



Screened data bases

Pubmed 2007 - 2022, ASCO 2010 – 2022, SABCS 2010 – 2021, Cochrane Data Base (2019)

Screened guidelines

1. Cardoso F, Paluch-Shimon S, Senkus E, et. al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020 Dec;31(12):1623-1649.
2. Thomssen C., Lüftner D, Untch M, et al. International Consensus Conference for Advanced Breast Cancer, Lisbon 2019: ABC5 Consensus - Assessment by a German Group of Experts. Breast Care (Basel). 2020
3. ASCO (American Association of Clinical Oncology, Practice Guidelines, 2021) <http://www.asco.org>
4. American Society of Clinical Oncology Clinical Practice Survivorship Guidelines, Endorsements and Adaptations: <https://www.asco.org/practice-policy/cancer-care-initiatives/prevention-survivorship/survivorship-compendium-0>
5. 2016 Updated American Society of Clinical Oncology/Oncology Nursing Society Chemotherapy Administration Safety Standards, Including Standards for Pediatric Oncology: <http://ascopubs.org/doi/pdfdirect/10.1200/JOP.2016.017905>
6. Hershman DL, Lacchetti C, Dworkin RH et al. American Society of Clinical Oncology. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014 Jun 20;32(18):1941-67.

7. NCCN (National Comprehensive Cancer Network , 2021): <http://www.nccn.org>
8. S3-Leitlinie: Supportive Therapie: Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3 – Februar 2020 AWMF-Registernummer: 032/054OL



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Supportive Care and Management of Side Effects

■ Versions 2002–2021:

Albert / Bauerfeind / Brunnert / Bischoff / Costa / Dall / Diel / Fersis /
Friedrich / Friedrichs / Gerber / Göhring / Hanf / Harbeck / Heinrich /
Hoover / Jackisch / Lisboa / Lück / Lüftner / von Minckwitz / Möbus /
Müller / Mundhenke / Nitz / Oberhoff / Rody / Schaller / Scharl / Schmidt
/ Schneeweiss / Schütz / Solomayer / Souchon / Stickeler / Thomssen /
Untch

■ Version 2022:


Harbeck / Reimer



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Guidelines - Evidence



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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>).

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

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

1. S3-Leitlinie Supportive Therapie:
Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3 – Februar 2020 AWMF-Registernummer: 032/054OL Zugriff 25.12.2021
https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.3.pdf
2. ESMO Clinical Practice Guidelines: Supportive and Palliative Care. www.esmo.org
3. Jordan K, Aapro M, Kaasa S, et al. European Society for Medical Oncology (ESMO) position paper on supportive and palliative care. Ann Oncol. 2018 Jan 1;29(1):36-43.
4. Schneider BJ, Naidoo J, Santomasso BD, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update. J Clin Oncol. 2021 Dec 20;39(36):4073-4126.




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Toxicity Assessment

- **Acute toxicity (NCI-CTCAE)**
- **Long term toxicity (ICPC, ICD-GM)**



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Toxicity Assessment

Acute Toxicity (according to WHO¹ or NCI-CTC²)

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

Grade	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 LoE 5 D AGO ++
(acc. ICPC³ following symptoms or acc. ICD-10-GM⁴ following diagnoses)

Acute Toxicity

1. WHO Handbook for reporting results of cancer treatment, NO 48 (1979) (WHO offset Publications, Geneva)
2. NCI, Bethesda, USA, Common Terminology Criteria for Adverse Events v5.0 (CTCAE; published 2017);
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50 (Download 18.01.2018)

Acute Toxicity – Assessment after each cycle of therapy


1. Cirillo M, Lunardi G, Coati F, et al: Management of oral anticancer drugs: Feasibility and patient approval of a specific monitoring program. Tumori 100: 243-248, 2014

Long-term toxicity

1. International Classification of Primary Care (ICPC) revised December 2016,
<http://www.who.int/classifications/icd/adaptations/icpc2/en/> (Download 18.01.2018) or
<http://www.globalfamilydoctor.com/groups/WorkingParties/wicc.aspx> (Download 18.01.2018)
2. Deutschen Institut für Medizinische Dokumentation und Information (DIMDI), ICD-10-GM Version 2017;
<https://www.dimdi.de/static/de/klassi/icd-10-gm/kodesuche/onlinefassungen/htmlgm2017/> (Download 18.01.2018)
3. Kenyon M, Mayer DK, Owens AK. Late and long-term effects of breast cancer treatment and surveillance management for the

general practitioner. J Obstet Gynecol Neonatal Nurs. 2014 May-Jun;43(3):382-98.

4. Hematopoietic Cell Transplantation Guidelines Taskforce, Auditory and Vision Guidelines Taskforce, Cardiopulmonary Guidelines Taskforce, Endocrine Guidelines Taskforce, Genitourinary and Renal Guidelines Taskforce, Oral, Dental, Gastrointestinal and Hepatic Guidelines Taskforce, et al. Late Effects Surveillance Recommendations among Survivors of Childhood Hematopoietic Cell Transplantation: A Children's Oncology Group Report. Author manuscript; available in PMC 2017 May 1. Published in final edited form as: Biol Blood Marrow Transplant. 2016 May; 22(5): 782–795.
5. Inge Spronk, Joke C Korevaar, Francois G Schellevis, et al. Evidence-based recommendations on care for breast cancer survivors for primary care providers: a review of evidence-based breast cancer guidelines. BMJ Open. 2017; 7(12): e015118.
6. M.J. Heins, J.C. Korevaar, P.M. Rijken, et al. For which health problems do cancer survivors visit their General Practitioner? European Journal of Cancer (2013) 49, 211– 218.



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Acute Toxicity (NCI CTCAE v 5.0, 2017)

- **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.

Activities of Daily Living (ADL)

- * 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.

1. NCI, Bethesda, USA, Common Terminology Criteria for Adverse Events v5.0 (CTCAE; published 2017); https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50 (Download 18.01.2018)

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Incidence of Side Effects

- **According to product information by MedDRA* classification**

* MedDRA - Medical Dictionary for Regulatory Activities

*MedDRA - Medical Dictionary for Regulatory Activities

<https://www.meddra.org/>



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Chemotherapy – Acute Toxicities I

DRUGS

SYSTEM ORGAN CLASS

	INFECTIONS AND INFESTATIONS	NEOPLASMS BEN., ALIGNANT AND UNSPECIFIED (INCL CYSTS & POLYPS)	IMMUNE SYSTEM 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
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 (sporadic)	4	3	-	5	4	4	4	3	3 4
Gemcitabine	4	-	5	1	-	4	-	4	-	-	2 2
Platinum-complexes											
Cisplatin	4	2	5	3	2	5	-	4	2	5	4 4
Carboplatin	4	-	5	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(1)	-	-	(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 to 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)

Side effect categories - MedDRA (Medical Dictionary for Regulatory Activities)

- MedDRA: <https://www.meddra.org/> bzw.
https://www.meddra.org/sites/default/files/guidance/file/intguide_20_1_english_0.pdf

Sources for product information (Download 19.01.2018)

- Cyclophosphamid: http://www.baxter.de/de_DE/assets/downloads/fachinformation/endoxan.pdf
- Methotrexat: https://www.gelbe-liste.de/produkte/MTX-HEXAL-10-mg-Tabletten_117469/fachinformation
- 5-Fluorouracil: https://www.gelbe-liste.de/produkte/Fluorouracil-HEXAL-50-mg-ml-Injektionsloesung-100-ml_546519/fachinformation
- Capecitabin: <https://www.zentiva.de/Produkte/Capecitabin-Zentiva/Downloads?id=a63946ee-51ce-46ac-8184-a468b705ed9b>
- Gemcitabin: <http://www.success-studie.de/b/downloads/Fachinfo/GemzarFI07Jan.pdf>
- Cisplatin: https://www.gelbe-liste.de/produkte/Cisplatin-Teva-1-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-100-ml_543960/fachinformation
- Carboplatin: <http://www.teva.de/index.php?eID=dumpFile&t=f&f=37532&g=-1&r=11068%2C11068&token=eefb22e78f1cc8d9935d59c087e80630146f49e>

8. Epirubicin:
9. Doxorubicin:
10. Liposomales Doxorubicin: https://www.gelbe-liste.de/produkte/Myocet-50-mg-Pulver-Dispersion-u-Loesungsmittel-fuer-ein-Konzentrat-zur-Herstellung-einer-Infusionsdispersion_359323/fachinformation
11. PEG-lipo. Doxorubicin: https://www.gelbe-liste.de/produkte/Caelyx-2-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-10-ml_121890/fachinformation
12. Mitoxantron: https://www.gelbe-liste.de/produkte/Mitoxantron-Teva-2-mg-ml-Injektionsloesung-15ml_543783/fachinformation
13. Paclitaxel: <https://medikamio.com/de-de/medikamente/paclitaxel-ratiopharm/pil>
14. Nab-Paclitaxel: https://www.gelbe-liste.de/produkte/Abbraxane-5-mg-ml-Pulver-zur-Herstellung-einer-Infusionssuspension_514889/fachinformation
15. Docetaxel: <https://mein.sanofi.de/produkte/Taxotere/Downloads?id=89447754-dfb2-450b-b35a-36950de8a74d>
16. Vinorelbin: <http://www.detect-studien.de/dokumente/d3/fachinfo/Navelbine.pdf>
17. Eribulin: http://www.detect-studien.de/dokumente/d4/fachinfo/Fachinfo_Eribulin_Halaven.pdf

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2. Petrelli F et al: Mortality, leukemic risk, and cardiovascular toxicity of adjuvant anthracycline and taxane chemotherapy in breast cancer: a meta-analysis. *Breast Cancer Res Treat*. 2012 Sep;135(2):335-46
3. Jim HS et al: Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. *J Clin Oncol*. 2012 Oct 10;30(29):3578-87
4. Cortes J, O'Shaughnessy J, Loesch D et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet*. 2011;377:914-23
5. Link, H. and S. Schmitz (2013). "Treatment of cancer-associated anaemia: results from a two-day cross-sectional survey in Germany." *Onkologie* 36(5): 266-272.
6. Fox P, Darley A, Furlong E, et al: The assessment and management of chemotherapy-related toxicities in patients with breast cancer, colorectal cancer, and Hodgkin's and non-Hodgkin's lymphomas: A scoping review. *Eur J Oncol Nurs*. 2017 Feb;26:63-82. doi: 10.1016/j.ejon.2016.12.008. Epub 2016 Dec 22.

7. Maeda S, Saimura M, Minami S, et al. Efficacy and safety of eribulin as first- to third-line treatment in patients with advanced or metastatic breast cancer previously treated with anthracyclines and taxanes. See comment in PubMed Commons below Breast. 2017 Jan 2;32:66-72. doi: 10.1016/j.breast.2016.12.017.
8. Zhang XH, Hao S, Gao B, et al. A network meta-analysis for toxicity of eight chemotherapy regimens in the treatment of metastatic/advanced breast cancer. Oncotarget. 2016 Dec 20;7(51):84533-84543. doi: 10.18632/oncotarget.13023.
9. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. Journal of Clinical Oncology 2011;29:4189- 4198
10. Crawford J.
11. NCCN, editor. NCCNR Practice Guidelines in Oncology - v.1.2011; Myeloid Growth Factors. National Comprehensive Cancer Network 2011. 18-7-2011.
12. Madeddu C, Deidda M, Piras A, et al. Pathophysiology of cardiotoxicity induced by nonanthracycline chemotherapy. J Cardiovasc Med (Hagerstown). 2016 May;17 Suppl 1 Special issue on Cardiotoxicity from Antiblastic Drugs and Cardioprotection:e12-e18. Review.

Chemotherapy – Acute Toxicities II												
DRUG	SYSTEM ORGAN CLASS											
	RESPIRAT. HORAC. & MEDIA- STINAL DIS.	GASTROINTESTINAL DIS. (NAUSEA, EMESIS)	HEPATO BILIARY DISORDERS	SKIN & SUBCUT. TIS. DISORD.	HAEMATOLOGICAL DISORDERS	CONNECTIVE TISSE DISORDERS	RENAL & URINARY DISORDERS	PREGN. PUEPER. & PERINATAL CONDIT.	REPRODUCTIVE & MALE DISORDERS	ADMINI- STRATION SITE DISORDERS	FAMILIAL GENET. DISORDERS	SPECIAL FEATURES
Alkylating antineoplastic agent												
Cyclophosphamide	2	4	4	5	-	5	-	4	5	-	-	Hyponatraemia
Anti-Metabolites												
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												
Cisplatin	4	5	4	4	-	5	-	3	5	-	-	Nephrotoxicity, ototoxicity, CIPN
Carboplatin	4	5	-	4	4	4	-	-	4	-	-	Colitis (nephrotoxicity)
Anthracyclines / Anthracyclines												
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	-	-	Palmar and plantar erythema (PPE)
PEG-lipo. Doxo.	4	5	-	5	4	-	-	4	5	-	-	Sec. AML, cardiomyopathy
Mitoxantrone	4	5	3	5	-	3	-	3	4	-	-	
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, myalgia
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

Listing and grading of side effects was performed according to the MedDRA-classification with the following categories of frequency: 1. Very rarely (<1/10,000); 2. rarely (≥ 1/10,000 to < 1/10,000); 3. occasionally (≥ 1/3,000 to < 1/1000); 4. frequently (≥ 1/100 to < 1/10); 5. very frequently (≥ 1/10).

unknown (based on available data incidence not assessable)

Abbreviations

AML = Acute myeloid Leucemia; DPD = Dihydropyrimidin-Dehydrogenase); CHF = congestive heart failure; CIPN = Chemotherapy-induced peripheral neuropathy; HFS = Hand-Foot-Syndrom; PPE = Palmar and plantar Erythema

Side effect categories - MedDRA (Medical Dictionary for Regulatory Activities)

1. MedDRA: <https://www.meddra.org/> bzw. https://www.meddra.org/sites/default/files/guidance/file/intguide_20_1_english_0.pdf

Sources for product information (Download 19.01.2018)

1. Cyclophosphamid: http://www.baxter.de/de_DE/assets/downloads/fachinformation/endoxan.pdf
2. Methotrexat: https://www.gelbe-liste.de/produkte/MTX-HEXAL-10-mg-Tabletten_117469/fachinformation
3. 5-Fluorouracil: https://www.gelbe-liste.de/produkte/Fluorouracil-HEXAL-50-mg-ml-Injektionsloesung-100-ml_546519/fachinformation
4. Capecitabin: <https://www.zentiva.de/Produkte/Capecitabin-Zentiva/Downloads?id=a63946ee-51ce-46ac-8184-a468b705ed9b>
5. Gemcitabin: <http://www.success-studie.de/b/downloads/Fachinfo/GemzarFI07Jan.pdf>


6. Cisplatin: https://www.gelbe-liste.de/produkte/Cisplatin-Teva-1-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-100-ml_543960/fachinformation
7. Carboplatin: <http://www.teva.de/index.php?eID=dumpFile&t=f&f=37532&g=-1&r=11068%2C11068&token=eebfb22e78f1cc8d9935d59c087e80630146f49e>
8. Epirubicin:
9. Doxorubicin:
10. Liposomales Doxorubicin: https://www.gelbe-liste.de/produkte/Myocet-50-mg-Pulver-Dispersion-u-Loesungsmittel-fuer-ein-Konzentrat-zur-Herstellung-einer-Infusionsdispersion_359323/fachinformation
11. PEG-lipo. Doxorubicin: https://www.gelbe-liste.de/produkte/Caelyx-2-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-10-ml_121890/fachinformation
12. Mitoxantron: https://www.gelbe-liste.de/produkte/Mitoxantron-Teva-2-mg-ml-Injektionsloesung-15ml_543783/fachinformation
13. Paclitaxel: <https://medikamio.com/de-de/medikamente/paclitaxel-ratiopharm/pil>
14. Nab-Paclitaxel: https://www.gelbe-liste.de/produkte/Abiraxane-5-mg-ml-Pulver-zur-Herstellung-einer-Infusionssuspension_514889/fachinformation
15. Docetaxel: <https://mein.sanofi.de/produkte/Taxotere/Downloads?id=89447754-dfb2-450b-b35a-36950de8a74d>
16. Vinorelbin: <http://www.detect-studien.de/dokumente/d3/fachinfo/Navelbine.pdf>
17. Eribulin: http://www.detect-studien.de/dokumente/d4/fachinfo/Fachinfo_Eribulin_Halaven.pdf

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2. Petrelli F et al: Mortality, leukemic risk, and cardiovascular toxicity of adjuvant anthracycline and taxane chemotherapy in breast cancer: a meta-analysis. Breast Cancer Res Treat. 2012 Sep;135(2):335-46
3. Jim HS et al: Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. J Clin Oncol. 2012 Oct 10;30(29):3578-87
4. Cortes J, O'Shaughnessy J, Loesch D et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011;377:914-23
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12. Madeddu C, Deidda M, Piras A, et al. Pathophysiology of cardiotoxicity induced by nonanthracycline chemotherapy. *J Cardiovasc Med (Hagerstown)*. 2016 May;17 Suppl 1 Special issue on Cardiotoxicity from Antiblastic Drugs and Cardioprotection:e12-e18. Review.



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

Oxford
LoE GR AGO
1a A ++

- **DPD (Dihydropyrimidin-Dehydrogenase) - Deficiency Testing (DPYD-Genotype or Phenotype)**

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

DPD Deficiency:

1. Rote-Hand-Brief vom 04.06.2020: <https://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RHB/2020/rhb-fluorouracil.html> (Zugriff am 17.01.2022)
2. García-Alfonso P, Saiz-Rodríguez M, Mondéjar R, et al. Consensus of experts from the Spanish Pharmacogenetics and Pharmacogenomics Society and the Spanish Society of Medical Oncology for the genotyping of DPYD in cancer patients who are candidates for treatment with fluoropyrimidines. Clin Transl Oncol. 2021 Nov 13.
3. Sharma BB, Rai K, Blunt H et al. Pathogenic DPYD Variants and Treatment-Related Mortality in Patients Receiving Fluoropyrimidine Chemotherapy: A Systematic Review and Meta-Analysis. Oncologist 2021 Dec;26(12):1008-1016.



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Endocrine Therapy – Toxicities

	INFECTIONS AND INFESTATIONS	NEOPLASMS BEN. AND MALIGNANT	UNSPECIFIED (INCL. CYSTS & POLYPS)	BLOOD & LYMPH. SYST. DISORDERS	IMMUNE SYSTEM 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
DRUG													
SERM													
Tamoxifen	-	3	4	-	3	5	-	4	4	-	-	4	
AI	-	-	-	-	-	4	4	5	5	4	-	4	5
Anastrozole	-	-	4	-	-	4	4	5	4	4	-	4	5
Exemestane	3	-	3	-	-	5	4	4	4	3	-	3	5
Letrozole	4	-	3	4	-	4	-	4	4	-	-	-	4
SERD													
Fulvestrant	4	-	3	4	-	4	-	-	4	-	-	-	4
DRUG	RESPIR., THORAC. & MEDIASTIN. DIS.	GASTROINT. DIS. (NAUSEA, EMESIS)	HEPATOBLILIARY DISORDERS	SKIN & SUBCUTIS DIS. (ALOPECIA) MUSCULOSKELETAL & CONNECTIVE TISSUE DISORDERS	RENAL DISORDERS	URINARY DISORDERS	PREGN. & PUERPER. COND.	PERINAT. COND.	PRODUCTS OF CONCEPTION	GENERAL DIS. & ADMINISTRATION SITE	FAM. & GENET. DISORD.	SPECIAL FEATURES	
SERM													
Tamoxifen	3	5	4	5	4	-	-	5	5	1	Hot flushes; rarely: endometrial Ca (>55y); thrombosis		
AI	-	5	4	5	5	-	-	5	5	-	Hot flushes, arthralgia, osteoporosis; cognition		
Anastrozole	-	5	4	5	5	-	-	5	5	-	Hot flushes, arthralgia, osteoporosis; cognition		
Exemestane	3	4	3	5	5	3	-	4	5	-	Hot flushes, arthralgia, osteoporosis; cognition		
Letrozole	-	5	5	4	4	4	-	3	5	-	Hitzewallungen		
SERD													
Fulvestrant	-	5	5	4	4	4	-	3	5	-	Hitzewallungen		

Listing and grading of side effects was performed according to 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)

Side effect categories- MedDRA (Medical Dictionary for Regulatory Activities)

1. MedDRA: <https://www.meddra.org/> bzw.
https://www.meddra.org/sites/default/files/guidance/file/intguide_20_1_english_0.pdf

Sources for product information (Download 19.01.2018)

1. Tamoxifen: https://www.gelbe-liste.de/produkte/Tamoxifen-20-mg-HEXAL-Filmtbl_8660/fachinformation
2. Anastrozol: <https://imedikament.de/anastrozol-ratiopharm-1-mg-filmtabletten/fachinformation>
3. Exemestan: http://www.success-studie.de/c/downloads/Fachinfo/FI_ExemestanAromasin.pdf
4. Letrozol: http://www.success-studie.de/b/downloads/Fachinfo/Femara_Juli_2014.pdf
5. Fulvestrant: https://www.gelbe-liste.de/produkte/Fulvestrant-HEXAL-250-mg-Injektionsloesung-in-einer-Fertigspritze_912622/fachinformation

Key-Toxicities – Antibodies and Antibody-Drug-Conjugates (HER2+)		
	Oxford	
	LoE	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
Trastuzumab-Emtansine (T-DM1)		
▪ Thrombocytopenia, hepatotoxicity, pyrexia, headache, pneumonitis, neuropathy	1b	A
Trastuzumab-Deruxtecan		
▪ Interstitial lung disease, neutropenia, nausea, alopecia	1b	A

Cardiotoxicity

1. Slamon D, Eiermann W, Robert N et al: Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 365:1273-1283, 2011
2. Procter M, Suter TM, de Azambuja, et al: Longer-term assessment of trastuzumab-related cardiac adverse events in the Herceptin Adjuvant (HERA) trial. J Clin Oncol 28: 3422-3428, 2010
3. Russell SD, Blackwell KL, Lawrence J, et al: Independent adjudication of symptomatic heart failure with the use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant therapy: a combined review of cardiac data from the National Surgical Adjuvant breast and Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials. J Clin Oncol 28: 3416-3421, 2010
4. Higa GM, Abraham J: Biological mechanisms of bevacizumab-associated adverse events. Expert. Rev Anticancer Ther 2009;9:999–1007
5. Martin M, Esteva FJ, Alba E, et al: Minimizing cardiotoxicity while optimizing treatment efficacy with trastuzumab: review and expert recommendations. Oncologist 2009;14:1–11
6. Untch M, Eidtmann H, du Bois A, et al: Cardiac safety of trastuzumab in combination with epirubicin and cyclophosphamide in women with metastatic breast cancer: results of a phase I trial. Eur J Cancer 2004; 40:988–97
7. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al.: Herceptin Adjuvant (HERA) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017

Mar 25;389(10075):1195-1205.

8. Pondé NF, Lambertini M, de Azambuja E. Twenty years of anti-HER2 therapy-associated cardiotoxicity. ESMO Open. 2016 Jul 21;1(4):e000073.

Troponin I

1. Cardinale D, Colombo A, Torrisi R, et al: Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. J Clin Oncol 28: 3910-3916, 2010

Lapatinib

1. Wu PA, Balagula Y, Lacouture ME, et al.: Prophylaxis and treatment of dermatologic adverse events from epidermal growth factor receptor inhibitors. Curr Opin Oncol 23:343-351, 2011
2. Von Minckwitz G, Eidtmann H, Loibl S et al: Integrating bevacizumab, everolimus, and lapatinib into current neoadjuvant chemotherapy regimen for primary breast cancer. Safety results of the GeparQuinto trial. Ann Oncol 22:301-306, 2011
3. Sherill B, Amonkar MM, Sherif B et al: Quality of life in hormone receptor-positive Her2-positive metastatic breast cancer patients during treatment with letrozole alone or in combination with lapatinib. Oncologist 15:944-953, 2010
4. Cameron D, Casey M, Olicka C et al: Lapatinib plus capecitabine in women with Her2-positive advanced breast cancer: Final survival analysis of a phase III randomized trial. Oncologist 15:924-934, 2010
5. Geyer CE, Forster J, Lindquist D; et al: Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 355:2733-2743, 2006

Pertuzumab


1. von Minckwitz G, Procter M, de Azambuja E, et al. APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER-2 Positive Breast Cancer. N Engl J Med. 2017 Jul 13;377(2):122-131.
2. Drucker AM, Wu S, Dang CT, et al.: Risk of rash with the anti-HER2 dimerization antibody pertuzumab: a meta-analysis. Breast Cancer Res Treat. 2012 Sep;135(2):347-54.
3. Baselga J, Cortes J, Kim S-B et al. Pertuzumab plus Trastuzumab plus Docetaxel for metastatic breast cancer. N Engl J Med 2012; 366:109-119

T-DM1

1. Verma S, Miles D, Gianni L, et al: EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012 Nov 8;367(19):1783-91.
2. von Minckwitz G, Huang CS, Mano MS, et al.; KATHERINE Investigators. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2018 Dec 5. doi: 10.1056/NEJMoa1814017

Trastuzumab-Deruxtecan

1. Cortes J et al. Trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients (Pts) with HER2+ metastatic breast cancer (mBC): Results of the randomized phase III DESTINY-Breast03 study. ESMO 2021, LBA1
2. Modi S, Saura C, Yamashita T, et al.: Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2020 Feb 13;382(7):610-621.
3. Tamura K, Tsurutani J, Takahashi S, et al.: Trastuzumab deruxtecan (ds-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: A dose-expansion, phase 1 study. Lancet Oncol 2019;20:816-826.



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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, %	All 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

Primary prophylaxis with loperamide

LoE	GR	AGO
2b	B	++

1. Chan A, Delagoge S, Holmes FA et al Neratinib after trastuzumab –based adjuvant therapy in patients with HER2 positive breast cancer (ExteNET): a multicentr, randomized, double.-blind, placebo controlled , phase III trial. Lancet Oncol 17(39: 367-377, 2016
2. Piccart-Gebhart M , Holmes E., Baselga J et al Adjuvant Lapatinib and Trastuzumab for Early Human Epidermal Growth Factor Receptor 2-positive Breast Cancer:Results From the Randomized Phase III Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Trial. JCO 34:1034-1042, 2015
3. Neratinib: FDA Produktinformation 2017

	Common Toxicities with anti-HER2-TKI: Tucatinib + Trastuzumab + Capecitabine	
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	Capecitabine + Tucatinib + Trastuzumab	
	Any grade (%)	≥ 3 grade (%)
	Any adverse event	99.3
	Diarrhea	55.2
	PPE syndrome	12.9
	Nausea	13.1
	Fatigue	3.7
	Vomiting	4.7
	Stomatitis	3.0
	Reduced appetite	2.5
	Headache	0.5
		0.5

1. Murthy RK, Loi S, Okines A, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med. 2020 Feb 13;382(7):597-609. doi: 10.1056/NEJMoa1914609. Epub 2019 Dec 11.

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Key-Toxicities – Antibodies and Antibody-Drug-Conjugates (HER2-)

Bevacizumab

- Hypertonus, proteinuria, bleeding, left ventricular dysfunction

Sacituzumab Govitecan

- (Febrile) neutropenia, leukopenia, anemia, diarrhea, nausea, alopecia

Oxford	
LoE	GR

2b B

1b A

Bevacizumab

1. Cortes J, Calvo V, Ramirez-Merino N et al: Adverse events risk associated with bevacizumab addition to breast cancer chemotherapy: a metanalysis. Ann Oncol. 2019 Jan 9. doi: 10.1093/annonc/mdy535
2. Hamilton EP, Blackwell KL: Safety of Bevacizumab in patients with metastatic breast cancer. Oncology 80:314-325, 2011
3. Syrigos KN, Karapanagiotu E, Boura P et al: Bevacizumab-induced hypertension. Biodrugs; 25:159-169, 2011
4. Blowers E, Hall K: Managing adverse events in the use of bevacizumab and chemotherapy. Br J Nurs 2009;18:351–6, 58
5. Miller K, Wang M, Gralow J, et al: Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 357: 2666-2676, 2007

Sacituzumab Govitecan...

1. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. N Engl J Med. 2021 Apr 22;384(16):1529-1541.

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

Palbociclib


1. Verma S, Bartlett CH, Schnell P, et al. Palbociclib in Combination With Fulvestrant in Women With Hormone Receptor-Positive/HER2-Negative Advanced Metastatic Breast Cancer: Detailed Safety Analysis From a Multicenter, Randomized, Placebo-Controlled, Phase III Study (PALOMA-3). Oncologist. 2016 Oct;21(10):1165-1175. Epub 2016 Jul 1.
2. N.Harbeck, J. Ettl, Palbociclib, CDK 4/ 6 Inhibition als neue Therapieoption bei Patientinnen mit fortgeschrittenem HR+/ Her – Mammakarzinom. Drug Report, 2017

Ribociclib

1. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med. 2016 Nov 3;375(18):1738-1748. Epub 2016 Oct 7.

Abemaciclib

1. Sledge GW, Jr., Toi M, Neven P, et al: Monarch 2: Abemaciclib in combination with fulvestrant in women with hr+/her2- advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol 2017;35:2875-2884.
2. Goetz MP, Toi M, Campone M, et al: Monarch 3: Abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol 2017;35:3638-3646.



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

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% (≥ G3 0.4% - 1 G5 event); control 1.2% (≥ G3 n = 1; 0%)

1. Raschi E, Fusaroli M, Ardizzoni A, et al. Cyclin-dependent kinase 4/6 inhibitors and interstitial lung disease in the FDA adverse event reporting system: a pharmacovigilance assessment. Breast Cancer Res Treat 2021 Feb;186(1):219-227.
2. Toi M, Harbeck N, Puig JM et al. Characterization of venous thromboembolic events (VTE), elevated aminotransferases (EAT) and interstitial lung disease (ILD) in monarchE. ESMO Breast 2021
3. Jahan N, Wongsasengsak S, Rehman A, et al. Relative risk of pneumonitis or interstitial lung disease (ILD) associated with the use of cyclin-dependent kinase inhibitors (CDK4/6i): A systematic review and meta-analysis of phase 3 randomized controlled trials. ASCO 2021, #1072



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


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

1. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). J Clin Oncol. 2020 Dec 1;38(34):3987-3998.
2. Toi M, Harbeck N, Puig JM et al. Characterization of venous thromboembolic events (VTE), elevated aminotransferases (EAT) and interstitial lung disease (ILD) in monarchE. ESMO Breast 2021



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QT Interval Prolongation: Ribociclib vs. Placebo

- **Post-baseline QT interval prolongation > 480 msec: 6.9% vs. 1.2% (incidence Ribo vs Placebo)**
- **Post-baseline QT interval prolongation > 500 msec: 1.5% vs. 0.3%**
- **Therapy discontinuation for QT interval prolongation: 0.3% vs. 0.6%**
- **QT interval prolongation is not associated with symptoms; however, QT interval prolongation stands for an elevated risk of life-threatening arrhythmia "*torsades de pointes*" (TdP)**

1. Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomized phase 3 trial. *Lancet Oncol.* 2018 Jul;19(7):904-915.
2. Slamon DJ, Neven P, Chia S, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone-Receptor-Positive, Human Epidermal Growth Factor Receptor-2 Negative Advanced Breasts Cancer: MONALEESA-3. *J Clin Oncol.* 2018 Aug 20;36(24):2465-2472.
3. Durairaj C, Ruiz-Garcia A, Gauthier ER, et al. Palbociclib has no clinically relevant effect on the QTc interval in patients with advanced breast cancer. *Anticancer Drugs.* 2018 Mar;29(3):271-280.
4. Trinkley KE, Page RL 2nd, Lien H, et al. QT interval prolongation and the risk of torsades de pointes: essentials for clinicians. *Curr Med Res Opin.* 2013 Dec;29(12):1719-26.

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	

1. Baselga J, Campone M, Piccart M et al Everolimus in postmenopausal hormone receptor positive advanced breast cancer N Engl J Med:366,: 520 -529, 2012



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Toxicities of PI3K Inhibitor Alpelisib in Combination with Endocrine Therapy

Alpelisib + Fulvestrant

UE, %	All Grade	Grad ≥/=3
Hyperglycemia	63,7%	32,7%
Diarrhea	57,7%	6,7%
Nausea	44,7%	2,5%
Decreased appetite	35,6%	< 1% SAE
Rash	35,5%	9,9%
Vomiting	27,1%	< 1% SAE
Weight loss	26,8%	3,9%
Stomatitis	24,6%	2,5%
Fatigue	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	++

Andre F, et al N Engl J Med 2019;380:1929-1940

1. H. S. Rugo, F. André, et al. Time Course and Management of Key Adverse Events During the Randomized Phase 3 SOLAR-1 Study of PI3K inhibitor Alpelisib Plus Fulvestrant in Patients With HR-Positive Advanced Breast Cancer in press, 2020
2. Andre F, Ciruelos E, Rubovszky G et al.:Alpelisib for pik3ca-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med 2019;380:1929-1940.
3. Mayer IA, Abramson V, Formisano L, et al.: A phase ib study of alpelisib (byl719), a pi3kalpha-specific inhibitor, with letrozole in er+/her2-negative metastatic breast cancer. Clin Cancer Res 2016.

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			<h3>Olaparib</h3>		
AE, %	all grades (%)	grade ≥3 (%)	AE, %	all grades (%)	grade ≥3 (%)
AE, overall	97.1	36.6	AE, overall	98,6	31,8
Neutropenia	27.3	9.3	neutropenia	34,6	20.9
Anemia	40.0	16.1	Anemia	52.8	39,2
Fatigue	28.8	2.9	Fatigue	50,3	1,7
Nausea	58.0	0	Nausea	48,6	0,3
Emesis	29.8	0	Emesis	24,8	2,4
Diarrhea	20.5	0.5	Diarrhea	22,0	0,7
Appetite loss	16.1	0	Appetite loss	21,3	0,3
Headache	20.0	1	Headache	32,5	1,7
Pyrexia	14.1	0	Back pain	21,0	2,4
Cough	17.1	0	Dyspnea	17,5	2,4
ALT elevated	11.2	1.5	Pleural effusion	2,1	1,7
AST elevated	9.3	2.4	PPE	1,4	0,3
PPE	0.5				
Treatm. discontinuation	4.9				

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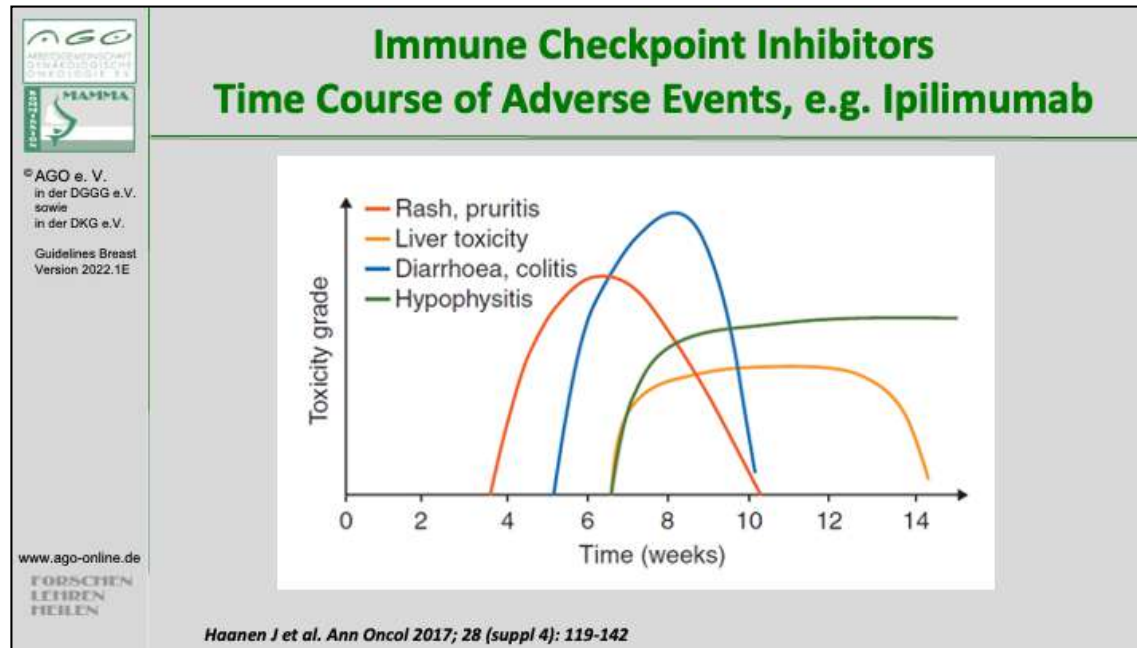
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Immune Checkpoint Inhibitors

- **Therapeutic approaches (antibodies)**
 - **PD-1 / PD-L1**
 - PD-1**
 - Nivolumab
 - Pembrolizumab
 - PD-L1**
 - Atezolizumab
 - Durvalumab
 - Avelumab

1. Haanen J, Carbone F, Robert C, et al, on behalf of the ESMO Guidelines Committee: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (suppl 4): 119-142. doi: ^0.1093/annonc/mdx225
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1. Haanen J, Carbonnel F, Robert C, et al. on behalf of the ESMO Guidelines Committee: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (suppl 4): 119-142.



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Immune Checkpoint Inhibitors – Side Effects –

■ **Adverse events \geq grade 3**

- diarrhea
- fatigue
- skin lesions (maculopapular exanthema, vitiligo, epidermolysis)
- pneumonitis
- colitis
- hypophysitis
- hepatitis
- nephritis
- thyroiditis (hyper- / hypothyroidism)
- Guillain-Barré syndrome
- cardiomyopathy
- myopathy – myalgia – rhabdomyolysis
- uveitis

1. Haanen J, Carbone F, Robert C, et al. on behalf of the ESMO Guidelines Committee: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (suppl 4): 119-142.

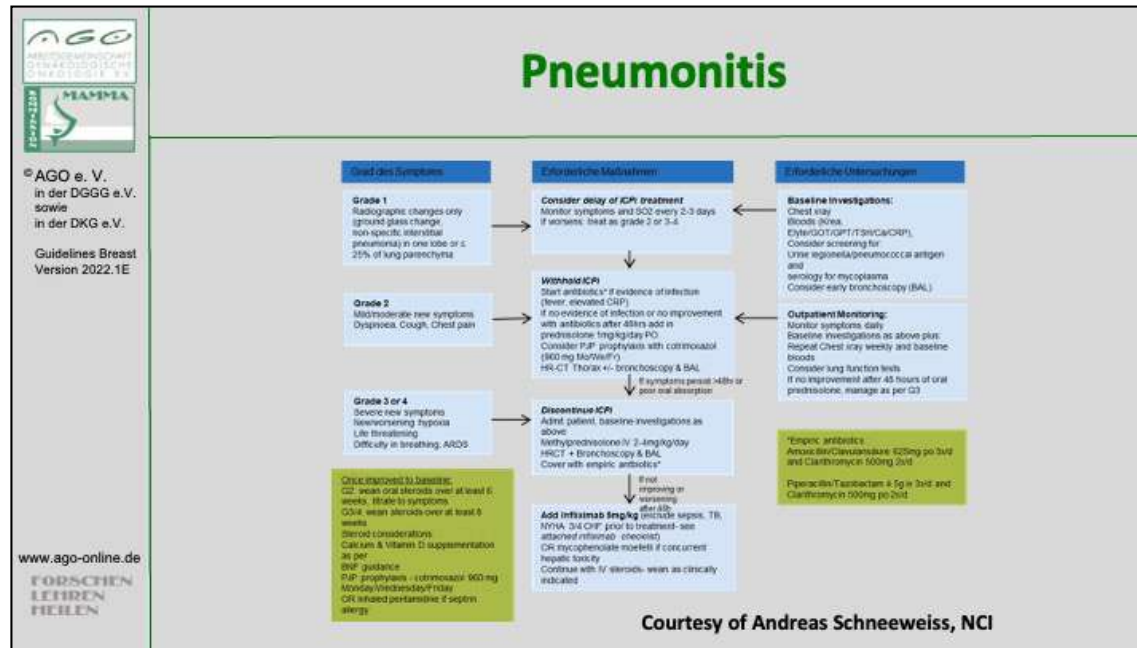
Immune Checkpoint Inhibitors Toxicities (Total in %)			
	atezolizumab	nivolumab	pembrolizumab
diarrhea	18.6%	13%	18%
colitis	1.1%	2%	1%
exanthema	18.6%	15%	< 1%
hepatotoxicity	0.3%	1%	0.5%
hypophysitis	< 0.1%	< 1%	0.5%
pneumonitis	3.1%	3%	2.9%
thyroid dysfunction	hyper- 1.7% hypo- 4.7%	hyper -1% hypo- 4%	hyper- 1.2% hypo- 8.3%
nephritis	< 1%	1%	0.7%
neuropathy	0.2%	< 1%	< 1%

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

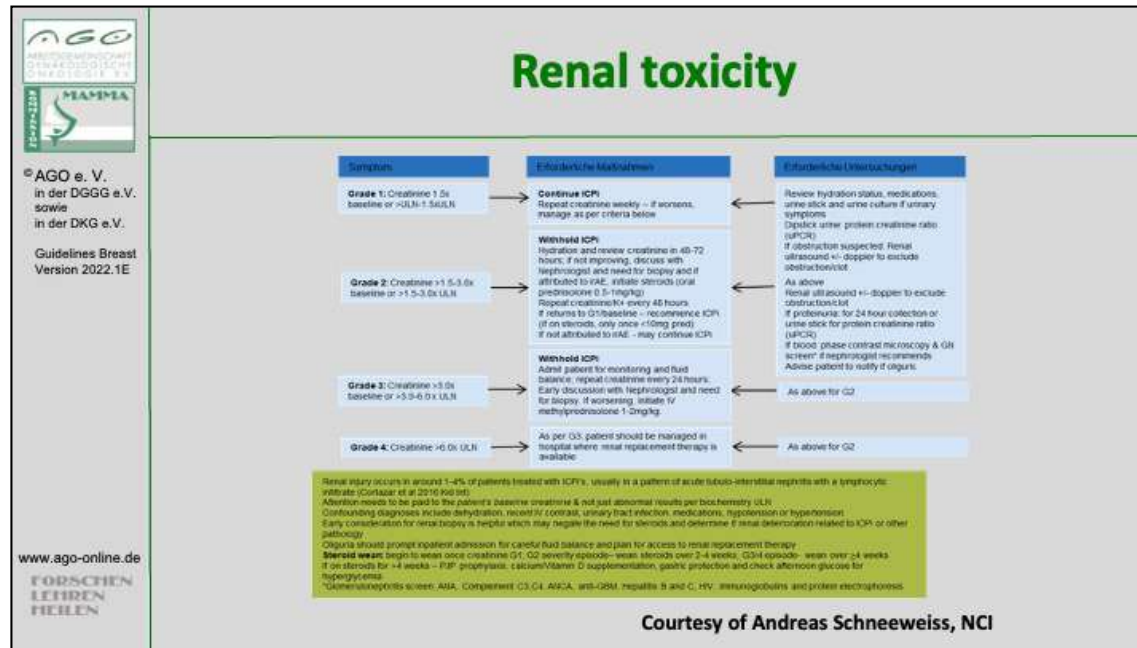
1. Atezolizumab: <https://www.fachinfo.de/suche/fi/021700>
2. Nivolumab: <https://www.fachinfo.de/suche/fi/020675>
3. Pembrolizumab: <https://www.fachinfo.de/suche/fi/020716>

	<h2 style="text-align: center;">Immune Checkpoint Inhibitors</h2> <h3 style="text-align: center;">Principles of Adverse Event Management</h3>	
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	1	<ul style="list-style-type: none"> supportive therapy close examination exclusion of infective complications patient information
	2	Like grade 1 but <ul style="list-style-type: none"> intermission of therapy until recovery of all irAE to grades 0-1 consider corticosteroids
	3	<ul style="list-style-type: none"> supportive therapy IV steroids (e.g. 1-2 mg/kg prednisolone) In case of no improvement within 48 h: <ul style="list-style-type: none"> 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

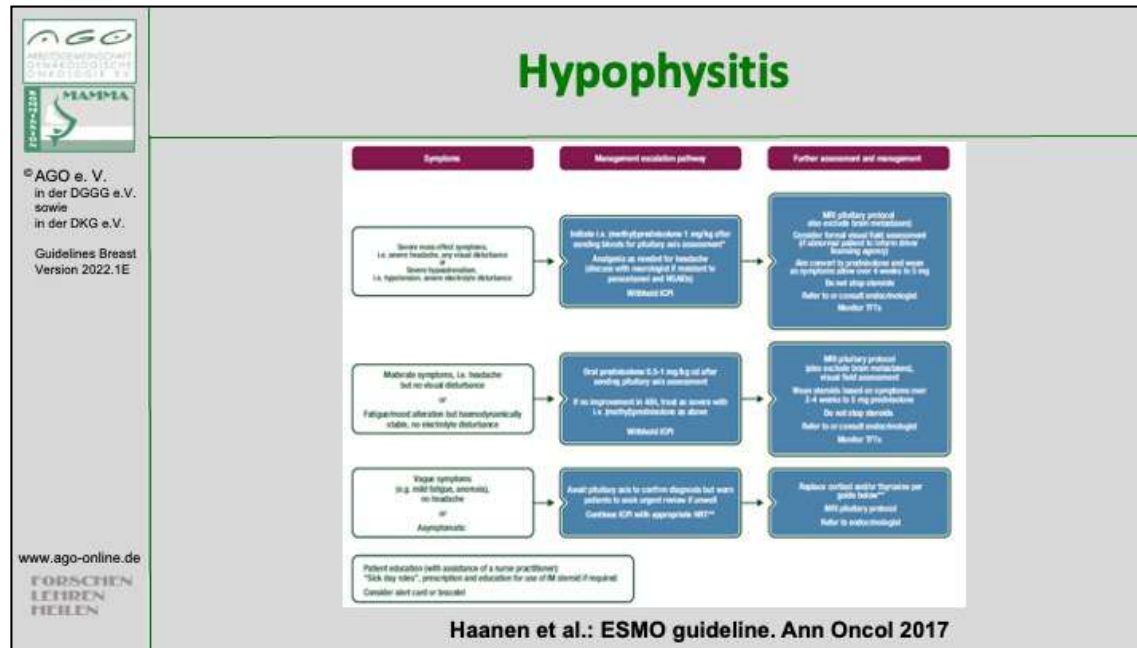
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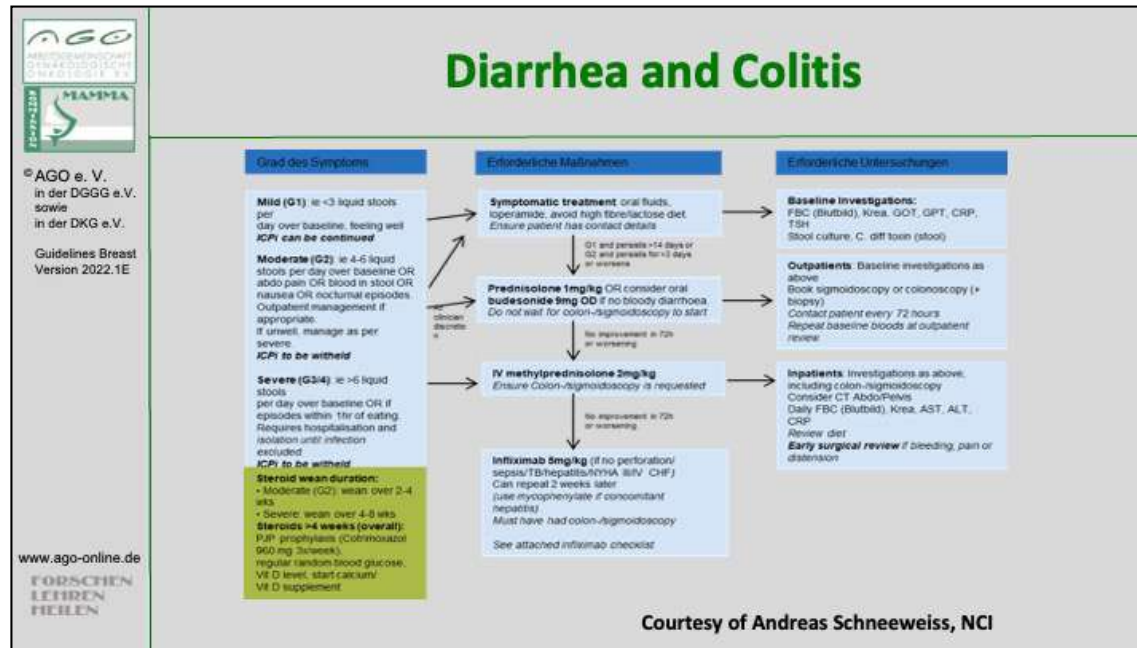
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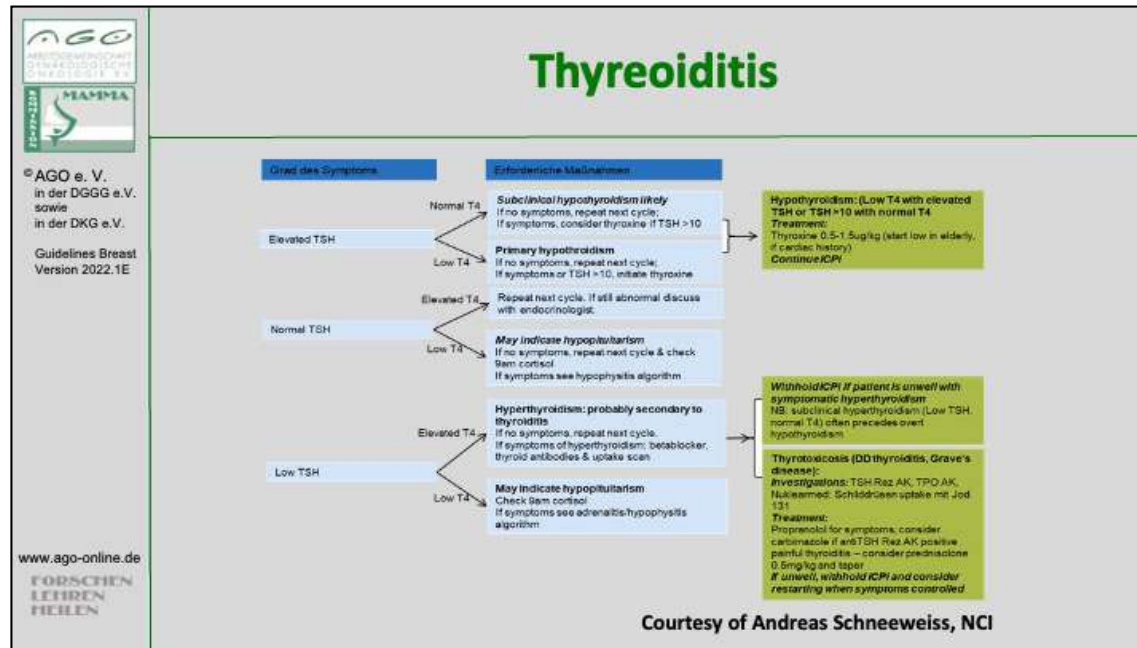
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Side Effects According Organ Systems

Incidence, Prevention, Therapy

1. Infections

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

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2. Giesen N, Sprute R, Rüthrich M et al. 2021 update of the AGIHO guideline on evidence-based management of COVID-19 in patients with cancer regarding diagnostics, viral shedding, vaccination and therapy. COVID-19 guideline panel of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO). Eur J Cancer. 2021 Apr;147:154-160.

Prophylaxis of Infections rarely Applicable to Patients with Solid Tumors (e.g. BC) ASCO Practice Guideline „Antimicrobial Prophylaxis...” 2018			
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	LoE	GR	AGO
	5	D	+
	<ul style="list-style-type: none"> Avoidance of highly infection-risking behavior or situations 		
	1a	B	-
	<ul style="list-style-type: none"> Prophylactic treatment in low-risk patients 		
	<ul style="list-style-type: none"> Prophylactic treatment in high-risk* patients (e.g. according to NCCN Guidelines) with <ul style="list-style-type: none"> Antibiotics Anti-fungal agents (triazole) Virostatics in solid tumors Granulocyte colony-stimulating factors 		
	1a	A	++
	1a	B	+/-
	5	D	-
	1a	A	++


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

ASCO:

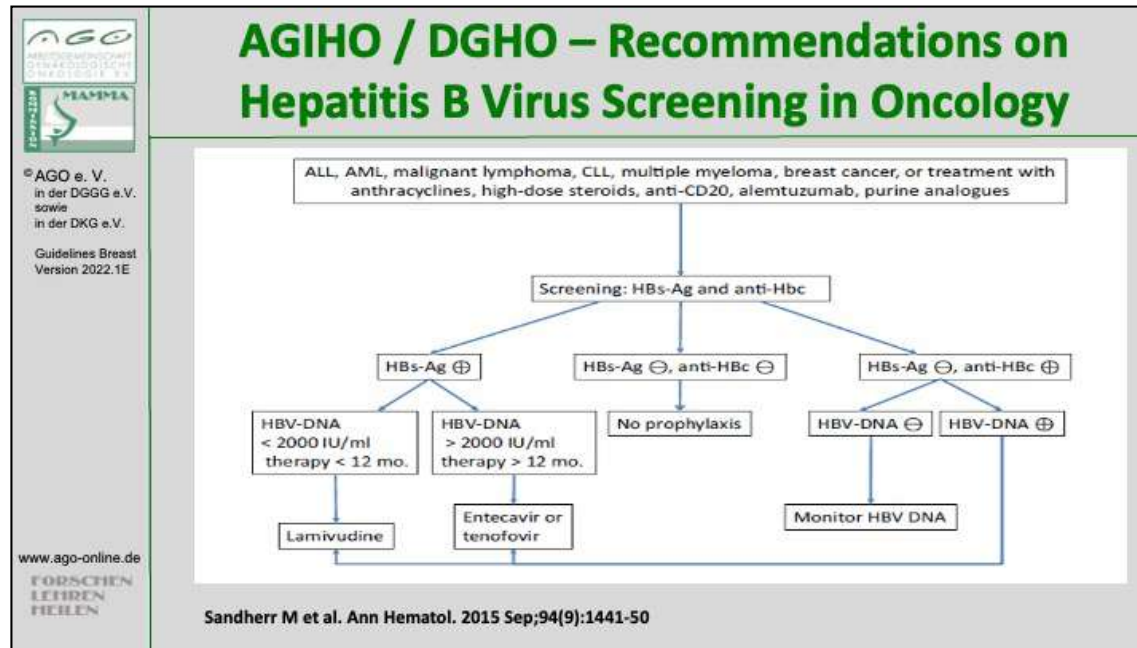
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NCCN:

1. NCCN Guidelines Version 1.2021 Prevention and Treatment of Cancer-Related Infections.
https://www.nccn.org/professionals/physician_gls/PDF/infections.pdf

Hepatitis B Virus Screening before Chemotherapy			
	Oxford		
	LoE	GR	AGO
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<ul style="list-style-type: none"> Hepatitis B virus screening before adjuvant chemotherapy (HBsAG, anti-HBC, anti-HBs) 	2c	B	+
<u>In case of positive serology or reactivation:</u>			
<ul style="list-style-type: none"> Prophylactic therapy with virustatic drugs if HBV-DNA detected (according AGIHO / DGHO – recommendations) 	1b	A	++
<ul style="list-style-type: none"> Hepatitis C virus screening before chemotherapy 	5	D	+/-

1. Sandherr M, Hentrich M, von Lilienfeld-Toal M, et al. Antiviral prophylaxis in patients with solid tumours and haematological malignancies--update of the Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO). Ann Hematol. 2015 Sep;94(9):1441-50.
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Side Effects According Organ Systems Incidence, Prevention, Therapy

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

Secondary Malignancies I	
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	LoE GR
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<ul style="list-style-type: none"> With regard to solid tumors, chemotherapy induced secondary malignancies are rare events 	2a
<ul style="list-style-type: none"> Alkylating agents increase the risk of leukemia dose- dependently to a total of 0.2–0.4% within 10–15 years 	2a
<ul style="list-style-type: none"> Anthracycline-containing regimens increase the risk of MDS and leukemia to 0.2–1.7% within 8 to 10 years 	2a
<ul style="list-style-type: none"> PARP-inhibitors are associated with an increased risk of AML and MDS to 0.5–1% 	2b
<ul style="list-style-type: none"> Radiotherapy increases the risk of leukemia by 0.2–0.4% in patients treated with anthracycline-containing chemotherapy 	2b
<ul style="list-style-type: none"> Tamoxifen approximately doubles the risk for developing endometrial cancer (in pts. older than 55 yrs. at start of therapy) 	2b


Statements 1-4

- Schaapveld M, Visser O, Louweman M et al.(2008) Risk of primary non breast cancers after breast cancer treatment: a dutch population-based study. J Clin Oncol 26: 1239-46.
- Kirova Y, De Rycke Y, Gambotti L et al.(2008) Second malignancies after breast cancer: the impact of different treatment modalities. B J Cancer 98: 870-4.
- Andersson M, Jensen M, Engholm G, et al (2008) Risk of secondary primary cancer among patients with early operable breast cancer registered or randomised in Danish Breast Cancer cooperative Group (DBCG) protocols of the 77, 82, 89 programmes during 1977-2001. Ann Oncol 47: 755-64.
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- Hershman D, Neugut A, Jacobson J et al.(2007) Acute myeloid leukemia or myelodysplastic syndrome following use of granulocyte colony-stimulating factors during breast cancer adjuvant chemotherapy. J Natl Cancer Inst 99: 196-205
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Tamoxifen and endometrial cancer

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Secondary Malignancies II (After Radiotherapy)

	Oxford LoE
<ul style="list-style-type: none"> ▪ Radiotherapy (PMRT, BET) may moderately enhance the risk of ipsilateral lung cancer and angiosarcoma (10-15/10.000) 5–10 years after treatment 	1a
<ul style="list-style-type: none"> ▪ Enhanced risk especially among ever smokers 	2b
<ul style="list-style-type: none"> ▪ No difference of secondary malignancy between PBI und WBI 	2c

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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)			
	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	

Leitlinie:

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, 2020, AWMF Registernummer: 032/054OL

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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 β: 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**

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Granulocyte Colony-Stimulating Factors			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Primary prophylaxis for expected febrile neutropenia (FN) <ul style="list-style-type: none"> If expected risk for FN 10–20% <ul style="list-style-type: none"> In case of individual risk factors If expected risk for FN > 20% (e.g. DAC, dose-dense CT) Secondary prophylaxis during chemotherapy (previous FN or neutropenia grade IV > 7 days) Therapeutic use for FN Start related to chemotherapy and duration <ul style="list-style-type: none"> Pegfilgrastim day 2 Lipegfilgrastim day 2 Filgrastim / Lenograstim from day 2–3 until ANC > 2–3 x 10⁹ 	1b	B	+/-
	3b	C	+
	1a	A	++
	1b	A	++
	1a	A	+/-
	1b	A	++
	1b	A	++
	1b	A	++

Relevante Leitlinien


1. S3-Leitlinie: Supportive Therapie:
Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3 – Februar 2020
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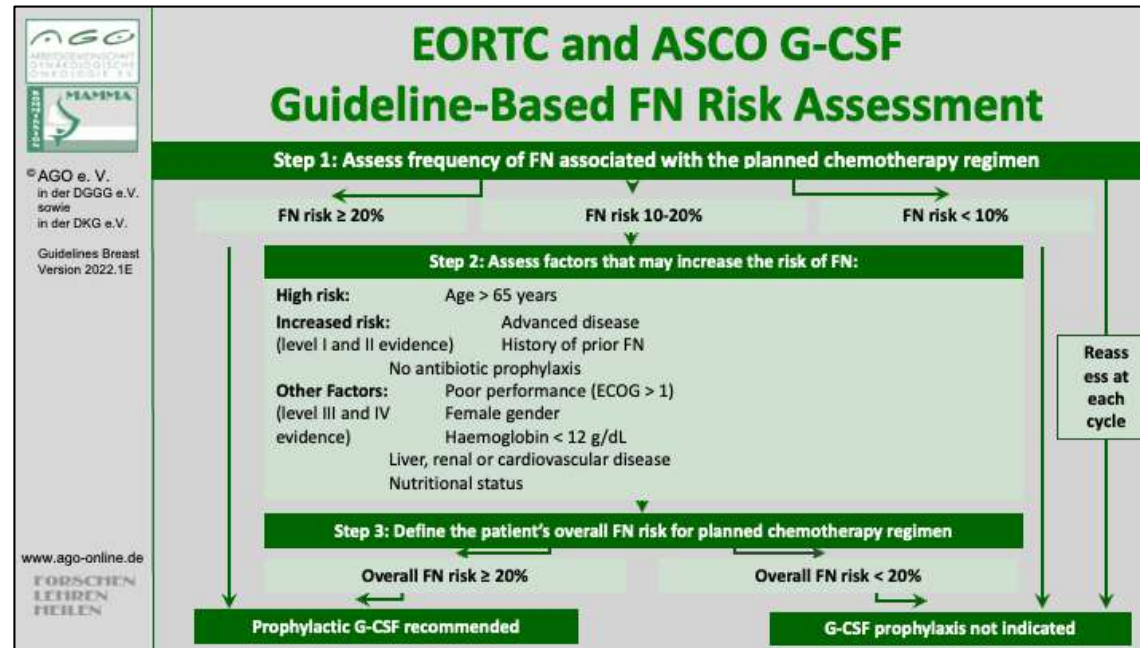
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	Management of Febrile Neutropenia			
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Guidelines Breast Version 2022.1E	Definition (oral temperature of > 38.5°C or two consecutive readings of > 38°C for 2 h in a patient with an ANC of < 500 cells/mm ³ or expected to fall to <500 cells/mm ³)			
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	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	+/-


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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)		

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Side Effects According Organ Systems

Incidence, Prevention, Therapy

5. Psychiatric Disorders

- Depression
- Fatigue
- Cognitive impairment
- Sleep disturbances

(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	+

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(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	+

Guideline:

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Fatigue is frequently present...

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Psycho-social interventions...

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(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, deterioration of cognitive performance was observed (espec. verbal memory)	1a	B

Therapiebedingte kognitive Störungen (sog. „Chemobrain“) häufig beschrieben

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(Therapy-associated) Sleep Disturbances		Oxford		
		LoE	GR	AGO
 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2022.1E</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<ul style="list-style-type: none"> ■ Sleep disturbances are a common problem in breast cancer patients during and after therapy (20–70%) 	2a	B	
	<ul style="list-style-type: none"> ■ Behavioral therapies demonstrated efficacy in treatment of insomnia and improved quality of life 	1b	A	++

Sleep disturbances are a common problem....

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Behavioral therapies have demonstrated efficacy.....

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Side Effects According Organ Systems Incidence, Prevention, Therapy

6. Nervous system disorders

- **Chemotherapy-Induced Peripheral Neuropathy (CIPN)**



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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)

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Chemotherapy-induced Peripheral Neuropathy – Prevention –			
	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

Reviews/Guidelines

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Non-medical prevention

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Kompression

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Elektro-Akupunktur

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Drug-based prevention

Venlafaxin

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Different substances

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Chemotherapy-induced Peripheral Neuropathy – Therapy –			
	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, pregabalin	1b	B	+/-
▪ Amitryptiline / nortriptyline, 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

Reviews / Leitlinien

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chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial." JAMA 309(13): 1359-1367.

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Funktionstraining

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Medikamentöse Therapie

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neuropathy. *Ann Pharmacother*. 2014 May;48(5):626-32.

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Gabapentin, Pregabalin:

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2. Nishikawa T, Hasegawa K, Shintani D, et al.: Combination Therapy of Pregabalin with Tramadol for Treatment of Peripheral Neuropathy in Patients with Gynecological Cancer Receiving Taxane Containing Chemotherapy. *Gan To Kagaku Ryoho*. 2017 Mar;44(3):227-231.

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Side Effects According Organ Systems Incidence, Prevention, Therapy

7. Cardiac Disorders

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/m ² 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, pre-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 toxicity	2b	B	+/-
▪ Betablocker-prophylaxis during anthracycline therapy	2a	B	+/-

Consensus recommendations:

1. Curigliano G, Lenihan D, Fradley M, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann Oncol 2020 Feb;31(2):171-190.

Statements

“Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.)”

“Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity”

1. van Dalen EC Different anthracycline derivatives for reducing cardiotoxicity in cancer patients. Cochrane Database Syst Rev. 2010 Mar 17;(3):CD005006. Review. Update in: Cochrane Database Syst Rev. 2010;(5):CD005006.

“Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently...”

1. Petrelli F: Mortality, leukemic risk, and cardiovascular toxicity of adjuvant anthracycline and taxane chemotherapy in breast cancer: a meta-analysis. Breast Cancer Res Treat. 2012 Sep;135(2):335-46
2. Azim HA Jr, de Azambuja E, Colozza M, et al.: Long-term toxic effects of adjuvant chemotherapy in breast cancer. Ann Oncol. 2011 Sep;22(9):1939-47.

“Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors.”

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6. Sautter-Bihl ML, Souchon R, Gerber B: Adjuvant therapy for women over age 65 with breast cancer. Dtsch Arztebl Int 108:365-371, 2011

“Monitoring of cardiac function before / during / after treatment: Echocardiography (LVEF or SF in %)”

1. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments: what the cardiologist needs to know. Nat Rev Cardiol. 2010 Oct;7(10):564-75. Review.
2. Slamon D: Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011 Oct 6;365(14):1273-83
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6. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Card

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1. Ponde N, Bradbury I, Lambertini M, et al. Cardiac biomarkers for early detection and prediction of trastuzumab and/or lapatinib-induced cardiotoxicity in patients with HER2-positive early-stage breast cancer: a NeoALTTO sub-study (BIG 1-06). Breast Cancer Res Treat. 2017 Dec 27.
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HEILEN

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)

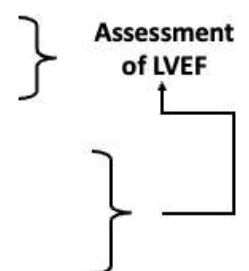
During trastuzumab

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

**Assessment
of LVEF**



Statement: Cardiac Monitoring (5 D ++)

Vote result of the AGO recommendation: 100%

1. Perez EA, Suman VJ, Davidson NE, et al.: Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol. 2008 Mar 10;26(8):1231-8. Epub 2008 Feb 4.
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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	-

Trastuzumab simultaneous to radiotherapy"

1. Halyard MY, Pisansky TM, Dueck AC: Radiotherapy and adjuvant trastuzumab in operable breast cancer: tolerability and adverse event data from the NCCTG Phase III Trial N9831. J Clin Oncol 27: 2638-2644, 2009
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"Trastuzumab simultaneous to epirubicin"

1. Untch M, Muscholl M, Tjulandin S, et al.: First-line trastuzumab plus epirubicin and cyclophosphamide therapy in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: cardiac safety and efficacy data from the Herceptin, Cyclophosphamide, and Epirubicin (HERCULES) trial. J Clin Oncol. 2010 Mar 20;28(9):1473-80.
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Breast. 2016 Oct;29:153-9. doi: 10.1016/j.breast.2016.07.017. Epub 2016 Aug 5.

“Trastuzumab simultaneous to doxorubicin”

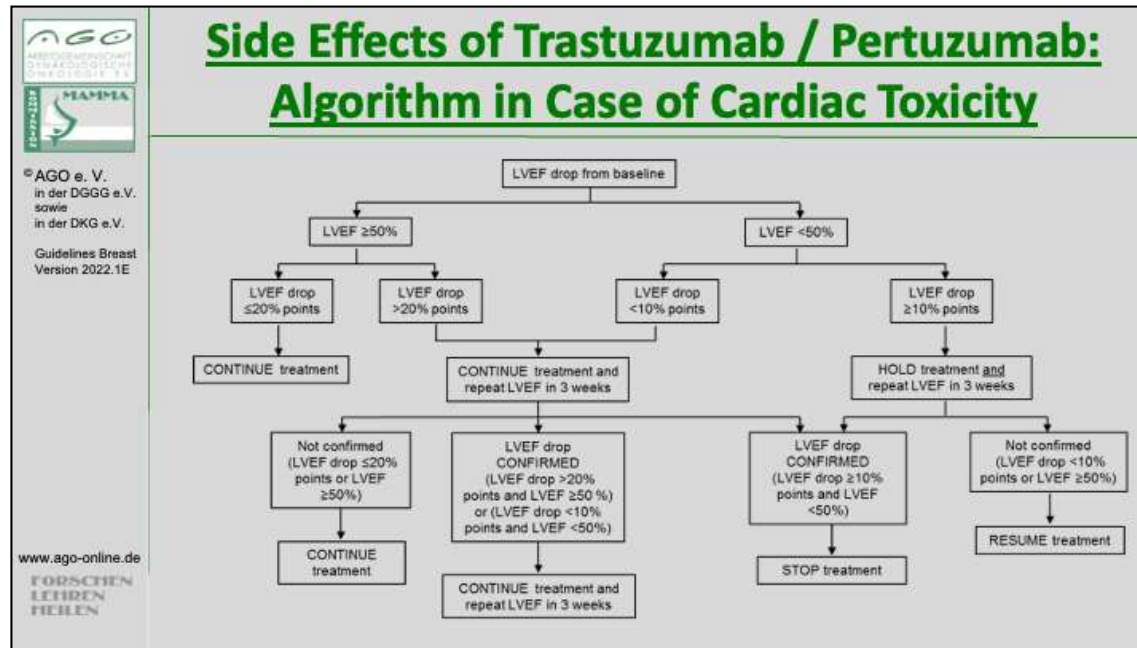
1. Slamon D, Eiermann W, Robert N, et al.: Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011 Oct 6;365(14):1273-83

“Anthracycline simultaneous to radiotherapy”

1. Toledano A, Garaud P, Serin D, et al.: Concurrent administration of adjuvant chemotherapy and radiotherapy after breast-conserving surgery enhances late toxicities: long-term results of the ARCOSEIN multicenter randomized study. Int J Radiation Oncology Biol. Phys. 2006; 65: 324-332.

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Side Effects According Organ Systems

Incidence, Prevention, Therapy

8. Gastrointestinal Disorders

- Nausea, Emesis
- Mucositis
 - Stomatitis (Everolimus)
- Diarrhea
- Constipation

Antiemetic Therapy			
http://www.mascc.org/antiemetic-guidelines www.onkosupport.de			
	Oxford		
	LoE	GR	AGO
▪ After assessment of emetic potential of chemotherapy protocol	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	+/-

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Olanzapine

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Antiemetic Therapy

<https://www.mascc.org/antiemetic-guidelines>

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-HT₃ = serotonin₃ receptor antagonist

DEX = DEXAMETHASONE

NK₁ = neurokinin₁ receptor antagonist such as APREPITANT or FOSAPREPITANT or ACUPITANT or NEPA (combination of netupitant and palonosetron)


OLZ = OLANZAPINE

DOP = drupamine receptor antagonist

NOTE: If the NK₁ receptor antagonist is not available for AC chemotherapy, palonosetron is the preferred 5-HT₃ 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



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DELAYED Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS
High Non-AC	DEX or (if APR 125mg for acute: (MCP + DEX) or (APR + DEX)) +/- OLZ*
High AC	NONE or (if APR 125mg for acute: DEX or APR) +/- OLZ*
Carboplatin	NONE or (if APR 125mg for acute: APR)
Oxaliplatin, or anthracycline, or cyclophosphamide	DEX can be considered
Moderate (other)	No routine prophylaxis
Low and Minimal	No routine prophylaxis

DEX = DEXAMETHASONE
MCP = METOCLOPRAMIDE
APR = APREPITANT
OLZ = OLANZAPINE

International Association of Supportive Care in Cancer
Supportive Care Guideline Gastro Cancer Therapy



<https://www.mascc.org/antiemetic-guidelines>

Supportive Therapy Antiemetics				
Wirkstoffgruppe	Substanz	Dosierung	Nebenwirkungen	Potenzial
Serotonin- antagonisten	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.	Kopfschmerzen, Diarrhoe, Flushsymptomatik Transaminasenanstieg Darmatonie in hoher Dosierung	sehr hoch
NK1-Antagonisten	Aprepitant Fosaprepitant Rolapitant	125 mg d1, 80 mg d 2-3 p.o. 150 mg d1 i.v. 180 mg d1 p.o.	Cytochrom-P-450- Aktivierung mit Dosis-reduktion von Dexamethason (2 x 8 mg). Keine Kombination mit Astemizol, Terfenadin, Cisaprid	sehr hoch
Dopamin- antagonisten/ substituierte Benzamide	Metoclopramid Alizaprid	bis zu 120 mg/24h als Dauerinfusion od. als Tropfen bis zu 300 mg i.v. oder p.o./24 h (6 Amp. od. 6 Tbl.)	Dyskinesien (Antidot: Biperiden) Angstreaktion, Depressionen, Diarrhoe	hoch
Oxazapine	Olanzapin	10mg/d for d1-4 Ggf. 5mg/d for d1-4	Sedation, weight gain	hoch
Phenothiazine/ Butyrophenone	Haloperidol	1-3 mg 4 x/d	Sedation, Senkung der Krampfschwelle, transiente Leberwerterhöhung	mäßig
Corticosteroide	Dexamethason Prednisolon	8-20 mg i.v. 1-3 x/d 100-250 mg i.v. 1-3 x/d	Blutzuckerentgleisung, psychotische Reaktionen, Flush, Blutdruckanstieg	mäßig
Benzodiazepine	Diazepam Lorazepam	bis zu 20 mg/d 0,5-1,0 mg/d	Sedation, Atemdepression	gering
NEPA (Netupitant and Palonosetron)	fixe Kombinations partner (oral)	NE 300 mg PA 0,5 mg		sehr hoch

Olanzapine

1. Slimano F, Netzer F, Borget I et al. Olanzapine as antiemetic drug in oncology: a retrospective study in non-responders to standard antiemetic therapy. Int J Clin Pharm 2018 Oct;40(5):1265-1271. doi: 10.1007/s11096-018-0649-1. Epub 2018 May 9.
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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“

	Oxford		
	LoE	GR	AGO
<p>■ 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.</p> <p>This entails:</p> <ol style="list-style-type: none"> 1. Patient: <ul style="list-style-type: none"> ■ Regular mouth washes (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 <p>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 / combinations</p>	<p style="color: green;">2b</p>	<p style="color: green;">++</p>	

Relevant practice guideline


Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, Februar 2020,

AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 27.12.2021)

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2. McGuire DB, Fulton JS, Park J, et al.: Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of basic oral care for the management of oral mucositis in cancer patients. Support Care Cancer 2013 Nov;21(11):3165-77.
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6. Nicolatou-Galitis, O., T. Sarri, J. Bowen, et al.: Systematic review of amifostine for the management of oral mucositis in cancer

patients. Support Care Cancer 2013; 21(1): 357-364.

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9. Yarom, N., A. Ariyawardana, A. Hovan, et al.: Systematic review of natural agents for the management of oral mucositis in cancer patients. Support Care Cancer 2013;21(11):3209-21.



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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

1. Rugo HS, Seneviratne L, Beck JT, et al: Prevention of everolimus-related stomatitis in women with hormone receptor-positive, her2-negative metastatic breast cancer using dexamethasone mouthwash (swish): A single-arm, phase 2 trial. *Lancet Oncol* 2017;18:654-662.
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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

Relevant practice guideline


Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, Februar 2020,

AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 27.12.2021)

1. <https://www.mascc.org/mascc-guidelines>
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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)**

Relevant practice guideline


Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, Februar 2020,

AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 27.12.2021)

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Constipation

Important Side Effect of Opioid Treatment

- **Bulging agents**
 - Psyllium, 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

Relevant practice guideline

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, Februar 2020,
2. AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 27.12.2021)



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Side Effects According Organ Systems

Incidence, Prevention, Therapy

9. Skin & Subcutaneous Tissue Disorders

(Alopecia)

Relevant practice guideline

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,
2. AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)

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

Relevant practice guidelines

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, Februar 2020,
2. AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 27.12.2021)
3. Lacouture ME, Sibaud V, Gerber PA, et al. Prevention and management of dermatological toxicities related to anticancer agents: ESMO Clinical Practice Guidelines. Ann Oncol 2021;32:157-170.

Scalp Cooling:

1. 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.
2. Rugo HS, Voigt J. Scalp Hypothermia for Preventing Alopecia During Chemotherapy. A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Clin Breast Cancer. 2018 Feb;18(1):19-28.
3. Rugo HS, Melin SA, Voigt J. Scalp cooling with adjuvant/neoadjuvant chemotherapy for breast cancer and the risk of scalp metastases: systematic review and meta-analysis. Breast Cancer Res Treat. 2017 Jun;163(2):199-205.



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Scalp Cooling: Scalp Cooling Alopecia Prevention Trial (SCALP) and 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)

1. 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.
2. Rugo HS, Voigt J. Scalp Hypothermia for Preventing Alopecia During Chemotherapy. A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Clin Breast Cancer. 2018 Feb;18(1):19-28.
3. Rugo HS, Melin SA, Voigt J. Scalp cooling with adjuvant/neoadjuvant chemotherapy for breast cancer and the risk of scalp metastases: systematic review and meta-analysis. Breast Cancer Res Treat. 2017 Jun;163(2):199-205.



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Side Effects According Organ Systems


Incidence, Prevention, Therapy

10. Musculoskeletal & connective tissue disorders

(see Chapter Osteooncology)

Relevant practice guideline

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, Februar 2020,
2. AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 27.12.2021)



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11. General Disorders & Administration Site Conditions

Relevant practice guideline

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,
2. AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)

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Extravasation of Potentially Necrotizing Compounds (Anthracyclines, Taxanes, Vinorelbine)

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- **Dexrazoxane for treatment of anthracycline-extravasations
(exception: liposomal Anthracyclines)**
- **Hyaluronic acid for treatment of taxane /
vinorelbine-extravasations (off-label use)**

Oxford		
LoE	GR	AGO
2b	B	++
3b	B	+

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Relevant practice guideline:


1. Hensley ML, Hagerty KL, Kewalramani T et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol. 2009 Jan 1;27(1):127-45.
2. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, 2020, AWMF Registernummer: 032/054OL

Dexrazoxane

1. Hensley ML, Hagerty KL, Kewalramani T, et al.: Cardioprotective effect of dexrazoxane in patients with breast cancer treated with anthracyclines in adjuvant setting: a 10-year single institution experience. J Clin Oncol. 2009 Jan 1;27(1):127-45.
2. Testore F, Milanese S, Ceste M, et al.: Dexrazoxane (Totect): FDA review and approval for the treatment of accidental extravasation following intravenous anthracycline chemotherapy. Oncologist. 2008 Apr;13(4):445-50.
3. Mouridsen HT, Langer SW, Buter J, et al.: Treatment of anthracycline extravasation with Savene (dexrazoxane): results from two prospective clinical multicentre studies. Ann Oncol. 2007 Mar;18(3):546-50.

Hyaluronsäure

siehe S3-Leitlinie, Kapitel 11: Paravasate.



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Extravasation of Chemotherapy Role of Dexrazoxane / Hyaluronic Acid

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

Relevant practice guideline

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, Februar 2020,
2. AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 27.12.2021)



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Side Effects According Organ Systems Incidence, Prevention, Therapy

11. Lung

Relevant practice guideline

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, 2020,
2. AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 17.01.2022)

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Drug-induced Pneumonitis, Interstitial Lung Disease (ILD)

- Diagnostic work-up with chest CT

Therapy according to grade and drug*

- Corticosteroids (start with ≥ 0.5 mg/kg/d prednisolone-equivalent)
- Dose hold or therapy discontinuation* (according to respective product information)

Oxford		
LoE	GR	AGO
1a	B	++


1a	B	++
		++

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Relevant practice guidelines:

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, 2020, AWMF Registernummer: 032/054OL
2. Skeoch S, Weatherley N, Swift AJ, et al. Drug-Induced Interstitial Lung Disease: A Systematic Review. J Clin Med. 2018 Oct 15;7(10):356.
3. Hackshaw MD, Danysh HE, Singh J, et al. Incidence of pneumonitis/interstitial lung disease induced by HER2-targeting therapy for HER2-positive metastatic breast cancer. Breast Cancer Res Treat. 2020 Aug;183(1):23-39.



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Management ILD Trastuzumab Deruxtecan

For asymptomatic ILD / pneumonitis (grade 1)*


- Consider corticosteroid treatment (eg, ≥ 0.5 mg/kg/day prednisolone or equivalent)
- Interrupt T-DXd until resolved to Grade 0, then:
 - If resolved in 28 days or less from date of onset, maintain dose
 - If resolved in greater than 28 days from date of onset, reduce dose one level

For symptomatic ILD / pneumonitis (grade 2 or greater)*

- Promptly initiate systemic corticosteroid treatment (eg, ≥ 1 mg/kg/day prednisolone or equivalent)
- Continue for at least 14 days followed by gradual taper for at least 4 weeks
- Permanently discontinue T-DXd in patients who are diagnosed with any symptomatic ILD / pneumonitis

* ENHERTU [prescribing information]. Daiichi Sankyo Inc., Basking Ridge, NJ and AstraZeneca Pharmaceuticals LP, Wilmington, DE, 2021.

1. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2020;382(7):610-621.
2. Modi S, Park H, Murthy RK, et al. Antitumor Activity and Safety of Trastuzumab Deruxtecan in Patients With HER2-Low-Expressing Advanced Breast Cancer: Results From a Phase Ib Study. J Clin Oncol. 2020 Jun 10;38(17):1887-1896.
3. Tarantino P, Modi S, Tolaney SM, et al. Interstitial Lung Disease Induced by Anti-ERBB2 Antibody-Drug Conjugates: A Review. JAMA Oncol. 2021 Dec 1;7(12):1873-1881.




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Further Supportive and Palliative Issues

- **Orphan symptom (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

1. Santini D, Armento G, Giusti R, et al. Management of orphan symptoms: ESMO Clinical Practice Guidelines for diagnosis and treatment. ESMO Open 2020 Nov;5(6):e000933.



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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.**

Klinische Ernährung

1. Arends J, Bertz H, Bischoff SC, et al. Klinische Ernährung in der Onkologie. S3-Leitlinie (AWMF Reg.: 073-006) Aktual Ernährungsmed. 2015; 40: e1–e74. https://www.dgem.de/sites/default/files/PDFs/Leitlinien/S3-Leitlinien/073-006l_S3_Klin_Ern%C3%A4hrung_in_der_Onkologie_2015-10.pdf (abgerufen 28.12.2021)
2. de Las Peñas R, Majem M, Perez-Altozano J, et al. SEOM clinical guidelines on nutrition in cancer patients (2018). Clin Transl Oncol. 2019 Jan;21(1):87-93.
3. van den Berg MMGA, Kok DE, Posthuma L, et al. Body composition is associated with risk of toxicity-induced modifications of treatment in women with stage I-IIIB breast cancer receiving chemotherapy. Breast Cancer Res Treat. 2019 Jan;173(2):475-481.



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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

Relevant practice guideline:

1. World Health Organization (2018). WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. World Health Organization. <https://apps.who.int/iris/handle/10665/279700>. Lizenz: CC BY-NC-SA 3.0 IGO (Zugriff 27.12.2021)
2. NCCN guideline: Adult cancer pain. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf (Zugriff 27.12.2021)
3. Horlemann J, Schürmann N. DGS Praxisleitlinien in der Schmerztherapie. Cannabis in der Schmerzmedizin v1.0. <https://dgs-praxisleitlinien.de/cannabis/> (Zugriff 27.12.2021)



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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.**
- **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 counselling.**

<https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/>

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Palliativmedizin für Patienten mit einer nicht-heilbaren Krebserkrankung, Langversion 2.2, September 2020, AWMF-Registernummer: 128/001OL, <https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/> (abgerufen am: 27.12.2021)