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Expert recommendations on treatment sequencing and challenging clinical scenarios in human epidermal growth factor receptor 2-positive (HER2-positive) metastatic breast cancer

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ABSTRACT

Human epidermal growth factor receptor 2 (HER2) overexpression and/or *ERBB2* gene amplification occurs in approximately 15–20% of breast cancers and is associated with poor prognosis. While the introduction of HER2-targeted therapies has significantly improved survival in patients with HER2-positive metastatic breast cancer, the incidence of brain metastases has increased due to patients living longer. Current recommendations sequence treatments by line of therapy, as well as by the status of brain metastases in patients with HER2-positive breast cancer. However, in the third-line treatment setting and beyond, there is a lack of clarity of the preferred choice of therapy. In clinical practice, clinicians may also encounter challenging scenarios where the optimal therapeutic approach has not been defined by clinical studies, so there is a need for clarity in such situations. Two consensus meetings of expert oncologists (12 from Europe and one from Canada) were convened to discuss these scenarios. We subsequently developed this article to present an overview of current treatment recommendations for HER2-positive metastatic breast cancer and give practical guidance on addressing challenging scenarios in a real-world setting. Based on our clinical experience, we provide a unanimous consensus concerning the treatment of elderly patients as well as those with brain-only metastases, leptomeningeal disease, oligometastatic disease, central nervous system oligo-progressive disease or *ERBB2*-mutant disease. We also discuss how to combine HER2-targeted therapy with endocrine therapy in patients with HER2-positive/hormone-receptor-positive disease, considerations for potential discontinuation of HER2-targeted therapy in patients with long-term remission and how to treat patients whose metastatic biopsy no longer confirms their HER2-positive status.

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Introduction

Worldwide, breast cancer is the most common cancer and the fifth leading cause of cancer-related death. In 2020, there were an estimated 2.3 million diagnoses of breast cancer (11.7 % of all new cancer cases) and 685,000 deaths due to breast cancer (6.9 % of all cancer-related deaths) globally [1]. Approximately 20–30 % of patients with early-stage breast cancer will progress to metastatic disease [2].

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer is defined as cancer that has an immunohistochemistry (IHC) score of 3 + or 2 + with a positive *in situ* hybridisation (ISH) score [3]. HER2 overexpression and/or *ERBB2* gene amplification is present in approximately 15–20 % of breast cancers [4,5], with results from a study published in 2022 suggesting that approximately 50 % of patients with HER2-positive breast cancer may present with *de novo* metastatic disease [6]. An analysis of the Epidemiological Strategy and Medical Economics cohort published in 2024 suggested the prevalence of HER2-positive disease may be slightly increased in younger patients; 26.8 % and 20.5 % of patients aged < 40 years and 40–69 years had HER2-positive disease, respectively [7]. HER2 positivity or *ERBB2* amplification are synonymous with oncogenic activation of the HER2 pathway; HER2 is, therefore, a well-established therapeutic target in metastatic breast cancer.

While HER2 activation has been associated with poor prognosis, the introduction of HER2-targeted therapies has significantly improved outcomes in patients with HER2-positive early and metastatic breast cancer [8,9]. For example, in the HERA trial of patients with HER2-positive early breast cancer, the 12-year overall survival (OS) rate was 79 % in patients who had received 1 year of adjuvant trastuzumab versus 73 % in the observation arm at a median follow-up of 11 years; the absolute gain in 12-year OS benefit was 6.5 % [8]. Moreover, in the CLEOPATRA trial, the 8-year OS rate was 37 % (95 % confidence interval [CI], 31–42) in patients with HER2-positive metastatic disease treated with trastuzumab, pertuzumab and docetaxel versus 23 % (95 % CI, 19–28) in those treated with trastuzumab and docetaxel [9]. Nevertheless, with improved systemic therapy and patients living longer, the cumulative incidence of brain metastases in HER2-positive breast cancer has increased, with approximately 50 % of patients estimated to develop brain metastases over the course of their disease [10]. Data from the KATHERINE trial suggest that the introduction of adjuvant trastuzumab emtansine (T-DM1) in high-risk early breast cancer may not have affected the overall incidence of CNS metastases [11].

According to guidelines from the European Society of Medical Oncology (ESMO), treatments should be selected by line of therapy and by the status of brain metastases in HER2-positive metastatic breast cancer [12]. In clinical practice, clinicians may encounter challenging scenarios such as treating elderly patients or those with brain-only metastases (including when to use systemic therapy), leptomeningeal disease (LMD), oligometastatic disease, CNS oligo-progressive disease or *ERBB2*-mutant disease. Moreover, clinicians may be faced with decisions concerning how to combine HER2-targeted therapy with endocrine therapy in patients with HER2-positive / hormone receptor (HR)-positive disease; considerations for potential discontinuation of HER2-targeted therapy in patients with long-term remission; and how to treat patients whose metastatic biopsy no longer confirms their HER2-positive status due to selection of HER2-negative clones under the pressure of treatment. The optimal therapeutic approach in these scenarios has not been determined by randomised clinical trials and is not covered by current treatment guidelines, so there is a need for clarity in such situations. Two consensus meetings of expert oncologists were convened to discuss these scenarios. We subsequently developed this article to present an overview of current treatment recommendations for HER2-positive metastatic breast cancer in Europe and Canada. We provide practical guidance concerning how to address challenging scenarios, for which there are no/limited clinical guidelines, in a real-world setting. Some of the presented treatment options represent off-label use based on our clinical experience.

Overview of current ESMO treatment guideline recommendations in HER2-positive metastatic breast cancer

An overview of the current ESMO guideline-recommended therapies, sequenced by line of therapy as well as by the status of brain metastases, is shown in Fig. 1. Considering the therapies used currently in HER2-positive early breast cancer, drug rechallenge may be applied in HER2-positive metastatic breast cancer [12], providing that the disease-free interval is ≥ 12 months after the last drug administration and that limited remaining toxicities exist.

First-line treatment options

The first-line metastatic treatment setting applies to patients with *de novo* metastatic disease, as well as to those whose disease has relapsed ≥ 12 months after prior HER2-targetting adjuvant therapy. Disease recurrence within 12 months of adjuvant therapy should receive additional scrutiny when choosing the next line of therapy.

The combination of trastuzumab and pertuzumab, which are both HER2-targeting monoclonal antibodies, added to a taxane (docetaxel or paclitaxel) for at least six cycles is recommended for patients who are candidates for chemotherapy, irrespective of HR status (ESMO-Magnitude of Clinical Benefit Scale [MCBS] 1A), based on results from the CLEOPATRA and PERUSE studies (Table 1) [9,12–14]. While the combination of trastuzumab and pertuzumab plus endocrine therapy is not currently approved by the European Medicines Agency (EMA), the ESMO guidelines recommend this combination as maintenance therapy in patients with HR-positive disease following the completion of chemotherapy; maintenance therapy should consist of trastuzumab and pertuzumab for those with HR-negative disease (MCBS 1A) [12]. Among patients with chemotherapy contraindications, treatment should only consist of trastuzumab and pertuzumab for patients with HR-negative disease, with additional endocrine therapy for those with HR-positive disease (MCBS 2B) [12]. Patients with metastatic recurrence within 6–12 months of receiving adjuvant trastuzumab and pertuzumab should be treated according to second-line therapy recommendations (MCBS 2B), while those who develop metastatic disease within 12 months of adjuvant trastuzumab (without pertuzumab) may receive first-line trastuzumab, pertuzumab, and a taxane or second-line therapy [12].

Patients with no, unknown, or stable brain metastases

Second-line treatment options

Following progression on trastuzumab, pertuzumab, and taxane therapy, trastuzumab deruxtecan (T-DXd) is the preferred therapy in the second-line setting (MCBS 1A), based on results from the DESTINY-Breast03 study (Table 1) [12,15].

T-DXd is an antibody-drug conjugate (ADC) that combines the HER2-targeting antitumour properties of trastuzumab with the cytotoxic activity of the topoisomerase I inhibitor DXd. Prior to the approval of T-DXd, T-DM1 was the standard of care in the second-line setting, primarily due to results of the EMILIA study (Table 1) [12,16,17]. T-DM1, an ADC composed of trastuzumab and the cytotoxic microtubule-inhibitory agent DM1, is now recommended in cases when T-DXdis unavailable (MCBS 1A) [12] or unsuitable (e.g., in patients with interstitial lung disease). The addition of tucatinib, a highly selective HER2 tyrosine kinase inhibitor (TKI), to T-DM1 in the second-line setting is currently under investigation in the phase 3 HER2CLIMB-02 (NCT03975647) trial. At the primary analysis, median progression-free survival (PFS) was significantly increased with tucatinib and T-DM1 (9.5 months) versus placebo and T-DM1 (7.4 months; hazard ratio, 0.76; 95 % CI, 0.61–0.95; p = 0.0163), suggesting potential clinical benefit [18]. While elevations in Grade ≥ 3 alanine aminotransferase (16.5 % vs 2.6 %) and aspartate aminotransferase (16.5 %

vs 2.6 %) were substantially greater with tucatinib and T-DM1 than placebo and T-DM1, these events were generally transient, manageable, and reversible. This combination may provide an alternative treatment option in the future for selected cases where T-DXd is unsuitable or unavailable (e.g., a patient with pre-existing interstitial lung disease); however, no final conclusion can currently be drawn for this combination as OS data were immature at the primary analysis [18].

Third- and later-line treatment options

Several treatment options exist for patients who have previously received treatment with trastuzumab, pertuzumab, and an ADC. The addition of tucatinib to trastuzumab and capecitabine was approved by the EMA after at least two prior anti-HER2 treatment regimens based on results from the HER2CLIMB study (Table 1; MCBS 1A) [12,19–21]. T-DXd(ESMO MCBS 3A) or T-DM1 (MCBS 1A) can also be considered for patients who have not received these agents in the second-line setting, based on results from the DESTINY-Breast01 and DESTINY-Breast02 trials, and TH3RESA trial, respectively (Table 1) [12,22–25].

The current ESMO guidelines do not indicate whether the tucatinib, trastuzumab, and capecitabine combination, T-DXd, or T-DM1 is preferred in the third-line setting. While country-specific clinical practice guidance is generally consistent with that of ESMO, the latest treatment guidelines in Austria, Canada, France, and Italy specifically note the tucatinib, trastuzumab, and capecitabine combination should be preferably used following second-line T-DXd [26–29]. In Germany, both the tucatinib, trastuzumab, and capecitabine combination and T-DXd have the highest grade of recommendation in the third-line setting [30]. The choice of third-line therapy is dependent on prior therapy; therefore, for patients with disease progression on second-line T-DXd, the tucatinib, trastuzumab, and capecitabine combination would be preferred [30]. In contrast, the Belgian treatment guidelines recommend either choice of the tucatinib, trastuzumab, and capecitabine combination or T-DM1 following T-DXd [31]. While there are currently no clinical trial data on tucatinib, trastuzumab, and capecitabine post T-DXd, recent real-world data investigating this approach in the third to fifth line setting have demonstrated the potential effectiveness of this treatment approach, with a median OS of approximately 13–14 months (Table 2 [32,33]). Moreover, a consensus paper published in 2024 reported that of 80 Italian and Spanish breast cancer experts surveyed, 98 % believed that the optimal treatment sequence in HER2 + metastatic breast cancer consisted of trastuzumab and pertuzumab, followed by T-DXd and subsequent tucatinib, trastuzumab and capecitabine [34].

Following progression on third-line therapy, combinations of lapatinib (a dual HER2 and epidermal growth factor receptor TKI) plus trastuzumab (MCBS 1B), trastuzumab plus chemotherapy (MCBS 3A), margetuximab (a HER2-targeted monoclonal antibody) plus chemotherapy (MCBS 1B) or neratinib (a pan-HER inhibitor) plus chemotherapy (MCBS 1C) would be reasonable to consider [12]. Of note, while the US Food and Drug Administration has approved the margetuximab plus chemotherapy and neratinib plus chemotherapy combinations, they are not currently licensed by the EMA [12].

Patients with active brain metastases

Unlike patients with stable brain metastases whose CNS disease is under control, a proportion of patients have active brain metastases, defined as new brain metastases or progressive brain metastases, that have not been subjected to CNS-directed therapy since the last documented progression [35].

Local therapeutic approaches, which include surgical resection, stereotactic radiotherapy (SRT) and whole-brain radiotherapy (WBRT; for selected cases only) should be considered in patients with active brain metastases who are eligible for local therapy [12]. Surgery should be followed by SRT to the resection cavity, regardless of whether the lesion was completely or partially resected (MCBS 1A) [12,36]. SRT is recommended for patients with 1–4 brain metastases (MCBS 1A) and should be considered in patients with 5–10 brain metastases providing

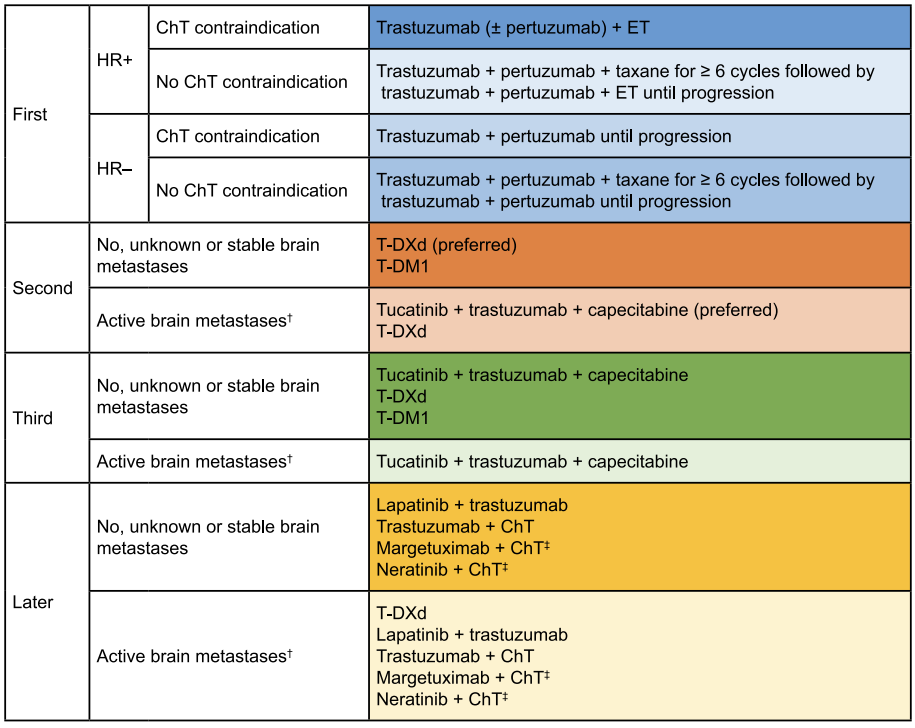

Fig. 1. Current ESMO guideline-recommended treatments by line of therapy and status of brain metastases in HER2-positive metastatic breast cancer. [12]. †Systemic therapy is recommended in patients with active brain metastases when local therapy is contraindicated. ‡FDA approved, not EMA approved. Abbreviations: ChT = chemotherapy; EMA, European Medicines Agency; ET = endocrine therapy; ESMO = European Society of Medical Oncology; FDA = U.S. Food and Drug Administration; HR = hormone receptor; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

Table 1
Clinical trial data supporting treatment approvals in HER2-positive metastatic breast cancer.

	CLEOPATRA [9,13]	**PERUSE** [14]	**DESTINY-Breast03** [15]	**EMILIA** [16,17]	**HER2CLIMB** [20,21]	**DESTINY-Breast01** [22]	**DESTINY-Breast02** [25]	**TH3RESA** [23,24]
Line of therapy	First	First	Second	Second	Third	Third	Third	Third
Trial design	Phase 3, randomised, double-blind	Phase 3b, single-arm, open-label	Phase 3, randomised, open-label	Phase 3, randomised, open-label	Phase 2, randomised, double-blind	Phase 2, single-arm, open-label	Phase 3, randomised, open-label	Phase 3, randomised, open-label
Active treatment	Pertuzumab + trastuzumab + docetaxel	Pertuzumab + trastuzumab + taxane (docetaxel, paclitaxel, or nab-paclitaxel)	T-DXd	T-DM1	Tucatinib + trastuzumab + capecitabine	T-DXd	T-DXd	T-DM1
Comparator	Placebo + trastuzumab + docetaxel	–	T-DM1	Lapatinib + capecitabine	Placebo + trastuzumab + capecitabine	–	Physician's choice	Physician's choice
Randomisation ratio	1:1	NA	1:1	1:1	2:1	NA	2:1	2:1
Patient population, N	*Pertuzumab + trastuzumab + docetaxel* 402 *Placebo + trastuzumab + docetaxel* 406	*All patients* 1436[†] *Docetaxel backbone* 775 *Paclitaxel backbone* 568 *Nab-paclitaxel backbone* 65	*T-DXd* 261 *T-DM1* 263	*T-DM1* 495 *Lapatinib + capecitabine* 496	*Tucatinib + trastuzumab + capecitabine* 410[‡] *Placebo + trastuzumab + capecitabine* 202[‡]	184	*T-DXd* 406[§] *Physician's choice* 202	*T-DM1* 404 *Physician's choice* 198
PFS	Median, months 18.5 vs 12.4 [13]	Median, months (95 % CI) *All patients* 20.7 (18.9–23.1) *Docetaxel backbone* 19.4 (16.9–22.1) *Paclitaxel backbone* (19.6–25.6) *Nab-paclitaxel backbone* 19.2 (11.7–37.1)	Median, months (95 % CI) NR (18.5–NE) vs 6.8 (5.6–8.2)	Median, months 9.6 vs 6.4 [16]	Median, months (95 % CI) 7.8 (7.5–9.6) vs 5.6 (4.2–7.1) [20]	Median, months (95 % CI) 16.4 (12.7–NR)	Median, months (95 % CI) 17.8 (14.3–20.8) vs 6.9 (5.5–8.4)	Median, months (95 % CI) 6.2 (5.59–6.87) vs 3.3 (2.89–4.14) [23]
OS	Median, months (95 % CI) 57.1 (50–72) vs 40.8 (36–48) [9]	Median, months (95 % CI) *All patients* 65.3 (60.9–70.9) *Docetaxel backbone* 66.5	12-month OS, % (95 % CI) 94.1 (90.3–96.4) vs 85.9 (80.9–89.7)	Median, months (95 % CI) 29.9 (26.3–34.1) vs 25.9 (22.7–28.3) [17]	Median, months (95 % CI) 24.7 (21.6–28.9) vs 19.2 (16.4–21.4) [21]	12-month OS,% (95 % CI) 86.2 (79.8–90.7)	Median, months (95 % CI) 39.2 (32.7–NE) vs 26.5 (21.0–NE)	Median, months (95 % CI) 22.7 (19.4–27.5) vs 15.8 (13.5–18.7) [24]

(*continued on next page*)

Table 1 (*continued*)

	CLEOPATRA [9,13]	PERUSE [14]	DESTINY-Breast03 [15]	EMILIA [16,17]	HER2CLIMB [20,21]	DESTINY-Breast01 [22]	DESTINY-Breast02 [25]	TH3RESA [23,24]
		(61.7–77.3)						
		Paclitaxel backbone 64.0 (56.6–72.2)						
		Nab-paclitaxel backbone 70.9 (39.7-NE)						
ORR	%	% (95 % CI)	% (95 % CI)	% (95 % CI)	% (95 % CI)	% (95 % CI)	%	%
	80.2 vs 69.3 [13]	*All patients* 79 (77–82)	79.7 (74.3–84.4) vs 34.2 (28.5–40.3)	43.6 (38.6–48.6) vs 30.8 (26.3–35.7) [16]	40.6 (35.3–46.0) vs 22.8 (16.7–29.8) [20]	60.9 (53.4–68.0)	70 vs 29	31 vs 9 [23]

Abbreviations: CI = confidence interval; NA = not applicable; NE = not estimable; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; T-DM1= trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

† One patient discontinued therapy immediately after the first pertuzumab administration and therefore received neither trastuzumab nor taxane, and seven additional patients discontinued all study treatments before receiving their first taxane dose. ‡The primary endpoint analysis population included 320 patients treated with tucatinib + trastuzumab + capecitabine and 160 patients treated with placebo + trastuzumab + capecitabine. §Two patients did not receive T-DXd and seven patients did not receive treatment of physician's choice.

Table 2
Real-world effectiveness data of the tucatinib, trastuzumab, and capecitabine combination following treatment with T-DXd in patients with HER2-positive metastatic breast cancer.

	Kaufman, et al (2023) [32]	Anders, et al (2023) [77]	Frenel, et al (2024) [33]
Real-world evidence source	Flatiron Health database between January 2017 and December 2022	Komodo Health Sentinel database between January 2017 and September 2022	Twelve French comprehensive cancer centres between August 2020 and December 2022
Patient population, N	35	61	86
Prior treatment lines	Median: 3 (Range: 1–10)	Median: 3 (IQR: 3–4)	Median: 4 (Range: 2–15)†
rwTTD	Median: 6.4 months (95 % CI, 3.5–9.4)	Median: 7.3 months (95 % CI, 3.2–9.5)	Not reported
rwPFS	Not reported	Not reported	Median: 5.0 months (95 % CI, 4.2–6.0)
rwTTNT	Median: 8.1 months (95 % CI, 4.5–11.5)‡	Median: 7.5 months (95 % CI, 5.0–13.3)‡	Median: 5.5 months (95 % CI, 4.8–7.2)
rwOS	Median: 13.9 months (95 % CI, 12.2–NR)	Not reported	Median: 13.4 months (95 % CI, 11.9–NR)

Abbreviations: CI = confidence interval; HER2 = human epidermal growth factor receptor 2; IQR = interquartile range; NR = not reached; PFS = progression-free survival; rwOS = real-world overall survival; rwPFS, real-world progression-free survival; rwTTNT = real-world time to next treatment; rwTTD = real-world time to treatment discontinuation; T-DXd = trastuzumab deruxtecan.

† Results are presented for the overall study population (N = 101) as specific results for the 86 patients who received the tucatinib, trastuzumab, and capecitabine combination following treatment with T-DXd were not reported. ‡Used as a proxy for PFS.

their total tumour volume is less than 15 mL (MCBS 2B) [12,36]. WBRT should be avoided as long as possible. WBRT should only be considered for patients with more than 10 brain metastases, not amenable to SRT, depending on the presence of neurological symptoms, size, number, and location of brain metastases as well as the choice and availability of CNS-active systemic therapy (MCBS 3B) [12,36].

The current systemic therapy should be continued in patients eligible for local therapy who have isolated progression of brain metastases without disease progression in other organs [12] (systemic therapy is usually interrupted briefly during irradiation [discussed in detail below]). However, patients with brain metastases as well as extracranial disease progression should usually be switched to the next line of systemic therapy [12]. Systemic therapy is recommended in patients with active brain metastases when local therapy is contraindicated [12].

The current ESMO guidelines note that the tucatinib, trastuzumab, and capecitabine combination is preferred for use earlier in the course of disease (second-line setting) for patients with brain metastases [12]. The tucatinib, trastuzumab, and capecitabine combination was the first regimen to demonstrate efficacy in patients with active brain metastases in the randomised HER2CLIMB trial (Table 3) [20,37,38]. In tucatinib, trastuzumab, and capecitabine-treated patients versus placebo-treated patients, median (95 % CI) OS was 21.4 (18.1–28.9) versus 11.8 (10.3–15.2) months in patients with active brain metastases (exploratory analysis) [38].

T-DXd also showed relevant efficacy in a small number of patients with active brain metastases in open-label, single-arm trials (Table 3) [39,40]. Based on these data, T-DXd is recommended for use in patients

Table 3
Efficacy of the tucatinib, trastuzumab, and capecitabine combination and T-DXd in patients with HER2-positive breast cancer and brain metastases.

	HER2CLIMB (NCT02614794) [20,37,38]	HER2CLIMB-02 (NCT03975647)[18]	DESTINY-Breast01 (NCT03248492) [78]	DESTINY-Breast02 (NCT03523585) [25]	DESTINY-Breast03 (NCT03529110) [79]	TUXEDO-1 (NCT04752059) [40]	DEBBRAH (NCT04420598) [39]	DESTINY-Breast12 (NCT04739761) [42]
Trial design	Phase 2, randomised, double-blind	Phase 3, randomised, double-blind	Phase 2, single-arm, open-label	Phase 3, randomised, open-label	Phase 3, randomised, open-label	Phase 2, single-arm, open-label	Phase 2, open-label, 5-cohort, non-comparative	Phase 3b/4, single-arm, open-label
Active treatment	Tucatinib + trastuzumab + capecitabine	Tucatinib + T-DM1	T-DXd	T-DXd	T-DXd	T-DXd	T-DXd	T-DXd
Comparator	Placebo + trastuzumab + capecitabine	Placebo + T-DM1	–	Physician's choice	T-DM1	–	–	–
BM inclusion criteria	Patients with baseline BM (including stable, progressing, or untreated BM not requiring local therapy)[†]	Patients with baseline BM (including stable, progressing, or untreated BM not requiring local therapy)[†]	Patients with baseline BM that were treated, asymptomatic and did not require therapy to control symptoms were eligible for enrolment. All treatment to control symptoms had to be completed ≥ 60 days before randomisation[†]	Patients with clinically inactive/ treated asymptomatic brain metastases[†,‡]	Patients with clinically inactive/ asymptomatic BM[†,§]	Patients with newly diagnosed BM or BM progressing after prior local therapy, measurable disease per RANO-BM criteria[‖]	Cohort 1: Patients with stable BM after local therapy Cohort 3: Patients with progressing BM after local therapy[‖]	BM cohort: Patients with baseline BM (including stable [previously treated] or active BM [untreated or previously treated and progressing])
Randomisation ratio	2:1	1:1	NA	2:1	1:1	NA	NA	NA
Overall patient population, N	*Tucatinib + trastuzumab + capecitabine* 410 *Placebo + trastuzumab + capecitabine* 202	*Tucatinib + T-DM1* 228 *Placebo + T-DM1* 235	184	*T-DXd* 406 *Physician's choice* 202	*T-DXd* 261 *T-DM1* 263	15	*All patients* 36[¶] *Cohort 1* 8 *Cohort 3* 9	504[#]
BM population, n	*Tucatinib + trastuzumab + capecitabine* *All BM* 198 *Stable BM* *80* *Active BM* 118 *Placebo + trastuzumab + capecitabine* *All BM* 93	*Tucatinib + T-DM1* *All BM* 99 *Stable BM* *49* *Active BM* 50 *Placebo + T-DM1* *All BM* 105 *Stable BM*	24	*T-DXd* 74 *Physician's choice* 36	*T-DXd* 43 *T-DM1* 39	15	17	*All patients* 263 *Stable BM* 157 *Active BM* 106

(*continued on next page*)

Table 3 (*continued*)

	HER2CLIMB (NCT02614794) [20,37,38]	HER2CLIMB-02 (NCT03975647)[18]	DESTINY-Breast01 (NCT03248492) [78]	DESTINY-Breast02 (NCT03523585) [25]	DESTINY-Breast03 (NCT03529110) [79]	TUXEDO-1 (NCT04752059) [40]	DEBBRAH (NCT04420598) [39]	DESTINY-Breast12 (NCT04739761) [42]
	Stable BM 37 *Active BM* 56	48 *Active BM* 57						
PFS (not CNS-specific) in patients with BM	Median, months (95 % CI) *All BM* 7.6 (6.2–9.5) vs 5.4 (4.1–5.7)[Δ] [20] *Stable BM* 7.5 (5.4–9.6) vs5.0 (2.0–5.6) *Active BM* 7.6 (5.7–8.5) vs 4.1 (3.1–4.3) [37]	Median, months (95 % CI) *All BM* 7.8 (6.7–10.0) vs 5.7(4.6–7.5)	Median, months (95 % CI) 18.1 (6.7–18.1)	Median, months (95 % CI) 13.9 (11.1–18.0) vs 5.6 (3.3–8.1)	Median, months (95 % CI) 15.0 (12.5–22.2) vs3.0 (2.8–5.8)	Median, months (95 % CI) 14 (11–not recorded)	16-week PFS, % (95 % CI) *Cohort 1* 87.5 (47.3–99.7) *Cohort 3* Not reported	12-month PFS, % (95 % CI) *All BM* (54.9–67.6) *Stable BM* 62.9 (54.0–70.5) *Active BM* (49.0–68.7)
OS in patients with BM	Median, months (95 % CI) *All BM* 21.6 (18.1–28.5) vs 12.5 (11.2–16.9) *Stable BM* 21.6 (15.3–42.4) vs 16.4 (10.6–21.6) *Active BM* 21.4 (18.1–28.9) vs 11.8(10.3–15.2) [38]	–	–	–	–	–	–	12-month OS, % (95 % CI) *All BM*90.3 (85.9–93.4) *Stable BM* 93.2 (87.7–96.3) *Active BM* 86.1 (77.6–91.5)
ORR (not CNS-specific) in patients with BM	–	–	% (95 % CI) 58.3 (36.6–77.9)	–	% (95 % CI) 67.4 (51.5–80.9) vs 20.5 (9.3–36.5)	–	% (95 % CI) *Cohort 1* 80.0	% (95 % CI) *All BM* 51.7

(*continued on next page*)

Table 3 (*continued*)

	HER2CLIMB (NCT02614794) [20,37,38]	HER2CLIMB-02 (NCT03975647)[18]	DESTINY-Breast01 (NCT03248492) [78]	DESTINY-Breast02 (NCT03523585) [25]	DESTINY-Breast03 (NCT03529110) [79]	TUXEDO-1 (NCT04752059) [40]	DEBBRAH (NCT04420598) [39]	DESTINY-Breast12 (NCT04739761) [42]
							(28.4–99.5) *Cohort 3* 66.7 (29.9–92.5)	(45.7–57.8) *Stable BM* 49.7 (41.9–57.5) *Active BM* 54.7 (45.2–64.2)
CNS-PFS in patients with BM	Median, months (95 % CI) *All BM* 9.9 (8.4–11.7) vs 4.2 (3.6–5.7) *Stable BM* 13.9 (9.7–24.9) vs 5.6 (3.0–NE) *Active BM* 9.6 (7.6–11.1) vs 4.0 (2.9–5.6) [38]	–	–	–	–	–	–	12-month CNS-PFS, % (95 % CI) *All BM* 58.9 (51.9–65.3) *Stable BM* 57.8 (48.2–66.1) *Active BM* 60.1 (49.2–69.4)
CNS ORR in patients with BM	% (95 % CI) *Active BM* 47.3 (33.7–61.2)vs 20.0 (5.7–43.7) [38]	–	% 50	–	% 65.7 vs 34.3	% (95 % CI) 78.6 (49.2–95.3)	% (95 % CI) *Cohort 1* Not reported *Cohort 3* 44.4 (13.7–78.8)	% (95 % CI) *All BM* 71.7 (64.2–79.3) *Stable BM* 79.2 (70.2–88.3) *Active BM* 62.3 (50.1–74.5)

Abbreviations: BM = brain metastases; CNS = central nervous system; NA = not applicable; NE = not estimable; NR = not reached; ORR = objective response rate; OS = overall survival; RANO = response assessment in neuro-oncology; PFS = progression-free survival.

† The study also included patients without BM. ‡The study initially allowed enrolment of patients with previously untreated and asymptomatic brain metastases; in a subsequent protocol amendment, inclusion of patients with active brain metastases was prohibited. §The study initially allowed enrolment of patients with previously locally untreated BMs; in a subsequent protocol amendment, prior local therapy for BM became mandatory. ‖The study specifically focussed on patients with BM; ¶Overall patient population, N = 36 (Cohort 1, N = 8; Cohort 2, N = 11; Cohort 3, N = 9; Cohort 4, N = 4; Cohort 5, N = 4). #Overall patient population, N = 504 (BM cohort, N = 263; Non-BM cohort, N = 241). ΔThe risk of disease progression or death was 52 % lower with tucatinib + trastuzumab + capecitabine versus placebo + trastuzumab + capecitabine (hazard ratio, 0.48; 95 % CI, 0.34–0.69). The difference between the two treatment groups was statistically significant ($p < 0.001$) [20].

Table 4
Recommendations for prospective studies to address evidence gaps across challenging clinical scenarios in HER2-positive metastatic breast cancer.

Challenging clinical scenario	Recommendations for prospective studies
Treatment of patients with brain metastases	• Combining and sequencing local and systemic therapy • Feasibility of avoiding local therapy by switching systemic therapy • Efficacyof tucatinib + trastuzumab + capecitabine vs T-DXd • Efficacy of T-DM1 following T-DXd • Efficacy of endocrine therapy in combination with novel agents, e.g., CDKis
Treatment of patients with LMD	• Sequencing local and systemic therapy • Role of intrathecal therapy (e.g., intrathecal trastuzumab; RCT)
Treatment of patients with oligometastatic disease	• Curative therapy in patients with *de novo* oligometastatic disease • Systemic therapy with local therapy vs systemic therapy without local therapy (RCT) • Continuation vs interruption of HER2-targeted therapy in patients with deep response to treatment (RCT) • De-escalating dose of HER2-targeted therapy in patients with deep response to treatment
Treatment of patients with CNS oligo-progressive disease	• Combining local and systemic therapy • Efficacy of local therapy plus continuation of ongoing systemic therapy vs local therapy plus switch of systemic therapy in the absence of extracranial progression (RCT) • Feasibility of avoiding local therapy by switching systemic therapy
Treatment of patients with HR-positive/HER2-positive disease	• Efficacy of endocrine-based therapies vs chemotherapy-based therapies, both combined with HER2-targeting therapy and administered upfront • Feasibility of switching to endocrine therapy combined with HER2-targeting agents following initial treatment with an ADC or chemotherapy • Efficacy of CDKis combined with endocrine and HER2-targeted therapy
Treatment of patients with *ERBB2*-mutant disease	• Efficacy of TKIs and ADCs (phase 2 studies)
Discontinuation and modification of anti-HER2 therapy in patients with long-term remission	• Preferred maintenance strategy • Feasibility of discontinuing/de-escalating dose of HER2-targeted therapy • Consider including patients with negative ctDNA samples • Potential addition of TKI agent to maintenance regimen for the prevention of brain metastases
Impact of stability of HER2 status over time	• Observational, international registry study to provide further insight into potential treatment approaches for patients with unstable HER2 expression • Central collection of tumour tissue should be encouraged

Abbreviations: ADC = antibody-drug conjugate; CDKi = cyclin-dependent kinase inhibitor; CNS = central nervous system; ctDNA = circulating tumour DNA; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; LMD = leptomeningeal disease; RCT = randomised controlled trial; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TKI = tyrosine kinase inhibitor.

with active brain metastases as well; treatment decisions may generally be based on both the CNS and extracranial disease burden [12,41]. In patients with predominant CNS disease, current guidance suggests that T-DXd use could follow disease progression on the tucatinib, trastuzumab, and capecitabine combination [12,41]. In contrast, use of T-DXd may be initially preferred in patients with predominantly extracranial disease, despite the presence of brain metastases [41]. The efficacy of T-DXd in patients with active brain metastases has recently been confirmed in a larger dataset from the non-randomised DESTINY-Breast12 trial; the 12-month OS rate was 86.1 % (95 % CI, 77.6–91.5) in patients with active brain metastases. The overall efficacy of T-DXd was similar in patients with active brain metastases compared with those without brain metastases in DESTINY-Breast12 [42]. Given these findings, T-DXd may become an additional standard of care for patients irrespective of the presence or absence of brain metastases in the second-line setting; however, the update of treatment guidelines is currently pending.

Treatment selection in HER2-positive metastatic breast cancer in real-world clinical practice

Challenging clinical scenarios

We conducted a survey among expert oncologists (12 from Europe and one from Canada) to guide clinicians in the management of challenging scenarios that they may encounter in clinical practice. Experts were selected based on their clinical experience in the treatment of HER2-positive metastatic breast cancer and their participation as investigators in clinical trials of HER2-directed therapies. The survey results were discussed at two roundtable meetings. Here we present a unanimous consensus and practical guidance on how to approach these scenarios.

While the patient groups described in the following sections typically represent a minority of the total population with HER2-positive metastatic breast cancer, their inclusion in clinical trials should be prioritised to generate further insight into how they should be treated optimally. We provide recommendations for prospective studies (Table 4) and other studies/analyses to address evidence gaps associated with each challenging scenario (Table 5). In addition, we highlight some potential factors to consider when designing studies in these specific patient groups (Table S1).

Treatment of patients with brain metastases

In a recent prospective cohort study of 147 patients with HER2-positive or triple-negative metastatic breast cancer, approximately 20 % had asymptomatic brain metastases [43]. In addition, median OS appeared to be greater among patients whose brain metastases were identified by surveillance rather than symptomatic detection (23.7 months vs 8.1 months; hazard ratio, 0.41; 95 % CI, 0.17–0.95; p = 0.04) [43]. While these results require further prospective investigation, they suggest that routinely screening patients for brain metastases may be beneficial, potentially contributing to improved therapeutic outcomes among patients with HER2-positive breast cancer. Indeed, the consensus among Italian and Spanish experts in 2024 was that asymptomatic screening for brain metastases should be undertaken to increase the likelihood of detecting brain metastases early in the course of disease [34].

Recent data on T-DXd provide additional evidence that the status of brain metastases (stable vs active) may be less relevant when selecting treatment than clinicians previously thought. In a pooled analysis of the DESTINY-Breast01, DESTINY-Breast02, and DESTINY-Breast03 trials, the intracranial objective response rate (ORR) of T-DXd was comparable between patients with treated or stable brain metastases (45.2 %) and those with untreated or active brain metastases (45.5 %) [44]. Moreover, in the primary analysis of the non-randomised phase 3b/4 DESTINY-Breast12 trial, T-DXd demonstrated overall and intracranial

Table 5
Recommendations for other studies/analyses to address evidence gaps across challenging clinical scenarios in HER2-positive metastatic breast cancer.

Challenging clinical scenario	Recommendations for other studies/analyses
Treatment of patients with brain metastases	• Potential synergy between systemic therapy and radiotherapy • Role of systemic therapy in patients with symptomatic brain metastases • Time to response and improvement in symptoms in patients with brain metastases • Rate of radionecrosis in pivotal trials of patients with brain metastases (e.g., DESTINY-Breast12, HER2CLIMB)
Treatment of patients with LMD	• Omics-based study of large cohort of patients with LMD from both primary and metastatic tumours to identify those at high risk of developing LMD • Role of ctDNA in CSF for diagnosis and guiding treatment strategies in patients with LMD
Treatment of patients with oligometastatic disease	• Duration of systemic therapy in patients with complete remission • Optimal timing of locoregional therapy
Treatment of patients with CNS oligo-progressive disease	• Longitudinal assessments of ctDNA in serum (potentially also CSF) to identify patients at high risk for disease progression
Treatment of elderly patients	• Role of comprehensive geriatric assessment in guiding treatment strategies • Potential differences in tumour biology, clinical behaviour, or response to treatment in elderly patients
Treatment of patients with HR-positive/HER2-positive disease	• Translational studies to identify predictive biomarkers (e.g., PAM50)
Treatment of patients with *ERBB2*-mutant disease	• Rate of *ERBB2* mutations, including in patients with brain metastases • Role of different *ERBB2* mutations in patients with or without HER2 amplification
Impact of stability of HER2 status over time	• Relevance of low HER2 expression over time • Activity of T-DXd in HER2 − disease • Correlation of HER2 expression with response to treatment • Perform subsequent biopsy upon disease progression to confirm whether HER2 positivity has been retained or lost

Abbreviations: ADC = antibody-drug conjugate; CNS = central nervous system; CSF = cerebrospinal fluid; ctDNA = circulating tumour DNA; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; LMD = leptomeningeal disease; PAM50 = Prediction Analysis of Microarray 50; T-DXd = trastuzumab deruxtecan; TKI = tyrosine kinase inhibitor.

clinical activity in patients with stable or active brain metastases. The 12-month PFS rate was 61.6 % (95 % CI, 54.9–67.6) in the overall brain metastases cohort, 62.9 % (95 % CI, 54.0–70.5) in patients with stable brain metastases, and 59.6 % (95 % CI, 49.0–68.7) in those with active brain metastases (Table 3) [42]. The intracranial ORR was 71.7 % (95 % CI, 64.2–79.3), 79.2 % (95 % CI, 70.2–88.3), and 62.3 % (95 % CI, 50.1–74.5) in the overall brain metastases cohort, patients with stable brain metastases, and patients with active brain metastases, respectively (Table 3) [42].

With these data on T-DXd, there are now two available systemic regimens that show relevant activity in patients with brain metastases. In clinical practice, the DESTINY-Breast12 data suggest that T-DXd may be used when indicated, regardless of the presence or absence of brain metastases. In addition to data from HER2CLIMB (discussed earlier), descriptive results from the primary analysis of HER2CLIMB-02 also suggest potential clinical benefit of combining tucatinib with.

T-DM1in the second-line setting for patients with brain metastases. Median PFS was 7.8 months (95 % CI, 6.7–10.0) with tucatinib and T-DM1 versus 5.7 months (95 % CI, 4.6–7.5) with placebo and T-DM1 (hazard ratio, 0.64; 95 % CI, 0.46–0.89; Table 3) [18].

Presently, there is no consensus concerning the optimal timing of administering combinations of radiotherapy and systemic therapy in breast cancer. However, recent evidence from a *meta*-analysis [45] as well as a retrospective cohort study [46] suggest that combining ADCs with intracranial radiation (stereotactic radiosurgery or SRT) may be associated with an increased risk of radionecrosis. While these findings warrant further investigation prospectively, they suggest that clinicians should exercise caution if they are considering treating patients with a combination of radiotherapy and an ADC.

In clinical practice currently, we usually do not administer local and systemic treatments simultaneously, with patients typically initiating systemic therapy following the completion of local therapy. For patients who experience progression of isolated brain metastases in the absence of extracranial progression, systemic therapy would usually be briefly interrupted, with the same agent being resumed following the completion of local therapy. However, some clinicians may consider changing systemic therapy to an agent with CNS activity in cases where CNS progression has occurred more than once, even when extracranial disease is controlled, given that the tucatinib, trastuzumab, and capecitabine combination and T-DXd have demonstrated efficacy in patients with both stable and active brain metastases [38,42,44]. This may be particularly relevant in cases where a significant volume of CNS metastases has developed. Some clinicians may also choose to delay radiotherapy by switching systemic therapy. In addition, some clinicians may maintain HER2-directed treatments during local therapy if they appear to control a relevant part of the disease.

Treatment of patients with LMD

The prognosis of patients with HER2-positive breast cancer and LMD is poorer than in those with active brain metastases. In retrospective analyses, estimates of OS have been reported to range from 4.4–20.0 months in patients with LMD [47,48] compared with approximately 24 months in those with brain metastases (without LMD) [49].

In the latest European Association of Neuro-Oncology (EANO)-ESMO guidelines concerning the management of LMD, current treatments recommended for patients with LMD include systemic pharmacotherapy (chemotherapy and targeted therapy), intrathecal pharmacotherapy, and radiotherapy [50]. Methotrexate, cytarabine, and thiotepa are commonly used intrathecal chemotherapeutic agents [50]. Some clinicians may administer intrathecal trastuzumab as monotherapy [51], or in combination with intrathecal chemotherapy in clinical practice. Radiotherapy typically comprises SRT, with craniospinal radiotherapy and WBRT being used in selected patients [50].

Based on our clinical experience, we believe that systemic pharmacotherapy would generally be preferred for patients with HER2-positive disease and LMD. The tucatinib, trastuzumab, and capecitabine combination has been included as a potential treatment option in the latest EANO-ESMO guidelines [50]. In the phase 2 TBCRC049 study, this combination was associated with a median OS of 11.9 months (95 % CI, 4.1–NR) in 17 patients with LMD [52]; ORR (per Response Assessment in Neuro-Oncology-leptomeningeal metastases criteria) was 38 % in 13 response-eligible patients [53].

Recent data suggest T-DXd could also have a role in the treatment of patients with LMD. In the phase 2 DEBBRAH study, median OS with T-DXdwas 13.3 months (95 % CI, 2.5–not reached [NR]) in 7 patients with HER2-positive or HER2-low breast cancer and LMD [54]. Moreover, in a Japanese retrospective medical chart review, median OS was not reached with T-DXd at a median follow-up of 12 months in 19 patients with HER2-positive breast cancer and LMD, 17 of whom had concomitant active brain metastases [55]. We believe systemic

pharmacotherapy should usually be administered to this patient subgroup indefinitely, or until patients choose to pursue best supportive care.

Treatment of patients with oligometastatic disease

Some clinicians may perform surgery with or without 'adjuvant' radiotherapy for selected patients with oligometastatic disease. Typically, surgery is considered in those with isolated sites of disease progression in the breast and/or axilla, where complete resection is feasible. Given the current lack of consensus and of established treatment protocols, other clinicians may prefer to use high-dose palliative or even high-dose radical radiotherapy for local disease and stereotactic radiosurgery with ablative doses or targeted ablation with microwave, radiofrequency, or cryotherapy to the oligometastatic disease. We believe the decision to administer local therapy should be made on a case-by-case basis, with local therapy only being considered in patients who otherwise maintain a good response to systemic therapy for at least 3–6 months. Prior to undergoing treatment, patients should be made aware that any OS benefit associated with local therapy is currently unknown. The prospective CHLOE study, which is currently underway in *de novo* oligometastatic HER2-positive breast cancer, is investigating the sequential effect of systemic therapy, primary tumour surgical resection, ablative radiation to known metastatic lesions, and additional systemic therapy [56].

Treatment of patients with CNS oligo-progressive disease

While some clinicians would prefer to treat patients with CNS oligo-progressive disease with a combination of systemic and local therapy, others would prefer to administer local therapy alone. Patients with stable extracranial disease should normally maintain their current systemic therapy and receive local therapy for CNS oligo-progressive lesions. However, following a second or third intracranial progression on trastuzumab-pertuzumab, clinicians could potentially consider switching patients to the tucatinib, trastuzumab, and capecitabine regimen or to T-DXd, particularly those who have a significant volume of disease. Clinicians may choose to start systemic therapy if their patient is not receiving ongoing systemic treatment at the appearance of their CNS oligo-progressive lesions. In the absence of supporting data, clinicians could potentially consider starting first-line systemic treatment when the CNS is the first site of relapse following treatment in the adjuvant setting. This may be particularly important in countries where access to funding for drugs with CNS activity requires prior treatment.

Treatment of elderly patients

Clinicians must tailor treatment to individual patients according to their Eastern Cooperative Oncology Group performance status, comorbidities, and personal preference as age alone should not be the driver of treatment choice. Clinicians use tools such as the G-8 score [57] and the Clinical Frailty Score [58] to assess the frailty level of elderly patients and inform their subsequent treatment decisions.

Optimal treatment strategies should balance disease control and toxicity. Therapies associated with better tolerability should be considered in more frail patients. In the first-line setting, we prefer endocrine therapy combined with trastuzumab, or trastuzumab and pertuzumab for patients with HR-positive disease.

Potentially, vinorelbine could be used instead of a taxane in the first-line setting. The phase 3 HERNATA study demonstrated that while there was no significant difference in median OS between a combination of trastuzumab plus docetaxel (35.7 months) or trastuzumab plus vinorelbine (38.8 months) in the first-line treatment of patients with HER2-positive advanced breast cancer, the vinorelbine combination was associated with significantly fewer treatment-related grade 3 or 4 adverse events than the docetaxel combination [59]. Vinorelbine was also investigated in combination with trastuzumab and pertuzumab in the first-line setting, in the phase 2 VELVET study [60,61]. The sequential administration of single-agent pertuzumab, trastuzumab, and vinorelbine was associated with an ORR of 74.2 % (95 % CI, 63.8–82.9), while co-administered pertuzumab and trastuzumab followed by vinorelbine led to an ORR of 63.7 % (95 % CI, 53.0–73.6) in patients with HER2-positive locally advanced or metastatic breast cancer [60,61]. Neither treatment regimen was associated with any unexpected safety signals [60,61]. Eribulin may also have the potential to provide a less toxic alternative to taxane-based combinations in the first-line setting in the future. In the phase 3 EMERALD trial of patients with locally advanced or metastatic HER2-positive breast cancer, median PFS was 14.0 months with eribulin combined with trastuzumab and pertuzumab versus 12.9 months with docetaxel/paclitaxel combined with trastuzumab and pertuzumab [62]. Adverse drug reactions were numerically lower with the eribulin-based regimen than the taxane-based regimen [62].

The addition of metronomic chemotherapy to the trastuzumab plus pertuzumab combination could potentially delay or replace use of taxanes in the first-line setting, in elderly patients [63]. In a phase 2 trial which enrolled patients aged $\geq$ 70 years or $\geq$ 60 years with confirmed functional restrictions, metronomic chemotherapy (oral cyclophosphamide) combined with trastuzumab plus pertuzumab was associated with prolonged median PFS (12.7 months [95 % CI, 6.7–24.8]) compared with trastuzumab plus pertuzumab alone (5.6 months [95 % CI, 3.6–16.8]) [63].

Some clinicians may prefer to administer T-DM1 rather than T-DXd to elderly patients, in the second-line setting. However, no new safety signals associated with T-DXd were observed in a recent retrospective analysis of 27 patients with advanced breast cancer with a median age of 74 years. These results, therefore, suggest increased age should not necessarily influence the decision of whether to administer T-DXd [64].

Treatments should be initiated at a lower dose in patients who are frail or who have comorbidities than in those with a better performance status. For example, we may initiate T-DXd at 4.4 mg/kg and then reduce the dose to 3.2 mg/kg in this patient subgroup during treatment. Moreover, while tucatinib appears to be well tolerated in this patient subgroup, the dose of capecitabine may need to be reduced (e.g., from a starting dose of 1000 mg/m^2 twice daily to 750 mg/m^2 twice daily) if gastrointestinal or cutaneous toxicities appear. Clinicians could also consider preplanned treatment holidays to improve toxicity in frail patients.

Treatment of patients with HR-positive/HER2-positive disease

Based on the PERTAIN study [65], we would consider administering endocrine therapy combined with trastuzumab plus pertuzumab as maintenance therapy to patients with HR-positive/HER2-positive disease following the completion of induction therapy (taxane-based chemotherapy combined with trastuzumab plus pertuzumab) in the first-line setting. Clinicians may consider starting with endocrine therapy combined with trastuzumab plus pertuzumab upfront in patients whose performance status declines or are unsuitable for chemotherapy, but this decision should be made on a case-by-case basis. However, it is important to note that this combination is not currently approved. We would not combine endocrine therapy with an ADC or the tucatinib, trastuzumab, and capecitabine combination regimen in the second- or third-line setting in the absence of evidence suggesting this would improve treatment efficacy, but may consider combining endocrine therapy with trastuzumab or lapatinib in later lines of therapy.

Treatment of patients with ERBB2-mutant disease

The overall frequency of *ERBB2* mutations in breast cancer is low; in a systematic literature review involving 12,905 patients with breast cancer, *ERBB2* mutations were identified in 2.7 % of patients [66]. It has been reported that *ERBB2* mutations are more common in patients with HER2-low or HER2-negative breast cancer than HER2-amplified disease (occurring mainly in patients with HR-positive/HER2-negative disease) [67,68], as well as in those with invasive lobular carcinoma rather than invasive ductal carcinoma [69,70]. The majority (~90 %) of *ERBB2*

mutations affect exons 19–20, which code for the tyrosine kinase domain, with the remaining mutations predominantly affecting exon 8, which codes for the extracellular domain [67].

As patients with breast cancer do not routinely undergo next-generation sequencing, the detection of *ERBB2* mutations is often missed. In the absence of an approved indication, clinicians currently do not have access to specific treatments for patients with *ERBB2*-mutant disease outside of a clinical trial.

In those cases where an *ERBB2* mutation has been identified, we may consider administering a TKI-containing regimen. Recent evidence suggests neratinib could potentially be considered in patients who do not have any other valid treatment options in the second-line setting and beyond, or in those who have not responded to other treatment. In the phase 2 multi-tumour SUMMIT trial, the addition of neratinib to fulvestrant and trastuzumab was associated with an ORR of 39 % (95 % CI, 26–52 %) and median PFS of 8.3 months (95 % CI, 6.0–15.1 months) in 57 patients with HR-positive/HER2-negative metastatic breast cancer with activating *ERBB2* mutations who had received prior cyclin-dependent kinase 4/6 inhibitor therapy [71]. Moreover, an ORR of 24 % (95 % CI, 7–50) with neratinib plus fulvestrant was observed in 17 patients with HR-positive/HER2-negative breast cancer who had received at least one line of therapy for advanced breast cancer, or who had relapsed within 12 months of neoadjuvant or adjuvant chemotherapy in the phase 2a plasmaMATCH trial [72]. In addition, in the open-label, phase 2 basket SGNTUC-019 (NCT04579380) trial, tucatinib combined with trastuzumab (plus fulvestrant in HR-positive disease) was associated with a confirmed ORR of 42 % (90 % CI, 27–58 %) and median PFS of 9.5 months (90 % CI, 5.4–13.8 months) in 31 patients with *ERBB2*-mutant metastatic breast cancer [73].

While there is currently limited evidence to support the use of an ADC in patients with *ERBB2*-mutant metastatic breast cancer, T-DXd demonstrated clinically meaningful improvements in terms of ORR (49.0 % [95 % CI, 39.0–59.1] with 5.4 mg/kg every 3 weeks [Q3W] and 56.0 % [95 % CI, 41.3–70.0] with 6.4 mg/kg Q3W) and median OS (19.5 months [95 % CI, 13.6–not estimable {NE}] with 5.4 mg/kg Q3W and NE [95 % CI, 12.1–NE] with 6.4 mg/kg Q3W) in 152 patients (5.4 mg/kg Q3W, n = 102; 6.4 mg/kg Q3W, n = 50) with *ERBB2*-mutant non-small-cell lung cancer in the phase 2 DESTINY-Lung02 trial [74]. The activity of T-DXd was also reported across multiple solid tumour types harbouring *ERBB2*-activating mutations in the phase 2 DESTINY-PanTumor01 trial. An ORR of 50 % was observed in the 20 patients with breast cancer, suggesting that further evaluation may be warranted [75].

Discontinuation and modification of anti-HER2 therapy in patients with long-term remission

There are currently no data from randomised controlled clinical trials concerning how long HER2-targeted therapy should be administered for in patients with prolonged responses. Therefore, we would recommend that treatment be continued indefinitely, especially in those without complete response to therapy, provided they agree, until the development of progressive disease or unacceptable toxicity. In a recent retrospective analysis, similar 5-year (90.5 % [95 % CI, 80.8–100]) and 10-year OS rates (87 % [95 % CI, 75.9–99.8]) were reported in 33 patients with HER2-positive metastatic breast cancer who had no evidence of disease following treatment with pertuzumab and/or trastuzumab for at least 5 years. These results support the notion that after 5 years, clinicians could potentially consider discontinuing treatment in patients with a complete response to therapy on a case-by-case basis if this is something the patient desires. The STOP-HER2 (NCT05721248)study, which is currently recruiting, will investigate the discontinuation of first-line HER2-targeted therapy in exceptional responders after at least 3 years of treatment [76].

We would normally only consider reducing the dose of therapy in patients who experience unacceptable toxicity (e.g., interstitial lung disease associated with T-DXd). Clinical trials investigating whether the dose of HER2-targeted therapy can be de-escalated in patients with a good response would, therefore, likely be useful. We would potentially consider switching patients to trastuzumab if they have been in remission for at least 2 years, or when the occurrence of treatment-related side effects increases.

Impact of stability of HER2 status over time

The decision concerning whether to continue HER2-targeted therapy in patients who lose HER2 positivity over time varies among clinicians and should be considered on a case-by-case basis.

Evaluating HER2 status at metastatic sites should increase the likelihood of patients receiving suitable treatment based on their latest disease profile [34]. Many clinicians would treat the patient according to their most recent biopsy in cases where there is a lack of concordance between the primary and metastatic biopsies. Some clinicians may stop HER2-targeted treatment among patients who have been receiving HER2-targeted therapy based on having a HER2-positive primary tumour if their biopsy was HER2-negative at the onset of metastases. We believe that in patients who previously stopped receiving HER2-targeted therapy, a subsequent biopsy should be performed at the time of next progression due to tumour heterogeneity and clonal dynamics. This would enable clinicians to confirm the latest status of HER2 expression (i.e., determine whether the relevant metastatic site has remained HER2-negative or become HER2-positive again) to guide systemic therapy recommendations.

Other clinicians may continue HER2-targeted treatment in patients who have lost HER2 over-expression or amplification over time. Trastuzumab may be continued as maintenance therapy in patients who have lost HER2 positivity. In addition, among patients with *de novo* metastatic breast cancer with a HER2-positive primary tumour biopsy and HER2-negative metastatic biopsy, HER2-targeted therapy may be continued in patients whose primary tumour was not resected.

Conclusions

Current recommendations exist across Europe and in Canada for sequencing treatments, by line of therapy as well as by brain metastases status [12] in patients with HER2-positive breast cancer. While there is a lack of clarity on the preferred choice of therapy in the third-line treatment setting and beyond, recent real-world evidence has demonstrated potential effectiveness of tucatinib, trastuzumab, and capecitabine post T-DXd [32,33,77], which should be confirmed prospectively. In the absence of guideline recommendations or specific randomised trials, we have provided practical guidance, based on our clinical experience, to address challenging scenarios that may be faced by clinicians in a real-world setting. However, some of the presented treatment options may represent off-label use; thus, clinicians are advised to check the given treatment options against their local regulations.

Owing to a lack of supporting data, clinical trials generating further evidence on the optimal therapeutic strategies, with a particular focus on the individualisation of treatment lines based upon disease volume, sites of disease and patient preference, when to administer systemic therapy to patients with CNS-only disease, and on the treatment of patients with LMD would likely be useful. Further insight into the impact of treatment sequencing on patient quality of life and long-term therapeutic outcomes is also likely to be useful to clinicians working in the field of HER2-positive metastatic breast cancer.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Rupert Bartsch** reports advisory roles at AstraZeneca, Daiichi Sankyo, Eisai, Eli Lilly, Grünenthal, MSD, Novartis, Pfizer, Pierre Fabre, Roche and Seagen; lecture honoraria from AstraZeneca, Daiichi Sankyo, Eisai, Eli Lilly, Grünenthal, MSD, Novartis, Pfizer, Pierre Fabre, Roche, and

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Appendix A. Supplementary data

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