Central Nervous System Disease in phase III studies for advanced HER2 Positive Breast Cancer: A Review

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Central nervous system disease in phase III studies for advanced HER2 positive breast cancer: A review

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ABSTRACT

Importance: The introduction of human epidermal growth factor receptor 2 (HER2) directed therapy has transformed the outcomes of patients with advanced breast cancer (BC). However, HER2 positive breast cancer has a predilection for the central nervous system (CNS) which is associated with significant morbidity and mortality. Understanding the intracranial activity of novel HER2 directed agents is key to developing treatments as well as possible preventative strategies for HER2-positive CNS disease.

Observations: Using protocols and data from published phase III clinical trials for locally advanced/metastatic HER2-positive breast cancer since the licensing of single agent trastuzumab for advanced BC we review the central nervous system related aspects. This includes CNS related entry criteria, use of baseline and on study cross-sectional imaging of the CNS and protocol and non-protocol defined CNS end points and reported data.

Conclusions: and Relevance: This review found heterogeneity between studies with regard to the entry criteria, use of CNS imaging and reported end points within the pivotal phase III studies. Based on these data, a standardisation of both entry criteria and end points with regard to the CNS should be developed and applied to future studies of HER2-positive advanced BC. Such an approach would enable the generation of comparable data and allow a meaningful analysis of different treatment approaches with regard to the CNS. This in turn would allow the development of the most optimal treatment approaches for HER2 positive CNS disease and ultimately the development of preventative strategies.

Disclaimers

Nil.

1. Introduction

Human epidermal growth factor receptor 2 positive (HER2-positive) breast cancer (BC) has a predilection for the central nervous system (CNS) with up to a fivefold increased risk of CNS disease as compared to luminal breast cancers [1,2]. Data from the Herceptin Adjuvant (HERA) study demonstrated that in 2% of patients the CNS was the first site of distant relapse [3]. Subsequent adjuvant studies with dual antibody therapy [4] as well as trastuzumab combined with the small molecule lapatinib [5], have not demonstrated any improvement or change in the proportion of patients presenting with the CNS as a site of initial relapse. The CNS as a site of initial relapse rises to 6% in higher risk patients defined by the presence of residual disease after neoadjuvant HER2 therapy [6] while the neoALTTO (BIG 1–06) study reported that 18% of all first event free survival events involved the CNS [7]: Data from the HERA study has also demonstrated that 47% of patients have evidence of CNS involvement at time of death [3]. While CNS disease can often be the sole site of disease progression [8] and its development is associated with significantly poorer outcomes [8,9].

Where the CNS is the sole site of progression, local treatment in the form of surgery and/or radiotherapy with continuation of anti-HER2 therapy is the standard of care [10]. Where there is progressive CNS disease, despite optimal local therapy, options are limited to either systemic therapy, enrolment in a clinical trial or best supportive care. Recent data has demonstrated the intracranial activity of tucatinib in combination with trastuzumab and capecitabine, which resulted in

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improved survival clinical outcomes in those who received tucatinib as compared to placebo [11]. However, despite the intracranial activity of tucatinib, patients still progress within the CNS and ongoing search into the treatment of CNS disease in HER2-positive BC patients is needed to further improve the outcomes of these patients and to ultimately develop preventive strategies.

Within this article we review the CNS study entry criteria, use or otherwise of baseline cross-sectional CNS imaging, the protocol mandated methodology for follow up of the CNS as well as the protocol defined end-points and data reported within the randomised phase III trials conducted since the advent of trastuzumab for locally advanced and metastatic HER2-positive breast cancer (MBC).

2. Methods

2.1. Search strategy and literature search

We undertook a review of the published literature since the licensing of trastuzumab for HER2-positive metastatic breast cancer. With searches of PubMed, Web of Science and Scopus databases performed up to March 15, 2022. References from all identified articles were also reviewed to check for other relevant studies with duplicates identified and removed.

2.2. Study selection

The inclusion criteria were any randomised phase III clinical trials which enrolled HER2-positive locally advanced and/or metastatic breast cancer patients since the licensing of single agent trastuzumab. Studies had to be published in English in a peer reviewed journal.

2.3. Data extraction

Publications and protocols (where available) were reviewed to extract the following information [1] entry criteria for patients with CNS disease [2]; if baseline CNS screening was utilised and the nature of any such cross-sectional imaging [3]; the proportion of patients with asymptomatic disease at screening [4]; any CNS disease related end-points [5]; CNS cross-sectional imaging on study and frequency of this [6] available data in CNS progression during the study.

3. Studies

Since the licensing of single agent trastuzumab for MBC in September 1998 [12] there have been seventeen peer reviewed published randomised phase III trials addressing the treatment of HER2-positive locally advanced and/or MBC [11,13–27]. These studies, based on the experimental arm, can be classified as follows, those investigating:

(1) Trastuzumab beyond progression plus a different chemotherapy regimen [24].
(2) Double anti-HER2 therapy (antibody in combination with either another antibody or a tyrosine kinase inhibitor) [13,18].
(3) An antibody drug-conjugate (ADC) [14–17].
(4) A tyrosine kinase inhibitors (TKI) targeting the epidermal growth factor receptor (EGFR) family in combination with chemotherapy [19–23,25].
(5) The TKI targeting mTOR, everolimus, in combination with trastuzumab and paclitaxel or vinorelbine [26,28].
(6) The TKI tucatinib in combination with trastuzumab and capecitabine [11].
(7) The TKI lapatinib in combination with the aromatase inhibitor letrozole [27].

3.1. Study protocols and primary end-points

12 of 17 (71%) study protocols were available [11,13,14,16,17,19,20,22,25–28] and where not available information from the published paper was utilised [15,18,21,23,24]. A summary of these studies with regard to design, key entry criteria and reported primary and secondary end point data are summarised in Table 1. In 16 of the 17 (94%) studies the primary end point was progression free survival (PFS) and/or overall survival (OS) [11,13–18,20–28]. The remaining study, CEREBREL, the only CNS metastases prevention trial, had a primary end point of the incidence of CNS metastasis as first site of relapse. As the sole CNS disease prevention study, analysis of the CNS data from CEREBREL was therefore done separately from the other 16 studies (Table 2).

3.2. Central nervous system entry criteria

All studies had entry criteria relating to the CNS or CNS disease (Tables 3 and 4). As the sole prevention study, CEREBREL excluded all patients who had active or previous history of CNS disease confirmed clinically or radiologically at study entry [19].

Heterogeneity with regard to entry criteria was seen in the non-prevention studies with 10 of 16 (63%) allowing the inclusion of patients with asymptomatic disease or stable CNS metastases which had previously been treated with local therapy [11,14,15,17,18,20,21,23,24,26], therefore excluding individuals with symptomatic or untreated asymptomatic CNS disease. In addition, the TH3RESA [15], EMILIA [14] and EGF100151 [23] studies excluded patients who had received treatment for CNS disease within one, two and three months prior to randomization respectively. Whilst the NEfERT-T study excluded patients, who had been commenced on corticosteroids or anticonvulsant therapy for CNS disease within one month of randomization ([20]).

6 of 16 (38%) non-prevention studies, CLEOPATRA, MARIANNE, MA.31, PH0EBE, BOLERO-1 and ALTERNATIVE excluded patients with either a history of, or, current CNS metastases, irrespective of any prior treatment [13,16,22,25,27,28], Tables 3 and 4

HER2CLIMB was the sole trial to allow entry of patients with symptomatic CNS metastasis as well as treated or untreated asymptomatic CNS metastases if their diameter was smaller than 2 cm [11]. Those patients with active CNS disease requiring immediate local intervention were permitted to receive local therapy prior to enrolment.

3.3. Protocol defined assessment of the CNS at study entry

Radiological assessment of the CNS prior to study entry and randomization was variable between studies. As expected, CEREBREL given its nature, mandated cross-sectional imaging of the CNS at baseline with magnetic resonance imaging (MRI). Of the other studies, only 3 of 16 (19%) trials, EMILIA [14], MA.31 [25] and HER2CLIMB [11], mandated radiological assessment of the CNS. The modality varied between these studies with HER2CLIMB utilising MRI [11] and EMILIA and MA.31 allowing the use of either computed tomography scan (CT) or MRI [14,25].

The remaining 13 studies only required cross-sectional imaging of the CNS as part of the study screening process if there was clinical suspicion of CNS disease [13,15–18,20–24,26–28]. Such an approach is subjective, and clinicians might be biased towards not assessing the CNS radiologically if it would result in the exclusion of the patient.

Of the 10 studies that allowed the inclusion of previously treated, stable and asymptomatic CNS disease, 8 (80%) did not require up to date imaging of the CNS at baseline ([15,17,18,20,21,23,24,26]).

3.4. Proportion of patients excluded from study entry due to protocol defined CNS criteria

CEREBREL excluded 39 of 540 (7.2%) patients due to the detection of asymptomatic CNS disease [19]. Of the other 16 studies, only MA.31

Table 1
Summary of the randomised phase III studies for HER-2 positive locally advanced and metastatic breast cancer since advent of single agent Trastuzumab.

Study/Author, year	Agents	Key entry criteria	Line of Therapy	Non-CNSEnd points	Study population (n)	Median FU (months)	Primary End-Point results
GBG 26	Trastuzumab + Capecitabine (TC)	**Inclusion:**	2nd line	**Primary:**	TC: 78	20.7	**Median PFS (months):**
		PD on >12 weeks treatment with trastuzumab		PFS			TC = 8.2 vs. C = 5.6
Von Minckwitz et al., 2009, 2011	vs				C: 78		(HR = 0.69 [95% CI, 0.48–0.97]. p = 0.0338)
	Capecitabine (C)			**Secondary:** OS CBR DoR			
CLEOPATRA	Trastuzumab, Pertuzumab and Docetaxel (TP)	**Exclusion:**	1st line	**Primary:**	TP: 402	30	**Median PFS (months):**
		Prior chemotherapy or biological therapy for advanced disease		PFS			TP = 18.7 vs. T = 12.4
Swain et al., 2015	vs				T: 406		(HR = 0.68 [95% CI, 0.58–0.80]. P < 0.001)
	Trastuzumab, Placebo and Docetaxel (T)			**Secondary:** OS ORR DoR Safety profile			
EGF104900	Lapatinib + Trastuzumab (LT)	**Inclusion:**	2nd line	**Primary:**	LT: 148	LT: 12.8	**Median PFS (weeks):**
		Disease progression on Trastuzumab		PFS			LT = 12.0 vs. L = 8.1
Blackwell et al., 2010	vs				L: 148	L: 8.7	(HR = 0.73 [95% CI, 0.57–0.93]. P = 0.008)
		Prior Anthracycline and Taxane treatment		**Secondary:**			
	Lapatinib (L)			ORR CBR OS Safety profile			
EMILIA	TDM-1	**Inclusion:**	2nd line	**Primary:**	TDM-1: 495	19	**Median PFS (months):**
		Prior Trastuzumab and Taxane treatment		PFS			TDM-1 = 9.6 vs. XL = 6.4
Verma et al., 2012	vs			OS	XL: 496		(HR = 0.65 [95% CI, 0.55–0.77]. P < 0.001)
		Exclusion:		Safety profile			
	Lapatinib + Capecitabine (XL)	Prior TDM-1, Lapatinib or Capecitabine treatment					**Median OS (months):**
				Secondary:			TDM-1 = 30.9 vs. XL = 25.1
				ORR			(HR = 0.68 [95% CI, 0.55–0.85]. P < 0.001)
				DoR CBR			
TH3RESA	TDM-1	**Inclusion:**	3rd line or more	**Primary:**	TDM-1: 404	7.2	**Median PFS (months):**
		Prior Trastuzumab, Lapatinib and a Taxane treatment		PFS			TDM-1 = 6.2 vs. PC = 3.3
Krop et al., 2014	vs			OS	PC: 198		(HR = 0.53 [95% CI, 0.42–0.66]. P < 0.0001)
		PD after ≥2 HER2 directed regimens					
	Physician's choice (PC)			**Secondary:**			**Median OS (months):**
				ORR			TDM-1 = Not estimable vs. PC = 14.9
		Exclusion:		6- and 12-month survival			(HR = 0.55 [95% CI, 0.37–0.33]. P = 0.0034)

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and TH3RESA reported the proportion of patients excluded as a result of not meeting the CNS entry criteria. MA.31 excluded 4 of 652 (0.6%) patients due to the identification of CNS disease following mandatory CNS imaging ([25]). While 107 of 370 (28.9%) patients were excluded from entering TH3RESA due to either having symptomatic and/or untreated CNS disease or having received treatment for CNS-disease within 1 months before randomization (15).

The EMILIA study, despite undertaking cross-sectional imaging of the CNS of all patients during screening, did not report the proportion of patients detected with asymptomatic disease, although an overall screen failure rate of 37.1% (585 of 1576) was reported ([14]. While, CLEOPATRA (13), EGF104900 [18], SOPHIA (17), BOLERO-1 [28] and BOLERO-3 [26] reported only overall screen failure rates (32.4%, 25.4%, 29.8%, 24.2% and 22.2% respectively) with no CNS specific

Table 1 (*continued*)

Study/Author, year	Agents	Key entry criteria	Line of Therapy	Non-CNSEnd points	Study population (n)	Median FU (months)	Primary End-Point results
		Prior TDM-1 treatment		Safety profile			
MARIANNE	TDM-1 + Pertuzumab (TDM-P)	**Exclusion:**	1st Line	**Primary:**	TDM-P: 363	35	**Median PFS (months):**
		Any prior anti-cancer treatment, excluding hormonal therapy for MBC		PFS			TDM-P = 15.2 vs. TDM-1 = 14.1 vs. TT = 13.7
Perez et al., 2017	vs			Safety profile	TDM-1: 367		
		Neoadjuvant and/or adjuvant Vinca alkaloid or Taxane chemotherapy <6 months before advanced breast cancer diagnosis					TDM-P vs. TT:
	TDM-1			**Secondary:**	TT: 365		(HR = 0.87 [97.5% CI, 0.69–1.08]. P = 0.14)
				OS			
	vs			ORR			TDM-1 vs. TT:
				DoR			(HR = 0.91 [97.5% CI, 0.73–1.13]. P = 0.31)
	Trastuzumab + Taxane (TT)						
							TDM-P vs. TDM-1: (HR = 0.91 [97.5% CI, 0.73–1.13])
SOPHIA	Margetuximab (M) + chemotherapy	**Inclusion:**	3rd line or more	**Primary:**	M: 266	15.6	**Median PFS (months):**
		Disease progression after ≥2 HER2 regimens (including Pertuzumab)		PFS			M = 5.7 vs. T = 4.4
Rugo et al., 2021	vs			OS	T: 270		(HR = 0.71 [95% CI, 0.58–0.86]. P < 0.001)
		1-3 lines of non-hormonal MBC therapy		**Secondary:**			
	Trastuzumab (T) + chemotherapy			ORR			**Median OS (months):**
				CBR			M = 21.6 vs. T = 19.8
				Safety			(HR = 0.89 [95% CI, 0.69–1.13]. P = 0.33)
CEREBREL	Lapatinib + Capecitabine (LC)	**Inclusion:**	2nd line or more	**Primary:**	LC: 251	Not stated	**Incidence of CNS-M as first site:**
		Prior Anthracycline and/or Taxane and/or Trastuzumab treatment		Incidence of CNS-M as first site of relapse			LC = 8 of 251 (3%) vs. TC = 12 of 250 (5%)
Pivot et al., 2015	vs				TC: 250		(OR = 0.65 [95% CI, 0.26–1.63]. P = 0.36)
				Secondary:			
	Trastuzumab + Capecitabine (TC)			PFS			
				OS			
				ORR			
				DoR			
EGF100151	Lapatinib + Capecitabine (LC)	**Inclusion:** PD after treatment with regimens that included an anthracycline, a taxane, and trastuzumab	2nd line or more	**Primary:**	LC: 198	30	**Median PFS (months):**
				PFS			LC = 6.2 vs. C = 4.3
Geyer et al.,	vs				C: 201		(HR = 0.57 [95% CI, 0.43–0.77]. p = 0.00013)
2006				**Secondary:**			
	Capecitabine (C)			OS			
Cameron et al., 2007, 2010				PFS			
				6 month PFS			
				CBR			
				QoL			
MA.31	Lapatinib + Taxane (L)	**Exclusion:**	1st line	**Primary:**	L: 326	21.5	**Median PFS (months):**
		Prior therapy with cytotoxics or biologics for recurrent or advanced disease		PFS			L = 9.0 vs. T = 11.3
Gelmon et al.,	vs				T: 326		(HR = 1.36 [95% CI, 1.13–1.65]. p = 0.001)
2015	Trastuzumab + Taxane (T)			**Secondary:**			
				OS			
				CBR			

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Table 1 (*continued*)

Study/Author, year	Agents	Key entry criteria	Line of Therapy	Non-CNSEnd points	Study population (n)	Median FU (months)	Primary End-Point results
				DoR QoL			
NEfERT-T	Neratinib + Paclitaxel (NP)	**Exclusion:**	1st line	**Primary:**	NP: 242	23	**Median PFS (months):**
		HER2 targeted or systematic treatment (excluding endocrine therapy or neo-adjuvant Trastuzumab or Lapatinib)		PFS			NP = 12.9 vs. TP = 12.9
Awada et al., 2016	vs				TP: 237		(HR = 1.02 [95% CI, 0.81–1.27]. P = 0.89)
	Trastuzumab + Paclitaxel (TP)			**Secondary:** ORR			
				CBR DoR Safety profile			
NALA	Neratinib + Capecitabine (NC)	**Inclusion:**	3rd line or more	**Primary:**	NC: 307	29.9	**Mean PFS (months):**
		Disease progression after ≥2 HER2 regimens		PFS			NC = 8.8 vs. LC = 6.6
Saura et al., 2020	vs			OS	LC: 314		(HR = 0.76 [95% CI, 0.63–0.93]. P = 0.0003)
	Lapatinib + Capecitabine (LC)			**Secondary:**			**Mean OS (months):**
				Safety ORR CBR			NC = 24.0 vs. LC = 22.2 (HR = 0.88 [95% CI, 0.72–1.07]. P = 0.2086)
PH0EBE	Pyrotinib + Capecitabine (PC)	**Inclusion:**	1st or 2nd line	**Primary:**	PC: 134	21.8	**Median PFS (months):**
		Trastuzumab and Taxane exposure		PFS			PC = 12.5 vs. LC = 6.8
Xu et al., 2021	vs				LC: 132		(HR = 0.39 [95% CI, 0.27–0.56]. P < 0.0001)
		Anthracycline treatment allowed, but not required		**Secondary:**			
	Lapatinib + Capecitabine (LC)			OS			
		Exclusion: Prior Capecitabine or TKI treatment		ORR Time to PD DoR			
		Anti-cancer treatment within 4 weeks of randomization		CBR			
				Safety profile			
BOLERO-1	Everolimus, Paclitaxel and Trastuzumab (EPT)	**Inclusion:**	1st line	**Primary:**	EPT: 480	41.3	**Median PFS in whole population (months):**
		Prior trastuzumab and/or chemotherapy allowed, but should be discontinued >12 months prior to randomization		PFS in whole population			EPT = 15.0 vs. PPT = 14.5
Hurvitz et al.,	vs				PPT: 239		(HR = 0.89 [95% CI, 0.73–1.08]. p = 0.1166)
2015		**Exclusion:**		PFS in hormone receptor negative subpopulation			
	Placebo, Paclitaxel and Trastuzumab (PPT)	Prior systemic therapy for					**Median PFS in hormone receptor negative subpopulation (months):**
		advanced disease		**Secondary:**OS ORR			EPT = 20.3 vs. PPT = 13.1 (HR = 0.66 [95% CI, 0.48–0.91]. p = 0.0049)
		Prior mTOR inhibitors for the treatment of cancer.		CBRDoR			
				Everolimus, paclitaxel + trastuzumab serum levels			
		History of central nervous system metastasis.		Time to deterioration of ECOG-PS Safety			

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Table 1 (*continued*)

Study/Author, year	Agents	Key entry criteria	Line of Therapy	Non-CNSEnd points	Study population (n)	Median FU (months)	Primary End-Point results
BOLERO-3 Andre et al., 2014	Everolimus, Vinorelbine and Trastuzumab (EVT) vs Vinorelbine and Trastuzumab (VT)	**Inclusion:** Resistance to trastuzumab Prior Taxane therapy **Exclusion:** Previous mTOR inhibitors or vinca alkaloid agents More than three prior chemotherapy lines for advanced disease	2nd line or more	**Primary:** PFS **Secondary:** OS ORR CBR Safety QoL	EVT: 284 VT: 285	20.2	**Median PFS (months):** EVT:7.0 vs. VT: 5.8 (HR = 0.78 [95% CI, 0.65–0.95]. p = 0.0067)
HER2CLIMB Murthy et al., 2020	Tucatinib, Trastuzumab, and Capecitabine (TTC) vs Placebo, Trastuzumab, and Capecitabine (PTC)	**Inclusion:** Trastuzumab, Pertuzumab and TDM-1 treatment **Exclusion:** Exposure to Capecitabine or TKI	3rd line or more	**Primary:** PFS **Secondary:** ORR Safety DoR CBR	TTC: 410 PTC: 202	14	**Median PFS (months):** TTC = 7.8 vs. PTC = 5.6 (HR = 0.54 [95% CI, 0.42–0.71]. P < 0.001)
ALTERNATIVE Johnston et al., 2009, 2020	Lapatinib + Trastuzumab + Letrozole (L) vs Placebo + Trastuzumab + Letrozole + (P)	**Inclusion:** Postmenopausal women Prior neoadjuvant/adjuvant anti-estrogen therapy Adjuvant aromatase inhibitors and/or trastuzumab provided it was completed >1 year before study entry **Exclusion:** Prior therapy for advanced or metastatic disease Extensive symptomatic visceral disease	1st line	**Primary:** PFS **Secondary:** ORR CBR OS Safety	L: 111 P: 108	21.6	**Median PFS (months):** L = 8.2 vs. P = 3.0 (HR = 0.71 [95% CI, 0.53–0.96]. p = 0.019)

FU, follow up; vs, versus; PFS, progression free survival; ORR, objective response rate; CBR, clinical benefit ratio; OS, overall survival; HR, hazard ratio; OR, odds ratio; CI, confidence interval; TDM-1, Trastuzumab emtansine; PD, progressive disease; CNS, central nervous system; CNS-M, central nervous system metastases; BM, brain metastases; HER2, human epidermal growth factor receptor 2; DoR, duration of response; MBC, metastatic breast cancer; TKI, tyrosine kinase inhibitor; mTOR, mechanistic target of rapamycin; ECOG-PS, eastern cooperative oncology group performance status; QoL, quality of life.

screen failure data presented please refer to Tables 3 and 4

3.5. Proportion of patients with CNS disease at randomization

3.5.1. Studies with mandatory CNS screening

As expected CEREBREL, excluded all patients with CNS disease following radiological assessment at baseline [19]. Within those studies that undertook CNS imaging prior to study entry, EMILIA enrolled 95 of 991 (10%) patients with asymptomatic CNS disease (all previously treated with radiotherapy) [14]; while 291 of 612 (48%) of patients enrolled into HER2CLIMB had CNS metastases [11]. These comprised 174 patients with active (untreated or treated progressing) CNS disease at baseline (174 of 612; 28%) and 117 patients with stable CNS disease (117 of 612; 19%) [11]. MA.31 identified and subsequently excluded 4 patients (0.6%) at baseline due to the presence of CNS metastasis [25].

3.6. Studies with no protocol mandated CNS screening

Where radiological screening of the CNS was not mandated, 12 of 13 (92%) reported the number of randomized patients with CNS disease, this varied from 0% to 13.2% of the randomized population [13,15–18,20–22,24,26–28], Table 4. EGF100151 was the only study not to report any data on the number of patients with CNS disease at study entry [23].

3.7. Protocol mandated monitoring of the CNS

Following randomization, studies varied in how the CNS was surveilled. As a CNS disease prevention trial, CEREBREL mandated regular cross-sectional imaging of the CNS with MRI at 12-weekly intervals until week 84, thereafter every 24 weeks.

Of the non-CNS prevention trials, only HER2CLIMB performed

Table 2
Summary of the reported CNS data from the phase III CNS metastases prevention study for HER-2 positive locally advanced and metastatic breast cancer since advent of single agent Trastuzumab.

Study	Protocol defined CNS entry criteria	Protocol defined CNS screening and on study CNS imaging requirements	Screen failures due to asymptomatic CNS disease	Number of patients with CNS disease at study entry	Protocol defined CNS End-Points	Results of protocol defined CNS End-Points
CEREBREL	**Exclusion:** CNS-M confirmed clinically or radiologically	Mandatory MRI Brain screening **On study radiological assessment:** MRI brain routinely performed at 12-week intervals until week 84, thereafter every 24 weeks.	LC: 7.4% (20 of 271) TC: 7.1% (19 of 269)	Patients recruited with CNS-M at study entry: 0	**Primary:** Incidence of CNS as site of first relapse **Secondary:** Time to first CNS progression Incidence of CNS progression at any time	**Incidence of CNS-M as first site:** LC = 8 of 251 (3%) vs. TC = 12 of 250 (5%) (OR = 0.65 [95% CI, 0.26–1.63]. P = 0.36) **Incidence of CNS-M at any time:** LC = 17 of 251 (7%) vs. TC = 15 of 250 (6%) (OR = 1.14 [95% CI, 0.52–2.51]. P = 0.86) **Median time to first CNS-M (months):** LC = 5.7 vs. TC = 4.4 (p-value not stated)

CNS, central nervous system; CNS-M, central nervous system metastases; LC, lapatinib + capecitabine; TC, trastuzumab + capecitabine; MRI, magnetic resonance imaging scan; vs, versus; CI, confidence interval; OR; odds ratio.

regular assessment of the CNS, consisting of MRI of the CNS initially at 6-weekly intervals until week 24 and then 9 weekly thereafter.

The remaining 15 (94%) studies (93%) did not have protocol defined CNS imaging as part of the follow up schedule. With CNS imaging only indicated if there was clinical suspicion of CNS progression at a clinical assessment. The time intervals between such clinical assessment varied between trials and were performed every 3 weeks ([24,26]), every 4 weeks ([18,27]), every 6 weeks ([14,15,17,21–23]), every 8 weeks ([20, 28]), every 9 weeks ([13,16]) or every 12 weeks ([25]). One study, MA.31 mandated CNS imaging on all patients who developed extra cranial disease progression to investigate for concurrent CNS progression. Despite this being within the protocol, the group commented that the compliance to this was poor; the specific proportion of patients who did not have CNS imaging was not reported ([25]).

3.8. CNS specific end points

CEREBREL was the only study with a specific primary CNS endpoint; which was the incidence of CNS metastases as the first site of relapse. In addition, the time from randomization to first CNS metastases and incidence of CNS progression at any time were recorded as secondary endpoints.

Only 4 of 16 (25%) non-CNS prevention trials had protocol defined CNS specific endpoints [11,20,21,25]. HER2CLIMB was sole study where assessment of the CNS formed part of the primary endpoint [11], with PFS based on a bi-compartmental assessment of both the CNS and non-CNS disease [11]. The remaining protocol defined endpoints were all secondary and varied between trials, these included [1] CNS progression free survival, time to progression, objective response rate, duration of response, clinical benefit rate [HER2CLIMB] [11]; [2] frequency of and time to symptomatic or progressive CNS lesions [NEfERT-T] [20], [3] time between randomization and the need for local intervention (radiotherapy, surgery, or CNS directed concomitant medications) for new or progressive baseline CNS disease [NALA] [21], and [4] time to CNS metastasis at the time of first progression and incidence of CNS metastasis at time of progression [MA.31] [25]. The remaining 12 studies did not have protocol defined CNS end point [13–18,22–24,26–28], although 6 of these 12 (50%) reported non-protocol defined CNS data [13–15,18,22,23]. No data related to the CNS was reported for six studies; GBG26 [24], MARIANNE [16], SOPHIA [17], BOLERO-1 [28], BOLERO-3 [26], ALTERNATIVE [27], and.

3.9. Terminology for CNS endpoints

9 of 13 (69%) studies which have not undertaken CNS screening have used the term ‘no CNS disease’ [13,15,17,18,20–22,24,26] to describe the population with no history of CNS involvement at study entry however given the lack of CNS screening, the lack of objective information to demonstrate ‘no CNS disease’ and the likelihood the study population contain patients with asymptomatic CNS disease it would be more appropriate to label such patient populations ‘asymptomatic/no CNS disease’. While 4 of 13 (31%) studies which did not perform a CNS screen used the term “new CNS metastases” to describe those patients who are diagnosed with CNS disease during the study [13, 20–22]. However, in these circumstances given asymptomatic disease that has progressed on study cannot be differentiated from new CNS metastasis the term ‘CNS disease diagnosed on study’ would seem a more appropriate description.

It also needs to be remembered that any reported CNS endpoints and observations in studies which did not screen or monitor the CNS will only be able to report data related to progression and not benefit in those with asymptomatic or previously treated disease. This will also potentially prevent important observations of both clinical activity as well as primary prevention.

4. Results of protocol defined CNS end points

4.1. Tyrosine kinase inhibitors in combination with chemotherapy

Within the CEREBEL study lapatinib in combination with capecitabine (LC) when compared to trastuzumab in combination with capecitabine (TC) was found not to significantly reduce the incidence of new CNS metastasis as the first site (LC = 8 of 251 (3%) vs. TC = 12 of 250 (5%): OR = 0.65 [95% CI, 0.26–1.63]. P = 0.36) or CNS metastasis at any time during the study (LC = 17 of 251 (7%) vs. TC = 15 of 250 (6%): OR = 1.14 [95% CI, 0.52–2.51]. P = 0.86) [19]. It should be noted that CEREBEL was powered to detect a difference in CNS event rate of 20% versus 12%, based on observations from the randomised comparison of lapatinib-capecitabine versus capecitabine alone [23,29]. However, the low CNS event rate within CEREBEL the study meant that it was significant underpowering for the primary end point. A key reason for this

Table 3
Summary of the reported CNS data from the randomised phase III studies for HER-2 positive locally advanced and metastatic breast cancer since advent of single agent Trastuzumab where baseline cross sectional imaging of the CNS was mandatory.

Study	Protocol defined CNS entry criteria	Protocol defined CNS screening and on study CNS imaging requirements	Screen failures due to asymptomatic CNS disease	Number of patients with CNS disease at study entry	Protocol defined CNS End-Points	Results of protocol defined CNS End-Points
EMILIA	**Inclusion:** Asymptomatic CNS-M previously treated with radiotherapy **Exclusion:** Symptomatic or untreated CNS-M CNS-M treatment within 2 months before randomization	Mandatory CT or MRI Brain at baseline **On study radiological assessment:** CT or MRI brain not routinely performed, only when clinically indicated	Patients screened: 1576 Patients randomly assigned: 991 585 (37.1%) patients excluded. Specific data on screen failures due to asymptomatic CNS disease was not outlined.	Patients recruited with CNS-M at study entry: 95 Randomized: TDM-1: 45 XL: 50	None	**No protocol defined CNS end-points** **Exploratory CNS data: Development of CNS disease in patients with:** CNS-M at baseline population: TDM-1 = 10 of 45 (22.2%) vs. XL = 8 of 50 (16.0%). No CNS-M at baseline population: TDM-1 = 9 of 450 (2%) vs. XL = 3 of 446 (0.7%) **Median PFS (months):** Population with CNS-M at baseline: TDM-1 = 5.9 vs. XL = 5.7 (HR = 1.00 [95% CI, 0.54–1.84]. P = 1.000) **Median OS (months):** Population with CNS-M at baseline: TDM-1 = 26.8 vs. XL = 12.9 (HR = 0.38 [95% CI, 0.18–0.80]. P = 0.008)
MA.31	**Exclusion:** CNS-M confirmed radiologically	Mandatory CT or MRI Brain at baseline **On study radiological assessment:** CT or MRI brain not routinely performed, only when: 1) clinically indicated (presence of symptoms), 2) mandated at the time of disease progression, regardless of the site of progression.	Patients randomly assigned: 652 4 (0.61%) patients excluded due to CNS-M	Patients recruited with CNS-M at study entry: 0	**Secondary:** Time to CNS-M at the time of first progression Incidence of CNS-M at the time of progression	**Time to CNS-M at the time of first progression (months):** L = 8.77 [95% CI, 0.00–32.69]vs. T = 11.10 [95% CI, 0.00–38.54]*P* -value not stated **Incidence of CNS-M at the time of progression:** L = 44 of 178 (24.7%) vs. T = 52 of 157 (33.1%)*P* -value not stated
HER2CLIMB	**Inclusion:** Asymptomatic CNS-M (untreated, not needing immediate local therapy) Previously treated brain metastases not needing immediate local therapy Active CNS-M (untreated or treated progressing) Untreated CNS-M >2 cm in diameter could be enrolled with approval from the medical monitor. **Exclusion:** Symptomatic CNS-M requiring immediate local intervention (these patients could receive treatment and be enrolled subsequently) Leptomeningeal disease	Mandatory MRI Brain screening **On study radiological assessment:** MRI brain routinely performed at 6-week intervals until week 24, thereafter every 9 weeks (in patients with CNS-M on baseline MRI brain).	No data provided	Patients recruited with CNS-M at study entry: 291 Active CNS-M at baseline: 174 Stable CNS-M at baseline: 117 Randomized: TTC: 118 active CNS-M 80 stable CNS-M PTC: 56 active CNS-M 37 stable CNS-M	**Primary:** None **Secondary:** To assess the effect of each arm in patients with brain metastases at baseline	**All CNS-M at baseline (n = 291)** Median PFS (months): TTC = 7.6 (IQR, 4.2 to 11.8) vs. PTC = 5.4 (IQR 3.0 to 7.5)*P* -value not stated Exploratory estimated 1-year CNS-PFS: TTC = 40.2% (95% CI, 29.5%–50.6%) vs. PTC = 0% Median CNS-PFS (months): TTC = 9.9 vs. PTC = 4.2 (HR = 0.32 [95% CI, 0.22–0.48]. P < 0.00001) Exploratory estimated 1-year OS: TTC = 70.1% (95% CI, 62.1%–76.7%) vs. PTC = 46.7% (95% CI, 33.9%–58.4%) **Active CNS-M at baseline (n = 174)** Estimated 1-year CNS-

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Table 3 (*continued*)

Study	Protocol defined CNS entry criteria	Protocol defined CNS screening and on study CNS imaging requirements	Screen failures due to asymptomatic CNS disease	Number of patients with CNS disease at study entry	Protocol defined CNS End-Points	Results of protocol defined CNS End-Points
						PFS: TTC = 35.0% (95% CI, 23.2%–47.0%) vs. PTC = 0% Median CNS-PFS (months): TTC = 9.5 (95% CI, 7.5–11.1 months) vs. PTC = 4.1 (95% CI, 2.9–5.6 months). HR not reported Exploratory estimated 1-year OS: TTC = 71.7% (95% CI, 61.4%–79.7%) vs. PTC = 41.1% (95% CI, 25.5%–56.1%) **Stable CNS-M at baseline (n = 117)** Exploratory estimated 1-year CNS-PFS: TTC = 53.3% (95% CI, 31.4%–71.0%) vs. PTC = 0% Median CNS-PFS (months): TTC = 13.9 (95% CI, 9.7–32.2 months) vs. PTC = 5.6 (95% CI, 3.0–5.9 months). HR not reported Exploratory estimated 1-year OS: TTC = 67.6% (95% CI, 53.8%–78.0%) vs. PTC = 55.6% (95% CI, 34.1%–72.6%)

CNS, central nervous system; CNS-M, central nervous system metastases; CT, computed tomography scan; MRI, magnetic resonance imaging scan; vs, versus; TDM-1, trastuzumab emtansine; XL, lapatinib + capecitabine; TTC, tucatinib + trastuzumab + capecitabine; PTC, placebo + trastuzumab + capecitabine; PFS, progression free survival; CI, confidence interval; OS, overall survival; HR, hazard ratio; IQR, interquartile range.

is likely the use of CNS screening at baseline which resulted in 7.2% of patients being diagnosed with asymptomatic brain metastases. Such CNS screening was not undertaken in the randomised comparison of lapatinib-capecitabine versus capecitabine alone [29].

Within MA31 lapatinib (L) plus a taxane, was resulted in a numerically lower incidence of new CNS metastasis at time of disease progression at any site when compared to trastuzumab (T) plus a taxane, (L = 44 of 178 (24.7%) vs. T = 52 of 157 (33.1%). No reported p-value). While, lapatinib increased the time to CNS metastasis at the time of first progression (L = 8.77 [95% CI, 0.00–32.69]vs. T = 11.10 [95% CI, 0.00–38.54]. No reported p-value) [25]. Data from both NEfERT-T and NALA studies demonstrate that neratinib has intracranial activity ([20, 21]). With the combination of neratinib plus paclitaxel (NP) significantly reducing CNS disease progression as defined as either new CNS metastases or progression of baseline disease as compared to trastuzumab and paclitaxel (TP) (NP = 20 of 242 (8.3%) vs. TP = 41 of 237 (17.3%). (RR = 0.48 [95% CI, 0.29–0.79]. P = 0.002)) ([20]). However, it should be noted that at study entry twice as many patients had prior CNS disease in the TP arm as compared to NP arm (Table 4) and therefore this could have resulted in more frequent CNS imaging and therefore the detection of more CNS disease. While in NALA the combination of neratinib and capecitabine (NC) similarly significantly reduced the cumulative incidence of CNS metastases which required treatment interventions as compared to Lapatinib and Capecitabine (LC) (NC = 22.8% vs. LC = 29.2%, (HR = 0.78 [95% CI, 0.60–1.01]. P = 0.043)) [21].

When taken together NEfERT-T and NALA would suggest neratinib is more active than lapatinib at controlling intracranial disease [20,21]. Given both NEfERT-T and NALA did not perform CNS screening or regular CNS imaging it is not possible to determine if the intracranial effects of neratinib are in part due to the prevention of brain metastasis or the control or regression of asymptomatic intracranial disease present at study entry.

4.2. HER2 antibody treatment in combination with a HER2 tyrosine kinase inhibitor

HER2CLIMB demonstrated that the addition of tucatinib to trastuzumab and capecitabine improved median PFS in patients with CNS metastases at baseline. This benefit was demonstrated in all patients with CNS metastases at baseline (TTC = 9.9 months vs. PTC = 4.2 months, (HR = 0.32 [95% CI, 0.22–0.48]. P < 0.00001)) and also when these patients were subdivided into those with active (TTC = 9.5 (95% CI, 7.5–11.1 months) vs. PTC = 4.1 (95% CI, 2.9–5.6 months), HR not reported) and stable (TTC = 13.9 (95% CI, 9.7–32.2 months) vs. PTC = 5.6 (95% CI, 3.0–5.9 months), HR not reported) CNS disease. These data therefore establishing that the addition of a HER2 TKI, tucatinib, to anti-HER2 antibody therapy with chemotherapy is more efficacious than HER2-therapy antibody alone with chemotherapy in regards to controlling CNS disease.

Table 4
Summary of the reported CNS data from the randomised phase III studies for HER-2 positive locally advanced and metastatic breast cancer since advent of single agent Trastuzumab where baseline cross sectional imaging of the CNS was not mandated and only performed if clinically indicated.

Study	Protocol defined CNS entry criteria	Screen failures due to CNS disease	Number of patients with CNS disease at randomization	Protocol defined CNS End-Points	Results of post-hoc CNS analysis
GBG 26	**Inclusion:** CNS-M, if adequately controlled by surgery and/or radiotherapy with complete resolution of symptoms and of all steroids.	No data provided	Patients recruited with CNS-M at study entry: 3 Randomized: TC: 1 C: 2	None	No CNS data reported
CLEOPATRA	**Exclusion:** CNS -M confirmed clinically or radiologically	Patients screened: 1196 Patients randomly assigned: 808 388 (32.4%) patients excluded. Specific data on screen failures due to asymptomatic CNS disease was not outlined.	Patients recruited with CNS-M at study entry: 0	None	**Proportion with CNS progression:** TP = 55 of 402 (13.7%) vs. T = 51 of 406 (12.6%) **Median time to develop CNS-M (months):** TP = 15.0 vs. T = 11.9 (HR = 0.58 [95% CI, 0.39–0.85]. P = 0.0049) **Median OS (months):** Population who developed CNS-M: TP = 34.4 vs. T = 26.3 (HR = 0.66 [95% CI, 0.39–1.11]. P = 0.1139)
EGF104900	**Inclusion:** Asymptomatic CNS-M **Exclusion:** Symptomatic CNS-M	Patients screened: 397 Patients randomly assigned: 296 101 (25.4%) patients excluded. Further breakdown on screen failures due to asymptomatic CNS disease was not outlined.	Patients recruited with CNS-M at study entry: 36 Randomized: LT: 16 L: 20	None	**Proportion with CNS progression:** CNS-M at baseline population: LT = 9 of 16 (56%) vs. L = 15 of 20 (75%) No CNS-M at baseline population: No reported data
TH3RESA	**Inclusion:** Asymptomatic CNS-M previously treated with radiotherapy **Exclusion:** Symptomatic or previously untreated CNS-M CNS-M treatment within 1 months before randomization	107 of 370 (28.9%)	Patients recruited with CNS-M at study entry: 67 Randomized: TDM-1: 40 PC: 27	None	**Proportion with CNS events:** CNS-M at baseline population: TDM-1 = 24 of 40 (60.0%) vs. PC = 16 of 27 (59.3%) No CNS-M at baseline population: CNS data not reported **Median PFS (months):** Population with CNS-M at baseline: TDM-1 = 5.8 vs. PC = 2.9 (HR = 0.47 [95% CI, 0.24–0.89]. P = not stated)
MARIANNE	**Exclusion:** Asymptomatic or symptomatic CNS-M that are untreated, are progressive, or require any type of therapy (radiation, surgery, or steroids).	No data provided	Patients recruited with CNS-M at study entry: 0	None	No CNS data reported
SOPHIA	**Inclusion:** Asymptomatic CNS-M previously treated with surgery or radiotherapy **Exclusion:** Symptomatic CNS-M	Patients screened: 763 Patients randomly assigned: 536 227 (29.8%) patients excluded. Specific data on screen failures due to asymptomatic CNS disease was not outlined.	Patients recruited with CNS-M at study entry: 71 Randomized: M: 37 T: 34	None	No CNS data reported
EGF100151	**Inclusion:** Stable CNS-M defined as asymptomatic and off systemic steroids and anticonvulsants for at least 3 months **Exclusion:** Known history/ clinical evidence of leptomeningeal carcinomatosis	No data provided	No data provided	None	**CNS disease as first progression event:** LC = 4 of 198 (2%) vs. C = 13 of 201 (6%). P = 0.045.
NEfERT-T	**Inclusion:** Asymptomatic CNS-M previously treated with surgery or radiotherapy **Exclusion:** Symptomatic CNS-M Use of steroids or anticonvulsant within 1 months before randomization	No data provided	Patients recruited with CNS-M at study entry: 18 Randomized: NP: 6 TP: 12	**Primary:** None **Secondary:** Frequency of and time to symptomatic or progressive CNS lesions	**Proportion with CNS progression:** NP:20 of 242 (8.3%) vs. TP = 41 of 237 (17.3%). (RR = 0.48 [95% CI, 0.29–0.79]. P = 0.002) **Estimated Kaplan-Meier 2-year incidence of CNS-M:** NP = 16.3% vs. TP = 31.2% (HR = 0.45 [95% CI, 0.26–0.78]. P = 0.004)
NALA	**Inclusion:** Stable and asymptomatic CNS-M **Exclusion:** Symptomatic or unstable CNS-M	No data provided	Patients recruited with CNS-M at study entry: 101 Randomized: NC: 51 LC: 50	**Primary:** None **Secondary:** Time to intervention for metastatic CNS disease (radiotherapy, surgery, or CNS-directed concomitant medications)	**Intervention for CNS disease, cumulative incidence:** NC = 22.8% vs. LC = 29.2%. (HR = 0.78 [95% CI, 0.60–1.01]. P = 0.043)

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Table 4 (*continued*)

Study	Protocol defined CNS entry criteria	Screen failures due to CNS disease	Number of patients with CNS disease at randomization	Protocol defined CNS End-Points	Results of post-hoc CNS analysis
PH0EBE	**Exclusion:** CNS -M confirmed clinically or radiologically	No data provided	Patients recruited with CNS-M at study entry: 0	None	**New CNS-M:** PC = 3 of 134 (2%) vs. LC = 3 of 132 (2%). No other CNS data reported
BOLERO-1	**Exclusion:** CNS -M confirmed clinically or radiologically	Patients screened: 948 Patients randomly assigned: 719 229 (24.2%) patients excluded. Specific data on screen failures due to asymptomatic CNS disease was not outlined.	Patients recruited with CNS-M at study entry: 0	None	No CNS data reported
BOLERO-3	**Inclusion:** Previously treated asymptomatic CNS-M, provided that the last treatment for CNS-M was completed >8 weeks prior to randomization **Exclusion:** Symptomatic CNS-M or evidence of leptomeningeal disease.	Patients screened: 731 Patients randomly assigned: 569 162 (22.2%) patients excluded. Specific data on screen failures due to asymptomatic CNS disease was not outlined.	Patients recruited with CNS-M at study entry: 27 Randomized: ETV: 21 TV: 6	None	No CNS data reported
ALTERNATIVE	**Exclusion:** CNS -M confirmed clinically or radiologically	No data provided	Patients recruited with CNS-M at study entry: 0	None	No CNS data reported

CNS, central nervous system; CNS-M, central nervous system metastases; vs, versus; TP, trastuzumab + pertuzumab + docetaxel; T, trastuzumab + placebo + docetaxel; TDM-1, trastuzumab emtansine, PC, physician's choice; M, margetuximab + chemotherapy; T, trastuzumab + chemotherapy; LT, lapatinib + trastuzumab; L, lapatinib; NP, neratinib + paclitaxel; TP, trastuzumab + paclitaxel; NC, neratinib + capecitabine; LC, lapatinib + capecitabine; PFS, progression free survival; CI, confidence interval; OS, overall survival; HR, hazard ratio; RR, relative risk.

5. Results of non-protocol defined post hoc and exploratory analysis related to CNS disease

5.1. Doublet anti-HER2 therapy

Within the CLEOPATRA study, the addition of pertuzumab to trastuzumab did not result in a reduction in the proportion of patients with CNS progression [TP = 55 of 402 (13.7%) vs. T = 51 of 406 (12.6%) No reported p-value]. Although significant increase in the median time to the development of CNS disease was reported when compared to trastuzumab alone (15.0 months vs. 11.9 months; HR = 0.58 [95% CI, 0.39–0.85]. P = 0.0049)) ([13,30]). Subsequent, multivariate analysis, found only the number of metastatic sites (≤3 versus >3) was significantly associated with the development of CNS metastases (HR: 0.42; 95% CI,28–0.63 P=<0.0001). However, given the relatively small number of CNS events as first site of disease limits the sensitivity of these analysis to detect differences in time to event by subgroups (30). In those patients with CNS metastasis at baseline, the median overall survival was superior within the combination therapy treatment arm [TP = 34.4 vs. T = 26.3 (HR = 0.66 [95% CI, 0.39–1.11]. P = 0.1139)]. Therefore, while doublet HER2 antibody treatment does prevent CNS disease it does seem to potentially slow their development as well as improve the outcomes of those with disease at baseline. The latter likely reflecting the ability of HER2 antibodies to access the CNS after prior local therapy.

5.2. Antibody drug-conjugate

In a retrospective, exploratory analysis of the EMILIA study the proportion of patients developing new CNS disease was found to be 0.7% (3 of 446) in the capecitabine and lapatinib arm as compared to 2% (9 of 450) with T-DM1 ([14]). The overall shorter PFS for capecitabine and lapatinib as compared to T-DM1 could have influenced and decreased the possibility of detecting new CNS disease within this arm. While in those patients with CNS metastases at baseline, a smaller proportion developed CNS progression on study with TDM-1 than capecitabine and lapatinib; 22.2% (10 of 45) and 16.0% (8 of 50), respectively ([14]).

While the PFS was similar between the treatment arms in the subgroup of patients with CNS metastases at baseline (TDM-1 = 5.9 months vs. XL = 5.7 months, (HR = 1.00 [95% CI, 0.54–1.84]. P = 1.000)), a significantly longer overall survival was observed within this subgroup with TDM-1 as compared to capecitabine and lapatinib (TDM-1 = 26.8 months vs. XL = 12.9 months, (HR = 0.38 [95% CI, 0.18–0.80]. P = 0.008)) (14).

While specific data related to the CNS was not presented within the TH3RESA study, PFS data for those patients with treated asymptomatic brain metastasis did form part of the subgroup analyses ([15]). This demonstrated that there was no significant difference in progression events between T-DM1 and physicians' choice of treatment (TDM-1 = 24 of 40 (60.0%) as compared TPC 16 of 27 (59.3%) No reported p-value). While the risk of disease progression was similar between arms there was a numerically longer median PFS with TDM-1 as compared to physicians' choice for those with CNS disease (TDM-1 = 5.8 months vs. PC = 2.9 months (HR = 0.47 [95% CI, 0.24–0.89]. P = not stated)) [15]. With regard to overall survival in patients with baseline brain metastases the median overall survival was 17.3 months for patients assigned to trastuzumab emtansine and 12.6 months for those assigned to treatment of physician's choice (HR 0.62 [95% CI 0.34–1.13]) [15].

No CNS specific data has been reported to date for TDM-1 in combination with pertuzumab versus single agent TDM-1 ([16]), or for margetuximab versus trastuzumab ([17]).

5.3. Tyrosine kinase inhibitors in combination with chemotherapy

Within EGF100151 the addition of lapatinib to capecitabine was associated with a significantly lower incidence of CNS disease as first site of progression in EGF100151 (LC = 4 of 198 (2%) vs. C = 13 of 201 (6%). P = 0.045) [23].

While PH0EBE reported the proportion of patients presenting with new brain metastases on study was similar between the pyrotinib and lapatinib arms (PC = 3 of 134 (2%) vs. LC = 3 of 132 (2%)) ([22]).

5.4. HER2 antibody treatment in combination with a HER2 tyrosine kinase inhibitor

EGF104900 performed an exploratory analysis of the benefit of lapatinib in combination with trastuzumab as compared to lapatinib

alone based on the site of metastatic disease [31]. With regard to CNS disease the proportion of patients with baseline CNS disease who had CNS progression, was numerically lower with lapatinib in combination with trastuzumab as compared to lapatinib alone (LT = 9 of 16 (56%) vs. L = 15 of 20 (75%) no reported p-value) [31]. Median overall survival for patient with CNS disease at baseline was longer for the combination as compared to for lapatinib alone (LT 11.9 months vs L: 8.7 months). While the absence of brain metastasis was a significant predictor of OS benefit by univariate analysis (HR: 0.64 0.44 to 0.92 (p = 0.0175), the benefits of lapatinib in combination with trastuzumab were of similar magnitude in relation to reducing the risk of death in patients with and without brain metastasis [31].

5.5. Tyrosine kinase inhibitor plus HER2 antibody plus chemotherapy

Further exploratory data analysis was performed from the HER2-CLIMB trial which highlighted that tucatinib was associated with a superior estimated 1-year PFS (TTC = 40.2% (95% CI, 29.5%–50.6%) vs. PTC = 0%, No reported p-value) and estimated 1-year OS (TTC = 70.1% (95% CI, 62.1%–76.7%) vs. PTC = 46.7% (95% CI, 33.9%–58.4%)) in all patients with CNS metastases at baseline. This was also seen within the active and stable CNS metastases at baseline subdivisions (Table 3) [32].

5.6. Studies with no reported CNS data

No data pertaining to CNS disease was reported from the GBG26 trial which investigated the use of trastuzumab beyond progression in combination with chemotherapy [24], the addition of everolimus to trastuzumab and paclitaxel or vinorelbine [26,28] or for adding lapatinib to trastuzumab plus endocrine therapy [27].

5.7. On-going studies

There are currently eight ongoing randomised phase III studies for advanced HER2 positive breast cancer registered on clinicaltrials.gov (Table 5). These studies, like those published, demonstrate heterogeneity in regard to CNS entry criteria, use of baseline and on-study cross-sectional CNS imaging and the specific CNS targeted end points. Only 1 of 8 (13%) studies, TULIP, excludes patients with either a previous history of, or current CNS disease at baseline. With only 3 of these 8 (38%) studies having protocol defined CNS end points; DESTINY-B12 (NCT: NCT04739761), NRG-BR004 (NCT: NCT03199885) and PATINA (NCT: NCT02947685).

6. Conclusion

Data from randomised control trials of HER2 directed therapies can provide an opportunity to both understand the prevalence of asymptomatic CNS disease secondary to HER2 positive breast cancer as well as the activity of novel HER2 therapies in CNS disease and potentially identify agents which might lower the risk or have a protective effect against CNS disease. As patients live longer with metastatic HER2-positive breast cancer as a result of treatment advances, the management and treatment of CNS disease is becoming increasingly important given the cumulative risk of such disease [33] and the often solitary nature of CNS progression [8]. Currently, most phase III studies, both completed and on-going, have restrictive CNS entry criteria, rely on clinical acumen regarding the need to screen for CNS disease or not and do not monitor the CNS. While reported CNS end points are heterogenous and in the vast majority are unplanned post hoc analysis [13,14,18,22,23,32,34]. Such an approach disadvantages patient who may wish to avoid local therapy such as whole brain radiotherapy, those with CNS disease that is progressing following either local treatment or prior HER2 directed therapy. While opportunities to gain insights into the CNS activity of novel HER2 directed therapies via randomised studies is lost, leading to a reliance on single cohort phase II or phase IIb studies [35–40] or real world data [41–44] for CNS related data for novel agents. In fact, it can now be argued in the case of metastatic HER2 positive breast cancer that studies that exclude patents with CNS disease actually limit their generalizability to a real-world population. The American Society of Clinical Oncology (ASCO)-Friends of Cancer Research Brain Metastases Working Group recommended in 2017 that eligibility within studies should be more inclusive of patients with brain metastasis [45]. While the guidance provided by the Response Assessment in Neuro- Oncology Brain Metastases (RANO-BM) can aid in both designing a clinical trial on systemic therapy involving CNS disease [46]. A number of response assessment criteria can be used to assess CNS disease in the context of studies these include. RECIST 1.1, modified RECIST 1.1 and the RANO criteria [47–49], these are summarised in supplementary table 1 [50].

Limitation of the review are that given we limited our review to phase III studies data from phase 1 B/II trials are not included within the article. Given we only included peer reviewed and published data studies key data from studies such as DESTINY Breast 03 and TULIP which have been the such of oral presentation have not been fully reviewed and discussed. Although their design and details have been summarised in Table 5.

In summary

Our review has demonstrated heterogeneity in regard to how the CNS is handled within phase III clinical trials in HER2 positive breast cancer. This heterogeneity remains in the current ongoing studies which yet to be peer reviewed. The HER2CLIMB is an exemplar study given it undertook CNS screening, had permissive CNS entry criteria and collected CNS specific endpoints. Such an approach should be considered the norm for future studies for advanced HER2 positive breast cancer not only to ensure that clinically relevant CNS populations are included but that relevant CNS specific data is collected and reported. Such an approach would result in a contemporaneous evidence base on which to base and guide the treatment of patients with CNS disease secondary to HER2 positive breast cancer. It would also mean patients with CNS disease are not placed at a disadvantage in terms of being able to enter clinical trials. The sequential therapeutic improvements seen in the management of extra cranial disease make the need for such an evidence based increasingly needed.

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Final approval of manuscript

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Table 5
Summary of key CNS related information for ongoing randomised phase III studies for HER-2 positive locally advanced and metastatic breast cancer.

Study/NCT number	Agents	Key non-CNS entry criteria	CNS related entry criteria	Protocol defined CNS screening at baseline	Non-CNS End points	CNS specific end points
HER2CLIMB-02 NCT03975647	Tucatinib + TDM-1 vs TDM-1	**Inclusion:** Prior treatment with a taxane and trastuzumab in any setting **Exclusion:** Prior treatment with tucatinib, afatinib, trastuzumab deruxtecan Prior treatment with lapatinib or neratinib within 12 months of starting study treatment	**Inclusion:** CNS criteria based on baseline MRI brain: - No BM - Untreated BM not needing immediate local therapy - Previously treated BM which remain stable since treatment or may have progressed since prior local CNS therapy however there is no clinical indication for immediate re-treatment with local therapy If newly identified CNS disease received local treatment then there should be an adequate washout period before day of first dosing: ≥7 days since SRS or gamma knife ≥21 days since whole brain radiotherapy ≥28 days since surgical resection **Exclusion:** Untreated brain lesions >2 cm in size Use of corticosteroids for BM symptoms control Known or suspected leptomeningeal disease	Yes	**Primary:** PFS **Secondary:** OS ORR DoR CBR Number of patients with adverse events	Nil
TULIP NCT03262935	Trastuzumab duocarmazine vs Physician's choice	**Inclusion:** Female patients only Disease progression during or after at least two HER2-targeting treatment regimens or after TDM-1	**Exclusion:** Untreated BM Symptomatic BM BM requiring steroids to manage symptoms Treatment for BM within 8 weeks prior to randomization	Not stated	**Primary:** PFS **Secondary:** OS ORR Patient reported outcomes for health related quality of life	Nil
DESTINY-B02 NCT03523585	Trastuzumab deruxtecan vs Trastuzumab + capecitabine vs Lapatinib + capecitabine	**Inclusion:** Previous treatment with TDM-1 **Exclusion:** Previous treatment with capecitabine	**Inclusion:** Inactive CNS-M **Exclusion:** Active CNS-M (either untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms).	Not stated	**Primary:** PFS **Secondary:** OS ORR DoR	Nil
DESTINY-B03 NCT03529110	Trastuzumab deruxtecan vs TDM-1	**Inclusion:** Previous treatment with trastuzumab and taxane in the advanced/metastatic setting, or, progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and Taxane **Exclusion:** Treatment with anti-HER2 ADC in the metastatic setting	**Inclusion:** Inactive CNS-M Treated asymptomatic CNS-M who require no treatment with corticosteroids or anticonvulsants **Exclusion:** Active CNS-M (either untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms).	Not stated	**Primary:** PFS **Secondary:** OS ORR DoR	Nil
DESTINY-B09 NCT04784715	Trastuzumab deruxtecan vs Trastuzumab deruxtecan + pertuzumab vs Taxane + pertuzumab + traztuzumab	**Inclusion:** No prior chemotherapy or HER2-targeted therapy or only 1 previous line of endocrine therapy in the metastatic setting	**Inclusion:** Clinically inactive or previously treated CNS-M that are asymptomatic **Exclusion:** Clinically active CNS-M	Not stated Not stated	**Primary:** PFS **Secondary:** OS ORR DoR Time to second progression or death Health related quality of life	Nil

(*continued on next page*)

Table 5 (*continued*)

Study/NCT number	Agents	Key non-CNS entry criteria	CNS related entry criteria	Protocol defined CNS screening at baseline	Non-CNS End points	CNS specific end points
DESTINY-B12 NCT04739761	Trastuzumab deruxtecan in patients with no baseline CNS-M vs Trastuzumab deruxtecan in patients with baseline CNS-M	**Inclusion** Disease progression on no more than 2 lines/regimens of therapy in the metastatic setting (excluding tucatinib). **Exclusion:** Prior exposure to tucatinib treatment	**Inclusion** Either: no evidence of BM, or untreated BM on screening brain MRI/CT scan not needing immediate local therapy or previously treated stable or progressing BM If radiotherapy is required for BMs, there should be an adequate washout period before day of first dosing: ≥7 days since SRS or gamma knife ≥21 days since whole brain radiotherapy **Exclusion:** Known or suspected leptomeningeal disease Neurologically unstable BM Poorly controlled generalized or complex partial seizures (>1/ week) Ongoing use of systemic corticosteroids for control of symptoms of BMs Untreated brain lesions >2.0 cm in size		**Primary:** ORR in patients without BM at baseline PFS in patients with BM at baseline **Secondary:** OS DoR	**Secondary:** Time to next progress (CNS or extra-cranial) or death Time to new BM/ progression of baseline BM Duration of treatment on subsequent lines of therapy Incidence of new symptomatic CNS-M during treatment in participants without BM at baseline CNS-PFS in patients with BM at baseline Number of patients with adverse events with BM at baseline
NRG-BR004 NCT03199885	Atezolizumab + pertuzumab + trastuzumab + taxane therapy vs Placebo + pertuzumab + trastuzumab + taxane therapy		**Inclusion:** Brain metastases, if they meet all the following criteria: - Four or fewer metastatic sites to CNS - Largest unexcised tumour does not exceed 3 cm - No metastases to brain stem, midbrain, pons, medulla or the optic nerves and chiasm - Must have measurable disease outside the CNS, based on RECIST 1.1, as determined by the site, which has not been irradiated - If patient presented with symptoms from CNS-M, the symptoms must have resolved with initiation of steroids and initial local therapy (surgery, radiation therapy, or both) - May have received administration of trastuzumab OR lapatinib concurrently with radiation therapy for brain metastases. Toxicities related to lapatinib if administered, should be =< grade 1 per the CTCAE v5.0, and the lapatinib must have been completed at least 2 weeks prior to study entry - No history of intracranial haemorrhage or spinal cord haemorrhage - No neurosurgical resection or brain biopsy within 10 days prior to study entry **Exclusion:** - Leptomeningeal carcinomatosis Brain metastases, if they meet any of the following criteria: - Symptoms from CNS-M have not resolved prior to study entry - Five or more clearly identified foci of metastases to the brain	No MRI/CT brain must be obtained in patients if clinical suspicion of CNS-M. Neuroimaging is recommended but not required in asymptomatic patients	**Primary:** PFS **Secondary:** OS ORR DoR Frequency of adverse events	**Secondary:** Cumulative incidence of brain metastases

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Table 5 (*continued*)

Study/NCT number	Agents	Key non-CNS entry criteria	CNS related entry criteria	Protocol defined CNS screening at baseline	Non-CNS End points	CNS specific end points
			- Largest unexcised tumour exceeds 3 cm - Spinal cord metastases - Medical Oncologist plans to employ HER2-directed tyrosine kinase inhibitor as component of systemic therapy - Metastatic disease limited to CNS			
PATINA NCT02947685	Palbociclib + trastuzumab/ pertuzumab + letrozole, anastrozole, exemstane or fulvestratnt vs Placebo + trastuzumab/ pertuzumab + letrozole, anastrozole, exemstane or fulvestratnt	**Exclusion:** Prior therapy with any CDK 4/ 6 inhibitor	**Inclusion:** History or presence of asymptomatic CNS-M, provided they meet all of the following: - Disease outside the CNS is present. - No evidence of interim progression between the completion of induction therapy and the screening radiographic study - No history of intracranial haemorrhage or spinal cord haemorrhage - Not requiring anti-convulsant for symptomatic control - Minimum of 3 weeks between completion of CNS radiotherapy and Cycle 1 Day 1 and recovery from significant (Grade ≥3) acute toxicity with no ongoing requirement for corticosteroid	Not stated	**Primary:** PFS **Secondary:** OS 3 and 5 year survival probabilities ORR DoR CBR Safety	Nil

CNS, central nervous system; CNS-M, central nervous system metastases; CT, computed tomography scan; MRI, magnetic resonance imaging scan; vs, versus; TDM-1, trastuzumab emtansine; PFS, progression free survival; OS, overall survival; ORR, objective response rate; CBR, clinical benefit ratio; BM, brain metastases; SRS, stereotactic radiosurgery; ADC, antibody drug conjugate.

Declaration of competing interest

TB: None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.03.013.

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