Screened data bases

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

Screened guidelines

ABC Consensus Guidelines for Advanced Breast Cancer (ABC 1-4)

-Cardoso F, Costa A, Senkus E, Aapro M, André F, Barrios CH, Bergh J, Bhattacharyya G, Biganzoli L, Cardoso MJ, Carey L, Corneliussen-James D, Curigliano G, Dieras V, El Saghir N, Eniu A, Fallowfield L, Fenech D, Francis P, Gelmon K, Gennari A, Harbeck N, Hudis C, Kaufman B, Krop I, Mayer M, Meijer H, Mertz S, Ohno S, Pagani O, Papadopoulos E, Peccatori F, Penault-Llorca F, Piccart MJ, Pierga JY, Rugo H, Shockney L, Sledge G, Swain S, Thomssen C, Tutt A, Vorobiof D, Xu B, Norton L, Winer E. 3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). Ann Oncol. 2017 Jan 1;28(1):16-33.

-ABC 4: Breast Care Feb 2018 (in press)

ASCO (American Association of Clinical Oncology, Practice Guidelines, 2016) http://www.asco.org

-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

-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
-Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, Chauhan C, Gavin P, Lavino A, Lustberg MB, Paice J, Schneider B, Smith ML, Smith T, Terstriep S, Wagner-Johnston N, Bak K, Loprinzi CL; 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.
CMA (Canadian Medical Association , 2016): http://www.cmaj.ca
NCCN (National Comprehensive Cancer Network , 2018): http://www.nccn.org
NCI (National Cancer Institute , 2017): http://www.cancer.gov
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

- **Supportive Therapie - Version 2002 - 2017:**
  Bauerfeind / Bischoff / Costa / Dall / Diel / Fersis / Hanf / Heinrich / Jackisch / von Minckwitz / Möbus /Nitz / Oberhoff / Rody / Schaller / Scharl / Schmidt / Schütz

- **Nebenwirkungen der Therapie - Versionen 2004–2017:**
  Albert / Bischoff / Brunnert / Costa / Dall / Friedrich / Friedrichs / Gerber / Göhring / Huober / Jackisch / Lisboa / Lück / Müller / Nitz / Schmidt / Solomayer / Souchon / Stickeler / Untch

- **Version 2018:**
  Thomssen / Diel / Nitz / Lüftner / Bischoff

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HEILEN

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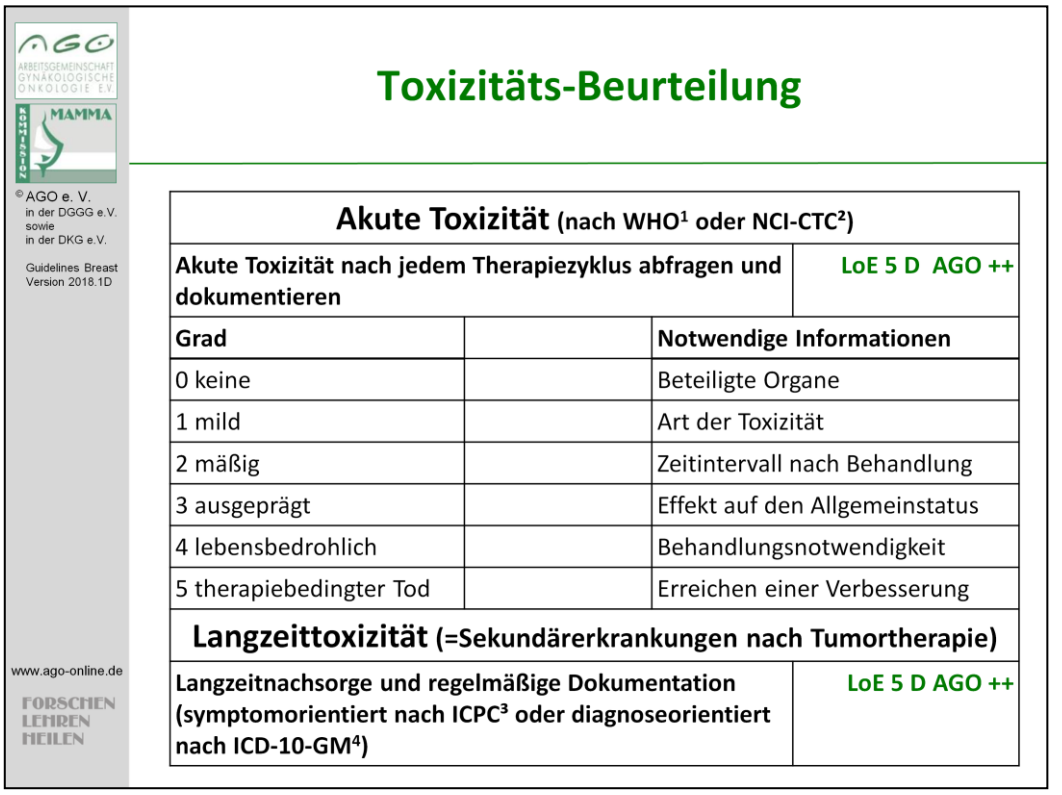
- **Leitlinien - Umfeld**

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)

- **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)

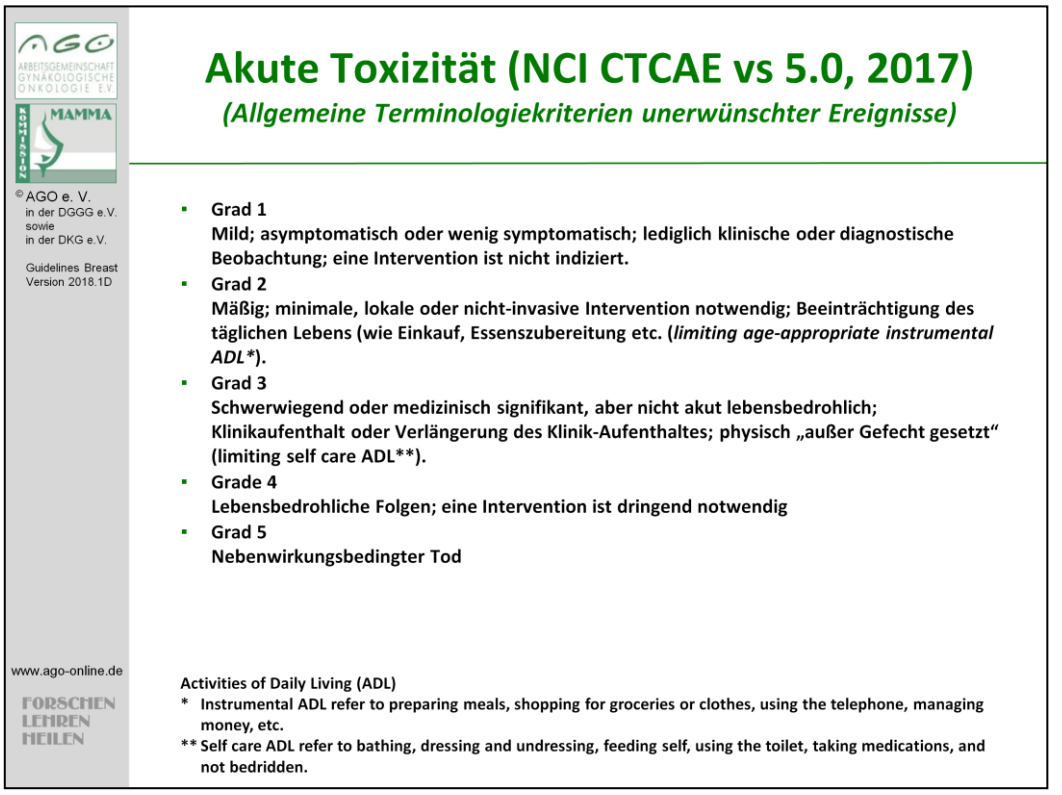
Akute Toxizität nach jedem Therapiezyklus abfragen

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

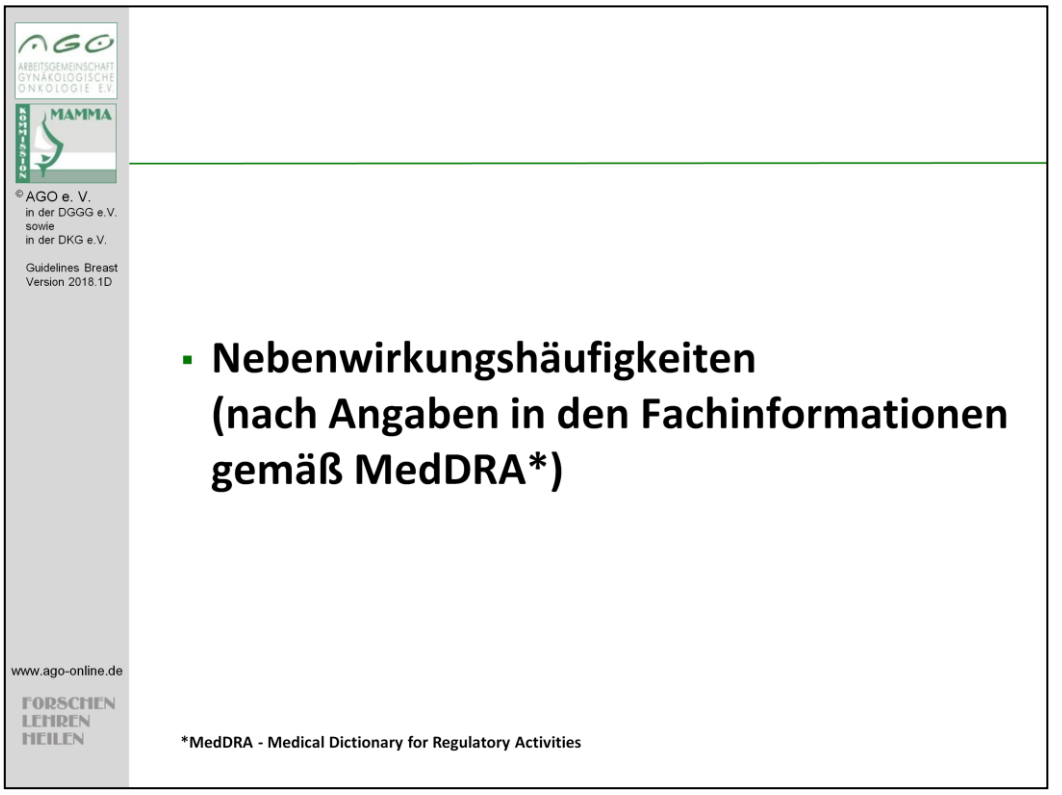
Langzeittoxizität

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.

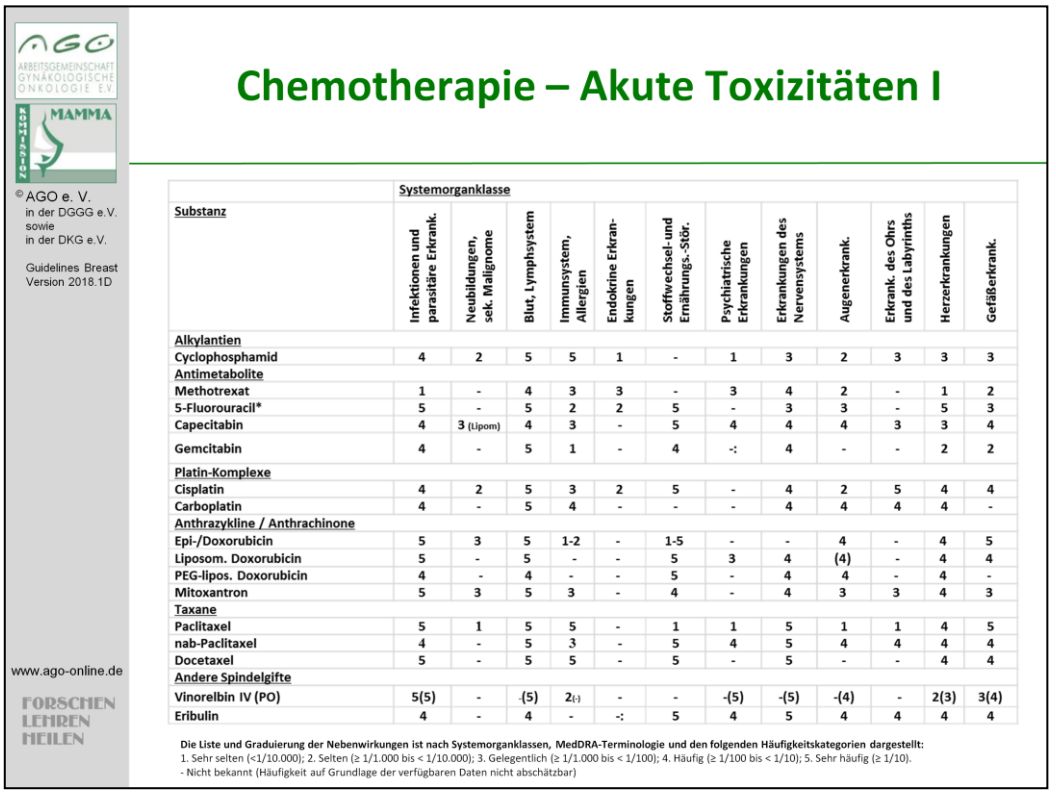


1. NCI, Bethesda, USA, Common Terminology Criteria for Adverse Events v5.0 (CTCAE; published 2017); https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50 (Download 18.01.2018)



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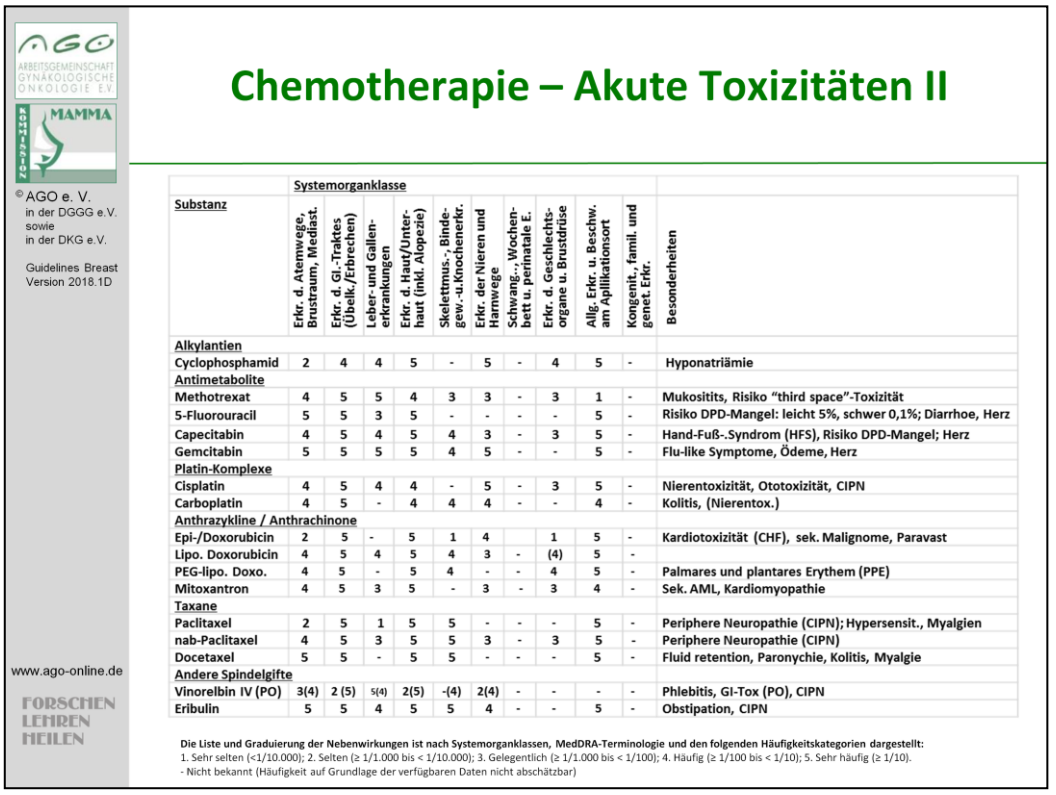
12. Madeddu C, Deidda M, Piras A, et al. Pathophysiology of cardiotoxicity induced by nonanthracycline chemotherapy. J Cardiovasc Med (Hagerstown). 2016 May;17 Suppl 1 Special issue on Cardiotoxicity from Antiblastic Drugs and Cardioprotection:e12-e18. Review.



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:
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- 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

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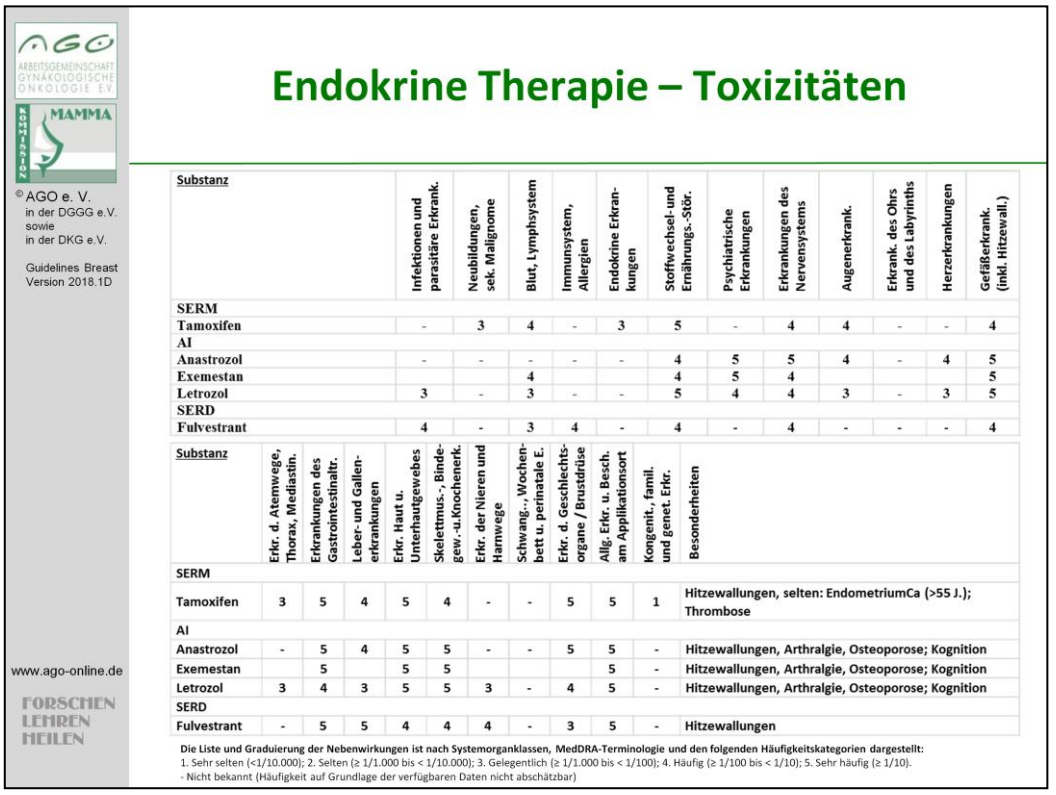
12. Madeddu C, Deidda M, Piras A, et al. Pathophysiology of cardiotoxicity induced by nonanthracycline chemotherapy. J Cardiovasc Med (Hagerstown). 2016 May;17 Suppl 1 Special issue on Cardiotoxicity from Antiblastic Drugs and Cardioprotection:e12-e18. Review.



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Guidelines Breast
Version 2018.1D

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FORSCHEN
LEHREN
HEILEN

Endokrine Therapie – Toxizitäten

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

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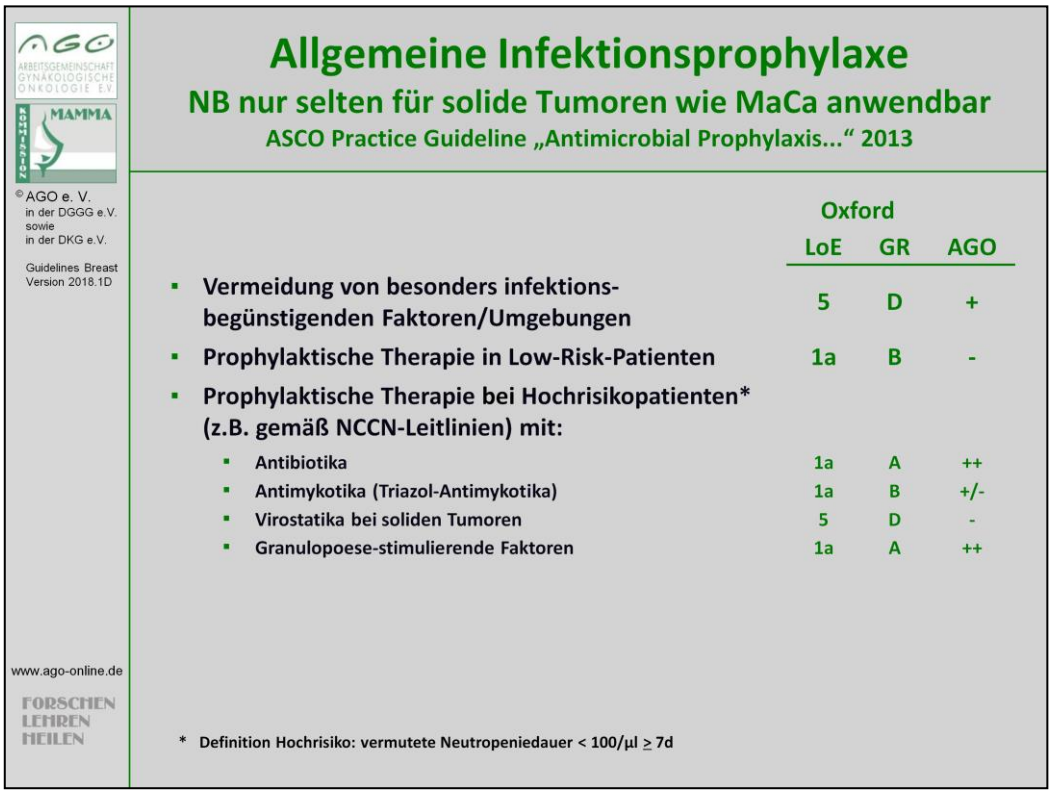
Nebenwirkungen nach Organsystemen
Inzidenz, Prävention, Therapie

1. Infektionen u. parasitäre Erkrankungen

- Allgemeine Infektionsprophylaxe
- Hepatitis B-Screening

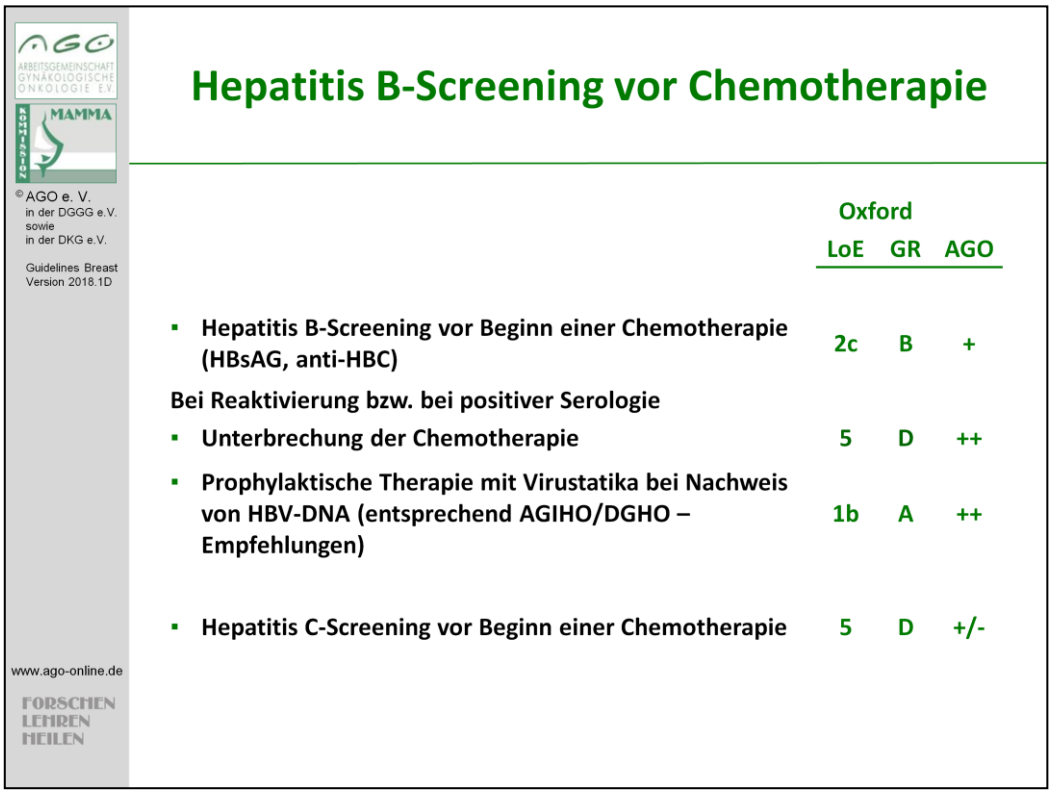


ASCO:

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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2. Robert-Koch-Institut. Epidemiologisches Bulletin**.** 20. Juli 2015 / Nr. 29
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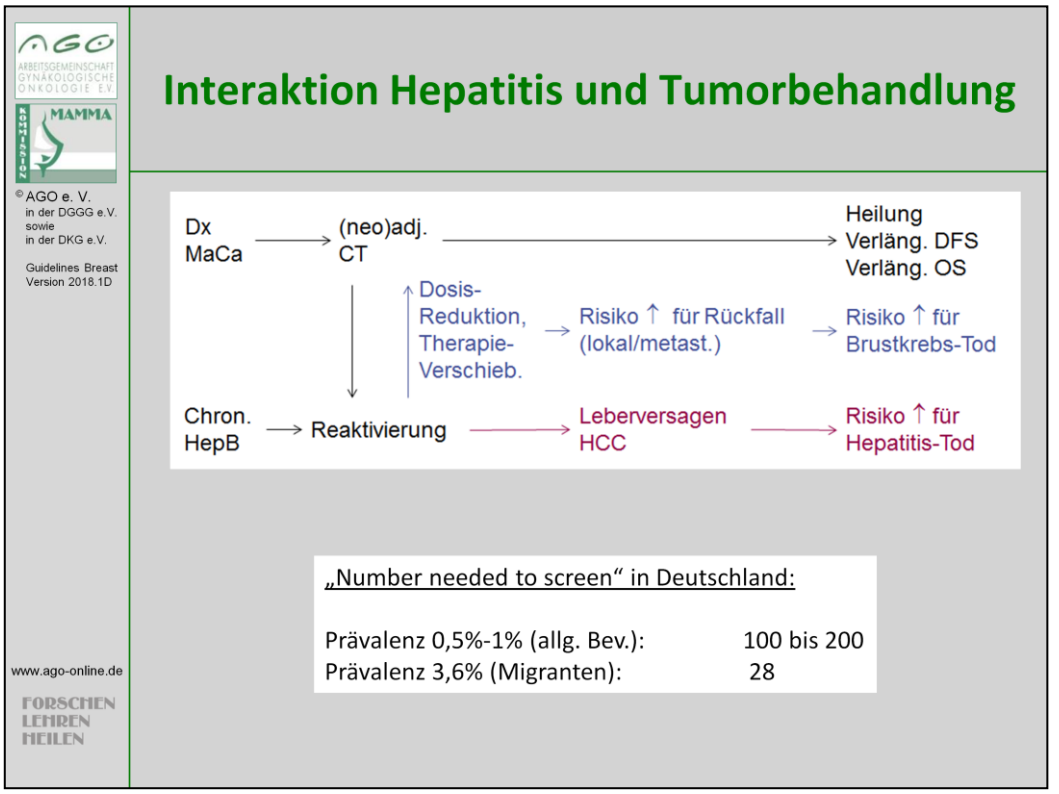

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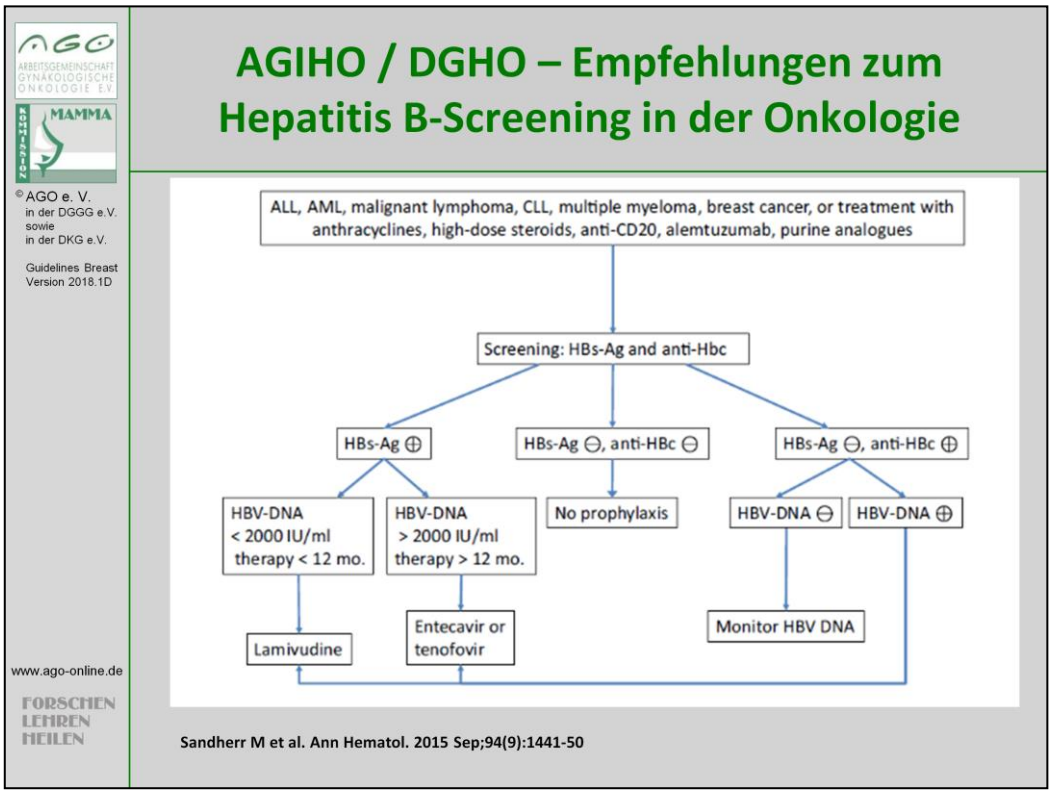

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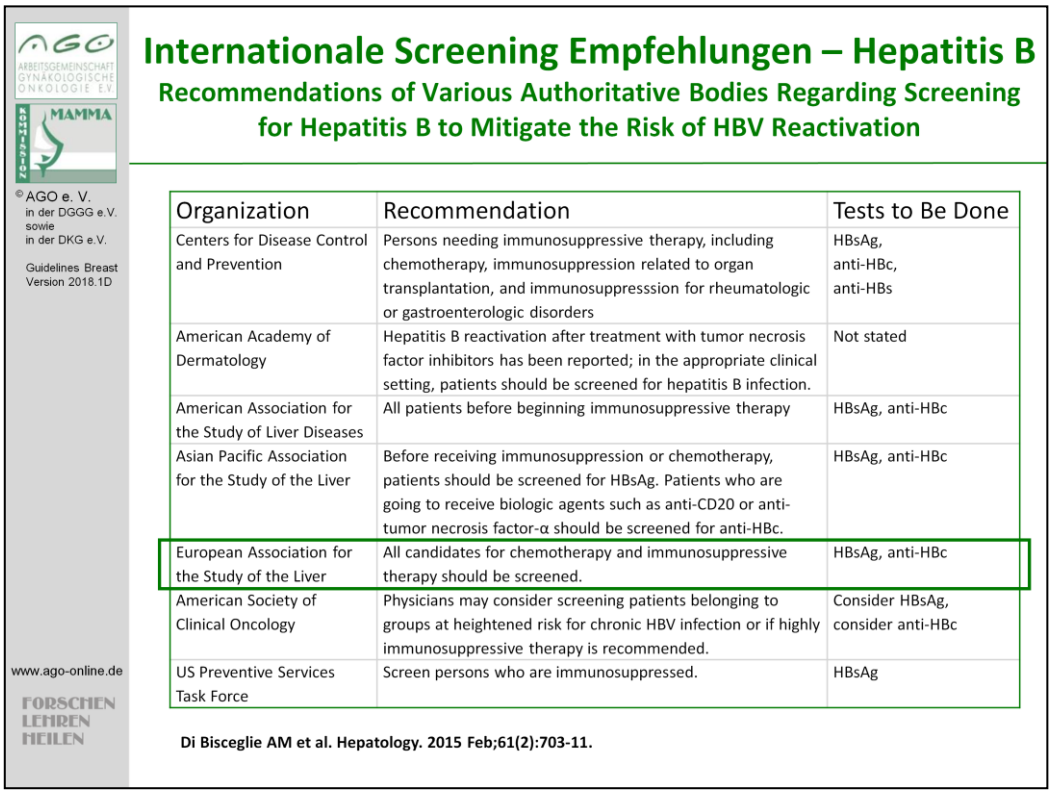

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Guidelines Breast
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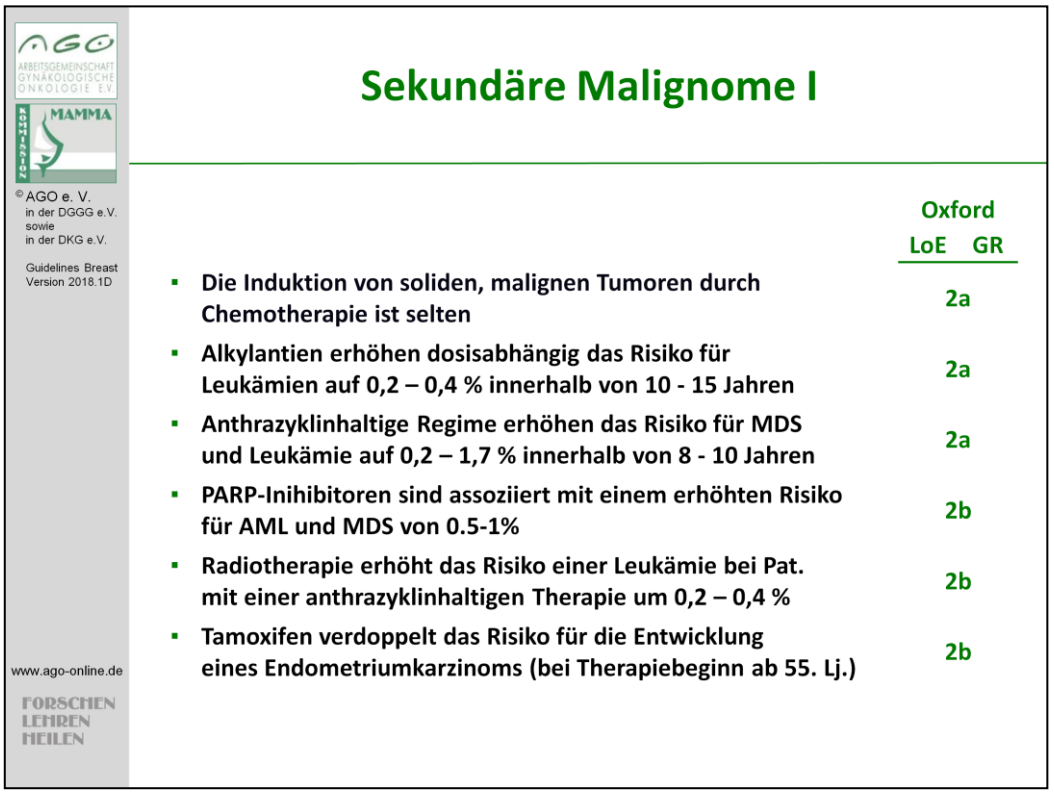
Nebenwirkungen nach Organsystemen
Inzidenz, Prävention, Therapie

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



Statements 1-4

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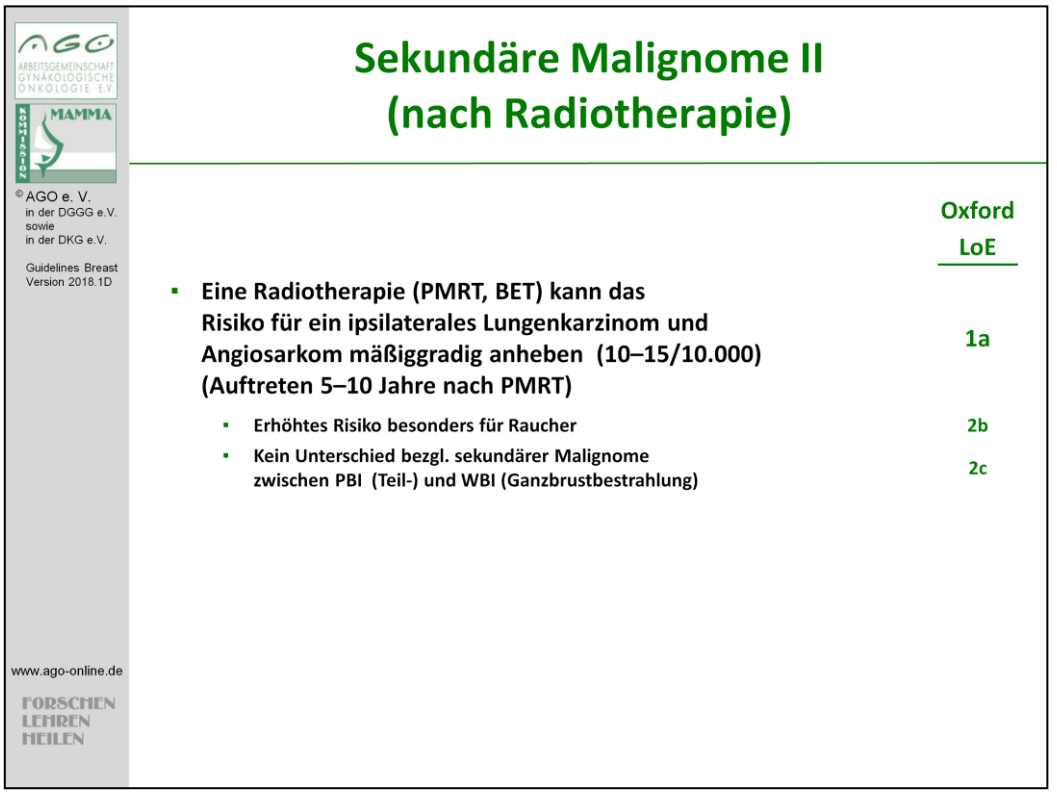

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Guidelines Breast
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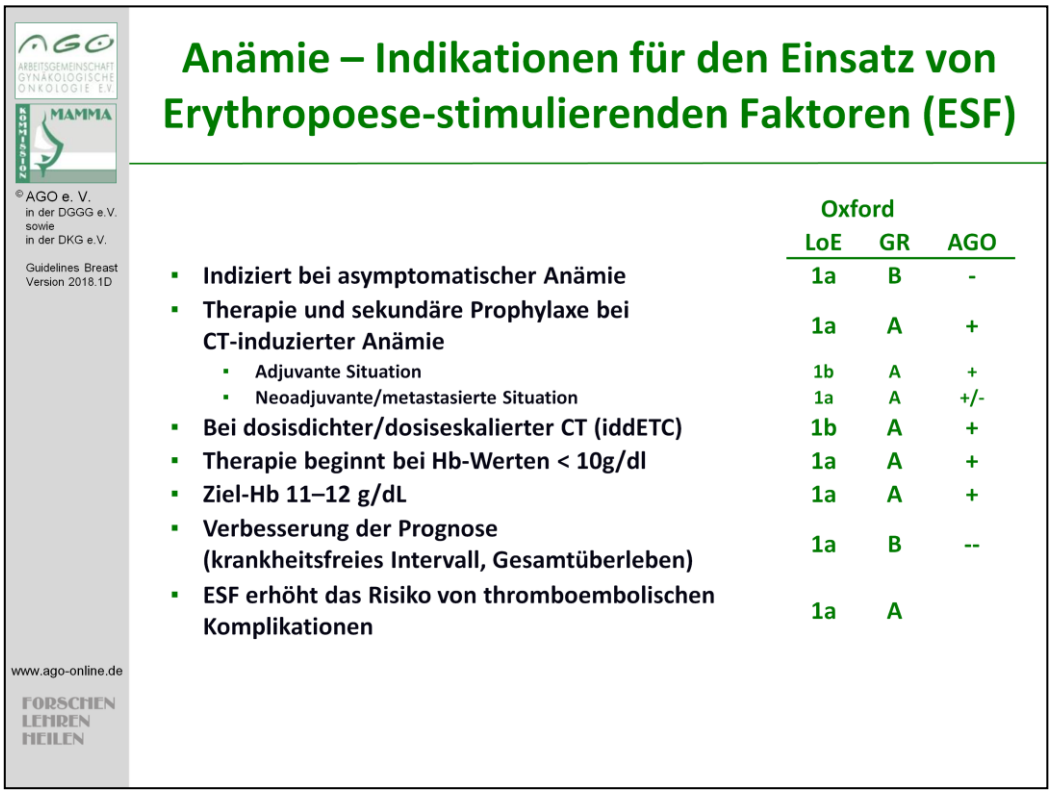
Nebenwirkungen nach Organsystemen
Inzidenz, Prävention, Therapie

3. Erkrankungen des Blutes und des Lymphsystems

- Anämie
- Neutropenie
- Febrile Neutropenie



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hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. J Clin Oncol. 2005;23:5960–5972.

Relevante Leitlinien

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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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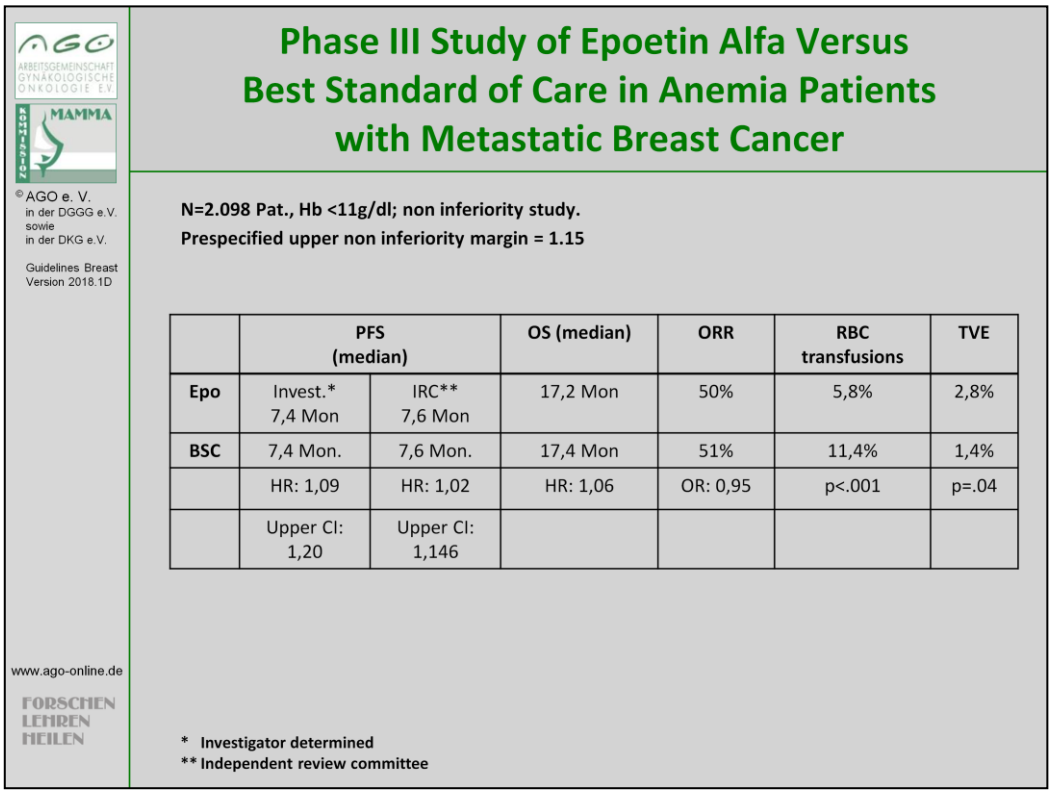

Phase III Study of Epoetin Alfa Versus Best Standard of Care in Anemia Patients with Metastatic Breast Cancer

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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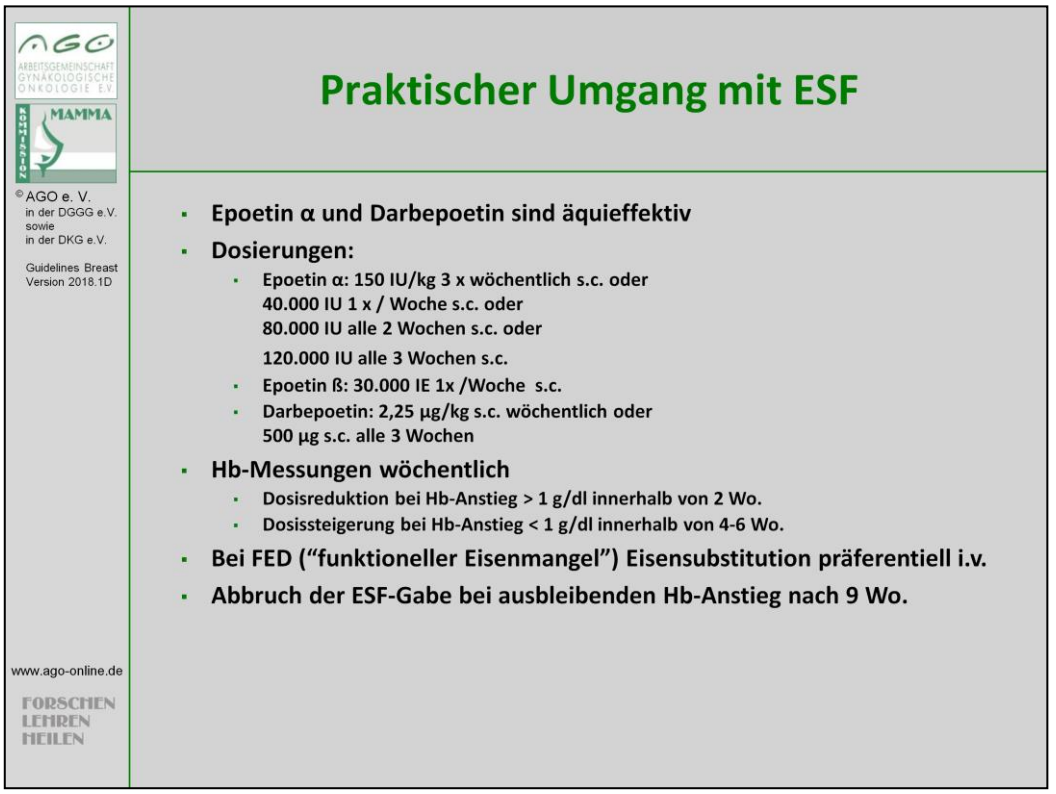

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<u>Relevante Leitlinien</u>

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Cancer- and Chemotherapy-Induced Anemia. Version 2.2018 (https://www.nccn.org/professionals/physician_gls/pdf/anemia.pdf)
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   J Clin Oncol 2010; 28: 4996–10
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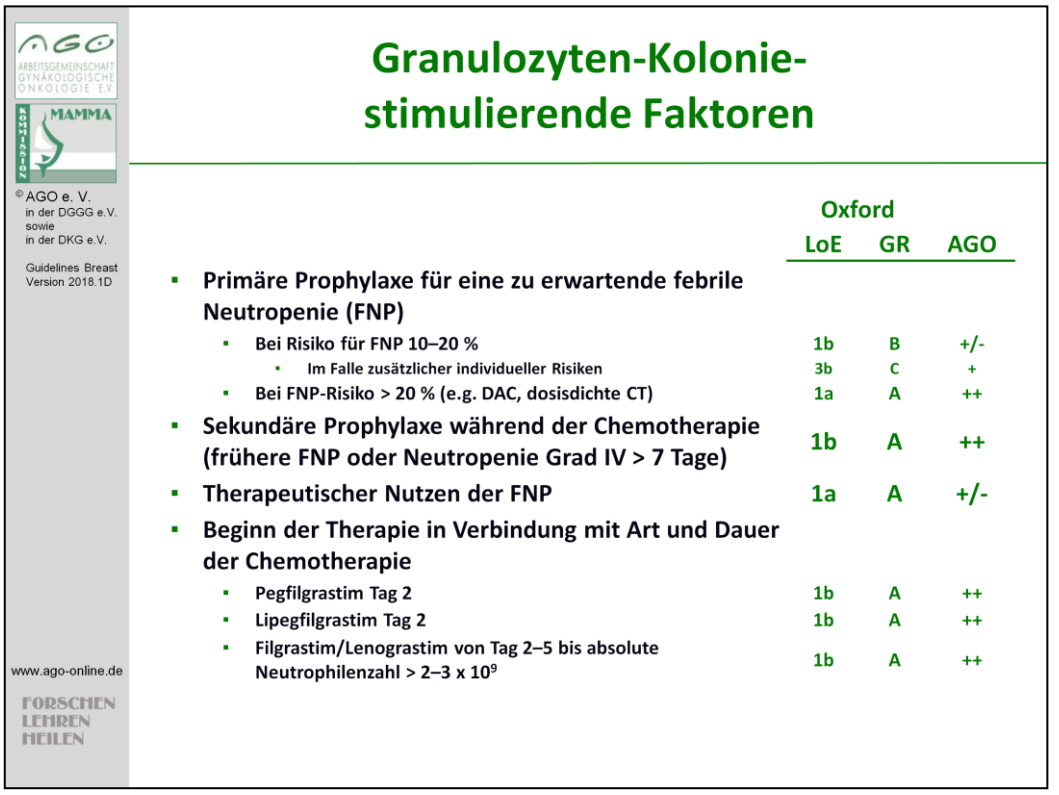
   Oncologist 2008;13(Suppl):33–36.



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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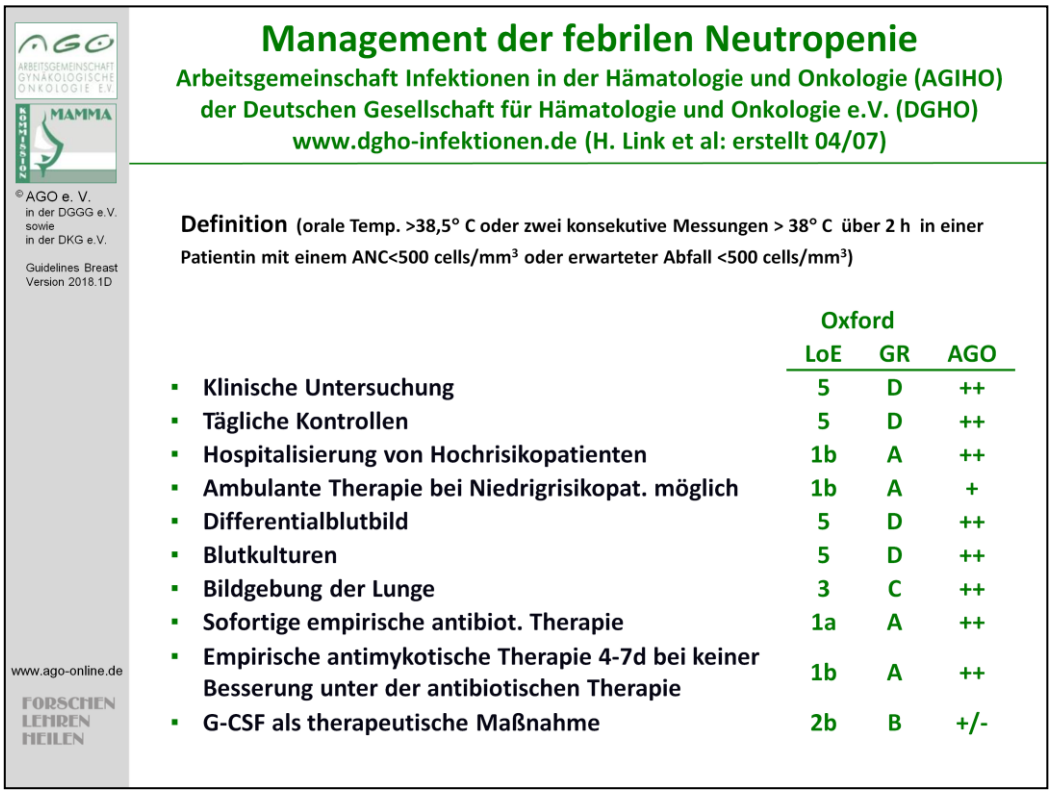

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Empirische Antibiotikatherapie

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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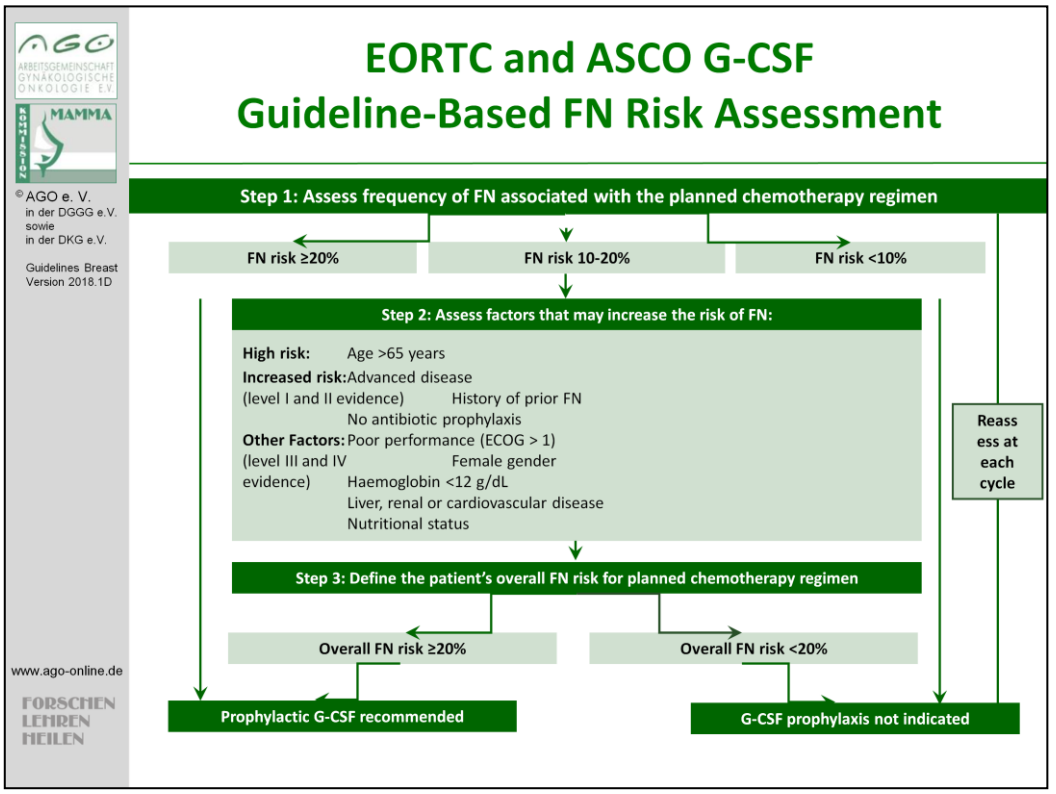

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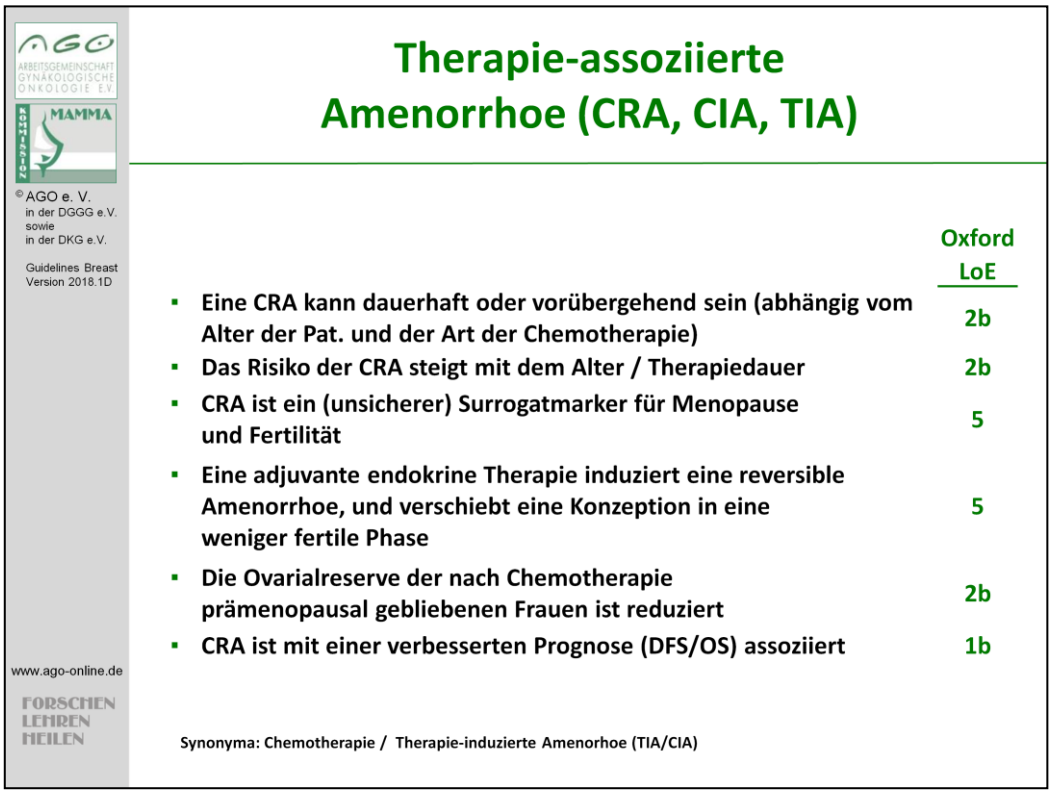
4. Endokrine Erkrankungen



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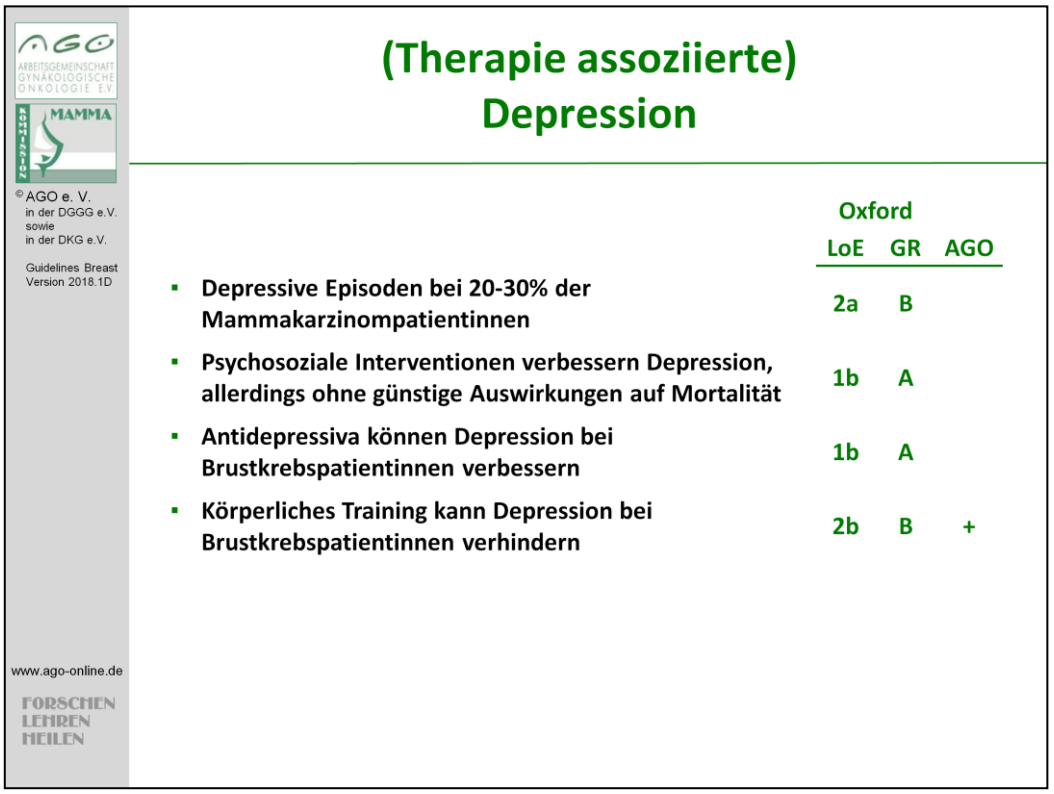
Nebenwirkungen nach Organsystemen
Inzidenz, Prävention, Therapie

5. Psychiatrische Erkrankungen

- Depression
- Fatigue
- Kognitive Störungen
- Schlafstörungen



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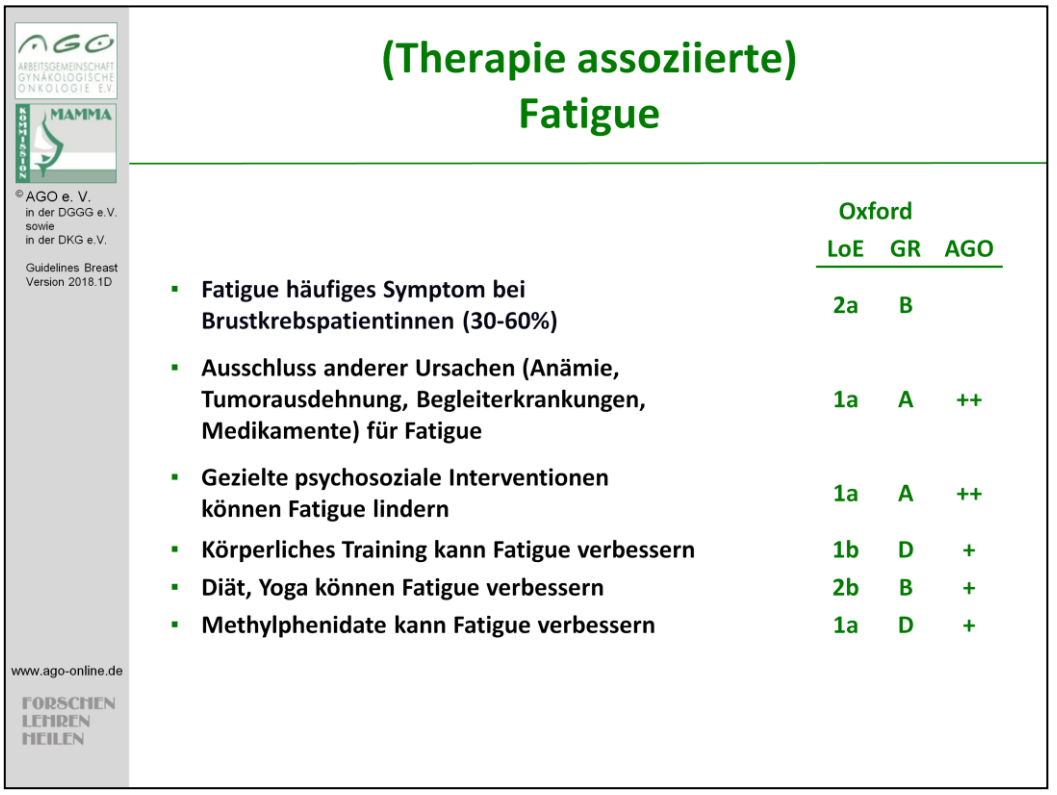

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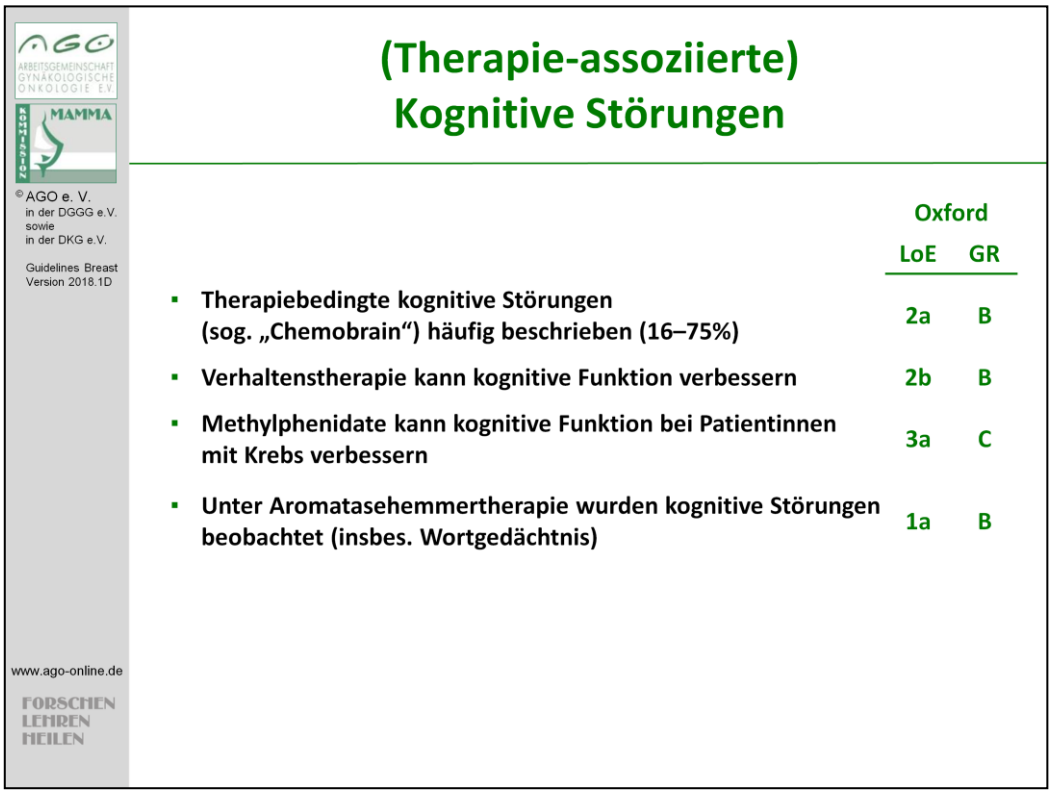

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<u>Methylphenidate kann kognitive Funktion bei Patientinnen mit Krebs verbessern</u>

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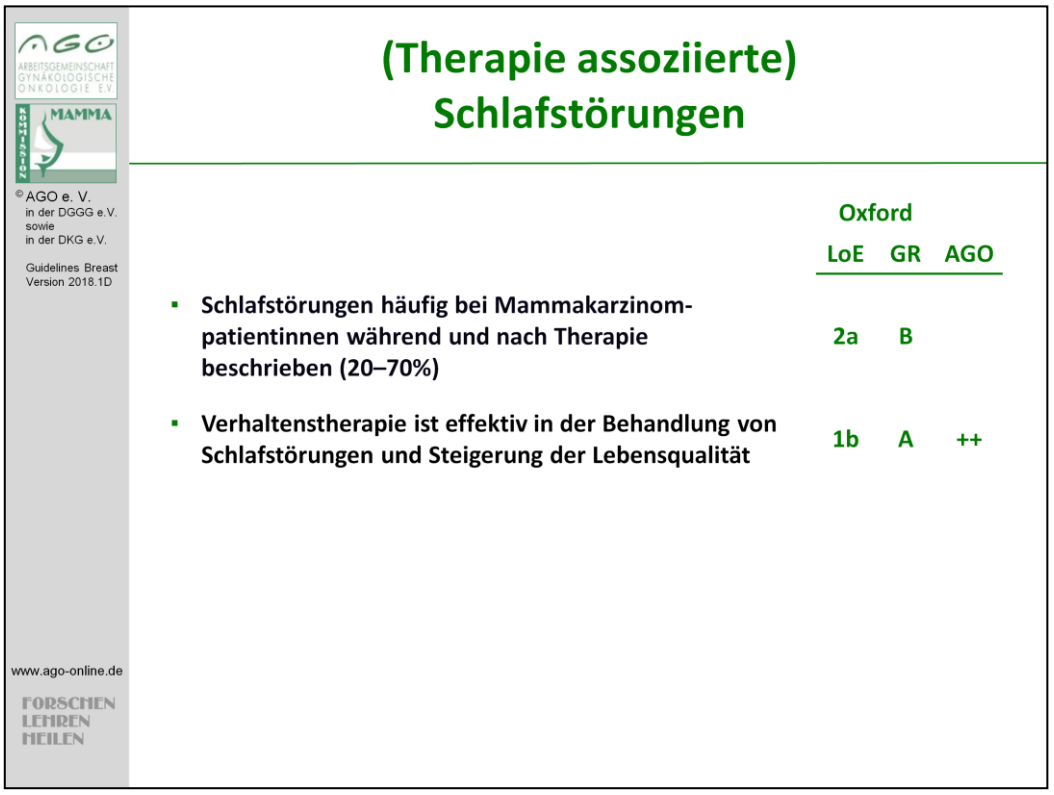

<u>Sleep disturbances are a common problem….</u>

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<u>Behavioral therapies have demonstrated efficacy…..</u>

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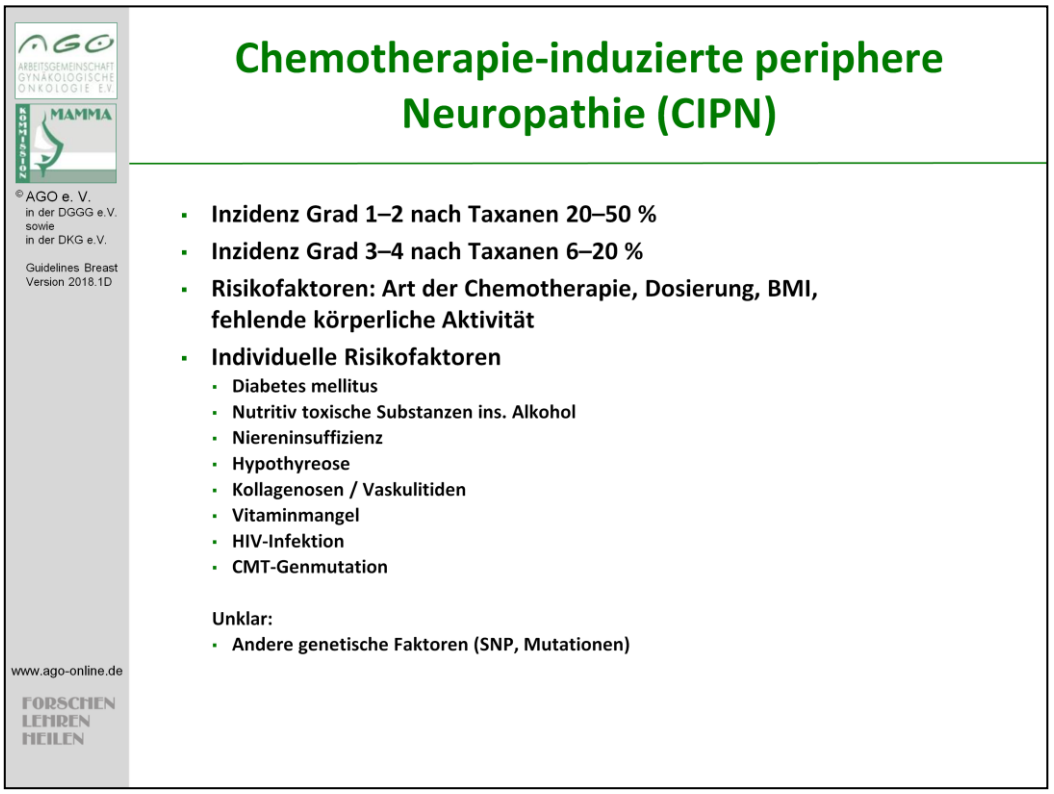
Guidelines Breast
Version 2018.1D

Nebenwirkungen nach Organsystemen
Inzidenz, Prävention, Therapie

6. Erkrankungen des Nervensystems

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



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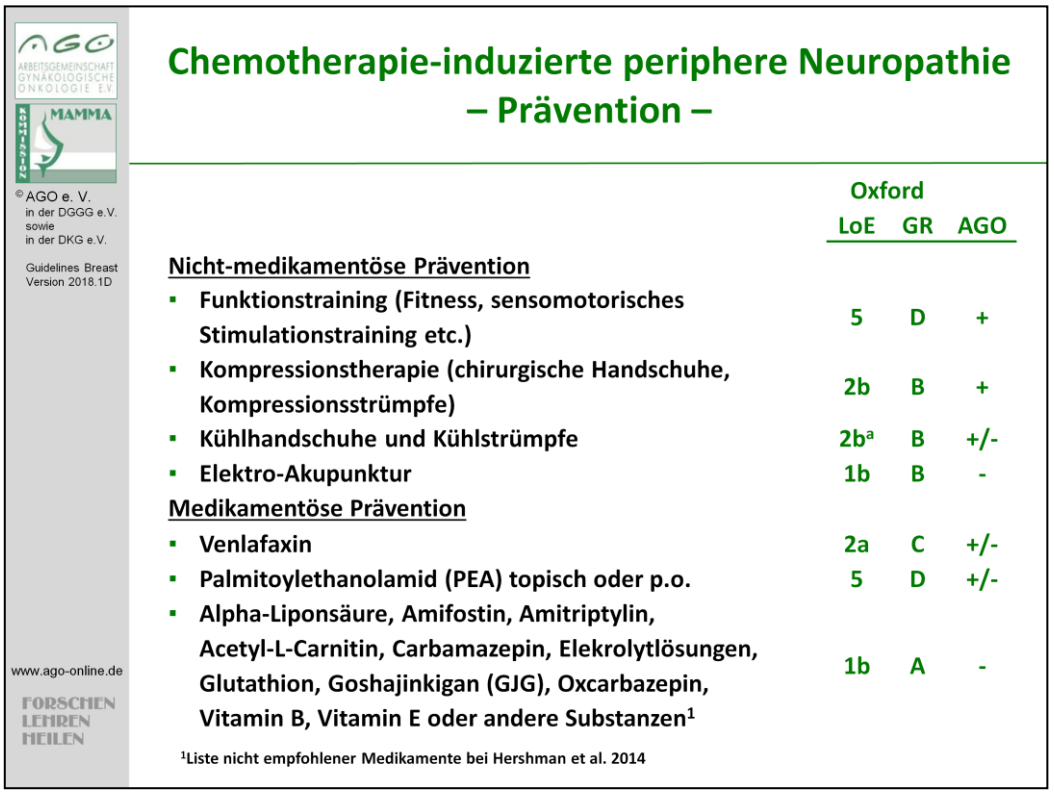

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Nicht-medikamentöse Prävention

Funktionstraining

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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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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

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Acetyl-L-Carnitin

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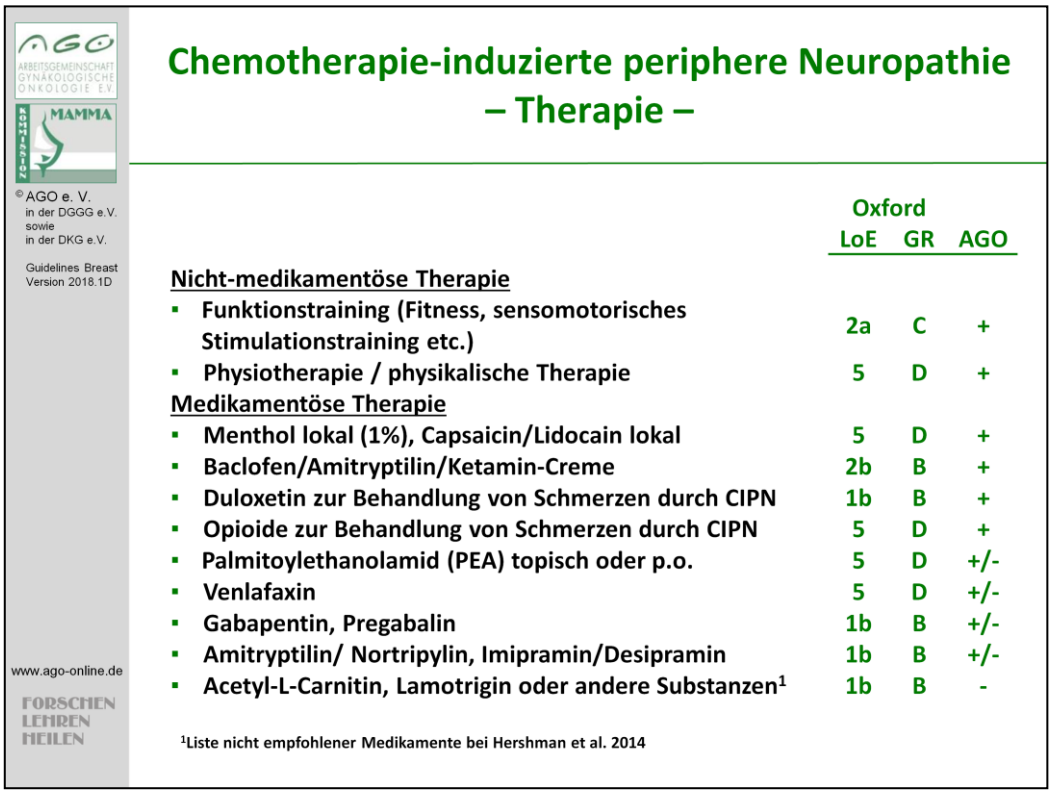

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Nicht-medikamentöse Therapie

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.

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Menthol / Capsaicin

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Baclofen/Amitryptilin/Ketamin-Creme

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Duloxetin

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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. J Pharmacol Exp Ther. 2007 Feb;320(2):599-606
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Gabapentin, Pregabalin:

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Acetyl-L-Carnitin, Lamotrigin oder andere Substanzen:

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Guidelines Breast
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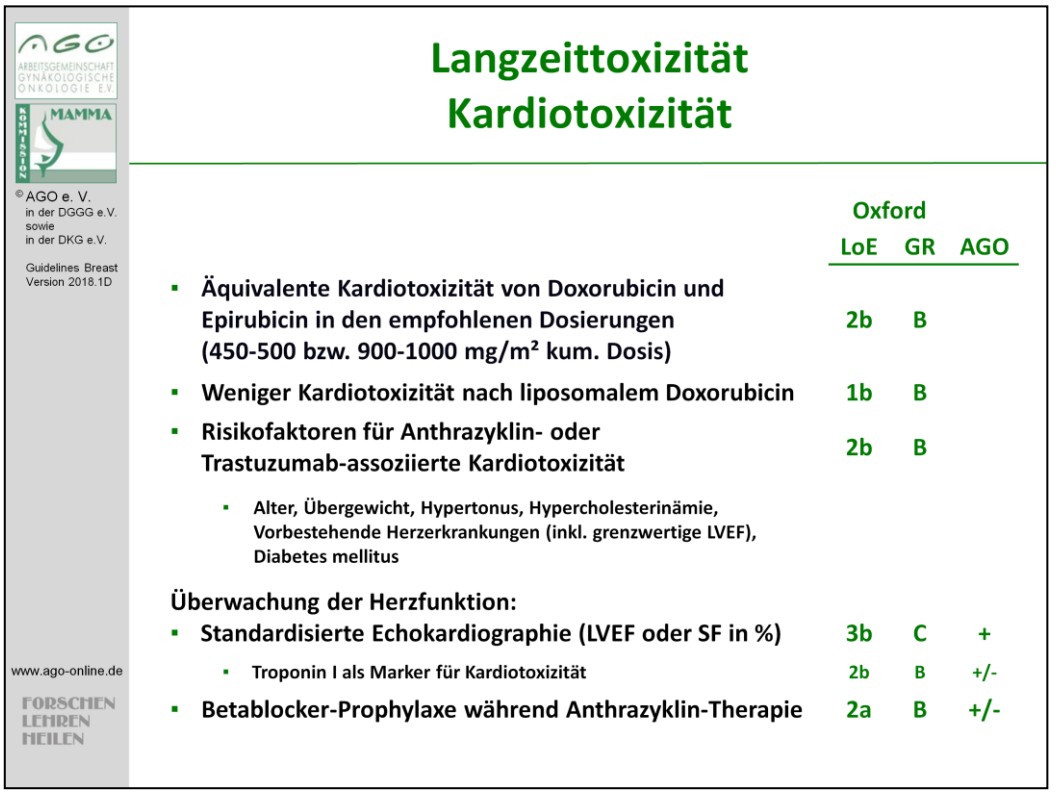
7. Herzerkrankungen



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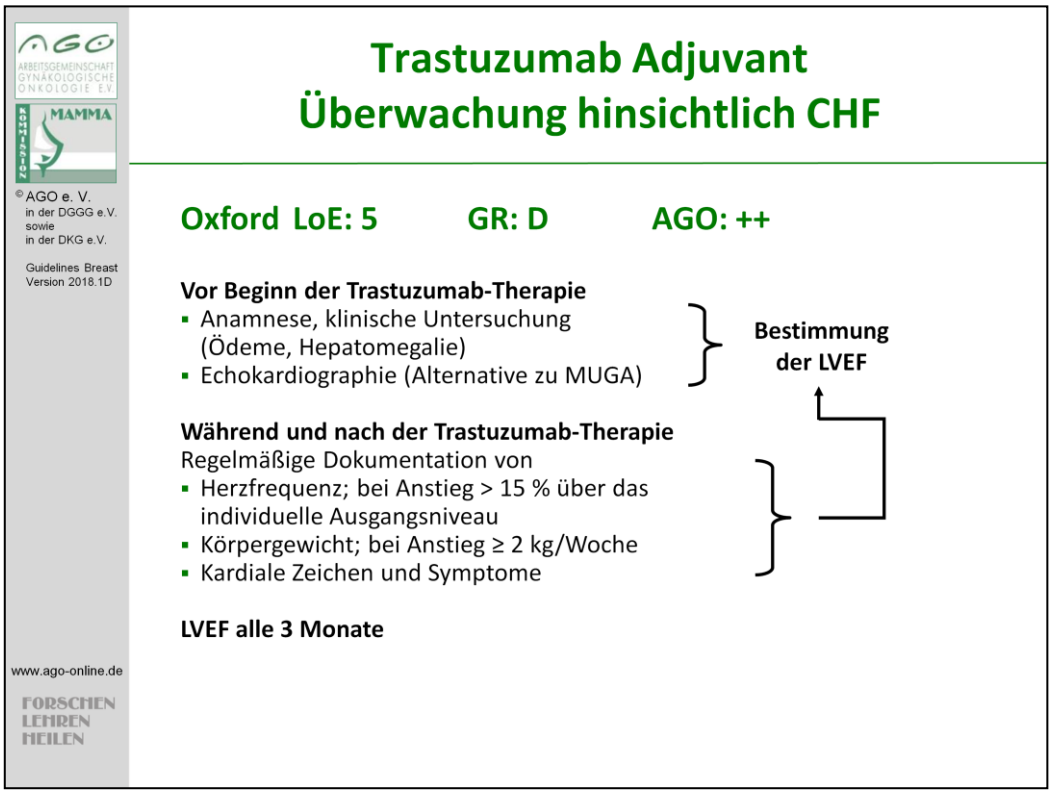

Statement: Cardiac Monitoring (5 D ++)
Vote result of the AGO recommendation: 100%

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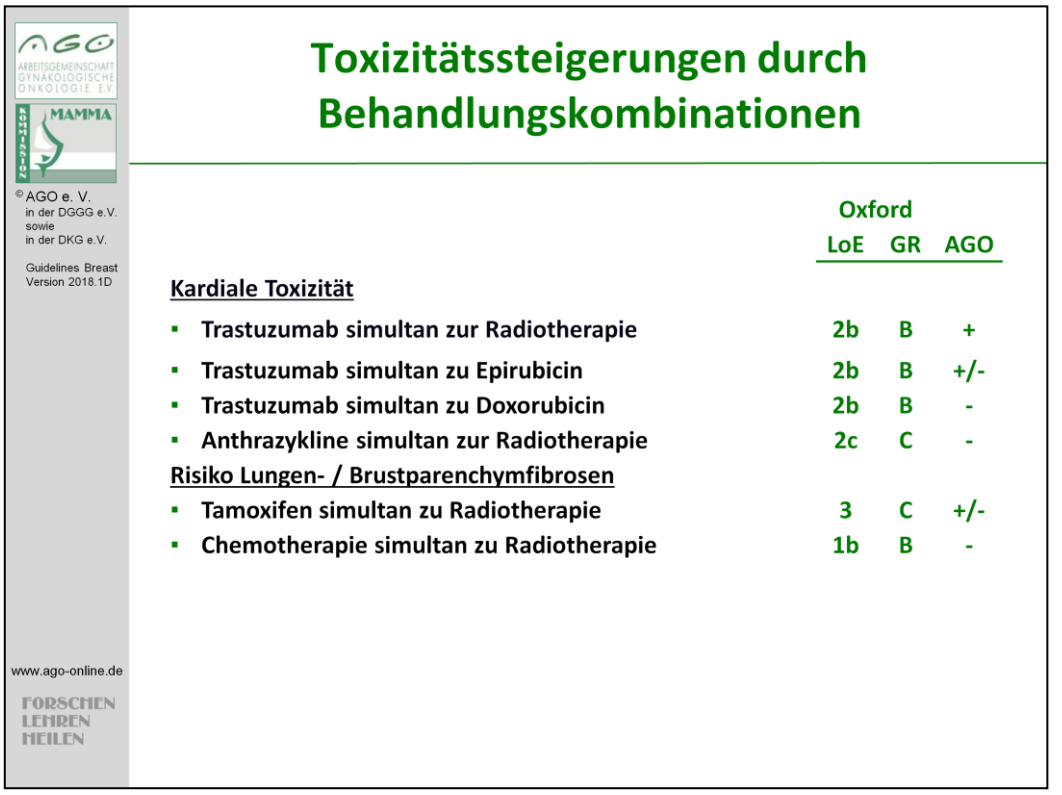

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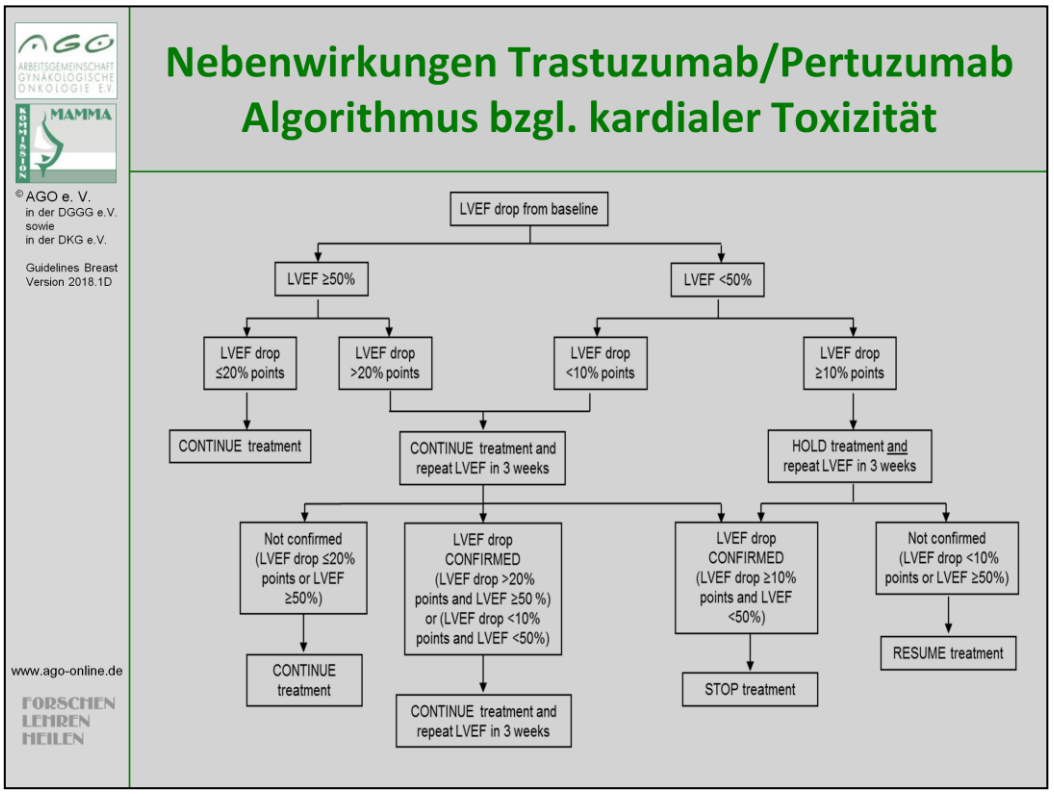

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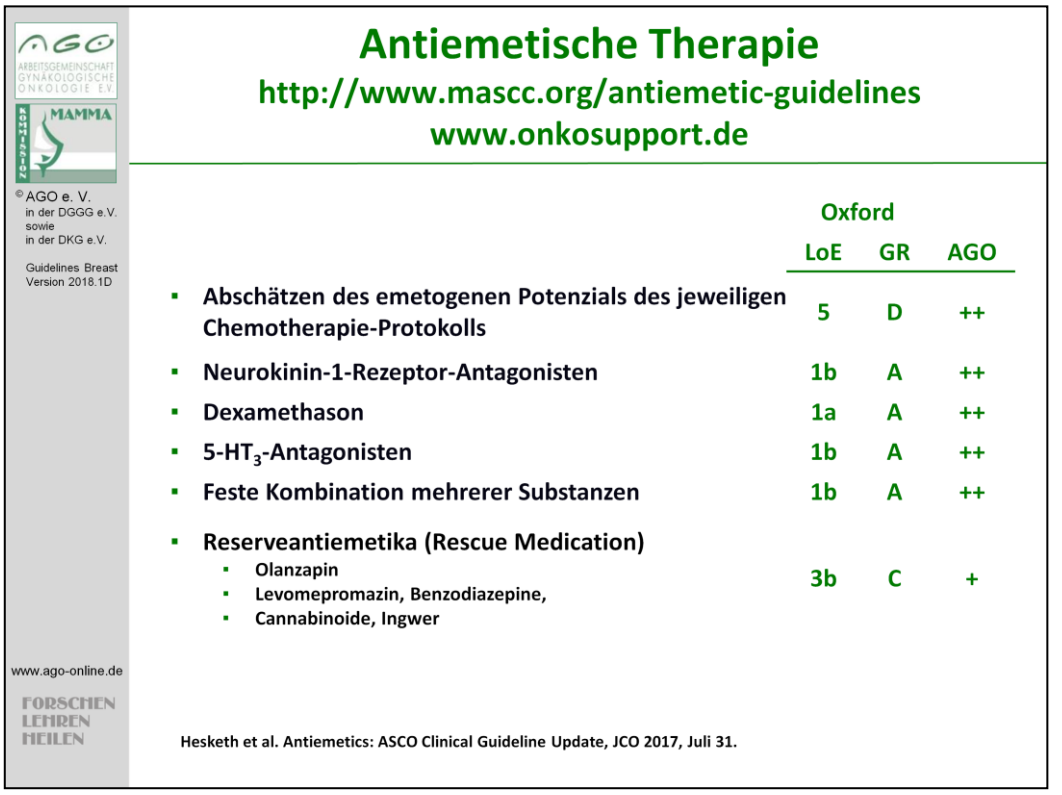
Nebenwirkungen nach Organsystemen
Inzidenz, Prävention, Therapie

8. Erkrankungen des Gastrointestinaltrakts

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



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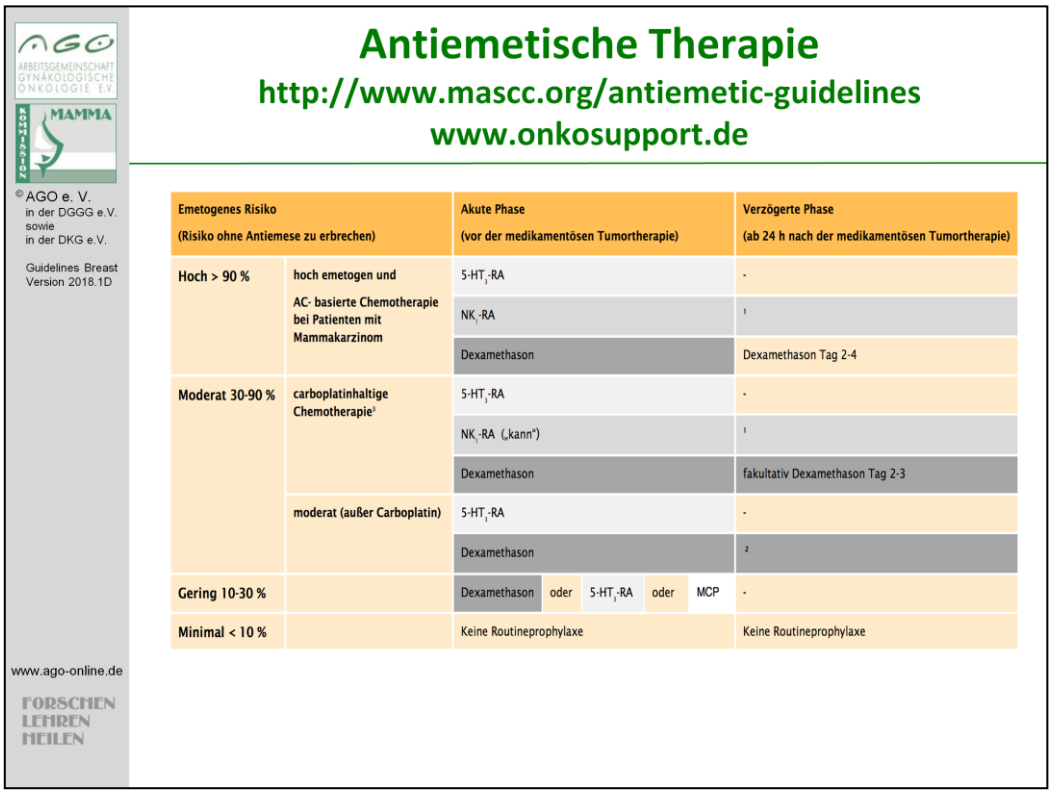

Emetogenes Risiko (Risiko ohne Antiemese zu erbrechen)		Akute Phase (vor der medikamentösen Tumortherapie)	Verzögerte Phase (ab 24 h nach der medikamentösen Tumortherapie)
Hoch > 90 %	hoch emetogen und AC- basierte Chemotherapie bei Patienten mit Mammakarzinom	5-HT$_3$-RA	-
		NK$_1$-RA	[1]
		Dexamethason	Dexamethason Tag 2-4
Moderat 30-90 %	carboplatinhaltige Chemotherapie[3]	5-HT$_3$-RA	-
		NK$_1$-RA („kann")	[1]
		Dexamethason	fakultativ Dexamethason Tag 2-3
	moderat (außer Carboplatin)	5-HT$_3$-RA	-
		Dexamethason	[2]
Gering 10-30 %		Dexamethason oder 5-HT$_3$-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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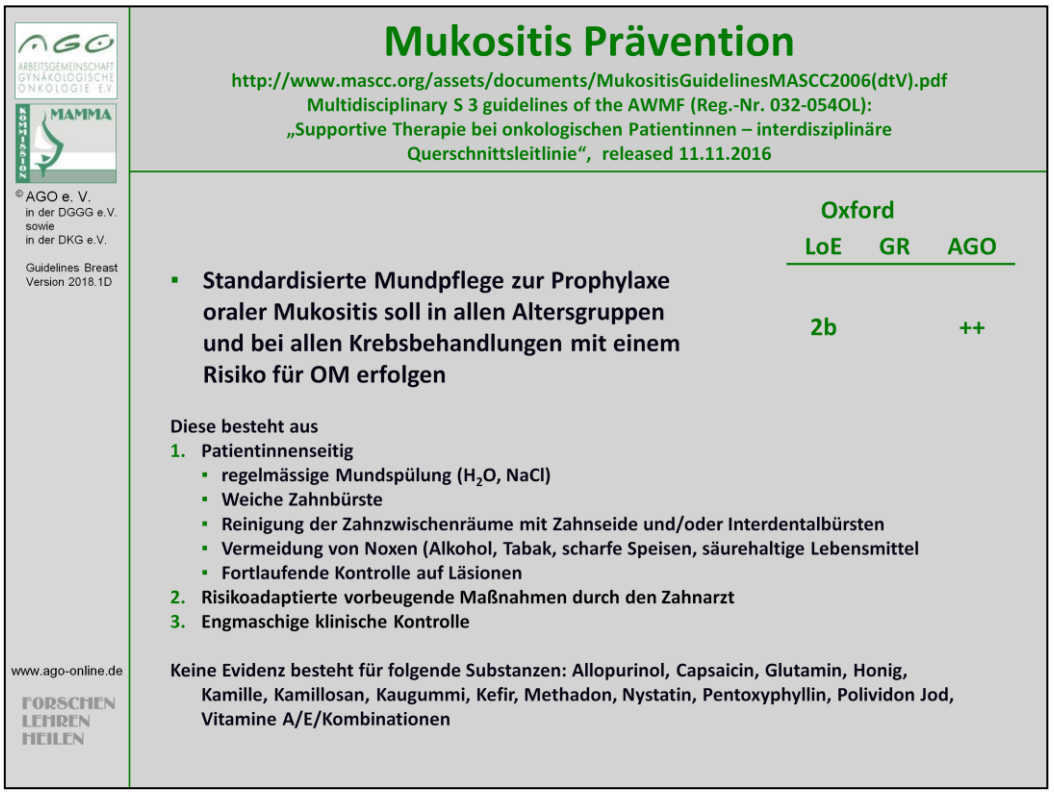

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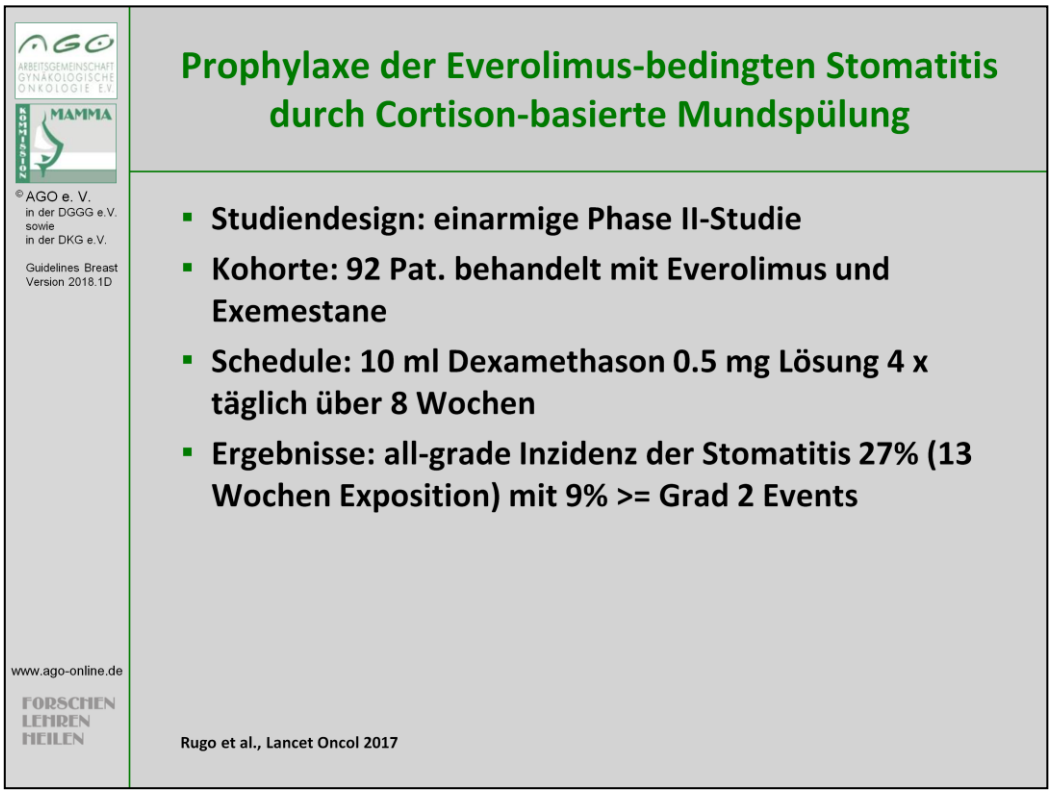

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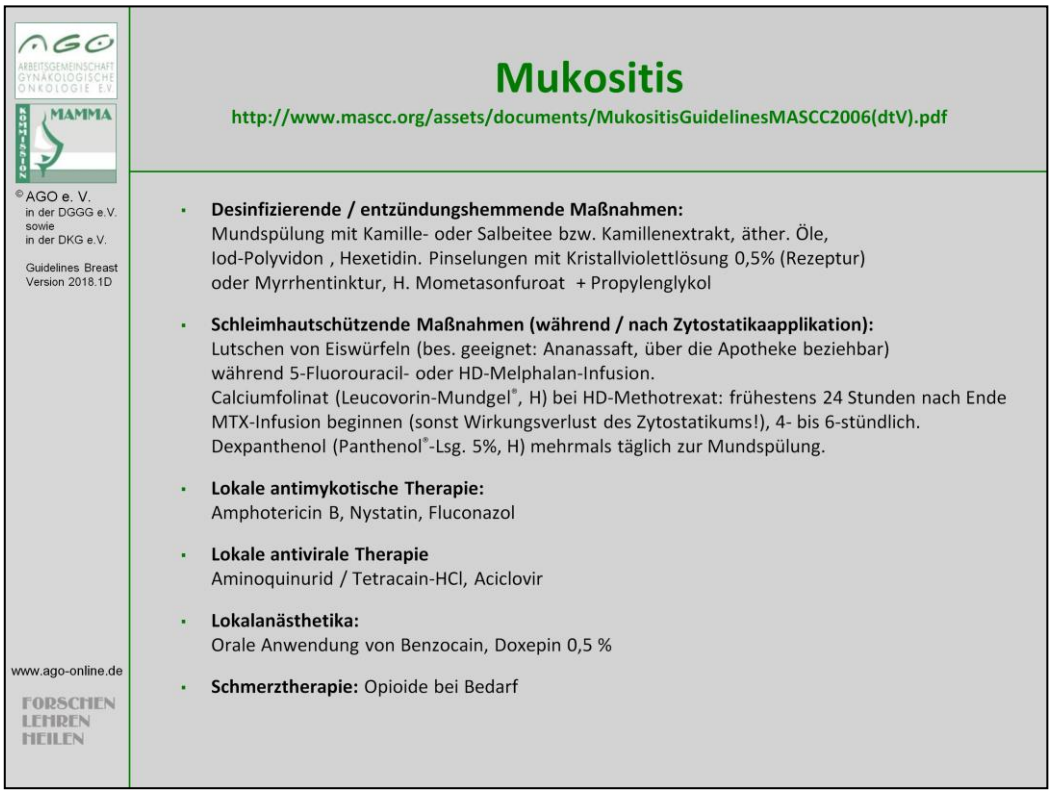

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Guidelines Breast
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Obstipation

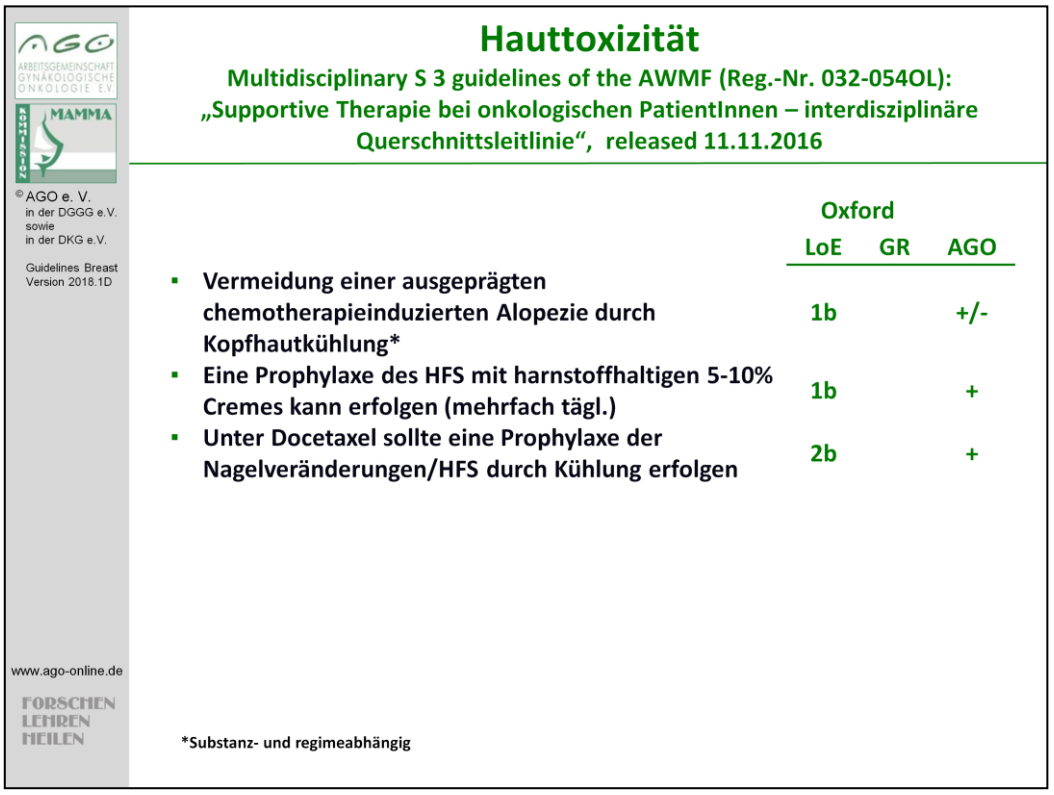
Wichtige Nebenwirkung einer Opiattherapie

- **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 2018.1D

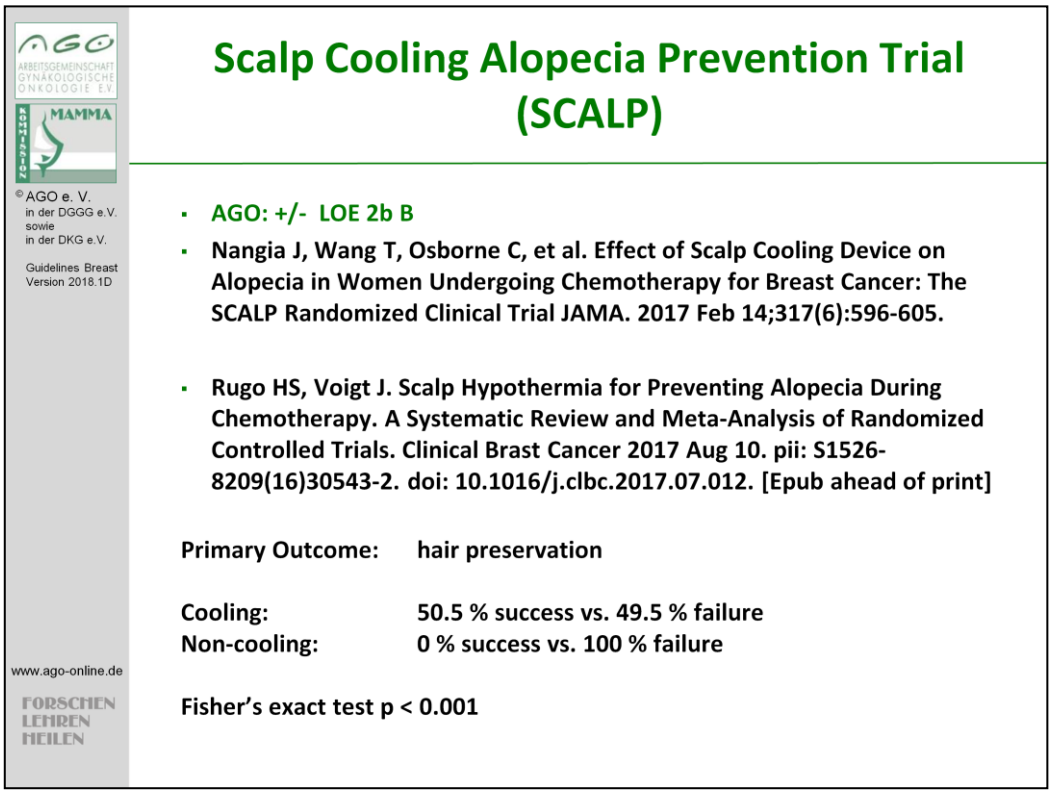
Nebenwirkungen nach Organsystemen
Inzidenz, Prävention, Therapie

9. Erkrankungen der Haut und des Unterhautgewebes



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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Guidelines Breast
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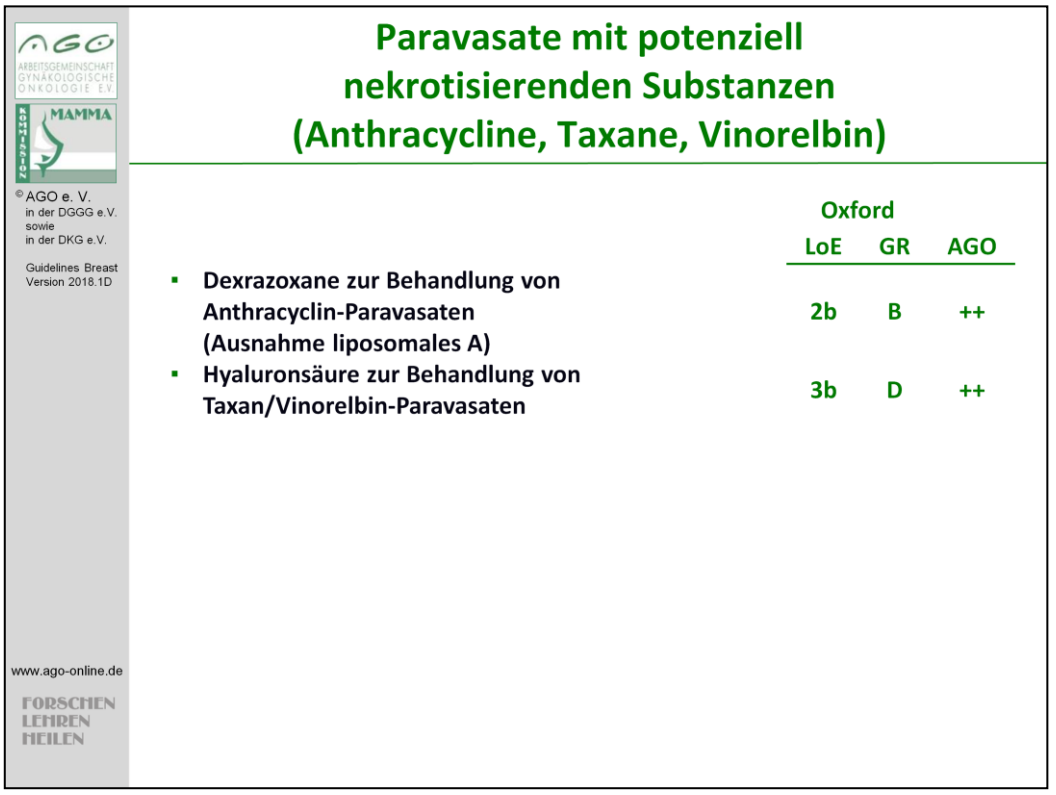
Nebenwirkungen nach Organsystemen
Inzidenz, Prävention, Therapie

10. Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen

(siehe Kapitel Osteoonkologie)

Guidelines Breast
Version 2018.1D

11. Allgemeine Erkrankungen und Beschwerden am Verabreichungsort



Relevant practice guideline:

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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.
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Hyaluronsäure

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Guidelines Breast
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Paravasate
Dexrazoxane/Hyaluronsäure

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.

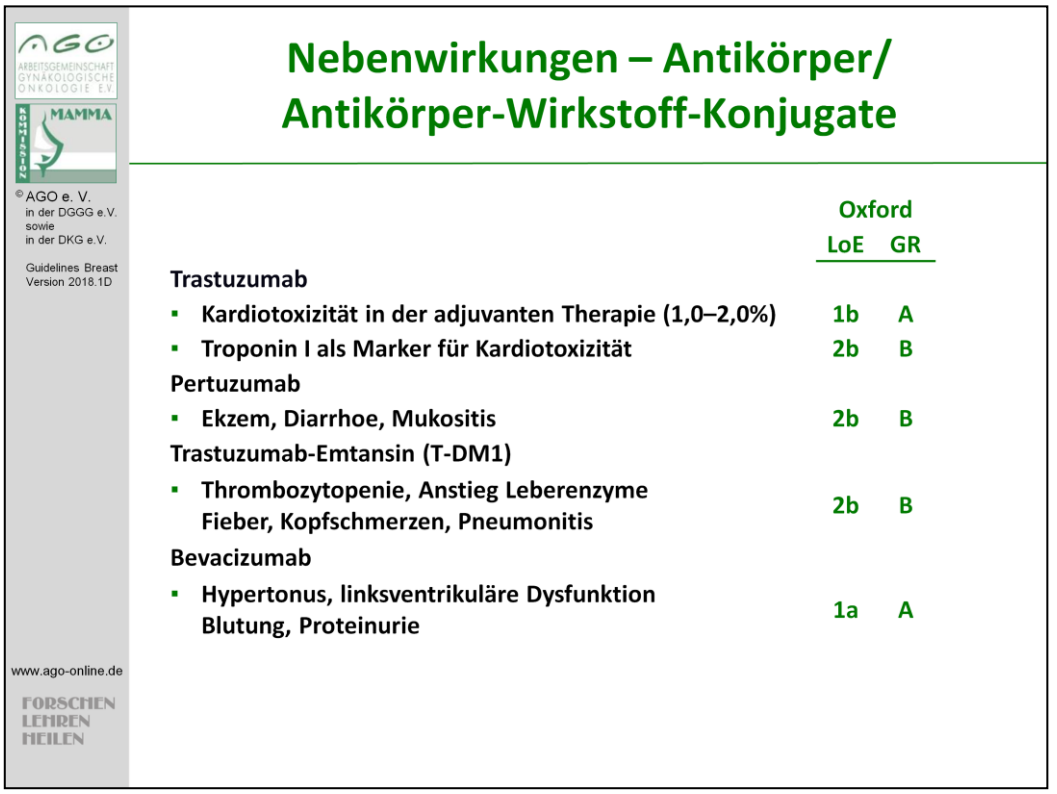
Lokale Kälte: Eispackung 6-stündlich jeweils für 15 Min. für 3 Tage oder: 24 h Abdeckung mit Eisbeuteln

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**

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



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4. Higa GM, Abraham J: Biological mechanisms of bevacizumab-associated adverse events. Expert. Rev Anticancer Ther 2009;9:999–1007
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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

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Lapatinib…
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Everolimus

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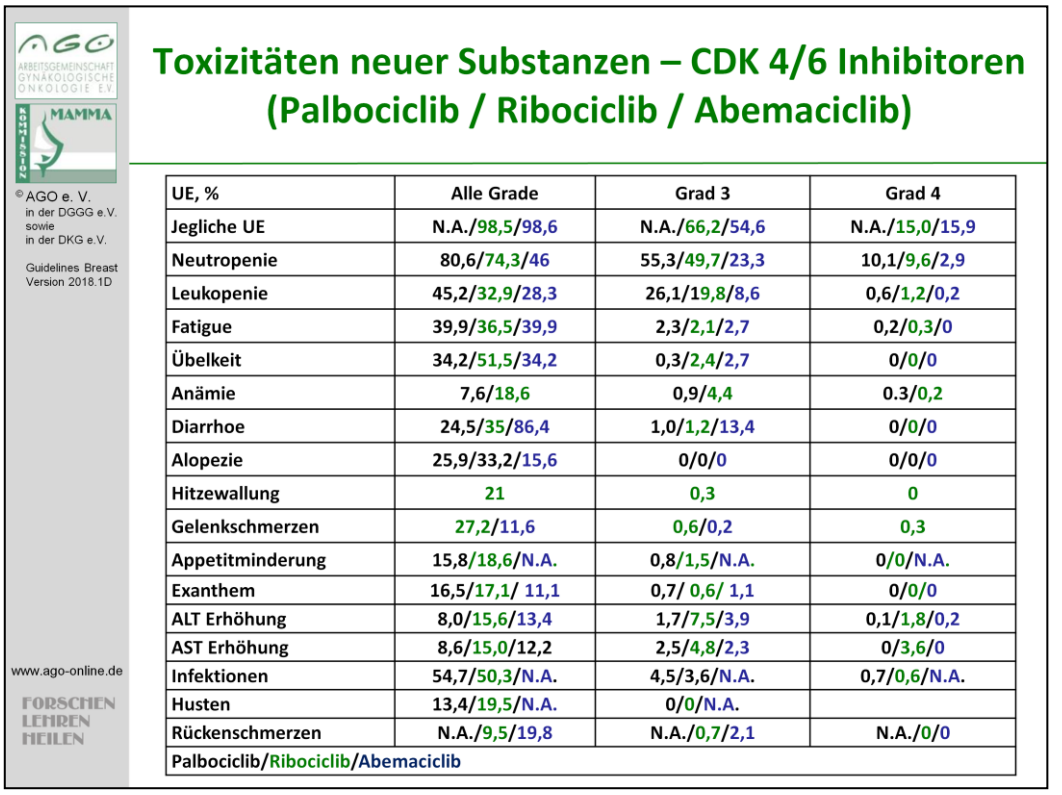

Toxizitäten neuer Substanzen – CDK 4/6 Inhibitoren (Palbociclib / Ribociclib / Abemaciclib)

UE, %	Alle Grade	Grad 3	Grad 4
Jegliche UE	N.A./98,5/98,6	N.A./66,2/54,6	N.A./15,0/15,9
Neutropenie	80,6/74,3/46	55,3/49,7/23,3	10,1/9,6/2,9
Leukopenie	45,2/32,9/28,3	26,1/19,8/8,6	0,6/1,2/0,2
Fatigue	39,9/36,5/39,9	2,3/2,1/2,7	0,2/0,3/0
Übelkeit	34,2/51,5/34,2	0,3/2,4/2,7	0/0/0
Anämie	7,6/18,6	0,9/4,4	0.3/0,2
Diarrhoe	24,5/35/86,4	1,0/1,2/13,4	0/0/0
Alopezie	25,9/33,2/15,6	0/0/0	0/0/0
Hitzewallung	21	0,3	0
Gelenkschmerzen	27,2/11,6	0,6/0,2	0,3
Appetitminderung	15,8/18,6/N.A.	0,8/1,5/N.A.	0/0/N.A.
Exanthem	16,5/17,1/ 11,1	0,7/ 0,6/ 1,1	0/0/0
ALT Erhöhung	8,0/15,6/13,4	1,7/7,5/3,9	0,1/1,8/0,2
AST Erhöhung	8,6/15,0/12,2	2,5/4,8/2,3	0/3,6/0
Infektionen	54,7/50,3/N.A.	4,5/3,6/N.A.	0,7/0,6/N.A.
Husten	13,4/19,5/N.A.	0/0/N.A.	
Rückenschmerzen	N.A./9,5/19,8	N.A./0,7/2,1	N.A./0/0
Palbociclib/Ribociclib/Abemaciclib			

Palbociclib

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

Ribociclib

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

Abemaciclib

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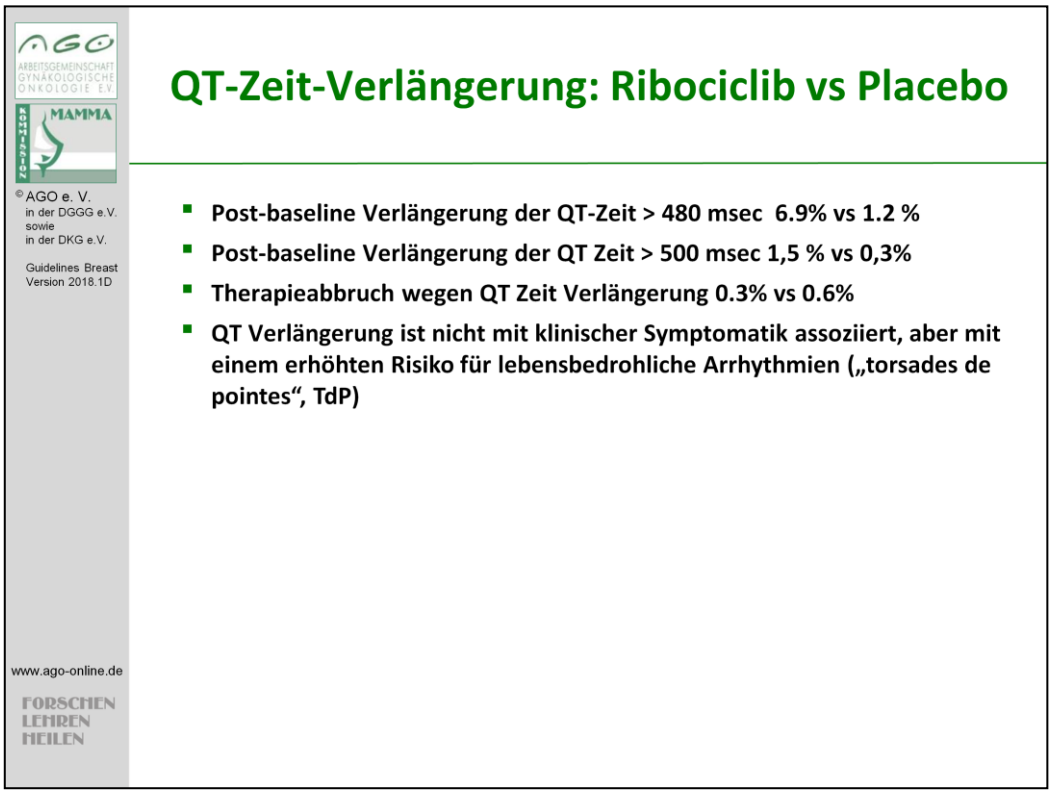

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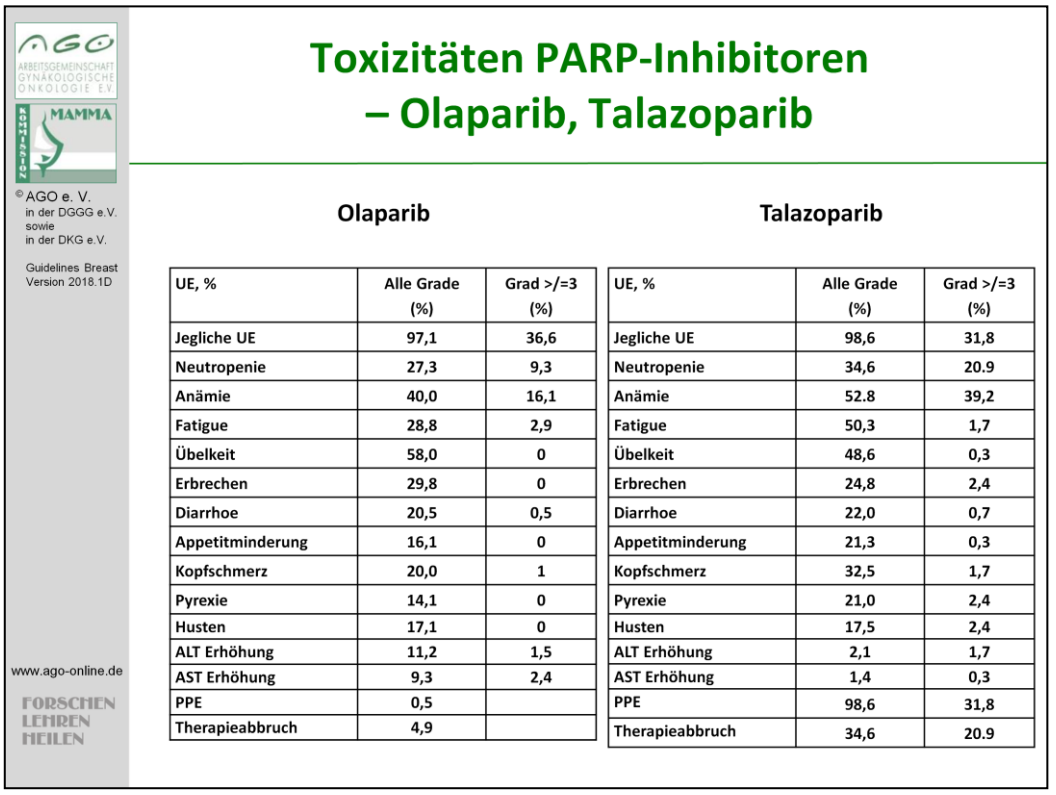
2. SABCS GS02-05, 2017

Toxizitäten neuer Substanzen: mTOR-Inhibitor (Everolimus)

Guidelines Breast
Version 2018.1D

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

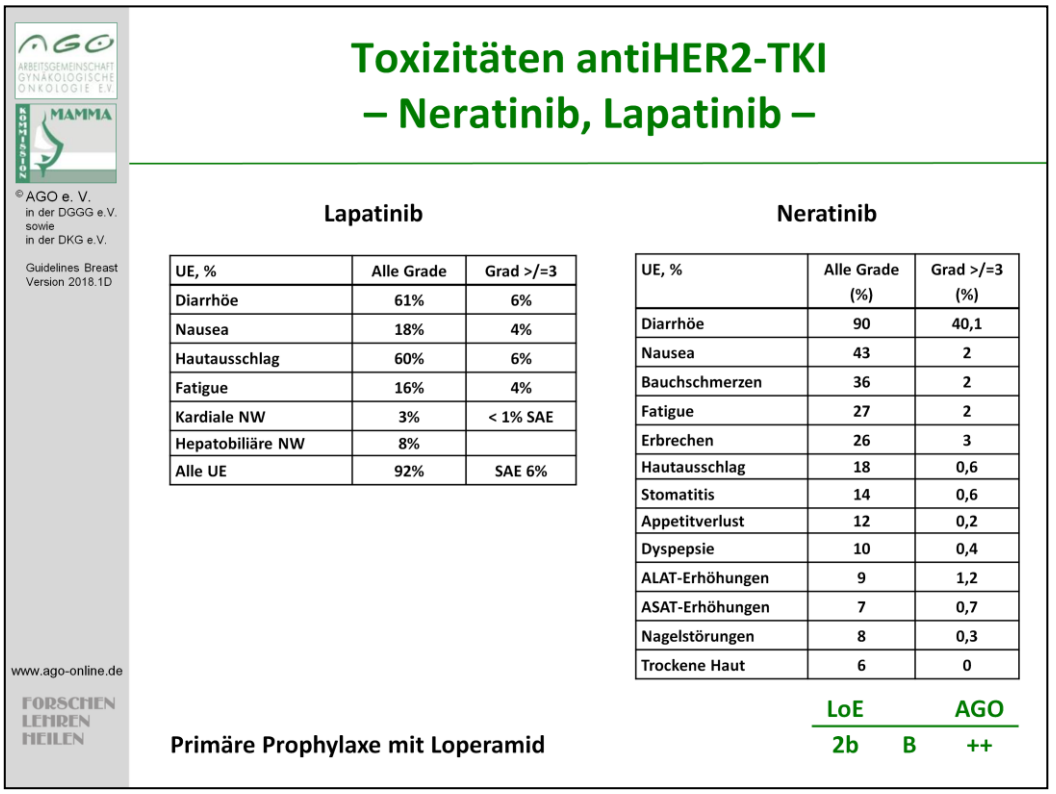
Olaparib

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 J, Rugo H, Ettl J et al EMBRACA: A phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician's choice of therapy in patients with advanced germline BRCA-mutation breast cancer SABCS GS06-07, 2017
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



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
2. Lancet Oncol 17(39: 367-377, 2016
3. Piccart M, Holmes FA, Baselga J et al First results from the phase III ALTTO trial (BIG 2-06; NCCTG [Alliance] N063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T→L), or their combination (T+L) in the adjuvant treatment of HER2-positive early breast cancer (EBC) ASCO LBA 4, 2014
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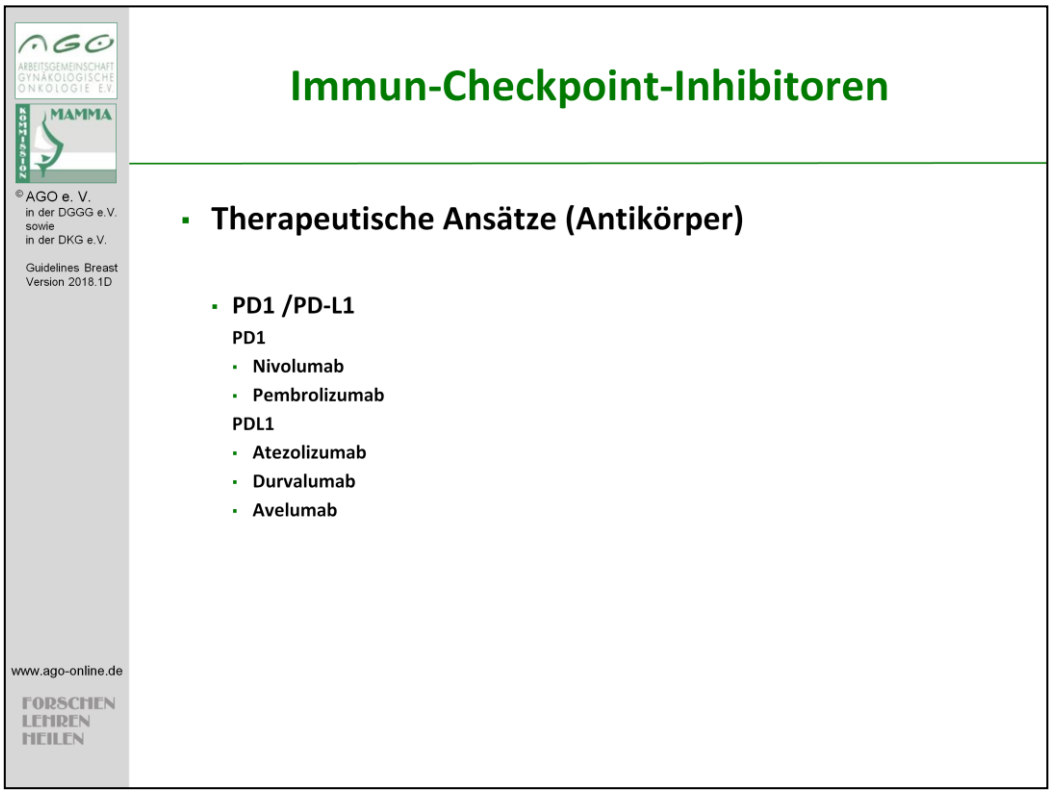
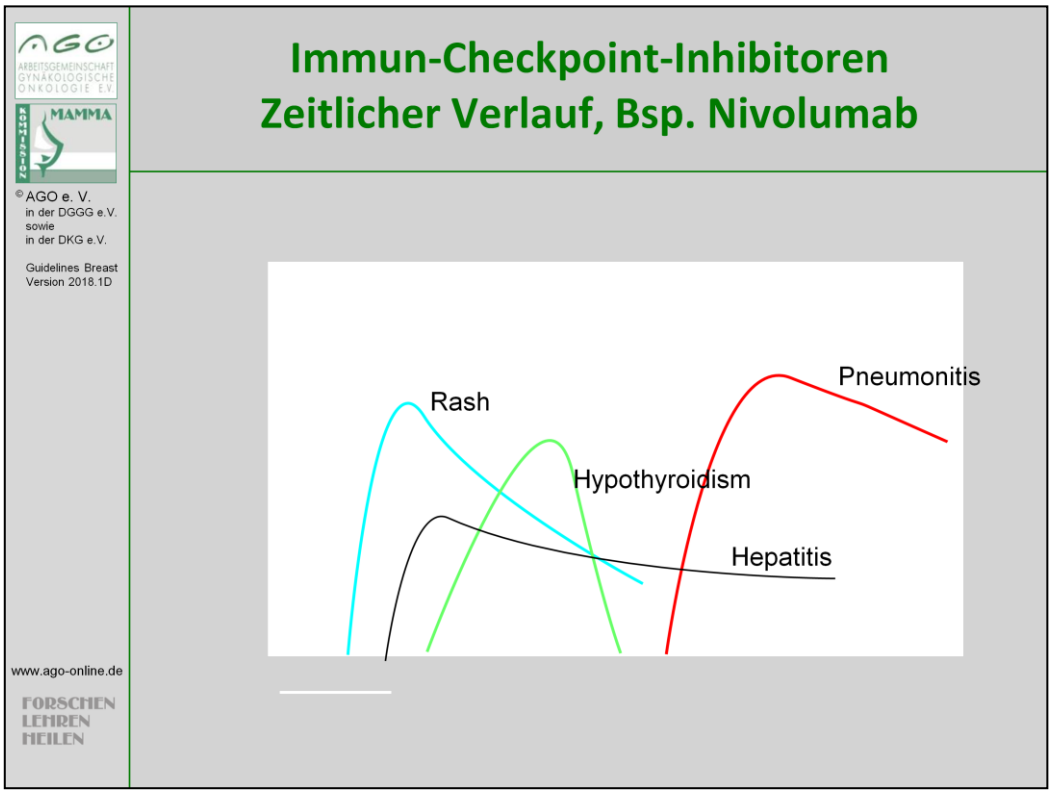
5. and/or Trastuzumab Treatment Optimization Trial
6. JCO 34:1034-1042, 2015

7. Neratinib: FDA Produktinformation 2017



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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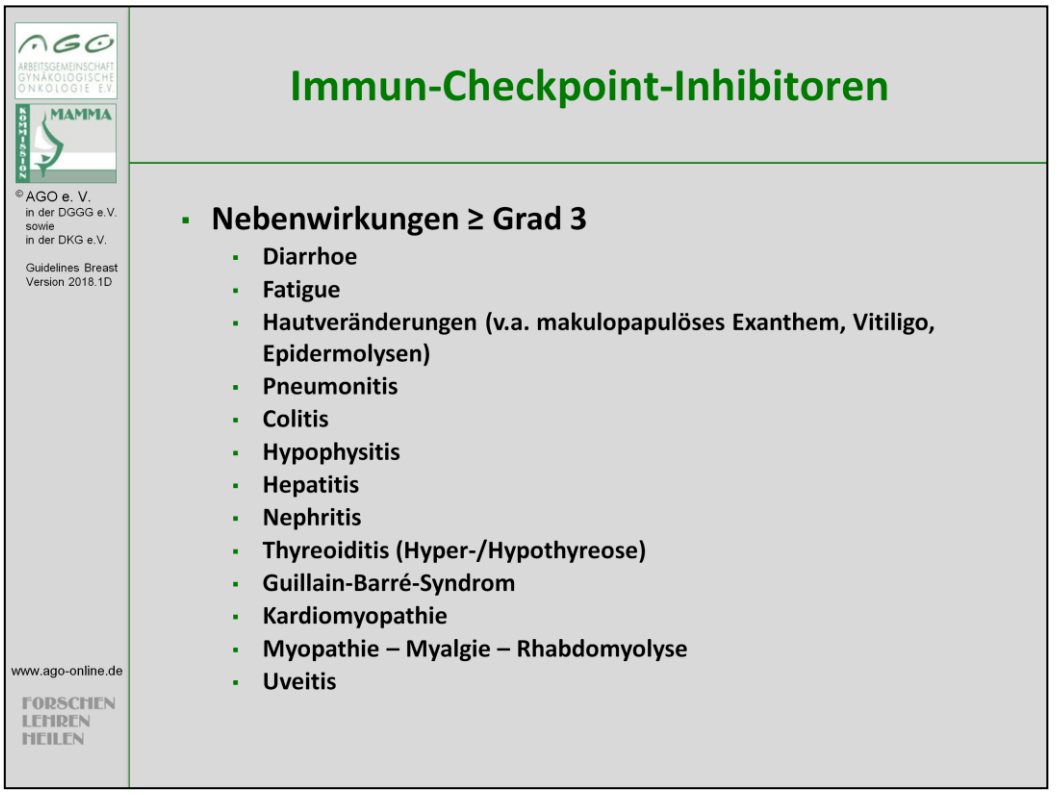

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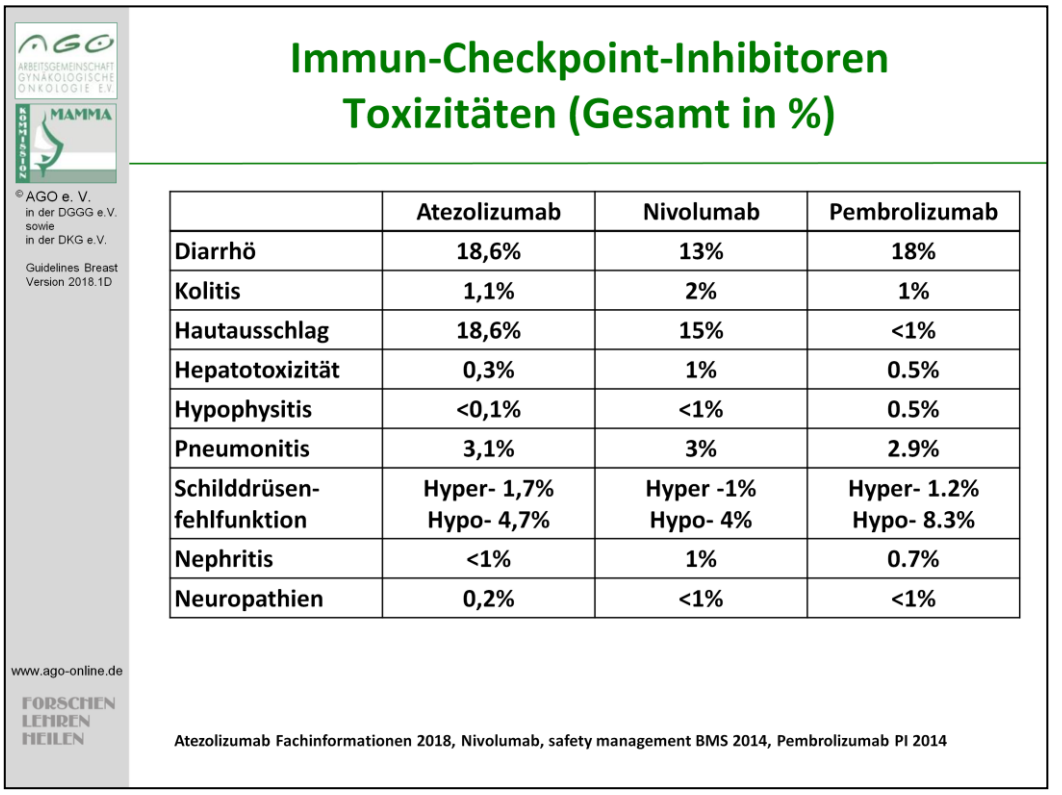
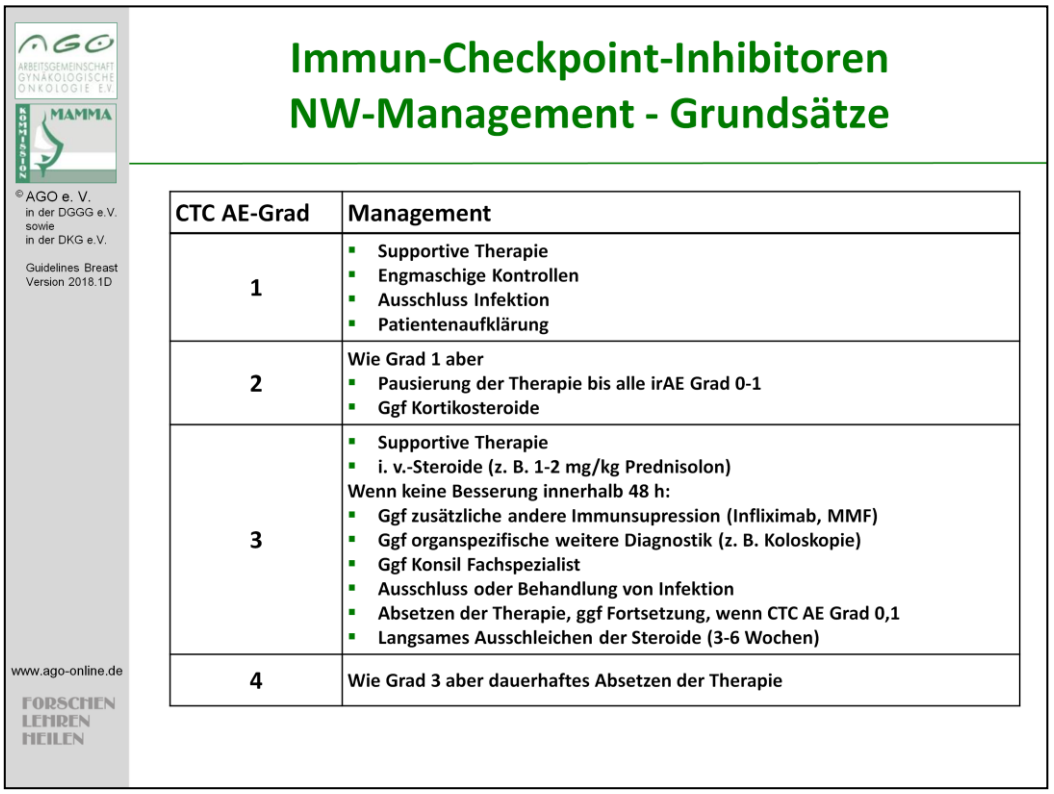


Immun-Checkpoint-Inhibitoren Toxizitäten (Gesamt in %)

	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

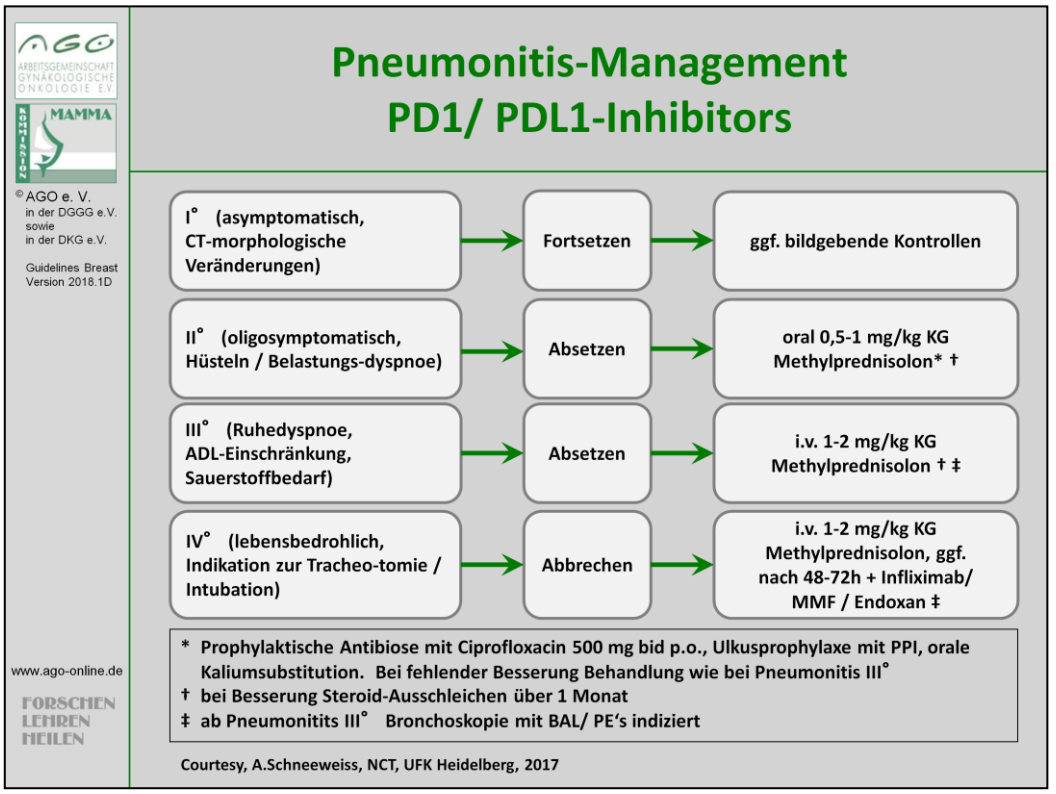
Atezolizumab: https://www.fachinfo.de/suche/fi/021700
Nivolumab: https://www.fachinfo.de/suche/fi/020675
Pembrolizumab: https://www.fachinfo.de/suche/fi/020716



Immun-Checkpoint-Inhibitoren
NW-Management - Grundsätze

CTC AE-Grad	Management
1	▪ Supportive Therapie ▪ Engmaschige Kontrollen ▪ Ausschluss Infektion ▪ Patientenaufklärung
2	Wie Grad 1 aber ▪ Pausierung der Therapie bis alle irAE Grad 0-1 ▪ Ggf Kortikosteroide
3	▪ Supportive Therapie ▪ i. v.-Steroide (z. B. 1-2 mg/kg Prednisolon) Wenn keine Besserung innerhalb 48 h: ▪ Ggf zusätzliche andere Immunsupression (Infliximab, MMF) ▪ Ggf organspezifische weitere Diagnostik (z. B. Koloskopie) ▪ Ggf Konsil Fachspezialist ▪ Ausschluss oder Behandlung von Infektion ▪ Absetzen der Therapie, ggf Fortsetzung, wenn CTC AE Grad 0,1 ▪ Langsames Ausschleichen der Steroide (3-6 Wochen)
4	Wie Grad 3 aber dauerhaftes Absetzen der Therapie

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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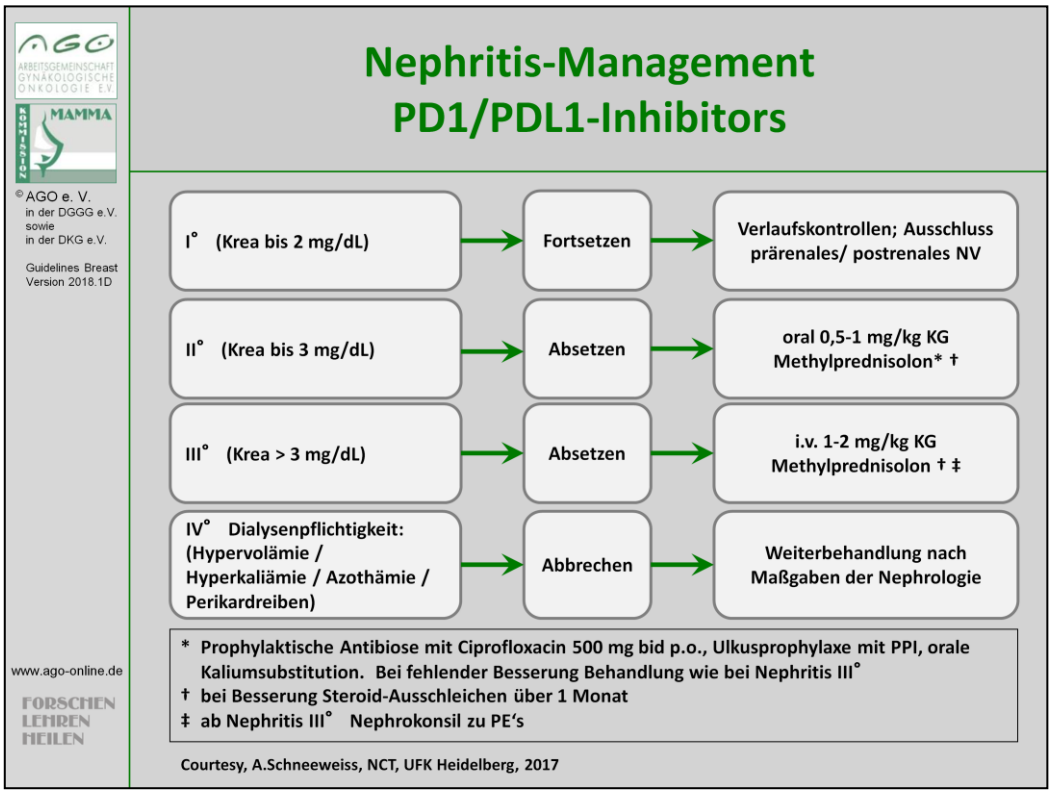

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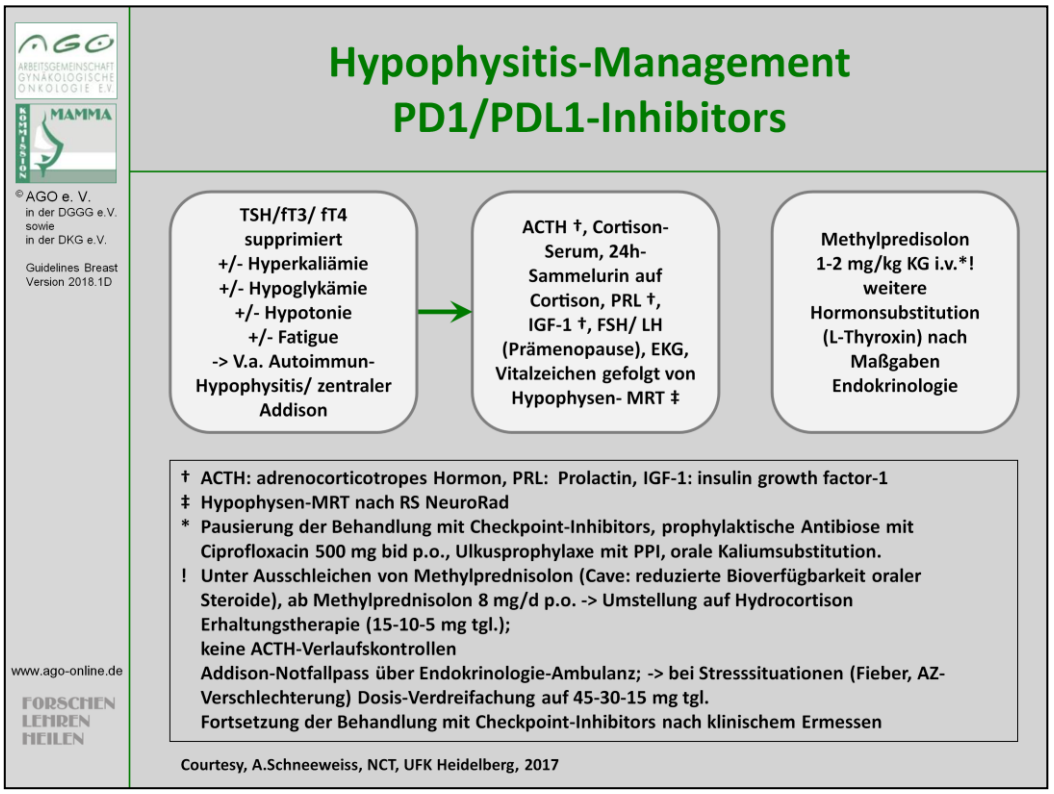

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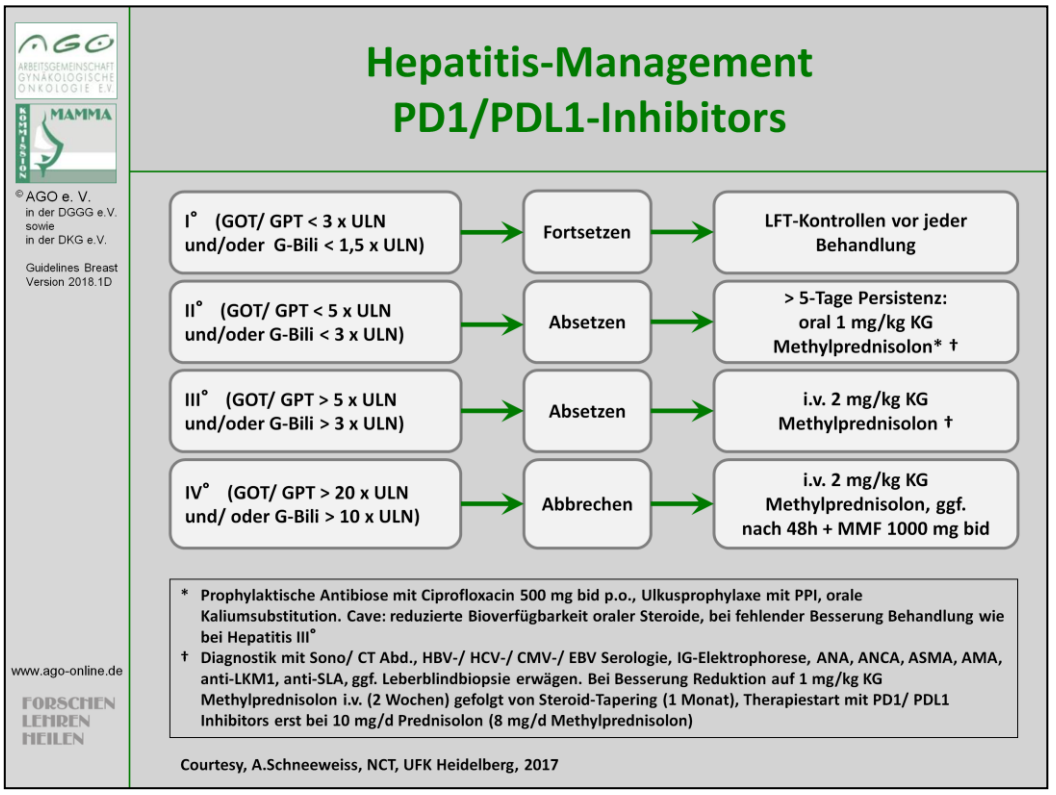

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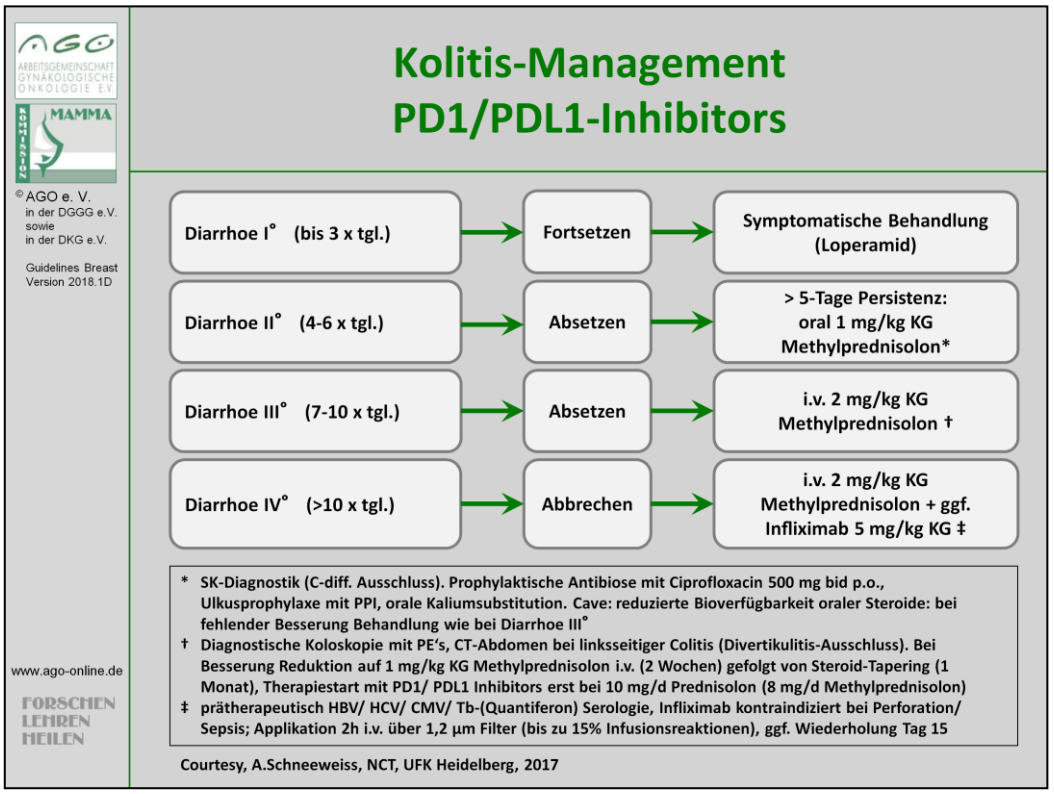

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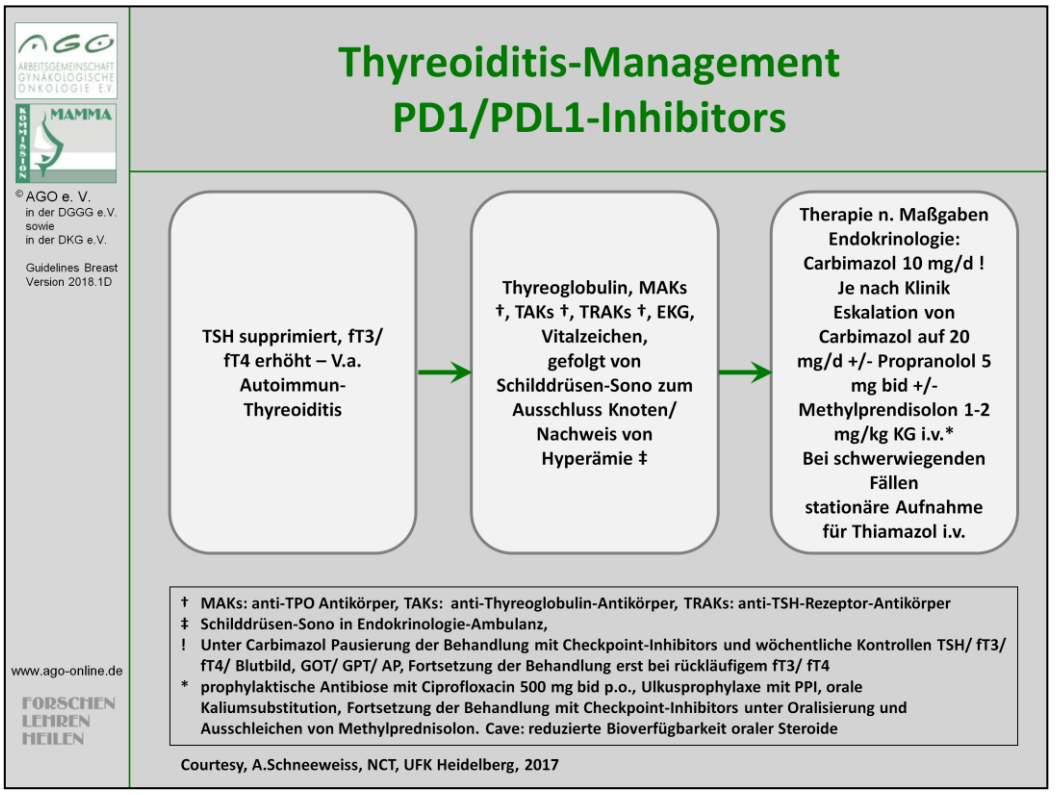

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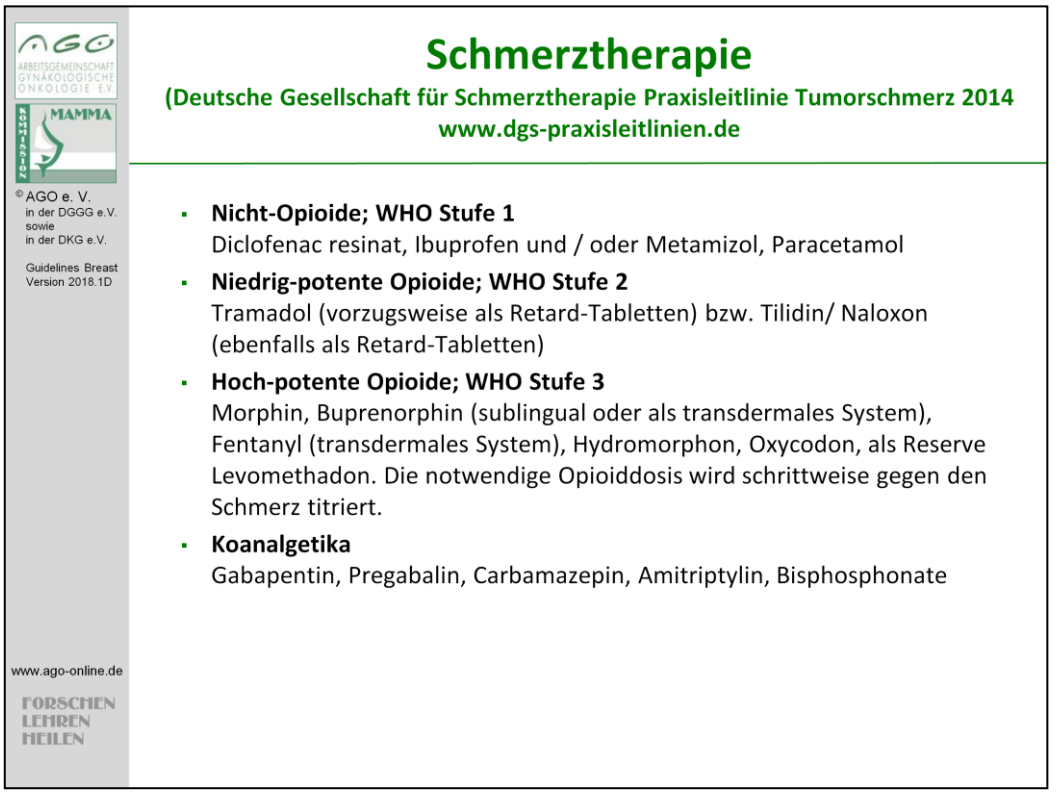
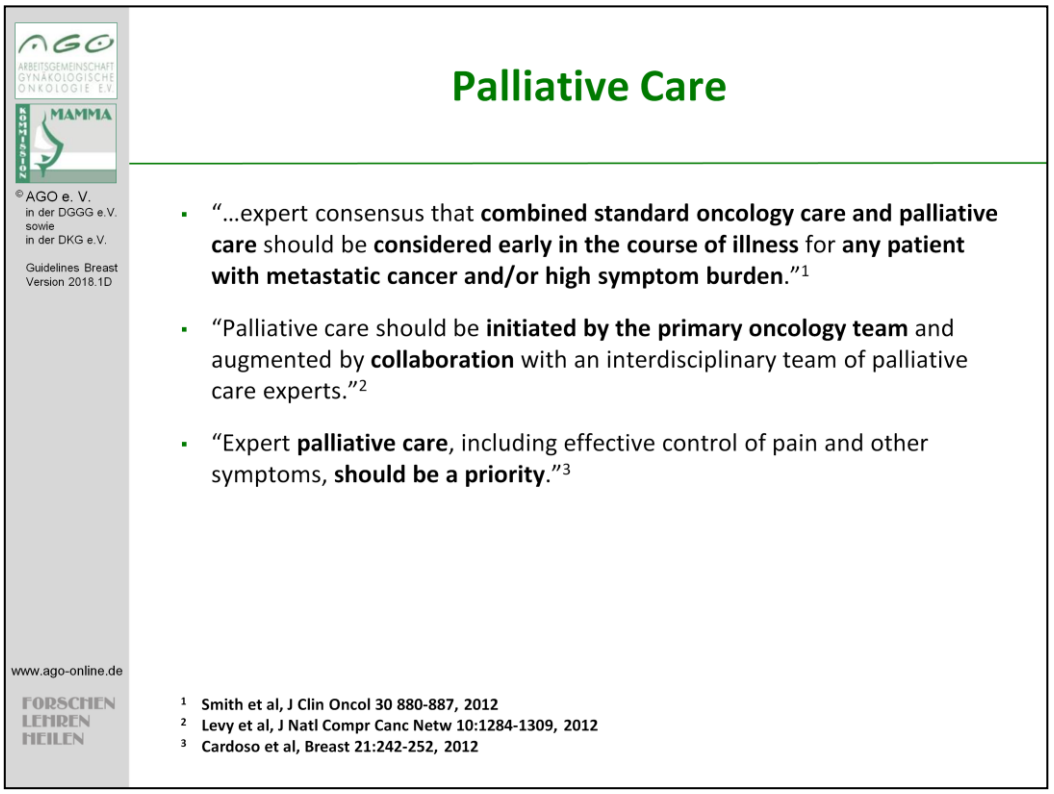
- **Andere supportive und palliative Fragestellungen**
  - **Schmerztherapie**
  - **Palliative Care**



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