#### HER2-targeted therapy prolongs survival in patients with HER2-positive breast cancer and intracranial metastatic disease: a systematic review and meta-analysis

### Background

- Intracranial metastatic disease (IMD) is a serious and known complication of human epidermal growth factor receptor 2 (HER2)-positive breast cancer with up to 50% of patients developing IMD over their lifetime.<sup>1</sup>
- IMD negatively impacts prognosis: the median survival for patients with HER2-positive metastatic breast cancer is 26.3 months with IMD versus 44.6 months without brain involvement.<sup>1,2</sup>
- Treatment has historically been limited to surgical resection and radiotherapy; the role for chemotherapy has generally been disappointing.<sup>3-6</sup>
- The finding of prolonged survival with HER2 inhibition in women with HER2-positive metastatic breast cancer<sup>7-11</sup> and the increased permeability of novel HER2 inhibitors into the brain<sup>12</sup> have led to interest in HER2-targeted therapy as treatment of IMD from HER2-positive metastatic disease<sup>13,14</sup>; However, little is known about effects of HER2-targeted therapy for IMD.

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## Objective

To evaluate the effects of HER2-targeted therapy on survival, response, and safety outcomes in patients with HER2-positive breast cancer and IMD.

# Methods

- MEDLINE, EMBASE, CENTRAL, and grey literature sources were searched for interventional and observational studies reporting survival, response, and safety outcomes for patients with IMD receiving HER2-targeted therapy.
- Eligible outcomes were pooled through metaanalysis and covariate effects were examined through forest plot stratification and meta-regression.
- Evidence quality of comparative outcomes was evaluated using GRADE.

- Our analyses showed that HER2-targeted therapy is associated with prolonged overall survival, notable response proportions, and an adverse event rate that may depend on drug structure.
- Our results were consistent with previous reviews of trastuzumab and lapatinib for IMD from HER2-positive breast cancer.<sup>15,16</sup>
- Future studies should aim to obtain high quality data regarding the efficacy of systemic therapy for the treatment of breast cancer patients with IMD, including intracranial outcomes.

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-targeted was associated with the following:

- olonged overall survival (HR 0.47; 95% CI, 0.39–0.56)
- RCTs (HR 0.63; 95% CI, 0.46–0.86; n = 392; GRADE, high)
- Observational studies (HR 0.45; 95% CI, 0.37–0.54; n = 2341; GRADE, low)
- prolonged progression-free survival (HR 0.52; 95% CI, 0.27–1.02)
- RCTs (HR 0.74; 95% CI, 0.29–1.90; n = 392; GRADE, low)
- Observational studies (HR 0.32; 95% CI, 0.19–0.55; n = 83; GRADE, low)
- racranial objective response rate of 19% (95% CI, 12–27%)
- racranial disease control rate of 62% (95% CI, 55–69%)
- racranial complete response rate of 0% (95% CI, 0–0.01%)
- ade 3+ adverse event rate of 26% (95% CI, 11-45%)
- f bias was high in 40% (39/97) of studies.

#### Adverse Events



# Discussion

- More liberal inclusion of patients with IMD should also be considered in the design of future clinical trials.<sup>17-19</sup>

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## Results

Intracr	ania	al O	bje	ctive F	Response	Rate	
Study	Cases	Total	CNS ORR	95% CI	CNS C (propor	)RR tion)	Weight
Retrospective cohort study							
Le Scodan. R. et al. 2011	0	23	0.00	[0.00: 0.15]	<b></b>		3.0%
Okines, A. et al. 2018	0	13	0.00	[0.00: 0.25]	<b>B</b>		2.7%
Fabi, A. et al. 2018	13	53	0.25	[0.14: 0.38]			3.3%
Mailliez, A. et al. 2016	4	14	0.29	[0.08; 0.58]			2.7%
Metro, G. et al. 2011	7	22	0.32	[0.14; 0.55]	-		3.0%
Huang, C. et al. 2010	9	26	0.35	[0.17; 0.56]			3.0%
Mc, Cabe Y. et al. 2016	4	10	0.40	[0.12; 0.74]			2.5%
Riahi, H. et al. 2010	23	31	0.74	[0.55; 0.88]			3.1%
Fixed effect model		192	0.28	[0.21; 0.34]			
Random effects model			0.25	[0.09; 0.46]			23.2%
Heterogeneity: $I^2 = 88\%$ , $\tau^2 = 0.0^{-1}$	795, <i>p</i> <	0.01					
Single-arm interventional tri	al				1		
de Azambuja, E. et al. 2013	0	15	0.00	[0.00; 0.22]			2.7%
Bonneau, C. et al. 2018	0	14	0.00	[0.00; 0.23]			2.7%
Lin, N. et al. 2008	1	39	0.03	[0.00; 0.13]			3.2%
Yardley, D. et al. 2018	0	5	0.00	[0.00; 0.52]	P 1	_	1.9%
Van Swearingen, A. et al. 2018	3 1 	26	0.04	[0.00; 0.20]			3.0%
Lin, N. et al. 2009	15	237	0.06	[0.04; 0.10]			3.5%
Leone, J. et al. 2019	1	21	0.05	[0.00; 0.24]			2.9%
Freedman, R. et al. 2019	3	40	0.07	[0.02; 0.20]			3.2%
Metzger, O. et al. 2017	3	36	0.08	[0.02; 0.22]			3.2%
Giotta, F. et al. 2010	1	14	0.07	[0.00; 0.34]			2.7%
Lin, N. et al. 2016	4	37	0.11	[0.03; 0.25]			3.2%
Morikawa, A. et al. 2019	1	11	0.09	[0.00; 0.41]			2.5%
Falchook, G. et al. 2013	1	10	0.10	[0.00; 0.45]			2.5%
Ro, J. et al. 2012	8	47	0.17	[0.08; 0.31]			3.3%
Sutherland, S. et al. 2010	/	33	0.21	[0.09; 0.39]			3.1%
101, IVI. et al. 2009	2	10	0.20	[0.03; 0.56]			2.5%
Lin, N. et al. 2011	5	22	0.23	[0.08; 0.45]			3.0%
MacPherson, I. et al. 2019	1	5	0.20	[0.01; 0.72]			1.9%
Barisch, R. et al. 2008	I E	5 10	0.20	[0.01; 0.72]			1.9%
	С 1	19	0.20			_	2.9%
Showley H at al. 2010	1 7	4 01	0.20	[0.01, 0.01]			1./ % 0.00/
Borgoo V et al. 2019	7	2 I 1 /	0.33	[0.13, 0.57]			2.9%
Naskhlotashvili D at al 2010	5	14	0.30	[0.13, 0.03]			2.7 % 1 00/-
Murthy P at al 2019	2	10 10	0.40	[0.05, 0.05]			1.9% 2.6%
Bachelot T et al. 2010	5 24	12	0.42	[0.15, 0.72]	• •		2.0% 2.0%
Christodoulou C et al 2017	24 7	42 10	0.57	[0.41, 0.72]		-	0.2 /0 2 6%
Lin N et al 2013	י 22	28	0.50	[0.20, 0.00]			2.0/o . 3.1%
Fixed effect model	22	20 79/	0.79	[0.33, 0.32]		-	J. I /0
Random effecte model		104	0.13	[0.10, 0.13]			76 8%
Heterogeneity: $l^2 = 83\%$ , $\tau^2 = 0.04$	460, <i>p</i> <	0.01	0.17	[0.10, 0.20]			1 0.0 /0
Fixed offect medel		070	045	[0 49. 0 40]			
Fixed effects model		910	U.15 0 10	[U.13; U.18] [0 12: 0 27]			 100 00/
Heterogeneity: $l^2 = 950/c^2 = 0.01$	507 n -	0 01	0.19	[0.12, 0.27]			100.0%
Residual heterogeneity: $I^2 = 85\%$			0 0.2 0.4	0.6 0.8			

# Limitations

Patients with IMD from HER2-positive breast cancer were a subgroup in many of the included studies and therefore, outcomes for these patients were often few and secondary.

Several outcomes key to clarifying the role of HER2targeted therapy in the management of IMD were under-reported among included studies, such as comparative response and safety outcomes, and CNSspecific clinical features and mortality.

Many outcomes were reported in formats that precluded meta-analysis.





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#### **Overall Survival**

No Study (HER2	. patients therapy)	No. patients (control)	HR	(95% CI)	OS Hazard Ratio	Weight
Retrospective cohort stud	dy				1	
Griguolo, G. et al. 2018	22	10	0.12	[0.02; 0.69]		1.0%
Morikawa, A. et al. 2018	80	20	0.24	[0.14; 0.41]	_ <b></b> }	5.1%
Zhang, Q. et al. 2016	24	36	0.25	[0.12; 0.53]		3.5%
Zhang, C. et al. 2016	33	35	0.25	[0.13; 0.46]		4.3%
Park, Y. et al. 2009	40	37	0.28	[0.06; 1.20]	+	1.3%
Bartsch, R. et al. 2011	43	37	0.29	[0.16; 0.54]	- <u>i</u>	4.4%
Gori, S. et al. 2019	102	52	0.30	[0.19; 0.47]		5.7%
Gomes, D. et al. 2015	NR	NR	0.41	[0.28; 0.60]	- <del></del>	6.4%
Hayashi, N. et al. 2015	283	149	0.44	[0.35; 0.56]		7.7%
Kaplan, M. et al. 2015	20	30	0.46	[0.22; 0.96]		3.6%
Le Scodan, R. et al. 2011	32	20	0.49	[0.29; 0.83]	<del>•</del> •	5.1%
Mounsey, L. et al. 2018	76	47	0.61	[0.39; 0.96]		5.7%
Yap, Y. et al. 2012	115	165	0.62	[0.43; 0.89]	÷	6.5%
Miller, J. et al. 2017	82	17	0.70	[0.49; 0.99]	; <del></del> -	6.7%
Parsai, S. et al. 2019	50	76	0.71	[0.42; 1.21]	<del>}</del>	5.0%
Karam, I. et al. 2011	130	46	0.73	[0.50; 1.06]		6.4%
Yomo, S. et al. 2013	24	16	0.99	[0.33; 2.95]		2.1%
Hulsbergen, A. et al. 2020	8	7	1.88	[0.40; 8.75]	+ + +	1.2%
Fixed effect model	1164	800	0.48	[0.43; 0.53]	<b>♦</b>	
Random effects model			0.46	[0.37; 0.56]	<b>•</b>	81.6%
Heterogeneity: $I^2 = 61\%$ , $\tau^2 =$	0.1059, <i>p</i> <	0.01				
Randomized controlled tr	ial					
Murthy, R. et al. 2019	198	93	0.58	[0.40; 0.85]		6.4%
Chan, A. et al. 2019	64	37	0.74	[0.43; 1.27]	÷ =+	4.9%
Fixed effect model	262	130	0.63	[0.46; 0.86]	$\sim$	
Random effects model			0.63	[0.46; 0.86]		11.3%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$	, <i>p</i> = 0.47					
Prospective cohort study						
Brufsky, A. et al. 2011	258	119	0.33	[0.24; 0.45]		7.1%
Fixed effect model	258	119	0.33	[0.24; 0.45]		
Random effects model			0.33	[0.24; 0.45]		7.1%
Heterogeneity: not applicable					1 1 1 1	
Fixed effect model	1684	1049	0.47	[0.43; 0.52]		
Random effects model			0.47	[0.39; 0.56]	$\dot{\diamond}$	100.0%
Heterogeneity: $I^2 = 62\%$ , $\tau^2 =$	0.0977, <i>p</i> <	0.01		•		
Residual heterogeneity: $I^2 = 5$	9%, <i>p</i> < 0.0	1			0.1 0.5 1 2 1	0
	•			Favor	s HER2 therapy Favors c	ontrol

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