



Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Supportive Care and Management of Side Effects

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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 /
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- **Version 2022:**

Harbeck / Reimer

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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**



Toxicity Assessment

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

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

Long term toxicity (= secondary diseases after tumour therapy)

**Long term surveillance and documentation in regular intervals
(acc. ICPC³ following symptoms or acc. ICD-10-GM⁴ following diagnoses)**

LoE 5 D AGO ++

Acute Toxicity (NCI CTCAE v 5.0, 2017)

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- **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.

Incidence of Side Effects

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

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Chemotherapy – Acute Toxicities I

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DRUGS	SYSTEM ORGAN CLASS												
	INFECTIONS AND INFESTATIONS	NEOPLASMS BEN., ALIGNANT AND NSPECIFIED (INCL CYSTS & POLYPS)	BLOOD & LYMPH. SYST.	ISORDERS 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
<u>Alkylating antineoplastic agent</u>													
Cyclophosphamide	4	2	5	5	1	-	1	3	2	3	3	3	
<u>Anti-Metabolites</u>													
Methodreaxate	1	-	4	3	3	-	3	4	2	-	1	2	
5-Fluorouracil*	5	-	5	2	2	5	-	3	3	-	5	3	
Capecitabine	4	3 (Lipoma)	4	3	-	5	4	4	4	3	3	4	
Gemcitabine	4	-	5	1	-	4	-	4	-	-	2	2	
<u>Platinum-complexes</u>													
Cisplatin	4	2	5	3	2	5	-	4	2	5	4	4	
Carboplatin	4	-	5	4	-	-	-	4	4	4	4	-	
<u>Anthracyclines / Anthrachinones</u>													
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	
<u>Taxanes</u>													
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	
<u>Further tubulin-targeting drugs</u>													
Vinorelbine IV (PO)	5(5)	-	(5)	2(-)	-	-	(5)	(5)	(4)	-	2(3)	3(4)	
Eribulin	4	-	4	-	-	5	4	5	4	4	4	4	

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

Chemotherapy – Acute Toxicities II

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

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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

Endocrine Therapy – Toxicities

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SERM												
Tamoxifen	-	3	4	-	3	5	-	4	4	-	-	4
AI												
Anastrozole	-	-	-	-	-	4	5	5	4	-	4	5
Exemestane	-	-	4	-	-	4	5	4	4	-	-	5
Letrozole	3	-	3	-	-	5	4	4	3	-	3	5
SERD												
Fulvestrant	4	-	3	4	-	4	-	4	-	-	-	4

DRUG	RESPIR., THORAC. & MEDIASTIN. DIS. GASTROINT. DIS. (NAUSEA, EMESIS)	HEPATOBIILIARY DISORDERS	SKIN & SUBCUT.TIS. DIS. (ALOPECIA) MUSCULOSKEL ETAL & CONNECTIVE TISSUE DISORDERS RENAL & URINARY DISORDERS	PREGN., PUERPER. & PERINAT. COND. REPRODUCT. DISORDERS	GENERAL DIS. & ADMINISTRATIO N SITE CONDITIONS	CONGEN., FAMIL. & GENET. DISORD.	SPECIAL FEATURES				
SERM											
Tamoxifen	3	5	4	5	4	-	-	5	5	1	Hot flushes; rarely: endometrial Ca (>55y); thrombosis
AI											
Anastrozole	-	5	4	5	5	-	-	5	5	-	Hot flushes, arthralgia, osteoporosis; cognition
Exemestane	-	5	5	5	5	-	-	5	5	-	Hot flushes, arthralgia, osteoporosis; cognition
Letrozole	3	4	3	5	5	3	-	4	5	-	Hot flushes, arthralgia, osteoporosis; cognition
SERD											
Fulvestrant	-	5	5	4	4	4	-	3	5	-	Hitzewallungen

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 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)

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

Oxford	
LoE	GR

Trastuzumab

- Cardiotoxicity in the adjuvant setting (1.0–2.0%)
- Troponin I may identify patients at risk for cardiotoxicity

1b	A
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, neuropenia, nausea, alopecia

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

Primary prophylaxis with
loperamide

LoE	GR	AGO
2b	B	++

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

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

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

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Oxford	
LoE	GR

Bevacizumab

- Hypertonus, proteinuria, bleeding, left ventricular dysfunction

2b

B

Sacituzumab Govitecan

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

1b

A

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			

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

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

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

Overall incidence:

Systematic review of published data:

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

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

Monarch-E:

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

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

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Abemaciclib : All grade 2.3% (grade 3/4 1.2%)

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

Characterization of VTE (DVT or PE)*

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

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

QT Interval Prolongation: Ribociclib vs. Placebo

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- **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)**

Toxicities of mTOR-Inhibitor (Everolimus)

UE, %	All grades (%)	grade \geq 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

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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
Rush	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

Toxicities of PARP-Inhibitors – Olaparib, Talazoparib

Olaparib

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

Talazoparib

AE. %	all grades (%)	grade \geq 3 (%)
AE, overall	98,6	31,8
neutropenia	34,6	20,9
Anemia	52,8	39,2
Fatigue	50,3	1,7
Nuasea	48,6	0,3
Emesis	24,8	2,4
Diarrhea	22,0	0,7
Appetite loss	21,3	0,3
Headache	32,5	1,7
Back pain	21,0	2,4
Dyspnea	17,5	2,4
Pleural effusion	2,1	1,7
PPE	1,4	0,3

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Immune Checkpoint Inhibitors

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- **Therapeutic approaches (antibodies)**

- **PD-1 / PD-L1**

- PD-1**

- Nivolumab
 - Pembrolizumab

- PD-L1**

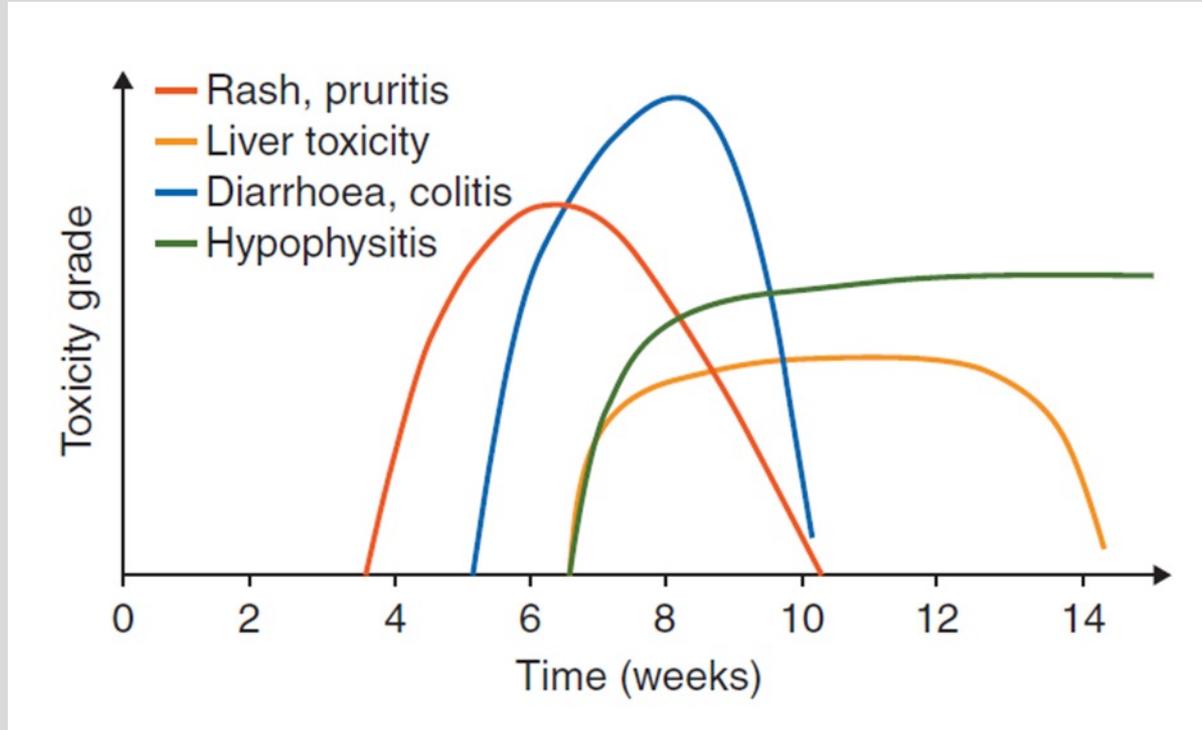
- Atezolizumab
 - Durvalumab
 - Avelumab

Immune Checkpoint Inhibitors

Time Course of Adverse Events, e.g. Ipilimumab

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Immune Checkpoint Inhibitors

– Side Effects –

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- **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**

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%

Immune Checkpoint Inhibitors

Principles of Adverse Event Management

CTC AE-Grade	Management
1	<ul style="list-style-type: none"> ▪ supportive therapy ▪ close examination ▪ exclusion of infective complications ▪ patient information
2	<p>Like grade 1 but</p> <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) <p>In case of no improvement within 48 h:</p> <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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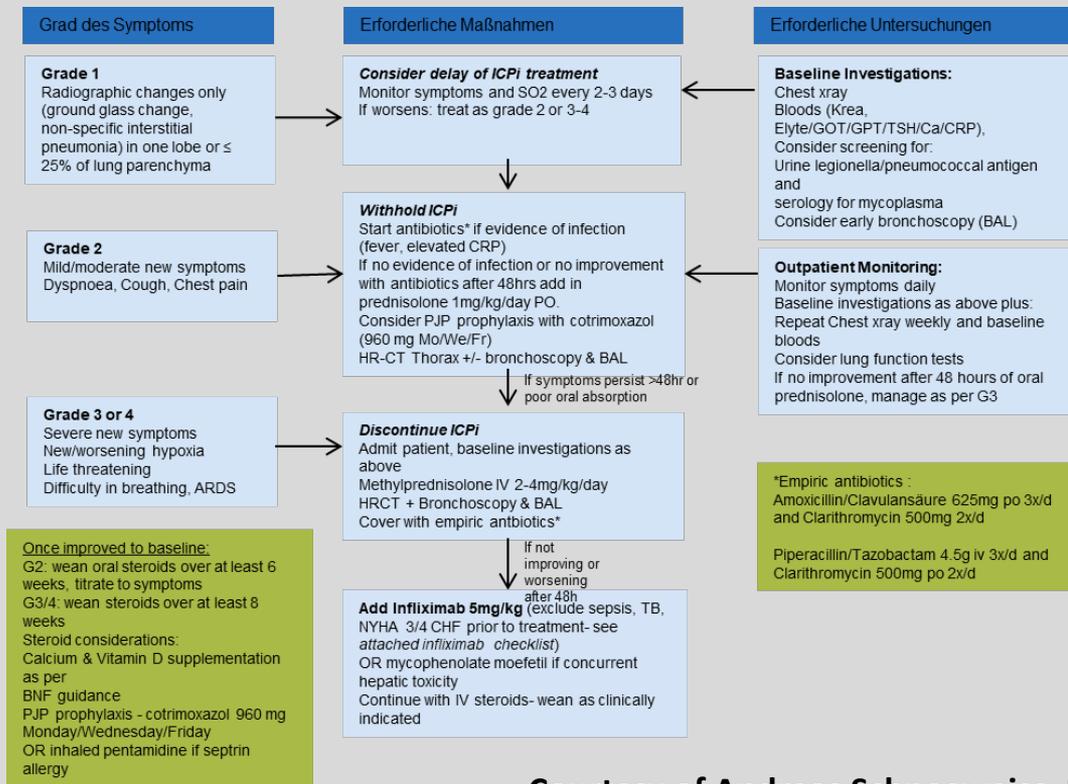
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Pneumonitis

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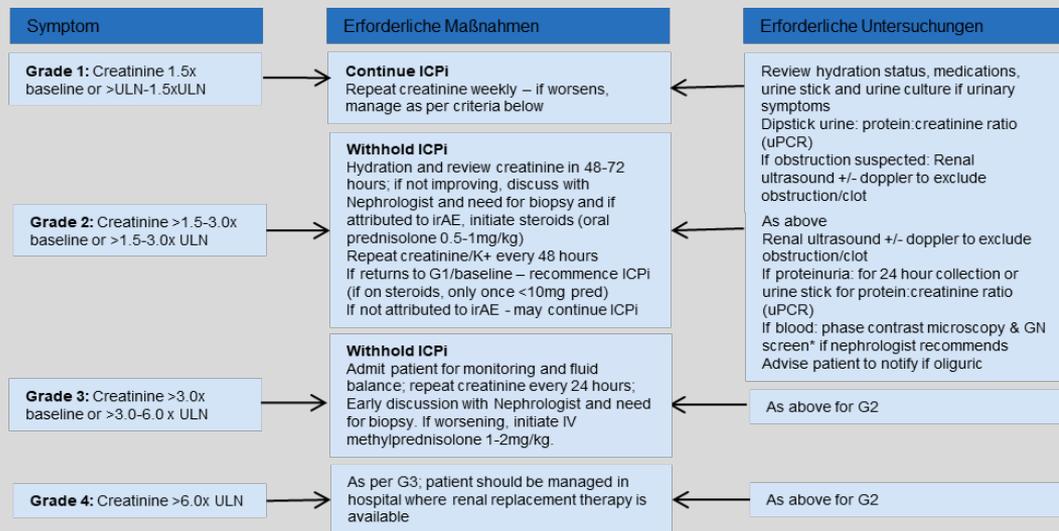
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Renal toxicity

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Renal injury occurs in around 1-4% of patients treated with ICPI's, usually in a pattern of acute tubulo-interstitial nephritis with a lymphocytic infiltrate (Cortazar et al 2016 Kid Int)

Attention needs to be paid to the *patient's baseline creatinine* & not just abnormal results per biochemistry ULN

Confounding diagnoses include dehydration, recent IV contrast, urinary tract infection, medications, hypotension or hypertension

Early consideration for renal biopsy is helpful which may negate the need for steroids and determine if renal deterioration related to ICPI or other pathology

Oliguria should prompt inpatient admission for careful fluid balance and plan for access to renal replacement therapy

Steroid wean: begin to wean once creatinine G1; G2 severity episode – wean steroids over 2-4 weeks; G3/4 episode- wean over ≥4 weeks

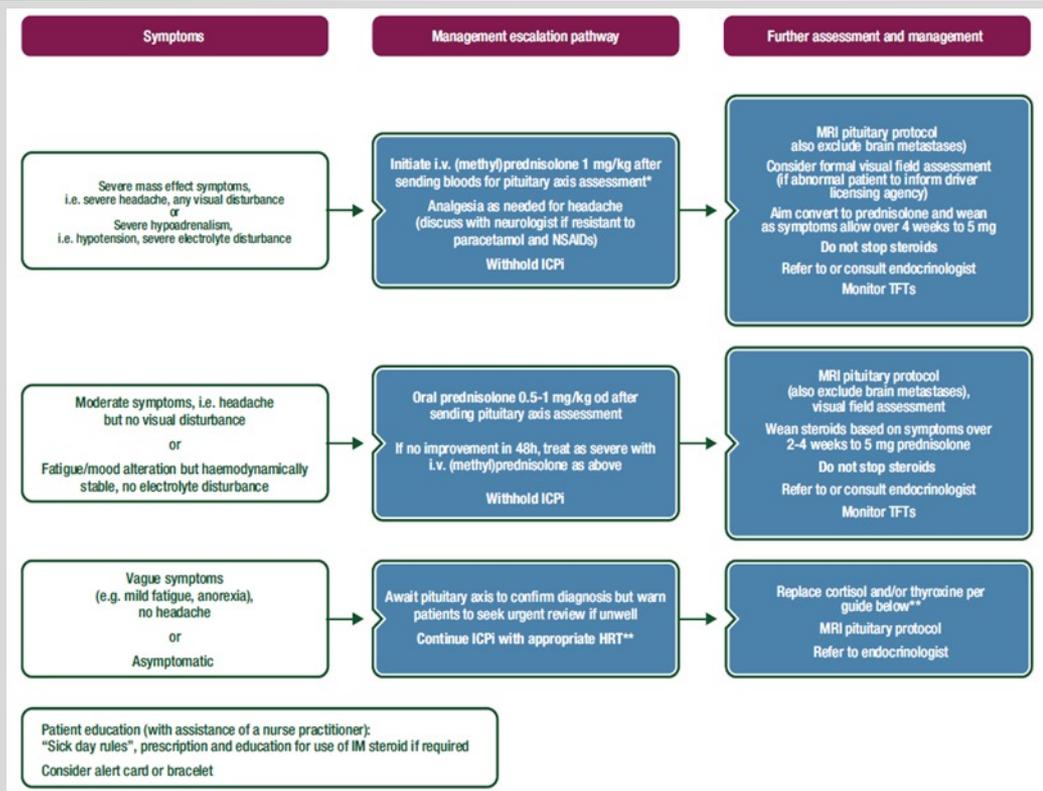
If on steroids for >4 weeks – PJP prophylaxis, calcium/vitamin D supplementation, gastric protection and check afternoon glucose for hyperglycemia

*Glomerulonephritis screen: ANA, Complement C3,C4, ANCA, anti-GBM, Hepatitis B and C, HIV, Immunoglobulins and protein electrophoresis

Hypophysitis

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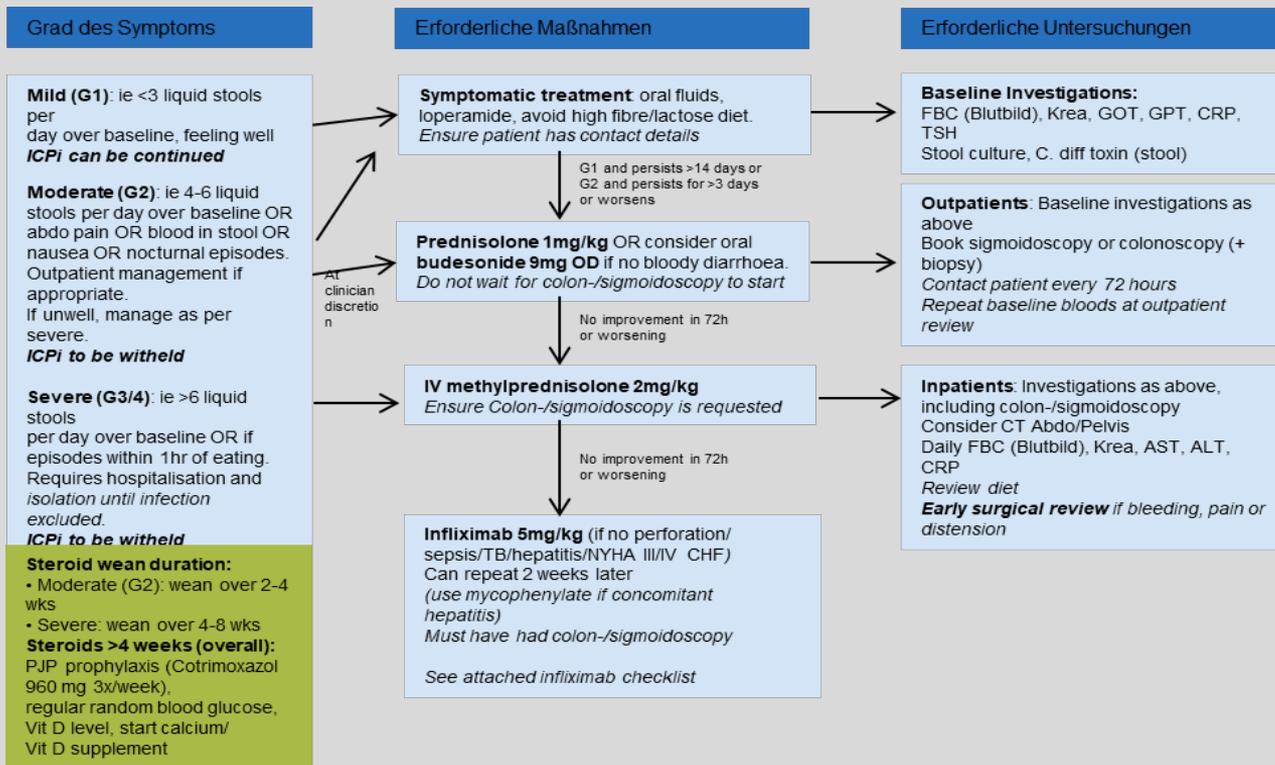
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Diarrhea and Colitis

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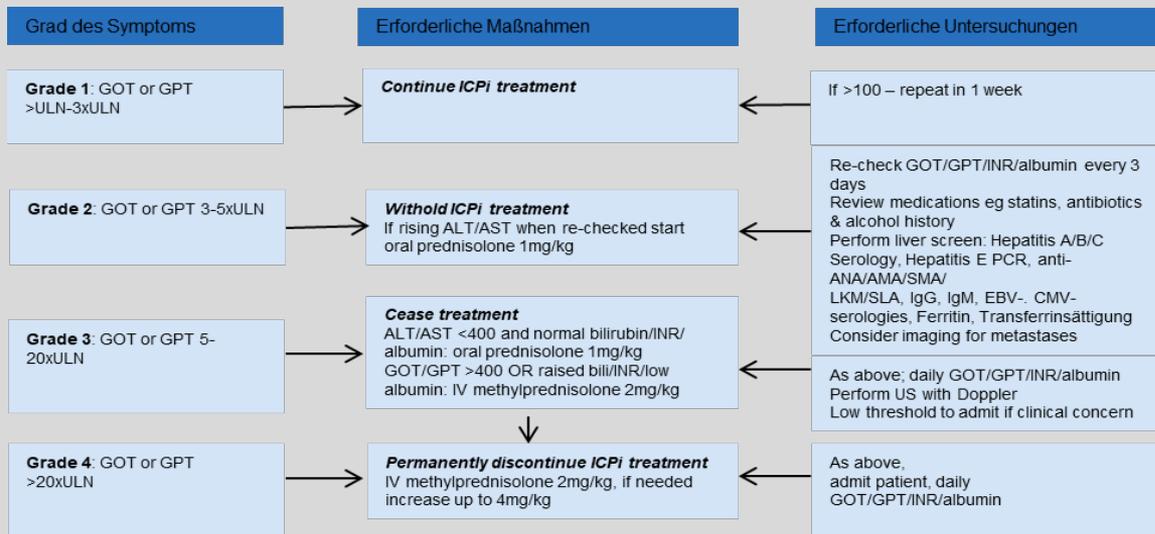
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Hepatitis

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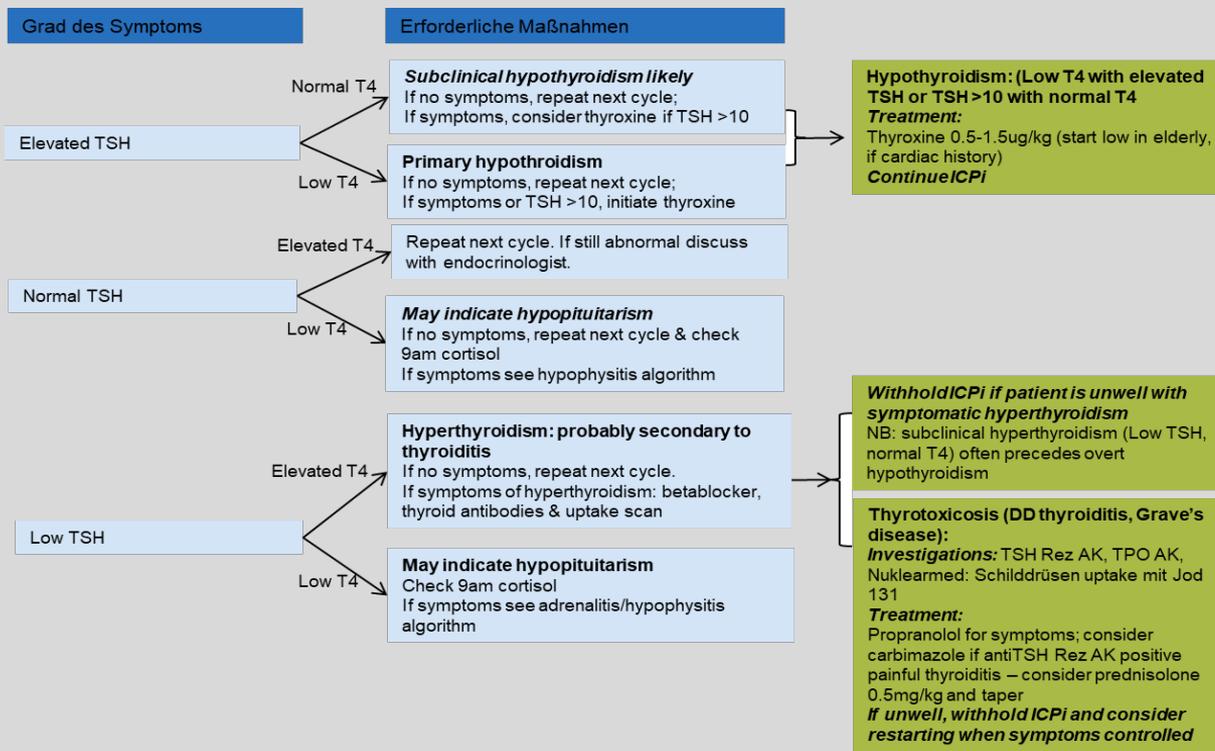
Steroid wean:

- G2: once G1, wean over 2 weeks; re-escalate if worsening; ICPI treatment may be resumed once prednisolone \leq 10mg
- G3/4: once improved to G2, can change to oral prednisolone and wean over 4 weeks; for G3: consider rechallenge with ICPI
- Worsening despite steroids:
 - if on oral – change to IV methylprednisolone
 - if on IV increase dose to up to 4 mg/kg methylprednisolone
 - consider adding mycophenolat mofetil (Cellcept) 500-1000mg BD (see attached MMF Guide)
- If worse on mycophenolat mofetil – consider addition of tacrolimus

Thyreoiditis

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1. Infections

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

Prophylaxis of Infections

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

ASCO Practice Guideline „Antimicrobial Prophylaxis...“ 2018

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	Oxford		
	LoE	GR	AGO
■ Avoidance of highly infection-risking behavior or situations	5	D	+
■ Prophylactic treatment in low-risk patients	1a	B	-
■ Prophylactic treatment in high-risk* patients (e.g. according to NCCN Guidelines) with			
■ Antibiotics	1a	A	++
■ Anti-fungal agents (triazole)	1a	B	+/-
■ Virostatics in solid tumors	5	D	-
■ Granulocyte colony-stimulating factors	1a	A	++

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

Hepatitis B Virus Screening before Chemotherapy



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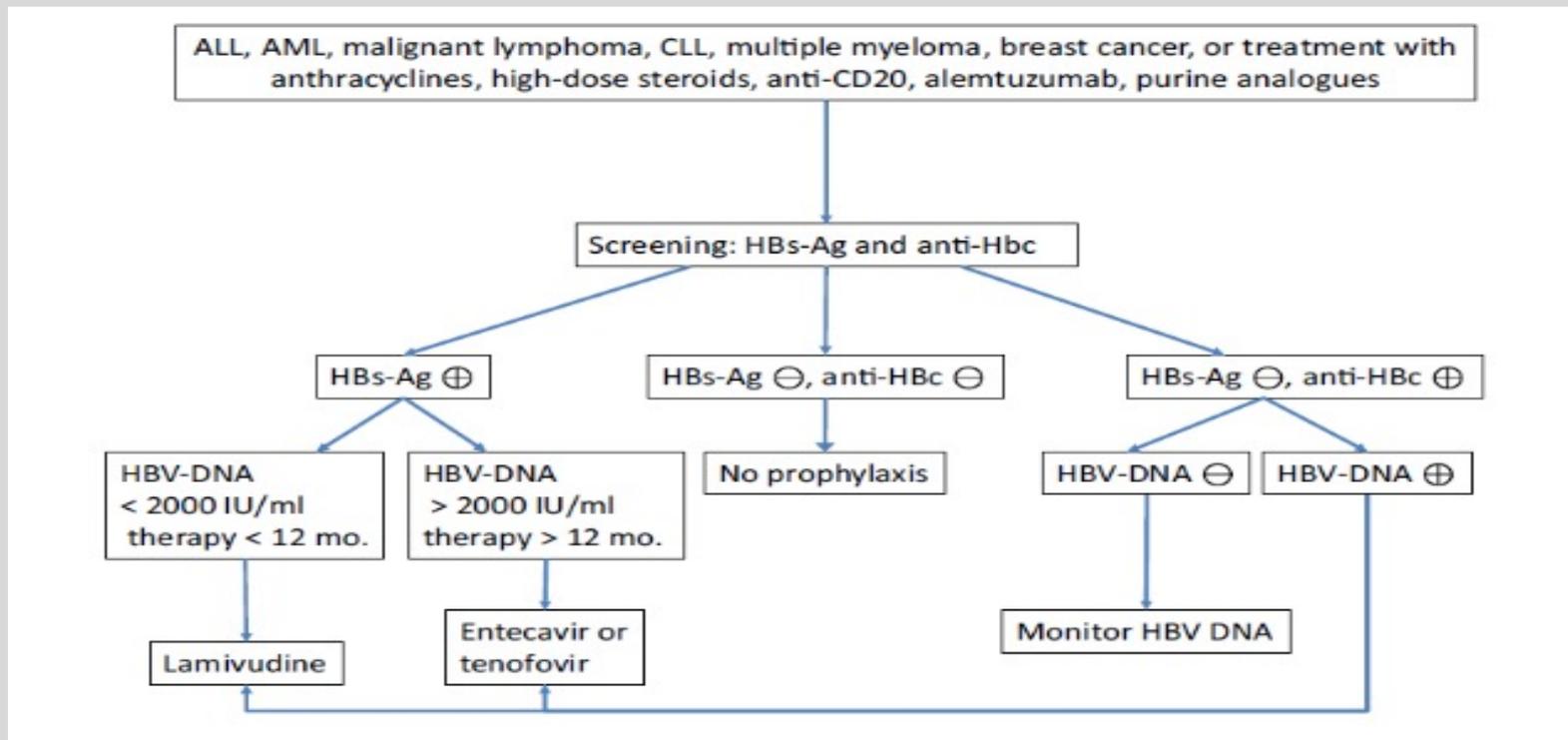
- **Hepatitis B virus screening before adjuvant chemotherapy (HBsAG, anti-HBC, anti-HBs)**

In case of positive serology or reactivation:

- **Prophylactic therapy with antiviral drugs if HBV-DNA detected (according AGIHO / DGHO – recommendations)**
- **Hepatitis C virus screening before chemotherapy**

Oxford		
LoE	GR	AGO
2c	B	+
1b	A	++
5	D	+/-

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





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

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Secondary Malignancies I

Oxford
LoE GR

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

Secondary Malignancies II (After Radiotherapy)

Oxford

LoE

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

1a

2b

2c

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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	

Practical Use of ESAs

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- **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 μ g/kg s.c. weekly or 500 μ g 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**

Granulocyte Colony-Stimulating Factors

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	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) 	1b	B	+/-
	3b	C	+
	1a	A	++
<ul style="list-style-type: none"> ■ Secondary prophylaxis during chemotherapy (previous FN or neutropenia grade IV > 7 days) 	1b	A	++
<ul style="list-style-type: none"> ■ Therapeutic use for FN 	1a	A	+/-
<ul style="list-style-type: none"> ■ 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	A	++
	1b	A	++
	1b	A	++

Management of Febrile Neutropenia

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

Definition (oral temperature of $> 38.5^{\circ}\text{C}$ or two consecutive readings of $> 38^{\circ}\text{C}$ for 2 h in a patient with an ANC of $< 500 \text{ cells/mm}^3$ or expected to fall to $< 500 \text{ cells/mm}^3$)

- **Clinical examination**
- **Daily evaluation**
- **Hospitalization of high-risk patients**
- **Homecare in low-risk patients**
- **Differential blood count**
- **Blood cultures**
- **Imaging of lungs**
- **Immediate initially empiric antibiotic therapy**
- **Empiric antifungal therapy 4–7 d in case of failure of antibiotic therapy**
- **G-CSF for treatment (not prophylactic)**

Oxford		
LoE	GR	AGO
5	D	++
5	D	++
1b	A	++
1b	A	+
5	D	++
5	D	++
3	C	++
1a	A	++
1b	A	++
2b	B	+/-



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

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

FN risk $\geq 20\%$

FN risk 10-20%

FN risk $< 10\%$

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

High risk: Age > 65 years

Increased risk: Advanced disease
(level I and II evidence) History of prior FN
No antibiotic prophylaxis

Other Factors: Poor performance (ECOG > 1)
(level III and IV evidence) Female gender
Haemoglobin < 12 g/dL
Liver, renal or cardiovascular disease
Nutritional status

Reassess at each cycle

Step 3: Define the patient's overall FN risk for planned chemotherapy regimen

Overall FN risk $\geq 20\%$

Overall FN risk $< 20\%$

Prophylactic G-CSF recommended

G-CSF prophylaxis not indicated

4. Toxicities / Ovaries

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Therapy-associated amenorrhea (CRA, CIA, TIA)

- CRA may be permanent or temporary (depending on age of the patient and type of chemotherapy)
- The risk of CRA increases with patient's age and duration of the chemotherapy
- CRA is an imperfect surrogate for menopause and fertility
- Adjuvant endocrine therapy with GnRHa induces reversible amenorrhea, but delays conception to a less fertile period
- Ovarian reserve of women who remain premenopausal after CTX is reduced
- CRA is associated with improved outcome (DFS / OS)

Oxford

LoE

2b

2b

5

5

2b

1b

Synonym: Chemotherapy related or induced / Treatment induced Amenorrhea (CRA, CIA, TIA)

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5. Psychiatric Disorders

- Depression
- Fatigue
- Cognitive impairment
- Sleep disturbances

(Therapy-associated) Depression

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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Depression is an often reported adverse event in breast cancer patients (20–30%) 	2a	B	
<ul style="list-style-type: none"> Psychological interventions are effective to improve mood, but not survival in distressed and depressed patients 	1b	A	
<ul style="list-style-type: none"> Antidepressants have shown to improve depression in breast cancer patients 	1b	A	
<ul style="list-style-type: none"> Regular exercise participation can prevent depression in breast cancer survivors 	2b	B	+

(Therapy-related) Fatigue

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- **Fatigue frequent in breast cancer patients (30–60%)**
- **Exclusion of somatic reasons (anemia, tumor burden, co-morbidity, medication) for fatigue**
- **Psycho-social interventions specifically addressing fatigue efficient in reducing fatigue**
- **Physical exercise can improve fatigue**
- **Yoga can improve fatigue**
- **Methylphenidate or corticosteroids (short-term) can improve fatigue**

	Oxford		
	LoE	GR	AGO
	2a	B	
	1a	A	++
	1a	A	++
	1b	D	+
	2b	B	+
	1a	D	+

(Therapy-associated) Cognitive Impairment

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	Oxford	
	LoE	GR
<ul style="list-style-type: none"> Therapy-related cognitive deficits (“chemobrain”) frequently described (16–75%) 	2a	B
<ul style="list-style-type: none"> Cognitive-behavioral therapy beneficial for cognitive function 	2b	B
<ul style="list-style-type: none"> Methylphenidate may improve cognitive function in cancer patients 	3a	C
<ul style="list-style-type: none"> Under therapy with aromatase inhibitors, deterioration of cognitive performance was observed (espec. verbal memory) 	1a	B

(Therapy-associated) Sleep Disturbances

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- Sleep disturbances are a common problem in breast cancer patients during and after therapy (20–70%)
- Behavioral therapies demonstrated efficacy in treatment of insomnia and improved quality of life

Oxford		
LoE	GR	AGO
2a	B	
1b	A	++

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6. Nervous system disorders

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

Chemotherapy-Induced Peripheral Neuropathy (CIPN)

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- **Incidence with taxanes:**
 - Grade 1–2: 20–50%
 - Grade 3–4: 6–20%
- **Risk factors: type and dose of chemotherapy, BMI, reduced physical activity**
- **Individual risk factors**
 - Diabetes mellitus
 - Nutritive-toxic compounds part. alcohol
 - Renal failure
 - Hypothyreosis
 - Collagenoses / vasculitis
 - Vitamine deficiency
 - HIV-Infection
 - CMT-Gen mutations

Unclear:

- Other genetic factors (SNPs, mutations)

Chemotherapy-induced Peripheral Neuropathy – Prevention –



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Non drug-based prevention

- **Functional training (physical fitness, sensomotoric stimulation training etc.)**
- **Compression treatment (tight surgical gloves, compression stockings)**
- **Cooling gloves and stockings**
- **Elektro-acupuncture**

Drug-based prevention

There is no drug-based prophylaxis available

- **Venlafaxine**
- **Palmitoylethanolamine (PEA) topically or PO**
- **A-lipoic-acid (thioctic acid), amifostine, amitriptyline, acetyl-L-car-nitine, carbamazepine, electrolyte solutions, glutathione, Goshajinkigan (GJG), oxcarbazepine, vitamine B, vitamine E, or other compounds¹**

	Oxford		
	LoE	GR	AGO
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	-
Venlafaxine	2a	C	+/-
Palmitoylethanolamine (PEA) topically or PO	5	D	+/-
A-lipoic-acid (thioctic acid), amifostine, amitriptyline, acetyl-L-car-nitine, carbamazepine, electrolyte solutions, glutathione, Goshajinkigan (GJG), oxcarbazepine, vitamine B, vitamine E, or other compounds ¹	1b	A	-

¹ For list of not recommended drugs, see Hershman et al. 2014

Chemotherapy-induced Peripheral Neuropathy – Therapy –



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Non drug-based therapy

- Functional training (physical fitness, sensomotoric stimulation training etc.)
- Physiotherapy / physical treatment
- acupuncture

Drug-based therapy

- Menthol locally (1%), capsaicin / lidocain locally
- Baclofen / amitryptiline / ketamin-gel
- Duloxetine for therapy of CIPN-induced pain
- Opioids for therapy of CIPN-induced pain
- Palmitoylethanolamine (PEA) topically or PO.
- Venlafaxine
- Gabapentin, pregabalin
- Amitryptiline / nortriptyline, imipramine / desipramine
- Acetyl-L-carnitine, lamotrigine, or other compounds¹

	Oxford		
	LoE	GR	AGO
Functional training (physical fitness, sensomotoric stimulation training etc.)	2a	C	+
Physiotherapy / physical treatment	5	D	+
acupuncture	2b	B	+
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



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7. Cardiac Disorders

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Cardiotoxicity as Long-term Side Effect

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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.) 	2b	B	
<ul style="list-style-type: none"> Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity 	1b	B	
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently: <ul style="list-style-type: none"> Elderly patients, obesity, hypertension, hypercholesterinemia, üre-existing cardiac disease (incl. borderline LVEF), diabetes mellitus 	2b	B	
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Monitoring of cardiac function: <ul style="list-style-type: none"> Standardized echocardiography (LVEF or SF in %) ECG (QT-interval) <ul style="list-style-type: none"> Troponin I as marker of cardiac toxicicty 	3b	C	+
	1a	A	+
	2b	B	+/-
<ul style="list-style-type: none"> Betablocker-prohylaxis during anthracycline therapy 	2a	B	+/-

Adjuvant Trastuzumab Cardiac Monitoring for CHF

Oxford LoE: 5

GR: D

AGO: ++

Before start of trastuzumab

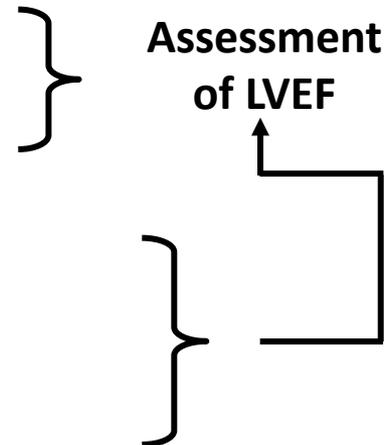
- History, physical examination (edema, hepatomegaly)
- Echocardiography (alternative to MUGA)

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



Feasibility of Treatment Combinations Considering Toxicities



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Regarding cardiac toxicity

- Trastuzumab simultaneous to radiotherapy
- Trastuzumab simultaneous to epirubicin
- Trastuzumab simultaneous to doxorubicin
- Anthracycline simultaneous to radiotherapy

Regarding lung and breast fibrosis

- Tamoxifen simultaneous to radiotherapy
- Chemotherapy simultaneous to radiotherapy

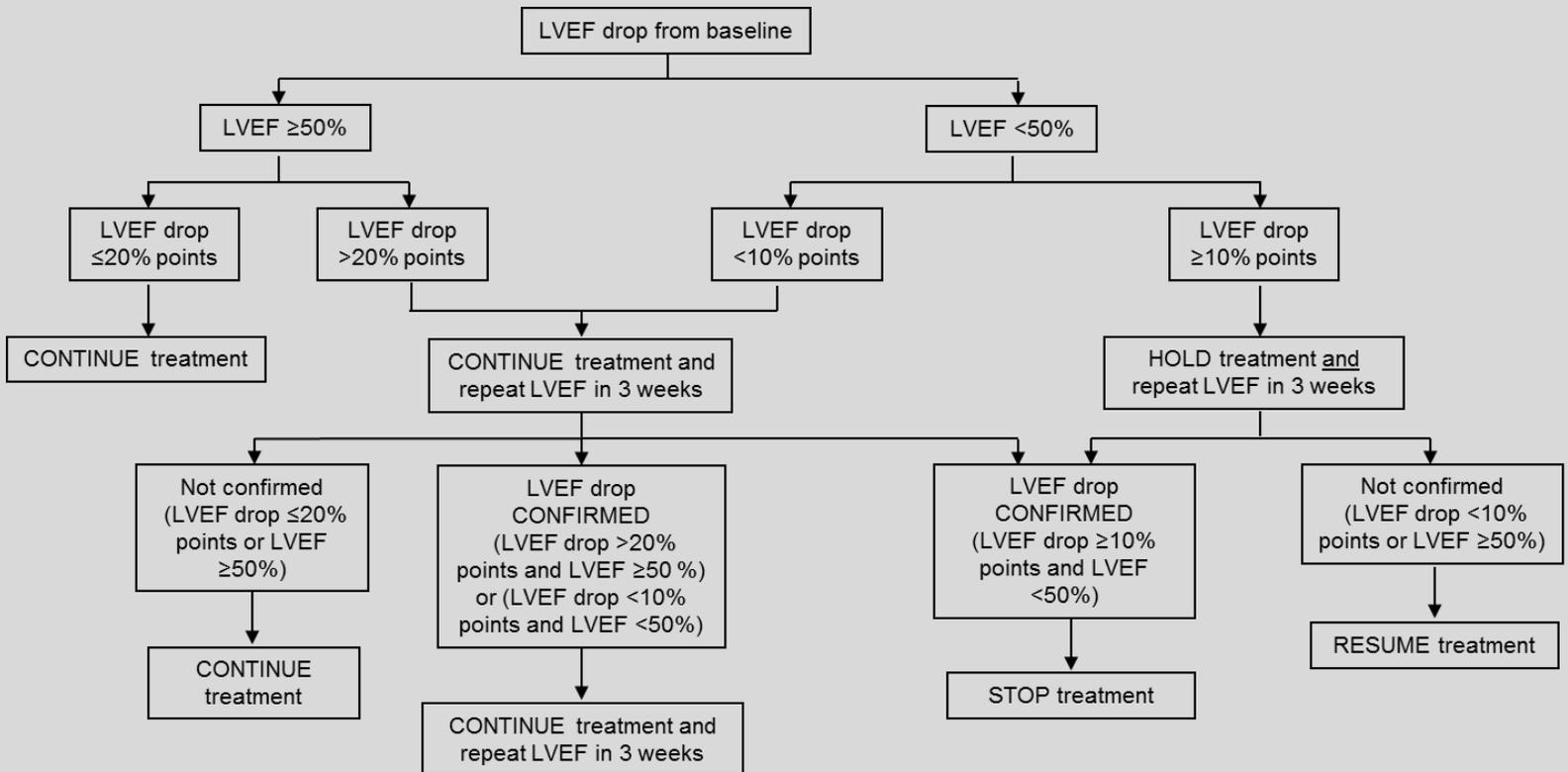
Oxford		
LoE	GR	AGO
2b	B	+
2b	B	+/-
2b	B	-
2c	C	-
3	C	+/-
1b	B	-

Side Effects of Trastuzumab / Pertuzumab: Algorithm in Case of Cardiac Toxicity



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8. Gastrointestinal Disorders

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



Antiemetic Therapy

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

www.onkosupport.de

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	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	+/-

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

ICPi=Immune Checkpoint inhibitor

Antiemetic Therapy

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

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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 ROLAPITANT or NEPA (combination of netupitant and palonosetron)

OLZ = OLANZAPINE

DOP = dopamine 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.

Antiemetic Therapy

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

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

Supportive Therapy

Antiemetics

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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	Olanzepin	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

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
2b		++

- **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.**

This entails:

1. **Patient:**
 - 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**

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

Prevention of Everolimus-Induced Stomatitis Using Corticosteroid-based Mouthwash

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- **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%), \geq grade 2 events 9% (BOLERO 27%)**

* Alternatively Hydrocortison: Hydrocortisonacetat-Suspension 0,5% with Lidocainhydrochlorid and Dexpanthenol (Germany: Arzneibuchrezeptur NRF 7.14.)

Mucositis

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- **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

Diarrhea

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- **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-Analagon 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)**

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

Side Effects According Organ Systems

Incidence, Prevention, Therapy

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9. Skin & Subcutaneous Tissue Disorders (Alopecia)

Skin Toxicities

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- **Avoidance of chemotherapy-induced alopecia by cooling the patient's scalp***
- **Prophylaxis of hand-foot-syndrome using urea containing lotions (5-10%)**
- **Prophylaxis of nail changes and hand-foot-syndrome by cooling hands during application of docetaxel**

Oxford		
LoE	GR	AGO
1b		+/-
1b		+
2b		+

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



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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)



Side Effects According Organ Systems

Incidence, Prevention, Therapy

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10. Musculoskeletal & connective tissue disorders

(see Chapter Osteooncology)

Side Effects According Organ Systems

Incidence, Prevention, Therapy

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11. General Disorders & Administration Site Conditions

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	+

Extravasation of Chemotherapy

Role of Dexrazoxane / Hyaluronic Acid

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Dexrazoxane for treatment of anthracyclines paravasates

Day 1: 1000 mg/m² (max. 2000 mg), IV 1–2 hrs

Day 2: 1000 mg/m² (max. 2000 mg), IV 1–2 hrs

Day 3: 500 mg/m² (max. 1000 mg), IV 1–2 hrs

Otherwise or if treatment with dexrazoxane is not indicated, following measures are recommended:

1. Local cooling: ice packs for 15 min every 6 hrs, for at least 3 days, alternatively: 24 h continuous ice cooling
2. Local application (with swab) of dimethylsulfoxid 99% (DMSO) every 3-4 hours for at least 3 days (better 14 days), allow it to air dry. The interval may be extended to 6 hours from day 4 onward.

Hyaluronic Acid in case of Taxan/Vinorelbin Paravasates:

- 1–10 Amp a 150 IU
- 1 ml dissolvent (e.g. NaCl 0.9%)
- Local anaesthesia
- No thermotherapy after taxanes
- Dry warmth 4 x daily 20 min during vincaalkaloids

Side Effects According Organ Systems

Incidence, Prevention, Therapy

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11. Lung

Drug-induced Pneumonitis, Interstitial Lung Disease (ILD)

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- Diagnostic work-up with chest CT

Oxford		
LoE	GR	AGO
1a	B	++

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)

1a	B	++
		++

Management ILD

Trastuzumab Deruxtecan

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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

Further Supportive and Palliative Issues

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- **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

Nutrition Deficiency

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- **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.**

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

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/>