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# Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

## Supportive Therapie und Nebenwirkungsmanagement

### Screened data bases

Pubmed 2007 - 2018, ASCO 2010 – 2018, SABCS 2010 – 2018, Cochrane Data Base (2017)

### Screened guidelines

1. ABC Consensus Guidelines for Advanced Breast Cancer (ABC 1-4): Cardoso F, Costa A, Senkus E et al. 3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). Ann Oncol. 2017 Jan 1;28(1):16-33.
2. Harbeck N, Lüftner D, Marschner N et al. ABC4 Consensus: assessment by a German Group of Experts. Breast Care (Basel). 2018 Mar;13(1):48-58.
3. ASCO (American Association of Clinical Oncology, Practice Guidelines, 2016) <http://www.asco.org>
4. American Society of Clinical Oncology Clinical Practice Survivorship Guidelines, Endorsements and Adaptations: <https://www.asco.org/sites/new-www.asco.org/files/content-files/practice-and-guidelines/documents/Survivorship-Summary-of-Recs-Binder.pdf>
5. 2016 Updated American Society of Clinical Oncology/Oncology Nursing Society Chemotherapy Administration Safety Standards, Including Standards for Pediatric Oncology: <http://ascopubs.org/doi/pdfdirect/10.1200/JOP.2016.017905>
6. Hershman DL, Lacchetti C, Dworkin RH et al. American Society of Clinical Oncology. Prevention and management of

chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014 Jun 20;32(18):1941-67.

7. CMA (Canadian Medical Association , 2016): <http://www.cmaj.ca>
8. NCCN (National Comprehensive Cancer Network , 2018): <http://www.nccn.org>
9. NCI (National Cancer Institute , 2017): <http://www.cancer.gov>
10. S3 Leitlinie Supportive Therapie: Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.1, 2017, AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff 29. Januar 2018)



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## Supportive Therapie und Nebenwirkungsmanagement

- **Version 2002–2018:**  
**Albert / Bauerfeind / Brunnert / Bischoff / Costa / Dall / Diel / Fersis / Friedrich / Friedrichs / Gerber / Göhring / Hanf / Heinrich / Huober / Jackisch / Lisboa / Lück / Lüftner / von Minckwitz / Möbus / Müller / Nitz / Oberhoff / Rody / Schaller / Scharl / Schmidt / Schütz / Solomayer / Souchon / Stickeler / Thomssen / Untch**
- **Version 2019:**  
**Harbeck / Schneeweiss**

# Inhaltsverzeichnis

- **Leitlinien**
- **Toxizitätsbeurteilung**
- **Inzidenz von Nebenwirkungen  
(nach Fachinformationen; MedDRA-Standard)**
- **Nebenwirkungen nach Organsystemen**
  - Inzidenz, Prävention, Therapie
- **Substanzspezifische Nebenwirkungen**
  - Zielgerichtete Substanzen
- **Andere Fragestellungen**
  - Schmerztherapie, Palliative Care


## ■ Leitlinien - Umfeld

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1. S3-Leitlinie: Supportive Therapie:

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.1, 2017, AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff 29. Januar 2018)

- **Toxizitätsbeurteilung**
  - **Akute Toxizität (NCI-CTCAE)**
  - **Langzeittoxizität (ICPC, ICD-GM)**



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# Toxizitäts-Beurteilung

Akute Toxizität (nach WHO <sup>1</sup> oder NCI-CTC <sup>2</sup> )		
Akute Toxizität nach jedem Therapiezyklus abfragen und dokumentieren		LoE 5 D AGO ++
Grad		Notwendige Informationen
0 keine		Beteiligte Organe
1 mild		Art der Toxizität
2 mäßig		Zeitintervall nach Behandlung
3 ausgeprägt		Effekt auf den Allgemeinzustand
4 lebensbedrohlich		Behandlungsnotwendigkeit
5 therapiebedingter Tod		Erreichen einer Verbesserung
Langzeittoxizität (=Sekundärerkrankungen nach Tumorthherapie)		
Langzeitnachsorge und regelmäßige Dokumentation (symptomorientiert nach ICPC <sup>3</sup> oder diagnoseorientiert nach ICD-10- GM <sup>4</sup> )		LoE 5 D AGO ++

## Akute Toxizität

1. WHO Handbook for reporting results of cancer treatment, N0 48 (1979) (WHO offset Publications, Geneva)
2. NCI, Bethesda, USA, Common Terminology Criteria for Adverse Events v5.0 (CTCAE; published 2017);  
[https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm#ctc\\_50](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50) (Download 18.01.2018)

## Akute Toxizität nach jedem Therapiezyklus abfragen


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

## Langzeittoxizität

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

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

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



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## Akute Toxizität (NCI CTCAE vs 5.0, 2017)

*(Allgemeine Terminologiekriterien unerwünschter Ereignisse)*

- **Grad 1**  
Mild; asymptomatisch oder wenig symptomatisch; lediglich klinische oder diagnostische Beobachtung; eine Intervention ist nicht indiziert.
- **Grad 2**  
Mäßig; minimale, lokale oder nicht-invasive Intervention notwendig; Beeinträchtigung des täglichen Lebens (wie Einkauf, Essenszubereitung etc. (*limiting age-appropriate instrumental ADL\**)).
- **Grad 3**  
Schwerwiegend oder medizinisch signifikant, aber nicht akut lebensbedrohlich; Klinikaufenthalt oder Verlängerung des Klinik-Aufenthaltes; physisch „außer Gefecht gesetzt“ (limiting self care ADL\*\*).
- **Grade 4**  
Lebensbedrohliche Folgen; eine Intervention ist dringend notwendig
- **Grad 5**  
Nebenwirkungsbedingter Tod

Activities of Daily Living (ADL)

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

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

1. NCI, Bethesda, USA, Common Terminology Criteria for Adverse Events v5.0 (CTCAE; published 2017); [https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm#ctc\\_50](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50) (Download 18.01.2018)



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- **Nebenwirkungshäufigkeiten  
(nach Angaben in den Fachinformationen  
gemäß MedDRA\*)**

\* MedDRA - Medical Dictionary for Regulatory Activities

\*MedDRA - Medical Dictionary for Regulatory Activities

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

# Chemotherapie – Akute Toxizitäten I

Substanz	Systemorganklasse											
	Infektionen und parasitäre Erkrank.	Neubildungen, sek. Malignome	Blut, Lymphsystem	Immunsystem, Allergien	Endokrine Erkrank- ungen	Stoffwechsel- und Ernährungs-Stör.	Psychiatrische Erkrankungen	Erkrankungen des Nervensystems	Augenerkrank.	Erkrank. des Ohrs und des Labyrinths	Herzerkrankungen	Gefäßerkrank.
<b>Alkylantien</b>												
Cyclophosphamid	4	2	5	5	1	-	1	3	2	3	3	3
<b>Antimetabolite</b>												
Methotrexat	1	-	4	3	3	-	3	4	2	-	1	2
5-Fluorouracil*	5	-	5	2	2	5	-	3	3	-	5	3
Capecitabin	4	3 (Lipom)	4	3	-	5	4	4	4	3	3	4
Gemcitabin	4	-	5	1	-	4	-	4	-	-	2	2
<b>Platin-Komplexe</b>												
Cisplatin	4	2	5	3	2	5	-	4	2	5	4	4
Carboplatin	4	-	5	4	-	-	-	4	4	4	4	-
<b>Anthrazykline / Anthrachinone</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	-
Mitoxantron	5	3	5	3	-	4	-	4	3	3	4	3
<b>Taxane</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>Andere Spindelgifte</b>												
Vinorelbin IV (PO)	5(5)	-	(5)	2(-)	-	-	(-5)	(-5)	(-4)	-	2(3)	3(4)
Eribulin	4	-	4	-	-	5	4	5	4	4	4	4

Die Liste und Graduierung der Nebenwirkungen ist nach Systemorganklassen, MedDRA-Terminologie und den folgenden Häufigkeitskategorien dargestellt:  
 1. Sehr selten (<1/10.000); 2. Selten (≥ 1/1.000 bis < 1/10.000); 3. Gelegentlich (≥ 1/1.000 bis < 1/100); 4. Häufig (≥ 1/100 bis < 1/10); 5. Sehr häufig (≥ 1/10).  
 - Nicht bekannt (Häufigkeit auf Grundlage der verfügbaren Daten nicht abschätzbar)

## Nebenwirkungskategorien - MedDRA (Medical Dictionary for Regulatory Activities)

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

[https://www.meddra.org/sites/default/files/guidance/file/intguide\\_20\\_1\\_english\\_0.pdf](https://www.meddra.org/sites/default/files/guidance/file/intguide_20_1_english_0.pdf)

## Quellen für die Fachinformationen (Download 19.01.2018)

Cyclophosphamid: [http://www.baxter.de/de\\_DE/assets/downloads/fachinformation/endoxan.pdf](http://www.baxter.de/de_DE/assets/downloads/fachinformation/endoxan.pdf)

Methotrexat: [https://www.gelbe-liste.de/produkte/MTX-HEXAL-10-mg-Tabletten\\_117469/fachinformation](https://www.gelbe-liste.de/produkte/MTX-HEXAL-10-mg-Tabletten_117469/fachinformation)

5-Fluorouracil: [https://www.gelbe-liste.de/produkte/Fluorouracil-HEXAL-50-mg-ml-Injektionsloesung-100-ml\\_546519/fachinformation](https://www.gelbe-liste.de/produkte/Fluorouracil-HEXAL-50-mg-ml-Injektionsloesung-100-ml_546519/fachinformation)

Capecitabin: <https://www.zentiva.de/Produkte/Capecitabin-Zentiva/Downloads?id=a63946ee-51ce-46ac-8184-a468b705ed9b>

Gemcitabin: <http://www.success-studie.de/b/downloads/Fachinfo/GemzarFI07Jan.pdf>

Cisplatin: [https://www.gelbe-liste.de/produkte/Cisplatin-Teva-1-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-100-ml\\_543960/fachinformation](https://www.gelbe-liste.de/produkte/Cisplatin-Teva-1-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-100-ml_543960/fachinformation)

Carboplatin: <http://www.teva.de/index.php?eID=dumpFile&t=f&f=37532&g=-1&r=11068%2C11068&token=eebfb22e78f1cc8d9935d59c087e80630146f49e>

Epirubicin:

Doxorubicin:

Liposomales Doxorubicin: [https://www.gelbe-liste.de/produkte/Myocet-50-mg-Pulver-Dispersion-u-Loesungsmittel-fuer-ein-Konzentrat-zur-Herstellung-einer-Infusionsdispersion\\_359323/fachinformation](https://www.gelbe-liste.de/produkte/Myocet-50-mg-Pulver-Dispersion-u-Loesungsmittel-fuer-ein-Konzentrat-zur-Herstellung-einer-Infusionsdispersion_359323/fachinformation)

PEG-lipo. Doxorubicin: [https://www.gelbe-liste.de/produkte/Caelyx-2-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-10-ml\\_121890/fachinformation](https://www.gelbe-liste.de/produkte/Caelyx-2-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-10-ml_121890/fachinformation)

Mitoxantron: [https://www.gelbe-liste.de/produkte/Mitoxantron-Teva-2-mg-ml-Injektionsloesung-15ml\\_543783/fachinformation](https://www.gelbe-liste.de/produkte/Mitoxantron-Teva-2-mg-ml-Injektionsloesung-15ml_543783/fachinformation)

Paclitaxel: <https://medikamio.com/de-de/medikamente/paclitaxel-ratiopharm/pil>

Nab-Paclitaxel: [https://www.gelbe-liste.de/produkte/Abbraxane-5-mg-ml-Pulver-zur-Herstellung-einer-Infusionssuspension\\_514889/fachinformation](https://www.gelbe-liste.de/produkte/Abbraxane-5-mg-ml-Pulver-zur-Herstellung-einer-Infusionssuspension_514889/fachinformation)

Docetaxel: <https://mein.sanofi.de/produkte/Taxotere/Downloads?id=89447754-dfb2-450b-b35a-36950de8a74d>

Vinorelbin: <http://www.detect-studien.de/dokumente/d3/fachinfo/Navelbine.pdf>

Eribulin: [http://www.detect-studien.de/dokumente/d4/fachinfo/Fachinfo\\_Eribulin\\_Halaven.pdf](http://www.detect-studien.de/dokumente/d4/fachinfo/Fachinfo_Eribulin_Halaven.pdf)

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1. Azim HA Jr, de Azambuja E, Colozza M, et al.: Long-term toxic effects of adjuvant chemotherapy in breast cancer. *Ann Oncol.* 2011 Sep;22(9):1939-47.
2. Petrelli F et al: Mortality, leukemic risk, and cardiovascular toxicity of adjuvant anthracycline and taxane chemotherapy in breast cancer: a meta-analysis. *Breast Cancer Res Treat.* 2012 Sep;135(2):335-46
3. Jim HS et al: Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. *J Clin Oncol.* 2012 Oct 10;30(29):3578-87
4. Cortes J, O'Shaughnessy J, Loesch D et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet.* 2011;377:914-23
5. Link, H. and S. Schmitz (2013). "Treatment of cancer-associated anaemia: results from a two-day cross-sectional survey in Germany." *Onkologie* 36(5): 266-272.
6. Fox P, Darley A, Furlong E, et al: The assessment and management of chemotherapy-related toxicities in patients with breast cancer, colorectal cancer, and Hodgkin's and non-Hodgkin's lymphomas: A scoping review. *Eur J Oncol Nurs.* 2017 Feb;26:63-82. doi:

- 10.1016/j.ejon.2016.12.008. Epub 2016 Dec 22.
7. Maeda S, Saimura M, Minami S, et al. Efficacy and safety of eribulin as first- to third-line treatment in patients with advanced or metastatic breast cancer previously treated with anthracyclines and taxanes. See comment in PubMed Commons below Breast. 2017 Jan 2;32:66-72. doi: 10.1016/j.breast.2016.12.017.
  8. Zhang XH, Hao S, Gao B, et al. A network meta-analysis for toxicity of eight chemotherapy regimens in the treatment of metastatic/advanced breast cancer. Oncotarget. 2016 Dec 20;7(51):84533-84543. doi: 10.18632/oncotarget.13023.
  9. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. Journal of Clinical Oncology 2011;29:4189- 4198
  10. Crawford J.
  11. NCCN, editor. NCCNR Practice Guidelines in Oncology - v.1.2011; Myeloid Growth Factors. National Comprehensive Cancer Network 2011. 18-7-2011.
  12. Madeddu C, Deidda M, Piras A, et al. Pathophysiology of cardiotoxicity induced by nonanthracycline chemotherapy. J Cardiovasc Med (Hagerstown). 2016 May;17 Suppl 1 Special issue on Cardiotoxicity from Antitubercular Drugs and Cardioprotection:e12-e18. Review.

## Chemotherapie – Akute Toxizitäten II

Substanz	Systemorganklasse										Besonderheiten
	Ehr. d. Atemwege, Brustraum, Mediast.	Ehr. d. GI-Traktes (Übelk./Erbrechen)	Leber- und Gallenerkrankungen	Ehr. d. Haut/Unterhaut (inkl. Alopecia)	Skelettmyos.- Bindegew.- u. Knochenmhr.	Ehr. der Nieren und Harnwege	Schwang.-, Wochenbett u. perinatale E.	Ehr. d. Geschlechtsorgane u. Brustdrüse	Allg. Ehr. u. Beschw. am Applikationsort	Kongenit., famili. und genet. Ehr.	
<b>Alkylantien</b>											
Cyclophosphamid	2	4	4	5	-	5	-	4	5	-	Hyponatriämie
<b>Antimetabolite</b>											
Methotrexat	4	5	5	4	3	3	-	3	1	-	Mukositis, Risiko "third space"-Toxizität
5-Fluorouracil	5	5	3	5	-	-	-	-	5	-	Risiko DPD-Mangel: leicht 5%, schwer 0,1%; Diarrhoe, Herz
Capecitabin	4	5	4	5	4	3	-	3	5	-	Hand-Fuß-Syndrom (HFS), Risiko DPD-Mangel; Herz
Gemcitabin	5	5	5	5	4	5	-	-	5	-	Flu-like Symptome, Ödeme, Herz
<b>Platin-Komplexe</b>											
Cisplatin	4	5	4	4	-	5	-	3	5	-	Nierentoxizität, Ototoxizität, CIPN
Carboplatin	4	5	-	4	4	4	-	-	4	-	Kollitis, (Nierentox.)
<b>Anthrazykline / Anthrachinone</b>											
Epi-/Doxorubicin	2	5	-	5	1	4	-	1	5	-	Kardiotoxizität (CHF), sek. Malignome, Paravast
Lipo. Doxorubicin	4	5	4	5	4	3	-	(4)	5	-	
PEG-lipo. Doxo.	4	5	-	5	4	-	-	4	5	-	Palmares und plantares Erythem (PPE)
Mitoxantron	4	5	3	5	-	3	-	3	4	-	Sek. AML, Kardiomyopathie
<b>Taxane</b>											
Paclitaxel	2	5	1	5	5	-	-	-	5	-	Periphere Neuropathie (CIPN); Hypersensit., Myalgien
nab-Paclitaxel	4	5	3	5	5	3	-	3	5	-	Periphere Neuropathie (CIPN)
Docetaxel	5	5	-	5	5	-	-	-	5	-	Fluid retention, Paronychie, Kolitis, Myalgie
<b>Andere Spindelgifte</b>											
Vinorelbin 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	-	Obstipation, CIPN

Die Liste und Graduierung der Nebenwirkungen ist nach Systemorganklassen, MedDRA-Terminologie und den folgenden Häufigkeitskategorien dargestellt:  
 1. Sehr selten (<1/10.000); 2. Selten (≥ 1/1.000 bis < 1/10.000); 3. Gelegentlich (≥ 1/1.000 bis < 1/100); 4. Häufig (≥ 1/100 bis < 1/10); 5. Sehr häufig (≥ 1/10).  
 - Nicht bekannt (Häufigkeit auf Grundlage der verfügbaren Daten nicht abschätzbar)

### Abkürzungen

AML = Akute myeloische Leukämie; DPD = Dihydropyrimidin-Dehydrogenase); CHF = Kardiomyopathie; CIPN = Chemotherapie induzierte periphere Neuropathie; HFS = Hand-Fuß-Syndrom; PPE = Palmares und plantares Erythem.

### Nebenwirkungskategorien - MedDRA (Medical Dictionary for Regulatory Activities)

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

[https://www.meddra.org/sites/default/files/guidance/file/intguide\\_20\\_1\\_english\\_0.pdf](https://www.meddra.org/sites/default/files/guidance/file/intguide_20_1_english_0.pdf)

### Quellen für die Fachinformationen (Download 19.01.2018)

Cyclophosphamid: [http://www.baxter.de/de\\_DE/assets/downloads/fachinformation/endoxan.pdf](http://www.baxter.de/de_DE/assets/downloads/fachinformation/endoxan.pdf)

Methotrexat: [https://www.gelbe-liste.de/produkte/MTX-HEXAL-10-mg-Tabletten\\_117469/fachinformation](https://www.gelbe-liste.de/produkte/MTX-HEXAL-10-mg-Tabletten_117469/fachinformation)

5-Fluorouracil: [https://www.gelbe-liste.de/produkte/Fluorouracil-HEXAL-50-mg-ml-Injektionsloesung-100-ml\\_546519/fachinformation](https://www.gelbe-liste.de/produkte/Fluorouracil-HEXAL-50-mg-ml-Injektionsloesung-100-ml_546519/fachinformation)


Capecitabin: <https://www.zentiva.de/Produkte/Capecitabin-Zentiva/Downloads?id=a63946ee-51ce-46ac-8184-a468b705ed9b>

Gemcitabin: <http://www.success-studie.de/b/downloads/Fachinfo/GemzarFI07Jan.pdf>  
 Cisplatin: [https://www.gelbe-liste.de/produkte/Cisplatin-Teva-1-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-100-ml\\_543960/fachinformation](https://www.gelbe-liste.de/produkte/Cisplatin-Teva-1-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-100-ml_543960/fachinformation)  
 Carboplatin: <http://www.teva.de/index.php?elD=dumpFile&t=f&f=37532&g=-1&r=11068%2C11068&token=eebf22e78f1cc8d9935d59c087e80630146f49e>  
 Epirubicin:  
 Doxorubicin:  
 Liposomales Doxorubicin: [https://www.gelbe-liste.de/produkte/Myocet-50-mg-Pulver-Dispersion-u-Loesungsmittel-fuer-ein-Konzentrat-zur-Herstellung-einer-Infusionsdispersion\\_359323/fachinformation](https://www.gelbe-liste.de/produkte/Myocet-50-mg-Pulver-Dispersion-u-Loesungsmittel-fuer-ein-Konzentrat-zur-Herstellung-einer-Infusionsdispersion_359323/fachinformation)  
 PEG-lipo. Doxorubicin: [https://www.gelbe-liste.de/produkte/Caelyx-2-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-10-ml\\_121890/fachinformation](https://www.gelbe-liste.de/produkte/Caelyx-2-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-10-ml_121890/fachinformation)  
 Mitoxantron: [https://www.gelbe-liste.de/produkte/Mitoxantron-Teva-2-mg-ml-Injektionsloesung-15ml\\_543783/fachinformation](https://www.gelbe-liste.de/produkte/Mitoxantron-Teva-2-mg-ml-Injektionsloesung-15ml_543783/fachinformation)  
 Paclitaxel: <https://medikamio.com/de-de/medikamente/paclitaxel-ratiopharm/pil>  
 Nab-Paclitaxel: [https://www.gelbe-liste.de/produkte/Abbraxane-5-mg-ml-Pulver-zur-Herstellung-einer-Infusionssuspension\\_514889/fachinformation](https://www.gelbe-liste.de/produkte/Abbraxane-5-mg-ml-Pulver-zur-Herstellung-einer-Infusionssuspension_514889/fachinformation)  
 Docetaxel: <https://mein.sanofi.de/produkte/Taxotere/Downloads?id=89447754-dfb2-450b-b35a-36950de8a74d>  
 Vinorelbin: <http://www.detect-studien.de/dokumente/d3/fachinfo/Navelbine.pdf>  
 Eribulin: [http://www.detect-studien.de/dokumente/d4/fachinfo/Fachinfo\\_Eribulin\\_Halaven.pdf](http://www.detect-studien.de/dokumente/d4/fachinfo/Fachinfo_Eribulin_Halaven.pdf)

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# Endokrine Therapie – Toxizitäten

Substanz	<div> <div>Infektionen und parasitäre Erkrank.</div> <div>Neubildungen, sek. Malignome</div> <div>Blut, Lymphsystem</div> <div>Immunsystem, Allergien</div> <div>Endokrine Erkrankungen</div> <div>Stoffwechsel- und Ernährungs-Stör.</div> <div>Psychiatrische Erkrankungen</div> <div>Erkrankungen des Nervensystems</div> <div>Augenerkrank.</div> <div>Erkrank. des Ohrs und des Labyrinths</div> <div>Herzkrankungen</div> <div>Gefäßkrank. (inkl. Hitzewall.)</div> </div>												
SERM													
Tamoxifen	-	3	4	-	3	5	-	4	4	-	-	4	
AI													
Anastrozol	-	-	-	-	-	4	5	5	4	-	4	5	
Exemestan	-	-	4	-	-	4	5	4	4	-	-	4	5
Letrozol	3	-	3	-	-	5	4	4	3	-	3	5	
SERD													
Fulvestrant	4	-	3	4	-	4	-	4	-	-	-	4	
Substanz	Erkr. d. Atemwege, Thorax, Mediastin.	Erkrankungen des Gastrointestinaltr.	Leber- und Gallenerkrankungen	Erkr. Haut u. Unterhautgewebes	Skelettmus-, Bindegew.-u. Knochenkr.	Erkr. der Nieren und Harnwege	Schwang., Wochenbett u. perinatale E.	Erkr. d. Geschlechtsorgane / Brustdrüse	Allg. Erkr. u. Besch. am Applikationsort	Kongenit., famil. und genet. Erkr.	Besonderheiten		
SERM													
Tamoxifen	3	5	4	5	4	-	-	5	5	1	Hitzewallungen, selten: EndometriumCa (>55 J.); Thrombose		
AI													
Anastrozol	-	5	4	5	5	-	-	5	5	-	Hitzewallungen, Arthralgie, Osteoporose; Kognition		
Exemestan	5	5	5	5	5	-	-	5	5	-	Hitzewallungen, Arthralgie, Osteoporose; Kognition		
Letrozol	3	4	3	5	5	3	-	4	5	-	Hitzewallungen, Arthralgie, Osteoporose; Kognition		
SERD													
Fulvestrant	-	5	5	4	4	4	-	3	5	-	Hitzewallungen		

Die Liste und Graduierung der Nebenwirkungen ist nach Systemorganklassen, MedDRA-Terminologie und den folgenden Häufigkeitskategorien dargestellt:

1. Sehr selten (<1/10.000); 2. Selten (≥ 1/1.000 bis < 1/10.000); 3. Gelegentlich (≥ 1/1.000 bis < 1/100); 4. Häufig (≥ 1/100 bis < 1/10); 5. Sehr häufig (≥ 1/10).

- Nicht bekannt (Häufigkeit auf Grundlage der verfügbaren Daten nicht abschätzbar)

## Nebenwirkungskategorien - MedDRA (Medical Dictionary for Regulatory Activities)

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

[https://www.meddra.org/sites/default/files/guidance/file/intguide\\_20\\_1\\_english\\_0.pdf](https://www.meddra.org/sites/default/files/guidance/file/intguide_20_1_english_0.pdf)

## Quellen für die Fachinformationen (Download 19.01.2018)

Tamoxifen: [https://www.gelbe-liste.de/produkte/Tamoxifen-20-mg-HEXAL-Filmtbl\\_8660/fachinformation](https://www.gelbe-liste.de/produkte/Tamoxifen-20-mg-HEXAL-Filmtbl_8660/fachinformation)

Anastrozol: <https://imedikament.de/anastrozol-ratiopharm-1-mg-filmtabletten/fachinformation>

Exemestan: [http://www.success-studie.de/c/downloads/Fachinfo/FI\\_ExemestanAromasin.pdf](http://www.success-studie.de/c/downloads/Fachinfo/FI_ExemestanAromasin.pdf)

Letrozol: [http://www.success-studie.de/b/downloads/Fachinfo/Femara\\_Juli\\_2014.pdf](http://www.success-studie.de/b/downloads/Fachinfo/Femara_Juli_2014.pdf)

Fulvestrant: [https://www.gelbe-liste.de/produkte/Fulvestrant-HEXAL-250-mg-Injektionsloesung-in-einer-Fertigspritze\\_912622/fachinformation](https://www.gelbe-liste.de/produkte/Fulvestrant-HEXAL-250-mg-Injektionsloesung-in-einer-Fertigspritze_912622/fachinformation)

# Nebenwirkungen nach Organsystemen

## Inzidenz, Prävention, Therapie

### 1. Infektionen u. parasitäre Erkrankungen

- Allgemeine Infektionsprophylaxe
- Hepatitis B-Screening



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## Allgemeine Infektionsprophylaxe

### NB nur selten für solide Tumoren wie MaCa anwendbar

#### ASCO Practice Guideline „Antimicrobial Prophylaxis...” 2013

	Oxford		
	LoE	GR	AGO
▪ Vermeidung von besonders infektionsbegünstigenden Faktoren/Umgebungen	5	D	+
▪ Prophylaktische Therapie in Low-Risk-Patienten	1a	B	-
▪ Prophylaktische Therapie bei Hochrisikopatienten* (z.B. gemäß NCCN-Leitlinien) mit:			
▪ Antibiotika	1a	A	++
▪ Antimykotika (Triazol-Antimykotika)	1a	B	+/-
▪ Virostatika bei soliden Tumoren	5	D	-
▪ Granulopoese-stimulierende Faktoren	1a	A	++


\* Definition Hochrisiko: vermutete Neutropeniedauer < 100/μl ≥ 7d

#### ASCO:

1. Flowers CR et al. Antimicrobial Prophylaxis and Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy\_Journal of Clinical Oncology, Vol 31, Issue 3 (February), 2013: 794-810. <https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/supportive-care-and-treatment-related-issues#/9966>

#### NCCN:

1. NCCN Guidelines Version 1.2018: Prevention and Treatment of Cancer-Related Infections. [https://www.nccn.org/professionals/physician\\_gls/pdf/infections.pdf](https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf)



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MAMMA

# Hepatitis B-Screening vor Chemotherapie

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- Hepatitis B-Screening vor Beginn einer Chemotherapie (HBsAG, anti-HBC)

Oxford		
LoE	GR	AGO
2c	B	+

## Bei Reaktivierung bzw. bei positiver Serologie

- Unterbrechung der Chemotherapie
- Prophylaktische Therapie mit Virustatika bei Nachweis von HBV-DNA (entsprechend AGIHO/DGHO – Empfehlungen)

5	D	++
1b	A	++

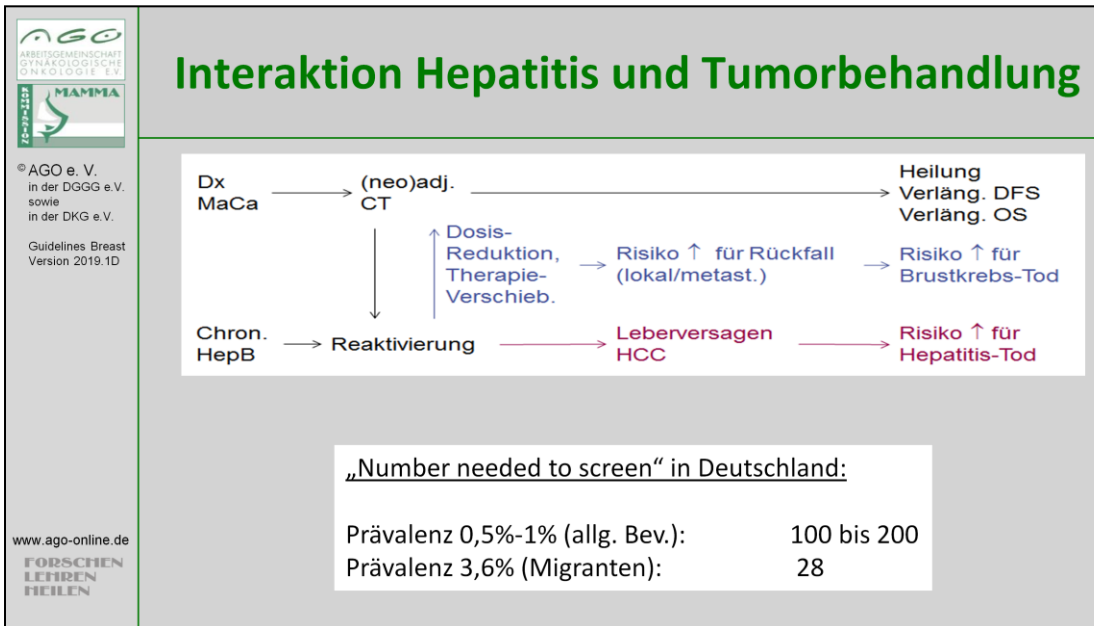
- Hepatitis C-Screening vor Beginn einer Chemotherapie

5	D	+/-
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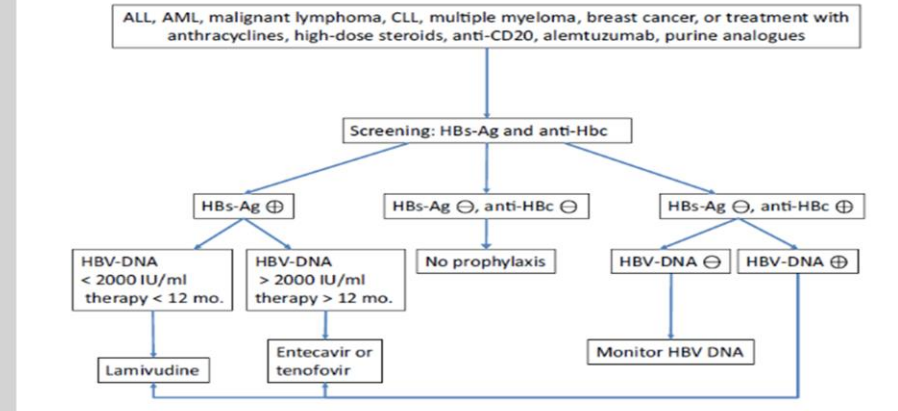
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1. Wong WW, Hicks LK, Tu HA et al. Hepatitis B virus screening before adjuvant chemotherapy in patients with early-stage breast cancer: a cost-effectiveness analysis. Breast Cancer Res Treat. 2015 Jun;151(3):639-52.

## AGIHO / DGHO – Empfehlungen zum Hepatitis B-Screening in der Onkologie



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# Internationale Screening Empfehlungen – Hepatitis B

## Recommendations of Various Authoritative Bodies Regarding Screening for Hepatitis B to Mitigate the Risk of HBV Reactivation

Organization	Recommendation	Tests to Be Done
Centers for Disease Control and Prevention	Persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic or gastroenterologic disorders	HBsAg, anti-HBc, anti-HBs
American Academy of Dermatology	Hepatitis B reactivation after treatment with tumor necrosis factor inhibitors has been reported; in the appropriate clinical setting, patients should be screened for hepatitis B infection.	Not stated
American Association for the Study of Liver Diseases	All patients before beginning immunosuppressive therapy	HBsAg, anti-HBc
Asian Pacific Association for the Study of the Liver	Before receiving immunosuppression or chemotherapy, patients should be screened for HBsAg. Patients who are going to receive biologic agents such as anti-CD20 or anti-tumor necrosis factor-α should be screened for anti-HBc.	HBsAg, anti-HBc
European Association for the Study of the Liver	All candidates for chemotherapy and immunosuppressive therapy should be screened.	HBsAg, anti-HBc
American Society of Clinical Oncology	Physicians may consider screening patients belonging to groups at heightened risk for chronic HBV infection or if highly immunosuppressive therapy is recommended.	Consider HBsAg, consider anti-HBc
US Preventive Services Task Force	Screen persons who are immunosuppressed.	HBsAg


**Di Bisceglie AM et al. Hepatology. 2015 Feb;61(2):703-11.**

1. Di Bisceglie AM, Lok AS, Martin P, et al. Recent US Food and Drug Administration warnings on hepatitis B reactivation with immune-suppressing and anticancer drugs: just the tip of the iceberg? Hepatology. 2015 Feb;61(2):703-11.
2. <https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/supportive-care-and-treatment-related-issues#/9811>
3. European Association For The Study Of The Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol. 2012 Jul;57(1):167-85.
4. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017 Aug;67(2):370-398.

# Nebenwirkungen nach Organsystemen

## Inzidenz, Prävention, Therapie

### 2. Gutartige, bösartige und nicht spezifizierte Neubildungen (einschl. Zysten und Polypen)

 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1D</p> <p>www.ago-online.de FORSCHEN LEHREN HEILEN</p>	Sekundäre Malignome I	
<ul style="list-style-type: none"> <li>▪ Die Induktion von soliden, malignen Tumoren durch Chemotherapie ist selten</li> <li>▪ Alkylantien erhöhen dosisabhängig das Risiko für Leukämien auf 0,2 – 0,4 % innerhalb von 10 - 15 Jahren</li> <li>▪ Anthrazyklinhaltige Regime erhöhen das Risiko für MDS und Leukämie auf 0,2 – 1,7 % innerhalb von 8 - 10 Jahren</li> <li>▪ PARP-Inhibitoren sind assoziiert mit einem erhöhten Risiko für AML und MDS von 0.5-1%</li> <li>▪ Radiotherapie erhöht das Risiko einer Leukämie bei Pat. mit einer anthrazyklinhaltigen Therapie um 0,2 – 0,4 %</li> <li>▪ Tamoxifen verdoppelt das Risiko für die Entwicklung eines Endometriumkarzinoms (bei Therapiebeginn ab 55. Lj.)</li> </ul>	Oxford	
	LoE	GR
		2a
		2a
		2a
		2b
		2b
		2b


#### Statements 1-4

1. Schaapveld M, Visser O, Louweman M et al.(2008) Risk of primary non breast cancers after breast cancer treatment: a dutch population-based study. J Clin Oncol 26: 1239-46.
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4. Beadle G, Baade P, Fritschi L(2009) Acute myeloid leukemia after breast cancer: a population-based comparison with hematological malignancies and other cancers. Ann Oncol 20: 103-9.
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## Sekundäre Malignome II (nach Radiotherapie)

Oxford  
LoE

<ul style="list-style-type: none"> <li>▪ Eine Radiotherapie (PMRT, BET) kann das Risiko für ein ipsilaterales Lungenkarzinom und Angiosarkom mäßiggradig anheben (10–15/10.000) (Aufreten 5–10 Jahre nach PMRT)</li> <li>▪ Erhöhtes Risiko besonders für Raucher</li> <li>▪ Kein Unterschied bezgl. sekundärer Malignome zwischen PBI (Teil-) und WBI (Ganzbrustbestrahlung)</li> </ul>	<p style="color: green;">1a</p> <p style="color: green;">2b</p> <p style="color: green;">2c</p>
-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------

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Nov;55(11):1331-1337. Epub 2016 Jul 5.

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# Nebenwirkungen nach Organsystemen

## Inzidenz, Prävention, Therapie

### 3. Erkrankungen des Blutes und des Lymphsystems

- Anämie
- Neutropenie
- Febrile Neutropenie

## Anämie – Indikationen für den Einsatz von Erythropoese-stimulierenden Faktoren (ESF)


	Oxford		
	LoE	GR	AGO
▪ Indiziert bei asymptomatischer Anämie	1a	B	-
▪ Therapie und sekundäre Prophylaxe bei CT-induzierter Anämie	1a	A	+
▪ Adjuvante Situation	1b	A	+
▪ Neoadjuvante/metastasierte Situation	1a	A	+/-
▪ Bei dosisdichter/dosiseskalierter CT (iddETC)	1b	A	+
▪ Therapie beginnt bei Hb-Werten < 10g/dl	1a	A	+
▪ Ziel-Hb 11–12 g/dL	1a	A	+
▪ Verbesserung der Prognose (krankheitsfreies Intervall, Gesamtüberleben)	1a	B	--
▪ ESF erhöht das Risiko von thromboembolischen Komplikationen	1a	A	

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## Phase III Study of Epoetin Alfa Versus Best Standard of Care in Anemia Patients with Metastatic Breast Cancer

**N=2.098 Pat., Hb <11g/dl; non inferiority study.**  
**Prespecified upper non inferiority margin = 1.15**

	PFS (median)		OS (median)	ORR	RBC transfusions	TVE
<b>Epo</b>	Invest.* 7,4 Mon	IRC** 7,6 Mon	17,2 Mon	50%	5,8%	2,8%
<b>BSC</b>	7,4 Mon.	7,6 Mon.	17,4 Mon	51%	11,4%	1,4%
	HR: 1,09	HR: 1,02	HR: 1,06	OR: 0,95	p<.001	p=.04
	Upper CI: 1,20	Upper CI: 1,146				

\* Investigator determined  
\*\* Independent review committee

1. Leyland-Jones B, Bondarenko I et al. J Clin Oncol 2016 (34): 1197-1209



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## Praktischer Umgang mit ESF

- **Epoetin α und Darbepoetin sind äquieffektiv**
- **Dosierungen:**
  - Epoetin α: 150 IU/kg 3 x wöchentlich s.c. oder  
40.000 IU 1 x / Woche s.c. oder  
80.000 IU alle 2 Wochen s.c. oder  
120.000 IU alle 3 Wochen s.c.
  - Epoetin β: 30.000 IE 1x /Woche s.c.
  - Darbepoetin: 2,25 µg/kg s.c. wöchentlich oder  
500 µg s.c. alle 3 Wochen
- **Hb-Messungen wöchentlich**
  - Dosisreduktion bei Hb-Anstieg > 1 g/dl innerhalb von 2 Wo.
  - Dosissteigerung bei Hb-Anstieg < 1 g/dl innerhalb von 4–6 Wo.
- **Bei FED (“funktioneller Eisenmangel”) Eisensubstitution präferentiell i.v.**
- **Abbruch der ESF-Gabe bei ausbleibenden Hb-Anstieg nach 9 Wo.**

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Granulozyten-Kolonie-stimulierende Faktoren			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>Primäre Prophylaxe für eine zu erwartende febrile Neutropenie (FNP) <ul style="list-style-type: none"> <li>Bei Risiko für FNP 10–20 % <ul style="list-style-type: none"> <li>Im Falle zusätzlicher individueller Risiken</li> </ul> </li> <li>Bei FNP-Risiko &gt; 20 % (e.g. DAC, dosisdichte CT)</li> </ul> </li> <li>Sekundäre Prophylaxe während der Chemotherapie (frühere FNP oder Neutropenie Grad IV &gt; 7 Tage)</li> <li>Therapeutischer Nutzen bei FNP</li> <li>Beginn der Therapie in Verbindung mit Art und Dauer der Chemotherapie <ul style="list-style-type: none"> <li>Pegfilgrastim Tag 2</li> <li>Lipegfilgrastim Tag 2</li> <li>Filgrastim/Lenograstim von Tag 2–5 bis absolute Neutrophilenzahl &gt; 2–3 x 10<sup>9</sup></li> </ul> </li> </ul>			
	1b	B	+/-
	3b	C	+
	1a	A	++
	1b	A	++
	1a	A	+/-
	1b	A	++
	1b	A	++
	1b	A	++



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## Relevante Leitlinien


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## Statements 1-4

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## Management der febrilen Neutropenie

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)  
(H. Link et al: erstellt 04/07)

**Definition** (orale Temp. > 38,5° C oder zwei konsekutive Messungen > 38° C über 2 h in einer Patientin mit einem ANC < 500 cells/mm<sup>3</sup> oder erwarteter Abfall < 500 cells/mm<sup>3</sup>)

	Oxford		
	LoE	GR	AGO
▪ Klinische Untersuchung	5	D	++
▪ Tägliche Kontrollen	5	D	++
▪ Hospitalisierung von Hochrisikopatienten	1b	A	++
▪ Ambulante Therapie bei Niedrigrisikopat. möglich	1b	A	+
▪ Differentialblutbild	5	D	++
▪ Blutkulturen	5	D	++
▪ Bildgebung der Lunge	3	C	++
▪ Sofortige empirische antibiot. Therapie	1a	A	++
▪ Empirische antimykotische Therapie nach 4-7d bei keiner Besserung unter der antibiotischen Therapie	1b	A	++
▪ G-CSF als therapeutische Maßnahme	2b	B	+/-

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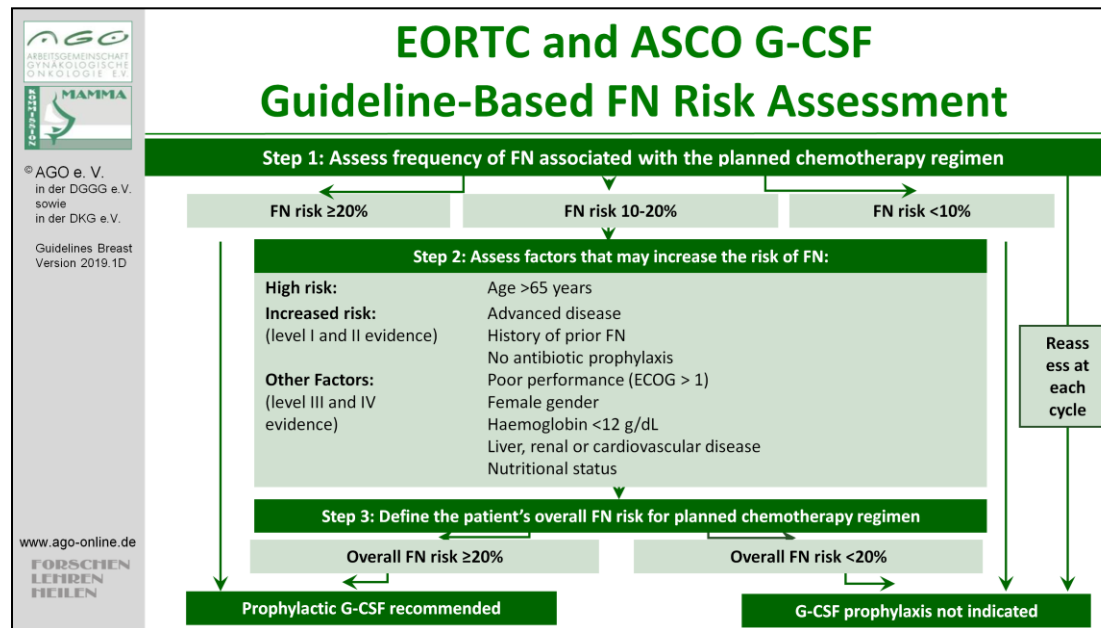
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## Empirische Antibiotikatherapie

**Die Empfehlungen zur empirischen Antibiotikatherapie unterliegen einem infektionsbiologisch bedingten Wechsel und bedürfen der beständigen fachkundigen Anpassung.**

Die 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) gibt aktuelle Hinweise.



### EORTC and ASCO G-CSF Guideline-Based FN Risk Assessment (Folie 29/81)

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# Nebenwirkungen nach Organsystemen

## Inzidenz, Prävention, Therapie

### 4. Endokrine Erkrankungen

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	<ul style="list-style-type: none"> <li>▪ Eine CRA kann dauerhaft oder vorübergehend sein (abhängig vom Alter der Pat. und der Art der Chemotherapie)</li> <li>▪ Das Risiko der CRA steigt mit dem Alter / Therapiedauer</li> <li>▪ CRA ist ein (unsicherer) Surrogatmarker für Menopause und Fertilität</li> <li>▪ Eine adjuvante endokrine Therapie mit einem GnRHa induziert eine reversible Amenorrhoe, und verschiebt eine Konzeption in eine weniger fertile Phase</li> <li>▪ Die Ovarialreserve der nach Chemotherapie prämenopausal gebliebenen Frauen ist reduziert</li> <li>▪ CRA ist mit einer verbesserten Prognose (DFS/OS) assoziiert</li> </ul> <p>Synonyma: Chemotherapie / Therapie-induzierte Amenorrhoe (TIA/CIA)</p>	<p><b>Oxford LoE</b></p> <p><b>2b</b></p> <p><b>2b</b></p> <p><b>5</b></p> <p><b>5</b></p> <p><b>2b</b></p> <p><b>1b</b></p>

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# Nebenwirkungen nach Organsystemen

## Inzidenz, Prävention, Therapie

### 5. Psychiatrische Erkrankungen

- Depression
- Fatigue
- Kognitive Störungen
- Schlafstörungen

	(Therapie assoziierte) Depression		
	LoE	GR	AGO
 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<ul style="list-style-type: none"> <li>Depressive Episoden bei 20–30% der Mammakarzinompatientinnen</li> <li>Psychosoziale Interventionen verbessern Depression, allerdings ohne günstige Auswirkungen auf Mortalität</li> <li>Antidepressiva können Depression bei Brustkrebspatientinnen verbessern</li> <li>Körperliches Training kann Depression bei Brustkrebspatientinnen verhindern</li> </ul>	<p>2a</p> <p>1b</p> <p>1b</p> <p>2b</p>	<p>B</p> <p>A</p> <p>A</p> <p>B +</p>

#### Statements 1-4

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(Therapie assoziierte) Fatigue			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>Fatigue häufiges Symptom bei Brustkrebspatientinnen (30–60%)</li> </ul>	2a	B	
<ul style="list-style-type: none"> <li>Ausschluss anderer Ursachen (Anämie, Tumorausdehnung, Begleiterkrankungen, Medikamente) für Fatigue</li> </ul>	1a	A	++
<ul style="list-style-type: none"> <li>Gezielte psychosoziale Interventionen können Fatigue lindern</li> </ul>	1a	A	++
<ul style="list-style-type: none"> <li>Körperliches Training kann Fatigue verbessern</li> </ul>	1b	D	+
<ul style="list-style-type: none"> <li>Diät, Yoga können Fatigue verbessern</li> </ul>	2b	B	+
<ul style="list-style-type: none"> <li>Methylphenidate kann Fatigue verbessern</li> </ul>	1a	D	+



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	(Therapie-assoziierte) Kognitive Störungen	
	LoE	GR
<ul style="list-style-type: none"> <li>Therapiebedingte kognitive Störungen (sog. „Chemobrain“) häufig beschrieben (16–75%)</li> <li>Verhaltenstherapie kann kognitive Funktion verbessern</li> <li>Methylphenidate kann kognitive Funktion bei Patientinnen mit Krebs verbessern</li> <li>Unter Aromatasehemmertherapie wurden kognitive Störungen beobachtet (insbes. Wortgedächtnis)</li> </ul>	2a	B
	2b	B
	3a	C
	1a	B

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

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#### Verhaltenstherapie kann kognitive Funktion verbessern

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### Methylphenidate kann kognitive Funktion bei Patientinnen mit Krebs verbessern

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### Unter Aromatasehemmertherapie wurden kognitive Störungen beobachtet

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## (Therapie assoziierte) Schlafstörungen

Oxford		
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2a	B	
1b	A	++

- **Schlafstörungen häufig bei Mammakarzinom-patientinnen während und nach Therapie beschrieben (20–70%)**
- **Verhaltenstherapie ist effektiv in der Behandlung von Schlafstörungen und Steigerung der Lebensqualität**

### Sleep disturbances are a common problem....

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Behavioral therapies have demonstrated efficacy.....


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# Nebenwirkungen nach Organsystemen

## Inzidenz, Prävention, Therapie

### 6. Erkrankungen des Nervensystems

- Chemotherapie induzierte periphere Neuropathie (CIPN)



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## Chemotherapie-induzierte periphere Neuropathie (CIPN)

- Inzidenz Grad 1–2 nach Taxanen 20–50 %
- Inzidenz Grad 3–4 nach Taxanen 6–20 %
- Risikofaktoren: Art der Chemotherapie, Dosierung, BMI, fehlende körperliche Aktivität
- Individuelle Risikofaktoren
  - Diabetes mellitus
  - Nutritiv toxische Substanzen ins. Alkohol
  - Niereninsuffizienz
  - Hypothyreose
  - Kollagenosen / Vaskulitiden
  - Vitaminmangel
  - HIV-Infektion
  - CMT-Genmutation
- Unklar:
  - Andere genetische Faktoren (SNP, Mutationen)

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# Chemotherapie-induzierte periphere Neuropathie – Prävention –

	Oxford		
	LoE	GR	AGO
<b><u>Nicht-medikamentöse Prävention</u></b>			
▪ Funktionstraining (Fitness, sensomotorisches Stimulationstraining etc.)	5	D	+
▪ Kompressionstherapie (chirurgische Handschuhe, Kompressionsstrümpfe)	2b	B	+
▪ Kühllhandschuhe und Kühlstrümpfe	2b <sup>a</sup>	B	+/-
▪ Elektro-Akupunktur	1b	B	-

## **Medikamentöse Prävention**

▪ Venlafaxin	2a	C	+/-
▪ Palmitoylethanolamid (PEA) topisch oder p.o.	5	D	+/-
▪ Alpha-Liponsäure, Amifostin, Amitriptylin, Acetyl-L-Carnitin, Carbamazepin, Elektrolytlösungen, Glutathion, Goshajinkigan (GJG), Oxcarbazepin, Vitamin B, Vitamin E oder andere Substanzen <sup>1</sup>	1b	A	-

<sup>1</sup> Liste nicht empfohlener Medikamente bei Hershman et al. 2014

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	Oxford		
	LoE	GR	AGO
<b><u>Nicht-medikamentöse Therapie</u></b>			
▪ Funktionstraining (Fitness, sensomotorisches Stimulationstraining etc.)	2a	C	+
▪ Physiotherapie / physikalische Therapie	5	D	+
<b><u>Medikamentöse Therapie</u></b>			
▪ Menthol lokal (1%), Capsaicin/Lidocain lokal	5	D	+
▪ Baclofen/Amitriptylin/Ketamin-Creme	2b	B	+
▪ Duloxetine zur Behandlung von Schmerzen durch CIPN	1b	B	+
▪ Opioide zur Behandlung von Schmerzen durch CIPN	5	D	+
▪ Palmitoylethanolamid (PEA) topisch oder p.o.	5	D	+/-
▪ Venlafaxin	5	D	+/-
▪ Gabapentin, Pregabalin	1b	B	+/-
▪ Amitriptylin/ Nortriptylin, Imipramin/Desipramin	1b	B	+/-
▪ Acetyl-L-Carnitin, Lamotrigin oder andere Substanzen <sup>1</sup>	1b	B	-
<sup>1</sup> Liste nicht empfohlener Medikamente bei Hershman et al. 2014			

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#### *Opioide*

#### *Palmitoylethanolamid (PEA)*

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# Nebenwirkungen nach Organsystemen

## Inzidenz, Prävention, Therapie

### 7. Herzerkrankungen

Langzeittoxizität Kardiotoxizität			
	Oxford		
	LoE	GR	AGO
▪ Äquivalente Kardiotoxizität von Doxorubicin und Epirubicin in den empfohlenen Dosierungen (450-500 bzw. 900-1000 mg/m <sup>2</sup> kum. Dosis)	2b	B	
▪ Weniger Kardiotoxizität nach liposomalem Doxorubicin	1b	B	
▪ Risikofaktoren für Anthrazyklin- oder Trastuzumab-assoziierte Kardiotoxizität	2b	B	
▪ Alter, Übergewicht, Hypertonus, Hypercholesterinämie, Vorbestehende Herzerkrankungen (inkl. grenzwertige LVEF), Diabetes mellitus			
Überwachung der Herzfunktion:			
▪ Standardisierte Echokardiographie (LVEF oder SF in %)	3b	C	+
▪ Troponin I als Marker für Kardiotoxizität	2b	B	+/-
▪ Betablocker-Prophylaxe während Anthrazyklin-Therapie	2a	B	+/-



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## Statements

“Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m<sup>2</sup> cum. dose, resp.)”

“Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity”

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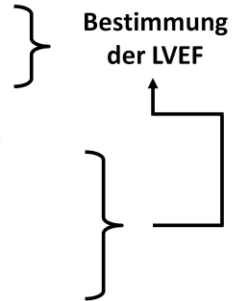
## Trastuzumab Adjuvant Überwachung hinsichtlich CHF

**Oxford LoE: 5**
**GR: D**
**AGO: ++**

**Vor Beginn der Trastuzumab-Therapie**

- Anamnese, klinische Untersuchung (Ödeme, Hepatomegalie)
- Echokardiographie (Alternative zu MUGA)

**Bestimmung der LVEF**



**Während und nach der Trastuzumab-Therapie**

Regelmäßige Dokumentation von


- Herzfrequenz; bei Anstieg > 15 % über das individuelle Ausgangsniveau
- Körpergewicht; bei Anstieg ≥ 2 kg/Woche
- Kardiale Zeichen und Symptome

**LVEF alle 3 Monate**

Statement: Cardiac Monitoring (5 D ++)

Vote result of the AGO recommendation: 100%

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

	Oxford		
	LoE	GR	AGO
<b><u>Kardiale Toxizität</u></b>			
▪ Trastuzumab simultan zur Radiotherapie	2b	B	+
▪ Trastuzumab simultan zu Epirubicin	2b	B	+/-
▪ Trastuzumab simultan zu Doxorubicin	2b	B	-
▪ Anthrazykline simultan zur Radiotherapie	2c	C	-
<b><u>Risiko Lungen- / Brustparenchymfibrosen</u></b>			
▪ Tamoxifen simultan zu Radiotherapie	3	C	+/-
▪ Chemotherapie simultan zu Radiotherapie	1b	B	-

### “Trastuzumab simultaneous to radiotherapy”

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

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“Trastuzumab simultaneous to doxorubicin”

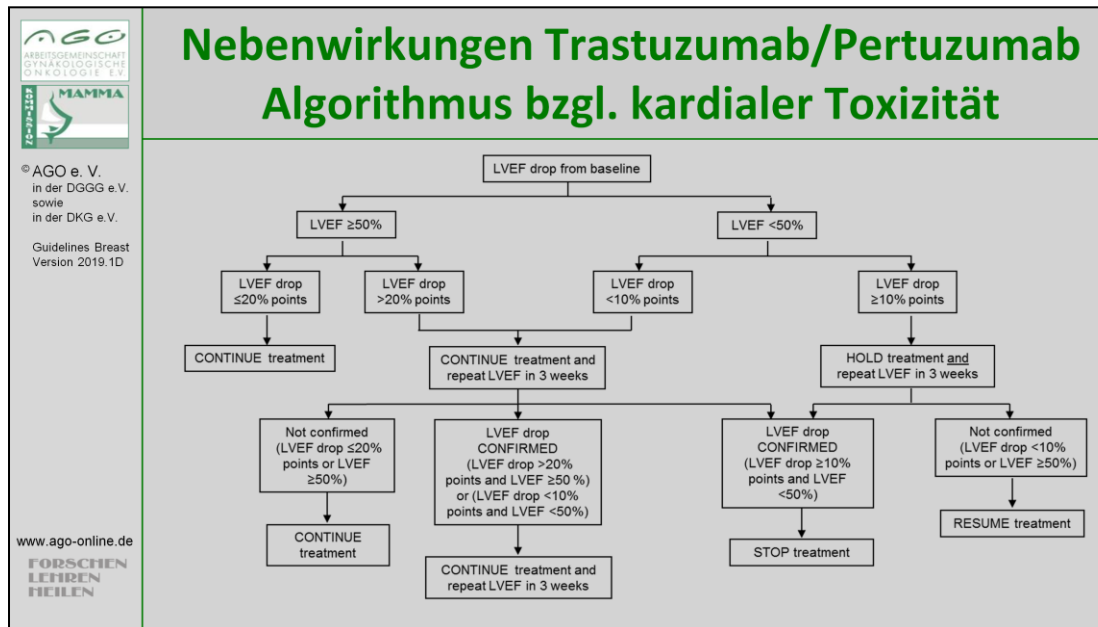
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“Anthracycline simultaneous to radiotherapy”

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

“Tamoxifen simultaneous to radiotherapy”

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  2. Varga Z, Cserháti A, Kelemen G, et al.: Role of systemic therapy in the development of lung sequelae after conformal radiotherapy in breast cancer patients. Int J Radiat Oncol Biol Phys. 2011 Jul 15;80(4):1109-16.
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## Nebenwirkungen nach Organsystemen

### Inzidenz, Prävention, Therapie

#### 8. Erkrankungen des Gastrointestinaltrakts

- Nausea, Emesis (Übelkeit, Erbrechen)
- Mukositis
  - Stomatitis (Evrolimus)
- Diarrhoe
- Obstipation



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# Antiemetische Therapie


<http://www.mascc.org/antiemetic-guidelines> [www.onkosupport.de](http://www.onkosupport.de)

	Oxford		
	LoE	GR	AGO
▪ <b>Abschätzen des emetogenen Potenzials des jeweiligen Chemotherapie-Protokolls</b>	5	D	++
▪ <b>Neurokinin-1-Rezeptor-Antagonisten</b>	1b	A	++
▪ <b>Dexamethason</b>	1a	A	++
▪ <b>5-HT<sub>3</sub>-Antagonisten</b>	1b	A	++
▪ <b>Feste Kombination mehrerer Substanzen</b>	1b	A	++
▪ <b>Reserveantiemetika (Rescue Medication)</b>			
▪ Olanzapin	3b	C	+
▪ Levomepromazin, Benzodiazepine,			
▪ Cannabinoide, Ingwer			

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# Antiemetische Therapie

<http://www.mascc.org/antiemetic-guidelines> [www.onkosupport.de](http://www.onkosupport.de)

Emetogenes Risiko (Risiko ohne Antiemese zu erbrechen)		Akute Phase (vor der medikamentösen Tumorthherapie)	Verzögerte Phase (ab 24 h nach der medikamentösen Tumorthherapie)
Hoch > 90 %	hoch emetogen und AC- basierte Chemotherapie bei Patienten mit Mammakarzinom	5-HT <sub>3</sub> -RA	-
		NK <sub>1</sub> -RA	1
		Dexamethason	Dexamethason Tag 2-4
Moderat 30-90 %	carboplatinhaltige Chemotherapie <sup>1</sup>	5-HT <sub>3</sub> -RA	-
		NK <sub>1</sub> -RA („kann“)	1
		Dexamethason	fakultativ Dexamethason Tag 2-3
	moderat (außer Carboplatin)	5-HT <sub>3</sub> -RA	-
		Dexamethason	2
Gering 10-30 %		Dexamethason oder 5-HT <sub>3</sub> -RA oder MCP	-
Minimal < 10 %		Keine Routineprophylaxe	Keine Routineprophylaxe

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# Supportive Therapie

## Antiemetika

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
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



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## Mukositis Prävention

[http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006\(dtV\).pdf](http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006(dtV).pdf)


Multidisciplinary S 3 guidelines of the AWMF (Reg.-Nr. 032-054OL): „Supportive Therapie bei onkologischen Patientinnen – interdisziplinäre Querschnittsleitlinie“, released 11.11.2016

	Oxford		
	LoE	GR	AGO
<p>▪ <b>Standardisierte Mundpflege zur Prophylaxe oraler Mukositis soll in allen Altersgruppen und bei allen Krebsbehandlungen mit einem Risiko für OM erfolgen</b></p> <p>Diese besteht aus</p> <ol style="list-style-type: none"> <li>1. Patientinnenseitig               <ul style="list-style-type: none"> <li>▪ regelmässige Mundspülung (H<sub>2</sub>O, NaCl)</li> <li>▪ Weiche Zahnbürste</li> <li>▪ Reinigung der Zahnzwischenräume mit Zahnseide und/oder Interdentalbürsten</li> <li>▪ Vermeidung von Noxen (Alkohol, Tabak, scharfe Speisen, säurehaltige Lebensmittel)</li> <li>▪ Fortlaufende Kontrolle auf Läsionen</li> </ul> </li> <li>2. Risikoadaptierte vorbeugende Maßnahmen durch den Zahnarzt</li> <li>3. Engmaschige klinische Kontrolle</li> </ol> <p>Keine Evidenz besteht für folgende Substanzen: Allopurinol, Capsaicin, Glutamin, Honig, Kamille, Kamillosan, Kaugummi, Kefir, Methadon, Nystatin, Pentoxiphyllin, Polividon Jod, Vitamine A/E/Kombinationen</p>	2b		++

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analgesics for the management of oral mucositis in cancer patients. Support Care Cancer 2013; 21(11): 3191-3207.

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## Prophylaxe der Everolimus-bedingten Stomatitis durch Cortison-basierte Mundspülung

- **Studiendesign:** einarmige Phase II-Studie
- **Kohorte:** 92 Pat. behandelt mit Everolimus und Exemestane
- **Schedule:** 10 ml Dexamethason 0.5 mg Lösung  
4 x täglich über 8 Wochen
- **Ergebnisse:** all-grade Inzidenz der Stomatitis 27%  
(13 Wochen Exposition) mit 9%  $\geq$  Grad 2 Events

Rugo et al., Lancet Oncol 2017

1. Rugo et al., Lancet Oncol 2017



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## Mukositis

[http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006\(dtV\).pdf](http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006(dtV).pdf)

- **Desinfizierende / entzündungshemmende Maßnahmen:**  
Mundspülung mit Kamille- oder Salbeitee bzw. Kamillenextrakt, äther. Öle, Iod-Polyvidon, Hexetidin. Pinselungen mit Kristallviolett-Lösung 0,5% (Rezeptur) oder Myrrhentinktur, H. Mometasonfuroat + Propylenglykol
- **Schleimhautschützende Maßnahmen (während / nach Zytostatikaapplikation):**  
Lutschen von Eiswürfeln (bes. geeignet: Ananassaft, über die Apotheke beziehbar) während 5-Fluorouracil- oder HD-Melphalan-Infusion. Calciumfolinat (Leucovorin-Mundgel®, H) bei HD-Methotrexat: frühestens 24 Stunden nach Ende MTX-Infusion beginnen (sonst Wirkungsverlust des Zytostatikums!), 4- bis 6-stündlich. Dexpantenol (Panthenol®-Lsg. 5%, H) mehrmals täglich zur Mundspülung.
- **Lokale antimykotische Therapie:**  
Amphotericin B, Nystatin, Fluconazol
- **Lokale antivirale Therapie**  
Aminoquinurid / Tetracain-HCl, Aciclovir
- **Lokalanästhetika:**  
Orale Anwendung von Benzocain, Doxepin 0,5 %
- **Schmerztherapie:** Opiode bei Bedarf

1. [http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006\(dtV\).pdf](http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006(dtV).pdf)
2. RV Lalla, J Bowen, RV Lalla, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2014; 120:1453-61
3. McGuire DB, Fulton JS, Park J, et al; Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of basic oral care for the management of oral mucositis in cancer patients. Support Care Cancer 2013 Nov;21(11):3165-77.
4. Jensen, S. B., V. Jarvis, Y. Zadik, et al. Systematic review of miscellaneous agents for the management of oral mucositis in cancer patients. Support Care Cancer 2013;21(11): 3223-3232.
5. Leenstra, J. L., R. C. Miller, R. Qin, et al.: Doxepin rinse versus placebo in the treatment of acute oral mucositis pain in patients receiving head and neck radiotherapy with or without chemotherapy: a phase III, randomized, double-blind trial (NCCTG-N09C6 [Alliance]). J Clin Oncol 2014;32(15): 1571-1577.
6. Nicolatou-Galitis, O., T. Sarri, J. Bowen, et al.: Systematic review of amifostine for the management of oral mucositis in cancer patients. Support Care Cancer 2013; 21(1): 357-364.
7. Peterson, D. E., K. Ohn, J. Bowen, et al.: Systematic review of oral cryotherapy for management of oral mucositis caused by cancer therapy. Support Care Cancer 2013; 21(1): 327-332.
8. Saunders, D. P., J. B. Epstein, S. Elad, et al.: Systematic review of antimicrobials, mucosal coating agents, anesthetics, and

analgesics for the management of oral mucositis in cancer patients. Support Care Cancer 2013; 21(11): 3191-3207.

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



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# Diarrhoe

- **Adsorbantien**
  - Carbo medicinalis, Kaolin / Pektin, Al-Mg-Silikathydrat
- **Analgetica, Opioide**
  - Loperamid Codein , Morphin i.v. , Tinktura opii, Butylscopolamin
- **Pseudomembranöse Kolitis**
  - Metronidazol oder bei Versagen Vancomycin

1. D. E. Peterson, C. B. Boers-Doets, R. J. Bensadoun, et al. on behalf of the ESMO Guidelines Committee Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up Annals of Oncology 2015;26 (Supplement 5): v139–v151.
2. Stein A, Voigt W, Jordan K. Chemotherapy-induced diarrhea: pathophysiology, frequency and guideline-based management Ther Adv Med Oncol 2010;2(1) 51-63
3. Coyle, V. M., D. Lungulescu, C. Toganel, et al. (2013). "A randomised double-blind placebo-controlled phase II study of AGI004 for control of chemotherapy-induced diarrhoea." Br J Cancer 2013;108(5);1027-1033.
4. Hoff, P. M., D. F. Saragiotto, C. H. Barrios, et al. (2014). "Randomized Phase III Trial Exploring the Use of Long-Acting Release Octreotide in the Prevention of Chemotherapy-Induced Diarrhea in Patients With Colorectal Cancer: The LARCID Trial." J Clin Oncol 2014;32;1006-11
5. Kee, B. K., J. S. Morris, R. S. Slack, et al. "A phase II, randomized, double blind
6. trial of calcium aluminosilicate clay versus placebo for the prevention of diarrhea in patients with metastatic colorectal cancer treated with irinotecan." Support Care Cancer 2015;23;661-70.
7. Middleton, G., S. Brown, C. Lowe, T. et al. (2013). "A randomised phase III trial of the pharmacokinetic biomodulation of irinotecan using oral ciclosporin in advanced colorectal cancer: results of the Panitumumab, Irinotecan & Ciclosporin in COLOrectal cancer therapy trial (PICCOLO)." Eur J Cancer 2013, 49(16): 3507-3516.

# Obstipation


## Wichtige Nebenwirkung einer Opiattherapie

- **Quellmittel**
  - Flohsamen, Leinsamen (geschrotet)
- **Osmotisch wirksame Laxanzien**
  - Macrogol > Lactulose (Cochrane Review LoE 1a AGO +)
  - Orale Kontrastmittel: Ultima ratio z.B. Natriumamidotrizoat
  - Sorbit
- **Stimulierende Laxanzien**
  - Sennesfrüchte, Rizinusöl, Bisacodyl, Natriumpicosulfat
- **Stuhlweichmacher**
  - Gleitmittel z.B. Paraffin
- **Opiod-Rezeptorantagonist bei Opiatobstipation**
  - Methylnaltrexone

# Nebenwirkungen nach Organsystemen

## Inzidenz, Prävention, Therapie

### 9. Erkrankungen der Haut und des Unterhautgewebes



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## Hauttoxizität

**Multidisciplinary S 3 guidelines of the AWMF (Reg.-Nr. 032-054OL): „Supportive Therapie bei onkologischen PatientInnen – interdisziplinäre Querschnittsleitlinie“, released 11.11.2016**

	Oxford LoE	GR	AGO
▪ Vermeidung einer ausgeprägten chemotherapie-induzierten Alopecie durch Kopfhautkühlung*	1b		+/-
▪ Eine Prophylaxe des HFS mit harnstoffhaltigen 5-10% Cremes kann erfolgen (mehrfach tägl.)	1b		+
▪ Unter Docetaxel sollte eine Prophylaxe der Nagelveränderungen/HFS durch Kühlung erfolgen	2b		+


\* Substanz- und regimeabhängig

### Scalp Cooling:

1. Nangia J, Wang T, Osborne C, et al. Effect of Scalp Cooling Device on Alopecia in Women Undergoing Chemotherapy for Breast Cancer: The SCALP Randomized Clinical Trial JAMA. 2017 Feb 14;317(6):596-605.
2. Rugo HS, Voigt J. Scalp Hypothermia for Preventing Alopecia During Chemotherapy. A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Clin Breast Cancer. 2018 Feb;18(1):19-28.
3. Rugo HS, Melin SA, Voigt J. Scalp cooling with adjuvant/neoadjuvant chemotherapy for breast cancer and the risk of scalp metastases: systematic review and meta-analysis. Breast Cancer Res Treat. 2017 Jun;163(2):199-205.

### Relevant practice guideline

1. Multidisciplinary S 3 guidelines of the AWMF (Reg.-Nr. 032-054OL):
2. „Supportive Therapie bei onkologischen PatientInnen - interdisziplinäre Querschnittsleitlinie“, released 11.11.2016



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## Scalp Cooling: Scalp Cooling Alopecia Prevention Trial (SCALP) und Metaanalysen

**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  $p < 0.001$

**Zwei Metaanalysen: AGO: +/- LOE 1b**

- Scalp cooling reduced relative risk (RR) of alopecia by 43% (RR, 0.57; 95% CI, 0.45-0.72;  $I^2 = 11\%$ ;  $P < .00001$ ). (Rugo & Voigt, Clinical Breast Cancer 2018; 18(1): 19-28.)
- Incidence rate of scalp metastasis (SC vs. no-SC) 0.61% vs. 0.41%;  $P = 0.43$ . (Rugo & Voigt; BCRT 2017)

1. Nangia J, Wang T, Osborne C, et al. Effect of Scalp Cooling Device on Alopecia in Women Undergoing Chemotherapy for Breast Cancer: The SCALP Randomized Clinical Trial JAMA. 2017 Feb 14;317(6):596-605.
2. Rugo HS, Voigt J. Scalp Hypothermia for Preventing Alopecia During Chemotherapy. A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Clin Breast Cancer. 2018 Feb;18(1):19-28.
3. Rugo HS, Melin SA, Voigt J. Scalp cooling with adjuvant/neoadjuvant chemotherapy for breast cancer and the risk of scalp metastases: systematic review and meta-analysis. Breast Cancer Res Treat. 2017 Jun;163(2):199-205.

## Nebenwirkungen nach Organsystemen


### Inzidenz, Prävention, Therapie

#### 10. Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen *(siehe Kapitel Osteoonkologie)*

# Nebenwirkungen nach Organsystemen

## Inzidenz, Prävention, Therapie

### 11. Allgemeine Erkrankungen und Beschwerden am Verabreichungsort



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## Paravasate mit potenziell nekrotisierenden Substanzen (Anthracycline, Taxane, Vinorelbin)

	Oxford LoE	GR	AGO
▪ <b>Dexrazoxane zur Behandlung von Anthracyclin-Paravasaten (Ausnahme liposomales A)</b>	<b>2b</b>	<b>B</b>	<b>++</b>
▪ <b>Hyaluronsäure zur Behandlung von Taxan/Vinorelbin-Paravasaten</b>	<b>3b</b>	<b>D</b>	<b>++</b>

### Relevant practice guideline:

1. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants.

### Dexrazoxane

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

Hyaluronsäure

...

# Paravasate

## Dexrazoxane/Hyaluronsäure

### Dexrazoxane zur Behandlung von Anthracyclin-Paravasaten

Tag 1: 1000 mg/m<sup>2</sup> (max. 2000 mg), IV 1–2 Stunden

Tag 2: 1000 mg/m<sup>2</sup> (max. 2000 mg), IV 1–2 Stunden

Tag 3: 500 mg/m<sup>2</sup> (max. 1000 mg), IV 1–2 Stunden

In anderen Fällen bzw. in denen eine Therapie mit Dexrazoxan nicht indiziert ist, gelten für die Anthrazyklin-Paravasate die folgenden Maßnahmen.


Lokale Kälte: Eispackung 6-stündlich jeweils für 15 Min. für 3 Tage oder: 24 h Abdeckung mit Eisbeuteln

Lokale Applikation von Dimethylsulfoxid ( DMSO ) 99% mit Watteträger 3- bis 4-stündlich für mind. 3 Tage (besser 14 Tage) auftragen und an der Luft trocknen lassen. Das Intervall kann ab Tag 4 auf 6 Stunden verlängert werden.

### Hyaluronsäure bei Taxan/Vinorelbin-Paravasaten:

- 1-10 Amp a 150 IU
- 1 ml Lösungsmittel (z.B. NaCl 0.9%)
- Lokalanästhesie
- Keine Thermotherapie bei Taxanen, trockene Wärme 4 x täglich 20 min bei Vincaalkaloiden

- **Substanzspezifische Nebenwirkungen**
  - Antikörper und Antikörper-Wirkstoff-Konjugate (ADC)
  - CDK 4/6-Inhibitoren
  - PARP-Inhibitoren
  - Small molecules (TKI, mTOR-Inhibitor)
  - Immun-Checkpoint-Antikörper

Nebenwirkungen – Antikörper/ Antikörper-Wirkstoff-Konjugate		
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	<b>Trastuzumab</b>	<b>Oxford</b>
	▪ Kardiotoxizität in der adjuvanten Therapie (1,0–2,0%)	<b>LoE GR</b>
	▪ Troponin I als Marker für Kardiotoxizität	
	<b>Pertuzumab</b>	
	▪ Ekzem, Diarrhoe, Mukositis	<b>1b A</b>
	<b>Trastuzumab-Emtansin (T-DM1)</b>	
	▪ Thrombozytopenie, Anstieg Leberenzyme Fieber, Kopfschmerzen, Pneumonitis, Polyneuropathie	<b>1b A</b>
	<b>Bevacizumab</b>	
	▪ Hypertonus, linksventrikuläre Dysfunktion Blutung, Proteinurie	<b>1a A</b>

#### Cardiotoxicity....

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

Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet*. 2017 Mar 25;389(10075):1195-1205.

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

#### Troponin I....

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

#### Bevacizumab ....

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

#### Lapatinib...

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

2743, 2006

#### Pertuzumab


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

#### T-DM1

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

#### Everolimus

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



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# Toxizitäten neuer Substanzen – CDK 4/6 Inhibitoren (Palbociclib / Ribociclib / Abemaciclib)

UE, %	Alle Grade	Grad 3	Grad 4
<b>Neutropenie</b>	79,5/ <b>74,3</b> /41,3	56,1/ <b>49,7</b> /19,6	10,4/ <b>9,6</b> /1,5
<b>Leukopenie</b>	39,0/ <b>32,9</b> /20,8	24,1/ <b>19,8</b> /7,3	0,7/ <b>1,2</b> /0,3
<b>Anämie</b>	24,1/ <b>18,6</b> /28,4	5,2/0,9/5,8	0,2/ <b>0,3</b> /0
<b>Thrombopenie</b>	15,5/ <b>5,7</b> /10,0	1,4/0,6/2,0	0,2/0/ <b>&lt;1,0</b>
<b>Fatigue</b>	37,4/ <b>36,5</b> /40,1	1,8/2,1/1,8	0/0,3/0
<b>Übelkeit</b>	35,1/ <b>51,5</b> /38,5	0,2/2,4/0,9	0/0/0
<b>Erbrechen</b>	15,5/ <b>29,3</b> /28,4	0,5/3,6/1,2	0/0/0
<b>Diarrhoe</b>	26,1/ <b>35,0</b> /81,3	1,4/1,2/9,5	0/0/0
<b>Alopezie</b>	32,9/ <b>33,2</b> /26,6	-	-
<b>Exanthem</b>	17,8/ <b>17,1</b> / 14,0	0,9/0,6/ <b>&lt;1,0</b>	0/0/0
<b>ALT Erhöhung</b>	9,9/ <b>15,6</b> /15,6	1,7/7,5/5,8	0,1/ <b>1,8</b> /0,3
<b>AST Erhöhung</b>	9,7/ <b>15,0</b> /15,0	2,5/4,8/3,0	0/0,9/0
<b>Infektionen</b>	60/ <b>50,3</b> /39,1	6,0/3,6/4,0	1/0,6/0,9
<b>QT Prolongation</b>	N.A./7,5/N.A.	N.A./3,0/N.A.	N.A./0/N.A.

Palbociclib/Ribociclib/Abemaciclib

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### Palbociclib


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

### Ribociclib

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

### Abemaciclib

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



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## QT-Zeit-Verlängerung: Ribociclib vs Placebo

- Post-baseline Verlängerung der QT-Zeit > 480 msec 6.9% vs 1.2 %
- Post-baseline Verlängerung der QT Zeit > 500 msec 1,5 % vs 0,3%
- Therapieabbruch wegen QT Zeit Verlängerung 0.3% vs 0.6%
- QT Verlängerung ist nicht mit klinischer Symptomatik assoziiert, aber mit einem erhöhten Risiko für lebensbedrohliche Arrhythmien („torsades de pointes“, TdP)

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

<div>  <b>Toxizitäten neuer Substanzen: mTOR-Inhibitor (Everolimus)</b> </div>			
<div>  <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1D</p> <p>www.ago-online.de</p> <p><b>FORSCHEN LEHREN HEILEN</b></p> </div>	UE, %	Alle Grade (%)	Grad >=3 (%)
	Stomatitis	11,6	1,6
	Ausschlag	7,4	0,02
	Anämie	3,3	1,3
	Fatigue	6,8	0,8
	Übelkeit	5,6	0
	Erbrechen	2,9	0
	Diarrhoe	6,2	0,02
	Appetitminderung	6,0	0,02
	Kopfschmerz	3,9	0
	Gewichtsverlust	3,9	0
	Dyspnoe	3,8	0,08
	Arthralgie	3,3	0
	Epistaxis	3,1	0
	Ödem	2,9	0
	Obstipation	2,6	
	Pyrexie	2,9	0
	Husten	4,5	0
	ALT Erhöhung	2,6	0
	Pneumonitis	0,2	0
	Asthenie	2,4	0,04
	Dysgeusie	4,3	0

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

## Toxizitäten PARP-Inhibitoren – Olaparib, Talazoparib

### Olaparib

UE, %	Alle Grade (%)	Grad >=3 (%)
Jegliche UE	97,1	36,6
Neutropenie	27,3	9,3
Anämie	40,0	16,1
Fatigue	28,8	2,9
Übelkeit	58,0	0
Erbrechen	29,8	0
Diarrhoe	20,5	0,5
Appetitminderung	16,1	0
Kopfschmerz	20,0	1
Pyrexie	14,1	0
Husten	17,1	0
ALT Erhöhung	11,2	1,5
AST Erhöhung	9,3	2,4
PPE	0,5	
Therapieabbruch	4,9	

### Talazoparib

UE, %	Alle Grade (%)	Grad >=3 (%)
Jegliche UE	98,6	31,8
Neutropenie	34,6	20,9
Anämie	52,8	39,2
Fatigue	50,3	1,7
Übelkeit	48,6	0,3
Erbrechen	24,8	2,4
Diarrhoe	22,0	0,7
Appetitminderung	21,3	0,3
Kopfschmerz	32,5	1,7
Pyrexie	21,0	2,4
Husten	17,5	2,4
ALT Erhöhung	2,1	1,7
AST Erhöhung	1,4	0,3
PPE	98,6	31,8
Therapieabbruch	34,6	20,9

1. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med. 2018 Aug 23;379(8):753-763.
2. Robson M, Im SA, Senkus E et al. Olaparib for metastatic breast cancer in patients with germline BRCA mutation N Engl J Med 377: 523-533, 2017

# Toxizitäten antiHER2-TKI – Neratinib, Lapatinib –

## Lapatinib


UE, %	Alle Grade	Grad >=3
Diarrhöe	61%	6%
Nausea	18%	4%
Hautausschlag	60%	6%
Fatigue	16%	4%
Kardiale NW	3%	< 1% SAE
Hepatobiliäre NW	8%	
Alle UE	92%	SAE 6%

## Neratinib

UE, %	Alle Grade (%)	Grad >=3 (%)
Diarrhöe	90	40,1
Nausea	43	2
Bauchschmerzen	36	2
Fatigue	27	2
Erbrechen	26	3
Hautausschlag	18	0,6
Stomatitis	14	0,6
Appetitverlust	12	0,2
Dyspepsie	10	0,4
ALAT-Erhöhungen	9	1,2
ASAT-Erhöhungen	7	0,7
Nagelstörungen	8	0,3
Trockene Haut	6	0

Primäre Prophylaxe mit Loperamid LoE AGO  
2b B ++

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



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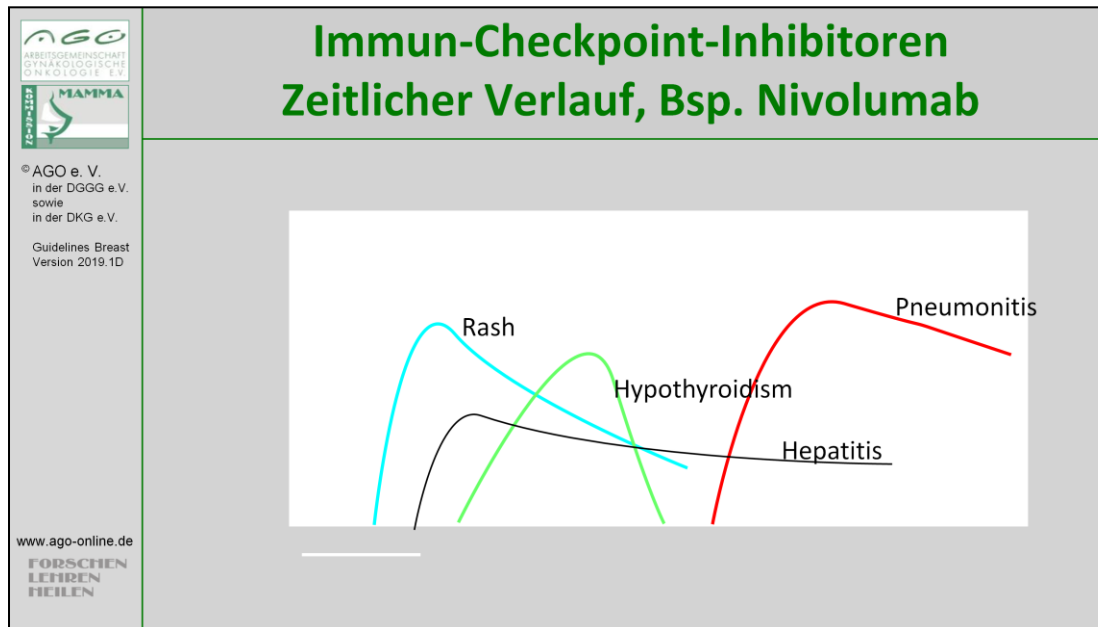
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# Immun-Checkpoint-Inhibitoren


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- **Therapeutische Ansätze (Antikörper)**
  - **PD1 /PD-L1**
    - PD1**
      - Nivolumab
      - Pembrolizumab
    - PDL1**
      - Atezolizumab
      - Durvalumab
      - Avelumab


1. Haanen J, Carbone F, Robert C, et al, on behalf of the ESMO Guidelines Committee: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (suppl 4): 119-142. doi: 10.1093/annonc/mdx225



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



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## Immun-Checkpoint-Inhibitoren

- **Nebenwirkungen ≥ Grad 3**
  - Diarrhoe
  - Fatigue
  - Hautveränderungen (v.a. makulopapulöses Exanthem, Vitiligo, Epidermolysen)
  - Pneumonitis
  - Colitis
  - Hypophysitis
  - Hepatitis
  - Nephritis
  - Thyreoiditis (Hyper-/Hypothyreose)
  - Guillain-Barré-Syndrom
  - Kardiomyopathie
  - Myopathie – Myalgie – Rhabdomyolyse
  - Uveitis

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

## Immun-Checkpoint-Inhibitoren Toxizitäten (Gesamt in %)


	Atezolizumab	Nivolumab	Pembrolizumab
<b>Diarrhö</b>	<b>18,6%</b>	<b>13%</b>	<b>18%</b>
<b>Kolitis</b>	<b>1,1%</b>	<b>2%</b>	<b>1%</b>
<b>Hautausschlag</b>	<b>18,6%</b>	<b>15%</b>	<b>&lt;1%</b>
<b>Hepatotoxizität</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>Schilddrüsen- fehlfunktion</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>Neuropathien</b>	<b>0,2%</b>	<b>&lt;1%</b>	<b>&lt;1%</b>

Atezolizumab Fachinformationen 2018, Nivolumab, safety management BMS 2014, Pembrolizumab PI 2014

Atezolizumab: <https://www.fachinfo.de/suche/fi/021700>

Nivolumab: <https://www.fachinfo.de/suche/fi/020675>

Pembrolizumab: <https://www.fachinfo.de/suche/fi/020716>



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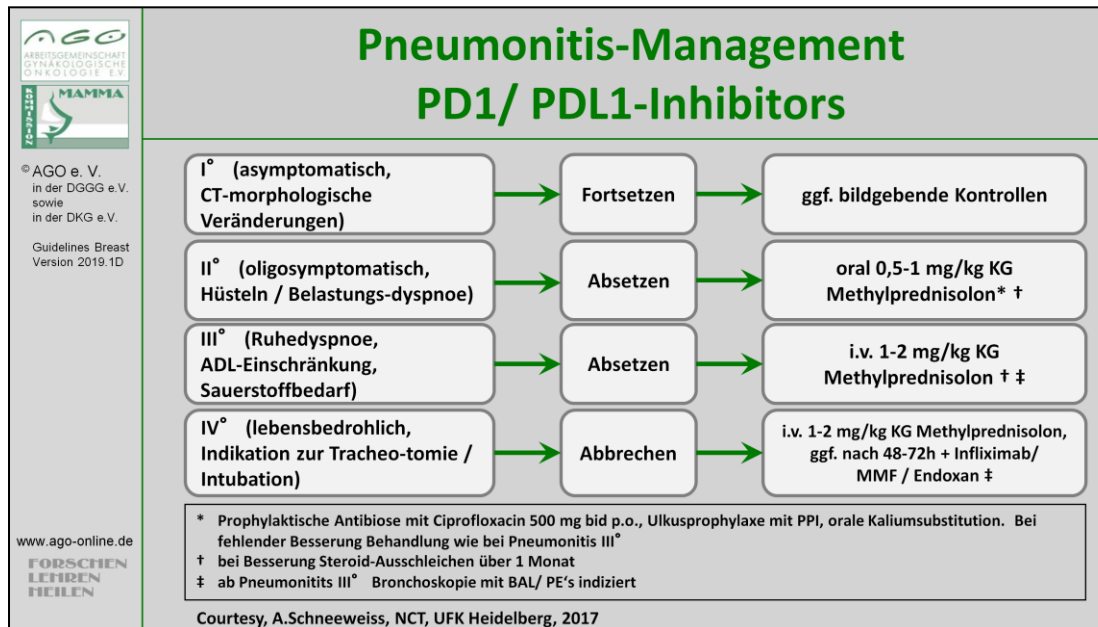
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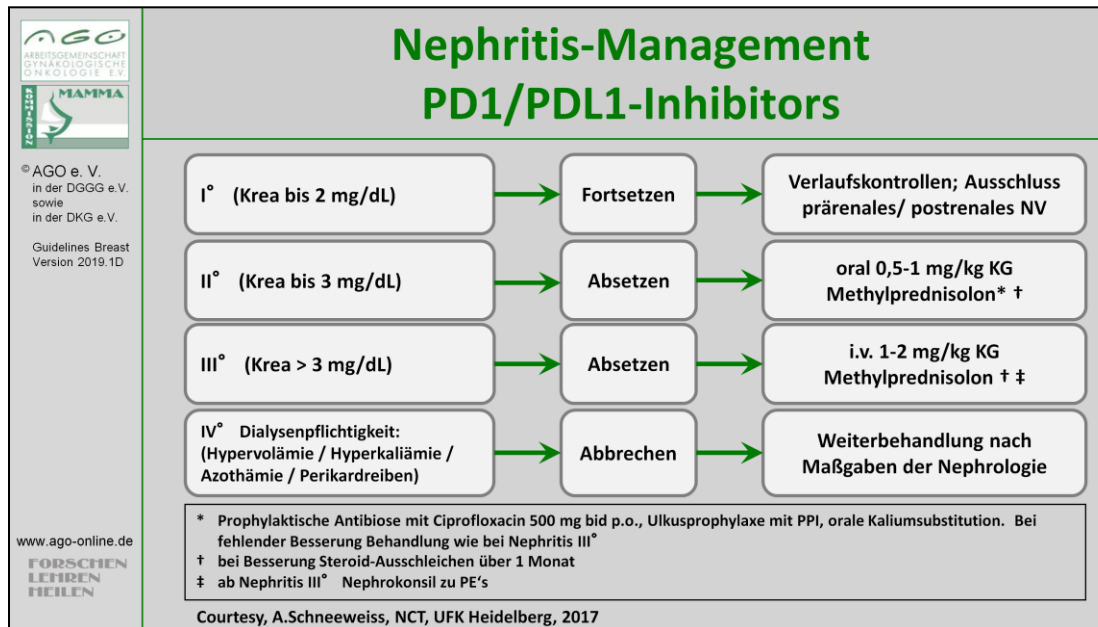
## Immun-Checkpoint-Inhibitoren NW-Management - Grundsätze

CTC AE-Grad	Management
<b>1</b>	<ul style="list-style-type: none"> <li>▪ Supportive Therapie</li> <li>▪ Engmaschige Kontrollen</li> <li>▪ Ausschluss Infektion</li> <li>▪ Patientenaufklärung</li> </ul>
<b>2</b>	Wie Grad 1 aber <ul style="list-style-type: none"> <li>▪ Pausierung der Therapie bis alle irAE Grad 0-1</li> <li>▪ Ggf Kortikosteroide</li> </ul>
<b>3</b>	<ul style="list-style-type: none"> <li>▪ Supportive Therapie</li> <li>▪ i. v.-Steroide (z. B. 1-2 mg/kg Prednisolon)</li> </ul> Wenn keine Besserung innerhalb 48 h: <ul style="list-style-type: none"> <li>▪ Ggf zusätzliche andere Immunsuppression (Infliximab, MMF)</li> <li>▪ Ggf organspezifische weitere Diagnostik (z. B. Koloskopie)</li> <li>▪ Ggf Konsil Fachspezialist</li> <li>▪ Ausschluss oder Behandlung von Infektion</li> <li>▪ Absetzen der Therapie, ggf Fortsetzung, wenn CTC AE Grad 0,1</li> <li>▪ Langsames Ausschleichen der Steroide (3-6 Wochen)</li> </ul>
<b>4</b>	Wie Grad 3 aber dauerhaftes Absetzen der Therapie

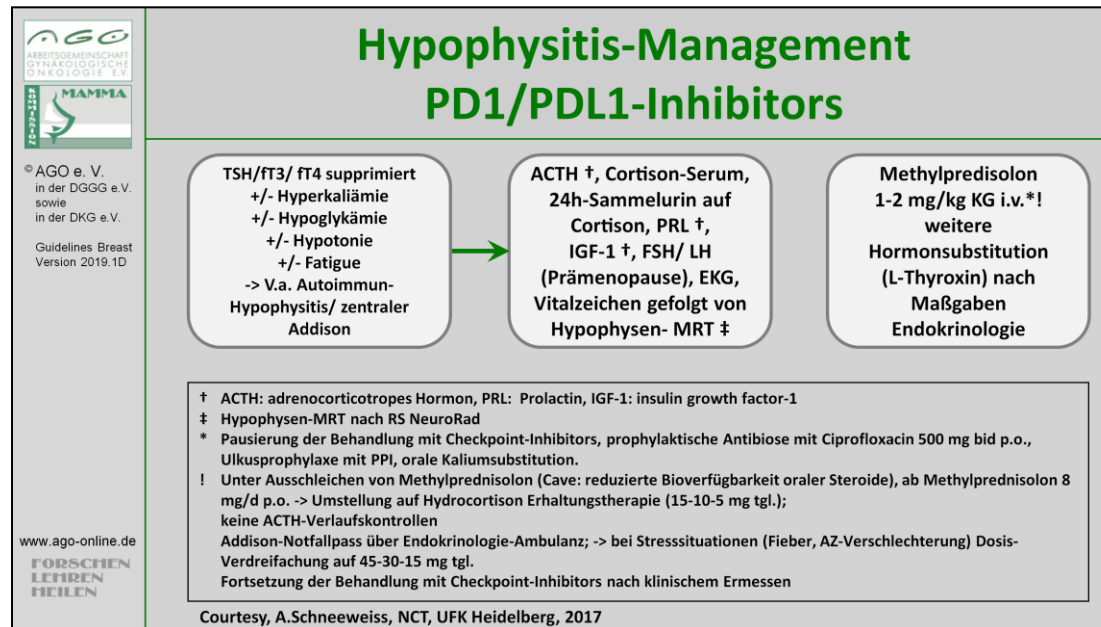
1. Haanen J, Carbone F, Robert C, et al. on behalf of the ESMO Guidelines Committee: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (suppl 4): 119-142.



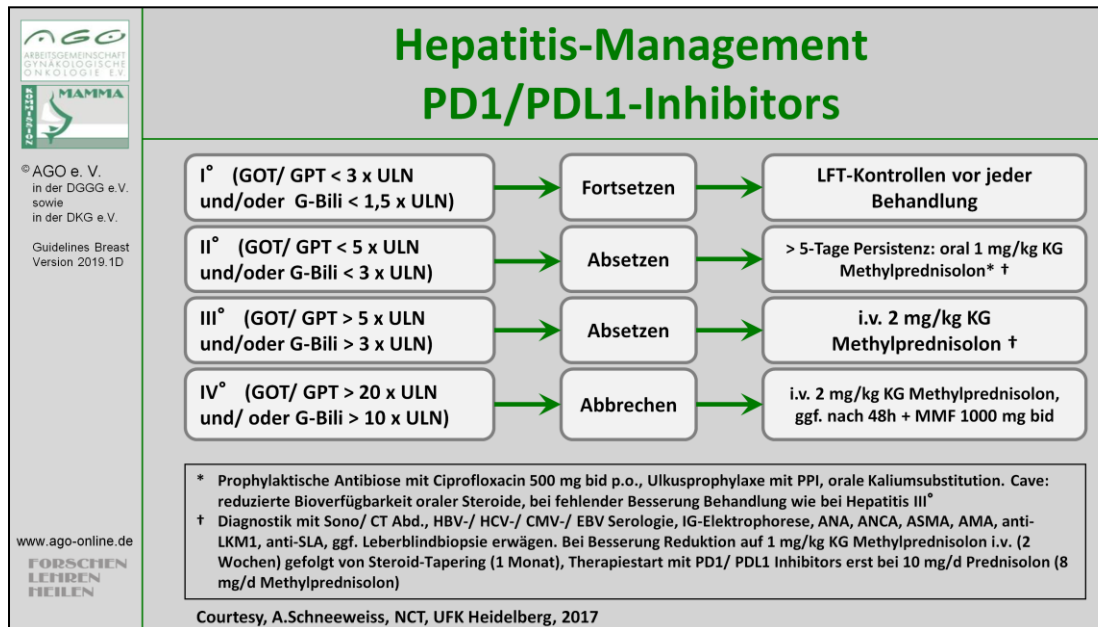
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2. Postow M, Sidlow R, Hellmann M: Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018; 378(2): 158-168. doi: 10.1056/NEJMra1703481



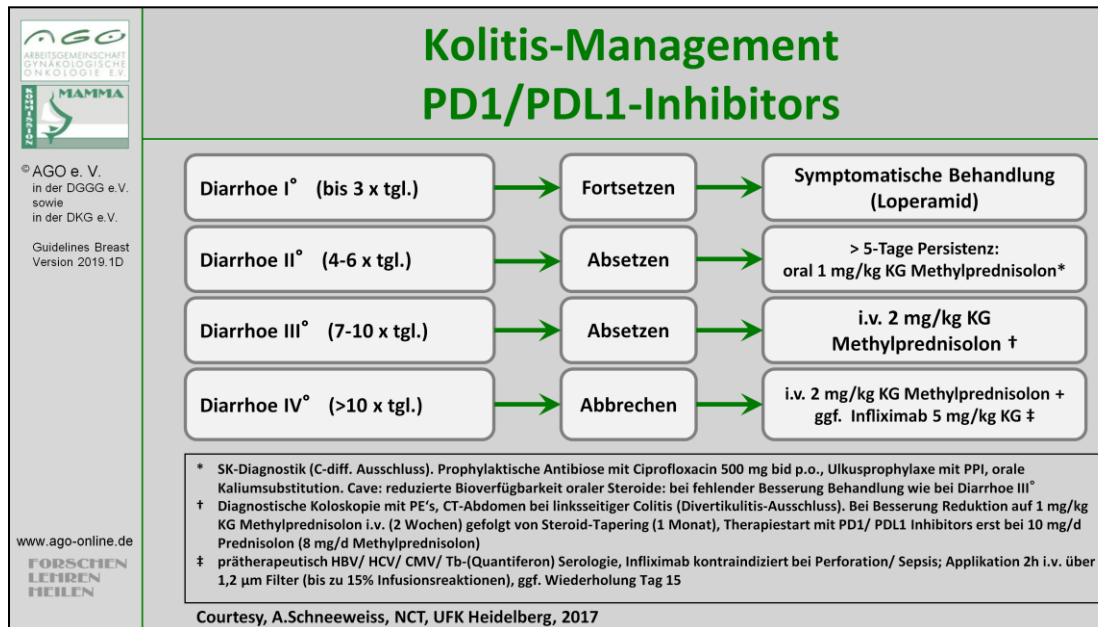
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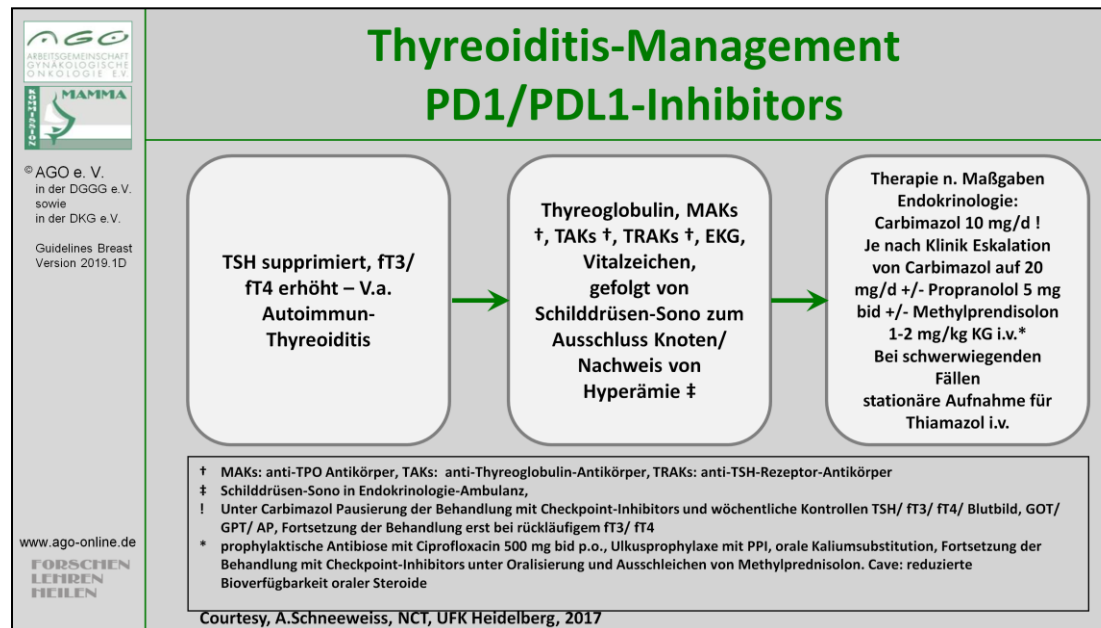
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1. Haanen J, Carbone F, Robert C, et al. on behalf of the ESMO Guidelines Committee: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (suppl 4): 119-142.
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-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



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# Schmerztherapie

(Deutsche Gesellschaft für Schmerztherapie Praxisleitlinie Tumorschmerz 2014  
[www.dgs-praxisleitlinien.de](http://www.dgs-praxisleitlinien.de))

- **Nicht-Opioide; WHO Stufe 1**  
Diclofenac resinat, Ibuprofen und / oder Metamizol, Paracetamol
- **Niedrig-potente Opioide; WHO Stufe 2**  
Tramadol (vorzugsweise als Retard-Tabletten) bzw. Tilidin/ Naloxon (ebenfalls als Retard-Tabletten)
- **Hoch-potente Opioide; WHO Stufe 3**  
Morphin, Buprenorphin (sublingual oder als transdermales System), Fentanyl (transdermales System), Hydromorphon, Oxycodon, als Reserve Levomethadon. Die notwendige Opioiddosis wird schrittweise gegen den Schmerz titriert.
- **Koanalgetika**  
Gabapentin, Pregabalin, Carbamazepin, Amitriptylin, Bisphosphonate

### Relevant practice guideline

Deutsche Gesellschaft zum Studium des Schmerzes, [www.dgss.org](http://www.dgss.org)

## Palliative Care

- "...expert consensus that **combined standard oncology care and palliative care** should be **considered early in the course of illness** for any patient with metastatic cancer and/or high symptom burden."<sup>1</sup>
- "Palliative care should be **initiated by the primary oncology team** and augmented by **collaboration** with an interdisciplinary team of palliative care experts."<sup>2</sup>
- "Expert **palliative care**, including effective control of pain and other symptoms, **should be a priority**."<sup>3</sup>

<sup>1</sup> Smith et al, J Clin Oncol 30 880-887, 2012

<sup>2</sup> Levy et al, J Natl Compr Canc Netw 10:1284-1309, 2012

<sup>3</sup> Cardoso et al, Breast 21:242-252, 2012

1. Smith et al, J Clin Oncol 30 880-887, 2012
2. Levy et al, J Natl Compr Canc Netw 10:1284-1309, 2012
3. Cardoso et al, Breast 21:242-252, 2012