Editorial Commentary

A potential central nervous system niche for trastuzumab deruxtecan in patients with HER2-expressing non-small cell lung cancer

Anna-Maria Lazaratos[1,2], David J. H. Bian[3], Kevin Petrecca[4], Marie-Christine Guiot[4], Matthew Dankner[2,3]^

[1]Department of Medicine, Université de Montreal, Montreal, QC, Canada; [2]Rosalind and Morris Goodman Cancer Institute, McGill University, Montreal, QC, Canada; [3]Department of Internal Medicine, Faculty of Medicine and Health Sciences, McGill University, Montreal, QC, Canada; [4]Montreal Neurological Institute-Hospital, McGill University, Montreal, QC, Canada

Correspondence to: Matthew Dankner, MD, PhD. Rosalind and Morris Goodman Cancer Institute, McGill University, 1160 Pine Ave. West, Montreal, QC H3A 1A3, Canada; Department of Internal Medicine, Faculty of Medicine and Health Sciences, McGill University, Montreal, QC, Canada. Email: matthew.dankner@mail.mcgill.ca.

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Trastuzumab deruxtecan (TDXd) is an antibody-drug conjugate that has become a component of the treatment armamentarium for a subset of patients with human epidermal growth factor receptor 2 (HER2)-overexpressing and HER2-mutated solid tumors, including those with brain metastases (1). HER2 is amplified, mutated, or overexpressed in approximately 2–5%, 1–4%, and 8–23% of non-small cell lung cancer (NSCLC) specimens, respectively (2-4). For this reason, trials that employed the HER2-targeted therapies trastuzumab, pertuzumab and trastuzumab emtansine (T-DM1), as well as tyrosine kinase inhibitors, notably afatinib, poziotinib, neratinib and pyrotinib, have been performed for this subgroup of patients, albeit with limited success (5) (*Table 1*).

TDXd has emerged as an effective treatment option for breast cancer and other solid tumors with HER2 overexpression or mutation (6). The phase II DESTINY-Lung01 trial enrolled patients with HER2-overexpressing (characterized by an immunohistochemistry (IHC) score of 2+ or 3+) or HER2-mutated unresectable or metastatic NSCLC, and treated them with TDXd administered at a dose of 5.4 or 6.4 mg/kg (*Table 1*) (7,8). Importantly, patients with stable brain metastases were eligible in this trial, but responses to treatment were determined systemically with no intracranial response data presented.

In the HER2-mutated cohort of the DESTINY-Lung01 study wherein patients were treated exclusively with the 6.4 mg/kg dose, TDXd resulted in an overall response rate (ORR) of 55%, a median progression-free survival (PFS) of 8.2 months and a median overall survival (OS) of 17.8 months (7). Thirty-three patients in the HER2-mutated cohort with stable brain metastases exhibited an ORR of 54.5%, a median PFS of 7.1 months, and a median OS of 13.8 months (7). The DESTINY-Lung02 trial subsequently evaluated the efficacy of TDXd administered at a dose of 5.4 *vs.* 6.4 mg/kg in patients with advanced HER2-mutated NSCLC and found an ORR of 49% and 56% in the cohort of patients receiving TDXd at a dose of

^ ORCID: 0000-0003-4869-5895.

Table 1 Clinical trial data of HER2-targeted therapies in patients with HER2-overexpressing or mutated NSCLC

Trial/study/NCT	Patient population	HER2-targeted treatment	ORR, mPFS and mOS	
			All patients	Patients with brain metastases
Monoclonal antibody targeting HER2				
Lara *et al.*, no NCT ID, PMID: 14967075	HER2-positive (2+ or 3 by immunohistochemistry) NSCLC	Trastuzumab	N=4, mOS: 5.7 months	Patients with active BM were excluded. Inactive/treated BM were eligible but data not described
Gatzemeier *et al.*, no NCT ID, PMID: 14679114	Patients with untreated advanced or metastatic HER2-positive (2+ or 3 by immunohistochemistry) NSCLC	Trastuzumab, gemcitabine, and cisplatin	N=51, ORR: 36%, mPFS: 6.1 months, mOS: 12.2 months	Patients with BM were excluded
Van Berge Henegouwen *et al.*, NCT02925234, PMID: 35716537	Advanced pre-treated HER2-mutant NSCLC	Trastuzumab and pertuzumab	N=24, ORR: 8.3%, mOS: 10 months	Patients with active BM were excluded. Inactive/treated BM were eligible, but data not described
Antibody-drug conjugate targeting HER2				
Hotta *et al.*, no NCT ID, PMID: 29313813	HER2-overexpressing (2+ or 3+ by immunohistochemistry) relapsed NSCLC	T-DM1	N=15, ORR: 20%, mPFS: 2 months, mOS: 10.9 months	Not described
Peters *et al.*, NCT02289833, PMID: 30206164	HER2-overexpressing (2+ or 3 by immunohistochemistry) previously treated advanced NSCLC	T-DM1	N=49, ORR: 6.7%, mPFS: 2.6 months, mOS: 12.2 months	Patients with BM were excluded
Li *et al.*, NCT02675829, PMID: 29989854	HER2-mutant locally advanced, recurrent, or metastatic NSCLC	T-DM1	N=18, ORR: 44%, mPFS: 5 months	2 patients had active untreated BM at enrollment, but both patients had progression of disease systemically and in the brain at first response assessment
Iwama *et al.*, JapicCTI-194620, PMID: 34959152	HER2-mutant (HER2 exon 20 insertion mutations) locally advanced, recurrent, or metastatic NSCLC	T-DM1	N=22, ORR: 38.1%, mPFS: 2.8 months, mOS: 8.1 months	N=9 but BM-specific data not described
Li *et al.*, NCT02675829, PMID: 32213539	HER2-mutant or amplified lung cancer	T-DM1	N=49, ORR: 51%, mPFS: 5 months	Not described
Smit *et al.*, Destiny-Lung01, HER2 overexpression cohort, NCT03505710, PMID: 38547891	HER2-overexpressing (2+ or 3+ by immunohistochemistry) unresectable or metastatic NSCLC	TDXd 5.4 and 6.4 mg/kg	5.4 mg/kg: N=41, ORR: 34.1%, mPFS: 6.7 months, mOS: 11.2 months; 6.4 mg/kg: N=49, ORR: 26.5%, mPFS: 5.7 months, mOS: 12.4 months	5.4 mg/kg: N=12, ORR: 50%, mPFS: 7.1 months, mOS: 13.5 months; 6.4 mg/kg: N=17, ORR: 29%, mPFS: 4.6 months, mOS: not reached
Li *et al.*, Destiny-Lung01, HER2 mutant cohort, NCT03505710, PMID: 34534430	Metastatic HER2-mutant NSCLC that was refractory to standard treatment	TDXd 6.4 mg/kg	N=91, ORR: 55%, mPFS: 8.2 months, mOS: 17.8 months	N=33, ORR: 54.5%, mPFS: 7.1 months, mOS: 13.8 months

Table 1 *(continued)*

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Trial/study/NCT	Patient population	HER2-targeted treatment	ORR, mPFS and mOS	
			All patients	Patients with brain metastases
Goto *et al.*, Destiny-Lung02, NCT04644237, PMID: 37694347	Patients with previously treated HER2-mutant metastatic NSCLC	TDXd 5.4 and 6.4 mg/kg	5.4 mg/kg: N=102, ORR: 49%, mOS: 19.5 months; 6.4 mg/kg: N=50, ORR: 56%, mOS: NE	5.4 mg/kg: N=35, ORR: 60%; 6.4 mg/kg: N=22, ORR: 45.5%
Planchard *et al.*, Destiny-Lung03, NCT04686305, no PMID (conference abstract)	Pretreated HER2-overexpressing unresectable, locally advanced or metastatic, nonsquamous NSCLC	TDXd 5.4 mg/kg	N=36, ORR: 44.4%, mPFS: 8.2 months, mOS: 14.7 months	N=9 but BM-specific data not described
Anti-HER2 tyrosine kinase inhibitors				
Dziadziuszko *et al.*, NCT02369484, PMID: 30825613	Advanced NSCLC harboring HER2 exon 20 mutations	Afatinib	N=13, mPFS: 15.9 months, mOS: 56 months	N=1 but BM-specific data not described
Elamin *et al.*, NCT03066206, PMID: 34550757	HER2 exon 20 mutant advanced NSCLC	Poziotinib	N=30, ORR: 43%, mPFS: 5.5 months, mOS: 15 months	Inactive/treated BM were eligible, but data not described
Le *et al.*, NCT03318939, PMID: 34843401	Advanced or metastatic NSCLC	Poziotinib	N=90, ORR: 27.8 months, mPFS: 5.5 months	N=14, ORR: 28.6%, mPFS: 7.4 months
Heymach *et al.*, NCT03066206, DOI: 10.1016/j.jtho.2018.08.243	HER2 exon 20 mutant NSCLC	Poziotinib	N=12, ORR: 50%	Not described
Hyman *et al.*, NCT01953926, PMID: 29420467	HER2-mutant lung cancer	Neratinib	N=26, ORR: 3.8%, mPFS: 5.5 months	Not described
Gandhi *et al.*, NCT00838539, PMID: 24323026	HER2-mutant advanced NSCLC	Neratinib + temsirolimus	N=43, ORR: 16.2%, mPFS: 4.1 months, mOS: 15.8 months	Inactive/treated BM were eligible, but data not described
Zhou *et al.*, NCT02834936, PMID: 32614698	Stage IIIB or IV HER2-mutant lung adenocarcinoma who were previously treated with platinum-based chemotherapy	Pyrotinib	N=60, ORR: 30%, mPFS: 6.9 months, mOS: 14.4 months	N=12, ORR: 25.0%, mPFS: 5.5 months, mOS: 6.9 months

HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; NCT, National Clinical Trial Identifier Number; ORR, overall response rate; mPFS, median progression-free survival; mOS, median overall survival; BM, brain metastases; T-DM1, trastuzumab emtansine; TDXd, trastuzumab deruxtecan; NE, not evaluable; PMID, PubMed Identifier.

5.4 and 6.4 mg/kg respectively (9). Thirty-five patients with stable brain metastases exhibited an ORR of 60% when receiving TDXd at a dose of 5.4 mg/kg, while 22 patients with stable brain metastases displayed an ORR of 45.5% when receiving TDXd at a dose of 6.4 mg/kg (9).

In the HER2-overexprresing cohort of the DESTINY-Lung01 study, the authors describe 39 patients with a HER2 IHC score of 2+ and 10 patients with a HER2 IHC score of 3+ in the cohort of patients receiving TDXd at a dose of 6.4 mg/kg, as well as 24 patients with a HER2 IHC score of 2+ and 17 patients with a HER2 IHC score of 3+ in the cohort of patients receiving TDXd at a dose of 5.4 mg/kg (8). Patients with HER2-overexpressing NSCLC receiving TDXd at a dose of 5.4 mg/kg exhibited an ORR of 34.1%, a median PFS of 6.7 months and a median OS of 11.2 months, while those receiving TDXd at a dose of 6.4 mg/kg exhibited

an ORR of 26.5%, a median PFS of 5.7 months and a median OS of 12.4 months (8). Patients receiving TDXd at a dose of 5.4 mg/kg with a HER2 IHC score of 2+ or 3+ exhibited an ORR of 21% and 53%, a median PFS of 4.5 and 7.5 months, and a median OS of 10.6 and 12.5 months respectively (8). When TDXd was administered at a dose of 6.4 mg/kg, patients with a HER2 IHC score of 2+ or 3+ exhibited an ORR of 28% and 20%, a median PFS of 5.9 and 4.2 months, and a median OS of 16.8 and 11.7 months respectively (8). Twelve patients with stable brain metastases receiving TDXd at a dose of 5.4 mg/kg exhibited an ORR of 50%, a median PFS of 7.1 months and a median OS of 13.5 months, while the 17 receiving TDXd at a dose of 6.4 mg/kg exhibited an ORR of 29%, a median PFS of 4.6 months, and a median OS of that was not reached.

Recently, the first results from the TDXd single-agent arm of the DESTINY-Lung03 trial were presented and build upon these results (10,11). This study enrolled patients with unresectable or metastatic non-squamous NSCLC with HER2 2+ or 3+ and treated them with TDXd at 5.4 mg/kg (10,11). ORR was 44.4%, median duration of response (DOR) was 12.2 months, median PFS was 8.2 months, and median OS was 14.7 months (10,11). Among patients with HER2 3+ status, ORR was 56.3% and mDOR was 12.5 months (10,11). Importantly, response rates were higher in patients who received prior epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (68.4% *vs.* 17.8%) (10,11).

Together, the conclusion of these studies posits that TDXd is more effective in patients with HER2-mutated NSCLC compared to patients with HER2-overexpressing tumors. However, it is difficult to fully understand the differences in outcomes in the HER2-overexpression cohorts of DESTINY-Lung01 and DESTINY-Lung03 without full publication of the DESTINY-Lung03 results, where outcomes in patients with HER2 3+ was closer to what was seen in patients with HER2-mutations (7). If indeed TDXd is more effective in NSCLC patients with HER2–mutations compared to HER2-overexpresion, this may be explained by the fact that pre-clinical data has shown that in NSCLC, HER2 activating mutations drive rapid recycling of HER2 receptors, leading to more rapid internalization and cleavage of DXd from the trastuzumab antibody (12).

For the time being, TDXd has begun to gain acceptance for use in patients with metastatic NSCLC whose tumors harbor HER2-mutations in the absence of randomized data (13-15). However, the same cannot be said for HER2-overexpressing NSCLC, where outcomes with TDXd appear to be closer to what may be expected with standard of care chemoimmunotherapy in these patients (16). Furthermore, rare but well-described cases of lethal toxicities with TDXd represent an additional drawback of using TDXd in the absence of definitive data showing superiority compared to other therapeutic agents (17). Notably, TDXd has been associated with interstitial lung disease in a minority of patients but poses a risk of severe outcomes. A recent meta-analysis reported interstitial lung disease in 11.6% of patients receiving TDXd, with 6.4% of these events being grade 5 (17). These findings underscore the importance of careful patient monitoring and early intervention when administering TDXd.

Despite this, it is possible that patients with HER2-overexpressing NSCLC with central nervous system (CNS) metastases represent a population uniquely poised to derive benefit from TDXd compared to other agents, with further study. The results of the DESTINY-Lung01 and DESTINY-Lung02 trials suggest that TDXd exhibits comparable activity in NSCLC patients with stable brain metastases compared to the rest of the cohort at large. These findings are similar to what has been observed in other cancer types, such as breast cancer, where TDXd has demonstrated robust intracranial activity (1,18-21). This distinguishes TDXd from other anti-cancer therapies that possess limited intracranial activity. Therefore, patients with NSCLC harboring HER2-overexpression may stand to benefit from TDXd compared to alternative agents, exclusively if they have CNS metastases.

In order to better understand the subset of patients with NSCLC brain metastases who may be able to derive benefit from treatment with TDXd, we performed IHC on a tissue microarray containing 109 lung cancer brain metastasis specimens, with representative images shown in *Figure 1A*. When applying the IHC staining criteria used in the DESTINY-Lung01 study, we found that 6% of patients with lung cancer brain metastases exhibit HER2 2+ (4%) or 3+ (2%) staining (*Figure 1B*). Thus, this represents a significant patient population who may stand to derive clinical benefit from TDXd. Furthermore, an additional 18% of patients had 1+ HER2 staining. While these patients were not included in the DESTINY-Lung studies, it is possible that TDXd may possess meaningful activity in these patients as well, as it does in HER2-low and HER2-ultralow breast cancer (22,23).

Together, it is apparent that additional studies are required to better understand TDXd's role in HER2-overexpressing NSCLC. This includes the publication

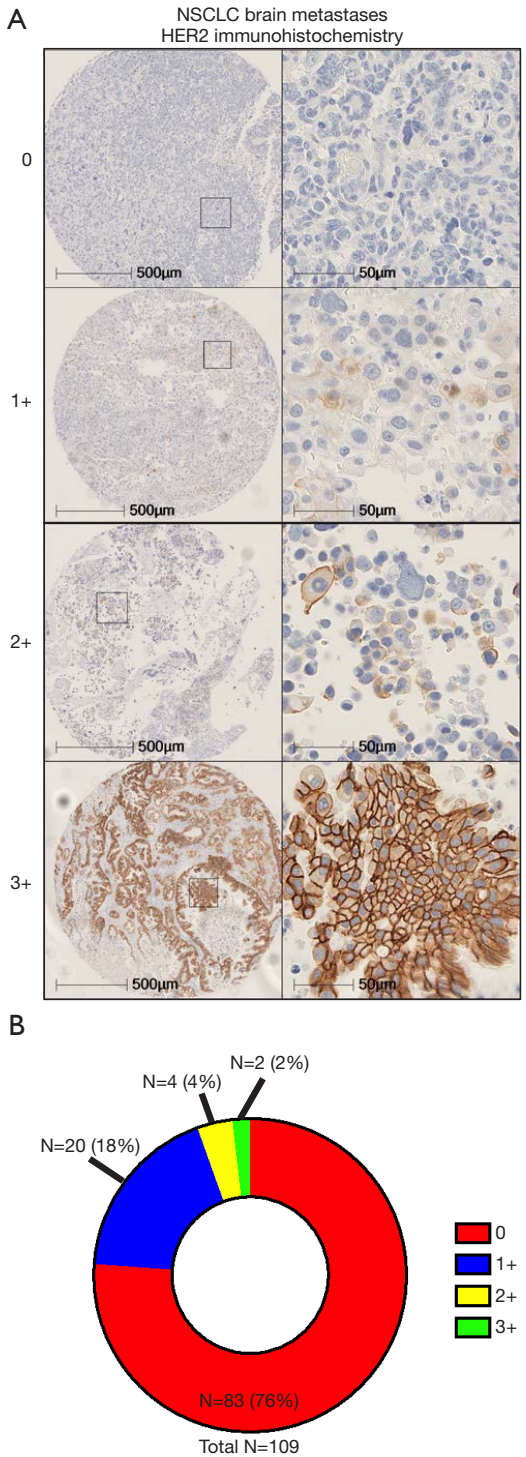

Figure 1 Immunohistochemistry for HER2 on lung cancer brain metastasis specimens. (A) Representative images of 0, 1+, 2+ and 3+ HER2 staining in NSCLC brain metastases. (B) Proportion of NSCLC brain metastases with 0, 1+, 2+ and 3+ HER2 staining. NSCLC, non-small cell lung cancer; HER2, human epidermal growth factor receptor 2.

of intracranial response outcomes of patients with brain metastases included in the DESTINY-Lung01, 02 and 03 studies, new studies with robust pharmacodynamics specifically for patients with CNS metastases that uses reproducible criteria to define intracranial response, and trials that combine TDXd with other agents to augment HER2 expression or receptor recycling. Furthermore, such studies for patients with brain metastases should be performed in a multidisciplinary context that considers radiotherapy and surgical modalities, and also take into consideration the fact that HER2 expression levels may change in intracranial compared to extracranial lesions in the same patient (24).

HER2 immunohistochemistry was performed using anti-HER2 clone 790-2991 (Roche) using Ventana Benchmark Ultra Autostainer, on a tissue microarray derived from 109 surgically resected lung cancer brain metastases, in duplicate 1.5 mm cores from each patient, arranged across two tissue blocks. Operations performed on all patients occurred at the Montreal Neurological Institute-Hospital between 2007 and 2019. HER2 scoring was performed by a board-certified pathologist according to the recommendations of Bartley *et al.* (25), as was performed in the DESTINY-Lung01 trial. An immunohistochemistry score of 3+ was defined as strong complete, basolateral, or lateral membranous reactivity in at least 10% of tumour cells, an immunohistochemistry score of 2+ was defined as weak-to-moderate complete, basolateral, or lateral membranous reactivity in at least 10% of tumour cells, and an immunohistochemistry score of 1+ was defined as faint/barely perceptible membranous reactivity in ≥10% of tumor cells; cells are reactive only in part of their membrane.

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