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Current indications and future perspectives for antibody-drug conjugates in brain metastases of breast cancer

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ABSTRACT

Breast cancer is one of the main cause of cerebral and leptomeningeal metastases, the prognosis of which remains poor to this day. Most studies excluded patients with active brain metastases (BM) and particularly with leptomeningeal metastases (LM) explaining the lack of therapeutic innovation in this area. Currently, the standard management of patients with BM of breast cancer is based on the combination of surgery, radiotherapy and systemic treatments. Recently, third-generation of Antibody-Drug Conjugates (ADCs), have revolutionized the management of metastatic breast cancer. Trastuzumab deruxtecan and Sacituzumab govitecan have indeed shown significant improvements of survival outcomes and can now be used in a wide range of breast cancer subtypes. However, few data are available on the efficacy of third-generation ADCs on BM and LM of breast cancer. As the field of ADCs is rapidly evolving, with new constructs entering the late clinical development, in this review we describe the efficacy of approved and novel promising conjugates on patients with BM and LM of breast cancer.

Introduction

Brain metastases (BM) frequently occur in patients with advanced solid tumors, leading to significant morbidity and mortality. Although the incidence of BM varies across tumor histologies, it is estimated that 10 to 25% of patients with metastatic cancer will develop BM during the course of their disease [1–3]. Among these tumors, breast cancer (BC) ranks as the second most common cause of BM, following lung cancer. Autopsy studies, considering both symptomatic and asymptomatic lesions, estimate the incidence of BM in BC to be around 20 to 30% [4,5]. Among metastatic breast cancers (mBC), HER2 positive and triple-negative subtypes are associated with a higher risk of BM (about 30% for each) than luminal subtype (15%) [5].Typically, BM is a late event in the disease course. The median time between the diagnosis of mBC and the onset of BM is approximately 53 months for luminal subtype, 34 months for HER2-positive subtype, and 25 months for triple-negative breast cancer (TNBC) [6]. With the availability of more effective systemic therapies for breast cancer, patients are living longer, resulting in a steady increase in the incidence of BM [7]. Despite therapeutic advancements, patients with BM from BC continue to have a poor prognosis. The median survival varies depending on tumor subtypes, ranging from 7 to 9 months for hormone-receptor positive (HR+)/HER2-negative BC, 16 to 19 months for HR+/HER2-positive BC, 11 to 13 months for hormone-receptor negative (HR-)/HER2-positive BC, and less than 5 months for TNBC [8–10].

This poor prognosis is partly attributed to the presence of the blood–brain barrier (BBB), which acts as a protective shield for brain tissue, making it difficult for conventional chemotherapy to penetrate. It has long been believed that large molecules have limited ability to cross the BBB due to its physiological and electrical properties. The BBB, along with the blood-cerebrospinal fluid barrier, plays a crucial role in maintaining brain homeostasis and microenvironment equilibrium through various mechanisms [11]. These mechanisms include specific characteristics of brain endothelial cells (such as the absence of intracellular fenestrations, presence of tight junctions, and limited pinocytosis activity), differences in protein composition compared to the peripheral circulation resulting in electrical resistance, and the presence of drug efflux transporters (e.g., P-glycoprotein) that restrict the entry of certain molecules, including chemotherapies, into the brain [12–14]. However, some studies have suggested that at the site of metastatic disease, the BBB may be compromised and transformed into a blood-tumor barrier (BTB) [15]. In addition, mBC is a heterogeneous

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Table 1
Efficacy of ADC in patients with HER2+/HER2-low metastatic breast cancer and brain metastases across.

Author Date	Trial name Phase	ADC	Main inclusion criteria	Number of patient with BM	Outcome in patients with BM	Response criteria
HER2						
Krop et al. 2015	EMILIA Phase III	T-DM1	-HER2 + advanced breast cancer -Previously treated with trastuzumab -HR positive or negative -Treated, asymptomatic CNS metastases	45	mOS: 26.8 months (HR 0.38; 95%CI 0.18—–0.79; p = 0.0081) mPFS: 5.9 months) (HR 1.00; 95%CI 0.54–1.84; p = 1.000)	RECIST v1.0
Krop et al. 2017	TH3RESA Phase III	T-DM1	-HER2 + advanced breast cancer −2 or more HER2-directed regimens in the advanced setting -CNS metastasis had to be treated and not symptomatic -HR positive or negative	40	mPFS 5.8 months (HR 0.47, 95%CI; 0.24–0.89)	RECIST v1.1
Montemurro et al. 2020	KAMILLA Phase IIIb	T-DM1	-HER2 + locally advanced/metastatic breast cancer -Prior HER2-targeted therapy and chemotherapy - Untreated, asymptomatic BM or controlled brain disease -HR positive or negative	398 126 with measurable lesions	IC-ORR 21.4% IC-CR 2.4% mPFS 5.5 months (95%CI 5.3–5.6) mOS 18.9 months (95%CI 17.1–21.3)	RECIST v1.1
Jacobson et al. 2022	DESTINY-BREAST03 Phase III	T-DM1	- HER2-overexpressed metastatic breast cancer -Previously treated with trastuzumab and a taxane -BM eligible if clinically stable, previously treated brain metastases -HR positive or negative	39	IC-ORR 33.3% IC-CR 2.8% mPFS 3.0 months (HR 0.25, 95%CI 0.13–0.45)	RECIST v1.1
Bartsch et al. 2015	- Retrospective	T-DM1	-HER2 + invasive breast cancer -Newly diagnosed or progressive BM -HR positive or negative	10 (8 active BM)	IC-ORR 70% IC-PR 30% IC-PFS 5 months (95%CI 3.69–6.32) OS NR	RANO-BM
Jacot et al. 2016	- Retrospective	TDM-1	-HER2 + invasive breast cancer -BM -HR positive or negative	39 36 with previous local therapy	mPFS 6.1 months (95%CI 5.2–18.3) mOS NR	RECIST v1.1
Jerusalem et al. 2020	DESTINY-BREAST01 Phase II	T-DXd	- HER2+, unresectable or metastatic breast cancer -Had received previous treatment with T-DM1 -HR positive or negative -CNS metastases had to be treated and asymptomatic	24	IC-ORR 41.2% mPFS 18.1 months (95%CI 6.7–18.1)	RECIST, version 1.1
–	DESTINY-BREAST02 Phase III	T-DXd	-HER2 unresectable and/or metastatic breast cancer - previously treated with TDM-1 - HR positive or negative - Brain metastases had to be clinically inactive and/or treated.	74	mPFS 13.9 months (HR 0.35, 95%CI 0.20–0.61)	RECIST v1.1
Jacobson et al. 2022	DESTINY-BREAST03 Phase III	T-DXd	- HER2-overexpressed metastatic breast cancer -Previously treated with trastuzumab and a taxane -BM eligible if clinically stable, previously treated brain metastases -HR positive or negative	43	IC-ORR 63.9% IC-CR 27.8% mPFS 15.0 months (HR 0.25, 95%CI 0.13–0.45)	RECIST v1.1
Modi et al. 2022	DESTINY-BREAST04 Phase III	T-DXd	-HER2-low metastatic breast cancer -Had received one or two previous lines of chemotherapy -HR positive or negative -CNS metastases had to be treated and not symptomatic	24	mPFS 8.1 months (HR 0.71, 95%CI 0.28–1.8)	RECIST v 1.1
Diéras, et al. 2022 Epaillard, et al. 2022	DAISY Phase II	T-DXd	-Advanced breast cancer -Clinically inactive BM *cohort 1: HER2+ *cohort 2: HER2-low -HR positive or negative	*cohort 1: 12 *cohort 2: 10	*cohort 1: mPFS 13 months (95% CI 7.1-NR) *cohort 2: mPFS 4.1 months (95% CI 2.3–11.7)	RECIST v1.1
Kabraji et al. 2022	- Retrospective	T-DXd	-Metastatic breast cancer - known stable or active/ progressive brain metastases -HR positive or negative	17	IC-ORR 73.3% mIC PFS NR	RANO-BM

ADC: Antibody-Drug Conjugate, Bm: Brain Metastases, TDM-1: trastuzumab-emtansine; HER2+: HER2-overexpressed, HR: hormone receptor, CNS: central nervous system, mOS: median overall survival, mPFS: median progression free survival, IC-ORR: intracranial overall response rate, IC-CR: intracranial complete response, IC-

PR: intracranial partial response, IC-PFS: intracranial progression free survival, NR: not reached, T-DXd: Trastuzumab deruxtecan, CI: confidence interval, mIC PFS: median intracranial progression free survival.

disease, with behavior that can differ from the primary cancer due to genetic and immunohistochemical changes occurring during the process of metastatic invasion. These modifications can also influence the risk of developing BM [19–21]. Previous studies have also indicated that the tumor microenvironment of BM in mBC, particularly the immune microenvironment, is associated with patients' prognosis and may vary across triple-negative, HER2-positive, and luminal breast cancer subtypes [16].

These resistance mechanisms and the poor prognosis of BC patients with BM partly explain why, historically, most clinical trials assessing the effectiveness of standard chemotherapies have excluded patients with symptomatic or active brain metastases. However, efforts have been made to develop novel techniques capable of overcoming these challenges, including strategies to penetrate the blood–brain barrier (BBB) and utilize nanoparticles that are not eliminated by efflux systems. One approach involves the direct administration of certain chemotherapies into the cerebrospinal fluid through procedures such as lumbar punctures or Ommaya reservoirs. However, these techniques often have limited effectiveness, are technically demanding to implement (requiring repeated lumbar punctures or surgical procedures), and carry a significant risk of complications, including mechanical obstructions (25%), meningeal infections (ranging from 5.5% to 8%), or hemorrhages [17].

Nowadays, the standard management of patients with BM from solid cancers is based on a multidisciplinary approach that may combine surgery, radiotherapy (stereotactic radiosurgery or whole brain radiation) and systemic treatments depending on the primary site [9,18]. In recent years, several small molecules with the ability to passively penetrate the BBB have emerged in clinical development [19] as has the combination of neratinib with capecitabine [20]. Additionally, among the cyclin-dependent kinase inhibitors, abemaciclib has shown promising results in patients with hormone-positive, HER2-negative metastatic breast cancer (mBC). It exhibited an intracranial clinical benefit rate of 24% and achieved a volumetric reduction of brain metastatic target lesions by $\geq$ 20% [21].

Furthermore, among the emerging therapeutic classes, antibody-drug conjugates (ADC) have emerged as a highly promising strategy in the treatment of various solid tumors, including BC. Owing their complex activity across tumors with heterogeneous target expression, a wealth of study investigated their efficacy on brain metastases. While previous research on monoclonal antibodies and their derivatives in glioblastoma has yielded mixed results, the newer generation ADC, which employ more potent payloads, offer improved prospects for penetrating the blood–brain barrier (BBB) [22,23]. Studies conducted in breast cancer have demonstrated that despite their relatively large size, ADC molecules are capable of reaching brain metastases and delivering substantial doses of cytotoxic payloads.

In this review, we provide a comprehensive summary of the most notable preclinical and clinical evidence pertaining to the efficacy of ADC in BM from BC. Additionally, we discuss ongoing studies that are investigating novel ADC and combinations of ADC with other therapeutic approaches in this specific context.

Activity of ADC on brain metastases of breast cancer: Preclinical data

Some ADC have demonstrated promising results in the treatment of BM, as observed in preclinical models. For instance, Askoxylakis et al. conducted a study where female nude mice with brain metastases were treated with Ado-trastuzumab-emtansine (T-DM1) or Trastuzumab [24]. T-DM1 exhibited superior outcomes compared to Trastuzumab, with prolonged cerebral progression-free survival (60daysversus10days) and overall survival (112daysversus28days). Another anti-HER2 antibody-tubulysin conjugate, bHER2-ATC, was tested in a preclinical murine model of brain metastasis, resulting in a substantial decrease in the size of large BM (70 to 85%) and micrometastases (53 to 92%) [25]. Furthermore, Trastuzumab Deruxtecan (T-DXd) has also demonstrated efficacy in the treatment of brain metastases of breast cancer in a patient-derived xenografts model. In a recently published trial, the authors evaluated the activity of T-DXd at the dose of 10 mg/kg every 3 weeks in 2 PDX-models of HER2 + BC brain metastases, with either positive or negative ER, in a HER-2-low BC brain metastases PDX model and in a T-DM1 resistant HER2 + BC brain metastases PDX. T-DXd substantially reduced tumor size and prolonged the animal survival in both HER2 + PDX models, as compared to vehicle control (OS 77.5 days vs. 155.5 days, $p = 0.0067$ and 67 days vs. 154 days, $p = 0.0018$, in the ER-pos and ER-neg respectively), showing a prevalent cytotoxic effect on the brain metastases. Similar activity was observed in the HER2-low PDX and in the T-DM1 resistant model [26].

Leveraging these promising preclinical results, several clinical trials have explored the efficacy of ADC in patients with brain and/or leptomeningeal metastasis from different subtypes of breast cancer.

Clinical activity of currently approved ADC on brain metastases of breast cancer

Targeting HER2

Table 1 provides an overview of clinical trials involving patients with HER2+/HER2-low mBC treated with ADC. Given that up to 50% of patients with HER2-overexpressed (HER2+) metastatic breast cancer can develop BM over the whole disease course, a number of prospective and retrospective studies investigated the activity of T-DM1, the first ADC approved in BC, on central nervous system (CNS) lesions [27]. T-DM1 is composed of Trastuzumab and DM1, a cytotoxic anti-microtubule agent, linked through a thioether uncleavable linker [28].

The pivotal EMILIA trial [29,30] compared T-DM1 to lapatinib plus capecitabine in 991 patients with HER2 + BC previously treated with trastuzumab and taxanes. Thanks to the substantial improvement of median PFS (9.6 vs 6.4 months; HR 0.65, 95%CI 0.55–0.77; $p < 0.001$) and median OS (29.9 vs 25.9 months; HR 0.75, 95%CI 0.64–0.88; $p < 0.001$), this trial established at that time T-DM1 as the recommended second-line treatment in metastatic HER2 + BC. The study also included 95 patients with previously treated and asymptomatic central nervous system metastases. In this subset the treatment with T-DM1 ($n = 45$) led to a median progression free survival (mPFS) of 5.9 months (vs 5.7 in the control arm, $n = 50$) (HR 1.00; 95% CI 0.54–1.84; $p = 1.000$), and a mOS 26.8 months (versus 12.9) (HR 0.38, 95%CI 0.18—–0.79; $p = 0.0081$) [30].

In the TH3RESA trial, T-DM1 compared favorably to treatment of physician's choice (TPC) in patients with HER2 + advanced breast cancer pretreated with at least two HER2 directed regimens [31]. The mPFS in the T-DM1 group was 6.2 months and 3.3 in the control arm ($n = 198$) (HR 0.53, 95%CI 0.422–0.661; $p < 0.0001$). The mOS was not reached in the T-DM1 group vs 14.9 months inTPC. The study included patients with asymptomatic treated CNS metastasis. In the T-DM1 ($n = 40$) arm and the control arm ($n = 27$), the mPFS was 5.8 months vs 2.9 months respectively (HR 0.47, 95%CI; 0.24–0.89).

In the KAMILLA [32] phase IIIb trial, which included 2002 patients treated with T-DM1, 398 patients presented brain metastasis (untreated and asymptomatic or controlled), of whom 126 had measurable brain lesions according to RECIST v1.1. In this subgroup, the intracranial overall response rate (IC-ORR) was 21.4% (intracranial complete response [IC-CR] 2.4%), the mPFS was 5.5 months (95%CI 5.3–5.6) and the mOS 18.9 months (95%CI 17.1–21.3).

Bartsh et al. [33] and Jacot et al. [34] reported two retrospective

Table 2
Prospective clinical trials with ADC on patients with active BM or LMs from breast cancer.

Author Date	Trial name Phase	ADC	Inclusion criteria	Number of patient	Outcome	Response criteria
HER2						
Pérez-García et al. 2022	DEBBRAH Phase II	T-DXd	- HER2 + **or HER2-low** advanced breast cancer cohort 1: HER2 + with stable BM after local therapy (RT or surgery) cohort 2: HER2 + or HER2–low asymptomatic untreated BM cohort 3: HER2 + with progressing BM after local therapy *cohort 4: HER2-low with progressing BM after local therapy* *cohort 5: HER2 + or HER2-low with leptomeningeal carcinomatosis* -HR positive or negative	*cohort 1: 8 *cohort 2: 4 *cohort 3: 9	*cohort 1: 16wk PFS 87.5% IC-PD 12.5% *cohort 2: IC-ORR 50% *cohort 3: IC-ORR 44.4% IC-ORR active BM 46.2%	RANO-BM
Bartsch et al. 2022	TUXEDO-1 Phase II	T-DXd	- HER2 + breast cancer -Previous exposure to trastuzumab and pertuzumab -HR positive or negative -Newly diagnosed untreated BM or progressing after previous local therapy, and no indication for immediate local therapy	15 (ITT) 14 (PP)	ITT: IC-ORR 73.3% IC-CR 13.3% IC-PR 60% IC-SD 20% PP: IC-ORR 78.6% mPFS 14 months mOS NR	RANO-BM

ADC: Antibody-Drug Conjugate, T-DXd: Trastuzumab deruxtecan, HER2+: HER2-overexpressed, BM: Brain Metastases; RT: radiotherapy, HR: hormone receptor, wk: week, PFS: progression free survival, IC-PD: intracranial progressive disease, IC-ORR: intracranial overall response rate, ITT: intention to treat, PP: per protocol, IC-CR: intracranial complete response, IC-PR: intracranial partial response, IC-SD: intra cranial stable disease, mOS: median overall survival, mPFS: median progression free survival, NR: not reached.

cohorts of patients presenting an advanced or metastatic HER2 + breast cancer treated with T-DM1. In the first, for the 10 patients presenting newly diagnosed brain metastasis (2asymptomaticand8progressive), the IC-ORR was 70% and the IC mPFS was 5 months (95%CI 3.69–6.32). In the second, 39 patients with brain metastasis (including 36 previously treated with surgery and/or radiotherapy) received T-DM1. After a median follow-up of 8.1 months, the mPFS was 6.1 months (95%CI 5.2–18.3), and at 1 year, 58% patients were still alive.

Thanks to cutting-edge technologies that have led to the recent development of more active ADC, an increasing number of studies have investigated the efficacy of 3rd generation ADC on BM. Trastuzumab Deruxtecan (T-DXd) conjugates a humanized monoclonal antibody targeting HER-2 to a topoisomerase I inhibitor through a tetrapeptide-based cleavable linker, with a high drug-to-antibody ratio of 8 (versus 3 to 4 for T-DM1).

The first impressive results of T-DXd were reported in heavily pretreated patients with HER2 + breast cancer included in the phase II, dose-escalating, DESTINY-Breast01 trial [35], in which mPFS of 16.4 months (95%CI, 12.7 to not reached) far exceeded that of standard therapies. Overall, the mPFS of the 24 patients with treated and asymptomatic brain metastasis at baseline was 18.1 months (95%CI 6.7–18.1). In the 17 patients with measurable brain metastasis at baseline the IC-ORR was 41.2% [36].

Further compelling results derived from the phase III studies DESTINY-Breast02 [37] and DESTINY-Breast03. The first trial randomized patients with unresectable and/or metastatic HER2 + breast cancer previously treated with TDM-1 to T-DXd (n = 406) or a doublet treatment according to physician's choice (Trastuzumab / Capecitabine or Lapatinib / Capecitabine) (n = 202). Both mPFS and OS were significantly prolonged with T-DXd [mPFS: 17.8 months vs 6.9 (HR 0.36, 95%CI 0.28–0.45; p < 0.000001) and mOS 39.2 months vs 26.5 (HR 0.66, 95%CI 0.50–0.86; p = 0.0021)]. Patients with clinically inactive and treated BM could be included. The mPFS of the 74 patient with BM at baseline in the group T-DXd was 13.9 months and 5.6 months for the 36 of the control arm (HR 0.35, 95% CI 0.20–0.61).

DESTINY-Breast03 [38] trial compared TDM-1 to T-DXd in 524 patients with HER2 + mBC that had previously received Trastuzumab and a taxane. The mPFS was not reached in the group T-DXd (95%CI 18.5 to could not be estimated) and 6.8 months in the TDM-1 group (95%CI 5.6–8.2). Overall 82 patients had clinically stable and previously treated brain metastases [39]. In the TDM-1 group (n = 39), the IC-ORR, the IC-CR and the mPFS were 33.3%, 2.8% and 3.0 months respectively versus 63.8%, 27.8% and 15.0 months (HR 0.25, 95% CI 0.13–0.45) in the group T-DXd (n = 43).

Destiny-Breast04 [40] phase III trial included patients with HER2-low (immunohistochemistry scores of 1 + or 2+/in situ hybridization non amplified) unresectable and/or metastatic breast cancer that had received one or two previous lines of chemotherapy. A total of 557 patients were randomized between T-DXd and chemotherapy according to physician's choice. The mPFS was 9.9 months (95%CI 9.0–11.3) of the T-DXd group (n = 373) versus 5.1 months (95%CI 4.2–6.8) for the control arm (n = 184) (HR 0.5, 95%CI 0.40–0.63; p < 0.001) and mOS was 23.4 months (95%CI 20.0–24.8) and 16.8 months (95% CI 14.5–20.0) respectively (HR 0.64; 95%CI 0.49–0.84, p = 0.001). Thirty-two patients presented treated asymptomatic brain metastasis; mPFS was 8.1 months in 24 patients of the group T-DXd and 4.8 in the group T-DM1 (n = 8) (HR 0.71, 95% CI 0.28–1.8) (sponsor internal data).

DAISY [41,42] was a phase II trial in which patients treated for a metastatic breast cancer were included in the 3 cohorts according to HER2 status: cohort 1 (HER2+, n = 12), cohort 2 (HER2-low, n = 10) and cohort 3 (HER2 0, n = 2), whatever the HR status. In the subgroup of patients with brain metastases at study entry, we reported a mPFS of 13 months (95% CI 7.1-NR) and 4.1 months (95%CI 2.3–11.7) in cohort 1 and cohort 2, respectively [43].

Kabraji et al. reported the results of a retrospective series of 157 patients with brain metastasis from breast cancer treated with T-DXd. The IC-ORR was 73.3% and median IC-PFS was not reached [26].

Interestingly, two prospective clinical trials have specifically investigated the efficacy of T-DXd on brain metastases and/or leptomeningeal metastases from breast cancer (Table 2): DEBBRAH trial and the TUXEDO-1 trial.

DEBBRAH is an ongoing phase II trial in which patients with

Table 3
Trials with new ADC constructs on brain metastases of breast cancer.

Author Date	Trial name Phase	ADC	Inclusion criteria	Number of patient	Outcome	Response criteria
LRP1						
Miller et al. 2016 *Unpublished*	HERMIONE Phase II	MM-302	-HER2- overexpressed locally advanced/metastatic breast cancer -Anthracycline-naïve -Treated, stable, asymptomatic CNS metastases may be considered.	Unknown	Unknown	Unknown
Kumthekar et al. 2020	- Phase II	ANG1005	-Breast cancer, known HER2 and HR status, -Recurrent brain metastases with or without leptomeningeal carcinomatosis after targeted therapy	72 (ITT) 60 (PP)	PP: IC-ORR 8% mPFS 3,8 months	RECIST v1.1

ADC: Antibody-Drug Conjugate, CNS: central nervous system, HR: hormone receptor, ITT: intention to treat, PP: per protocol, IC-ORR: intracranial overall response rate, mPFS: median progression free survival.

advanced or metastatic breast cancer are included in five cohorts based on HER2 expression and metastatic brain status, regardless of their HR status. Cohort 1 is composed of patients with HER2 + mBC and stable brain metastasis after local therapy (radiotherapy and/or surgery); cohort 2 of patients with HER2 + or HER2–low mBC, with asymptomatic and untreated brain metastasis; cohort 3 of patients with HER2 + mBC and progressing brain metastasis after local therapy (radiotherapy and/or surgery); cohort 4 of patients with HER2-low mBC and progressing brain metastasis after local therapy and cohort 5 patients with HER2 + or HER2-low mBC and leptomeningeal carcinomatosis. For cohort 1, primary endpoint was 16-week PFS and IC-ORR for cohorts 2, 3 and 4. So far study results have been published in 2022 [44] for the cohorts 1 (n = 8), 2 (n = 4) and 3n = 9). The 16-week PFS for the cohort 1 determined by RANO-BM criteria, was 87.5% (95%CI, 47.399.7; p < 0 0.001) while IC-ORR in patients with active BM (cohort 2 and 3, n = 13) was 46.2% (95%CI, 19.2–74.9). A recent abstract showed updated data from cohorts 2 (n = 6) and 4 (n = 7) [45]. IC-ORR of the cohort 2 was 66.7% (95% CI, 22.3–95.7) and 33.3% (95% CI, 4.3–77.7; p = 0.033) for the cohort 4.

The phase II TUXEDO-1 trial [46] included patients with HER2 + breast cancer previously treated with both Trastuzumab and Pertuzumab and presenting brain metastasis untreated or resistant to surgery and/or radiotherapy. The primary endpoint was IC-ORR to T-DXd according to RANO-BM criteria. The IC-ORR was 73.3%: two patients had an IC-CR (13.3%), nine an IC-PR (60%) and three a IC-SD (20%), the clinical benefice rate was 92.9% and the mPFS was 14 months (95%CI 11.0 to not recorded). A post-hoc analysis showed a 100% IC-ORR in patients with newly diagnosed brain metastases not treated with local therapy.

Targeting Trop-2

The trophoblast cell-surface antigen 2 (Trop-2) is a transmembrane glycoprotein transducing an intracellular calcium signal. While it is expressed at low levels in normal tissue, it is overexpressed in a wide range of epithelial tumors, including 80% of BC cases. Retrospective studies have demonstrated that Trop-2 overexpression is associated with a worse prognosis, as it is involved in the regulation of mesenchymal-to-epithelial transcription, which contributes to tumor invasiveness and growth [47]. Sacituzumab govitecan is a first-in-class ADC directed against Trop-2, composed of an anti-Trop-2 antibody coupled to a topoisomerase-I inhibitor, SN-38, the active metabolite of irinotecan [48].

In the ASCENT phase II trial [49], Sacituzumab govitecan was administered as treatment for unresectable, locally advanced or metastatic triple-negative breast cancer who presented a progressive disease after at least two standard chemotherapy regimens. At total of 468 patients without BM were randomized to Sacituzumab govitecan (n = 235) or physician's choice: eribulin, vinorelbine, capecitabine, or gemcitabine (n = 233). The mPFS and mOS were 5.6 (95%CI 4.3–6.3) and 12.1 months (95%CI, 10.7–14.0) with Sacituzumab govitecan versus 1.7 (95%CI 1.5–2.6) and 6.7 months (95%CI 5.8–7.7) with standard chemotherapy (HR 0.41, 95%CI 0.32–0.52; p < 0.001 and 0.48, 95%CI 0.38–0.59; p < 0.001). Sixty-one patients with stable brain metastasis for at least 4 weeks before treatment were eligible for the trial but excluded from the primary end-point analysis. The mPFS and mOS of these patients were 2.8 (95%CI 1.5–3.9) and 6.8 (95%CI 4.7–14.1) months respectively in the SG group versus 1.6 (95%CI 1.3–2.9) and 7.5 months (95%CI, 4.7–11.1) in the chemotherapy group (HR 0.65, 95%CI, 0.35–1.22 and HR 0.87, 95%CI, 0.47–1.63) [50].

Rugo et al. reported at ASCO 2022 the first result of the TROPICS-02 study evaluating Sacituzumab govitecan in locally advanced or metastatic HR+ / HER2 negative or low breast cancer [51]. In this trial, patients were randomized to receive Sacituzumab govitecan (n = 272) or mono-chemotherapy at physician's choice: capecitabine, vinorelbine, gemcitabine, eribulin (n = 271). Median PFS of the overall cohort was 5.5 months in the SG group versus 4.0 in the control arm (HR 0.66, 95% CI, 0.53–0.83, p = 0.0003). BM were not an exclusion criteria. As of today, no data are available on the outcome of patients with brain metastases.

In addition, in 2023, di Mauro et al. reported the case report of a patient with metastatic relapse of her initially localized triple-negative breast cancer [52]. This 59-year-old patient with BRCA2 germline mutation, developed multiple symptomatic brain metastases 3 months after initiation of a first-line chemotherapy regimen with carboplatin and paclitaxel. She was then treated with SG combined with whole-brain radiotherapy. After 10 months of treatment, extra cerebral tumor progression was noted, but an intracranial response persisted.

Efficacy of new ADC constructs on brain metastases of breast cancer

MM-302 is a HER2-directed PEGylated antibody–liposomal doxorubicin conjugate that is meant to selectively deliver doxorubicin to HER2-overexpressing tumor cells, limiting the exposure of healthy cells such as cardiomyocytes. As it targets a different epitope of trastuzumab, in HERMIONE phase II trial [53], MM-302 was combined with Trastuzumab as treatment for HER2 + locally advanced or metastatic breast cancer. Patients with central nervous system metastasis could be included if treated and asymptomatic. As this trial is unpublished, no data are available concerning this association on brain metastasis.

ANG1005, a novel peptide–drug conjugate composed of paclitaxel liked to Angiopep-2 has been tested in a phase II trial [54]. Of the 72 patients in the intention to treat population with breast cancer (HER2 and HR positive or negative) and recurrent brain metastases with or without leptomeningeal carcinomatosis after targeted therapy, 60 were analyzed in the per protocol analysis (HER2 + 48.3%, HER2- 51.7% including 21.7% of TNBC). The IC-ORR was 8% (14% for HER2 + and 3% for HER2-, 8% for TNBC) with no IC-CR. The median IC-PFS was 3.8 months (95%CI 3.9–4.8) (4.7 and 3.6 months fort HER2 + and -

Table 4
Ongoing trials with adc in brain metastasis of breast cancer.

Trial name Phase	ADC	Inclusion criteria	ClinicalTrials.gov Identifier
HER2			
DESTINY-BREAST12 Phase III	T-DXd	-Advanced/metastatic HER2-overexpressed breast cancer - Brain metastases may be included: exclusion if untreated and > 2.0 cm; ongoing use of systemic corticosteroids for control of symptoms of BM; requiring immediate local therapy; have poorly controlled neurologic symptoms. -Progressed on prior anti-HER2-based regimens and who received no more than 2 lines/regimens of therapy in the metastatic setting	NCT04739761
DESTINY-BREAST07 Phase Ib/II	T-DXd +/- Durvalumab / Paclitaxel / Pertuzumab / Tucatinib	-Advanced/metastatic HER2-overexpressed breast cancer-Brain metastases may be included if stable (modules 0 – 5), or untreated brain metastases not needing local therapy or previously treated brain metastases that have progressed since prior local therapy (module 6 and 7) .	NCT04538742
HER2CLIMB04 Phase II	T-DXd + Tucatinib	-HER2-overexpressed Breast Cancer-Clinically inactive brain metastases, may be included: untreated brain metastases not needing immediate local therapy or previously treated brain metastases with local therapy (stable or progressive but without clinical indication for immediate re-treatment with local therapy) .	NCT04539938
BIRTH Phase I	TDM-1 + brain RT	-HER2-overexpressed Breast Cancer -Non operable brain Metastases mandatory.	NCT02135159
HER2BAT Phase I/II	TDM-1 +/- Afatinib	-HER2-overexpressed Breast Cancer -Active brain Metastases mandatory.	NCT04158947
Phase I/II	TDM-1 +/- Temozolomide	-HER2-overexpressed Breast Cancer -Brain metastasis recently treated with stereotactic radiation or surgery mandatory.	NCT03190967
KIARA Phase II	TDM-1	-HER2-overexpressed Breast Cancer-Brain Metastases mandatory: cohort 1 (oligosymptomatic or asymptomatic not requiring immediate local therapy), cohort 2 (progression after previous local therapy)	NCT03203616
KATE3 Phase III	T-DM1 +/- Atezolizumab	-HER2-overexpressed Breast Cancer PD-L1 positive -Asymptomatic brain Metastases may be included	NCT04740918
HER2CLIMB02 Phase III	T-DM1 +/- Tucatinib	-HER2-overexpressed Breast Cancer + PD-L1 positive -Brain Metastases: stable not needing immediate local therapy or previously treated may be included	NCT03975647
ACE-Breast-03 Phase II	ARX788	-HER2-overexpressed, Metastatic Breast Cancer - Previously treated with T-DXd -Subjects with stable brain metastases may be included	NCT04829604
Phase I	ZN-A-1041 +/- Capecitabine	-HER2-positive Breast Cancer -Clinically inactive brain metastases, may be included	NCT04487236
Phase I	GQ1001	- HER2-positive Breast Cancer - Clinically active brain metastases may be included	NCT04450732
TROP 2			
S2007 Phase II	Sacituzumab Govitecan	-HER2 negative metastic breast cancer -Brain metastasis that has not been irradiated or has progressed despite prior radiation therapy mandatory.	NCT04647916
Neuro/ Sacituzumab Govitecan/ Breast Brain Metastasis/ Glioblastoma Phase 0	Sacituzumab Govitecan	-Brest cancer -Brain metastasis mandatory.	NCT03995706
TROPION-Breast01 Phase III	Dato-DXd	-Inoperable or metastatic HR-Positive, HER2-negative breast cancer -Treated with one or two prior lines of systemic chemotherapy -Clinically inactive brain metastases, may be included	NCT05104866
TROPION Breast02 Phase III	Dato-DXd	-Locally recurrent inoperable or Metastatic Triple-negative Breast Cancer	NCT05374512

(*continued on next page*)

Table 4 (*continued*)

Trial name Phase	ADC	Inclusion criteria	ClinicalTrials.gov Identifier
		-Clinically inactive brain metastases, may be included	
TROPION-PanTumor01 Phase II	Dato-DXd	-HR-positive Breast Cancer or TN Breast Cancer -Clinically inactive brain metastases, may be included	NCT03401385
HER3			
ICARUS-BREAST Phase II	Patritumab Deruxtecan	-HER3 Positive Metastatic Breast Cancer -Clinically inactive brain metastases, may be included	NCT04965766
Phase II	Patritumab Deruxtecan	-HER3 Positive Metastatic Breast Cancer	NCT02980341
Phase II	Patritumab Deruxtecan	- Locally advanced or mBC -Treated and stable brain metastases, may be included.	NCT04699630
FRα			
Phase I-II	MORAb-202	-Metastatic Triple Negative Breast Cancer -Treated and stable brain metastases, may be included	NCT04300556
Phase I	AMT-151	-Metastatic Triple Negative Breast Cancer -Treated and stable brain metastases, may be included	NCT05498597
Phase I-II	PRO1184	-Metastatic Breast Cancer (TNBC, HR + and HER2+) -Brain Metastasis may be included	NCT05579366
LRP1			
Phase II	GRN1005	-Breast Cancer -Brain Metastases mandatory	NCT01679743
Phase II	ANG1005	-Breast Cancer-Recurrent brain metastases mandatory (not requiring immediate neurosurgery)	NCT02048059
	ANG1005	-Breast Cancer-Recurrent brain metastases mandatory (not requiring immediate neurosurgery)	NCT02755987
LIV-1			
Phase I	Ladiratuzumab vedotin	-Metastatic Breast Cancer	NCT01969643
Nectin-4			
Phase II	Enfortumab vedotin	-Metastatic Breast Cancer (HR+/HER2 − or TNBC) -Clinically inactive brain metastases, may be included	NCT04225117
CEACAM5			
Phase II	Tusamitamab ravtansine	-Metastatic Breast Cancer -Treated and stable brain metastases, may be included	NCT04659603
ROR1			
Phase I-II	NBE-002	-Metastatic Triple Negative Breast Cancer -Treated and stable brain metastases, may be included	NCT04441099
ROR2			
Phase I-II	CAB-ROR2-ADC	-Metastatic Triple Negative Breast Cancer -Treated and stable brain metastases, may be included	NCT03504488
B7-H3			
Phase I-II	MGC018	-Metastatic Triple Negative Breast Cancer -Treated and stable brain metastases, may be included	NCT03729596
B7-H4			
Phase I-II	SGN-B7H4V	-Metastatic Breast Cancer (HR+/HER2 − or TNBC) -Clinically inactive brain metastases, may be included	NCT05194072

ADC: Antibody-Drug Conjugate, T-DXd: Trastuzumab deruxtecan, BM: Brain Metastases, TDM-1: trastuzumab-emtansine, RT: radiotherapy, Dato-DXd: Datopotamab deruxtecan, mBC: metastatic breast cancer, TNBC: triple negative breast cancer, HR: hormone receptor, HER2+: HER2-overexpressed, HER2−: HER2 not overexpressed.

respectively). Table 3 summarizes the two trials.

Many trials evaluating ADC in breast cancer are currently ongoing. Table 4 summarizes those in which patients with brain metastases are eligible for inclusion. The main targets of ADC are HER2 and TROP2. Although several studies are specifically evaluating the efficacy of ADC in breast cancer patients with brain metastases, the majority of ongoing trials with new ADC constructs are including patients with treated and inactive brain metastases and still exclude patients with leptomeningeal disease. Only very few studies allow the inclusion of patients with active BM or LMs. To the best of our knowledge ANGLeD (NCT03613181) is the only Phase III trial specifically investigating the activity of ANG1005, in the treatment of newly diagnosed LMs in patients with HER2-negative breast cancer.

A wealth of studies are also evaluating the combination of ADCs with other compounds, such as target therapies, immune checkpoint inhibitors and chemotherapies, with the intent of enhancing the ADC distribution and penetration in the tumor tissue, the target expression and internalization, the payload activity of eliciting the antitumor immunity induced by the ADC. The combination of ADC and chemotherapy in breast cancer was studied in the TEAL trial, in which patients with early-stage HER2 + breast cancer were treated with T-DM1 plus nab-paclitaxel and lapatinib in neo adjuvant setting. The RCB 0 or 1 rate was 100% among the 14 evaluable patients [55]. Several studies have investigated the combination of ADC and targeted therapies, notably in HER2 + breast cancer. In the MARIANNE trial [56] the addition of pertuzumab to TDM-1 did not significantly increase OS in patients with HER2 + metastatic breast cancer: 53.7 months for the group treated with TDM-1 + pertuzumab versus 51.8 months for the TDM-1 group alone. The NSABP Foundation Trial FB-10 [57] evaluated the TDM-1 neratinib combination in patients with HER2 + metastatic breast cancer who progressed after treatment with trastuzumab, pertuzumab and a taxane. Of the 19 evaluable patients, 13 (63%) showed an objective response to the combination. In a poster [58], Anders et al. report on the pre-clinical and early clinical results of the combination of ZN-1041, an

oral anti-HER2 tyrosine kinase inhibitor, and ADC (TDM-1 or T-DXd). The toxicity data did not reveal any new side effects beyond what is already known for these treatments, suggesting that further, more advanced studies can be conducted to explore the effectiveness of these combinations. In the TNBC, the combination of sacituzumab govitecan and talazoparib is currently being evaluated in a phase I/II trial (NCT04039230). Immune checkpoint inhibitors show promising result in mBC notably with BM. Brastianos et al. recently published the result of a phase II trial evaluating pembrolizumab as a monotherapy treatment in BM of divers tumor [59]. Among the 57 included patients, 35 had a mBC (16 HER2+, 11 TNBC, 8 HR + HER- or unlnown) with untreated BM (n = 4) or with recurrent and progressive BM (n = 31). Thirty-seven percent (90%CI 24–52%) had intracranial benefit and 5 and a survival superior to 2 years (2 with HER2+, 2 with TNBC and 1 with HER-/HR+). Immune checkpoint inhibitors and ADC were also evaluated mostly in HER2 + and TNBC. In the KATE2 study, the addition of atezolizumab to TDM-1 didn't show an improvement of mPFS in patients with advanced HER2 + BC: mPFS 8.2 months (95%CI 5.8–10.7) in the combination group versus 6.8 months (4.0–11.1) for TDM-1 group (HR 0.82, 95% CI 0.55–1.23; p = 0.33) [60]. T-DXd and nivolumab were combined in a phase 1b study including patients with pretreated HER2 + or HER2-low BC. The confirmed ORR of the 48 patientes was 65.6% (95%CI, 46.8–81.4) for HER2 + patients and 50% (95% CI, 24.7–75.3) for HER2-low (CITER). BEGONIA is an ongoing trial evaluating datopotamab deruxtecan associated to durvalumab in metastatic TNBC [61]. Confirmed ORR of the 23 patients was 57% with 54% in response at 12 months and mPFS was 7.3 months (95% CI 5.4–13.8).

Conclusions and perspectives

In recent years, the advent of novel ADC has significantly transformed the treatment landscape for metastatic breast cancer and holds great promise for improving survival outcomes [62].

However, the management of brain metastases remains a significant challenge. Many studies have either excluded patients with central nervous system involvement or failed to report specific intracranial data when included. Furthermore, there is a paucity of studies specifically investigating the efficacy of third-generation ADC in patients with active brain metastases or leptomeningeal disease.

Nonetheless, the limited available data thus far present promising findings, demonstrating notable activity of ADC in patients with active brain metastases. Given the poor prognosis associated with central nervous system involvement and the effectiveness of ADC, it is imperative to intensify the exploration of these novel treatments in this patient population. Therefore, substantial efforts should be dedicated to designing well-designed clinical trials in this context.

However, caution is warranted in the development of future ADC that specifically target brain tumors. The challenges of crossing the blood–brain barrier make it crucial to consider the homogeneity of these ADC and the drug-to-antibody ratio, as highlighted by recent research conducted by Anami et al. using a preclinical model [63]. These factors should be taken into account when designing future generations ADC.

Currently, numerous phase I, II, and even III studies are underway, specifically evaluating the activity of new ADC, either alone or in combination, in patients with cerebral metastases. The findings of these studies are eagerly anticipated, as they hold the potential to further advance our understanding and treatment options for brain metastases.

CRediT authorship contribution statement

N. Epaillard: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **J. Bassil:** Data curation, Writing – original draft. **B. Pistilli:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: BP: Consulting/Advisor: Puma Biotechnology, Novartis, Myriad Genetics, Pierre Fabre; Personal fees: Novartis, AstraZeneca, MSD Oncology, Pfizer; Research funding: Daiichi-Sankyo, Puma Biotechnology, Novartis, Merus, Pfizer, AstraZeneca.

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References

[1] Ostrom QT, Wright CH, Barnholtz-Sloan JS. Chapter 2 - Brain metastases: epidemiology. In: Schiff D, van den Bent MJ, éditeurs. Handbook of Clinical Neurology [Internet]. Elsevier; 2018 [cité 9 déc 2022]. p. 27-42. (Metastatic Disease of the Nervous System; vol. 149). Disponible sur: https://www.sciencedirect.com/science/article/pii/B9780128111611000025.
[2] Sacks P, Rahman M. Epidemiology of Brain Metastases. Neurosurg Clin N Am Oct 2020;31(4):481–8.
[3] Tabouret E, Chinot O, Metellus P, Tallet A, Viens P, Gonçalves A. Recent Trends in Epidemiology of Brain Metastases: An Overview. Anticancer Res 2012:8.
[4] Cheng X, Hung MC. Breast cancer brain metastases. Cancer Metastasis Rev déc 2007;26(3–4):635–43.
[5] Kuksis M, Gao Y, Tran W, Hoey C, Kiss A, Komorowski AS, et al. The incidence of brain metastases among patients with metastatic breast cancer: a systematic review and meta-analysis. Neuro Oncol 1 juin 2021,;23(6):894–904.
[6] Kwon HC, Oh SY, Kim SH, Lee S, Kwon KA, Choi YJ, et al. Clinical Outcomes and Breast Cancer Subtypes in Patients with Brain Metastases. Onkologie 2010;33(4):146–52.
[7] Brufsky AM, Mayer M, Rugo HS, Kaufman PA, Tan-Chiu E, Tripathy D, et al. Central Nervous System Metastases in Patients with HER2-Positive Metastatic Breast Cancer: Incidence, Treatment, and Survival in Patients from registHER. Clin Cancer Res. 15 juill 2011;17(14):4834-43.
[8] Darlix A, Louvel G, Fraisse J, Jacot W, Brain E, Debled M, et al. Impact of breast cancer molecular subtypes on the incidence, kinetics and prognosis of central nervous system metastases in a large multicentre real-life cohort. Br J Cancer. 10 déc 2019;121(12):991-1000.
[9] Niikura N, Hayashi N, Masuda N, Takashima S, Nakamura R, Watanabe K, et al. Treatment outcomes and prognostic factors for patients with brain metastases from breast cancer of each subtype: a multicenter retrospective analysis. Breast Cancer Res Treat août 2014;147(1):103–12.
[10] Watase C, Shiino S, Shimoi T, Noguchi E, Kaneda T, Yamamoto Y, et al. Breast Cancer Brain Metastasis—Overview of Disease State, Treatment Options and Future Perspectives. Cancers. 3 mars 2021;13(5):1078.
[11] Pardridge WM. The blood-brain barrier: Bottleneck in brain drug development 2005;2(1):12.
[12] Shibata S. Ultrastructure of capillary walls in human brain tumors. Acta Neuropathol 1989;78(6):561–71.
[13] Bart J, Groen HJM, Hendrikse NH, van der Graaf WTA, Vaalburg W, de Vries EGE. The blood-brain barrier and oncology: new insights into function and modulation. Cancer Treatment Reviews déc 2000;26(6):449–62.
[14] Liebner S, Fischmann A, Rascher G, Duffner F, Grote EH, Kalbacher H, et al. Claudin-1 and claudin-5 expression and tight junction morphology are altered in blood vessels of human glioblastoma multiforme. Acta Neuropathol 3 sept 2000,;100(3):323–31.
[15] Achrol AS, Rennert RC, Anders C, Soffietti R, Ahluwalia MS, Nayak L, et al. Brain metastases. Nat Rev Dis Primers déc 2019;5(1):5.
[16] Griguolo G, Tosi A, Dieci MV, Fineberg S, Rossi V, Ventura A, et al. A comprehensive profiling of the immune microenvironment of breast cancer brain metastases. Neuro Oncol 1 déc 2022,;24(12):2146–58.
[17] Lishner M, Perrin RG, Feld R, Messner HA, Tuffnell PG, Elhakim T, et al. Complications associated with Ommaya reservoirs in patients with cancer. The Princess Margaret Hospital experience and a review of the literature. Arch Intern Med janv 1990;150(1):173–6.
[18] Le Rhun E, Guckenberger M, Smits M, Dummer R, Bachelot T, Sahm F, et al. EANO–ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol Nov 2021;32(11):1332–47.
[19] Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med 13 févr 2020,;382(7):597–609.

[20] Saura C, Oliveira M, Feng YH, Dai MS, Chen SW, Hurvitz SA, et al. Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With ≥ 2 HER2-Directed Regimens: Phase III NALA Trial. JCO 20 sept 2020,;38(27):3138–49.

[21] Tolaney SM, Sahebjam S, Le Rhun E, Bachelot T, Kabos P, Awada A, et al. A Phase II Study of Abemaciclib in Patients with Brain Metastases Secondary to Hormone Receptor-Positive Breast Cancer. Clin Cancer Res 15 Oct 2020,;26(20):5310–9.

[22] Abounader R, Schiff D. The blood-brain barrier limits the therapeutic efficacy of antibody-drug conjugates in glioblastoma. Neuro Oncol 1 déc 2021,;23(12):1993–4.

[23] Parakh S, Nicolazzo J, Scott AM, Gan HK. Antibody Drug Conjugates in Glioblastoma – Is There a Future for Them? Front Oncol. 3 déc 2021;11:718590.

[24] Askoxylakis V, Ferraro GB, Kodack DP, Badeaux M, Shankaraiah RC, Seano G, et al. Preclinical Efficacy of Ado-trastuzumab Emtansine in the Brain Microenvironment. JNCI: Journal of the National Cancer Institute [Internet]. févr 2016 [cité 17 nov 2022];108(2). Disponible sur: https://academic.oup.com/jnci/article-lookup/doi/10.1093/jnci/djv313.

[25] Gril B, Wei D, Zimmer AS, Robinson C, Khan I, Difilippantonio S, et al. HER2 antibody-drug conjugate controls growth of breast cancer brain metastases in hematogenous xenograft models, with heterogeneous blood–tumor barrier penetration unlinked to a passive marker. Neuro Oncol 26 Nov 2020,;22(11):1625–36.

[26] Kabraji S, Ni J, Sammons S, Murthy RK, Winer EP, Anders CK, et al. Preclinical and clinical efficacy of trastuzumab deruxtecan in breast cancer brain metastases (BCBM). 1.

[27] Pasquier D, Darlix A, Louvel G, Fraisse J, Jacot W, Brain E, et al. Treatment and outcomes in patients with central nervous system metastases from breast cancer in the real-life ESME MBC cohort. European Journal of Cancer janv 2020;125:22–30.

[28] Lewis Phillips GD, Li G, Dugger DL, Crocker LM, Parsons KL, Mai E, et al. Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. Cancer Res 15 Nov 2008,;68(22):9280–90.

[29] Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. N Engl J Med 8 Nov 2012,;367(19):1783–91.

[30] Krop IE, Lin NU, Blackwell K, Guardino E, Huober J, Lu M, et al. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. Annals of Oncology janv 2015;26(1):113–9.

[31] Krop IE, Kim SB, González-Martín A, LoRusso PM, Ferrero JM, Smitt M, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. The Lancet Oncology juin 2014;15(7):689–99.

[32] Montemurro F, Delaloge S, Barrios CH, Wuerstlein R, Anton A, Brain E, et al. Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial☆. Ann Oncol Oct 2020;31(10):1350–8.

[33] Bartsch R, Berghoff AS, Vogl U, Rudas M, Bergen E, Dubsky P, et al. Activity of T-DM1 in Her2-positive breast cancer brain metastases. Clin Exp Metastasis Oct 2015;32(7):729–37.

[34] Jacot W, Pons E, Frenel JS, Guiu S, Levy C, Heudel PE, et al. Efficacy and safety of trastuzumab emtansine (T-DM1) in patients with HER2-positive breast cancer with brain metastases. Breast Cancer Res Treat juin 2016;157(2):307–18.

[35] Modi S, Park H, Murthy RK, Iwata H, Tamura K, Tsurutani J, et al. Antitumor Activity and Safety of Trastuzumab Deruxtecan in Patients With HER2-Low–Expressing Advanced Breast Cancer: Results From a Phase Ib Study. JCO. 10 juin 2020;38(17):1887-96.

[36] Jerusalem G, Park YH, Yamashita T, Hurvitz SA, Chen S, Cathcart J, et al. 138O CNS metastases in HER2-positive metastatic breast cancer treated with trastuzumab deruxtecan: DESTINY-Breast01 subgroup analyses. Annals of Oncology mai 2020;31:S63–4.

[37] Daiichi Sankyo, Inc. A Phase 3, Multicenter, Randomized, Open-label, Active-controlled Study of Trastuzumab Deruxtecan (DS-8201a), an Anti-HER2-antibody Drug Conjugate, Versus Treatment of Investigator's Choice for HER2-positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated With T-DM1 [Internet]. clinicaltrials.gov; 2022 août [cité 12 janv 2023]. Report No.: NCT03523585. Disponible sur: https://clinicaltrials.gov/ct2/show/NCT03523585.

[38] Cortés J, Kim SB, Chung WP, Im SA, Park YH, Hegg R, et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. N Engl J Med 24 mars 2022,;386(12):1143–54.

[39] Jacobson A. Trastuzumab Deruxtecan Improves Progression-Free Survival and Intracranial Response in Patients with HER2-Positive Metastatic Breast Cancer and Brain Metastases. The Oncologist. 28 mars 2022;27(Supplement_1):S3-4.

[40] Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med 7 juill 2022,;387(1):9–20.

[41] Diéras V, Deluche E, Lusque A, Pistilli B, Bachelot T, Pierga JY, et al. Trastuzumab deruxtecan (T-DXd) for advanced breast cancer patients (ABC), regardless of HER2 status: A phase II study with biomarkers analysis (DAISY). :1.

[42] Diéras V, Deluche E, Lusque A, Pistilli B, Bachelot T, Pierga JY, et al. Abstract PD8-02: Trastuzumab deruxtecan (T-DXd) for advanced breast cancer patients (ABC), regardless HER2 status: A phase II study with biomarkers analysis (DAISY). Cancer Res 15 févr 2022;;82(4_Supplement):PD8-02.

[43] Epaillard N, Lusque A, Pistilli B, André F, Bachelot T, Pierga JY, et al. 260P Antitumor activity of trastuzumab deruxtecan (T-DXd) in patients with metastatic breast cancer (mBC) and brain metastases (BMs) from DAISY trial. Ann Oncol 1 sept 2022;;33:S656.

[44] Pérez-García JM, Vaz Batista M, Cortez P, Ruiz-Borrego M, Cejalvo JM, de la Haba-Rodriguez J, et al. Trastuzumab deruxtecan in patients with central nervous system involvement from HER2-positive breast cancer: The DEBBRAH trial. Neuro Oncol 26 mai 2022;;noac144.

[45] Pérez-García JM, Batista MV, Cortez-Castedo P, Borrego MR, Cejalvo JM, de la Haba-Rodríguez J, et al. Abstract PD7-02: Trastuzumab Deruxtecan in patients with Unstable Central Nervous System Involvement from HER2-Low Advanced Breast Cancer: The DEBBRAH Trial. Cancer Res 1 mars 2023;;83(5_Supplement):PD7-02.

[46] Bartsch R, Berghoff AS, Furtner J, Marhold M, Bergen ES, Roider-Schur S, et al. Trastuzumab deruxtecan in HER2-positive breast cancer with brain metastases: a single-arm, phase 2 trial. Nat Med sept 2022;28(9):1840–7.

[47] Remšík J, Binó L, Kahounová Z, Kharaishvili G, Šimečková Š, Fedr R, et al. Trop-2 plasticity is controlled by epithelial-to-mesenchymal transition. Carcinogenesis 13 déc 2018,;39(11):1411–8.

[48] Bardia A, Mayer IA, Vahdat LT, Tolaney SM, Isakoff SJ, Diamond JR, et al. Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer. N Engl J Med 21 févr 2019,;380(8):741–51.

[49] Bardia A, Hurvitz SA, Tolaney SM, Loirat D, Punie K, Oliveira M, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. N Engl J Med 22 avr 2021,;384(16):1529–41.

[50] Targeted Oncology [Internet]. 2020 [cité 28 févr 2023]. Sacituzumab Govitecan Shows PFS Benefit for Patients With mTNBC and Brain Metastases. Disponible sur: https://www.targetedonc.com/view/sacituzumab-govitecan-shows-pfs-benefit-for-patients-with-mtnbc-and-brain-metastases.

[51] Rugo HS, Bardia A, Marmé F, Cortes J, Schmid P, Loirat D, et al. Primary results from TROPiCS-02: A randomized phase 3 study of sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (Pts) with hormone receptor–positive/HER2-negative (HR+/HER2-) advanced breast cancer. :1.

[52] di Mauro P, Schivardi G, Pedersini R, Laini L, Esposito A, Amoroso V, et al. Sacituzumab govitecan and radiotherapy in metastatic, triple-negative, and BRCA-mutant breast cancer patient with active brain metastases: A case report. Front. Oncol 20 févr 2023;;13:1139372.

[53] Miller K, Cortes J, Hurvitz SA, Krop IE, Tripathy D, Verma S, et al. HERMIONE: a randomized Phase 2 trial of MM-302 plus trastuzumab versus chemotherapy of physician's choice plus trastuzumab in patients with previously treated, anthracycline-naïve, HER2-positive, locally advanced/metastatic breast cancer. BMC Cancer déc 2016;16(1):352.

[54] Kumthekar P, Tang SC, Brenner AJ, Kesari S, Piccioni DE, Anders C, et al. ANG1005, a Brain-Penetrating Peptide-Drug Conjugate, Shows Activity in Patients with Breast Cancer with Leptomeningeal Carcinomatosis and Recurrent Brain Metastases. Clin Cancer Res 15 juin 2020,;26(12):2789–99.

[55] Patel TA, Ensor JE, Creamer SL, Boone T, Rodriguez AA, Niravath PA, et al. A randomized, controlled phase II trial of neoadjuvant ado-trastuzumab emtansine, lapatinib, and nab-paclitaxel versus trastuzumab, pertuzumab, and paclitaxel in HER2-positive breast cancer (TEAL study). Breast Cancer Res 2019;21:100.

[56] Perez EA, Barrios C, Eiermann W, Toi M, Im YH, Conte P, et al. Trastuzumab emtansine with or without pertuzumab versus trastuzumab with taxane for human epidermal growth factor receptor 2–positive advanced breast cancer: Final results from MARIANNE. Cancer 2019;125(22):3974–84.

[57] Abraham J, Montero AJ, Jankowitz RC, Salkeni MA, Beumer JH, Kiesel BF, et al. Safety and Efficacy of T-DM1 Plus Neratinib in Patients With Metastatic HER2-Positive Breast Cancer: NSABP Foundation Trial FB-10. J Clin Oncol 10 Oct 2019,;37(29):2601–9.

[58] Lin NU, Chand A, Fu T, Zhu D, Wang Z, Zhou D, et al. Preclinical and early clinical data of ZN-1041 in combination with trastuzumab deruxtecan to treat breast cancer with or without CNS metastases. Journal of Clinical Oncology [Internet]. 31 mai 2023 [cité 20 juin 2023]; Disponible sur: https://ascopubs.org/doi/pdf/10.1200/JCO.2023.41.16_suppl.1041?role=tab.

[59] Brastianos PK, Kim AE, Giobbie-Hurder A, Lee EQ, Lin NU, Overmoyer B, et al. Pembrolizumab in brain metastases of diverse histologies: phase 2 trial results. Nat Med 2 juin 2023,:1–10.

[60] Emens LA, Esteva FJ, Beresford M, Saura C, De Laurentiis M, Kim SB, et al. Trastuzumab emtansine plus atezolizumab versus trastuzumab emtansine plus placebo in previously treated, HER2-positive advanced breast cancer (KATE2): a phase 2, multicentre, randomised, double-blind trial. Lancet Oncol Oct 2020;21(10):1283–95.

[61] Schmid P, Im SA, Armstrong A, Park YH, Chung WP, Nowecki Z, et al. BEGONIA: Phase 1b/2 study of durvalumab (D) combinations in locally advanced/metastatic triple-negative breast cancer (TNBC)—Initial results from arm 1, d+paclitaxel (P), and arm 6, d+trastuzumab deruxtecan (T-DXd). JCO. 20 mai 2021;39(15_suppl):1023-1023.

[62] Grinda T, Rassy E, Pistilli B. Antibody-Drug Conjugate Revolution in Breast Cancer: The Road Ahead. Curr Treat Options Oncol 2023;24(5):442–65.

[63] Anami Y, Otani Y, Xiong W, Ha SYY, Yamaguchi A, Rivera-Caraballo KA, et al. Homogeneity of antibody-drug conjugates critically impacts the therapeutic efficacy in brain tumors. Cell Rep 24 mai 2022;;39(8):110839.