Guidelines Breast
Version 2023.1D

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ZNS-Metastasen beim Mammakarzinom

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ZNS-Metastasen beim Mammakarzinom

- **Versionen 2003-2022:**
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- **Version 2023:**
  Fehm / Krug

ZNS-Metastasen beim Mammakarzinom

- **Das Mammakarzinom ist zweithäufigste Ursache von ZNS-Metastasen.**
- **In Autopsie-Kollektiven:**
  - **Parenchymale ZNS-Metastasen: ~ 30–40 %**
  - **Leptomeningeale ZNS-Metastasen: 5–16 %**
- **Stetig steigende Inzidenz (10 % ⇨ 40 %)**
- **Anstieg der Inzidenz verursacht durch:**
  - **Effektivere Behandlungsoptionen der extrazerebralen Metastasen**
  - **Vermehrter Einsatz der MR-Diagnostik**
- **Keine Evidenz für Hirnmetastasen-Screening bei asymptomatischen Patientinnen.**
- **Datenlage für Behandlung von ZNS-Metastasen des Mammakarzinoms ist unbefriedigend, da Studien meist nicht Mammakarzinom-spezifisch. Teilnahme an der deutschen Registerstudie zu ZNS-Metastasen Mammakarzinom empfohlen (www.gbg.de).**

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Incidence of Brain Metastases among Patients with Metastatic Breast Cancer – Meta-Analysis of 25 Trials between 2010-2020

Subtype	No patients	Incidence per patient-year	Pooled cumulative incidence	Median follow-up (months)
HER2 positive (all)	5971	13% 95% CI: 0.22–0.38	31%	31
HR- / HER2 positive	2092	13% 95% CI: 0.08–0.20	-	-
HR+ / HER2 positive	3480	8% 95% CI: 0.05–0.13	-	-
HR- / HER2 negative	4102	13% 95% CI: 0.09–0.20	32% 95% CI: 0.19–0.49	33
HR+ / HER2 negative	14656	5% 95% CI: 0.03–0.08	15% 95% CI: 0.078–0.27	33

Kuksis M, Gao Y, Tran W et al. Neuro Oncol. 2021 Jun 1;23(6):894-904

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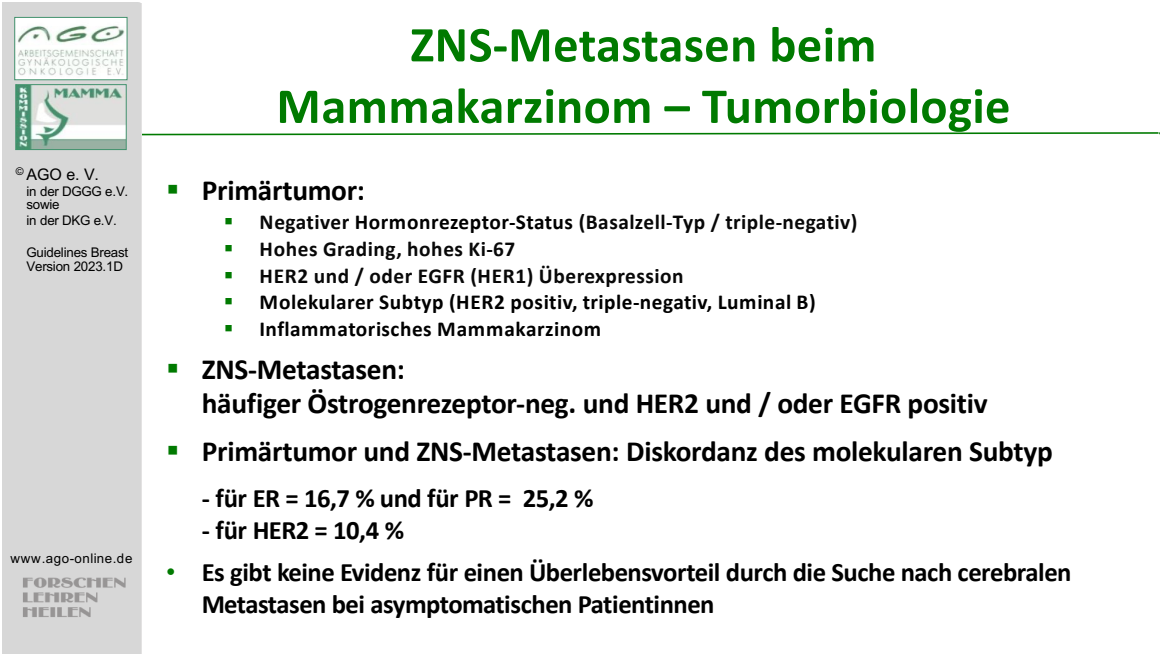

Risk factors (see also references slide CNS incidence)

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Brain metastases (BM) are more likely to be estrogen receptor negative, and overexpress HER2 or EGFR

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There is no evidence for BM-screening in asymptomatic BC-patients

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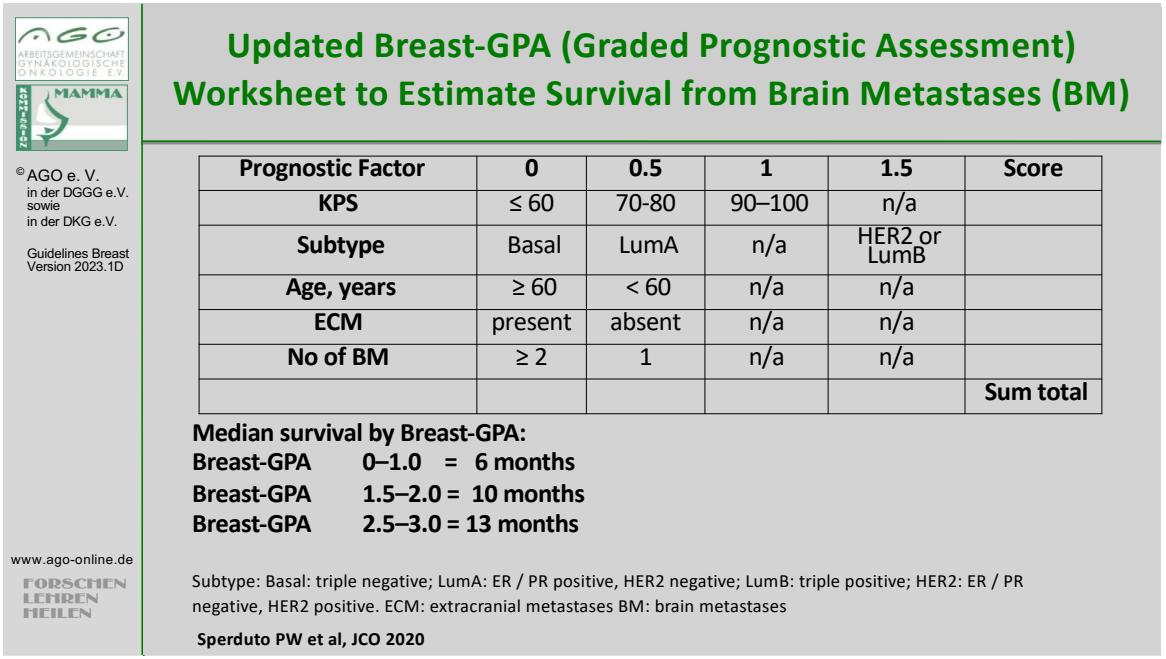

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Updated Breast-GPA (Graded Prognostic Assessment)
Worksheet to Estimate Survival from Brain Metastases (BM)

Prognostic Factor	0	0.5	1	1.5	Score
KPS	≤ 60	70-80	90–100	n/a	
Subtype	Basal	LumA	n/a	HER2 or LumB	
Age, years	≥ 60	< 60	n/a	n/a	
ECM	present	absent	n/a	n/a	
No of BM	≥ 2	1	n/a	n/a	
					Sum total

Median survival by Breast-GPA:
Breast-GPA 0–1.0 = 6 months
Breast-GPA 1.5–2.0 = 10 months
Breast-GPA 2.5–3.0 = 13 months

Subtype: Basal: triple negative; LumA: ER / PR positive, HER2 negative; LumB: triple positive; HER2: ER / PR negative, HER2 positive. ECM: extracranial metastases BM: brain metastases

Sperduto PW et al, JCO 2020

Breast-GPA

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Prognostic Factors for Survival

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Singuläre Hirnmetastasen und Oligohirnmetastasen*

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	Oxford		
	LoE	GR	AGO
Alleinige Lokaltherapie: SRS (≤ 4 cm) oder SRT	1b	B	++
Singuläre Metastase	1b	B	++
OP (wenn indiziert) + Bestrahlung des Tumorbetts (ohne WBRT)			
Oligometastasen	1b	B	++
OP (wenn indiziert) + Bestrahlung des Tumorbetts und SRS oder SRT der nicht-resezierten Metastasen (ohne WBRT)			
WBRT + Boost (SRS, SRT) oder Resektion + WBRT	2a	B	+
Alleinige WBRT	2b	B	+
Patientinnen mit ungünstiger Prognose und/oder schlechtem Allgemeinzustand			
Hippocampusschonung (bei günstiger Prognose)**	1b	B	+

* Oligohirnmetastasierung oder limitierte Metastasierung bezieht sich vor allem auf bis zu 4 Hirnmetastasen, unter bestimmten Voraussetzungen bis zu 10 (Gesamtvolumen < 15 ml)
** Ausschlusskriterium: Metastasen in der Hippocampus-Region
[SRS = stereotactic radiosurgery (einzeitig); SRT = stereotactic radiotherapy (fraktioniert), WBRT = whole brain radiotherapy]

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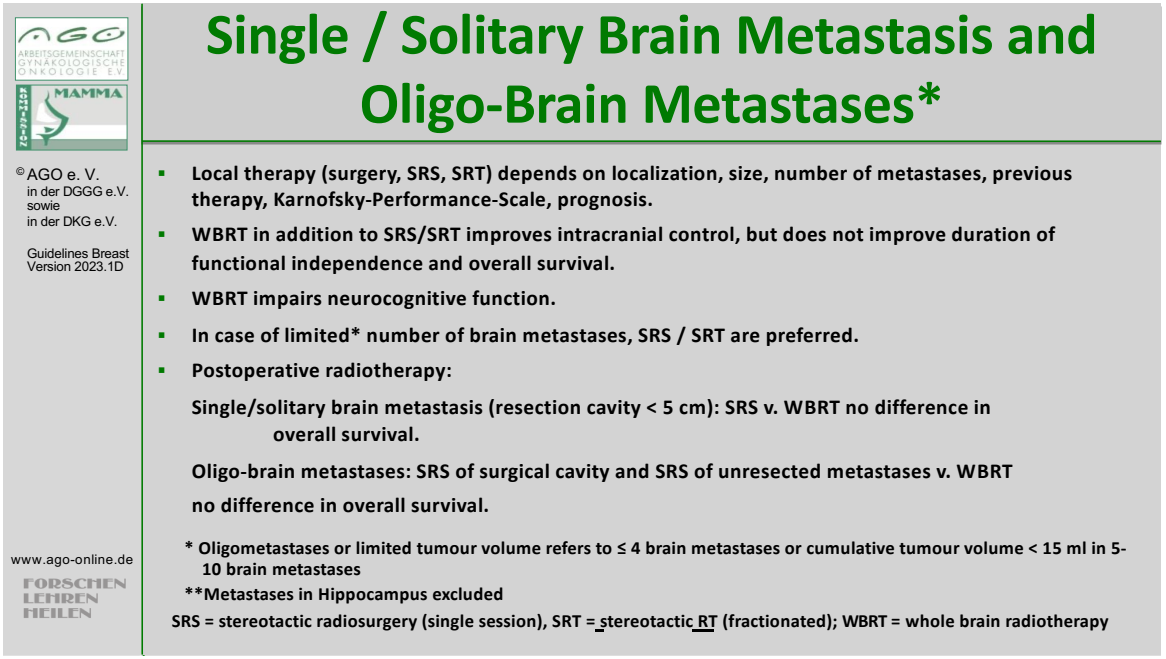

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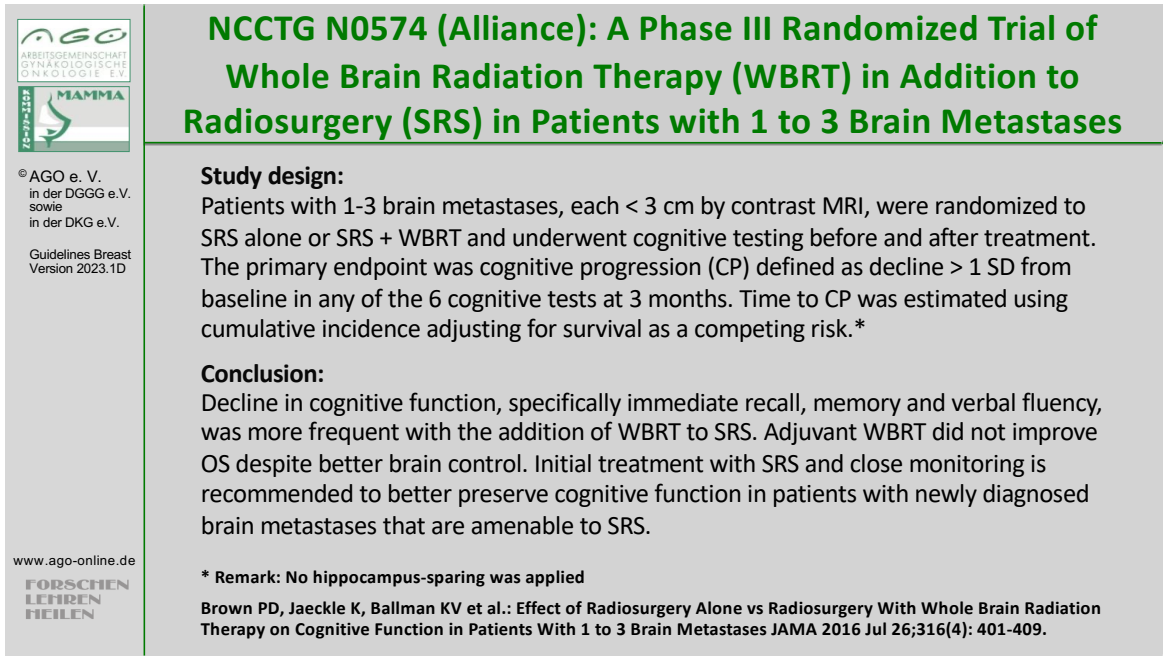

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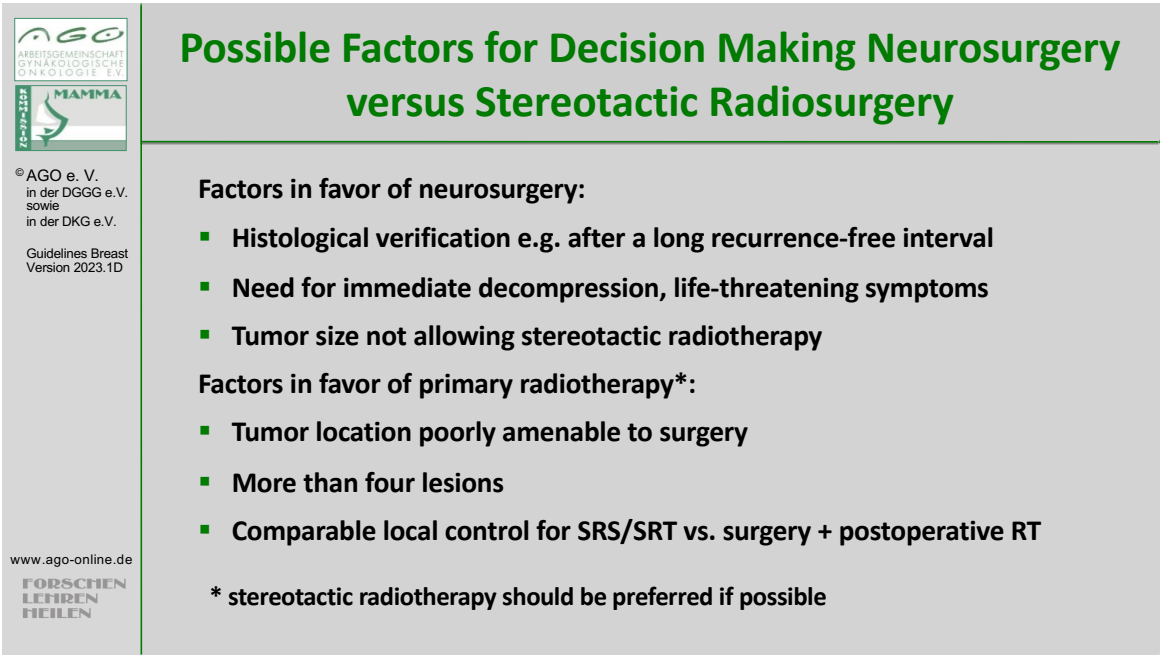

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Multiple Hirnmetastasen falls stereotaktische Strahlentherapie nicht sinnvoll möglich ist

	Oxford		
	LoE	GR	AGO
▪ **WBRT (supportiv Steroide[1])**	1a	A	++
▪ **Hippocampusschonung[2] (bei günstiger Prognose)**	1b	B	+
▪ **Glukokortikoide allein[1]**	3a	B	+/-
▪ **Systemtherapie als alleinige Primärbehandlung**	3a	D	+/-
• **bei asymptomatischen Hirnmetastasen oder asymptomatischem zerebralen Progress (gilt nur bei HER2 positiv)[3]**	2b	C	+
▪ **Radiochemotherapie**	3b	C	-
▪ **Erneute WBRT bei Rezidiv[4]**	4	C	+/-

[1] Symptomadaptiert; [2]Ausschlusskriterium: Metastasen in der Hippocampus-Region; [3]vorausgesetzt: Schema mit nachgewiesener Aktivität bei aktiven Hirnmetastasen; [4] Falls lokale Therapien (OP, SRS, SRT) im Rezidivfall nicht sinnvoll, möglich in Einzelfällen abhängig vom Intervall der vorangegangen Bestrahlung, Vorbelastung und Lokalisation

SRS = stereotactic radiosurgery; SRT = stereotactic radiotherapy (fractionated); WBRT= whole brain radiotherapy

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Systemic treatment alone for pts with newly diagnosed or progressive asymptomatic brain metastases

1. 1. Murthy RK, Loi S, Okines A et al., Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer, N Engl J Med 2020; 382(7):597-609
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1. Ammirati M, Cobbs CS, Linskey ME et al.: The role of retreatment in the management of recurrent/progressive brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010, 96:85-96.
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<u>Re-Bestrahlung bei Rezidiv</u>

1. Huang, Z., B. Sun, G. Shen et al.: Brain metastasis reirradiation in patients with advanced breast cancer. J Radiat Res 2016. Oct 5. [Epub ahead of print] DOI 10.1093/jrr/rrw087
2. Minniti, G., C. Scaringi, S. Paolin et al.: Repeated stereotactic radiosurgery for patients with progressive brain metastases. J Neurooncol 2016; 126(1): 91-97.
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Symptomatische Therapie von Hirnmetastasen

	Oxford		
	LoE	GR	AGO
▪ **Antikonvulsiva nur bei Anfallssymtomatik**	3a	C	+
▪ **Glukokortikoide nur, wenn Symptome und / oder Verdrängungseffekt (Dexamethason mit größter Evidenz)**	3a	C	++
▪ **Für Pat. mit schlechter Prognose best supportive care, und / oder palliative Versorgung ohne weitere Therapie als Option**	5	D	+

Anticonvulsants

1. Lobos-Urbina D, Kittsteiner-Manubens L, Pena J: Is primary prevention with antiepileptic drugs effective in brain tumors or brain metastases? Medwave 2017;17:e6871.
2. Soffietti R, Abacioglu U, Baumert B et al.: Diagnosis and treatment of brain metastases from solid tumors: Guidelines from the european association of neuro-oncology (eano). Neuro Oncol 2017;19:162-174.

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Guidelines Breast
Version 2023.1D

Klinische Einordnung von Hirnmetastasen

Stabile Hirnmetastase (Definition: RECIST / RANO): Stabilisierung nach vorangehender Behandlung der Hirnmetastase(n)

Stabile Hirnmetastase (Definition analog DESTINY-Breast03-Studie): stabile Hirnmetastasen 2 Wochen nach Ganzhirnbestrahlung, keine Symptome, keine Medikation mit Kortikosteroiden, Antikonvulsiva

Aktive Hirnmetastase (Definition analog HER2Climb-Studie):

lokal vorbehandelt: progrediente oder neue Hirnmetastase(n), bei denen keine sofortige erneute lokale Behandlung indiziert ist
oder
lokal unbehandelte Hirnmetastase(n), für die keine sofortige lokale Behandlung indiziert ist.

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4. Hurvitz S., Kim SB, Chung WP et al. :Trastuzumab deruxtecan (T-DXd; DS-8201a) vs. trastuzumab emtansine (T-DM1) in patients (pts) with HER2+ metastatic breast cancer (mBC): subgroup analyses from the randomized phase 3 study DESTINY-Breast03, General Session 3, SABCS 2021

Systemische Therapie von Hirnmetastasen: Allgemeine Grundsätze

	Oxford LoE	GR	AGO
▪ **Interdisziplinäre Behandlungsplanung (Tumorboard)**	5	D	++
▪ **<u>Systemtherapie</u> als alleinige Primärbehandlung**	3a	D	+/-
▪ **bei asymptomatischen Hirnmetastasen oder asymptomatischem zerebralen Progress (gilt nur bei HER2 positiv)***	2b	C	+
▪ **Beibehalten des aktuellen Therapieschemas bei Erstdiagnose zerebraler Metastase und bei extrazerebral stabiler Erkrankungssituation****	2c	C	+

***vorausgesetzt: Schema mit nachgewiesener Aktivität bei aktiven Hirnmetastasen**
****vorausgesetzt: Adäquate lokale Therapie der Hirnmetastasen**

1. Le Rhun E, Guckenberger M, Smits M et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol. 2021;32(11):1332-1347.
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<u>Systemic treatment alone for pts with newly diagnosed or progressive asymptomatic brain metastases</u>

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Systemische Therapie bei Hirnmetastasen: HER2 positiv

	Oxford		
	LoE	GR	AGO
▪ Tucatinib + Trastuzumab + Capecitabin*	2b	B	+
▪ Trastuzumab-Deruxtecan**	2b	B	+
▪ Trastuzumab-Deruxtecan*	2b	C	+/-
▪ T-DM1**	2b	B	+/-
▪ Lapatinib + Capecitabin*	2b	B	+/-
▪ Neratinib + Capecitabin*	2b	B	+/-
▪ Neratinib + Paclitaxel**	2b	B	+/-
▪ High-dose Trastuzumab + Pertuzumab*	2b	C	-

*Wirksamkeit bei aktiven und stabilen Hirnmetastasen basierend auf Studieneinschlußkriterien vorhanden
**Wirksamkeit bei stabilen Hirnmetastasen basierend auf Studieneinschlußkriterien vorhanden

Tucatinib + Trastuzumab + Capecitabin:

1. Murthy RK, Loi S, Okines A et al., Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer, N Engl J Med 2020; 382(7):597-609
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T-DM1:

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Lapatinib + Capecitabin:

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Trastuzumab + Pertuzumab:

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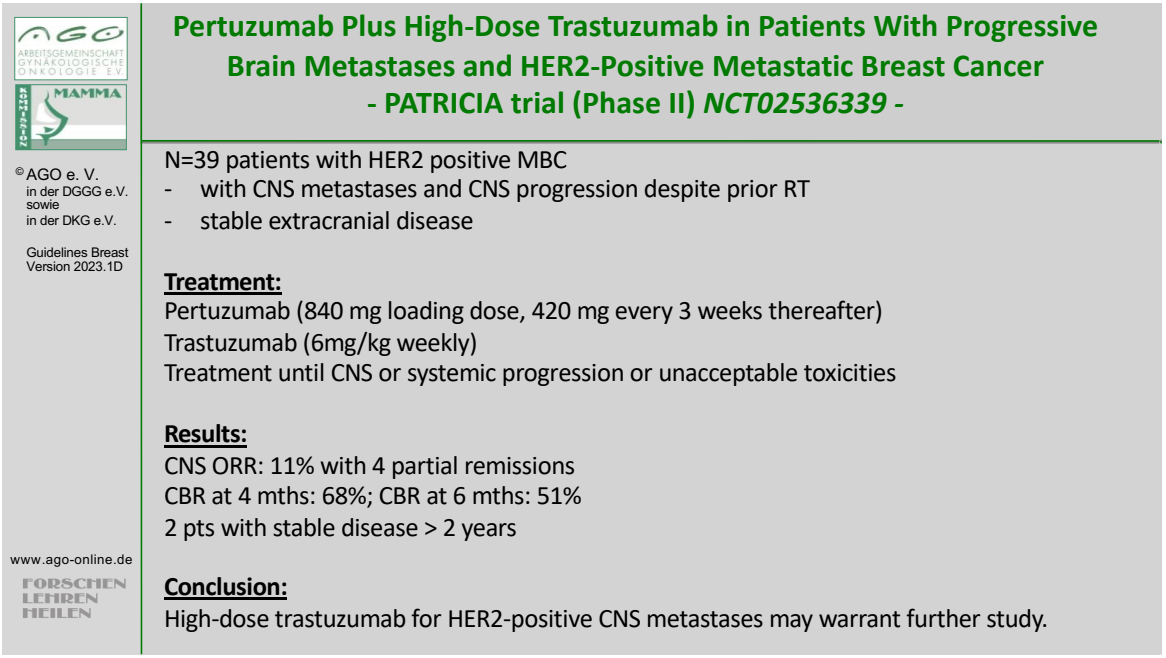

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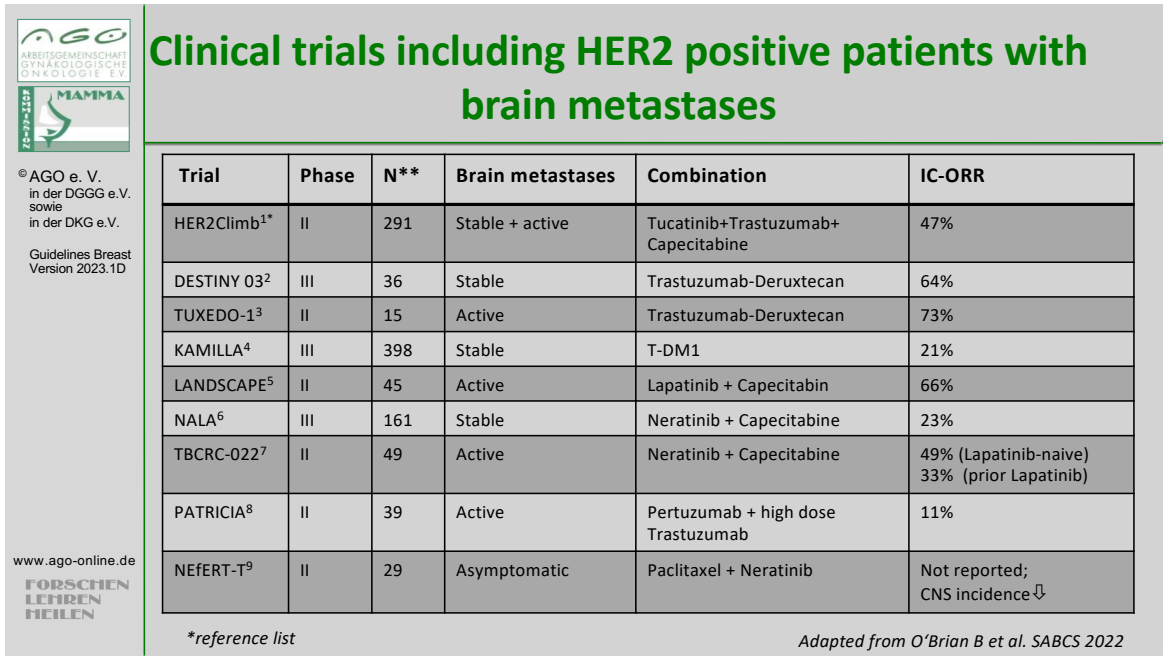

Clinical trials including HER2 positive patients with brain metastases

Trial	Phase	N**	Brain metastases	Combination	IC-ORR
HER2Climb[1*]	II	291	Stable + active	Tucatinib+Trastuzumab+ Capecitabine	47%
DESTINY 03[2]	III	36	Stable	Trastuzumab-Deruxtecan	64%
TUXEDO-1[3]	II	15	Active	Trastuzumab-Deruxtecan	73%
KAMILLA[4]	III	398	Stable	T-DM1	21%
LANDSCAPE[5]	II	45	Active	Lapatinib + Capecitabin	66%
NALA[6]	III	161	Stable	Neratinib + Capecitabine	23%
TBCRC-022[7]	II	49	Active	Neratinib + Capecitabine	49% (Lapatinib-naive) 33% (prior Lapatinib)
PATRICIA[8]	II	39	Active	Pertuzumab + high dose Trastuzumab	11%
NEfERT-T[9]	II	29	Asymptomatic	Paclitaxel + Neratinib	Not reported; CNS incidence⇩

*reference list

Adapted from O'Brian B et al. SABCS 2022

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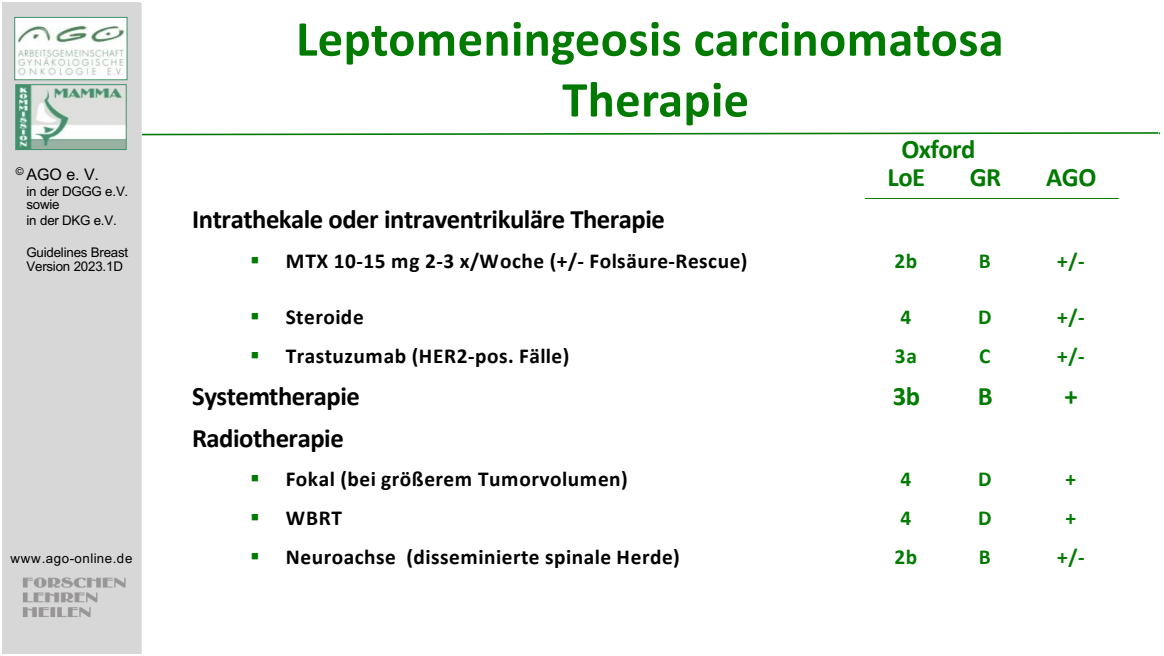

Leptomeningeosis carcinomatosa
Therapie

	Oxford LoE	GR	AGO
Intrathekale oder intraventrikuläre Therapie			
▪ MTX 10-15 mg 2-3 x/Woche (+/- Folsäure-Rescue)	2b	B	+/-
▪ Steroide	4	D	+/-
▪ Trastuzumab (HER2-pos. Fälle)	3a	C	+/-
Systemtherapie	3b	B	+
Radiotherapie			
▪ Fokal (bei größerem Tumorvolumen)	4	D	+
▪ WBRT	4	D	+
▪ Neuroachse (disseminierte spinale Herde)	2b	B	+/-

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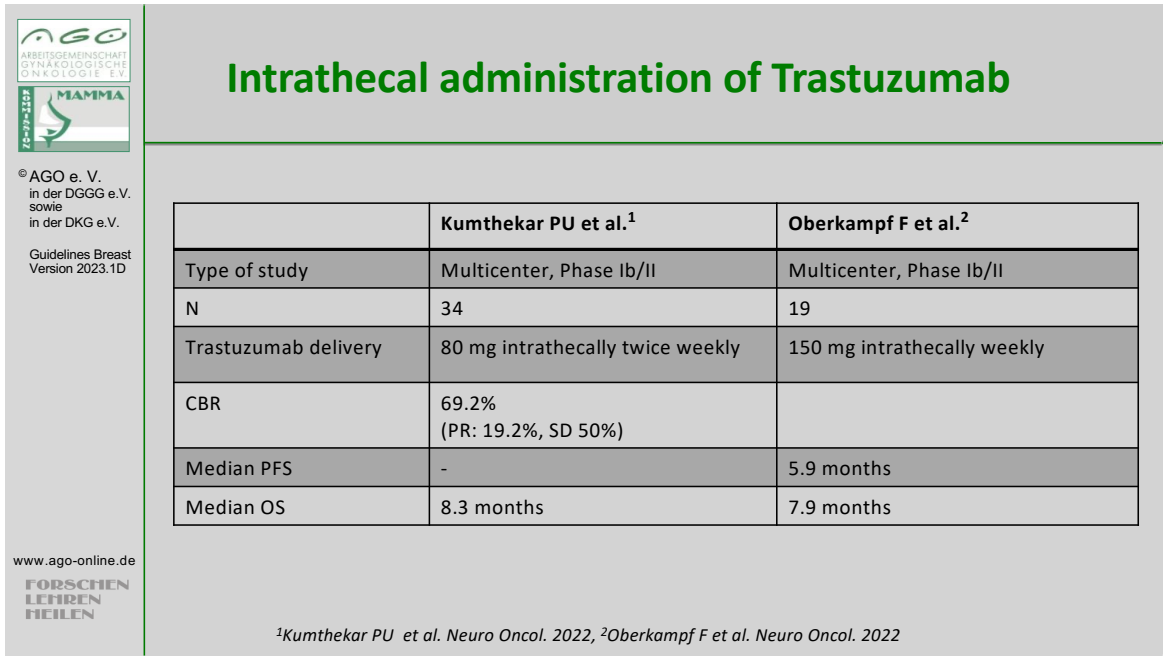

Intrathecal administration of Trastuzumab

	Kumthekar PU et al.[1]	Oberkampf F et al.[2]
Type of study	Multicenter, Phase Ib/II	Multicenter, Phase Ib/II
N	34	19
Trastuzumab delivery	80 mg intrathecally twice weekly	150 mg intrathecally weekly
CBR	69.2% (PR: 19.2%, SD 50%)	
Median PFS	-	5.9 months
Median OS	8.3 months	7.9 months

[1]Kumthekar PU et al. Neuro Oncol. 2022, [2]Oberkampf F et al. Neuro Oncol. 2022

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