

Tratamento sistêmico para metástase cerebral e carcinomatose meníngea em tumores HER2+

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Declaração de conflito de interesses

Clinical study: Daiichi Sankyo, MSD, Roche

Consultant: AstraZeneca, Daiichi Sankyo, Genomic Health, Gilead, Libbs, Lilly, MSD, Novartis, Pfizer, Roche

Travel expenses: AstraZeneca, Roche

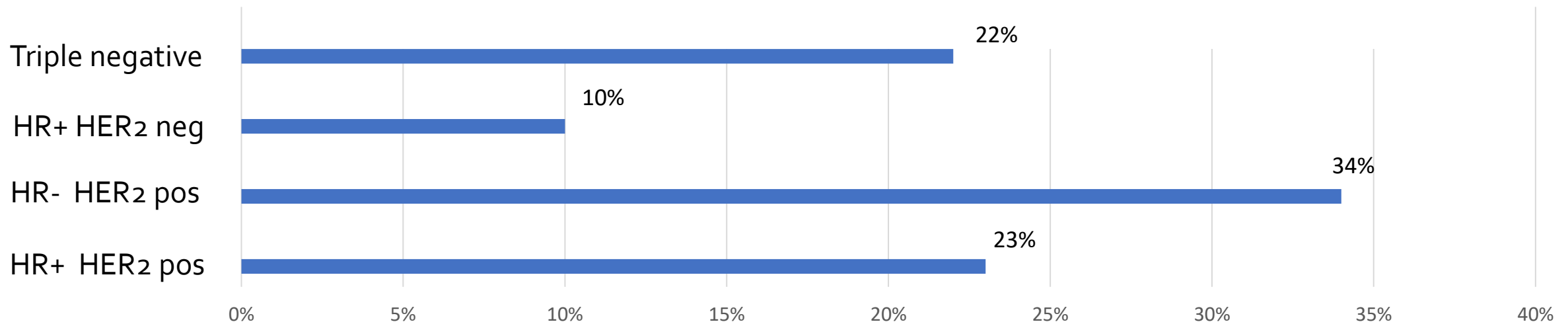
Personal opinion may not reflect the Instituto Nacional de Câncer orientation

Real world cohort of patients with metastatic breast cancer

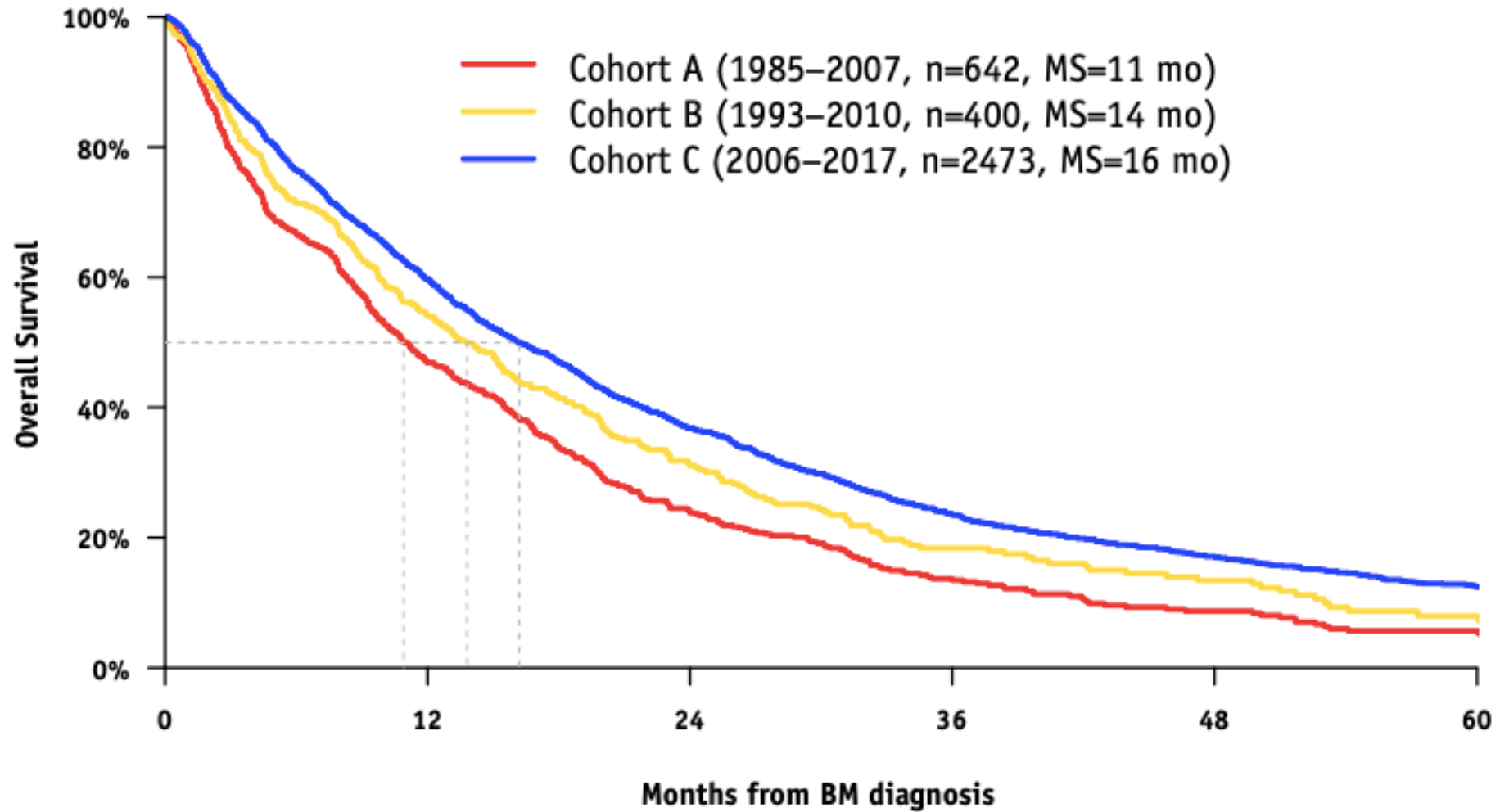
18075 patients

6.1% brain metastases @ index date

The cumulative incidence of brain metastases at 60 months

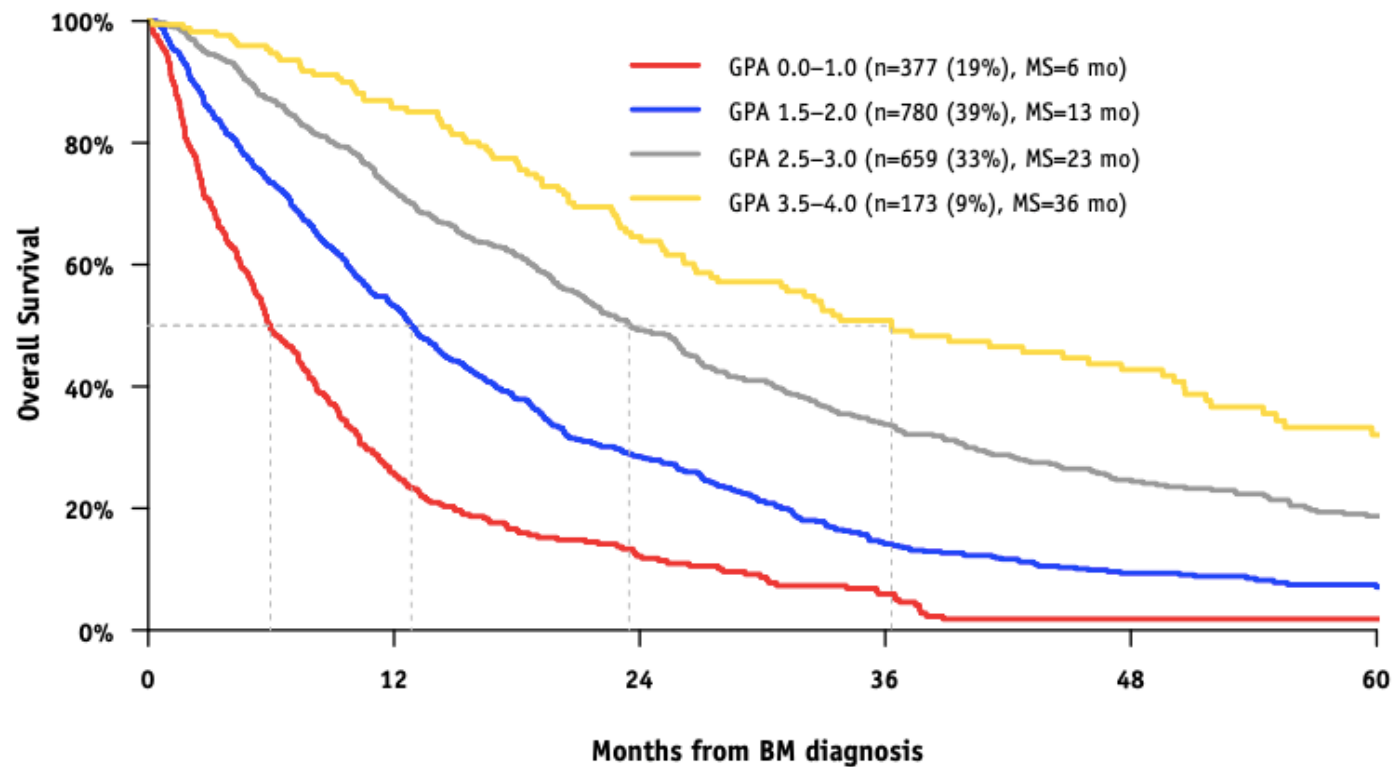


The prognosis of breast cancer patients with brain metastases is improving over time



Estimating the prognosis of breast cancer patients with brain metastases (Breast GPA)

Factor	0	0.5	1.0	1.5
KPS	≤60	70-80	90-100	NA
Subtype	Basal	Luminal A	NA	HER2, Luminal B
Age	≤60	<60	NA	NA
No. BM	>1	1	NA	NA
ECM	Present	Absent		





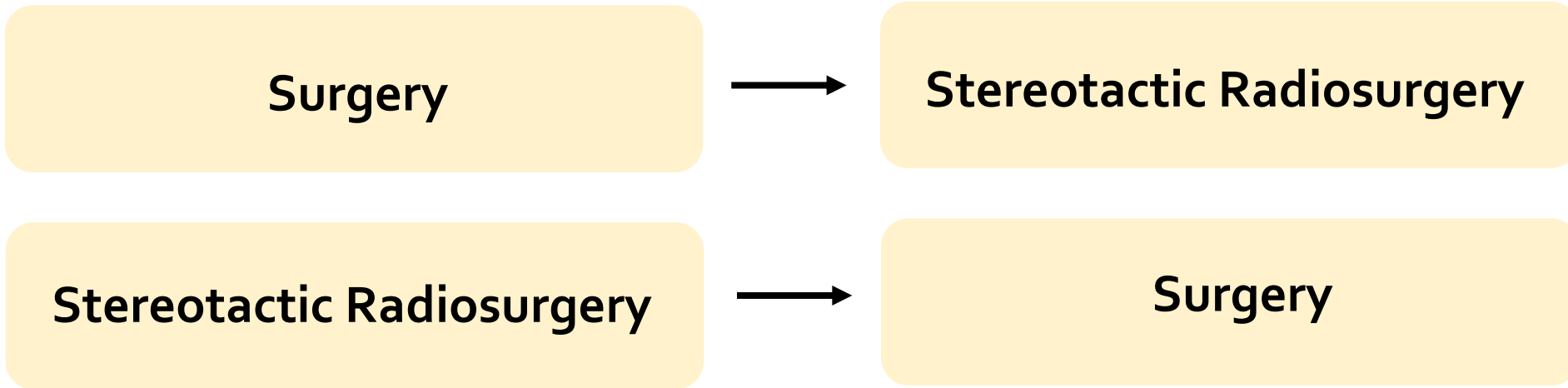
To screen or Not to screen?

Invited Commentary

June 8, 2023

The Emerging Paradigm of Preoperative Stereotactic Radiosurgery for Resectable Brain Metastases

Shearwood McClelland III, MD^{1,2}; Debra Nana Yeboa, MD^{3,4}

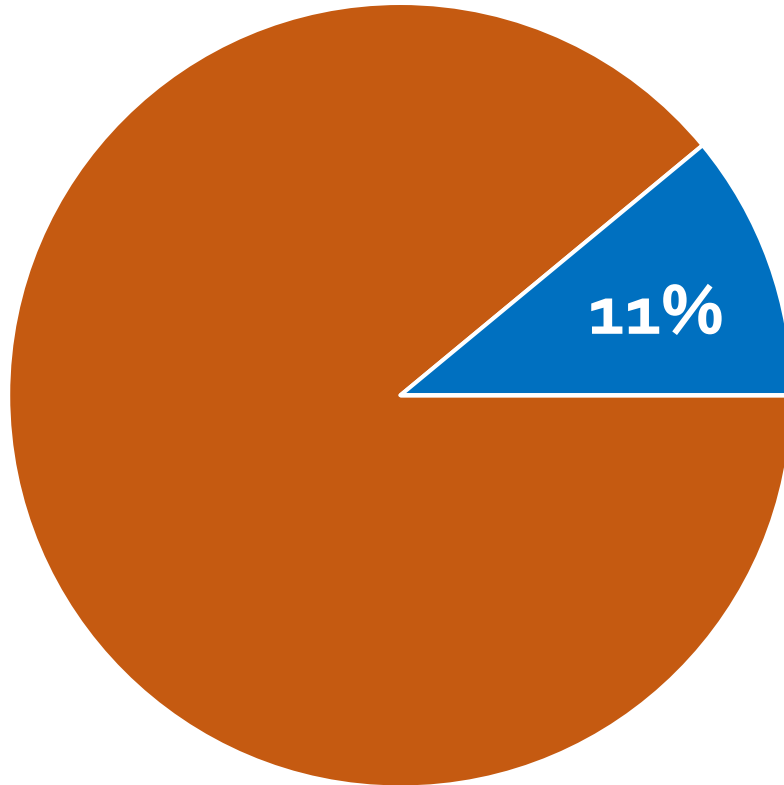


MD Anderson Cancer Center ([NCT03741673](#))

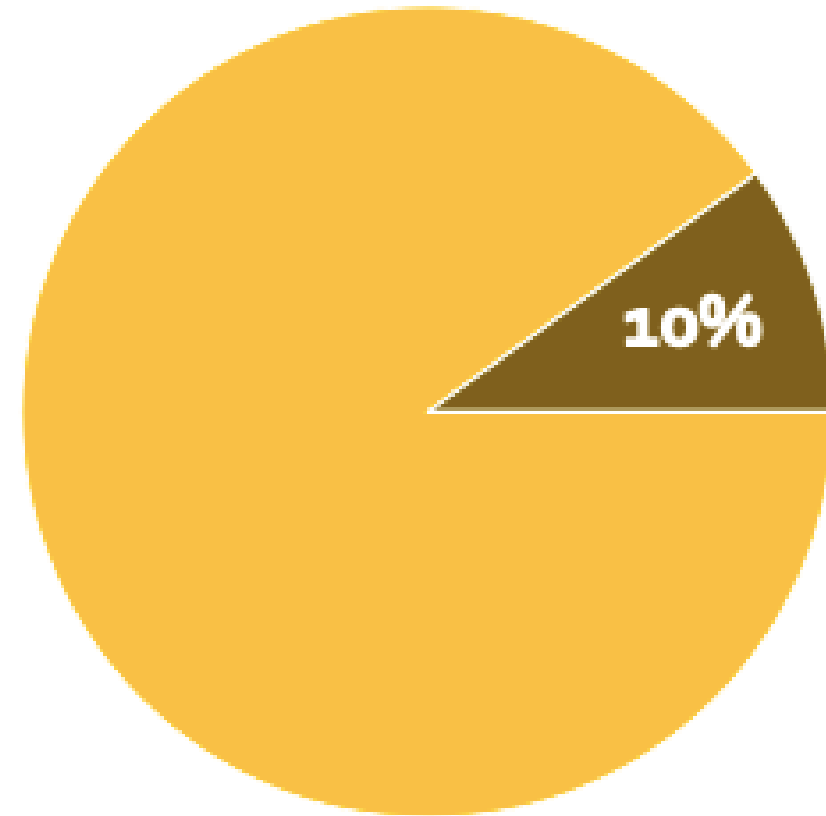
NRG Oncology ([NCT05438212](#))

Discordance between primary tumor and brain metastases

15 articles
1373 patients

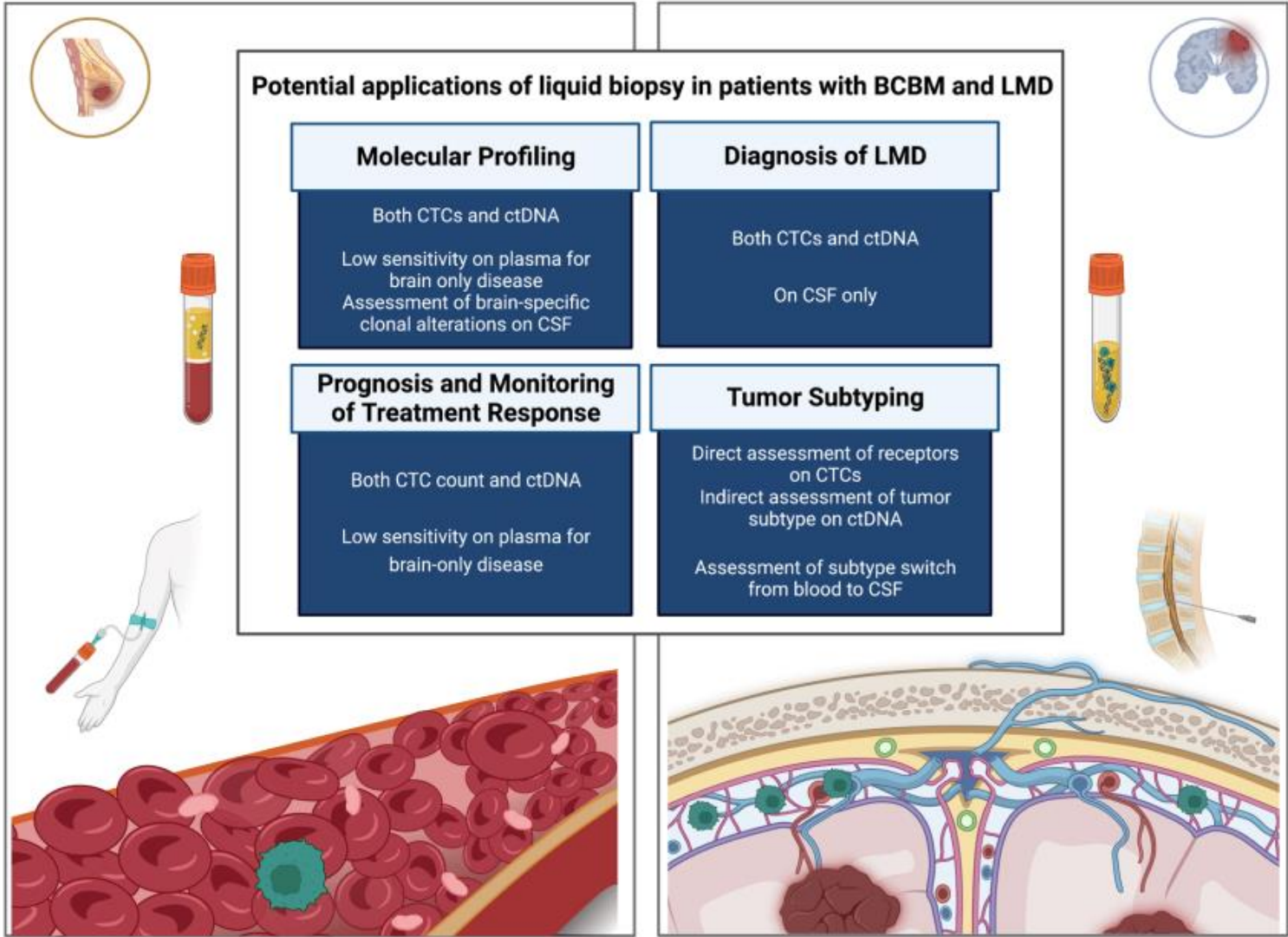


ER loss



HER2 gain

Liquid biopsy for brain metastases and leptomeningeal disease



SPECIAL ARTICLE

5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5)★

In patients with HER2-positive ABC who develop brain metastases with stable extracranial disease, systemic therapy should not be changed.

I/D

95%

SPECIAL ARTICLE

5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5)★

For patients with HER2-positive ABC where brain metastases are the only site of recurrence, the addition of ChT to local therapy is not known to alter the course of the disease and is not recommended.

I/D

83%

SPECIAL ARTICLE

5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5)★

It is recommended to re-start the anti-HER2 therapy (trastuzumab) if this had been stopped.	I/B	83%
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SPECIAL ARTICLE

EANO—ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours[☆]

- Systemic treatment of asymptomatic or oligosymptomatic BMs should be considered to delay WBRT in HER2-positive breast cancer patients with a preserved general status [EANO: III, C; ESMO: III; B].

Systemic Treatment for HER2-Positive Breast Cancer with Brain Metastases

	n	PFS
LANDSCAPE (Lapatinib + Cape)	44	6.2 months
EMILIA (T-DM ₁)	45	5.9 months
KAMILLA (T-DM ₁)	126	5.5 months
NALA (Neratinib + Cape)	51	7.8 months
PHENIX (Pirotinib + Cape)	21	6.9 months
HER2 CLIMB (Tucatinib + Trast + Cape)	198	9.9 months
T-DXd (meta-analysis)	319	15 months

Bachelot T. Lancet Oncol. 2013. Krop IE. Ann Oncol. 2015. Freedman RA. J Clin Oncol 2019. Yan M. TBCR 2020
Montemurro F. Ann Oncol 2020. Lin NU. J Clin Oncol 2020. Hurvitz SA. Oncologist 2021. Michelon I. ESMO Open 2024

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T-DXd: a systematic review and meta-analysis

ORR according to the study design (n = 202)

Study	N	Total	Weight	Proportion	95% CI
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Retrospective studies

ROSET-BM	38	72	27.9%	0.53	(0.41-0.64)
Nakajima 2022	4	8	6.4%	0.50	(0.20-0.80)
DAISY	11	12	3.2%	0.92	(0.59-0.99)
Kabraji 2023	5	11	8.4%	0.45	(0.20-0.73)
Random effects model			46.0%	0.56	(0.39-0.72)

Heterogeneity: $I^2 = 40\%$, $\tau^2 = 0.2128$, $\chi^2_3 = 5$ ($P = 0.17$)

Clinical trials

DEBBRAH	12	18	11.4%	0.67	(0.43-0.84)
DESTINY-Breast01	14	24	15.0%	0.58	(0.38-0.76)
DESTINY-Breast03	29	43	20.3%	0.67	(0.52-0.80)
TUXEDO-1	11	14	7.4%	0.79	(0.51-0.93)
Random effects model			54.0%	0.66	(0.56-0.75)

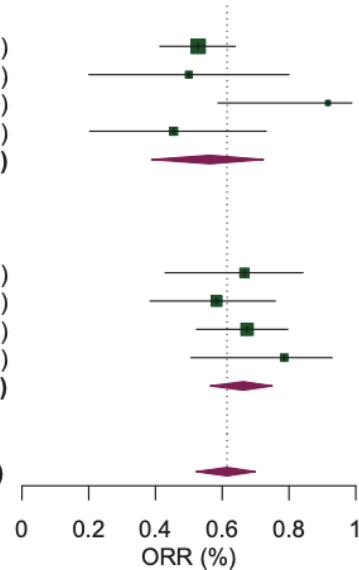
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi^2_3 = 1.61$ ($P = 0.66$)

Random effects model **100.0%**

Heterogeneity: $I^2 = 28\%$, $\tau^2 = 0.0777$, $\chi^2_7 = 9.69$ ($P = 0.21$)

Test for subgroup differences: $\chi^2_1 = 1.01$, $df = 1$ ($P = 0.31$)

0.61 (0.52-0.70)



ORR in patients with stable (n = 95) versus active (n = 109) BMs

Study	N	Total	Weight	Proportion	95% CI
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Stable

ROSET-BM	8	11	6.3%	0.73	(0.41-0.91)
DEBBRAH	4	5	2.5%	0.80	(0.31-0.97)
DESTINY-Breast-01	14	24	14.6%	0.58	(0.38-0.76)
DESTINY Breast 03	29	43	21.0%	0.67	(0.52-0.80)
DAISY	11	12	2.8%	0.92	(0.59-0.99)
Random effects model			47.2%	0.68	(0.57-0.77)

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi^2_4 = 3.93$ ($P = 0.42$)

Active

ROSET-BM	38	72	31.4%	0.53	(0.41-0.64)
DEBBRAH	8	13	8.6%	0.62	(0.34-0.83)
TUXEDO-1	11	14	6.8%	0.79	(0.51-0.93)
Kabraji 2023	7	10	6.1%	0.70	(0.38-0.90)
Random effects model			52.8%	0.60	(0.48-0.72)

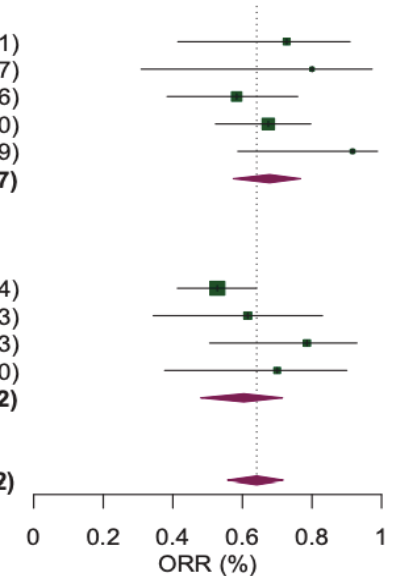
Heterogeneity: $I^2 = 19\%$, $\tau^2 = 0.0576$, $\chi^2_3 = 3.7$ ($P = 0.30$)

Random effects model **100.0%**

Heterogeneity: $I^2 = 16\%$, $\tau^2 = 0.0456$, $\chi^2_8 = 9.56$ ($P = 0.30$)

Test for subgroup differences: $\chi^2_1 = 0.89$, $df = 1$ ($P = 0.35$)

0.64 (0.56-0.72)

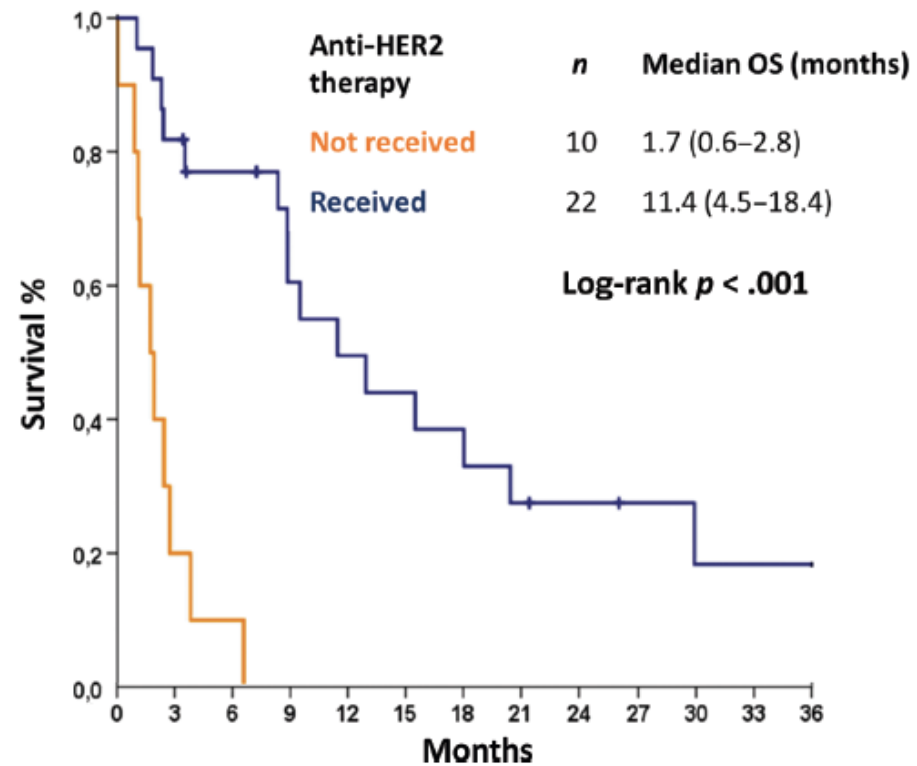


overall response of 61%

median PFS of 15 months

Leptomeningeal disease: HER2 positive BC

HER2+ BC showed a trend toward better prognosis (median OS 8.4 vs. 3.2 months, $p = .066$)



Anti-HER2 Rx independente prognostic factor

Systemic Treatment for HER2-Positive Breast Cancer with Leptomeningeal Disease

Treatment	n	PFS	OS
Intratechal Trastuzumab	19	6 months	8 months
Intratechal Trastuzumab	23	3 months	11 months
Neratinib + Capecitabine	10	4 months	10 months
Tucatinib + Trastuzumab + Capecitabine	17	7 months	12 months
T-DXd (DEBBRAH cohort 5)	7 (3 HER2-low)	9 months	13 months

Ongoing trials

DEBBRAH trial: T-DXd in different cohorts of patients

DESTINY-12 trial: T-DXd in real-world stable and active BM

HER2CLIMB-02 trial: combination of tucatinib and T-DM1

HER2CLIMB-04 trial: combination of tucatinib and T-DXd

❖ Study proposal: Treatment and outcome of HER2 pos breast cancer with CNS metastases in Brazil

Pending questions

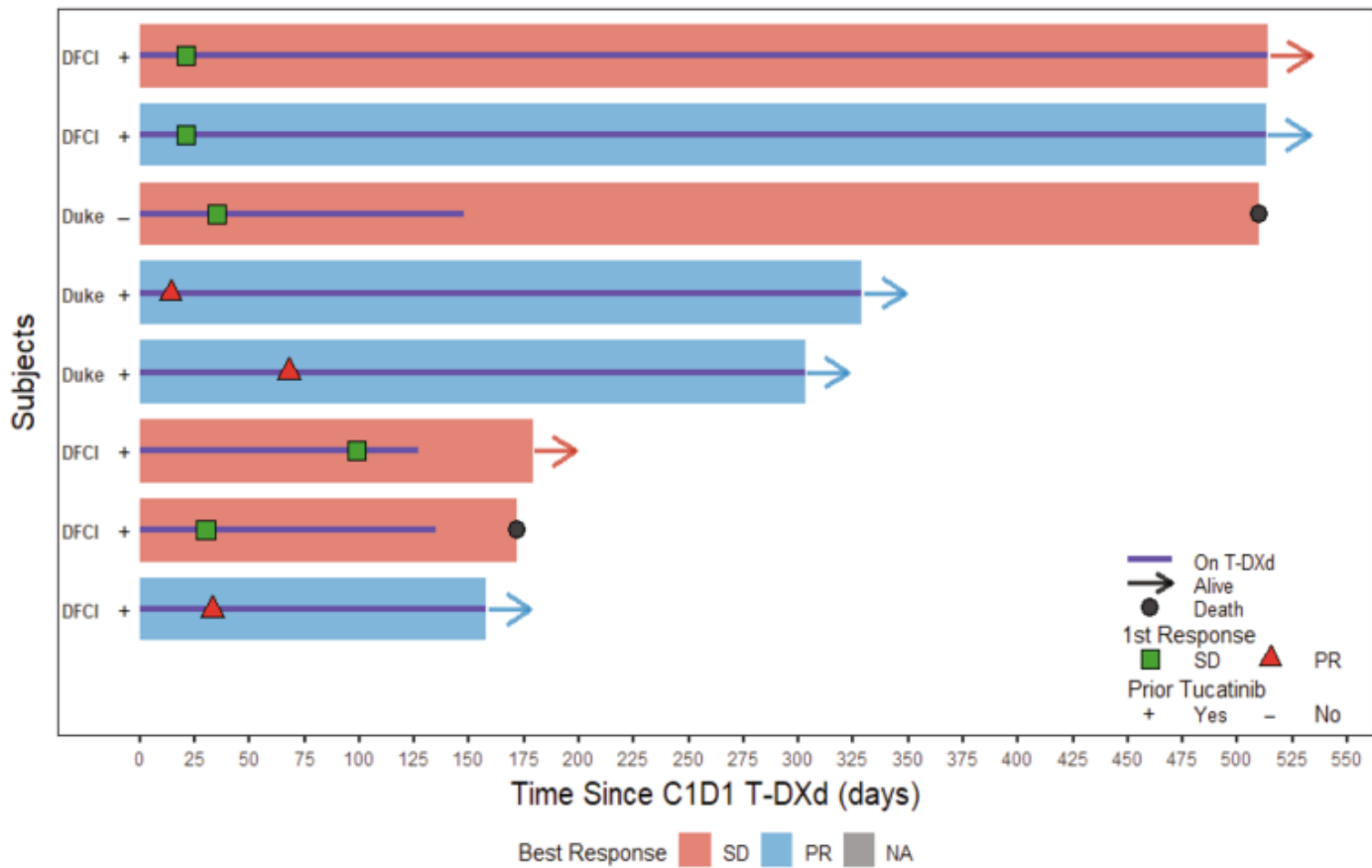
assessment of HER2 status change in brain metastases and LMD

role and sequence of radiation therapy in view of improvement in systemic treatment

the optimal sequencing of systemic therapies

Metástase cerebral e carcinomatose meníngea em tumores HER2+

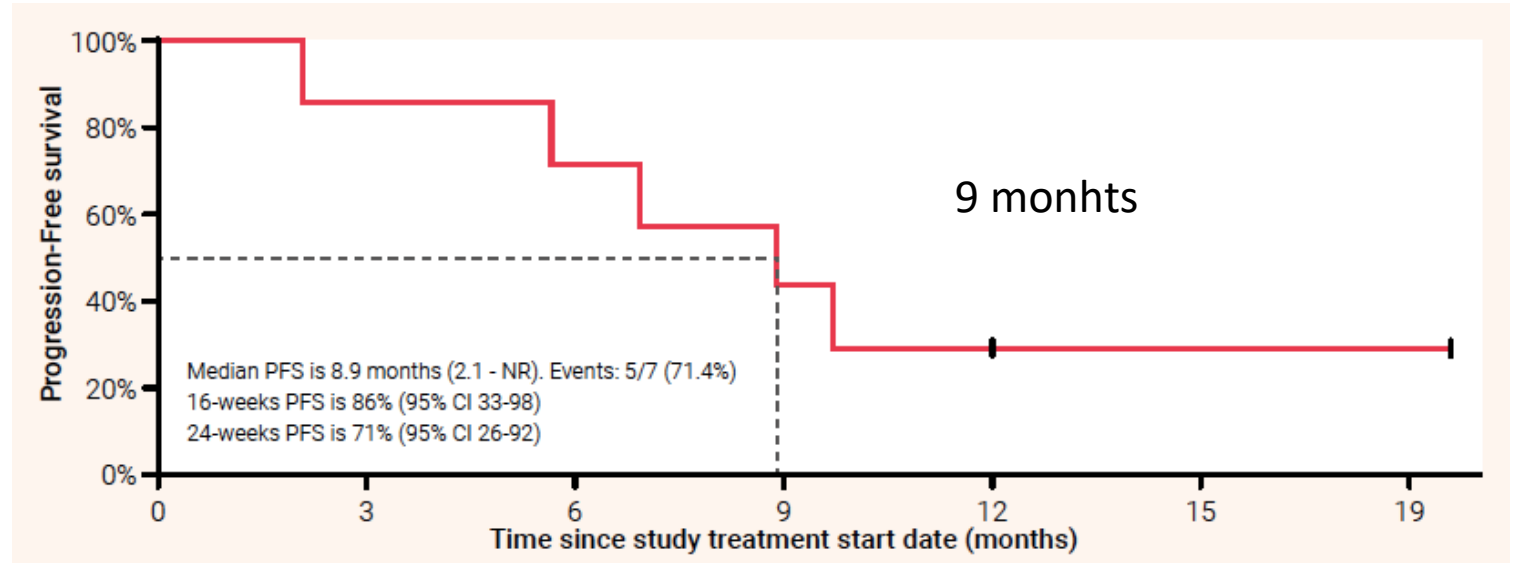
- Causas importantes de morbidade e mortalidade
- Começamos a vislumbrar melhorias nesse cenário, às custas de tratamentos mais eficazes



Median time on T-DXd 8 months
 OS from 1st cycle of T-DXd 10 months
 OS from diagnosis of LM 16 months

Cohort 5 DEBBRAH study: leptomeningeal carcinomatosis

HER2-low (n=4)
HER-2 pos (n=3)



- ▶ 71% prolonged stabilization
- ▶ Of the 5 pts that progressed, none had intracranial progression
- ▶ At data cutoff, 19% pts remained on therapy

