Editorial Commentary

Trastuzumab deruxtecan in HER2 overexpressing non-small cell lung cancer (NSCLC)

Omali Pitiyarachchi[1]^, Aaron C. Tan[2,3]^

[1]School of Biomedical Sciences, Faculty of Medicine and Health, UNSW Sydney, Sydney, Australia; [2]Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore; [3]Duke-NUS Medical School, Singapore, Singapore

Correspondence to: Asst. Prof. Aaron C. Tan, MBBS, PhD, FRACP. Division of Medical Oncology, National Cancer Centre Singapore, 30 Hospital Blvd, Singapore 168583, Singapore; Duke-NUS Medical School, Singapore, Singapore. Email: aaron.tan@singhealth.com.sg.

Comment on: Smit EF, Felip E, Uprety D, *et al.* Trastuzumab deruxtecan in patients with metastatic non-small-cell lung cancer (DESTINY-Lung01): primary results of the HER2-overexpressing cohorts from a single-arm, phase 2 trial. Lancet Oncol 2024;25:439-54.

Keywords: HER2 overexpression; non-small cell lung cancer (NSCLC); antibody drug conjugate (ADC)

Submitted Oct 19, 2024. Accepted for publication Jan 15, 2025. Published online Feb 24, 2025.
doi: 10.21037/tlcr-24-968
View this article at: https://dx.doi.org/10.21037/tlcr-24-968

The number of alterations being tested in advanced non-small cell lung cancer (NSCLC) is expanding largely due to therapeutic development and the availability of targeted therapies adopted as standard of care. HER2-positive NSCLC reflects a clinically and biologically heterogenous subset of this disease with HER2 alterations occurring as gene mutations, gene amplifications or protein overexpression with little correlation between the types (1,2). HER2 activation by any of the above mechanisms leads to downstream activation of the Ras/MAPK, PI3K/Akt, and the Janus kinase-STAT (Jak-STAT) signalling pathways propagating tumour progression in NSCLC. The distinct biological differences and response to therapies of these modes of HER2 activation place an impetus on the importance of testing for the different alterations (3).

HER2 overexpression is observed in 8–23% of NSCLC, defined by HER2 immunohistochemistry (IHC) staining with a score of 3+ or 2+, and infers a poor prognosis (4). The wide range of prevalence of HER2 overexpression may be a reflection on the lack of standardisation in HER2 IHC scoring in NSCLC, with the current scoring methods extrapolated from breast and gastrointestinal cancers (5). Secondly, HER2 amplifications are present in 2–5% of NSCLC, and may be higher in patients who develop resistance due to prior exposure to EGFR tyrosine kinase inhibitors (TKIs) (1). HER2 amplifications can be detected using fluorescence in situ hybridization (FISH), silver in situ hybridization (SISH), or with alternatives such as next generation sequencing (NGS), chromogenic in situ hybridization and quantitative real-time reverse transcription polymerase chain reaction for HER2 mRNA. HER2 amplification is defined by a HER2:chromosome 17 ratio of ≥2.0 detected by FISH and in NSCLC, HER2 mutations and HER2 amplification are mutually exclusive (1); both are associated with female sex, Asian ethnicity, non-smoker status, and moderate to poorly differentiated adenocarcinoma (2). In addition, there is no correlation between HER2 overexpression and amplification in NSCLC which is unlike that seen in breast cancer (1). Finally, activating HER2 mutations are seen in approximately 1–4% of NSCLC, with HER2 exon 20 insertion mutations being the most common activating mutation comprising 89%. HER2 mutations are detected using NGS, and are generally associated with light or never smoking history and adenocarcinoma or adenosquamous histology (6); HER2 mutations may infer a worse prognosis compared with EGFR and ALK mutated NSCLC (1,7). The clinical manifestations may also differ; for example, with invasion of the pleura linked with HER2 overexpressing or amplified NSCLC, and central nervous system (CNS) metastasis

^ ORCID: Omali Pitiyarachchi, 0000-0001-6693-9756; Aaron C. Tan, 0000-0001-7292-1114.

more commonly associated with HER2 mutations.

Prior trials evaluating treatment options for HER2 overexpressing (IHC 2+/3+) advanced or metastatic non-squamous NSCLC refractory to standard of care have been underwhelming. Trastuzumab monotherapy (8) showed little clinical benefit, nor did the combination of chemotherapy with trastuzumab such as the phase II study using gemcitabine-cisplatin (9), and with combined anti-HER2 therapy using pertuzumab (10). Selective HER2 TKIs have looked promising and in their nature have EGFR sparing activity; however, the advent of antibody drug conjugates (ADCs) translated to a paradigm shift in how we treated tumours with HER2 alterations. A phase II study assessing the response to T-DM1 (3) at a dose of 3.6 mg/kg given 3 weekly showed an objective response rate (ORR) of 20% (n=4/20) in patients with tumours scored as HER2 IHC3+; whereas there were no responders with HER2 IHC2+. Interestingly, most of the patients who responded had either a co-occurring amplification or mutation of HER2 in addition to overexpression. Exploratory analysis of levels of HER2 mRNA expression did not reveal a cutoff for response (3).

Trastuzumab deruxtecan (T-DXd), a newer generation HER2 ADC, consisting of a humanised anti-HER2 IgG1 monoclonal antibody with a tetrapeptide-based cleavable linker and a novel topoisomerase I inhibitor payload, with a drug to antibody ratio of 8:1 (11). Binding of T-DXd to the HER2 receptor leads to internalisation then endocytosis, followed by cleavage of the ADC within endosomes and/or lysosomes resulting in the release of the payload from within these respectively. This results in cell death, and the bystander effect. The higher drug antibody ratio compared to previous ADCs such as trastuzumab emtansine (T-DM1), improved drug stability in the circulation, and the bystander effect potential therefore results in improved pharmacological features (11). T-DXd was first approved for use in HER2 positive breast cancer as defined by HER2 overexpression or amplification with demonstrated efficacy in patients with active CNS disease (12), in patients who have previously received HER2 treatment (13,14), and HER2 low breast cancer (15). T-DXd has also been adopted as an effective treatment option in gastric/gastroesophageal junction adenocarcinoma (16). In NSCLC, results from DESTINY-Lung02 led to US Food and Drug Administration (FDA) accelerated approval of T-DXd in 2022 and provided the first available therapy for HER2-mutant NSCLC (ESMO-Magnitude of Clinical Benefit Scale v1.1 score: 3) in the second line setting after progression on a platinum-doublet with or without an immune checkpoint inhibitor (ICI) (17). The importance of dose optimisation was highlighted in this study, with the lower dose of T-DXd, 5.4 mg/kg resulting in similar efficacy but lower adverse events specifically with pneumonitis or interstitial lung disease (ILD), and thus the dose approved.

Smit *et al.* (18) recently published data from DESTINY-Lung01, an open-label, multi-centre, phase II study evaluating the activity of T-DXd in patients with unresectable and/or metastatic non-squamous NSCLC with no suitable standard of care options. This study included two cohorts of participants enrolled sequentially, with Cohort 1 receiving 6.4 mg/kg T-DXd and Cohort 1a the lower dose of 5.4 mg/kg, both administered every 3 weeks. A comparison of the two cohorts is presented in *Table 1*. HER2 status as determined by IHC showed a greater IHC3+ proportion in 20% in Cohort 1 *vs.* 41% Cohort 1a, and HER2 amplification (by FISH) in 34% Cohort 1 *vs.* 24% Cohort 1a.

The primary endpoint demonstrated an ORR of 26.5% [95% confidence interval (CI): 15.0–41.1%] in Cohort 1 and 34.1% (95% CI: 20.1–50.6%) in Cohort 1a as assessed by independent central review. Median treatment duration was 5.5 months in Cohort 1a which was 1.4 months longer compared with Cohort 1 perhaps reflective of the tolerability of the lower dose (*Table 1*). Responses [ORR, disease control rate, duration of response (DOR), progression-free survival] assessed by independent central review were similar to investigator assessed responses. There were also lower rates of neutropenia, pneumonia, and drug related adverse events in Cohort 1a, with up to two dose reductions permitted in each cohort. Of particular interest is the rate of pneumonitis and ILD, with numerically more patients experiencing Grade 1 or 2 pneumonitis/ILD with the higher dose, 7 *vs.* 1 patient but the number of patients who died due to pneumonitis/ILD were similar, 3 *vs.* 2 patients, thus even at the dose of 5.4 mg/kg every 3 weeks, vigilant monitoring for T-DXd related pneumonitis/ILD is vital. Prompt cessation of drug is required with any grade pneumonitis/ILD, and drug rechallenge should only be attempted with Grade 1 toxicity, and again only if full resolution to Grade 0 and within 18 weeks. Notably, any participants with a history of pneumonitis or ILD that was not related to an infective process were excluded from the study.

Based on the results from this study (18), as well as DESTINY-PanTumour02 and DESTINY-CRC02, the FDA granted accelerated tumour agnostic approval in April

Table 1 Summary of key data from Cohorts 1 and 1a from DESTINY-Lung01 (18)

Characteristics	Cohort 1 (n=49)	Cohort 1a (n=41)
T-DXd dose	6.4 mg/kg i.v. every 3 weeks	5.4 mg/kg i.v. every 3 weeks
Age (years), median [IQR]	63 [58–68]	62 [56–66]
Sex: male, n [%]	30 [61]	22 [54]
Race: White, n [%]	31 [63]	31 [76]
Treatment duration (months), median (IQR)	4.1 (1.4–7.1)	5.5 (1.4–8.7)
Follow-up (months), median (range)	12.0 (5.4–22.4)	10.6 (4.5–13.5)
Confirmed ORR (RECIST v1.1), % (95% CI); n/total	26.5% (15.0–41.1%); 13/49 PR	34.1% (20.1–50.6%); 14/41: 2 CR, 12 PR
Disease control rate, n (%); 95% CI	34 (69.4); 54.6–81.8%	32 (78.0); 62.4–89.4%
Mean DOR, months (95% CI)	5.8 (4.3–NE)	6.2 (4.2–9.8)
Median PFS, months (95% CI)	5.7 (2.8–7.2)	6.7 (4.2–8.4)
Median OS, months (95% CI)	12.4 (7.8–17.2)	11.2 (8.4–NE)
TEAE ≥ Grade 3, n [%]		
Neutropenia	12 [24]	0 [0]
Pneumonia	6 [12]	2 [5]
Fatigue	6 [12]	3 [7]
PD	6 [12]	4 [10]
Dyspnoea	5 [10]	2 [5]
Deaths due to TEAEs, n [%]	10 [20]	7 [17]
Drug-related TEAEs ≥G3, n [%]	26 [53]	9 [22]
Drug-related SAEs, n [%]	10 [20]	3 [7]
TEAEs leading to discontinuation, n [%]		
Pneumonitis	7 [14]	2 [5]
PD	2 [4]	3 [7]
Drug-related ILD/pneumonitis, n [%]		
Grade 1	2 [4]	0 [0]
Grade 2	5 [10]	1 [2]
Deaths (Grade 5)	3 [6]	2 [5]

All responses shown here are by independent central review. T-DXd, trastuzumab deruxtecan; IQR, interquartile range; ORR, objective response rate; CI, confidence interval; DOR, duration of response; PFS, progression-free survival; OS, overall survival; TEAE, treatment emergent adverse event; PD, progressive disease; SAE, serious adverse event; ILD, interstitial disease; PR, partial response; CR, complete response; NE, not evaluable.

2024 for T-DXd at a dose of 5.4 mg/kg given 3 weekly for adult patients with unresectable or metastatic HER2 IHC3+ expressing tumours who have had prior treatment with no viable options remaining. DESTINY-PanTumor02 (19), and DESTINY-CRC02 (20) showed an ORR of 51.4% (95% CI: 41.7–61.0%), and 46.9% (95% CI: 34.3–59.8%) respectively and a median DOR of 19.4 months (range, 1.3 to 27.9+ months), and 5.5 months (range, 1.3+ to 9.7+ months). As HER2 overexpression accounts for a greater proportion of HER2 alterations in NSCLC compared to HER2 amplifications or mutations, the use of T-DXd in this setting has the potential to benefit many patients and

thus represents a transformative era in the treatment of advanced/metastatic NSCLC for patients with no suitable standard of care options. With respect to treatment sequencing, although T-DXd has a tumour agnostic approval for HER2 overexpressing (IHC3+) solid tumours, in order to progress T-DXd forward to the first line setting we see this requiring a randomized control trial.

The main limitation in Cohorts 1 and 1a of DESTINY-Lung01 were the small sample sizes, with 49 and 41 patients in each cohort respectively. Although participants with stable brain metastases were included in the study, intracranial activity was not assessed and may have added further data to the CNS penetration activity of T-DXd (12). The demographics of the study participants revealed a predominantly white population, with Asians patients constituting 13 (27%) and 4 (10%) in Cohort 1 and 1a respectively. This is important given the potentially higher risk of pneumonitis/ILD in certain patient populations such as Japanese patients (21). Notably however T-DXd studies in other tumours such as the subgroup analysis of DESTINY-Breast03 hasn't specifically suggested disproportionate toxicities in Asian patients (22).

Archival tissue was used from the diagnostic tumour specimen for HER2 assessment, and study participants had received on average three lines of systemic therapy prior to study enrolment. Almost all patients had received platinum-based chemotherapy (92% in Cohort 1, 98% in Cohort 1a), anti-programmed cell death 1/programmed death-ligand 1 (anti-PD-1/PD-L1) (73%, 80%), docetaxel (24%, 22%), and HER2 or EGFR TKI (29%, 17%). To determine whether HER2 overexpression can change following exposure to prior systemic therapies in NSCLC, analysis of HER2 expression both at diagnosis and at the time of disease progression would need to occur. Re-biopsy upon disease progression and subsequent HER2 testing could reveal instances where HER2 overexpression has been lost with treatment exposure or identify patients who were not initially defined as having HER2 overexpression based on the assessment of diagnostic tumour tissue such as seen in breast cancer (23,24). Fresh tumour biopsy may also be used to identify resistance mechanisms with the alternative of cell-free DNA assessment where appropriate. Notable examples of HER2 overexpression as a potential resistance mechanism to prior therapy include in EGFR TKI resistance in EGFR mutated NSCLC (25). However, large in-depth studies of paired pre- and post-treatment samples evaluating HER2 overexpression are lacking.

Comparisons across studies are also affected by the difference in scoring methods and assays used as there is a lack of standardisation in HER2 overexpression analysis in NSCLC. The scoring criteria set by the CAP-ASCP-ASCO (College of American Pathologists-American Society for Clinical Pathology-the American Society of Clinical Oncology) HER2 testing guideline for gastroesophageal cancer is most commonly implemented in assessing HER2 overexpression in NSCLC, and this was implemented in DESTINY-Lung01 (26). The recommendation from this guideline is for ISH testing when the IHC result for HER2 is equivocal, i.e., 2+, whereas for IHC3+ it is not recommended. HER2 amplification by FISH was only detected in 23% of HER2 IHC 3+ participants in Cohort 1 from DESTINY-Lung01 and 77% of HER2 IHC2+. This poses the question whether a tumour specific HER2 scoring system needs to be validated (27). Furthermore, more sensitive assays to detect HER2 expression may have utility in NSCLC, given the discordance between HER2 overexpression and amplification in NSCLC (28). In gastroesophageal cancers, areas of low-grade tumour are more likely to be associated with HER2 positivity, and multiple areas may require testing if there is tumour grade variability within the specimen, and this should be taken into consideration for HER2 scoring other tumour types. In addition, DESTINY-PanTumour02 demonstrated discordant results between investigator and centrally assessed HER2 IHC, which improved from 59% concordance for IHC3+ between local and central laboratories, to 73% when both laboratories used the HercepTest (Glostrup, Denmark) as opposed to a local HER2 IHC assay (29). With respect to the specific HER2 antibody used (29), DESTINY-Lung01 utilised the ultraVIew Universal DAB Detection Kit (Tucson, AZ, USA) with an investigational version of the PATHWAY HER2/neu (4B5) antibody (by Ventana Medical Systems, Tucson, AZ, USA), whereas other studies have used the HercepTest kit (Glostrup, Denmark) (9,30). On a practical level, kit dependent variation in HER2 overexpression and different scoring methods may affect a patient's eligibility for HER2 targeted therapies.

With respect to timing of testing for HER2 overexpression, it is not routinely performed upfront in NSCLC as the initial clinical management would not differ based on currently available evidence. For newly diagnosed lung adenocarcinoma, large cell carcinoma and NSCLC not otherwise specific (NOS), the National Comprehensive Cancer Network (NCCN) guideline for NSCLC does however recommend broad molecular profiling including

for HER2 mutations in addition to EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, and RET; this molecular profiling panel could also be considered in all patients with squamous cell carcinoma (31). The latest 2025 version of the NCCN guideline, have now included HER2 IHC as part of the broad molecular profiling panel (31). However, the optimal timing of testing remains at some point during progression, as the timing should be balanced with tissue conservation. In DESTINY-Lung01, circulating tumour (ct) DNA was performed in a retrospective manner to detect co-occurring mutations in addition to HER2 overexpression. This was restricted to HER2, EGFR, BRAF, KRAS, and NRAS mutations and ALK and ROS1 fusions (18). In Cohort 1 and 1a respectively, 10 (21%) and 6 (15%) EGFR mutations, 7 (15%) and 13 (33%) KRAS mutations were detected; and patients with HER2 mutations where not included in these cohorts. Co-mutations were present in 3 patients, with EGFR and KRAS seen in 2 patients, and KRAS and BRAF in 1 patient. Antitumour responses was demonstrated in patients with and without co-occurring mutations, but the numbers of participants with these were small. In patients who have had targeted therapies for NSCLC with targetable alterations, upon disease progression, it may be suitable to test for alternate mechanisms of resistance including *HER2* amplification with a fresh biopsy specimen. Whether HER2 testing is performed on the diagnostic specimen or a fresh biopsy in patients with NSCLC without a targetable alteration who develop disease progression, is an evolving area as we know from breast cancer data that exposure to prior treatments including chemotherapy and/or targeted therapies may alter the expression of HER2 (24).

Based on the current evidence from DESTINY-Lung01 (18) in patients with HER2 overexpressing NSCLC including squamous cell carcinoma, the current recommendation for sequencing of treatments would be after standard of care has been exhausted, with at least 2 lines of therapy, i.e., after first line chemoimmunotherapy and docetaxel. However, as targetable alterations such as EGFR mutations can co-occur with HER2 overexpression, the sequencing in this setting after first line targeted therapies is less clear. In addition, other ADCs such as datopotamab deruxtecan have demonstrated efficacy in patients with actionable genomic alterations, after targeted therapies and platinum-based chemotherapy (32,33). In breast cancer, T-DXd has shown efficacy after treatment with another ADC (34), therefore identifying the optimal sequence of therapies in NSCLC incorporating T-DXd warrants continued investigation.

The results from DESTINY-Lung01 Cohorts 1 and 1a add value to a previous void in the treatment of patients with HER2 overexpressing advanced/metastatic NSCLC (18). There are further trials in progress and a selected list of HER2 targeted trials inclusive of participants with HER2 overexpressed NSCLC is shown in *Table 2*. This includes trials evaluating zongertinib and BAY2927088, both HER2 TKIs which have been granted US FDA breakthrough therapy designation in HER2 mutated NSCLC. Moreover, other avenues worth exploring include dual payload ADCs which have shown potential in pre-clinical studies with dual conjugation exerting greater cytotoxic potential in overcoming treatment resistance. Further developments with the choice of payload using cytotoxic alternatives such as targeted agents, e.g., BCL-XL inhibitors (41), are under investigation. Bispecific anti-HER2 antibodies have also shown promise with the rationale to increase selectivity of binding with dual tumour-associated antigens. For example, *in vivo* studies have shown anti-tumour activity of YH012, a human bispecific anti-HER2/TROP2 antibody, in cell line-derived and patient-derived xenografts of NSCLC (42). Notably, zenocutuzumab, a HER2-HER3 bispecific antibody has recently been granted FDA accelerated approved for advanced NRG1 fusion positive NSCLC (43)—although efficacy in HER2 overexpressed NSCLC with this compound is lacking.

The results from DESTINY-Lung01 may transform the landscape in the management of patients with previously treated HER2-overexpressed advanced/metastatic or unresectable NSCLC, with the lower dose of T-DXd 5.4 mg/kg serving a balance between managing toxicity and achieving efficacy in a pre-treated patient population. Responses were seen with either HER2 IHC 3+ or 2+ and with co-existing HER2 amplifications, prior treatment with anti-PD-1 or anti-PD-L1, and the presence of stable brain metastases. However, the strongest evidence and indeed the FDA accelerated approval is for HER2 IHC3+ overexpressing tumours including NSCLC, and therefore this recommendation should be adhered to. The results of this study have addressed a critical gap in the management of NSCLC with HER2 overexpression. Yet to be illuminated is the optimal sequence of systemic therapies in HER2 altered NSCLC, the feasibility and timing of testing for HER2 IHC, whether drug combination strategies should be utilised, and whether responses can be seen in HER2 low NSCLC. As a heterogenous disease with differential responses to HER2 targeted therapies, further

Table 2 HER2 targeted trials

Study	Patient population	Design	Drug(s)	Primary endpoint
In progress				
DESTINY-Lung03 (35) (NCT04686305)	First line; HER2 overexpressed advanced/ metastatic non-squamous NSCLC	Phase 1b	T-DXd + durvalumab + chemotherapy	Frequency of AEs and SAEs
U106 (36) (NCT04042701)	2 cohorts with NSCLC [HER2-expressing (IHC ≥1+) or HER2-mutated], treatment naïve (no anti-PD-1, -PD-L1, or -HER2). Also includes 2 breast cohorts	Phase 1b; open-label, multicenter, nonrandomized, multidose, 2-part study	T-DXd + pembrolizumab	Part 1: dose escalation, recommended dose for expansion. Part 2: cORR by independent central review
DESTINY-Lung04 (37) (NCT05048797)	First line; HER2 mutated (exon19 or exon 20) unresectable, locally advanced, or metastatic NSCLC	Phase 3; open-label RCT	T-DXd in first line compared to SOC (platinum, pemetrexed, pembrolizumab)	PFS (blinded ICR) RECIST V1.1
Beamion LUNG-1 (38) (NCT04886804)	HER2 specific TKI; phase 1a—HER2 aberration-positive (gene mutations, rearrangements, amplification, or overexpression) solid tumours. Ib—HER2 mutated advanced/metastatic NSCLC	Phase Ia/Ib	Zongertinib (BI 1810631)	Phase 1a—MTD, DLTs. Phase 1b—ORR (central independent review, investigator review and according to RANO-BM by central independent review)
Completed				
HUDSON (39) (NCT03334617)	Second line; HER2 biomarker matched patients	Phase 2; multidrug umbrella study	T-DXd + durvalumab	HER2 expressing cohort n=23. Confirmed ORR 26.1% (80% CI: 14.3–41.3%), mPFS 2.8 mo (80% CI: 2.2–5.5), mOS 9.5 mo (80% CI: 6.6–12.4). HER2 mutated cohort n=20. Confirmed ORR 35% (80% CI: 20.7–51.8%); mPFS 5.7 mo (80% CI: 5.5–6.5); mOS 10.6 mo (80% CI: 8.9–NC)
SOHO-01 (40) (NCT05099172)	HER2 mutant; pretreated patients	Phase I/II study—expansion cohort	BAY2927088	ORR 70%; 95% CI: 51.3–84.4%. Median DOR not reached (median F/U 8 mo)

NSCLC, non-small cell lung cancer; IHC, immunohistochemistry; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor; RCT, randomised controlled trial; T-DXd, trastuzumab deruxtecan; SOC, standard of care; AEs, adverse events; SAEs, serious adverse events; cORR, confirmed objective response rate; PFS, progression-free survival; ICR, investigator confirmed response; MTD, maximum tolerated dose; DLT, dose-limiting toxicity; ORR, objective response rate; RANO-BM, Response Assessment in Neuro-Oncology for Brain Metastases; CI, confidence interval; mPFS, median PFS; mOS, median overall survival; mo, months; NC, non-calculable; F/U, follow-up.

molecular characterisation may aid in the understanding of the subtypes of HER2 altered NSCLC. A push to achieve consensus regarding HER2 overexpression testing and scoring is vital for not only study comparisons but to ensure fair eligibility for patients. On the global scale, inequity and access to drug is an ongoing issue if not available via insurance or universal healthcare. Despite the unanswered questions, the significant advancements in the treatment of HER2 altered NSCLC is showing promise for better patient outcomes.

Acknowledgments

None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Lung Cancer Research*. The article has undergone external peer review.

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-968/prf

Funding: None.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-968/coif). A.C.T. reports institutional funding from AstraZeneca, Takeda; consulting fees from Amgen, Pfizer, Bayer; honoraria from Roche, AstraZeneca, Guardant, Merck, Amgen, Takeda. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Li BT, Ross DS, Aisner DL, et al. HER2 Amplification and HER2 Mutation Are Distinct Molecular Targets in Lung Cancers. J Thorac Oncol 2016;11:414-9.
2. Riudavets M, Sullivan I, Abdayem P, et al. Targeting HER2 in non-small-cell lung cancer (NSCLC): a glimpse of hope? An updated review on therapeutic strategies in NSCLC harbouring HER2 alterations. ESMO Open 2021;6:100260.
3. Peters S, Stahel R, Bubendorf L, et al. Trastuzumab Emtansine (T-DM1) in Patients with Previously Treated HER2-Overexpressing Metastatic Non-Small Cell Lung Cancer: Efficacy, Safety, and Biomarkers. Clin Cancer Res 2019;25:64-72.
4. Kim EK, Kim KA, Lee CY, et al. The frequency and clinical impact of HER2 alterations in lung adenocarcinoma. PLoS One 2017;12:e0171280.
5. College of American Pathologists. CAP-ASCP-ASCO HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma Guideline 2016. Available online: https://www.cap.org/protocols-and-guidelines/cap-guidelines/current-cap-guidelines/her2-testing-and-clinical-decision-making-in-gastroesophageal-adenocarcinoma
6. Tan AC, Saw SPL, Chen J, et al. Clinical and Genomic Features of HER2 Exon 20 Insertion Mutations and Characterization of HER2 Expression by Immunohistochemistry in East Asian Non-Small-Cell Lung Cancer. JCO Precis Oncol 2022;6:e2200278.
7. Comprehensive molecular profiling of lung adenocarcinoma. Nature 2014;511:543-50.
8. Langer CJ, Stephenson P, Thor A, et al. Trastuzumab in the treatment of advanced non-small-cell lung cancer: is there a role? Focus on Eastern Cooperative Oncology Group study 2598. J Clin Oncol 2004;22:1180-7.
9. Gatzemeier U, Groth G, Butts C, et al. Randomized phase II trial of gemcitabine-cisplatin with or without trastuzumab in HER2-positive non-small-cell lung cancer. Ann Oncol 2004;15:19-27.
10. Hainsworth JD, Meric-Bernstam F, Swanton C, et al. Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa Multiple Basket Study. J Clin Oncol 2018;36:536-42.
11. Ogitani Y, Aida T, Hagihara K, et al. DS-8201a, A Novel HER2-Targeting ADC with a Novel DNA Topoisomerase I Inhibitor, Demonstrates a Promising Antitumor Efficacy

with Differentiation from T-DM1. Clin Cancer Res 2016;22:5097-108.
12. Harbeck N, Ciruelos E, Jerusalem G, et al. Trastuzumab deruxtecan in HER2-positive advanced breast cancer with or without brain metastases: a phase 3b/4 trial [published correction appears in Nat Med. 2024 Dec;30(12):3780.
13. Modi S, Saura C, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med 2020;382:610-21.
14. Cortés J, Kim SB, Chung WP, et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. N Engl J Med 2022;386:1143-54.
15. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med 2022;387:9-20.
16. Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. N Engl J Med 2020;382:2419-30.
17. Li BT, Smit EF, Goto Y, et al. Trastuzumab Deruxtecan in HER2-Mutant Non-Small-Cell Lung Cancer. N Engl J Med 2022;386:241-51.
18. Smit EF, Felip E, Uprety D, et al. Trastuzumab deruxtecan in patients with metastatic non-small-cell lung cancer (DESTINY-Lung01): primary results of the HER2-overexpressing cohorts from a single-arm, phase 2 trial. Lancet Oncol 2024;25:439-54.
19. Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial. J Clin Oncol 2024;42:47-58.
20. Raghav K, Siena S, Takashima A, et al. Trastuzumab deruxtecan in patients with HER2-positive advanced colorectal cancer (DESTINY-CRC02): primary results from a multicentre, randomised, phase 2 trial. Lancet Oncol 2024;25:1147-62.
21. Powell CA, Modi S, Iwata H, et al. Pooled analysis of drug-related interstitial lung disease and/or pneumonitis in nine trastuzumab deruxtecan monotherapy studies. ESMO Open 2022;7:100554.
22. Iwata H, Xu B, Kim SB, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in Asian patients with HER2-positive metastatic breast cancer. Cancer Sci 2024;115:3079-88.
23. Mittendorf EA, Wu Y, Scaltriti M, et al. Loss of HER2 amplification following trastuzumab-based neoadjuvant systemic therapy and survival outcomes. Clin Cancer Res 2009;15:7381-8.
24. Tarantino P, Ajari O, Graham N, et al. Evolution of HER2 expression between pre-treatment biopsy and residual disease after neoadjuvant therapy for breast cancer. Eur J Cancer 2024;201:113920.
25. de Langen AJ, Jebbink M, Hashemi SMS, et al. Trastuzumab and paclitaxel in patients with EGFR mutated NSCLC that express HER2 after progression on EGFR TKI treatment. Br J Cancer 2018;119:558-64.
26. Bartley AN, Washington MK, Colasacco C, et al. HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline From the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology. J Clin Oncol 2017;35:446-64.
27. Jørgensen JT, Egebjerg K, Lænkholm AV, et al. Human Epidermal Growth Factor Receptor 2 Pan Tumor Indication for Trastuzumab Deruxtecan. J Clin Oncol 2024;42:4130-3.
28. Liu M, Vathiotis I, Robbins CJ, et al. Quantitative Measurement of HER2 Expression in Non-Small Cell Lung Cancer With a High-Sensitivity Assay. Mod Pathol 2024;37:100556.
29. Makker V, Lee JY, Oh DY, Oaknin A, Puvvada SD, Cecchi F, et al. 148P DESTINY-PanTumor02 study of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-expressing solid tumors: Exploratory biomarker analyses of HER2 expression and gene amplification in tissue and plasma. Annals of Oncology. 2023;34:S239-S40.
30. Li BT, Meric-Bernstam F, Bardia A, et al. Trastuzumab deruxtecan in patients with solid tumours harbouring specific activating HER2 mutations (DESTINY-PanTumor01): an international, phase 2 study. Lancet Oncol 2024;25:707-19.
31. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (Non-Small Cell Lung Cancer Version 1.2025). Available online: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
32. Ahn MJ, Tanaka K, Paz-Ares L, et al. Datopotamab Deruxtecan Versus Docetaxel for Previously Treated Advanced or Metastatic Non-Small Cell Lung Cancer: The Randomized, Open-Label Phase III TROPION-Lung01 Study. J Clin Oncol 2025;43:260-72.
33. Paz-Ares L, Ahn MJ, Lisberg AE, et al. 1314MO TROPION-Lung05: Datopotamab deruxtecan (Dato-DXd) in previously treated non-small cell lung cancer (NSCLC) with actionable genomic alterations (AGAs). Ann Oncol 2023;34:S755-S756.
34. Hurvitz SA, Hegg R, Chung WP, et al. Trastuzumab

deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. Lancet 2023;401:105-17.
35. Planchard D, Brahmer JR, Yang JCH, et al. 1507TiP Phase Ib multicenter study of trastuzumab deruxtecan (T-DXd) and immunotherapy with or without chemotherapy in first-line treatment of patients (pts) with advanced or metastatic nonsquamous non-small cell lung cancer (NSCLC) and HER2 overexpression (OE): DESTINY-Lung03. Ann Oncol 2023;34:S848-S849.
36. Borghaei H, Besse B, Bardia A, et al. P01.02 Trastuzumab Deruxtecan Plus Pembrolizumab in Advanced/Metastatic Breast or Non-Small Cell Lung Cancer: A Phase 1b Study. J Thorac Oncol 2021;16:S236.
37. Li BT, Ahn MJ, Goto K, et al. Open-label, randomized, multicenter, phase 3 study evaluating trastuzumab deruxtecan (T-DXd) as first-line treatment in patients with unresectable, locally advanced, or metastatic non–small cell lung cancer (NSCLC) harboring HER2 exon 19 or 20 mutations (DESTINY-Lung04). J Clin Oncol 2022;40:TPS9137.
38. Heymach J, Opdam F, Barve MA, et al. Phase Ia/Ib trial of zongertinib (BI 1810631), a HER2-specific tyrosine kinase inhibitor (TKI), in patients (pts) with HER2 aberration-positive solid tumors: Updated Phase Ia data from Beamion LUNG-1, including progression-free survival (PFS) data. J Clin Oncol 2024;42:8514.
39. Cheema P, Hartl S, Koczywas M, et al. 695 Efficacy and safety of trastuzumabderuxtecan (T-DXd) with durvalumab inpatients with non-small cell lung cancer (her2altered NSCLC) WHO progressed on anti-PD1/PDL1 therapy (HUDSON). J Immunother Cancer 2023;11:A787.
40. Girard N, Kim TM, Kim HR, et al. Safety and anti-tumor activity of BAY 2927088 in patients with HER2-mutant NSCLC: Results from an expansion cohort of the SOHO-01 phase I/II study. J Clin Oncol 2024;42:LBA8598.
41. Tolcher AW, Carneiro BA, Dowlati A, et al. A first-in-human study of mirzotamab clezutoclax as monotherapy and in combination with taxane therapy in relapsed/refractory solid tumors: Dose escalation results. J Clin Oncol 2021;39:3015.
42. Shang C, An G, Guo Y, et al. Abstract 2977: A first-in-class anti-HER2/TROP2 bispecific antibody-drug conjugate (YH012) exhibits potent anti-tumor efficacy. Cancer Res 2023;83:2977.
43. Schram A, Goto K, Kim DW, et al. 1315MO Durable efficacy of zenocutuzumab, a HER2 x HER3 bispecific antibody, in advanced NRG1 fusion-positive (NRG1+) non-small cell lung cancer (NSCLC). Ann Oncol 2023;34:S756-S757.

Cite this article as: Pitiyarachchi O, Tan AC. Trastuzumab deruxtecan in HER2 overexpressing non-small cell lung cancer (NSCLC). Transl Lung Cancer Res 2025;14(2):314-322. doi: 10.21037/tlcr-24-968