Screened data bases

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

Screened guidelines

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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)

Supportive Therapie und Nebenwirkungsmanagement

Guidelines Breast
Version 2019.1D

- **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
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  Harbeck / Schneeweiss

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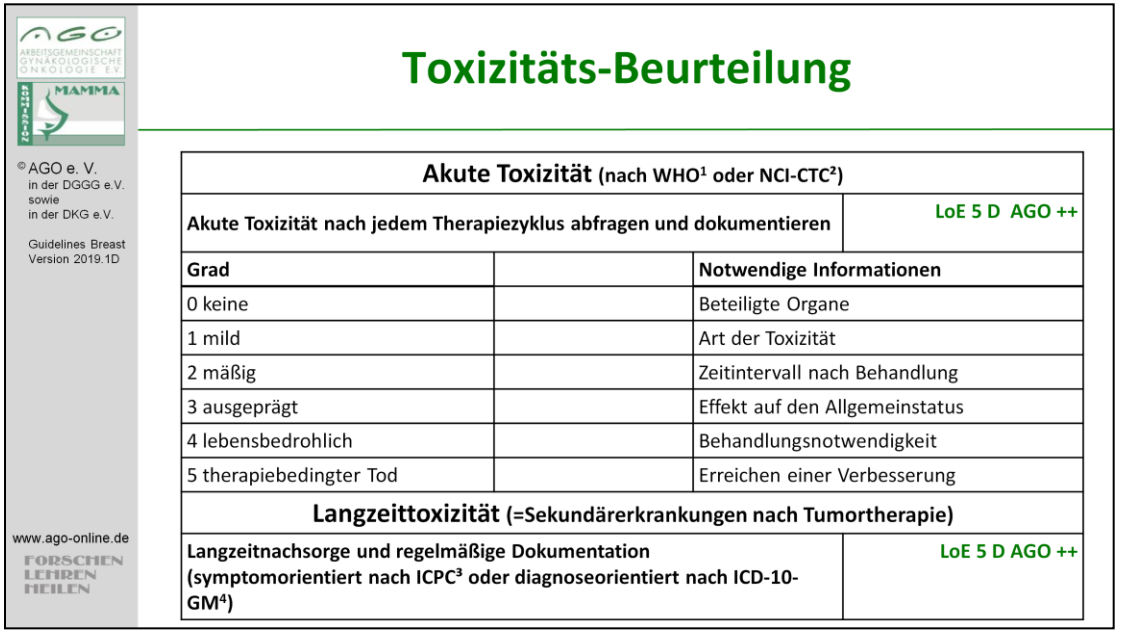
- **Leitlinien - Umfeld**

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)

Guidelines Breast
Version 2019.1D

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



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 (Download 18.01.2018)

Akute Toxizität nach jedem Therapiezyklus abfragen

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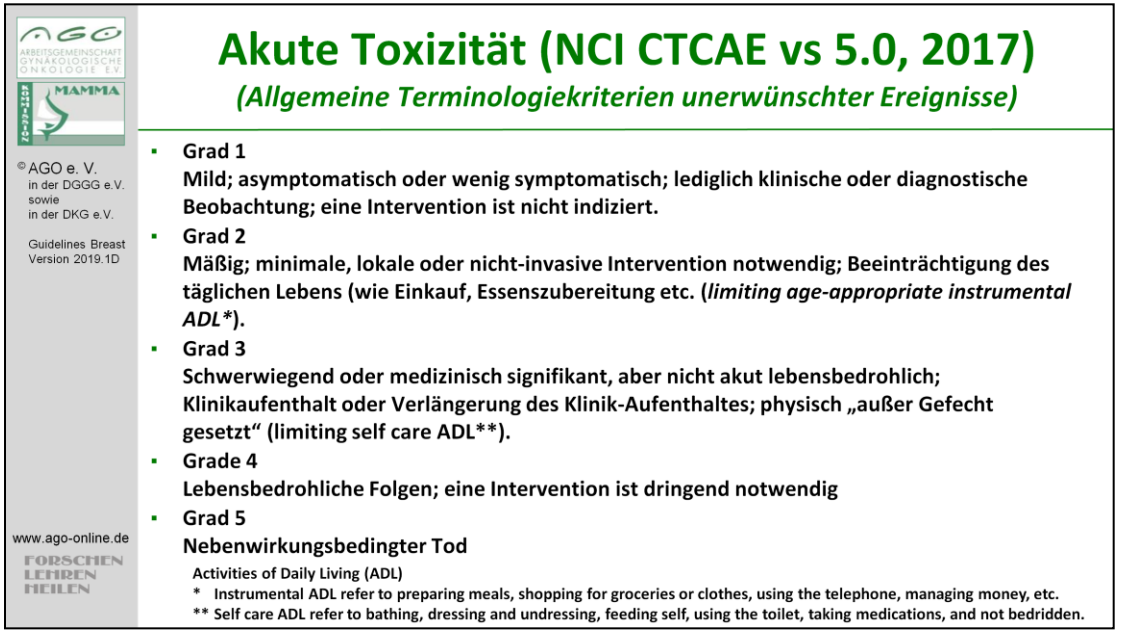
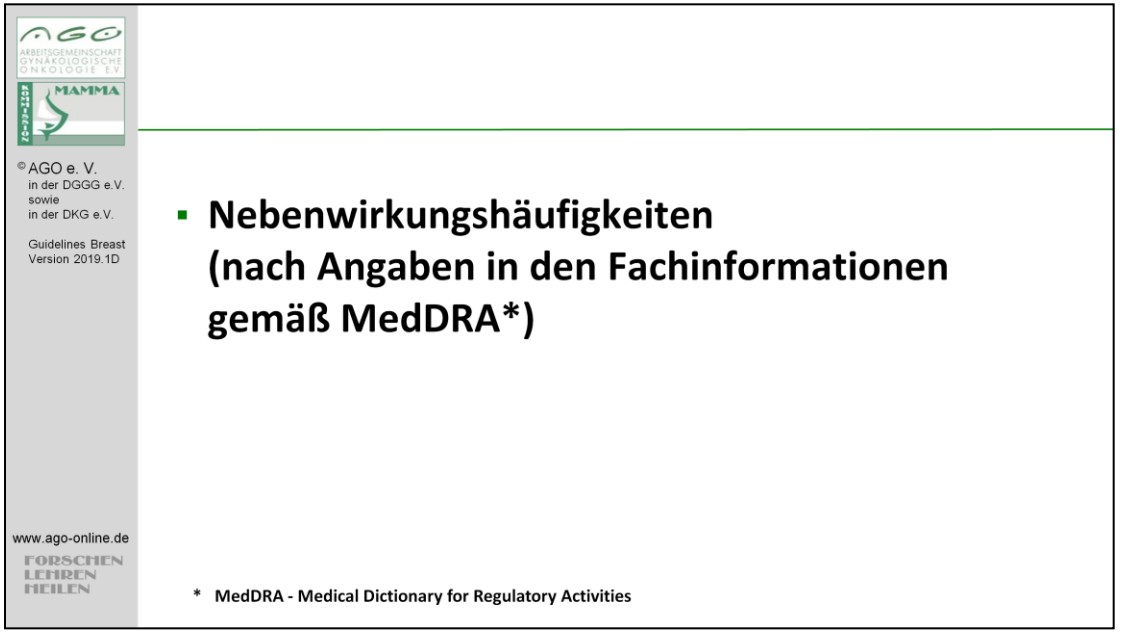
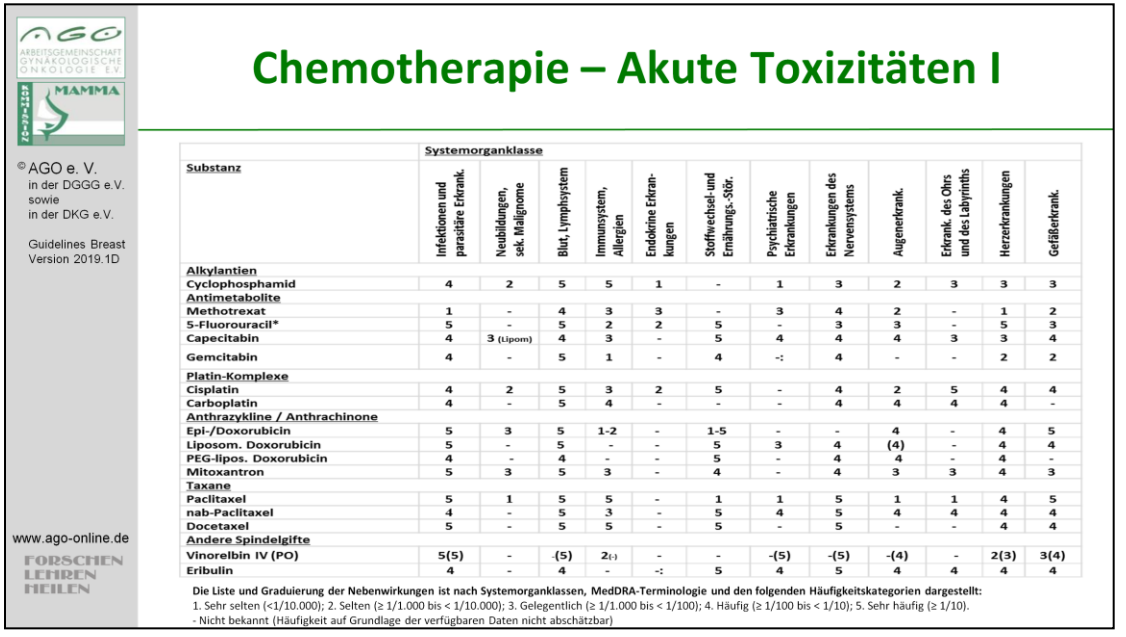


1. NCI, Bethesda, USA, Common Terminology Criteria for Adverse Events v5.0 (CTCAE; published 2017); https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50 (Download 18.01.2018)



*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 Erkrankungen	Stoffwechsel- und Ernährungs.-Stör.	Psychiatrische Erkrankungen	Erkrankungen des Nervensystems	Augenerkrank.	Erkrank. des Ohrs und des Labyrinths	Herzerkrankungen	Gefäßerkrank.
Alkylantien												
Cyclophosphamid	4	2	5	5	1	-	1	3	2	3	3	3
Antimetabolite												
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
Platin-Komplexe												
Cisplatin	4	2	5	3	2	5	-	4	2	5	4	4
Carboplatin	4	-	5	4	-	-	-	4	4	4	4	-
Anthrazykline / Anthrachinone												
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
Taxane												
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
Andere Spindelgifte												
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

Quellen für die Fachinformationen (Download 19.01.2018)
Cyclophosphamid: http://www.baxter.de/de_DE/assets/downloads/fachinformation/endoxan.pdf
Methotrexat: https://www.gelbe-liste.de/produkte/MTX-HEXAL-10-mg-Tabletten_117469/fachinformation
5-Fluorouracil: https://www.gelbe-liste.de/produkte/Fluorouracil-HEXAL-50-mg-ml-Injektionsloesung-100-ml_546519/fachinformation
Capecitabin: https://www.zentiva.de/Produkte/Capecitabin-Zentiva/Downloads?id=a63946ee-51ce-46ac-8184-a468b705ed9b
Gemcitabin: http://www.success-studie.de/b/downloads/Fachinfo/GemzarFI07Jan.pdf
Cisplatin: https://www.gelbe-liste.de/produkte/Cisplatin-Teva-1-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-100-ml_543960/fachinformation
Carboplatin: http://www.teva.de/index.php?eID=dumpFile&t=f&f=37532&g=-1&r=11068%2C11068&token=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
PEG-lipo. Doxorubicin: 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
Paclitaxel: https://medikamio.com/de-de/medikamente/paclitaxel-ratiopharm/pil
Nab-Paclitaxel: https://www.gelbe-liste.de/produkte/Abraxane-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

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

10.1016/j.ejon.2016.12.008. Epub 2016 Dec 22.
7. Maeda S, Saimura M, Minami S, et al. Efficacy and safety of eribulin as first- to third-line treatment in patients with advanced or metastatic breast cancer previously treated with anthracyclines and taxanes.See comment in PubMed Commons below Breast. 2017 Jan 2;32:66-72. doi: 10.1016/j.breast.2016.12.017.
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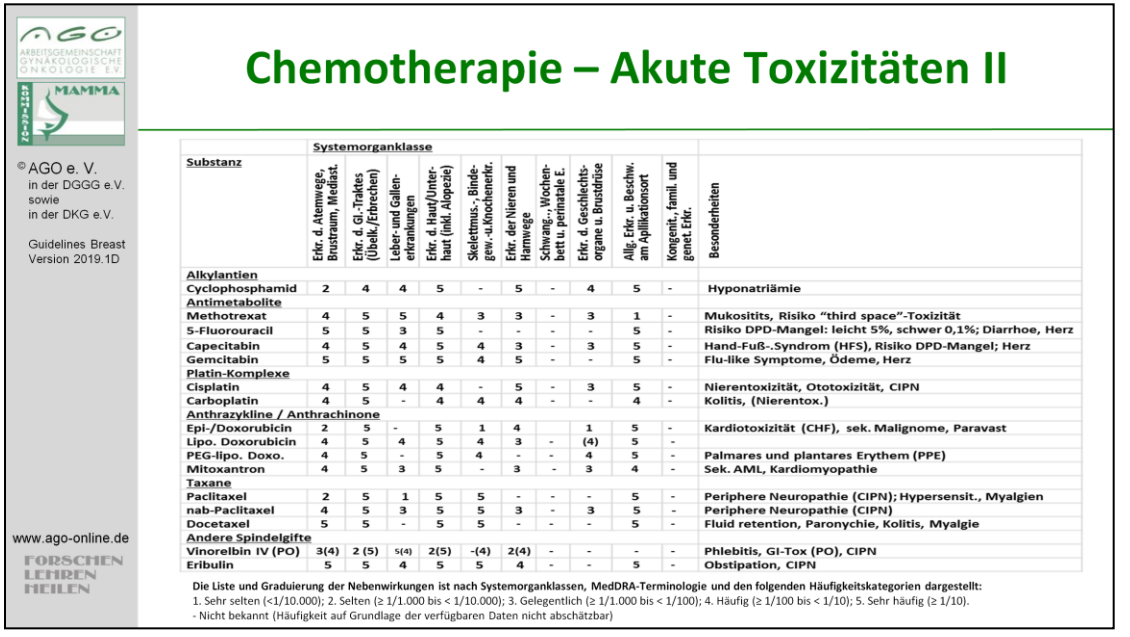
12. Madeddu C, Deidda M, Piras A, et al. Pathophysiology of cardiotoxicity induced by nonanthracycline chemotherapy. J Cardiovasc Med (Hagerstown). 2016 May;17 Suppl 1 Special issue on Cardiotoxicity from Antiblastic Drugs and Cardioprotection:e12-e18. Review.



Chemotherapie – Akute Toxizitäten II

Substanz	Systemorganklasse: Erkr. d. Atemwege, Brustraum, Mediast.	Erkr. d. GI.-Traktes (Übelk./Erbrechen)	Leber- und Gallenerkrankungen	Erkr. d. Haut/Unterhaut (inkl. Alopezie)	Skelettmus.-, Bindegew.-u.Knochenerkr.	Erkr. der Nieren und Harnwege	Schwang., Wochenbett u. perinatale E.	Erkr. d. Geschlechtsorgane u. Brustdrüse	Allg. Erkr. u. Beschw. am Applikationsort	Kongenit., famil. und genet. Erkr.	Besonderheiten
Alkylantien											
Cyclophosphamid	2	4	4	5	-	5	-	4	5	-	Hyponatriämie
Antimetabolite											
Methotrexat	4	5	5	4	3	3	-	3	1	-	Mukositits, 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
Platin-Komplexe											
Cisplatin	4	5	4	4	-	5	-	3	5	-	Nierentoxizität, Ototoxizität, CIPN
Carboplatin	4	5	-	4	4	4	-	-	4	-	Kolitis, (Nierentox.)
Anthrazykline / Anthrachinone											
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
Taxane											
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
Andere Spindelgifte											
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)

<u>Abkürzungen</u>

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

<u>Nebenwirkungskategorien - MedDRA (Medical Dictionary for Regulatory Activities)</u>

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

<u>Quellen für die Fachinformationen (Download 19.01.2018)</u>

Cyclophosphamid: http://www.baxter.de/de_DE/assets/downloads/fachinformation/endoxan.pdf

Methotrexat: https://www.gelbe-liste.de/produkte/MTX-HEXAL-10-mg-Tabletten_117469/fachinformation

5-Fluorouracil: https://www.gelbe-liste.de/produkte/Fluorouracil-HEXAL-50-mg-ml-Injektionsloesung-100-ml_546519/fachinformation

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

Gemcitabin: http://www.success-studie.de/b/downloads/Fachinfo/GemzarFI07Jan.pdf
Cisplatin: https://www.gelbe-liste.de/produkte/Cisplatin-Teva-1-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-100-ml_543960/fachinformation
Carboplatin: http://www.teva.de/index.php?eID=dumpFile&t=f&f=37532&g=-1&r=11068%2C11068&token=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
PEG-lipo. Doxorubicin: 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
Paclitaxel: https://medikamio.com/de-de/medikamente/paclitaxel-ratiopharm/pil
Nab-Paclitaxel: https://www.gelbe-liste.de/produkte/Abraxane-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

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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
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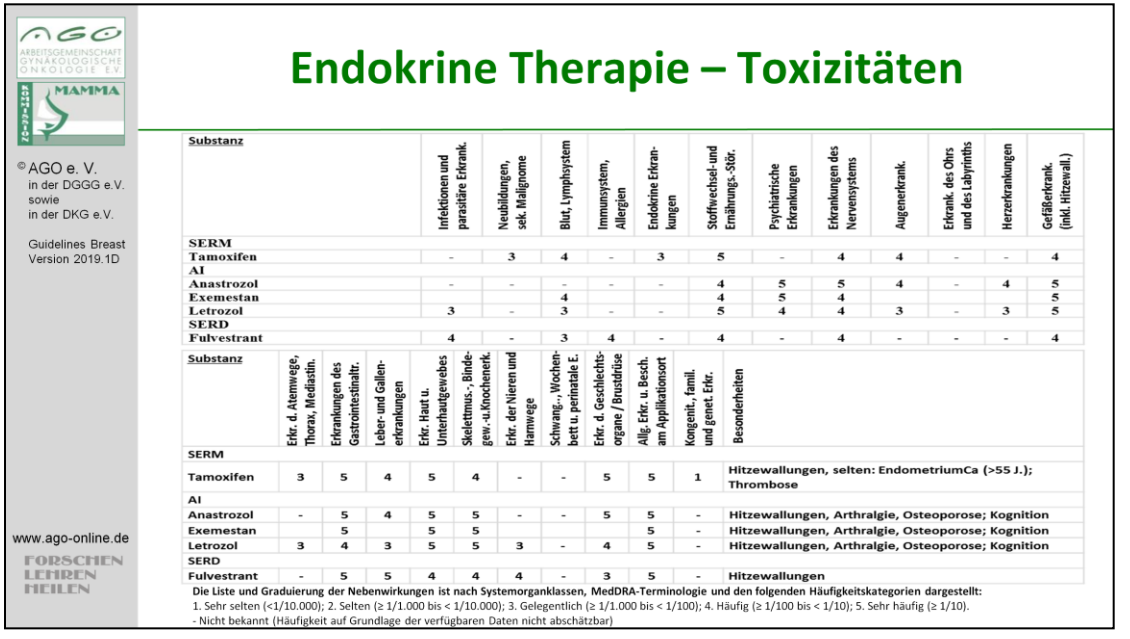
12. Madeddu C, Deidda M, Piras A, et al. Pathophysiology of cardiotoxicity induced by nonanthracycline chemotherapy. J Cardiovasc Med (Hagerstown). 2016 May;17 Suppl 1 Special issue on Cardiotoxicity from Antiblastic Drugs and Cardioprotection:e12-e18. Review.



Endokrine Therapie – Toxizitäten

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Substanz	Infektionen und parasitäre Erkrank.	Neubildungen, sek. Malignome	Blut, Lymphsystem	Immunsystem, Allergien	Endokrine Erkrankungen	Stoffwechsel- und Ernährungs.-Stör.	Psychiatrische Erkrankungen	Erkrankungen des Nervensystems	Augenerkrank.	Erkrank. des Ohrs und des Labyrinths	Herzerkrankungen	Gefäßerkrank. (inkl. Hitzewall.)
SERM												
Tamoxifen	-	3	4	-	3	5	-	4	4	-	-	4
AI												
Anastrozol	-	-	-	-	-	4	5	5	4	-	4	5
Exemestan			4			4	5	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.Knochenerk.	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	-	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)

<u>Nebenwirkungskategorien - MedDRA (Medical Dictionary for Regulatory Activities)</u>
MedDRA: https://www.meddra.org/ bzw.
https://www.meddra.org/sites/default/files/guidance/file/intguide_20_1_english_0.pdf

<u>Quellen für die Fachinformationen (Download 19.01.2018)</u>
Tamoxifen: 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
Letrozol: 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

Nebenwirkungen nach Organsystemen
Inzidenz, Prävention, Therapie

1. Infektionen u. parasitäre Erkrankungen

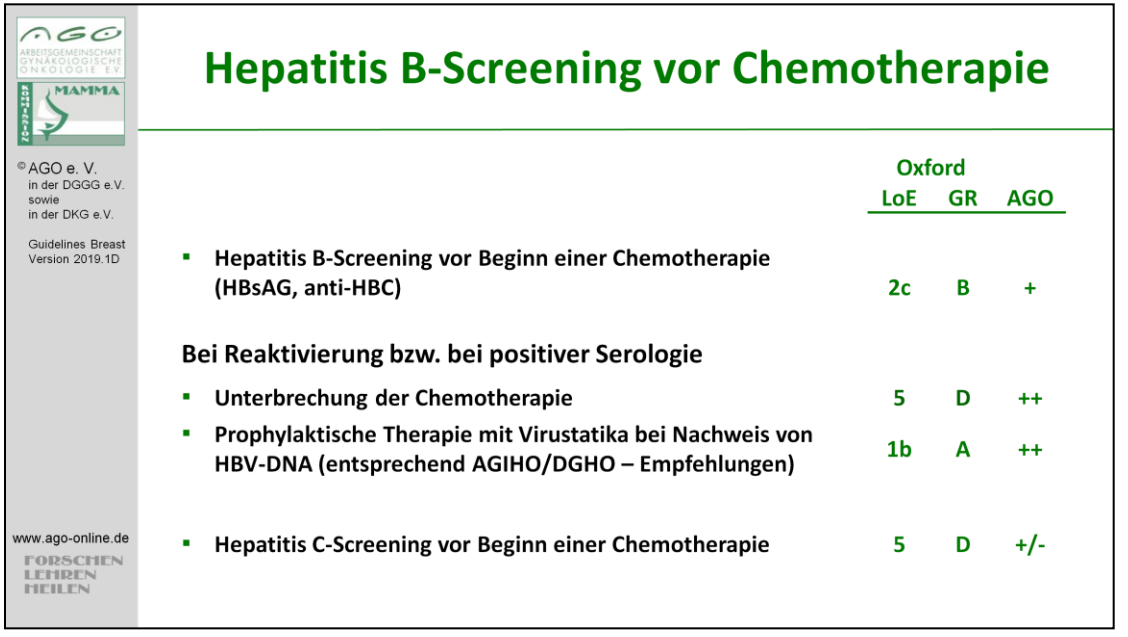
- Allgemeine Infektionsprophylaxe
- Hepatitis B-Screening

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



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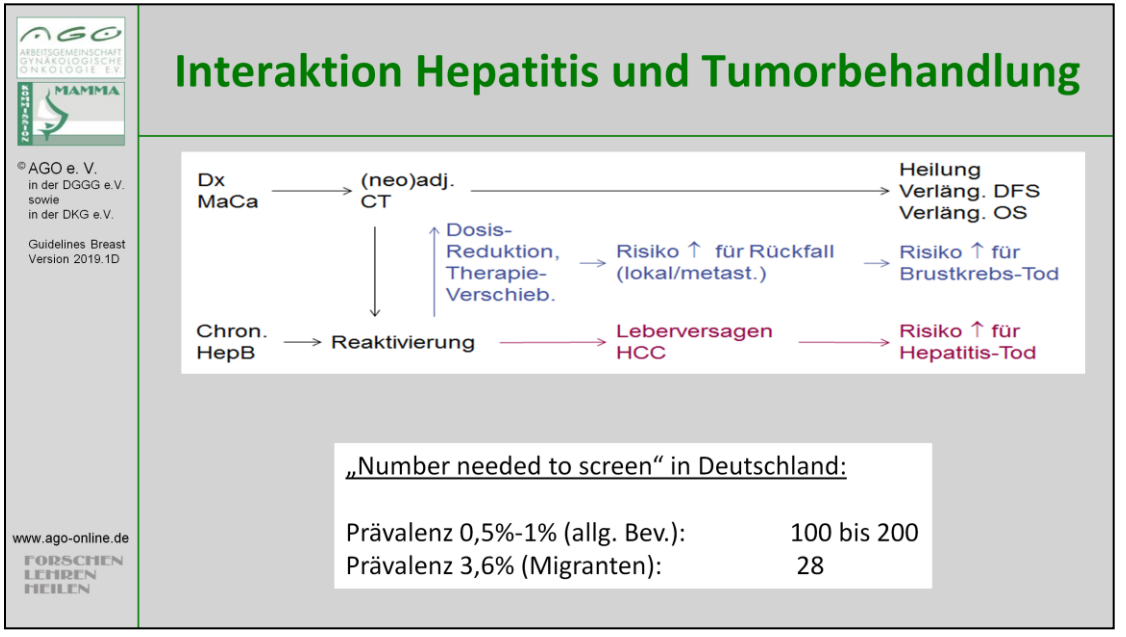

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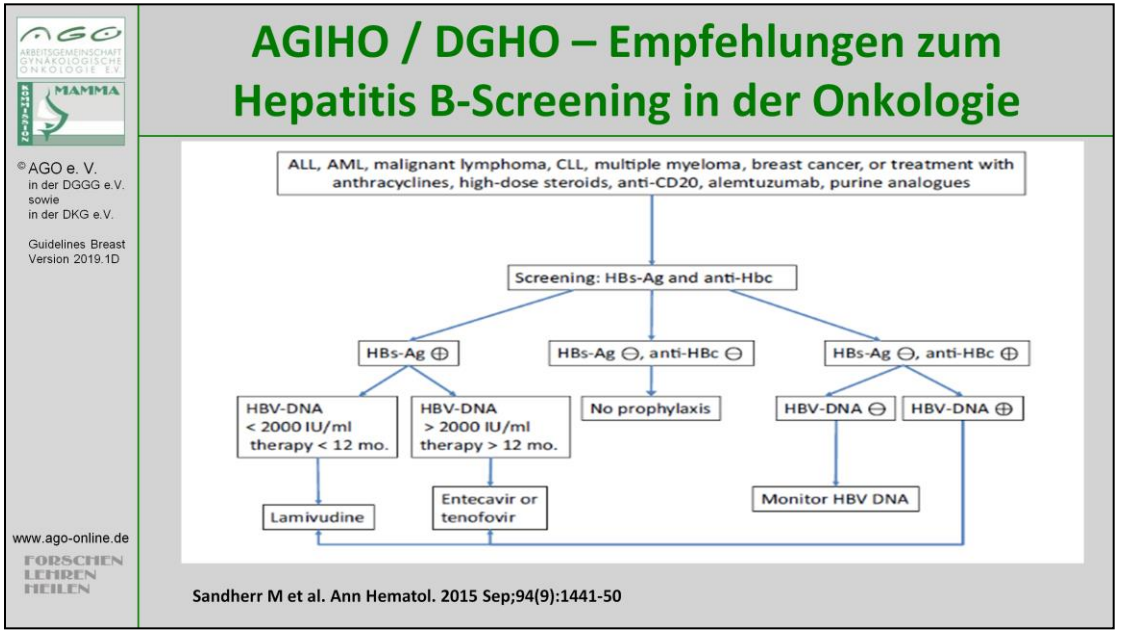

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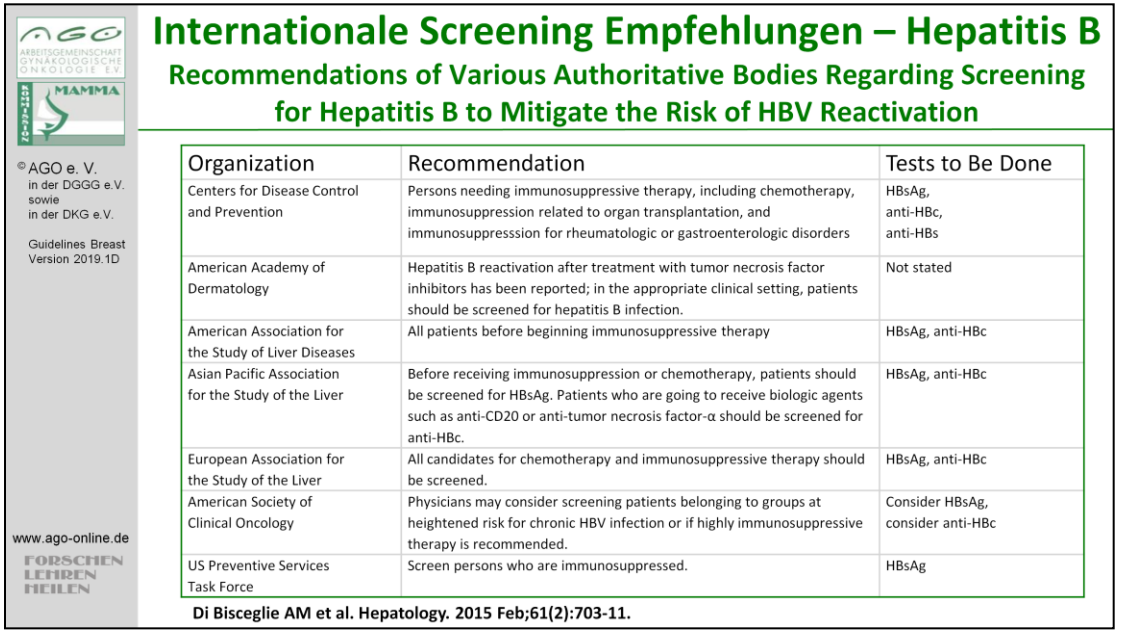

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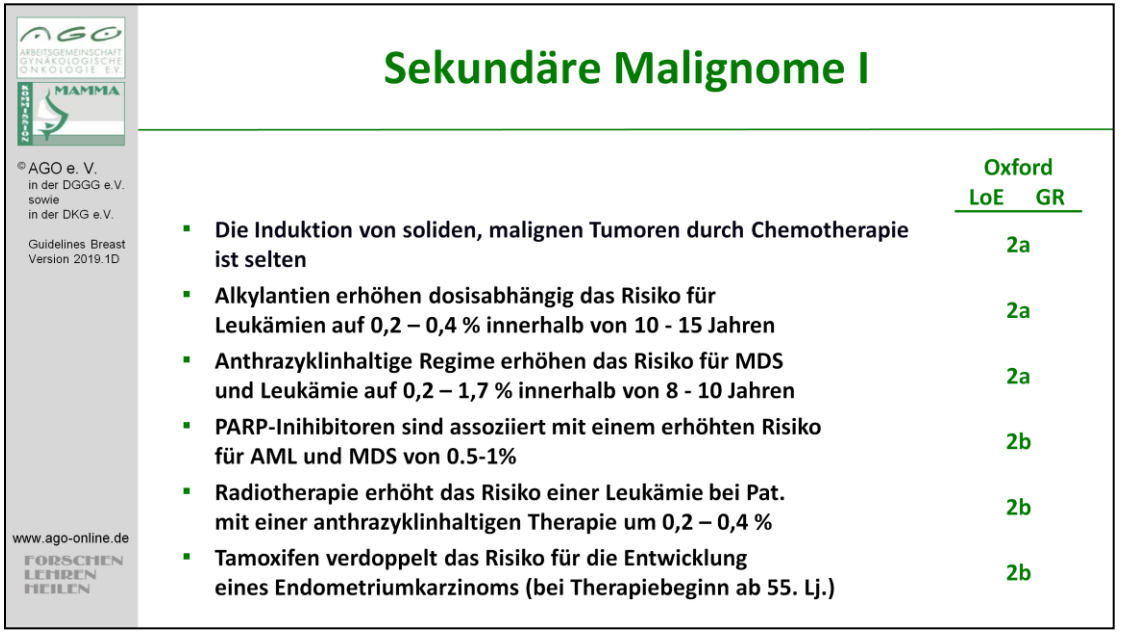
Guidelines Breast
Version 2019.1D

Nebenwirkungen nach Organsystemen

Inzidenz, Prävention, Therapie

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



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Tamoxifen and endometrial cancer

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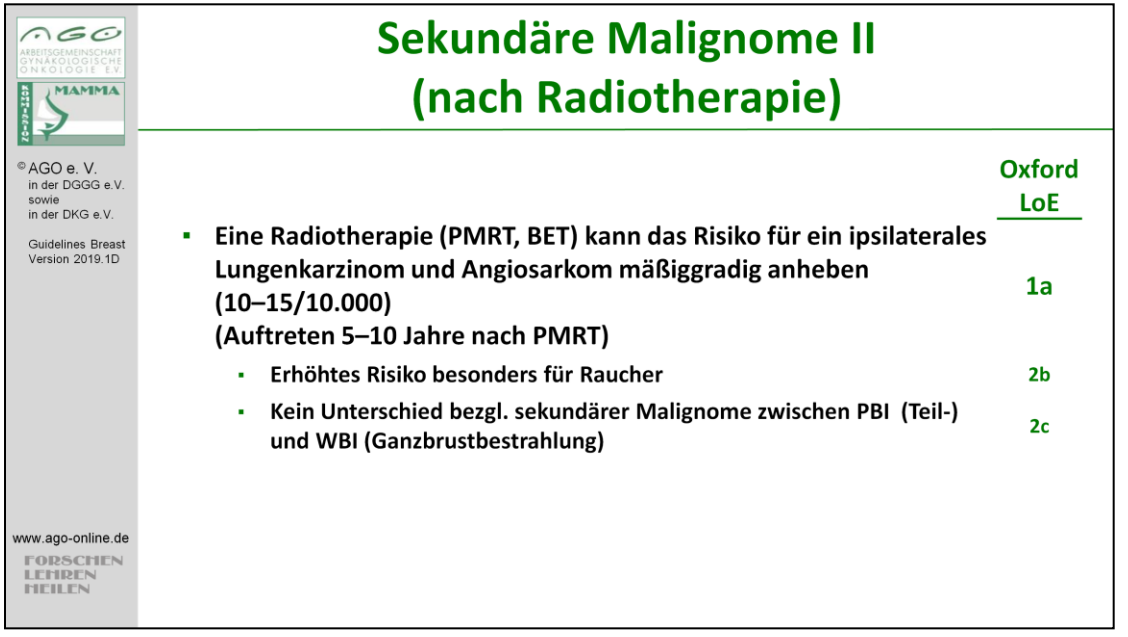

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Guidelines Breast
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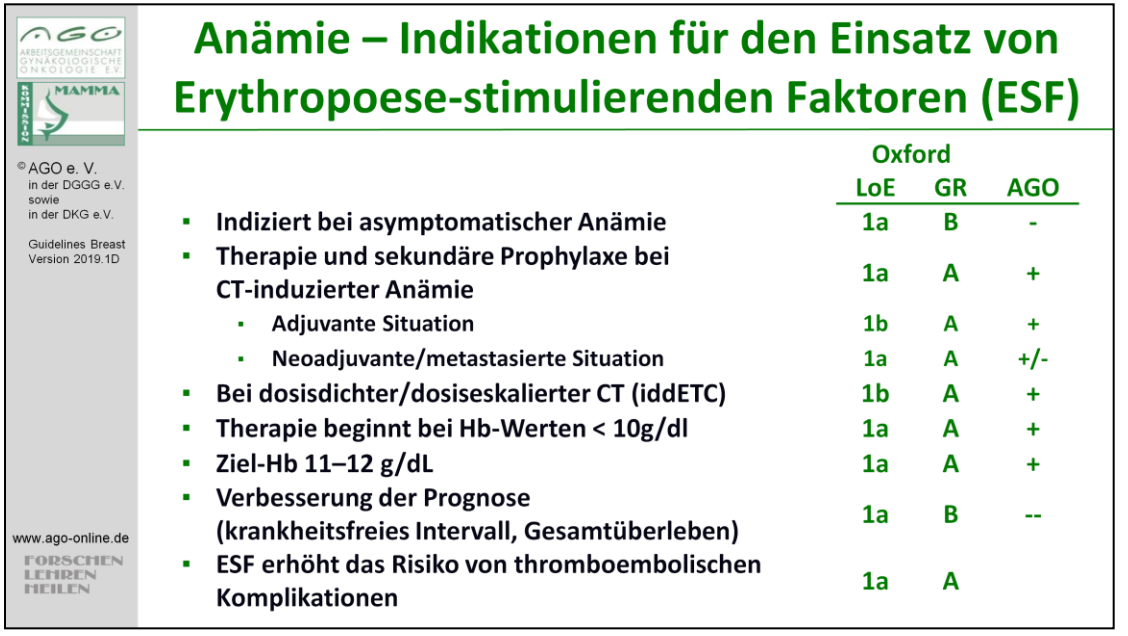
Nebenwirkungen nach Organsystemen
Inzidenz, Prävention, Therapie

3. Erkrankungen des Blutes und des Lymphsystems

- Anämie
- Neutropenie
- Febrile Neutropenie



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2. Rodgers GM, Gilreath JA et al: Cancer- and chemotherapy-induced anemia. NCCN Clinical Practice Guidelines in Oncology 2.2015. Available from: URL: http://www.nccn.org
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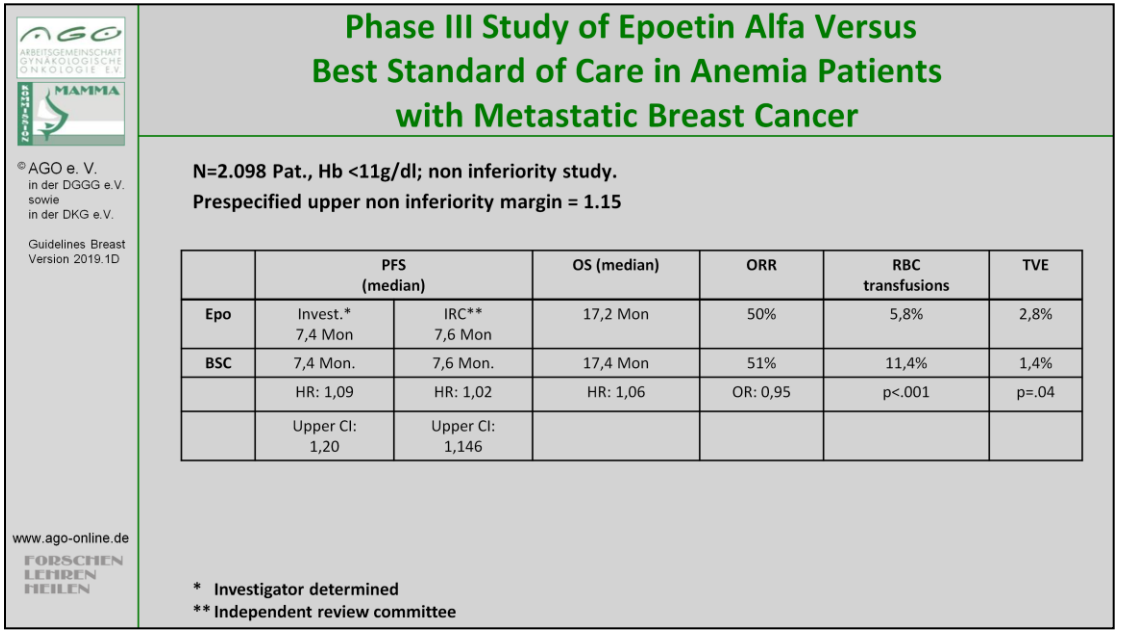

Phase III Study of Epoetin Alfa Versus Best Standard of Care in Anemia Patients with Metastatic Breast Cancer

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
Epo	Invest.* 7,4 Mon	IRC** 7,6 Mon	17,2 Mon	50%	5,8%	2,8%
BSC	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**

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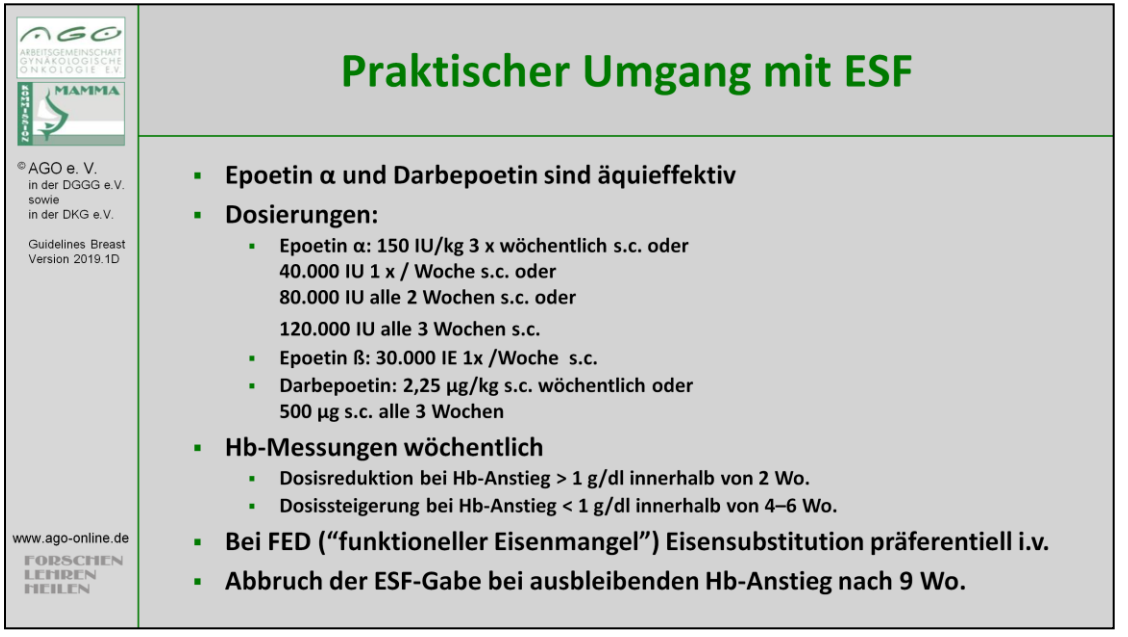

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<u>Relevante Leitlinien</u>

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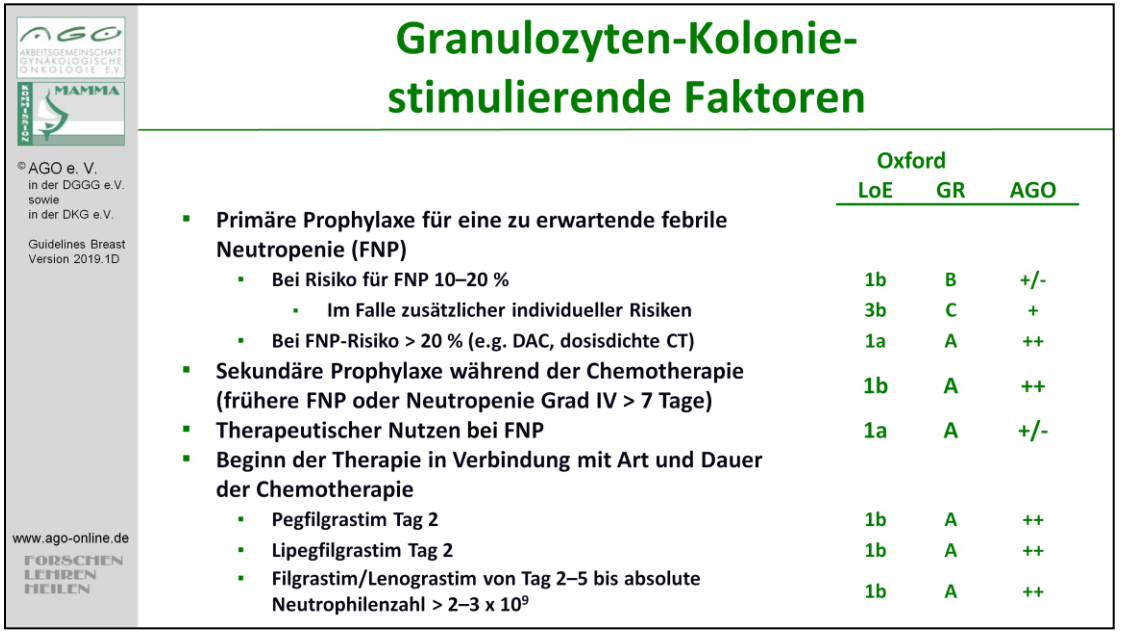

Relevante Leitlinien

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)
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Statements 1-4

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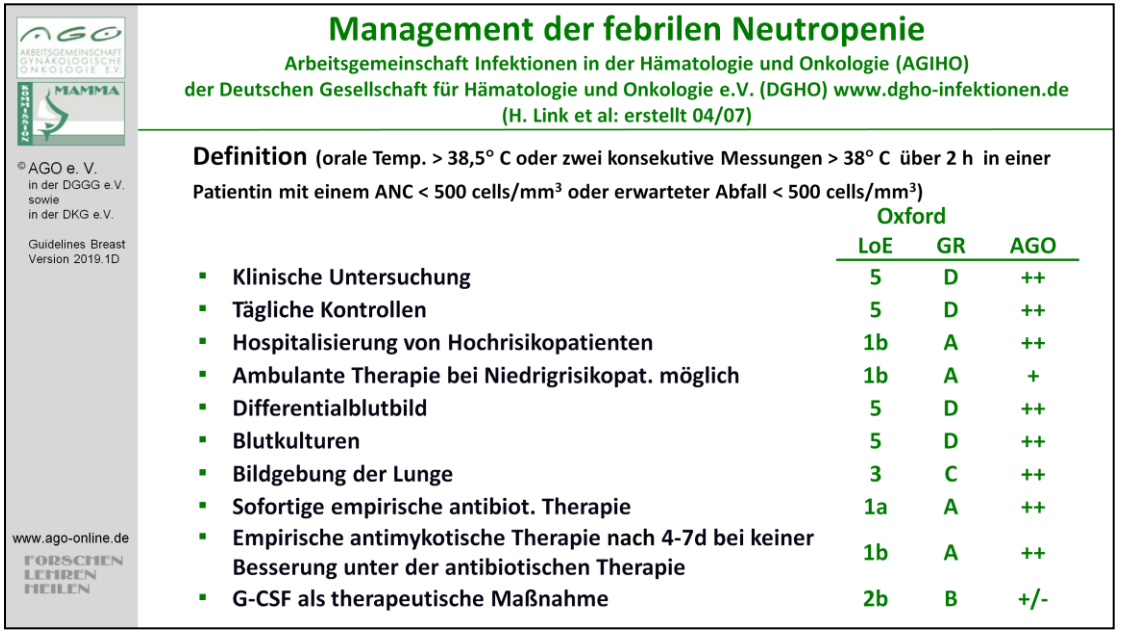

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Empirische Antibiotikatherapie

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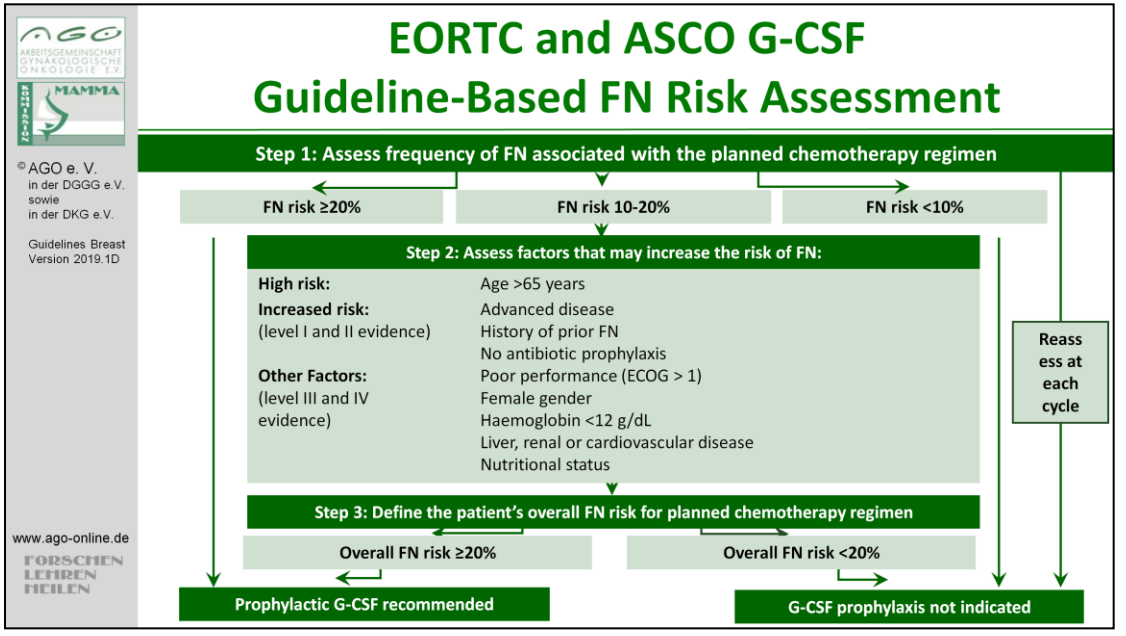
Die Empfehlungen zur empirischen Antibiotikatherapie unterliegen einem infektionsbiologisch bedingten Wechsel und bedürfen der beständigen fachkundigen Anpassung.

Die Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO) www.dgho-infektionen.de gibt aktuelle Hinweise.



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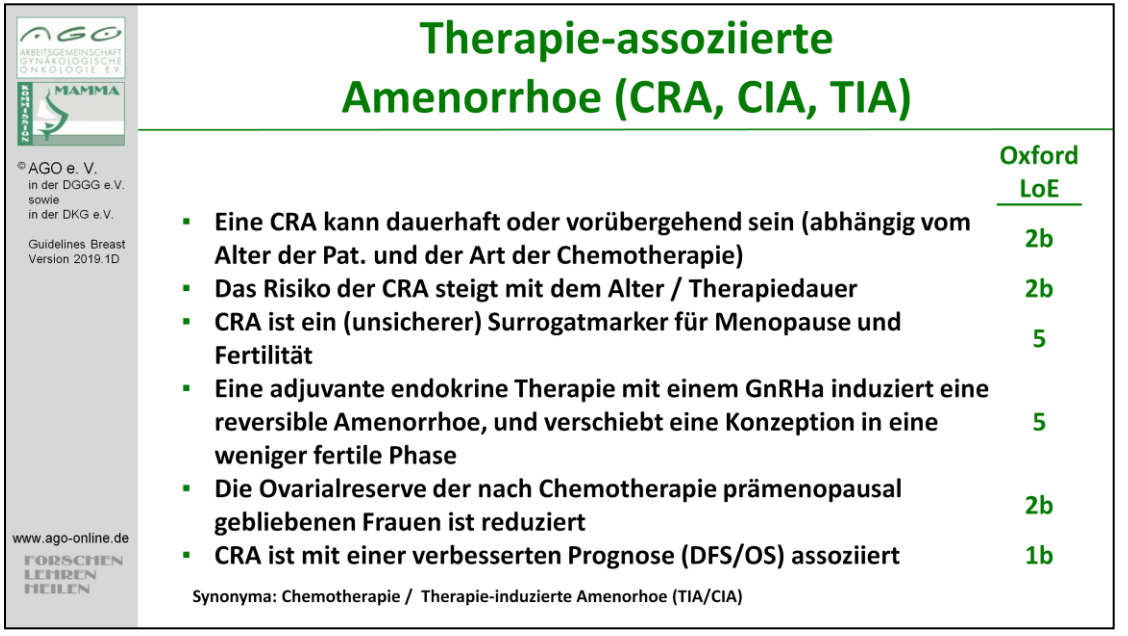
4. Endokrine Erkrankungen



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Guidelines Breast
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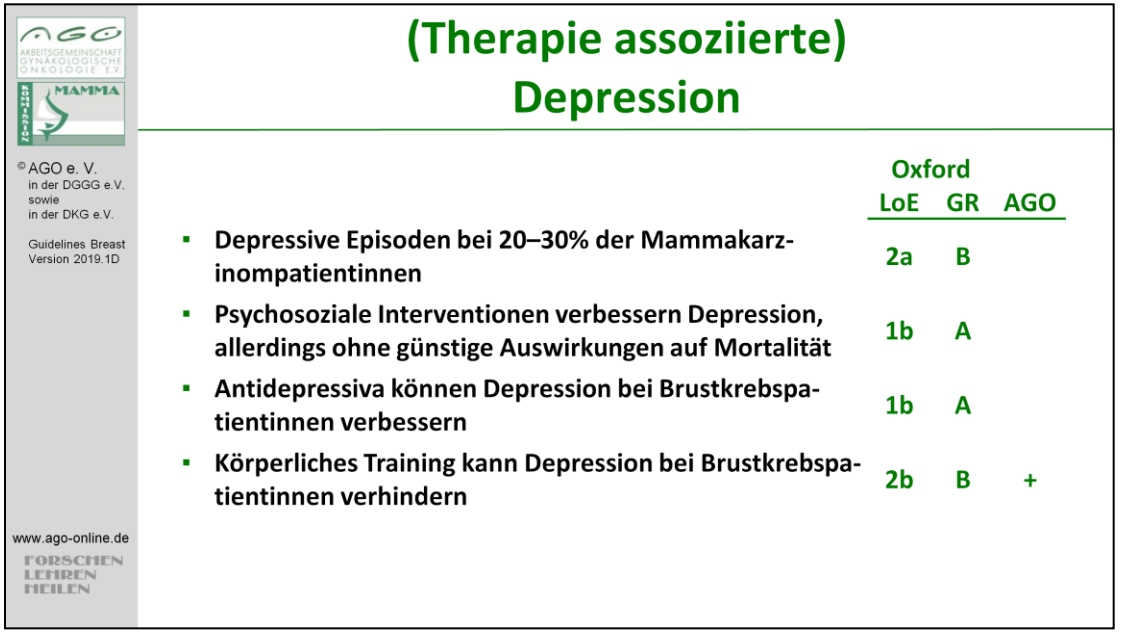
Nebenwirkungen nach Organsystemen
Inzidenz, Prävention, Therapie

5. Psychiatrische Erkrankungen

- Depression
- Fatigue
- Kognitive Störungen
- Schlafstörungen



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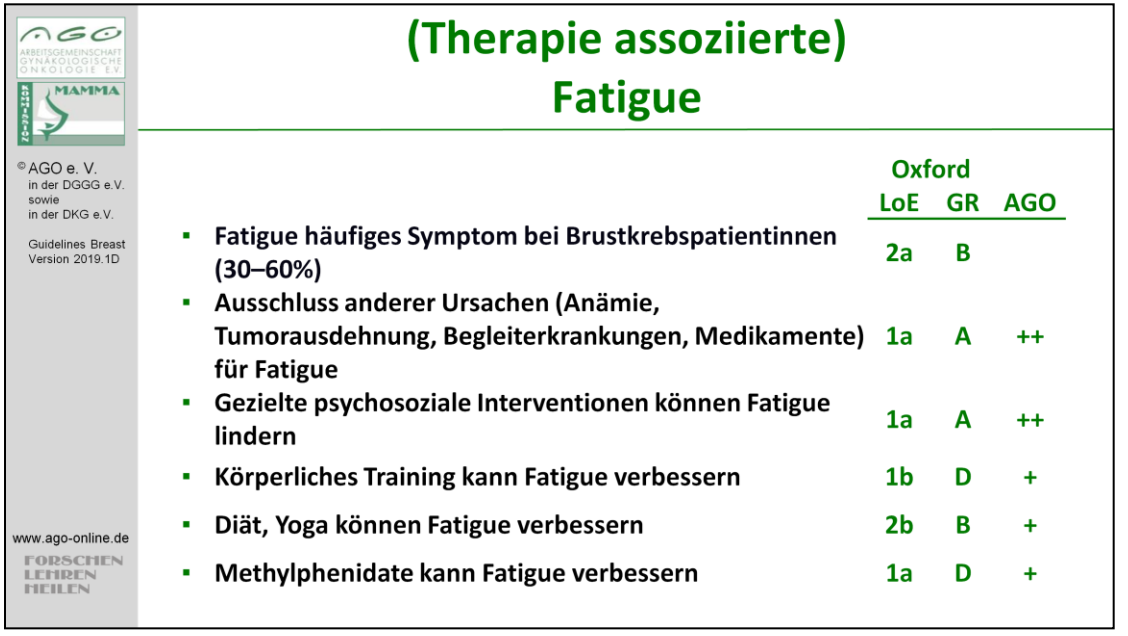

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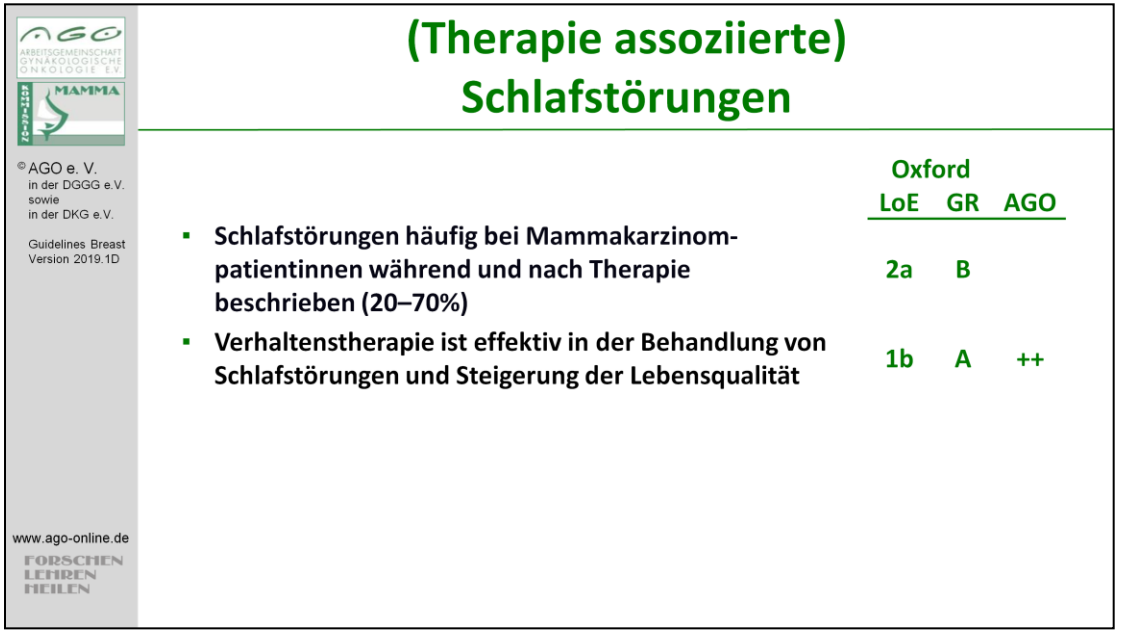

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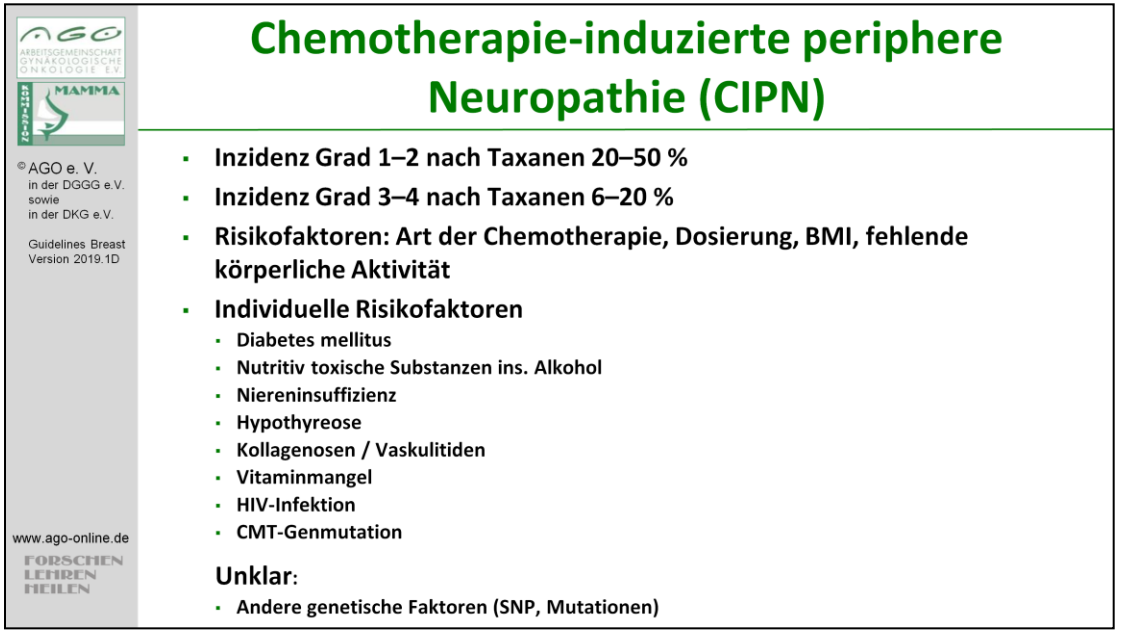
Guidelines Breast
Version 2019.1D

Nebenwirkungen nach Organsystemen
Inzidenz, Prävention, Therapie

6. Erkrankungen des Nervensystems

- **Chemotherapie induzierte periphere Neuropathie (CIPN)**



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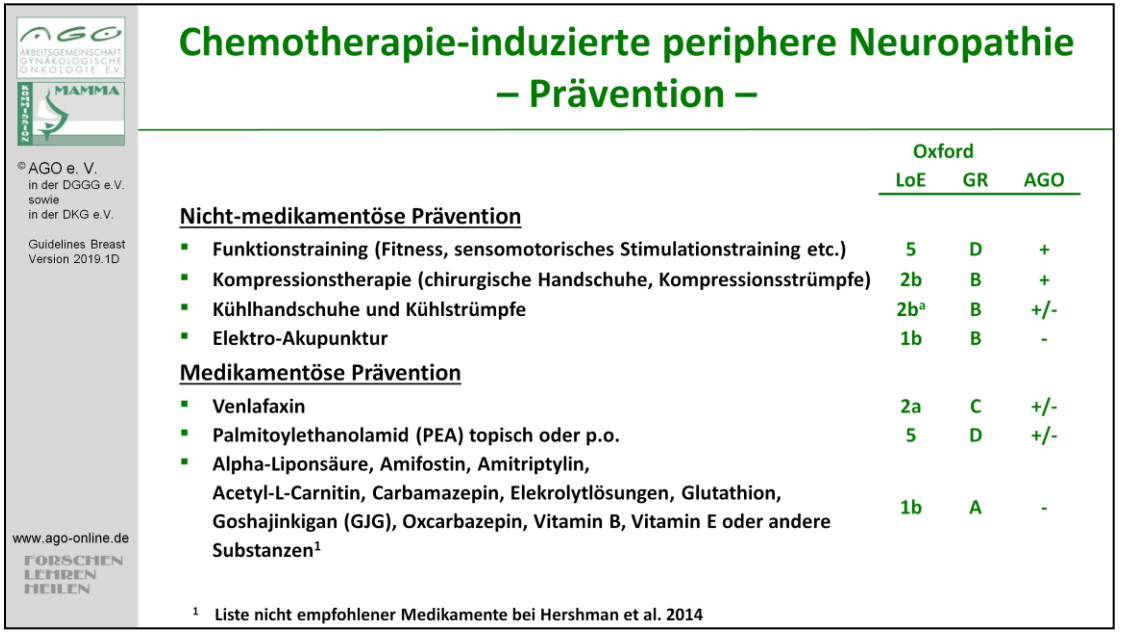

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Nicht-medikamentöse Prävention

Funktionstraining

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1. Hanai A, Ishiguro H, Sozu T et al. (2016) The effects of frozen gloves and socks on paclitaxel-induced peripheral neuropathy among patientswith breast cancer: A selfcontrolled clinical trial. J ClinOncol 34(suppl): (abstr 10022). http://meetinglibrary.asco.org/content/166655-176.
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Elektro-Akupunktur

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Medikamentöse Prävention

Venlafaxin

1. Aziz MT, Good BL, Lowe DK. Serotonin-norepinephrine reuptake inhibitors for the management of chemotherapy-induced peripheral neuropathy. Ann Pharmacother. 2014 May;48(5):626-32.
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3. Gallagher HC, Gallagher RM, Butler M, et al.: Venlafaxine for neuropathic pain in adults. Cochrane Database Syst Rev. 2015 Aug 23;(8):CD011091.

Palmitoylethanolamid (PEA)

1. Lombardi G, Miglio G, Varsaldi F, et al.: Oxyhomologation of the amide bond potentiates neuroprotective effects of the endolipid N-palmitoylethanolamine.
   J Pharmacol Exp Ther. 2007 Feb;320(2):599-606
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Verschiedene Substanzen

1. Schloss J, Colosimo M, Vitetta L. Herbal medicines and chemotherapy induced peripheral neuropathy (CIPN): A critical literature review. Crit Rev Food Sci Nutr. 2017 Apr 13;57(6):1107-1118.
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1. Hershman DL, Unger JM, Crew KD, et al.: Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for the prevention of taxane-induced neuropathy in women undergoing adjuvant breast cancer therapy. J Clin Oncol. 2013 Jul 10;31(20):2627-33.
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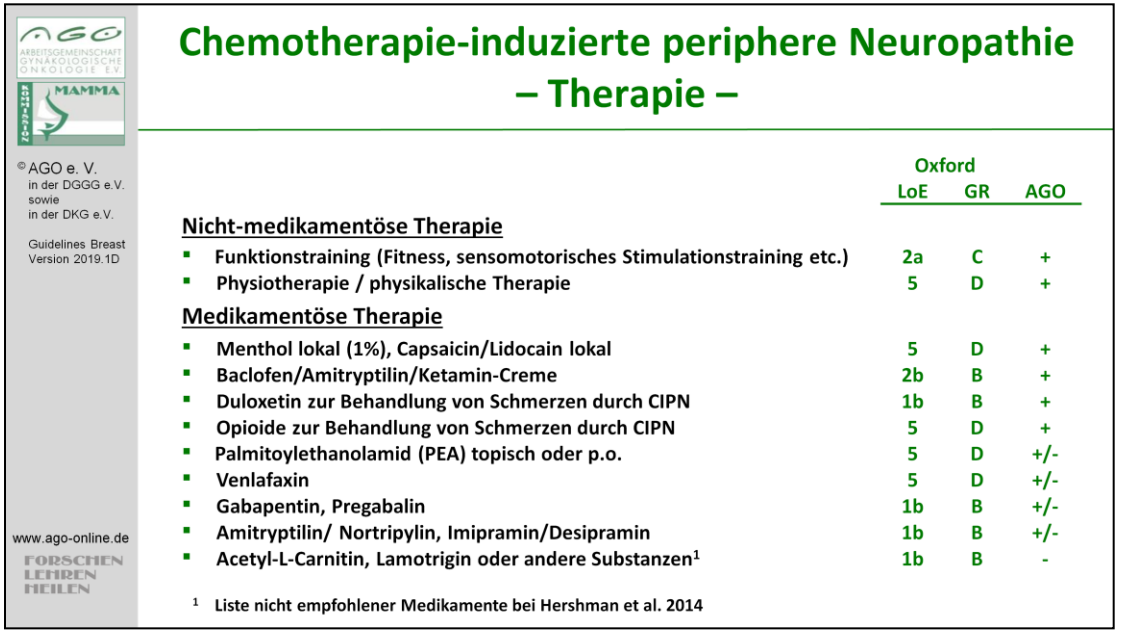

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Nicht-medikamentöse Therapie

Funktionstraining

1. Duregon F, Vendramin B, Bullo V, et al.: Effects of exercise on cancer patients suffering chemotherapy-induced peripheral neuropathy undergoing treatment: A systematic review. Crit Rev Oncol Hematol. 2018 Jan;121:90-100.

Medikamentöse Therapie

Menthol / Capsaicin

1. Fallon MT, Storey DJ, Krishan A, et al.: Cancer treatment-related neuropathic pain: proof of concept study with menthol--a TRPM8 agonist. Support Care Cancer. 2015 Sep;23(9):2769-77
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Baclofen/Amitryptilin/Ketamin-Creme

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Duloxetin

1. Smith EM, Pang H, Cirrincione C, et al.: Alliance for Clinical Trials in Oncology. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA. 2013 Apr 3;309(13):1359-67

Opioide

Palmitoylethanolamid (PEA)

1. Lombardi G, Miglio G, Varsaldi F, et al.: Oxyhomologation of the amide bond potentiates neuroprotective effects of the endolipid N-palmitoylethanolamine.
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Venlafaxin

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Gabapentin, Pregabalin:

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Amitryptilin/Nortriptylin

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Acetyl-L-Carnitin, Lamotrigin oder andere Substanzen:

1. Rao RD, Flynn PJ, Sloan JA, et al.: Efficacy of lamotrigine in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled trial, N01C3. Cancer. 2008 Jun 15;112(12):2802-8
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Guidelines Breast
Version 2019.1D

Nebenwirkungen nach Organsystemen
Inzidenz, Prävention, Therapie

7. Herzerkrankungen

Statements

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

"Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity"

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

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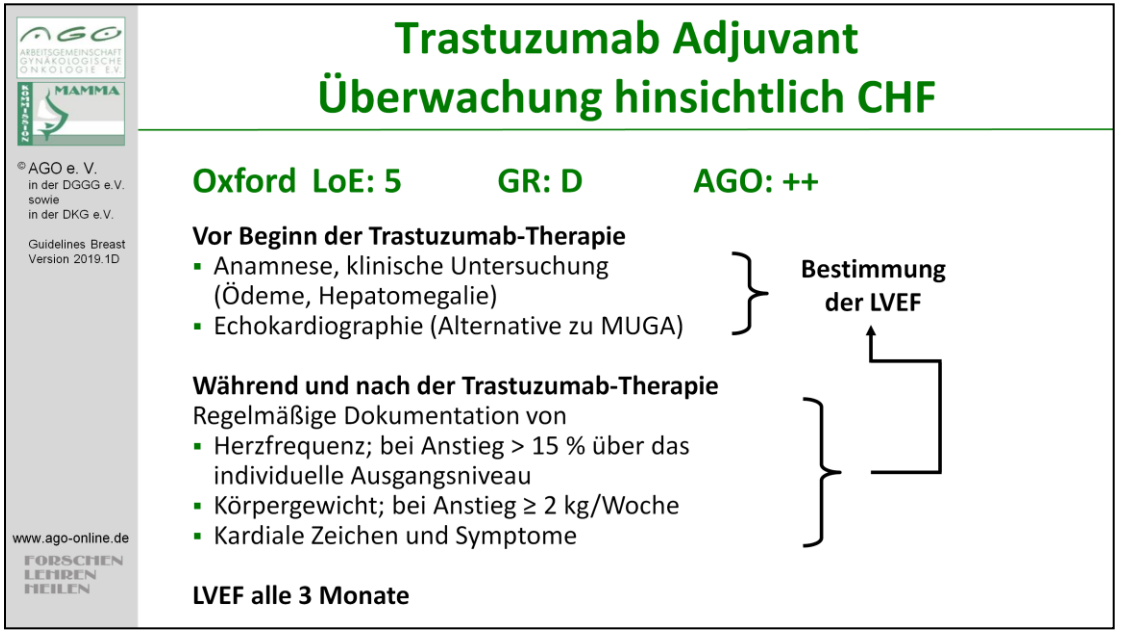

Statement: Cardiac Monitoring (5 D ++)
Vote result of the AGO recommendation: 100%

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Toxizitätssteigerungen durch Behandlungskombinationen

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

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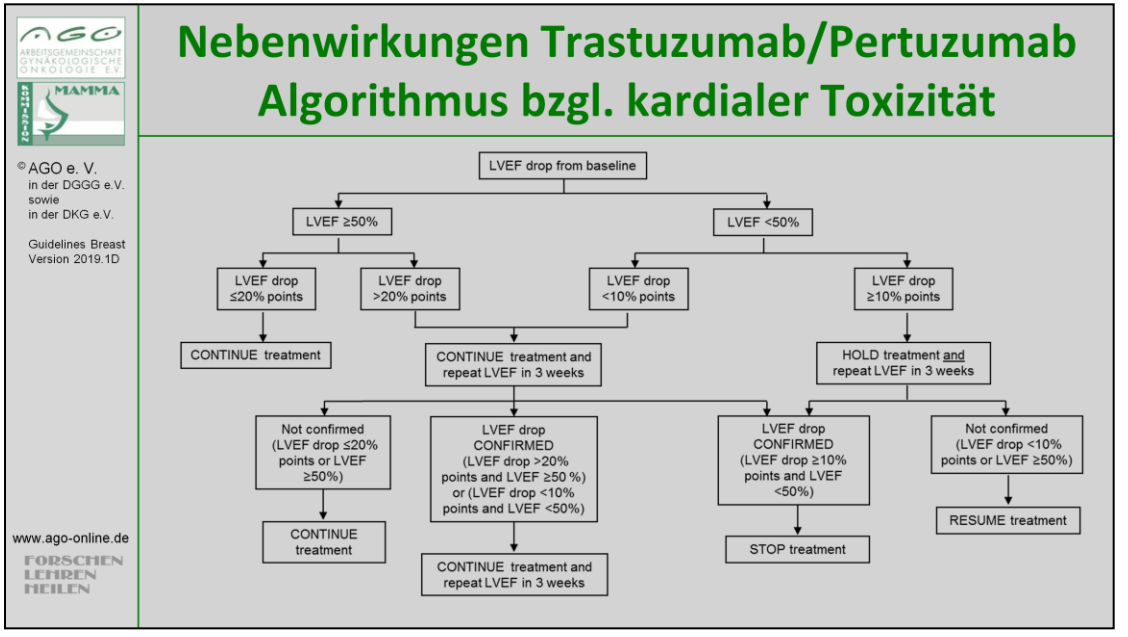

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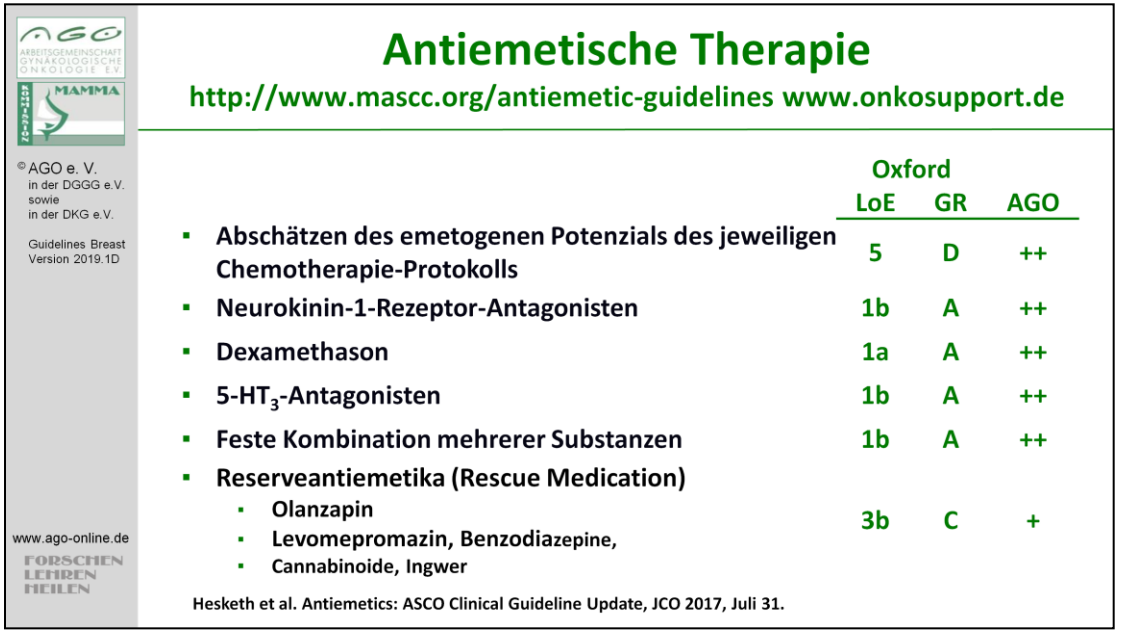
Guidelines Breast
Version 2019.1D

Nebenwirkungen nach Organsystemen
Inzidenz, Prävention, Therapie

8. **Erkrankungen des Gastrointestinaltrakts**
   - **Nausea, Emesis (Übelkeit, Erbrechen)**
   - **Mukositis**
     - **Stomatitis (Evrolimus)**
   - **Diarrhoe**
   - **Obstipation**



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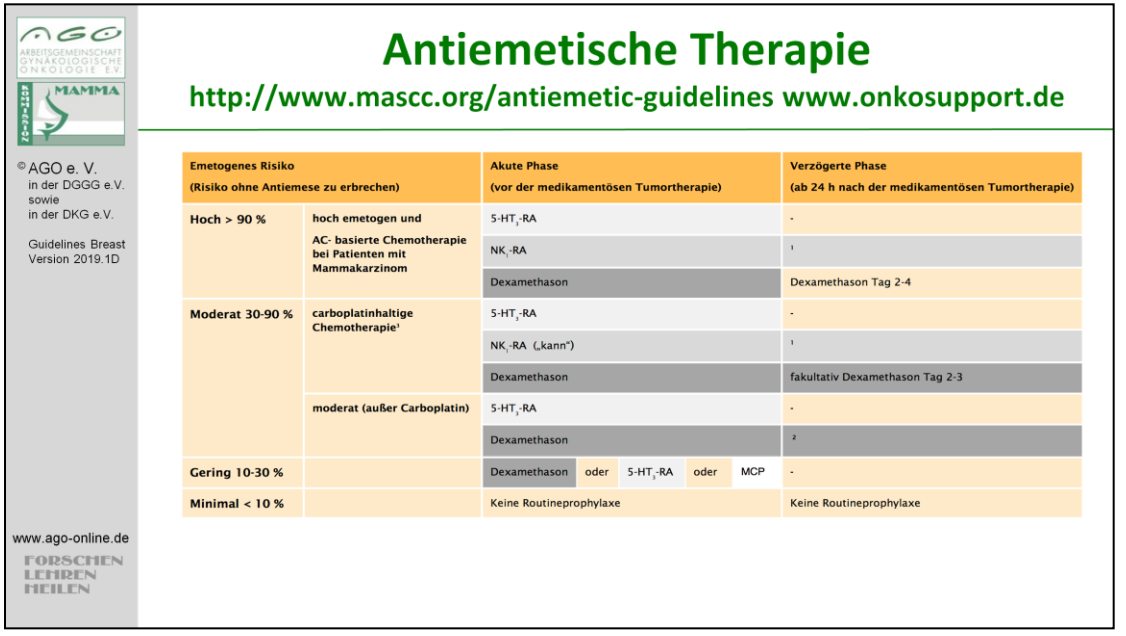

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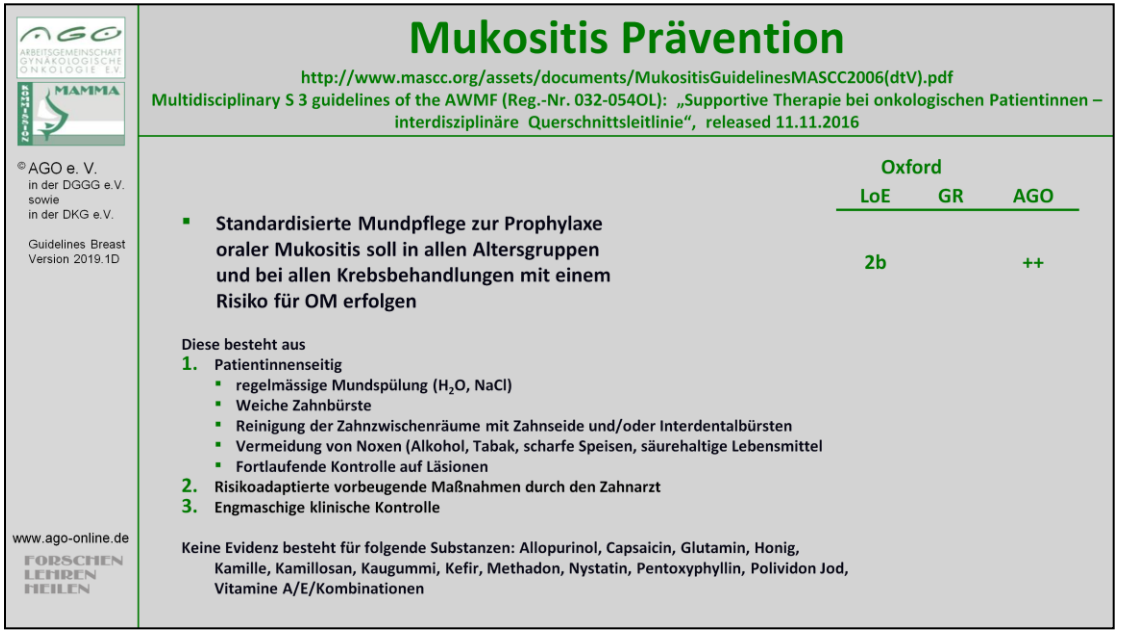
Supportive Therapie
Antiemetika

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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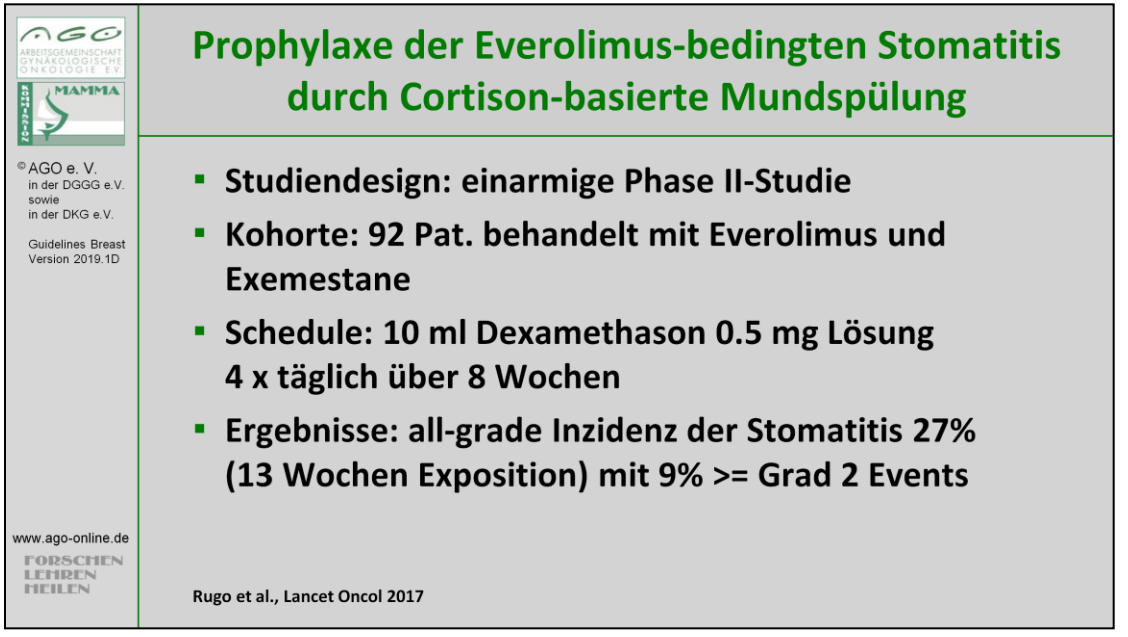

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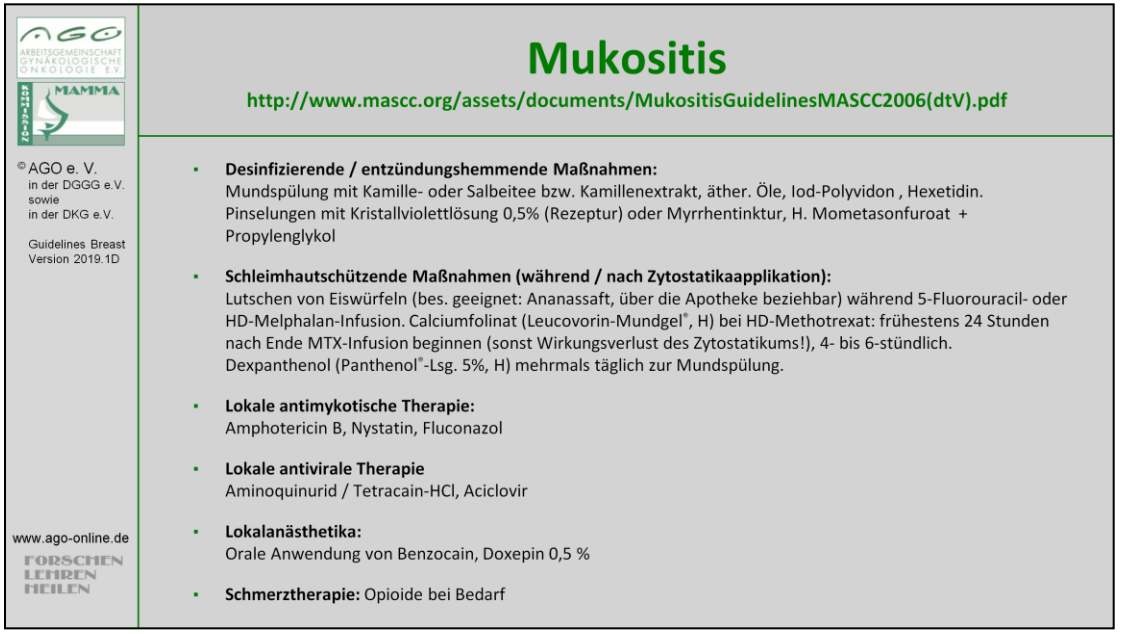

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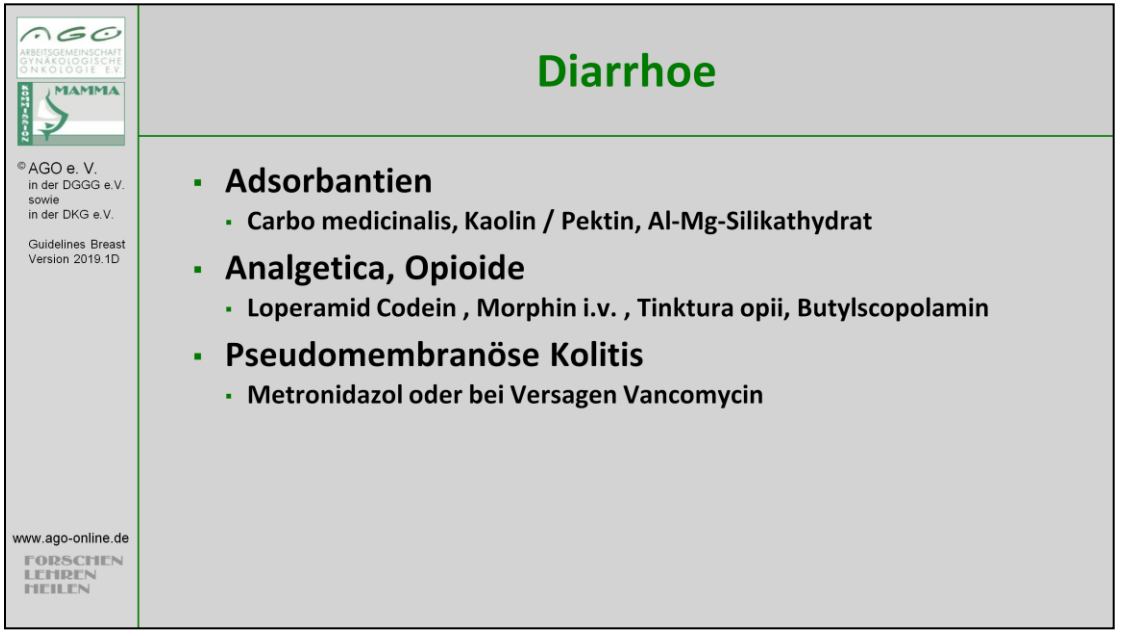

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Obstipation

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

Guidelines Breast
Version 2019.1D

Guidelines Breast
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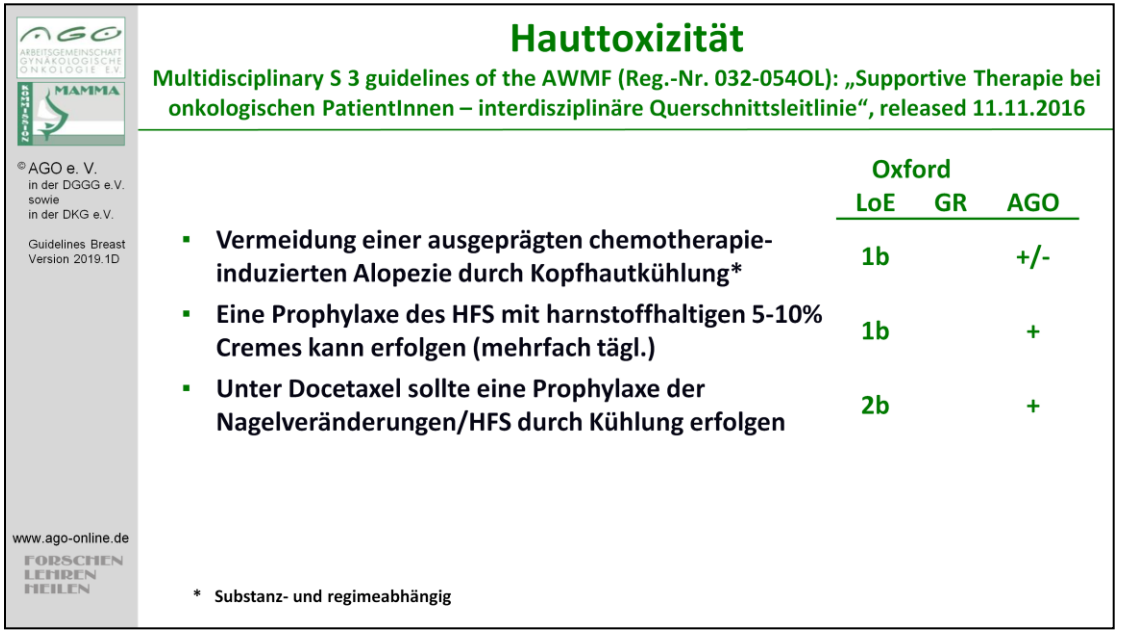
9. Erkrankungen der Haut und des Unterhautgewebes

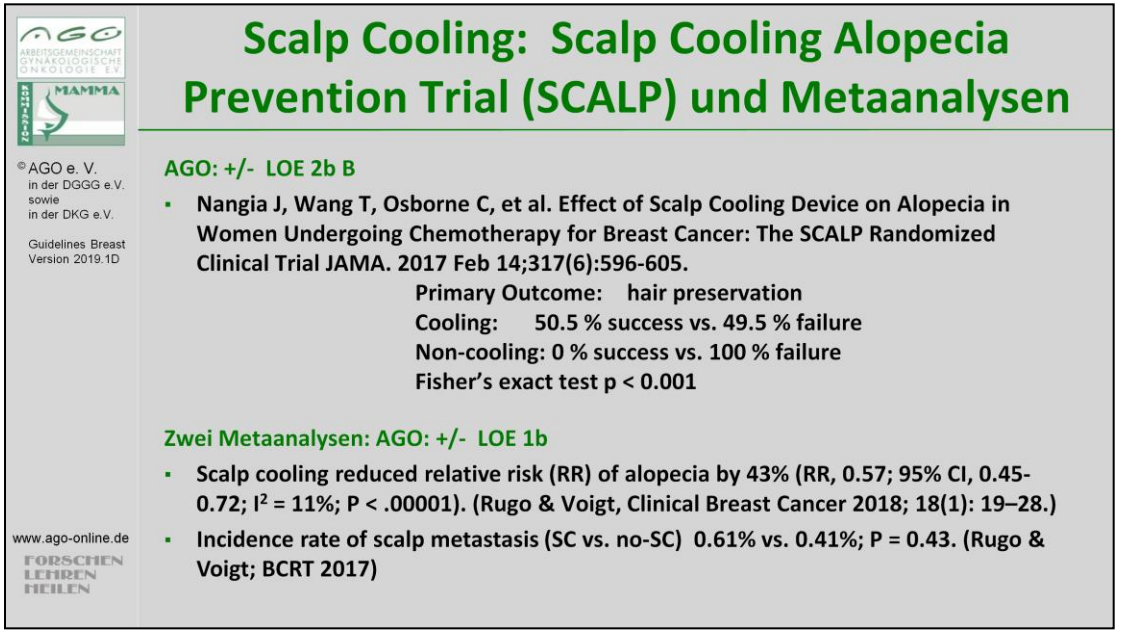


Scalp Cooling:

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



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.

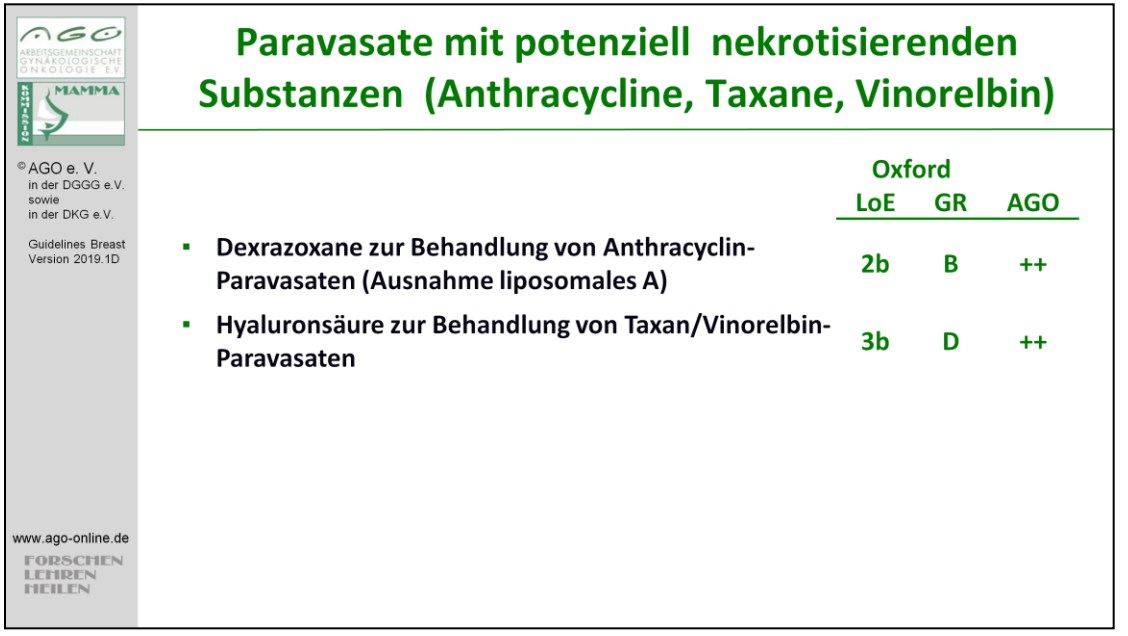
Nebenwirkungen nach Organsystemen
Inzidenz, Prävention, Therapie

10. Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen

(siehe Kapitel Osteoonkologie)

Guidelines Breast
Version 2019.1D

11. Allgemeine Erkrankungen und Beschwerden am Verabreichungsort



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.
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Hyaluronsäure

…

Paravasate
Dexrazoxane/Hyaluronsäure

Guidelines Breast
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Dexrazoxane zur Behandlung von Anthracyclin-Paravasaten

Tag 1: 1000 mg/m² (max. 2000 mg), IV 1–2 Stunden

Tag 2: 1000 mg/m² (max. 2000 mg), IV 1–2 Stunden

Tag 3: 500 mg/m² (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 Lösungsmittelt (z.B. NaCl 0.9%)**
- **Lokalanaesthesie**
- **Keine Thermotherapie bei Taxanen, trockene Wärme 4 x täglich 20 min bei Vincaalkaloiden**

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FORSCHEN
LEHREN
HEILEN

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

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
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Troponin I….
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T-DM1

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Everolimus

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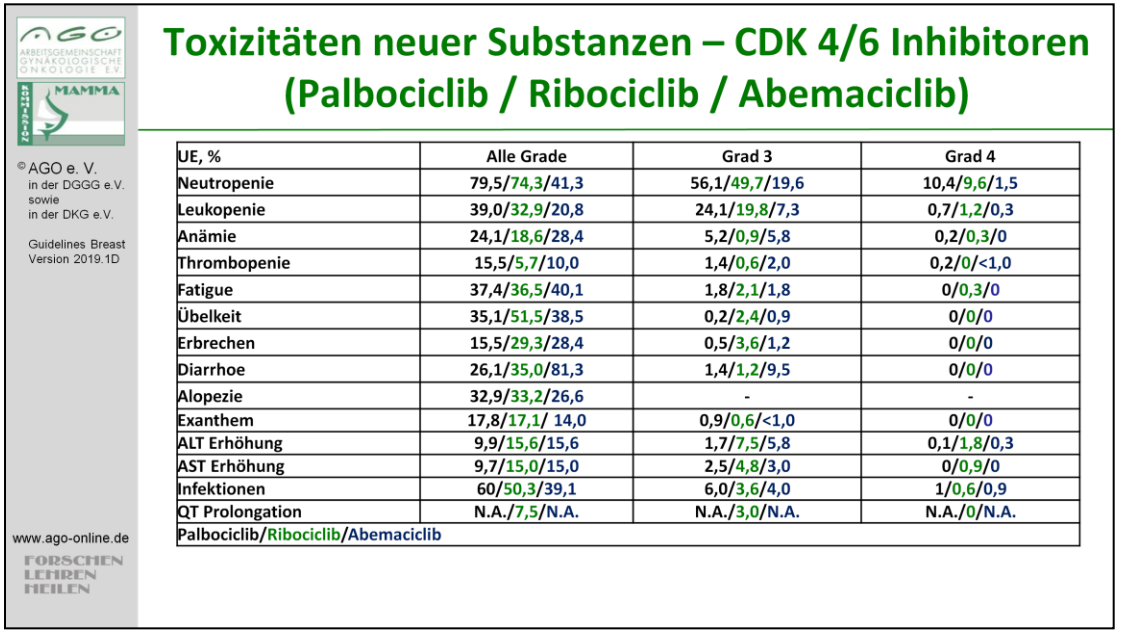

UE, %	Alle Grade	Grad 3	Grad 4
Neutropenie	79,5/74,3/41,3	56,1/49,7/19,6	10,4/9,6/1,5
Leukopenie	39,0/32,9/20,8	24,1/19,8/7,3	0,7/1,2/0,3
Anämie	24,1/18,6/28,4	5,2/0,9/5,8	0,2/0,3/0
Thrombopenie	15,5/5,7/10,0	1,4/0,6/2,0	0,2/0/<1,0
Fatigue	37,4/36,5/40,1	1,8/2,1/1,8	0/0,3/0
Übelkeit	35,1/51,5/38,5	0,2/2,4/0,9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

Palbociclib

1. Verma S, Bartlett CH, Schnell P, et al. Palbociclib in Combination With Fulvestrant in Women With Hormone Receptor-Positive/HER2-Negative Advanced Metastatic Breast Cancer: Detailed Safety Analysis From a Multicenter, Randomized, Placebo-Controlled, Phase III Study (PALOMA-3). Oncologist. 2016 Oct;21(10):1165-1175. Epub 2016 Jul 1.
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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.

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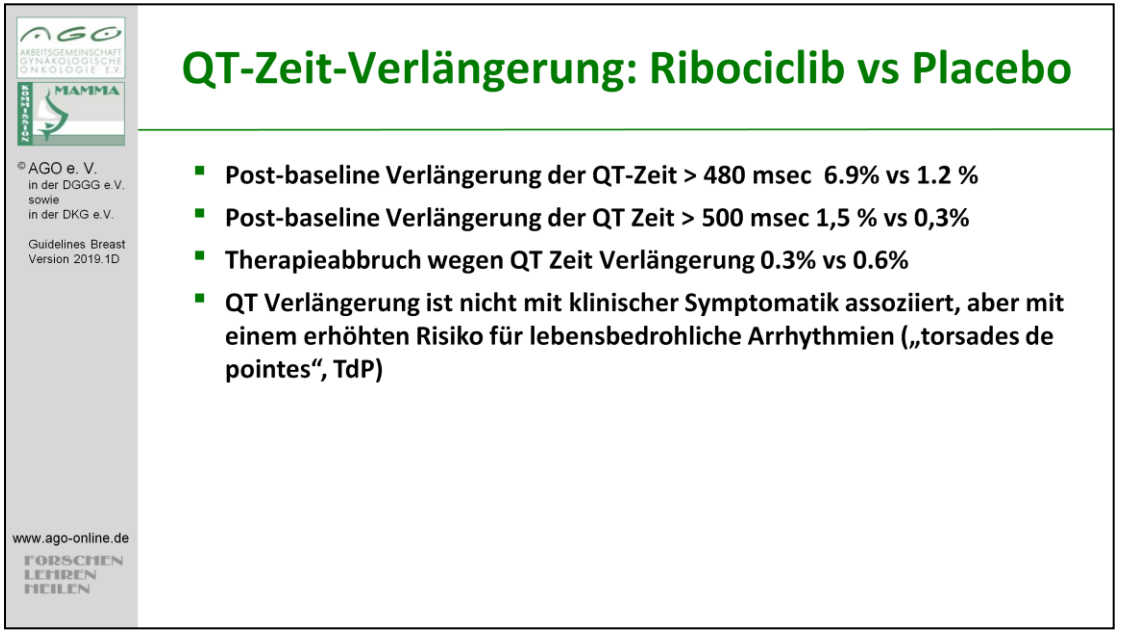

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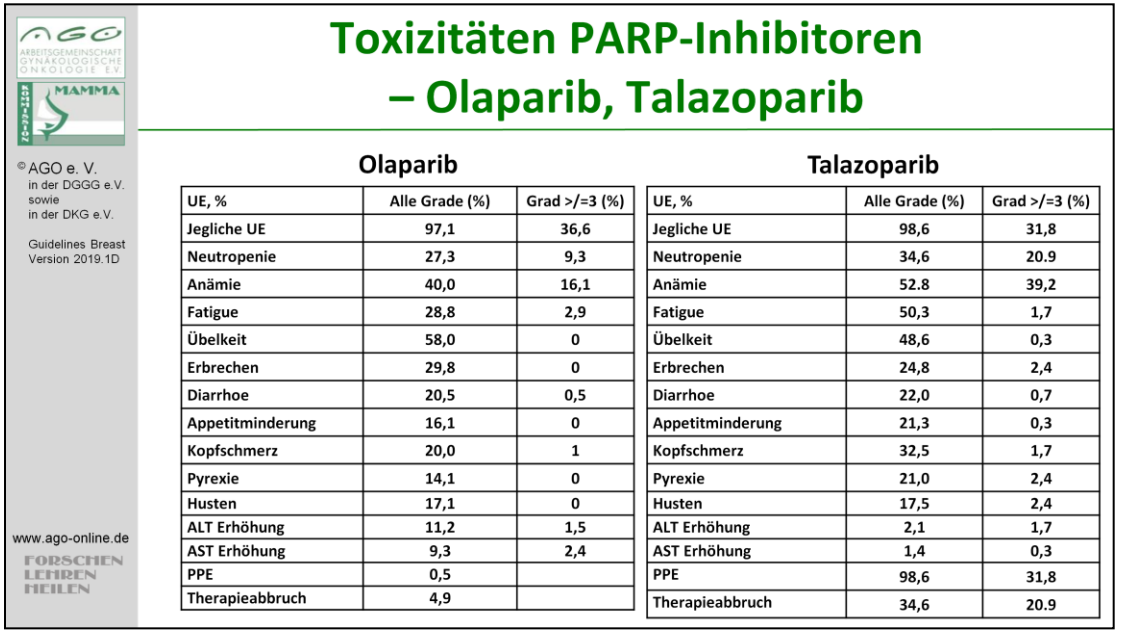
Toxizitäten neuer Substanzen: mTOR-Inhibitor (Everolimus)

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

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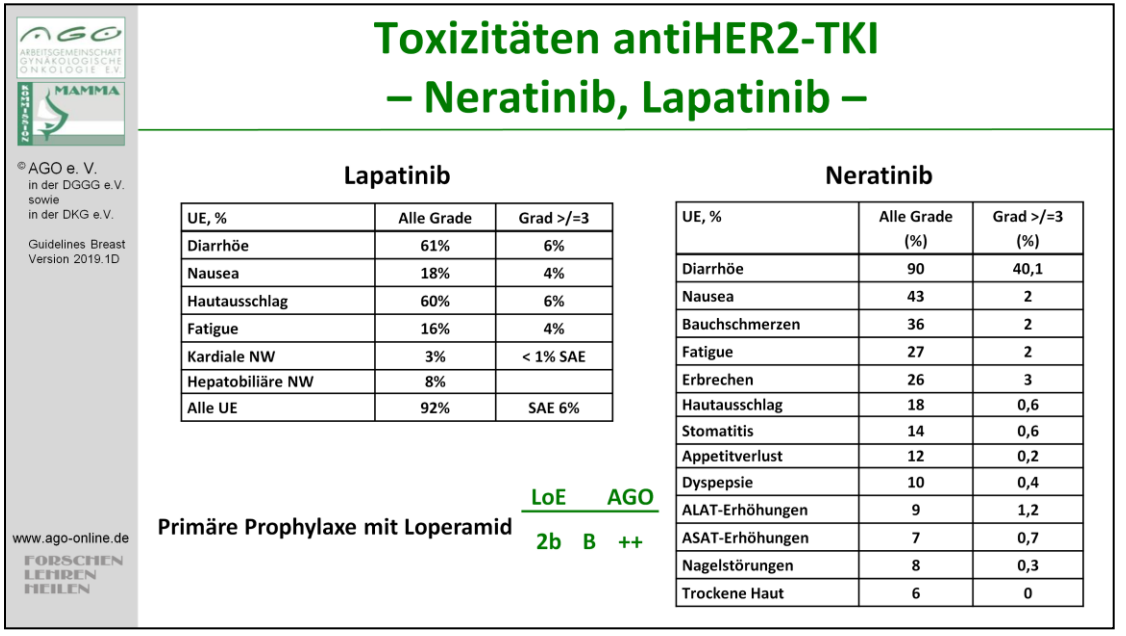

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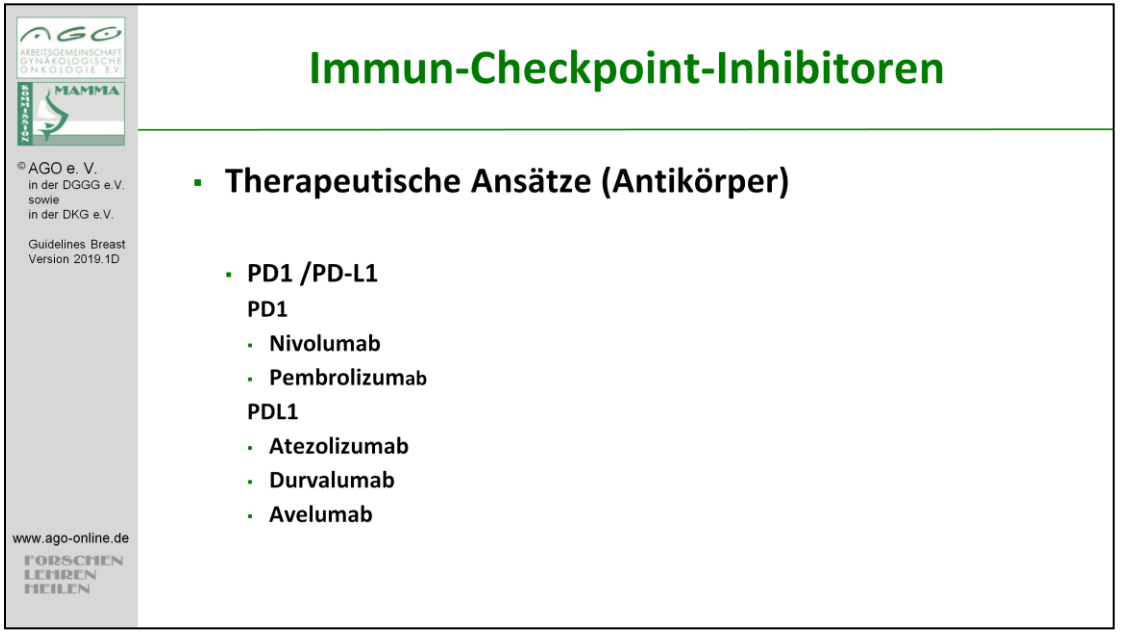
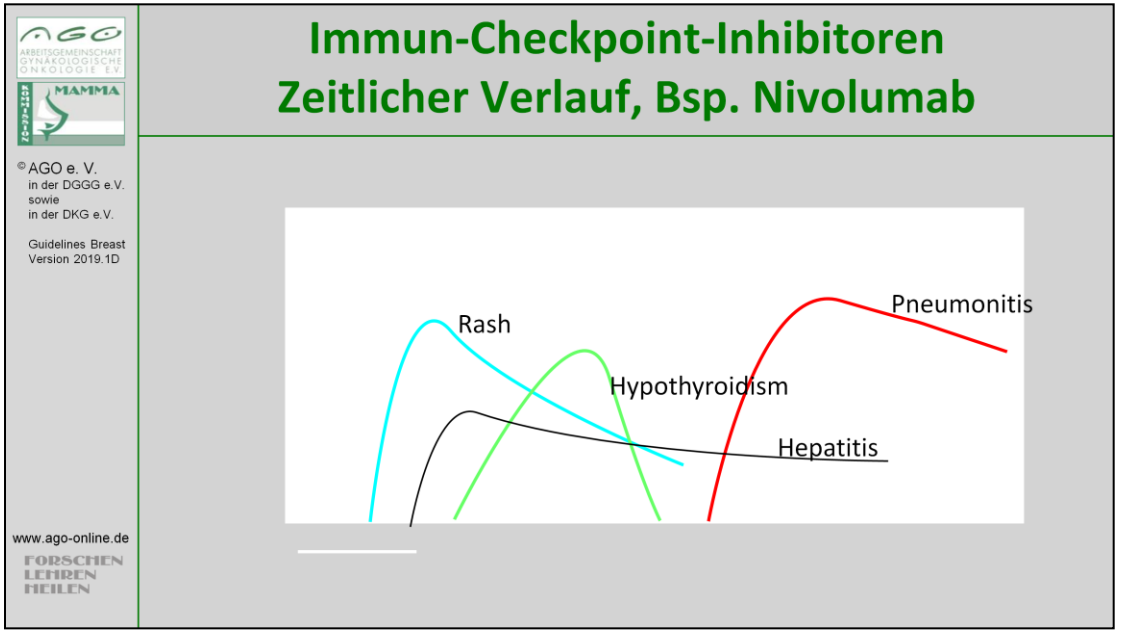


1. Haanen J, Carbonnel F, Robert C, et al, on behalf of the ESMO Guidelines Committee: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelöines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (suppl 4): 119-142. doi: ^0.1093/annonc/mdx225



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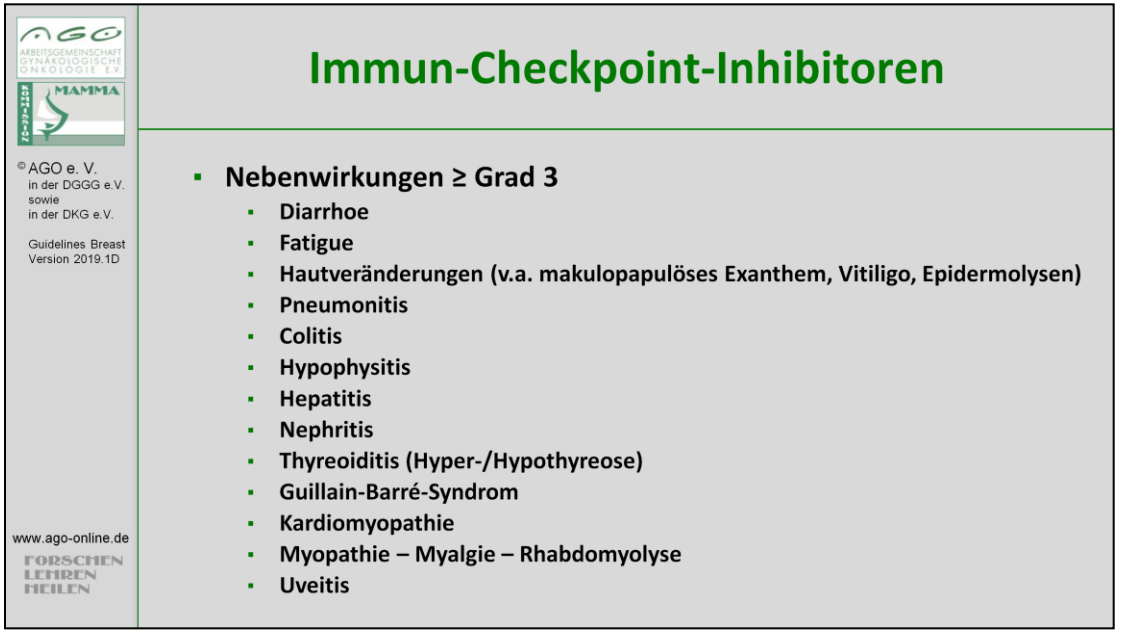

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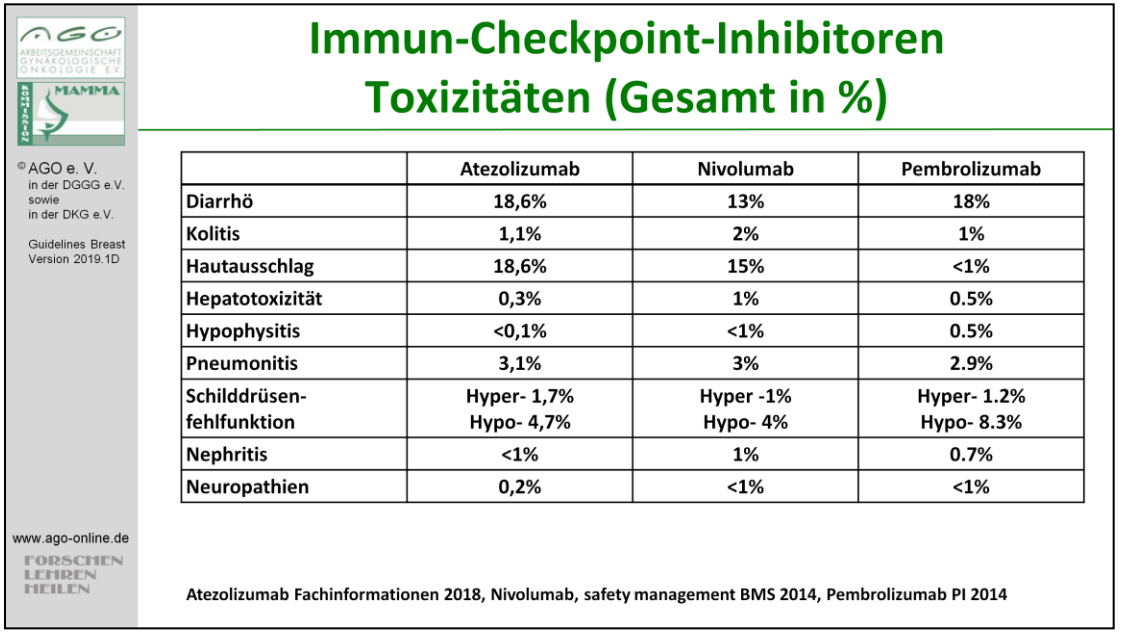
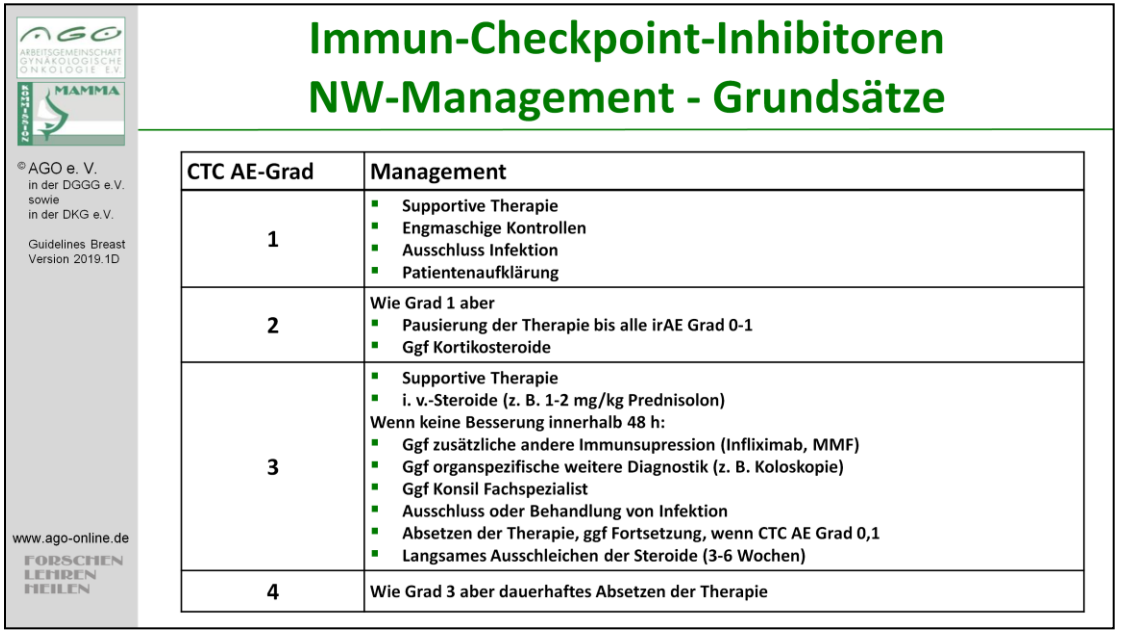


Immun-Checkpoint-Inhibitoren
Toxizitäten (Gesamt in %)

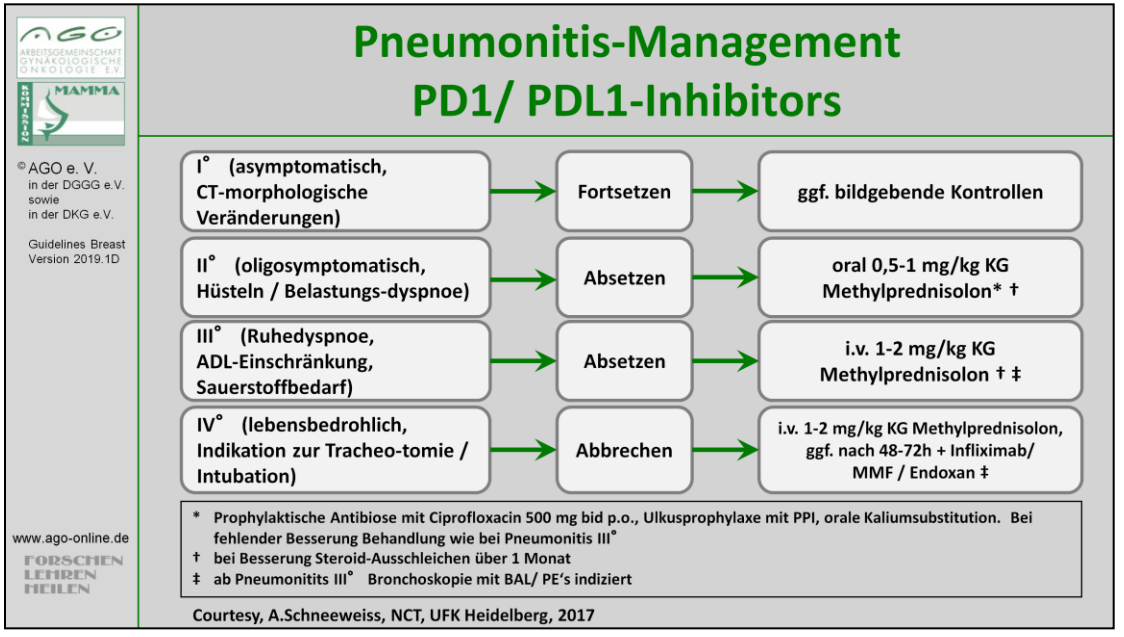
	Atezolizumab	Nivolumab	Pembrolizumab
Diarrhö	18,6%	13%	18%
Kolitis	1,1%	2%	1%
Hautausschlag	18,6%	15%	<1%
Hepatotoxizität	0,3%	1%	0.5%
Hypophysitis	<0,1%	<1%	0.5%
Pneumonitis	3,1%	3%	2.9%
Schilddrüsen-fehlfunktion	Hyper- 1,7% Hypo- 4,7%	Hyper -1% Hypo- 4%	Hyper- 1.2% Hypo- 8.3%
Nephritis	<1%	1%	0.7%
Neuropathien	0,2%	<1%	<1%

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



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



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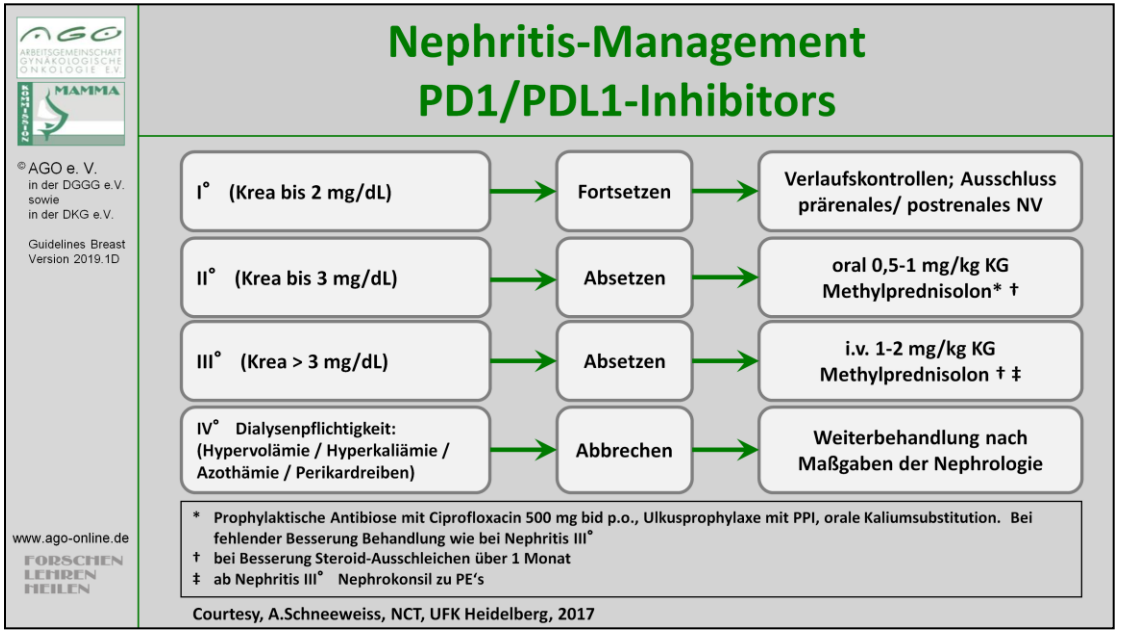

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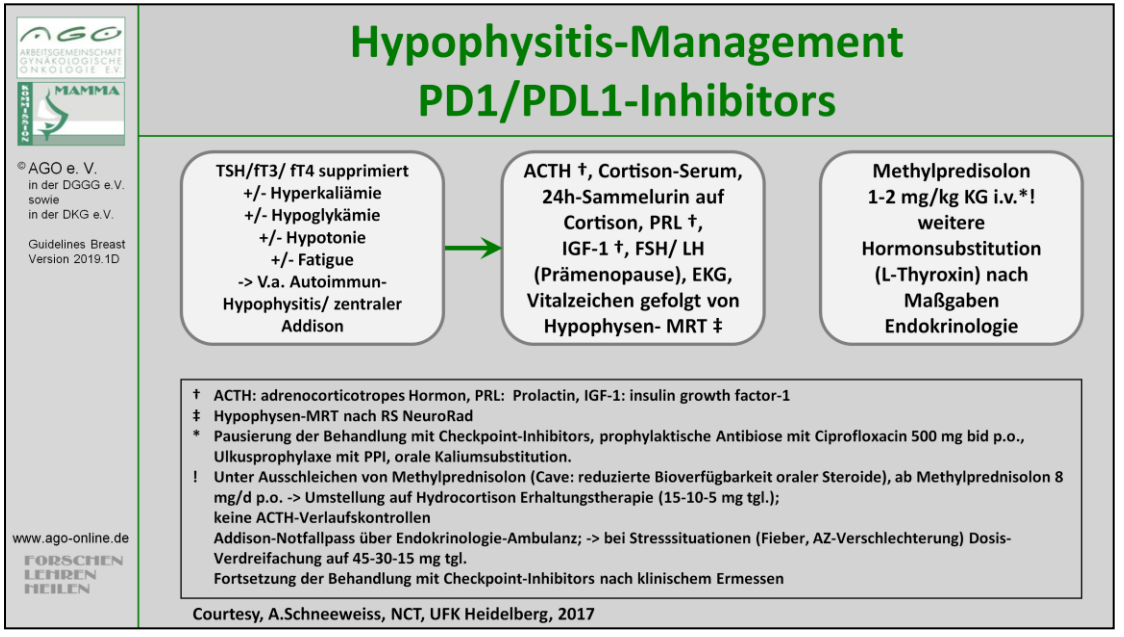

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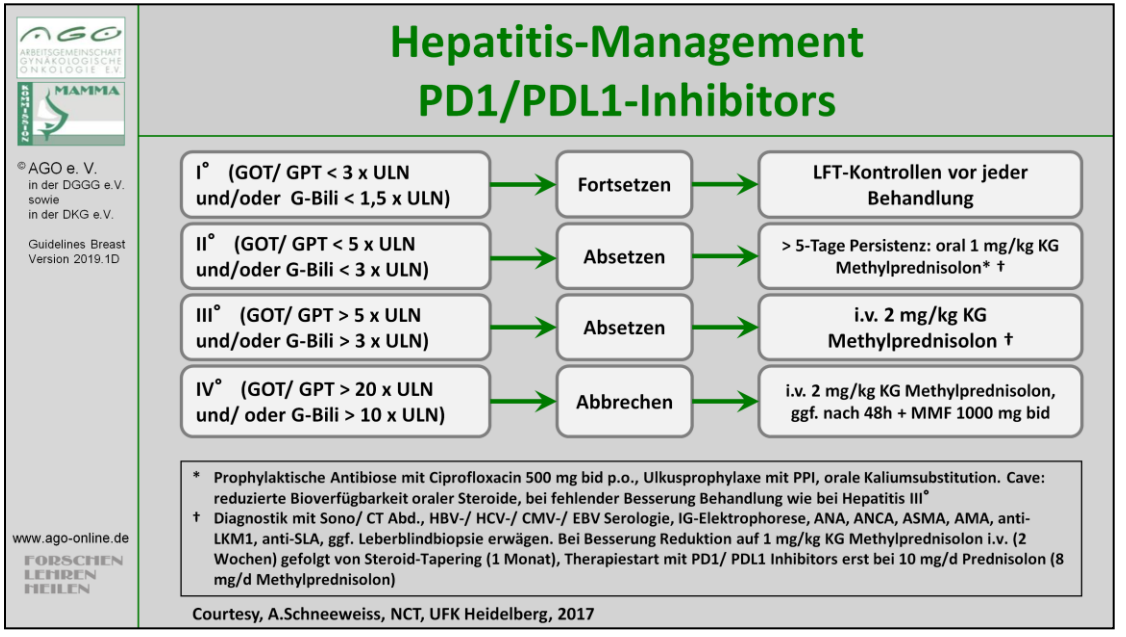

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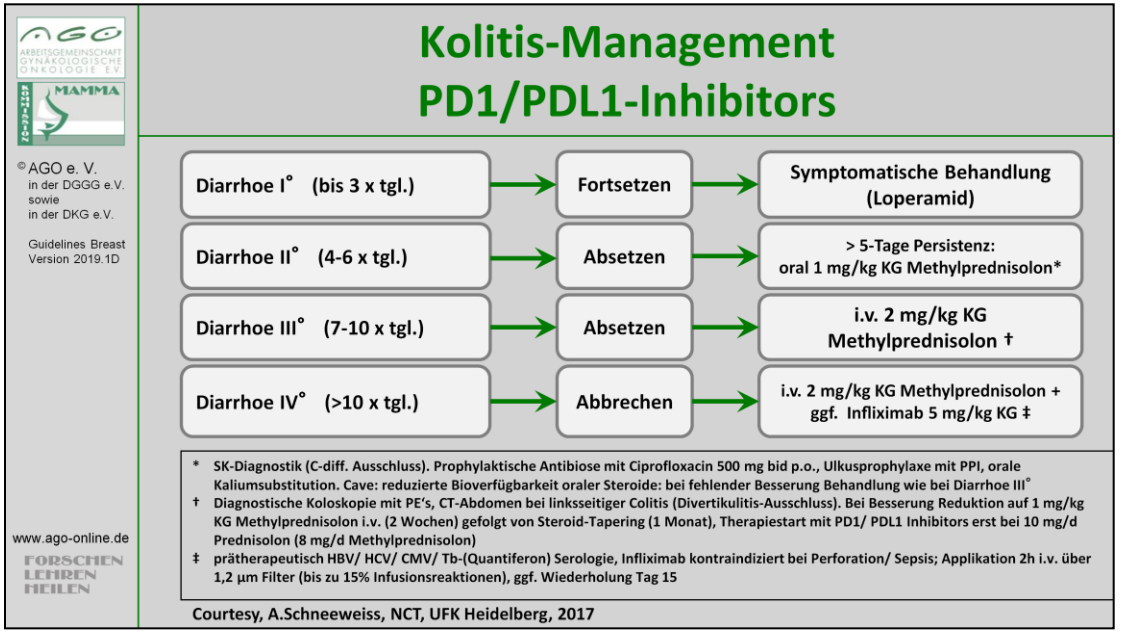

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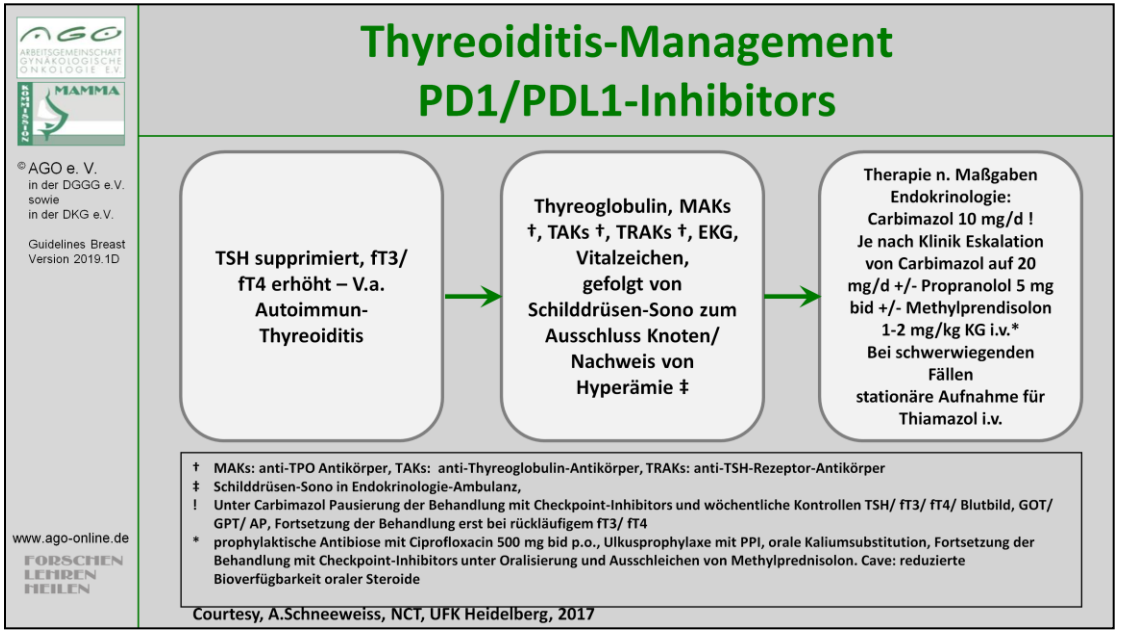

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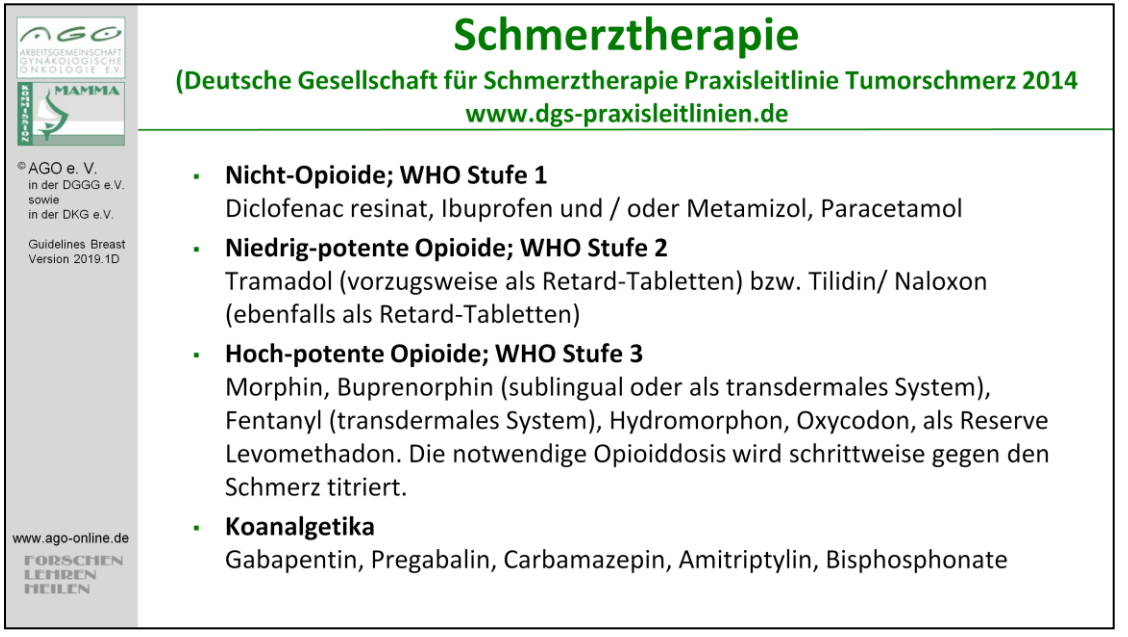
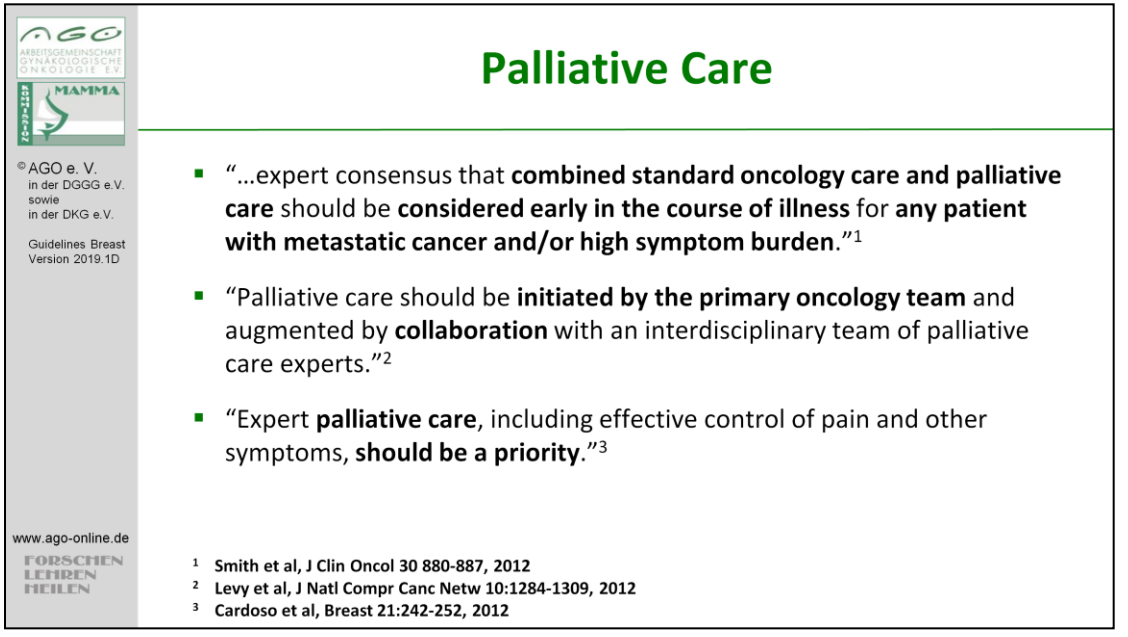
Guidelines Breast
Version 2019.1D

- **Andere supportive und palliative Fragestellungen**
  - **Schmerztherapie**
  - **Palliative Care**



Relevant practice guideline

Deutsche Gesellschaft zum Studium des Schmerzes, www.dgss.org



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