

# Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Guidelines Breast  
Version 2025.1E

## Supportive Care and Management of Side Effects

# Supportive Care and Management of Side Effects

- **Versions 2002–2024:**

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- **Version 2025:**

**Fasching / Schütz**

# Guidelines – Evidence

**Supportive therapy is a patient centered healthcare provision, which addresses the prevention and therapy of therapy related adverse events. The aim should be the treatment of side effects and an improvement of quality of life and a better therapy management of cancer therapies. LoE 5D, AGO++**

**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 Grade

## Acute Toxicity (according to WHO<sup>1</sup> or NCI-CTCAE<sup>2</sup>)

**Acute toxicities should be asked for and documented after every treatment course**

**LoE 5 D AGO ++**

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

## Long term toxicity (= secondary diseases after tumour therapy)

**Long term surveillance and documentation in regular intervals  
(acc. ICPC<sup>3</sup> following symptoms or acc. ICD-10-GM<sup>4</sup> following diagnoses)**

**LoE 5 D AGO ++**



# Toxicity Assessment

## Acute Toxicity (NCI CTCAE v 6.0, 2020)

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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.**

**ADL = Activities of Daily Living**

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

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

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# Use of eHealth in Breast Cancer Patients

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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>Use of DiGA to improve quality of life during and after breast cancer therapy</li> </ul>	1b	B	+
<ul style="list-style-type: none"> <li>PRO-based management for reduction of therapy-associated side effects and for improvement of quality of life</li> </ul>	1b	A	+
<ul style="list-style-type: none"> <li>PRO-based management for improvement of survival in metastatic breast cancer</li> </ul>	1b	B	+/-

\* See current DiGA status / reimbursement

# Toxicities after Therapies

## Chemotherapy – Acute Toxicities I

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DRUGS	SYSTEM ORGAN CLASS												
	INFECTIONS AND INFESTATIONS	NEOPLASMS BEN. ALIGNANT AND NSPECIFIED (INCL. CYSTS & POLYPS)	YMPH. SYST. ISORDERS IMMUNE SYSTEM (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		
<b><u>Alkylating antineoplastic agent</u></b>													
Cyclophosphamide	4	2	5	5	1	-	1	3	2	3	3	3	
<b><u>Anti-Metabolites</u></b>													
Methotrexate	1	-	4	3	3	-	3	4	2	-	1	2	
5-Fluorouracil*	5	-	5	2	2	5	-	3	3	-	5	3	
Capecitabine	4	3 (Lipoma)	4	3	-	5	4	4	4	3	3	4	
Gemcitabine	4	-	5	1	-	4	-	4	-	-	2	2	
<b><u>Platinum-complexes</u></b>													
Cisplatinum	4	2	5	3	2	5	-	4	2	5	4	4	
Carboplatin	4	-	5	4	-	-	-	4	4	4	4	-	
<b><u>Anthracyclines / Anthrachinones</u></b>													
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	
<b><u>Taxanes</u></b>													
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	
<b><u>Further tubulin-targeting drugs</u></b>													
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)

# Toxicities after Therapies

## Chemotherapy – Acute Toxicities II

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DRUG	RESPIRAT., HORAC. & MEDIA- STINAL DIS.	GASTROINT.DISO RD. (NAUSEA, EMESIS)	HEPATOBIILIARY DISORDERS	SKIN & SUBCUT. TIS. DISORD. (ALOPECIA) MUSCULOSKELE TAL & CONNECTIVE TISSUE	RENAL & URINARY DISORDERS	PREGN., PUERPER. & PERINATAL CONDIT.	REPRODUCT. SYS. & BREAST DISORDERS GENERAL	DISORD. & ADMINI- STRATION SITE	CONDITIONS CONGEN., FAMILIAL GENET. DISORDERS	SPECIAL FEATURES	
<b>SYSTEM ORGAN CLASS</b>											
<b>Alkylating antineoplastic agent</b>											
Cyclophosphamide	2	4	4	5	-	5	-	4	5	-	Hyponatraemia
<b>Anti-Metabolite</b>											
Methotrexate	4	5	5	4	3	3	-	3	1	-	Mucositis, risk of "third space"-toxicity
5-Fluorouracil	5	5	3	5	-	-	-	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
<b>Platinum-complexes</b>											
Cisplatin	4	5	4	4	-	5	-	3	5	-	Nephrotoxicity, ototoxicity, CIPN
Carboplatin	4	5	-	4	4	4	-	-	4	-	Colitis (nephrotoxicity)
<b>Anthracyclines / Anthrachinones</b>											
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	-	Sec. AML, cardiomyopathy
<b>Taxanes</b>											
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
<b>Further tubulin-targeting drugs</b>											
Vinorelbine IV (PO)	3(4)	2 (5)	5(4)	2(5)	-(4)	2(4)	-	-	-	-	Phlebitis, GI-Tox (PO), CIPN
Eribulin	5	5	4	5	5	4	-	-	5	-	Constipation, CIPN

- unknown (based on available data incidence not assessable)

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# Toxicities after Therapies

## Diagnostics\* before 5-FU (i.v.) / Capecitabine-Therapy

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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

# Toxicities after Therapies

## Endocrine therapy

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- **Adherence and persistence should be specifically supported**
- **Side effects of endocrine therapies decrease adherence and should be one focus of the therapy management**
- **Adherence and Persistence have an influence on the prognosis**

Oxford		
LoE	GR	AGO
<b>2b</b>	<b>B</b>	<b>++</b>
<b>2a</b>	<b>B</b>	<b>+</b>
<b>1b</b>	<b>B</b>	<b>NA</b>

# Toxicities after Therapies

## Endocrine Therapy – Toxicities

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

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

1. Very rarely (< 1/10,000); 2. rarely (≥ 1/1,000 to < 1/10,000); 3. occasionally (≥ 1/1,000 to < 1/100); 4. frequently (≥ 1/100 to < 1/10); 5. very frequently (≥ 1/10).

- unknown (based on available data incidence not assessable)

# Toxicities after Therapies

## Endocrine Therapy – Toxicities

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

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

1. Very rarely (< 1/10,000); 2. rarely (≥ 1/1,000 to < 1/10,000); 3. occasionally (≥ 1/1,000 to < 1/100); 4. frequently (≥ 1/100 to < 1/10); 5. very frequently (≥ 1/10).

- unknown (based on available data incidence not assessable)

# Toxicities after Therapies

## Key-Toxicities – Antibodies

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

# Toxicities after Therapies

## Side effects of 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	++

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# Toxicities after Therapies

## 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

# Toxicities after Therapies Antibody-Drug-Conjugates

Oxford

LoE      GR

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## Sacituzumab Govitecan

- (Febrile) neutropenia, leukopenia, anemia, diarrhea, nausea/vomiting, alopecia, fatigue

1b

A

## Trastuzumab-Emtansin (T-DM1)

- Thrombozytopenia, elevation liver enzymes, pyrexia, headache  
pneumonitis, neuropathy, fatigue

1b

A

## Trastuzumab-Deruxtecan

- Interstitial lung disease, neutropenia, nausea/vomiting, alopecia, fatigue

1b

A

# Treatment Specific Side Effects 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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# Treatment Specific Side Effects

## 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%)

# Treatment Specific Side Effects

## Venous Thromboembolic Events: Adjuvant Abemaciclib

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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

# Treatment Specific Side Effects

## QT-Interval-Prolongation: Ribociclib 600 mg vs. Placebo

- **Post-baseline prolongation QT-interval > 480 msec 6.9% vs. 1.2%**
- **Post-baseline prolongation QT-interval > 500 msec 1.2% vs. 0.3%**
- **Dicsontinuation due to QT-interval prolongation 0.3% vs. 0.6%**
- **Prolongation of QT-interval is not associated with clinical symptoms, but with an increased risk of the life-threatening arrhythmia torsades de pointes (TdP)**
- **Ribociclib in the adjuvant setting is used with 400 mg and has Grade 3/4 QT-Interval prolongations in 0.2% of the cases**
- **Use of QT check tools might be helpful ([www.arzneimitteltherapie.de](http://www.arzneimitteltherapie.de))**

# Treatment Specific Side Effects

## 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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# Treatment Specific Side Effects

## Alpelisib/Capivasertib + Endocrine Therapy

	Alpelisib + Fulvestrant		Capivasertib + Fulvestrant	
UE, %	All Grade	Grad >/=3	All Grade	Grad >/=3
Hyperglycemia	63,7%	32,7%	16,3 %	2,3 %
Diarrhea	57,7%	6,7%	72,4 %	9,3 %
Nausea	44,7%	2,5%	34,6 %	0,8 %
Decreased appetite	35,6%	< 1% SAE	16,6 %	0,3 %
Rush	35,5%	9,9%	38 %	12,1 %
Vomiting	27,1%	< 1% SAE	20,6 %	1,7 %
Weight loss	26,8%	3,9%	-	-
Stomatitis	24,6%	2,5%	14,6 %	2,0%
Fatigue	24,3%	3,5	20,8 %	0,6 %
Asthenia	20,4%	1,8	13,2 %	1,1 %
Alopecia	19,7%	0	-	-
Mucositis	18,3%	2,1	-	-
Headache	-	-	16,9 %	0,3 %

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

LoE	GR	AGO
2b	B	++

# Treatment Specific Side Effects

## 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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# Treatment Specific Side Effects

## Immune Checkpoint Inhibitors (ICI)

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- **Therapeutic approaches (antibodies)**

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

- PD-1**

- Nivolumab (not approved for the treatment of breast cancer)
      - Pembrolizumab (approved for early and advanced TNBC)

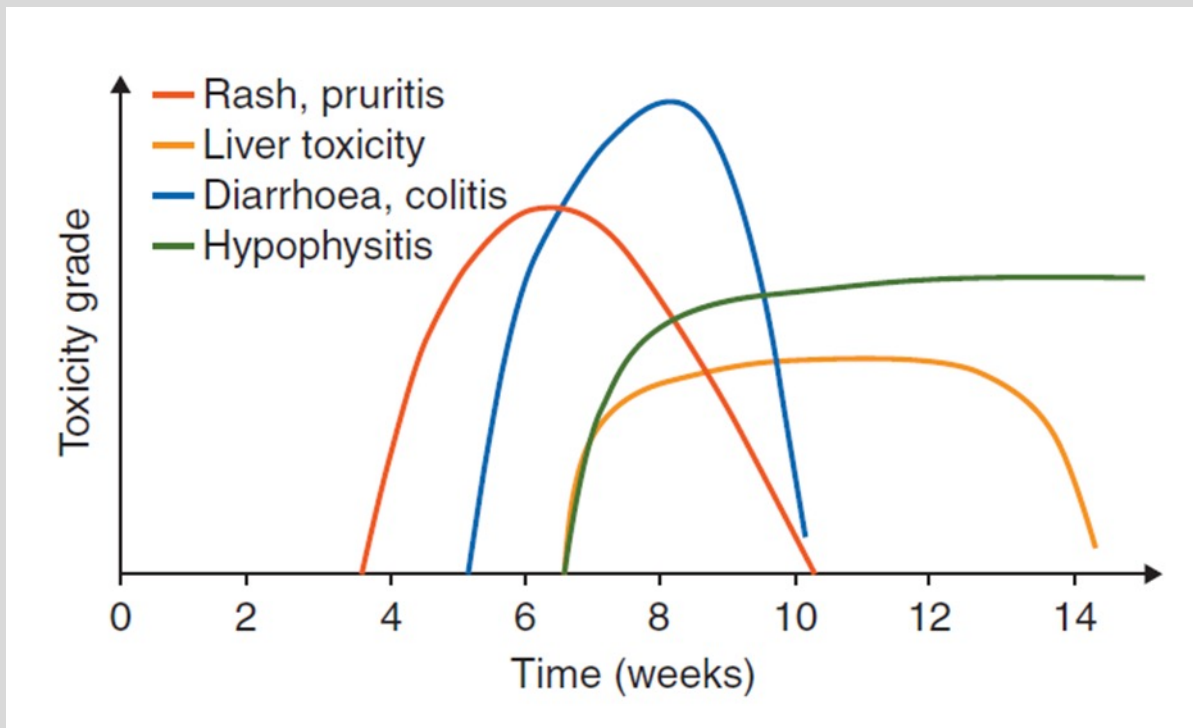
- PD-L1**

- Atezolizumab (approved for advanced TNBC)
      - Durvalumab (not approved for the treatment of breast cancer)
      - Avelumab (not approved for the treatment of breast cancer)

# Treatment Specific Side Effects Immune Checkpoint Inhibitors (ICI) Time Course of Adverse Events, e.g. Ipilimumab

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# Treatment Specific Side Effects

## Immune Checkpoint Inhibitors (ICI)

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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**

# Treatment Specific Side Effects Immune Checkpoint Inhibitors (ICI)

## Toxicities (Total in %)

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

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HEILEN**

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

# Treatment Specific Side Effects

## Immune Checkpoint Inhibitors (ICI)

### Principles of Adverse Event Management

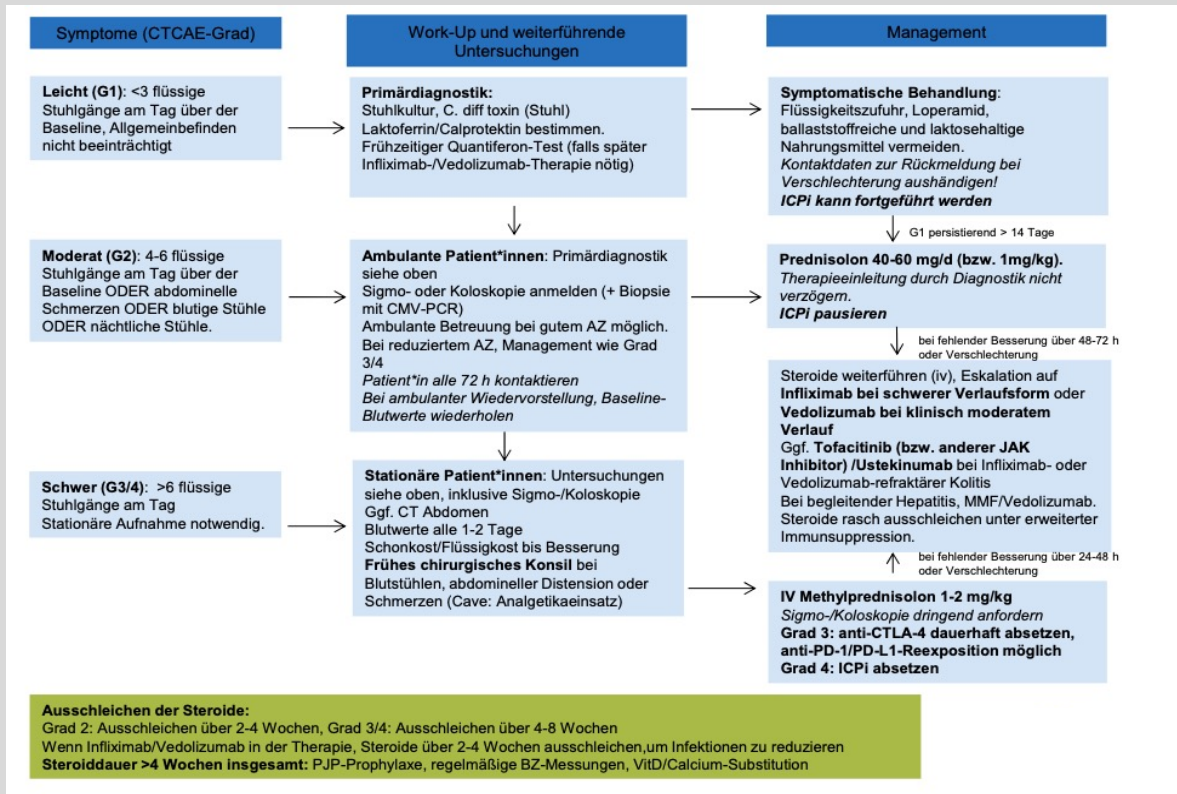
CTC AE-Grade	Management
1	<ul style="list-style-type: none"><li>▪ supportive therapy</li><li>▪ close examination</li><li>▪ exclusion of infective complications</li><li>▪ patient information</li></ul>
2	Like grade 1 but <ul style="list-style-type: none"><li>▪ intermission of therapy until recovery of all irAE to grades 0-1</li><li>▪ consider corticosteroids</li></ul>
3	<ul style="list-style-type: none"><li>▪ supportive therapy</li><li>▪ IV steroids (e.g. 1-2 mg/kg prednisolone)</li></ul> In case of no improvement within 48 h: <ul style="list-style-type: none"><li>▪ consider additional immunosuppressive therapy (infliximab, MMF)</li><li>▪ consider further organ specific diagnostics (eg. colonoscopy)</li><li>▪ consider specialists consultations</li><li>▪ exclusion or treatment of infection</li><li>▪ stop of treatment, re-initiation after recovery to CTC AE grades 0, 1</li><li>▪ slow reduction of steroids (3-6 weeks)</li></ul>
4	Like grade 3 but persistent withdrawal of therapy

# Treatment Specific Side Effects

## ICI: Diarrhoea and Colitis

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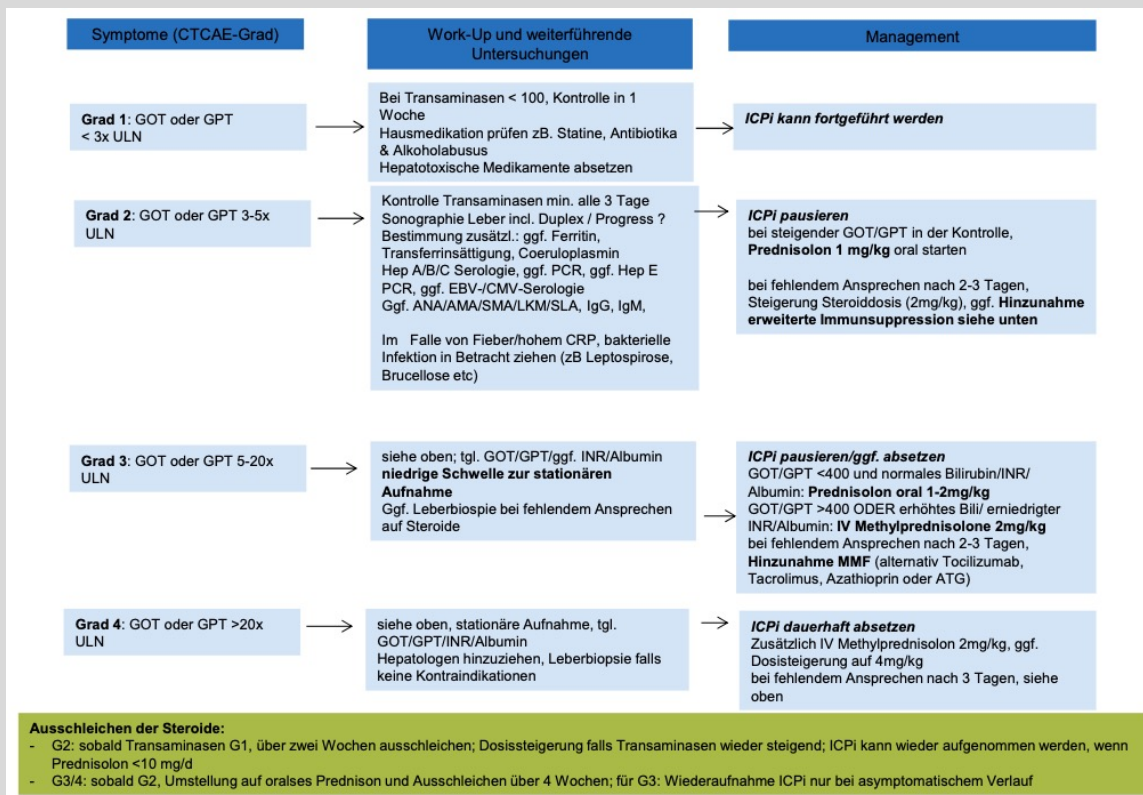


# Treatment Specific Side Effects

## ICI: Hepatitis

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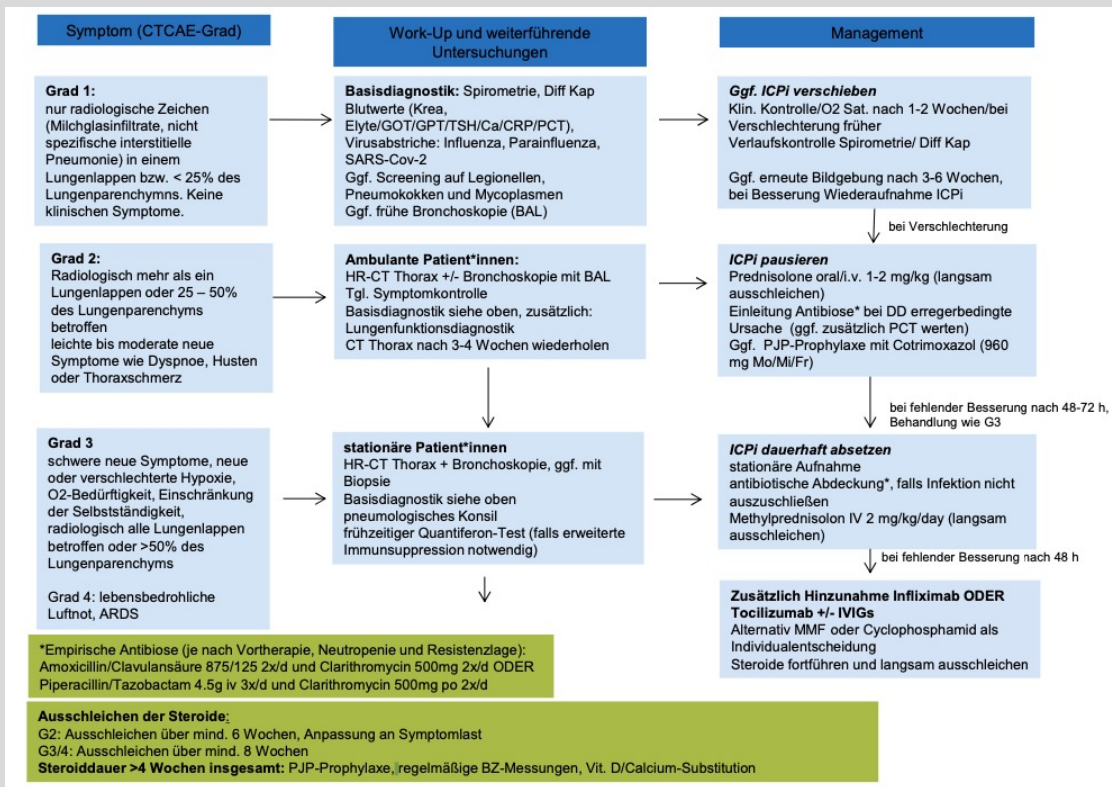


# Treatment Specific Side Effects

## ICI: Pneumonitis

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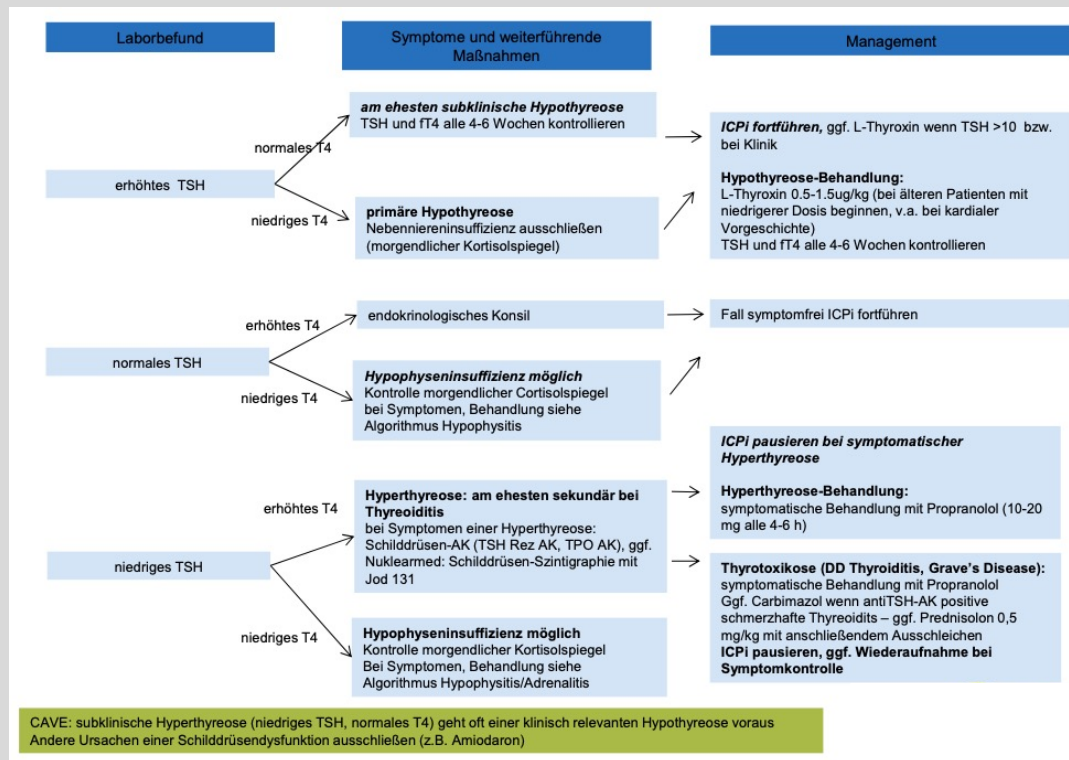


# Treatment Specific Side Effects

## ICI: Thyreoiditis

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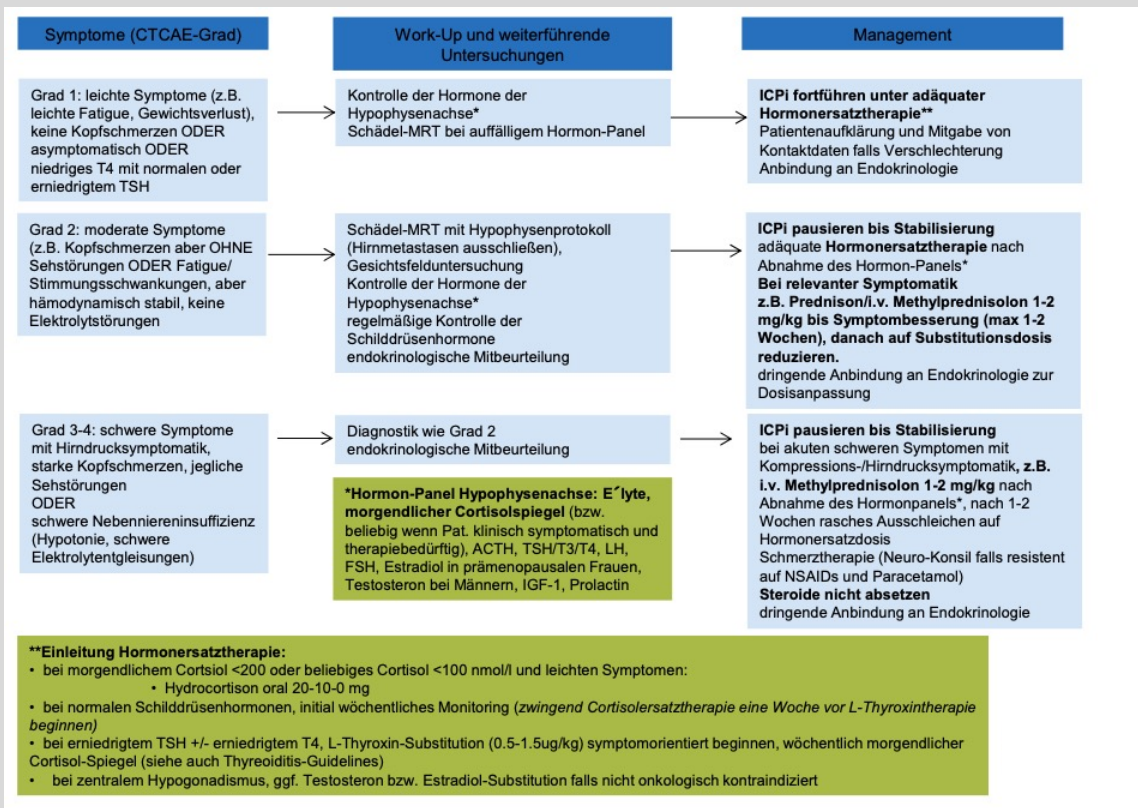


# Treatment Specific Side Effects

## ICI: Hypophysitis

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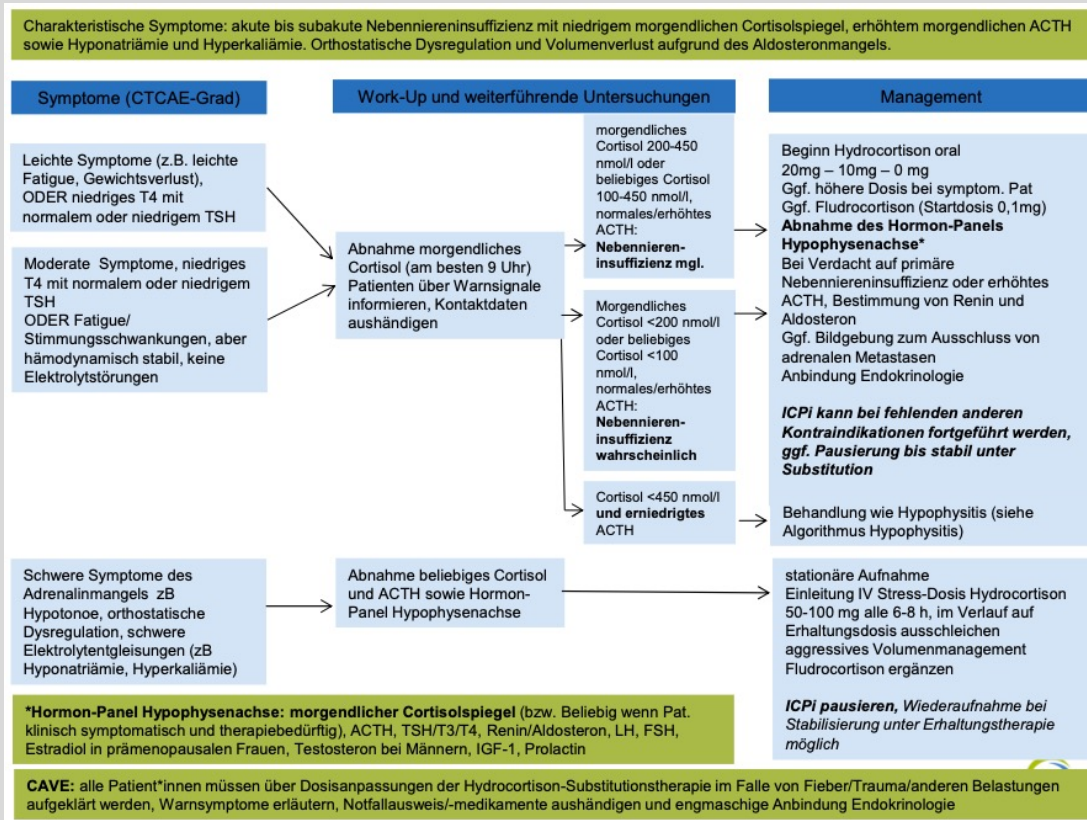


# Treatment Specific Side Effects

## ICI: Adrenalitis

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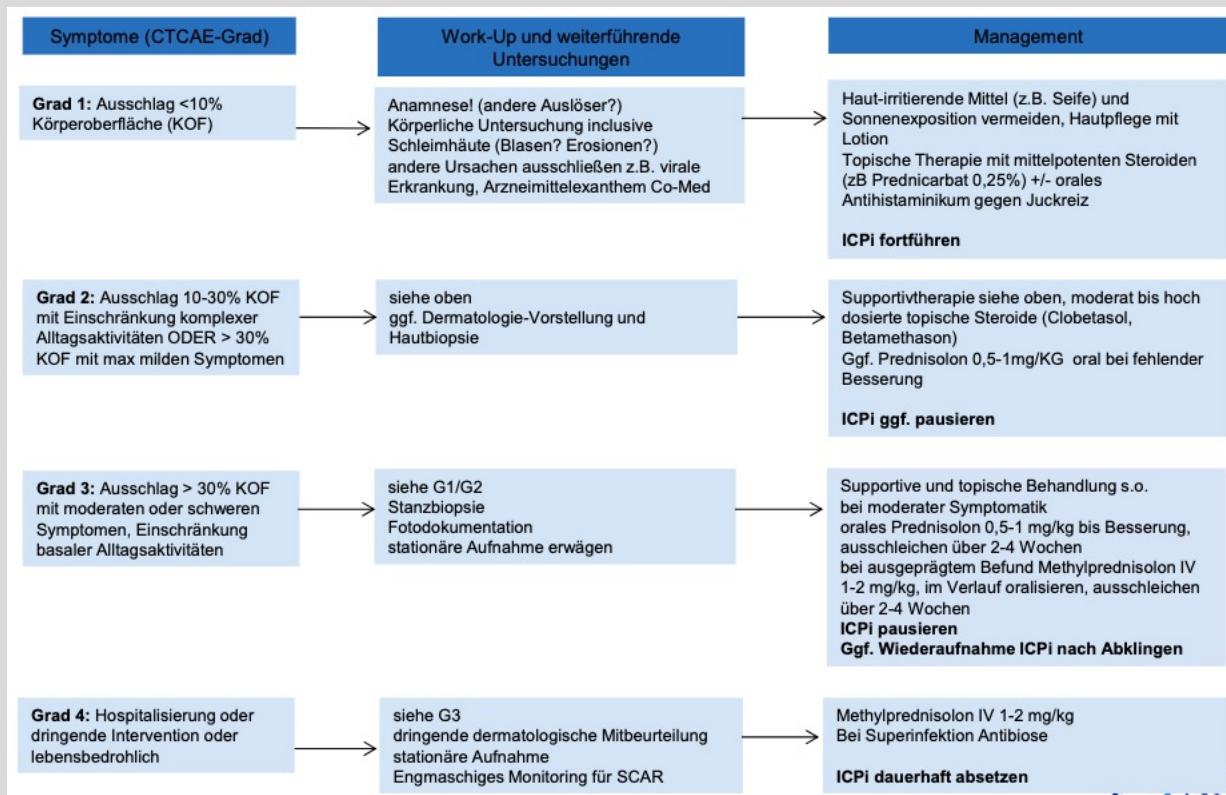


# Treatment Specific Side Effects

## ICI: Cutaneous Toxicity

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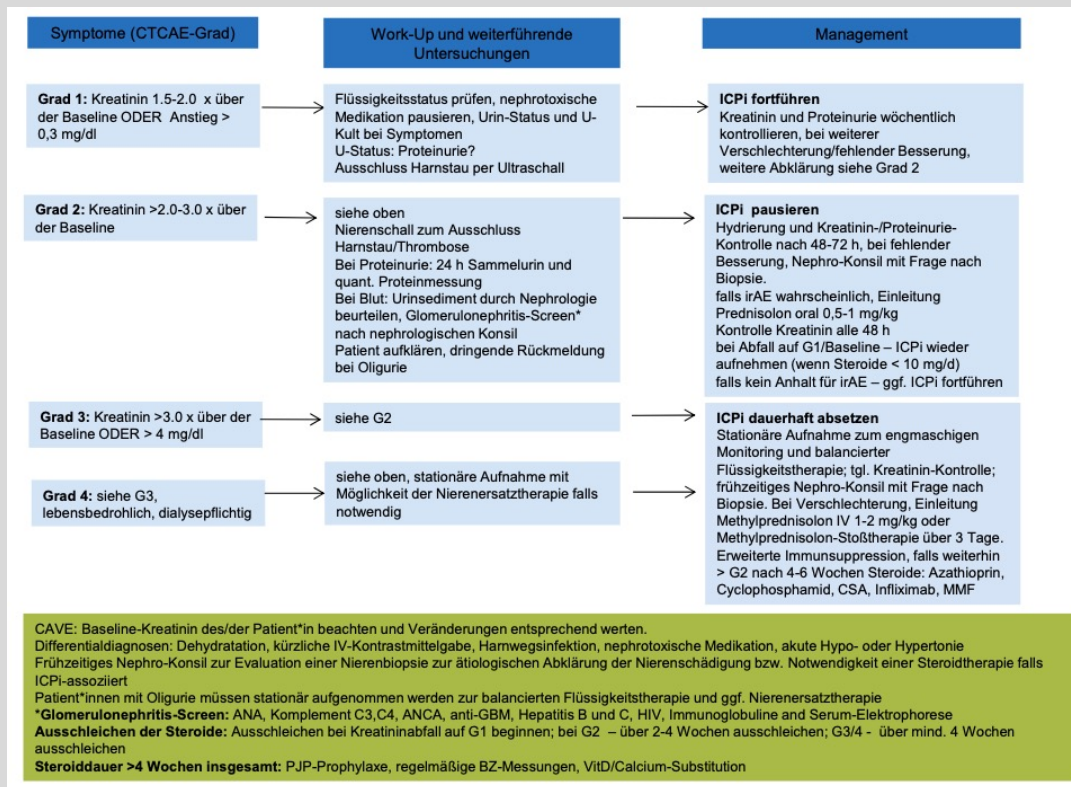


# Treatment Specific Side Effects

## ICI: Nephrotoxicity

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# Treatment Specific Side Effects

## ICI: Arthritis, Arthralgia, Myalgia

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Symptome (CTCAE-Grad)	Work-Up und weiterführende Untersuchungen	Management
<p>Grad 1: leichte Gelenk- oder Muskelschmerzen mit Entzündungszeichen, Schwellung oder leichter funktionaler Einschränkung</p>	<p>Komplette rheumatologische Anamnese mit DD wie unten aufgelistet Klinische Untersuchung aller Gelenke und Hautstatus Ggf. Röntgen bzw. Bildgebung zum Metastasenausschluss falls notwendig. Autoimmun-Panel (siehe unten) und CK</p>	<p>Schmerztherapie mit Metamizol +/- NSAID (z.B. Ibuprofen, Diclofenac, Celecoxib) (CAVE: Nierenfunktion prüfen, Comedikation mit ASS vermeiden) Bei unzureichender Einstellung, Einleitung Prednisolon 5-10 mg oral UND/ODER ggf. intraartikuläre Steroidinjektion in große Gelenke <b>ICPI fortführen, Verlaufsmonitoring Rheuma-Untersuchung, CRP/BSG alle 4-6 Wochen</b></p>
<p>Grad 2: moderate Schmerzen mit oben genannten Begleitsymptomen, Einschränkung der Tätigkeiten des täglichen Lebens</p>	<p>Anamnese, klinische Untersuchung und Autoimmunes-Panel/CK siehe oben Ultraschall +/- MRT der betroffenen Gelenke Rheumatologisches Konsil</p>	<p>Schmerztherapie steigern (CAVE: Nierenfunktion prüfen) Einleitung Prednisolon bei Leichter Klinik 10-20mg/Tag, ansonsten 0,5-1 mg/kg über 2-3 Wochen, bei fehlender Besserung, Behandlung wie G3/4 <b>Ggf. ICPI pausieren</b> und Wiederaufnahme bei Symptomkontrolle und Steroide &lt; 10 mg Prednisolon, Verlaufsmonitoring siehe oben</p>
<p>Grad 3: starke Schmerzen; potentiell irreversible Gelenkschädigung, Einschränkung der häuslichen Selbstversorgung, deutliche Einschränkungen</p>	<p>siehe Grad 2 dringliche rheumatologische Mitbeurteilung</p>	<p>Einleitung Prednisolon 1(-2) mg/kg bei fehlender Besserung innerhalb von 1 Woche/frustranem Ausschleichen nach 2 Wochen oder Verschlechterung, erweiterte Immunsuppression mit Rheumatologie besprechen (zB Infliximab, MTX, Tocilizumab, Adalimumab, Sulfasalazin, Azathioprin, Etanercept, Hydroxychloroquin) <b>ICPI pausieren, ggf. dauerhaft absetzen</b></p>
<p>Grad 4: Myositis und schwere Organbeteiligung</p>		

**Zu bedenkende Differentialdiagnosen in der Evaluation der inflammatorischen Arthropathie:**

- Rheumatoide Arthritis (seropositiv oder seronegativ) – normalerweise symmetrische Beteiligung der kleinen Gelenke
- periphere Spondyloarthritis (seronegativ) – häufig asymmetrisch, Beteiligung der großen Gelenke
- Reaktive Arthritis – postinfektiös (Diarrhoe oder Harnwegsinfektion) mit asymmetrischer Beteiligung der großen Gelenke und/oder der Augen
- Bindegeweberkrankungen zB systemischer Lupus erythematosus (SLE), Myositis oder Dermatomyositis
- Psoriasisarthritis- normalerweise kleine Gelenke, Beteiligung der distalen Interphalangealgelenke, assoziiert mit Hautläsionen der Kopfhaut oder an den Streckseiten
- virale Arthritis (zB Parvovirus B19) oder postinfektiös (zB post-Streptokokken)

**Nicht-inflammatorische Differentialdiagnosen:**

- Gicht, Pseudogicht, Trauma, Osteoarthritis – alle gehen normalerweise mit einer Monoarthritis mit Rötung einher (Ausnahme Gicht mehrere Gelenke möglich)

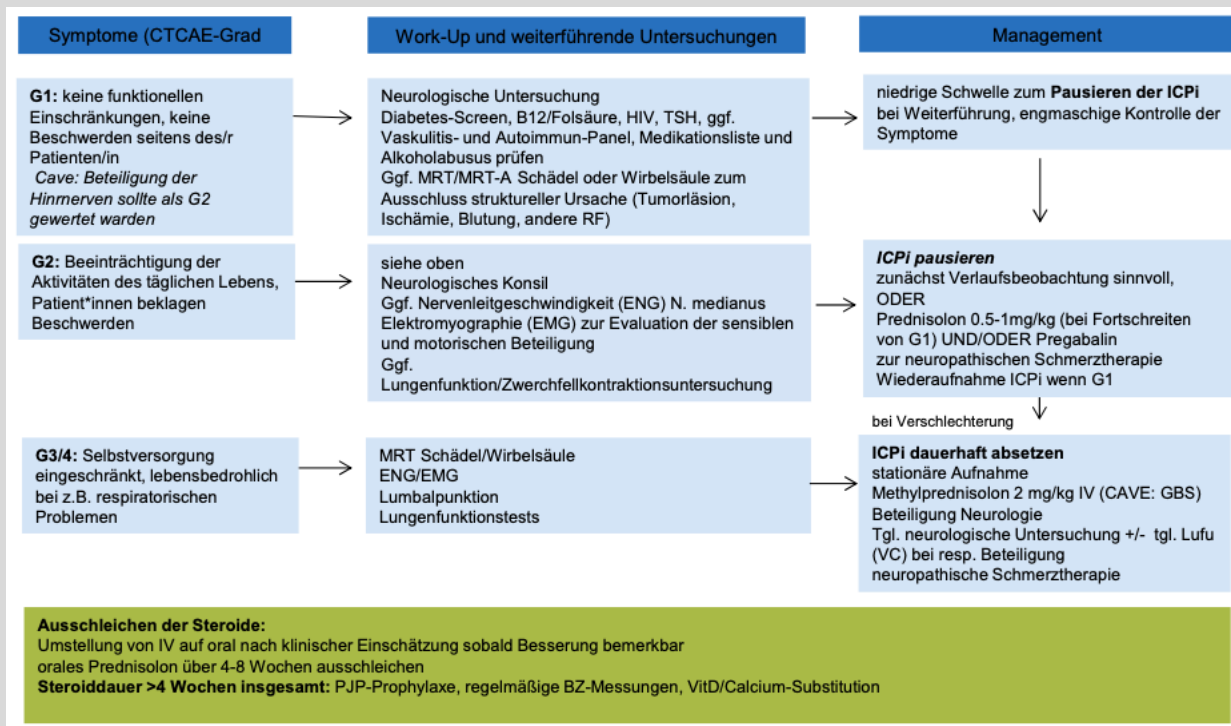
**Autoimmun-Panel:**  
ANA, dsDNA, ENA, C3/4, Rheumafaktor, Anti-Citrullinisches-Peptid Ab, BSG, CRP, ANCA, Hep B/C, Harnsäure, CK, sCD25, bei Verdacht auf Sarkoidose ACE, Calcium und 25-OH-D3

# Treatment Specific Side Effects

## ICI: Peripheral Neurotoxicity (I)

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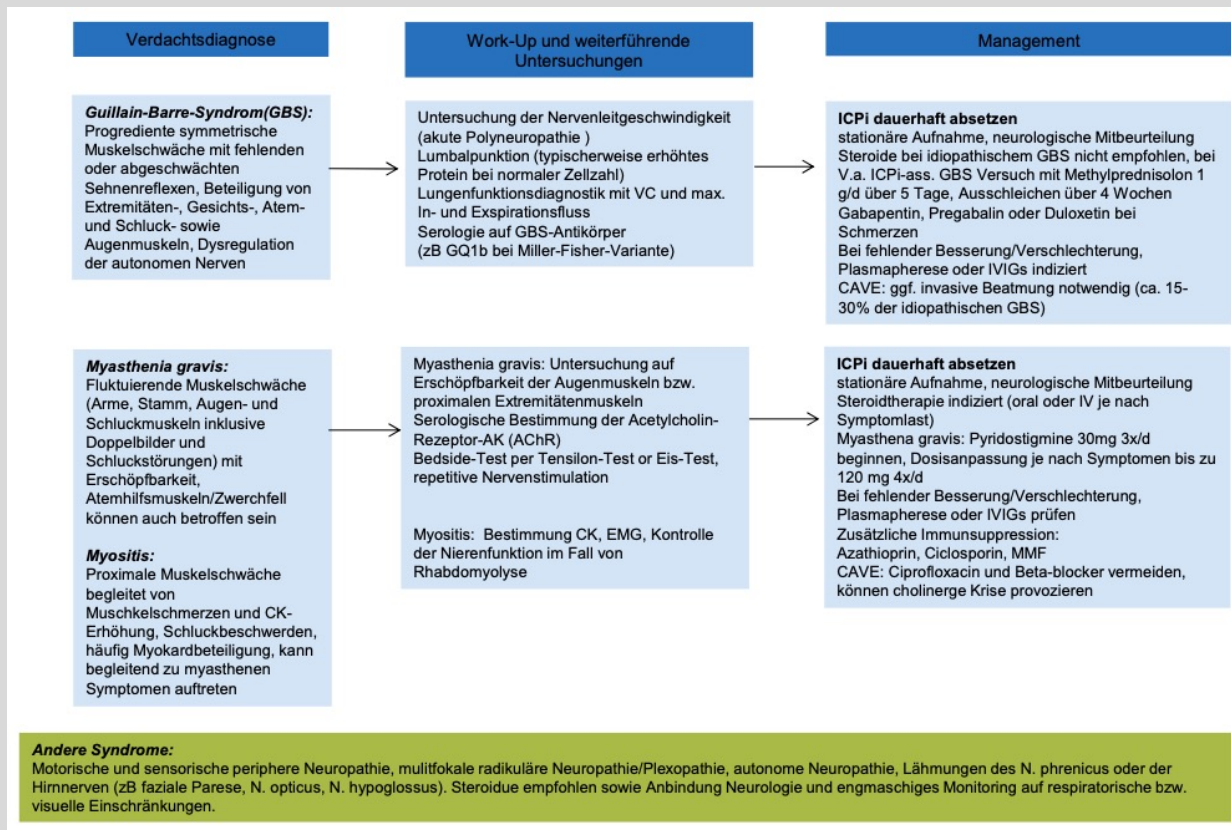


# Treatment Specific Side Effects

## ICI: Peripheral Neurotoxicity (II)

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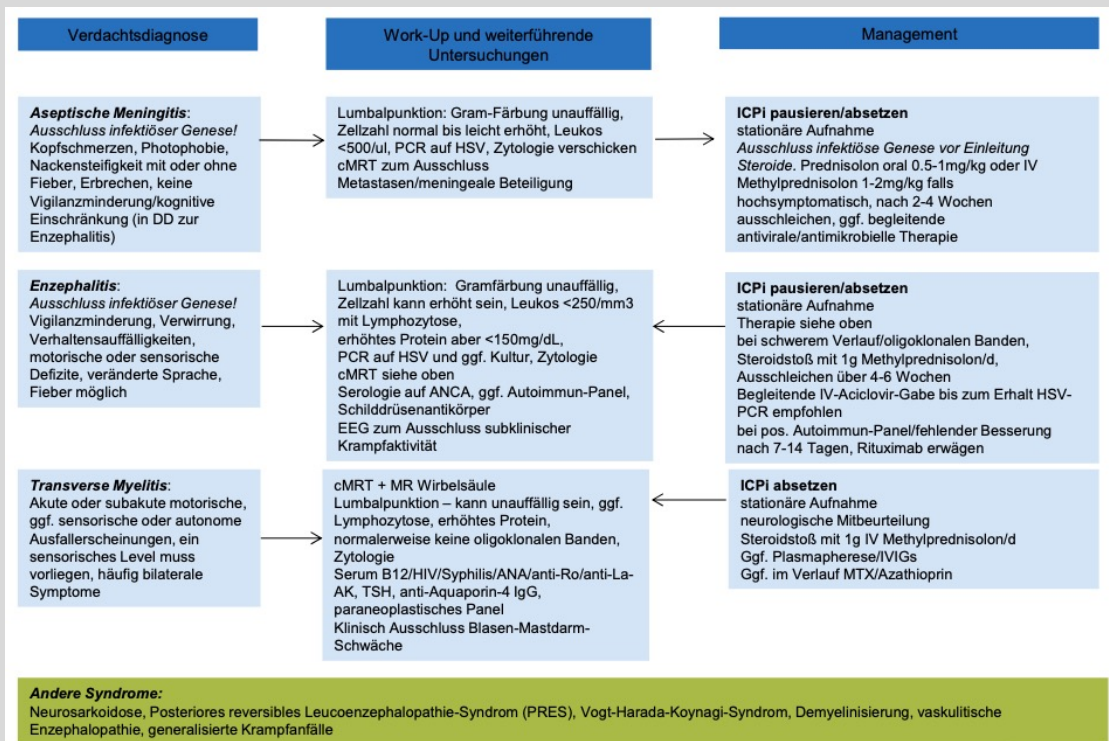


# Treatment Specific Side Effects

## ICI: Central Neurotoxicity

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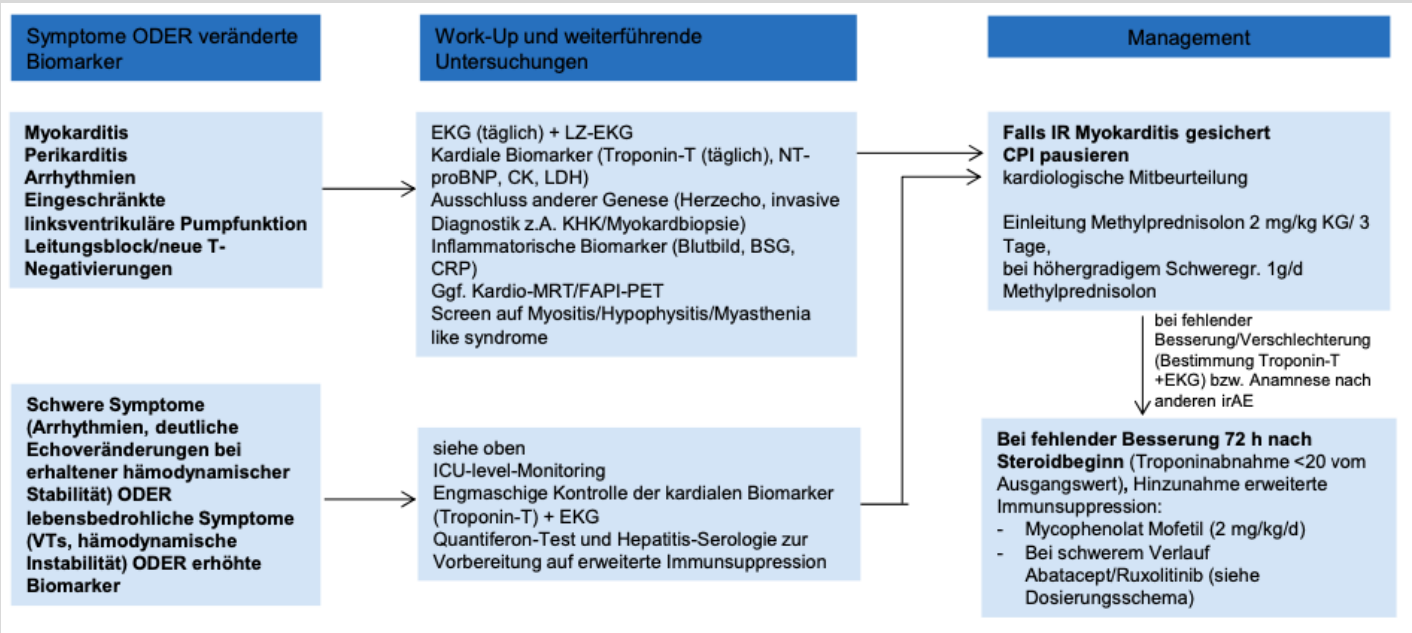


# Treatment Specific Side Effects

## ICI: Cardiovascular Toxicity

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# Side Effects According to Organ Systems

## Infections

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

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

# Side Effects According to Organ Systems

## 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

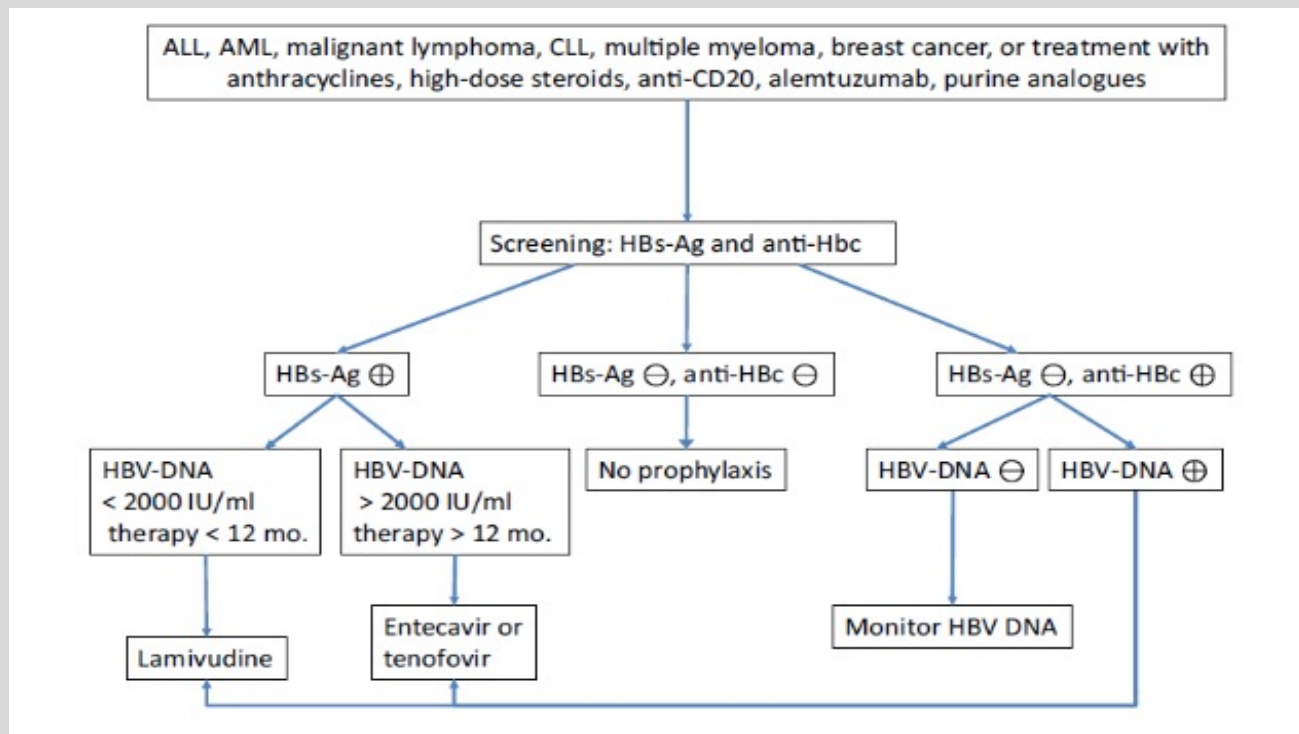
LoE GR AGO

2c B +

1b A ++

5 D +/-

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



# Side Effects According to Organ Systems

## Incidence, Prevention, Therapy

---

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

# Side Effects According to Organ Systems

## 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
- **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

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# Side Effects According to Organ Systems

## 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

# Side Effects According to Organ Systems

## Blood and Lymphatic System Disorders



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### 3. Blood and Lymphatic System Disorders

- Anemia
- Neutropenia
- Febrile Neutropenia (FN)

# Side Effects According to Organ Systems

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

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

# Organ Specific Side effects

## Practical Use of ESAs

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- **Epoetin  $\alpha$  and Darbepoetin are equieffective**
- **Dosage:**
  - **Epoetin  $\alpha$ : 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  $\beta$ : 30.000 IE weekly s.c.**
  - **Darbepoetin: 2,25  $\mu$ g/kg s.c. weekly or 500  $\mu$ 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**

# Side Effects According to Organ Systems

## Granulocyte Colony-Stimulating Factors

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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>■ <b>Primary prophylaxis for expected febrile neutropenia (FN)</b> <ul style="list-style-type: none"> <li>■ If expected risk for FN 10–20%                             <ul style="list-style-type: none"> <li>■ In case of individual risk factors</li> </ul> </li> <li>■ If expected risk for FN &gt; 20% (e.g. DAC, dose-dense CT)</li> </ul> </li> <li>■ <b>Secondary prophylaxis during chemotherapy (previous FN or neutropenia grade IV &gt; 7 days)</b></li> <li>■ <b>Therapeutic use for FN</b></li> <li>■ <b>Start related to chemotherapy and duration</b> <ul style="list-style-type: none"> <li>■ Pegfilgrastim day 2</li> <li>■ Lipegfilgrastim day 2</li> <li>■ Filgrastim / Lenograstim from day 2–3 until ANC &gt; 2–3 x 10<sup>9</sup></li> </ul> </li> </ul>	<p>1b</p> <p>3b</p> <p>1a</p> <p>1b</p> <p>1a</p> <p>1b</p> <p>1b</p> <p>1b</p>	<p>B</p> <p>C</p> <p>A</p> <p>A</p> <p>A</p> <p>A</p> <p>A</p>	<p>+/-</p> <p>+</p> <p>++</p> <p>++</p> <p>+/-</p> <p>++</p> <p>++</p> <p>++</p>

# 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](http://www.dgho-infektionen.de)

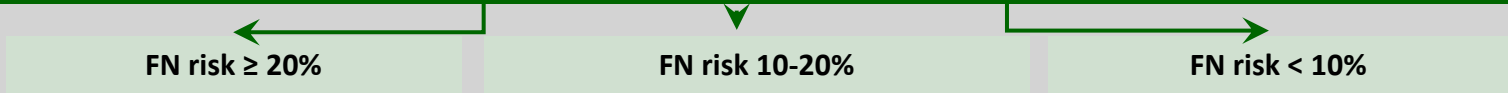
**Definition** (oral temperature of  $> 38.5^{\circ}\text{C}$  or two consecutive readings of  $> 38^{\circ}\text{C}$  for 2 h in a patient with an ANC of  $< 500 \text{ cells/mm}^3$  or expected to fall to  $< 500 \text{ cells/mm}^3$ )

Oxford

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

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

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



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

- High risk:** Age > 65 years
- Increased risk:** (level I and II evidence)
  - Advanced disease
  - History of prior FN
  - No antibiotic prophylaxis
- Other Factors:** (level III and IV evidence)
  - Poor performance (ECOG > 1)
  - Female gender
  - Haemoglobin < 12 g/dL
  - Liver, renal or cardiovascular disease
  - Nutritional status

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



**Prophylactic G-CSF recommended**

**G-CSF prophylaxis not indicated**

**Reassess at each cycle**

# Side Effects According to Organ Systems

## 4. Toxicities / Ovaries

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### Therapy-associated amenorrhea (CRA, CIA, TIA)

Oxford

LoE

- CRA may be permanent or temporary (depending on age of the patient and type of chemotherapy) 2b
- The risk of CRA increases with patient's age and duration of the chemotherapy 2b
- CRA is an imperfect surrogate for menopause and fertility 5
- Adjuvant endocrine therapy with GnRHa induces reversible amenorrhea, but delays conception to a less fertile period 5
- Ovarian reserve of women who remain premenopausal after CTX is reduced 2b
- CRA is associated with improved outcome (DFS / OS) 1b

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

# Side Effects According to Organ Systems

## Psychiatric Disorders

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## 5. Psychiatric Disorders

- Depression
- Fatigue
- Cognitive impairment
- Sleep disturbances

# Side Effects According to Organ Systems (Therapy-associated) Depression



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	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	+

# Side Effects According to Organ Systems (Therapy-related) Fatigue



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	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	+

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# Side Effects According to Organ Systems (Therapy-associated) Cognitive Impairment

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

# Side Effects According to Organ Systems (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	++

# Side Effects According to Organ Systems

## Chemotherapy-Induced Peripheral Neuropathy (CIPN)

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## 6. Nervous system disorders

- Chemotherapy-Induced Peripheral Neuropathy (CIPN)

# Side Effects According to Organ Systems

## 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)

# Side Effects According to Organ Systems

## Prevention of Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Oxford

LoE GR AGO

### 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

5	D	+
2b	B	+
2b <sup>a</sup>	B	+
1b	B	-

### 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 compounds<sup>1</sup>

2a	C	+/-
5	D	+/-
1b	A	-

<sup>1</sup> For list of not recommended drugs, see Hershman et al. 2014

# Side Effects According to Organ Systems

## Therapy of Chemotherapy-induced Peripheral Neuropathy

	Oxford		
	LoE	GR	AGO
<b>Non drug-based therapy</b>			
▪ Functional training (physical fitness, sensomotoric stimulation training etc.)	2a	C	+
▪ acupuncture	2b	B	+
<b>Drug-based therapy</b>			
▪ Menthol locally (1%), capsaicin / lidocain locally	5	D	+
▪ Capsaicin	2b	B	+
▪ Duloxetine for therapy of CIPN-induced pain	1b	B	+
▪ Opioids for therapy of CIPN-induced pain	5	D	+
▪ Gabapentin, pregabalin	1b	B	+/-
▪ Amitriptyline / nortriptyline, imipramine / desipramine	1b	B	+/-
▪ Acetyl-L-carnitine, lamotrigine, or other compounds <sup>1</sup>	1b	B	-

<sup>1</sup> For list of not recommended drugs, see Hershman et al. 2014

# Side Effects According to Organ Systems

## Cardiac Disorders

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## 7. Cardiac Disorders

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# Side Effects According to Organ Systems

## Cardiotoxicity as Long-term Side Effect



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

# Side Effects According to Organ Systems

## Adjuvant Trastuzumab Cardiac Monitoring for CHF

**Oxford LoE: 5**

**GR: D**

**AGO: ++**

### Before start of trastuzumab

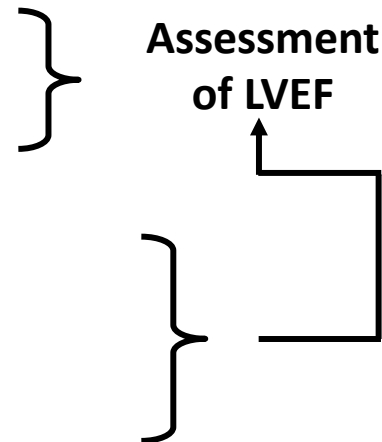
- History, physical examination (edema, hepatomegaly)
- Echocardiography (alternative to MUGA)

### During trastuzumab

#### Regular assessment of

- Heart rate increase > 15% above individual base level
- Body weight increase  $\geq 2$  kg/week
- Cardiac signs and symptoms

### 3 monthly assessment of LVEF



# Side Effects According to Organ Systems

## Feasibility of Treatment Combinations Considering Toxicities

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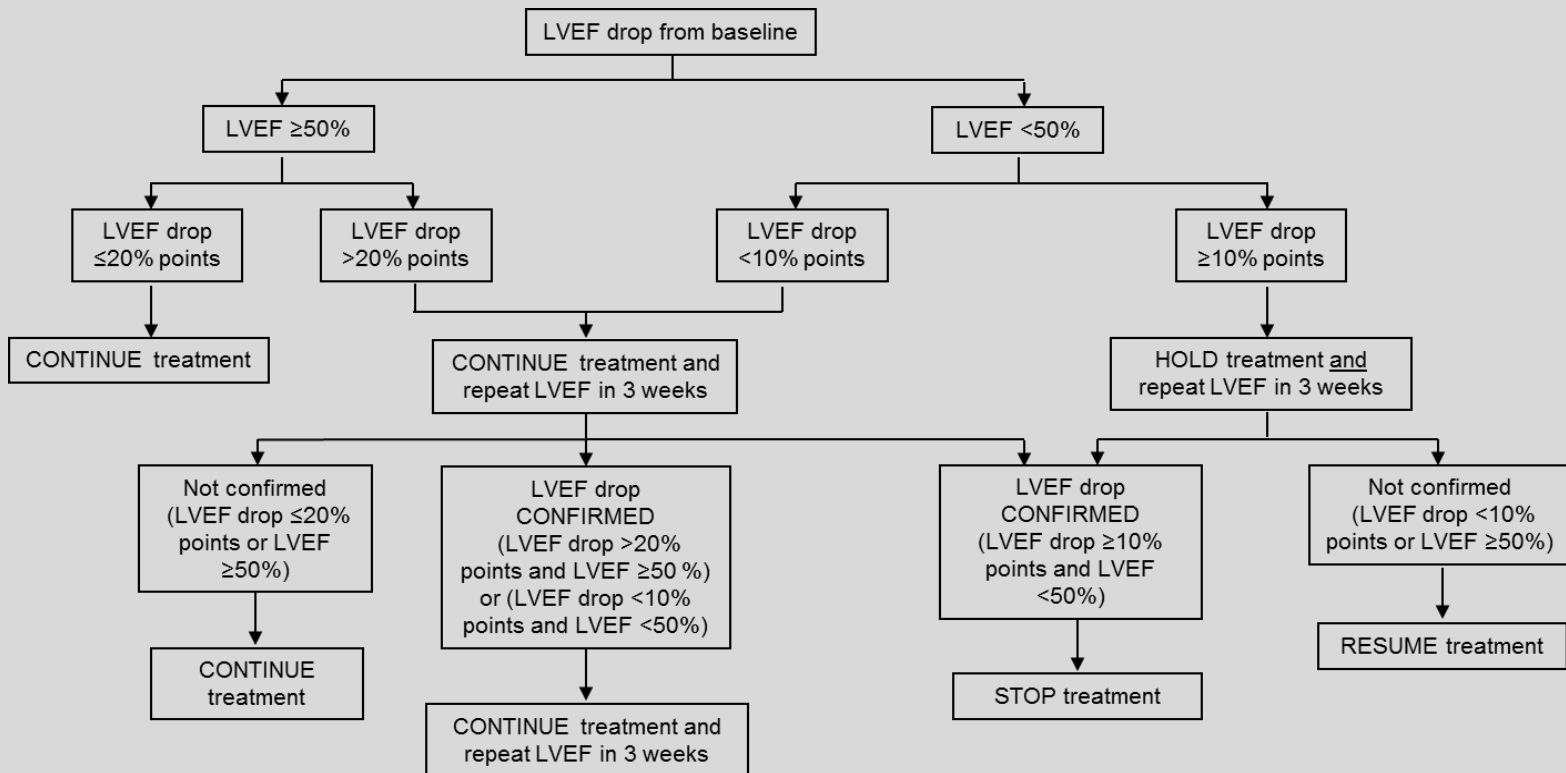
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	Oxford		
	LoE	GR	AGO
<b><u>Regarding cardiac toxicity</u></b>			
▪ Trastuzumab simultaneous to radiotherapy	2b	B	+
▪ Trastuzumab simultaneous to epirubicin	2b	B	+/-
▪ Trastuzumab simultaneous to doxorubicin	2b	B	-
▪ Anthracycline simultaneous to radiotherapy	2c	C	-
<b><u>Regarding lung and breast fibrosis</u></b>			
▪ Tamoxifen simultaneous to radiotherapy	3	C	+/-
▪ Chemotherapy simultaneous to radiotherapy	1b	B	-

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

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# Side Effects According to Organ Systems

## Nausea, Emesis, Mucositis, Diarrhoea, Constipation

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## 8. Gastrointestinal Disorders

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

# Side Effects According to Organ Systems

## Antiemetic Therapy (MASCC and ASCO)

Oxford

LoE GR AGO

<ul style="list-style-type: none"> <li>▪ After assessment of emetic potential of therapy protocol (p.o., i.v., s.c., i.m.)</li> </ul>	5	D	++
<ul style="list-style-type: none"> <li>▪ Neurokinin-1-receptor-antagonists</li> </ul>	1b	A	++
<ul style="list-style-type: none"> <li>▪ Dexamethasone (also in chemotherapy combinations with ICPI)</li> </ul>	1a	A	++
<ul style="list-style-type: none"> <li>▪ 5-HT<sub>3</sub>-antagonists</li> </ul>	1b	A	++
<ul style="list-style-type: none"> <li>▪ Fixed antiemetic combination therapy</li> </ul>	1b	A	++
<ul style="list-style-type: none"> <li>▪ Rescue Medication                             <ul style="list-style-type: none"> <li>▪ Olanzapine</li> <li>▪ Levomepromazine, benzodiazepines</li> <li>▪ Cannabinoids, ginger</li> </ul> </li> </ul>	1b	A	+
	3b	C	+
	3b	C	+/-

ICPI = Immune Checkpoint inhibitor



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# 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 <sub>3</sub>	+	DEX	+	NK <sub>1</sub> +/- OLZ*
High AC	5-HT <sub>3</sub>	+	DEX	+	NK <sub>1</sub> +/- OLZ*
Carboplatin	5-HT <sub>3</sub>	+	DEX	+	NK <sub>1</sub>
Moderate (other than carboplatin)	5-HT <sub>3</sub>	+	DEX		
Low	5-HT <sub>3</sub>	or	DEX	or	DOP
Minimal	No routine prophylaxis				

5-HT<sub>3</sub> = serotonin<sub>3</sub> receptor antagonist

DEX = DEXAMETHASONE

NK<sub>1</sub> = neurokinin<sub>1</sub> receptor antagonist such as APREPITANT or FOSAPREPITANT or ROLAPITANT or NEPA (combination of netupitant and palonosetron)

OLZ = OLANZAPINE

DOP = dopamine receptor antagonist

NOTE: If the NK<sub>1</sub> receptor antagonist is not available for AC chemotherapy, palonosetron is the preferred 5-HT<sub>3</sub> 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

# Antiemetic Therapy

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

## DELAYED Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS
High Non-AC	<b>DEX</b> or (if APR 125mg for acute: ( <b>MCP</b> + <b>DEX</b> ) or ( <b>APR</b> + <b>DEX</b> )) +/- <b>OLZ*</b>
High AC	NONE or ( if APR 125mg for acute: <b>DEX</b> or <b>APR</b> ) +/- <b>OLZ*</b>
Carboplatin	NONE or (if APR 125mg for acute: <b>APR</b> )
Oxaliplatin, or anthracycline, or cyclophosphamide	<b>DEX can be considered</b>
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	Antiemetic potential
Serotonin-antagonists	Ondansetron Tropisetron Granisetron Palonosetron	8 mg i.v., 2 x 4-8 mg p.o. 5 mg i.v., 5 mg p.o. 1-3 mg i.v. 0.25 mg i.v.	Headache, diarrheea, flush, elevated transaminases, intestinal atony (higher doses)	Very high
NK1-Antagonists	Aprepitant  Fosaprepitant Rolapitant	125 mg d1, 80 mg d 2-3 p.o. 150 mg d1 i.v. 180 mg d1 p.o.	Activation of cytochrome-P-450-, dose reduction of dexamethasone (2 x 8 mg). No combination with Astemizole, Terfenadine, Cisaprid	Very high
Dopamin-antagonists/ substituted Benzamides	Metoclopramid  Alizaprid	Up to 120 mg/24h als continuous infusion or drop  bis zu 300 mg i.v. oder p.o./24 h ( 6 Amp. od. 6 Tbl.)	Dyskinesia (Antidote: Biperiden)  Anxiety, depression, diarrhoea	high
Oxazapine	Olanzepin	10mg/d for d1-4 Ggf. 5mg/d for d1-4	Sedation, weight gain	high
Phenothiazine/ Butyrophenone	Haloperidol	1-3 mg 4 x/d	Sedation, reduction of seizure threshold, transient elevation of liver enzymes	intermediate
Corticosteroids	Dexamethasone  Prednisolone	8-20 mg i.v. 1-3 x/d  100-250 mg i.v. 1-3 x/d	Hyperglycaemia, psychosis, flush, hypertension	intermediate
Benzodiazepine	Diazepam Lorazepam	Up to 20 mg/d 0,5-1,0 mg/d	Sedation, respiratory depression	Low
NEPA (Netupitant and Palonosetron)	Fixed combination	NE 300 mg PA 0,5 mg		Very high

# Mucositis Prevention

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

Multidisciplinary S3 guidelines of the AWMF (Reg.-Nr. 032-054OL): „Supportive Therapie bei onkologischen Patientinnen – interdisziplinäre Querschnittsleitlinie“

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 (H<sub>2</sub>O, 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

# 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

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- **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 to Organ Systems

## Skin & Subcutaneous Tissue Disorders

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## 9. Skin & Subcutaneous Tissue Disorders (Alopecia)

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# Side Effects According to Organ Systems

## 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		+

\* Substance- and regimen specific

# Scalp Cooling: Scalp Cooling Alopecia Prevention Trial (SCALP) and 3 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 to Organ Systems

## Musculoskeletal & Connective Tissue Disorders

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## 10. Musculoskeletal & connective tissue disorders

*(see Chapter Osteooncology)*

# Side Effects According to Organ Systems

## General Disorders & Administration Site Conditions

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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/m<sup>2</sup> (max. 2000 mg), IV 1–2 hrs**

**Day 2: 1000 mg/m<sup>2</sup> (max. 2000 mg), IV 1–2 hrs**

**Day 3: 500 mg/m<sup>2</sup> (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 to Organ Systems

## Lung

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## 11. Lung

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# Drug-induced Pneumonitis, Interstitial Lung Disease (ILD)

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Guidelines Breast  
Version 2025.1E

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>Diagnostic work-up with chest CT as a consequence of any grade of clinical symptoms</li> </ul>	1a	B	++
<b>Therapy according to grade and drug*</b>			
<ul style="list-style-type: none"> <li>Corticosteroids (start with <math>\geq 0.5</math> mg/kg/d prednisolone-equivalent)</li> </ul>	1a	B	++
<ul style="list-style-type: none"> <li>Dose hold or therapy discontinuation* (according to respective product information)</li> </ul>	1b	B	++

# Management ILD -Trastuzumab Deruxtecan

## Monitor for suspected ILD/P



- Interrupt T-DXd if ILD/P is suspected
- Rule out ILD/P if radiographic changes consistent with ILD/P or if acute onset of new or worsening pulmonary symptoms develop

## Confirm ILD/P by evaluation

- High-resolution CT, pulmonologist consultation, blood culture and CBC, bronchoscopy or BAL, PFTs and pulse oximetry, arterial blood gases, PK analysis of blood sample (as clinically indicated and feasible)<sup>a</sup>
- **All ILD/P events regardless of severity or seriousness should be followed until resolution including after drug discontinuation**

## Manage ILD/P

Grade 1	Grade 2 (symptomatic)	Grade 3 or 4
<ul style="list-style-type: none"> <li>• <b>Interrupt T-DXd</b></li> <li>• T-DXd can be resumed if the ILD/P resolves to grade 0                             <ul style="list-style-type: none"> <li>– If resolved in ≤28 days from onset, maintain dose</li> <li>– If resolved in &gt;28 days from onset, reduce dose by 1 level<sup>b</sup></li> </ul> </li> </ul>	<p><b>Permanently discontinue T-DXd</b></p>	<p><b>Permanently discontinue T-DXd</b></p>
<ul style="list-style-type: none"> <li>• <b>Discontinue T-DXd</b> if ILD/P occurs beyond day 22 and has not resolved within 49 days from the last infusion</li> </ul>		
<p>↓</p> <ul style="list-style-type: none"> <li>• Monitor and closely follow-up in 2-7 days for onset of clinical symptoms and pulse oximetry</li> <li>• Consider:                             <ul style="list-style-type: none"> <li>– Follow-up imaging in 1-2 weeks, or as clinically indicated</li> <li>– Starting systemic glucocorticoids (e.g. ≥0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over ≥4 weeks</li> </ul> </li> </ul> <p><i>If diagnostic observations worsen despite initiation of corticosteroids, then follow grade 2 guidelines.</i></p>	<ul style="list-style-type: none"> <li>• Promptly start systemic glucocorticoids (e.g. ≥1 mg/kg/day prednisone or equivalent) for ≥14 days until complete resolution of clinical and chest CT findings, followed by gradual taper over ≥4 weeks</li> <li>• Monitor symptoms closely</li> <li>• Re-image as clinically indicated</li> <li>• If worsening or no improvement in clinical or diagnostic observations in 5 days:                             <ul style="list-style-type: none"> <li>– Consider increasing dose of glucocorticoids (e.g. 2 mg/kg/day prednisone or equivalent), and administration may be switched to i.v. (e.g. methylprednisolone)</li> <li>– Reconsider additional workup for alternative etiologies as described above</li> <li>– Escalate care as clinically indicated</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Hospitalization required</li> <li>• Promptly start empirical high-dose methylprednisolone i.v. treatment (e.g. 500-1000 mg/day for 3 days), followed by ≥1.0 mg/kg/day of prednisone (or equivalent) for ≥14 days or until complete resolution of clinical and chest CT findings, followed by gradual taper over ≥4 weeks</li> <li>• Re-image as clinically indicated</li> <li>• If still no improvement within 3-5 days:                             <ul style="list-style-type: none"> <li>– Reconsider additional workup for alternative etiologies as described above</li> <li>– Consider other immunosuppressants (e.g. infliximab or mycophenolate mofetil) and/or treat per local practice</li> </ul> </li> </ul>
<p>We suggest considering steroids for selected grade 1 cases that show extensive lung involvement or in patients at increased risk for progression of ILD/P</p>		

# 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
  - CNS metastases (see chapter)
- **Please note the AWMF S3 Guideline for supportive therapies**

# Palliative Care

- **All patients should be offered palliative care after the diagnosis of a non-curable cancer, regardless of whether a tumour-specific therapy is carried out.**
- **In patients with incurable disease advance care planning (incl. advance directive) should be recommended.**
- **Specialized palliative care should be integrated into oncological decision-making processes, e.g. by participating in interdisciplinary tumor conferences.**
- **Patients with incurable cancer who are cared for in structures of specialized palliative care (palliative care ward, specialized outpatient care such as SAPV) should have access to oncological counselling.**

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