Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

FORSCHEN
LEHREN
HEILEN

Herausgegeben von der Kommission Mamma
(vertreten durch: Wolfgang Janni)
der Arbeitsgemeinschaft Gynäkologische Onkologie e.V.
in der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe e.V.
sowie der Deutschen Krebsgesellschaft e.V.

Inhaltsverzeichnis

Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Empfehlungen der AGO Kommission Mamma

FORSCHEN
LEHREN
HEILEN

ARBEITSGEMEINSCHAFT GYNÄKOLOGISCHE ONKOLOGIE E.V.

KOMMISSION MAMMA

Oxford Levels of Evidence (LoE)

LoE	Therapy/Prevention, Aetiology/Harm	Prognosis
1a	Systematic review (with homogeneity) of randomised controlled trials	Systematic review (with homogeneity) of inception cohort studies; clinical decision rule validated in different populations
1b	Individual randomised controlled trials (with narrow Confidence Interval)	Individual inception cohort study with ≥ 80% follow-up; clinical decision rule validated in a single population
1c	All or none	All or none case-series
2a	Systematic review (with homogeneity) of cohort studies	Systematic review (with homogeneity) of either retrospective cohort studies or untreated control groups in randomised controlled trials
2b	Individual cohort study (including low quality randomised controlled trials; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in a randomised controlled trials; Derivation of clinical decision rule or validated on split-sample only
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research
3a	Systematic review (with homogeneity) of case-control studies	
3b	Individual Case-Control Study	
4	Case-series (and poor quality cohort and case-control studies)	Case-series (and poor quality prognostic cohort studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Guidelines Breast
Version 2024.1

Oxford Grades of Recommendation (GR)

A	consistent level 1 studies
B	consistent level 2 or 3 studies ***or*** **extrapolations from level 1 studies**
C	level 4 studies ***or*** **extrapolations from level 2 or 3 studies**
D	level 5 evidence ***or*** **troublingly inconsistent or inconclusive studies of any level**

Guidelines Breast
Version 2024.1

AGO Grades of Recommendation

++	This investigation or therapeutic intervention is highly beneficial for patients, can be recommended without restriction, and should be performed.
+	This investigation or therapeutic intervention is of limited benefit for patients and can be performed.
+/-	This investigation or therapeutic intervention has not shown benefit for patients and may be performed only in individual cases. According to current knowledge a general recommendation cannot be given.
-	This investigation or therapeutic intervention can be of disadvantage for patients and might not be performed.
--	This investigation or therapeutic intervention is of clear disadvantage for patients and should be avoided or omitted in any case.

Guidelines Breast
Version 2024.1

Abbreviations – I

A	Doxorubicin
ACC	Adenoid-zystisches Karzinom (adenoid cystic carcinoma)
ADH	Atypische duktale Hyperplasie
ADL	Aktivitäten des täglichen Lebens (activities of daily life)
ADM	Azelluläre dermale Matrix
ADP	atypische epitheliale Proliferation vom duktalen Typ
AHT	Arterielle Hypertonie
AI	Aromataseinhibitor
AK	Antikörper
ALH	Atypische lobuläre Hyperplasie
A_{lip}	Liposomales Doxorubicin
ALND	Axilläre Lymphknotendissektion
AML	akute myeloische Leukämie
ANC	Absolute Neutrophilenzahl
APBI	Akzelerierte Teilbrustbestrahlung
APR	Aprepitant
AR	Androgenrezeptor
ARDS	Acute Respiratory Distress Syndrome
ASS	Acetylsalicylsäure
AT	Anthrazyklin/Taxan
AZ	Allgemeinzustand
BAL	Bronchoalveoläre Lavage
BC	Mammakarzinom (breast cancer)
BCFI	Brustkrebs-freies Intervall

Guidelines Breast
Version 2024.1

Abbreviations – II

BCI	Breast Cancer Index
BCS	Brusterhaltende Operation (breast-conserving surgery)
BCT	Brusterhaltende Therapie (breast-conserving therapy)
BEO	Brusterhaltende Operation
BET	Brusterhaltende Therapie
Bev	Bevacizumab
BfARM	Bundesinstitut für Arzneimittel und Medizinprodukte
BIA-ALCL	Brustimplantat-assoziiertes anaplastisches großzelliges Lymphom
BMI	Body Mass Index
BP	Bisphosphonat
BR	Brustrekonstruktion
BSE	Selbstuntersuchung (breast self-examination)
BZ	Brustkrebszentrum
C	Cyclophosphamid
Ca.	Karzinom
CAM	Komplementäre und alternative Medizin
Cap	Capecitabin
CBE	klinische Brustuntersuchung (clinical breast examination)
CDK4/6i	Cyklin-abhängige Kinase 4/6-Inhibitor
CESM	Kontrastmittel-verstärkte spektrale Mammographie (contrast enhanced spectral Mammography)
CEUS	Kontrastmittel-Sonographie (contrast enhanced ultrasound)
cfDNA	zellfreie DNA
CGA	Umfassende geriatrische Einschätzung (Comprehensive Geriatric Assessment)
CHF	Kardiomyopathie (congestive heart failure)

Guidelines Breast
Version 2024.1

Abbreviations – III

CHOP	Cyclophosphamid, Doxorubicin, Vincristin, Prednison
CI	Konfidenzintervall (Confidence interval)
CIA	Chemotherapie-induzierte Amenorrhoe
CIPN	Chemotherapie-induzierte periphere Neuropathie
CISH	Chromogene in situ-Hybridisierung
CMF	Cyclophosphamid, Methotrexat, 5-Fluorouracil
CNB	Stanzbiopsie (core needle biopsy)
COX2	Cyclooxygenase-2
CPS	Combined positive score
CRA	Chemotherapie-induzierte Amenorrhoe (chemotherapy-related amenorrhea)
CSL	Komplexe sklerosierende Läsion
CT	Computertomographie
CTC	Zirkulierende Tumorzellen
CTS	Category of tumor marker study
CTS5	Clinical Treatment Score 5
CTx	Chemotherapie
CUP	Cancer of unknown primary
D	Docetaxel
DAC	Docetaxel, Doxorubicin, Cyclophosphamid
DBT	Digitale Brust-Tomosynthese
DCIS	Duktales Carcinoma in situ
DDFS	Distant disease free survival
DDT	Dichlordiphenyltrichlorethan
DES	Diethylstilbestrol

Abbreviations – IV

DEX	Dexamethason
DFS	Krankheitsfreies Überleben
DHEA	Dehydroepiandrosteron
DIEP	Deep Inferior Epigastric Perforator (Lappen)
DK-FBEK	Deutsches Konsortium für Familiären Brust- und Eierstockkrebs
DM	Digitale Mammographie
DM	Fernmetastasierung
Dmab	Denosumab
DMSO	Dimethylsulfoxid
DOP	Dopaminrezeptor-Antagonist
DPD	Dihydropyrimidin-Dehydrogenase
DS-GPA	Diagnosis-specific Graded Prognostic Assessment
DTC	Disseminierte Tumorzellen
DXA	Dual-Röntgen-Absorptiometrie
E	Epirubicin
E2	Estradiol
EAT	Erweiterte adjuvante endokrine Therapie
eBC	Frühes Mammakarzinom
EBUS	Endobronchialer Ultraschall
ECS	Extrakapsuläres Tumorwachstum
EFS	Event-freies Überleben
EGFR	Epidermaler Wachstumsfaktorrezeptor
EIC	Extensive intraduktale Komponente
EK	Einschlusskriterien

Abbreviations – V

ELEE	Geschätzte lebenslange Estrogen-Exposition (Estimated lifetime estrogen exposure)
EM Ca	Endometriumkarzinom
EMA	European Medicines Agency
ER	Estrogenrezeptor
ESF	Erythropoese-stimulierender Faktor
ETx	Endokrine Therapie
F	5-Fluorouracil
F/U	Follow up
FBC	Blutbild (full blood count)
FCI	Fasciocutaneous Infragluteal Flap
FDA	Food and Drug Administration
FDG-PET	^{18}F-2-Fluor-2-Desoxyglucose-Positronen-Emissions-Tomographie
FEA	Flache epitheliale Atypie
FED	Funktioneller Eisenmangel
FFPE	Formalin-fixiertes Paraffin-eingebettetes Gewebe
FISH	Fluoreszenz-in-situ-Hybridisierung
FN	Febrile Neutropenie
FSH	Follikelstimulierendes Hormon
FSRT	Fraktionierte stereotaktische Radiotherapie
Ful	Fulvestrant
G-CSF	Granulozyten-Kolonie-stimulierender Faktor
GC-HBOC	German Consortium for Hereditary Breast and Ovarian Cancer
GCP	Gute klinische Praxis (Good Clinical Practice)

Abbreviations – VI

GEP	Gexexpressionsprofil
GI	Gastrointestinal
GJG	Goshajinkigan
GKP	Gute klinische Praxis
GKV	Gesetzliche Krankenversicherung
GnRH	Gonadotropin-Releasing-Hormon
GnRHa	Gonadotropin-Releasing-Hormon-Agonist
GR	Oxford Grade of Recommendation
HER2	Human epidermal growth factor receptor 2
HFS	Hand-Fuß-Syndrom
HR	Hazard Ratio
HR	Hormonrezeptor
HRQoL	Gesundheitsbezogene Lebensqualität (Health-related quality of life)
HRT	Hormonersatztherapie
HT	Hormontherapie
IADL	The Lawton Instrumental Activities of Daily Living Scale
IBC	Inflammatorisches Mammakarzinom
IBR	Sofortrekonstruktion (immediate breast reconstruction)
IBTR	Ipsilaterales Brustrezidiv (Ipsilateral Breast Tumor Recurrence)
IC	Immunzellen
ICG	Indocyaningrün
ICG	Infraklavikulärgrube
ICPi	Immuncheckpointinhibitor

Guidelines Breast
Version 2024.1

Abbreviations – VII

iddETC	Epirubicin, Paclitaxel, Cyclophosphamid, dosis-dicht, dosis-intensiviert
iDFS	invasives krankheitsfreies Überleben
IGAP	Inferior gluteal artery perforator
IHC	Immunhistochemie
ILC	Invasives lobuläres Karzinom
ILRR	Ipsilaterales lokoregionäres Rezidiv
IMC	Mammaria interna Region (internal mammary lymph node chain)
IMRT	Intensitätsmodulierte Radiotherapie
IOERT	Intraoperative Elektronen-Radiotherapie
IORT	Intraoperative Radiotherapie
IR	Implantat-Rekonstruktion
irAE	Immunbezogenes unerwünschtes Ereignis (Immune-related adverse event)
ISH	In-situ-Hybridisierung
ITC	Isolierte Tumorzellen
IUD	Intrauterine device
KFU	Krebsfrüherkennungsuntersuchung
Lap	Lapatinib
LCIS	Lobuläres Carcinoma in situ
LH	Luteinisierendes Hormon
LHRH	Luteinisierendes-Hormon-Releasing-Hormon
LIN	Lobuläre intraepitheliale Neoplasie
LITT	Laser-induzierte Tumortherapie
LK	Lymphknoten

Guidelines Breast
Version 2024.1

Abbreviations – VIII

LN	Lobuläre Neoplasie
LoE	Evidenzlevel (level of evidence)
LR	Lokalrezidiv
LRFI	Lokalrezidiv-freies Intervall
LVEF	Links-ventrikuläre Ejektionsfraktion
LVI	Lymphovaskuläre Invasion
MaCa	Mammakarzinom
MAK	Mamillen-Areola-Komplex
mBC	metastasierter Brustkrebs
MBSR	Mindfulness-Based Stress Reduction
MCP	Metoclopramid
MDS	Myelodysplastisches Syndrom
ME	Mastektomie
MedDRA	Medical Dictionary for Regulatory Activities
MF	Multifokalität
MG	Mammographie
MMF	Mycophenolate mofetil
MPA	Medroxyprogesteronacetat
MPE	Maligner Pleuraerguss
MRI	Magnetresonanztomographie (magnetic resonance imaging)
MRM	Modifiziert radikale Mastektomie
MRT/MR	Magnetresonanztomographie
MS	Mammasonographie
MSI	Mikrosatelliteninstabilität

Abbreviations – IX

MTX	Methotrexat
MUGA	Multigated acquisition
MZ	Multizentrizität
n.a.	nicht verfügbar (not available)
n.r.	nicht berichtet (not reported)
n.s.	Nicht signifikant
NabPac	Nab-Paclitaxel
NACT	Neoadjuvante Chemotherapie
NEPA	Netupitant / Palonosetron
NET	Neoadjuvante endokrine Therapie
NGS	Next-Generation-Sequencing
NK1	Neurokinin-1
NNT	Number needed to treat
NSAID	Nicht-steroidale Antiphlogistika (non-steroidal anti-inflammatory drug)
NSM	Mamillensparende Mastektomie (nipple-sparing mastectomy)
NST	Kein spezieller Typ (no special type)
NW	Nebenwirkung
NX	Vinorelbin, Capecitabin
OC	Ovarialkarzinom
OFS	Ovarialfunktions-Suppression
OLZ	Olanzapin
OM	Orale Mukositis
ONJ	Kieferosteonekrose (osteonecrosis of the jaw)

Abbreviations – X

OP	Operation
OPS	Onkoplastische brusterhaltende Operation
OR	Odds Ratio
OS	Gesamtüberleben (overall survival)
OSNA	One Step Nucleic Acid Amplification
Pac	Paclitaxel
PAF	Population attributable fractions
PAI-1	Plasminogen-Aktivator-Inhibitor Typ 1
PARP	Poly-ADP-Ribose-Polymerase
PARPi	PARP-Inhibitor
PBI	Partielle Brustbestrahlung (partial breast irradiation)
PCO	Polycystic Ovarian Syndrome
pCR	pathologische Komplettremission
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death 1 ligand 1
PE	Probeentnahme
PEA	Palmitoylethanolamid
PET-CT	Positronen-Emissions-Tomographie-Computertomographie
PFS	Progressionsfreies Überleben
PJP	Pneumocystis jiroveci-Pneumonie
PLAC	Placebo
PMMA	Polymethylmethacrylat
PMRT	Post-Mastektomie Radiotherapie
POI	Prämature Ovarialinsuffizienz

Abbreviations – XI

PPE	Palmares und plantares Erythem
PPV	Positiver prädiktiver Wert
PR	Progesteronrezeptor
PROM	Patient-reported outcome measures
PT	Phylloides-Tumor
PTV	Zielvolumen (Planning Target Volume)
PVP	Povidon
Pw	Paclitaxel weekly
Pz	Pertuzumab
QA	Quality assurance
QoL	Lebensqualität (quality of life)
RFA	Radiofrequenzablation
RFID	Radiofrequenz-Identifikation
RFS	Rezidivfreies Überleben
RR	Relatives Risiko
RRBM	Risiko-reduzierende bilaterale Mastektomie
RRCM	Risikoreduzierende kontralaterale Mastektomie
RRSO	Risiko-reduzierende bilaterale Salpingo-Oophorektomie
RS	Recurrence Score
RT	Radiotherapie
RT-PCR	Reverse-Transkriptase-Polymerase-Kettenreaktion
SAE	Schwerwiegendes unerwünschtes Ereignis

Abbreviations – XII

SAPV	Spezialisierte ambulante Palliativversorgung
SCC	Plattenepithelkarzinom (squamous cell carcinoma)
SCG	Supraklavikulärgrube
SD	Standardabweichung (Standard deviation)
SGAP	Superior gluteal artery perforator (Lappen)
SIEA	Superficial inferior epigastric artery (Lappen)
SIR	Standardized incidence ratio
SIRT	Selektive interne Radiotherapie
SLN	Sentinel-Lymphknoten
SLNE	Sentinel-Lymphknoten-Exzision
SM	Synthetische Mammographie
SNP	Single Nucleotide Polymorphism
SNRI	Serotonin-Noradrenalin-Wiederaufnahmehemmer
SPIO	Superparamagnetic Iron Oxide
SRE	Skeletal-related events
SRS	Stereotactic radiosurgery
SRS-VMAT	Stereotactic radiosurgery with volumetric modulated arc therapy
SSE	Symptomatic skeletal events
SSI	Wundinfektion (surgical site infection)
SSM	Hautsparende Mastektomie (Skin sparing mastectomy)
SSRI	Selektive Serotonin-Wiederaufnahmehemmer
TAD	Targeted Axillary Dissection
Tam	Tamoxifen
TB	Tuberkulose

Guidelines Breast
Version 2024.1

Abbreviations – XIII

TBP	Treatment beyond progression
TCHP	Docetaxel, Carboplatin, Trastuzumab, Pertuzumab
TDLU	Terminale duktulolobuläre Einheit
TdP	Torsade de Pointes
TENS	Transkutane elektrische Nervenstimulation
TFI	Therapiefreies Intervall
TFT	Schilddrüsenfunktionstest
TIA	Therapie-induzierte Amenorrhoe
TIL	Tumor-infiltrierende Lymphozyten
TLNE	Targeted Lymph Node Excision
TMG	Transverse Musculocutanaeus Gracilis (Lappen)
TN	triple-negativ
TNBC	triple-negatives Mammakarzinom
TRAM	Transverser Rectus abdominus Muskel (Lappen)
TTR	Zeit zum Rezidiv (time to recurrence)
TxCHP	Paclitaxel, Carboplatin, Trastuzumab, Pertuzumab
Tz	Trastuzumab
UCT	Unkonventionelle Therapie
UE	Unerwünschtes Ereignis
ÜL	Überleben
uPA	Urokinase-Typ Plasminogen Aktivator
uPCR	Urin-Protein:Kreatinin-Ratio
VAB	Vakuumbiopsie (vacuum-assisted breast biopsy)

Abbreviations – XIV

VAB	Vakuumbiopsie (vacuum-assisted breast biopsy)
VATS	Videoassistierte Thorakoskopie
VUS	Variante unklarer Signifikanz (variant of unknown significance)
WBI	Ganzbrustbestrahlung (whole breast irradiation)
WBRT	Ganzhirnradiatio (whole brain radiotherapy)
ZNS	Zentrales Nervensystem

Guidelines Breast
Version 2024.1

Members of the AGO Breast Committee

Guidelines Breast
Version 2024.1

Members of the Breast Committee 1

- Prof. Dr. Ute-Susann Albert, Würzburg
- Prof. Dr. M. Banys-Paluchowski, Lübeck
- Dr. Ingo Bauerfeind, Landshut
- Prof. Dr. Jens-Uwe Blohmer, Berlin
- Prof. Dr. Wilfried Budach, Düsseldorf
- Prof. Dr. Peter Dall, Lüneburg
- Prof. Dr. Nina Ditsch, Augsburg
- PD Dr. Eva Fallenberg, München
- Prof. Dr. Peter Fasching, Erlangen
- Prof. Dr. Tanja Fehm, Düsseldorf
- Prof. Dr. Michael Friedrich, Krefeld
- Prof. Dr. Bernd Gerber, Rostock
- PD Dr. Oleg Gluz, Mönchengladbach
- Prof. Dr. Nadia Harbeck, München
- Prof. Dr. Andreas Hartkopf, Tübingen
- Prof. Dr. Jörg Heil, Heidelberg
- Prof. Dr. Jens Huober, St. Gallen
- Prof. Dr. Christian Jackisch, Offenbach
- Prof. Dr. Wolfgang Janni, Ulm
- Prof. Dr. Cornelia Kolberg-Liedtke, Berlin
- Prof. Dr. Hans H. Kreipe, Hannover (DGP)
- PD Dr. David Krug, Kiel
- Prof. Dr. Thorsten Kühn, Esslingen
- Prof. Dr. Sherko Kümmel, Essen

Guidelines Breast
Version 2024.1

Members of the Breast Committee 2

- Prof. Dr. Sibylle Loibl, Neu-Isenburg / Frankfurt
- Prof. Dr. Diana Lüftner, Berlin
- Prof. Dr. Michael Lux, Paderborn
- Prof. Dr. Nicolai Maass, Kiel
- Prof. Dr. Volkmar Müller, Hamburg
- Prof. Dr. Christoph Mundhenke, Bayreuth
- Prof. Dr. Ulrike Nitz, Mönchengladbach
- Prof. Dr. T.-W. Park-Simon, Hannover
- Prof. Dr. Toralf Reimer, Rostock
- Prof. Dr. Kerstin Rhiem, Köln
- Prof. Dr. Achim Rody, Lübeck
- Prof. Dr. Marcus Schmidt, Mainz
- Prof. Dr. Andreas Schneeweiss, Heidelberg (AIO)
- Prof. Dr. Florian Schütz, Speyer
- Prof. Dr. H. Peter Sinn, Heidelberg (Pathologie)
- Prof. Dr. Christine Solbach, Frankfurt
- Prof. Dr. Erich F. Solomayer, Homburg
- Prof. Dr. Elmar Stickeler, Aachen
- Prof. Dr. Marc Thill, Frankfurt
- Prof. Dr. Christoph Thomssen, Halle
- Prof. Dr. Michael Untch, Berlin
- Prof. Dr. Isabell Witzel, Zürich
- Prof. Dr. Achim Wöckel, Würzburg
- PD Dr. Rachel Würstlein

Guidelines Breast
Version 2024.1

Previous Members of the Breast Committee 1

- Prof. Dr. Werner Audretsch, Düsseldorf
- PD Dr. Joachim Bischoff, Dessau
- Dr. Michael Böhme, Magdeburg
- Dr. Klaus E. Brunnert, Osnabrück
- Prof. Dr. Dr. Serban D. Costa, Magdeburg
- Prof. Dr. Ingo J. Diel, Mannheim
- PD Dr. Nikos Fersis, Duisburg
- PD Dr. Kay Friedrichs, Hamburg
- Prof. Dr. Uwe-Jochen Göhring, Bonn
- Prof. Dr. Volker Hanf, Fürth
- Dr. Georg Heinrich, Fürstenwalde
- Prof. Dr. Walter Jonat, Kiel (DKH)
- Dr. Hans Junkermann, Heidelberg
- Prof. Dr. Manfred Kaufmann, Frankfurt
- Dr. Björn-Wieland Lisboa, Düsseldorf
- Prof. Dr. Hans-Joachim Lück, Hannover
- Prof. Dr. Gunter von Minckwitz, Neu-Isenburg / Düsseldorf
- Prof. Dr. Volker Möbus, Frankfurt
- Prof. Dr. Markus Müller-Schimpfle, Frankfurt
- PD Dr. Carsten Oberhoff, Essen

Previous Members of the Breast Committee 2

- **Dr. Mahdi Rezai, Düsseldorf**
- **Prof. Dr. Gerhard Schaller, München**
- **Prof. Dr. Anton Scharl, Amberg**
- **Prof. Dr. Rita Schmutzler, Köln**
- **Prof. Dr. Ingrid Schreer, Hamburg**
- **Prof. Dr. H. Seegenschmiedt, Essen**
- **Prof. Dr. W. Simon, Stuttgart**
- **Prof. Dr. Rainer Souchon, Berlin**
- **Prof. Dr. Frederik Wenz, Freiburg**

Potential Conflict of Interest (COI)

- **The members of the editing committee of these guidelines are specialists in diagnosis, treatment, and research in breast cancer. Most of the members therefore have cooperations with industry. Thus, potential conflict of interest cannot be excluded.**
- **In order to minimize potential bias within the statements we followed the pre-defined rules:**
  - **These guidelines are strictly based on available evidence from the scientific literature.**
  - **The chapters of each edition were prepared by annually alternating teams of authors.**
  - **Each statement and the correspondent AGO-recommendations were thoroughly discussed within the entire group and accepted by majority decisions.**
  - **Each member of the editing committee is required to submit a written declaration of his/her conflicts of interests to an elected internal COI committee on an annual basis.**
  - **Members who do not submit a COI declaration may not participate in the guideline preparation.**

Potential Conflicts of Interest (COI) 2023 - 2024

Guidelines Breast
Version 2024.1

All members of the AGO Breast Committee have submitted their COI report for the past year. Members of the AGO Breast Committee indicated that they have received support (e.g. research funding, lecture or consulting honoraria etc.) from the following commercial entities:

Abbvie, AGE, Agendia, Amgen, Apogheva, aQua-Institut GmbH, Art Tempi communications GmbH, AstraZeneca, Atheneum, Aurikamed, Aventis, Bayer, Becton/Dickinson, Berliner Krebsgesellschaft, best practice onkologie, BGGF, Biom'Up, BioNTech, BLÄK, BMBF, BMMC, BMS (Head and Neck Cancer), Brands Minds Media Communication, b-rayZ, Brustkrebs Deutschland e. V. , BZKF, Cairn Surgical, Canon, Carl Zeiss Meditec, Cellegene, Chugai, Clarivate Analytics Ltd, ClearCut, Clinsol, Clovis, ConEvent, Daiichi-Sankyo, DeltaMed Nord, Deutsche Akademie für Senologie e.V., Deutsche Kresbshilfe, DFG, Dialog Service GmbH, Dracentus, DSI, Eickeler-Kongress, EirGenix, Eisai, Eli Lilly, Endomag, EPG Communication, ESMO, ESO, Esteve, EU (alles an Institution), EUSOBI, Excact Sciences, Funding, FuxWinter, GBA, GBG, GedeonRichter, Genentech (Institutionell), Georg Thieme Verlag GmbH, German Breast Group, Gilead, Grünethal, GSK, Hexal, high5med GmbH, Hologic, If-Kongress Management GmbH, I-Med-Institute, Inivata, institutionell Celegene, institutionell DSI, iOMEDICO AG, IQTIG6, Janssen, Jörg Eickeler, Klinikum Chemnitz, Krebsstiftung NRW, Laborarztpraxis Walther et al., LÄK Hessen Akademie, Lilly, LMU Klinikum/Studienzentrale, Loreal, Mammotome, MCI, Med Concept, med update GmbH, Medac, MedConcept GmbH, Medi-Seminar, Medscape, Menari-Group, Menarini, Merck (Head and Neck cancer), Merck KGaA, Merit-Medical, MSD, MTE, Mylan, Myriad Genetics, NCO, Neodynamics, NOGGO e.V., Novartis, Olema, Oncolgy, Onko-Interbetportal, Onkowissen, OnkoZert, Organon, Palleos, Pantarhei Bioscience, Paxman, Pfizer, pfm Medical, Phaon, Piere Fabre, PINK, Pomme Med, PRAEGNENT / ClinSol, primus Relay Therapeutics, Research Grant, Resitu, RG-Gesellschaft, Roche, Roland Berger GmbH, RTI Surgical, Saarl. Krebsgesellschaft, Samantree, Samsung, Sandoz, Sankyo, Sanofi, Sanofi Genzyme, Sanofi-Aventis, Seagen, Seattle Genetics, Sidekick Health, Sirius Medical, SLK Kliniken Heilbronn GmbH, SPCC Grant, Springer Verlag, Stemline – Menarini, Stemline Therapeutics, Storz, StreamedUp GmbH, Syantra, Sysmex, Teva, UKA, Universitätsklinikum Ulm, Vericyte, Viatris, Vifor, Vovartis Best Academy, WSG, Zeneca, ZP Therapeutics, Zuckschwerdt Verlag, Zuelligpharma. The Committee did not consider any of the reported support to represent a conflict of interest that would preclude participation in AGO Breast Committee discussions or voting.

Guidelines Breast
Version 2023.1

How to Use these Slides

- **The AGO Breast Committee encourages everyone to use these slides for his or her own information, improvement of patient care, medical education, presentations, and publications.**
- **For presentations, the slides should only be used in their original version and layout, e.g. by using a PDF-copy of each slide. The AGO-signet ("logo") should not be modified or erased. Extracting single phrases or parts of the slides may change the guideline content and is therefore not allowed.**
- **The following citation needs to be used: *"AGO Breast Committee. Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer. Recommendations 2024. www.ago-online.de"***
- **Prior to any print media or electronic publication (except for oral presentations), the corresponding tables or figures have to be submitted to the chairman of the AGO Breast Committee in order to obtain written permission (currently at *direktion.frauenklinik@uniklinik-ulm.de*).**
- **A summary of the slides is availabe as publication in the journal „Breast Care“.**
- **Speaking of patients implicates that female / male / diverse gender is included.**

Guidelines Breast
Version 2024.1

Editor & Copyright

Kommission „Mamma“ der
Arbeitsgemeinschaft für gynäkologische
Onkologie
(AGO)
www.ago-online.de

Address for correspondence:

Univ.-Prof. Dr. med. Wolfgang Janni
Frauenklinik, Dpt. Obst&Gyn
Universitätsklinikum Ulm
Prittwitzstr. 43 | 89075 Ulm
P +49 731 500 58500 | F +49 731 500 58502
direktion.frauenklinik@uniklinik-ulm.de

Prof. Dr. Volkmar Müller
Universitätsklinikum Hamburg-Eppendorf
Martinistr. 52 | 20246 Hamburg
P +49 40 7410-52510 | F +49 40 7410-54355
v.mueller@uke.de

Editorial Assistance: **Dr. Kristina Veselinovic**

Guidelines Breast
Version 2024.1E

Options for Primary Prevention: Modifiable Lifestyle Factors

Prevention

- **Versions 2011–2023:**
  Albert / Dall / Diel / Gerber / Hanf / Maass / Mundhenke / Rhiem / Solbach / Solomayer / Thomssen / von Minckwitz / Albert

- **Version 2024:**
  Fasching / Solomayer

Guidelines Breast
Version 2024.1E

Risk Factors

- Female
- Family history of cancer
- Breast density
- Older age
- Genetics
- Lower number of births or no pregnancy
- Advanced age at first full term delivery
- Alcohol intake
- Nicotine
- Steroid hormone therapy
- Oral contraceptive use
- Hormone therapy (estrogen / gestagen combination) in postmenopausal women
- Adipositas in postmenopausal women
- Personal history of breast lesions
  - Non-proliferative lesions
  - Proliferative lesions w/o atypia
  - High risk lesions (ADH, LIN)
  - Breast cancer (DCIS, Inv. BC)
- Chest irradiation
- Air pollution (PM2,5)

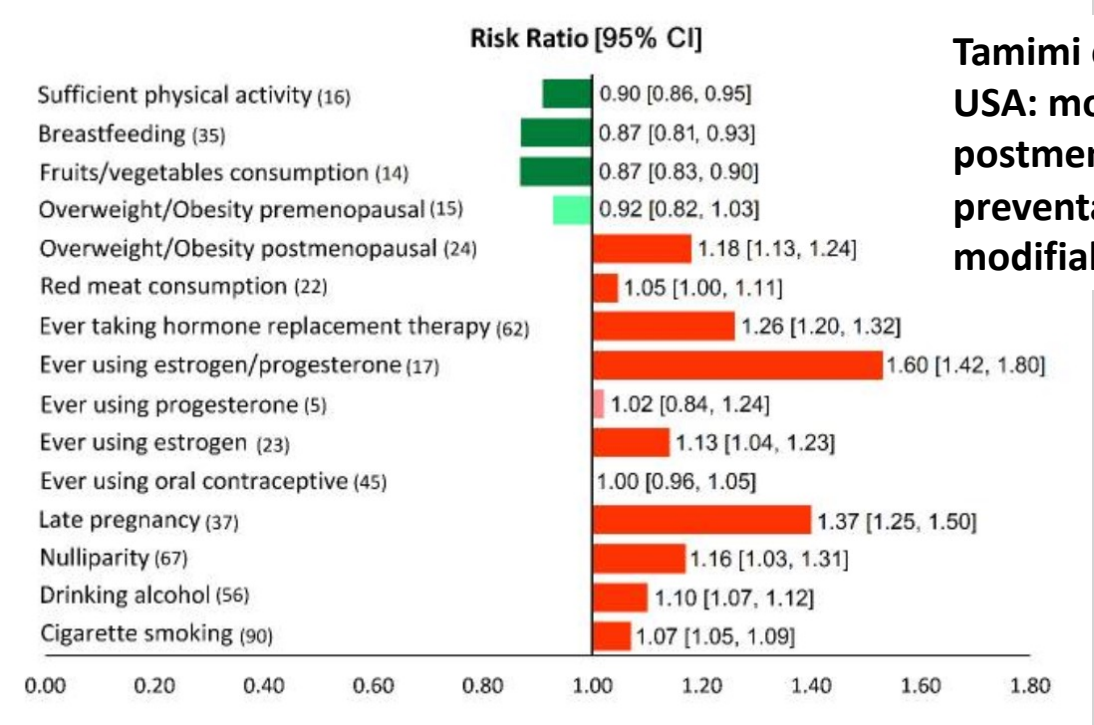
Guidelines Breast
Version 2024.1E

Protective factors

- **Full terminated pregnancies**
- **Early terminated pregnancies**
- **Regulary physical movement**
- **Breastfeeding**

Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies

Guidelines Breast
Version 2024.1E

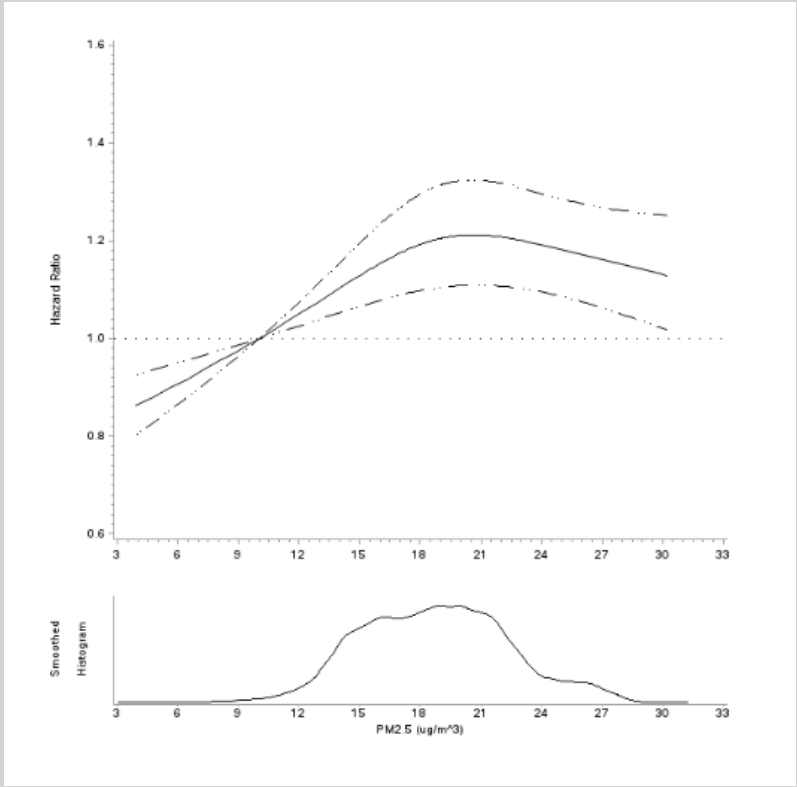


Tamimi et al, 2016
USA: more than a third of postmenopausal breast cancers are preventable through changes in modifiable risk factors

Poorolajal J et al. J Res Health Sci. 2021 Jul 20;21(3):e00520.

Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies

Guidelines Breast
Version 2024.1E



196 905 Teilnehmerinnen von denen 15 870 Mammakarzinom hatten. Durchschnittliche PM2.5 Werte in der Wohnregion. Medianes Follow up von 20,7 Jahren

A 10 ug/m^3 increase in PM2.5 was statistically significantly associated with overall breast cancer incidence (HR: 1.08, 95% CI: 1.02 to 1.13). The association was evident for estrogen receptor–positive (H = 1.10, 95% CI: 1.04 to 1.17) but not estrogen receptor–negative tumors (HR: 0.97, 95% CI: 0.84 to 1.13)

White et al. JNCI 2023; DOI: https://doi.org/10.1093/jnci/djad170

Guidelines Breast
Version 2024.1E

Pregnancy Related Factors

List of factors that are still being clarified

Prevention	Oxford LoE	Oxford GR
▪ Any full-term pregnancy	2b	B
▪ High number of pregnancies	2b	B
▪ Young age at first full-term pregnancy	2b	B
▪ Breast feeding (protective if total breast-feeding time exceeds 1.5-2 years)	3a	B
▪ Lower birth weight of the first born (3000-3500 vs. > 4500g RR = 1.53)	2b	B
▪ Lower length of pregnancy first born (26-31. WOP vs. 40-41. WOP; HR = 2.38, p = 0.03)	2b	B

Guidelines Breast
Version 2024.1E

Impact of Breastfeeding on Breast Cancer Risk

- **Breastfeeding reduces the risk of breast cancer by 4.3% for every 12 months of breastfeeding, which is in addition to the 7.0% decrease in risk observed for each birth.**
- **Breastfeeding has been shown to primarily reduce the risk of Triple- Negative Breast Cancer (20%) as well as in carriers of BRCA1 mutations (22– 50%).**
- **An estimated 4.7% of breast cancer cases in the UK are caused by not breastfeeding.**

From: Stordal B. Cancer Med. 2022 Sep 26.

Medical endocrine Prevention for Women at Increased Risk

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Tamoxifen for women > 35 years: Risk reduction of invasive BC, DCIS and LN	1a	A	+*
▪ Raloxifen for postmenopausal women: Risk reduction of invasive BC only	1b	A	+*
▪ AI for postmenopausal women	1b	A	+**

* Risk situation as defined in NSABP P1-trial (1.66% in 5 years) or according to #Tyrer-Cuzick model (IBIS-II)

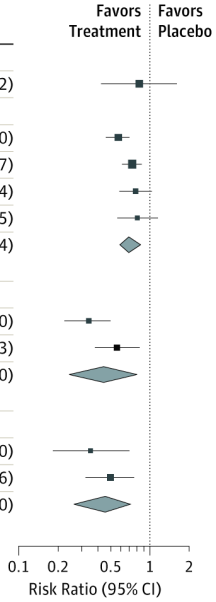
** Significant risk reduction was seen for anastrozole for ovarian and endometrial cancer, as well as skin, colorectal, hematologic, thyroid and urinary tract cancers. Chemopreventive regimes should only be offered after individual and comprehensive counseling. The net benefit strongly depends on risk status, age and pre-existing risk factors for side effects.

Medical Endocrine Prevention

Guidelines Breast
Version 2024.1E

Risk Reduction of Invasive Breast Cancer: Meta-analysis of Primary Prevention Trials

Source	Trial	Mean, y: Intended Treatment Duration	Mean, y: Total Follow-up	No. With Invasive Breast Cancer/Total Participants (%): Treatment	No. With Invasive Breast Cancer/Total Participants (%): Placebo	Rate per 1000 Women-Years: Treatment	Rate per 1000 Women-Years: Placebo	Risk Ratio (95% CI)
Tamoxifen, low dose								
DeCensi et al,[41] 2013	HOT	5	6.2	18/938 (1.9)	22/946 (2.3)	3.13	3.78	0.83 (0.42-1.62)
Tamoxifen								
Fisher et al,[82] 2005	NSABP-1	5	6.1	145/6681 (2.2)	250/6707 (3.7)	3.59	6.29	0.57 (0.46-0.70)
Cuzick et al,[74] 2015	IBIS-I	5	16.0	214/3579 (6.0)	289/3575 (8.1)	3.86	5.29	0.73 (0.61-0.87)
Powles et al,[83] 2007	Marsden	5	13.2	82/1238 (6.6)	104/1233 (8.4)	4.80	6.10	0.78 (0.58-1.04)
Veronesi et al,[84] 2007	Italian	4[a]	11.2	53/2700 (2.0)	66/2708 (2.4)	1.77	2.21	0.80 (0.56-1.15)
Combined I^2 = 38.7%; Q = 4.9 for heterogeneity; P = .18								0.69 (0.59-0.84)
Raloxifene								
Martino et al,[45] 2004	MORE/CORE	4 or 8[b]	5.4[b]	40/5129 (0.8)	58/2576 (2.3)	1.40	4.20	0.34 (0.22-0.50)
Barrett-Connor et al,[48] 2006	RUTH	5.1[a]	5.6	40/5044 (0.8)	70/5057 (1.4)	1.43	2.49	0.56 (0.38-0.83)
Combined I^2 = 66.4%; Q = 3.0 for heterogeneity; P = .08								0.44 (0.24-0.80)
Aromatase inhibitor								
Goss et al,[44] 2011	MAP.3	5[c]	2.9	11/2285 (0.5)	32/2275 (1.4)	1.66	4.85	0.35 (0.18-0.70)
Cuzick et al,[4] 2014	IBIS-II	5	5	32/1920 (1.7)	64/1944 (3.3)	3.29	6.62	0.50 (0.32-0.76)
Combined I^2 = 0.0%; Q = 0.8 for heterogeneity; P = .39								0.45 (0.26-0.70)



Nelson et al. JAMA. 2019;322(9):868-886. doi:10.1001/jama.2019.5780

Guidelines Breast
Version 2024.1E

Medical Primary non-hormonally Prevention*

	Oxford		
	LoE	GR	AGO
▪ ASS	2a	B	+/-
▪ COX2-Inhibitors	2a	B	+/-
▪ Bisphosphonates	2b	B	+/-
▪ Vitamin D	2b	B	+/-
▪ Statins	2b	B	-

* No approval, consider side effects

Guidelines Breast
Version 2024.1E

Medical non-endocrine Prevention

Kehm RD et al., Regular use of aspirin and other non-steroidal anti-inflammatory drugs and breast cancer risk for women at familial or genetic risk: a cohort study. Breast Cancer Res. 2019 Apr. 18;21(1):52

Prospective multinational cohort study, n = 5606, healthy women questionaire, regular intake of ASS, NSAID, COX2-inhibitors

Regular ASS-intake: HR 0.61, CI 0.33-1.14, breast cancer incidence
Regular COX2-inhibitors : HR 0.39, CI 0.15-0.97, breast cancer incidence other NSAIDs: n.s.
[independent of BRCA-status]

Guidelines Breast
Version 2024.1E

Prevention by Changing Lifestyle Factors: Body Mass Index / Diet

	Oxford		
	LoE	GR	AGO
▪ **Maintaining normal weight (BMI at 18.5-25 kg/m²)***	2a	B	++
▪ **Premenopausal**	3a	B	+/-
▪ **Postmenopausal**	2a	B	++
▪ **Prevention / screening and treatment of diabetes mellitus type II (reduction of breast cancer incidence and mortality)**	2b	B	++

* Amount of body fat can be increased in people with normal BMI and correlates with breast cancer risk

The risk of breast, ovarian and endometrial cancer in obese women submitted to bariatric surgery: a meta-analysis

B Ishihara, D Farah, M Fonseca and A Nazário, Surg Obes Relat Dis 2020;16(10):1596-1602

- **Meta-analysis, of a total of 150,537 patients in the bariatric surgery arm and 1,461,938 women in the control arm.**
- **The risk of breast cancer was reduced by 49 % [RR: 0.39 (95 % CI [0.31 to 0.56]; I^2 = 90 %; 7 studies).**
- **The risk of ovarian cancer was reduced by 53 % [RR: 0.47 (95 % CI [0.27 to 0.81]; I^2 = 0 %; 3 studies).**
- **The risk of endometrial cancer was reduced by 67 % [RR: 0.33 (95 % CI [0.21 to 0.51]; I^2 = 88 %; 7 studies).**

Association of Body Fat and Risk of Breast Cancer in Postmenopausal Women With Normal Body Mass Index: A Secondary Analysis of a Randomized Clinical Trial and Observational Study.

Iyengar NM et al.: JAMA Oncol. 2019 Feb 1;5(2):155-163

- **WHI substudy**
- **Among the 3460 women included in the analysis (mean [SD] age, 63.6 [7.6] years), multivariable-adjusted hazard ratios for the risk of invasive breast cancer were 1.89 (95 % CI, 1.21-2.95) for the highest quartile of whole-body fat and 1.88 (95 % CI, 1.18-2.98) for the highest quartile of trunk fat mass.**
- **The corresponding adjusted hazard ratios for ER-positive breast cancer were 2.21 (95 % CI, 1.23-3.67) and 1.98 (95 % CI, 1.18-3.31), respectively.**

Guidelines Breast
Version 2024.1E

Prevention by Changing Lifestyle Factors: Diet

* As recommended by German Society of Nutrition (DGE)
** Recommended as a part of healthy nutrition

	Oxford LoE	GR	AGO
▪ Preference of a balanced diet*	2b	B	+
▪ Mediterranean Diet	2a	B	+
▪ Dietary components			
▪ Olive oil (extra virgin olive oil), as part of mediterranean diet	2b	B	+
▪ Fat reduced food	2a	B	+
▪ Reduced consumption of red meat	2b	C	+
▪ Nuts / peanuts (> 10g/d) (peanut butter without effect)	2b	B	+
▪ Fiber containing food	2a	B	+
▪ Vitamin D substitution for prevention (MaCa HR1,02)	1b	B	+/-
▪ Vegetables / fruits **	2a	B	+/-
▪ Phytoestrogens / soy	2a	B	+/-
▪ Vegetarian / vegan diet (no significant risk reduction)	2b	C	+/-
▪ Coffee (no significant reduction)	2a	B	+/-
▪ Supplementation of vitamins, minerals, trace elements	2a	B	-

Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease

N Engl J Med. 2019 Jan 3;380(1):33-44. doi: 10.1056/NEJMoa1809944. Epub 2018 Nov 10.

Randomized, placebo-controlled trial, with a two-by-two factorial design, of vitamin D_3 (cholecalciferol) at a dose of 2000 IU per day and marine n-3 (also called omega-3) fatty acids at a dose of 1 g per day

Primary end points were invasive cancer of any type and major cardiovascular events

25,871 participants

median follow-up of 5.3 years

124 breast cancers (Vit D group) vs. 122 (placebo group) Hazard Ratio: 1,02

Olive Oil Consumption and Breast Cancer Risk

Guidelines Breast
Version 2024.1E

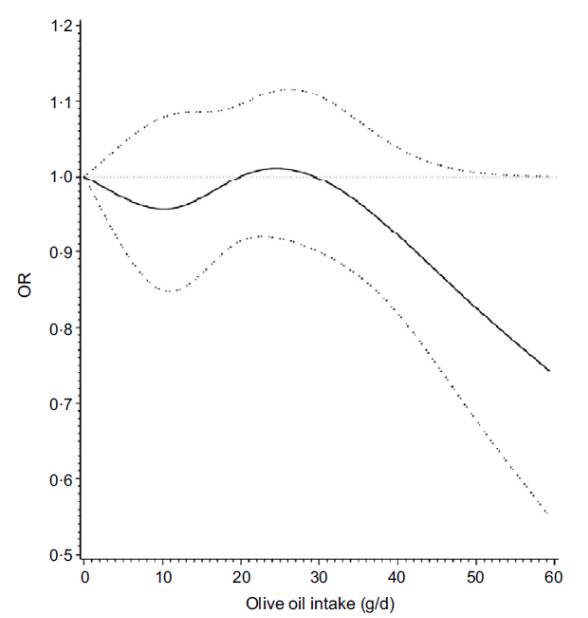


Fig. 5. Dose–response relationship between olive oil intake and breast cancer.

Table 3. Subgroup analyses for case–control studies of olive oil and breast cancer

Group	Number of studies	OR	95 % CI	I^2 (%)	$P_{for\ heterogeneity}$
Location					
Italy, Spain, Greece	4	0·60	0·39, 0·95	85	<0·001
Other countries	4	1·06	0·72, 1·57	58	0·07
Source of controls					
Hospital based	5	0·94	0·69, 1·28	65	0·02
Population based	3	0·57	0·28, 1·19	90	<0·001
Number of cases					
<500 cases	5	0·71	0·37, 1·39	89	<0·001
≥500 cases	3	0·80	0·67, 0·95	0	0·47
Exposure assessment					
Assessed amount consumed	5	0·75	0·48, 1·15	88	<0·001
Assessed frequency consumed	3	0·77	0·39, 1·51	69	0·04
Adjustment for total energy					
Adjusts for total energy	5	0·67	0·46, 0·98	83	<0·001
No adjustment for total energy	3	0·98	0·50, 1·91	69	0·04

1. **Amount of olive oil consumption correlates to breast cancer risk (not significant)**
2. **The source / quality of the olive oil (mediterranean vs others) seems to be relevant (or the origin of the data)**
3. **It is difficult to separate between use of olive oil and general adherence to a mediterranean diet.**

Sealy N et al. British Journal of Nutrition (2021), 125, 1148–1156

Prevention by Modifying Lifestyle Risk Factors: Alcohol

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Reduction of alcohol intace reduces risk of breast cancer (ideal < 10g/d, class II evidence)	2a	B	+
Particularly for			
▪ ER+ / PR+ tumors	2a	B	
▪ Invasive lobular tumors	2a	B	

Nature, Nurture and cancer risks: Genetic and nutritional contributions to cancer

Theodoratou, E.: Annu Rev Nutr. 2017 August 21; 37: 293–320.
doi:10.1146/annurev-nutr-071715-051004

No association was classified as convincing (class I). The association between alcohol intake and ER+ breast cancer was classified as highly suggestive (Class II) based on a meta-analysis of 20 prospective studies (≥ 30 g/d of alcohol consumption versus non-drinkers

RR (95% CI): 1.35 (1.23, 1.48, p-value = 5.2×10^{-10}, I^2 = 26 %,

$P_{\text{small effect bias}} = 0.184$, $P_{\text{excess significance bias}} = 4 \times 10^{-8}$)

Guidelines Breast
Version 2024.1E

Prevention by Modifying Lifestyle Risk Factors: Smoking

Oxford		
LoE	GR	AGO
2a	B	++

- **Never smoking reduces risk of breast cancer (~ 15-24% reduction of lifetime risk)**

- **Young women smoking have a 60% increased risk of BC, when smoking > 10 years before the first childbirth (vs. never smokers)**

Smoking and Risk of Breast Cancer in the Generations Study Cohort

Jones, M.E.:Breast Cancer Res. 2017 Nov 22;19(1):118. doi: 10.1186/s13058-017-0908-4.

102,927 women recruited 2003–2013

average of 7.7 years of follow-up

The HR (reference group was never smokers) was
1.14 (95% CI 1.03–1.25; *P* = 0.010) for ever smokers,
1.24 (95% CI 1.08–1.43; *P* = 0.002) for starting smoking at ages < 17 years
1.23 (1.07–1.41; *P* = 0.004) for starting smoking 1–4 years after menarche

Women with a family history of breast cancer (ever vs never smokers HR 1.35; 95% CI 1.12–1.62; *P* = 0.002) had a significantly larger HR … than women without (ever smoker vs never smoker HR 1.07; 95% CI 0.96–1.20; *P* = 0.22).

Guidelines Breast
Version 2024.1E

Prevention by Modifying Lifestyle Risk Factors: Physical Activity

	Oxford		
	LoE	GR	AGO
▪ **Physical exercise** **(Metabolic equivalents to 3–5 hrs moderate pace walking per week)**	2a	B	++

These effects also apply to *BRCA1/2* mutation carriers and for women with an increased family risk.

Recreational Physical Activity Is Associated with Reduced Breast Cancer Risk in Adult Women at High Risk for Breast Cancer: A Cohort Study of Women Selected for Familial and Genetic Risk.

Kehm RD et al.: Cancer Res. 2020 Jan 1;80(1):116-125. doi: 10.1158/0008-5472.CAN-19-1847. Epub 2019 Oct 2.

- **Prospective cohort study**
- **n = 15 550, women with fam. Hx of breast cancer**
- **multiplicative interactions of physical activity with predicted absolute breast cancer familial risk based on pedigree data and with BRCA1 and BRCA2 mutation status**
- **Higher physical activity → 20% reduction of breast cancer incidence**
- **(HR0.80, CI 0.68-0.93), independent of BRCA-status or pedigree risk**

Prevention by Modifying Lifestyle Risk Factors: Hormone Therapy in Postmenopausal Women

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
Avoiding hormonal therapy in postmenopausal women			
Avoiding estrogen / progestin combinations	1b	A	+
Avoiding estrogens only (no increased, possibly reduced breast cancer risk, but increased risk for endometrial cancer, if not hysterectomized)	1b	A	+/-

Epigenome-wide association study for lifetime estrogen exposure identifies an epigenetic signature associated with breast cancer risk.

Johansson A et al.: Clin Epigenetics. 2019 Apr 30;11(1):66.

Epidemiological data from EPIC-Italy (n = 31,864)
Study: estimated lifetime estrogen exposure

Method: epigenome-wide association study, blood DNA samples, n = 216 , and 440 healthy controls

Results: an estimated 5% increase in breast cancer risk per 1-year longer ELEE (OR = 1.05, 95% CI 1.04-1.07, P = $3x10^{-12}$) in EPIC-Italy.
694 CpG sites were associated with ELEE (FDR Q < 0.05)

Prevention of Hormones in Postmenopausal Patients

Guidelines Breast
Version 2024.1E

	N	MC-RR (95%CI)	Further information
WHI WHI: JAMA 2002, JAMA 2017	~ 27 000	1.3 (1,0-1,6)	1.3 (1.1-1,6) coronary events 1.4 (1,1-1,9) insults 2.1 (1,4-3,3) pulmonary embolism 2.1 (1,5-2,9) deep vein thrombosis
HERS Hulley S: JAMA 2002	I 2763 RCT, med. 4.1 yrs. II 2321 open-label, 2.7 yrs.	1.2 (0.95-1.5)	med. age 67 yrs. no secondary prevention side effects as comp. to WHI + cholcystectomy↗
Million Women Beral V: Lancet 2003	1.084 110 ~ 50 % HRT 4.1 J. follow-up	1.66 (1.6-1.8)	EPC > E mode of applic. not relevant duration > 5 yrs. Tibolon RR 1.45 (1.2-1.7)
EPIC Int J Cancer 2010	1.153 747 person-years	1.4 (1.2-1.6) 1.8 (1.4-2.2)	E-Mono EPC > E
Metaanalyse Nelson HD: JAMA 2002	16 Studies	1.21-1.40	side effects as compared to WHI +

Chlebowski et al., Climacteric 2015, 18:336-8
Chlebowski et al., J Natl Compr Canc Netw 2015, 13:917-24
Manson JE et al., JAMA 2017; 318: 927-938

Prevention of Hormones (EGC) in Postmenopausal Patients

Guidelines Breast
Version 2024.1E

	N	MC-RR (95% CI)	Further statements
CLEAR-study (NSW) **Case-Control-Study, retrospect. Australia**	**1236 BC cases**	2.09 (1.57-2.78)	current user
		1.03 (0.82-1.28)	past user
		2.62 (1.56-4.38)	E/P combination
		1.80 (1.21-2.68)	E only

Salagame et al., Int J Cancer. 2016;138(8):1905-14

Prevention by Modifying Lifestyle Risk Factors: Oral Contraception (OC)

Guidelines Breast
Version 2024.1E

	Oxford LoE
▪ OC does <u>not</u> increase the risk of mortality from breast cancer	1a
▪ <u>Risk</u> of breast cancer slightly increased, risk of ovarian, endometrial cancer is decreased	1a$^{(-)}$

Guidelines Breast
Version 2024.1E

Risk Reduction for Ipsi- and Contralateral Breast Cancer

Rationale: Women with breast cancer have an increased risk for a second primary

Additional preventive effect by	Oxford LoE	Oxford GR	Oxford AGO
▪ Tamoxifen	1a	A	+
▪ Aromatase inhibitors	1a	A	+
▪ Suppression of ovarian function + Tamoxifen	1b	B	+

Risk reduction for ipsi- and contralateral second breast cancers ("second primaries")

	Locali-zation	HR / RR	95% CI	p-value	ref.
Tamoxifen (vs nil)	ipsilat.	0.47	SE 0.08	0.00001	EBCTCG 2005
	contralat.	0.71	SE 0.06	< 0.00001	
Tamoxifen (vs nil) ER+ or unknown	ipsilat.	n.d.	n.d.	-	EBCTCG 2005
	contralat.	0.61	0.50–0.73	-	
Aromatase inhibitor (vs Tam)	ipsilat.	0.74	0.58 - 0.95	0.020	EBCTCG 2015
	contralat.	0.62	0.48 - 0.80	0.0003	
GnRH-agonist + tamoxifen (vs Tam)	ipsilat.		11.8 vs 16.7%	-	Cochrane 2020
	contralat.	0.56	0.29- 1.07	-	

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

Breast Cancer Risk, Genetics and Prevention

Breast Cancer Risk and Prevention

Guidelines Breast
Version 2024.1E

- **Versions 2003–2023:**
  Albert / Bischoff / Blohmer / Dall / Ditsch / Fasching / Fehm / Gerber / Kiechle / Maass / Müller-Schimpfle / Mundhenke / Park-Simon / Rhiem / Rody / Schmidt / Schmutzler / Schütz / Stickeler / Thomssen / Witzel

- **Version 2024:**
  Gluz / Untch

Guidelines Breast
Version 2024.1D

gBRCA-Testing – Therapeutic Consequences

Oxford LoE: 1b GR: A AGO: ++

gBRCA-Testing should be performed irrespective of family history, if it has therapeutic consequences

Guidelines Breast
Version 2024.1E

Therapy of Germline Mutation-Associated Breast Cancer

	Oxford		
	LoE	GR	AGO
▪ Breast conserving surgery according common standard (adequate local tumor control in long time follow up, ~10 years observation)	2a	B	+
▪ Systemic therapy according to common standard	3a	B	+
▪ gBRCA mutation status is predictive for neoadjuvant chemotherapy in early TNBC	2b	B	
▪ gBRCA mutation status is predictive for Carboplatin (vs. Docetaxel) in metastatic breast cancer	1b	B	
PARP inhibitor (Her2-negative carcinoma):			
▪ eBC high risk:			
▪ Olaparib (in case of *gBRCA1/2* mutation)*	1b	A	++
▪ MBC:			
▪ Olaparib, Talazoparib in *gBRCA 1/2* mutation	1b	A	++
▪ Olaparib in s*BRCA 1/2* mutation (somatic mutation)	2b	B	+/-
▪ Olaparib in *PALB2* germ line mutation	2b	B	+/-

EBC: Early Breast Cancer; MBC: Metastatic Breast Cancer; * Use according to study inclusion criteria and approval

Indication for Genetic Testing of *BRCA1/2* Genes and Possibly Further Risk Genes?

(Part 1 of 2 – testing according to family history)

Oxford LoE: 2b GR: B AGO: ++

Families with (each from one family branch) at least*

- three women with breast cancer independent of age
- two women with breast cancer, one diagnosed before the 51st birthday
- one woman affected by breast and one by ovarian cancer or
- one woman affected by breast and ovarian cancer or
- two women affected by ovarian cancer or
- one woman affected by bilateral breast cancer, first before 51st birthday
- one woman affected by breast cancer before the 36th birthday or
- one man affected by breast cancer

- Inclusion criteria of the German Consortium of Hereditary Breast and Ovarian Cancer (GCHBOC) based on a *BRCA1/2* mutation prevalence ≥ 10% tested in 21,401 families. All mutation carriers should be registered in scientific databases, to validate the inclusion and exclusion criteria (including population-based studies).

Guidelines Breast
Version 2024.1E

Indication for Genetic Testing of *BRCA1/2* Genes and Possibly Further Risk Genes?

(Part 2 of 2 - testing according to disease)

Guidelines Breast
Version 2024.1E

Oxford LoE: 2b GR: B AGO: ++

- **Other recommended criteria:**
  - **own disease of triple negative breast cancer diagnosed before 60th birthday**
  - **own disease of ovarian cancer before 80th birthday**
  - **if therapeutically relevant (e.g. PARPi; *gBRCA1* and *gBRCA2* only; possibly *gPALB2*)**

Extended Indication for Genetic Testing of the Genes *BRCA1, BRCA2, TP53, PALB2, CDH1, PTEN, STK11* and Further Risk Genes

Guidelines Breast
Version 2024.1D

- **Genetic Testing can be performed in patients with**
  - **Age at first diagnosis ≤ 65 years, irrespective of family history**
  - **Triple-negative histology and age at first diagnosis > 60 years, especially in families with further breast cancer cases (irrespective of age at diagnosis)**
  - **Invasive lobular histology and diffuse gastric cancer in the family history**
  - **In families with pancreatic cancer history and high risk prostate cancer history**
  - **Ashkenazi jews**

Cave: frequent VUS and decreased penetrance

Checklist for Recording a Possible Hereditary Burden of Breast and / or Ovarian Cancer

Guidelines Breast
Version 2024.1E

Name Patientin/Patient: **Geburtsdatum:**

DKG KREBSGESELLSCHAFT Zertifizierung

A. Patient/in und deren Geschwister / Kinder

Auftreten bei Patientin/Patient	Anzahl	Gewichtung	Ergebnis
eines Mammakarzinoms bei der Patientin **vor** dem 36. Geburtstag		3	0
eines triple-negativen Mammakarzinoms bei der Patientin vor dem 60. Geburtstag*		3	0
eines unilateralen Mammakarzinoms bei der Patientin **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei der Patientin, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei der Patientin **nach** dem 51. Geburtstag		1	0
eines uni- oder bilateralen Mammakarzinoms bei dem Patienten (männlich)		2	0
eines Ovarialkarzinoms bei der Patientin vor dem 80. Geburtstag*		3	0
eines Ovarial-/Tuben-/primären Peritonealkarzinoms bei der Patientin		2	0
Auftreten bei Kindern, Geschwistern und deren Kindern			
eines Mammakarzinoms bei Schwestern/Töchtern/Nichten **vor** dem 36. Geburtstag		3	0
eines unilateralen Mammakarzinoms bei Schwestern/Töchtern/Nichten **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei Schwestern/Töchtern/Nichten, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei Schwestern/Töchtern/Nichten **nach** dem 51. Geburtstag		1	0
eines uni- oder bilateralen Mammakarzinoms bei Brüdern/Söhnen/Neffen		2	0
eeines Ovarial-/Tuben-/primären Peritonealkarzinoms bei Schwestern/Töchtern/Nichten		2	0
		A	0

B. Mütterliche Linie (incl. Mutter)

Auftreten	Anzahl	Gewichtung	Ergebnis
eines Mammakarzinoms bei einer Angehörigen **vor** dem 36. Geburtstag		3	0
eines unilateralen Mammakarzinoms bei einer Angehörigen **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei einer Angehörigen, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei einer Angehörigen **nach** dem 51. Geburtstag		1	0
eines Mammakarzinoms bei einem angehörigen Mann		2	0
eines Ovarial-/Tuben-/primären Peritonealkarzinoms bei einer Angehörigen		2	0
Summe weitere mütterliche Linie			
		B	0

C. Väterliche Linie (incl. Vater)

Auftreten	Anzahl	Gewichtung	Ergebnis
eines Mammakarzinoms bei einer Angehörigen **vor** dem 36. Geburtstag		3	0
eines unilateralen Mammakarzinoms bei einer Angehörigen **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei einer Angehörigen, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei einer Angehörigen **nach** dem 51. Geburtstag		1	0
eines Mammakarzinoms bei einem angehörigen Mann		2	0
eines Ovarial-/Tuben-/primären Peritonealkarzinoms bei einer Angehörigen		2	0
Summe väterliche Linie			
		C	0

D. Der höhere Wert aus B und C — D: 0

E. Summe aus A und D = Risiko-Score — A+D: 0

Ausfüllhinweis

Zunächst wird die Anzahl bekannter Erkrankungsfälle bei den Geschwistern und Kindern, einschließlich der aktuellen Erkrankung der Patientin sowie in der mütterlichen und väterlichen Linie erfragt.

Diese Zahlen werden mit den jeweiligen Gewichtungen multipliziert. Dann wird die Summe aus diesen Ergebnissen errechnet und in die Felder A und B und C eingetragen.

Der höhere der beiden Werte aus den Feldern B und C wird in Feld D eingetragen.

Der Gesamtscore errechnet sich dann aus der Summe der Felder A und D.
Eine Risikoberatung in den ausgewiesenen Zentren ist bei Scores ≥ 3 Punkten zu empfehlen

*Diese Einschlusskriterien gelten nur in Kooperation mit den Zentren des Deutschen Konsortiums Familiärer Brust- und Eierstockkrebs bzw. mit den zertifizierten FBREK-Zentren , die diese im Rahmen der Wissen generierenden Versorgung validieren. Die anderen Einschlusskriterien entsprechen den Vorgabe des EBM.

Version: 11. Januar 2022 (C)
Ärztekammer Westfalen-Lippe,
Deutsche Krebsgesellschaft,
Deutsche Gesellschaft für Senologie,
Deutsches Konsortium für Erblichen Brust- und Eierstockkrebs

Online checklist for familial breast and ovarian cancer:

Source: Deutsche Krebsgesellschaft e.V.

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Risk Estimation for Syndrome-Associated Breast Cancer (non-BRCA)

Oxford		
LoE	GR	AGO
2b	B	++

History and family history over at least three generation (including age of first disease)

- **Characteristic disease**
  - **Breast and ovarian cancer**
- **Further disease**
  - **Pancreatic, thyroid, colorectal, stomache, hepatobilear, urogenital, lung cancer, melanoma, osteosarcoma, leukemia, lymphoma**
  - **Kidney cancer**
  - **Testinal cancer**
  - **Endometrial cancer**
  - **Prostate cancer**

Non BRCA-Associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer

Syndrome	Gene	Risk for malignancy
Li Fraumeni	*TP53*	Breast, endometrium, colorectal, small intestine, stomach, hepato biliary, skin, osteosarcoma, soft tissue sarcoma, urogenital, CNS, ACC, leukemia, lymphoma, lung
Cowden	*PTEN*	Breast, endometrium, thyroid, colorectal, kidney, melanoma
Hereditary diffuse gastric cancer syndrome	*CDH1*	Hereditary diffuse gastric cancer, lobular invasive breast cancer
Peutz-Jeghers Syndrome	*STK11/ LKB1*	Colorectal, small intestine, stomach, pancreas, testicle, endometrium
Lynch	*MLH1, MSH2, MSH6, PMS2, EPCAM*	Endometrium, ovary, colorectal, small intestine, stomach, hepato biliary, pancreas, kidney, urogenital, CNS
Ataxia telangiectasia (AT-Syndrome)	*ATM*	Breast cancer, leukemia, stomach, melanoma, sarcoma
Franconi Anämie	*BRCA2, BRIP1, RAD51C, PALB2*	AML, MDS, SCC, medulloblastoma, nephroblastoma, breast, pancreas, ovary

Guidelines Breast
Version 2024.1E

Non-Directive Counseling Regarding Preventive Measures

Guidelines Breast
Version 2024.1E

AGO ++

According to:

- **The Genetic Diagnostic Law**
- **The Medical Devices Act (e.g. risk assessment)**
- **Application of software for risk calculation requires professional training and experience**

Communicate:

- **Absolute cancer risks within a manageable timeframe**
- **Risk and benefit of a multimodal intensive surveillance program**
- **Risk and benefit of preventive clinical methods**
- **Competing risks, e.g. risk of disease progression in relation to risk of a secondary primary in case women already affected by primary breast cancer**

Allow appropriate time for consideration

Guidelines Breast
Version 2024.1E

Current Clinical Impact of Further Risk Genes

- **Further moderate and low-risk gene variants are most likely transmitted by an oligo- or polygenic trait.**
- **The penetrance of such genes depends on the own and family cancer history.**
- **Individual low-risk variants increase the risk of disease only insignificantly. They have a multiplicative effect, so that the analysis of multiple gene regions (polygenic risk score, PRS) will be of clinical relevance.**

	Oxford		
	LoE	GR	AGO
▪ Clinical genetic testing of moderate-risk genes, e.g. gene panels	1b	B	+
▪ Clinical genetic testing for low-risk variants (polygenic risk score, PRS)	2b	B	+*
▪ Referral to specialised centers	5	D	+

* Currently, moderately penetrant genes and low-risk variants should only be examined in the context of prospective cohort studies, such as that of the German consortium, in order to assess the clinical benefit.

Pathogenic Variants with Moderate to High Lifetime Risk for Breast Cancer

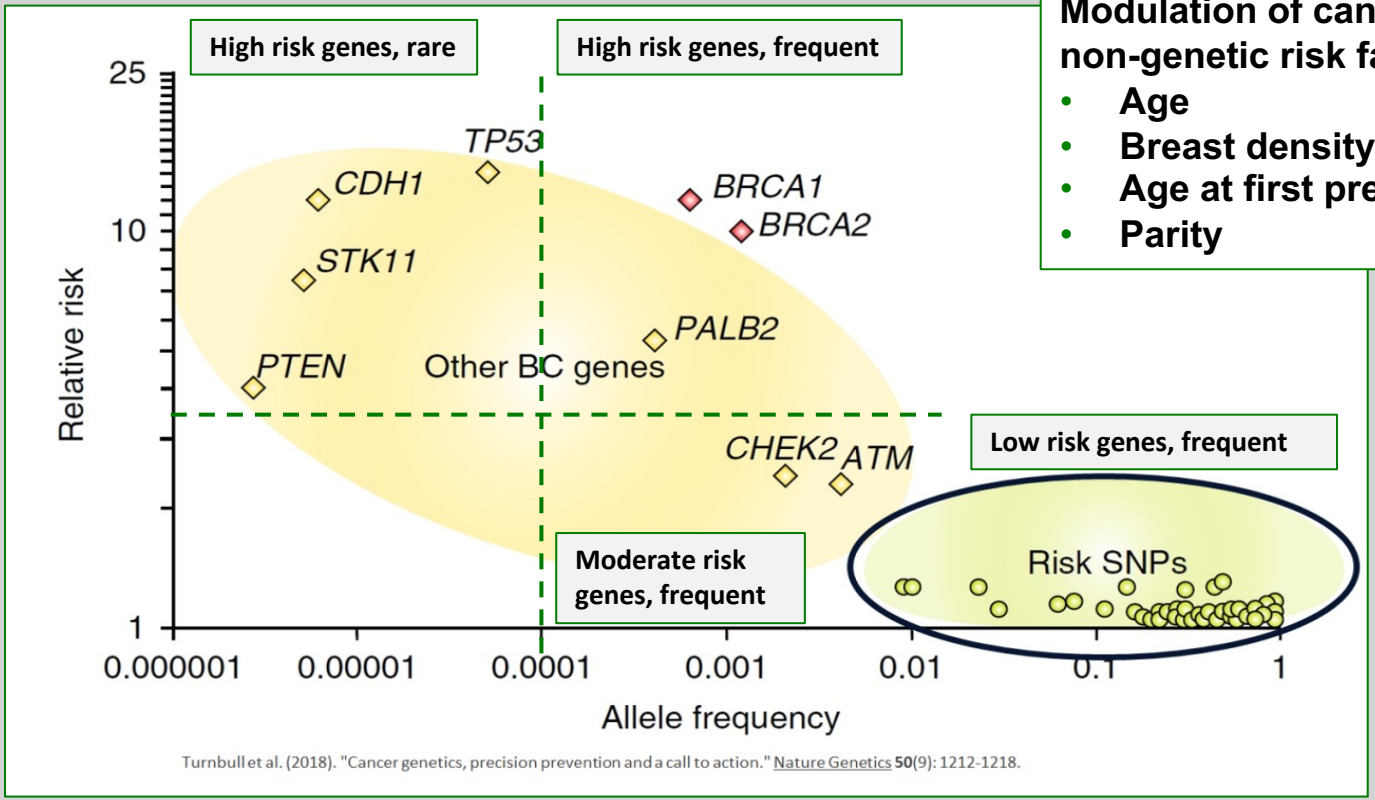
	Oxford		
	LoE	GR	AGO
Age-related risks for breast cancer			
▪ high: ***BRCA1, BRCA2, PALB2***			
▪ high: ***CDH1, PTEN, TP53; STK11***			
▪ moderate: ***ATM, CHEK2***			
▪ moderate: B***ARD1, RAD51C, RAD51D***			
Clinical benefit* of a genetic test			
▪ ***BRCA1, BRCA2***	1b	A	++°
▪ ***PALB2***	3a	B	+°
▪ ***CDH1, PTEN, TP53, STK11***	3b	B	+°
▪ ***ATM, BARD1, CHEK2, RAD51C, RAD51D***	3a	B	+/- °

* Take into account the effectiveness of preventive measures and competing risks when making clinical decisions.

° Participation in prospective registries or studies is highly recommended.

State of research: Relevance of Genetic and non-Genetic Risk Factors

Guidelines Breast
Version 2024.1E



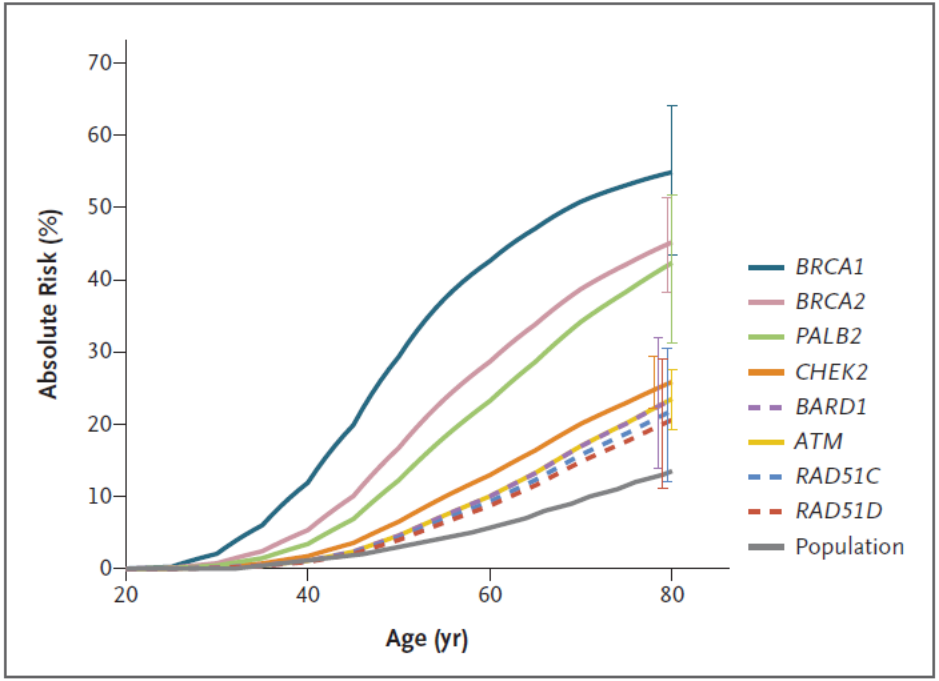
Turnbull et al. (2018). "Cancer genetics, precision prevention and a call to action." Nature Genetics 50(9): 1212-1218.

Modulation of cancer risk by non-genetic risk factors, e.g.:

- **Age**
- **Breast density**
- **Age at first pregnancy**
- **Parity**

Estimated Cumulative Risk of Breast Cancer with Protein-Truncating Variants in 8 Genes

Guidelines Breast
Version 2024.1E



Shown are cumulative risks of breast cancer through 80 years of age for protein-truncating variants in 8 genes that had significant evidence of an association with breast cancer overall, on the basis of estimated odds ratios from population-based studies. Baseline absolute risks were derived from population incidences in the United Kingdom in 2016. The I bars indicate 95 % confidence intervals.

Dorling L, Carvalho S, Allen J et al. Breast-Cancer Risk Genes — Association Analysis in More than 113,000 Women. January 20, 2021 DOI: 10.1056/NEJMoa1913948

Guidelines Breast
Version 2024.1E

Breast Cancer Risk Category
Definition of Moderate / High Risk for Breast Cancer

Breast cancer risk category

	Near population risk of breast cancer	Moderate risk of breast cancer	High risk of breast cancer
Lifetime risk from age 20	Less than 17%	Greater than 17% but less than 30%	30% or greater
Risk between ages 40 and 50	Less than 3%	3 to 8%	Greater than 8%

NICE (National Institute for Health and Care Excellence) guidance: Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer
Clinical guideline [CG164] Published: 25 June 2013 Last updated: 20 November 2019

IARC - Classification of Sequence Variants (Plon et al., Human Mutation, 2008)

Guidelines Breast
Version 2024.1E

Proposed Classification System for Sequence Variants Identified by Genetic Testing		
Class	**Description**	**Probability of being pathogenic**
5	Definitely pathogenic	> 0,99
4	Likely pathogenic	0,95-0,99
3	Uncertain	0,05-0,949
2	Likely not pathogenic or of little clinical significance	0,001-0,049
1	Not pathogenic or no of clinical significance	< 0,001

Only class 4 and class 5 variants are considered clinically relevant.
Class 3 are considered as Variants of Unknown Significance (VUS).

Variant of Unknown Significance (VUS): Problems and Questions

- „A Variant of Unknown Significance (VUS IARC class 3) is a genetic variant with unknown clinical relevance.“ (Plon et al. Hum Mutat 2008)
- Most VUS are extremely rare (≤ 3 variants in > 80 % of families)
- Classification of sequence variants should be performed according to the IARC classification system
- Frequency of VUS (IARC class 3) increases with numbers of tested genes
- Clinical interpretation and decision making depending on the IARC classification system is not standardized yet
- In silico prediction tools (PolyPhen2, SIFT) are not adequate or sufficient for clinical decision making
- Additional analyses are required, e.g. in vitro splicing assay, functional assay, segregation analysis, co-occurence analysis, large case / control studies

Guidelines Breast
Version 2024.1E

Guidelines Breast
Version 2024.1E

Multimodal Intensive Surveillance Program*

		Oxford LoE	Oxford GR	AGO
▪ Program for BRCA-mutation carriers without BC				
▪ For the detection of early stage cancers		2b	B	++
▪ Clinical breast exam	≥ 25 years	Semi-annually		
▪ Sonography	≥ 25 years	Semi-annually		
▪ Mammogram	≥ 40 years	Every 1-2 years**		
▪ Breast MRI	≥ 25 years	Annually		
▪ For improvement of metastasis-free interval		2b	B	+
▪ Radiotherapy of thoracic wall in the childhood (e.g. M. Hodgkin)		2a	B	++

* The multimodal early detection program should be carried out for women with a pathogenic mutation in risk genes and those with an increased calculated risk without a mutation within the framework of transparent quality assurance and appropriate evaluation;

** According to the recommendation of the German Consortium 2022: Depending on the assessability of the breast, the glandular parenchyma density and the previous mammographic findings every 1-2 years from the 40th-45th Age, under 40 years only after strict individual indication.

High-Risk Breast Cancer Surveillance with MRI

Guidelines Breast
Version 2024.1E

	30-39 years		40-49 years		≥ 50 years	
	Detection rate (‰)	PPV (%)	Detection rate (‰)	PPV (%)	Detection rate (‰)	PPV (%)
BRCA1	43.2	29.4	21.8	25.5	30.5	33.3
BRCA2	22.7	23.3	24.3	27.5	16.3	23.5
BRCA1/2-non carriers with high risk	2.9	2.8	7.4	6.8	10.9	13.8

PPV: Positive predictive value

Detection performance of annual multimodality screening rounds with MRI by risk group and age.

Bick U, Engel C, Krug B, et al. High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. *Breast Cancer Res Treat*. 2019;175(1):217–228. doi:10.1007/s10549-019-05152-9

Guidelines Breast
Version 2024.1E

Modified Surveillance Program for *BRCA*-neg. Women at Moderate to High Risk or Survivors of Hodgkin Disease

Rationale:

- **Increased risk of breast cancer after chest irradiation because of Hodgkin lymphoma in childhood (9–18 years)**
- **Increased risk of breast or ovarian cancer in women from BRCA1/2 negative families at risk that is, however, lower than in women from BRCA1/2 positive families**
- **Referral to centres of the GC-HBOC or cooperating centres for the evaluation of structured surveillance and follow-up**

Multimodal Surveillance Program for Female Carriers of Pathogenic BRCA Mutations after Unilateral Breast Cancer

Guidelines Breast
Version 2024.1E

	Oxford LoE	GR	AGO
▪ **Multimodal intensive surveillance program***			
▪ **For detection of early stage breast cancers**	2a	B	++
▪ **Clinical breast exam**	Semi-annually		
▪ **Sonography**	Semi-annually		
▪ **Mammogram**	Every 1-2 years**		
▪ **Breast MRI (until ACR1)**	Annually		
▪ **For mortality reduction (10-year survival)**	3a	C	+/-

* Aftercare should be carried out within the framework of transparent quality assurance and corresponding evaluation.

** According to the recommendation of the German Consortium 2022: Depending on the assessability of the breast, the glandular parenchyma density and the previous mammographic findings every 1-2 years from the 40th-45th Age, under 40 years only after strict individual indication.

Surveillance for Male Carriers of Pathogenic BRCA Mutations*

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
Currently, no specific surveillance is recommended → Early detection of cancer as part of standard care			
▪ **BRCA1/2 mutation carrier: explanation of risks for cancer disease including male family members**	5	D	++
▪ **For breast cancer: self examination**	5	D	+
▪ **For prostate cancer: Compare German Guideline program**	5	D	+

The lifetime risk of breast cancer in the general male population is 0.1%. *BRCA1* mutation carriers have a risk of breast cancer of about 1% and an up to 1.8 to 3.75 times higher risk for prostatic cancer ≤ 65y. *BRCA 2* mutation carriers have an up to 5–7% lifetime risk for breast cancer and an up to 2.5 to 8.6 times higher risk for prostatic cancer ≤ 65y.

* **Follow-up care / surveillance should be carried out as part of transparent quality assurance and appropriate evaluation.**

Guidelines Breast
Version 2024.1E

Surgical Prevention

	Oxford		
	LoE	GR	AGO
▪ Risk-reducing unilateral or bilateral mastectomy (RRME) without the presence of clearly defined genetic risk factors	2a	B	-*
▪ Axillary dissection or Sentinel lymph node excision during RRME	2a	B	--

* study participation recommended

Guidelines Breast
Version 2024.1E

Surgical Prevention for Healthy Female *BRCA1/2* Mutation Carriers

	Oxford LoE	Oxford GR	AGO
▪ **Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)****	2a	B	
▪ **Reduces OvCa incidence and mortality**			++*
▪ **Reduces overall mortality**			++*
▪ **Risk-reducing bilateral mastectomy (RR-BM)**			
▪ **Reduces BC incidence**	2b	B	+*
▪ **Reduces BC mortality in *BRCA1* mutation carriers*****	2b	B	+*

* Study participation recommended

** The RR-BSO is recommended from about 35 years for *BRCA1* and from about 40 years for *BRCA2* mutation carriers, taking into account the age of ovarian cancer diagnosis in the family and the family planning status.

*** No reduction in mortality could be shown for BRCA2 mutation carriers. RRBM counselling should be individualised.

Risk-reducing Interventions for BRCA1/2 Female Mutation Carriers Affected by Breast Cancer

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)	2b	B	+*
▪ Reduces OvCa incidence and mortality			
▪ Reduces overall mortality (contradictory results for reduction of cl BC incidence)			
▪ Prophylactic contralateral mastectomy (RR-CM)*	2b	B	+*
▪ Reduces BC incidence and mortality			
▪ Tamoxifen (reduces contralateral BC incidence)	2b	B	+/-*
▪ Indication for RR-CM should consider age at onset of first breast cancer in affected gene	2a	B	++*
▪ RR-BM after ovarian cancer	4	C	+/-**

* Study participation recommended

** Depends on tumor stage (FIGO I/II), recurrence free interval (≥ 5 yrs.), age

Improved Overall Survival After Contralateral Risk-reducing Mastectomy in *BRCA1/2* Mutation Carriers with a History of Unilateral Breast Cancer: A Prospective Analysis

Guidelines Breast
Version 2024.1E

Analysis[a]	Group	Person years of observation	Deaths	Mortality[b] (95% CI)	HR (95% CI)
(a)	Surveillance	3007	65	21.6 (16.9-27.6)	Ref
	CRRM	1975	19	9.6 (6.1-15.1)	0.43 (0.26-0.72)[c] 0.49 (0.29-0.82)[d]
(b)	Surveillance	2673	56	21.0 (16.1-27.2)	Ref.
	CRRM	1837	18	9.8 (6.2-15.5)	0.46 (0.27-0.79)[c] 0.55 (0.32-0.95)[d]

[a] Analysis (a) is the main analysis with start of observation being either the date of primary breast cancer (PBC) diagnosis or the date of DNA diagnosis, whichever came first. In the additional analysis (b), the observation starts either 2 years after PBC or at the date of DNA diagnosis, whichever came first, to exclude patients who presented with distant metastases or died within 2 years after PBC diagnosis (*n* = 17).

[b] Per 1000 person years of observation.

[c] Univariate analysis.

[d] Multivariate analysis, adjusted for risk-reducing salpingo-oophorectomy. The following variables did not meet the criteria for incorporation in the multivariate Cox model as described in the Methods section, and were therefore not included in the multivariate analysis: type of mutation, year of birth, age at DNA diagnosis, age at PBC diagnosis, T-status, presence of positive lymph nodes, differentiation grade, hormone receptor status, HER2 status and treatments administered for PBC.

Abbreviations: CRRM, contralateral risk-reducing mastectomy; HR, Hazard ratio; CI, confidence interval.

We conclude that CRRM is associated with improved overall survival in BRCA1/2 mutation carriers with a history of PBC. Further research is warranted to develop a model based on age at diagnosis and tumour and treatment characteristics that can predict survival benefit for specific subgroups of patients, aiming at further personalized counselling and improved decision making.

Medical Prevention for Women at Increased Risk

Guidelines Breast
Version 2024.1E

	Oxford LoE	Oxford GR	AGO
▪ Tamoxifen for women > 35 years: Risk reduction of invasive BC, DCIS and LN	1a	A	+*
▪ Raloxifen for postmenopausal women: Risk reduction of invasive BC only	1b	A	+*
▪ AI for postmenopausal women	1b	A	+**

* Risk situation as defined in NSABP P1-trial (1.66% in 5 years) or according to #Tyrer-Cuzick model (IBIS-II)

** Significant risk reduction was seen for anastrozole for ovarian and endometrial cancer, as well as skin, colorectal, hematologic, thyroid and urinary tract cancers. Chemopreventive regimes should only be offered after individual and comprehensive counseling. The net benefit strongly depends on risk status, age and pre-existing risk factors for side effects.

Guidelines Breast
Version 2024.1E

Early Detection and Diagnosis

Guidelines Breast
Version 2024.1E

Early Detection and Diagnosis

- **Versions 2005–2023:**
  Albert / Blohmer / Fallenberg / Fersis / Gerber / Junkermann / Kühn / Maass / Müller-Schimpfle / Scharl / Schreer / Wöckel

- **Version 2024:**
  Fallenberg / Heil

Guidelines Breast
Version 2024.1E

Early Detection with Mammography

Age	Interval	Oxford		AGO
		LOE	GR	
< 40	na	-	-	--
40-44	na	1b	B	-
45–49	24-36	1a	A	+#
50–75*	24	1a	A	++
> 75**	24	4	C	+/-#

* National Mammography-Screening-Program
** health status + life expectancy more than 10 years
# clear indication necessary, or indicated if screening age is adapted

Guidelines Breast
Version 2024.1E

Early Detection in Asymptomatic Women
Digital Breast Tomosynthesis, Endpoint: cancer detection rate

	Oxford		
	LOE	GR	AGO
Digital Breast Tomosynthesis (DBT ± SM)*	1a	A	+
Replacing FFDM by synthetic MG in addition to DBT	1a	A	++

The complete DBT dataset of images has to be available for judgment / reporting, the synthetic mammography only is not sufficient.

* **Sign. higher sensitivity, heterogeneous specificity, and higher costs [machine, evaluation, archiving] of DBT in comparison to Full-Field Digital Mammography (FFDM)**
Dose reduction due to calculated synthetic 2D mammography (SM) instead of additional FFDM, no significant reduction of interval cancers to date

Guidelines Breast
Version 2024.1E

AI for cancer detection

	Oxford		
	LOE	GR	AGO
AI in screening			
Second reader of mammography	1b	B	+/-
To reduce workload (AI only)	2b	B	-
Tomosynthesis: stand alone or second reader	2a	B	-

Breastcancer: incidence and mortality risk

Guidelines Breast
Version 2024.1E

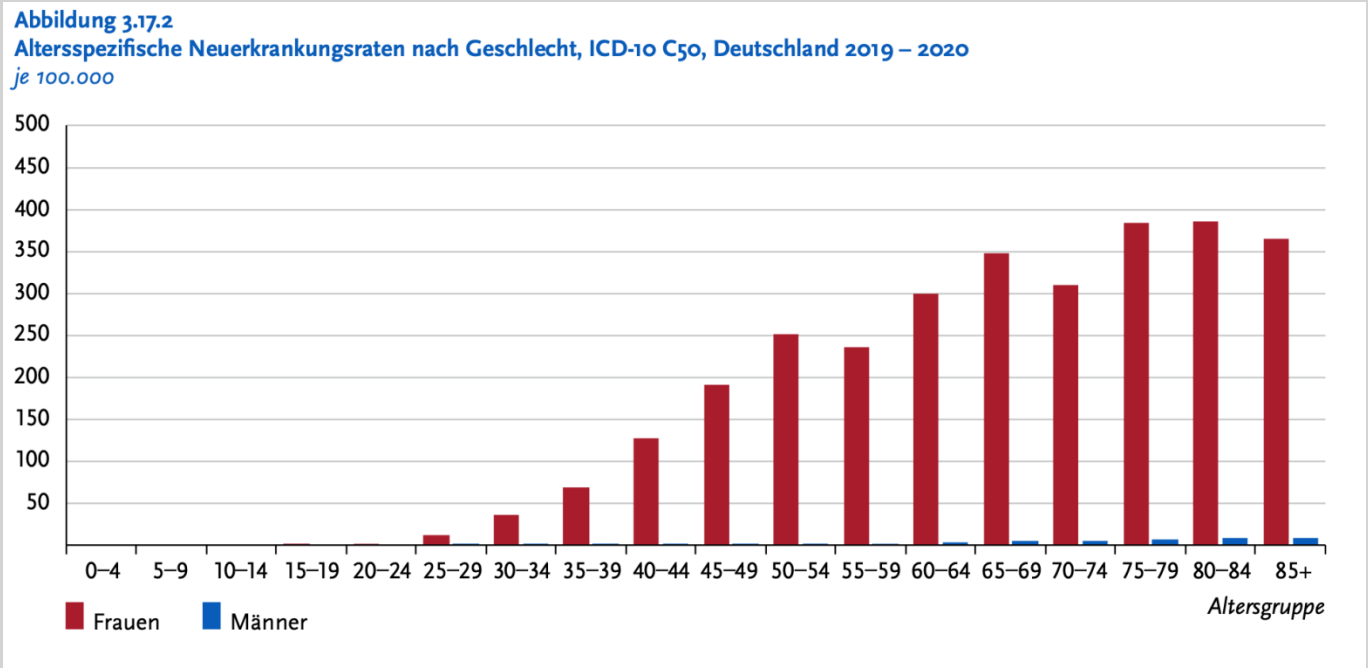
Tabelle 3.17.2
Erkrankungs- und Sterberisiko in Deutschland nach Alter und Geschlecht, ICD-10 C50, Datenbasis 2019

	Erkrankungsrisiko				Sterberisiko			
Frauen im Alter von	**in den nächsten 10 Jahren**		**jemals**		**in den nächsten 10 Jahren**		**jemals**	
35 Jahren	1,0 %	(1 von 99)	13,1 %	(1 von 8)	0,1 %	(1 von 1.000)	3,5 %	(1 von 28)
45 Jahren	2,2 %	(1 von 45)	12,3 %	(1 von 8)	0,2 %	(1 von 410)	3,5 %	(1 von 29)
55 Jahren	2,8 %	(1 von 35)	10,4 %	(1 von 10)	0,4 %	(1 von 230)	3,3 %	(1 von 31)
65 Jahren	3,4 %	(1 von 29)	8,2 %	(1 von 12)	0,8 %	(1 von 130)	3,0 %	(1 von 34)
75 Jahren	3,6 %	(1 von 28)	5,6 %	(1 von 18)	1,3 %	(1 von 77)	2,5 %	(1 von 40)
Lebenszeitrisiko			13,2 %	(1 von 8)			3,5 %	(1 von 28)
Männer im Alter von	**in den nächsten 10 Jahren**		**jemals**		**in den nächsten 10 Jahren**		**jemals**	
35 Jahren	< 0,1 %	(1 von 29.250)	0,1 %	(1 von 750)	< 0,1 %	(1 von 319.800)	< 0,1 %	(1 von 2.500)
45 Jahren	< 0,1 %	(1 von 11.400)	0,1 %	(1 von 760)	< 0,1 %	(1 von 44.700)	< 0,1 %	(1 von 2.500)
55 Jahren	< 0,1 %	(1 von 4.000)	0,1 %	(1 von 790)	< 0,1 %	(1 von 24.400)	< 0,1 %	(1 von 2.600)
65 Jahren	< 0,1 %	(1 von 2.300)	0,1 %	(1 von 890)	< 0,1 %	(1 von 8.400)	< 0,1 %	(1 von 2.600)
75 Jahren	0,1 %	(1 von 1.700)	0,1 %	(1 von 1.100)	< 0,1 %	(1 von 5.650)	< 0,1 %	(1 von 3.000)
Lebenszeitrisiko			0,1 %	(1 von 750)			< 0,1 %	(1 von 2.500)

From:https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2023/kid_2023_c50_brust.pdf?__blob=publicationFile

Breastcancer: Age specific new Cancer cases

Guidelines Breast
Version 2024.1E



From:https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2023/kid_2023_c50_brust.pdf?__blob=publicationFile

Mammography-Screening
Benefit and Harm

Guidelines Breast
Version 2024.1E

Data background: Breast Cancer Surveillance Consortium Registry Data per 10.000 Women screened over 10 years

Age	40-49	50-59	60-69	70-74
Breast cancer death avoided (CI 95%)	3 (0-9)	8 (2-17)	21 (11-32)	13 (0-32)
False-positive (n)	1212	932	808	696
Breast biopsies (n)	164	159	165	175
False-negative (n)	10	11	12	13

Siu Al on behalf of the USPSTF 2016, 164:279–296

Guidelines Breast
Version 2024.1E

Early Detection (normal risk) Sonography / MRI

	Oxford LoE	Oxford GR	Oxford AGO
▪ Screening-Breast sonography allone	5	D	--
▪ Automated 3D-sonography	3a	C	-
▪ Breast sonography as an adjunct:			
▪ Dense mammogram (heterogeneously dense, extremely dense)	2a	B	++
▪ Elevated risk	1b	C	++
▪ Mammographic lesion	2b	B	++
▪ Second-look US (MRI-only detected lesions)	2b	C	++
▪ MRI if screening MG is negative and breast composition: extremely dense* 45–75 LJ	1b	B	+

* Definition of extremely dense corresponds to BIRADS-density category D, heterogeneously dense to BIRADS-category C according to ACR BI-RADS-Atlas 5th ed. 2013

Guidelines Breast
Version 2024.1E

Early Detection (normal risk)
Clinical Breast Examination (CBE)

	Oxford		
	LoE	GR	AGO
As stand alone procedure			
▪ Self-examination	1a	A	-*
▪ Clinical breast examination (CBE) by health professionals outside checkup for cancer	1a	C	-*
▪ Clinical breast examination (CBE) by health professionals during checkup for cancer	1a	B	++
▪ Medical palpation by blind / visually impaired persons	3b	C	-
CBE because of mammographic / sonographic lesion	5	D	++
CBE in combination with imaging	1a	A	++

* May increase breast awareness

Guidelines Breast
Version 2024.1E

Assessment of Breast Symptoms or Lesions

	Oxford		
	LoE	GR	AGO
▪ Clinical examination	3b	B	++
▪ Mammography	1b	A	++
▪ Tomosynthesis***	2a	B	+
▪ Contrast-enhanced mammography (alone or as adjunct)	2a	B	+
▪ Sonography	2b	B	++
▪ Elastography (shear-wave) *	2b	B	+
▪ Automated 3D-sonography	3b	B	+/-
▪ MRI**	2b	B	+
▪ Minimally invasive biopsy	1b	A	++

* Adjunct assessment

** If clinical examination, mammography and sonography incl. needle biopsy do not allow a clear assesment

*** Replacement of additional FFDM with SM

Guidelines Breast
Version 2024.1E

Pre-therapeutic Assessment of Breast

	Oxford		
	LoE	GR	AGO
▪ Clinical examination	5	D	++
▪ Mammography (completion of the imaging)	2b	B	++
▪ + Tomosynthesis (DBT)***	2b	B	+
▪ Contrast-enhanced mammography (alone) adjusted with regards of radiation sensitivity of patient and availability*	2a	B	+
▪ Sonography (breast)	2b	B	++
▪ MRI*	1b	A	+
▪ Minimally invasive biopsy**	1b	A	++
▪ Breast-CT	4	D	-
▪ Axillary PET (PET-CT, PET-MR)	2b	B	-

* MRI- or CEM guided vacuum biopsy is mandatory in case of MRI- or CEM detected additional lesions (in house or with cooperations).
Individual decision for patients at high familiar risk, with dense breast (density C / D), lobular invasive tumors, suspicion of multilocular disease.

** Histopathology of additional lesions if relevant for treatment

*** Replacement of additional FFDM with SM

Guidelines Breast
Version 2024.1E

Pre-therapeutic Assessment Axilla

	Oxford		
	LoE	GR	AGO
▪ Clinical examination	5	D	++
▪ Mammography	2b	B	-
▪ + Tomosynthesis***	2b	B	-
▪ CEM (alone) after unclear resection (Rx) if available	2a	B	-
▪ Ultrasound (Axilla#)	2a#	B	++
▪ MRI	1b	A	+
▪ CNB Axilla, if suspicious LN and marking of the node if TAD planned ≤3 susp. LK	2b	B	++
▪ Breast-CT	4	D	-
▪ PET CT / MRI for axillary LN	2b	B	-

*** Replacement additional DM through SM

Guidelines Breast
Version 2024.1E

Pre-therapeutic Staging

	Oxford		
	LoE	GR	AGO
▪ History and clinical examination	5	D	++
Only in case of high metastatic potential and/or symptoms and/or indication for (neo-) adjuvant chemotherapy and/or antibody-therapy:			
▪ CT scan of thorax / abdomen / pelvis	2a	B	+
▪ Bone scan	2b	B	+
▪ Chest X-ray	5	C	+/-
▪ Liver ultrasound	5	D	+/-
▪ Further investigation in case of additonal suspicious lesions (e.g. liver-MRI, CEUS*, biopsy etc.)	2a	B	+
▪ FDG-PET or FDG-PET-CT** FDG-PET-MRI**	2b	B	+/-
▪ Whole body MRI	4	C	+/-

* Contrast enhanced ultrasound

** especially in patients with high tumor stage (III) if available

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

Pathology

Pathology

- **Versions 2004–2023:**
  Blohmer / Costa / Fehm / Friedrichs / Harbeck / Huober / Kreipe / Lück / Maass/Schneeweiss/ Sinn / Thomssen / Schmidt

- **Version 2024:**
  Harbeck / Kreipe / Sinn

Guidelines Breast
Version 2024.1E

Preanalytics: Fixation

	Oxford		
	LoE	GR	AGO
▪ Minimize time to fixation (cold ischemia time)	5	D	++
▪ Minimal fixation time of 6 hours for optimal antigen preservation	5	D	++
▪ Optimal fixation time 6 - 72 h for core biopsies	5	D	++
▪ Optimal fixation time for resection specimens: 12 - 72 h	5	D	++
▪ Use of neutral buffered formalin	5	D	++

Guidelines Breast
Version 2024.1E

Use of Breast Cytology*

	Oxford		
	LoE	GR	AGO
▪ Nipple secretion	5	D	+
▪ Tumor	5	D	-
▪ Cyst	5	D	+/-
▪ Lymph node	5	D	+/-

* Ultrasound-guided core biopsy recommended

Guidelines Breast
Version 2024.1E

Workup: Core Needle Biopsies (US-guided or stereotactic)

	Oxford		
	LoE	GR	AGO
▪ Routine workup in step sections (14G: 1–3 step sections / 11G, 8G: 6–8 step sections)	5	D	++
▪ Correlation with imaging (density, calcifications), use of B-classification	1b	B	++
▪ Frozen section diagnosis on core biopsies	5	D	--
▪ Routine evaluation of ER/PR and HER2 status	3b	C	++
▪ Turn-around time < 24 h (histology)	5	D	+

Guidelines Breast
Version 2024.1E

Workup: Breast-Conserving Specimens

	Oxford		
	LoE	GR	AGO
▪ Slicing perpendicular to the longitudinal axis (or perpendicular to the nipple-peripheral axis in case of spherical specimens)	5	D	++
▪ Systematic sampling, at least 1 tissue block every 1 cm	5	D	++
▪ Inking of resection margins. Sampling of resection margins	5	D	++
▪ Documentation after slicing using specimen radiography, photo documentation or diagram	5	D	+

Guidelines Breast
Version 2024.1E

Workup: Mastectomy Specimens

	Oxford		
	LoE	GR	AGO
▪ Margins always to be sampled	5	D	++
▪ Skin close to tumor			
▪ Deep margin			
▪ Other margins, if close (< 1 cm)			
▪ Attention to soft tissue margins in skin sparing mastectomy	5	D	++
▪ Routine sampling of uninvolved quadrants, skin above tumor, and retroareolar region	5	D	++
▪ Systematic sampling in prophylactic mastectomies (patients with BRCA-1/2 mutation)	5	D	++

Guidelines Breast
Version 2024.1E

Workup: Sentinel Node Biopsy

	Oxford		
	LoE	GR	AGO
▪ Full workup using step sections of ≤ 500 µm on paraffin embedded tissue	5	D	++
▪ Cytokeratin immunohistochemistry			
▪ If suspicious, to detect micrometastases	2b	B	+
▪ For micrometastasis detection after NACT	2b	B	+
▪ As a routine procedure	5	D	+/-
▪ Frozen section (compromises paraffin histomorphology)			
▪ If clinical consequences	5	D	+
▪ If no clinical consequences from frozen section (e.g. cT1 or cT2 and cN0 and BCT)	5	D	-
▪ Imprint cytology instead of, or in addition to frozen section	3b	C	+/-
▪ RT-PCR for epithelial genes	4	D	-
▪ OSNA	3b	B	-

Workup: Intraoperative pathological evaluation and frozen sections

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ **Sentinel node biopsy for invasive cancer (compromises final paraffin histomorphology)**			
▪ If clinical consequences	5	D	+
▪ No clinical consequences	5	D	-
▪ **Closest margin of resection**			
▪ If macroscopically < 1 cm	5	D	+
▪ If macroscopically > 1 cm	5	D	-
▪ **Lesions ≥ 1 cm, without core biopsy**	5	D	+
▪ **Non-palpable lesions or lesions < 1 cm**	5	D	--
▪ **Conservation of fresh tissue (tumor banking)**	5	D	+

Guidelines Breast
Version 2024.1E

Reporting: Histologic Tumor Type

Oxford		
LoE	GR	AGO
3b	C	++

- **Histologic tumor typing according to WHO-Classification, (5th ed., 2019)**
  - **Partial special differentiation:**
    > 50% NST component
    and < 50% special tumor type (minor component)
  - **Mixed differentiation:**
    > 50% special tumor type
    and < 50% NST component
    Example: mucinous breast cancer, mixed type
  - **Pure types:**
    > 90% special tumor type
    Examples: tubular or cribriform Ca.

Ductal TNBC: Comparable survival rates and similar response rates to chemotherapy for ER = 0% compared to ER 1% - <10%

Guidelines Breast
Version 2024.1E

Reference	Patients	Results
Villegas, S. L. *Eur J Cancer* **148**, 159–170 (2021) DOI: 10.1016/j.ejca.2021.02.020	Neoadjuvant clinical trial cohorts (n = 2765) comparing neg. ER/PR (<1%) vs. ER/PR low pos. (ER and/or PR <9%) vs. strong-pos. (ER or PR >= 10%) HR expression.	Low HR-positive, HER2-negative tumours had a similar clinical behavior compared to TNBC, showing high pCR rates and poor survival and also a basal-like gene expression signature. Patients with low HR-positive tumours should be regarded as candidates for therapy strategies targeting TNBC.
Dieci, M. V. et al. Npj Breast Cancer 7, 101 (2021) DOI: 10.1038/s41523-021-00308-7	406 patients with ER < 10% HER2-negative BC. Pat. Were categorized in ER-negative (ER < 1%; N = 364) and ER-low positive (1–9%, N = 42).	No difference was observed in overall survival (OS) according to ER expression levels (5-years OAS 82.3% vs. 76.7% for ER-negative and ER-low positive BC, respectively, p = 0.8). Our results suggest the use of a 10% cut-off, rather than <1%, to define triple-negative BC (TNBC).
Reddy, S. M. *et al.* *British Journal of Cancer* **118**, 17–23 (2018) DOI: 10.1038/bjc.2017.379	Stage I-III TNBC pat. (n=873) who were disease free at 5 years from diagnosis. Recurrence-free interval (RFI), r.f. survival (RFS), and distant r.f. survival (DRFS) rates were calculated.	After a disease-free interval of 5 years, patients with low hormone receptor-pos. cancers had a higher risk of late events as measured by RFS, and similar risk by RFI or DRFS, compared to TNBC survivors.

Guidelines Breast
Version 2024.1E

Rare histological TNBC subtypes show divergent tumor differentiation patterns and clinical behavior

Apocrine TNBC

- Luminal phenotype (no basal markers)
- High expression of the androgen receptor
- Low tumor proliferation
- Poor response to chemotherapy
- Better prognosis than ductal TNBC

Metaplastic TNBC

- See chapter 15 Special Situations

Rare and salivary-type TNBC

- Tumors with divergent clinical behavior and specific genetic alterations
- Mostly low tumor proliferation
- Poor response to conventional chemotherapy
- Experimental treatment according to the molecular pathology (e.g. NTREK for secretory ca.)

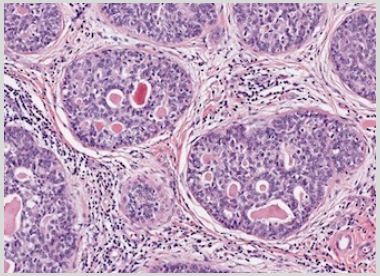
Apocrine TNBC: More favorable survival and poor response to adjuvant chemotherapy

Reference	Patients	Results
Saridakis, A. *et al.* *Ann Surg Oncol* **28**, 5610–5616 (2021). DOI: 10.1245/s10434-021-10518-9	Women with invasive apocrine cancer were retrospectively identified from the Surveillance, Epidemiology, and End Results (SEER) database. N= 533 triple-negative apocrine cancers were identified.	Half of apocrine tumors are triple negative, but these have more favorable features and much better survival than non-apocrine triple-negative cancers. Compared with non-apocrine triple-negative, apocrine triple-negative patients were much older, with smaller, lower-grade tumors and much better survival (86% vs. 74%).
Montagna, E. et al. *Breast* **53**, 138–142 (2020). DOI: 10.1038/s41523-021-00308-7	406 patients with ER < 10% HER2-negative BC. Pat. Were categorized in ER-negative (ER < 1%; N = 364) and ER-low positive (1–9%, N = 42).	The outcome of selected apocrine triple negative breast cancer patients who did not received adjuvant chemotherapy is excellent and supports a treatment de-escalation.
Mills, A. M., et al. *Am J Surg Pathol* **40**, 1109–1116 (2016). DOI: 10.1097/pas.0000000000000671	All pure apocrine carcinomas diagnosed during a 10-year period were reviewed, and clinicopathologic characteristics were compared with a control group of 26 non-apocrine TNBC cases. Twenty apocrine carcinomas were identified (~0.8% of all breast cancers).	Apocrine TNBC had a favorable clinical prognosis, with 80% of patients showing no evidence of disease-related morbidity or mortality (mean follow-up: 45.2 mo). Pure apocrine carcinomas represent a clinicopathologically distinct subgroup of triple-negative breast cancer characterized by AR positivity.

Rare and salivary-type TNBC: Tumors with divergent clinical behavior and specific genetic alterations

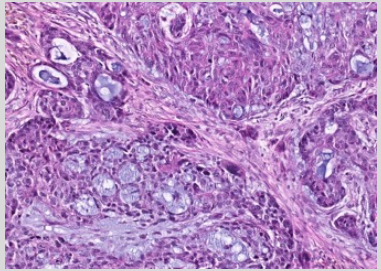
Guidelines Breast
Version 2024.1E

Adenoid-cystic carcinoma



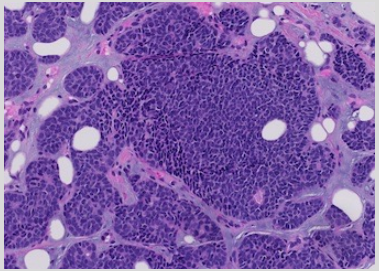
MYB-NFIB
MYBL1 rearrangements
MYB gene amplification

Secretory carcinoma



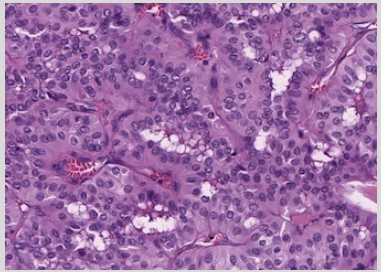
ETV6-NTRK3
gene fusions

Polymorphous carcinoma



PRKD1 E710D
PRKD1/PRKOZ/PRKD3
rearrangements

Tall cell carcinoma with reversed polarity



IDH2 hotspot mutations

Guidelines Breast
Version 2024.1E

Reporting: Grade of Malignancy

	Oxford		
	LoE	GR	AGO
▪ Use of Nottingham grading system (Elston & Ellis 1991) for all types of invasive breast cancer (incl. status post neoadjuvant systemic therapy)	5	D	++
▪ In case of very little tumor tissue, pure nuclear grading or additional criteria, such as Ki-67 proliferation fraction, may be used	5	D	++
▪ Grading of DCIS, e.g. according to WHO-Classification, (5th ed., 2019)	5	D	++
▪ Reporting of tumor grade in numeric form (e.g. G3)	5	D	++

Guidelines Breast
Version 2024.1E

Reporting: Tumor Size and Total Extent of Tumor

	Oxford		
	LoE	GR	AGO
▪ Reporting of invasive tumor size taking into account macroscopic and histologic findings and clinical imaging results	5	D	++
▪ Additional reporting of total extent of invasive carcinoma in case of satellite nodules or multifocality	5	D	++
▪ Reporting of size of non-invasive component (DCIS or LCIS) when DCIS or LCIS component is extensive (more than 2x invasive Ca)	5	D	++

Guidelines Breast
Version 2024.1E

Reporting: pTNM

Oxford		
LoE	GR	AGO
5	D	++

- **Use of current UICC classification (8th ed.)**

  pT 1-3: Invasive tumor size (largest focus in case of multifocality or multicentricity)

  pT4: Invasion of dermis alone does not qualify as pT4. Criteria for pT4a/b/c/d must be met.

  pT4d: Negative skin biopsy does not rule out pT4d (inflammatory carcinoma).

  pM: pM1 indicates any non-regional disease, except 2nd primary contralateral. Use of MX is not recommended.

Reporting: Margins of Resection and R-Classification

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Evaluation of distance to all resection margins macroscopically and close margins histologically (< 1 cm)	5	D	++
▪ Reporting of minimal distance to resection margin and its topography	5	D	++
▪ R-Classification	5	D	++

R0: No residual tumor

R1: Microscopic invasive or noninvasive carcinoma involving resection margin

RX: Presence of residual tumor cannot be assessed (e.g. tumor in multiple specimens)

Guidelines Breast
Version 2024.1E

Reporting: Lymphovascular Invasion

	Oxford		
	LoE	GR	AGO
▪ L1: Lymphovascular invasion L0: No lymphovascular invasion	5	D	++
▪ IHC for evaluation of lymphovascular invasion	3b	C	-
▪ Differentiation of peritumoral and extensive lymphovascular invasion	3b	C	++
▪ Reporting of venous invasion (V0/V1) optional, prognostic significance not established	5	D	+

Guidelines Breast
Version 2024.1E

Reporting: Evaluation of Tumor-Infiltrating Lymphocytes (TIL)

Oxford		
LoE	GR	AGO
5	D	+/-

- **Identification of tumors with predominant lymphocytic infiltrate (> 50%) in tumor stroma (according to Salgado et al.*)**

  Consider only lymphocytic infiltrate in tumor stroma and not at the invasion front

  Do not consider central fibrosis and necrotic areas

  Report average of lymphocytic infiltrate as percentage

* Salgado, R., Denkert, C., Demaria, S., Sirtaine, N., Klauschen, F., Pruneri, G., et al. (2014). The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Annals of Oncology

Reporting: Evaluation after Neoadjuvant Chemotherapy

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Identification of tumor bed, otherwise ypTX	4	D	++
▪ Reporting of tumor size as total extent of tumor bed area involved by infiltrates of residual vital invasive carcinoma	4	D	++
▪ pCR when absence of invasive Ca. and absence of angioinvasion or LN metastases. Presence of ypTis should be recorded	2b	D	+
▪ Use of IHC to identify tumor residues (lymphnodes)	2b	B	+/-
▪ Reporting of ypTN after neoadjuvant systemic therapy	5	D	++
▪ Repeat IHC for ER, PR, and HER2	5	D	+/-
▪ Intraoperative frozen section (reduced sensitivity)	5	D	-
▪ Tumorregression-Scores: RCB-Score or Sataloff-Score	4	D	+/-

Guidelines Breast
Version 2024.1E

Predictive pathology of endocrine responsiveness

	Oxford		
	LoE	GR	AGO
▪ Immunhistochemical detection of estrogen- and progesterone-receptors in paraffin-embedded tissue; scored as percentage of positive tumor cell nuclei (ER positive if ≥ 1%, low positivity ≥ 1% to 10%; PR positive if ≥10%)	1a	A	++
▪ Detection of endocrine responsiveness by Ki-67 decrease to ≤ 10% after 3-4 weeks of preoperative endocrine therapy in primary breast cancer	1b	A	+
▪ Detection of secondary, i.e. acquired endocrine resistance by analysis of activating ESR-1 mutations in liquid biopsy or metastatic tissue	1b	A	+

Guidelines Breast
Version 2024.1E

HER2-Analysis by IHC

	Oxford		
	LoE	GR	AGO
▪ 3+ staining pattern: HER2+ if strong complete circular membrane staining of > 10% invasive cells	1a	A	++
▪ 2+ staining pattern: If > 10% circular but moderate/weak membrane staining or ≤ 10% strong staining, U-shaped staining in micropapillary carcinoma: ISH required (CISH, SISH, FISH)	1a	A	++
▪ 1+ staining pattern: with >10 % incomplete membrane staining that is weak or barely perceptible (caveat: reproducibility).	1a	A	+
▪ 0 grade staining: to be confirmed by second determination in case that Trastuzumab-Deruxtecan treatment* is considered	5	D	++
▪ HER2-low: 1+ oder 2+ /ISH negativ	1b	A	++

* Due to heterogeneity and therapeutic relevance

Guidelines Breast
Version 2024.1E

HER2-Analysis by ISH when IHC 2+

	Oxford		
	LoE	GR	AGO
▪ **Single-Color In-Situ-Hybridisation (ISH):**	3a	C	++
▪ HER2+ if signal counts ≥ 6 in at least 20 cohesive cells			
▪ negative if signal counts < 4 signals/nucleus			
▪ 2-Color ISH recommended for ≥ 4 and < 6 signals/nucleus			
▪ **Two-Color In-Situ-Hybridisation (ISH):**	3a	D	++
▪ Group 1: Ratio ≥ 2.0 and signals/nucleus ≥ 4.0 -> HER2+			
▪ Group 2: Ratio ≥ 2.0 and signals/nucleus < 4.0 -> HER2- (no benefit of anti-HER2 therapy)			
▪ Group 3: Ratio < 2.0 and signals/nucleus ≥ 6.0 -> HER2+ (but benefit of anti-HER2 therapy not certain)			
▪ Group 4: Ratio < 2.0 and signals/nucleus ≥ 4.0 und < 6 -> HER2- (no benefit of anti-HER2 therapy)			
▪ Group 5: Ratio < 2.0 und signals/nucleus < 4.0 -> HER2-			

Guidelines Breast
Version 2024.1E

HER2 testing by validated dual-probe ISH assay when IHC = 2+

Batch controls and on-slide controls show appropriate hybridization

HER2/CEP17 ratio ≥ 2.0

Group 1	Group 2
Average *HER2* copy number ≥ 4.0 signals/cell	Average *HER2* copy number < 4.0 signals/cell
	mostly
HER2 positive	HER2 negative

HER2/CEP17 ratio < 2.0

Group 3	Group 4	Group 5
Average *HER2* copy number ≥ 6.0 signals/cell	Average *HER2* copy number ≥ 4.0 - < 6.0 signals/cell	Average *HER2* copy number <4.0 signals/cell
mostly	mostly	
HER2 positive	HER2 negative	HER2 negative

Guidelines Breast
Version 2024.1E

HER2 Testing on Core Biopsies

False positive immunohistochemical labeling may occur in core biopsies. Therefore, methods of individual laboratories should be validated by comparison of core biopsies and resection specimens. Background staining should be evaluated by comparison with normal duct epithelium.

Alternatively, all G1 and G2 cases with HER2 3+ in core biopsies may be analyzed by ISH or may be re-evaluated in the resection specimen.
False positivity is likely when HER+ was reported in G1 tumors of the following types: Infiltrating ductal or lobular carcinoma, ER and PR positive, Tubular (at least 90% pure), Mucinous (at least 90% pure) Cribriform (at least 90% pure), Adenoid cystic carcinoma (90% pure).

In case of discrepancy between core biopsy and specimen, the HER2 overexpressing sample should be re-evaluated by a different method. If still discrepancy – anti-HER2-treatment if amplified in one of both samples. Expected rate of HER2-overexpression: 15% HER2 positive

Guidelines Breast
Version 2024.1E

Additional Special Studies: Molecular Analysis of HER2 Status

	Oxford		
	LoE	GR	AGO
▪ Therapy decisions should only be based on IHC and ISH	1a	A	++
▪ Evaluation of HER2 using validated gene expression test kits	3b	B	-
▪ Evaluation of HER2-amplification by RNA-sequencing	5	D	-
▪ Use of molecular HER2-testing for subtyping	3b	B	+/-

Guidelines Breast
Version 2024.1E

Special Studies: Evaluation of Ki-67 Score

	Oxford		
	LoE	GR	AGO
▪ Counting of tumor nuclei at the invasion front	5	D	++
▪ Semiquantitative eyeballing or counting of labelled cells in core needle biopsies	2	A	++
▪ Consideration of weakly stained tumor nuclei	5	D	++
▪ Reporting of Ki-67 positive nuclei as percentage	5	D	++
▪ Establishing of laboratory standards and cut-off values	5	D	++
▪ Use of image analysis for objective Ki-67 evaluation	5	D	+
▪ Determination of Ki-67 dynamics after short term (2-4 weeks) endocrine therapy*	1b	B	+

* See chapter Neoadjuvant Systemic Therapy

Guidelines Breast
Version 2024.1E

Predictive PD-L1 determination in metastatic triple negative breast cancer

Immunohistochemical assay	Oxford LoE	Oxford GR	Oxford AGO
Metastatic or primary tumor tissue	**2**	**A**	**++**
Detection with antibodies equivalent to registration trials	**3**	**B**	**+**
Combined positive score (CPS) for pembrolizumab indication Divide: positive tumor cells + macrophages + lymphocytes / number of tumor cells x 100	**2**	**A**	**++**
Cut-off value: CPS ≥ 10	**1b**	**A**	
Immune Score (IC) for atezolizumab indication: Cytoplasmic staining of the leucocyte stromal infiltrate (lymphocytes, macrophages, plasma cells, granulocytes outside of abscesses) in relation to the tumor volume	**2**	**A**	**++**
Cut-off value: IC ≥ 1%	**1b**	**A**	

Mutational studies* in mBC: „Precision medicine“ for targeted therapies

Guidelines Breast
Version 2024.1E

Altered genes	Therapeutic relevance	Gene region	Material	Oxford		
				LOE	GR	AGO
BRCA1, BRCA2	Olaparib, Talazoparib Olaparib	All exons	Germline: Blood cells Somatic: Tissue	1b 2b	A B	++ +
PALB2	Olaparib		Germline: Blood cells	2b	B	+
PIK3CA	Alpelisib	Exons 7, 9 and 20	Primary tumor, metastases, plasma	1b	A	++
AKT1, PTEN, PIK3CA	Capivasertib		Primary tumor, metastases, plasma	1b	A	+
HER2-mutation (independent of HER2-status)	Neratinib, lapatinib	Kinase- and extracellular domains; S310, L755, V777, Y772_A775dup	Primary tumor, metastases, plasma particul. lobular BC	4	C	+/-
ESR1	Resistance against AI Response to Elacestrant	Exons 4, 7 and 8	Metastases, plasma Metastases, plasma	2b 1b	B B	+ ++
NTRK gene fusion	Larotrectinib, entrectinib	Fusion- and splice variants	Tumor tissue, particul. secretory breast cancer	2a	B	+
MSI	Pembrolizumab	Microsatellite-instability	Tissue	2a	B	+

* Ideally panel diagnostics

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

Prognostic and Predictive Factors

Guidelines Breast
Version 2024.1E

Prognostic and Predictive Factors

- **Versions 2002–2023:**
  Costa / Fasching / Fersis / Friedrichs / Gerber / Gluz / Göhring / Harbeck / Jackisch / Janni / Kolberg-Liedtke / Kreipe / Loibl / Lück / Mundhenke / Nitz / Rody / Schaller / Schmidt / Schmutzler / Schneeweiss / Simon / Solomayer / Thill / Thomssen / Untch / Witzel / Wöckel

- **Version 2024:**
  Thill / Friedrich / Kreipe

Guidelines Breast
Version 2024.1E

Definition

A **Prognostic Factors** is associated with the probability of the course of the disease (e.g. disease-free or progression-free survival, overall survival). The probability can be influenced by therapy.

A **Predictive Factor** is associated with the probability of the effect of a given therapy.

Guidelines Breast
Version 2024.1E

“Low absolute risk implies low absolute benefit”

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet 379: 432-444, 2012

Guidelines Breast
Version 2024.1E

Quality Criteria

- **Biological hypothesis**
- **Simple and standardized assessment method, quality assurance (QA) of the test**
- **Prospectively planned statistical evaluation (primary goal)**
- **Validation of clinical significance according to**
  - **„Oxford Level of Evidence (LoEOx2001)“ criteria and „Grades of Recommendation (GR)“**
  - **„Grades of Recommendation (GR)“ as well as modified LoE criteria for the use in archived specimen (LoE2009) and category of tumor marker study (CTS)**
- **Clinical relevance for treatment decisions**

in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2024.1E

Prognostic Factors for an Ipsilateral Recurrence after DCIS I

	LoE
Resection margins	1a
Age	1a
Size	1a
Grade	1a
Comedo necrosis	1a
Method of diagnosis	1a
Focality	1a
HER2-overexpression	1a
ER / PR (positive vs. negative)	1a

#see chapter „DCIS“

Prognostic Factors for an Ipsilateral Recurrence after DCIS II

Guidelines Breast
Version 2024.1E

	LoE
Hereditary breast cancer risk	2a
Premenopausal at time of DCIS diagnosis	2a
High BMI	2a
High breast density	2a
Growth pattern (cribriform / solid versus „clinging“ / micro-papillary)	2b
Residual tumor-associated microcalcifications	2b
Architecture	2b
(modified) Van Nuys Prognostic Index/ mitotic rate	2b
Palpable DCIS	2b
ER-, HER2+, Ki-67+	2b
Scores: DCIS, Oncotype DX Breast DCIS Score (12 genes); CCP (23 genes)	2b
MSKCC Nomogram	2b
▪ DCISionRT	2b
Intrinsic subtypes (luminal A, B, HER2+, triple negative)	2b
DCIS compared to invasive carcinoma with higher risk of contralateral BC	2b
High number of TILs	2b

#see chapter „DCIS“

Early Breast Cancer (M0) – eBC
Prognostic Factors I

Factor	Oxford LoE$_{Ox2001}$	Oxford GR	AGO
▪ Tumor size - pT	1a	A	++
▪ Axillary lymph node status - pN	1a	A	++
▪ Histological tumor type (mucinous, tubular etc.)	2b	B	++
▪ Grade (Elston & Ellis) - G	2a	B	++
▪ Age	2a	B	++
▪ Histologically proven peritumoral lymphatic vessel and vascular invasion (L1 V1)	1b	B	++
▪ pCR after NACT* in (luminal-B-like, HER2+, TN)	1a	A	++
▪ Increased risk of recurrence in invasive-lobular BC, cT3/4, N+	2a	B	+/-
▪ Obesity (BMI > 30 kg/m²)	1b	B	+
▪ Margins (resection status) - R0 / R1	1a	A	+

* NACT = Neoadjuvant Chemotherapy

Guidelines Breast
Version 2024.1E

Early Breast Cancer (M0) - eBC
Prognostic Factors II

Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ ER / PR	1a	A	++
▪ HER2 (IHC, ISH)	1a	A	++
▪ ER / PR / HER2/ Ki-67 to assess the intrinsic type with regards to tumor histology and biology	2b	B	++
▪ Proliferation markers			
▪ Ki-67 before, during, or after treatment	1a	B	+
▪ Ki-67 Re-Evaluation after short term preoperative endocrine therapy (2-4 weeks) (ypT and ypN)*	1a	B	+

* Biomarker and Multi Gene Expression test should be evaluated on core needle biopsy prior endocrine therapy

Reproducibility – Quality Assurance is Key for Clinical Decision Making

- ER / PR: concordance central vs local is high (97%; Plan B, SABCS 2014)
- Grade: concordance central vs local is 68% (PlanB, JCO 2016)
- HER2: frequency of false-positive test results 6% (ASCO /CAP JCO 2013)
- Impact of routine pathologic review in N0 BC: 20% changes: grade 40%, LVI 26%, N 15%, margin 12% (JCO 2012)
- pN0 from MIRROR study: pN0 was upstaged in 22%, in central pathology review (Ann Oncol 2012)
- Ki67:
  - Inter- and intraobserver variability in measurement of Ki-67 is high (J Nat. Cancer Institute 2011)
  - High reproducibility for low and high Ki67 levels (J Pathol 2002)
  - Standardized methodology improves analytical validity (JNCI 2020)

Guidelines Breast
Version 2024.1E

Guidelines Breast
Version 2024.1D

Predictive pathology of endocrine responsiveness

	Oxford		
	LoE	GR	AGO
▪ Immunhistochemical detection of estrogen- and progesterone-receptors in paraffin-embedded tissue; scored as percentage of positive tumor cell nuclei (ER positive if ≥ 1%, low positivity ≥ 1% to 10%; PR positive if ≥10%)	1a	A	++
▪ Detection of endocrine responsiveness by Ki-67 decrease to ≤ 10% after 3-4 weeks of preoperative endocrine therapy in primary breast cancer	1b	A	+
▪ Detection of secondary, i.e. acquired endocrine resistance by analysis of activating ESR-1 mutations in liquid biopsy or metastatic tissue	1b	A	+

see chapter „Pathology“

Guidelines Breast
Version 2024.1E

Early Breast Cancer (M0) - eBC
Prognostic Factors III

Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ Gene expression profiles (GEP, multigene assays, gene signatures)			
▪ MammaPrint® (N0-1)	1b	A	+*
▪ Oncotype DX® (N0-1, HR+ HER2-)	1b	A	+*
▪ EndoPredict® (N0-1, HR+, HER2 -)	2b	B	+*
▪ Prosigna® (N0-1, HR+, HER2 -)	2b	B	+*
▪ Breast Cancer Index^{SM} (N0-1, HR+ HER2-)**	2b	B	+/-*
▪ IHC4 (ER / PR / HER2 / Ki-67) (validated for central testing)	2b	B	+/-
▪ PREDICT® algorithm (https://breast.predict.nhs.uk/)	1b	A	+
▪ HER2DX (HER2+)	2b	B	+/-
▪ Clinical-pathological score for lobular breast cancer (nodal status, tumor size, lymphovascular invasion LVI)	2b	B	+/-
▪ CTS5 Clinical Treatment Score**	2b	B	+
▪ CPS-EG Score	2b	B	+
▪ RCB Score	2a	B	+

* Should only be used in the context of clinical-pathological criteria (tumor size, nodal involvement, grade, Ki-67, ER, PR, HER2)
** Estimation of late recurrence

Guidelines Breast
Version 2024.1E

Early Breast Cancer (M0) - eBC
Prognostic Factors IV

Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ Disseminated tumor cells (DTC, in bone marrow)	1a	A	+/-
▪ Circulating tumor cells (CTC, in blood, Cell Search®)*	1b	A	+/-
▪ CTC before NACT (regarding OS, DDFS, LRFI)	1b	B	+/-
▪ Therapy decisions based on CTC phenotypes	3a	C	-
▪ Cell-free DNA (cfDNA, ctDNA in blood, prognostic for DFS, PFS, DDFS, OS)	2a	B	+/-

* Validated clinical data only available for this assay

Commercially Available Molecular Tests

	70 gene signature (MammaPrint®) $	21 gene Recurrence score (Oncotype DX®) $	8 gene signature (Endopredict®) $	PAM 50 (Prosigna®) $	Breast Cancer Index® (BCI) $
Provider	Agendia	Genomic Health	Sividon (Myrirads)	NanoString	Biotheranostics
Type of assay	70-gene assay	21-gene recurrence score	11-gene assay	50-gene assay	5 + 2 (MGI+H/I)
Type of tissue	fresh frozen (technical validation for FFPE available)	FFPE	FFPE	FFPE	FFPE
Technique	Microarrays for RNA	qRT-PCR	q-RT-PCR	Direct hybridization (nCounter®)	q-RT-PCR
Central lab	yes	yes	no	no	yes
Indication and population studied	prognostic N-/+, < 70 Jahre	prognostic N-/+, ER+ endocrine treated	prognostic (pre-) postmenopausal N-/+, ER+ HER2- endocrine treated	prognostic postmenopausal N-/+, ER+ HER2- endocrine treated	Prognostic pT1-3pNo – pN1 ER+ / HER2– Endocrine treated
Risk classes	Low – high	RS (Low – intermediate – high)	Low – high	ROR (Low – inter-mediate – high), molecular types	Low - high
Clinical Validation	Yes	yes	yes	yes	Yes
Registration	FDA clearance as “In Vitro Diagnostic Multivariate Index Assay (IVDMIA)« CE-Mark (fresh tissue and FFPE)	Clinical Laboratory Improvement Amendments (CLIA) + College of American Pathologists (CAP)-accredited ref lab	CE-Mark	CE-Mark FDA 510(k) Clearance	Service Mark (SM)

$ **Validated clinical data only available for this assay**

Guidelines Breast
Version 2024.1E

Commercially Available Molecular Tests

Guidelines Breast
Version 2024.1E

	70 gene signature (MammaPrint®) $	21 gene Recurrence score (Oncotype DX®) $	8 gene signature (Endopredict®) $	PAM 50 (Prosigna®) $	Breast Cancer Index® (BCI)
Prognosis after 5 yrs (late recurrences)	not separately shown	yes	yes	yes	yes
Predictive impact (chemotherapy benefit)	poorly validated	yes	not shown	not shown	EAT after 5 yrs
Prospective-retrospective evidence (% of recruited patients)	Multicenter validation	NSABP B-14 **(14%)** NSABP B-20 **(28%)** ECOG 9127 SWOG 8814 **(40%)** ATAC **(30%)**	ABCSG 6 **(19%)** ABCSG 8 **(36%)** GEICAM-9906 **(45%)** ATAC **(10%)**	MA.12 **(59%)** MA.5 **(66%)** ABCSG 8 **(44%)** ATAC **(16%)**	TransATTOM **(11%)**
Prospective evidence	MINDACT (N0, N1) (8y DFS, OS)	TAILORx (12 y DFS, OS), N0, RS ≤ 25 vs. ≥ 26 PlanB (N0 highrisk/N+) (5 y DFS, OS) RxPONDER (5 y DFS, OS), N1, RS ≤ 25 vs. ≥ 26) ADAPT (5 y DFS, OS), N0-1, RS 0-11; RS 12-25 / Ki67 response	–	–	--

$ **Validated clinical data only available for this assay**

Prospective Clinical Trials (Oncotype DX® [TAILORx, PlanB, RxPONDER, ADAPT], MammaPrint® [MINDACT])

Guidelines Breast
Version 2024.1E

Prognosis in low-risk groups excellent for both tests: ~ 94% 5 J. DFS with only adjuvant endocrine therapy (ET)

	TailorX	RxPONDER	PlanB	ADAPT	MINDACT
Follow-up	median 7.5 years	median 5.1 years	5-year-DFS	median 60 months	median 8.7 years
Trial design (biomarker question)	pN0; Randomization RS 11-25 (+/- CTX)	pN1; Randomization RS0-25 (+/- CTX)	Prospective ODX testing: ET alone in RS 0-11 pN0-1	Non-inferiority (iDFS) ET alone: RS 0-11 vs RS12-25/ET response	Prospectively defined 5y-DMFS threshold for ET alone
Percentage clinically defined low-risk group	6615/9427 (70.2%, adj-online)	all 1-3 involved lymph nodes	all clincial CTX indication (pN0-1)	all clincial chemotherapy (CTX) indication (c/pN0-1)	3336/ 6693 (49.8%, adj-online)
Percentage high clinical risk and low genomic risk (clinical CTX indication)	16.7% (RS 0–10)	42.8% (RS 0-13)	15.3% (RS 0–11)	ET-trial (pN0-1): all RS 0-25, i.e. low genomic risk with ET alone	23.2% (high clinical/low genomic risk)
Test failure rate	n.r.	n.r.	2.9%	n.r.	26% (fresh frozen)
Percentage genomically intermediate-risk group (only for Oncotype DX, ODX)	69.1% (RS 11–25)	57.2% (RS 14-24)	60.4% (RS 12–25)	Included only RS 0-11 (37.9%) or RS 12-25/ET response (62.1%)	n.a.
Percentage genomically high-risk group (only for Oncotype DX)	14.3% (RS ≥ 26)	n.a.	24.3% (RS ≥ 26)	n.a.	27.0% (high clinical and high genomic risk)
12-year follow-up	reported	n.r.	n.r.	n.r.	n.r.

Guidelines Breast
Version 2024.1E

Adjuvant Endocrine Therapy
Predictive Factors for DFS

Therapy	Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ Endocrine therapy	▪ ER / PR status [%]	1a	A	++
	▪ IHC staining intensity (ER/PR)	1a	A	-
	▪ Ki-67 Re-Evaluation after short preoperative endocrine therapy (2-4 weeks) (ypT and ypN)*	1b	A	+
▪ Extended endocrine therapy (EAT)	▪ Breast Cancer Index® MammaPrint	2b	B	+/-
▪ Tamoxifen	▪ CYP2D6-polymorphism	2b	B	-
▪ Ovarian ablation or suppression	▪ Menopausal status	1c	A	++
▪ Aromatase inhibitors vs. tamoxifen	▪ Menopausal status	1c	A	++
	▪ ER / PR / HER2 as single factors	1c	A	-
	▪ Invasiv-lobular breast cancer	2b	B	+
	▪ Ki-67 high	2b	B	+/-
	▪ Obesity (BMI > 30 kg/m²)	2b	B	+/-

Guidelines Breast
Version 2024.1E

Adjuvant Chemotherapy and Targeted Therapy Predictive Factors for DFS

Therapy	Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ Adjuvant Chemotherapy	70-Gene-signature (Mammaprint®)	1b	A	+
	21-Gene-signature (Oncotype DX RS®)	1b	A	+
	EPclin (Endopredict®)	2b	B	+
	PAM-50 (Prosigna®)	2b	B	+
	Histological type (lobular vs. NST)	2b	B	-
	TIL´s in TNBC	2b	B	+/-
▪ Anti-HER2-Therapy	HER2 (IHC, ISH)	1a	A	++
▪ PARP-Inhibitors	gBRCA1/Mutation (HER2 neg.)	1a	A	+

*Consider decision according to age/menopausal status, prospective evidence available for Mammaprint and OncotypeDX only (see next slide)

Results for prospectively evaluated biomarkers (LOE1a) in early HR+/HER2- breast cancer

Guidelines Breast
Version 2024.1E

biomarker/ signature	Population (HR+/HER2- patients)	therapy options
Mammaprint (MINDACT n=2140)	Clinically high/genomic low risk (n=1550) N0-1, age >50 yrs N0-1, age ≤50 yrs (patients with OFS in the ET arm: 26%)	 ET, no adjuvant CT adjuvant CT→ET*: 2.6% CT-benefit in 5-y DDFS (93.6 vs. 96.2%)
Oncotype DX (TAILORx n=6711)	TailorX (T1b-T2, N0, 74% clinically low risk, 13% OFS in premenopausal women)) N0, RS 0-25 age>50 yrs. N0 RS 0-15 age ≤50 yrs N0 RS 16-25 age ≤50 yrs	 ET, no adjuvant CHT ET, no adjuvant CHT adjuvant CT→ET*: (3.2-3.4% CT-benefit in 5-y DRFI (93→95-96% 5 y DRFI, in RS 16-20 if clinical high risk only, 16-20: HR=1.4 (n.s.), 21-25: HR=2.19 (sign) for ET vs. CT→ET
RxPonder (n=5018)	RxPonder: N1 RS 0-25: postmenopausal RS 0-25: premenopausal (patients with OFS in the ET arm: 19%)	ET, no adjuvant CT (neo)adjuvant CT→ET* 2.4% CT benefit in 5-y DRFI (5-y DRFI 93.9 vs. 96.3%, HR=0.062, p=0.02) explorative analysis: no effect of CT age 50 and older ($p_{interaction}$ 0.06)
RS + KI-67post (ADAPT, n=2290 endocrine treated)	clinically intermediate/high risk , RS 0-25 (RS 12, 25+$Ki67_{post}$≤10%) N0-1, age>50 yrs N0, RS 0-11 and age ≤50 yrs N0, RS 12-25 with $Ki67_{post}$≤10% and age ≤50 yrs N1: RS 0-25 (+ Ki-67_{post} ≤10% in RS 12-25) and age ≤50 yrs N1: RS 0-25 and ki-67_{post}>10%	 ET, no adjuvant CT adjuvant ET, no adjuvant CT adjuvant ET+/- OFS, if RS >16 or clinically high risk +/- CT: 5-yr-DDFS: 97% with ET alone, no significant difference between RS 0-15 and 16-25 adjuvant ET+OFS or CT→ET 5-yrs. DDFS 97% with ET alone (neo)adjuvant CT→ET

* If CT is refused: alternative ET+OFS

DDFS=distant-disease-free-survival, DRFI= distant recurrence free interval, ET= endocrine treatment, CT= chemotherapy, OFS= ovarian function suppression, RS= Recurrence Score

Neoadjuvant Systemic Chemotherapy (NACT)
Predictive Factors for pCR I

Factor	pCR* Probability	Oxford LoE	Oxford GR	Oxford AGO
▪ Young age	↑	1a	A	+
▪ Obesity	↓	2a	B	+
▪ cT1 / cT2 tumors o. N0 o. G3	↑↑	1a	A	++
▪ Negative hormone receptor status	↑↑	1a	A	++
▪ Triple negative breast cancer	↑↑	1a	A	++
▪ Positive HER2-status	↑↑	1a	A	++
▪ Early clinical response	↑	1b	A	+
▪ Lobular tumor type	↓	1a	A	+
▪ Metaplastic tumor type	↓↓	4	C	+

* High (↑) or very high (↑↑) probability to reach pCR, low (↓) or very low (↓↓) probability to reach pCR
See aso chapter „Prognostic and predictive factors“

Guidelines Breast
Version 2024.1E

Neoadjuvant Systemic Chemotherapy (NACT) Predictive Factors for pCR II

Factor	pCR* Probability	Oxford LoE	Oxford GR	Oxford AGO
▪ Gene expression profiles (gene signatures) (Mammaprint®(+ Blueprint®), Endopredict® Oncotype DX®, Prosigna®, PAM50®, Breast Cancer Index^{SM})	↑	2b	B	+/-
▪ HER2DX (27 genes, response to trastuzumab/pertuzumab	↑	2b	B	+/-
▪ Ki-67	↑	2b	B	+
▪ Tumor infiltrating lymphocytes**	↑	2a	B	+
▪ *PIK3CA* mutation (for HER2-positive BC)	↑	2a	B	+/-
▪ *gBRCA*-mutation (for the effect of chemotherapy)	↑	2b	B	+
▪ *gBRCA*-mutation (for the effect of platinum)	↔	2b	B	+/-

* High (↑) or very high (↑↑) probabililty of pCR, low (↓) or very low (↓↓) probabililty of pCR

** Defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front (lymphocytes make up > 50% of stroma area)

Guidelines Breast
Version 2024.1E

Metastatic Breast Cancer (mBC)
Prognostic Factors

Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ Circulating tumor cells (CTC in blood, Cell Search®)			
▪ Prognosis	1a	A	+
▪ Early response assessment (3w)	1b	B	+
▪ Therapy decision solely based on dynamics of CTC numbers over time or CTC phenotype	1b	A	-*
▪ Cell-free DNA (cfDNA in blood)	2a	A	+/-

* Study participation recommended

Treatment of Metastatic Breast Cancer
Markers for Indication

Guidelines Breast
Version 2024.1E

Therapy	Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ Endocrine therapy	ER / PR (prim. tumor, better: metastasis)	1a	A	++
	Response to prior therapy	2b	B	++
▪ Elacestrant	Autocrine receptor mutation (*ESR1*) (metastases, plasma)	1b	B	++
▪ Alpelisib	*PIK3CA* mutation (prim. tumor, metastases, plasma)	1b	A	++
▪ Capivasertib	*PIK3CA, AKT1, PTEN* alterations (primary tumor, metastases, plasma)	1b	A	+
▪ Trastuzumab Deruxtecan	HER2-low or HER2-positive	1b	A	++
▪ Chemotherapy	Response to prior therapy	1b	A	++
▪ Anti-HER2-therapy	HER2 (prim. tumor, better: metastasis)	1a	A	++
▪ Checkpoint-Inhibitors	PD-L1 positivity# (IC, CPS) in TNBC (primary tumor or metastasis)	1b	B	++
	MSI/TMB	3	C	+
▪ PARP-Inhibitors	g*BRCA1/2*-mutation	1a	A	++
	sBRCA1/2/gPALB2	2b	B	+

Mutation Diagnostics* in mBC: „Precision Medicine“ for Targeted Therapies

Guidelines Breast
Version 2024.1E

Altered genes	Therapeutic relevance	Gene region	Material	Oxford		
				LOE	GR	AGO
BRCA1, BRCA2	Olaparib, Talazoparib Olaparib	All exons	Germline: Blood cells Somatic: Tissue	1b 2b	A B	++ +
PALB2	Olaparib		Germline: Blood cells	2b	B	+
PIK3CA	Alpelisib	Exons 7, 9 and 20	Primary tumor, metastases, plasma	1b	A	++
AKT1, PTEN, PIK3CA	Capivasertib		Primary tumor, metastases, plasma	1b	A	+
HER2-mutation (independent of HER2-status)	Neratinib, lapatinib	Kinase- and extracellular domains; S310, L755, V777, Y772_A775dup	Primary tumor, metastases, plasma particul. lobular BC	4	C	+/-
ESR1	Resistance against AI Response to Elacestrant	Exons 4, 7 and 8	Metastases, plasma Metastases, plasma	2b 1b	B B	+ ++
NTRK gene fusion	Larotrectinib, entrectinib	Fusion- and splice variants	Tumor tissue, particul. secretory breast cancer	2a	B	+
MSI	Pembrolizumab	Microsatellite-instability	Tissue	2a	B	+

* Ideally panel diagnostics # see chapter „pathology“

Decision guidance prosepectively evaluated biomarkers (LOE1a) and therapy options (mBC)

Guidelines Breast
Version 2024.1E

Biomarker / Signature-therapy option	**Subtyp / Population**	**Therapy option**
PDL-L1 ≥ 1%	TNBC	Firtst line Atezolizumab + nab Paclitaxel
CPS > 10	TNBC	First line Pembro + chemotherapy
PIK3CA mutation	HR+ / HER2-	Fulvestrant + Alplisib after failure offirst line ET
BRCA1/2 mutation (OlympiAD, EMBRACA)	HER2 –	Olaparib, Talazoparib

Therapy-Relevant Mutational Analysis for „Actionable“ Genomic Alterations in BC

Guidelines Breast
Version 2024.1E

Diagnostic Tool*	Outcome	Oxford LoE	Oxford GR	AGO
Evidence from studies with other cancer patients („tumor-agnostic testing“)				
▪ Companion Diagnostics for therapies of other tumor entities (e.g. BRAF, FGFR1, …)	Efficacy of diverse therapies	4	D	+/-**
▪ Large Panel Gene Analysis (e.g. FoundationOne, GPS Cancer, NeoSelect, Molecular Health Guide, local „hand-selected„ panels)	Efficacy of diverse therapies, prognosis	3a	C	+/-**
▪ Next Generation Sequencing (NGS) (recommended only in Tier 1 + 2)	Efficacy of evaluated drugs	1b	B	+/-**

* Assessment method for somatic mutations (tumor tissue, cf-DNA) is not taken into consideration for LoE

** Participation in clinical trials or structured registries recommended

Joint Consensus Recommendations of AMP, ACMG, ASCO and CAP for Reporting Genetic Variants in Cancer

Guidelines Breast
Version 2024.1E

Tier	LoE		Explanation
Tier 1	A.1	Biomarkers that predict response or resistance to FDA-approved therapies for a specific type of cancer	Variants of strong clinical significance
	A.2	Biomarkers included in professional guidelines that predict response to therapies for a specific type of tumor	
	B	Biomarkers that predict response or resistance to therapies for a specific type of tumor based on well-powered studies with consensus from experts in the field	
Tier 2	C.1	Biomarkers that predict response or resistance to therapies approved by the FDA or professional societies for a different type of tumor	Variants of potential clinical significance
	C.2	Biomarkers that serve as inclusion criteria for clinical trials	
	D	Biomarkers that show plausible therapeutic significance based on preclinical studies	
Tier 3		Not observed at a significant allele frequency in the general or specific subpopulation databases, or pan-cancer or tumor-specific variant databasis. No convincing publised evidence or cancer association	Variants of unknown clinical significance
Tier 4		Observed at significant allele frequency in the general or specific subpopulation Databases. No existing published evidence of cancer association	Benign or likely benign variants

Guidelines Breast
Version 2024.1E

Lesions of Uncertain Malignant Potential (B3)

(ADH, LIN, FEA, Papilloma, Radial Scar/Complex Sclerosing Lesion)

Lesions of Uncertain Malignant Potential (B3)

Guidelines Breast
Version 2024.1E

Versionen 2005–2023:

Albert / Audretsch / Bauerfeind / Brunnert / Ditsch / Fallenberg / Fersis / Friedrich / Friedrichs / Gerber / Huober / Kolberg-Liedtke / Kreipe / Maass / Nitz / Reimer / Rody / Schmidt / Schreer / Sinn / Thomssen

Version 2024:

Friedrich / Sinn

Pathology Reporting for Minimal Invasive Biopsies

Guidelines Breast
Version 2024.1E

B-Classification*

B1 = Unsatisfactory or normal tissue only

B2 = Benign lesion

B3 = Lesion of uncertain malignant potential

B4 = Suspicion of malignancy

B5 = Malignant

- **B5a = Non-invasive**
- **B5b = Invasive**
- **B5c = In situ / invasion not assessable**
- **B5d = Non epithelial, metastatic**

* **AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V. (Hrsg.). Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Langversion 4.4, Juni 2021**

Guidelines Breast
Version 2024.1D

B3-Lesions

1. **Lesions with increased risk of associated DCIS or invasive carcinoma**
   - Atypical ductal hyperplasia (ADH) or atypical epithelial proliferation of ductal type (classification possibly as B4, depending on extent of lesion)
   - Flat epithelial atypia (FEA)
   - Lobular neoplasia (LIN; LN; now subdivided into ALH and LCIS, no differentiation according to older nomenclature) classical and non-classical type
   - Atypical apocrine adenosis
2. **Potentially heterogeneous lesions with risk of incomplete sampling**
   - Cellular fibroepithelial lesion or phyllodes tumour without evidence of malignancy
   - Intraductal papilloma with / without atypia (possibly also B4, depending on the extent of the lesion)
   - Radial scar or complex sclerosing lesion (unless the radial scar only microscopically, not radiologically detected: B2)
   - Hemangioma
3. **Rare Lesions**
   - Adenomyoepithelioma, nipple adenoma, microglandular adenosis, mucocele-like lesion, nodular fasciitis, desmoid-type fibromatosis, spindle cell lesion of unknown significance

Guidelines Breast
Version 2024.1E

Management after Minimally Invasive Biopsy

	Oxford		
	LoE	GR	AGO
▪ **Interdisciplinary conference: Concordant findings in pathology and imaging?**			
▪ yes: proceed according to histologic type and dimension of lesion	3a	C	++
▪ no: open biopsy	3a	C	++
Vacuum-assisted biopsy (after core biopsy)	5	D	+

Guidelines Breast
Version 2024.1E

Strategy after Diagnosis of ADH in Biopsy Sypecimen

	Oxford		
	LoE	GR	AGO
ADH in core- / vacuum-assisted biopsy:			
▪ **Open excisional biopsy**	3a	C	++
▪ **Open excisional biopsy may be omitted, if all following requirements apply:** a) No mass-lesion radiologically, and b) a small lesion (≤ 2 TDLU*) in vacuum biopsy, and c) complete removal of imaging abnormality	5	C	+/-
ADH at margins in open biopsy specimen:			
▪ **No further surgery, if incidental finding accompanies invasive or intraductal carcinoma**	3a	C	+

* Terminal ductal-lobular unit

Guidelines Breast
Version 2024.1E

Lobular Intraepithelial Neoplasia (LIN / LCIS)

- Includes:
  - Atypical lobular hyperplasia
  - Classical lobular carcinoma in situ (LIN, classical variant)
  - Non-Classical lobular carcinoma in situ (LIN, classical variant)
- LIN 1–3 classification is not sufficiently validated prognostically
- Non-Classical LIN (pleomorphic LIN, florid LIN) are classified as lesions with elevated risk → potentially **B5a**
- Indicator / precursor lesion:
  Ipsi- and contralaterally increased breast cancer risk:
  7x after 10 years

Guidelines Breast
Version 2024.1E

Upgrade rates* for B3 lesions

* i.e., upgrade to malignant diagnosis when excised

Risk lesion	Upgrade rate to in situ or invasive Ca	References
Atypical lobular hyperplasia (ALH)	5%	[1]
Classical lobular neoplasia (C-LCIS)	4 - 16%	[1-3]
Non-classical lobular neoplasia (pleomorphic, florid LCIS, NC-LCIS)	33 - 39%	[3, 4]
Atypical ductal hyperplasia (ADH)	23%	[1]
Flat epithelial atypia (FEA)	0 - 14%	[5, 6]
Papilloma	12%	[7]
- no atypia	6 - 10%	[7, 8]
- atypia	21 -29%	[8, 9]
Radial scar or complex sclerosing lesion	7 - 11%	[10-12]
- no atypia	5%	[12]
- atypia	25%	[13]

Guidelines Breast
Version 2024.1E

Risk of malignant disease during follow-up*

* i.e. ipsilateral or contralateral disease irrespective of localization of prior lesion

Risk lesion	Upgrade rate to in situ or invasive Ca
LIN/LCIS	7x / 10 yrs (ipsi-/contralateral)
Atypical ductal hyperplasia (ADH)	3-5x / 10 years (ipsi-/contralateral)
Papilloma	
• no atypia	4.6% (ipsilateral)
• atypia	13% (ipsilateral)

Guidelines Breast
Version 2024.1E

LCIS with elevated risk

- **Non-classical LCIS:**
  - **Pleomorphic LCIS: high-grade cellular atypia, common involvement of ducts with comedo necrosis and microcalcifications**
  - **Florid LCIS: involvement of multiple lobuli with a maximum extension until confluence and involvement of ductuli and neighboring TDLU**
- **Microinvasion in classical and non-classical LCIS*:**
  - **classical LCIS: n = 11**
  - **florid LCIS: n = 4**
  - **pleomorphic LCIS: n = 1**

Microinvasion in 0.37% of all LCIS (n = 4310) and in 0.43% among all invasive lobular breast cancers (n = 3740).

* **Ross DS & Hoda SA. Am J Surg Pathol 2011; 35: 750–6.**

Guidelines Breast
Version 2024.1E

Strategy after Diagnosis of LIN / LCIS

	Oxford LoE	Oxford GR	Oxford AGO
LIN / LCIS in core- / vacuum-assisted biopsy:			
▪ No further measures if LIN (LCIS, classical variant) with involvement of ≤ 3 TDLU (terminal ductulo-lobular unit) in vacuum biopsy and concordant with imaging.	2b	C	++
▪ Open excisional biopsy, with pleomorphic LIN, florid LIN (LIN 3), or LIN with comedo type necrosis or if not concordant with imaging findings.	2b	C	++
LIN / LCIS at margins of resection specimen (BCT):			
▪ No further surgery.	2a	C	++

Exceptions:

a) Pleomorphic, florid, or LIN / LCIS with necrosis

b) Imaging abnormality is not removed

Strategy after Diagnosis of FEA

	Oxford LoE	Oxford GR	Oxford AGO
FEA in core biopsy / vacuum-assisted biopsy:			
Open excisional biopsy	2b	B	+
Open excisional biopsy may be omitted under the following circumstances: a. a small lesion (≤ 2 TDLU* in vacuum biopsy) <u>and</u> b. Complete or near complete removal of imaging abnormality	2b	B	+
FEA at margins in resection specimen:			
No further surgery, unless calcifications have not been completely removed	3b	C	++

* TDLU = Terminal ductal-lobular unit

Guidelines Breast
Version 2024.1E

Papilloma

- **Includes:** Central and peripheral papilloma > 2 mm, atypical intraductal papilloma (B3)
- To be **distinguished from** peripheral micropapilloma arising in the TDLU, size ≤ 2 mm, may be multiple
- To be distinguished from papilloma with DCIS, from intraductal papillary carcinoma, and from encapsulated papillary carcinoma
- **Precursor lesion:**
  May be associated with in-situ or invasive cancer (up to 6% without atypia if concordant imaging, up to 30% with atypia), increased ipsilateral risk for cancer (up to 4.6% and up to 13% in case of atypical papilloma) .

Guidelines Breast
Version 2024.1E

Strategy after Diagnosis of Papilloma

	Oxford		
	LoE	GR	AGO
▪ **Papilloma without atypia in core needle or vacuum biopsy:**			
→ **no further therapy, if biopsy sufficiently representative (100mm3) and concordant with imaging**	2b	C	+
▪ **Multiple papillomas (>2 mm)**			
→ **open biopsy**	3a	C	++
▪ **Papilloma with atypia in core needle or vacuum biopsies:**			
→ **open biopsy**	3a	C	++
▪ **Papilloma at resection margin:**			
→ **no published data available**			

Guidelines Breast
Version 2024.1E

Radially Sclerosing Lesion

- **Benign pseudoinfiltrative lesion with central fibroelastic core and radial configuration.**
- **Includes:**
  - **radial scar (usually ≤ 1 cm)**
  - **complex sclerosing lesion (> 1 cm)**
- **Additional risk factor in patients with benign epithelial hyperplasia (proliferating breast disease)**
- **Risk for upgrade in open biopsy after diagnosis of a radial sclerosing lesion, depending on the size of the needle (CNB) or method (VAB) and additional atypia: 1–18%**

Strategy after Diagnosis of Radial Scar, Complex Sclerosing Lesion (CSL)

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ **Radial scar / CSL in core- / vacuum-assisted biopsy:**			
▪ **Open excisional biopsy**	3a	C	+
▪ **Without atypia**	3a	C	+
▪ **With atypia**	3a	C	++
→ **Omission of open excisional biopsy if small (< 5mm) lesion or (near) complete removal of imaging abnormality**	5	C	+
▪ **Radial scar / CSL at margins in resection specimen:**			
→ **No further surgery**	3b	C	++

Guidelines Breast
Version 2024.1E

Breast Cancer Early Detection: Follow-up Imaging for Women Age 50–69 Years with B3-Lesions

	Oxford		
	LoE	GR	AGO
▪ **FEA, non-atypical papilloma, radial sclerosing lesion**			
▪ Screening mammography	5	C	++
▪ **LIN / LCIS**			
▪ Mammography (12 months)	3a	C	++
▪ **ADH**			
▪ Mammography (12 months)	3a	C	++
▪ Women with LIN and ADH should be informed about their elevated risk of breast cancer	3a	C	++

Medical Prevention for Patients with Increased Risk of DCIS or Invasive Carcinoma

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Tamoxifen 20 mg/d (5 yrs) for women > 35 years	1a	A	+/-
▪ Low-dose Tamoxifen 5 mg/d* (3 years) independent of menopausal status	1b	B	+/-
▪ Aromatase inhibitors (Exemestane, Anastrozole) for postmenopausal women	1a	A	+/-
▪ Raloxifen for postmenopausal women: Risk reduction of invasive BC only	1a	A	+/-**

Medical prevention should only be offered after individual and comprehensive counseling; overall benefit depends on classification, age, and pre-existing conditions that may influence occurrence of side effects.

* 5 mg Tablet not available; alternatively 10 mg p.o. q2d

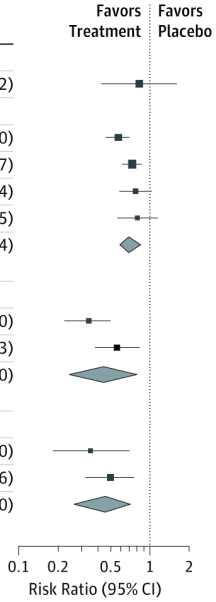
** Risk situation as defined in NSABP P1-trial (1.66% in 5 years)

Medical endocrine Prevention

Guidelines Breast
Version 2024.1D

Risk Reduction of Invasive Breast Cancer: Meta-analysis of Primary Prevention Trials

Source	Trial	Mean, y: Intended Treatment Duration	Mean, y: Total Follow-up	No. With Invasive Breast Cancer/Total Participants (%): Treatment	No. With Invasive Breast Cancer/Total Participants (%): Placebo	Rate per 1000 Women-Years: Treatment	Rate per 1000 Women-Years: Placebo	Risk Ratio (95% CI)
Tamoxifen, low dose								
DeCensi et al,[41] 2013	HOT	5	6.2	18/938 (1.9)	22/946 (2.3)	3.13	3.78	0.83 (0.42-1.62)
Tamoxifen								
Fisher et al,[82] 2005	NSABP-1	5	6.1	145/6681 (2.2)	250/6707 (3.7)	3.59	6.29	0.57 (0.46-0.70)
Cuzick et al,[74] 2015	IBIS-I	5	16.0	214/3579 (6.0)	289/3575 (8.1)	3.86	5.29	0.73 (0.61-0.87)
Powles et al,[83] 2007	Marsden	5	13.2	82/1238 (6.6)	104/1233 (8.4)	4.80	6.10	0.78 (0.58-1.04)
Veronesi et al,[84] 2007	Italian	4[a]	11.2	53/2700 (2.0)	66/2708 (2.4)	1.77	2.21	0.80 (0.56-1.15)
Combined I^2 = 38.7%; Q = 4.9 for heterogeneity; P = .18								0.69 (0.59-0.84)
Raloxifene								
Martino et al,[45] 2004	MORE/CORE	4 or 8[b]	5.4[b]	40/5129 (0.8)	58/2576 (2.3)	1.40	4.20	0.34 (0.22-0.50)
Barrett-Connor et al,[48] 2006	RUTH	5.1[a]	5.6	40/5044 (0.8)	70/5057 (1.4)	1.43	2.49	0.56 (0.38-0.83)
Combined I^2 = 66.4%; Q = 3.0 for heterogeneity; P = .08								0.44 (0.24-0.80)
Aromatase inhibitor								
Goss et al,[44] 2011	MAP.3	5[c]	2.9	11/2285 (0.5)	32/2275 (1.4)	1.66	4.85	0.35 (0.18-0.70)
Cuzick et al,[4] 2014	IBIS-II	5	5	32/1920 (1.7)	64/1944 (3.3)	3.29	6.62	0.50 (0.32-0.76)
Combined I^2 = 0.0%; Q = 0.8 for heterogeneity; P = .39								0.45 (0.26-0.70)



Nelson et al. JAMA. 2019;322(9):868-886. doi:10.1001/jama.2019.5780

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2024.1E

Ductal Carcinoma in Situ (DCIS)

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2024.1E

Ductal Carcinoma In Situ (DCIS)

Versions 2002–2023:

Audretsch / Bauerfeind / Blohmer / Brunnert / Budach / Costa/ Ditsch / Fersis / Friedrich / Gerber / Hanf / Junkermann / Kühn / Lux / Maass / Möbus / Mundhenke / Nitz / Oberhoff / Scharl / Schütz / Solbach / Solomayer / Souchon / Thill / Thomssen / Wenz

Version 2024:

Budach / Gerber

in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2024.1E

DCIS - Pretherapeutic Assessment

	Oxford		
	LoE	GR	AGO
Mammography	1b	B	++
Magnification view of microcalcifications	4	C	++
Increased detection rate of G1 / G2 DCIS by full-field digital mammography (versus screen-film)	2b	B	+
Ultrasound (to rule out an accompanying invasive component)	4	C	++
For tumors with a solid part	4	C	++
MRI to determine the extension and planning of surgery	1a	B	+/-
Clinical examination	5	D	++
Stereotactic core needle / vacuum biopsy (VAB)	2b	B	++
Specimen radiography	2b	B	++
Marker (clip) left at biopsy site for localization if lesion is completely removed	5	D	++
Interdisciplinary board presentation	5	D	++

DCIS – Upstaging, ipsi- / Contralateral Events und Mortality

Guidelines Breast
Version 2024.1E

Upstaging to BC %	Ipsilateral events (cum. incidence) %	Contralateral events (cum. incidence) %	BC-specific mortality % (95% CI)
5-25.9	*10 years*: BCS: 24.6 BCS and radiotherapy: 9.6 *20 years:* BCS: 30.6 BCS and radiotherapy: 18.2	*10 years:* 4.8-6.4 *15 years*: 6.4-~11	*10 years*: 0.9 (0.7-1.1) (BCS) 0.8 (0.7-1.0) (BCS and radiotherapy) 1.3 (1.1-1.5) (unilateral mastectomy)

~ 50% of all ipsilateral events are invasive.

Breast cancer specific mortality is 3,3%.

Women with DCIS have a 1.8-3-fold increased risk of death compared to normal population/women without DCIS. Risk is greater for young and black women.

Association of a Diagnosis of Ductal Carcinoma In Situ With Death From Breast Cancer

Giannakeas V, Sopik V, Narod SA. JAMA Netw Open. 2020 Sep 1;3(9):e2017124

144,524 women treated for DCIS, 1,540 women died of breast cancer,
cohort study included data for women who had first primary DCIS diagnosed between 1995 and 2014 from the SEER registries database (use of ET is not reported),
retrospective analysis,
results:

- **standardized mortality ratio for death from breast cancer among women with DCIS was 3.36 (95% CI, 3.20-3.53),**
- **risk is greater for young and black women,**
- **4,502 (3.1%) ipsilateral invasive recurrences, resulting in a 20-year actuarial risk of 13.9%,**
- **5,527 (3.8%) contralateral invasive breast cancers, resulting in a 20-year actuarial risk of 11.3%,**
- **women with DCIS had a 3-fold increased risk of death from breast cancer compared to women without DCIS.**

Risk Factors for Upstaging from DCIS to Invasive Cancer in Final Surgical Specimen

in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2024.1E

	Oxford LoE
Higher risk	
▪ DCIS without microcalcification in core needle or vaccum biopsy	3b
▪ Microcalcification ≥ 11,5 mm	3b
▪ Presentation as tumor in MRI	3b
▪ Increased Ki-67 (≥ 20%)	3b
▪ PR negative	3b
▪ High peak contrast enhancement on MRI	3b
▪ Irregularly shaped, non-circumscribed, heterogeneous or margin-enhancing tumors with intratumoral high signal intensity or peritumoral edema on MRI	3b
▪ Biopsy technique: diagnosis by core needle biopsy versus vacuum biopsy (smaler sampling volume)	3b
▪ High platelet-lymphocyte ratio	3b
Lower risk	
▪ Removal ≥ 90% of the microcalcifications by vacuum biopsy	3b

in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2024.1E

Good Clinical Practice (GCP)

Surgical excision (BCS or mastectomy) is the standard treatment for DCIS.

Adjuvant treatment (radiotherapy, endocrine treatment) must be discussed with the patient individually. Adverse effects should be weighted against risk reduction.

Guidelines Breast
Version 2024.1E

Surgical Treatment for Histologically Proven DCIS I

	Oxford		
	LoE	GR	AGO
Excisional biopsy (wire guided)	2b	B	++
Localization with wire-free procedure	3b	C	+/-
Bracketing wire localization in large lesions	3a	C	+
Specimen radiography	2b	B	++
Intraoperative ultrasound (pre-op visible lesion)	3a	C	+/-
Immediate re-excision in case of incomplete resection (specimen radiography)	1c	B	++
Intraoperative frozen section (in individual cases for margin assessment)	3a	D	+/-
Interdisciplinary board presentation	2b	C	++

Open biopsy in suspicious lesions (mammographic microcalcifications, suspicious US, MRI etc.) without preoperative needle biopsy should be avoided

Surgical Treatment for Histologically Proven DCIS II

in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
Histologically clear margins (Ris0)	1a	A	++
Multifocal DCIS: BCS if feasible	2b	B	+
Re-excision required for close margin in case of BCS and radiotherapy (≤ 2 mm in paraffin section)*	2b	C	+
Mastectomy**			
Large lesions confirmed by multiple biopsies; no clear margins after re-excision	2a	B	++
SLNE			
Mastectomy	3b	B	+
BCS	3b	B	--
In case of DCIS in the male breast	5	D	+/-
ALND	2b	B	--

* Individual approach taking into account age, tumor size, grading and implementation of radiation, especially in case of no subsequent radiation

** Patients who present with a palpable mass have a significantly higher potential for occult invasion (26%), multicentricity and local recurrence

in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2024.1E

Prognostic Factors for an Ipsilateral Recurrence after DCIS I

	LoE
Resection margins	**1a**
Age	**1a**
Size	**1a**
Grade	**1a**
Comedo necrosis	**1a**
Method of diagnosis	**1a**
Focality	**1a**
HER2-overexpression	**1a**
ER / PR (positive vs. negative)	**1a**

See also chapter “Prognostic Faktors“

Prognostic Factors for an Ipsilateral Recurrence after DCIS II

in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2024.1E

	LoE
Hereditary breast cancer risk	2a
Premenopausal at time of DCIS diagnosis	2a
High BMI	2a
High breast density	2a
Growth pattern (cribriform / solid versus „clinging“ / micro-papillary)	2b
Residual tumor-associated microcalcifications	2b
Architecture	2b
(modified) Van Nuys Prognostic Index/ mitotic rate	2b
Palpable DCIS	2b
ER-, HER2+, Ki-67+	2b
Scores: DCIS, Oncotype DX Breast DCIS Score (12 genes); CCP (23 genes)	2b
MSKCC Nomogram	2b
▪ DCISionRT	2b
Intrinsic subtypes (luminal A, B, HER2+, triple negative)	2b
DCIS compared to invasive carcinoma with higher risk of contralateral BC	2b
High number of TILs	2b

See also chapter “Prognostic Faktors“

Guidelines Breast
Version 2024.1E

DCIS – Radiotherapy Statements

Radiotherapy has no impact on survival	**LoE 1a**
Radiotherapy reduces the risk of ipsilateral (invasive and non invasive) recurrences by 50 %	**LoE 1a**
The number needed to treat (for ipsilateral breast recurrence) is 9 (over all risk groups).	

Guidelines Breast
Version 2024.1E

DCIS – Adjuvant Radiotherapy

	Oxford LoE	GR	AGO
Radiotherapy after:			
Breast conserving surgery (BCS)	1a	A	++
Mastectomy	2b	B	--
Radiotherapy procedure:			
Conventionally fractionated radiotherapy (50 Gy in 25 fract.)	1a	A	+
Hypofractionated radiotherapy (40-42,5 Gy in 15-16 fract.)	1a	A	+
Radiotherapy boost of the tumor bed	1b	B	+/-
in case of risk factors* (absolute benefit 5-y-RFS 4 %, rate of fibrosis significant increased)	1b	B	+/-
without risk factors	2b	B	-
Partial breast irradiation [age ≥ 50y, DCIS ≤ 3 cm, G1-2, R0 (≥ 5 mm), unifocal / unicentric]	1b	B	+

Side effects and disadvantages must be weighed against risk reduction. Omitting radiotherapy implies elevated risk for local recurrence without effect for overall survival even in the subset of „good risk" patients. Lack of level-1 evidence supporting the omission of adjuvant radiotherapy in selected low-risk cases: < 2.5 cm, low and intermediate nuclear grade, mammographically detected.

*** < 50 years or ≥ 50 years and diagnosis based on symptoms, ≥ 15 mm, multifocality, palpable tumor, resection margins < 10 mm, G2 / 3, central necrosis, comedo type**

in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2024.1E

DCIS – Adjuvant Systemic Treatment

Adjuvant endocrine treatment has no impact on survival (RR 1.11; 95% CI 0.89-1.39)	LoE 1a
Endocrine treatment may have a small effect on ipsilateral invasive (HR 0.79; 95% CI 0.62-1.01) and DCIS (HR 0.75; 95% CI 0.61-0.92) recurrences	LoE 1a
Endocrine treatment for DCIS has an effect on contralateral invasive (RR 0.57; 95% CI 0.39-0.83) and non-invasive (RR 0.50; 95% CI 0.28-0.87) cancer	LoE 1a
The number needed to treat for any ipsilateral breast event is 15	LoE 1a
The number needed to treat to prevent invasive breast cancer is 29 for anastrozole vs. 59 for tamoxifen*	LoE 1b

* within 12 years; according to IBIS II-trial

Guidelines Breast
Version 2024.1E

DCIS – Adjuvant Systemic Treatment

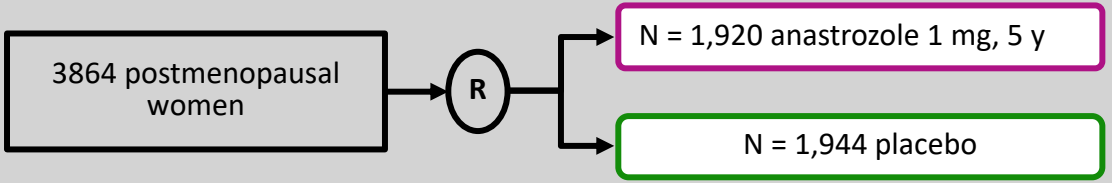
	Oxford		
	LoE	GR	AGO
Tamoxifen (only ER+) 20 mg	1a	A	+/-*
Tamoxifen (only ER+) 5 mg for 3 years	2b	B	+/-*
Aromatase inhibitor (only ER+) in postmenopausal women only	1b	A	+/-*#
Trastuzumab (only HER2+)	5	D	--

* Indication for treatment depends on risk factors, side effects and patient preference

\# Anastrozole versus Tamoxifen: Anastrozole higher fracture rate (OR 1.34), Tamoxifen higher rate of stroke (OR 3.10) and TIA (OR 3.10)

Use of Anastrozole for Breast Cancer Prevention (IBIS-II): Long-Term Results of a Randomised Controlled Trial

Cuzick J et al, Lancet 2020

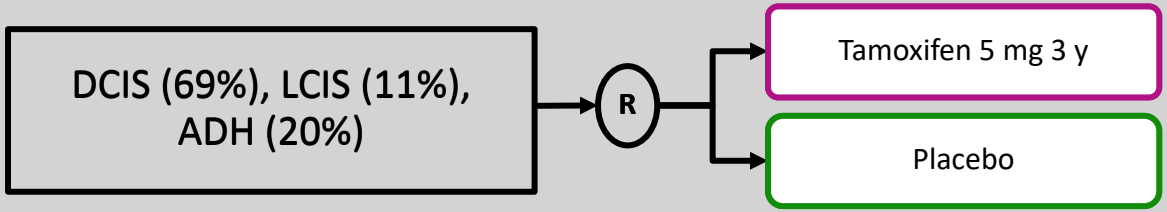


N = 3,864 postmenopausal women at inceased risk for breast cancer,
median follow-up of 131 months,
results:

- **49% reduction of all breast cancers with anastrozole (HR 0.51, 95% CI 0.39–0.66, p < 0.0001),**
- **significant reduction in incidence for anastrozole for ductal carcinoma in situ (HR 0.41, 0.22–0.79, p = 0.0081), especially for oestrogen-positive (HR 0.22, 0.07–0.65, p = 0.0062),**
- **5-year adherence anastrozole 74.6% vs. 77.0% for placebo,**
- **no difference in major side effects (fractures, mycardial infarctions, deep vein thrombosis, pulmonary embolism),**
- **NNT to prevent one breast cancer during 12 years: 29 (anastrozole) vs. 59 (tamoxifen).**

Low Dose Tamoxifen (5 mg) in Premalignant Lesions

Lazzeroni M et al: J Clin Oncol 2023



- **N = 500,**
- **follow-up 9.7 years,**
- **results:**
  - Events: 66 breast cancers (15 in situ; 51 invasive) were diagnosed: Tam 25 and Placebo 41; hazard ratio: 0.58; 95% CI, 0.35 to 0.95; log-rank *P* = .03).
  - Contralateral BC incidence: Tam 6 vs. Plac 16 (HR, 0.36; 95% CI, 0.14 - 0.92; *P* = .025)
  - NNT to prevent one case of breast event with tam 22 in 5 and 14 in 10 years.
  - Severe adverse event: no significant differences
  - Adherence Tam 65% vs. PLAC 61%.

Guidelines Breast
Version 2024.1E

Therapy of Local DCIS Recurrence after Tumorectomy

	Oxford		
	LoE	GR	AGO
After Radiation:			
Simple mastectomy	3a	C	+
+ SLNE	5	D	+
Secondary breast conserving surgery	4	C	+/-
Without radiation after first tumorectomy			
Treatment like primary disease	3	C	++

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

In collaboration with:

AWOgyn

Breast Cancer Surgery
Oncological Aspects

Breast Cancer Surgery
Oncological Aspects

Guidelines Breast
Version 2024.1E

In collaboration with:

- **Versions 2002–2023:**
  Banys-Paluchowski / Bauerfeind / Blohmer / Böhme / Brunnert / Costa / Ditsch / Fallenberg / Fersis / Friedrich / Gerber / Hanf / Janni / Junkermann / Kaufmann / Kühn / Kümmel / Möbus/ Nitz / Rezai / Simon / Solomayer / Thomssen / Thill / Untch / Wöckel

- **Version 2024**
  Rody / Schütz

Breast Cancer Surgery
Oncological Aspects

Guidelines Breast
Version 2024.1E

In collaboration with:

AGO: ++

Surgery is one sub-step out of multiple steps in breast cancer treatment. Thus, both diagnostic and oncological expertise are an essential requirement for every breast surgeon.

AGO: +

Avoidance of a significant delay in cancer treatment

AGO: ++

Surgical therapy decisions should be made in the context of a multimodal therapy concept; in particular, the waiver of diagnostic measures (e.g. SLNE) should be decided as part of a preoperative, interdisciplinary tumor conference.

Pre-therapeutic Assessment of Breast

Guidelines Breast
Version 2024.1E

In collaboration with:

	Oxford LoE	GR	AGO
▪ Clinical examination	5	D	++
▪ Mammography (completion of the imaging)	2b	B	++
▪ + Tomosynthesis (DBT)***	2b	B	+
▪ Contrast-enhanced mammography (alone) adjusted with regards of radiation sensitivity of patient and availability*	2a	B	+
▪ Sonography (breast#)	2b#	B	++
▪ MRI*	1b	A	+
▪ Minimally invasive biopsy**	1b	A	++
▪ Breast-CT	4	D	-
▪ Axillary PET (PET-CT, PET-MR)	2b	B	-

* MRI- or CEM guided vacuum biopsy is mandatory in case of MRI- or CEM detected additional lesions (in house or with cooperations). Individual decision for patients at high familiar risk, with dense breast (density C / D), lobular invasive tumors, suspicion of multilocular disease.

** Histopathology of additional lesions if relevant for treatment

*** Replacement of additional FFDM with SM

Pre-therapeutic Assessment Axilla

Guidelines Breast
Version 2024.1E

In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ Clinical examination	5	D	++
▪ Mammography	2b	B	-
▪ + Tomosynthesis***	2b	B	-
▪ CEM (alone) after unclear resection (Rx) if available	2a	B	-
▪ Ultrasound (Axilla#)	2a#	B	++
▪ MRI	1b	A	+
▪ CNB Axilla, if suspicious LN and marking of the node if TAD planned ≤ 3 susp. LK	2b	B	++
▪ Breast-CT	4	D	-
▪ PET CT / MRI for axillary LN	2b	B	-

*** Replacement additional DM through SM

Pre-therapeutic Staging

	Oxford LoE	Oxford GR	AGO
▪ History and clinical examination	5	D	++
Only in case of high metastatic potential and/or symptoms and/or indication for (neo-) adjuvant chemotherapy and/or antibody-therapy:			
▪ CT scan of thorax / abdomen / pelvis	2a	B	+
▪ Bone scan	2b	B	+
▪ Chest X-ray	5	C	+/-
▪ Liver ultrasound	5	D	+/-
▪ Further investigation in case of additonal suspicious lesions (e.g. liver-MRI, CEUS*, biopsy etc.)	2a	B	+
▪ FDG-PET or FDG-PET-CT** FDG-PET-MRT**	2b	B	+/-
▪ Whole body MRI	4	C	+/-

* Contrast enhanced ultrasound

** especially in patients with high tumor stage (III) if available

Guidelines Breast
Version 2024.1E

In collaboration with:

Evidence of Surgical Procedure

	Oxford LoE	Oxford GR
▪ Survival rates after lumpectomy + RT are at least equivalent to those after (modified) radical mastectomy	1a	A
▪ Local recurrence rates after skin sparing mastectomy are equivalent to those after mastectomy	2b	B
▪ Conservation of the NAC (nipple areola complex) is an adequate surgical procedure, if R0 resection is achieved	2b	C

Breast-Conserving Surgery (BCS): Options to Localize Non-Palpable Lesions

Guidelines Breast
Version 2024.1E

In collaboration with:

	Oxford LoE	GR	AGO
▪ Wire-guided localization	1a	A	++
▪ Wireless intraoperative ultrasound-guided localization*	1a	A	++
▪ Other procedures:**			
Radar reflectors	2b	B	+/-
Magnetic marker*** Paramagnetic markers***	2b	B	+/-
MagSeed™ (compared with wire localization)***	1b	A	+
Radiofrequency-based markers (RFID)***	2b	B	+/-
Radionuclide-guided localization (ROLL)	1a	A	+/-
Radioactive seeds****	1a	A	+/-

* The lesion must be sonographically visualized by the same examiner pre- and intraoperatively in its whole extension. Adequate equipment and training of the surgeon are mandatory.

** according to approval

*** not suitable for MRI-based response assessment under NACT

**** not approved in Germany

Localization Methods for non-Palpable Breast Cancer: a Meta-Analysis

Guidelines Breast
Version 2024.1E

In collaboration with:

Athanasiou et al. Eur J Surg Onc 2021:

- Meta-analysis of RCTs
- 18 studies with 3112 patients
- Pairwise and network meta-analysis

Ultrasound-guided surgery vs. wire-guided surgery:

- decreased positive margin both in the pairwise [OR = 0.19 (0.11, 0.35); P < 0.01] and network meta-analysis [OR = 0.19 (0.11, 0.60)]
- a statistically significant reduction in re-operation rate [OR = 0.19 (0.11, 0.36); P < 0.01] and operative time [MD = -4.24 (-7.85, -0.63); P = 0.02]

Ultrasound-guided surgery vs. ROLL / RSL:

- a statistically significant reduction in positive margin compared to ROLL [OR = 0.19 (0.11,0.6)] and RSL [OR = 0.26 (0.13, 0.52)]

„Ultrasound-guided surgery has potential benefits in reduction of positive surgical margin, the rest of the techniques seem to have equivalent efficacy."

Breast-Conserving Surgery (BCS): Resection Margins

Guidelines Breast
Version 2024.1E

In collaboration with:

	Oxford LoE	Oxford GR	AGO
Invasive breast cancer without extensive intraductal component (EIC)*			
Aim: tumor-free margins ("no ink on tumor" is sufficient even in case of unfavorable tumor biology)	2a	A	++
Re-excision for invasive or non-invasive tumor cells reaching margin (final histology)	2a	B	++
Invasive breast cancer with EIC*			
Re-excision for invasive or non-invasive tumor cells reaching margin (final histology)	2a	B	++
Re-excision in case of a close margin of the intraductal component (< 2 mm on final histology)**	2a	B	-

* No clear definition of EIC in the literature. Increased risk of local recurrence in case of EIC with at least twice the greatest dimension of the invasive tumor component (definition according to the German S3 guideline).

** Individual approach with consideration of patient's age and tumor extent

Breast-Conserving Surgery (BCS): Surgical and Technical Aspects

Guidelines Breast
Version 2024.1E

In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ Specimen radiography and / or -sonography in non-palpable lesions and / or tumor-associated microcalcifications*	2b	B	++
▪ Intraoperative ultrasound to increase negative margin rates in non-palpable lesions	1a	A	+
▪ Intraoperative ultrasound to increase negative margins rates in palpable lesions (with smaller resection volumes)	1b	B	+
▪ Surgical clip marking of the tumor bed if boost or partial breast irradiation is indicated	2b	B	+
▪ Intraoperative margin evaluation (with Margin Probe®)	1b	A	+/-
▪ Therapeutic stereotactic excision alone	4	D	--

* Mandatory also for probe-guided detection systems (magnetic seeds, radar reflectors, RFID, radioactive seeds, ROLL)

Breast-Conserving Surgery (BCS) without Neoadjuvant Therapy

Guidelines Breast
Version 2024.1E

In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ Multifocality / Multicentricity (R0 resection of all lesions required)	2b	B	+
▪ Positive microscopic margins after repeated excision	2b	B	--
▪ Inflammatory breast cancer	2b	B	--

For surgery after neoadjuvant chemotherapy see chapter „Neoadjuvant chemotherapy“

Axillary Lymph Node Dissection (ALND) without Neoadjuvant Chemotherapy

Guidelines Breast
Version 2024.1E

In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ Endpoint: Survival (if patient receives adequate multimodal therapy)	3	D	-
▪ Endpoint: Staging	3	A	-
▪ Endpoint: Locoregional control	2a	A	+/-
▪ pN+ (histologically confirmed pre-surgery)	2a	B	+
▪ cN0 pN0 (i+) (sn)	1b	A	--
▪ cN0 pN1mi (sn)	2b	B	--
▪ cN0 pN1 (sn) (T1/2 , < 3 SN+*, BCS + RT + adequate systemic therapy)	1b	A	-
▪ cN0 pN1 (sn) and mastectomy (no chestwall radiotherapy)	1b	B	+**
▪ cN0 pN1 (sn) and mastectomy (T1/2, < 3 SN+, chestwall radiotherapy)	5	D	+/-**
▪ ALND indicated, but not feasible			
▪ Radiotherapy according to AMAROS trial (validated for cN0 pN1sn)	1b	B	+

* ACOSOG Z0011 trial protocol without clear definition of gross extra nodal disease
** Study participation recommended

Guidelines Breast
Version 2024.1E

In collaboration with:

Axillary Surgery and NACT

cN status (before NACT)	pN status (before NACT)	ycN status (after NACT)	Axillary surgery (after NACT)	AGO	ypN status (after NACT and surgery)	Surgical consequence based on histopathology	Oxford LoE	Oxford GR	AGO
cN0*	No surgery before NACT	ycN0	SLNE	++	ypN0 (sn)	none	2b	B	++
					ypN0 (i+) (sn)	ALND	2b	C	+/-
					ypN1mi (sn)	ALND	2b	C	+
					ypN1 (sn)	ALND	2b	C	++

* Study participation in EUBREAST-01 recommended

Axillary Surgery and NACT (cN+)

cN status (before NACT)	pN status (before NACT)	ycN status (after NACT)	Axillary surgery (after NACT)	AGO	ypN status (after NACT and surgery)	Surgical consequence based on histopathology	Oxford LoE	Oxford GR	AGO
cN+*	$pN+_{CNB}$	ycN0	ALND	+	ypN0 / ypN+	none	2b	B	++
			TAD	+	ypN0	none	2b	B	+
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ inkl. ypN1mi	ALND	2b	B	+
			SLNE	+/-	ypN0	none	2b	B	+/-
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ inkl. ypN1mi	ALND	2b	B	+
			TLNE	+/-	ypN0	none	2b	B	+/-
					ypN0 (i+)	ALND	3b	B	+/-
					ypN+ inkl. ypN1mi	ALND	3b	B	+
		ycN+**	ALND	++	ypN0 / ypN+	none	2b	B	++

* Study participation in AXSANA recommended, ** Cave: In 30.3% false-positive findings, consider CNB if necessary

Guidelines Breast
Version 2024.1E

In collaboration with:

www.ago-online.de
FORSCHEN
LEHREN
HEILEN

Guidelines Breast
Version 2024.1E

In collaboration with:

Targeted Axillary Dissection (TAD) = TLNE + SLNE

	Oxford		
	LoE	GR	AGO
▪ Core needle biopsy and marking of suspicious lymph nodes (LN)	2b	B	++
▪ Marking of multiple LN if more than one LN is suspicious	2b	B	+/-
▪ Evidence for comparison of different markers (clip / coil, carbon, magnetic seed, radar reflector, radiofrequency-based marker etc.) is insufficient *	2b	B	
▪ TAD in case of 1-3 suspicious LN before NACT	2b	B	+
▪ TAD in case of ≥ 4 suspicious LN before NACT	5	D	+/-
▪ Full workup using step sections of ≤ 500 µm on paraffin embedded tissue	5	D	++
▪ Immunohistochemistry for ITC detection	5	D	+/-
▪ ALND in case of pre- or intraoperatively undetectable marker	5	D	+
▪ Further intervention to retrieve lost marker (incl. after ALND)	5	D	-
▪ TLNE only without SLNE	2B	B	+/-

* Study participation in AXSANA recommended

Sentinel Lymph Node Excision (SLNE) Indications I

Guidelines Breast
Version 2024.1E

In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ Clinically / sonographically negative axilla (cN0)	1b	A	++
▪ cT 1–2	2b	A	++
omission of SLNE according to SOUND trial	1b	B	+
▪ cT 3–4c	3b	B	+
▪ Multifocal / multicentric breast cancer	2b	B	+
▪ DCIS			
▪ Mastectomy	3b	B	+
▪ BCT	3b	B	-
▪ DCIS in male	5	D	+/-
▪ Male breast cancer	2b	B	+
▪ Omission of axillary intervention in elderly patients (≥ 70 yrs., co-morbidities, pT1, HR+)	3b	B	+/-

Sentinel lymph node biopsy vs no axillary surgery in patients with small breast cancer and negative results on ultrasonography of axillary lymph nodes
The SOUND Randomized Clinical Trial

Gentilini et al. JAMA Oncology, 2023

Guidelines Breast
Version 2024.1D

In Zusammen-
arbeit mit:

- Prospective noninferiority phase 3 randomized clinical trial
- cT1a-c, preoperative negative axillary ultrasound = cN0 (ultrasound)
- 1463 patients included, 1405 intention-to-treat analysis, 708 SLNB, 697 no-SLNB
- Median age 60 years (52-68 years), median tumor size 1.1 cm (0,8-1.5 cm)
- Tumor biology: 87,8% HR+/HER2 neg.
- Results
  - Follow up 5.7 years (5.0-6.8 years), positive LN SLNB-group 13.7% (≥ 4 LN 0.6%)
  - No statistical difference according to BCT, mastectomy, hormone therapy (97.9% vs. 98.9%) chemotherapy (20.1 vs. 17.5%), radiotherapy (98.0 vs. 97.6%)
  - **5 years DDFS 97.7% SLNB group vs. 98.0% in no-SLNB group (p = 0.67, HR 0.84, 90CI 0.45-1.54, noninferiority p = 0.02)**
  - Locoregional relapse 1.7% SLNB group vs. 1.6% in no-SLNB group
  - Axilla recurrence 1.7% SLNB group vs. 1.6% in no-SLNB group
  - Distant metasases 1.8% SLNB group vs. 2.0% in no-SLNB group
  - Deaths 3.0% SLNB group vs. 2.6% in no-SLNB group
- **CAVE: ultrasonography of axilla might be difficult, no details of radiotherapy presented, impact on systemic treatment decisions possible (e.g. CDK4/6 inhibitors), longer follow up needed**

Sentinel Lymph Node Excision (SLNE) Indications II

	Oxford		
	LoE	GR	AGO
▪ During pregnancy and / or breast feeding (only ^{99m}Tc-colloid, no patent or methylene blue dye, no data to SPIO or ICG)	3	C	++
▪ After prior tumor excision	2b	B	+
▪ After prior major breast surgery (e.g. reduction mammoplasty)	3b	C	+/-
▪ Ipsilateral breast recurrence after prior BCS and prior SLNE	4	D	-
▪ SLNE in the mammary internal chain	2b	B	-
▪ After axillary surgery	3b	B	+/-
▪ Prophylactic bilateral / contralateral mastectomy	3b	B	--
▪ Inflammatory breast cancer	3b	C	-

Sentinel Lymph Node Excision (SLNE) Marking

Guidelines Breast
Version 2024.1E

In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ ^{99m}Tc Kolloid	1a	A	++
▪ Preoperative lymphoscintigraphy (added infomation limited, but mandatory by legal regulations)*	1b	A	+
▪ Patent blue dye	1a	A	+/-
▪ Indocyanin green (ICG)°	2a	B	+
▪ SPIO#	2a	B	+
▪ Methylene blue	2a	B	+/-

* In Germany required for quality assurance of nuclear medicine

\# SPIO: Superparamagnetic Iron Oxide (Caveat: impaired MRI-sensitivity during follow-up)

° no approval for LN marking in the axilla, off-label

Guidelines Breast
Version 2024.1E

In collaboration with:

Surgical Approach in the Neoadjuvant Setting

	Oxford		
	LoE	GR	AGO
▪ Early marking of tumor (incl. detailed topographic documentation)	5	D	++
▪ Surgical removal of tumor / representative excicion of post-therapeutic, marked tumor area	2b	C	++
▪ Tumor resection in new margins	2b	C	++
▪ Microscopically clear margins	2a	B	++

For „Surgery after neoadjuvant chemotherapy“ see chapter „Neoadjuvant chemotherapy“

Begin of Adjuvant Therapy after Primary Surgery

Guidelines Breast
Version 2024.1E

In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ Start adjuvant systemic therapy and radiotherapy (RT) as soon as possible (asap) after surgery	1b	A	++
▪ Start of adjuvant chemotherapy +/- HER2 therapy asap after surgery, prior to RT	1b	A	++
▪ Without cytotoxic therapy +/- anti-HER2 therapy:			
▪ Start adjuvant RT within 6–8 weeks after surgery	2b	B	++
▪ Start endocrine therapy after surgery asap	5	D	++
▪ Endocrine therapy concurrent with RT	2b	B	+

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

In collaboration with:

Oncoplastic and Reconstructive Breast Surgery

Oncoplastic and Reconstructive Breast Surgery

Guidelines Breast
Version 2024.1E

In collaboration with:

- **Versions 2002–2023:**
  Audretsch / Bauerfeind / Blohmer / Brunnert / Dall / Ditsch / Fersis / Friedrich / Gerber / Hanf/ Heil / Kühn / Kümmel / Lux / Nitz / Rezai / Rody / Scharl / Solbach / Thill / Thomssen / Wöckel

- **Version 2024:**
  Banys-Paluchowski / Solbach

Definition of oncoplastic surgery

Guidelines Breast
Version 2024.1E

In collaboration with:

Use of plastic surgical techniques at the time of tumor removal to improve aesthetic and quality of life outcomes without compromising oncological safety.

Focus on favorable scar placement, adequate soft tissue formation, choice of a suitable reconstructive technique (taking radiation therapy into consideration) and contralateral symmetrization.

Classifications

1. Hoffmann / Wallwiener (2009):
Classification by reconstructive surgery complexity with respect to breast conservation and mastectomy

2. Clough et al. (2010):
Oncoplastic classification for breast conservation according to relative resection volume: Level 1: < 20 % of breast volume resection („simple oncoplastic surgery“) and Level 2 > 20 % of breast volume resection with quadrant per quadrant techniques of mastopexy

3. American Society of Society of Breast Surgeons (2019):
Level 1: < 20% breast tissue removed; Level 2: 20–50% of breast tissue removed; Volume replacement: > 50% of breast tissue removed

Hoffmann D et al., BMC 2009; Clough KB et al., Ann Surg Oncol 2010; Chatterjee A et al. Ann Surg Oncol 2019

Oncoplastic Breast-Conserving Surgery (OPS)

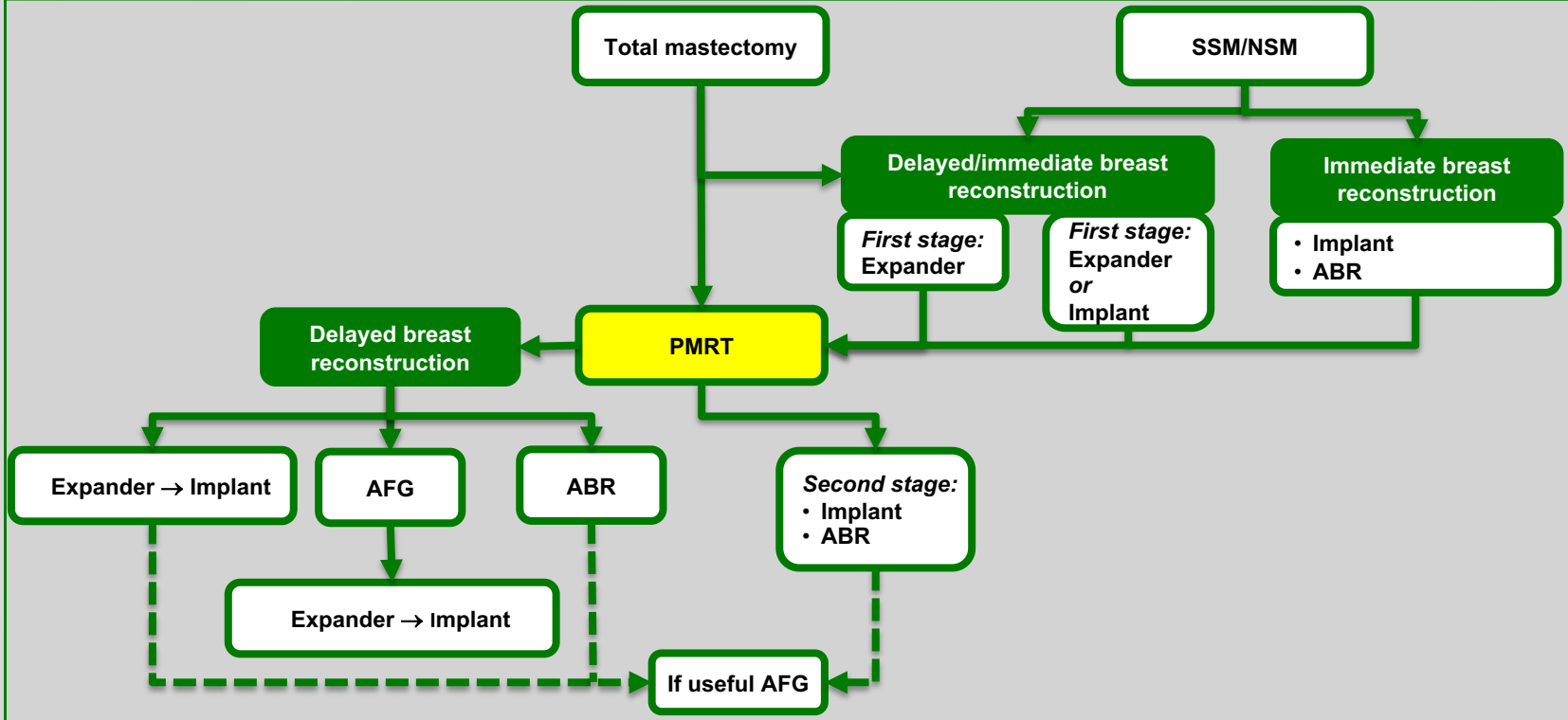
Guidelines Breast
Version 2024.1E

In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ OPS may replace mastectomy in selected patients	2b	B	+
▪ also in case of multicentric / multifocal tumors	2b	B	+
▪ OPS and BCS have equivalent oncological safety	2a	B	++
▪ Complication rates of OPS and BCS are similar	2a	B	+/-

Options for Breast Reconstruction When Radiotherapy is Planned

For patients who ask for breast reconstruction and are scheduled to undergo radiotherapy*



*Influencing factors: tumor related factors, breast size/shape, skin flap, previous surgery/RT, BMI, comorbidities, patient wishes, physical activities, oncological situation; ABR, autologous breast reconstruction; AFG, autologous fat grafting; PMRT, post mastectomy radiotherapy; SSM/NSM, skin sparing/nipple sparing mastectomy

Guidelines Breast
Version 2024.1E

In collaboration with:

AWOgyn

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Breast Reconstruction Principles
Good Clinical Practice

Guidelines Breast
Version 2024.1E

In collaboration with:

AGO: ++

- **Planning of breast reconstruction by interdisciplinary tumor board before mastectomy**
- **Counseling regarding all surgical techniques, including advantages and disadvantages**
- **Preference for autologous reconstruction after radiotherapy or if radiotherapy is planned**
- **Offer second opinion**
- **Discussion of neoadjuvant treatment (if indicated based on tumor biology) in case of unfavorable breast-tumor relation**
- **Consideration of contralateral breast:**
  - **Discuss symmetrization procedures**
- **Preference for less radical surgical technique with stable long-term aesthetic result (prefer BCS / OPS over mastectomy)**
- **Avoid delay of adjuvant therapy due to reconstruction**
- **Assessment of outcome, e.g. Patient Reported Outcome (PRO)**
- **Oncologic safety is not impaired**

Mastectomy and Reconstruction Options

Guidelines Breast
Version 2024.1E

In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ Heterologous reconstruction *	2a	B	+
▪ Autologous reconstruction	2a	B	+
▪ Pedicled flap reconstruction	2a	B	+
▪ Free flap reconstruction (including vascular anastomoses)	2a	B	+
▪ Autologous reconstruction combined with implant placement	3a	C	+/-

Caveat: BMI > 30, smoking, diabetes, radiotherapy, age, bilateral mastectomy

*** Documentation in implant registry**

Germany: https://www.bundesgesundheitsministerium.de/implantateregister-deutschland,
Mandatory documentation of breast implants in the Medical Implants Registry begins on 1st July 2024

Guidelines Breast
Version 2024.1E

In collaboration with:

Timing of Reconstruction

	Oxford		
	LoE	GR	AGO
▪ Immediate breast reconstruction	3b	B	++
▪ Prevention of postmastectomy syndrome			
▪ Delayed breast reconstruction (2-step)	3b	B	++
▪ No interference with adjuvant (CHT, RT)			
▪ Disadvantage: loss of skin envelope			
▪ „Delayed-immediate“ breast reconstruction (placeholder before definitive reconstruction)	3b	B	+

Timing of Implant-Based Reconstruction and Radiotherapy

	Oxford		
	LoE	GR	AGO
▪ **Implant reconstruction**	2a	B	+
▪ **without radiotherapy**	2a	B	++
▪ **prior to radiotherapy**	2a	B	+
▪ **following radiotherapy**	2b	B	+/-
▪ **following secondary mastectomy after breast-conserving therapy**	2a	B	+/-

Antibiotics and Breast Reconstruction

	Oxford		
	LoE	GR	AGO
Heterologous reconstruction:			
▪ Perioperative antibiotic prophylaxis (max. 24 h)	1a	A	+
▪ Extended antibiotic prophylaxis > 24 h	2a	B	+/-
Autologous reconstruction:			
▪ Perioperative antibiotic prophylaxis (max. 24 h)	2b	B	+
▪ Extended antibiotic prophylaxis > 24 h	2a	B	+/-

Tranexamic Acid in Complex Breast Surgery

Guidelines Breast
Version 2024.1E

In collaboration with:

	Oxford		
	LoE	GR	AGO
Prevention of:			
▪ **Hematoma**	2a	B	+/-
▪ **Seroma**	2a	B	+/-
No increased risk for thromboembolic complications in patients without history of thromboembolic events	2a	B	+

CAVE: Dosage and application routes (local, i.v., oral) differ between studies, consider history of thromboembolic events

Breast Implant-associated Diseases

Guidelines Breast
Version 2024.1E

In collaboration with:

BIA-ALCL = Breast implant-associated anaplastic large cell lymphoma

BIA-SCC = Breast implant-associated squamous cell carcinoma

SSBI = Systemic Symptoms Associated with Breast Implants

Synonyms:

Breast Implant Illness (BII); Autoimmune syndrome induced by adjuvants (ASIA); Shoenfeld's syndrome; Silicone implant incompatibility syndrome (SIIS)

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL)

Guidelines Breast
Version 2024.1E

In collaboration with:

- Peripheral non-Hodgkin's T-cell lymphoma arising around a textured breast implant or in a patient with a history of a textured surface device
- Number of global cases reported as MDR (medical device regulation) to the FDA by 30.06.2023: 1264 with 63 deaths
- Approximately 35,000,000 implant carriers worldwide
  (According to a survey by the International Society of Aesthetic Plastic Surgeons (ISAPS) 2023: 2,174,616 augmentations worldwide were performed)
- Prevalence and incidence vary greatly, as the number of women with implants can only be estimated
- The current lifetime risk ranges between 1:355 and 1:86,029 patients with textured implants
- Time interval between last implantation and lymphoma diagnosis: 8 years (median)
- 5-year-OS 89-92 %
- Clinical presentation
  - Frequently periprosthetic seroma, breast asymmetry
  - in rarer cases tumor, regional lymphadenopathy, skin rash and/or capsular contracture
- Tumor cells are CD30-positive / ALK-negative
- Obligation to notify the BfArM as SAE according to §3 MPSV*

* Germany: BfArM https://www.bfarm.de/SharedDocs/Formulare/DE/Medizinprodukte/BIA-ALCL-Meldung.html

BIA-ALCL – Diagnosis

	Oxford		
	LoE	GR	AGO
▪ Breast ultrasound (assessment of new seromas > 1 year after implant placement, solid lesions, axillary lymph nodes)	3a	D	++
▪ Cytology of late seromas ▪ Assessment of min. 50 ml ▪ Complete assessment incl. BIA-ALCL specific cytologic diagnostic (CD 30+) ▪ Flow cytometry (T-cell clone)	3a	D	++
▪ Core needle biopsy of solid lesions	3a	D	++
▪ Breast-MRI in confirmed cases	3a	D	++
▪ Staging (PET-CT, alternatively: CT [neck, chest, abdomen, pelvis])	3a	D	++
▪ Lymphoma assessment in resected tissue and histologic staging	3a	D	++
▪ Documentation of the implant in the Implant Registry *	5	D	++

* Germany: https://www.bfarm.de/SharedDocs/Formulare/DE/Medizinprodukte/BIA-ALCL-Meldung.html

Guidelines Breast
Version 2024.1E

In collaboration with:

AWOgyn

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

BIA-ALCL – Therapy

Guidelines Breast
Version 2024.1E

In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ Case discussion in a multidisciplinary tumor board in the presence of a lymphoma specialist	5	D	++
▪ Implant resection and complete capsulectomy including tumorectomy	3a	C	++
▪ Contralateral implant removal and capsulectomy in case of bilateral implants (4-6% bilateral BIA-ALCL)	4	D	+/-
▪ Resection of suspicious lymph nodes, no routine use of sentinel node biopsy or axillary lymph node dissection	4	D	++
▪ Systemic therapy depending on disease stage	4	D	+
▪ Radiotherapy in unresectable tumors	5	D	+/-

BIA-ALCL Treatment Pathways

Outcome

- BIA-ALCL confirmed
- Indeterminate
  - Options: Further imaging US / MRI / Repeat biopsy, Tertiary referral
- Negative for BIA-ALCL
  - Treatment of infection / benign seroma (serial aspiration, implant exchange with capsulectomy)

Workup

- Referral to experienced breast cancer center
- PET-CT & breast MRI
- Routine bloods (+/- bone marrow bx)
- MTD Discussion
- Clinical suspicion remains
  - Consider diagnostic capsulectomy

Surgery

- En-bloc capsulectomy and complete excision (mass)
- +/- other breast +/- axilla biopsy (SNB not recommended)
- Histological Staging (Clemens et al. 2016)
- MTD Discussion
- Reports to BfArM (Germany), manufacturers, PROFILE registry (USA); MedWatch (FDA)

Adjuvant Therapy

- Stage I : No further treatment
- Stage II - IV: Consider adjuvant treatment
- Chemo-immunotherapy
- Radiotherapy for positive margins / irresectable thoracic wall infiltration but N0/M0

Follow-up

- Clinical follow-up (ultrasound / CT scan) 3–6 m for 2 y, afterwards for 5 y
- PET-CT if symptomatic

Treatment as per systemic ALCL regimes

24-36 Gy in 15 fractions

TNM Staging of BIA-ALCL

	TNM-Kategorie	Definition
Tumor extent (cT/pT)	T1	Confined to seroma or a layer on luminal side of capsule
	T2	Early capsule infiltration
	T3	Cell aggregates or sheets infiltrating the capsule
	T4	Lymphoma infiltrates beyond the capsule
Regional lymph nodes (cN/pN)	N0	No lymph node involvement
	N1	One regional lymph node positive
	N2	Multiple regional lymph nodes positive
Metastasis (cM/pM)	M0	No distant spread
	M1	Spread to other organs or distant sites

Stage	Definition
IA	T1 N0 M0
IB	T2 N0 M0
IC	T3 N0 M0
IIA	T4 N0 M0
IIB	T1-3 N1 M0
III	T4 N1-2 M0
IV	T any N any M1

Guidelines Breast
Version 2024.1E

In collaboration with:

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Breast Implant Capsule-Associated Squamous Cell Carcinoma

Guidelines Breast
Version 2024.1E

In Zusammenarbeit mit:

- By March 22, 2023, the FDA had reported 19 cases of BIA-SCC; 21 cases were described up to 5/2023 (J Surg Oncol. 2023;128(4):495-501)
- BIA-SCC occurred approximately 7 to 42 years after initial implant placement (median time 18 years) in aesthetic and reconstructive cases
- BIA-SCC was located in the capsule around the breast implant, often in the posterior aspect
- There is not a consistent type of implant (textured vs. smooth), content (silicone vs. saline), or location (subglandular vs. retropectoral) that is associated with BIA-SCC
- Periprosthetic fluid should be sent for CK5/6 and p63, should be rich in keratin and cytology should display abnormal squamous cells
- Initial presentation with breast pain, erythema and swelling
- Overall poorer prognosis
  - 7/21 cases had recurrent cancer within 12 months after definitive resection
  - in a review of 18 cases the estimated 12-month mortality rate was 23.8% (calculated from 10 cases with survival data reported)
- In this limited cohort it is difficult to ascribe prognostic factors, but extracapsular extension does appear to be a concerning finding.

Systemic Symptoms Associated with Breast Implants = SSBI

Breast Implant Illness (BII); Autoimmune syndrome induced by adjuvants (ASIA); Shoenfeld's syndrome; Silicone implant incompatibility syndrome (SIIS);

Guidelines Breast
Version 2024.1E

In Zusammenarbeit mit:

- Summarize a variety of systemic symptoms that have been reported by some women following reconstruction or augmentation with breast implants, independent of the type of implant, filling, shape or surface characteristics, with an onset anywhere from immediately after implantation to years later

- The most frequent systemic symptoms reported in the FDA MDR database (sorted by frequency more to less common):

>40%	Fatigue
>30%	Joint pain
>20%	Brain fog, Autoimmune diseases, Hair loss
10-20%	Depression, Rash, Headache, Weight changes

- Currently SSBI are not recognized as a formal medical diagnosis
- SSBI remain a diagnosis of exclusion, there are no specific tests or defined criteria to characterize it
- Any persistent symptoms reported by patients with breast implants should be evaluated for other medical diseases prior to consider implant removal surgery
- Breast implant explantation can show significant improvement of systemic complaints as well as improvement of overall quality of life

BIA-ALCL – EUSOMA-Recommendation

- **Despite an increase of BIA-ALCL in association with textured implants the use of textured implants is still permitted!**

„For the moment, textured implants can safely continue to be used with patient's fully informed consent, and that women that have these type of implants already in place don't need to remove or substitute them, which would undoubtedly cause harm to many tens of thousands of women, to prevent an exceptionally rare, largely curable and currently poorly understood disease."

Guidelines Breast
Version 2024.1E

In collaboration with:

AWOgyn

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Implant Position, Meshes and ADMs in Implant-Based Reconstruction: Outcome QoL / Complication Rate

Guidelines Breast
Version 2024.1E

In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ **Insufficient evidence to conclude superiority of the prepectoral or subpectoral approach**	3a	C	+/-
▪ **Acellular dermal matrix (ADM)**			
▪ **subpectoral**	1b	A	+/-
▪ **prepectoral**	2b	B	+/-
▪ **Synthetic meshes**			
▪ **subpectoral**	2b	B	+/-
▪ **prepectoral**	2b	B	+/-

Guidelines Breast
Version 2024.1E

In collaboration with:

Lipotransfer

	Oxford		
	LoE	GR	AGO
▪ Lipotransfer following mastectomy and reconstruction	2a	B	+
▪ Lipotransfer after breast-conserving therapy	2a	B	+
▪ Autologous adipose derived stem cells (ASCs)-enriched fat grafting vs. without stem cells	2a	B	+/-

Guidelines Breast
Version 2024.1E

In collaboration with:

Pedicled Flap Reconstruction

	Oxford		
	LoE	GR	AGO
▪ TRAM, latissimus dorsi flap (both can be performed as muscle-sparing techniques)	2a	C	+
▪ Delayed TRAM in high-risk patients	3a	B	+
▪ Ipsilateral pedicled TRAM	2a	B	+
▪ Omentum Flap	4	C	+/-
▪ Radiotherapy:			
▪ Breast reconstruction following radiotherapy	2a	B	+
▪ Breast reconstruction prior to radiotherapy	2a	B	+/-

(higher rates of fibrosis, wound healing disorders, liponecrosis and reduced aesthetic outcome)

Guidelines Breast
Version 2024.1E

In collaboration with:

Free Flaps for Reconstruction

	Oxford		
	LoE	GR	AGO
▪ **DIEP** (deep inferior epigastric artery perforator)	2a	B	+
▪ **Free TRAM** (transverse rectus abdominis myocutaneus)	2a	B	+
▪ **SIEA** (superficial inferior epigastric artery)	3a	C	+/-
▪ **Glutealis flaps (SGAP** [superior gluteal artery perforator] / **IGAP** [inferior gluteal artery perforator]**, FCI** [fasciocutaneous infragluteal])	4	C	+/-
▪ **Free gracilis flap (TMG,** transverse myocutaneous gracilis**)**	4	C	+/-
▪ **PAP** (profunda artery perforator)	2b	B	+/-
▪ **Omentum Flap**	4	C	+/-
Use of ICG* to assess flap perfusion	2a	B	+

Advantages

- **DIEP and free TRAM are potentially muscle-sparing procedures. DIEP has a lower rate of abdominal hernias, especially in obese patients**

Disadvantages

- **Time- and personnel consuming microsurgical procedures, intensified postoperative monitoring**

* **ICG: indocyanin green**

Pedicled versus Free Tissue Transfer

Guidelines Breast
Version 2024.1E

In collaboration with:

Oxford		
LoE	GR	AGO
3a	A	++

- **Muscle-sparing techniques and accuracy of abdominal wall closure lead to low rates of late donor site complications independent of method used**
- **Autologous abdominal-based reconstructions have highest satisfaction rates (PROM)**
- **Donor site morbidity (e.g. impaired muscle function) has to be taken into consideration with all flap techniques**

Skin-/ Nipple-Sparing Mastectomy (SSM / NSM) and Reconstruction

	Oxford LoE	Oxford GR	AGO
Skin-/nipple-sparing Mastectomy (SSM / NSM)			
Oncologically safe (equivalent recurrence rate as in total mastectomy in suitable patients)	2b	B	++
Higher QoL	2b	B	++
NAC can be preserved under special conditions	2b	B	++
Feasible after mastopexy / reduction mammoplasty	4	C	++
Use of ICG* to predict skin necrosis	1b	B	+
Skin incisions → different possibilities:			
Periareolar			
Hemi-periareolar with / without medial / lateral extension			
Reduction pattern: „inverted-T“ or vertical			
Inferior lateral approach, inframammary fold			
Lowest incidence of complications	2b	B	+

* ICG = Indocyanine Green

Mastectomy + Reconstruction

Risk of complications with the addition of radiotherapy

Autologous reconstruction		Implant-based reconstruction	
Endpoint	**Risk Ratio with addition of radiotherapy (95%-CI)**	**Endpoint**	**Risk Ratio with addition of radiotherapy (95%-CI)**
Wound infection	1.14 (NA)	Wound infection	2.49 (1.43,4.35)
Secondary surgery	1.62 (1.06, 2.48)	Secondary surgery	1.64 (1.17-2.31)
Reconstructive failure	0.80 (NA)	Reconstructive failure	2.89 (1.30,6.39)
Volume loss	8.16 (4.26,15.63)		
Fat necrosis	1.91 (1.45, 2.52)		
		Capsular contracture	5.17 (1.93,13.80)
		ME skin flap nekrosis	1.62 (1.27, 2.08)
		Implant extrusion	3.44 (2.18, 5.43)

Further risks of autologous reconstruction:
Distorsion of breast shape, fibrosis, vascular complications
Autologous reconstruction is favored in terms of patient satisfaction and and assessment of the aesthetic outcome.

NA: not available

Guidelines Breast
Version 2024.1E

In Zusammenarbeit mit:

AWOgyn

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Prevention and Therapy of Capsular Contracture

Guidelines Breast
Version 2024.1E

In collaboration with:

	Oxford LoE	Oxford GR	AGO
Prevention			
Textured implantats (Caveat: BIA-ALCL)	1a	A	+
Acellular Dermal Matrix (ADM) vs. nil	2a	B	+
Synthetic mesh vs. nil	3a	C	+
Topical antibiotics / antiseptics	2a	B	+
PVP (Povidone-Iodine)	2a	B	+/-
Leukotriene-antagonists	2a	B	+/-
Breast massage	3a	C	-
Surgical interventions			
Capsulectomy	3b	C	+
Capsulotomy (Caveat: exclusion of BIA-ALCL)	3b	C	+

Seroma after Implant-Based Reconstruction I

Guidelines Breast
Version 2024.1E

In collaboration with:

AWOgyn

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

	Oxford	
	LoE	GR
▪ Incidence: approx. 5-10 % (2-50 %)	2a	B
Influencing factors:		
▪ History of radiation increases risk (RR approx. 3)	2a	B
▪ Obesity increases risk (e.g. BMI > 30 vs. < 30; RR approx. 3)	2a	B
▪ Use of ADM increases risk (RR approx. 3)	2a	B
▪ Use of expander with smooth surface increases risk (RR approx. 5)	3b	C
▪ History of neoadj. chemotherapy does not appear to increase risk	2a	B
▪ Prepectoral approach does not appear to increase risk	2b	B

Guidelines Breast
Version 2024.1E

In collaboration with:

Seroma after Implant-Based Reconstruction II

	Oxford		
	LoE	GR	AGO
Prevention			
▪ Drain	3b	C	+
▪ Drain removal at < 30ml per 24 hours	2b	B	+
Therapy			
▪ Evacuation of serma by FNA or re-insertion of drain	4	C	+
▪ Pressure dressing	5	D	+/-
▪ Revision surgery with capsulectomy (ultima ratio)	5	D	+
▪ Revision surgery with implant removal (ultima ratio)	5	D	+

Skin necrosis after mastectomy

Guidelines Breast
Version 2024.1E

In collaboration with:

	Oxford		
	LoE	GR	AGO
Prevention			
▪ Local nitroglycerin *	1a	A	+
▪ Closed-incision negative pressure therapy (ciNPT)	2a	B	+/-
▪ Local dimethylsulfoxid	2b	B	+/-
▪ Oral cilostazol	2b	B	+/-
▪ Preoperative local heat preconditioning	2b	B	+/-

* Dose and regimen vary between studies, off-label

Efficacy and safety of topical nitroglycerin in the prevention of mastectomy flap necrosis – a systematic review and meta-analysis

Wang P et al. Sci Rep 2020

- 7074 patients (3 randomized clinical trials, 2 retrospective cohort studies)
- Intervention: transdermal nitroglycerin treatment (ointment; 4.5-45 mg nitroglycerin, applied immediately after end of surgery and in some studies in the first postoperative period until day 6)
- Nitroglycerin significantly reduced the mastectomy flap necrosis rate (immediate breast reconstruction [IBR]: OR, 0.48, 95% CI, 0.33–0.70, P < 0.01)
- Full-thickness flap necrosis rate in patients receiving IBR was significantly lower in the nitroglycerin group than in the control group (OR, 0.42; 95% CI, 0.25–0.70; P < 0.01)

Guidelines Breast
Version 2024.1E

In collaboration with:

Siliconomas

- In breast parenchyma or regional lymph nodes, rarely in distant organs (pleura, ribs, muscles)
- Incidence unclear
- May occur with or without implant rupture (“silicone bleeding”)
- Migration of silicone to the lymph nodes takes 6-10 years
- Risk of malignancy is not increased

	Oxford		
	LoE	GR	AGO
▪ Asymptomatic siliconomas do not require removal	2b	B	+
▪ Complete removal of implant and silicone gel (in capsule, if possible) in case of implant rupture	2b	B	+

Surgical Prevention

	Oxford		
	LoE	GR	AGO
▪ Risk-reducing unilateral or bilateral mastectomy (RRME) without the presence of clearly defined genetic risk factors	2a	B	-*
▪ Axillary dissection or Sentinel lymph node excision during RRME	2a	B	--

* study participation recommended

Surgical Prevention for Healthy Female *BRCA1/2* Mutation Carriers

Guidelines Breast
Version 2024.1E

In collaboration with:

	Oxford LoE	Oxford GR	AGO
▪ **Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)****	2a	B	
▪ Reduces OvCa incidence and mortality			++*
▪ Reduces overall mortality			++*
▪ **Risk-reducing bilateral mastectomy (RR-BM)**			
▪ Reduces BC incidence	2b	B	+*
▪ Reduces BC mortality in *BRCA1* mutation carriers***	2b	B	+*

* Study participation recommended

** The RR-BSO is recommended from about 35 years for *BRCA1* and from about 40 years for *BRCA2* mutation carriers, taking into account the age of ovarian cancer diagnosis in the family and the family planning status.

*** No reduction in mortality could be shown for BRCA2 mutation carriers. RRBM counselling should be individualised.

Risk-reducing Interventions for BRCA1/2 Female Mutation Carriers Affected by Breast Cancer

Guidelines Breast
Version 2024.1E

In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)	2b	B	+*
▪ Reduces OvCa incidence and mortality			
▪ Reduces overall mortality (contradictory results for reduction of cl BC incidence)			
▪ Prophylactic contralateral mastectomy (RR-CM)*	2b	B	+*
▪ Reduces BC incidence and mortality			
▪ Tamoxifen (reduces contralateral BC incidence)	2b	B	+/-*
▪ Indication for RR-CM should consider age at onset of first breast cancer in affected gene	2a	B	++*
▪ RR-BM after ovarian cancer	4	C	+/-**

* Study participation recommended
** Depends on tumor stage (FIGO I/II), recurrence free interval (≥ 5 yrs.), age

Guidelines Breast
Version 2024.1E

Adjuvant Endocrine-based Therapy in pre- and postmenopausal Patients

Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

Guidelines Breast
Version 2024.1E

- **Versions 2002–2023:**
  Bauerfeind / Dall / Diel / Fasching / Fersis / Fehm / Friedrich / Friedrichs / Gerber / Göring / Hanf/ Harbeck / Huober / Jackisch / Lisboa / Loibl / Lück / Lux / Maass / von Minckwitz / Möbus / Müller / Nitz / Oberhoff / Schaller / Scharl / Schneeweiss / Schütz / Solomeyer / Stickeler / Thomssen / Untch

- **Version 2024:**
  Lux / Wöckel

Guidelines Breast
Version 2024.1E

Assessment of Steroid Hormone Receptor Status

Oxford LoE: 1 GR: A AGO: ++

Endocrine responsive – hormone receptor positive
Immunhistology (ER and/or PgR)

0%	pos. cells:	endocrine resistant
1–10%	pos. cells:	possibly endocrine sensitive
> 10%	pos. cells:	endocrine sensitive
Unknown hormone receptor status:		endocrine sensitive

If ER negative / PR positive (> 10% positive cells): reassess IHC status
If ER low (1-10%): Implications for therapy should be recommended in the pathology report

Adjuvant Endocrine Therapy
Assessment of Menopausal Status

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
Assessment of menopausal status:			
▪ **Menstruation history**			++
▪ **FSH, E2**			++

Guidelines Breast
Version 2024.1E

Adjuvant Endocrine Therapy

	Oxford		
	LoE	GR	AGO
▪ Endocrine responsive	1a	A	++
▪ Endocrine doubtful responsiveness	3b	D	+
▪ Endocrine therapy sequentially after CT	2a	B	+
▪ Endocrine therapy simultaneous to anti-HER2 therapy (w/o chemotherapy)	2b	B	+
▪ Not sensitiv to endocrine therapy	1a	A	--

Guidelines Breast
Version 2024.1E

General Principles in Adjuvant Endocrine Therapy AGO ++

- **Adjuvant endocrine therapy is divided into initial therapy (years 1-5), extended adjuvant therapy (EAT, years 6-10+) and adjuvant endocrine-based treatment (years 1-2).**
- **Standard treatment duration is 5 years.**
- **Extended therapy and initial adjuvant endocrine-based therapy should be considered based on individual risks and benefits.**
- **Duration, choice & sequence of AI or Tam or the combination with GnRHa mainly depend on menopausal status, tolerability, and risk of recurrence.**
- **Switch to another better tolerated endocrine treatment (Tam or AI) or Tam low dose is better than stopping endocrine therapy altogether.**
- **AI should be used as first treatment in patients, in case of lobular cancers and / or high risk of recurrence.**
- **To date, there is no sufficiently validated biomarker for identification of patients at risk for early versus late recurrence.**

Guidelines Breast
Version 2024.1E

Premenopausal Patients
Initial Adjuvant Endocrine Therapy (Year 1-5)

	Oxford LoE	Oxford GR	AGO
▪ **Low recurrence risk:**			
▪ **Tamoxifen for 5 years**	1a	A	++
▪ **Increased recurrence risk:**			
▪ **OFS 2-5 years* + tamoxifen for 5 years**	1a	A	++
▪ **OFS# + AI for 5 years**	1a	A	++
▪ **GnRHa monotherapie** (If severe contraindications for Tam exist, compared to no therapy)	1a	B	+

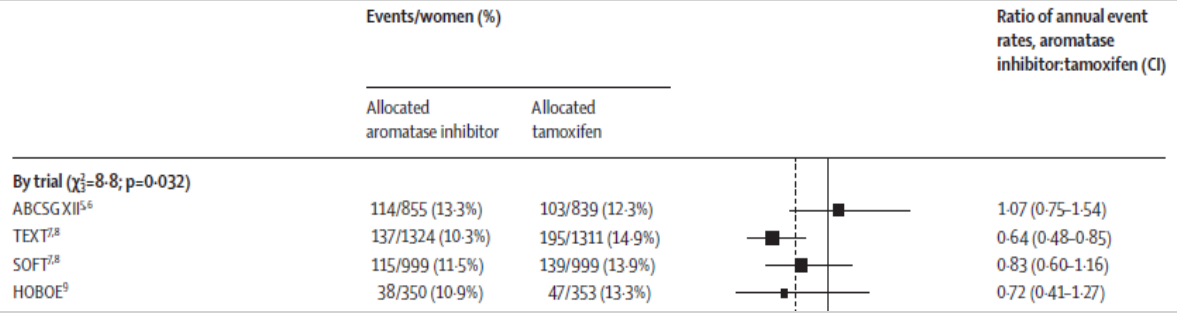
OFS: ovarian function suppression;

* as long as tolerated and the patient is clearly premenopausal after chemotherapy if ovarian function resumes within 24 months. The application of chemotherapy in the trials served as surrogate for high recurrence risk

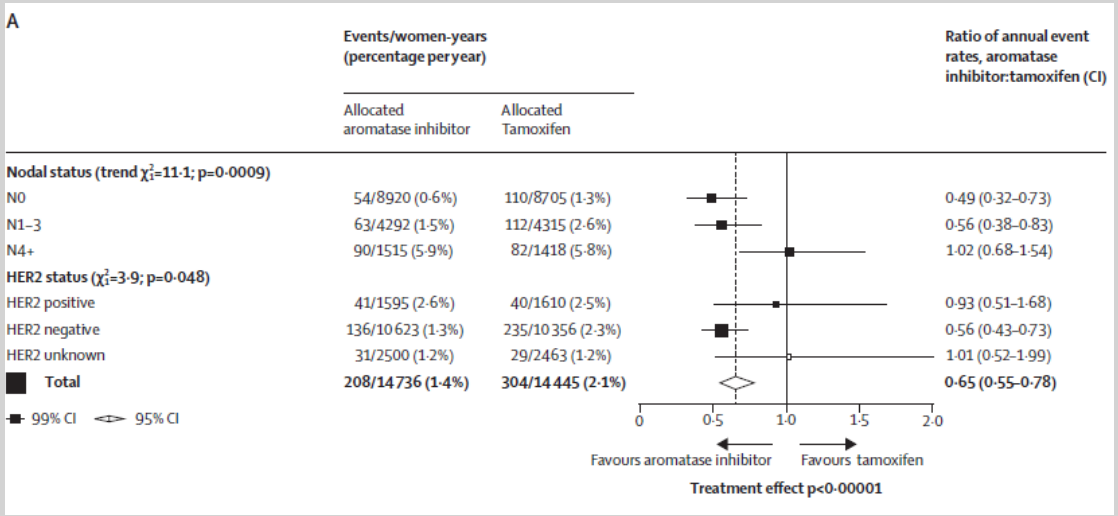
\# in premopausal women AI only in combination with OFS

Adjuvant endocrine therapy in premenopausal patients (OFS + TAM / AI)

Guidelines Breast
Version 2024.1E



	Events/women (%)		Ratio of annual event rates, aromatase inhibitor:tamoxifen (CI)
	Allocated aromatase inhibitor	Allocated tamoxifen	
By trial (χ^2_3=8·8; p=0·032)			
ABCSG XII[5,6]	114/855 (13·3%)	103/839 (12·3%)	1·07 (0·75–1·54)
TEXT[7,8]	137/1324 (10·3%)	195/1311 (14·9%)	0·64 (0·48–0·85)
SOFT[7,8]	115/999 (11·5%)	139/999 (13·9%)	0·83 (0·60–1·16)
HOBOE[9]	38/350 (10·9%)	47/353 (13·3%)	0·72 (0·41–1·27)



A

	Events/women-years (percentage per year)		Ratio of annual event rates, aromatase inhibitor:tamoxifen (CI)
	Allocated aromatase inhibitor	Allocated Tamoxifen	
Nodal status (trend χ^2_1=11·1; p=0·0009)			
N0	54/8920 (0·6%)	110/8705 (1·3%)	0·49 (0·32–0·73)
N1–3	63/4292 (1·5%)	112/4315 (2·6%)	0·56 (0·38–0·83)
N4+	90/1515 (5·9%)	82/1418 (5·8%)	1·02 (0·68–1·54)
HER2 status (χ^2_1=3·9; p=0·048)			
HER2 positive	41/1595 (2·6%)	40/1610 (2·5%)	0·93 (0·51–1·68)
HER2 negative	136/10623 (1·3%)	235/10356 (2·3%)	0·56 (0·43–0·73)
HER2 unknown	31/2500 (1·2%)	29/2463 (1·2%)	1·01 (0·52–1·99)
Total	**208/14736 (1·4%)**	**304/14445 (2·1%)**	**0·65 (0·55–0·78)**

99% CI 95% CI

0 0·5 1·0 1·5 2·0

Favours aromatase inhibitor Favours tamoxifen

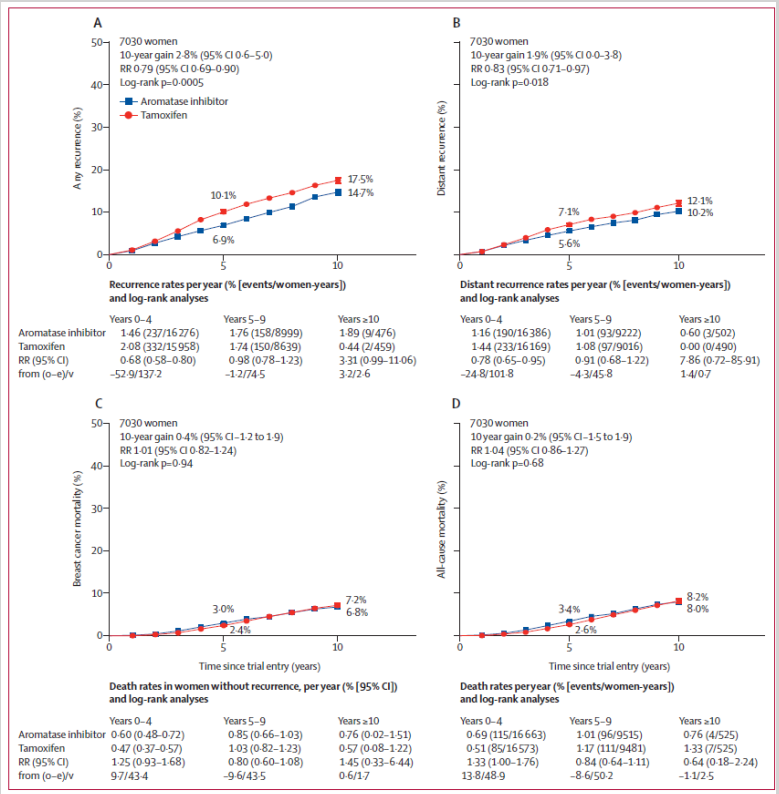
Treatment effect p<0·00001

EBCTCG: Lancet Oncol. 2022;23:382-392

Adjuvant endocrine therapy in premenopausal patients (OFS + TAM / AI)

Guidelines Breast
Version 2024.1E

Any recurrence



Distant recurrence

Breast cancer mortality

All-case mortality

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

EBCTCG: Lancet Oncol. 2022;23:382-392

Guidelines Breast
Version 2024.1E

Postmenopausal Patients
Initial Adjuvant Endocrine Therapy (Years 1-5)

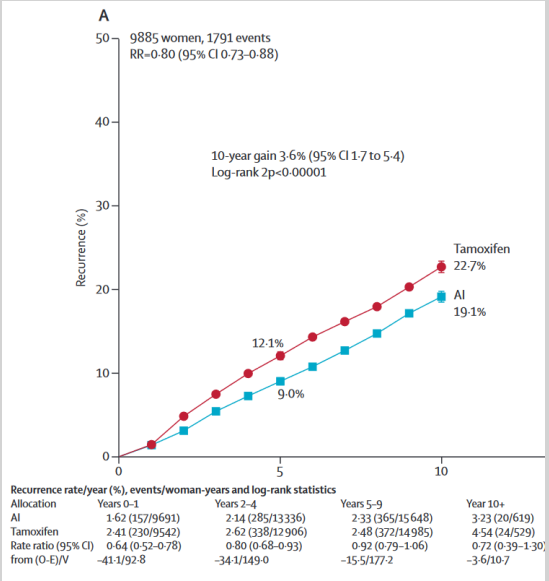
	Oxford		
	LoE	GR	AGO
▪ **Aromatase inhibitor (AI) for first 5 years**	1a	A	++
▪ Non steroidal-AI in lobular cancer	2b	B	+
▪ High risk of recurrence	2b	B	+
▪ **Sequential therapy for first 5 years ***	1a	A	++
▪ Tam (2-3 yrs.) followed by AI to complete 5 years	1a	A	++
▪ AI (2-3 yrs.) followed by tamoxifen to complete 5 years	1b	C	++
▪ **Tamoxifen 20 mg/d for 5 years****	1a	A	+

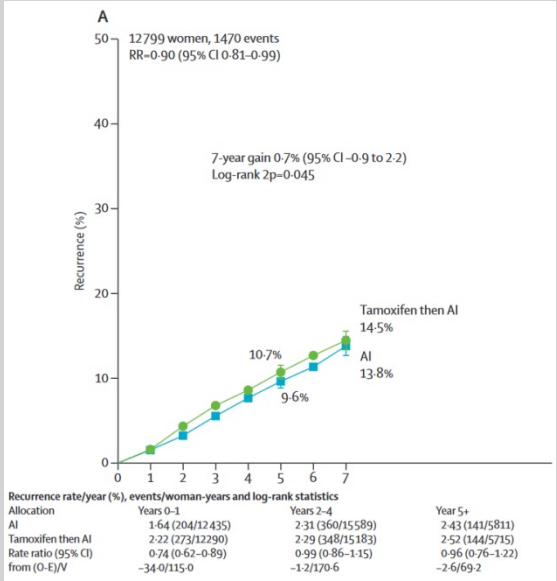
* **in postmenopausal patients, AI should be integrated in the first five years**

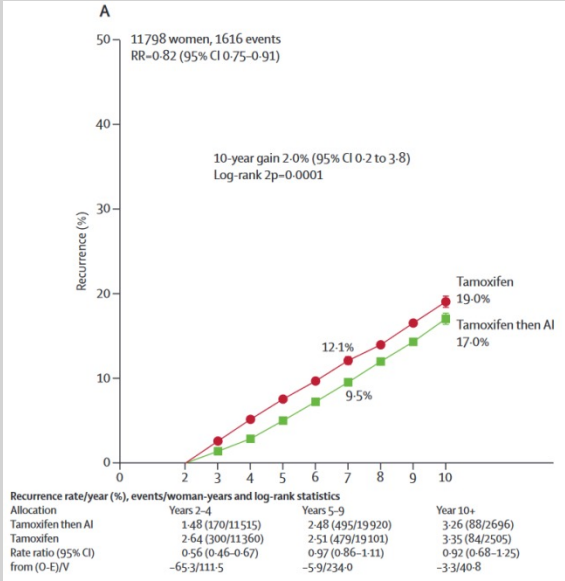
** **Tamoxifen may be offered to individual patients with very low risk of recurrence or if contraindications for AI are present**

Aromatase Inhibitor vs. Tamoxifen vs. Sequential Therapy - 5 years up-front Therapy

Guidelines Breast
Version 2024.1E







Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet. 2015 Oct 3;386(10001):1341-52.

Adjuvante Endocrine-Based Therapy with CDK4/6 Inhibitors and PARP Inhibitors

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
In patients with increased risk of recurrence, characteristics and drug doses corresponding to study criteria			
▪ **Abemaciclib for 2 years***	1b	B	+
▪ **Olaparib for 1 year in patients with *gBRCA1/2* mutations****	1b	B	++

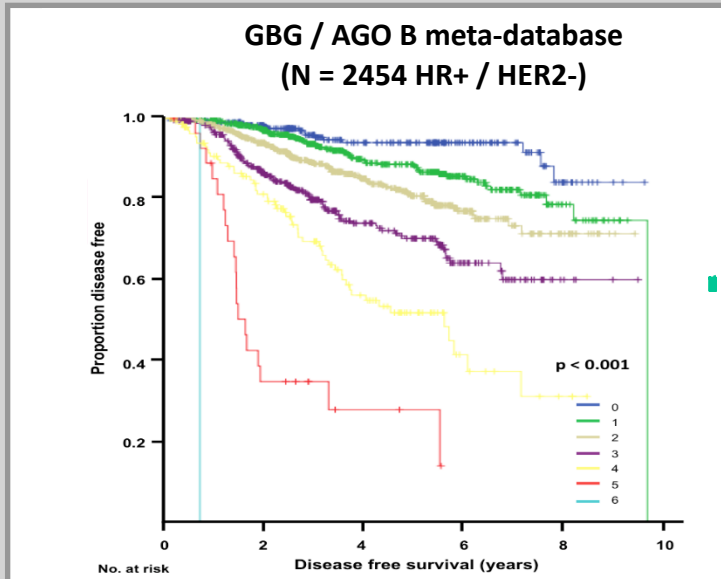
* corresponding to MonarchE-Study
** corresponding to OlympiA-Study

How to calculate CPS+EG Score?

Guidelines Breast
Version 2024.1E

Point assignment for CPS+EG score

Clinical Stage		
I	0	T1N0; T0N1mi, T1N1mi
IIA	0	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2N2
IIIB	2	T4N0-2
Pathologic Stage		
0	0	T0/isN0
I	0	T1N0; T0N1mi, T1N1mi
IIA	1	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2 N2
IIIB	1	T4 N0-N2
Tumor Biologic Factors		
ER negative	1	
Nuclear grade 3	1	



25%

Mittendorf EA, J Clin Oncol 2011;29:1956-1962
Marmé F, et al. Eur J Cancer 2021;153:203-212

Adjuvant / Post-Neoadjuvant Treatment with CDK4/6i

Guidelines Breast
Version 2024.1E

	monarchE	PALLAS	PENELOPE[B]	NATALEE
N	5,637	5,600	1,250	5,101
CDK4/6i	Abemaciclib	Palbociclib	Palbociclib	Ribociclib
% of pts. with NACT	37%	n.r.	100%	n.a.
Duration of CDK4/6i treatment	24 months	24 months	12 months	36 months
Follow-up	42.0 months	24 months	43 months	33.3 months
Discontinuation rate	30.6%	42%	20%	35.5%
Discontinuation rate due to AE_{CDKi}	18.5%	27%	5%	19.5%
IDFS-HR (95%-CI)	0.664 (0.578-0.762) p < 0.0001	0.96 (0.81-1.14) p = 0.65	0.93 (0.74-1.16) p = 0.525	0.749(0,628-0.892) P=0.0006
2-yrs IDFS	92.7% vs. 89.9%	n.r.	88% vs. 78%	93.5% vs. 92.0%
3-yrs IDFS	89.2% vs. 84.4%	88% vs. 89%	81% vs. 78%	90.7% vs. 87.6%
4-yrs IDFS	85.8% vs. 79.4%	84.2% vs. 84.5%	73% vs. 72%	

IDFS: invasive disease-free survival

Guidelines Breast
Version 2024.1E

Premenopausal Patients
Extended Adjuvant Endocrine Therapy (EAT) (Years 6–10)

	Oxford		
	LoE	GR	AGO
In case of high risk of recurrence			
▪ 5 years tamoxifen after 5 years tamoxifen	1a	A	++
▪ 2,5 – 5 years AI after 5 years tamoxifen in initially premenopausal patients who obtain validated postmenopausal status during course of therapy	1b	B	+
▪ 5 years tamoxifen after 5 years of endocrine therapy + OFS	5	D	+

Guidelines Breast
Version 2024.1E

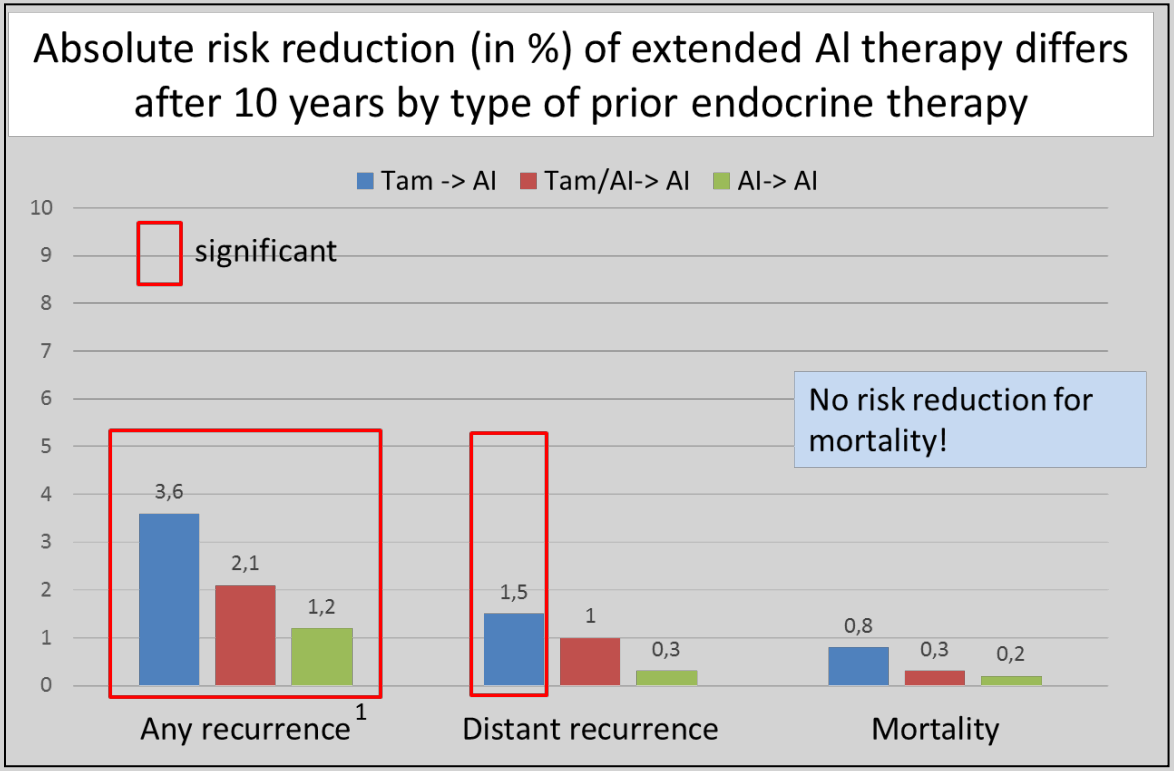
Postmenopausal Patients
Extended Adjuvant Endocrine Therapy (EAT) (Years 6–10)

	Oxford		
	LoE	GR	AGO
In case of high risk of recurrence			
▪ 5 years tamoxifen after 5 years tamoxifen	1a	A	+
▪ 2–5 years AI after 5 years tamoxifen	1a	A	++
▪ After initial AI-containing therapy (upfront or switch), prolongation of endocrine therapy with AI in total for 7-8 years*			
▪ High-risk of recurrence and good tolerability of AI, good bone health	1a	A	+
▪ Low-risk, poor tolerabilty of AI	1a	A	-
▪ Interruption of endocrine treatment up to 3 months during EAT with AI	1b	B	+/-

* Up to date, no impact on OS

Extended Aromatase Inhibitor Treatment following 5 or more Years of Endocrine Therapy: A Metaanalysis of 22192 Women in 11 Randomised Trials (EBCTCG)

Guidelines Breast
Version 2024.1E



[1] *(new primary breast cancer, local and distant recurrence)*

Gray R et al. SABCS 2018 (GS3-03)

Decision Criteria for Extended Adjuvant Therapy

Guidelines Breast
Version 2024.1E

Factors indicating a clinical benefit from EAT:

- Adjuvant tamoxifen therapy only
- Condition after chemotherapy (indicating high risk)
- Positive lymph node status and / or T2 / T3 tumors
- Elevated risk of recurrence based on immunohistochemical criteria or based on multi-gene expression assays
- High CTS5-score
- BCI (H/I) (Breast Cancer Index)

Further decision criteria:

- Wish of patient
- up to now well tolerated AI therapy,
- good bone health
- younger age
- adherence

Ovarian Protection with GnRHa and Fertility Preservation in Premenopausal Patients Receiving (Neo)-Adjuvant Chemotherapy (CT)

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ **CTx + GnRHa (preservation of ovarian function) (GnRHa application > 2 weeks prior to chemo-therapy, independent of hormone receptor status)**	1a	A	+
▪ **CTx + GnRHa (preservation of fertility)**	2a	B	+/-
▪ **Fertility preservation counselling including referral of all potential patients to appropriate reproductive specialists (ART; further information *https://fertiprotekt.com/english; S2k guideline Fertility protection in patients with malignancies*)**			++

Guidelines Breast
Version 2024.1E

Fertility Preservation and Assisted Reproductive Therapy (ART)

- Oncologic safety[1] -

	Oxford LoE	Oxford GR	AGO
▪ **Pretreatment approaches to preserve fertility**			
GnRHa	1a	A	++
Cryopreservation of ovarian tissue with subsequent transplantation[2]	4	D	+
Cryopreservation of oocytes (unfertilized / fertilized) after ovarian stimulation	2a	C	+
▪ **ART after breast diagnosis of breast cancer**	4	C	+/-

[1] Evidence is limited due to studies with poor quality e.g. (prospective randomized trials are not feasible)
[2] Risk of relapse caused by transplantation of ovarian tissue containing tumor cells from the original malignancy; removal of transplanted ovarian tissue is necessary in patients with BRCA1/2 mutations due to increased risk of ovarian cancer

Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

Guidelines Breast
Version 2024.1E

Temporary interruption of adjuvant endocrine treatment (ET) after 18-30 month of ET, allowing a wash out period of 3 months, the attempt to get pregnant in a period of up to 2 years for those women with the desire to get pregnant does not impact short-term breast cancer outcome.

AGO +

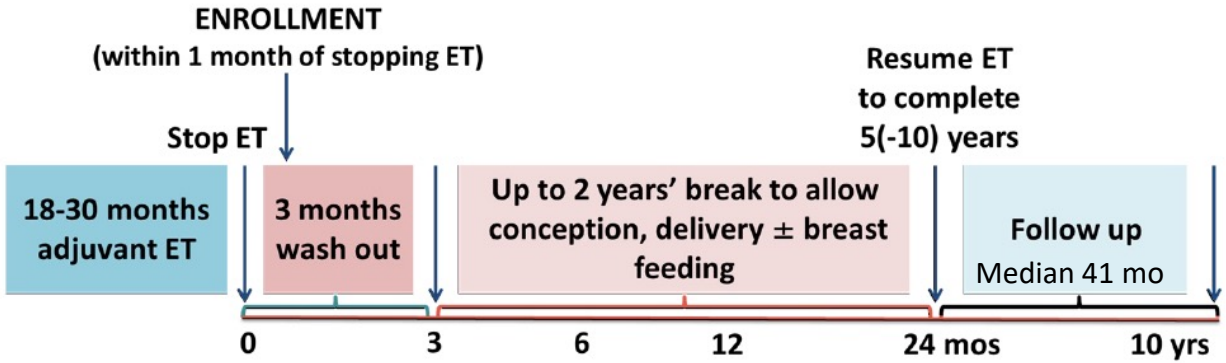
Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

Guidelines Breast
Version 2024.1E

Study design

AGO +

N=516



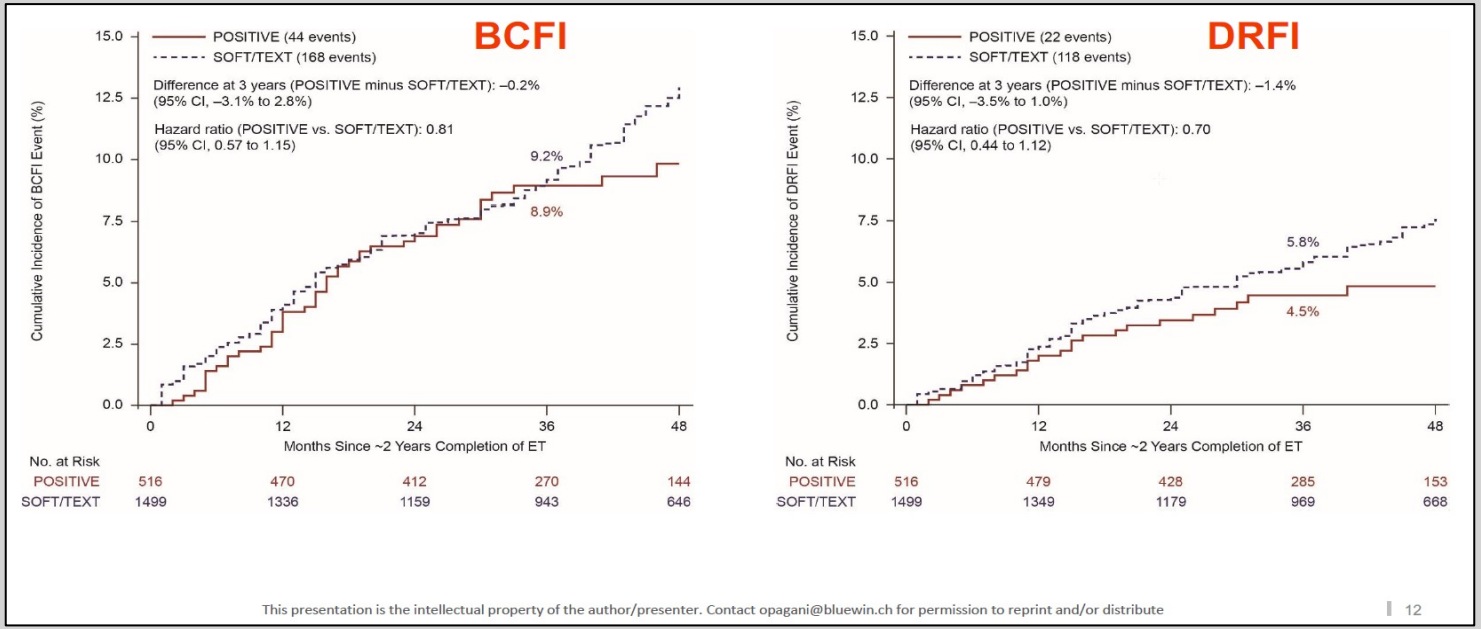
- Premenopausal women (≤42 years at study entry) wishing to get pregnant
- At least 18 months and no more than 30 months of prior adjuvant ET for stage I-III HR+ BC
- Up to 2 years to attempt pregnancy, conceive, deliver, and breastfeed, including
- 3-months washout period
- If no pregnancy by 1 y., fertility assessment recommended
- ET resumption strongly recommended after pregnancy to complete planned 5-10 yrs.

Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

Guidelines Breast
Version 2024.1E

Pregnancies outcome: 317 (64% of all women) had at least one live birth, 62% reported breast feeding, 2% showed birth defects

BREAST CANCER OUTCOMES – POSITIVE & SOFT/TEXT



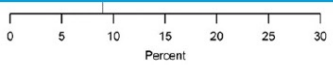
Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

Guidelines Breast
Version 2024.1E

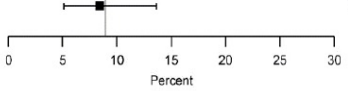
3- YEAR BCFI CUMULATIVE INCIDENCE – POSITIVE only

- 3-year BCFI varied according to clinical-pathological characteristics

Subgroup	No. Events / Total No. Patients	3-Year BCFI Cumulative Incidence Percent (95% CI)
Overall	44/516	8.9 (6.7–11.9)
Age at enrollment (years)		
<35	14/177	9.1 (5.4–14.9)
35–39	18/221	7.7 (4.8–12.3)
40–42	12/118	11.2 (6.5–18.9)
BMI at enrollment (kg/m²)*		
<25	34/371	9.5 (6.8–13.2)
25 to <30	7/90	8.0 (3.9–16.1)
≥30	3/49	7.2 (2.4–20.9)
BRCA status		
BRCA Positive	5/38	14.5 (6.3–31.6)
Other mutation	4/21	10.5 (2.7–35.9)
No documented mutation†	35/457	8.4 (6.1–11.5)
HER2 status		
Positive	6/134	4.9 (2.2–10.6)
Negative	38/382	10.4 (7.6–14.1)
Nodal status		
pN0	21/342	6.6 (4.3–10.0)
pN+ 1–3	18/151	12.6 (8.1–19.3)
pN+ 4–9	5/23	18.7 (7.4–42.6)



Subgroup	No. Events / Total No. Patients	3-Year BCFI Cumulative Incidence Percent (95% CI)
Tumor size (cm)‡		
≤2	24/331	7.6 (5.1–11.2)
>2 to ≤5	16/161	10.3 (6.3–16.5)
>5	4/21	21.1 (8.3–47.6)
Tumor grade‡		
1 (BRE 3–5)	5/89	6.4 (2.7–14.8)
2 (BRE 6–7)	21/252	8.9 (5.8–13.6)
3 (BRE 8–9)	18/172	10.4 (6.6–16.2)
Breast surgery		
Mastectomy	29/233	12.7 (8.9–17.9)
Breast conservation	15/283	5.7 (3.4–9.5)
Prior endocrine therapy		
SERM alone	20/215	9.9 (6.4–15.1)
SERM+OFS	20/184	11.4 (7.4–17.4)
AI+OFS	1/82	1.2 (0.2–8.4)
Other	3/35	8.8 (2.9–24.9)
Prior chemotherapy		
Anthracycline (A) based	8/36	19.4 (9.8–36.5)
Taxane (T) based	4/66	6.7 (2.5–16.9)
Both A and T based	16/215	8.4 (5.2–13.4)
Neither A or T based	0/3	
None	16/196	8.4 (5.1–13.6)



Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

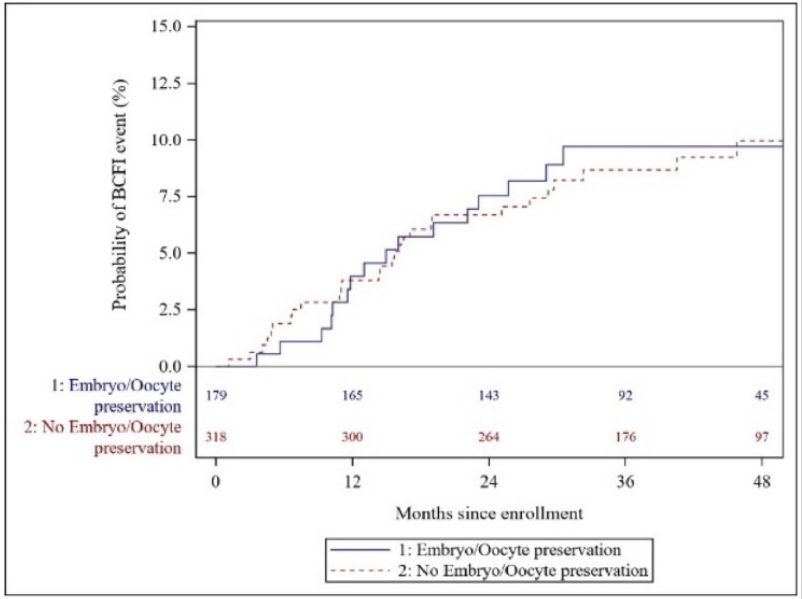
Guidelines Breast
Version 2024.1E

Ovarian stimulation and breast cancer outcome – results from the POSITIVE trial

1) As part of embryo/oocyte cryopreservation - after BC diagnosis

At 3-years, BCFI-events cumulative incidence

- **9.7%** (95% CI: 6.0% to 15.4%) for the 179 patients who underwent ovarian stimulation
- **8.7%** (95% CI: 6.0% to 12.5%) for the 318 patients who did not



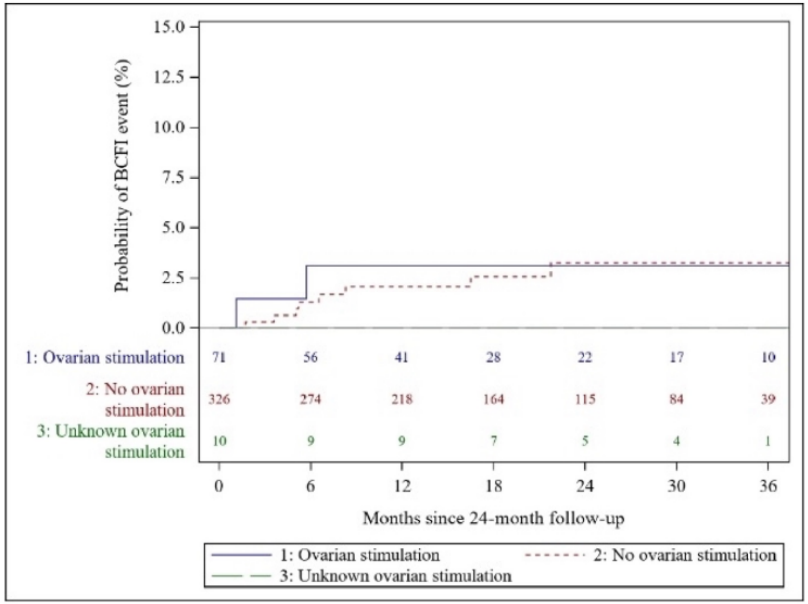
Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

Guidelines Breast
Version 2024.1E

Ovarian stimulation and breast cancer outcome – results from the POSITIVE trial

2) As part of ART - after enrollment

- **397 patients alive and BC free at 24-months (landmark analysis)**
  - 2 BC events amongst 71 patients in the ovarian stimulation group
  - 8 BC events amongst 326 patients in the non-ovarian stimulation group



Guidelines Breast
Version 2024.1E

Adjuvant Cytotoxic and Targeted Therapy

Adjuvant Cytotoxic and Targeted Therapy

Guidelines Breast
Version 2024.1E

- **Versions 2002 – 2023:**
  Albert / Dall / Fasching / Fehm / Gluz/ Harbeck / Jackisch /Janni / Kümmel / Loibl / Lux / von Minckwitz / Möbus / Müller / Nitz / Rody / Schmidt / Schneeweiss / Simon / Schütz / Solomayer / Stickeler / Thill / Thomssen / Untch

- **Version 2024:**
  Loibl / Lüftner

Guidelines Breast
Version 2024.1E

Strategies for Differentiated Systemic Treatment in the Curative Situation

If chemotherapy is indicated systemic treatment before surgery (neoadjuvant) should be preferred; study participation recommended

	AGO
▪ **HR+ / HER2- and „low recurrence-risk"**	
▪ **Endocrine therapy without chemotherapy**	++
▪ **HR+ / HER2- and „high recurrence-risk"**	
▪ **Endocrine / endocrine-based therapy (abemaciclib)**	++
▪ **Patients with indication for chemo-endocrine therapy***	
▪ **Conventionally dosed AT-based chemotherapy (q3w)**	+
▪ **Dose dense chemotherapy (including weekly schedule)**	++
▪ **Triple-negative (TNBC)**	
▪ **Conventional dosed AT-based chemotherapy (q3w)**	+
▪ **Sequential AT-based chemotherapy (incl. weekly schedule)**	++
▪ **Neoadjuvant platinum-containing chemotherapy**	+
▪ **Neoadjuvant platinum-containing chemotherapy with ICPI (Pembrolizumab)**	+
▪ **gBRCA1/2mut (HR+/HER- or TNBC respectively[1])**	
▪ **Olaparib[1] postneoadjuvant**	++
▪ **HER2+**	
▪ **Trastuzumab (plus Pertuzumab in N+ or NACT)**	++
▪ **Sequential AT-based chemotherapy with concurrent T + anti-HER2 therapy**	++
▪ **Anthracycline-free, chemotherapy + anti-HER2 therapy**	++

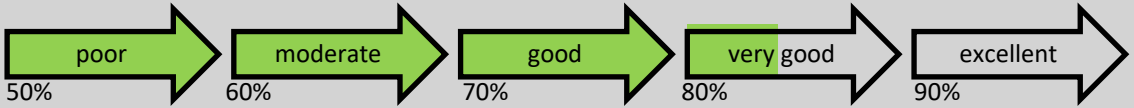
[1]according to approval or study population (if not approved), *see prognosis chapter

Guidelines Breast
Version 2024.1E

Lee-Schonberg Index
https://eprognosis.ucsf.edu/leeschonberg-result.php

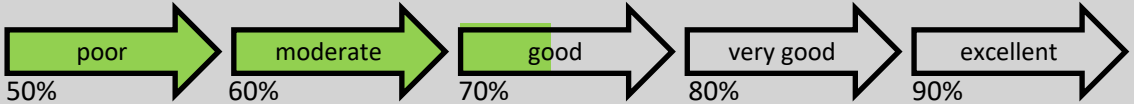
Lee Index

- This index was developed in 11,701 community-dwelling adults from the eastern, western and central United States who were interviewed in the Health Retirement Survey in 1998 (mean age 67, 57% female, 81% white, 12% 4-year mortality).
- The index was internally validated in 8009 Health Retirement Survey interviewees from the southern United States (mean age 67, 57% female, 71% white, 13% 4-year mortality) and externally validated in 7042 English Longitudinal Study on Ageing interviewees.
- Discrimination: This risk calculator sorts patients who died from patients who lived correctly 82% of the time (c-statistic). The life expectancy calculator sorts patients who lived longer from patients who lived shorter correctly 78-80% of the time in the validation studies
- Calibration: The model was well calibrated across all risk levels with less than 3% difference between estimated and actual mortality rates.



Schonberg Index

- This index was developed in 16,077 community dwelling older adults who responded to the 1997-2000 National Health Interview (NHIS) (27% >80 years old, 60% female, 85% white, 17% 5-year mortality)
- The index was internally validated in a random sample of 8038 from respondents from the same data source from 2001-2004 and followed through 2006 (27% >80 years old, 60% female, 85% white, 17% 5-year mortality). The index was internally validated in 16,063 respondents from the original development cohort and 8,027 respondents from the original validation cohort from 1997-2000 and followed through 2011 (10 and 14-year mortality).
- Discrimination: This risk calculator sorts patients who died within 5 years from patients who lived correctly 75% of the time (c-statistic). The discrimination was the same in the independent validation study. For 10 year and 14 year mortality the calculator sorts patients correctly 73% and 72% of the time.
- Calibration: The model was well calibrated across all risk levels with less than 10% difference between estimated and actual mortality.



Guidelines Breast
Version 2024.1E

Lee-Schonberg Index
https://eprognosis.ucsf.edu/leeschonberg-result.php

Risk Calculator questions

1. How old is your patient?
2. What is the sex of your patient?
3. What is your patient‘s BMI?
4. Which best describes your patient's health in general?
5. Does your patient have chronic lung disease, such as emphysema or chronic bronchitis?
6. Has your patient ever had cancer (excluding minor skin cancers)?
7. Does your patient have congestive heart failure?
8. Does your patient have diabetes or high blood sugar?
9. Which best describes your patient's cigarette use?
10. Does your patient have difficulty walking 1/4 mile (several city blocks) without help from other people or special equipment?
11. During the past 12 months, how many times was your patient hospitalized overnight?
12. Because of a physical, mental or emotional problem, does your patient need the help of others in handling routine needs such as everyday household chores, doing necessary business, shopping, or getting around for other purposes?
13. Because of a health or memory problem, does your patient have difficulty managing money - such as paying bills and keeping track of expenses?
14. Because of a health or memory problem, does your patient have difficulty with bathing or showering?
15. Because of a health problem, does your patient have difficulty pushing or pulling large objects like a living room chair?

(Neo)Adjuvant Chemotherapy: in Small, Node-Negative Tumors (T1)

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ **Indication for chemotherapy in**			
▪ **TNBC**			
▪ > 10 mm neoadjuvant preferred	2b	B	++
▪ > 5–10 mm neoadjuvant or adjuvant	2b	B	+
▪ ≤ 5 mm adjuvant	2b	B	+/-
▪ **HER2+ in combination with trastuzumab**			
▪ > 10 mm neoadjuvant or adjuvant	1a	A	++
▪ > 5–10 mm adjuvant	2b	B	+
▪ ≤ 5 mm adjuvant	2b	B	+/-

Adjuvant Chemotherapy without Trastuzumab: Overview

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Dose-dense anthracycline / taxane based (incl. weekly) chemotherapy	1a	A	++
▪ Conventional anthracycline / taxane based (q3w)	1a	A	+
▪ „Tailored“ anthracycline-/ taxane based	1b	B	+/-
▪ If anthracyclines are not a preferred option			
▪ Docetaxel plus cyclophosphamide	1b	B	++
▪ Paclitaxel mono weekly	1b	B	+/-
▪ CMF	1a	A	+/-

Gray R et al., Lancet 2019

Early Breast Cancer Trialists' Cooperative Group (EBCTCG)
Increasing the dose-density of adjuvant chemotherapy: an EBCTCG meta-analysis

Same chemotherapy drugs and doses **(n = 10,004)**

Recurrence-free survival: 10-y Gain 4.3% (95%-C.I. 2.2 – 6.5)
(RR = 0.83; 95%-C.I. 0.76 – 0.91; p < 0.0001)
Overall survival: 10-y Gain 2.8% (95%-C.I. 0.8 – 4.8)
(RR = 0.86; 95%-C.I. 0.77 – 0.96; p = 0.0054)

ER negative: **10-y Gain 4.7%** (95%-C.I. 2.3 – 7.1)
ER positive: **10-y Gain 3.1%** (95%-C.I. 1.5 – 4.7)

Guidelines Breast
Version 2024.1E

Recommended Dose-dense and / or Dose-escalated, Sequential Adjuvant Chemotherapy

	Oxford		
	LoE	GR	AGO
Dose-dense regimen			
▪ A_{60} x 4 → Pac_{175} x 4 → C_{600} x 4 q2w	1b	A	++
▪ A_{60}C q2w x 4 → Pac_{175} q2w x 4	1b	B	++
▪ E_{90}C q2w x 4 → Pac_{175} q2w x 4	1b	A	++
▪ E_{90}C q2w x 4 → Pac_{80} q1w x 12	1b	B	++
▪ $NabPac_{125}$ x 8-12 → E_{90}C q2(3)w x 4	1b	B	+
Dose-dense and dose-escalated regimen (N ≥ 4+)			
▪ E_{150} → Pac_{225} → C2000 q2w	1b	A	++

Recommended Conventional Regimens for Adjuvant Chemotherapy

Guidelines Breast
Version 2024.1E

		Oxford LoE	Oxford GR	AGO
Anthrazyklin-/ taxan-based regimen				
▪ *EC q3w x 4 → Pac q1w x 12		2b	B	++
▪ AC q3w x 4 → Pac q1w x 12		1b	A	++
▪ AC → D qw3	$A_{60}C$ q3w x 4 → D_{100} x 4	1b	A	+
▪ *EC → D qw3	$E_{90}C$ q3w x 4 → D_{100} x 4	1b	B	+
▪ DAC	$D_{75}A_{50}C$ q3w x 6	1b	A	+[a]
Anthrazyklin-free regimen				
▪ 6 x DC corresponds to EC → D or 3 x (F)EC-> 3 x Doc	D_{75} C_{600} x 6	1b	B	+
▪ 4 x DC >> 4 x AC	D_{75} C_{600} x 4	1b	B	+
▪ Pac mono	P_{80} q1w x 12	1b	B	+/-
▪ CMF		1a	A	+/-
Taxan-free regimen				
▪ EC (q3-2w) x 4-6	$E_{90}C_{600}$ x 4-6	2b[(a)]	B	+

* Extrapolation from doxorubicin trials

Guidelines Breast
Version 2024.1E

Adjuvant Chemotherapy
Other Drugs

	Oxford LoE	Oxford GR	AGO
▪ **Capecitabine-containing regimen in TNBC***			
▪ adjuvant / neoadjuvant	1a	A	+/-
▪ postneoadjuvant in non-pCR patients**			
▪ With non-pCR after A-T-containing chemotherapy	1a	A	++
▪ With non-pCR after platinum +/- pembrolizumab-containing therapy	5	D	+/-
▪ Anthracycline-free adjuvant therapy in TNBC (combination with taxan)	1b	B	+
▪ Anthracycline-based adjuvant therapy in TNBC	5	D	+/-
▪ **5- fluorouracile added to EC / AC**	1b	A	--

* DPYD genotyping for the identification of a DPD Deficiency
** in stage II-III without platinum/pembrolizumab-based pretreatment

Van Mackelenbergh M et al., J Cancer 2022

Effects of capecitabine as part of neo- / adjuvant chemotherapy
Meta-analysis of individual patient data from 12 randomized trials (n = 15,457)

HR for DFS overall 0.952 (95%-C.I. 0.895-1.012, p = 0.115)
X add. 0.888 (95%-C.I. 0.817-0.965, p = 0.005)
X instead 1.035 (95%-C.I. 0.945-1.134, p = 0.455)

HR for OS overall 0.892 (95%-C.I. 0.824-0.965, p = 0.005)
X add. 0.837 (95%-C.I. 0.751-0.933, p = 0.001)
X instead 0.957 (95%-C.I. 0.853-1.073, p = 0.450)

Significance only for TNBC overall DFS 0.886 (95%-C.I. 0.789-0.994, p = 0.040)
OS 0.828 (95%-C.I. 0.720-0.952, p = 0.008)
X add.: DFS 0.818 (95%-C.I. 0.713-0.938, p = 0.004)
OS 0.778 (95%-C.I. 0.657-0.921, p = 0.004)

Guidelines Breast
Version 2024.1E

Adjuvant HER2-directed Treatment

	Oxford LoE	Oxford GR	Oxford AGO
Trastuzumab + Pertuzumab			
pN+	1b[a]	B	++
pN-	1b[a]	B	+/-
Neratinib			
1 year after 1 year trastuzumab (HR-positive, stage II-III)	1b	B	+
1 year after trastuzumab / pertuzumab / T-DM1 (HR-positive, stage II-III)	5	D	+/-

Guidelines Breast
Version 2024.1E

(Neo)Adjuvant Treatment with Trastuzumab / Pertuzumab

	Oxford		
	LoE	GR	AGO
Start of treatment			
▪ Simultaneously with taxanes	1a	A	++
▪ Sequentially up to 3 months after chemotherapy	1b	B	+
Duration			
▪ For 1 year	1a	A	++
▪ For 0.5 years (Trastuzumab)	1a	A	+
▪ For 2 years	1b	A	-

(Neo)Adjuvant Treatment with Trastuzumab +/- Pertuzumab: Chemotherapy regimen

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
Trastuzumab simultaneously with			
▪ paclitaxel / docetaxel after AC / EC	1a	A	++
▪ P q1w 12 x in pT < 2 cm, pN0	2b	B	+
▪ docetaxel and carboplatin	1b	A	+
Trastuzumab + Pertuzumab simultaneously with			
▪ paclitaxel q1w (or docetaxel q3w) after EC / AC	1b	B	++
▪ docetaxel+ carboplatin	1b	B	++
▪ taxanes dose-dense	2b	B	+
Radiotherapy concurrently with Trastuzumab / Pertuzumab	1a	A	++

Postneoadjuvant Therapy HR+ / HER2-

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
HR positive (pCR and non-pCR)			
▪ Endocrine therapy according to menopausal state (s. chap. 10)	1a	A	++
▪ Abemaciclib for 2 yrs + endocrine therapy if high risk of recurrence[1]	1b	B	+
▪ Olaparib for 1 yr + endocrine therapy (g*BRCA1/2*^{MUT}, if non-pCR and CPS-EG Score ≥ 3)[2]	1b	A	++
▪ Capecitabine (non-pCR)	1b	A	+/-

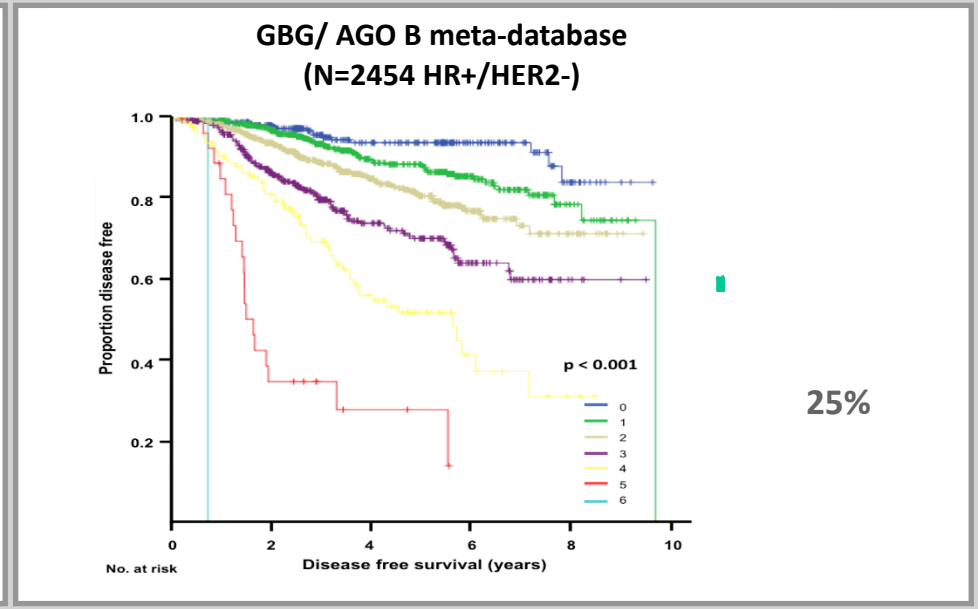
1 According inclusion criteria monarchE-study,
2 According inclusion criteria OlympiA-study

How to calculate CPS+EG Score?

Guidelines Breast
Version 2024.1E

Point assignment for CPS+EG score

Clinical Stage		
I	0	T1N0; T0N1mi, T1N1mi
IIA	0	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2N2
IIIB	2	T4N0-2
Pathologic Stage		
0	0	T0/isN0
I	0	T1N0; T0N1mi, T1N1mi
IIA	1	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2 N2
IIIB	1	T4 N0-N2
Tumor Biologic Factors		
ER negative	1	
Nuclear grade 3	1	



Mittendorf EA, J Clin Oncol 2011;
Marmé F, et al. Eur J Cancer 2016

Adjuvant / Post-Neoadjuvant Treatment with CDK4/6i

Guidelines Breast
Version 2024.1E

	monarchE	PALLAS	PENELOPE[B]	NATALLEE
N	5,637	5,600	1,250	5101
CDK4/6i	Abemaciclib	Palbociclib	Palbociclib	Ribociclib
% of pts. with NACT	37%	n.r.	100%	88%
Duration of CDK4/6i treatment	24 months	24 months	12 mths	36 months
Follow-up	42.0 months	24 months	43 months	33.3 months
Discontinuation rate	28%	42%	20%	35.5%
Discontinuation rate due to AE_{CDKi}	17%	27%	5%	19.5%
IDFS-HR (95%-CI)	0.664 (0.578-0.762) p < 0.0001	0.96 (0.81-1.14) p = 0.65	0.93 (0.74-1.16) p = 0.525	0.749 (0,628-0.892) p = 0.0006
2-yrs IDFS	92.7% vs. 89.9%	n.r.	88% vs. 78%	93.5% vs. 92.0%
3-yrs IDFS	89.2% vs. 84.4%	88% vs. 89%	81% vs. 78%	90.7% vs. 87.6%
4-yrs IDFS	85.8% vs. 79.4%	84.2% vs. 84.5%	73% vs. 72%	

IDFS: invasive disease-free survival

Guidelines Breast
Version 2024.1E

Postneoadjuvant Therapy TNBC

	Oxford LoE	Oxford GR	AGO
pCR			
▪ Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)	1b	B	+
Non-pCR			
▪ Capecitabine (q3w up to 8 courses)*			
▪ With non-pCR after A-T-containing chemotherapy*	1a	A	++
▪ With non-pCR after platinum +/- pembrolizumab-containing therapy	5	D	+/-
▪ Platinum salts (carboplatin or cisplatin) q3w after AT-pretreatment	1b	B	+/-
▪ Olaparib (*gBRCA^{MUT}*)[1]	1b	A	++
▪ Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)	1b	B	+

[1] according inclusion criteria of OlympiA trial, advantage especially with platinum-free NACT

* in stage II-III without platinum/pembrolizumab-based pretreatment

Guidelines Breast
Version 2024.1E

Postneoadjuvant Therapy HER2-positive

	Oxford LoE	Oxford GR	AGO
pCR			
▪ Low risk: Trastuzumab (to complete 12 mths)	2a	C	++
▪ High risk (cN+): Trastuzumab + Pertuzumab (to complete 12 mths)	2b	C	+
▪ Neratinib after 1 year Trastuzumab (HR-positive, stage II-III)*	2b	B	+/-
non-pCR			
▪ T-DM1	1b	B	++
▪ Trastuzumab + Pertuzumab (to complete 12 mths)	2b	C	+
▪ Additional HER2-directed therapy after 1 yr (extended adjuvant th.)			
▪ Neratinib after Trastuzumab (HR-positive, stage II-III)*	2b	B	+
▪ Neratinib after other HER2-directed therapies (HR-positive, stage II-III)*	5	D	+/-

* In combination with standard endocrine treatment

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

Neoadjuvant
(Primary) Systemic Therapy

Guidelines Breast
Version 2024.1E

Neoadjuvant Systemic Therapy

- **Versions 2002–2023:**
  Bauerfeind / Blohmer / Costa / Dall / Fasching / Fehm / Fersis / Friedrich / Göhring / Harbeck / Heinrich / Huober / Jackisch / Kaufmann / Liedtke / Loibl / Lux / von Minckwitz / Müller / Mundhenke / Nitz / Schneeweiss / Schütz / Solomayer / Stickeler / Untch / Thill / Thomssen

- **Version 2024:**
  Jackisch / Stickeler

Guidelines Breast
Version 2024.1E

Strategies for Differentiated Systemic Treatment in the Curative Situation

If chemotherapy is indicated systemic treatment before surgery (neoadjuvant) should be preferred; study participation recommended

	AGO
▪ **HR+ / HER2- and „low recurrence-risk"**	
▪ **Endocrine therapy without chemotherapy**	++
▪ **HR+ / HER2- and „high recurrence-risk"**	
▪ **Endocrine / endocrine-based therapy (abemaciclib)**	++
▪ **Patients with indication for chemo-endocrine therapy***	
▪ **Conventionally dosed AT-based chemotherapy (q3w)**	+
▪ **Dose dense chemotherapy (including weekly schedule)**	++
▪ **Triple-negative (TNBC)**	
▪ **Conventional dosed AT-based chemotherapy (q3w)**	+
▪ **Sequential AT-based chemotherapy (incl. weekly schedule)**	++
▪ **Neoadjuvant platinum-containing chemotherapy**	+
▪ **Neoadjuvant platinum-containing chemotherapy with ICPI (Pembrolizumab)**	+
▪ **gBRCA1/2mut (HR+/HER- or TNBC respectively[1])**	
▪ **Olaparib[1]**	++
▪ **HER2+**	
▪ **Trastuzumab (plus Pertuzumab in N+ or NACT)**	++
▪ **Sequential AT-based chemotherapy with concurrent T + anti-HER2 therapy**	++
▪ **Anthracycline-free, chemotherapy + anti-HER2 therapy**	++

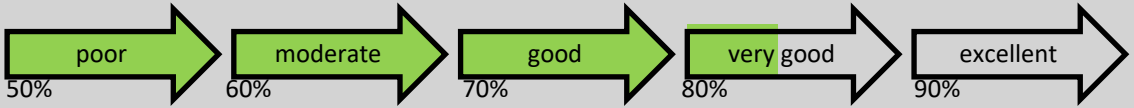
[1]according to approval or study population (if not approved), *see prognosis chapter

Guidelines Breast
Version 2024.1E

Lee-Schonberg Index
https://eprognosis.ucsf.edu/leeschonberg-result.php

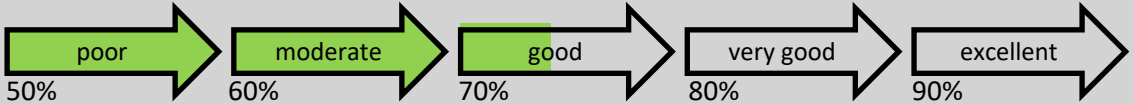
Lee Index

- This index was developed in 11,701 community-dwelling adults from the eastern, western and central United States who were interviewed in the Health Retirement Survey in 1998 (mean age 67, 57% female, 81% white, 12% 4-year mortality).
- The index was internally validated in 8009 Health Retirement Survey interviewees from the southern United States (mean age 67, 57% female, 71% white, 13% 4-year mortality) and externally validated in 7042 English Longitudinal Study on Ageing interviewees.
- Discrimination: This risk calculator sorts patients who died from patients who lived correctly 82% of the time (c-statistic). The life expectancy calculator sorts patients who lived longer from patients who lived shorter correctly 78-80% of the time in the validation studies
- Calibration: The model was well calibrated across all risk levels with less than 3% difference between estimated and actual mortality rates.



Schonberg Index

- This index was developed in 16,077 community dwelling older adults who responded to the 1997-2000 National Health Interview (NHIS) (27% >80 years old, 60% female, 85% white, 17% 5-year mortality)
- The index was internally validated in a random sample of 8038 from respondents from the same data source from 2001-2004 and followed through 2006 (27% >80 years old, 60% female, 85% white, 17% 5-year mortality). The index was internally validated in 16,063 respondents from the original development cohort and 8,027 respondents from the original validation cohort from 1997-2000 and followed through 2011 (10 and 14-year mortality).
- Discrimination: This risk calculator sorts patients who died within 5 years from patients who lived correctly 75% of the time (c-statistic). The discrimination was the same in the independent validation study. For 10 year and 14 year mortality the calculator sorts patients correctly 73% and 72% of the time.
- Calibration: The model was well calibrated across all risk levels with less than 10% difference between estimated and actual mortality.



Guidelines Breast
Version 2024.1E

Lee-Schonberg Index
https://eprognosis.ucsf.edu/leeschonberg-result.php

Risk Calculator questions

1. How old is your patient?
2. What is the sex of your patient?
3. What is your patient‘s BMI?
4. Which best describes your patient's health in general?
5. Does your patient have chronic lung disease, such as emphysema or chronic bronchitis?
6. Has your patient ever had cancer (excluding minor skin cancers)?
7. Does your patient have congestive heart failure?
8. Does your patient have diabetes or high blood sugar?
9. Which best describes your patient's cigarette use?
10. Does your patient have difficulty walking 1/4 mile (several city blocks) without help from other people or special equipment?
11. During the past 12 months, how many times was your patient hospitalized overnight?
12. Because of a physical, mental or emotional problem, does your patient need the help of others in handling routine needs such as everyday household chores, doing necessary business, shopping, or getting around for other purposes?
13. Because of a health or memory problem, does your patient have difficulty managing money - such as paying bills and keeping track of expenses?
14. Because of a health or memory problem, does your patient have difficulty with bathing or showering?
15. Because of a health problem, does your patient have difficulty pushing or pulling large objects like a living room chair?

Anthracycline-free Taxan / Carboplatin based Regimen for HER2+

Guidelines Breast
Version 2024.1E

Regimen	Ppts. (n)	pCR rate (%)	OUTCOME
6 x TCH (TRIO B07)	34	47	Not published
6 x TCHP (TRYPHAENA)	75	64	3-yr-DFS: 90%
6 x TCHP (KRISTINE - TRIO - 021)	221	56	3-yr-EFS: 94.2
4 x TCHP (NSABP- B52; nur HR+)	155	41	Not published
9 x TxCHP (TRAIN-2)	206	68	3-yr-EFS: 93.6%

T Docetaxel, Tx Paclitaxel, C Carboplatin, H Trastuzumab, P Pertuzumab

Guidelines Breast
Version 2024.1E

Neoadjuvant Systemic Chemotherapy Clinical Benefit

	Oxford	
	LoE	GR
▪ Leads to improvement of prognosis by individualization of neoadjuvant and post-neoadjuvant therapy (data most consistent for HER2pos and TNBC)	1b	A
▪ Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and number of cycles), if the postneoadjuvant therapy is not stratified according to pathologic response	1a	A
▪ Pathological complete response is associated with improved survival	1b	A
▪ The RCB Score and the class of RCB are subtype independent prognostic factors	2a	B
▪ Can achieve operability in primary inoperable tumors	1b	A
▪ Improved options for breast conserving surgery	1b	A
▪ Decreases rate of axillary lymphadenectomies lymphonodectomies	2b	B
▪ Allows individualization of therapy according to mid-course treatment effect	1b	B

Guidelines Breast
Version 2024.1E

Neoadjuvant Systemic Chemotherapy - Indications

	Oxford		
	LoE	GR	AGO
▪ If similar postoperative adjuvant chemotherapy is indicated	1b	A	++
▪ To allow a risk adapted postoperative therapy (data most consistent for HER2 pos and TNBC)	1b	A	++
▪ Inflammatory breast cancer	2b	B	++
▪ Inoperable breast cancer	1c	A	++
▪ Large operable breast cancer requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation	1b	B	++

Neoadjuvant Systemic Chemotherapy (NACT)
Predictive Factors for pCR I

Guidelines Breast
Version 2024.1E

Factor	pCR* Probability	Oxford LoE	Oxford GR	Oxford AGO
▪ Young age	↑	1a	A	+
▪ Obesity	↓	2a	B	+
▪ cT1 / cT2 tumors o. N0 o. G3	↑↑	1a	A	++
▪ Negative hormone receptor status	↑↑	1a	A	++
▪ Triple negative breast cancer	↑↑	1a	A	++
▪ Positive HER2-status	↑↑	1a	A	++
▪ Early clinical response	↑	1b	A	+
▪ Lobular tumor type	↓	1a	A	+
▪ Metaplastic tumor type	↓↓	4	C	+

* High (↑) or very high (↑↑) probability to reach pCR, low (↓) or very low(↓↓) probability to reach pCR; See aso chapter „Prognostic and predictive factors“

Guidelines Breast
Version 2024.1E

Neoadjuvant Systemic Chemotherapy (NACT) Predictive Factors for pCR II

Factor	pCR* Probability	Oxford LoE	Oxford GR	AGO
▪ Gene expression profiles (gene signatures) (Mammaprint®(+ Blueprint®), Endopredict® Oncotype DX®, Prosigna®, PAM50®, Breast Cancer Index^{SM})	↑	2b	B	+/-
▪ HER2DX (27 genes, response to trastuzumab / pertuzumab)	↑	2b	B	+/-
▪ Ki-67	↑	2b	B	+
▪ Tumor infiltrating lymphocytes**	↑	2a	B	+
▪ *PIK3CA* mutation (for HER2-positive BC)	↑	2a	B	+/-
▪ *gBRCA*-mutation (for the effect of chemotherapy)	↑	2b	B	+
▪ *gBRCA*-mutation (for the effect of platinum)	↔	2b	B	+/-

* High (↑) or very high (↑↑) probabililty of pCR, low (↓) or very low (↓↓) probabililty of pCR

** Defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front (lymphocytes make up > 50% of stroma area)

Guidelines Breast
Version 2024.1E

Neoadjuvant Systemic Chemotherapy Recommended Regimens

	Oxford		
	LoE	GR	AGO
▪ Use of adjuvant standard regimens for NACT*	1a	A	++
▪ Taxane mono followed by anthracycline (reverse order)	4	D	+/-
▪ Platinum in TNBC (cT1 / cN+ or cT2) (irrespective of BRCA status)	1b	A	+
▪ Platinum in TNBC (from cT1 / cN+ or cT2) (irrespective of BRCA status)	1a	A	+
▪ Nab-paclitaxel weekly instead of paclitaxel qw1 (in TNBC)	1a	A	+
▪ Pembrolizumab in combination with carbo / paclitaxel → 4x EC q3w (TNBC**)	1b	B	+

* See chapter Adjuvant Chemotherapy;
** > 2 cm or cN+, PD-L1 independent

Guidelines Breast
Version 2024.1E

Recommended Regimen in Triple Negative Breast Cancer

	Oxford		
	LoE	GR	AGO
Non-platinum-containing regimen			
ddEC x 4 → $pacli_{80}$ q1w x 12	1b	B	++
$NabPac_{125}$ q1w x 12 → $E_{90}C$ q(2)3w x 4	1b	B	+/-
Platinum-containing regimen			
$NabPac_{125}$ / $carbo_{AUC\ 2}$ q1w x 8 → ddEC x 4	1b	B	+
$Pacli_{80}$ q1w x 12 / $carbo_{AUC\ 6}$ q3w x 4 → ddAC / ddEC x 4	1b	B	+
Docetaxel / $carbo_{AUC6}$ q3w x 6 or paclitaxel/$carbo_{AUC1,5}$ q1w x18	2b	B	+
$NabPac_{1oo}$ / $carbo_{AUC\ 6}$ q4w x 4	2b	C	+
Checkpoint inhibitors			
$Pembro_{200}$ q3w + Pac_{80} / $carbo_{AUC\ 1,5}$ q1w x 12 → $E_{90}C$ q3w x 4	1b	B	+
$Pembro_{200}$ q3w + Pac_{80} q1w x 12 / $carbo_{AUC\ 5}$ q3w → $E_{90}C$ q3w x 4	1b	B	+

ICPi plus Neoadjuvant Chemotherapy for Patients with Triple Negative Breast Cancer

Guidelines Breast
Version 2024.1E

	GeparNuevo	IMpassion031	Keynote 522	neoTRIP
Phase	II	III	III	II
N	174	333	602 (pCR) 1174 (EFS)	280
Prim. endpoint	pCR	pCR	pCR + EFS	EFS
CPi	Durvalumab (24-26 weeks)	Atezolizumab (1 y)	Pembrolizumab (1 y)	Atezolizumab (24 weeks)
Chemo	$NabPac_{125}$ q1w x12 → EC q2w x4	$NabPac_{125}$q1w x12 → EC q2w x4	Pac q1w x12 + carbo q3w AUC 5 or q1w AUC 1,5 → AC/EC q3w x4	$NabPac_{125}$ + carbo AUC 2 q1w d1 and d8
Inclusion criteria	cT1b-cT4a-d	cT2-cT4, cN0-cN3	cT1cN1-2 or cT2 N0-2	cT1cN1; cT2cN1; cT3cN0
PD-L1 positive	87%	46%	83%	56%
pCR ITT	53.4% vs. 44.2% Δ 10.8% (n.s.)	57.6% vs. 41.2% Δ 16.5% (p < 0.01)	64.8% vs. 51.2% Δ 13.6% (p < 0.00055)	48.6% vs. 44.4% Δ 4.2% (n.s.)
pCR PD-L1 positive	58% vs. 50%	69% vs. 49%	69% vs. 55%	33,9% vs. 35.4%
pCR PD-L1 negative	44% vs. 18%	48% vs. 34%	45% vs. 30%	32% vs. 32%
Follow up/EFS/iDFS (months)/HR EFS/iDFS	43.7 months iDFS: 0.48 (p = 0.0389)	24 months EFS: 85% vs. 80% 0.76 (n.s.)	63.1 months EFS: 81,3% vs. 72,3% 0.63 (p = 0.00031)	54 months EFS: 70.6% vs. 74.9 % 1.076 (p = 0.76)
EFS/iDFS adjusted to pCR/non-pCR	pCR 95.5% vs. 86.1% npCR 76.3% vs. 69.7%	---	pCR 92. 2% vs. 88.2 % npCR 62.6 % vs. 52.3 %	pCR vs. non pCR 90.3% vs. 55.7%

Guidelines Breast
Version 2024.1E

Neoadjuvant Systemic Therapy
Recommended Methods of Monitoring of Response

	Oxford		
	LoE	GR	AGO
▪ Breast ultrasound	2b	B	++
▪ Palpation	2b	B	++
▪ Mammography	2b	B	++
▪ MRI	2b	B	+
▪ PET(-CT)	2b	B	+/-
▪ Pretherapeutical marking of tumor region	5	D	++
▪ Pretherapeutical diagnostic core needle biopsy and marking in case of of cN+ (CNB) (in case TAD is planned for ≤ 3 suspect lymph nodes)	2b	B	++*

(CNB: core needle biopsy; TAD: targeted axillary dissection;
*study participation recommended (AXSANA /Eubreast 3 Trial)

Neoadjuvant Targeted Therapy in HER2 Positive Tumors

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Pertuzumab + trastuzumab in combination with chemotherapy (high-risk defined as cT2-4 and / or cN+)	2b	B	++
▪ Trastuzumab in combination with stand polychemotherapy (low-risk)*	1b	A	+
▪ Anti-HER2 agents without chemotherapy	2b	B	+/-

* Single agent chemotherapy combined with trastuzumub should preferably be used in the adjuvant setting

Guidelines Breast
Version 2024.1E

Neoadjuvant Chemotherapy
Treatment Strategies Based on Clinical Response

	Oxford		
	LoE	GR	AGO
In case of early response			
▪ Completion of neoadjuvant chemotherapy	1b	A	++
In case of no change:			
▪ Completion of neoadjuvant chemotherapy (NACT) followed by surgery	2b	C	++
▪ Continuation of NACT with non cross-resistant regimen	2b	B	+
▪ AC or EC x 4 → D x 4 or Pw x 12	2b	B	+
▪ DAC x 2 → NX x 4	1b	B	+
In case of disease progression			
▪ Re-evaluation of tumorbiological factors	5	D	+/-
▪ Stop NACT and proceed to surgery or radiotherapy	4	D	++
▪ Additional adjuvant chemotherapy with non cross-resistant regimen	4	D	+/-

Guidelines Breast
Version 2024.1E

Axillary Surgery and NACT

cN status (before NACT)	pN status (before NACT)	ycN status (after NACT)	Axillary surgery (after NACT)	AGO	ypN status (after NACT and surgery)	Surgical consequence based on histopathology	Oxford LoE	Oxford GR	AGO
cN0*	No surgery before NACT	ycN0	SLNE	++	ypN0 (sn)	none	2b	B	++
					ypN0 (i+) (sn)	ALND	2b	C	+/-
					ypN1mi (sn)	ALND	2b	C	+
					ypN1 (sn)	ALND	2b	C	++

* Study participation in EUBREAST-01 recommended

Axillary Surgery and NACT (cN+)

cN status (before NACT)	pN status (before NACT)	ycN status (after NACT)	Axillary surgery (after NACT)	AGO	ypN status (after NACT and surgery)	Surgical consequence based on histopathology	Oxford LoE	Oxford GR	AGO
cN+*	$pN+_{CNB}$	ycN0	ALND	+	ypN0 / ypN+	none	2b	B	++
			TAD	+	ypN0	none	2b	B	+
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ inkl. ypN1mi	ALND	2b	B	+
			SLNE	+/-	ypN0	none	2b	B	+/-
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ inkl. ypN1mi	ALND	2b	B	+
			TLNE	+/-	ypN0	none	2b	B	+/-
					ypN0 (i+)	ALND	3b	B	+/-
					ypN+ inkl. ypN1mi	ALND	3b	B	+
		ycN+**	ALND	++	ypN0 / ypN+	none	2b	B	++

* Study participation in AXSANA recommended, ** Cave: In 30.3% false-positive findings, consider CNB if necessary

Guidelines Breast
Version 2024.1E

Neoadjuvant Systemic Therapy
Loco-regional Surgery (Breast)

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Pretherapeutic discussion in a multidisciplinary tumor board (e.g. to define the surgical procedure)	1a	B	++
▪ Early marking of tumor (incl. detailed topographic documentation)	5	D	++
▪ Surgical removal of tumor / representative excicion of posttherapeutic, marked tumorareal	2b	C	++
▪ Tumor resection in new margins	2b	C	++
▪ Microscopically clear margins	2a	B	++

Guidelines Breast
Version 2024.1E

Neoadjuvant Systemic Therapy
Indications for Mastectomy

	Oxford		
	LoE	GR	AGO
▪ Positive margins after repeated excisions	3b	C	++
▪ Radiotherapy not feasible	5	D	++
▪ In case of clinical complete response			
▪ Inflammatory breast cancer (in case of pCR)	2b	C	+/-
▪ Multicentric lesions	2b	C	+/-
▪ cT4a-c breast cancer	2b	B	+/-

Guidelines Breast
Version 2024.1E

Neoadjuvant Systemic Therapy
Timing of Diagnosis, Surgery and Radiotherapy

	Oxford		
	LoE	GR	AGO
Initiation of therapy Delay of therapy associated with worse prognosis	2b	B	+
Timing of surgery 4-8 weeks after last course of chemotherapy	2a	B	++
Radiotherapy within 2 months after surgery	2b	B	++

Neoadjuvant endocrine Therapy (NET)
- Good clinical practice -

Guidelines Breast
Version 2024.1E

- **Suitable for patients who are**
  - **inoperable**
  - **not able or willing to undergo chemotherapy**
- **Data for premenopausal in contrast to postmenopausal patients is limited**
- **Optimale duration of NET is at least 4-6 months or until best repsonse or progression**
- **Choice of endocrine therapy is based on the menopausal status**
- **Ki-67 analysis after preoperative short term endocrine therapy for 2 to 4 weeks may predict response to endocrine treatment (prognostic / predictive evaluation)**

Neoadjuvant Endocrine Therapy in Patients with Endocrine-responsive Breast Cancer

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ **Postmenopausal patients:**			
▪ **Optimizes the option for breast conserving therapy**	1b	A	+
▪ **Aromatase inhibitors (at least 6 months)**	1a*	B	+
▪ **Aromatase inhibitor + lapatinib (HER2+ BC)**	2b	B	+/-
▪ **Premenopausal patients**			
▪ **Tamoxifen**	2b	C	+
▪ **Aromatase inhibitors + LHRHa**	1b	C	+/-
▪ **Concurrent chemo-endocrine therapy**	1b	A	-
▪ **Ki-67 analysis after preoperative short term endocrine therapy for 2 to 4 weeks (Tam / AI ± GnRha) (prognostic / predictive evaluation information)**	1b	B	+
▪ **Prognostic score:**	1b	B	+
▪ **PEPI: pTN-Stage, ER expression and Ki-67 expression after neoadjuvant endocrine therapy**			

* **No long term results for neoadjuvant endocrine therapy (vs. adjuvant endocrine therapy)**

Guidelines Breast
Version 2024.1E

Postneoadjuvant Therapy HR+ / HER2-

	Oxford		
	LoE	GR	AGO
HR positive (pCR and non-pCR)			
▪ Endocrine therapy according to menopausal state (s. chap. 10)	1a	A	++
▪ Abemaciclib for 2 yrs + endocrine therapy[1]	1b	B	+
▪ Olaparib for 1 yr + endocrine therapy (g*BRCA1/2*^{MUT}, if non-pCR and CPS-EG Score ≥ 3)[2]	1b	A	++
▪ Capecitabine (non-pCR)	1b	A	+/-

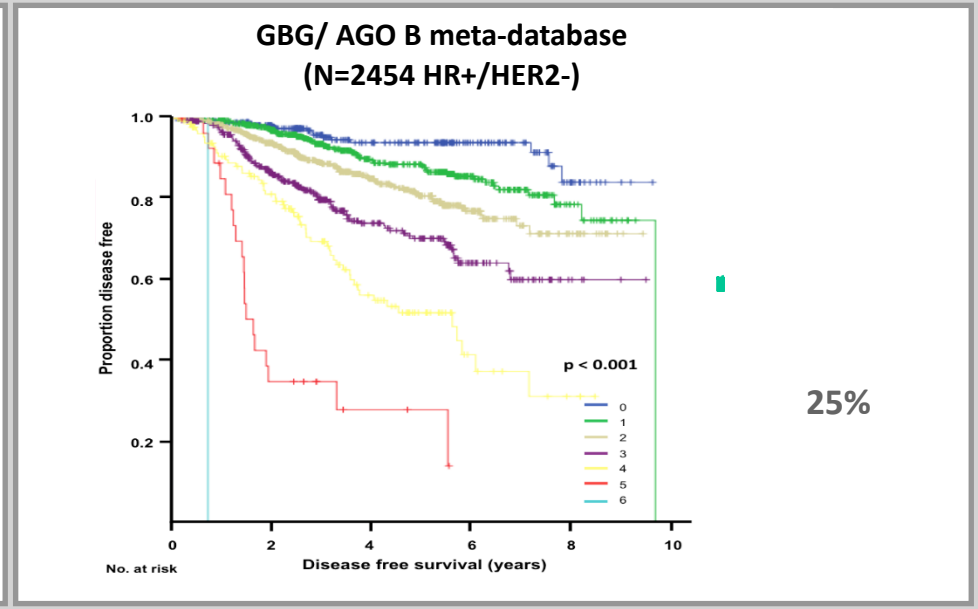
[1] According inclusion criteria monarchE-study,
[2] According inclusion criteria OlympiA-study

How to calculate CPS+EG Score?

Guidelines Breast
Version 2024.1E

Point assignment for CPS+EG score

Clinical Stage		
I	0	T1N0; T0N1mi, T1N1mi
IIA	0	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2N2
IIIB	2	T4N0-2
Pathologic Stage		
0	0	T0/isN0
I	0	T1N0; T0N1mi, T1N1mi
IIA	1	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2 N2
IIIB	1	T4 N0-N2
Tumor Biologic Factors		
ER negative	1	
Nuclear grade 3	1	



Mittendorf EA, J Clin Oncol 2011;
Marmé F, et al. Eur J Cancer 2016

Adjuvant / Post-Neoadjuvant Treatment with CDK4/6i

Guidelines Breast
Version 2024.1E

	monarchE	PALLAS	PENELOPE[B]	NATALLEE
N	5,637	5,600	1,250	5101
CDK4/6i	Abemaciclib	Palbociclib	Palbociclib	Ribociclib
% of pts. with NACT	37%	n.r.	100%	88%
Duration of CDK4/6i treatment	24 months	24 months	12 mths	36 months
Follow-up	42.0 months	24 months	43 months	33,3 months
Discontinuation rate	28%	42%	20%	35,5%
Discontinuation rate due to AE_{CDKi}	17%	27%	5%	19.5%
IDFS-HR (95%-CI)	0.664 (0.578-0.762) p < 0.0001	0.96 (0.81-1.14) p = 0.65	0.93 (0.74-1.16) p = 0.525	0.749(0,628-0.892) p = 0.0006
2-yrs IDFS	92.7% vs. 89.9%	n.r.	88% vs. 78%	93.5% vs. 92.0%
3-yrs IDFS	89.2% vs. 84.4%	88% vs. 89%	81% vs. 78%	90.7% vs. 87.6%
4-yrs IDFS	85.8% vs. 79.4%	84.2% vs. 84.5%	73% vs. 72%	

IDFS: invasive disease-free survival

Guidelines Breast
Version 2024.1E

Postneoadjuvant Therapy TNBC

	Oxford		
	LoE	GR	AGO
pCR			
▪ Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)	1b	B	+
Non-pCR			
▪ Capecitabine (q3w up to 8 courses)[1]			
▪ With non-pCR after A-T-containing chemotherapy[1]	1a	A	++
▪ With non-pCR after platinum +/- pembrolizumab-containing therapy	5	D	+/-
▪ Platinum salts (carboplatin or cisplatin) q3w after AT-pretreatment	1b	B	+/-
▪ Olaparib (*gBRCA*^{MUT})[2]	1b	A	++
▪ Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)	1b	B	++

[1] in stage II-III without platinum/pembrolizumab-based pretreatment
[2] according inclusion criteria of OlympiA trial, advantage especially with platinum-free NACT

Guidelines Breast
Version 2024.1E

Postneoadjuvant Therapy HER2-positive

	Oxford LoE	Oxford GR	AGO
pCR			
▪ Low risk: Trastuzumab (to complete 12 mths)	2a	C	++
▪ High risk (cN+): Trastuzumab + Pertuzumab (to complete 12 mths)	2b	C	+
▪ Neratinib after 1 year Trastuzumab (HR-positive, stage II-III)*	2b	B	+/-
non-pCR			
▪ T-DM1	1b	B	++
▪ Trastuzumab + Pertuzumab (to complete 12 mths)	2b	C	+
▪ Additional HER2-directed therapy after 1 yr (extended adjuvant th.)			
▪ Neratinib after Trastuzumab (HR-positive, stage II-III)*	2b	B	+
▪ Neratinib after other HER2-directed therapies (HR-positive, stage II-III)*	5	D	+/-

* In combination with standard endocrine treatment

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

Adjuvant Radiotherapy

Guidelines Breast
Version 2024.1E

Adjuvant Radiotherapy (RT)

- **Versions 2002 – 2023:**
  Blohmer / Budach / Friedrich / Friedrichs / Göhring / Huober / Janni / Krug / Kühn / Möbus / Rody / Scharl / Schmidt / Seegenschmiedt / Solbach / Souchon / Thomssen / Untch / Wenz

- **Version 2024:**
  Blohmer / Budach / Krug

Guidelines Breast
Version 2024.1E

Preliminary Note

- **The recommendations on adjuvant radiotherapy for breast cancer are based on a consensus discussion between AGO and DEGRO experts.**
- **For technical radiotherapy details, we refer to the corresponding updated DEGRO practical guidelines.**

Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer): Whole Breast Irradiation

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Radiotherapy of the affected breast	1a	A	++
▪ Moderately hypofractionated radiotherapy (total dose approx. 40 Gy in 15-16 fractions within 3-5 weeks	1a	A	++
▪ Ultra-hypofractionated RT (total dose 26 Gy in 5 fractions over one week = 1 fraction/day or 28.5 Gy in 5 fractions over 5 weeks = 1 fraction/week)	1b	B	+/-
▪ Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions in 5-6 weeks)	1a	B	+
▪ In case of life expectancy < 10 years and pT1, pN0, R0, ER / PR-positive, HER2-negative, endocrine therapy (all criteria), radiotherapy can be omitted after individual counseling, resulting in an increased risk for in-breast recurrence without imparing survival.	1a	B	+

Randomized controlled trials of radiotherapy omission after breast-conserving surgery in early breast cancer

Guidelines Breast
Version 2024.1E

Trial	N	Time-frame	Inclusion criteria	Follow up	Local recurrence (no RT)	Local recurrence (RT)	Hazard ratio
Toronto-British Columbia	769	1992-2000	≥ 50 years, T1/2 N0 R0 (ink) 80% HR+	5 y 8 y	7.7% 17.6%	0.6% 3.5%	8.3
BASO-II	204	1992-2000	< 70 J., T1, G1 L0	5 y	0.8% p.a.	0.2% p.a.	7.34
CALGB 9343	636	1994-1999	≥ 70 years, T1 (98%) cN0 ER+ (97%), R0 (ink)	5 y 10 y	4% 8%	1% 2%	5.55
ABCSG-8A	831	1996-2004	Postmenopausal T ≤ 3 cm N0, G1/2, ER+ and/or PR+	5 y 10 y	5.1% 7.5%	0.4% 2.5%	10.2
PRIME II	1326	2003-2009	≥ 65 years, T ≤ 3 cm N0, ER+ and/or PR+, R0 (≥1 mm)	5 y 10 y	4.3% 9.8%	1.3% 0.9%	10.4

Prospective observational studies of radiotherapy omission incorporating tumor biology and MRI

Trial	N	Time-frame	Inclusion criteria	Follow up	Local recurrence (95%-CI)
LUMINA	500	2013-2017	≥ 55 years, pT1 pN0 R0 (≥1 mm) **ER ≥1% PR ≥20% HER2 neg. Ki67 ≤ 13.25% (central lab)**	5 y	2.3% (1.2-4.1%)
IDEA	200	2015-2018	50-69 years, pT1 pN0 R0 (≥2 mm) **ER/PR pos. HER2 neg., Oncotype Dx RS ≤ 18**	5 y	50-59 y. 3.3% 60-69 y. 3.6%
PROSPECT	201	2011-2019	≥50 years, unifocal cT1 cN0, no LVI, no EIC, R0 (≥2 mm), ER/PR pos. and/or HER2-pos., **preoperative breast MRI**	5 y	1.0% (-5.4%)

- Discussion:
  - Confidence intervals of local recurrence (LR) rates overlap with control arms of previous trials.
  - Uncontrolled trials with limited follow up.
  - CALGB 9343 and PRIME II showed a doubling LR rates after 10 years vs. 5 years in the control arms and an increasing benefit of radiotherapy with longer follow-up.
  - In PRIME II, low ER expression was associated with an increased LR rate in the control arm.
  - Compliance for endocrine therapy was higher than expected in clinical routine.

Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer) – Boost Irradiation

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
Boost-RT (improves local control, no survival benefit)			
Premenopausal	1b	B	++
Postmenopausal, if > T1*, G3, HER2-positive, triple negative, EIC (at least 1 factor)	2b	B	+
Techniques			
Percutaneous boost (photons, electrons) as sequential boost	1a	A	++
Multicatheter brachytherapy-boost	1a	A	++
Percutaneous boost as simultaneous integrated boost (with hypofractionated whole-breast irradiation)	1b	B	+
Percutaneous boost as simultaneous integrated boost (with conventionally fractionated whole-breast irradiation)	1b	B	+
Intraoperative boost irradiation (followed by whole-breast irradiation)	2b	B	+
Intraoperative clip placement at the tumor bed if boost irradiation is indicated	2b	B	+

* continuous parameter with regard to risk of relapse

EORTC 22881-10882: Boost vs no Boost (Endpoint: Ipsilateral Breast Recurrence)

@20 yrs (95% C.I.)	Boost (n = 2.661)	No boost (n = 2.657)	Hazard Ratio (95% C.I.)
Overall Survival (Δ = -1.4%)	59.7% (56.3–63.0)	61.1% (57.6–64.3)	HR 1.05 (0.92–1.19) n.s.
Cumulative Risk of Ipsilateral Breast Tumour Recurrence			
All patients	12.0% (9.8–14.4)	16.4% (14.1–18.8)	HR=0.65 (0.52–0.81); p < 0.0001
≤ 40 years (Δ = 11.6%)	24.4% (14.9–33.8)	36.0% (25.8–46.2)	HR=0.56 (0.34–0.92); p = 0.003
41–50 years (Δ = 5.9%)	13.5% (9.5–17.5)	19.4% (14.7–24.1%)	HR=0.66 (0.45–0.98); p = 0.007
51–60 years (Δ = 2.96%)	10.3% (6.3–14.3)	13.2% (9.8–16.7)	HR=0.69 (0.46–1.04); p = 0.020
> 60 years (Δ = 3.0%)	9.7% (5.0–14.4)	12.7% (7.4–18.0)	HR=0.66 (0.42–1.04); p = 0.019

(Median F/U 17.2 y)

acc. to: Bartelink et al. Lancet Oncol 2015; 16: 47–56

Guidelines Breast
Version 2024.1E

EORTC 22881-10882: Boost vs. no Boost (Endpoint: Any First Recurrence)

@15 yrs/20 yrs (95% C.I.)	Boost (n = 2.661)		No boost (n = 2.657)	Hazard Ratio (95% C.I.)
Overall Survival (Δ = - 1.4%)	59.7% (56.3–63.0)		61.1% (57.6–64.3)	HR 1.05 (0.92–1.19) n.s.
Cumulative Risk of Any First Recurrence				
All patients (Δ ≥ 4%)	@15y @20y	28.1% 32,8%	32.1% 38.7%	HR = 0.92 (0.81-1.04), n.s.
≤ 40 years (Δ > 6%)	@15y @20y	41.5% 49.5%	48.1% 56.8%	HR = 0.80 (0.56-1.15) , n.s.
41–50 years	@15y @20y	34.0% 38.6%	35.6% 44.2%	HR = 0.91 (0.71-1.16), n.s.
51–60 years	@15y @20y	28.5% 34.7%	28.7% 36.2%	HR = 0.96 (0.76-1.21), n.s.
> 60 years	@15y @20y	27.4% 32.1%	29.1% 32.8%	HR = 0.94 (0.74-1.19), n.s.

(Median F/U 17.2 y)

acc. Bartelink et al. Lancet Oncol 2015; 16: 47–56. Suppl.

Moderate hypofractionation with simultaneous-integrated boost

	RTOG 1005 (ASTRO 2022)	**IMPORT-HIGH (Lancet 2023)**
Patient number	2262	2617
Schedule Breast	40 Gy in 15 fx	36 Gy in 15 fx 40 Gy in 15 fx
Schedule Boost	48 Gy in 15 fx	48 Gy in 15 fx vs. 53 Gy in 15 fx
Ipsilateral in-breast recurrence at 5 years	HR 1.32 (0.8-2.1) → Non-inferiority for SIB	HR 1.04 (0.56-1.92) → Non-inferiority for 48 Gy (absolute diff.) HR 1.76 (1.01-3.04) → Inferiority for SIB 53 Gy (absolute + relat.)
Toxicity	Toxicity grade ≥3 (ROTG) p = 0.79	Any moderate / marked breast AE p = 0.041 for SIB 48 Gy vs. sequential boost (less toxicity with SIB) p = 0.823 for SIB 53 Gy vs. sequential boost

Partial Breast Irradiation (PBI) after Breast Conserving Surgery (Invasive Cancer)

	Oxford		
	LoE	GR	AGO
▪ **Only for pT1 pN0 R0 G1-2, HR+, non-lobular, > 50 years, no extensive DCIS. For definition of target volume and practical conduct see DEGRO practical guidelines**			
▪ **Postoperative partial breast irradiation**			
▪ **Interstitial Multicatheter-Brachytherapy**	1b	A	+
▪ **Intracavitary balloon-technique**	2b	B	-
▪ **Intensity-modulated radiotherapy (IMRT) (5 x 6 Gy in 1.5 weeks)**	1b	A	+
▪ **3D-conformal radiotherapy (15 x 2.67 Gy in 3 weeks)**	1b	A	++
▪ **3D-conformal radiotherapy (10 x 3.85 Gy in 1 week)**	1b	A	-
▪ **Intraoperative Radiotherapy**			
▪ **As sole radiotherapy, during first breast surgery (IORT 50 kV, IOERT)**			
▪ **> 50 years**	1b	A	+/-
▪ **> 70 years**	1b	A	+
▪ **Intraoperative clip placement at the tumor bed if partial breasst irradiation is indicated**	2b	B	+

Meta-analyses on partial-breast irradiation

Guidelines Breast
Version 2024.1E

Meta-analysis of 13 studies with 15,561 patients comparing partial breast irradiation (PBI) and whole-breast irradiation (WBI), median follow-up 8.6 years; Odds Ratio (95%-confidence interval)

	Overall	EBRT	EBRT/BT	BT	IORT	Absolute diff.
Local recurrence (primary site)	1.01 (0.65-1.59)	0.85 (0.52-1.39)	0.84 (0.56-1.27)	0.87 (0.25-3.02)	**3.51 (1.36-9.11)**	+0.02%
Local recurrence (elswhere)	**2.21 (1.53-3.20)**	**2.26 (1.12-4.55)**	**2.07 (1.31-3.27)**	7.88 (0.42-146)	3.06 (0.1-91.59)	+0.64%

Meta-analysis of 11 studies with 15,438 patients comparing partial breast irradiation (PBI) and whole-breast irradiation (WBI); Hazard Ratio (95%-confidence interval)

	Overall	EBRT	EBRT/BT	BT	IORT
Overall survival	1.02 (0.89-1.16)	1.06 (0.83-.37)	1.10 (0.90-1.35)	0.64 (0.36-.12)	0.95 (0.72-1.24)

EBRT = external beam RT; BT = brachytherapy, IORT = intraoperative RT; EBRT/BT = both techniques were allowed on trial

Comparison of different techniques for partial breast irradiation

	Intraoperative radiotherapy	Multicatheter interstitial brachytherapy	External-beam radiotherapy
Advantages	• Shortest possible treatment time • Direct visualization of the tumor bed	• High conformality • Longest available follow-up	• Broad availability • Reproducibility
Disadvantages	• Lack of complete knowledge of risk factors (e.g. margin status, lympho-vascular invasion) • Potentially increased risk of fibrosis with additional whole-breast irradiation • Availability limited to specialized centers • Prolongation of anesthesia	• Availability limited to specialized centers with high expertise • Additional invasive procedure • Additional hospital stay • Risk of target miss due visualization of the tumor bed	• Risk of target miss due visualization of the tumor bed • Larger irradiated volume due to intra- and interfractional motion

Guidelines Breast
Version 2024.1E

Postmastectomy Radiotherapy (PMRT)* to the Chest Wall – Indication

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ > 3 tumor infiltrated lymph nodes (LN)	1a	A	++
▪ 1–3 tumor infiltrated LN (high-risk)	1a	A	+
▪ 1–3 tumor infiltrated LN (low-risk*)	5	D	+/-
▪ T3 / T4	1a	A	++
▪ pT3 pN0 R0 (and no additional risk factors)	2b	B	+/-
▪ If R0 is impossible to reach (for invasive tumor)	1a	A	++
▪ In young pts with high-risk features	2b	B	++
The indications for PMRT and regional RT are independent of adjuvant systemic treatment	1a	A	
Inflammatory breast cancer: PMRT and regional nodal irradiation	2c	B	++

* For definition of low-risk, see next slide Radiotherapy of the Chest Wall After Mastectomy (PMRT)

Guidelines Breast
Version 2024.1E

Postmastectomy Radiotherapy (PMRT)* to the Chest Wall* – Fractionation

	Oxford		
	LoE	GR	AGO
▪ Moderately hypofractionated radiotherapy (total dose approx. 40 Gy in 15-16 fractions within 3-5 weeks	1a	A	++
▪ After breast reconstruction	1b	B	+
▪ Ultra-hypofractionated RT (total dose 26 Gy in 5 fractions over one week = 1 fraction/day or 28.5 Gy in 5 fractions over 5 weeks = 1 fraction/week)	1b	B	+/-
▪ Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions in 5-6 weeks)	1a	B	+

* Regarding fractionation for regional nodal irradiation, refer to slide „Fractionation of Radiotherapy in Case of Regional Nodal Irradiation“.

Radiotherapy of the Chest Wall After Mastectomy (PMRT) in Case of 1-3 Axillary Lymph Node Metastases

Guidelines Breast
Version 2024.1E

PMRT can be omitted **LoE 3b B AGO +**	PMRT to be discussed **LoE 3b B AGO +/-**	PMRT recommended **LoE 3b B AGO +**
ER pos, G1, HER2 neg, pT1 (at least 3 criteria present)	Patients, who don't fulfill the mentioned criteria for high or low risk	≥ 45 y. AND > 25% pos. ax. Lnn in case of axillary dissection OR <45 y. AND (ER neg. OR>25% pos. ax. Lnn in case of axillary dissection OR medial tumor location)
Kyndi et al. 2009		Truong et al. 2005
		< 40 y. OR HER2 pos. OR lymphovascular invasion
		Shen H et al. 2015
		G3 OR lymphovascular invasion OR triple negative
		Different publications

Comment: In case of an indication for radiotherapy of regional lymph nodes, radiotherapy of the chest wall should also be administered

Guidelines Breast
Version 2024.1E

Boost in PMRT

	Oxford		
	LoE	GR	AGO
▪ An additional boost irradiation to a part of the chest wall has not been shown to improve DSS and overall survival	2a	B	
▪ An additional boost irradiation to a part of the chest wall should be given in case of of R1 / R2-resection, if secondary resection is not feasible	5	D	++
▪ In case of tumor extention to the pectoral resection margin, but no clinical signs of extention beyond the fascia, the resection margin should be regarded as R0 (provided, that the pectoral fascia was resected). A boost radiotherapy is not required in this situation	5	D	++

Radiotherapy of Axillary Lymph Nodes in Patients with Positive Sentinel-Lymph Nodes**, Who Did not Undergo Axillary Dissection

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
BCS and ACOSOG Z0011-criteria⁺ met	2b	B	+*
▪ **Radiotherapy of the breast including LN level 1 + 2 to 5 mm below the axillary vein (PTV)**			
BCS and ACOSOG Z0011-criteria⁺ not met	1b	B	++*
▪ **Radiotherapy of the axillary lymph nodes (analog AMAROS)**			
ME and chest wall RT indicated and ACOSOG Z011-criteria⁺ not met or ME and chest wall RT not planned			
▪ **Radiotherapy of the axillary lymph nodes (analog AMAROS)**	1b	B	++
≥ 3 pos. SLN			
▪ **Radiotherapy of the axillary lymph nodes (analog AMAROS)**	1b	B	+

* Study participation recommended

** Macrometastases

⁺ < T3, no palpable LN, R0, 1-2 positive SN, no NACT

Guidelines Breast
Version 2024.1E

Additional RT of the Axilla after Primary Surgery

(in case of an indication for RT of the breast/chest wall[1] +/- supra-/infraclavicular and internal mammary node RT[2])

Expansion of the PTV (planning target volume) to level I-II[3]

	Oxford		
	LoE	GR	AGO
pN-status			
pN0(sn) / pN1mic(sn)	1b	B	--
pN0/+ after ALND	1a	A	--
pN+(sn) in analogy to ACOSOG Z0011 (no ALND)	2b	B	+
pN+(sn) not fitting ACOSOG Z0011-criteria → RT in analogy to AMAROS[4] (no ALND)	1b	B	++
Extensive perinodal soft tissue involvement in the axilla	2b	B	+
Residual tumor in the axilla after ALND	5	D	++

[1]Incidental dose to parts of level i/II is inevitable. [2]The indication for supra-/infraclavicular and internal mammary node RT has to be assessed separately. [3]Cranial border 5 mm below the axillary vein. [4] < T3, no palpable LN, R0, 1-2 positive SN, no NACT, always in conjunction with supra-/infraclavicular RT

Guidelines Breast
Version 2024.1E

Additional RT of the Axilla after Neoadjuvant Therapy

(in case of an indication for RT of the breast/chest wall[1] +/- supra- / infraclavicular and internal mammary node RT[2])

Expansion of the PTV (planning target volume) to level I-II[3]

N-status pre/post NACT	pN-status	Oxford LoE	Oxford GR	AGO
cN0 / ycN0	ypN0(sn)	5	D	-
cN0 / ycN0	ypN1mic(sn) / ypN+(sn) (no ALND)	5	D	+[4]
$cN+_{CNB}$ / ycN0	ypN0 / ypN0(i+) (sn/TAD)	5	D	+/-[4]
$cN+_{CNB}$/ ycN0	ypN1mic(sn/TAD) / ypN+(sn/TAD) (no ALND)	5	D	+[4]
cN0/cN+	ypN0/+ after ALND	2b	B	-
cN0/cN+	Extensive perinodal soft tissue involvement in the axilla	2b	B	+
cN0/cN+	Residual tumor in the axilla after ALND	5	D	++

[1]Incidental dose to parts of level i/II is inevitable. [2]The indication for supra-/infraclavicular and internal mammary node RT has to be assessed separately. [3]Cranial border 5 mm below the axillary vein. [4]Study participation recommended.

Impact of axillary soft tissue involvement on regional recurrence

Guidelines Breast
Version 2024.1E

Naoum et al. J Clin Oncol 2023 Nov 15:JCO2301009. doi: 10.1200/JCO.23.01009.

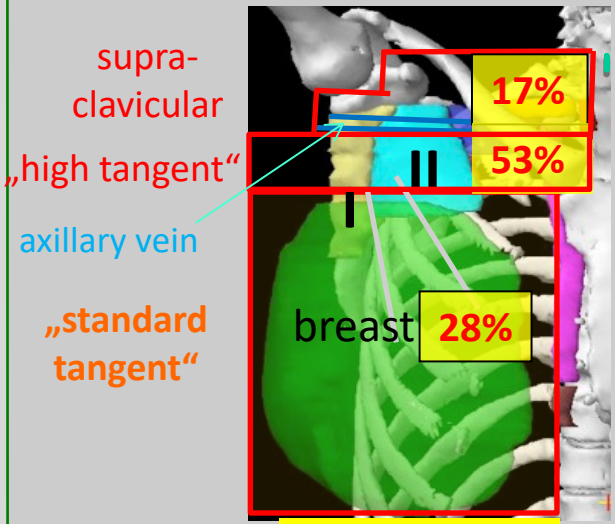
- Retrospective single center analysis, 2162 pat. with node-positive breast cancer treated 2000-2020.
- Analysis according to extracapsular extension (ECE) and axillary soft tissue involvement (AXT).
  - No ECE or AXT in 57.7%
  - ECE only in 24.9%
  - AXT only in 2.6%
  - ECE and AXT in 13.9%
- On multivariate analysis, AXT was significantly associated with distant failure (HR 1.61, $p < 0.001$), locoregional failure (HR 2.31, $p < 0.001$) and axillary failure (HR 3.33, $p = 0.003$).
- Regional nodal irradiation improved locoregional control in patients with ECT and/or AXT (HR 0.5, $p = 0.03$). Delivering a dose of < 50 Gy with conventional fractionation was associated with a higher risk of axillary failure.
- AXT was also associated with distant failure, locoregional failure and axillary failure in patients that underwent neoadjuvant chemotherapy.

Dose in the Axillary LN-levels I + II Using Different RT-Techniques

Guidelines Breast
Version 2024.1E

ACOSOG Z0011 Trial

45% micrometast. in the exp. arm



AMAROS

RT-volume
% of patients

Data from 228/856 pat.

	mean dose*	encompassed volume**
LN level 1		
AMAROS	> 95%	> 95%
high tangent	86%	79%
standard tangent	66%	51%
IMRT+	29%	1%
LN-level 2		
AMAROS	> 95%	> 95%
high tangent	71%	51%
standard tangent	44%	26%
IMRT+	7%	0%

* in relation to the prescribed dose in the breast

** % volume receiving the prescribed dose

\+ Lee et al. Medicine 2016 (3)

Jagsi (2): “The results of Z0011 should not be extrapolated to patients who receive RT using partial-breast or prone techniques, in which substantially less of the axilla is included”

Guidelines Breast
Version 2024.1E

Regional nodal irradiation

RT to the supra-/ infraclavicular and internal mammary region

	Oxford LoE	Oxford GR	AGO
≥ 4 involved axillary lymph nodes[1]	1a	A	++
1–3 involved axillary lymph nodes[1] • Central or medial tumor • HR-negative	1a	A	+
pN0 and premenopausal with central or medial tumor and G3 and HR-negative	1a	B	+
Clinical involvement of the above mentioned regions	2b	B	+
In case of left-sided breast cancer with elevated cardiac risk or if simultaneous HER2-targeted therapy is given	2b	A	-

[1] not applicable for micrometastases

Regional nodal irradiation: EBCTCG-metaanalysis 2023

	EBCTCG-metaanalysis („newer trials“, recruitment 1989 onwards)	
Patient number	12,167	
Median FU	13.7 years	
Design	7 randomized controlled trials and 1 national prospective cohort study	
Target volume	92% in the experimental arm had internal mammary irradiation	
Results	Absolute reduction at 15 years	Relative reduction
Any recurrence pN0 pN1-3 pN4+	2.6% 2.3% 2.9% 4.3%	RR 0.88 (95%-CI 0.81-0.95)
Breast-cancer mortality pN0 pN1-3 pN4+	3.0% 1.6% 2.7% 4.5%	RR 0.87 (95%-CI 0.80-0.94)
Mortality w/o recurrence	-3.0%	RR 0.90 (95%-CI 0.84-0.96)
Any death	-3.0%	RR 0.90 (95%-CI 0.84-0.96)

Guidelines Breast
Version 2024.1E

Guidelines Breast
Version 2024.1E

Fractionation of Radiotherapy in Case of Regional Nodal Irradiation

	Oxford		
	LoE	GR	AGO
▪ Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions within 5–6 weeks)	1a	A	++
▪ Moderately hypofractionated radiotherapy (total dose approx. 40–43.5 Gy in 15-16 fractions within 3–5 weeks)	1b	B	+
▪ Ultra-hypofractionated RT (total dose 26 Gy in 5 fractions over one week = 1 fraction/day)	2b	B	-

Hypofractionated regional nodal irradiation

Guidelines Breast
Version 2024.1E

	START-P/A/B subgroups	Wang et al.	DBCG Skagen 1 (Abstract)	HypoG-01
Patient number	864	820	2963	1265
Fractionation	39-42.9 Gy in 13-15 fx	43.5 Gy in 15 Fx	40 Gy in 15 Fx	40 Gy in 15 Fx
Median FU	10 years	58.5 months	3 years	3 years
Primary endpoint	Late normal tissue effects	Locoregional recurrence	Lymphedema at 3 years	Lymphedema at 3 years
Statistical design	Retrospective analysis	Non-inferiority	Non-inferiority	Non-inferiority
Results	No statistically significant differences for LRR or late normal tissue effects	Non-inferiority for LRR (primary analysis)	No increased risk of lymphedema or LRR (primary analysis)	Non-inferiority for lymphedema Superiority for LRR, DDFS, OS

Radiotherapy after NACT

Pretherapeutic	Posttherapeutic	RT-BCS	PMRT	RNI*	Oxford	
		AGO	AGO	AGO	LoE	GR
Locally advanced	pCR / no pCR	++	++	++	1a/1a/1a	A/A/A
cT1-3 cN1**	ypT+ ypN0	++	+	+/-[1]	1a/1b/1b	A/B/B
cT1-3 cN1**	ypT0/is ypN0	++	+/-[1]	+/-[1]	1a/1b/1b	A/B/B
cT1-3 cN0 / cN1** (Sonogr. obligatory)	ypN+ o. ypT3/4	++	+	+	1a/2b/2b	A/B/B
cT1-3 cN0 (Sonogr. obligatory)	ypT0/is ypN0	++	-	-	1a/2b/2b	A/B/B
cT1-3 cN0 (Sonogr. obligatory)	ypT1-2 ypN0	++	-	-	1a/2b/2b	A/B/B

Locally adcanced: T4 or cN2-N3

[1] Criteria for increased risk of relapse / benefit of locoregional radiotheray:
- Central/medial tumor, HR-negative, premenopausal, non-pCR in the breast, residual micrometastases in the axillary nodes, cT3

* Regarding coverage of axilla level I/II please also see slides „Additional RT of the axilla after primary surgery“ and „Additional RT of the axilla after neoadjuvant therapy“. ** = confirmed by core biopsy

Guidelines Breast
Version 2024.1E

Guidelines Breast
Version 2024.1E

Role of locoregional radiotherapy after neoadjuvant chemotherapy

Mamounas et al. SABCS 2023 – GS02-07 (NSABP B-51/RTOG 1304)

- Prospective randomized controlled trial, 1641 pts., 2013-2020, median follow-up 59.5 months
- cT1-3 cN1 (FNA/CNB) → ypN0 (SLNB/ALND) after standard neoadjuvant chemotherapy
- Randomization:
  - BCS: RT breast vs. RT breast + regional nodal irradiation
  - Mastectomy: No RT vs. Post-mastectomy RT + regional nodal irradiation
- Primary endpoint: Invasive breast cancer recurrence-free interval
  - 80% power to detect 4.6% absolute reduction (HR 0.65) – superiority trial, 172 events
- Patient characteristics: 80% cT1-2, 58% BCS, 55% SLNB, 78% pCR in breast, 20% TNBC, 20% Lum
- Results:
  - No improvement in BCRFI (HR 0.88), isolated locoregional recurrence-free interval (HR 0.37), distant recurrence-free interval (HR 1.00), DFS (1.06) and OS (HR 1.12)
- Discussion:
  - Short follow-up (benefit of RNI appeared in EBCTCG-metaanalysis after 10-15 years)
  - Underpowered for primary analysis (109/172 planned events)
  - Trial should have been designed as a non-inferiority trial
  - Underrepresented subgroups: cT3, ypT+
  - Not applicable to: cT4 cN2-3

Guidelines Breast
Version 2024.1E

Use of Concomitant Systemic Therapy with Adjuvant Locoregional Radiotherapy

	Oxford		
	LoE	GR	AGO
▪ Trastuzumab / Pertuzumab*	1a	A	++
▪ T-DM1	1b	A	+
▪ Tamoxifen	2b	B	+
▪ Aromatase inhibitors	2b	B	+
▪ Checkpoint inhibitors	2b	C	+
▪ Capecitabine**	2b	B	+
▪ CDK4/6-inhibitors***	4	C	+/-
▪ Olaparib****	2b	C	+/-

* Simultaneous parasternal RT should be avoided in patients with HER2-positive tumors and tumor-localisation on the left side

** With hypofractionated RT approx. 40 Gy, consider dose reduction of Capecitabine, Pat. with high risk for locoregional recurrence

*** In currently available phase III-trials (monarchE, PALLAS, Penelope-B) RT was given before initiation of CDK4/6-inhibitors. No definitive signs of significantly increased toxicity with concomitant RT in the palliative setting.

**** In currently available phase III-trials, RT was given before initiation of Olaparib.

Guidelines Breast
Version 2024.1E

Smoking and Risk of Secondary Lung Cancer

	Oxford		
	LoE	GR	AGO
▪ Increased risk of lung cancer secondary to breast cancer radiotherapy in smokers	1a	A	
▪ Inform patients about risk			++
▪ Recommend smoking cessation			++

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

Supportive Care and Management of Side Effects

Guidelines Breast
Version 2024.1E

Supportive Care and Management of Side Effects

- **Versions 2002–2023:**
  Albert / Bauerfeind / Brunnert / Bischoff / Costa / Dall / Diel / Fersis / Friedrich / Friedrichs / Gerber / Göhring / Hanf / Harbeck / Heinrich / Huober / Jackisch / Lisboa / Lück / Lüftner / Maass / von Minckwitz / Möbus / Müller / Mundhenke / Nitz / Oberhoff / Park-Simon / Reimer/ Rody / Schaller / Scharl / Schmidt / Schneeweiss / Schütz / Solomayer / Souchon / Stickeler / Thomssen / Untch

- **Version 2024:**
  Kolberg-Liedtke / Würstlein

Guidelines – Evidence

Specific national and international guidelines deal with various aspects of evidence-based supportive therapy of cancer patients.

Without claiming completeness, such guidelines will be quoted, with an emphasis on German guidelines.

Aspects concerning breast cancer patients will especially be highlighted.

The „Arbeitsgemeinschaft Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin der DKG“ should especially be highlighted (http://www.onkosupport.de).

<u>Multidisciplinary S 3 guidelines of the AWMF (Reg.-Nr. 032-054OL):</u>

- **S3-Leitlinie: Supportive Therapie bei onkologischen Patientinnen Langversion 1.3 –Februar 2020 AWMF-Registernummer: 032/054OL**

Guidelines Breast
Version 2024.1E

Toxicity Assessment

Acute Toxicity (according to WHO[1] or NCI-CTC[2])

Acute toxicities should be asked for and documented after every treatment course **LoE 5 D AGO ++**

Grade		Information required
0	none	organs involved
1	mild	type of toxicity
2	moderate	time interval after treatment
3	severe	effect on general health status
4	life threatening	treatment required
5	death	recovery achieved

Long term toxicity (= secondary diseases after tumour therapy)

Long term surveillance and documentation in regular intervals
(acc. ICPC[3] following symptoms or acc. ICD-10-GM[4] following diagnoses) **LoE 5 D AGO ++**

Acute Toxicity (NCI CTCAE v 5.0, 2017)

Guidelines Breast
Version 2024.1E

- **Grade 1**
  Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2**
  Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- **Grade 3**
  Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.**
- **Grade 4**
  Life-threatening consequences; urgent intervention indicated.
- **Grade 5**
  Death related to AE.

ADL = Activities of Daily Living

*** Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.**

**** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.**

Guidelines Breast
Version 2024.1E

Use of eHealth (DiGA)

	Oxford		
	LoE	GR	AGO
Use of DiGA to improve quality of life during and after breast cancer therapy	2b	B	+/-
Use of PROs for improved collection of therapy-associated side effects and quality of life	2b	B	+/-

* See current DiGA status / reimbursement

Chemotherapy – Acute Toxicities I

Guidelines Breast
Version 2024.1E

DRUGS	SYSTEM ORGAN CLASS											
	INFECTIONS AND INFESTATIONS	NEOPLASMS BEN., ALIGNANT AND NSPECIFIED (INCL CYSTS & POLYPS)	BLOOD & YMPH. SYST. ISORDERS	IMMUNE YSTEM DISORDERS (ALLERGIES)	ENDOCRINE DISORDERS	METABOLISM AND NUTRITION DISORDERS	PSYCHIATRIC DISORDERS	NERVOUS SYSTEM DISORDERS	EYE DISORDERS.	EAR AND LABYRINTH DISORDERS	CARDIAC DISORDERS	VASCULAR DISOR. INCL HOT FLUSHES
Alkylating antineoplastic agent												
Cyclophosphamide	4	2	5	5	1	-	1	3	2	3	3	3
Anti-Metabolites												
Methotrexate	1	-	4	3	3	-	3	4	2	-	1	2
5-Fluorouracil*	5	-	5	2	2	5	-	3	3	-	5	3
Capecitabine	4	3 (Lipoma)	4	3	-	5	4	4	4	3	3	4
Gemcitabine	4	-	5	1	-	4	-:	4	-	-	2	2
Platinum-complexes												
Cisplatinum	4	2	5	3	2	5	-	4	2	5	4	4
Carboplatin	4	-	5	4	-	-	-	4	4	4	4	-
Anthracyclines / Anthrachinones												
Epi-/Doxorubicin	5	3	5	1-2	-	1-5	-	-	4	-	4	5
Liposom. Doxorubicin	5	-	5	-	-	5	3	4	(4)	-	4	4
PEG-lipos. Doxorubicin	4	-	4	-	-	5	-	4	4	-	4	-
Mitoxanthrone	5	3	5	3	-	4	-	4	3	3	4	3
Taxanes												
Paclitaxel	5	1	5	5	-	1	1	5	1	1	4	5
nab-Paclitaxel	4	-	5	3	-	5	4	5	4	4	4	4
Docetaxel	5	-	5	5	-	5	-	5	-	-	4	4
Further tubulin-targeting drugs												
Vinorelbine IV (PO)	5(5)	-	-(5)	2(-)	-	-	-(5)	-(5)	-(4)	-	2(3)	3(4)
Eribulin	4	-	4	-	-:	5	4	5	4	4	4	4

Listing and grading of side effects was performed according the MedDRA-classification with the following categories of frequency: 1. Very rarely (<1/10,000); 2. rarely (≥ 1/1,000 to < 1/10,000); 3. occasionally (≥ 1/1,000 to < 1/100); 4. frequently (≥ 1/100 to < 1/10); 5. very frequently (≥ 1/10). - unknown (based on available data incidence not assessable)

Chemotherapy – Acute Toxicities II

	SYSTEM ORGAN CLASS										
DRUG	RESPIRAT., HORAC. & MEDIA-STINAL DIS.	GASTROINT.DISORD. (NAUSEA, EMESIS)	HEPATOBILIARY DISORDERS	SKIN & SUBCUT. TIS. DISORD. (ALOPECIA)	MUSCULOSKELETAL & CONNECTIVE TISSUE DISORDERS	RENAL& URINARY DISORDERS	PREGN., PUERPER. & PERINATAL CONDIT.	REPRODUCT. SYS. & BREAST DISORDERS	GENERAL DISORD. & ADMINI-STRATION SITE CONDITIONS	CONGEN., FAMILIAL GENET. DISORDERS	SPECIAL FEATURES
Alkylating antineoplastic agent											
Cyclophosphamide	2	4	4	5	-	5	-	4	5	-	Hyponatriaemia
Anti-Metabolitee											
Methotrexate	4	5	5	4	3	3	-	3	1	-	Mucositis, risk of "third space"-toxicity
5-Fluorouracil	5	5	3	5	-	-	-	-	5	-	Risk DPD-deficiency: light 5%, severe 0,1%; diarrhea, heart
Capecitabine	4	5	4	5	4	3	-	3	5	-	Hand-foot-syndrome (HFS), risk of DPD-deficiency; heart
Gemcitabine	5	5	5	5	4	5	-	-	5	-	Flu-like symptoms, edema, heart
Platinum-complexes											
Cisplatinum	4	5	4	4	-	5	-	3	5	-	Nephrotoxicity, ototoxicity, CIPN
Carboplatin	4	5	-	4	4	4	-	-	4	-	Colitis (nephrotoxicity)
Anthracyclines / Anthrachinones											
Epi-/Doxorubicin	2	5	-	5	1	4		1	5	-	Cardiotoxicity (CHF), sec. malign. diseases, extravasation
Lipo. Doxorubicin	4	5	4	5	4	3	-	(4)	5	-	
PEG-lipo. Doxo.	4	5	-	5	4	-	-	4	5	-	Palmar and plantar erythema (PPE)
Mitoxanthrone	4	5	3	5	-	3	-	3	4	-	Sec. AML, cardiomyopathy
Taxanes											
Paclitaxel	2	5	1	5	5	-	-	-	5	-	Peripheral neuropathy (CIPN); hypersensitivity, myalgia
nab-Paclitaxel	4	5	3	5	5	3	-	3	5	-	Peripheral neuropathy (CIPN)
Docetaxel	5	5	-	5	5	-	-	-	5	-	Fluid retention, paronychia, colitis, myalgie
Further tubulin-targeting drugs											
Vinorelbine IV (PO)	3(4)	2 (5)	5(4)	2(5)	-(4)	2(4)	-	-	-	-	Phlebitis, GI-Tox (PO), CIPN
Eribulin	5	5	4	5	5	4	-	-	5	-	Constipation, CIPN

- unknown (based on available data incidence not assessable)

Listing and grading of side effects was performed according the MedDRA-classification with the following categories of frequency: 1. Very rarely (<1/10,000); 2. rarely (≥ 1/1,000 to < 1/10,000); 3. occasionally (≥ 1/1,000 to < 1/100); 4. frequently (≥ 1/100 to < 1/10); 5. very frequently (≥ 1/10).

Guidelines Breast
Version 2024.1E

Diagnostics* before Start of 5-FU (i.v.) / Capecitabine-Therapy

	Oxford		
	LoE	GR	AGO
DPD (Dihydropyrimidin-Dehydrogenase) - Deficiency Testing (*DPYD*-Genotype or Phenotype)	1a	A	++

Phenotype determination (e.g. uracil in plasma / urine, determination of DPD-activity) are less standardized assays

Systematic review (cancer patients under 5-FU therapy):**

- **DPYD-variants (heterozygous or homozygous) 4.1%**
- **Therapy-associated mortality 2.3% (vs. 0.1% w/o DPYD-variants) – risk for therapy-associated death 25.6-fold increase**

* **Recommendation according to Medical Alert (Rote-Hand-Brief) 4.6.2020**

** **Sharma et al, Oncologist 2021**

Endocrine Therapy – Toxicities

	Tamoxifen	Anastrazole	Exemestane	Letrozole	Fulvestrant	Elacstrant
Infections / Infestations	-	-	-	3	4	-
Neoplasms (benin, malignant, unspecified)	3	-	-	-	-	-
Blood and lymphatic system disorders	4	-	4	3	3	-
Immune system disorders (allergies)	-	-	-	-	4	-
Endocrine disorders	3	-	-	-	-	5
Metabolism and nutrition disorders	5	4	4	5	4	5
Psychiatric disorders	-	5	5	4	-	5
Nervous system disorders	4	5	4	4	4	-
Eye disorders	4	4	-	3	-	-
Ear and lapyrinth disorders	-	-	-	-	-	-
Cardiac disorders	-	4	-	3	-	-
Vascular disorders (including hot flashes)	4	5	5	5	4	5

Listing and grading of side effects was performed according the MedDRA-classification with the following categories of frequency:
1. Very rarely (< 1/10,000); 2. rarely (≥ 1/1,000 to < 1/10,000); 3. occasionally (≥ 1/1,000 to < 1/100); 4. frequently (≥ 1/100 to < 1/10); 5. very frequently (≥ 1/10).
- unknown (based on available data incidence not assessable)

Guidelines Breast
Version 2024.1E

Endocrine Therapy – Toxicities

	Tamoxifen	Anastrazole	Exemestane	Letrozole	Fulvestrant	Elacstrant
Respiratory, thoracic and mediastinal disorders	3	-	-	3	-	-
Gastrointestinal disorders (nausea, emesis)	5	5	5	4	5	5
Hepatobiliary disorders	4	4	-	3	5	4
Skin and subcutis disorders (incl alopecia)	5	5	5	5	4	-
Musculosceletal and connective tissue	4	5	5	5	4	5
Renal and urinary disorders	-	-	-	3	4	-
Pregnancy, peurperal and perinatal disorders	-	-	-	-	-	-
Reproductive tract and breast disorders	5	5	-	4	3	-
General disorders / administration site conditions	5	5	5	5	5	-
Congenital, familiary and genetic disorders	1	-	-	-	-	-
Special features	*	**	**	**	***	
* Hot flushes; rarely endometrial cancer, thrombosis ** hot flashes, arthralgia, osteoporosis, cognition ***hot flushes						

Listing and grading of side effects was performed according the MedDRA-classification with the following categories of frequency:

1. Very rarely (< 1/10,000); 2. rarely (≥ 1/1,000 to < 1/10,000); 3. occasionally (≥ 1/1,000 to < 1/100); 4. frequently (≥ 1/100 to < 1/10); 5. very frequently (≥ 1/10).
- unknown (based on available data incidence not assessable)

Guidelines Breast
Version 2024.1E

Key-Toxicities – Antibodies

	Oxford LoE	Oxford GR
Trastuzumab		
▪ Cardiotoxicity in the adjuvant setting (1.0–2.0%)	1b	A
▪ Troponin I may identify patients at risk for cardiotoxicity	2b	B
Pertuzumab		
▪ Skin rash, diarrhea, mucositis	1b	A
Bevacizumab		
▪ Hypertension, proteinuria, bleeding, left ventricular dysfunction	1a	A

Toxicities of New Compounds: anti-HER2-TKI – Neratinib, Lapatinib –

Lapatinib

AE, %	All grades	Grade >/=3
Diarrhea	61%	6%
Nausea	18%	4%
Rash	60%	6%
Fatigue	16%	4%
Cardiac	3%	< 1% SAE
Hepatobiliary	8%	
All AE %	92%	SAE 6%

Neratinib

AE, %	Alle Grade	Grad >/=3
Diarrhea	90	40,1
Nausea	43	2
Abdominal pain	36	2
Fatigue	27	2
Emesis	26	3
Exanthema	18	0,6
Stomatitis	14	0,6
Appetite loss	12	0,2
Dyspepsia	10	0,4
ALAT elevated	9	1,2
ASAT elevated	7	0,7
Nail disorders	8	0,3
Dry skin	6	0

	LoE	GR	AGO
Primary prophylaxis with loperamide	2b	B	++

Guidelines Breast
Version 2024.1E

Common Toxicities with anti-HER2-TKI: Tucatinib + Trastuzumab + Capecitabine

Event	**Capecitabine + Tucatinib + Trastuzumab**	
	Any grade (%)	**≥ 3 grade (%)**
Any adverse event	99.3	55.2
Diarrhea	80.9	12.9
PPE syndrome	63.4	13.1
Nausea	58.4	3.7
Fatigue	45.0	4.7
Vomiting	35.9	3.0
Stomatitis	25.5	2.5
Reduced appetite	24.8	0.5
Headache	21.5	0.5

Key-Toxicities – Antibody-Drug-Conjugates

Guidelines Breast
Version 2024.1E

	Oxford LoE	Oxford GR
Sacituzumab Govitecan		
▪ (Febrile) neutropenia, leukopenia, anemia, diarrhea, nausea, alopecia, fatigue	1b	A
Trastuzumab-Emtansin (T-DM1)		
Thrombozytopenia, elevation liver enzymes, pyrrexia, headache pneumonitis, neuropathy, fatigue	1b	A
Trastuzumab-Deruxtecan		
Interstitial lung disease, neuropenia, nausea, alopecia, fatigue	1b	A

Toxicities of CDK 4/6 Inhibitors (Palbociclib / Ribociclib / Abemaciclib)

Guidelines Breast
Version 2024.1E

UE, %	All Grades	Grade 3	Grade 4
Neutropenia	79,5/74,3/41,3	56,1/49,7/19,6	10,4/9,6/1,5
Leukopenia	39,0/32,9/20,8	24,1/19,8/7,3	0,7/1,2/0,3
Anemia	24,1/18,6/28,4	5,2/0,9/5,8	0,2/0,3/0
Thrombocytopenia	15,5/5,7/10,0	1,4/0,6/2,0	0,2/0/< 1,0
Fatigue	37,4/36,5/40,1	1,8/2,1/1,8	0/0,3/0
Nausea	35,1/51,5/38,5	0,2/2,4/0,9	0/0/0
Vomiting	15,5/29,3/28,4	0,5/3,6/1,2	0/0/0
Diarrhea	26,1/35,0/81,3	1,4/1,2/9,5	0/0/0
Alopecia	32,9/33,2/26,6	-	-
Exantheme	17,8/17,1/14,0	0,9/0,6/< 1,0	0/0/0
ALT elevated	9,9/15,6/15,6	1,7/7,5/5,8	0,1/1,8/0,3
AST elevated	9,7/15,0/15,0	2,5/4,8/3,0	0/0,9/0
Infections	60/50,3/39,1	6,0/3,6/4,0	1/0,6/0,9
QT-prolongation	N.A./7,5/N.A.	N.A./3,0/N.A.	N.A./0/N.A.
Palbociclib/Ribociclib/Abemaciclib			

Interstitial Lung Disease (ILD) and CDK 4/6 Inhibitors

Guidelines Breast
Version 2024.1E

Pulmonary toxicity of cyclin-dependent kinase (CDK) 4/6 inhibitors from the publicly available FDA Adverse Event Reporting System (FAERS):

- 2.1% of all reports for abemaciclib; 0.3% of all reports palbociclib / ribociclib
- Increased reporting found for
  - CDK4/6 inhibitors vs. other drugs (ROR = 1.50; 95% CI = 1.28–1.74)
  - Abemaciclib vs other anticancer agents (4.70; 3.62–5.98).

Overall incidence:

Systematic review of published data:

CDK 4/6i: Any grade 1.64% (0.68% control). Pooled RR 2.26, 95% CI: 1.60-3.19, $p < 0.00001$

CDK 4/6i: Grade 3/4 0.28% (0.06% control). Pooled RR 2.35, 95% CI: 0.37-15.08, $p = 0.37$

Monarch-E:

Abemaciclib any grade 2.9% ($\geq$ G3 0.4% - 1 G5 event); control 1.2% ($\geq$ G3 n = 1; 0%)

Venous Thromboembolic Events: Adjuvant Abemaciclib (Monarch-E trial)

Guidelines Breast
Version 2024.1E

Abemaciclib : All grade 2.3% (grade 3/4 1.2%)
Control arm: All grade 0.5% (grade 3/4 0.1%)

Characterization of VTE (DVT or PE)*

- VTE by first ET = AI
  - Abemaciclib: any grade 1.7% (G3/4 0.9%)
  - Control arm: any grade 0.5% (G3/4 0.2%)
- VTE by first ET = tamoxifen
  - Abemaciclib: any grade 4.1% (G3/4 2.2%)
  - Control arm: any grade 0.7% (G3/4 0.4%)

* *DVT* is a composite term for several forms of venous thrombosis; *PE* is a composite term including embolism and pulmonary embolism

QT-Interval-Prolongation: Ribociclib vs. Placebo

Guidelines Breast
Version 2024.1E

Post-baseline prolongation QT-interval > 480 msec 6,9% vs. 1,2%

Post-baseline prolongation QT-interval > 500 msec 1,5% vs. 0,3%

Dicsontinuation due to QT-interval prolongation 0,3% vs. 0,6%

Prolongation of QT-interval is not associated with clinical symptoms, but with an increased risk of the life-threatening arrhythmia torsades de pointes (TdP)

Use of QT check tools might be helpful (www.arzneimitteltherapie.de)

Toxicities of mTOR-Inhibitor (Everolimus)

UE, %	All grades (%)	grade >/=3 (%)
Stomatitis	11,6	1,6
Exanthema	7,4	0,02
Anemia	3,3	1,3
Fatigue	6,8	0,8
Nausea	5,6	0
Emesis / Vomiting	2,9	0
Diarrhea	6,2	0,02
Loss of appetite	6,0	0,02
Headache	3,9	0
Weight loss	3,9	0
Dyspnea	3,8	0,08
Arthralgia	3,3	0
Epistaxis	3,1	0
Edema	2,9	0
Constipation	2,6	
Pyrexia	2,9	0
Cough	4,5	0
ALT Elevated	2,6	0
Pneumonitis	0,2	0
Asthenia	2,4	0,04
Dysgeusia	4,3	0

Guidelines Breast
Version 2024.1E

Guidelines Breast
Version 2024.1E

Toxicities of PI3K Inhibitor Alpelisib in Combination with Endocrine Therapy

Alpelisib + Fulvestrant

UE, %	All Grade	Grad >/=3
Hypergycemia	63,7%	32,7%
Diarrhea	57,7%	6,7%
Nausea	44,7%	2,5%
Decreased appetite	35,6%	< 1% SAE
Rush	35,5%	9,9%
Vomiting	27,1%	< 1% SAE
Weight loss	26,8%	3,9%
Stomatitis	24,6%	2,5%
Fatique	24,3%	3,5
Asthenia	20,4%	1,8
Alopecia	19,7%	0
Mucositis	18,3%	2,1

Regard recommendations for management of side effects (Diabetes mellitus, hyperglycemia, Insulin resistance und metabolic syndrom)

LoE	GR	AGO
2b	B	++

Toxicities of PARP-Inhibitors – Olaparib, Talazoparib

Guidelines Breast
Version 2024.1E

Olaparib

AE. %	all grades (%)	grade >/=3 (%)
AE, overall	97.1	36.6
Neutropenia	27.3	9.3
Anemia	40.0	16.1
Fatigue	28.8	2.9
Nausea	58.0	0
Emesis	29.8	0
Diarrhea	20.5	0.5
Appetite loss	16.1	0
Headache	20.0	1
Pyrexia	14.1	0
Cough	17.1	0
ALT elevated	11.2	1.5
AST elevated	9.3	2.4
PPE	0.5	
Treatm. discontinuation	4.9	

Talazoparib

AE. %	all grades (%)	grade >/=3 (%)
AE, overall	98,6	31,8
neutropenia	34,6	20.9
Anemia	52.8	39,2
Fatigue	50,3	1,7
Nuasea	48,6	0,3
Emesis	24,8	2,4
Diarrhea	22,0	0,7
Appetite loss	21,3	0,3
Headache	32,5	1,7
Back pain	21,0	2,4
Dyspnea	17,5	2,4
Pleural effusion	2,1	1,7
PPE	1,4	0,3

Guidelines Breast
Version 2024.1E

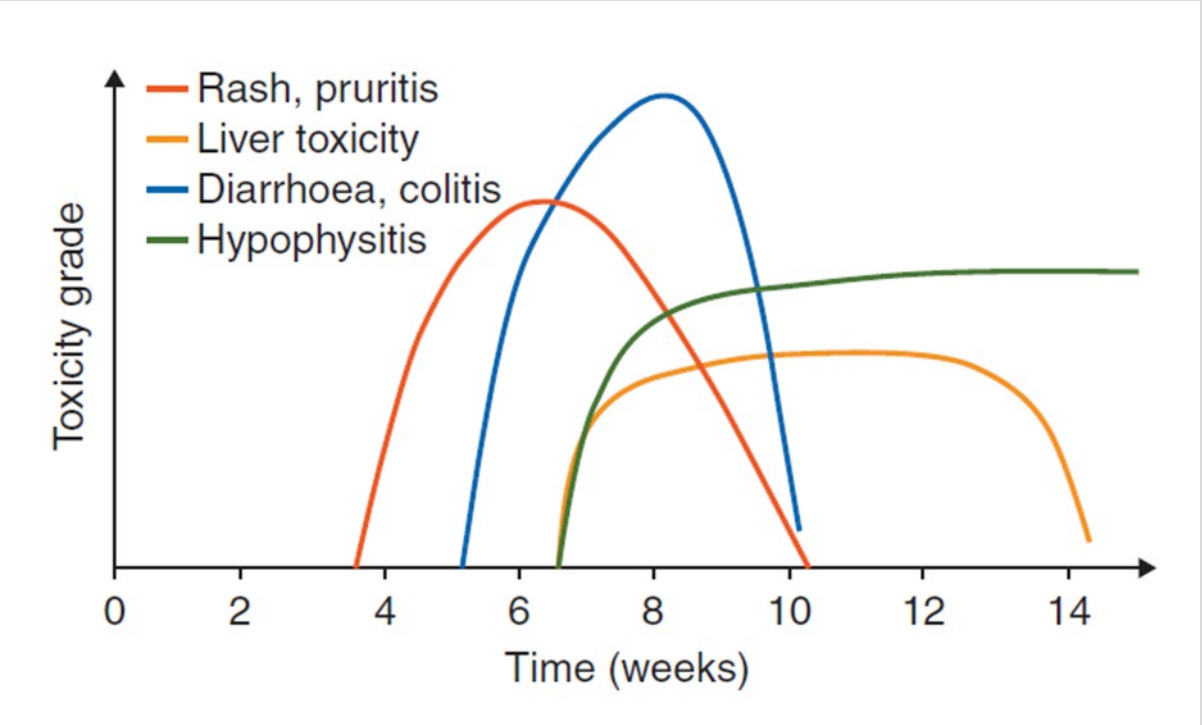
Immune Checkpoint Inhibitors

- **Therapeutic approaches (antibodies)**
  - **PD-1 / PD-L1**

    PD-1
    - **Nivolumab**
    - **Pembrolizumab**

    PD-L1
    - **Atezolizumab**
    - **Durvalumab**
    - **Avelumab**

Immune Checkpoint Inhibitors
Time Course of Adverse Events, e.g. Ipilimumab



Haanen J et al. Ann Oncol 2017; 28 (suppl 4): 119-142

Guidelines Breast
Version 2024.1E

Guidelines Breast
Version 2024.1E

Immune Checkpoint Inhibitors
– Side Effects –

- **Adverse events ≥ grade 3**
  - **diarrhea**
  - **fatigue**
  - **skin lesions (maculopapular exanthema, vitiligo, epidermolysis)**
  - **pneumonitis**
  - **colitis**
  - **hypophysitis**
  - **hepatitis**
  - **nephritis**
  - **thyreoiditis (hyper- / hypothyroidism)**
  - **Guillain-Barré syndrome**
  - **cardiomyopathy**
  - **myopathy – myalgia – rhabdomyolysis**
  - **uveitis**

Immune Checkpoint Inhibitors Toxicities (Total in %)

	atezolizumab	nivolumab	pembrolizumab
diarrhea	18.6%	13%	18%
colitis	1.1%	2%	1%
exanthema	18.6%	15%	< 1%
hepatoxicity	0.3%	1%	0.5%
hypophysitis	< 0.1%	< 1%	0.5%
pneumonitis	3.1%	3%	2.9%
thyroid dysfunction	hyper- 1.7% hypo- 4.7%	hyper -1% hypo- 4%	hyper- 1.2% hypo- 8.3%
nephritis	< 1%	1%	0.7%
neuropathy	0.2%	< 1%	< 1%

Atezolizumab technical product information 2018; Nivolumab, safety management BMS 2014; Pembrolizumab PI 2014

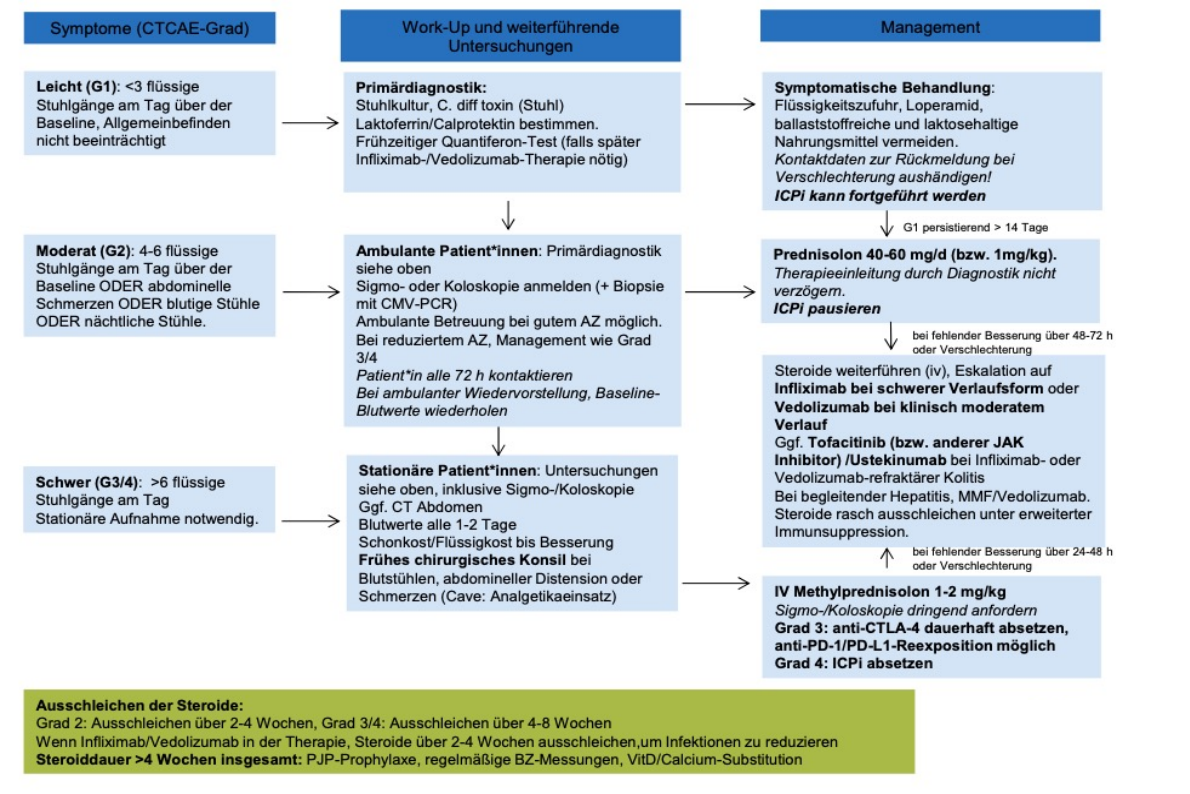
Guidelines Breast
Version 2024.1E

Immune Checkpoint Inhibitors
Principles of Adverse Event Management

CTC AE-Grade	Management
1	▪ supportive therapy ▪ close examination ▪ exclusion of infective complications ▪ patient information
2	Like grade 1 but ▪ intermission of therapy until recovery of all irAE to grades 0-1 ▪ consider corticosteroids
3	▪ supportive therapy ▪ IV steroids (e.g. 1-2 mg/kg prednisolone) In case of no improvement within 48 h: ▪ consider additional immunosuppressive therapy (infliximab, MMF) ▪ consider further organ specific diagnostics (eg. colonoscopy) ▪ consider specialists consultations ▪ exclusion or treatment of infection ▪ stop of treatment, re-initiation after recovery to CTC AE grades 0, 1 ▪ slow reduction of steroids (3-6 weeks)
4	Like grade 3 but persistent withdrawal of therapy

Guidelines Breast
Version 2024.1E

Diarrhoea and Colitis

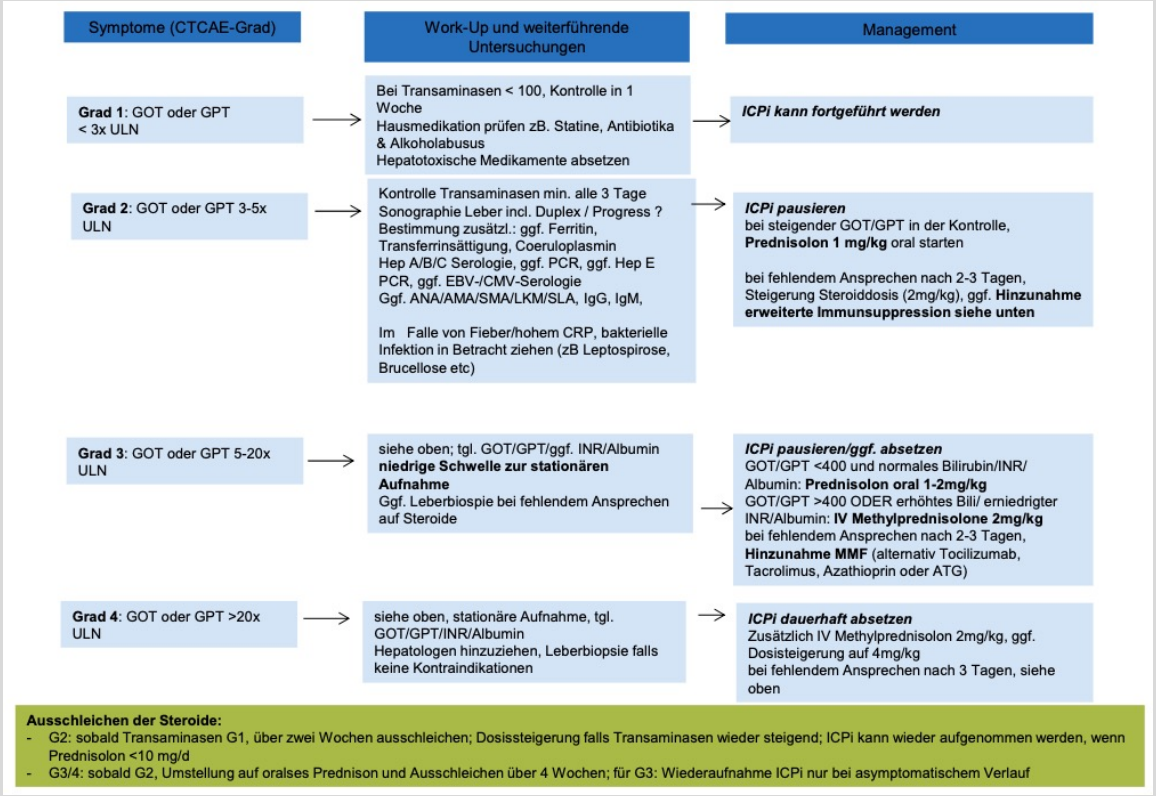


Guidelines Breast
Version 2024.1E

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Hepatitis

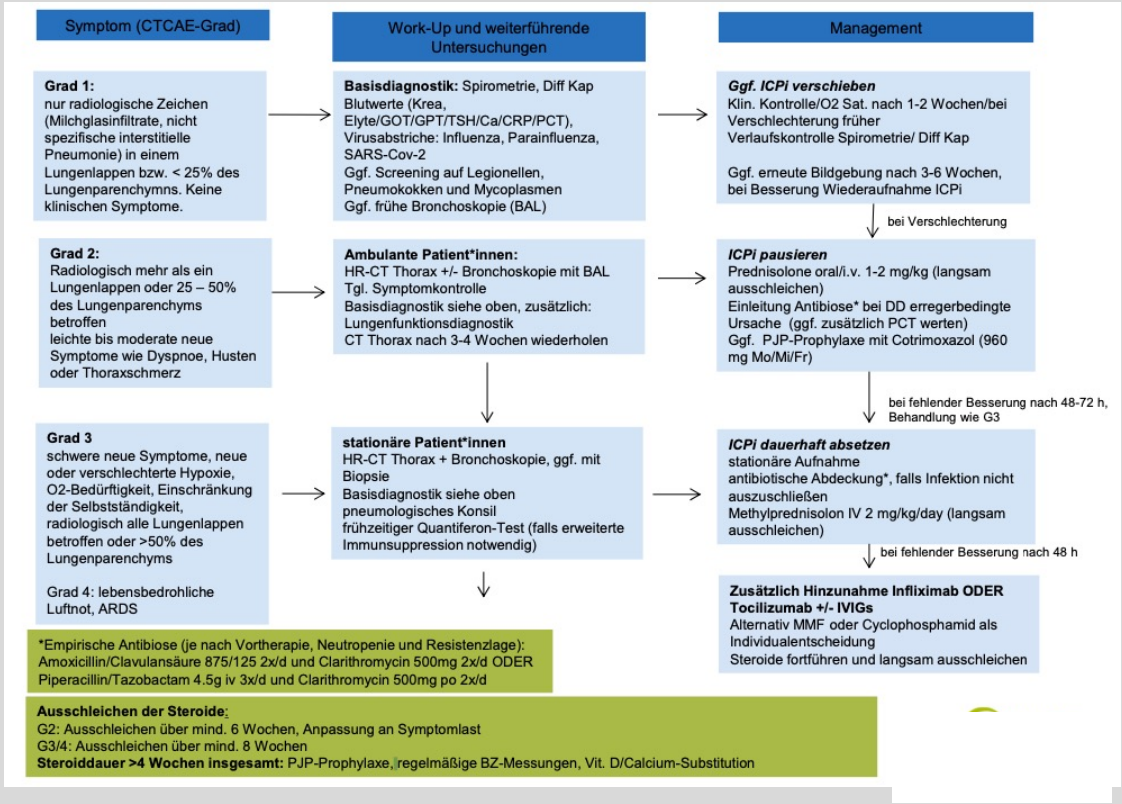


Symptome (CTCAE-Grad)	Work-Up und weiterführende Untersuchungen	Management
Grad 1: GOT oder GPT < 3x ULN	Bei Transaminasen < 100, Kontrolle in 1 Woche Hausmedikation prüfen zB. Statine, Antibiotika & Alkoholabusus Hepatotoxische Medikamente absetzen	***ICPi kann fortgeführt werden***
Grad 2: GOT oder GPT 3-5x ULN	Kontrolle Transaminasen min. alle 3 Tage Sonographie Leber incl. Duplex / Progress ? Bestimmung zusätzl.: ggf. Ferritin, Transferrinsättigung, Coeruloplasmin Hep A/B/C Serologie, ggf. PCR, ggf. Hep E PCR, ggf. EBV-/CMV-Serologie Ggf. ANA/AMA/SMA/LKM/SLA, IgG, IgM, Im Falle von Fieber/hohem CRP, bakterielle Infektion in Betracht ziehen (zB Leptospirose, Brucellose etc)	***ICPi pausieren*** bei steigender GOT/GPT in der Kontrolle, **Prednisolon 1 mg/kg** oral starten bei fehlendem Ansprechen nach 2-3 Tagen, Steigerung Steroiddosis (2mg/kg), ggf. **Hinzunahme erweiterte Immunsuppression siehe unten**
Grad 3: GOT oder GPT 5-20x ULN	siehe oben; tgl. GOT/GPT/ggf. INR/Albumin **niedrige Schwelle zur stationären Aufnahme** Ggf. Leberbiospie bei fehlendem Ansprechen auf Steroide	***ICPi pausieren/ggf. absetzen*** GOT/GPT <400 und normales Bilirubin/INR/ Albumin: **Prednisolon oral 1-2mg/kg** GOT/GPT >400 ODER erhöhtes Bili/ erniedrigter INR/Albumin: **IV Methylprednisolone 2mg/kg** bei fehlendem Ansprechen nach 2-3 Tagen, **Hinzunahme MMF** (alternativ Tocilizumab, Tacrolimus, Azathioprin oder ATG)
Grad 4: GOT oder GPT >20x ULN	siehe oben, stationäre Aufnahme, tgl. GOT/GPT/INR/Albumin Hepatologen hinzuziehen, Leberbiopsie falls keine Kontraindikationen	***ICPi dauerhaft absetzen*** Zusätzlich IV Methylprednisolon 2mg/kg, ggf. Dosisteigerung auf 4mg/kg bei fehlendem Ansprechen nach 3 Tagen, siehe oben

Ausschleichen der Steroide:
- G2: sobald Transaminasen G1, über zwei Wochen ausschleichen; Dosissteigerung falls Transaminasen wieder steigend; ICPi kann wieder aufgenommen werden, wenn Prednisolon <10 mg/d
- G3/4: sobald G2, Umstellung auf oralses Prednison und Ausschleichen über 4 Wochen; für G3: Wiederaufnahme ICPi nur bei asymptomatischem Verlauf

Guidelines Breast
Version 2024.1E

Pneumonitis

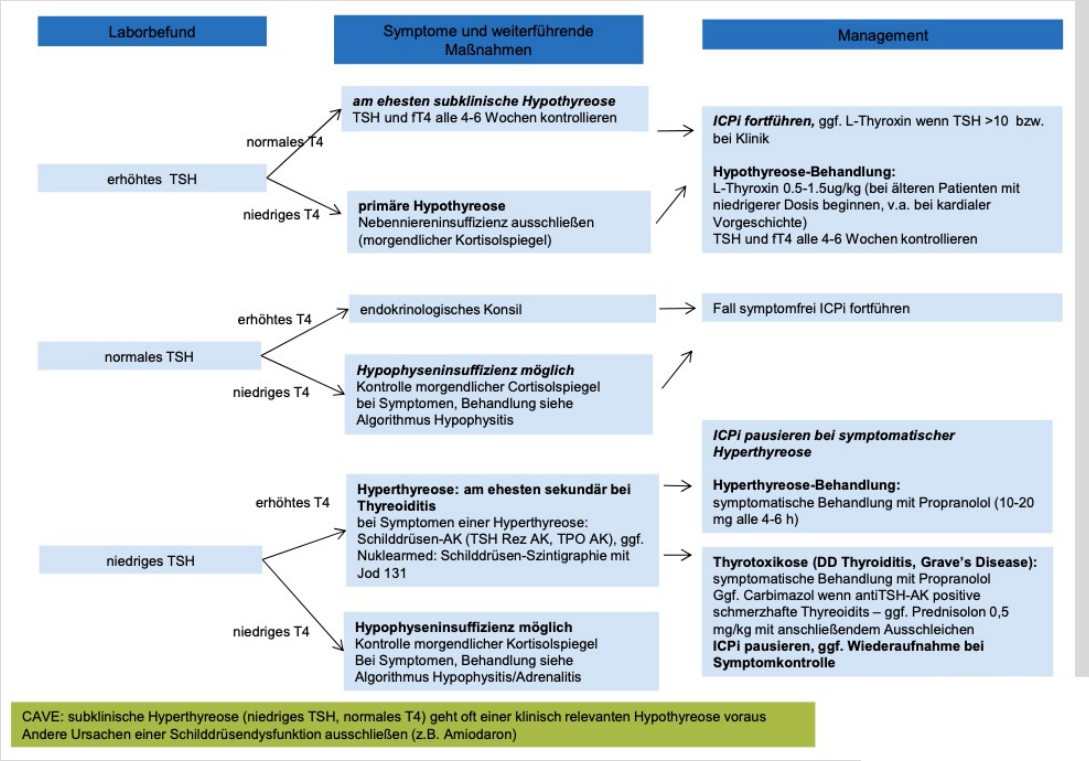


Guidelines Breast
Version 2024.1E

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Thyreoiditis

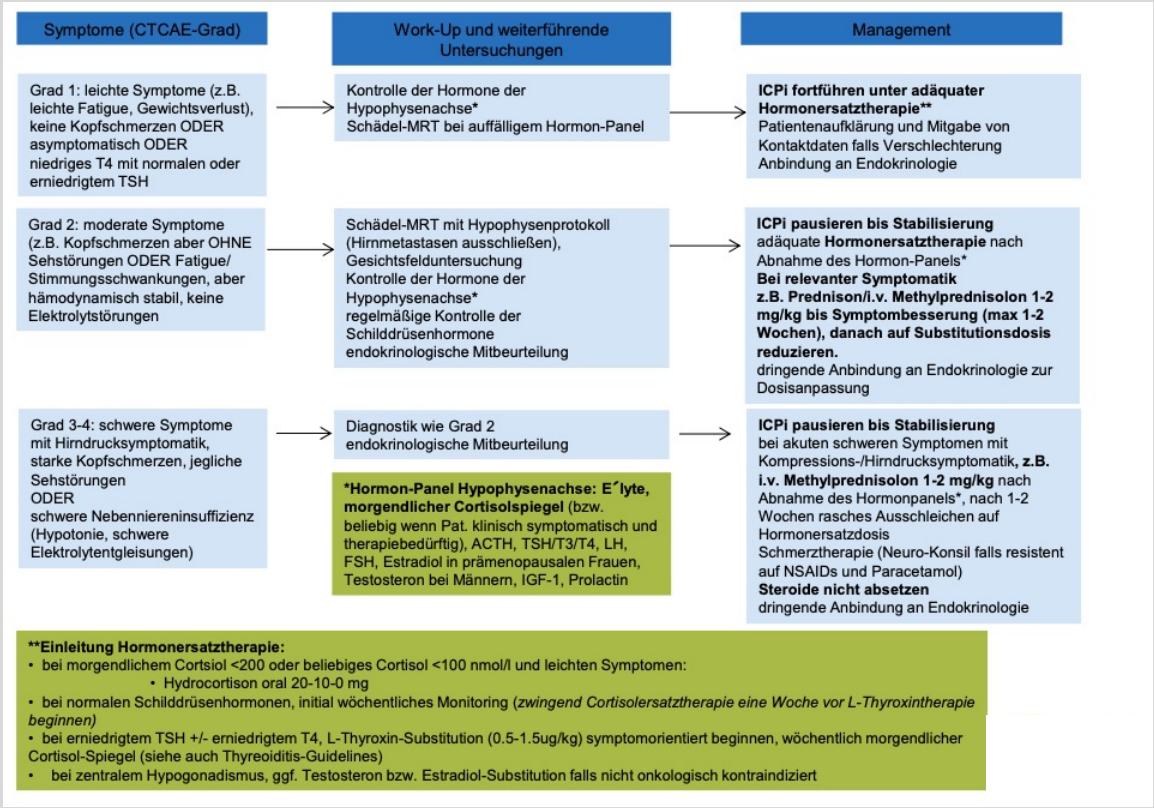


Guidelines Breast
Version 2024.1E

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Hypophysitis



Symptome (CTCAE-Grad)	Work-Up und weiterführende Untersuchungen	Management
Grad 1: leichte Symptome (z.B. leichte Fatigue, Gewichtsverlust), keine Kopfschmerzen ODER asymptomatisch ODER niedriges T4 mit normalen oder erniedrigtem TSH	Kontrolle der Hormone der Hypophysenachse* Schädel-MRT bei auffälligem Hormon-Panel	**ICPi fortführen unter adäquater Hormonersatztherapie**** Patientenaufklärung und Mitgabe von Kontaktdaten falls Verschlechterung Anbindung an Endokrinologie
Grad 2: moderate Symptome (z.B. Kopfschmerzen aber OHNE Sehstörungen ODER Fatigue/ Stimmungsschwankungen, aber hämodynamisch stabil, keine Elektrolytstörungen	Schädel-MRT mit Hypophysenprotokoll (Hirnmetastasen ausschließen), Gesichtsfelduntersuchung Kontrolle der Hormone der Hypophysenachse* regelmäßige Kontrolle der Schilddrüsenhormone endokrinologische Mitbeurteilung	**ICPi pausieren bis Stabilisierung** adäquate **Hormonersatztherapie** nach Abnahme des Hormon-Panels* **Bei relevanter Symptomatik z.B. Prednison/i.v. Methylprednisolon 1-2 mg/kg bis Symptombesserung (max 1-2 Wochen), danach auf Substitutionsdosis reduzieren.** dringende Anbindung an Endokrinologie zur Dosisanpassung
Grad 3-4: schwere Symptome mit Hirndrucksymptomatik, starke Kopfschmerzen, jegliche Sehstörungen ODER schwere Nebenniereninsuffizienz (Hypotonie, schwere Elektrolytentgleisungen)	Diagnostik wie Grad 2 endokrinologische Mitbeurteilung ***Hormon-Panel Hypophysenachse: E´lyte, morgendlicher Cortisolspiegel** (bzw. beliebig wenn Pat. klinisch symptomatisch und therapiebedürftig), ACTH, TSH/T3/T4, LH, FSH, Estradiol in prämenopausalen Frauen, Testosteron bei Männern, IGF-1, Prolactin	**ICPi pausieren bis Stabilisierung** bei akuten schweren Symptomen mit Kompressions-/Hirndrucksymptomatik, **z.B. i.v. Methylprednisolon 1-2 mg/kg** nach Abnahme des Hormonpanels*, nach 1-2 Wochen rasches Ausschleichen auf Hormonersatzdosis Schmerztherapie (Neuro-Konsil falls resistent auf NSAIDs und Paracetamol) **Steroide nicht absetzen** dringende Anbindung an Endokrinologie

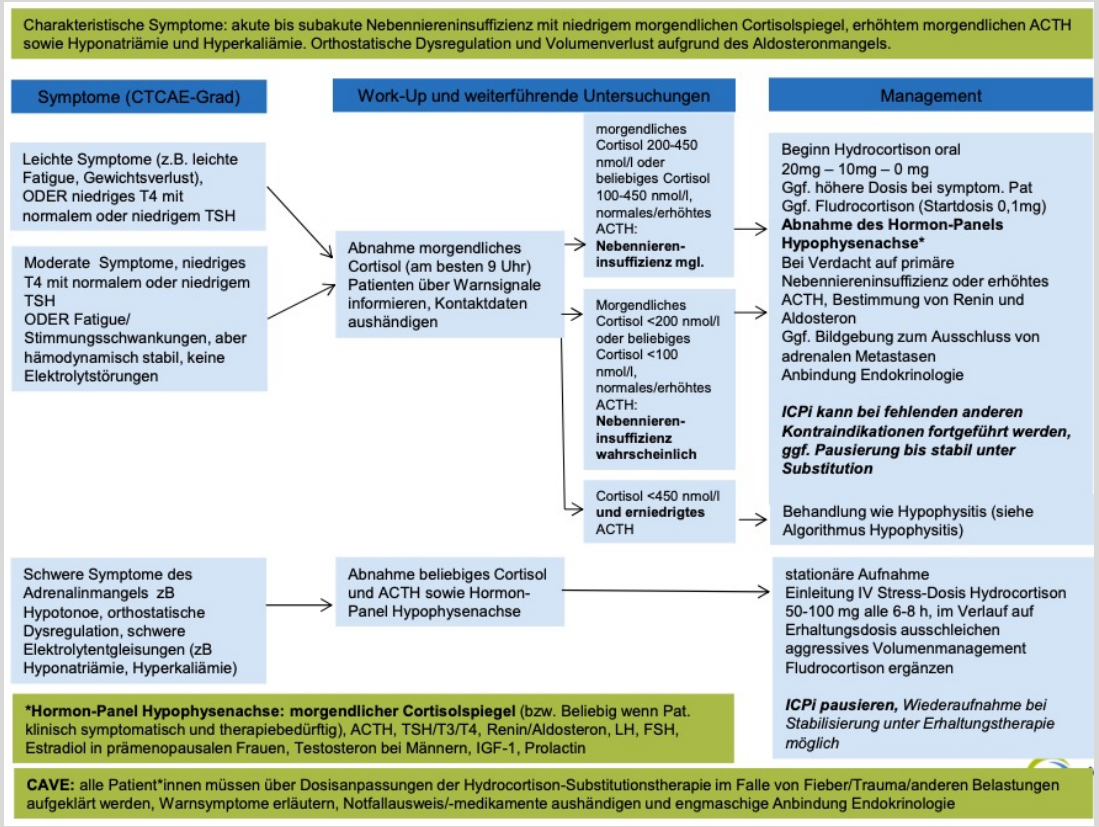
****Einleitung Hormonersatztherapie:**

- bei morgendlichem Cortsiol <200 oder beliebiges Cortisol <100 nmol/l und leichten Symptomen:
  - Hydrocortison oral 20-10-0 mg
- bei normalen Schilddrüsenhormonen, initial wöchentliches Monitoring (*zwingend Cortisolersatztherapie eine Woche vor L-Thyroxintherapie beginnen)*
- bei erniedrigtem TSH +/- erniedrigtem T4, L-Thyroxin-Substitution (0.5-1.5ug/kg) symptomorientiert beginnen, wöchentlich morgendlicher Cortisol-Spiegel (siehe auch Thyreoiditis-Guidelines)
- bei zentralem Hypogonadismus, ggf. Testosteron bzw. Estradiol-Substitution falls nicht onkologisch kontraindiziert

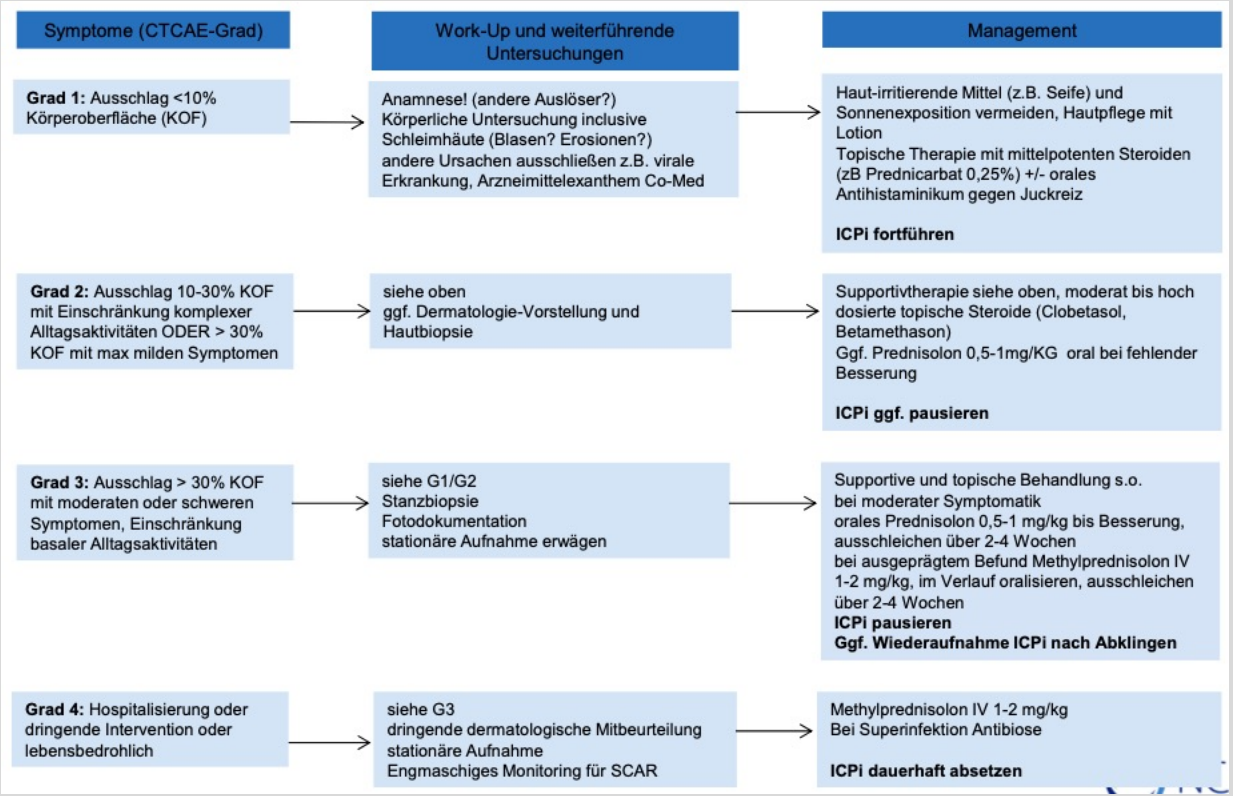
Guidelines Breast
Version 2024.1E

Adrenalitis

Guidelines Breast
Version 2024.1E



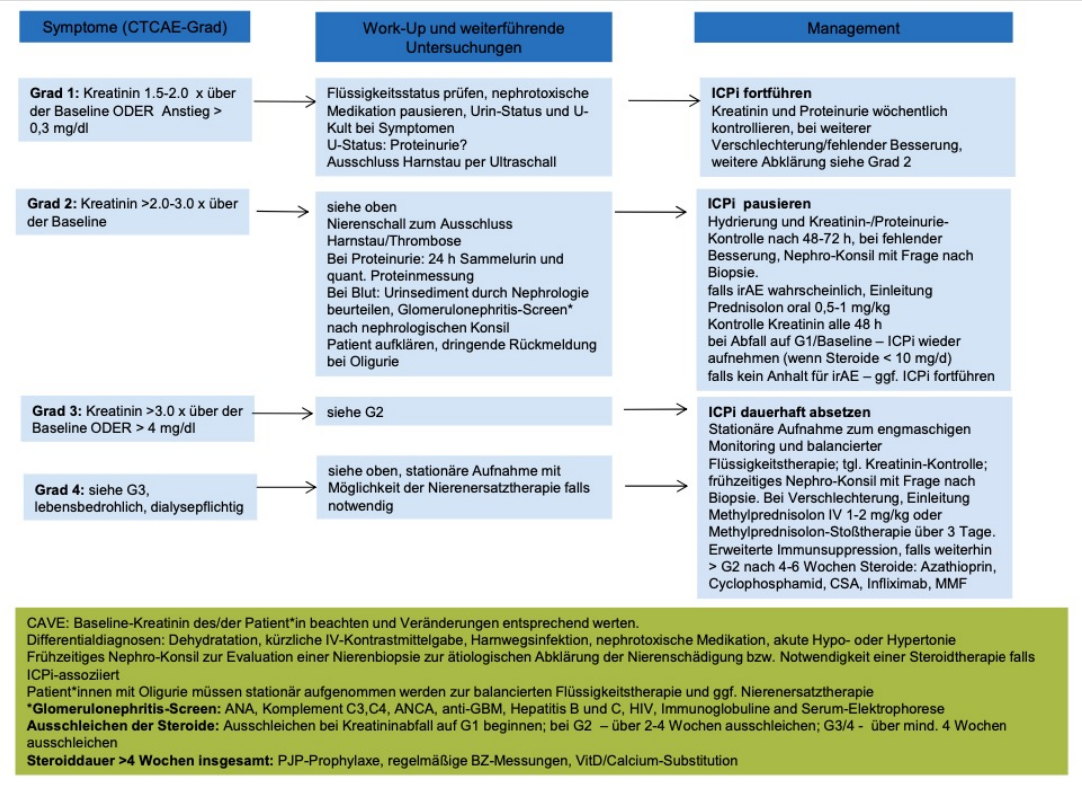
Cutaneous Toxicity



Symptome (CTCAE-Grad)	Work-Up und weiterführende Untersuchungen	Management
Grad 1: Ausschlag <10% Körperoberfläche (KOF)	Anamnese! (andere Auslöser?) Körperliche Untersuchung inclusive Schleimhäute (Blasen? Erosionen?) andere Ursachen ausschließen z.B. virale Erkrankung, Arzneimittelexanthem Co-Med	Haut-irritierende Mittel (z.B. Seife) und Sonnenexposition vermeiden, Hautpflege mit Lotion Topische Therapie mit mittelpotenten Steroiden (zB Prednicarbat 0,25%) +/- orales Antihistaminikum gegen Juckreiz **ICPi fortführen**
Grad 2: Ausschlag 10-30% KOF mit Einschränkung komplexer Alltagsaktivitäten ODER > 30% KOF mit max milden Symptomen	siehe oben ggf. Dermatologie-Vorstellung und Hautbiopsie	Supportivtherapie siehe oben, moderat bis hoch dosierte topische Steroide (Clobetasol, Betamethason) Ggf. Prednisolon 0,5-1mg/KG oral bei fehlender Besserung **ICPi ggf. pausieren**
Grad 3: Ausschlag > 30% KOF mit moderaten oder schweren Symptomen, Einschränkung basaler Alltagsaktivitäten	siehe G1/G2 Stanzbiopsie Fotodokumentation stationäre Aufnahme erwägen	Supportive und topische Behandlung s.o. bei moderater Symptomatik orales Prednisolon 0,5-1 mg/kg bis Besserung, ausschleichen über 2-4 Wochen bei ausgeprägtem Befund Methylprednisolon IV 1-2 mg/kg, im Verlauf oralisieren, ausschleichen über 2-4 Wochen **ICPi pausieren** **Ggf. Wiederaufnahme ICPi nach Abklingen**
Grad 4: Hospitalisierung oder dringende Intervention oder lebensbedrohlich	siehe G3 dringende dermatologische Mitbeurteilung stationäre Aufnahme Engmaschiges Monitoring für SCAR	Methylprednisolon IV 1-2 mg/kg Bei Superinfektion Antibiose **ICPi dauerhaft absetzen**

Guidelines Breast
Version 2024.1E

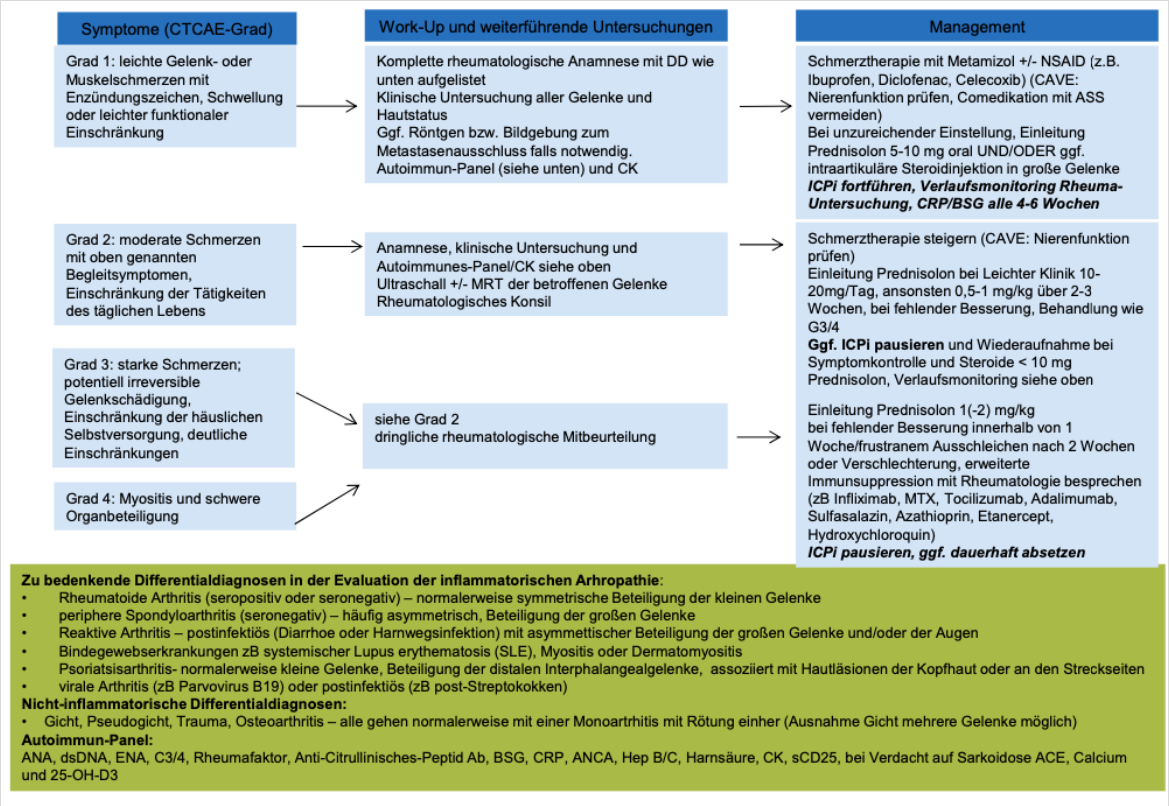
Nephrotoxicity



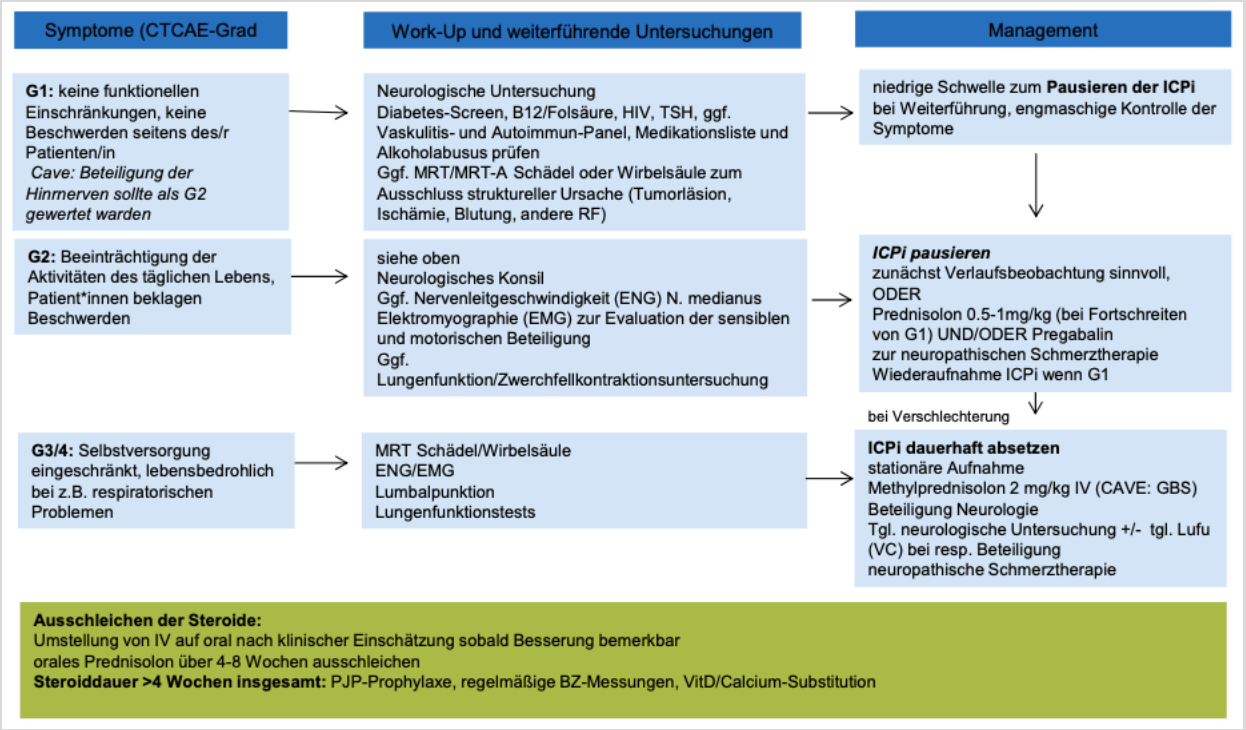
Guidelines Breast
Version 2024.1E

Arthritis, Arthralgia, Myalgia

Guidelines Breast
Version 2024.1E



Peripheral Neurotoxicity (I)



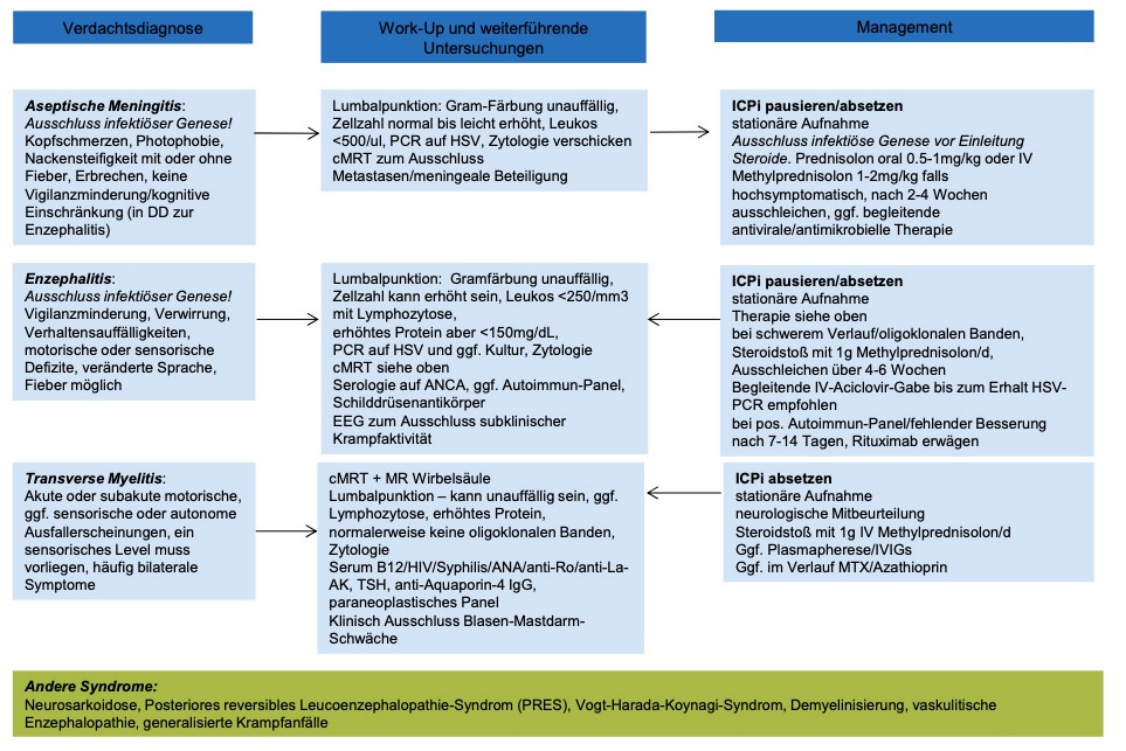
Peripheral Neurotoxicity (II)

Guidelines Breast
Version 2024.1E

Verdachtsdiagnose	Work-Up und weiterführende Untersuchungen	Management
Guillain-Barre-Syndrom(GBS): Progrediente symmetrische Muskelschwäche mit fehlenden oder abgeschwächten Sehnenreflexen, Beteiligung von Extremitäten-, Gesichts-, Atem- und Schluck- sowie Augenmuskeln, Dysregulation der autonomen Nerven	Untersuchung der Nervenleitgeschwindigkeit (akute Polyneuropathie) Lumbalpunktion (typischerweise erhöhtes Protein bei normaler Zellzahl) Lungenfunktionsdiagnostik mit VC und max. In- und Exspirationsfluss Serologie auf GBS-Antikörper (zB GQ1b bei Miller-Fisher-Variante)	**ICPi dauerhaft absetzen** stationäre Aufnahme, neurologische Mitbeurteilung Steroide bei idiopathischem GBS nicht empfohlen, bei V.a. ICPi-ass. GBS Versuch mit Methylprednisolon 1 g/d über 5 Tage, Ausschleichen über 4 Wochen Gabapentin, Pregabalin oder Duloxetin bei Schmerzen Bei fehlender Besserung/Verschlechterung, Plasmapherese oder IVIGs indiziert CAVE: ggf. invasive Beatmung notwendig (ca. 15-30% der idiopathischen GBS)
Myasthenia gravis: Fluktuierende Muskelschwäche (Arme, Stamm, Augen- und Schluckmuskeln inklusive Doppelbilder und Schluckstörungen) mit Erschöpfbarkeit, Atemhilfsmuskeln/Zwerchfell können auch betroffen sein ***Myositis:*** Proximale Muskelschwäche begleitet von Muschkelschmerzen und CK-Erhöhung, Schluckbeschwerden, häufig Myokardbeteiligung, kann begleitend zu myasthenen Symptomen auftreten	Myasthenia gravis: Untersuchung auf Erschöpfbarkeit der Augenmuskeln bzw. proximalen Extremitätenmuskeln Serologische Bestimmung der Acetylcholin-Rezeptor-AK (AChR) Bedside-Test per Tensilon-Test or Eis-Test, repetitive Nervenstimulation Myositis: Bestimmung CK, EMG, Kontrolle der Nierenfunktion im Fall von Rhabdomyolyse	**ICPi dauerhaft absetzen** stationäre Aufnahme, neurologische Mitbeurteilung Steroidtherapie indiziert (oral oder IV je nach Symptomlast) Myasthena gravis: Pyridostigmine 30mg 3x/d beginnen, Dosisanpassung je nach Symptomen bis zu 120 mg 4x/d Bei fehlender Besserung/Verschlechterung, Plasmapherese oder IVIGs prüfen Zusätzliche Immunsuppression: Azathioprin, Ciclosporin, MMF CAVE: Ciprofloxacin und Beta-blocker vermeiden, können cholinerge Krise provozieren

Andere Syndrome:
Motorische und sensorische periphere Neuropathie, mulitfokale radikuläre Neuropathie/Plexopathie, autonome Neuropathie, Lähmungen des N. phrenicus oder der Hirnnerven (zB faziale Parese, N. opticus, N. hypoglossus). Steroidue empfohlen sowie Anbindung Neurologie und engmaschiges Monitoring auf respiratorische bzw. visuelle Einschränkungen.

Central Neurotoxicity

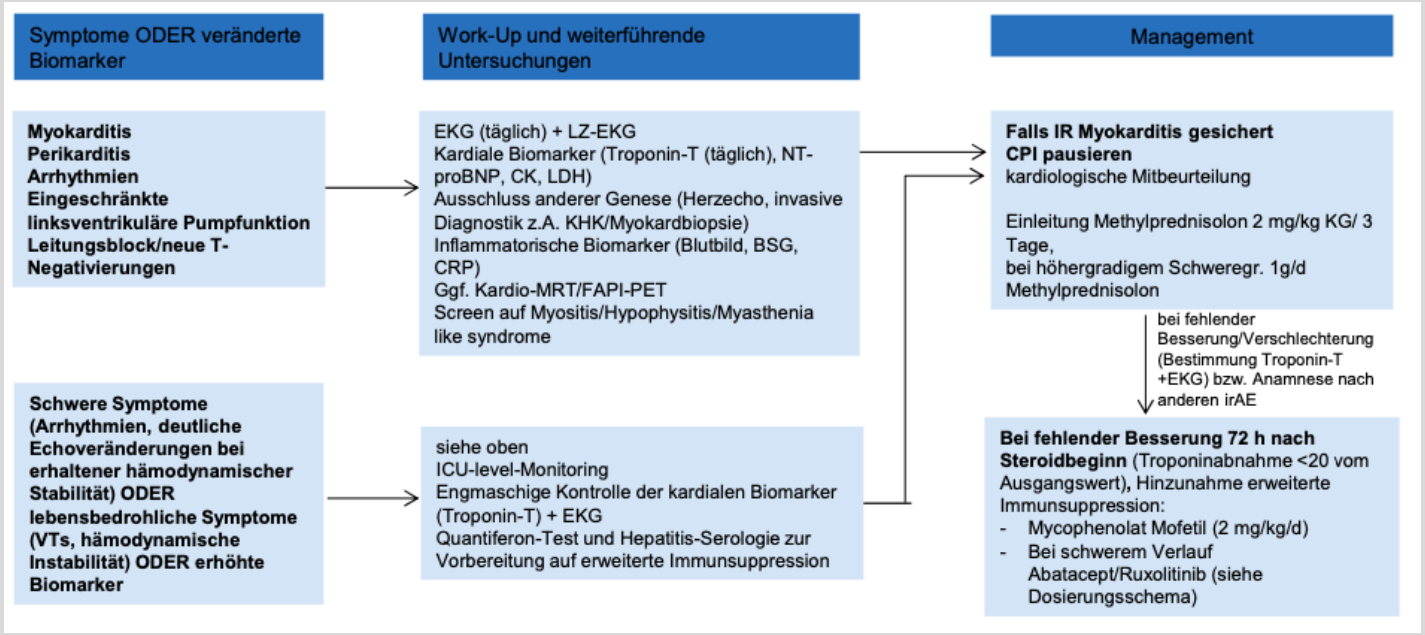


Guidelines Breast
Version 2024.1E

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Cardiovascular Toxicity



Guidelines Breast
Version 2024.1E

Side Effects According Organ Systems
Incidence, Prevention, Therapy

Guidelines Breast
Version 2024.1E

1. **Infections**
   - **General prophylaxis for infections**
   - **Hepatitis B virus screening**
   - **Covid-19 (see joint guidelines with DGHO)**

Guidelines Breast
Version 2024.1E

Prophylaxis of Infections rarely Applicable to Patients with Solid Tumors (e.g. BC)

ASCO Practice Guideline „Antimicrobial Prophylaxis...“ 2018

	Oxford		
	LoE	GR	AGO
▪ Avoidance of highly infection-risking behavior or situations	5	D	+
Review and potential update of vaccination status prior to initiation of therapy (according to recommendations by RKI, STIKO, DGHO	5	D	+
▪ Prophylactic treatment in low-risk patients	1a	B	-
▪ Prophylactic treatment in high-risk* patients (e.g. according to NCCN Guidelines) with			
▪ Antibiotics	1a	A	++
▪ Anti-fungal agents (triazole)	1a	B	+/-
▪ Virostatics in solid tumors	5	D	-
▪ Granulocyte colony-stimulating factors	1a	A	++

* High risk: estimated duration of neutropenia < 100/µl > 7d

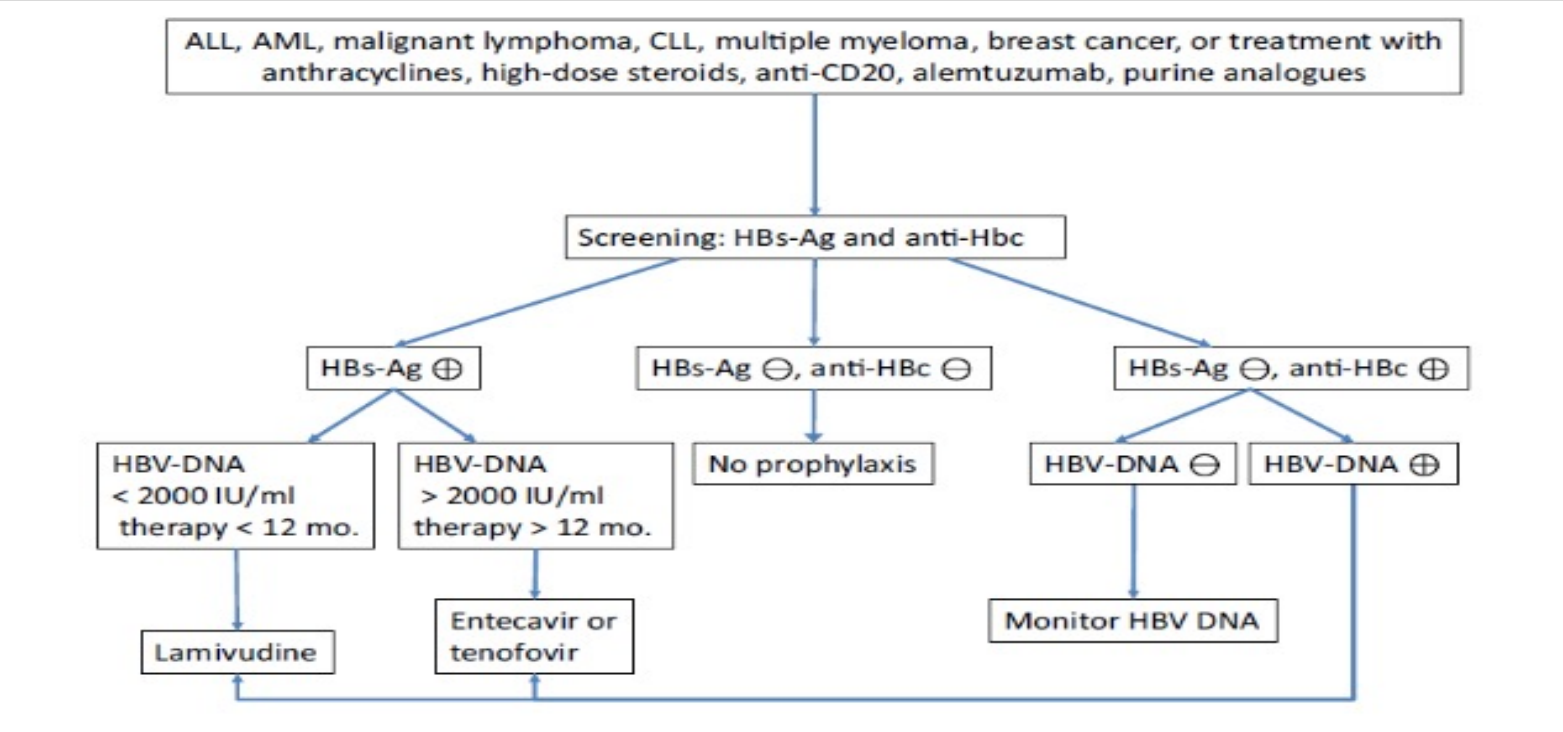
Guidelines Breast
Version 2024.1E

Hepatitis B Virus Screening before Chemotherapy

	Oxford		
	LoE	GR	AGO
▪ Hepatitis B virus screening before adjuvant chemotherapy (HBsAG, anti-HBC, anti-HBs)	2c	B	+
In case of positive serology or reactivation:			
▪ Prophylactic therapy with virustatic drugs if HBV-DNA detected (according AGIHO / DGHO – recommendations)	1b	A	++
▪ Hepatitis C virus screening before chemotherapy	5	D	+/-

AGIHO / DGHO – Recommendations on Hepatitis B Virus Screening in Oncology

Guidelines Breast
Version 2024.1E



Sandherr M et al. Ann Hematol. 2015 Sep;94(9):1441-50

Side Effects According Organ Systems
Incidence, Prevention, Therapy

Guidelines Breast
Version 2024.1E

2. Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

Guidelines Breast
Version 2024.1E

Secondary Malignancies I

	Oxford	
	LoE	GR
▪ With regard to solid tumors, chemotherapy induced secondary malignancies are rare events	2a	
▪ Alkylating agents increase the risk of leukemia dose- dependently to a total of 0.2–0.4% within 10–15 years	2a	
▪ Anthracycline-containing regimens increase the risk of MDS and leukemia to 0.2–1.7% within 8 to 10 years	2a	
▪ PARP-inhibitors are associated with an increased risk of AML and MDS to 0.5–1%	2b	
▪ Radiotherapy increases the risk of leukemia by 0.2–0.4% in patients treated with anthracycline-containing chemotherapy	2b	
▪ Tamoxifen approximately doubles the risk for developing endometrial cancer (in pts. older than 55 yrs. at start of therapy)	2b	

Guidelines Breast
Version 2024.1E

Secondary Malignancies II (After Radiotherapy)

	Oxford LoE
▪ Radiotherapy (PMRT, BET) may moderately enhance the risk of ipsilateral lung cancer and angiosarcoma (10-15/10.000) 5–10 years after treatment	1a
▪ Enhanced risk especially among ever smokers	2b
▪ No difference of secondary malignancy between PBI und WBI	2c

Guidelines Breast
Version 2024.1E

Side Effects According Organ Systems
Incidence, Prevention, Therapy

3. Blood and Lymphatic System Disorders

- Anemia
- Neutropenia
- Febrile Neutropenia (FN)

Anemia – Indications for Therapy with Erythropoiesis-stimulating Agents (ESAs)

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Indicated in asymptomatic anemia	1a	B	-
▪ Therapy and secondary prophylaxis in CTx-induced anemia	1a	A	+
▪ Adjuvant setting	1b	A	+
▪ Neoadjuvant / metastatic setting	1a	A	+/-
▪ In dose-dense / dose-escalated CTx (iddETC)	1b	A	+
▪ Treatment start at Hb-levels < 10 g/dL	1a	A	+
▪ Target Hb 11–12 g/dL	1a	A	+
▪ Improvement of outcome (DFS, OS)	1a	B	--
▪ Risk of thromboembolic events is increased by use of ESAs	1a	A	

Guidelines Breast
Version 2024.1E

Practical Use of ESAs

- **Epoetin α and Darbepoetin are equieffective**
- **Dosage:**
  - **Epoetin α: 150 IU/kg 3 x weekly s.c. or**
    40.000 IU 1 x /week s.c. or
    80.000 IU q2w s.c. or
    120.000 IU q3w s.c.
  - **Epoetin ß: 30.000 IE weekly s.c.**
  - **Darbepoetin: 2,25 µg/kg s.c. weekly or 500 µg s.c. q3w**
- **Weekly hematologic blood controls**
  - **Dose reduction if Hb-increase > 1g/dl within 2 weeks**
  - **Dose increase if Hb-increase < 1g/dl within 4-6 weeks**
- **In case of FID (“functional iron deficiency”) iron supplementation, preferably i.v.**
- **Stop ESA-treatment if there is no Hb increase after 9 weeks**

Guidelines Breast
Version 2024.1E

Granulocyte Colony-Stimulating Factors

	Oxford		
	LoE	GR	AGO
▪ **Primary prophylaxis for expected febrile neutropenia (FN)**			
▪ If expected risk for FN 10–20%	1b	B	+/-
▪ In case of individual risk factors	3b	C	+
▪ If expected risk for FN > 20% (e.g. DAC, dose-dense CT)	1a	A	++
▪ **Secondary prophylaxis during chemotherapy (previous FN or neutropenia grade IV > 7 days)**	1b	A	++
▪ **Therapeutic use for FN**	1a	A	+/-
▪ **Start related to chemotherapy and duration**			
▪ Pegfilgrastim day 2	1b	A	++
▪ Lipegfilgrastim day 2	1b	A	++
▪ Filgrastim / Lenograstim from day 2–3 until ANC > 2–3 x 10^9	1b	A	++

Management of Febrile Neutropenia

c.f. Recommendations by Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO) www.dgho-infektionen.de

Guidelines Breast
Version 2024.1E

Definition (oral temperature of > 38.5°C or two consecutive readings of > 38°C for 2 h in a patient with an ANC of < 500 cells/mm³ or expected to fall to <500 cells/mm³)

	Oxford		
	LoE	GR	AGO
▪ Clinical examination	5	D	++
▪ Daily evaluation	5	D	++
▪ Hospitalization of high-risk patients	1b	A	++
▪ Homecare in low-risk patients	1b	A	+
▪ Differential blood count	5	D	++
▪ Blood cultures	5	D	++
▪ Imaging of lungs	3	C	++
▪ Immediate initially empiric antibiotic therapy	1a	A	++
▪ Empiric antifungal therapy 4–7 d in case of failure of antibiotic therapy	1b	A	++
▪ G-CSF for treatment (not prophylactic)	2b	B	+/-

EORTC and ASCO G-CSF Guideline-Based FN Risk Assessment

Guidelines Breast
Version 2024.1E

Step 1: Assess frequency of FN associated with the planned chemotherapy regimen

FN risk ≥ 20% | **FN risk 10-20%** | **FN risk < 10%**

Step 2: Assess factors that may increase the risk of FN:

High risk:	Age > 65 years
Increased risk: (level I and II evidence)	Advanced disease History of prior FN No antibiotic prophylaxis
Other Factors: (level III and IV evidence)	Poor performance (ECOG > 1) Female gender Haemoglobin < 12 g/dL Liver, renal or cardiovascular disease Nutritional status

Step 3: Define the patient's overall FN risk for planned chemotherapy regimen

Overall FN risk ≥ 20% | **Overall FN risk < 20%**

Prophylactic G-CSF recommended

G-CSF prophylaxis not indicated

Reass ess at each cycle

Guidelines Breast
Version 2024.1E

4. Toxicities / Ovaries

Therapy-associated amenorrhea (CRA, CIA, TIA)

	Oxford LoE
▪ CRA may be permanent or temporary (depending on age of the patient and type of chemotherapy)	2b
▪ The risk of CRA increases with patient‘s age and duration of the chemotherapy	2b
▪ CRA is an imperfect surrogate for menopause and fertility	5
▪ Adjuvant endocrine therapy with GnRHa induces reversible amenorrhea, but delays conception to a less fertile period	5
▪ Ovarian reserve of women who remain premenopausal after CTX is reduced	2b
▪ CRA is associated with improved outcome (DFS / OS)	1b

Synonym: Chemotherapy related or induced / Treatment induced Amenorrhea (CRA, CIA, TIA)

Side Effects According Organ Systems
Incidence, Prevention, Therapy

Guidelines Breast
Version 2024.1E

5. Psychiatric Disorders

- Depression
- Fatigue
- Cognitive impairment
- Sleep disturbances

Guidelines Breast
Version 2024.1E

(Therapy-associated) Depression

	Oxford		
	LoE	GR	AGO
▪ Depression is an often reported adverse event in breast cancer patients (20–30%)	2a	B	
▪ Psychological interventions are effective to improve mood, but not survival in distressed and depressed patients	1b	A	
▪ Antidepressants have shown to improve depression in breast cancer patients	1b	A	
▪ Regular exercise participation can prevent depression in breast cancer survivors	2b	B	+

Guidelines Breast
Version 2024.1E

(Therapy-related) Fatigue

	Oxford		
	LoE	GR	AGO
▪ Fatigue frequent in breast cancer patients (30–60%)	2a	B	
▪ Exclusion of somatic reasons (anemia, tumor burden, co-morbidity, medication) for fatigue	1a	A	++
▪ Psycho-social interventions specifically addressing fatigue efficient in reducing fatigue	1a	A	++
▪ Physical exercise can improve fatigue	1b	D	+
▪ Yoga can improve fatigue	2b	B	+
▪ Methylphenidate or corticosteroids (short-term) can improve fatigue	1a	D	+

Guidelines Breast
Version 2024.1E

(Therapy-associated) Cognitive Impairment

	Oxford	
	LoE	GR
▪ Therapy-related cognitive deficits (“chemobrain”) frequently described (16–75%)	2a	B
▪ Cognitive-behavioral therapy beneficial for cognitive function	2b	B
▪ Methylphenidate may improve cognitive function in cancer patients	3a	C
▪ Under therapy with aromatase inhibitors, deterioriation of cognitive performance was observed (espec. verbal memory)	1a	B

Guidelines Breast
Version 2024.1E

(Therapy-associated) Sleep Disturbances

	Oxford		
	LoE	GR	AGO
▪ Sleep disturbances are a common problem in breast cancer patients during and after therapy (20–70%)	2a	B	
▪ Behavioral therapies demonstrated efficacy in treatment of insomnia and improved quality of life	1b	A	++

Guidelines Breast
Version 2024.1E

Side Effects According Organ Systems
Incidence, Prevention, Therapy

6. Nervous system disorders

- **Chemotherapy-Induced Peripheral Neuropathy (CIPN)**

Guidelines Breast
Version 2024.1E

Chemotherapy-Induced Peripheral Neuropathy (CIPN)

- **Incidence with taxanes:**
  - **Grade 1–2: 20–50%**
  - **Grade 3–4: 6–20%**
- **Risk factors: type and dose of chemotherapy, BMI, reduced physical activity**
- **Individual risk factors**
  - **Diabetes mellitus**
  - **Nutritive-toxic compounds part. alcohol**
  - **Renal failure**
  - **Hypothyreosis**
  - **Collagenoses / vasculitis**
  - **Vitamine deficiency**
  - **HIV-Infection**
  - **CMT-Gen mutations**

Unclear:

- **Other genetic factors (SNPs, mutations)**

Chemotherapy-induced Peripheral Neuropathy – Prevention –

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
Non drug-based prevention			
▪ Functional training (physical fitness, sensomotoric stimulation training etc.)	5	D	+
▪ Compression treatment (tight surgical gloves, compression stockings)	2b	B	+
▪ Cooling gloves and stockings	2b[a]	B	+
▪ Elektro-acupuncture	1b	B	-
Drug-based prevention			
There is no drug-based prophylaxis available			
▪ Venlafaxine	2a	C	+/-
▪ Palmitoylethanolamine (PEA) topically or PO	5	D	+/-
▪ A-lipoic-acid (thioctic acid), amifostine, amitriptyline, acetyl-L-car-nitine, carbamazepine, electrolyte solutions, glutathione, Goshajinkigan (GJG), oxcarbazepine, vitamine B, vitamine E, or other compounds[1]	1b	A	-

[1] For list of not recommended drugs, see Hershman et al. 2014

Chemotherapy-induced Peripheral Neuropathy – Therapy –

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
Non drug-based therapy			
▪ Functional training (physical fitness, sensomotoric stimulation training etc.)	2a	C	+
▪ Physiotherapy / physical treatment	5	D	+
▪ acupuncture	2b	B	+
Drug-based therapy			
▪ Menthol locally (1%), capsaicin / lidocain locally	5	D	+
▪ Baclofen / amitryptiline / ketamin-gel	2b	B	+
▪ Duloxetine for therapy of CIPN-induced pain	1b	B	+
▪ Opioids for therapy of CIPN-induced pain	5	D	+
▪ Palmitoylethanolamine (PEA) topically or PO.	5	D	+/-
▪ Venlafaxine	5	D	+/-
▪ Gabapentin, pregabaline	1b	B	+/-
▪ Amitryptiline / nortripyline, imipramine / desipramine	1b	B	+/-
▪ Acetyl-L-carnitine, lamotrigine, or other compounds[1]	1b	B	-

[1] For list of not recommended drugs, see Hershman et al. 2014

Guidelines Breast
Version 2024.1E

7. Cardiac Disorders

Guidelines Breast
Version 2024.1E

Cardiotoxicity as Long-term Side Effect

	Oxford		
	LoE	GR	AGO
▪ Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.)	2b	B	
▪ Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity	1b	B	
▪ Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently:	2b	B	
▪ Elderly patients, obesity, hypertension, hypercholesterinemia, üre-existing cardiac disease (incl. borderline LVEF), diabetes mellitus			
▪ Monitoring of cardiac function:			
▪ Standardized echocardiography (LVEF or SF in %)	3b	C	+
▪ ECG (QT-interval)	1a	A	+
▪ Troponin I as marker of cardiac toxicicty	2b	B	+/-
▪ Betablocker-prohylaxis during anthracycline therapy	2a	B	+/-

Guidelines Breast
Version 2024.1E

Adjuvant Trastuzumab
Cardiac Monitoring for CHF

Oxford LoE: 5 GR: D AGO: ++

Before start of trastuzumab

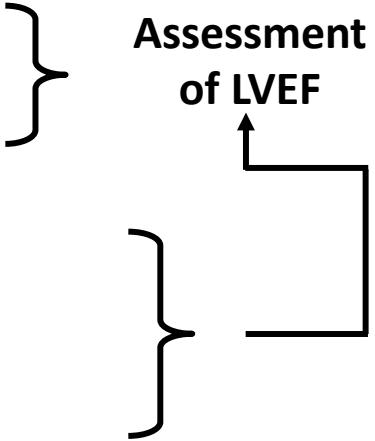
- History, physical examination (edema, hepatomegaly)
- Echocardiography (alternative to MUGA)

During trastuzumab

Regular assessment of

- Heart rate increase > 15% above individual base level
- Body weight increase ≥ 2 kg/week
- Cardiac signs and symptoms

3 monthly assessment of LVEF

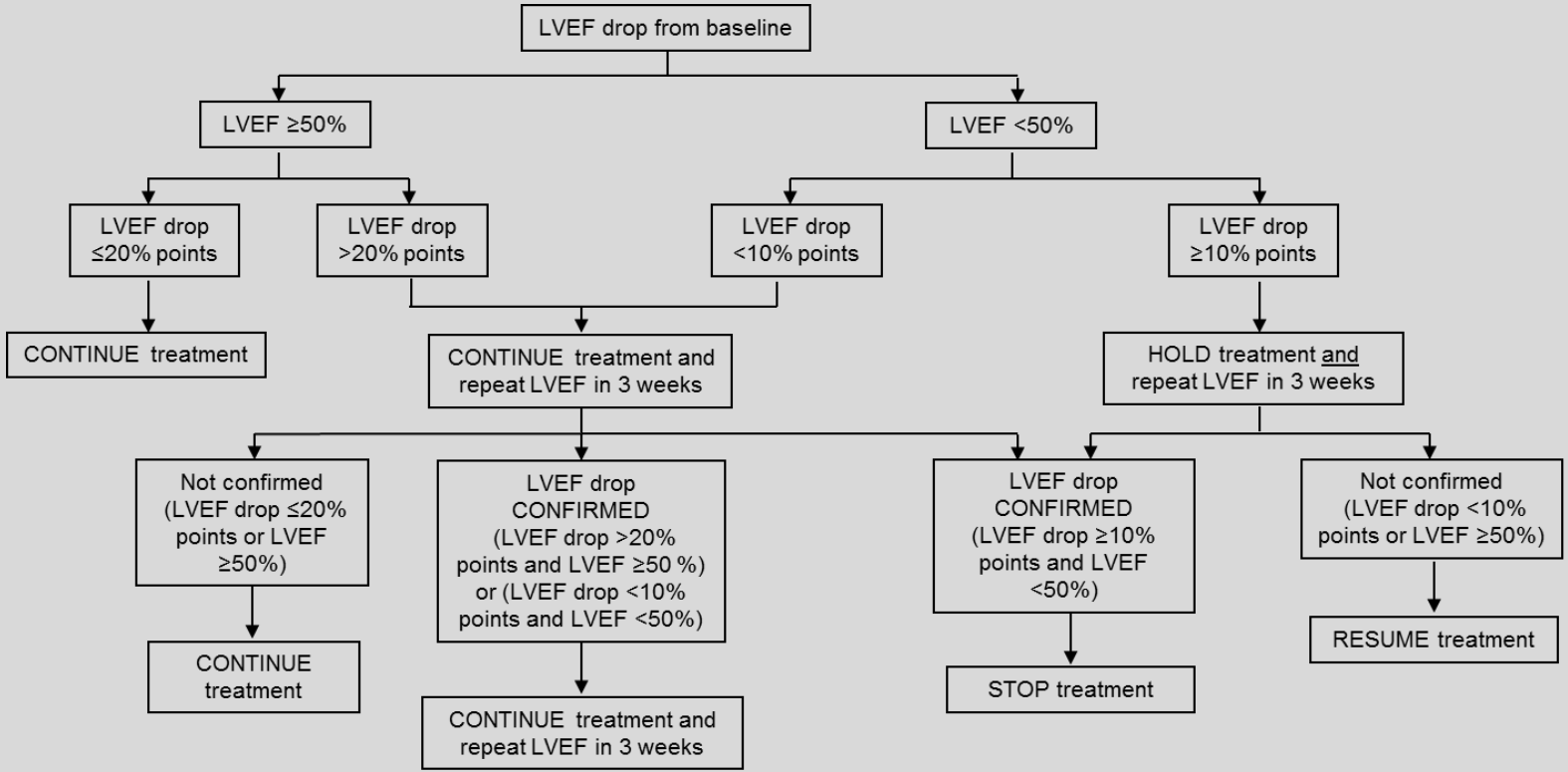


Guidelines Breast
Version 2024.1E

Feasibility of Treatment Combinations Considering Toxicities

	Oxford		
	LoE	GR	AGO
Regarding cardiac toxicity			
▪ Trastuzumab simultaneous to radiotherapy	2b	B	+
▪ Trastuzumab simultaneous to epirubicin	2b	B	+/-
▪ Trastuzumab simultaneous to doxorubicin	2b	B	-
▪ Anthracycline simultaneous to radiotherapy	2c	C	-
Regarding lung and breast fibrosis			
▪ Tamoxifen simultaneous to radiotherapy	3	C	+/-
▪ Chemotherapy simultaneous to radiotherapy	1b	B	-

Side Effects of Trastuzumab / Pertuzumab: Algorithm in Case of Cardiac Toxicity



Guidelines Breast
Version 2024.1E

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Guidelines Breast
Version 2024.1E

Side Effects According Organ Systems
Incidence, Prevention, Therapy

8. Gastrointestinal Disorders

- Nausea, Emesis
- Mucositis
  - Stomatitis (Everolimus)
- Diarrhea
- Constipation

Guidelines Breast
Version 2024.1E

Antiemetic Therapy

http://www.mascc.org/antiemetic-guidelines
www.onkosupport.de

	Oxford		
	LoE	GR	AGO
▪ After assessment of emetic potential of therapy protocol (p.o., i.v., s.c., i.m.)	5	D	++
▪ Neurokinin-1-receptor-antagonists	1b	A	++
▪ Dexamethasone (also in chemotherapy combinations with ICPi)	1a	A	++
▪ 5-HT_3-antagonists	1b	A	++
▪ Fixed antiemetic combination therapy	1b	A	++
▪ Rescue Medication			
▪ Olanzapine	1b	A	+
▪ Levomepromazine, benzodiazepines	3b	C	+
▪ Cannabinoids, ginger	3b	C	+/-

ICPi = Immune Checkpoint inhibitor

Antiemetic Therapy
https://www.mascc.org/antiemetic-guidelines

Guidelines Breast
Version 2024.1E

ACUTE Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS
High Non-AC	5-HT$_3$ + DEX + NK$_1$ +/- OLZ*
High AC	5-HT$_3$ + DEX + NK$_1$ +/- OLZ*
Carboplatin	5-HT$_3$ + DEX + NK$_1$
Moderate (other than carboplatin)	5-HT$_3$ + DEX
Low	5-HT$_3$ or DEX or DOP
Minimal	No routine prophylaxis

5-HT$_3$ = serotonin$_3$ receptor antagonist

DEX = DEXAMETHASONE

NK$_1$ = neurokinin$_1$ receptor antagonist such as APREPITANT or FOSAPREPITANT or ROLAPITANT or NEPA (combination of netupitant and palonosetron)

OLZ = OLANZAPINE

DOP = dopamine receptor antagonist

NOTE: If the NK$_1$ receptor antagonist is not available for AC chemotherapy, palonosetron is the preferred 5-HT$_3$ receptor antagonist.

* **OLZ:** Olanzapine may be added particularly if nausea is a concern.

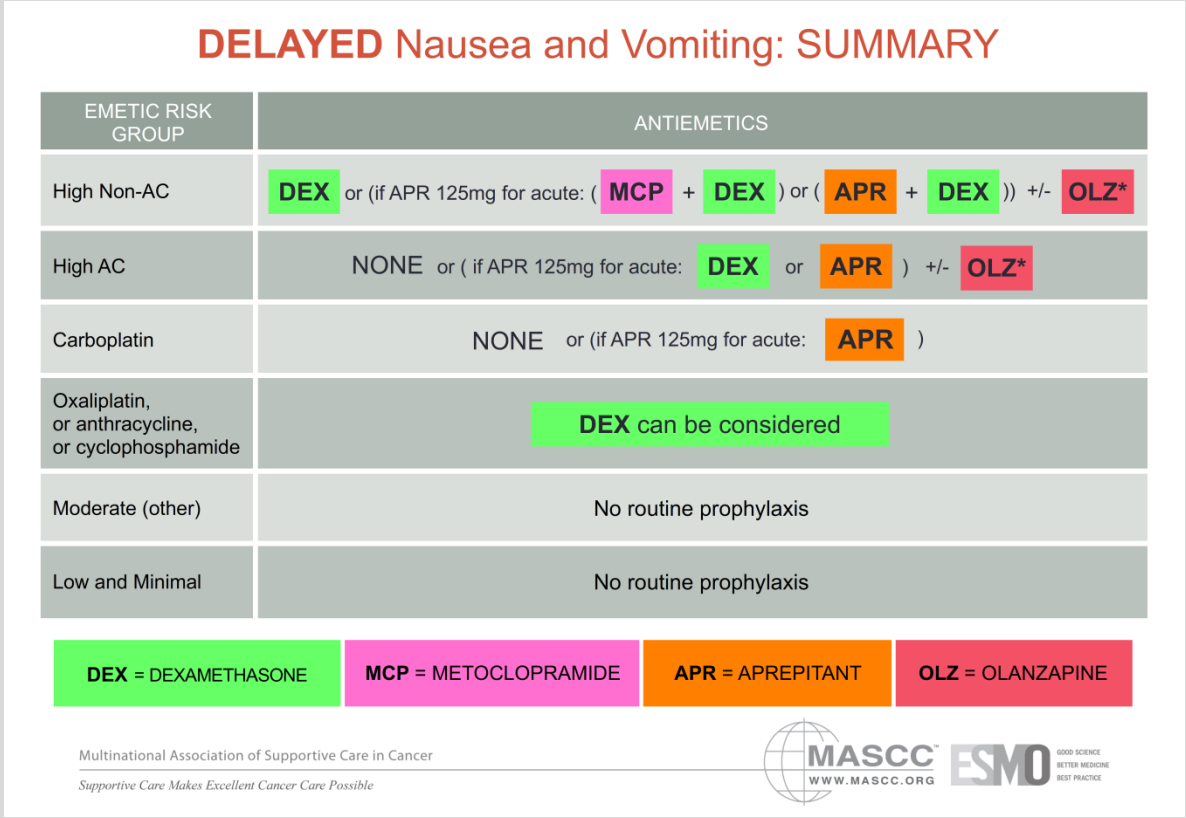
Multinational Association of Supportive Care in Cancer

Supportive Care Makes Excellent Cancer Care Possible

MASCC WWW.MASCC.ORG ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Antiemetic Therapy
https://www.mascc.org/antiemetic-guidelines

Guidelines Breast
Version 2024.1E



Supportive Therapy
Antiemetics

Wirkstoffgruppe	Substanz	Dosierung	Nebenwirkungen	Antiemetic potential
Serotonin-antagonists	Ondansetron Tropisetron Granisetron Palonosetron	8 mg i.v., 2 x 4-8 mg p.o 5 mg i.v., 5 mg p.o. 1-3 mg i.v. 0.25 mg i.v.	Headache, diarrheea, flush, elevated transaminases, intestinal atony (higher doses)	Very high
NK1-Antagonists	Aprepitant Fosaprepitant Rolapitant	125 mg d1, 80 mg d 2-3 p.o. 150 mg d1 i.v. 180 mg d1 p.o.	Activation of cytochrome-P-450-, dose reduction of dexamethasone (2 x 8 mg). No combination with Astemizole, Terfenadine, Cisaprid	Very high
Dopamin-antagonists/ substituted Benzamides	Metoclopramid Alizaprid	Up to 120 mg/24h als continuous infusion or drop bis zu 300 mg i.v. oder p.o./24 h (6 Amp. od. 6 Tbl.)	Dyskinesia (Antidote: Biperiden) Anxiety, depression, diarrhoea	high
Oxazapine	Olanzepin	10mg/d for d1-4 Ggf. 5mg/d for d1-4	Sedation, weight gain	high
Phenothiazine/ Butyrophenone	Haloperidol	1-3 mg 4 x/d	Sedation, reduction of seizure threshold, transient elevation of liver enzymes	intermediate
Corticosteroids	Dexamethasone Prednisolone	8-20 mg i.v. 1-3 x/d 100-250 mg i.v. 1-3 x/d	Hyperglycaemia, psychosis, flush, hypertension	intermediate
Benzodiazepine	Diazepam Lorazepam	Up to 20 mg/d 0,5-1,0 mg/d	Sedation, respiratory depression	Low
NEPA (Netupitant and Palonosetron)	Fixed combination	NE 300 mg PA 0,5 mg		Very high

Mucositis Prevention

https://www.mascc.org/mascc-guidelines

Multidisciplinary S3 guidelines of the AWMF (Reg.-Nr. 032-054OL): „Supportive Therapie bei onkologischen Patientinnen – interdisziplinäre Querschnittsleitlinie“

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ **Standardized mouth hygiene for prophylaxis of oral mucositis should be adhered to by all age groups and during all cancer-related therapies with any risk for oral mucositis.**	2b		++

This entails:

1. **Patient:**
   - **Regular mouth washs (H2O, NaCl)**
   - **Soft toothbrushes**
   - **Interdental care: flossing or using interdental brush**
   - **Avoidance of alcohol, tobacco, hot food, sour food**
   - **Regular screening for lesions**
2. **Risk adjusted prophylaxis by dentist**
3. **Continuous clinical control**

There is no evidence with regard to the use of one of the following compounds: allopurinol, capsaicin, glutamine, honey, camomile, camomile oil or extract, chewing gum, kefir, methadone, nystatin, pentoxifylline, povidone-iodine, vitamine A / E / combinationes

Prevention of Everolimus-Induced Stomatitis Using Corticosteroid-based Mouthwash

- **Study design: single arm phase II-trial (SWISH)**
- **Cohort: 92 pts., treated with everolimus 10 mg and exemestane 25 mg**
- **Schedule: 10 mL of alcohol-free dexamethasone 15 mg per 5 mL oral solution (swish for 2 min and spit) for at least 8–12 weeks***
- **Results: after 13 wks exposition all-grade incidence of stomatitis 27% (BOLERO 67%), ≥ grade 2 events 9% (BOLERO 27%)**

* **Alternatively Hydrocortison: Hydrocortisonacetat-Suspension 0,5% with Lidocainhydrochlorid and Dexpanthenol (Germany: Arzneibuchrezeptur NRF 7.14.)**

Rugo et al., Lancet Oncol 2017, , Jones et al. Oncologist 2019

Guidelines Breast
Version 2024.1E

Mucositis

https://www.mascc.org/mascc-guidelines

- **Desinfecting / antiphlogistic measures: :**
  Mouth rinsing with infusions of chamomile or salvia, extracts of chamomile, etheric oils, polyvidon-iodine, hexetidine. Local therapy with crystal violet solution 0.5% or tinctura myrrhei, H. mometasonfuroate + propylene glycol

- **Mucosa protecting measures (during / after application of chemotherapy):**
  Sucking ice cubes (especially from pineapple juice) during 5-fluorouracile- or HD-melphalane. Calcium folinate (Leucovorin-mouth gel®) every 4–6 hrs for HD-methotrexate:
  do not start earlier than 24 hours after end of MTX-Infusion (otherwise potential loss of efficacy of MTX!).
  Dexpanthenole (Panthenol®-Solution. 5%) mouth rinsing.

- **Local antimycotic treatment:**
  Amphotericin B, nystatin, fluconazole

- **Local antiviral treatment**
  Aminoquinuride / tetracaine-HCl , Aciclovir®

- **Local anaesthesia:**
  Benzocaine, Doxepin 0,5% p.o.

- **Pain Therapy:** Opioids if indicated

Guidelines Breast
Version 2024.1E

Diarrhea

- **Adsorbent agents**
  - **Carbo medicinalis; *caoline / pectine, Al-Mg-silicate hydrate***
- **Analgetics, opioids**
  - **Loperamide; *codeine, morphine IV, tinctura opii (tincture of opium), butylscopolamine***
- **Off-label: Somatostatin-Analogon Octreotid s.c. (starting at grade 3)**
- **Pseudomembranous colitis**
  - **Metronidazole *or (if not effective) vancomycin***

- **Initial dose escalation to reduce grade 3/4 diarrhea**
  - **CONTROL trial (dose escalation of neratinib: 120 mg/d day 1-7, 160 mg/d day 8-14, 240 mg/d afterwards)**

Guidelines Breast
Version 2024.1E

Constipation

Important Side Effect of Opioid Treatment

- **Bulging agents**
  - **Psylium, flaxseed (shredded)**
- **Osmotic laxatives**
  - **Macrogol > Lactulose (Cochrane review LoE 1a, AGO +)**
  - **Oral radio-opaque material: ultima ratio e.g. sodium amidotrizoate**
  - **Sorbitol**
- **Motility stimulating laxatives**
  - **Senna, Ricinus (Castrol Oil), Bisacodyl, sodium-picosulfate**
- **Emollients (Internal lubricants e.g. paraffin)**
- **Opioid-receptor-antagonists (in opioid-related constipation)**
  - **Methylnaltrexone**

Guidelines Breast
Version 2024.1E

9. Skin & Subcutaneous Tissue Disorders (Alopecia)

Guidelines Breast
Version 2024.1E

Skin Toxicities

	Oxford		
	LoE	GR	AGO
▪ Avoidance of chemotherapy-induced alopecia by cooling the patient‘s scalp*	1b		+/-
▪ Prophylaxis of hand-foot-syndrome using urea containing lotions (5-10%)	1b		+
▪ Prophylaxis of nail changes and hand-foot-syndrome by cooling hands during application of docetaxel	2b		+

* Substance- and regimen specific

Guidelines Breast
Version 2024.1E

Scalp Cooling: Scalp Cooling Alopecia Prevention Trial (SCALP) and 3 Metaanalyses

AGO: +/- LOE 2b B

Nangia J, Wang T, Osborne C, et al. Effect of Scalp Cooling Device on Alopecia in Women Undergoing Chemotherapy for Breast Cancer: The SCALP Randomized Clinical Trial JAMA. 2017 Feb 14;317(6):596-605.

Primary Outcome: hair preservation
Cooling: 50.5% success vs. 49.5% failure
Non-cooling: 0% success vs. 100% failure
Fisher's exact test $p < 0.001$

Two Meta-analyses: AGO: +/- LOE 1b

Scalp cooling reduced relative risk (RR) of alopecia by 43% (RR, 0.57; 95% CI, 0.45-0.72; $I^2 = 11\%$; $p < .00001$). (Rugo & Voigt, Clinical Breast Cancer 2018; 18(1): 19-28.)

Incidence rate of scalp metastasis (SC vs. no-SC) 0.61% vs. 0.41%; p = 0.43. (Rugo & Voigt; BCRT 2017)

Guidelines Breast
Version 2024.1E

10. Musculoskeletal & connective tissue disorders

(see Chapter Osteooncology)

Guidelines Breast
Version 2024.1E

11. General Disorders & Administration Site Conditions

Extravasation of Potentially Necrotizing Compounds (Anthracyclines, Taxanes, Vinorelbine)

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Dexrazoxane for treatment of anthracycline-extravasations (exception: liposomal Anthracyclines)	2b	B	++
▪ Hyaluronic acid for treatment of taxane / vinorelbine-extravasations (off-label use)	3b	B	+

Extravasation of Chemotherapy
Role of Dexrazoxane / Hyaluronic Acid

Guidelines Breast
Version 2024.1E

Dexrazoxane for treatment of anthracyclines paravasates

Day 1: 1000 mg/m² (max. 2000 mg), IV 1–2 hrs
Day 2: 1000 mg/m² (max. 2000 mg), IV 1–2 hrs
Day 3: 500 mg/m² (max. 1000 mg), IV 1–2 hrs

Otherwise or if treatment with dexrazoxane is not indicated, following measures are recommended:

1. **Local cooling: ice packs for 15 min every 6 hrs, for at least 3 days, alternatively: 24 h continuous ice cooling**
2. **Local application (with swab) of dimethylsulfoxid 99% (DMSO) every 3-4 hours for at least 3 days (better 14 days), allow it to air dry. The interval may be extended to 6 hours from day 4 onward.**

Hyaluronic Acid in case of Taxan/Vinorelbin Paravasates:

- **1–10 Amp a 150 IU**
- **1 ml dissolvent (e.g. NaCl 0.9%)**
- **Local anaesthesia**
- **No thermotherapy after taxanes**
- **Dry warmth 4 x daily 20 min during vincaalkaloids**

Side Effects According Organ Systems
Incidence, Prevention, Therapy

Guidelines Breast
Version 2024.1E

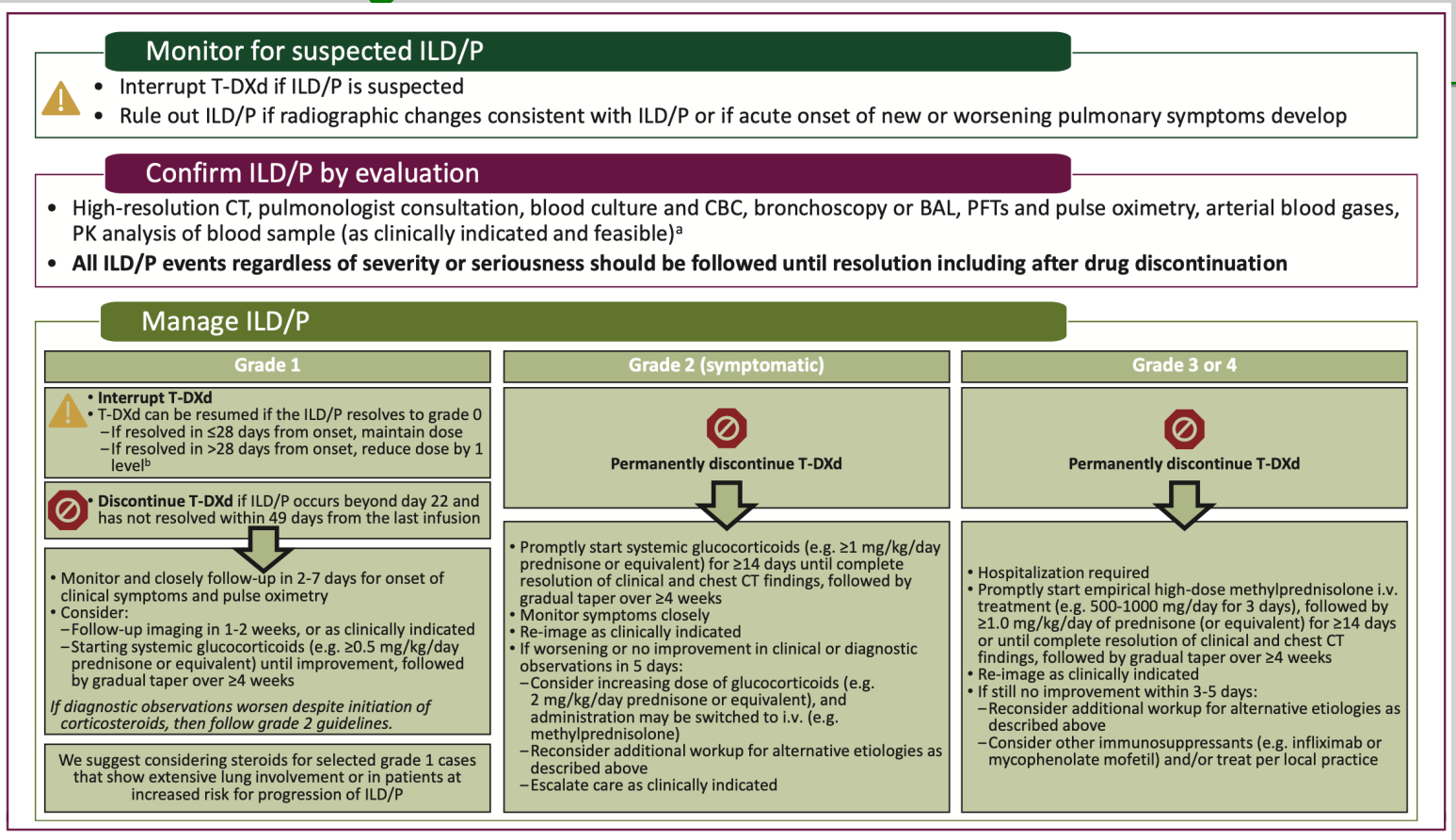
11. Lung

Guidelines Breast
Version 2024.1E

Drug-induced Pneumonitis, Interstitial Lung Disease (ILD)

	Oxford		
	LoE	GR	AGO
Diagnostic work-up with chest CT	1a	B	++
Therapy according to grade and drug*			
Corticosteroids (start with ≥ 0.5 mg/kg/d prednisolone-equivalent)	1a	B	++
Dose hold or therapy discontinuation* (according to respective product information)	1b	B	++

Management ILD -Trastuzumab Deruxtecan



- Rugo HS et al. ESMO Open. 2022 Aug;7(4):100553

Guidelines Breast
Version 2024.1E

Guidelines Breast
Version 2024.1E

Further Supportive and Palliative Issues

- **Orphan symptome (from ESMO-guideline for orphan symptoms 2020):**
  - **Muscle cramps**
  - **Myoclonus**
  - **Taste alterations**
  - **Dry mouth (Xerostomia)**
  - **Cough, Hiccup**
  - **Rectal tenesmus**
  - **Restless legs-syndrom**

- **Further issues**
  - **Nutrition**
  - **Pain management**
  - **Palliative Care**
  - **CNS metastases (see chapter)**

Guidelines Breast
Version 2024.1E

Nutrition Deficiency

- **Nutrient deficiency is a common medical problem affecting 15-40% of cancer patients. It impairs their quality of life and can affect the success of treatment.**
- **Integration of nutritional advice into clinical management recommended.**
- **For nutrition see S3 guideline Palliative care and supportive therapy.**

Guidelines Breast
Version 2024.1E

Analgesia

- **Non-opioids; WHO Step 1**
  Diclofenac resinate, ibuprofen and / or metamizole, paracetamol (acetaminophen)
- **Mild opioids; WHO Step 2**
  Tramadol (preferentially „retard“-formulations) or tilidine / naloxone (also as „retard“-formulations)
- **Strong opioids; WHO Step 3**
  Morphine, buprenorphine (sublingual or transdermal), fentanyl (transdermal), hydromorphone, oxycodone, as a back-up levomethadone. The dose of opioids should be titrated step by step according to the analgetic effect.
- **Additional drugs – „adjuvants“**
  Canabinoide, Gabapentin, pregabalin, carbamazepine, amitriptyline, bisphosphonates

Guidelines Breast
Version 2024.1E

Palliative Care

- **All patients should be offered palliative care after the diagnosis of a non-curable cancer, regardless of whether a tumour-specific therapy is carried out.**
- **In patients with incurable disease advance care planning (incl. advance directive) should be recommended.**
- **Specialized palliative care should be integrated into oncological decision-making processes, e.g. by participating in interdisciplinary tumor conferences.**
- **Patients with incurable cancer who are cared for in structures of specialized palliative care (palliative care ward, specialized outpatient care such as SAPV) should have access to oncological councelling.**

https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

Breast Cancer:
Specific Situations

Guidelines Breast
Version 2024.1E

Breast Cancer:
Specific Situations

- **Versions 2005–2023:**
  Dall / Ditsch / Fehm / Fersis / Friedrich / Gerber / Gluz / Göhring / Harbeck / Huober / Janni / Kolberg-Liedtke / Loibl / Lück / Lux / Maass / Mundhenke / Müller / Oberhoff / Rody / Scharl / Schmidt / Schneeweiss / Schütz / Sinn / Solomayer / Stickeler / Thomssen

- **Version 2024**
  Harbeck / Sinn / Thomssen

Guidelines Breast
Version 2024.1E

Content – Specific Situations

- Young patients ≤ 40 years
- Pregnancy and breast feeding-associated BC
- Elderly patients
  - Geriatric assessment
- Male patients
- Inflammatory breast cancer (IBC, cT4d)
- Occult breast cancer - axillary CUP („Cancer of Unknown Primary“)
- Paget‘s disease
- Malignant and Boderline Phylloides-Tumor
- Sarcoma, Angiosarcoma
- Metaplastisc breast cancer

Guidelines Breast
Version 2024.1E

Breast Cancer in Young Women ≤ 40 Years

	Oxford		
	LoE	GR	AGO
▪ Aggressive biological behavior with worse prognosis	2a	B	
▪ Local therapy independent of young age	2b	B	+
▪ Guidelines adapted (neo-)adjuvant systemic treatment (see respective chapters)	1b	A	++
▪ ET interruption (max. 2 years after at least 18 months of previous therapy) in case of desire to have children without short-term survival disadvantage	2b	B	+
▪ GnRHa as ovarian protection (see chapter gynecological problems)	1a	B	+
▪ Genetic and fertility counseling	2b	B	++
▪ Contraception counseling	2b	B	++

Breast Cancer During Pregnancy* or Breast Feeding – Diagnostics and Surgery

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Breast imaging and biopsy like as in non-pregnant patients (no general indication for MRI)	4	C	++
▪ Staging if indicated (bone scan after delivery)	5	D	+
▪ Full body MRI (without contrast agent)	4	C	+/-
▪ Surgery like in non-pregnant patients	4	C	++
▪ Sentinel node excision (technetium only)	2a	B	+
▪ SLNE during 1st trimester	5	D	+/-
▪ Sensitivity and specificity not established (during lactation); breast feeding should be avoided for 24 hrs	4	C	++
▪ Blue dye (not tested in pregnant animals or humans)	4	C	--

* Participation in register study recommended

Breast Cancer During Pregnancy or Breast Feeding - (Neo-)adjuvant Therapy

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Radiation therapy during pregnancy	4	C	-
▪ (Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant)			++
▪ Anthracyclines: AC	2b	B	++
▪ Dose-dense regimens with short-acting G-CSF	4	C	+/-
▪ Taxanes	2a	B	++
▪ Platinum salts (carboplatin, cisplatinum)	4	C	+/-
▪ MTX (e.g. CMF)	4	D	--
▪ Endocrine treatment	4	D	--
▪ HER2-targeted treatment	3a	C	--
▪ Checkpoint inhibitors	4	D	--
▪ Bisphosphonates, denosumab	4	D	--

Treatment (Chemotherapy, surgical procedure and radiotherapy) of patients with breast cancer during pregnancy should be as similar as possible to standard treatment of young, not pregnant patients with breast cancer.

Breast Cancer During Pregnancy* or Breast Feeding – Delivery and Breast-Feeding

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Delivery should be postponed until sufficient fetal maturation (avoid iatrogenic prematurity)	2b	C	++
▪ Termination of pregnancy does not improve maternal outcome	3b	C	
▪ Delivery mode like in healthy women; avoid delivery during chemotherapy-induced leucocyte nadir	4	C	++
▪ If further systemic therapy is needed after delivery, breast feeding may be contra-indicated depending on drug toxicities	5	D	++

* Participation in register study recommended

Breast Cancer and Pregnancy* or Breast Feeding – Family Planning

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Breast cancer patients of reproductive age should be offered fertility counseling before starting any kind of treatment	5	D	++
▪ Assisted reproductive treatment after breast cancer	4	D	+/-
▪ Success rates for getting pregnant and for delivering a child lower in breast cancer patients compared to non-cancer patients	3b	D	
▪ Breast cancer patients should not be advised against getting pregnant independent of their tumor‘s hormone receptor status and g*BRCA* status	2a	B	

* Participation in register study recommended

Breast Cancer During Pregnancy* and Breast Feeding - Outcome -

	Oxford LoE
▪ **BC during pregnancy**	
▪ **Prognosis is not worse if adequately treated**	3a
▪ **BC during lactation and within the first year after pregnancy**	
▪ **Prognosis worse than in BCP and if unrelated to pregnancy**	3a
▪ **Pregnancy / lactation after BC**	
▪ **Outcome not compromised**	3a

* **Participation in register study recommended**

Treatment for Fit Elderly Patients

(Life Expectancy > 5 yrs. and Acceptable Comorbidities)

	Oxford		
	LoE	GR	AGO
▪ **Clinical geriatric assessment**	2b	B	++
▪ **Treatment according to guidelines**	2a	C	++
▪ Surgery similar to „younger“ age	2b	B	++
▪ Endocrine treatment (HR+)	1a	A	++
▪ Chemotherapy (standard regimens)			
▪ ≤ 70 years	1a	A	+
▪ > 70 years (especially N+, ER / PR-)	2a	C	+*
▪ Radiotherapy	1a	A	+
▪ Omit radiotherapy after BCS if low-risk, and if endocrine treatment is administered	1b	B	+
▪ Anti-HER2-therapy	2b	C	+

* Study participation recommended

Guidelines Breast
Version 2024.1E

Treatment for Frail Patients

(Life Expectancy < 5 yrs., Substantial Comorbidities)

	Oxford		
	LoE	GR	AGO
▪ **Reduced standard treatment**	2b	C	++
▪ **Options extrapolated from trials in elderly:**			
▪ No breast surgery (consider endocrine therapy)	2b	C	+
▪ No axillary clearing (≥ 60 y, cN0, HR-pos)	2b	B	+
▪ No radiotherapy (Tumor size < 3 cm, pN0, HR-pos)	1b	B	++
▪ Hypofractionated radiotherapy	2b	B	+
▪ No chemotherapy if > 70 yrs. and negative risk-benefit analysis	2b	C	+

Guidelines Breast
Version 2024.1D

Geriatric Assessment

- **Ability to tolerate treatment varies greatly („functional reserve“)**
- **Comprehensive geriatric assessment describes a multidisciplinary evaluation of independent predictors of morbidity & mortality for older individuals (CGA)**
  - **Physical, mental, and psycho-social health**
  - **Basic activities of daily living (dressing, bathing, meal preparation, medication management, etc.)**
  - **Living arrangements, social network, access to support services**
- **General assessment tools:**
  - **Charlson Comorbidity Index (CCI, widely used; good predictor over a 10-year period)**
  - **12 prognostic indicators to estimate 4-year mortality risk**
  - **Short screening tests (more qualitative evaluation)**
    - **IADL (IADL = The Lawton Instrumental Activities of Daily Living Scale with 8 domains of function, that are measured)**
    - **G8 (Age plus Malnutrition Assessment, MNA)**
    - **Geriatric Prognostic Index (GPI), 3 parameters in oncological patients (food intake in the last 3 months, >3 prescribed drugs, moblity and autonomy)**
    - **Timed-up-and-go-test**
    - **Frailty Index (FI), Carolina Frailty Index (CFI)**

Links to current frailty scales:

CCI

IADL

G8

GPI

Timed up&go

FI

Male Breast Cancer*: Diagnostic Work-Up and Loco-Regional Therapy

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Diagnostic work-up as in women	4	C	+
▪ Ultrasound	2b	B	++
▪ Mammography	3b	C	+
▪ Standard-surgery: Mastectomy	4	C	++**
▪ BCT is an option (tumor / breast relation)	4	C	+**
▪ Sentinel-node excision (SLNE)	2b	B	+
▪ In occult breast cancer	2b	B	+
▪ Radiotherapy as in women (consider tumor / breast relation!)	4	C	+
▪ Genetic counseling (see genetics chapter)	2b	B	++
▪ Screening for 2nd malignancies according to guidelines	GCP		++

* Treatment in certified breast cancer centers recommended; ** Participation in register study recommended

Guidelines Breast
Version 2024.1E

Male Breast Cancer: Prognostic Factors

	Oxford		
	LoE	GR	AGO
▪ Nodal status	2b	A	++
▪ Age	2b	B	+
▪ Tumor size	2b	A	++
▪ ER / PR Expression	2b	A	++
▪ Ki-67 Expression	2b	C	+/-
▪ Grade	2b	C	+/-
▪ Genomic signatures	2b	B	+

Male Breast Cancer: Systemic Therapy

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ (Neo-)adjuvant chemotherapy as in women	2a	B	++
▪ HER2-targeted therapy (if HER2-positive)	5	D	++
▪ Endocrine therapy	4	D	++
▪ Tamoxifen	2b	B	++
▪ GnRHa and AI	4	C	+
▪ Aromatase inhibitors without GnRHa	2b	B	-
▪ Fulvestrant (metastatic BC)	4	C	+/-
▪ CDK4/6i (in combination)	2b	B	+
▪ Palliative chemotherapy as in women	4	C	++

Guidelines Breast
Version 2024.1E

Inflammatory Breast Cancer (IBC, cT4d)

	Oxford		
	LoE	GR	AGO
▪ Invasive BC and clinical signs of inflammation (e.g. ≥ 1/3 of the breast affected) determine stage cT4d			++
▪ Staging (including adequate breast imaging)	2c	B	++
▪ Skin punch biopsy (at least 2; detection rate < 75%)	2c	B	+
▪ Treatment according to guidelines (neoadjuvant or adjuvant – as in non-IBC)	2c	B	++
▪ Mastectomy after chemotherapy	2c	B	+
▪ Breast conserving therapy in case of pCR (individual)	2b	C	+/-
▪ Delayed breast reconstruction	3b	C	+
▪ Sentinel excision only	3b	C	-
▪ Radiotherapy of the chest wall including regional lymph nodes independent of therapy response	2c	B	++

Axillary Metastasis in Occult Breast Cancer (Axillary CUP) Diagnostic Imaging

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ **Breast imaging incl. Breast-MRI**	3	B	++
▪ **Exclude contralateral cancer**	3	B	++
▪ **Staging** (CT thorax / abdomen, pelvis, bone scan)	3	B	++
If histological diagnosis is not certain			
▪ **Exclude non-breast malignancy, especially in case of TNBC** (e.g. NEC, female genital tract, lung, thyroid gland, stomach, skin, ENT)	5	D	++
▪ **PET / PET-CT**	3b	B	+

Axillary Metastasis in Occult Breast Cancer (Cancer of Unknown Primary – Axillary CUP)

Guidelines Breast
Version 2024.1E

- **Incidence: < 1% of metastatic axillary disease**
- **In > 95% occult breast cancer, < 5% other primary**
- **Immunhistology**
  - **ER-positive: 55%**
  - **HER2 3+: 35%**
  - **Triple-negative: 38%**
- **Nodal status:**
  - **1 - 3 Ln-Met. in 48%**
  - **> 3 Ln-Met in 52%**
- **Outcome similar or better compared to breast cancer with similar tumor biology and tumor stage**

Axillary Metastasis in Occult Breast Cancer (ex. CUP)

Pathology, Molecular Pathology

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Immunohistochemistry (ER, PR, HER2, Ki-67, GATA)	5	D	++
▪ Immunohistochemistry (e.g. Ck5/6, Ck7, Ck20, SOX-10, PAX-8, TTF1, Synaptophysin etc.) to exclude other primary malignancies in case of TNBC phenotype or unusual histology, e.g. NEC, female genital tract, lung, ENT tumors, thyroid, stomach, skin	5	D	++
▪ Gene expression profiling for determination or primary site (e.g. CUPprint, Pathwork, TOT, CancerType)	2c	B	+/-
▪ NGS, epigenetics for determination of primary site (Panel-Sequencing, e.g. EPICup)	2c	B	+/-
▪ Prognostic gene expression tests	5	D	--

Axillary Metastasis in Occult Breast Cancer (Axillary CUP): Therapy

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Axillary dissection	3a	C	++
▪ Targeted axillary dissection after NACT (in case of clinical complete remission	3b	C	+/-
▪ Irradiation of regional lymph nodes according to breast cancer guidelines (AGO)	3b	B	+
▪ Breast irradiation if breast MRI is negative (acc. BCT)	2c	B	+
▪ Mastectomy if breast MRI is negative	3a	C	--
▪ (Neo-)adjuvant systemic therapy according to breast cancer guidelines (AGO)	5	D	++

„BCT“ in patients with axillary met‘s and occult primary (AxCUP, OBC)

Guidelines Breast
Version 2024.1E

Kim H, Park W, Kim SS et al. Prognosis of patients with axillary lymph node metastases from occult breast cancer analysis of multicenter data. Radiat Oncol J. 2021 Jun;39(2):107-112.
Retrospective analysis, n = 53 with AxCUP and OBC (adenocarcinoma); exclusion of a primary by extensive imaging. Eleven pts received blind upper quadrantectomy, 42 no breast surgery; 46 pts received whole breast irradiation (WBI), 7 did not; median F/U 85 months .
Result: 2 in-breast recurrences, 1 RLN rec., 1 combined in-breast and RLN, no distant metastases.
5 year DFS with WBI: 97.8% without WBI 83,3% (p = 0.01 univariate; in multivariate analysis nor biology nor extent of the disease nor therapy had a significant impact).
Discussion: ..in patients confirmed to have no lesion in the breast by contemporary imaging studies, it is necessary to include the ipsilateral breast in the radiation field in females with OBC presenting as AxCUP.

Tsai C, Zhao B, Chan T, Blair SL. Treatment for occult breast cancer: A propensity score analysis of the National Cancer Database. Am J Surg. 2020 Jul;220(1):153-160.
Given the equipoise in overall survival among the treatment options, we conclude that after axillary clearance, **breast preservation and radiation therapy alone may be sufficient** in the treatment of patients with occult breast cancer.

Guidelines Breast
Version 2024.1E

Paget‘s Disease of the Breast Diagnosis

„Mammary Paget Disease is a Sentinel Sign“

	Oxford		
	LoE	GR	AGO
▪ Histological verification by skin biopsy*			++
▪ Mammography, sonography	4	D	++
▪ MRI of the breast if other imaging negative	4	C	+
▪ Immunohistochemistry (ER, PR, HER2, CK7) to detect benign and HER2-negative cases	5	D	++

* including all skin strata (e.g. by punch biospy or wedge excision)

Guidelines Breast
Version 2024.1E

Paget‘s Disease of the Breast

- **Definition: Paget‘s disease of the breast is characterized by an intraepidermal tumor manifestation originating in intraductal or invasive breast cancer.**
- **Clinical presentation: skin eczema of the nipple, areola and surrounding skin; thickening, pigmentation and scaly skin**

Feature	Frequency
Presentation	Paget‘s disease with invasive Ca. (37-58%) Paget‘s disease mit DCIS (30-63%) Isolated Paget‘s disease (4-7%) Isolated Paget‘s disease with invasion (rare)
IHC	HER2-positive (83-97%) ER-positive (10-14%) AR-positive (71-88%)
Prognosis and tumor biology	Better in isolated Paget‘s disease Worse if in combination with invasive breast cancer or DCIS compared to isolated Paget‘s disease

Paget‘s Disease of the Breast Therapy

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
Paget‘s disease with underlying disease (invasive breast cancer, DCIS)			
▪ Therapy according to standard of underlying disease	5	D	++
▪ Surgery must achieve R0	1c	B	++
Isolated Paget‘s disease of the NAC:			
▪ Surgery must achieve R0	1c	B	++
▪ Surgical resection only, no adjuvant radiotherapy	4	D	++
▪ Sentinel-node excision (SLNE)	2b	B	--

Borderline and Malignant Phyllodes Tumor Diagnosis

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Mammography, sonography	3	C	++
▪ Diagnosis on core biopsy, grade determination on resection specimen	3	C	++
▪ Breast MRI	3	C	+/-
▪ Staging only malignant PT (CT thorax / abdomen, bone scan)	5	D	++

Guidelines Breast
Version 2024.1E

Borderline and Malignant Phyllodes Tumor

- Name derived from greek term of “Phyllon” (leaf) due to its lobulated histological aspect
- Differential diagnosis may be problematic on core biopsy
- Resection margin is independent prognostic parameter
- Comparable rates of recurrence in association with BCT or mastectomy
- In-Breast recurrence relatively frequently seen (10 - 30%)
- Distant metastasis relatively rare (< 10%) and almost exclusively seen in malignant phyllodes tumor.
- Adverse pathological criteria: marked stromal cellularity and overgrowth, increased nuclear atypia, presence of large necrohemorrhagic areas, and high mitotic activity associated with increased risk of distant recurrence

Phyllodes Tumor

- **Frequency 0.3 – 1% of all primary breast tumors**

parameter	frequencies
Grading (3-STEP histological grading system)	Benign (75%) Borderline (16%) Malignant (9%)
Median age at time of diagnosis	Benign PT: 39 y Borderline PT: 45 y Malignant PT: 47 y
Local recurrence	Benign PT: 4 – 17% Borderline PT: 14 – 25% Malignant PT: 23 – 30%
Metastasis	Benign PT: < 1% Borderline: PT: 1.6% Malignant PT: 16-22%

10 y OS: 86–90% (range: 57–100%) depending on subtype and unfavorable histological criteria

Borderline and Malignant Phyllodes Tumor Surgery

	Oxford		
	LoE	GR	AGO
▪ Fibroepithelial lesions with rapid growth or size > 3 cm should be excised (independently from the any CNB result)	5	D	++
▪ If the result of the CNB is unclear or suspicious for PT, excision with clear margins should be performed	5	D	++
▪ SLNE / Axillary dissection (if clinically unsuspicious)	4	C	--
▪ Treatment of local recurrence			
▪ R0 resection or simple mastectomy	4	C	++

Phyllodes Tumors of the Breast: Canadian National Consensus Document Using Modified Delphi Methodology

Guidelines Breast
Version 2024.1E

Canadian Phyllodes Tumor Consensus Panel (23 panelists): Example of one out of 109 state-ments on diagnosis and therapy of phyllodes tumors that were discussed (73 with consensus).

The following statements are referring to MALIGNANT phyllodes (diagnosed on biopsy)

If the diagnosis of malignant PT is known preoperatively, malignant PT should under-go wide excision (clinical 1 cm), with the goal of negative microscopic margins 87%

- In patients with negative margins who undergo wide excision (clinical 1cm) – if the
- microscopic margin is:
  - < 2 mm: reexcision of margin can be offered 82%
  - 2–10 mm: no re-excision should be offered 65%
  - > 10 mm: no reexcision should be offered 100%
- Patients with tumor on ink after breast conservation, should be offered reexcision (this includes "shelled out" and positive margins) 96%

Bogach J et al. Ann Surg Oncol. 2023 Oct;30(11):6386-6397.

Borderline and Malignant Phyllodes Tumor
- Margins -

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
■ **Intended lesion-free surgical margins are*** **- in borderline PT: ≥ 2 mm** **- in malignant PT: ≥ 10 mm**	2b	B	++
■ **Intended pathologically lesion-free margins are*** **- in borderline PT: negative („no ink on the tumor“)** **- in malignant PT: ≥ 2 mm**	2b	B	++
■ **Re-resection recommended** **- in borderline PT: if margin* positive („tumor on ink“)** **- in malignant PT: if margin < 2 mm**	2b	B	++

* Margins related to breast tissue only (but not to skin or to the thoracic wall)

Borderline and Malignant Phyllodes Tumor
- Adjuvant Radiotherapy -

Guidelines Breast
Version 2024.1E

Adjuvant radiotherapy of the breast and the thoracic wall is aimed at local control.

	Oxford		
	LoE	GR	AGO
■ **BCS, R0-resection** - Borderline PT: no - Malignant PT: yes (independently from the size of the lesion)	2b	B	+
■ **Mastectomy, R0-resection** - Borderline PT: no - Malignant PT: < 5 cm: no - Malignant PT: ≥ 5 cm: with aggressive pathology or growth	2b	B	+
■ **Mastectomy, R1-resection** - Borderline PT: no - Maligner PT: ja (independently from the size of the lesion)	2b	B	+

Borderline and Malignant Phyllodes Tumor
Systemic Adjuvant Therapy

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
Systemic adjuvant therapy (chemo, endocrine)			
Adjuvant endocrine therapy (irrespect. of ER/PR)	5	D	-
Adjuvant chemotherapy	4	C	-
Primary systemic therapy, if complete resection (R0) presumably cannot be achieved (Adriamycin/Ifosfamid)	4	C	+
Adjuvant Treatment of local recurrence			
Radiotherapy, chemotherapy after R1 resection	4	C	+/-
Distant metastasis (very rare)			
Multidisciplinary case discussion („Sarcoma board“)	5	D	++
Treatment like soft tissue sarcomas	4	C	++
Surgical resection of metastatic lesions	4	C	+

Guidelines Breast
Version 2024.1E

Primary Angiosarcoma of the Breast*
Diagnosis

	Oxford		
	LoE	GR	AGO
▪ Mammography, sonography to determine extent of disease	3a	C	--
▪ Preoperative MRI to determine the extent of disease	3a	C	++
▪ Diagnosis by core biopsy	3a	C	++
▪ Diagnosis by FNB	3a	C	--
▪ Staging (CT thorax & abd.; angiosarcoma: MRI brain)	4	D	++
▪ Prognostic factors: size, grade, margins	3a	C	++

* Therapy in specialized centers recommended

Guidelines Breast
Version 2024.1E

Sarcomas of the Breast

- **Not infrequently associated with familial syndromes (Li-Fraumeni, familial adenomatous polyposis, neurofibromatosis type 1)**
- **Primary sarcomas: angiosarcoma, undifferentiated sarcoma, leiomyosarcoma, liposarcoma, osteosarcoma**
- **Secondary malignancies of the breast:**
  - **Radiotherapy-Associated Angiosarcoma**
  - **Breast Implant Associated Large-Cell Anaplastic Lymphoma (BI-ALCL)**
- **Rare: intramammary sarcoma metastases**
- **Staging: TNM (UICC) or AJCC scheme of the soft tissue sarcoma analogous to sarcoma of the breast**
- **Grading: Analogous to the FNCLCC system for sarcoma or according to Rosen (1988) for angiosarcomas**

Guidelines Breast
Version 2024.1E

Primary Angiosarcoma of the Breast

- Most common primary sarcoma of the breast
- Young age (median: 24–46 years)
- Indistinct tumor borders
- Large tumor (median: 5–7 cm)
- Uncharacteristic findings on mammography and sonography
- High local recurrence risk, even after mastectomy
- More unfavorable prognosis than other primary sarcoma of the breast
- Metastasize early, often to the lung and liver

Primary Angiosarcoma of the Breast* Therapy

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Surgery with wide clear margins, mostly as mastectomy	2b	C	++
▪ Breast-conserving therapy	3a	C	-
▪ SLNE or axillary dissection if cN0	3a	C	--
▪ Adjuvant chemotherapy (anthracycline / taxane-based)	4	C	+/-
▪ Adjuvant radiotherapy if high risk (size > 5 cm, R1)	4	C	+/-

* Therapy in specialized centres recommended

Guidelines Breast
Version 2024.1E

Secondary Angiosarcoma of the Breast Therapy

	Oxford		
	LoE	GR	AGO
▪ Tumor resection (BCT / mastectomy)	3a	C	+
Radical surgery ist not associated with better outcome			
▪ (Neo-)adjuvant chemotherapy	3a	C	+/-
▪ Consider „trimodality treatment“ in case of locally advanced angiosarcoma (neoadjuvant taxanes => neoadjuvant radiochemotherapy => surgical resektion)	3a	C	+
▪ Adjuvant radiotherapy if high risk (size > 5 cm, R1)	2b	B	+/-
▪ Regional hyperthermia (to improve local control) plus chemotherapy and / or radiotherapy	2b	B	+/-

Trimodality Therapy Improves Disease Control in Radiation-Associated Angiosarcoma of the Breast (RAASB)

38 patients (median age 69 years) with RAASB; median F/U 5,6 y

- **Trimodality therapy** consisted of

(i) taxane induction therapy, followed by
(ii) concurrent taxane and irradiation therapy, followed by
(iii) surgical resection with wide margins.

Results:

- n = 16 trimodal therapy: pCR 12/16.
  Loc.rec.: 0/16; dist.met.: 1/16; death 1/16
  Wound break / sec. wound-healing: 100%
- n = 22 monotherapy/dual therapy:
  Loc.rec.: 10/22; dist.met.: 8/22; death 7/22
  Wound break / sec. wound-healing: 48% ($p < 0.001$)
- **RFS; 93.8% vs. 42.9%; P = 0.004; HR, 7.6 (95% CI: 1.3-44.2)**

Degnim AC, Siontis BL, Ahmed SK et al. Clin Cancer Res. 2023 Aug 1;29(15):2885-2893.

Secondary (Radiotherapy-associated) Angiosarcoma of the Breast

Guidelines Breast
Version 2024.1E

- **Cumulative incidence of radiotherapy-associated sarcoma: 3.2 per 1,000 after 15 years**
- **Clinical presentation**
  - **> 5 years after BCT or mastectomy with irradiation**
  - **usually intracutaneously or subcutaneously in the irradiation area with livid discoloration**
  - **multiple foci**
  - **most often in advanced stages (II - III)**
  - **metastasis mostly pulmonary**
  - **lymph node metastasis possible**
- **Prognosis is more unfavorable than in non-radiotherapy-associated sarcoma**
- **Survival: after 5 yrs. up to 50.5%, after 10 yrs. up to 25.2%**

Angiosarcoma of the Breast
Treatment of Local Recurrence and Metastases

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
Treatment of Local Recurrence:			
▪ R0 resection	4	C	++
▪ Adjuvant radiotherapy for high-risk patients (tumor size > 5 cm, R1)	4	C	+/-
Distant Metastases / Unresectable Tumors:			
▪ Treatment like as for soft tissue sarcomas (according to S3 guideline)	4	C	++
▪ Paclitaxel weekly / liposomal doxorubicin (as in angiosarcoma)	2b	B	+
▪ Antiangiogenic treatment (e.g. in angiosarcoma)	4	C	+/-
If clinically resistant to therapy			
▪ Molecular diagnostics (Multidisciplinary molecular board)	5	D	+

Guidelines Breast
Version 2024.1E

Metaplastic Breast Carcinoma
- High-Grade -

Consider reference pathology and subtyping.

	Oxford LoE	Oxford GR	AGO
▪ Surgical therapy and axillary staging as in case of NST	4	C	++
▪ Neoadjuvant chemotherapy (frequently chemoresistant)*			
▪ ER pos.	4	C	--
▪ ICPi (Pembrolizumab)-basierte PST (TNBC)	4	C	+/-
▪ HER2 pos. (inkl. Anti-HER2-Therapie)	4	C	+
▪ Adjuvant chemotherapy (frequently chemoresistant)	4	C	-
▪ Consider platin/taxane combination in case of mesenchymal differentiation (e.g. spindle cell)	4	C	+
▪ Adjuvant endocrine therapy if HR-positive	4	C	+
▪ Adjuvant radiotherapy according therapy of NST	4	C	+ +

* Note: control of local response in short intervals

Guidelines Breast
Version 2024.1E

Metaplastic Breast Carcinoma – Low Grade With Uncertain Malignant Potential (Fibromatous and Adenosquamous Ca.)*

	Oxford		
	LoE	GR	AGO
▪ Surgical therapy and axillary staging as in case of NST	4	C	++
▪ Adjuvant chemotherapy (frequently chemoresistant)	4	C	-
▪ Neoadjuvant chemotherapy (frequently chemoresistant)	4	C	- -
▪ Adjuvant endocrine therapy (not applicable, since triple-negative tumors)	4	C	-
▪ Adjuvant radiotherapy according therapy of NST	4	C	+

* Reference pathology recommended

Guidelines Breast
Version 2024.1E

Metaplastic Breast Cancer

Definition: Metaplastic transformation of epithelial tumor cells

- Epithelial differentiation: squamous cell carcinoma, spindle-cell carcinoma
- Heterologous (mesenchymal) differentiation: chondroid, osseous or otherwise metaplastic breast cancer

Clinical and pathological characteristics:

- < 1 % of malignant breast neoplasms
- Similar age group as NST breast cancer
- Localized, mostly palpable
- Rapidly growing, poor response to chemotherapy
- > 90 % triple-negative

Subtypes:

- Highly aggressive with squamous cell or high-grade spindle-cell differentiation
- Less aggressive (low-grade) with mesenchymal, low grade adenosquamous or fibromatosis-like differentiation

Frequent mutations:

- *TP53, EGFR, PIK3CA, PTEN*
- Possible association to *gBRCA1*-mutation/HRD-positivity

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

Breast Cancer Follow-Up

Guidelines Breast
Version 2024.1E

Breast Cancer Follow-Up

Versions 2002–2023:

Bauerfeind / Bischoff / Blohmer / Böhme / Costa / Diel / Friedrich / Gerber / Gluz / Hanf / Heinrich / Huober / Janni / Kaufmann / Kolberg-Liedtke / Kümmel / Lüftner / Lux / Maass / Möbus / Müller-Schimpfle/ Mundhenke / Oberhoff / Rody / Scharl / Solbach / Solomayer / Stickeler / Thomssen / Wöckel

Version 2024:

Mundhenke / Schmidt

Breast Cancer Follow-Up Objectives

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
Early detection of curable events			
▪ In-breast recurrence	1a	B	++
▪ Loco-regional recurrence*	1a	B	++
Early detection of contralateral cancers	1a	B	++
Early detection of metastasis			
▪ Early detection of symptomatic metastases	3b	C	+
▪ Early detection of asymptomatic metastases	1a	A	-

* loco-regional recurrence is associated with a higher risk of mortality in node-positive, PR-negative, younger patients and in patients with a short time between primary diagnosis and recurrence

Guidelines Breast
Version 2024.1E

Breast Cancer Follow-Up Objectives

	Oxford		
	LoE	GR	AGO
▪ Improve quality of life	2b	B	+
▪ Improve physical performance	2a	B	+
▪ Reduction and / or early detection of therapy-related side effects (such as osteoporosis, cardiac failure, fatigue, neurotoxicity, lymphedema, web axillary pain syndrome (abacterial lymphangitis), sexual disorders, cognitive impairment, sterility, and secondary tumors) and start of necessary therapies	2b	B	+
▪ Participation in interventional programs during follow-up for breast cancer survivors in order to maximize therapy adherence, assess life-style interventions, and improve quality of life	3b	B	+

Guidelines Breast
Version 2024.1E

Monitoring after Cardiotoxic Therapy (e.g. Anthracycliens, anti-HER2)

After anthracyclines / Trastuzumab:

- ECG and echocardiography:
  - 6, 12, 24 months and yearly up to 5 years after therapy
  - after 5th year, every 5 years and if patient is symptomatic
- If cardiovascular risk factors:
  - blood pressure at least yearly
  - lipids and HbA1c in serum yearly
- Modify risk factors if possible:
  - nicotine, body weight, bmi
- Education about individual risk profile and lifestyle

Risk factors:

radiotherapy of left breast, nicotine, hypertonus, diabetes mell., dyslipidaemia, adiposity, age > 60, cardiac diseases: reduced ejection fraction, post-myocardial infarction status , ≥ moderate heart defects

Breast Cancer Follow-Up Objectives

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
Evaluation of current adjuvant therapy	2b	B	++
incl. monitoring of adherence to endocrine therapies **Control of menopausal status, e.g. in case of CT-induced amenorrhea (FSH/2 or bleeding history) and addition of GnRH analogs (up to 2 years after CT) if premenopausal status in women < 45 years old, or switch to aromatase inhibitors (if postmenopausal)**			
Pro-active improvement of therapy adherence	5	D	++
Patient information about efficacy data for 5-10 years endocrine therapy			
Early therapy of side effects (sports, NSAIDs, vitamin D / calcium)			

Breast Cancer Follow-Up Objectives

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Psycho-social aspects of support and counseling	4	C	+
▪ Pregnancy, contraception, sexuality, quality of life, menopausal symptoms, fear of recurrence ▪ Inclusion of related persons (partner, family, friends, caregivers)			
▪ Second opinion regarding primary therapy	2c	B	++
▪ General counseling (e.g. changes in family history of breast, ovarian, prostate, pancreas carcinoma with new indication for genetic counseling, HRT, prophylactic surgery, breast reconstruction)	2c	C	+

Guidelines Breast
Version 2024.1E

Breast Cancer Follow-Up
Recommended Interventions

Interventions regarding lifestyle risks and comorbidity in order to reduce an unfavorable impact on disease outcome

	Oxford		
	LoE	GR	AGO
Treatment of type II-diabetes (> 25% undetected DM in postmenopausal BC patients, endocrine therapy improves risk for DM)	2a	B	++
Weight/lifestyle intervention (if BMI < 18.5 and > 30)	2a	B	+
Nightly fastening > 13 h	2b	B	+
Reduction of dietary intake (at least 15 % calories from fat) in HR-negative BC is associated with improved overall survival	2b	B	+
Stop smoking (smoking causes 2-fold increase in BC-specific and 4-fold increase in not directly BC-associated mortality)	2b	B	++
Alcohol consumption reduction (below 6g/d)	2b	B	+
Moderate sport (in patients with reduced physical activity prior to diagnosis) (at least 150 minutes/w, 2x/w)	1b	A	++
Distress reduction	3b	B	+

Guidelines Breast
Version 2024.1E

Nightly Fasting

Prolonged nightly fasting improves prognosis in breast cancer patients

retrospective cohort study:

2413 BC-pat. (no diabetes), nightly fasting more or less than 13 hrs

Fasting < 13 hrs: **HR 1.36, 36% increase of risk for recurrence**
HR 1.21, n.s. increase of risk for mortality

every 2-hrs-prolonged fasting was correlated with a 20% increase of sleeping duration

Marinac CR, Nelson SH, Breen CI et al. JAMA Oncol 2016: 2:1049-1055

Routine Follow-Up Examinations in Asymptomatic Patients

Guidelines Breast
Version 2024.1E

Tests:	Oxford LoE	GR	AGO
History (specific symptoms)	1a	A	++
Physical examination	1a	B	++
Breast self-examination	5	D	+
Mammography	1a	A	++
Sonography of the breast	2a	B	++
Routine MRI of the breast*	3a	B	+/-
Breast MRI if conventional imaging is inconclusive	3b	B	+
Pelvic examination	5	D	++
DXA-scan at baseline and repeat scan according to individual risk in women with premature menopause or women taking an AI	5	D	+

* Consider in case of increased risk (age < 50 y, HR-neg., diagnostic assessability C/D in mammography + ultrasound)

Routine Follow-Up Examinations in Asymptomatic Patients

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
Routine biochemistry (incl. tumor markers)	1a	A	-
Blood tests for monitoring of acute and late toxicities	5	D	+
Ultrasound of the liver/ Bone scan/ Chest X-ray	1a	A	-
CT of chest, abdomen, and pelvis	2a	D	-
Detection of isolated / circulating tumor cells	2a	D	-
ctDNA	2a	D	-
PET/ Whole body MRI	2b	B	-

Background for Toxicity Management

Tamoxifen:	Cholesterol, Triglycerides, Bilirubin, ALAT, ASAT, gamma-GT, Glucose
Aromatase inhibitors:	Cholesterol, Triglycerides, Bilirubin, ALAT, ASAT, gamma-GT
Anthracyclines:	pro-BNP, possibly Troponin
Trastuzumab:	pro-BNP, possibly Troponin
Checkpoint inhibitors:	Bilirubin, ALAT, ASAT, gamma-GT, Creatinine, TSH, fT3/T4, Myoglobin

Guidelines Breast
Version 2024.1E

Guidelines Breast
Version 2024.1E

Early Detection of Potentially Curable Events

	Oxford		
	LoE	GR	AGO
Locoregional recurrence (chest wall, in-breast):			
Incidence 7–20% (depending on time of F/U)			
Breast self-examination	5	D	+
Physical examination, mammography & US	1a	A	++
Magnetic resonance imaging (MRI)*	3a	B	+/-

* Consider in case of increased risk (age < 50 y, HR-neg., diagnostic assessability C/D in mammography + ultrasound)

Guidelines Breast
Version 2024.1E

Early Detection of Potentially Curable Events

	Oxford LoE	Oxford GR	Oxford AGO
Contralateral breast cancer:			
Relative risk: 2.5 - 5			
Incidence: 0.5 - 1.0 %/year			
Breast self-examination	5	D	+
Physical examination, mammography & US	1a	A	++
Routine breast MRI*	3b	B	+/-
▪ **Male breast cancer: analogous to BC in women****	5	D	+

* **Consider in case of increased risk: age < 50 y, HR-neg., diagnostic assessability C/D in mammography + ultrasound.**

** **See chapter "Breast Cancer Specific Situations"**

Guidelines Breast
Version 2024.1E

Early Detection of Potentially Curable Events

	Oxford		
	LoE	GR	AGO
Unrelated site carcinoma:			
MDS (RR 10.9), AML (RR 2.6–5.3), Colon RR 3.0; endometrium RR 1.6; ovary RR 1.5; lymphoma RR 7			
Screening for secondary malignancies according to current guidelines	**5**	**D**	**++**
Pelvic examination and PAP smear	**5**	**D**	**++**
Routine endometrial ultrasound / biopsy	**1b**	**B**	**-**

Follow-Up Care
for invasive / non-invasive Breast Cancer

Guidelines Breast
Version 2024.1E

Recommendations for asymptomatic pts.

(mod. according to ASCO-ACS recommendations 2016, NCCN 2021, ESMO 2019 and S3-guidelines 2017**)**

Clinical follow-up		**Follow-up***		**Screening/ Follow-up**
Years after primary therapy		**1 2 3**	**4 5**	**> 5**
History, physical examination, counseling		**every 3 months DCIS every 6 months**	**every 6 months**	**inv.: every 12 months**
Self-examination		**monthly**		
Imaging modalities and biochemistry		**indicated only if complaints, clinical findings, or suspicion of recurrence Monitoring of side effects of therapy**		
Mammo-graphy and additional sonography	**BCT****	**both sides: every 12 months**		
	Mastectomy	**contralateral every 12 months**		
Echocardiography		**6,12,24 months and yearly up to 5 years after completion of cardiotoxic therapy, after 5th year, every 5 years and if patient is symptomatic.**		

* Continued follow-up visits if still on adjuvant treatment

** In pts after breast-conserving therapy (BCT): First mammography 1 year after initial mammography or at least 6 months after completion of radiotherapy

Breast Cancer Follow-up
Duration and Breast Nurses

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
Duration of follow-up			
up to 5 years	1c	A	++
up to 10 years	1c	A	+
Surveillance by specialized breast nurses	2b	B	+/-*

* Studies recommended

Luminal-like, HER2-positive and Triple-negative Breast Cancer Patients

Guidelines Breast
Version 2024.1E

- **Intrinsic typing of breast cancer leads to subgroups with different course of disease. Thus, postoperative surveillance should be adapted to specific time-dependent hazards of recurrence.**
- **ER-positive patients have stable risk over many years requiring long term surveillance.**
- **However, patients with HER2-positive disease and TNBC have more risk in the early phase of follow-up and should therefore receive more intense surveillance in the first years of follow-up.**

Ribelles et al. BCR 2013

Guidelines Breast
Version 2024.1E

Loco-Regional Recurrence

Guidelines Breast
Version 2024.1E

Loco-Regional Recurrence

- **Versions 2002–2023:**
  Audretsch / Bauerfeind / Blohmer/ Brunnert / Budach / Costa / Dall / Ditsch/ Fehm / Fersis / Friedrich / Harbeck / Heil / Gerber / Gluz / Göhring / Hanf / Kühn/ Lisboa / Lux / Maass / Mundhenke / Rezai / Rody / Simon / Solbach / Solomayer / Souchon / Thomssen / Wenz / Wöckel

- **Version 2024:**
  Dall / Kühn

Guidelines Breast
Version 2024.1E

Loco-Regional Recurrence Incidence and Prognosis

Localization	10-y. incidence (%)	5-y. Overall Survival (%)
Ipsilateral recurrence[1] (post BEO + irradiation)	**10 (2–20)**	**65 (45–79)**
Chest wall[1] (post mastectomy)	**4 (2–20)**	**50 (24–78)**
As above plus supraclavicular fossa[2] Axilla:	**34**	**49 (3-y. OS)**
After **ALND[1]**	**1 (0.1–8)**	**55 (31–77)**
After **SLNE[4]**	1	**93**
Multiple localizations[2]	**16 (8–19)**	**21 (18–23)**

[1] Haffty et al. Int J Radiat Oncol Biol Phys 21(2):293-298, 1991;
[2] Reddy JP. Int J Radiat Oncol Biol Phys 80(5):1453-7, 201;
[3] Karabali-Dalamaga S et al. Br Med J 2(6139):730-733,1978;
[4] Andersson Y, et al. Br J Surg 99(2):226-31,2012

Guidelines Breast
Version 2024.1E

Loco-Regional Recurrence Staging

	Oxford		
	LoE	GR	AGO
Examinations before treatment			
▪ Tissue biopsy	3b	B	++
▪ Re-assessment of ER, PR, HER2	3b	B	++
▪ Complete re-staging (slice imaging*)	2b	B	++
▪ „Liquid biopsy“	5	D	-

* Standard: CT thorax / abdomen / pelvis and bone scan, in certain cases whole body MRI or ^{18}F FDG PET-CT may be used

Risk Factors for another Relapse*

	Oxford		
	LoE	GR	AGO
▪ Tumor size	2a	B	
▪ Multifocality	2a	B	
▪ Localisation	2b	B	
▪ Negative progesterone receptor	3b	B	
▪ High grade	3b	C	
▪ Omitted radiotherapy at first recurrence	3b	C	
▪ Inappropiate systemic treatment at first recurrence	3b	C	
Parameters of the locally recurrent tumor to define the risk for distant metastasis / survival			
▪ Early (< 2-3 yrs.) vs. late recurrence	2b	B	
▪ LVSI / Grade / ER-neg / positive margins (if ≥ 2 factors positive)	3b	B	
Predictive factors for treatment considerations			
▪ HER2	2b	B	++
▪ ER and PR	2b	B	++

* Risk factors for local relapse see chapter “prognostic factors”

Guidelines Breast
Version 2024.1E

Ipsilateral Locoregional Recurrence Surgical Treatment

	Oxford		
	LoE	GR	AGO
▪ After mastectomy: wide exzision (aim R0)	3b	B	++
▪ After BCS:			
▪ Mastectomy (aim: R0)	3b	B	++
▪ Re-BCS with tumor-free margins (R0) +partial breast irradiation*	2b	B	+
▪ Re-BCS with tumor-free margins (R0)	2b	B	+/-
▪ rcN0:			
▪ Axillary intervention after prior AxDiss	4	C	-
▪ Re-SLNE after prior SLNE	2a	B	-
▪ in histologically confirmed axillary recurrence: Excision with clear margins	5	C	+
▪ Palliative surgery in M1-situation or R0 not achievable (e.g. pain, ulceration, psychosocial indication)	5	D	+

* After consideration of risk factors for repeated relapse (time from primary diagnosis, tumor size)

Guidelines Breast
Version 2024.1E

Mastectomy vs. BCS + Partial Breast Irradiation

- **1327 pts. from 7 European countries with first local recurrence 01/1995 - 06/2017**
- **ME vs. BCS + Brachytherapy**
- **Propensity Score matched control (1:1): clinical and histopathological factors**
- **Primary endpoint: 5-y OS; secondary endpoints: e.g. 5-y-DFS, complications**
- **Median follow-up 75.4 months**
- **No differences in 5-y OS and sec. Endpoints: 5-y -OS: 88 vs. 87%**
- **cumulative incidence 2. recurrence: 2.3 vs. 2.8%**
- **5-y incidence of mastectomy after 1. recurrence 3.1%**

Hannoun-Levi et al. Int J Radiat Oncol Biol Phys. 2020

Loco-regional Recurrence after R0-Resection - Systemic Treatment

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
According to pathohistological re-evaluation of the recurrent tumor (ER, PR, HER2) and in consideration of time from primary diagnosis, pre-treatment, co-morbidities and patient's preference			
▪ Endocrine therapy in endocrine responsive tumors	2b	B	++
▪ Chemotherapy (consider preoperative) in case of first HR-negative relapse	2b	B	+
▪ In case of HER2-positive disease, chemotherapy + HER2-targeted therapy	5	D	+

Loco-Regional Recurrence Chemotherapy

- **CALOR Trial update (CHT vs. no CHT)**
  - **n = 163 (2003 - 2010), median follow-up of 9 years, all R0 resection**
  - **Time interval until recurrence: 3.6 years (ER neg)**
    6.8 years (ER pos)
  - **CHT is effective in ER neg disease (primary tumor and recurrence)**
  - **CHT is not effective in ER pos disease (primary tumor and recurrence)**
  - **The results were independent from the site of recurrence, previous chemotherapy and time interval from primary surgery**

Wapnir IL et al. J Clin Oncol 2018, Vol 36, issue 2, pp 1073-1079

Loco-Regional Recurrence Chemotherapy

- **CALOR Trial update**

	ER-positive			ER-negative		
Endpoint	**CT**	**No-CT**	**HR (95% CI)**	**CT**	**No-CT**	**HR (95% CI)**
10-yr DFS	**50%**	**59%**	**1.07 (0.57 – 2.00)**	**70%**	**34%**	**0.29 (0.13 – 0.67)**
	Interaction P-Value =0.013					
10-yr OS	**76%**	**66%**	**0.70 (0.32 – 1.55)**	**73%**	**53%**	**0.48 (0.19 – 1.20)**
	Interaction P-value =0.53					
10-yr BCFI	**58%**	**62%**	**0.94 (0.47 – 0.85)**	**70%**	**34%**	**0.29 (0.13 – 0.67)**
	Interaction P-value = 0.034					

Wapnir IL et al. J Clin Oncol 2018, Vol 36, issue 2, pp 1073-1079

Guidelines Breast
Version 2024.1E

Locoregional Recurrence in Case of R1-Resection / Inoperability – Systemic Treatment

	Oxford		
	LoE	GR	AGO
According to pathohistological re-evaluation of the recurrent tumor (ER, PR, HER2)			
▪ **Endocrine based therapy in endocrine responsive tumors corresponding to metastatic disease**	2b	B	++
▪ **Chemotherapy and targeted therapy (pre- or postoperative) corresponding to metastatic disease**	2b	B	++

Resectable ipsilateral Breast Tumor Recurrence after BCS – Radiotherapy

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
After Re-BCS			
▪ Whole breast irradiation (in case of no prior adjuvant radiotherapy)	3b	C	++
▪ Repeated (2.)-breast irradiation (Partial breast irradiation, brachytherapy/ external beam RT, in case of prior adjuvant radiotherapy) *	2b	B	+
After mastectomy			
▪ Radiation of chest wall +/- regional lymph nodes (in case of no prior adjuvant radiotherapy, according to risk factors)	2b	B	+
▪ Radiation dose escalation	3b	C	-
▪ Repeated (2.) irradiation			
▪ in case of R0 resection (according to risk factors)	3b	B	+/-
▪ in case of R1-resection (e.g. as brachytherapy)	3b	B	+
▪ Additional regional hyperthermia (especially for R1-resections)	2a	B	+/-

* Preoperative consultation with Radiation Oncology to determine if re-irradiation is possible.
** In Sites listed on the DKG Website
https://www.krebsgesellschaft.de/deutsche-krebsgesellschaft-wtrl/deutsche-krebsgesellschaft/ueber-uns/organisation/sektion-b-arbeitsgemeinschaften/iah.html

Guidelines Breast
Version 2024.1E

Resectable Thoraxic Wall Recurrence after Mastectomy and Axillary Recurrence – Radiotherapy

	Oxford		
	LoE	GR	AGO
Thoracic wall recurrence after mastectomy			
▪ No prior radiotherapy			
▪ Curative situation: Radiotherapy to the thoracic wall +/- regional nodal irradiation	2b	B	+
▪ Re-irradiation of the thoracic wall	3b	B	+/-
▪ R0-resection	3b	B	+/-
▪ R1-resection (e.g. brachytherapy)	3b	B	+
▪ Additional regional hyperthermia (especially for R1-resections)*	2a	B	+
Axillary recurrence			
▪ Radiotherapy to the axilla (R0-resection)			
▪ No prior radiotherapy to the axilla	3b	C	+
▪ Prior radiotherapy to the axilla	5	D	+/-

* In Sites listed on the DKG Website
https://www.krebsgesellschaft.de/deutsche-krebsgesellschaft-wtrl/deutsche-krebsgesellschaft/ueber-uns/organisation/sektion-b-arbeitsgemeinschaften/iah.html

Guidelines Breast
Version 2024.1E

Unresectable Loco-Regional Recurrence (cM0) Locoregional Treatment

	Oxford		
	LoE	GR	AGO
▪ Radiotherapy with curative intent (If no prior RT given)	2b	B	++
▪ Additional systemic treatment to increase the efficacy of RT	3b	C	+
▪ Repeat Irradiation (if prior RT given)	3b	B	+
▪ Additional regional hyperthermia*	2a	B	+
▪ Intra-arterial chemotherapy	4	C	+/-
▪ Electrochemotherapy	3b	C	+/-

* In Sites listed on the DKG Website
https://www.krebsgesellschaft.de/deutsche-krebsgesellschaft-wtrl/deutsche-krebsgesellschaft/ueber-uns/organisation/sektion-b-arbeitsgemeinschaften/iah.html

Guidelines Breast
Version 2024.1E

Endocrine based and targeted Therapy of Metastatic Breast Cancer

Endocrine-based and targeted Therapy of Metastatic Breast Cancer

Guidelines Breast
Version 2024.1E

- **Versions 2002–2023:**

  Albert / Banys-Paluchowski / Bischoff / Dall / Fasching / Fersis / Friedrich / Gerber / Huober / Janni / Jonat / Kaufmann / Kolberg-Liedtke / Loibl / Lüftner/ Lück / Lux / von Minckwitz / Möbus / Müller / Mundhenke / Nitz / Schmidt / Schneeweiß / Schütz / Stickeler / Thill / Untch / Witzel / Wöckel

Version 2024:

Fehm / Hartkopf

Endocrine-based and targeted Therapy of Metastatic Breast Cancer

Guidelines Breast
Version 2024.1E

Endocrine-based therapy is the first treatment option in patients with hormone receptor (HR) positive / HER2-negative metastatic breast cancer.

Oxford LoE: 1a **GR: A** **AGO: ++**

Impending organ failure and/or symptomatic visceral metastases do not necessarily represent an indication for chemotherapy, and endocrine-based therapy can be used individually for endocrine-sensitive disease.

Oxford LoE: 2b **GR: B** **AGO: +**

Caveat: Receptor status-may change during the course of disease. Histology of recurrent site should be obtained whenever possible.

Guidelines Breast
Version 2024.1E

Comparison ER / PR and HER2 Metastasis vs. Primary Tumor (n = 5.521)

Meta-analysis based on 39 (mostly retrospective) analyses, exclusively comparing primary tumor and metastasis (no lymph nodes):

Pooled discordance proportions were:

- 19,3% (95 % CI 1⁄4 15.8% to 23.4%) for ER
- 30,9% (95% CI1⁄4 26.6% to 35.6%) for PR
- 10,3% (95% CI 1⁄4 7.8% to 13.6%) for HER2

Pooled proportions of tumors shifting from positive to negative

- 22.5% (95% CI = 16.4% to 30.0%) for ER
- 49.4% (95% CI = 40.5% to 58.2%) for PR
- 21.3% (95% CI = 14.3% to 30.5%)) for HER2

Pooled proportions of tumors shifting from negative to positive

- 21.5% (95% CI = 18.1% to 25.5%) for ER
- 15.9% (95% CI = 11.3% to 22.0%) for PR
- 9.5% (95% CI = 7.4% to 12.1%) for HER2

Guidelines Breast
Version 2024.1E

Endocrine Therapy (ET)
General Considerations

- **Within all lines of treatment, treatment options should consider prior endocrine therapies, age and comorbidities as well as the respective approval status.**

- **Premenopausal patients treated with GnRH analogues or after ovarectomy can be treated like postmenopausal patients.**

- **In this chapter, the recommendations refer to pre- and postmenopausal women, unless menopausal status is explicitly mentioned (in premenopausal patients, the combination with GnRH analogues is usually carried out).**

Endocrine Resistance in Metastatic Breast Cancer

Guidelines Breast
Version 2024.1E

Primary endocrine resistance:

- **Relapse within 2 years of adjuvant endocrine treatment (ET)**
- **Progressive disease within first 6 months of first-line ETx for MBC**

Secondary (required) endocrine resistance:

- **Relapse while on adjuvant ET but after the first 2 years or a relapse within 12 months after completing adjuvant ET**
- **PD ≥ 6 months after initiation of ET for MBC**

Guidelines Breast
Version 2024.1E

Endocrine Therapy in Premenopausal Patients with HER2-Negative Metastatic Breast Cancer

	Oxford		
	LoE	GR	AGO
▪ GnRHa + Fulvestrant + CDK4/6i	2b	B	++
▪ GnRHa + AI + Ribociclib	1b	B	++
▪ GnRHa + AI + Palbociclib / Abemaciclib	3b/5	C	+
▪ GnRHa + Tamoxifen + Palbociclib / Abemaciclib	2b	B	+/-
▪ GnRHa + Tamoxifen	1a	A	+
▪ Tamoxifen	2b	B	+/-
▪ GnRHa + AI (first + second line)	2b	B	+
▪ GnRHa + Fulvestrant	1b	B	+
▪ Aromataseinhibitors without OFS	3	D	- -

Endocrine-Based Therapy with CDK4/6-Inhibitor for Postmenopausal Patients with HER2-Negative Metastatic Breast Cancer

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ **Ribociclib**			
▪ + non-steroidal AI	1b	A	++
▪ + Fulvestrant	1b	A	++
▪ **Abemaciclib**			
▪ + non-steroidal AI	1b	A	+
▪ + Fulvestrant	1b	A	++
▪ **Palbociclib**			
▪ + non-steroidal AI	1b	A	+
▪ + Fulvestrant	1b	A	+

CDK4/6 Inhibitors in First-line Studies

Guidelines Breast
Version 2024.1D

	Paloma-2	Monarch-3	Monaleesa-2	Monaleesa-7
Treatment arms	Letrozole +/- palbociclib	Nonsteroidal AI +/- abemaciclib	Letrozole+/- ribociclib	Goserelin + nonsteroidal AI or tamoxifen +/- ribociclib
Patients	666	493	668	672
Randomization	2:1	2:1	1:1	1:1
Primary endpoint	PFS	PFS	PFS	PFS
Menopausal status	post	post	post	pre
Progression-free survival (months, m)	27.6 vs. 14.5 m (+ 13.1 m) (HR 0.563)	29.0 vs. 14.8 m (+ 14.2 m) (HR 0.53)	25.3 vs. 16.0 m (+ 9.3 m) (HR 0.568)	23.8 vs. 13.0 m (+ 10.8 m) (HR 0.55)
Overall survival (months, m)	53.9 vs. 51.2 m (+ 2.7 m) (HR 0.956, **n.s.**)	66,8 vs. 53,7 m (+ 13,1 m) (HR 0,804 **n.s.**)	63.9 vs. 51.4 m (+ 12.5 m) (HR 0.76)	58.7 vs. 48.0 m (+ 10.7 m) (HR 0.76)

Endocrine-Based Therapy with CDK4/6-Inhibitor for Patients with HER2-Negative Metastatic Breast Cancer

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
■ Abemaciclib monotherapy*	3	C	+/-
■ CDK4/6-Inhibitor beyond progression in the metastatic situation (with change of the endocrine therapy partner)	2b^{-}	B	+/-
■ CDK4/6-Inhibitor switch based on toxicity	5	D	+/-

- Indicated after progression on prior endocrine therapy and prior chemotherapy in the metastatic setting (according to study inclusion criteria)

CDK4/6 Inhibitors beyond Progression

Guidelines Breast
Version 2024.1E

	MAINTAIN (Phase II)	PACE (Phase II)	PALMIRA (Phase II)
N	119	166	198
CDK4/6i	**Palbo → Ribo (86%)** Ribo → Ribo (14%)	**Palbo → Palbo (93%)** Ribo → Palbo (4%) Abema → Palbo (3%)	**Palbo → Palbo (100%)**
Endocine therapy	**AI → Fulvestrant (83%)** Fulvestrant → AI (27%)	**AI → Fulvestrant (100%)**	**AI → Fulvestrant (88%)** Fulvestrant → AI (12%)
initial treatment duration ≥12 months	67%	78%	85%
Median PFS ET alone	2.76 (2.66-3.25) mo	4.8 (2.1-8.2) mo	3.6 (2.7-4.2) mo
Median PFS ET + CDK4/6i beyond progression	5.29 (3.02-8.12) mo	4.6 (3.6-5.9) mo	4.2 (3.5-5.8) mo
HR	0.57 (0.39-0.95)	1.11 (0.74-1.66)	0.8 (0.6-1.1)
p-value	0.006	0.62 (ns)	0.206 (ns)

Guidelines Breast
Version 2024.1D

Second- and Subsequent-Line Endocrine-based Therapies for HR Pos. / HER2-Neg. Metastatic Breast Cancer

(No mutations / alterations required)

	Oxford		
	LoE	GR	AGO
▪ **CDK4/6i + ET***	1A	A	++
▪ **Everolimus**			
▪ + Exemestane	1b	A	+
▪ + Tamoxifen / Fulvestrant	2b	B	+
▪ + Letrozole	2b	B	+/-
▪ **CDK4/6i beyond progression**	2b	B	+/-
▪ **Endocrine monotherapy (AI / Fulvestrant) after CDK4/6i-therapy**	1b	B	+/-

*** if not given in 1st line setting**

Second- and Subsequent-Line Therapies for HR Pos. / HER2 Neg. Metastatic Breast Cancer

(Specific mutations / alterations required)

Guidelines Breast
Version 2024.1D

	Oxford		
	LoE	GR	AGO
▪ ***ESR1*-mutated and CDK4/6i-pretreatment**			
Elacestrant*	**1b**	**B**	**+**
▪ ***PIK3CA*-mutated**			
Alpelisib + Fulvestrant	**1b**	**B**	**+**
▪ **Alterations in *PIK3CA, AKT1, or PTEN***			
Capivasertib + Fulvestrant**	**1b**	**B**	**+**
▪ ***gBRCA*-mutated**			
Olaparib	**1b**	**A**	**++**
Talazoparib	**1b**	**A**	**++**

* *particularly in patients who experienced prolonged PFS on the prior lines of ET and CDK 4/6 inhibitors*

** *no EMA approval yet (01/2024)*

Further Endocrine Treatment Options for HR Pos. / HER2 Neg. Metastatic Breast Cancer: First and Subsequent Lines

(in case no combination or targeted therapies are possible)

Guidelines Breast
Version 2024.1D

	Oxford		
	LoE	GR	AGO
▪ Fulvestrant 500 mg	1b	B	+
▪ Aromatase inhibitor*	1a	A	+
▪ Tamoxifen	1a	A	+
▪ Fulvestrant 250 mg + Anastrozole	1b	B	+/-
▪ ET + Bevacizumab as 1st-line treatment	1b	B	+/-
▪ Repeat prior endocrine treatments	5	D	+/-

*** There is no evidence for superiority of a single aromatase inhibitor**

Endocrine-Based Therapy in HER2-Positive Metastatic Breast Cancer Patients

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Abemaciclib + Fulvestrant + Trastuzumab (≥ 3rd line, after T-DM1)	2b	B	+
▪ Aromatase inhibitor + Trastuzumab + Pertuzumab	2b	B	+
▪ Aromatase inhibitor + Trastuzumab	1b	B	+/-
▪ Aromatase inhibitor + Lapatinib	1b	B	+/-
▪ Fulvestrant + Lapatinib	1b	B	+/-

Poor efficacy of endocrine therapy alone.
Consider induction chemotherapy + anti-HER2-therapy (followed by endocrine + anti-HER2-therapy as maintenance therapy)!
Combination with GnRH agonists recommended in the premenopause.

Concomitant or Sequential Endocrine-Cytostatic Treatment

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Concomitant endocrine-cytotoxic treatment	1b	A	-
▪ May increase response rate and progression free interval but not overall survival			
▪ May increase toxicity			
▪ Endocrine maintenance therapy after chemotherapy +/- anti-HER2 therapy-induced response +/- anti-HER2 therapy	2b	B	+
▪ Bevacizumab maintenance plus endocrine therapy after remission with chemotherapy and bevacizumab	1b	B	+/-

Guidelines Breast
Version 2024.1E

Chemotherapy With or Without Targeted Drugs* in Metastatic Breast Cancer

* Substances without published evidence based on at least one phase III/II b trial were omitted

Chemotherapy ± Targeted Drugs in Metastatic Breast Cancer

Guidelines Breast
Version 2024.1E

- **Versions 2002–2023:**
  Albert / Bischoff / Dall / Fehm / Fersis / Friedrichs / Harbeck / Jackisch / Janni / Kolberg-Liedtke/ Loibl / Lüftner / Lux / von Minckwitz / Möbus / Müller / Rody / Schaller / Scharl / Schmidt / Schmutzler / Schneeweiss / Schütz / Stickeler / Thill / Thomssen / Untch

- **Version 2024:**
  Park-Simon / Schmidt

Guidelines Breast
Version 2024.1E

Metastatic Breast Cancer (mBC)
Disease-Free and Overall Survival

	Oxford LoE
▪ In MBC, an increase in survival over time has been shown in clinical trials	1b
▪ Multiple lines of sequential therapy are beneficial (at least same efficacy, less toxicity)	1b
▪ Targeted drugs in combination with chemotherapy can induce substantial survival benefits	1b

Guidelines Breast
Version 2024.1E

Metastatic Breast Cancer
Endocrine Resistance

Primary endocrine resistance:

- **Relapse within 2 years of adjuvant endocrine treatment (ET)**
- **Progressive disease within first 6 months of first-line ET for MBC**

Secondary (required) endocrine resistance:

- **Relapse while on adjuvant ET but after the first 2 years or a relapse within 12 months after completing adjuvant ET**
- **PD ≥ 6 months after initiation of ET for MBC**

Treatment of Metastatic Breast Cancer
Markers for Indication

Guidelines Breast
Version 2024.1D

Therapy	Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ Endocrine therapy	ER / PR (prim. tumor, better: metastasis)	1a	A	++
	Response to prior therapy	2b	B	++
▪ Elacestrant	Autocrine receptor mutation (*ESR1*) (metastases, plasma)	1b	B	++
▪ Alpelisib	*PIK3CA* mutation (prim. tumor, metastases, plasma)	1b	A	++
▪ Capivasertib	*PIK3CA, AKT1, PTEN* alterations (primary tumor, metastases, plasma)	1b	A	+
▪ Trastuzumab Deruxtecan	HER2-low or HER2-positive	1b	A	++
▪ Chemotherapy	Response to prior therapy	1b	A	++
▪ Anti-HER2-therapy	HER2 (prim. tumor, better: metastasis)	1a	A	++
▪ Checkpoint-Inhibitors	PD-L1 positivity# (IC, CPS) in TNBC (primary tumor or metastasis)	1b	B	++
	MSI/TMB	3	C	+
▪ PARP-Inhibitors	g*BRCA1/2*-mutation	1a	A	++
	s*BRCA1/2/gPALB2*	2b	B	+

Guidelines Breast
Version 2024.1E

Metastatic Breast Cancer
Treatment Rationale

Oxford LoE: 1b **GR: A** **AGO: ++**

- **Mono-Chemotherapy:**
  - Favorable therapeutic index*
  - Indicated in case of
    - Slow, not life-threatening progression
    - Insensitivity to or progression during endocrine therapy
- **Poly-Chemotherapy:**
  - Unfavorable therapeutic index
  - Indicated to achieve rapid remission in the case of
    - Extensive symptoms
    - Visceral crisis (ABC-5 definition)
  - Survival benefit in comparison to sequential single-agent therapies with the same compounds not proven

* Therapeutic index evaluates overall efficacy, toxicity, and impact on quality of life

Definition of Visceral Crisis (ABC 5)

- **Visceral crisis** is defined as severe organ dysfunction, as assessed by signs and symptoms, laboratory studies and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important organ compromise leading to a clinical indication for the most rapidly efficacious therapy.

Guidelines Breast
Version 2024.1E

Guidelines Breast
Version 2024.1E

Metastatic Breast Cancer
Systemic Therapy

GR: A **AGO: ++**

- **Evaluate compliance before and during therapy (especially in patients of older age, with reduced performance status, or significant co-morbidities and secondary primaries)**
- **Assess subjective and objective toxicities, symptoms, and performance as well as quality of life (QoL) status repeatedly**
- **Use dosages according to published protocols**
- **Assess tumor burden at baseline and approx. every 2 months, i.e. every 2-4 cycles. In slowly growing disease, longer intervals are acceptable.**

Guidelines Breast
Version 2024.1E

Metastatic Breast Cancer
Duration of Cytotoxic Therapy

	Oxford		
	LoE	GR	AGO
▪ As long as therapeutic index* remains positive	1a	A	++
▪ Treatment until progression	2b	B	+
▪ Treatment until best response	2b	B	+/-
▪ Change to alternative regimen before progression	2b	B	+/-
▪ Stop therapy in case of	1c	A	++
▪ Progression			
▪ Non tolerable toxicity			

* Therapeutic index evaluates overall efficacy, toxicity, and impact on quality of life

Guidelines Breast
Version 2024.1E

Chemotherapy in mBC
General Considerations - Drug Selection

AGO: ++

- **Participation in clinical trials is recommended**
- **The choice of systemic therapy depends on:**
  - **ER/PR, HER2, PD-L1-Status, g*BRCA*-Status (evtl. s*BRCA*-Status, evtl. PALB2), *PIK3CA*, *AKT*, *PTEN* , evtl. MSI, NTRK, ggf. m*ESR1*, other (NGS Panel preferred)**
  - **Prior therapies (and their toxicities)**
  - **Disease-free interval after end of adjuvant treatment**
  - **Progression-free interval achieved by the previous line of therapy**
  - **Disease aggressiveness and localization of metastases**
  - **Estimated life expectancy**
  - **Co-morbidities (including organ dysfunction)**
  - **Patient preferences and expectations**

Guidelines Breast
Version 2024.1E

mBC - HER2-negative / HR-positive
1st-Line Chemotherapy (if indicated)

	Oxford LoE	Oxford GR	AGO
Monotherapy:			
Paclitaxel (q1w), Docetaxel (q3w)	1a	A	++
Doxorubicin, epirubicin, Peg-liposomal doxorubicin (A_{lip})	1b	A	++
Vinorelbine	3b	B	+
Capecitabine	2b	B	+
Nab-paclitaxel	2b	B	+
Polychemotherapy:			
A + T	1b	A	++
Paclitaxel + capecitabine	2b	B	+
Docetaxel + capecitabine after adj. A	1b	A	+
T + gemcitabine after adj. A	2b	B	++
A + C or A_{lip} + C	1b	B	++

Guidelines Breast
Version 2024.1E

mBC - HER2-negative / HR-positive: Chemotherapy after Anthracycline Treatment*

	Oxford		
	LoE	GR	AGO
▪ Paclitaxel q1w	1a	A	++
▪ Docetaxel q3w	1a	A	++
▪ Capecitabine	2b	B	++
▪ Nab-paclitaxel	2b	B	++
▪ Peg-liposomal doxorubicin*	2b	B	+
▪ Eribulin	1b	B	+
▪ Vinorelbine	2b	B	+
▪ Docetaxel + Peg-liposomal doxorubicin	1b	B	+/-

* Independent whether anthracyclines were used in adjuvant or 1st line metastatic situation

mBC - HER2-negative / HR-positive:
Chemotherapy after Pretreatment *

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Trastuzumab-Deruxtecan (if HER2-low)	1b	A	++
▪ Sacituzumab Govitecan	1b	A	++
▪ Capecitabin	2b	B	+
▪ Eribulin	1b	B	+
▪ Vinorelbine	2b	B	+
▪ (Peg)-liposomal Doxorubicin	2b	B	+
▪ Taxane re-challenge**	2b	B	+
▪ Anthracycline re-challenge**	3b	C	+
▪ Metronomic therapy (e.g. cyclophos. + MTX)	2b	B	+

* See approval details for previous therapy
** at least 1 year recurrence free after adjuvant therapy

Guidelines Breast
Version 2024.1E

mBC - HER2-negative / HR-positive*

	Trastuzumab Deruxtecan HR-pos / HER2-low (331 patients)	Hazard Ratio relative to control	Sacituzumab-Gov. HR-pos / HER2-neg (272 patients)	Hazard Ratio relative to control
previous lines of chemotherapy in mBC	all patients		all patients	
1 line	61%	0.66 for OS	0%	
2 lines			44%	0.85 for OS n.s.
≥ 2 lines	40%	0.76 for OS n.s.		
≥ 3 lines			60%	0.75 for OS
PFS (months)	9.6	0.37	5.5	0.66
OS (months)	23.9	0.69	14.4	0.79

* Data from two different phase 3 studies with differently pretreated patients
kA: keine Angabe, n.s.: not significant, PFS: Progression free survival, OS: Overall survival

Guidelines Breast
Version 2024.1E

Triple Negative mBC PD-L1+
Independent of Germline Mutation in *BRCA 1/2* or *PALB2*

	Oxford LoE	Oxford GR	AGO
▪ Pembrolizumab + Chemotherapy* first-line PD-L1 CPS ≥ 10# (if TFI ≥ 6 months)	1b	B	++
▪ Atezolizumab + Nab-Paclitaxel first-line PD-L1 IC ≥ 1# (if TFI ≥ 12 months)	1b	B	+
▪ Atezolizumab + Paclitaxel first-line PD-L1 IC ≥ 1#	1b[a]	B	-
▪ Pembrolizumab monotherapy (after chemotherapy w/o previous immune oncology based therapy) in case of CPS ≥ 20#	1b[a]	B	+/-

\# (see chapter „Pathology“)
* nab-Paclitaxel or Paclitaxel or Carboplatin / Gemcitabine
TFI = therapy-free interval

Triple Negative mBC Independent of PD-L1 Status and Germline Mutations in *BRCA 1/2* or *PALB2**

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Sacituzumab Govitecan ≥ 2 TL	1b	A	++
▪ Bevacizumab 1st line in combination with			
▪ Paclitaxel (weekly)	1b	B	+
▪ Capecitabine	1b	B	+
▪ nab-Paclitaxel	2b	B	+/-
▪ Carboplatin (vs. Docetaxel)	1b	B	+/-
▪ Gemcitabin / Cisplatin (vs. Gem / Pac)	1b	A	+
▪ Nab-Paclitaxel / Carboplatin (vs. Carbo / Gem)	2b	B	+
▪ Trastuzumab Deruxtecan (in HER2 low)	2b	C	+

* according to label

Guidelines Breast
Version 2024.1E

Treatment Options in mBC with BRCA 1/2 or gPALB2 Mutation

	Oxford		
	LoE	GR	AGO
▪ **Carboplatin (vs. docetaxel) (if Platinum-naive)**	1b	B	+
▪ **PARP-Inhibitors (HER2-negative mBC)**			
▪ **HER2-negative, g*BRCA 1/2* mutation**			
▪ **Olaparib**	1b	A	++
▪ **Talazoparib**	1b	A	++
▪ **s*BRCA* 1/2 mutation**			
▪ **Olaparib**	2b	B	+/-
▪ ***gPALB2* mutation**			
▪ **Olaparib**	2b	B	+/-

Guidelines Breast
Version 2024.1E

HER2-pos. mBC

1st line without Pretreatment or after Trastuzumab

	Oxford		
	LoE	GR	AGO
Primary metastatic			
▪ Docetaxel + Trastuzumab + Pertuzumab	1b	A	++
▪ Paclitaxel (weekly) + Trastuzumab + Pertuzumab	2b	B	++
▪ nab-Paclitaxel + Trastuzumab + Pertuzumab	2b	C	+
After Trastuzumab in the adjuvant setting (TFI > 6 months)			
▪ Docetaxel + Trastuzumab + Pertuzumab	1b	A	++
▪ Paclitaxel (weekly) + Trastuzumab + Pertuzumab	2b	B	++
▪ nab-Paclitaxel + Trastuzumab + Pertuzumab	2b	C	+
▪ Vinorelbin + Trastuzumab + Pertuzumab	3b	B	+
After pretreatment with only Trastuzumab in the adjuvant setting (TFI ≤ 6 months)			
▪ Trastuzumab Deruxtecan (T-DXd)	4	D	+
▪ T-DM1	2b	B	+/-
▪ Chemotherapy + Trastuzumab + Pertuzumab	4	D	+/-

Guidelines Breast
Version 2024.1E

HER2-pos. mBC

1st line after Trastuzumab / Pertuzumab +/- TDM-1

	Oxford		
	LoE	GR	AGO
After Trastuzumab / Pertuzumab in the (neo-)adjuvant setting			
▪ Re-induction CTx + Trastuzumab + Pertuzumab (TFI > 6-12 months)	4	D	++
▪ Trastuzumab Deruxtecan (T-DXd)	4	D	+
▪ T-DM1 (TFI < 6-12 months)	5	D	+/-
▪ Capecitabine + Lapatinib	1b	B	+/-
After Trastuzumab / Pertuzumab in the (neo-)adjuvant setting and T-DM1 in the post-neoadjuvant setting			
▪ Re-induction CTx + Trastuzumab + Pertuzumab (TFI > 6-12 months)	4	D	+
▪ T-DXd	5	D	+
▪ Tucatinib + Capecitabine + Trastuzumab	5	D	+
▪ Capecitabine + Lapatinib	5	D	+/-

Guidelines Breast
Version 2024.1E

HER2-pos. mBC

2nd line

	Oxford		
	LoE	GR	AGO
▪ Trastuzumab Deruxtecan (T-DXd)	1b	B	++
▪ Tucatinib + Trastuzumab + Capecitabine (after pretreatment with T-DM1)	1b	B	++
▪ Tucatinib + T-DM1	1b	B	+/-
▪ T-DM 1	1b	A	+
▪ Capecitabine + Lapatinib / Trastuzumab	1b	B	+/-
▪ TBP: 2nd line Chemotherapy* + Trastuzumab / Pertuzumab	2b	B	+/-
▪ Trastuzumab + Pertuzumab	2b	B	+/-
▪ Trastuzumab + Lapatinib (HR neg.)	2b	B	+/-

* e.g. Taxane; Vinorelbin; Taxane / Carboplatin; Capecitabine; Capecitabin / Docetaxel (Toxizität!)

Guidelines Breast
Version 2024.1E

HER2-pos. mBC

≥ third-line

Depending on the previous therapy (substance)	Oxford LoE	Oxford GR	Oxford AGO
▪ Tucatinib + Trastuzumab + Capecitabine	1b	B	++
▪ Trastuzumab Deruxtecan	1b	B	++
▪ T-DM 1	1b	A	+
▪ Capecitabine + Trastuzumab / Lapatinib	1b	B	+
▪ Capecitabine + Neratinib	1b	B	+/-

HER2-pos. mBC

No Chemotherapy Possible or Desired

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Trastuzumab + Aromatase inhibitor (HR+)	2b	B	+/-
▪ Lapatinib + Aromatase inhibitor (HR+)	2b	B	+/-
▪ Aromatase inhibitor + Trastuzumab + Pertuzumab (HR+)	2b	B	+
▪ Abemaciclib + Trastuzumab + Fulvestrant	2b	B	+
▪ Trastuzumab + Pertuzumab	2b	B	+/-
▪ Trastuzumab + Lapatinib (HR neg.)	2b	B	+
▪ Trastuzumab mono	2b	B	+/-

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

Osteooncology and Bone Health

Guidelines Breast
Version 2024.1E

Osteooncology and Bone Health

- **Versionen 2002–2023:**

  Banys-Paluchowski / Bischoff / Böhme / Brunnert / Dall / Diel / Fehm / Fersis / Friedrich/ Friedrichs / Hanf / Harbeck / Huober / Jackisch / Janni / Kolberg-Liedtke / Lux / Maass / Nitz / Oberhoff / Reimer / Schaller / Scharl / Schütz / Seegenschmiedt / Solbach / Solomayer / Souchon

- **Version 2024:**

  Reimer / Rhiem

Guidelines Breast
Version 2024.1E

Bisphosphonates in Metastatic Breast Cancer

	Oxford		
	LoE	GR	AGO
▪ Therapy of hypercalcemia	1a	A	++
▪ Reduction of skeletal events / complications	1a	A	++
▪ Reduction of bone pain	1a	A	++
▪ Increasing bone pain-free survival	1a	A	++
▪ Treatment beyond osseous progression	5	D	++
▪ Use of bone resorption marker for therapy monitoring	5	D	-
▪ Bisphosphonates alone for pain control	5	D	-

Guidelines Breast
Version 2024.1E

Denosumab in Metastatic Breast Cancer

	Oxford		
	LoE	GR	AGO
▪ Therapy of hypercalcemia	1a	A	++
▪ Reduction of skeletal events / complications	1a	A	++
▪ Reduction of bone pain	1a	A	++
▪ Increasing bone pain-free survival	1b	A	++
▪ Treatment beyond progression	5	D	+
▪ Progression while on bisphosphonates	4	C	+/-
▪ Use of bone resorption markers for therapy monitoring	5	D	-
▪ Denosumab alone for pain control	5	D	-

Guidelines Breast
Version 2024.1E

Skeletal Metastases
Treatment with Radionuclids

	Oxford		
	LoE	GR	AGO
▪ **Tumor progression after standard treatment of multiple / disseminated metastases and intolerable bone pain**	1b	B	+
▪ ^{186}Rhenium-hydroxyethyliden-diphosphonat	2b	B	+
▪ ^{153}Samarium	1b	B	+
▪ ^{89}Strontium	1b	B	+
▪ ^{223}Radium	2b	B	+
▪ ^{177}Lu-EDTMP	2b	C	+
▪ ^{188} Rhenium-HEDP	1b	B	+

Cave: the potential benefits should be weighed against the risk of myelosuppression and pancytopenia

Longer-Interval vs. Standard Dosing of Bone-Targeted Agents

Guidelines Breast
Version 2024.1E

- **CALGB 70604 trial: n = 1822 patients with metastatic breast cancer, metastatic prostate cancer, or multiple myeloma, 795 completed the study**

  SRE after 2 years: 29.5% zoledronic acid every 4 weeks
  28.6% zoledronic acid every 12 weeks

- **OPTIMIZE-2 trial: n = 416 women with metastatic breast cancer, prior exposure to zoledronate or pamidronate for approx. 1 year or more**

  SRE after 1 year: 22.0% zoledronic acid every 4 weeks
  23.2% zoledronic acid every 12 weeks

- **REaCT-BTA trial: n = 263 metastatic cancer (160 breast, 103 prostate)**

  Denosumab (n = 148), zoledronate (n = 63) or pamidronate (n = 52) q4w vs. q12w

  Primary endpoint (non-inferiority of q12w vs. q4w in HRQoL) reached

  Cumulative SSE after 1 year: 7.6% bone-targeted agent every 4 weeks
  16.6% bone-targeted agent every 12 weeks (p = 0.27)

Guidelines Breast
Version 2024.1E

Bone Modifying Agents for the Therapy of Bone Metastases

	Oxford		
	LoE	GR	AGO
▪ Clodronate PO 1600 mg daily	1a	A	++
▪ Clodronate IV 1500 mg q3w / q4w	1a	A	++
▪ Pamidronate IV 90 mg			
▪ q3w / q4w	1a	A	++
▪ q12w	2b	B	+/-
▪ Ibandronate IV 6 mg q3w / q4w	1a	A	++
▪ Ibandronate PO 50 mg daily	1a	A	++
▪ Zoledronate IV 4 mg			
▪ q4w	1a	A	+
▪ q12w	1a	A	++
▪ Denosumab 120 mg SC			
▪ q4w	1a	A	++
▪ q12w	1b	B	+/-
▪ Other dosing or schedules, e.g. from adjuvant trials or therapy of osteoporosis	5	D	--
▪ Planned sequential therapy with multiple agents	2b	B	+/-

Guidelines Breast
Version 2024.1E

Metastatic Bone Disease of the Spine

Indications for surgery

Oxford LoE: 2b **GR: C** **AGO: ++**

- **Spinal cord compression**
  - **With progressive neurological symptoms**
  - **With pathological fractures**
- **Instability of the spine**
- **Lesions in pre-irradiated parts of the spine**

Guidelines Breast
Version 2024.1E

Bone Metastases Acute Spinal Cord Compression / Paraplegia

	Oxford		
	LoE	GR	AGO
▪ **Decompression surgery, reduction of tumor volume, stabilization surgery (< 24 h) and irradiation of the spine**	2b	C	++
▪ **Irradiation of the spine (< 24 h)** ▪ Radiatiotherapy regimen (1 x 8-10 Gy vs. multiple fractions) depending on prognosis, performance status and patient‘s preference	3b	C	++
▪ **Immediate start of treatment**	1c	D	++
▪ **Steroids (start at first symptoms)** **- Dexamethasone 16-24 mg/d, then reduction over 2 weeks**	2a	C	+

Clinical trials have included patients with different tumor entities!

Guidelines Breast
Version 2024.1E

Surgery for Bone Metastases
Technical Aspects

Spine and limbs

Oxford LoE: 3b **GR: C** **AGO: +**

- Marrow splints
- Plate osteosynthesis
- Compound osteosynthesis (replacement by PMMA and osteosynthesis)
- Vertebral replacement by titanspacer
- Tumor-Endoprothesis
- Vertebroplasty / Kyphoplasty +/- thermoablation of the tumor
- Kypho-IORT (in studies only)
- Resection of involved bone in oligometastatic disease (sternum, ribs, vertebrae)

Metastatic Bone Disease
Recurrent Bone Pain after RT

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
Recurrent bone pain in pre-irradiated parts of the skeleton			
▪ Single dose RT *	3b	C	++
▪ Fractionated RT *	3b	C	++
▪ Radionuclide therapy	2b	B	+
▪ Magnetic resonance-guided focused ultrasound	1b	B	+
▪ Radiofrequency ablation	4	C	+
▪ Cryoablation	4	C	+

* Dose and fractionation depending on location, interval from first radiotherapy (RT), and dose and fractionation of first RT

Side-Effects and Toxicity: Bisphosphonates (BP) and Denosumab (Dmab)

Guidelines Breast
Version 2024.1E

	LoE
▪ Renal function deterioration due to IV-aminobisphosphonates	1b
▪ Osteonecrosis of the jaw (ONJ) mostly under IV-BP and Dmab therapy (1.4 – 2.8% / 1.3 – 3.2%)	1b
▪ Association with (simultaneous) anti-angiogenetic therapies	3b
▪ Severe hypocalcemia (Dmab > BPs)	1b
▪ Acute Phase Reaction (IV Amino-BPs, Dmab) 10–30%	1b
▪ Gastrointestinal side effects (oral BPs) 2–10%	1b
▪ Atypical femur fractures (absolute risk of 11 per 10,000 person years of BP use)	2b
▪ Increased fracture risk after discontinuation of Dmab	3b
▪ Extremely rare: Uveitis / Scleritis under BP treatment	4

Guidelines Breast
Version 2024.1E

Metastatic Bone Disease: Radiotherapy (RT)

	Oxford		
	LoE	GR	AGO
Bone metastases			
▪ With fracture risk	1a	B	++
▪ With functional impairment	1a	B	++
▪ With bone pain	1a	B	++
Single dose RT = fractionated RT	2a	B	++
▪ With neuropathic bone pain	1b	B	++
▪ Asymptomatic isolated bone metastasis	2b	B	+/-
▪ Reduction of radiation-induced pain flare-up by dexamethasone	1b	B	+
▪ Radiotherapy in combination with hyperthermia	2b	B	+/-

Limited studies included breast cancer patients!

Guidelines Breast
Version 2024.1D

Prophylactic Radiation Therapy versus Standard of Care for Patients with High-Risk Asymptomatic Bone Metastases

A multicenter randomized controlled Phase II clinical trial

- **Cohort:** 78 adult patients (24% breast) with high-risk bone metastases (n = 122), stratified by histology and planned SOC (systemic therapy or observation), randomly assigned in a 1:1 ratio to receive RT to asymptomatic bone metastases or SOC alone
- **Results:** 1 year: RT vs. SOC: SRE in one of 62 bone metastases (1.6%) vs. 14 of 49 bone metastases (29%) ($P < .001$) with significantly fewer patients hospitalized for SRE in the RT arm compared with the SOC arm (0 *v* 4, $P = .045$); median follow-up of 2.5 years: OS was significantly longer in the RT arm (hazard ratio [HR], 0.49; 95% CI, 0.27 to 0.89; $P = .018$)

Common Side Effects during Treatment with Bisphosphonates / Denosumab

Guidelines Breast
Version 2024.1E

Drug	Acute phase-reaction	Kidney Tox.	Upper GI-tract	Diarrhea	ONJ	
Clodronate 1500 IV	0	+	0	0	0	Non-Amino.
Clodronate 1600 PO	0	0	+	+	0	Non-Amino.
Ibandronate 50 mg PO	0	0	+	0	0	Aminobisph.
Ibandronate 6 mg IV	+	0	0	0	+	Aminobisph.
Zoledronate 4 mg IV (q4w or q12w)	+	+	0	0	+	Aminobisph.
Pamidronate 90 mg IV	+	+	0	0	+	Aminobisph.
Zoledronate 4 mg IV q6m	+	0	0	0	0	Aminobisph.
Denosumab 120 mg SC q4w	+	0	0	+	+	

Cave: Hypocalcemia under antiresorptive therapy in pts with bone metastases!

Recommendations for Prevention of Osteonecrosis of the Jaw (ONJ)

Guidelines Breast
Version 2024.1E

Oxford LoE: 2a **GR: A** **AGO: ++**

- **During bisphosphonate or denosumab treatment, avoid any elective dental procedures involving jaw bone manipulations during treatment with bisphosphonates or denosumab**
- **Optimize dental status before start of bisphosphonate or denosumab treatment**
- **Inform patients about ONJ risk and educate about early symptom reporting**
- **In case of high risk for ONJ, use oral bisphosphonate**
- **Recommend good oral hygiene, limiting alcohol intake and quit smoking**
- **Under adjuvant bisphosphonate therapy, ONJ is rare (< 1%)**

AGSMO patientenbezogener Laufzettel
https://www.onkosupport.de/asors/content/e4125/e4405

Guidelines Breast
Version 2024.1E

Adjuvant Bone Targeted Therapy for Improvement of Prognosis

	Oxford		
	LoE	GR	AGO
Clodronate (oral)			
Postmenopausal patients*	1a	A	+
Premenopausal patients	1a	B	+/-
Aminobisphosphonate (IV or oral)			
Postmenopausal patients*	1a	A	+
Premenopausal patients	1a	B	+/-
Denosumab (6 x 120 mg/3–4w + 14 x 120 mg/3m)			
Stage II and III postmenopausal patients	1b	B	-
Denosumab (60 mg SC q6m)			
Postmenopausal patients undergoing AI therapy	1b	B	+/-

* independent of the intrinsic subtype

Guidelines Breast
Version 2024.1E

Dosage of Adjuvant Bisphosphonates for Improvement of Survival*

- **Non-Aminobisphosphonates:**
  - **Clodronate PO 1600 mg/d (Bonefos / Clodronic acid)**
  - **Clodronate PO 1040 mg/d (Ostac / Clodronic acid)**

- **Aminobisphosphonates:**
  - **Zoledronate IV 4 mg/6 m (Zometa / Zoledronic acid)**
  - **Ibandronate PO 50 mg/d (Bondronat / Ibandronic acid)**
  - **Pamidronate PO (orally not available in most countries)**
  - **Risedronate PO 35 mg/w*(Actonel / Risedronic acid)**
  - **Alendronate PO 70 mg/w (Fosamax / Alendronic acid)**
  - **Optimal duration yet to be defined; in adjuvant studies duration of BP treatment varied from 2–5 years**

***Utilisation of the NHS Predict Tool to estimate the effect of bisphosphonate use on overall survival, https://breast.predict.nhs.uk/tool**

Guidelines Breast
Version 2024.1D

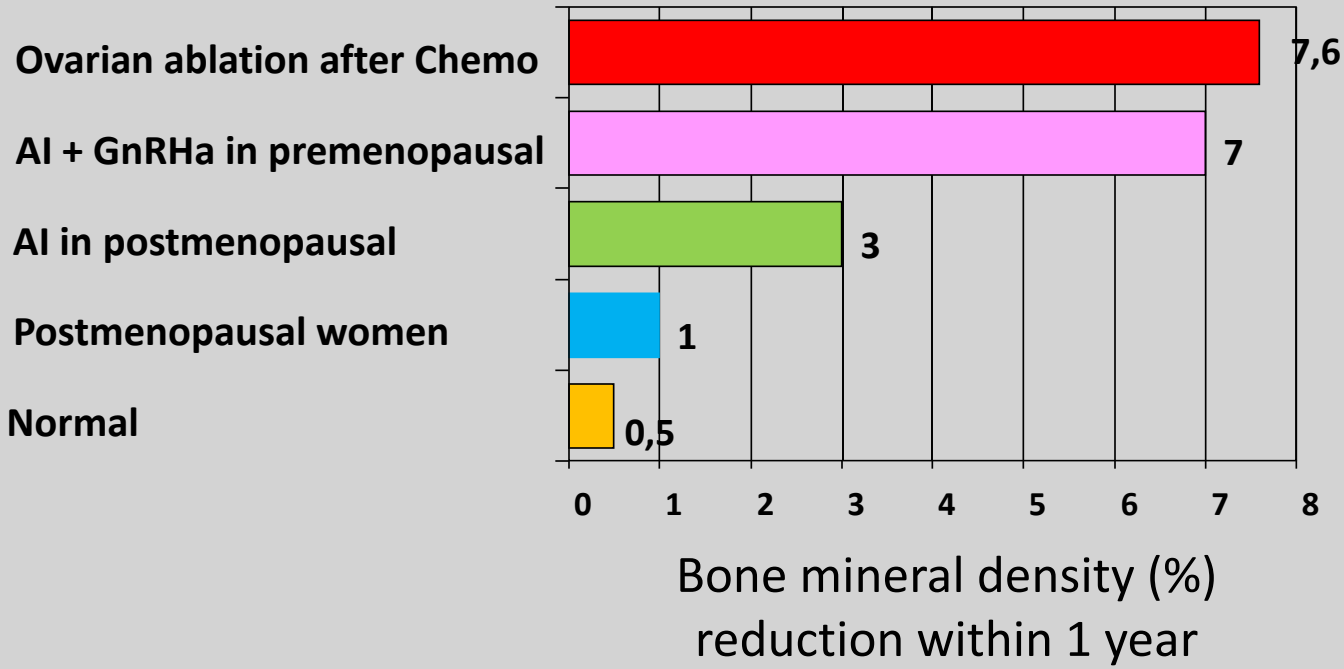
SUCCESS A trial

(*Friedl et al., JAMA Oncol 2021; 7: 1149-1157*)

	2 y ZOL (n = 1.447) **(4 mg IV every 3 mo for 2 y)**	**5 y ZOL (n = 1.540)** **(4 mg IV every 3 mo for 2 y +** **4 mg IV every 6 mo for 3 y)**
Survival	**No differences for DFS, OS, DDFS**	
Bone recurrences	n = 28	n = 25
Adverse Events		
Grade III/IV	n = 98 (5.1% of patients)	n = 159 (7.6% of patients)
SRE bone pain	3.7%	8.3%
Arthralgia	3.1%	5.1%
Fractures	n = 3	n = 14
ONJ	n = 5	n = 11

Reduction in Bone Density of Individual Agents

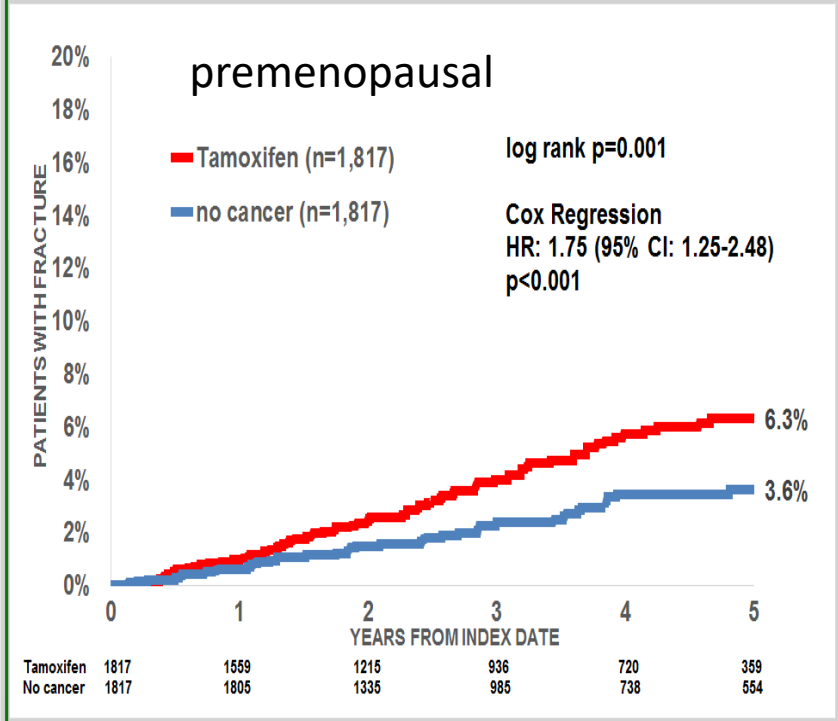
Guidelines Breast
Version 2024.1E

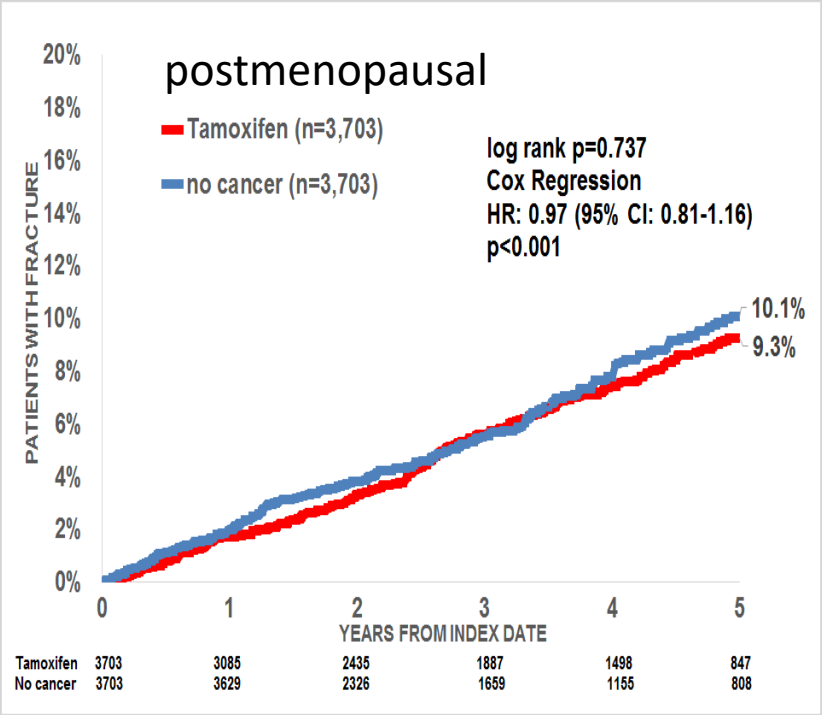


(1) Kanis JA Osteoporosis 22, 1997, (2) Gnant M SABCS 2004, (3) Shapiro CL, JCO 19:3305, 2001

Risk of Osteoporosis and Tamoxifen
(Fracture Risk)

Guidelines Breast
Version 2024.1E





Kyvernitakis et al Osteoporosis Int 2018

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ **Bisphosphonates**			
▪ Therapy	1b	B	++
▪ Prevention (2–5 yrs)	1b	A	+
▪ after discontinuation of Denosumab (1-2 years)	3c	C	+
▪ **Denosumab**			
▪ Therapy	1b	B	++
▪ Prevention (up to max. 3 yrs)	1b	A	+/-
▪ **Hormone replacement therapy**	5	D	-
▪ **Vitamin K2 substitution**	2b	B	-
▪ **Clinical risk assessment for osteoporosis at baseline according to DVO S3 – guidelines (as of 09/2023)**			++
▪ **Routine determination of 25-hydroxyvitamin D levels**	3d	B	+/-
▪ **DXA-scan at baseline in pts with endocrine therapy and / or premature menopause**	5	D	+
▪ **Antiresorptive therapy according to DVO S3 – guidelines (as of 09/2023)**			++
▪ **Repeat DXA-scan based on risk**	5	D	+

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis

Guidelines Breast
Version 2024.1E

Further recommendations (based on DVO-guidelines as of 09/2023)*

	Oxford		
	LoE	GR	AGO
▪ Physical activity	4	C	++
▪ Avoiding immobilisation	4	C	++
▪ Calcium (1000–1500 mg/d)**	4	C	++
▪ Vitamine D3 suppl. (800 U/d)	4	C	++
▪ Quit smoking, reduction of alcohol	2b	B	++
▪ Avoid BMI < 20 kg/m^2	3b	C	++
▪ Bisphosphonates after discontinuation of Denosumab (1-2 years)	3c	C	+
▪ Drugs approved for osteoporosis treatment in adults (see next slide)			

* https://dv-osteologie.org/osteoporose-leitlinien

** if nutritional supply is insufficient (in combination with Vit D3 only)

Effect of Denosumab Discontinuation

FREEDOM / FREEDOM Extension Trial

n = 1001, ≥ 2 dose of Denosumab or placebo, follow up ≤ 7 months after discontinuation treatment

Vertebral fracture rate per 100 participant year:

- 1.2 during denosumab therapy
- 7.1 after denosumab therapy
- 8.5 placebo

Non vertebral fracture rate per 100 participant year:

- 2.8 after denosumab vs. 3.8 placebo (n.s.)

Multiple vertebral fracture (% of all vertebral fractures):

- **60.7% after denosumab therapy vs. 38.7% placebo; p = 0.049**

Cummings SR et al. J Bone Miner Res 2017

Medical Treatment of Osteoporosis

Guidelines Breast
Version 2024.1E

	Oxford LoE	Oxford GR	AGO
▪ Alendronate 70 mg PO/w*	1b	B	++
▪ Zoledronate 5 mg IV/12m*	1b	B	++
▪ Ibandronate 150 mg PO/m*	1b	B	++
▪ Ibandronate 3 mg IV/3 m	1b	B	++
▪ Risedronate 35 mg PO/w*	1b	B	++
▪ Denosumab 60 mg SC/6m*	1b	B	++
▪ Raloxifene 60 mg PO/d (improves spine only)	1b	B	+/-
▪ Parathyroid hormone 100 µg SC/d	1b	B	+
▪ Strontium ranelate 2 g PO/d**	1b	B	+
▪ Teriparatide 20 µg SC/d	1b	B	+
▪ Romosozumab 210mg s.c./m for 12m***	1b	B	+

* Drugs tested in clinical studies with breast cancer patients and tumor therapy-induced osteoporosis

** Elevated risk of myocardial infarction (MI); only for to postmenopausal pts. with severe osteoporosis + high fracture risk

*** Elevated risk of MI and CVI; only for postmenopausal. pts with severe osteoporosis + high fracture risk

Indication for Osteoporosis Drug Therapy

(as of 09/2023)

Guidelines Breast
Version 2024.1D

DVO Guideline Osteoporosis 2023

Short version including:

- **Risk factor table for therapy threshold determination**
- **Tables for determining therapy thresholds (women, men)**

https://dv-osteologie.org/osteoporose-leitlinien

Guidelines Breast
Version 2024.1E

Sites of Metastases

Sites Of Metastases
Specific Approaches to Metastatic Disease

- **Versions 2002–2023:**
  Albert / Bauerfeind / Bischoff / Böhme / Brunnert / Dall / Diel / Fehm / Fersis / Friedrich / Friedrichs / Gerber / Hanf / Janni / Kolberg-Liedtke / Kreipe / Loibl / Lück / Lüftner / Lux / Maass / Mundhenke / Oberhoff / Park-Simon / Rezai / Rody / Schaller / Schütz / Seegenschmiedt / Solbach / Solomayer / Souchon / Thomssen

- **Version 2024:**
  Bauerfeind / Reimer

Guidelines Breast
Version 2024.1E

Guidelines Breast
Version 2024.1E

Sites of Metastases

- Liver and lung metastases
- Malignant pleural and pericardial effusions
- Ascites
- Bone marrow involvement
- Soft tissue metastases
- Contralateral axillary metastasis

See also chapters „CNS Metastases “ and „Locoregional Recurrence” (Loco-Regional Recurrence Treatment Options in Non Curative Cases)“ and ,,Osteooncology”

Guidelines Breast
Version 2024.1E

General Treatment Aspects of Metastases

	Oxford		
	LoE	GR	AGO
▪ Histological verification	3	B	++
▪ Cytological verification, if histology not possible	3	B	+
▪ Systemic therapy preferred	2a	B	++*
▪ Consider surgery of metastases in case of good response to palliative treatment, oligometastases (cave: no clear definition available)	2b	C	+/-
▪ Stereotatic Radiotherapy for patients with oligometastases	2b	B	+/-
▪ Local-interventional ablative procedure	3b	C	+/-
▪ Local treatment in the case of pain, exulceration, persistence after systemic treatment, bowel obstruction, hydrocephalus occlusus, spinal cord compression	5	D	+/-
▪ Systemic treatment after surgery	2c	B	++

* See chapters with systemic treatment recommendations

Different Definitions of Oligometastatic Disease (OMD)

Guidelines Breast
Version 2024.1E

Societies / Organisations or inclusion criteria of prospective clinical trials (selection)	
ESMO	limited or low-volume metastatic disease; up to five lesions in total, not necessarily in the same organ; all potentially amenable to receive local treatment
ESTRO/ASTRO	1-5 metastatic lesions; controlled primary tumor optional, all metastatic sites must be safely treatable
ESTRO/EORTC OligoCare project	Different clinical scenarios of OMD: synchronous vs. metachronous, repeat vs. de novo OMD, oligorecurrence vs. oligoprogression, oligopersistence vs. oligoprogression, induced vs. genuine OMD.
ABC-7	Low volume metastatic disease (up to 5 lesions and not necessarily in the same organ), potentially amenable for local treatment, aimed at achieving a complete remission status; highly dependent on the imaging method used. **Note:** OMD sites need to be solid; excludes pleural effusions, ascites, leptomeningeal disease.
SABR-COMET trial (NCT05784428)	$\leq$ 5 metastatic sites; small subset for breast cancer patients (n = 18)
NRG-BR002 trial (NCT02364557)	controlled locoregional disease and $\leq$ 4 metastases (standard imaging), $\leq$ 12 months systemic therapy without progression
OLIGOMA trial (NCT04495309)	up to 5 clinically manifest metastases, maximum of 3 cerebral metastases known

Guidelines Breast
Version 2024.1E

Local Therapy in Primary Metastatic Disease

	Oxford		
	LoE	GR	AGO
▪ **Surgery (R0) of the primary tumor (individualized procedure in case of oligometastatic disease)**			
▪ In case of bone metastases only	1b	B	+/-
▪ In case of visceral metastases	1b	B	-
▪ **Axillary surgery for cN1**	3b	B	+/-
▪ **Sentinel biopsy if cN0**	5	D	-
▪ **Radiotherapy of the primary tumor**			
▪ Alone (without surgery)	3a	C	+/-
▪ After local surgical treatment with BCS or mastectomy (according to adjuvant indication)	2c	B	+/-

Randomized Phase III Trials
ST +/- Surgery of the Primary Tumor

Guidelines Breast
Version 2024.1E

Trial	n	Therapy prior to randomization	Local Control	Improved OS Primary Endpoint	QoL
ECOG 2108 *[1,2] (USA/Kanada) 2001-2016	256	4-8 months systemic therapy	yes	no	ns
Tata Memorial Hospital *[3] (India) 2005-2012	350	chemotherapy	yes	no	-
MF07-01 *[4,5,6,7] (Turkey) 2008-2012	278	no systemic therapy	no 10 y LRP: LRT 1% vs 14% ST, s	10 y fu OS: LRT 19% vs. ST 5%, s (HR+, Her2-, < 55 y, solitary bone only metastasis)	ns
ABCSG-28#*[8.9] (Austria) 2010-2019	90	no systemic therapy	yes	no	ns
JCOG 1017 (Japan) 2011-2018	410	primary ST	Completed, results not reported so far		

ns not significant, s: significant #trial terminated due to poor recruitment
ST = systemic therapy, LRT= locoregional therapy, LRP = locoregional progression

Prospective Registry Study (Bone only)

Trial	n	Randomization	Local Control	Improved OS Primary Endpoint	QoL
BOMET MF 14-01# 2014-	505	ST vs LRT (LRT+ST vs. ST+LRT)	yes	3 y fu: improved OS in the LRT group (HR 0.40) HR+, Her2-; Her2+ subgroups, no benefit in triple neg. patients	-

ST = systemic therapy, LRT = locoregional therapy,

Guidelines Breast
Version 2024.1E

Liver Metastases
Local Therapy

	Oxford		
	LoE	GR	AGO
▪ Resection of liver metastases (R0)	3a	B	+/-
• HR-positive: chemotherapy-sensitive, long disease-free interval, absence of extrahepatic disease, ≤ 3 metastases			
• HER2-positive: age < 50 y, metastases < 5 cm, no further metastases			
▪ Interventional regional chemotherapy (TACE)*	3b	C	+/-
▪ Interventional regional radiotherapy (SIRT/TARE)*	3a	B	+/-
▪ Stereotactic Radiotherapy with VMAT (SRS-VMAT), other modalities*	2a	B	+/-
▪ Regional ablative procedures (RFA, MWA)	3b	C	+/-
▪ IRE, LITT, HIFU	5	D	-
▪ Cryoablation	3b	C	-

* interdisciplinary decision

Guidelines Breast
Version 2024.1E

Pulmonary Metastases
Local Therapy

	Oxford		
	LoE	GR	AGO
▪ Before any local therapy: staging and biopsy, histology for exclusion of second tumor	3a	B	+
▪ Resection of pulmonary metastases by VATS or conventional resection			
▪ In case of multi-locular metastatic disease	3a	B	-
▪ In case of single / few unilateral metastasis	3a	B	+/-
▪ Thermoablation (CT-guided RFA, LITT)	3b	C	+/-
▪ Regional radiotherapy (stereotactic radiotherapy with volumetric intensity modulated arc therapy (SRS-VMAT))	2a	B	+/-

* VATS = video-assisted thoracic surgery

Guidelines Breast
Version 2024.1E

Malignant Pleural Effusion (MPE)
Local Therapy

	Oxford		
	LoE	GR	AGO
▪ If short life expectancy, less invasive procedures should be considered	4	C	++
▪ VATS and Talcum-pleurodesis*	1b	B	++
▪ Continuous pleural drainage	2a	B	++
▪ Chemical pleurodesis*			
▪ Talcum powder	1a	B	+
▪ Intrathoracic chemotherapy	2b	C	+/-
▪ Povidone-iodine (20 ml of 10% solution)	1b	B	+
▪ Serial thoracocentesis	4	C	+/-

* Adequate pain-relief
VATS: video-assisted thoracoscopic surgery

Guidelines Breast
Version 2024.1E

Malignant Ascites
Local Therapy

	Oxford		
	LoE	GR	AGO
Ascites:			
▪ **Puncture, drainage in symptomatic patiens**	4	D	++
▪ **Continous drainage of ascites**	3b	D	+
▪ **Systemic therapy**	3b	D	++
▪ **Local chemotherapy**	3b	D	-

Guidelines Breast
Version 2024.1E

Malignant Pericardial Effusion
Local Therapy

Symptomatic pericardial effusion:	Oxford LoE	Oxford GR	Oxford AGO
▪ Drainage, fenestration	3b	B	++
▪ Combination with optimized systemic therapy	4	C	++
▪ VATS (video-assisted thoracic surgery)	4	C	+
▪ Ultrasound-guided puncture and instillation of cytotoxic / targeted compounds			
▪ Bleomycin, cisplatinum, mitomycin C, mitoxantrone etc., Bevacizumab	4	C	+/-

Guidelines Breast
Version 2024.1E

Bone Marrow Infiltration Associated with Pancytopenia

	Oxford		
	LoE	GR	AGO
▪ **Weekly chemotherapy with*:**			
▪ **Epirubicin, Doxorubicin, Paclitaxel**	4	D	++
▪ **Capecitabine**	4	D	++
▪ **HER2-positive:**			
▪ **anti-HER2-treatment**	5	D	++
▪ **Hormone receptor-positive:**			
▪ **Endocrine-based therapy**	3b	C	+

* **Consider pre-treatment**

Guidelines Breast
Version 2024.1E

Soft Tissue Metastasis
Local Therapy

	Oxford		
	LoE	GR	AGO
▪ **Surgery of limited locoregional metastasis (e.g. skin, muscular, nodal) with complete resection (R0) after exclusion of further metastases**	4	C	+/-
▪ **Radiotherapy in*:**			
▪ **Soft tissue metastases**	3b	C	+/-
▪ **Paresis, spinal cord compression**	2b	C	++
▪ **Plexus infiltration**	3b	C	++

*** Ecception: acute indication for surgery**

Guidelines Breast
Version 2024.1E

Oligo-Metastases
Contralateral Axillary Metastasis

“Contralateral axillary nodal metastasis (in the absence of contralateral primary) as initial diagnosis of recurrent disease is considered stage 4 metastatic breast cancer.
However, after prior local therapy to ipsilateral axilla for early breast cancer, subsequent metachronous contralateral axillary nodal metastasis, either alone or concurrent with an in-breast ipsilateral recurrence, could be considered and treated as a regional metastasis (due to altered lymphatic drainage), and has the potential for long survival or cure with a multidisciplinary approach”

ABC-7 (2023): LoE: Expert opinion/NA (85%)

Guidelines Breast
Version 2024.1E

CNS Metastases in Breast Cancer

Guidelines Breast
Version 2024.1E

CNS Metastases in Breast Cancer

- **Versions 2003-2023:**
  Bauerfeind / Bischoff / Diel / Ditsch / Fehm / Friedrich / Gerber / Huober / Krug / Loibl / Lück / Lüftner / Maass / Müller / Nitz / Park-Simon / Jackisch / Jonat / Junkermann / Rody / Schütz / Solbach / Stickeler / Witzel

- **Version 2024:**

  Maass / Witzel

Guidelines Breast
Version 2024.1E

CNS Metastases in Breast Cancer

- **Breast cancer is the 2nd most common cause of CNS metastases.**
- **In metastatic breast cancer patients:**
  - **Parenchymal CNS metastases: ~ 30–40%**
  - **Leptomeningeal CNS metastases: ~ 5–16%**
- **Increasing incidence (up to 40%)**
- **Increasing incidence due to**
  - **More effective treatment of extra-cerebral sites with improved prognosis**
  - **Increasing use of MRI for diagnostic evaluation**
- **Lack of specific knowledge about treatment of brain metastases in breast cancer since most studies are not breast cancer specific. Therefore, participation in the German registry study is recommended (www.gbg.de).**

Incidence of Brain Metastases among Patients with Metastatic Breast Cancer – Meta-Analysis of 25 Trials between 2010-2020

Guidelines Breast
Version 2024.1E

Subtype	No patients	Incidence per patient-year	Pooled cumulative incidence	Median follow-up (months)
HER2 positive (all)	5971	13% 95% CI: 0.22–0.38	31%	31
HR- / HER2 positive	2092	13% 95% CI: 0.08–0.20	-	-
HR+ / HER2 positive	3480	8% 95% CI: 0.05–0.13	-	-
HR- / HER2 negative	4102	13% 95% CI: 0.09–0.20	32% 95% CI: 0.19–0.49	33
HR+ / HER2 negative	14656	5% 95% CI: 0.03–0.08	15% 95% CI: 0.078–0.27	33

Kuksis M, Gao Y, Tran W et al. Neuro Oncol. 2021 Jun 1;23(6):894-904

Guidelines Breast
Version 2024.1E

CNS Metastases in Breast Cancer
Tumour biology

- **Primary Tumor:**
  - **Negative hormone receptor status (basal-like cell type / triple-negative)**
  - **High grade, high Ki-67 index**
  - **HER2 and / or EGFR (HER1) overexpression**
  - **Molecular subtype (Luminal B, HER2 positive, triple-negative)**
  - **Inflammatory breast cancer**
- **Brain metastases are more likely estrogen receptor negative and overexpress HER2 and / or EGFR.**
- **Discordance of molecular subtype between primary tumor and brain metastases: for ER = 16.7%, for PR = 25.2% and HER2 = 10.4%**
- **There is no evidence for a survival benefit of BM-screening in asymptomatic BC-patients.**

Updated Breast-GPA (Graded Prognostic Assessment) Worksheet to Estimate Survival from Brain Metastases (BM)

Guidelines Breast
Version 2024.1E

Prognostic Factor	0	0.5	1	1.5	Score
KPS	≤ 60	70-80	90–100	n/a	
Subtype	Basal	LumA	n/a	HER2 or LumB	
Age, years	≥ 60	< 60	n/a	n/a	
ECM	present	absent	n/a	n/a	
No of BM	≥ 2	1	n/a	n/a	
					Sum total

Median survival by Breast-GPA:

Breast-GPA 0–1.0 = 6 months
Breast-GPA 1.5–2.0 = 13 months
Breast-GPA 2.5–3.0 = 24 months
Breast-GPA 3.5–4.0 = 36 months

Subtype: Basal: triple negative; LumA: ER / PR positive, HER2 negative; LumB: triple positive; HER2: ER / PR positive, HER2 positive ECM: extracranial metastases BM: brain metastases

Sperduto PW et al. JCO 2020

Guidelines Breast
Version 2024.1E

Single / Solitary Brain Metastasis and Oligo-Brain Metastases*

	Oxford		
	LoE	GR	AGO
Local therapy alone: SRS (< 2-3 cm) oder SRT (>2-4 cm)	1b	B	++
Single / Solitary Metastasis:	1b	B	++
Resection (if indicated) + irradiation of the tumor bed (without WBRT)			
Oligo-Brain Metastases:	1b	B	++
Resection (if indicated) + irradiation of the tumor bed and SRS or SRT of unresected metastases (without WBRT)			
WBRT + Boost (SRS, SRT) or resection + WBRT	2a	B	+
WBRT alone	2b	B	+
Patients with reduced general condition and limited life expectancy			
Hippocampal-sparing (if prognosis is favourable)**	1b	B	+

*** Oligometastases or limited tumour volume refers to ≤ 4 brain metastases or cumulative tumour volume < 15 ml in 5-10 brain metastases**

**** Metastases in hippocampus excluded**

SRS = stereotactic radiosurgery (single session), SRT = stereotactic RT (fractionated); WBRT = whole brain radiotherapy

Single / Solitary Brain Metastasis and Oligo-Brain Metastases*

Guidelines Breast
Version 2024.1E

- **Local therapy (surgery, SRS, SRT) depends on localization, size, number of metastases, previous therapy, Karnofsky-Performance-Scale, prognosis.**
- **WBRT in addition to SRS/SRT improves intracranial control, but does not improve duration of functional independence and overall survival.**
- **WBRT impairs neurocognitive function.**
- **In case of limited* number of brain metastases, SRS / SRT are preferred.**
- **Postoperative radiotherapy:**

  Single/solitary brain metastasis (resection cavity < 5 cm): SRS v. WBRT no difference in overall survival.

  Oligo-brain metastases: SRS of surgical cavity and SRS of unresected metastases v. WBRT

  no difference in overall survival.

*** Oligometastases or limited tumour volume refers to ≤ 4 brain metastases or cumulative tumour volume < 15 ml in 5-10 brain metastases**

****Metastases in Hippocampus excluded**

SRS = stereotactic radiosurgery (single session), SRT = stereotactic RT (fractionated); WBRT = whole brain radiotherapy

Radiation necrosis (RN) after stereotactic radiotherapy

Incidence and imaging characteristics

- **RN should be considered in case of suspected progression of previously irradiated brain metastases as differential diagnosis**
- **Increase in contrast enhancement on MRI/CT, edema present, typically appearing 6-18 months after RT, progressive course without adequate treatment, correlation with radiotherapy plan is essential**
- **Additional imaging (i.e. FET-PET,CT/MRI perfusion) may be considered.**
- **Incidence 5-10% after SRS/SRT, approx. half of the patients are symptomatic**

Risk factors

- **Increasing diameter of treated metastases, previous irradiation (whole-brain radiotherapy or previous stereotactic radiotherapy to the same lesion), SRS for metastases >3 cm (prefer SRT), association with concurrent systemic treatment equivocal**

Management (in close coordination with treating radiation oncologist)

- **Follow-up with MRI is warranted in asymptomatic cases with uncritical size and location**
- **In symptomatic patients and/or critical size/location, interdisciplinary management is essential. Options include dexamethasone, bevacizumab (off label), and surgery.**

Adapted from Bernhardt et al. Strahlenther Onkol 2022. 198: 971-883.

Guidelines Breast
Version 2024.1E

Possible Factors for Decision Making Neurosurgery versus Stereotactic Radiosurgery

Factors in favor of neurosurgery:

- **Histological verification e.g. after a long recurrence-free interval**
- **Need for immediate decompression, life-threatening symptoms**
- **Tumor size not allowing stereotactic radiotherapy**

Factors in favor of primary radiotherapy*:

- **Tumor location poorly amenable to surgery**
- **More than four lesions**
- **Comparable local control for SRS/SRT vs. surgery + postoperative RT**

*** stereotactic radiotherapy should be preferred if possible**

Guidelines Breast
Version 2024.1E

Multiple Brain Metastases if Stereotactic Radiotherapy is not indicated

	Oxford		
	LoE	GR	AGO
▪ WBRT (supportive steroids[1])	1a	A	++
▪ Hippocampal-sparing radiotherapy[2] (if prognosis is favourable)	1b	B	+
▪ Corticosteroids alone[1]	3a	B	+/-
▪ Systemic therapy alone	3a	D	+/-
▪ For newly diagnosed or progressive asymptomatic brain metastases (only for HER2 breast cancer)[3]	2b	C	+
▪ Radiochemotherapy for intracerebral control	3b	C	-
▪ WBRT in case of recurrence[4]	4	C	+/-

[1]adapted to symptoms; [2]metastases in hippocampus excluded; [3]only if regimens with proven clinical activity in active brain metastases are used; [4]can be discussed depending on time-interval from first radiation, prior dose, and localization if local therapy (surgery, SRS, FSRT) is not indicated and / or possible

SRS = stereotactic radiosurgery; SRT = stereotactic radiotherapy (fractionated); WBRT = whole brain radiotherapy

Guidelines Breast
Version 2024.1E

Symptomatic Therapy of Brain Metastases

	Oxford		
	LoE	GR	AGO
▪ Anticonvulsants only if symptoms of seizures	3a	C	+
▪ Glucocorticoids only if symptoms and / or mass effect (Dexamethasone with best evidence)	3a	C	++
▪ For patients with bad prognosis and reduced physical common conditions best supportive care is an option	5	D	+

Guidelines Breast
Version 2024.1E

Clinical Classification of Brain Metastases

Stable brain metastases (definition: RECIST / RANO):
stabilization after treatment of brain metastases.

Stable brain metastases (definition: DESTINY-BREAST03):
stable brain metastases ≥ 2 weeks after whole brain radiotherapy, asymptomatic, no requirement of corticosteroid or anticonvulsant therapy

Active brain metastases (definition: HER2Climb):
locally pretreated brain metastases with progressive disease or newly diagnosed brain metastases not needing immediate local therapy
or
untreated brain metastases not needing immediate local therapy

Guidelines Breast
Version 2024.1E

Systemic Therapy of Brain Metastases

	Oxford		
	LoE	GR	AGO
▪ Interdisciplinary treatment planning (tumor board)	5	D	++
▪ Systemic therapy alone as primary treatment	3a	D	+/-
▪ For newly diagnosed or progressive asymptomatic brain metastases (only for HER2-positive breast cancer)*	2b	C	+
▪ Continuation of the current systemic therapy if first diagnosis of brain metastasis and stable extracranial disease**	2c	C	+

*only if regimens with proven clinical activity in active brain metastases are used
** only in case of adequate local treatment of brain metastases

Systemic Therapy of Brain Metastases: HER2 positive

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Tucatinib + Trastuzumab + Capecitabine*	2b	B	+
▪ Trastuzumab-Deruxtecan**	2b	B	+
▪ Trastuzumab-Deruxtecan*	2b	C	+/-
▪ T-DM1 **	2b	B	+/-
▪ Lapatinib + Capecitabine*	2b	B	+/-
▪ Neratinib + Capecitabine*	2b	B	+/-
▪ Neratinib + Paclitaxel**	2b	B	+/-
▪ High-dose Trastuzumab + Pertuzumab*	2b	C	-

* efficacy demonstrated in active and stable brain metastases based on trial inclusion criteria

** efficacy demonstrated in stable asymptomatic brain metastases based on trial inclusion criteria

Clinical trials including HER2 positive patients with brain metastases

Trial	Phase	N**	Brain metastases	Combination	IC-ORR
HER2Climb[1,2*]	II	291	Stable + active	Tucatinib+Trastuzumab+ Capecitabine	47%
HER2Climb02[3]	III	204	Stable + active	Tucatinib + T-DM1	42%
DESTINY-B03[4]	III	36	Stable	Trastuzumab-Deruxtecan	64%
TUXEDO-1[5]	II	15	Active	Trastuzumab-Deruxtecan	73%
DEBBRAH[6]	II	21	Stable + active	Trastuzumab-Deruxtecan	46.2% (active) 66.7% (all patients)
KAMILLA[7]	III	398	Stable	T-DM1	21%
LANDSCAPE[8]	II	45	Active	Lapatinib + Capecitabin	66%
NALA[9]	III	161	Stable	Neratinib + Capecitabine	23%
TBCRC-022[10]	II	49	Active	Neratinib + Capecitabine	49% (Lapatinib-naive) 33% (prior Lapatinib)
PATRICIA[11]	II	39	Active	Pertuzumab + high dose Trastuzumab	11%
NEfERT-T[12]	II	29	Asymptomatic	Paclitaxel + Neratinib	Not reported; CNS incidence⇩

**reference list*

Adapted from O'Brian B et al. SABCS 2022

Guidelines Breast
Version 2024.1E

Leptomeningeal Carcinomatosis: Therapy

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
Intrathecal or ventricular therapy			
▪ MTX 10–15 mg 2–3 x/ week (+/- folinic acid rescue)	2b	B	+/-
▪ Steroids	4	D	+/-
▪ Trastuzumab (HER2 pos. disease)	3a	C	+/-
Systemic therapy	3b	B	+
Radiotherapy			
▪ Focal (bulky disease)	4	D	+
▪ WBRT	4	D	+
▪ Neuroaxis Craniospinal irradiation (disseminated spinal lesions)	2b	B	+/-

Intrathecal administration of Trastuzumab

	Kumthekar PU et al.[1]	**Oberkampf F et al.[2]**
Type of study	Multicenter, Phase Ib/II	Multicenter, Phase Ib/II
N	34	19
Trastuzumab delivery	80 mg intrathecally twice weekly	150 mg intrathecally weekly
CBR	69.2% (PR: 19.2%, SD 50%)	
Median PFS	-	5.9 months
Median OS	8.3 months	7.9 months

[1]Kumthekar PU et al. Neuro Oncol. 2022, [2]Oberkampf F et al. Neuro Oncol. 2022

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

Complementary Therapy Survivorship

Complementary Therapy – Hormonal Treatment and Alternatives in Breast Cancer Survivors – Survivorship

Guidelines Breast
Version 2024.1E

- **Versions 2002–2023:**

  Albert / Bauerfeind / Blohmer / Dall/ Fersis / Friedrich / Gerber / Göhring / Hanf / Heil / Janni / Kümmel / Lück / von Minckwitz / Nitz / Oberhoff / Rhiem / Scharl / Schmidt / Schütz / Solomayer / Thomssen

- **Version 2024:**

  Kümmel / Thomssen

Guidelines Breast
Version 2024.1E

CAM

„Integrative Oncology“

„Unconventional methods“

CAM
Complementary + alternative medicine

Complementary

In addition to scientifically based medicine

Alternative

Instead of scientifically based medicine

UCT
Unconventional Tx

Unconventional

Unproven outsider methods

Guidelines Breast
Version 2024.1E

Good Clinical Practice

All patients should be consulted as early as possible and in the course of the process repeatedly on the interest in information complementary medical measures and, if interested, reliable sources of information should be referred.

S3 LL “Komplementärmedizin in der Behandlung von onkologischen PatientInnen“

Guidelines Breast
Version 2024.1E

General Considerations

	Oxford		
	LoE	GR	AGO
▪ CAM instead of loco-regional interventions	2b	B	--
▪ CAM instead of systemic treatment	2b	B	--

- **Diagnostic procedures in connection with complementary and alternative therapy concepts without evidence (e.g. iris diagnostics, bioresonance) should not be recommended.**
- ***During anti-cancer treatment:*** **Beware of drug interactions**

Guidelines Breast
Version 2024.1E

Complementary Therapy
Pre- and Postoperative

	Oxford		
	LoE	GR	AGO
Preoperative:			
▪ Hypnosis (reduces anxiety, pain, nausea)	1b	B	+
Postoperative:			
▪ Acupuncture (pain relief, anxiety)	1b	B	+
▪ Acupuncture (nausea, vomiting)	2b	B	+
▪ Massage therapy (pain relief)	2b	C	+/-
▪ Early postoperative exercise reduces upper-limb dysfunction (beware: increased wound drainage)	1a	A	+
▪ Physical exercise			
▪ to reduce breast cancer related secondary lymphedema	1a	A	+
▪ as a prophylaxis of lymphedema	1b	B	+/-
▪ Prophylactic lymphatic drainage	1b	B	--
▪ Yoga (arm and shoulder pain)	2b	C	+
▪ Music therapy (reduces pain after mastectomy)	2b	C	+/-

Guidelines Breast
Version 2024.1E

Complementary Treatment
While on Cancer Treatment – Impact on Toxicity I

During anti-cancer treatment: Beware of drug interactions

	Oxford LoE	Oxford GR	Oxford AGO
▪ **Mistletoe (Viscum album)** in order to reduce side effects	1a	B	+/-
▪ **Thymic peptides** lower risk of severe infections	1a	B	+/-
▪ **Ginseng** reduces fatigue; note: interacts with cytochrome P enzymes e.g. CYP 3A4	2b	B	-
▪ **Ganoderma Lucidum** reduces fatigue, note: inhibits cytochrome P enzymes (e.g. CYP 3A4)	1a	B	-
▪ **L-Carnitine**			
▪ peripheral neuropathy	1b	B	--
▪ treatment of fatigue	1b	B	-
▪ **Melatonin** (reduces fatigue, improve sleep, depressive symptoms, cognition)	2a	B	+/-
▪ **Curcumin** adjunct to reduce radiation-induced dermatitis	1b	B	+/-
▪ **Ginger** adjunct to guideline-oriented medication to treat chemotherapy induced nausea & vomiting – beware of drug interactions	1b	C	+/-

Guidelines Breast
Version 2024.1E

Complementary Treatment
While on Cancer Treatment – Impact on Toxicity II

	Oxford		
	LoE	GR	AGO
▪ **Antioxidant supplements**	1b	B	-
• **various antioxidative extracts** (to reduce anthracyclin-induced cardiotoxicity)	1b	B	-
▪ **High dose vitamin C**	1b	C	-
▪ **Vitamine E**	2b	B	-
▪ **Selenium** (for alleviating therapy side effects)	1b	B	-
▪ **Co-Enzyme Q 10** (fatique, QoL)	1b	B	-
▪ **Proteolytic enzymes** (for reduction of chemotherapy-induced toxicity)	2b	B	-
▪ **Chinese herbal medicine improves wound healing ***	1b	B	--
▪ **Oxygen and ozone therapy**	3	C	--
▪ **Short-term fasting** (under 3 week chemotherapy cycle - Qol, Fatigue)	2b	B	+/-**

* **Application of substances or combinations not tested in Germany**
** **Treatment in clinical trials recommended**

Guidelines Breast
Version 2024.1E

Additional Complementary Therapy of Side Effects Related to Cancer Treatments

	Oxford		
	LoE	GR	AGO
▪ **Cannabis-based drugs (against pain, emesis/nausea)**	1b	A	+/-
▪ **Chinese medicinal herbs** (to treat the side effects of chemotherapy and endocrine therapy)	**1b**	**B**	**-**
▪ **Homoeopathic medicine** (against therapy-related side effects / placebo effect)	**1b**	**B**	**+/-**
▪ **Topical Silymarin (**to prevent acute dermatitis during radiotherapy)	**2b**	**B**	**+/-**
▪ **Massage** (to improve on fatigue, pain, anxiety, nausea)	**1b**	**B**	**+/-**
▪ **Transcutaneous Electrical Nerve stimulation (TENS)** (against cancer pain)	**1a**	**B**	**+/-**
▪ **Hydrotherapy** (for supportive skin care)	**2b**	**B**	**+/-**

* Cave! Overviews or meta-analyses with purely Chinese-language original works cannot be verified by the Commission Mamma

Additional Complementary Therapy of Side Effects Related to Cancer Treatments

Guidelines Breast
Version 2024.1E

Acupuncture** in order to improve	Oxford LoE	Oxford GR	AGO
▪ Chemotherapy-induced nausea and vomiting			
▪ (Electro/Ear)-Acupuncture as adjunct to entiemetic treatment	1b	B	+
▪ (Ear-)Acupressure as adjunct to entiemetic treatment	1b	B	+
▪ Pain			
▪ Cancer pain	1b	B	+
▪ Aromatase-inhibitor – induced athralgia	1a	B	+
▪ Fatigue	1a	B	+
▪ Acupressure	1b	B	+
▪ Cognitive Dysfunction	2b	C	+/-
▪ Sleep Problems	2b	C	+/-
▪ Menopause syndrome (under treatment)	1b	B	+ *
▪ to improve on frequency and severity of hot flashes	1b	B	+/-
▪ Leucopenia (Moxibustion)	2b	B	-
▪ Treatment of chemotherapy induced polyneuropathy			
▪ prophylactically	1b	B	-
▪ therapeutically	2b	B	+/-
▪ Chronic lymph edema after breast cancer treatment	2b	B	+/-

* data only post treatment
** Cave! Overviews or meta-analyses with purely Chinese-language original works cannot be verified by the Mamma Commission

Guidelines Breast
Version 2024.1E

Complementary Treatment
Mind-Body Medicine I

	Oxford LoE	GR	AGO
MBSR (Mindfulness-Based Stress Reduction) Program improves quality of life, coping strategies, attentiveness, and lowers stress, anxiety (incl. fear of recurrence), depression, fatigue, and sleep disturbances	1a	A	+
Physical exercise / sport min. 3x/week moderate endurance training in combination with workout exercises (2x per week) improve quality of life, cardio-respiratory fitness, physical performance, sleep, pain, depression, lymphedema, fatigue, cognition, weight-control	1a	A	++

Complementary Treatment
Mind-Body Medicine II

Guidelines Breast
Version 2024.1E

	Oxford LoE	GR	AGO
Relaxation techniques Reduction of anxiety, depressivity and nausea, improvement of quality of life, sleep, reduction of psychological stress	2b	C	+/-
Yoga Improves quality of life, sleep, anxiety, depression, CIPN, lymphedema and especially fatigue	1b	A	+
Qi Gong May improve quality of life, fatigue, and mood	2a	B	+/-
Tai Chi Improves quality of life, muscular strength, sleep	2a	B	+/-
Hypnosis Improves fatigue and muscle weakness under radiotherapy; also reduces distress	1b	A	+

Guidelines Breast
Version 2024.1E

CAM
Prevention of Recurrence / Improvement of Overall Survival I
Modifiable Lifestyle Factors

	Oxford		
	LoE	GR	AGO
▪ **Physical exercise** (equivalent to 3–5 hrs moderate walking per week) improves DFS and OS, cardio-respiratory fitness, physical functioning	2a	A	++
▪ **Reduce smoking**	2b	A	+
▪ **Reduce alcohol consumption (< 6 g/day)**	2b	A	+

Guidelines Breast
Version 2024.1E

Modifiable Lifestyle Factors

Nutrition after Breast Cancer Diagnosis

Prevention of Recurrence / Improvement of Overall Survival II

	Oxford		
	LoE	GR	AGO
▪ **Adherence to normal BMI / weight loss if overweight, irrespective of HR-status**	1a	A	++
▪ **Low fat diet** dietary counseling recommended	1a	B	+
▪ **Increased fiber intake (e.g. Flaxseed)**	2a	B	+
▪ **Adherence to general nutrition guidelines** (e.g. DGE, WCRF) similar to a Mediterranean Diet	2a	B	++
▪ **Nightly Fasting**	2b	C	+/-
▪ **Dietary extremes**	2a	B	--

Guidelines Breast
Version 2024.1E

Complementary Treatment

Prevention of Recurrence / Improvement of Overall Survival III.1

Dietary Supplements – Herbal Therapies

During anti-cancer treatment: Beware of drug interactions	Oxford LoE	Oxford GR	AGO
Post treatment vitamine / antioxidant supplements does not appear to be associated with increased risk of recurrence (beware of drug / treatment interactions)	2b	B	
Smokers on antioxidant supplements are at higher risk for lung cancer	1b	A	
For Prevention of BC Recurrence:			
▪ **Antioxidants**	2a	B	+/-
▪ **Vitamine supplementation in patients on a balanced diet** (esp. Vitamine C, E)	2a	B	+/-
▪ **Vitamine D (after Vit D level)**	2b	B	+/-
▪ **Soy-food** (natural source of phytoestrogenes)	2a	B	+/-
– **food or concentrates containing ≥ 100 mg) isoflavones per day**	2a	B	-
▪ **Black Cohosh** (Cimicifuga racemosa)	3b	C	+/-
▪ **Antioxidant supplements** (after completion of radiotherapy)	2b	B	+/-
▪ **Green tea**	3a	C	+/-
▪ **Selenium**	2b	B	+/-

Guidelines Breast
Version 2024.1E

Complementary Treatment

Prevention of Recurrence / Improvement of Overall Survival III.2

Dietary Supplements – Herbal Therapies

During anti-cancer treatment: Beware of drug interactions

	Oxford		
	LoE	GR	AGO
▪ **Trace elements and minerals**	2b	B	-
▪ **Artificial carotenoids**	2b	B	-
▪ **Proteolytic enzymes** (Papain, Trypsin, Chymotrypsin)	3b	B	-
▪ **Mistletoe** (Viscum album)	1b	C	-
▪ **Thymic peptides** (impact on OS)	2a	B	-
▪ **Oxygen- and ozone therapy**	5	D	- -
▪ **Laetrile (**Amygdalin, „Vitamine B17“)	1c	D	- -
▪ **Methadone**	5	D	--
▪ **TCM-Herbs ***	2b	C	--
▪ **Cancer bush** (Sutherlandia frutescens), **Devil's claw** (Harpagophytum procumbens), **Rooibos tea** (Aspalathus linearis), **Bambara groundnut** (Vignea subterranean)	4	C	-
▪ **Incense**	5	D	-
▪ **Curcuma, curcumine**	2b	C	-

*** Cave! Reviews with original Chinese studies and herbal mixtures without knowledge of interactions**

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

Gynecological Issues in Breast Cancer Patients

Gynecologic Issues in Breast Cancer Patients

Guidelines Breast
Version 2024.1E

- **Versions 2015–2023:**
  Albert / Bauerfeind / Blohmer / Fehm / Fersis / Gerber / Hanf / Huober/ Loibl / Maas / Mundhenke/ Reimer / Rody / Scharl / Stickeler / Thill / Thomssen / Witzel
- **Version 2024:**
  Huober / Mundhenke

Hormone (Replacement) Therapy (HT) of Estrogen Deficiency after Diagnosis of Breast Cancer

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
Systemic hormone (replacement-) therapy			
▪ **Endocrine responsive disease (ER pos.)**	1a	B	-
▪ **Combined treatment TAM plus low dose HT**	2b	B	+/-
▪ **Endocrine non-responsive disease (ER neg.)**	1a	B	+/-
▪ **Tibolone**	1b	A	- -
Topical vaginal application of			
▪ **Estriol** (E3 0.03 mg as treatment course*)	2b	B	+/-
▪ **DHEA locally**	2b	B	-
▪ **Testosterone locally**	2b	B	-
▪ **Estradiol (E2)** during AI therapy	4	C	-

* **4 weeks daily 1 x 1, followed by 8 weeks 3 x 1 per week –** Note:. Elevated E3-blood levels only with start of therapy; oncological endpoints were not studied. Non-hormonal alternatives should be preferred, see slide „Sexual Health“

Further Medical Approaches to Reduce Menopausal Symptoms I

Guidelines Breast
Version 2024.1E

Medical approaches* (reduction of hot flushes)	Oxford LoE	Oxford GR	Oxford AGO
Selective serotonin reuptake inhibitors and serotonin-(noradrenalin) reuptake inhibitors (SSRI-SNRI): reduce hot flashes in BC patients			
Venlafaxine	1a	A	+
Desvenlafaxine, Sertraline, Escitalopram	1b	A	+/-
Gabapentin (patients using TAM)	1a	A	+
Oxybutynine (2.5 mg / 5 mg)	1b	A	+/-
Pregabalin	1b	A	+/-
Clonidine 0.05-0.15 mg/die (patients uasing TAM)	2a	B	+/-
MPA (i.m. 500 mg single shot) (most potent, but endocrine agent!)	1b	A	+/-
Omega-3 fatty acids	1b	A	+/-
Vitamin E	1b	A	-
Medical approaches (other treatment goals)			
Melatonin (improvement in sleep quality)	2b	C	+
Duloxetine (treating arthralgias while on AI)	1b	B	+

* **Note: Substantial placebo-effect has been proven (23-57%)** LoE 1b A +

CAM* - Approaches to Reduce Menopausal Symptoms II

* Complementary and Alternative Medicine

Guidelines Breast
Version 2024.1E

During anti-cancer treatment: Beware of drug interactions!	Oxford LoE	Oxford GR	Oxford AGO
▪ **Soy-derived phytoestrogens – isoflavonoids***			
Hot flushes	1b	B	-
Sleep disturbance	1b	B	+/-
Topical vaginal application	1b	B	+/-
▪ **Red Clover isoflavonoids***			
Hot flushes, sleep disturbance	1b	B	+/-
▪ **Flaxseed-supplementation** (40 g/d) (in HR+ ≤ 10 g/d) (reduces relapses, no effect on hot flashes)	2b	B	+/-
▪ **Black Cohosh for hot flushes**	1b	B	+/-
▪ **Black cohosh + St. John's Wort** (fixed combination)	1b	B	+/-
▪ **St. John's Wort** (pharmacokinetic interference with endocrine therapy, cyctotoxic drugs, and tyrosin kinase inhibitors)	1b	B	+/-
▪ **Ginseng root** (Panax ginseng or P. quinquefolius)	1b	B	-
▪ **Bromelain + Papain + Selenium + Lectin (for AI induced joint symptoms)**	3b	B	+
▪ **Homeopathic medicine to reduce hot flushes** (consider placebo-effect)	1b	B	+/-

* might stimulate BC, especially in endocrine responsive disease

Guidelines Breast
Version 2024.1E

General Approaches to Reduce Menopausal Symptoms III - Integrative Oncology Aspects

General approaches:

	Oxford LoE	GR	AGO
▪ Physical exercise	1a	A	++
▪ Cognitive behavioral therapy (CBT), hypnosis	1a	A	++
▪ Mind body-medicine (yoga, education, counselling, mindfulness training)	1b	B	+
▪ Short interruption of endocrine therapy in case of unacceptable side effects	5	D	+
(Electro) Acupuncture			
▪ Aromatase-inhibitor treatment induced arthralgia	1a	B	+
▪ Hot flushes	2a	B	+
▪ Anxiety, Depression	2b	B	+
▪ Sleep	2a	C	+

* as in SOLE Trial

Ovarian Protection with GnRHa and Fertility Preservation in Premenopausal Patients Receiving (Neo)-Adjuvant Chemotherapy (CT)

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ **CTx + GnRHa (preservation of ovarian function) (GnRHa application > 2 weeks prior to chemo-therapy, independent of hormone receptor status)**	1a	A	+
▪ **CTx + GnRHa (preservation of fertility)**	2a	B	+/-
▪ **Fertility preservation counselling including referral of all potential patients to appropriate reproductive specialists (further information *https://fertiprotekt.com/english; S2K Guideline Fertility preservation in oncology*)**			++

Guidelines Breast
Version 2024.1E

Fertility preservation and assisted reproductive therapy (ART)

- Oncological safety[1]-

	Oxford LoE	Oxford GR	AGO
▪ **Pretreatment approaches to preserve fertility**			
GnRHa	1a	A	++
Cryopreservation of ovarian tissue with subsequent transplantation[2]	4	D	+
Cryopreservation of oocytes (unfertilized / fertilized) after ovarian stimulation	2a	C	+
▪ **ART after diagnosis of breast cancer**	4	C	+/-

[1]Evidence is limited due to studies with poor quality e.g. (prospective randomized trials are not feasible)
[2] Risk of relapse caused by transplantation of ovarian tissue containing tumor cells from the original malignancy; Removal of transplanted ovarian tissue is necessary in patients with BRCA1/2 mutations due to increased risk of ovarian cancer

Oncological Safety of controlled ovarian stimulation (COS) or assisted reproductive therapy (ART)

Guidelines Breast
Version 2024.1E

N = 15 studies including 4643 patients undgoing COS or ART (assisted reproductive therapy)

COS before starting treatment (n=11 studies):

Reduced risk of recurrence RR 0.58, 95% CI 0,46-0,73

Reduced risk of mortality RR 0.54, 95% CI 0,38-0,76

No detrimental effect on EFS 0,76, 95% CI 0,55-1,06

- Subgroup of HR positive pts. HR 0.36, 95% CI 0.20–0.65

ART after treatment (n=4 studies):

Reduced risk of recurrence (RR 0.34, 95% CI 0.17-0.70)

No detrimental effect EFS (HR 0.43, 95% CI 0.17-1.11).

Conclusion: COS at diagnosis or ART following breast cancer treatment completion does not appear to be associated with any detrimental prognostic effect in young women

Arecco et al. Human Reprod 2022

Ovarian Protection – Synopsis of Randomized Trials

Guidelines Breast
Version 2024.1E

	ZORO	PROMISE	Munster et al. - US	POEMS	Option
Patient number	60 (60 HR-)	281 (50 HR-)	49 (13 HR-) of 124	218 (218 HR-)	227 (126 HR-)
Age median	38 years	39 years	39 years	Premenop. < 50 years	premenopausal
Treatment	goserelin	triptorelin	triptorelin	goserelin	goserelin
Start of treatment	> 2 weeks prior to cht	> 1 week prior to cht	> 1 week prior to cht	> 1 week prior to cht	> 1 week prior to cht
Primary Endpoint	menstruation at month 6 after chemotherapy	rate of early menopause at month 12 after cht	menstruation rate within 2 years after cht	Ovarian failure at 2 yrs after cht	Amenorrhea with elevated FSH levels between 12 and 24 months
Primary objective	to detect 30% absolute increase of menstruation rate	to detect at least 20% absolute reduction in early menopause	to detect 20% difference in amenorrhea rate – from 10% to 30%		To detect 20%-25% absolute reduction in early menopause
Multivar. analysis	age as only independent predictive factor	treatment as only independent predictive factor	n.d.	Treatment as only Independent predictive factor	Age, total cyclophosphamide dose and baseline AMH
Resumption of menses at month 12	83% with LHRH vs. 80% w/o	93% with LHRHa vs. 74% w/o	74% with LHRH vs. 68% w/o	78% with LHRH vs. 75% w/o; at 2 years; 22% with LHRH vs. 8%	78% with LHRHa vs. 62% amnorrhea rate between month 12 and 24
Median time to restoration of menses (months)	6.1 with LHRHa vs. 6.8 w/o; p = 0.30	not reached with LHRH vs. 6.7 w/o; p = 0.07	5.8 with LHRH vs. 5.0 w/o; p = 0.58	n.d.	n.d.
Cyclophosph. dose	4600 vs. 4700 mg	4080 vs. 4008 mg	n.r.	n.a.	5940 vs. 5940 mg

Guidelines Breast
Version 2024.1E

Assessment of Ovarian Reserve

	Oxford		
	LoE	GR	AGO
Tests for fertility assessment			
▪ Anti-Mullerian Hormone	1b	B	+
▪ Antral follicle count	3b	B	+
▪ FSH	2b[a]	B	+
▪ Combined test procedures for assessment of ovarian reserve*	5	C	+
Decreased ovarian reserve in BRCAmt carriers	2b	B	

* Tests are suggested for women > 35 y and infertility for 6-12 months; the tests do not predict failure to conceive. They should be used in counselling patients and to provide a rough estimate of the fertility window. Results may decrease patient referral time to infertility centers.

Contraceptive Options for Women after Diagnosis of Breast Cancer

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Barrier methods	5	D	+
▪ Sterilization (tubal ligation / salpingectomy / vasectomy)	5	D	+
▪ Non-hormonal intrauterine devices (IUDs)	3b	D	+
▪ Levonorgestrel-releasing IUDs	2b	C	-
▪ Removal in newly diagnosed patients	4	D	+/-
▪ Timing methods	5	D	-
▪ Injectable progestin-only contraceptives	5	D	-
▪ Progestin-only oral contraceptives	5	D	-
▪ Combined oral contraceptives	5	D	-
▪ Options of emergency contraception			
▪ Copper intrauterine device (Copper-IUD)	5	D	+
▪ Levonorgestrel, Ulipristal orally	5	D	+

Sexual Health / Vaginal Dryness

Evaluation	Oxford LoE	Oxford GR	AGO
▪ **Assessment of sexual dysfunction**	5	D	+
▪ **Use of patient-reported questionnaires**	4	C	+
Therapy of dyspareunia and vaginal dryness			
▪ **Psychoeducational support, group therapy, sexual counselling, marital counselling, psychotherapy**	1b	B	+
▪ **Topical vaginal treatment**			
▪ **Non-hormonal lubricants / moisturizers** (also with physiotherapy)	1b	B	+
▪ **Estriol** (E3 0.03 mg as treatment course*)	2b	B	+/-
▪ **DHEA local application**	2b	B	-
▪ **Testosterone local application**	2b	B	-
▪ **Estradiol** (E2) during AI therapy	4	C	-
▪ **Fractionated microablative CO2-Laser / Vaginal Erbium:YAG-Laser**	2a	B	+/-

* **4 weeks daily 1 x 1, followed by 8 weeks 3 x 1 per week –** Note:. Elevated E3-blood levels only with start of therapy; oncological endpoints were not studied. Non-hormonal alternatives should be preferred.

Einschätzung der sexuellen Gesundheit[1]

- **Kurze Checkliste Sexueller Symptome für Frauen (BSSC-W)[2]**
- **Screening-Fragebogen zur Sexualfunktion insgesamt**

1. Sind Sie zufrieden mit Ihrem Sexualleben? ***Ja – Nein***

Wenn nein, dann beantworten Sie bitte die nächsten Fragen:

2. Seit wann/wie lange sind Sie mit Ihrem Sexualleben unzufrieden? **.....**

3a. Ihr Problem im Sexualleben ist: *(eins oder mehrere markieren)*

1. Problem mit weniger oder gar kein Interesse bzw. Lust 0
2. Problem mit reduzierter Empfindlichkeit / Sensibilität im Genitalbereich (Gefühl) 0
3. Problem mit verringerter vaginaler Lubrikation (Trockenheit der Scheide) 0
4. Problem, einen Orgasmus zu erreichen 0
5. Probleme mit Schmerzen beim Geschlechtsverkehr 0
6. Andere Probleme oder Sorgen .....

3b. Welche Probleme stören Sie am meisten? *Bitte ankreuzen:* *1 – 2 – 3 – 4 – 5 – 6*

4. Wollen Sie über diese Probleme mit Ihrem Arzt/Ihrer Ärztin reden? ***Ja – Nein***

- **Sexual Complaints Screener For Women (SCS-W)[3,4]**
- **FSFI-19, FSFI-6[5,6]**

Guidelines Breast
Version 2024.1E

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

Health Literacy and Communication

Health Literacy

- **Versions 2020-2023:**
  Bauerfeind / Maass / Rhiem / Schmidt / Schütz

- **Version 2024:**
  Albert / Ditsch

Consulting patient advocates of the AGO-Patient-Taskforce:

R. Haidinger, Brustkrebs Deutschland e.V.

B. Welter, mamazone e.V.

Health Literacy Definition

“Health literacy is linked to literacy and entails people’s knowledge, motivation and competences to access, understand, appraise, and apply health information in order to make judgments and take decisions in everyday life concerning healthcare, disease prevention and health promotion to maintain or improve quality of life during the life course.”

Sørensen et al., (2012)

Health Literacy Model

(according to Sörensen)

Guidelines Breast
Version 2024.1E

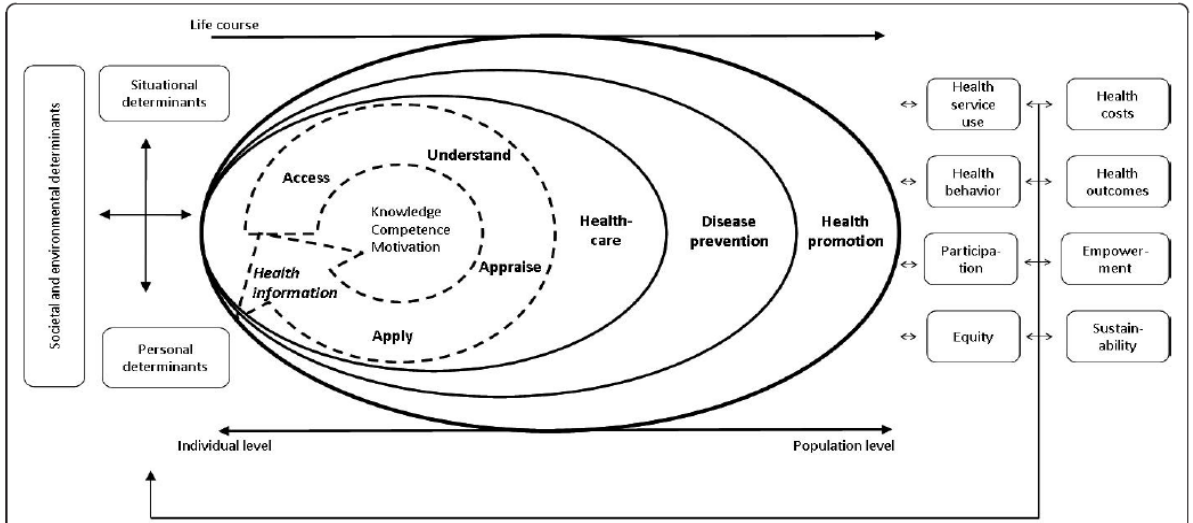


Figure 1 Integrated model of health literacy–see separate file.

Competencies

Access: seek, find, obtain health information.

Understand: Understanding the health information received

Appraise: Interpret, select, assess, review health information

Apply: Use health information to make decisions that support and improve health

Sørensen K, Van den Broucke S, Fullam J, Doyle G, Pelikan J, Slonska Z, Brand H. Health literacy and public health: A systematic review and integration of definitions and models. BMC Public Health. 2012, 12:80

Health Literacy

Health literacy is influenced both by individual abilities and skills ("personal health literacy") and by the demands and complexity of the living environment and systems ("organizational health literacy").

- The more developed health literacy is, the better a person can **inform** himself or herself about health (e.g. prevention, therapy) in everyday life, **form** an **opinion** and **make self-determined decisions** that maintain or improve the quality of life and health throughout the self-determined course of life ("personal health literacy") .

- However, the extent of health literacy of a person depends not only on his or her individual prerequisites and acquired competencies, but especially on the **professional quality, appropriateness, comprehensibility, form of communication and availability of the information provided** ("organizational health literacy").

Guidelines Breast
Version 2024.1E

Digital Health Literacy

Definition

Digital health literacy is the ability to search for, find, understand and evaluate health-related information in relation to digital applications and digital information services and to apply the acquired knowledge to solve a health problem.

Guidelines Breast
Version 2024.1E

Implemetation of Health Literacy

Reasons cited for overuse, underuse and misuse in the health care system include the weak position of patients (SVR 2001).

In the context of health literacy, the patient is

- more autonomous **actor and co-designer**
- the one who takes **responsibility** and an **active role** in medical decisions
- the person who extracts the **individually relevant meaning** from professionally offered information and **behaves in accordance with individual ideas about** certain health situations
- the one whose **digital health literacy** (e.g. media literacy, critical judgement) – as well as that of health professionals – should be supported.

SVR - Council of Experts for the Assessment of Developments in the Health Care System

Health Literacy

Patient-centered Communication

Aim of a physician-patient communication: enable a self-determined decision based on sufficient health competence (Shared Decision Making)

Oxford	
LoE	AGO
3a	+

Doctor-patient communication is key for acquiring health competence. It is the basis for successful oncological treatment and support. Core elements are, for example:

- **Non-directive communication** - i.e. those seeking advice have the right to choose their own goals in life, even if they contradict generally accepted, even evidence-based, recommendations after well-founded consideration.
- **Comprehensible communication** - i.e. geared to the level of knowledge, reception habits, competence requirements and preferences of the different patients

Guidelines Breast
Version 2024.1E

Health Literacy

Basic Principles of Patient-centered Communication

- Communicate information truthfully and empathetically
- Impart medical evidence-based knowledge in lay language
- Critical debate of pseude-scientific recommendations
- Active listening
- Showing empathy
- actively listening and expressing empathy
- Find out if and how the patient wants to be informed about his / her situation
- use understandable language avoiding or explaining technical terms
- Continuously improve understanding through e.g. repetitions, breaks, summary, comprehensible information material
- Encourage asking questions and expressing feelings
- Identifying individual stresses, problems and needs
- Motivating self-determination and personal activities ("empowerment")
- Giving hope for healing and relief
- Offer further assistance (e.g. psycho-oncology, self-help)

Guidelines Breast
Version 2024.1E

Health Literacy

Evidence-based Information

Evidence-based information in health care should be used to answer patients' questions in an understandable way. They are based on the current state of knowledge and are free from influence:

<u>requirement for evidence-based health information as a discrimination against pseudo-scientific recommendations:</u>

- **The information on services or products may not be used directly or indirectly for marketing purposes.**
- **The systematic search corresponds to the questions relevant to the target group.**
- **The selection of evidence suitable for the research question is justified.**
- **An undistorted presentation of the results relevant to the patients (e.g. side-effects, mortality, complaints, complications, health-related QoL) is available.**
- **The presentation of uncertainties is appropriate in terms of content and language.**
- **The presentation of results is clearly separated from the derivation of recommendations.**
- **Consideration of current evidence to communicate figures, risk information and probabilities.**
- **there must be sufficient time for the decision.**
- **The possibility that the measure may be refused must not be a reason for withholding information.**

Guidelines Breast
Version 2024.1E

Health Literacy

Communication

Non-directive and evidence-based doctor-patient communication geared to the current needs, values, problems, resources and preferences of patients has beneficial effects.

	Oxford LoE
▪ Reduction of fear	2b
▪ Trust in treating oncologists is increased	2b
▪ Treatment satisfaction is increased	2a
▪ Therapy adherence is increased	2a
▪ Decision making is improved	2a
▪ Mental complaints are improved	2a

Guidelines Breast
Version 2024.1E

Health Literacy

Communication Training

	Oxford LoE	AGO
Qualified training measures can help to promote communicative skills.		+
communication training for doctors can e.g.		
▪ **Enhance empathy**	2a	
▪ **Extend and enrich communication skills**	2a	
▪ **Increase patient satisfaction (information, support, consideration of concerns)**	2b	
▪ **Improve transmission of information**	2b	

Informed Decision Making

Guidelines Breast
Version 2024.1E

An informed decision is made when an individual

- understands the disease referred to
- understands what the medical management involves
- including the benefits, risks, limitations, alternatives and uncertainties;
- has considered his/her preferences and
- makes the decision in accordance with these,
- is of the opinion that one has participated in the decision to the desired extent and
- made the decision voluntarily and with the highest degree of personal autonomy.

Guidelines Breast
Version 2024.1E

Health Literacy

Shared Decision Making - Participatory Decision

	Oxford LoE	Oxford GR	AGO
▪ Patients want to be integrated actively involved into decision making at an early stage and open discussions about prognosis, treatment options, and quality of life	1b	A	
▪ Doctors should motivate patients to ask questions, demand clarification, express emotions, opinions, and preferences	3b	C	+
• Active involvement of caregivers/trusted persons	4	C	+

Shared Decision – Meta-analysis of Frequency and Influencing Factors

Guidelines Breast
Version 2024.1E

Method:

- 8 databases for studies about breast cancer patients' surgical decisional control preferences and shared decision making preference
- Meta-analysis of the frequency of preferred and actual shared decision making and decision congruence was performed (descriptive analysis)
- Fourteen original studies were included

Results:

- overall pooled frequency of the preferred shared decision making: 48.1% (95%CI 33.5%, 62.6%)
- the actual shared decision making 38.1% (95%CI 33.9%, 42.2%)
- pooled frequency of the decision congruence between preferred and actual decision styles was 61.7% (95%CI 54.6%, 68.8%).

Descriptive analysis findings indicated that the influencing factors of shared decision making included individual factors, surgeon-patient communication factors, and health setting factors.

Guidelines Breast
Version 2024.1E

Decision Aids

Decision aids address

- a wide range of preventive, diagnostic and therapeutic applications
- are offered as brochures, decision charts, videos or computer programs
- contain information on advantages and disadvantages, available options and instructions for individualized decision-making
- are used individually or as components of structured counseling or training.

The minimum quality standards are evidence-based, complete, unbiased and comprehensible.

Medical decision aids do not replace medical advice.

Guidelines Breast
Version 2024.1E

Health Literacy
Decision Aids for Patients

	Oxford LoE	AGO
The use of decision support in the physician-patient communication		+
▪ improves knowledge about treatment options	1a	
▪ reduces the decision conflict	1a	
▪ improves the level of information	1a	
▪ increases the feeling about the clarity of personal values	1a	
▪ encourages a more active role in decision-making	2b	
▪ improves risk perception	2b	
▪ improves the match between the chosen option and the patient's values	3a	

Guidelines Breast
Version 2024.1E

Health Literacy

Decision coaching

	Oxford		
	LoE	GR	AGO
			+

The use of decision coaching by health professionals based on evidence-based patient information can improve the decision-making process of patients.

Decision coaching is able to improve

▪ the knowledge of patients	2a	B
▪ the active role of patients in the process of decision making	2b	B

Use of eHealth (DiGA)

	Oxford		
	LoE	GR	AGO
▪ Use of DiGA to improve quality of life during and after breast cancer therapy	2b	B	+/-
▪ Use of PROs for improved collection of therapy-associated side effects and quality of life	2b	B	+/-

* See current DiGA status / reimbursement

Diagnosis and Treatment of Patients with Early and Advanced Breast Cancer

Guidelines Breast
Version 2024.1E

Therapy Algorithms

Preamble:

Therapy options shown in the algorithms are based on the current AGO recommendations, but cannot represent all evidence-based treatment options, since prior therapies, performance status, comorbidities, patient preference, special tumor biology etc. must be taken into account for the actual treatment choice. Normally only recommendations with the recommendation grades AGO+ and AGO++ are taken into account.

In individual cases, other evidence-based treatment options (not listed here) may also be appropriate and justified. After failure of effective standard treatments discussion in a molecular tumor board should be considered.

Regardless of approval status, the algorithms only take into account drugs that were available in Germany at the time the algorithm was last updated.

Guidelines Breast
Version 2024.1E

Therapy Algorithms

- **Version 2021-2023:**
  Schneeweiss / Bauerfeind / Fehm / Müller / Thill / Thomssen / Witzel / Wöckel / Janni
- **Version 2024:**
  Schneeweiss/ Müller with the Breast Committee of the AGO

- **Format legend:**
  - Text — **Definitions, features, parameters**
  - Text — **Therapy with grade of recommendation AGO+ or AGO++**
  - Text — **Therapy with grade of recommendation AGO+/- (case by case decision)**
  - **Recommended path with grade of recommendation AGO+ oder AGO++**
  - **Crossing without transition**
  - **Path of case by case decision (grade of recommendation AGO+/-)**
  - **Arrow points to the next therapy option**
  - *AGO++* — **AGO grade of recommendation of this path**

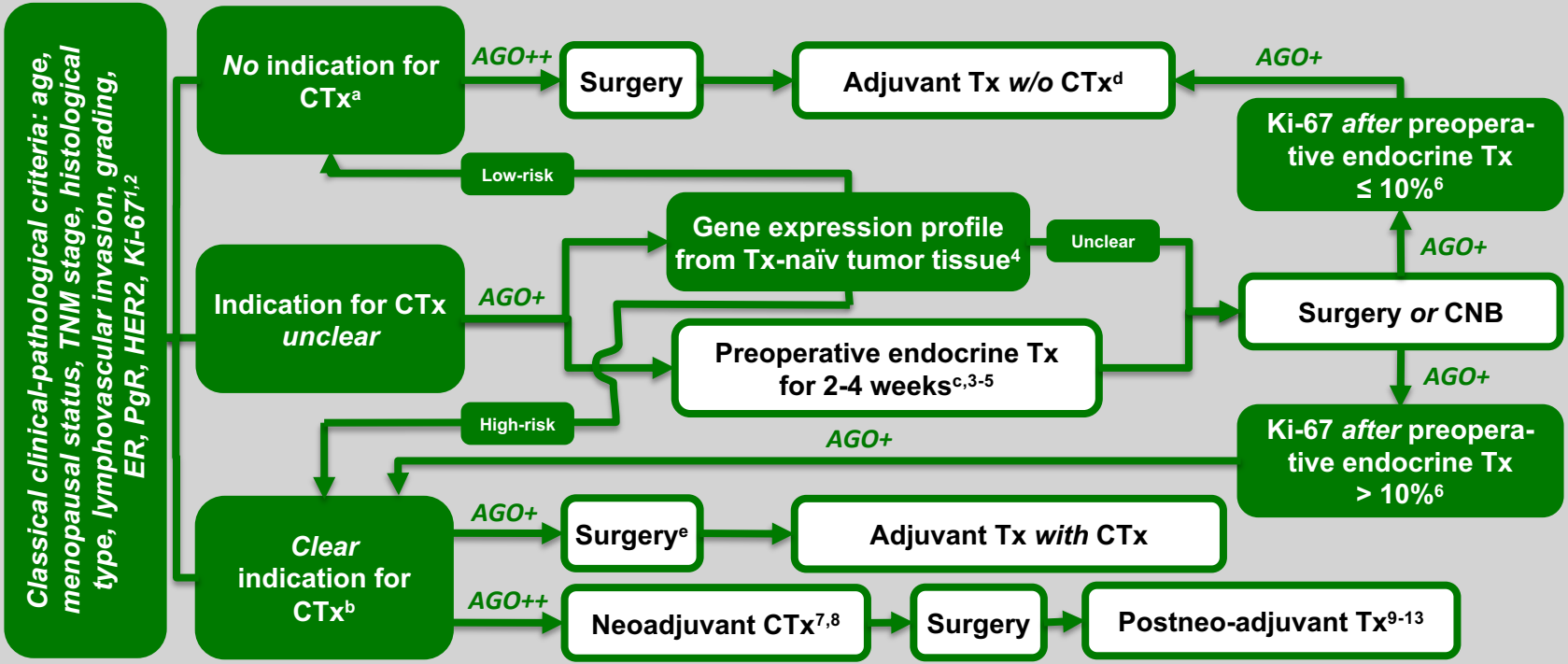
Guidelines Breast
Version 2024.1E

Content

- **Early breast cancer**
  - Therapy of HR-positive, HER2-negative early breast cancer: strategies
  - Therapy of HER2-positive early breast cancer
  - Therapy of early triple-negative breast cancer
  - Axillary surgery and neoadjuvant chemotherapy (NACT)
  - Adjuvant endocrine therapy in premenopausal patients
  - Adjuvant endocrine therapy in postmenopausal patients

- **Metastatic breast cancer**
  - HR-positive / HER2-negative metastatic breast cancer: strategies
  - HR-positive / HER2-negative metastatic breast cancer: endocrine-based first line treatment
  - HER2-positive metastatic breast cancer: 1st-3rd-line
  - Triple-negative metastatic breast cancer

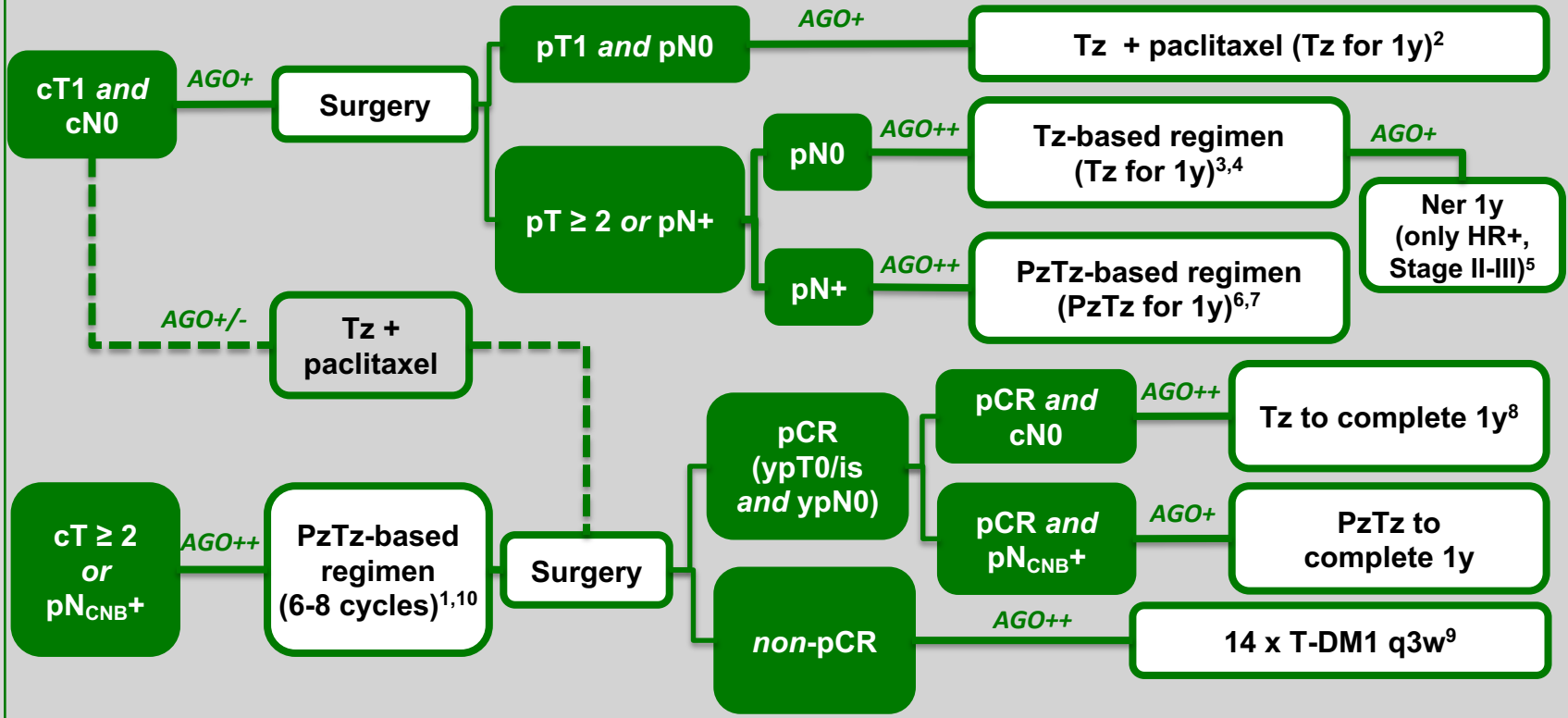
Therapy of HR-positive, HER2-negative Early Breast Cancer: Strategies



CNB, Stanzbiopsie (core needle biopsy); CTx, chemotherapy; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2 2; HR, Hormonrezeptor; Tx, therapy; w/o, without; [a]e.g.. ≤cT1c cN0-1 G1-2 Ki-67 ≤ 5% *or* -if sitaution unclear- low-risk gene expression profile; [b]e.g. inoperable tumor *or* ≥ 4 clinically involved axillary nodes *or* G3 and Ki-67 ≥ 35% *or* -if situation unclear- high-risk gene expression profile; [c]standard endocrine Tx; [d]if no change of prognostic factors after surgery; [e]if not already done.

Guidelines Breast
Version 2024.1E

Therapy of HER2-positive Early Breast Cancer

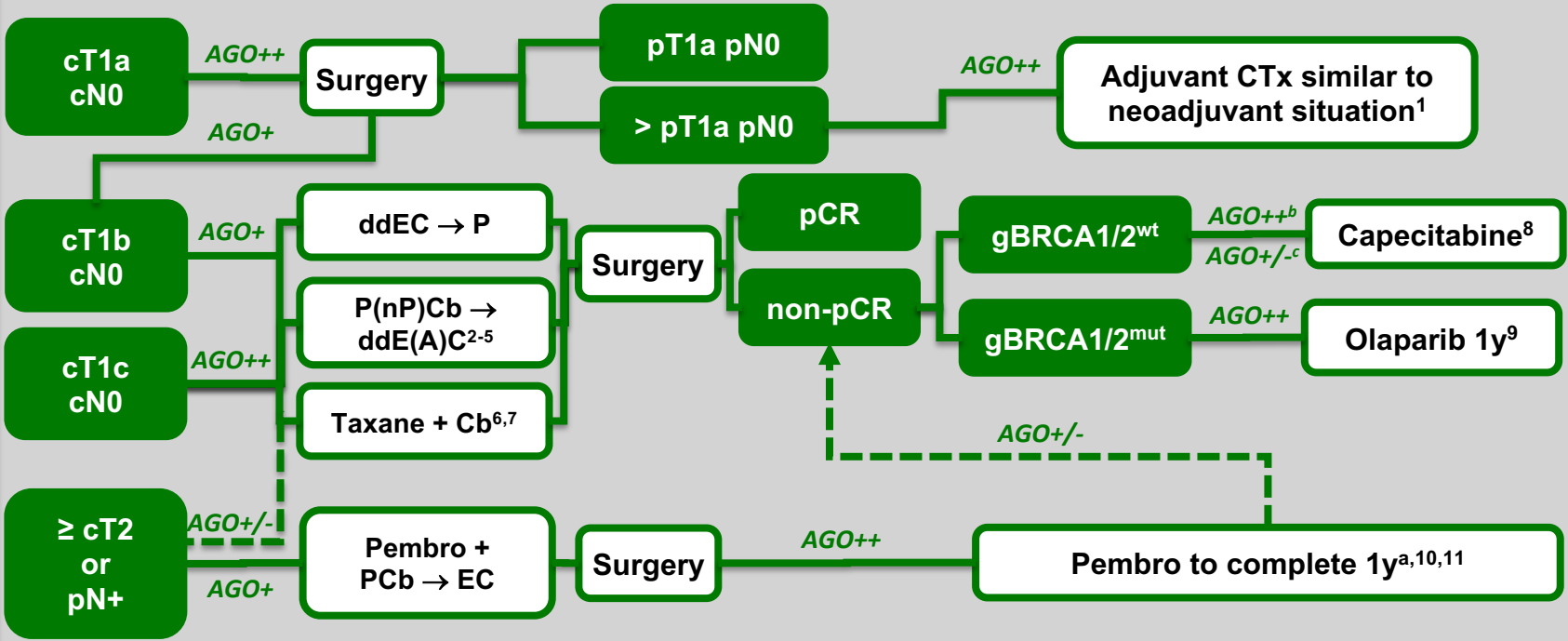


CNB, core needle biopsy; HR, hormone receptor; Ner, Neratinib; pCR, pathological complete response; Pz, Pertuzumab; q3w, every 3 weeks; T-DM1, Trastuzumab emtansine; Tz, Trastuzumab; y, year; if HR+ adjuvant endocrine therapy

Guidelines Breast
Version 2024.1E

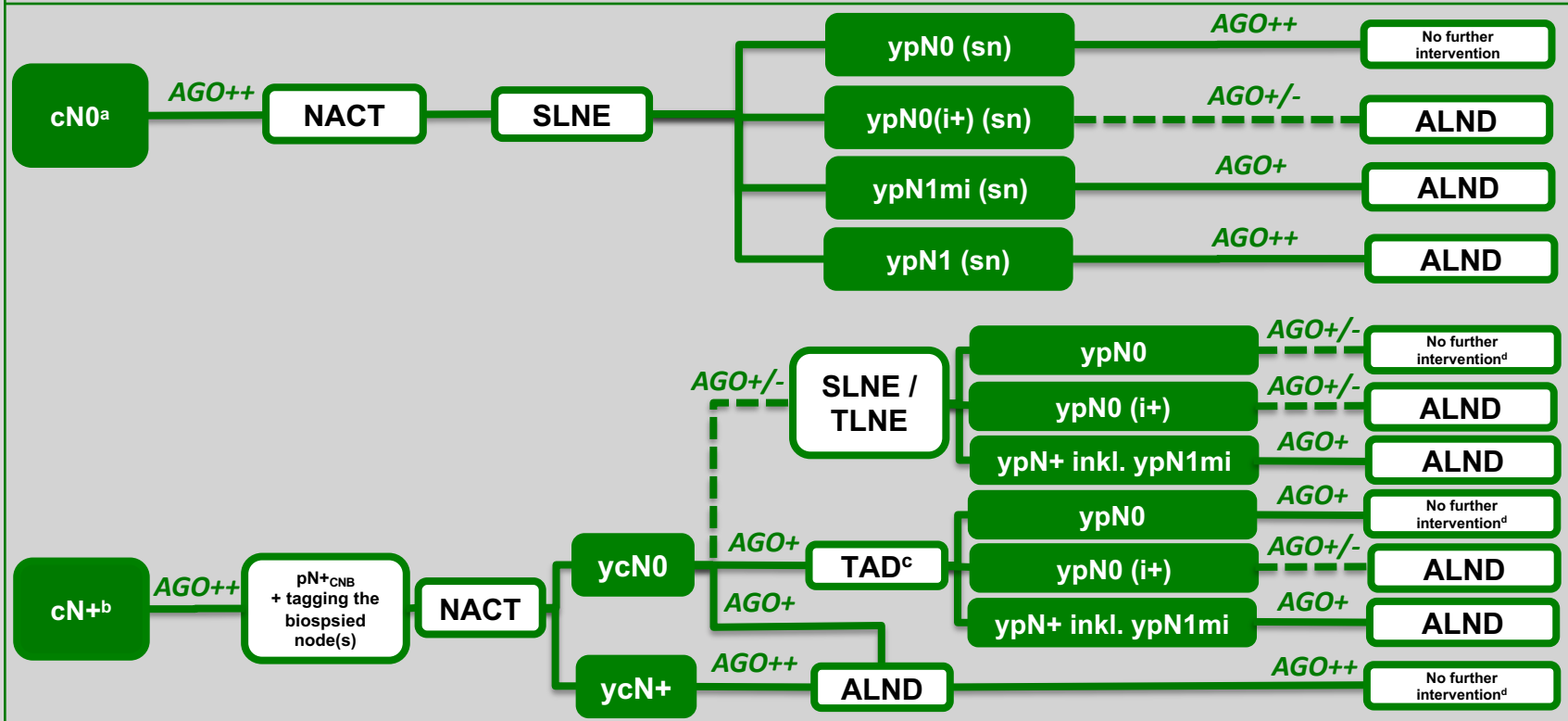
Therapy of Triple-negative Early Breast Cancer

Guidelines Breast
Version 2024.1E



A, doxorubicin; C, cyclophosphamide; Cb, carboplatin; CTx, chemotherapy; dd, dose dense (every 2 weeks); E, epirubicin; mut, mutated; nP, nab-paclitaxel; Pembro, pembrolizumab; P, paclitaxel; wt, wild type; y, year; [a] if Pembrolizumab was started before surgery; [b] after A/T-containing chemotherapy; [c] after chemotherapy with platinum and/or pembrolizumab.

Axillary Surgery and Neoadjuvant Chemotherapy (NACT)



ALND, axillary lymph node dissection; CNB, core needle biopsy; NACT, neoadjuvant chemotherapy; sn, sentinel node; SLNE, sentinel lymph node excision; TAD , targeted axillary dissection (SLNE + TLNE); TLNE, targeted lymph node excision; [a] participation in EUBREAST-01 study recommended; [b] participation in AXSANA study recommended; [c] TAD in case of 1-3 suspicious lymph nodes before NACT: +, in case of ≥ 4 suspicious lymph nodes before NACT: +/-; [d] for radiotherapy procedures see recommendations for radiotherapy.

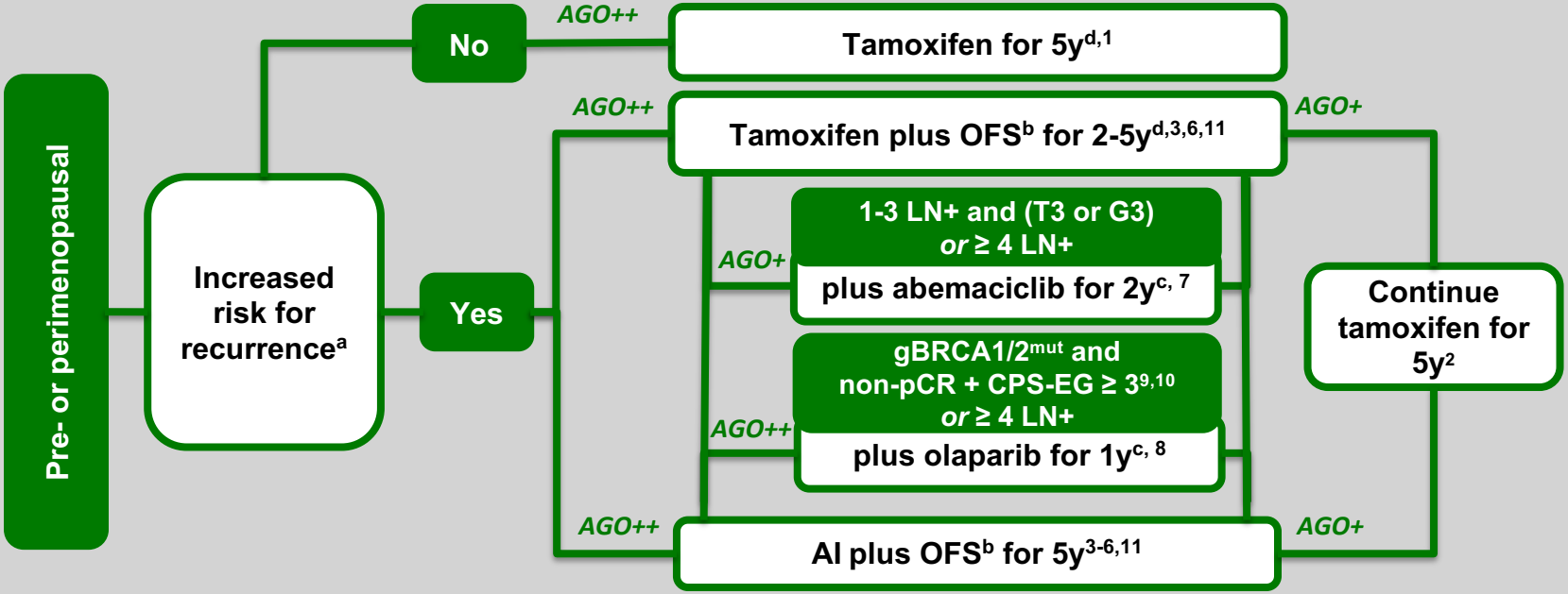
Guidelines Breast
Version 2024.1E

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

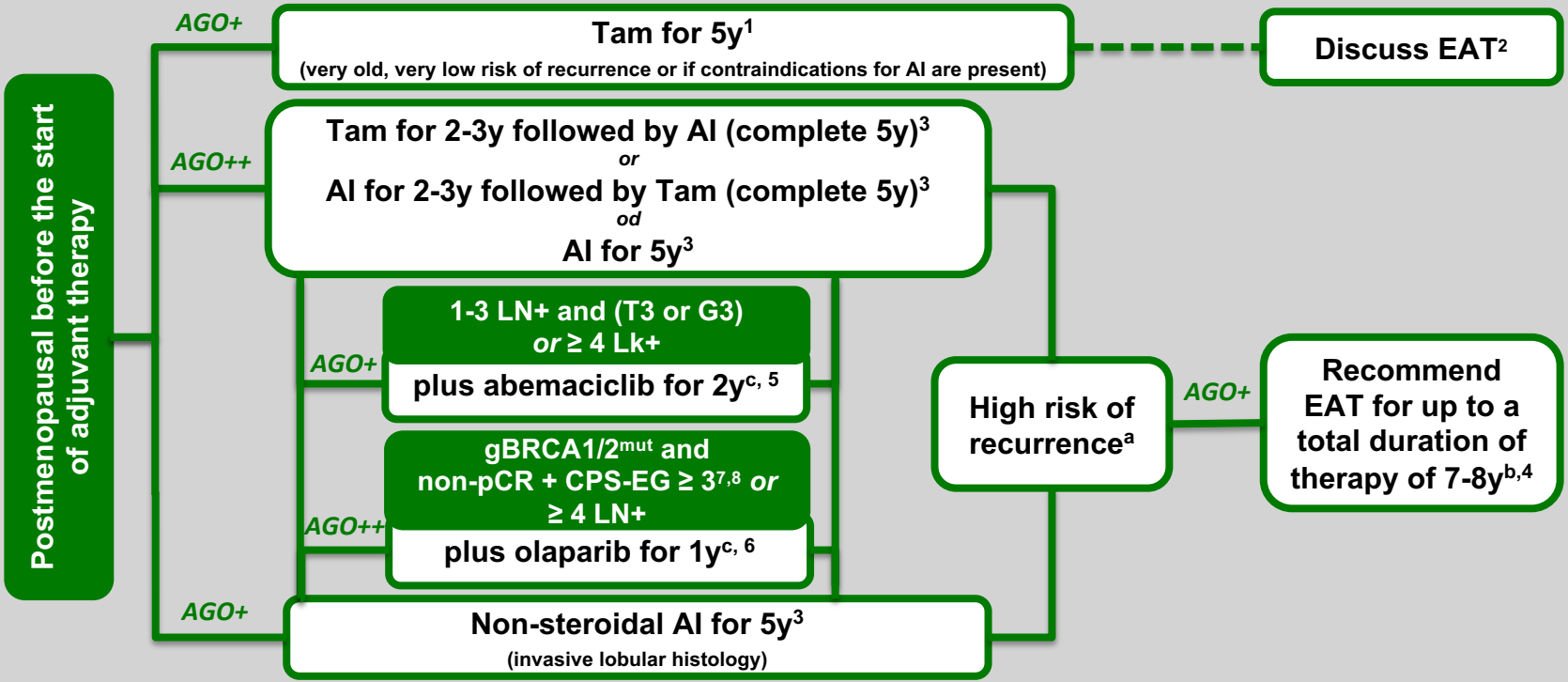
Adjuvant Endocrine-based Therapy in Premenopausal Patients

Guidelines Breast
Version 2024.1E



AI, aromatase inhibitor; CPS-EG, clinical pathological stage + estrogen receptor status and grade score; gBRCA1/2[mut], germ line BRCA1/2 mutation; LN, lymph node; OFS, ovarian function suppression; pCR, pathologic complete response; y, years; [a]Administration of chemotherapy was a surrogate marker for higher risk of recurrence in clinical trials; [b]OFS also in case of remaining or recurring ovarian function within 24 months after chemotherapy induced amenorrhea; [c]only HER2-negative; [d]In case patients wish to become pregnant interruption of adjuvant endocrine therapy after 18 months for a maximum of 2 years is possible without short-term survival disadvantage with a median F/U of only 3.5 years (AGO+).

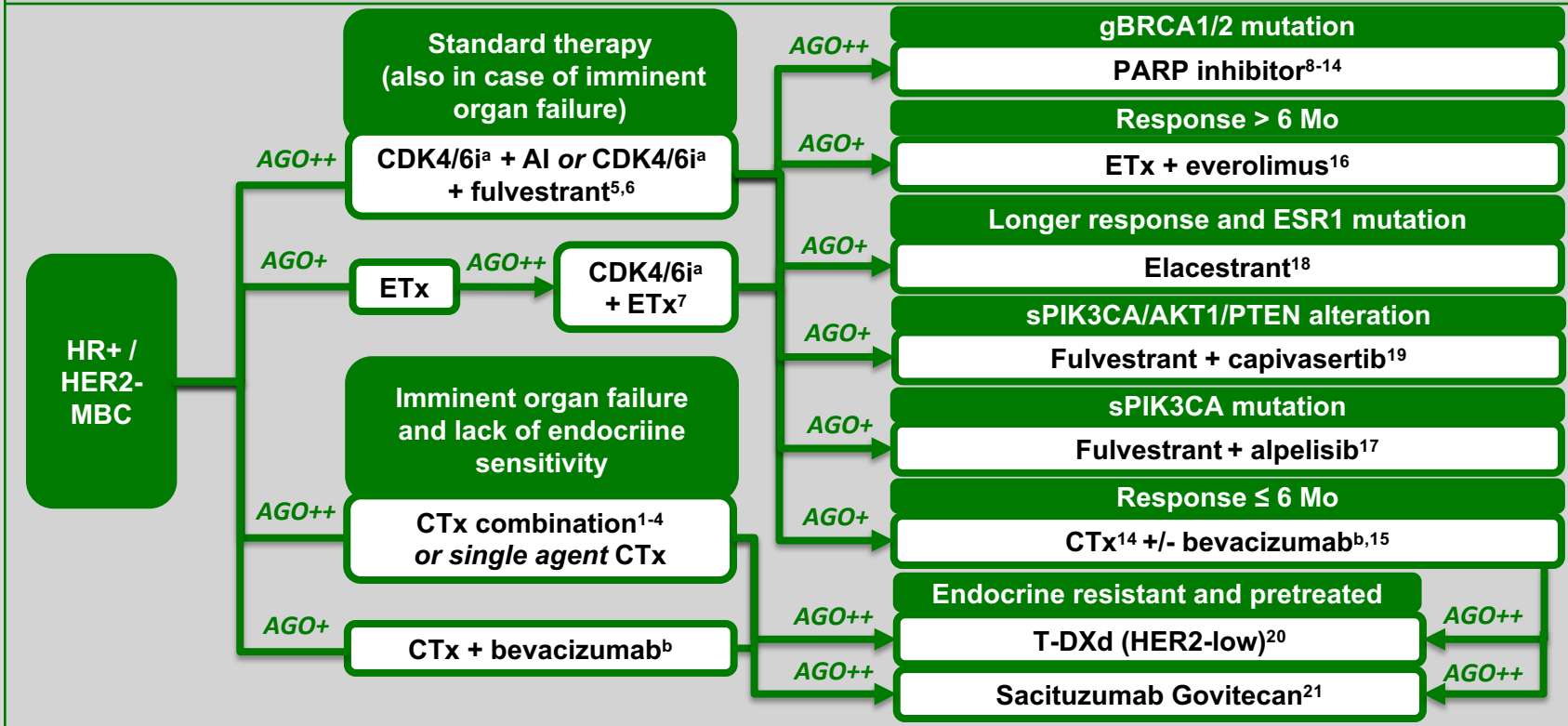
Adjuvant Endocrine-based Therapy in Postmenopausal Patients



AI, aromatase inhibitor; CPS-EG, clinical pathological stage + estrogen receptor status and grade score; EAT, extended adjuvant therapy; gBRCA1/2^{mut}, germ line BRCA1/2 mutation; LN, lymph node; Tam, tamoxifen; y, years; [a] decision criteria may include: condition after neo(adjuvant) chemotherapy (indicating high risk), positive lymph node status, T2/T3 tumors, elevated risk of recurrence based on immuno-histochemical criteria or based on multi-gene expression assays, high CTS5-Score; [b] up to date no impact on overall survival; [c] only HER2 negative.

Guidelines Breast
Version 2024.1E

HR-positive/HER2-negative Metastatic Breast Cancer: Strategies

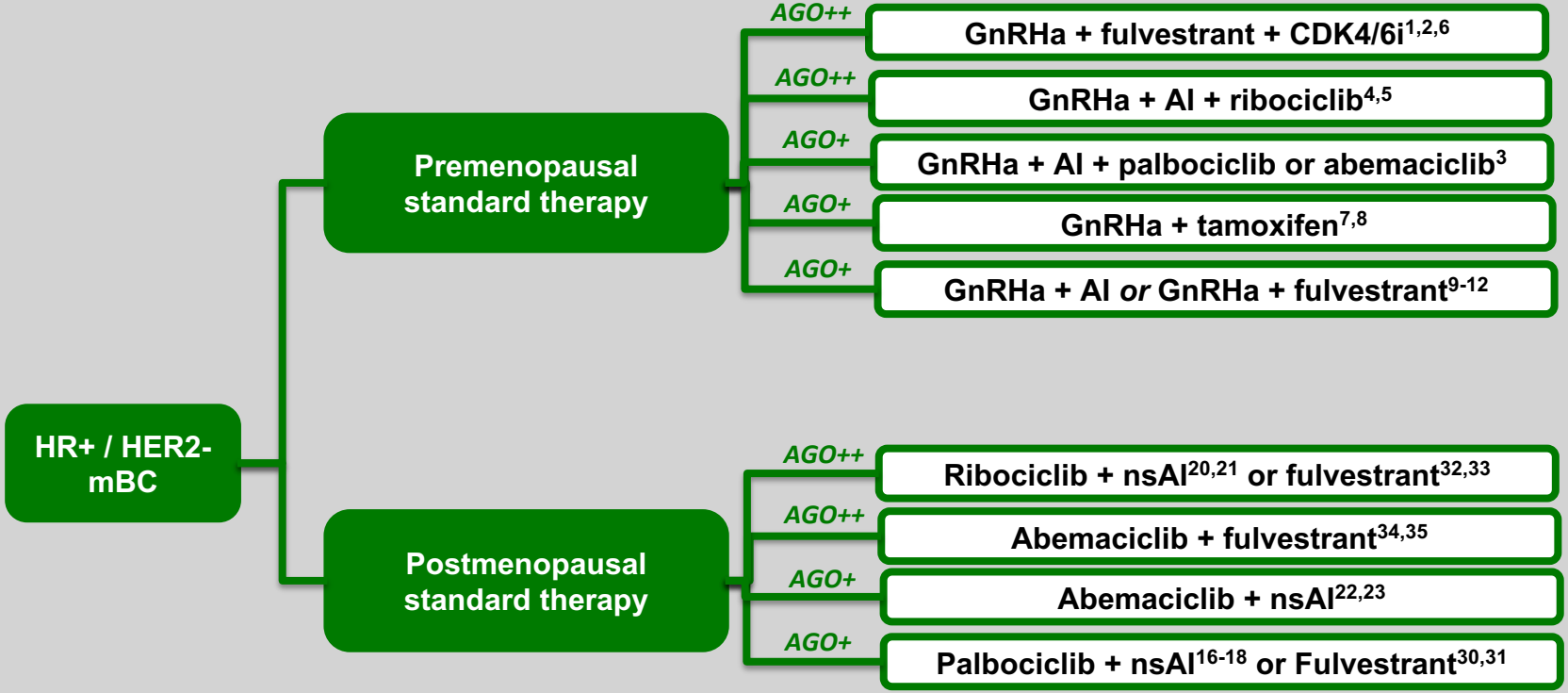


AI, aromatase inhibitor; CDK4/6i, CDK4/6 inhibitor; CTx, chemotherapy; ETx, endocrine therapy; gBRCA1/2 mutation, germ line BRCA1/2 mutation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mBC, metastatic breast cancer; mo, months; sPIK3CA mutation, somatic PIK3CA mutation; sPIK3CA/AKT1/PTEN alteration, somatic PIK3CA/AKT1/PTEN alteration; T-DXd, trastuzumab deruxtecan; [a] if premenopausal add ovarian function suppression; [b] bevacizumab + paclitaxel or + capecitabine.

Guidelines Breast
Version 2024.1E

HR-positive / HER2-negative Metastatic Breast Cancer: Endocrine-based First Line Treatment

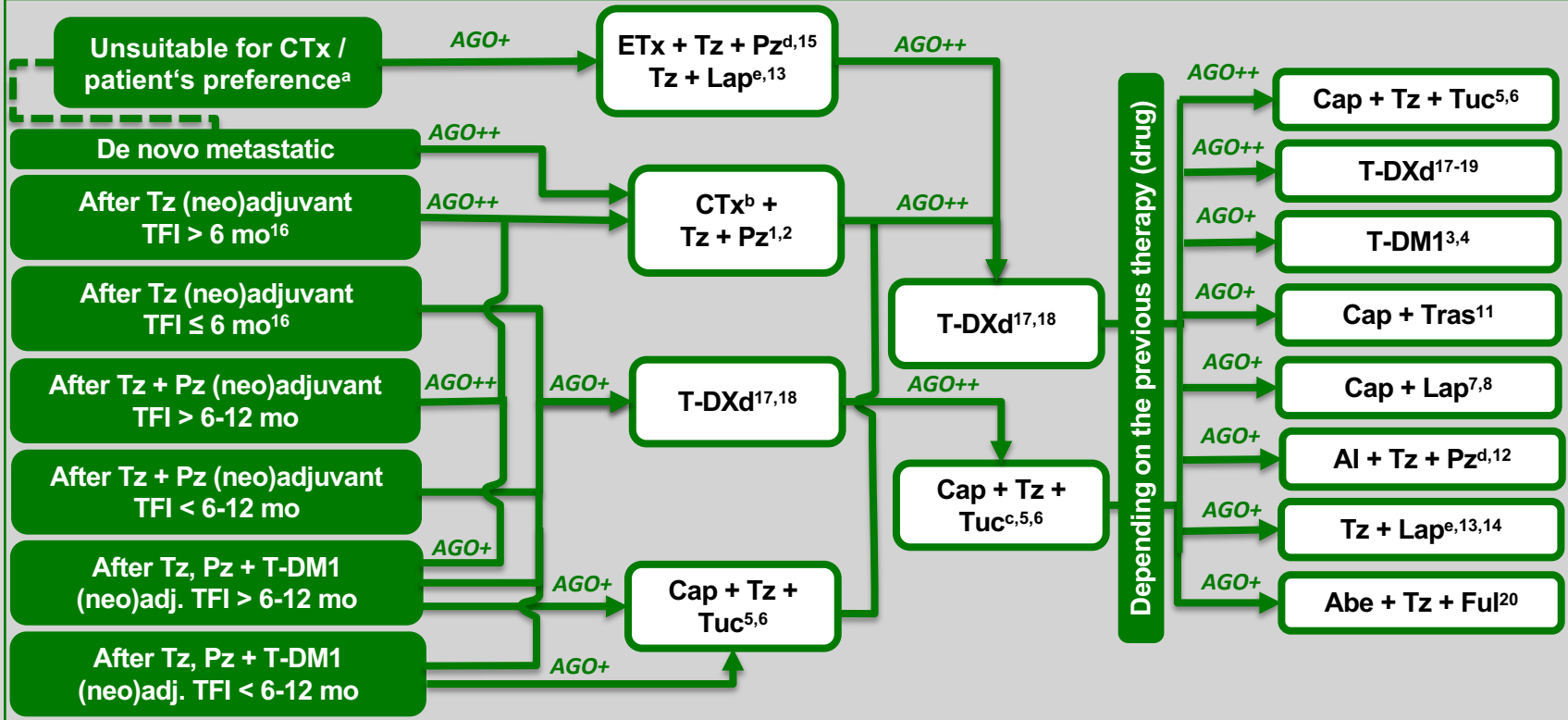
Guidelines Breast
Version 2024.1E



AI, aromatase inhibitor; CDK4/6i, CDK4/6 inhibitor; GnRHa, GnRH agonist; HR, hormone receptor; ns, non-steroidal; mBC, metastatic breast cancer; mo, months; TFI, treatment-free interval.

HER2-positive Metastatic Breast Cancer: 1st-3rd-line

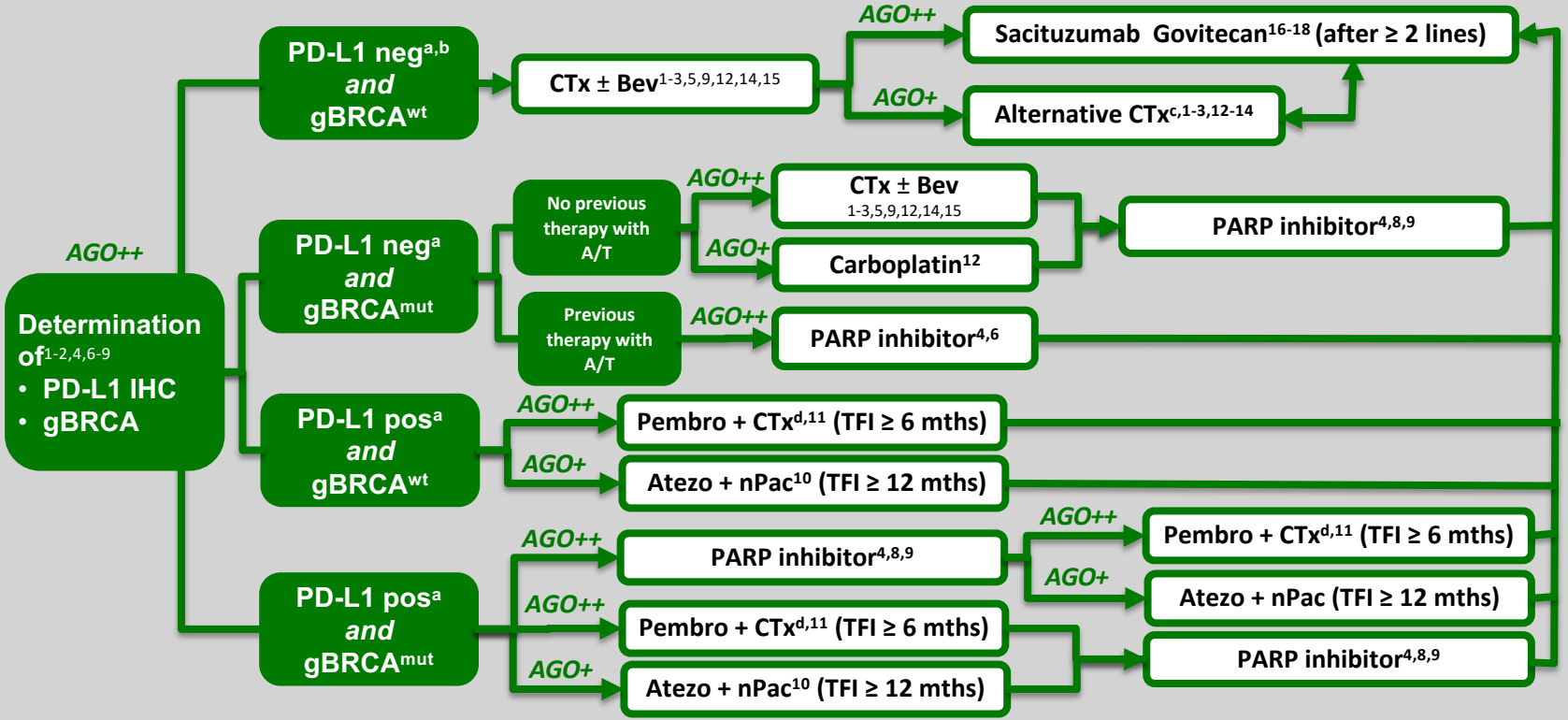
Guidelines Breast
Version 2024.1E



Abe, Abemaciclib; AI, aromatase inhibitor; Cap, capecitabine; CTx, chemotherapy; ETx, endocrine therapy; Ful, Fulvestrant; HR, hormone receptor; Lap, lapatinib; mo, months; Ner, neratinib; Pz, pertuzumab; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TFI, treatment-free interval; Tuc, tucatinib; Tz, trastuzumab; [a] no overall survival benefit, consider induction chemotherapy; [b] docetaxel (++), paclitaxel (++) or nab-paclitaxel (+); [c] only after T-DM1; [d] only if HR pos; [e] only if HR neg.

Triple-negative Metastatic Breast Cancer

Guidelines Breast
Version 2024.1E



A, anthracycline; Atezo, atezolizumab; Bev, bevacizumab; CTx, chemotherapy; gBRCA, germ line BRCA status; IHC, immunohistochemistry; mths, months; mut, mutated; neg, negative; ; nPac, nab-paclitaxel; Pembro, pembrolizumab; PD-L1, programmed cell death ligand 1; pos, positive; T, taxane; TFI, treatment-free interval; wt, wild type; [a]Pembro: CPS < 10 (neg) oder CPS ≥ 10 (pos), Atezo: IC < 1% (neg), IC ≥ 1% (pos); [b]PD-L1 pos with a TFI < 6-12 Mo; [c]use of not previously used compounds or regimen; [d]nPac, Pac or Carboplatin+Gemcitabin.