Title

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REVIEW

Spotlight on Trastuzumab Deruxtecan (DS-8201, T-DXd) for *HER2* Mutation Positive Non-Small Cell Lung Cancer

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Abstract: Human epidermal growth factor receptor 2 (*HER2*) is a proto-oncogene that, when mutated or overexpressed, plays an important role in oncogenesis. The landscape of *HER2*-positive breast cancer has changed dramatically over the past 2 decades with the FDA approval of a growing number of agents (antibodies, tyrosine kinase inhibitors, and antibody-drug conjugates) targeting the *HER2* receptor. *HER2* inhibition has also been approved for *HER2*-positive gastric cancer. *HER2* is amplified in 9% and mutated in 3% of lung cancer. Historically, *HER2*-targeted therapy for lung cancer with trastuzumab, pertuzumab, and trastuzumab emtansine has failed to demonstrate a survival benefit. Trastuzumab deruxtecan (T-DXd) is a novel antibody–drug conjugate with a tetrapeptide linker, which delivers a topoisomerase I inhibitor with a drug-to-antibody ratio of 7~8. The potency of the active payload, as well as its significant bystander effect, resulted in significant anti-tumor activity. The DESTINY-Lung01 trial evaluated T-DXd in *HER2*-positive non-squamous non-small cell lung cancer (NSCLC) and reported a progression-free survival of 14 months in *HER2*-mutated NSCLC, earning its breakthrough designation by the FDA. In this review, we will discuss the structural characteristics, pharmacodynamics, and pharmacokinetics of T-DXd. We will also shed light on the preclinical and ongoing clinical trials of T-DXd along with future directions in the management of *HER2* positive lung cancer.

Keywords: T-DXd, DS8201, antibody drug conjugate, *HER2*

Introduction

Human epidermal growth factor receptor 2 (*HER2)* is a transmembrane glycoprotein receptor with intracellular tyrosine kinase activity,[1] belonging to the epidermal growth factor receptor (*EGFR*) family. It is encoded by *ERBB2* gene on chromosome 17. Activation of this receptor tyrosine kinase family triggers a cascade of subcellular signal transduction pathways controlling epithelial cell growth, differentiation, motility, and likely angiogenesis in several cell lineages[2–5] (Figure 1). Overexpression of *HER2* activates the phosphoinositide 3-kinase/protein kinase B (*PI3K/Akt*) pathway, favoring cell proliferation by inhibiting apoptosis. Besides its potentiation as a proliferative effect, *HER2* contributes to metastasis by promoting secretion of the matrix metalloproteases and up-regulating specific angiogenic factors, including vascular endothelial growth factor (*VEGF*).[6–8]

HER2 in Malignancy

HER2 can be activated through amplification or mutation.[9] Overexpression of *HER2* plays a central role in pathogenesis of about 30% of breast cancers[10] and

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has been the poster child for success in the development of targeted drug therapy. In non-small cell lung cancer (NSCLC), *HER2* overexpression has been implicated in approximately 20% of adenocarcinoma subtypes. Additionally, *HER2* dysregulation has been identified as a mechanism of resistance in *EGFR* tyrosine kinase inhibitor (TKI) therapy targeted with osimertinib.[11] *HER2* amplification, as an *EGFR*-independent mechanism, has been identified in 5% and 2% of patients with acquired resistance to second- and first-line osimertinib, respectively.[12,13] The familial relationship between *EGFR* and *HER2* and their potential to heterodimerize (Figure 1) provides an elegant rationale for the development of resistance.

HER2 Testing

Tissue testing for overexpression includes immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH) for amplification. *HER2* mutation, usually comprising an in-frame insertion in exon 20,[14] is assessed by next-generation sequencing.[15] Patterns for *HER2* overexpression by IHC are scored as IHC 0/1+ (negative/low), IHC 2+ (equivocal) or IHC 3+ (positive). For FISH assessment, positivity for *HER2* amplification is defined by a *HER2*:CEP17 (centromere probe 17) ratio of ≥2.[16] In adenocarcinoma of the lung, *HER2* protein overexpression, defined as moderate or strong (2+/3+) membranous staining, was the most frequently reported in up to 20% of cases, whereas *HER2* amplification and mutation represented 9% and 3% of cases, respectively.[9] While the prevalence of *HER2* mutation is near that of breast cancer (2%)[17] and gastric adenocarcinoma (3%)[18], prevalence of amplification is lower (20–30%[19] and up to 34%,[20] respectively). To assist in the detection of such targetable biomarkers, liquid biopsy (Guardant360 CDx) has recently been validated for use in lung cancer. In the NILE study, comprehensive cell-free DNA (cfDNA) analysis from patients with newly diagnosed metastatic NSCLC was compared to standard of care tissue genotyping. Use of cfDNA successfully identified guideline-recommended biomarkers, including *HER2* alterations, at similar rates to tissue testing with a faster turnaround time.[21] As opposed to tissue biopsy, cfDNA analysis carries several advantages including easy sampling, mitigation of potential heterogeneity in intra-tumoral *HER2* expression/amplification, and avoidance of biopsy complications. The ease of sampling has increased the frequency of detecting targetable mutations, including *HER2*.

HER2-Targeted Therapy

HER2-targeted agents have significantly improved the prognosis of *HER2*-positive breast cancer. As documented by Seah et al, the overall survival of *HER2*-positive metastatic breast cancer patients increased to 4.5 years.[22] NCCN guidelines have also incorporated the addition of *HER2* inhibition in the first-line setting to *HER2*-expressing gastric cancers. Unfortunately, such success has yet to be replicated in lung cancer, and there are currently no FDA-approved *HER2*-targeted therapies in this setting. The anti-*HER2* monoclonal antibody trastuzumab was evaluated in combination with gemcitabine/cisplatin in treatment-naïve NSCLC patients with no evidence of improved clinical activity,[23] as well as in combination with docetaxel in those who progressed on platinum-based therapy with disappointing results.[24] A Phase II randomized clinical trial showed no difference in response rate or median survival between trastuzumab with docetaxel and trastuzumab with paclitaxel in previously untreated patients.[25] More recently, however, the combination of trastuzumab and paclitaxel in *EGFR*-mutated and *HER2*-expressing (≥ IHC1+) NSCLC that progressed on first-line TKI therapy demonstrated acceptable tolerability with a promising objective response rate of 46%.[26] Pertuzumab, a *HER2* dimerization inhibitor that binds to a separate domain, initially showed antitumor activity in preclinical studies of NSCLC.[27] Despite a promising Phase I clinical trial,[28] two phase II trials of pertuzumab monotherapy in previously treated NSCLC patients showed no response.[29,30] The combination of pertuzumab and erlotinib initially showed a response rate of 20% in *EGFR*-mutated NSCLC in a Phase 1b trial,[31] but the combination was not pursued after unacceptable toxicity was demonstrated in a subsequent phase II trial.[32]

Trastuzumab Emtansine (T-DM1) was the first antibody–drug conjugate (ADC) tested in advanced *HER2*-mutated NSCLC. A phase II trial compared the efficacy of T-DM1 by *HER2* expression and showed a modest response rate of 20% in metastatic NSCLC expressing *HER2* 3+ by IHC, but the response was not seen in those with 2+ IHC. Moreover, no PFS or OS advantage was observed in either cohort.[33,34] Another phase II trial in *HER2*-positive NSCLC including IHC 3+, exon 20 mutated, and IHC 2+ with positive FISH was terminated due to lack of efficacy of T-DM1.[35] To date, only one trial

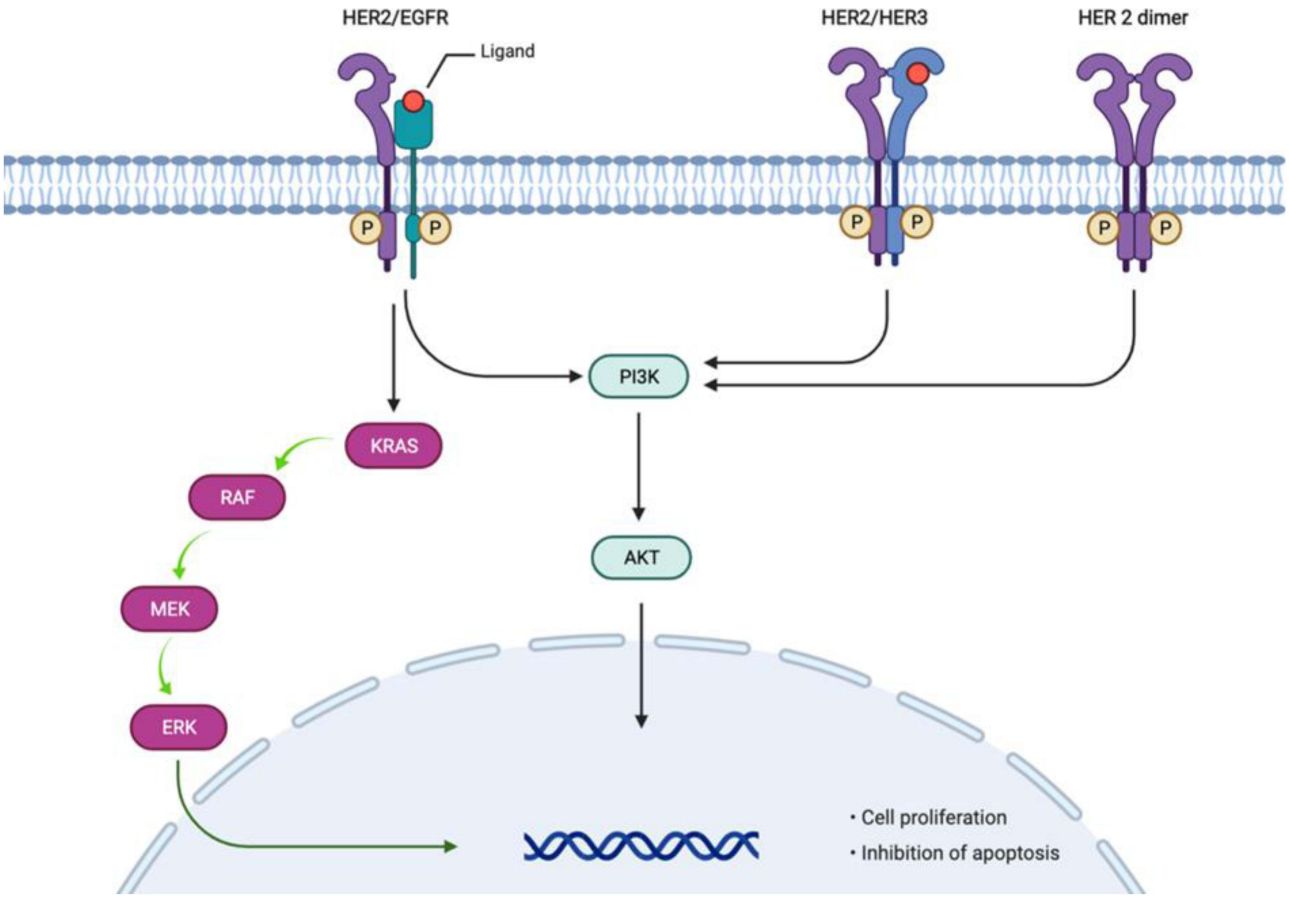

Figure 1 HER2 signaling pathway (Adapted from "HER2 Signaling Pathway", by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates).

by Li et al demonstrated an encouraging median PFS of 5 months in this setting.[36] Clinical efficacy was also demonstrated in *HER2*-amplified NSCLC.[37]

Trastuzumab Deruxtecan

Trastuzumab deruxtecan (T-DXd) was originally developed by Daiichi Sankyo (now being co-developed with AstraZeneca) as a novel antibody–drug conjugate (ADC) targeting *HER2*. T-DXd gained FDA approval in December 2019 for unresectable or metastatic *HER2*-positive breast cancer after two or more prior lines of anti-*HER2* therapy[38]. In the Phase II trial evaluating T-DXd in *HER2*-positive metastatic breast cancer patients who had received previous treatment with trastuzumab emtansine, the median duration of response to T-DXd was 14.8 months (95% CI, 13.8 to 16.9) and the median duration of progression-free survival was 16.4 months (95% CI, 12.7 to not reached).[39] Subsequently, the FDA approved T-DXd (famtrastuzumab deruxtecan-nxki) in January 2021 for locally advanced or metastatic *HER2* positive gastric or gastroesophageal junction (GEJ) adenocarcinoma based on the results of DESTINY-Gastric01.[40] In this trial, T-DXd was superior to single-agent chemotherapy (irinotecan or paclitaxel) as a third (or later) line treatment for *HER2*-positive gastric and GEJ adenocarcinoma with a median OS of 12.5 months in the T-DXd arm compared to 8.4 months in the chemotherapy arm (HR 0.59; 95% CI: 0.39, 0.88, p=0.0097) and ORR of 40.5% with T-DXd compared to 11.3% in those treated with chemotherapy. T-DXd was also evaluated in *HER2*-positive refractory colon cancer patients (phase II DESTINY-CRC01 trial) and showed promising results with ORR of 45% at a median follow-up of 27 weeks.[41] T-DXd is currently under investigation in numerous tumor types including biliary tract, urothelial bladder cancer, cervical cancer, endometrial cancer, ovarian cancer, pancreatic cancer (NCT04482309), and lung cancer.[42]

This review will focus on the role of T-DXd in lung cancer. We will discuss the structural characteristics, pharmacodynamics, and pharmacokinetics of T-DXd, and shed light on the preclinical and ongoing clinical trials of T-DXd along with the future directions in the management of *HER2*-positive lung cancer.

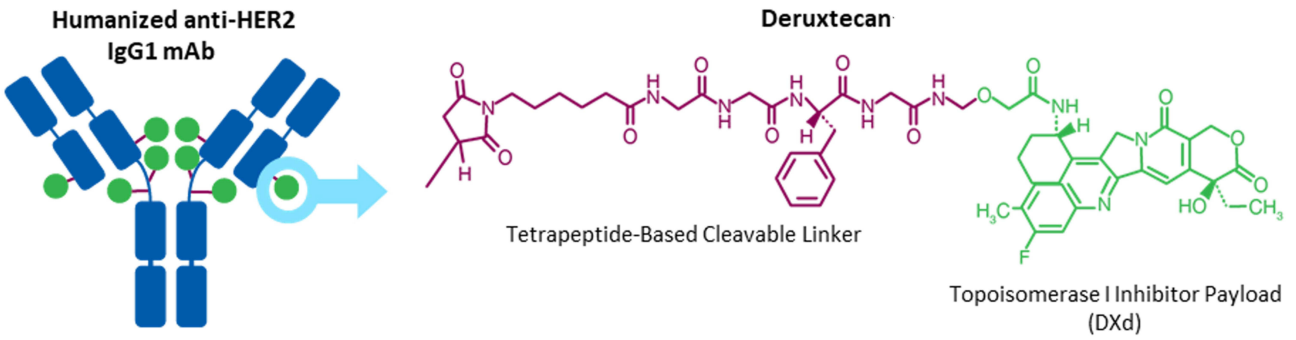

Figure 2 Structure of Trastuzumab Deruxtecan.
Notes: Reproduced with permission from Egbert F. Smit, Kazuhiko Nakagawa, Misako Nagasaka, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-mutated metastatic non-small cell lung cancer (NSCLC): Interim results of DESTINY-Lung01. J Clin Oncol. 2020;38(15_suppl):9504. copyright 2020, Wolters Kluwer Health, Inc.[56]

Structural Characteristics of T-DXd

Trastuzumab deruxtecan (previously called DS-8201a) is an antibody–drug conjugate (ADC) composed of three portions: an anti-*HER2* antibody, a maleimide peptide linker, and a cytotoxic payload (DX-8951f)[43,44] (Figure 2). The anti-*HER2* antibody, MAAL-9001, is a humanized monoclonal immunoglobulin G1 with the same amino acid sequence as trastuzumab. Binding to *HER2* positive tumor cells by MAAL-9001 leads to drug endocytosis.[44] The tetrapeptide linker conjugates the cytotoxic load to the antibody. When circulating in the blood stream, the linker remains stable; however, once inside the cell, cleavage by lysosomal cathepsins releases the cytotoxic payload. Since cathepsins are upregulated in tumor cells, selective targeting of these cells occurs and limits systemic toxicity.[45,46] DX-8951f, and its derivative MAAA-1181a (DXd), are topoisomerase I inhibitors of 10-fold potency compared to the active metabolite of irinotecan (SN-38) in vitro.[38] The payload-linker complex is connected to the antibody by cysteine-based residues. Drug-to-antibody ratio (DAR) is defined by the maximum number of payload molecules that are attached to the antibody. One of the key characteristics of T-DXd is a higher DAR (~7 to 8) compared with other ADCs, enhancing antitumor activity.[43] Additionally, the lipophilic nature of DXd allows for a significant bystander effect.[47]

Pharmacodynamics

By binding to *HER2*-positive tumor cells, the antigen-ADC complex undergoes endocytosis and the tetrapeptide linker is cleaved by lysosomal cathepsins, releasing the payload. DXd, in turn, inhibits DNA replication and induces apoptosis through binding of topoisomerase I-DNA complex (Figure 3). In in vitro pharmacologic studies,[48] DXd inhibited DNA topoisomerase I with an IC50 of 0.31 µmol/L (vs 2.78 for SN-38). In addition, MAAL-9001 blocks Akt phosphorylation, leading to cell growth inhibition. Chk1 and Histone HAX2.X phosphorylation is also stimulated by DXd, resulting in DNA damage. Therefore, T-DXd combines the pharmacological activity of MAAL-9001, the antibody component, and MAAA-1181a, the cytotoxic part, by exhibiting *HER2*-specific cell growth inhibition and antitumor activity, respectively. In a *HER2*-positive gastric cancer NCI-N87 model,[48] tumor regression was observed with T-DXd but not with T-DM1, which was attributed to the difference in payload mechanism of action.

Pharmacokinetics

Pharmacokinetic profiles of T-DXd were studied in *HER2*-positive tumor-bearing mice.[49] Following IV administration of T-DXd, the pharmacokinetic profiles of the T-DXd and the total antibody (conjugated and unconjugated) were almost similar, indicating that the bio-linker is stable in circulation. This observation may be a significant factor in limiting systemic exposure and toxicity of DXd.

Biodistribution studies using radiolabeled T-DXd demonstrated tumor-specific distribution and long-term retention. DXd was the main catabolite released from T-DXd in tumors, with exposure levels at least five times higher than those in normal tissues and seven times higher than those achieved by a non-targeted control ADC. After IV administration of DXd, there was rapid clearance from the circulation (T1/2: 1.35 h) and excretion was mainly through feces in its intact form.

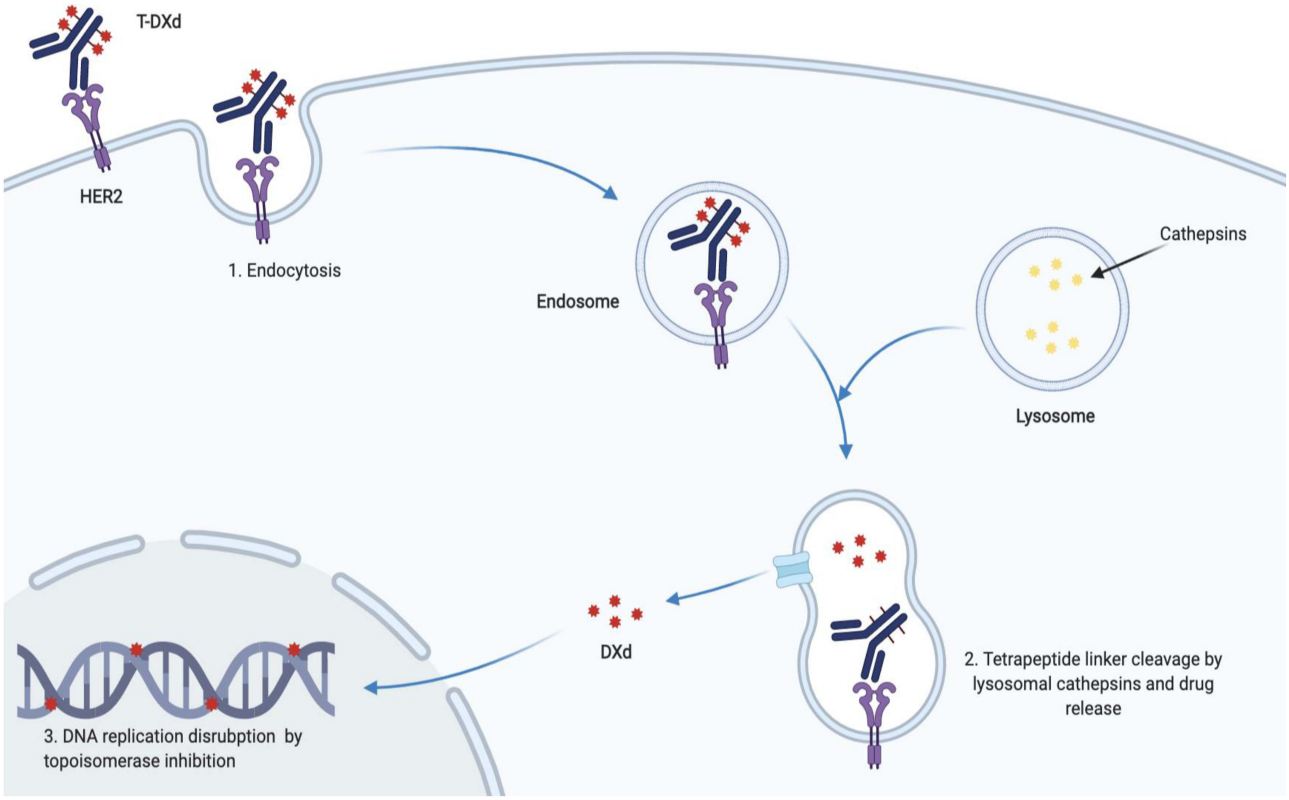

Figure 3 Trastuzumab Deruxtecan mechanism of action (Adapted from "Antibody–Drug Conjugate Drug Release", by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates).

DXd is primarily metabolized by cytochrome P450 (CYP) 3A4 in vitro. Organic anion transporting peptide (OATP) was proposed to be responsible for payload uptake by the liver.[50] Trastuzumab degradation is proposed to be similar to that of endogenous IgG. Clearance of T-DXd is approximately 0.42 L/day.[38] Decreased clearance and prolonged half-life of T-DXd were associated with higher dosing, indicating a non-linear process. DXd did not exhibit inhibition or induction potential of CYP1A2 or CYP2B6.[50] No antibodies against T-DXd were detected in the blood. The recommended dose based on clinical studies in metastatic breast and gastric cancers is 5.4 mg/kg and 6.4 mg/kg, respectively.[51]

Preclinical Studies

Antitumor efficacy of T-DXd was correlated with *HER2* protein expression, not *HER2* gene amplification.[38] Activity was even detected in cell lines expressing low levels of *HER2*.[52] Due to the high membrane permeability of DXd, bystander killing by T-DXd was observed in vitro. Within the tumor tissue, *HER2*-negative cells that are adjacent to *HER2*-positive cells were affected.[47,52] This finding, which has not been demonstrated in T-DM1, is clinically significant in tumors with *HER2* heterogeneity.[53] In addition, T-DM1 resistant xenograft models were sensitive to T-DXd. In N87-TDMR (T-DM1 resistant gastric cell line), efflux of the payload due to upregulation of cell pumps was suggested to be the mechanism of resistance to T-DM1. Thus, the activity of T-DXd was proposed to be either from low interaction between DXd and efflux pumps, or compensation for efflux activity by high DAR.[54] Antitumor activity of T-DXd was even detected in low *HER2* expression.[48,52]

Clinical Trials

Multiple investigational studies are being conducted in NSCLC either as monotherapy or in conjugation with other drug classes (Table 1).

Phase I/II Trials

T-DXd was investigated in a basket phase I study of multiple types of *HER2*-expressing or mutant solid tumors.[55] Out of 18 patients with NSCLC, 11 harbored *HER2* mutations, with the most common being exon 20

Table 1 Clinical Trials of Trastuzumab Deruxtecan in Non-Small Cell Lung Cancer (NSCLC)

NCT	Title	Phase	Combination Therapy	Status
04644237	A Phase 2, Multicenter, Randomized Study of Trastuzumab Deruxtecan in Subjects with *HER2*-mutated Metastatic Non-small Cell Lung Cancer (NSCLC) (DESTINY- LUNG02)	II	N/A	Recruiting
03505710	A Phase 2, Multicenter, Open-Label, 2-Cohort Study of Trastuzumab Deruxtecan (DS-8201a), an Anti-*HER2* Antibody Drug Conjugate (ADC), for *HER2*-Over-Expressing or -Mutated, Unresectable and/or Metastatic Non-Small Cell Lung Cancer (NSCLC) (DESTINY- LUNG01)	II	N/A	Active, not recruiting[56]
04042701	A Phase 1b, Multicenter, Two-Part, Open-Label Study of Trastuzumab Deruxtecan (DS-8201a), An Anti-Human Epidermal Growth Factor Receptor-2 (*HER2*)-Antibody Drug Conjugate (ADC), In Combination with Pembrolizumab, An Anti-PD-1 Antibody, In Subjects with Locally Advanced/Metastatic Breast or Non-Small Cell Lung Cancer (NSCLC)	Ib	Pembrolizumab	Recruiting
04686305	A Phase Ib Multicenter, Open-label Dose-escalation Study to Evaluate the Safety and Tolerability of Trastuzumab Deruxtecan (T-DXd) and Durvalumab in Combination with Cisplatin, Carboplatin or Pemetrexed in First-line Treatment of Patients with Advanced or Metastatic Non-squamous Non-small Cell Lung Cancer (NSCLC) and Human Epidermal Growth Factor Receptor 2 Overexpression (*HER2+*) (DESTINY- Lung03)	Ib	• Durvalumab • Durvalumab + Cisplatin • Durvalumab + Carboplatin • Durvalumab + Pemetrexed	Active, not recruiting
03334617	An Open-Label, Multi-Drug, Biomarker-Directed, Multi-Centre Phase II Umbrella Study in Patients with Non-Small Cell Lung Cancer, Who Progressed on an Anti-PD-1/PD-L1 Containing Therapy (HUDSON)	II	Durvalumab	Recruiting

insertions. IHC score for *HER2* expression was 1+ in 8 patients, 2+ in one, and 3+ in two patients. Five had an IHC score of 0 and two patients lacked evaluation of *HER2* expression. Only five patients had been previously treated with *HER2*-targeted therapy. T-DXd was dosed at 6.4 mg/kg. Confirmed objective response rate (ORR) for all tumor types was 55.6%, and median PFS was 11.3 months (95% CI, 7.2–14.3 months). However, response to treatment in *HER2*-mutant NSCLC was more evident with ORR and disease control rate (DCR) of 72.7% and 90.9%, respectively. Treatment-related adverse events were reported in two patients only (11.1%). It was concluded that T-DXd was clinically active and well tolerated across multiple types of tumors, particularly *HER2*-mutant NSCLC.[55]

The DESTINY-Lung01 trial evaluated T-DXd at a dose of 6.4 mg/kg in two separate cohorts of non-squamous NSCLC: *HER2*-mutated and *HER2*-overexpressed (IHC 2 + and IHC 3+). Patients with central nervous system metastases were eligible, unless untreated, symptomatic, or requiring corticosteroids or anticonvulsants. From May 21, 2018 until data cutoff on November 25th, 2019, 42 patients with *HER2*-mutant NSCLC were enrolled and interim data for this group were presented at the ASCO 2020 meeting. The median number of prior lines of therapy was 2 and included platinum-based chemotherapy, as well as PD-1 and PD-L1 inhibitors. Twenty-six patients had confirmed response (61.9%) with DCR of 90.5% (95% CI, 77.4–97.3%) and a median PFS of 14 months. In addition, median duration of response (DOR) was not achieved at the time of data cutoff.[56] Given these results, T-DXd was granted a breakthrough therapy designation in May 2020 for patients with metastatic *HER2*-mutated NSCLC who progressed on or after platinum-based chemotherapy and is currently listed on the NCCN guidelines.[57]

Updated results for the *HER2*-overexpressing cohort were presented at IASLC WCLC in January 2021. ORR and DCR from the 49 enrolled patients were lower than that of the *HER2*-mutant cohort (24.5% and 69.1%, respectively) with a median duration of response of 6 months. Median PFS was 5.4 months (Table 2). Ultimately, T-DXd, at 6.4mg/kg, demonstrated antitumor activity in this cohort.[58]

Table 2 Comparison of DESTINY-Lung01 Trial Results Between HER-Mutant and HER2-Overexpressing Cohorts

DESTINY-Lung01		
	HER Mutation	***HER2* Overexpression**
Patients (n)	42	49
Objective response rate Complete response Partial response	n = 26 (61.9%) n = 1 n = 25	n = 2 (24.5%) n = 1 n = 11
Duration of response	Not reached	6 months
Disease control rate	90.5%	69.1%
Progression-free survival	14 months	5.4 months
Dose interruption	n = 25 (59.5%)	n = 26 (53.1%)
Dose reduction	n = 16 (38.1%)	n = 17 (34.7%)
Dose discontinuation	n = 10 (23.8%)	n = 11 (22.4%)
Treatment emergent adverse events Nausea Alopecia Anemia Decreased appetite Decreased neutrophil count Fatigue	n = 42 (100%) n = 32 (76.2%) n = 20 (47.6%) n = 18 (42.9%) n = 18 (42.9%) n = 18 (42.9%) -	n = 49 (100%) n = 29 (59.2%) - - n = 19 (38.8%) - n = 16 (32.7%)
Grade 3 adverse events Decreased neutrophil count Anemia Fatigue	n = 27 (64.3%) n = 11 (26.2%) n = 7 (16.7%) -	n = 36 (73.5%) n = 10 (20.4%) - n = 5 (10.2%)

Safety, Tolerability, and Toxicity Profile

In the DESTINY-Lung01 study, interim data from the *HER2*-mutant group reported grade 3 treatment-related adverse events in over half of the participants (64.3%), including neutropenia and anemia. Out of the 42 enrolled patients, development of Interstitial Lung Disease (ILD) was demonstrated in 5 patients (All grade 2). Due to treatment-emergent adverse events (TEAEs), 10 patients had to discontinue treatment (23.8%) and 16 received dose-reduction (38.1%), while 25 had dose-interruptions (59.5%).[56] Updated safety results in 49 patients with *HER2*-overexpression demonstrated nausea, decreased appetite, and fatigue as the most common TEAE. Grade ≥3 TEAEs were reported in 73.5% of patients and included neutropenia and fatigue. T-DXd dose had to be reduced or interrupted in 17 and 26 patients, respectively. Compared to the *HER2*-mutant cohort, the incidence of ILD was slightly higher (16.3% vs 11.5%), and grade 4 severity was reported in 3 patients (Table 3). Despite the demonstrated tolerability, ILD remains a concerning and serious adverse event.[58]

In a phase I dose–escalation study, 24 patients with breast, gastric, and gastroesophageal cancers were treated with different doses of T-DXd. Gastrointestinal and hematological events were reported. Three patients experienced serious adverse events: intestinal perforation, febrile neutropenia, and cholangitis. Three patients had to discontinue treatment due to drug-induced toxicity, including thrombocytopenia and pneumonitis. Higher doses were more heavily associated with high-grade adverse events. Unlike trastuzumab, cardiac toxicity was not observed across all cohorts.[45]

In a recent trial in patients with low *HER2*-expressing breast cancer, T-DXd was administered at 5.4 mg/kg or 6.4 mg/kg. Eleven out of 54 participants (20.4%) discontinued therapy due to adverse events, most commonly pneumonitis and ILD. Grade III toxicity, in addition to

Table 3 ILD Incidence Rate and Grading Among DESTINY Trials

	DESTINY-Breast01	DESTINY-Gastric01	DESTINY-Lung01	
			HER2 Mutation	*HER2* Overexpression
Number of treated patients	184	125	42	49
T-DXd dose	5.4 mg/kg	6.4 mg/kg	6.4 mg/kg	6.4 mg/kg
Number of patients with ILD	25 (13.6%)	12 (10%)	5 (11.5%)	8 (16.3%)
ILD Grading				
I	20 (80%)	9 (75%)		2 (25%)
II			5 (100%)	3 (37.5%)
III	1 (4%)	2 (16.7%)		
IV		1 (8.3%)		
V	4 (16%)			3 (3.75%)

Notes: Pneumonitis grading: Grade 1: asymptomatic; clinical or diagnostic observations only; intervention not indicated; Grade 2: symptomatic; medical intervention indicated; limiting instrumental ADL; Grade 3: severe symptoms; limiting self-care ADL*; oxygen indicated; Grade 4: life-threatening respiratory compromise; urgent intervention indicated (eg, tracheostomy or intubation); Grade 5: death. Shading refers to no ILD reported at the specific grade.

treatment discontinuation and interruption, were more frequently reported in the high-dose group. Drug-induced ILD occurred in eight patients (14.8%), all in the 6.4 mg/kg cohort, leading to death in three patients despite corticosteroid therapy.[59]

In the DESTINY-Breast01 trial, T-DXd was evaluated at a dose of 5.4 mg/kg in 184 patients. Leukopenia, anemia, fatigue, and nausea were the most commonly observed grade ≥3 toxicities. Febrile neutropenia was witnessed in three patients. Grade 2 and 3 systolic dysfunction was reported in 3 asymptomatic patients, whose ejection fraction recovered after holding therapy. Nine patients (4.9%) had QT interval prolongation. ILD and pneumonitis were the main reasons for treatment discontinuation. Treatment-induced ILD was reported in 25 patients (13.6%), predominantly of low-grade severity. Median time of onset was 193 days with median time to recovery of 34 days. Recovery was demonstrated in seven patients (28%).[39] Of the 20 patients who were reported to have ILD of grade 2 or higher, 13 received glucocorticoids and 7 were hospitalized with four deaths (2.2% of the patients) attributable to interstitial lung disease.[39]

Hematologic toxicity was similar in DESTINY-Gastric01, where 125 patients received T-DXd at a dose of 6.4 mg/kg. Six patients developed febrile neutropenia. Treatment-related systolic dysfunction was not demonstrated. ILD or pneumonitis were reported in 12 participants (10%), none of grade 5 severity; median time until the date of onset was 84.5 days. Eight cases had recovered or were recovering at the time of analysis.[40]

Ongoing T-DXd Trials

Results of the phase I DESTINY-Lung01 trial achieved breakthrough designation status for the use of T-DXd in metastatic *HER2*-mutated NSCLC progressing on platinum-based therapy, and full FDA approval is anticipated with the completion of the subsequent DESTINY-Lung02 trial. T-DXd has been approved at a dose of 5.4 mg/kg for metastatic *HER2*-positive breast cancer and 6.4 mg/kg for gastric cancer. DESTINY-Lung02 (NCT0464437), a randomized phase II study comparing the two dose levels of 5.4 or 6.4 mg/kg, has started enrolling in March 2021 (Figure 4). Patients who have received at least one line of platinum-based therapy are eligible with the primary endpoint being objective response rates.

The optimal sequencing of T-DXd and chemo-immunotherapy in *HER2*-mutated NSCLC will likely be addressed in future trials. Few trials are looking into whether combining T-DXd with immunotherapy or chemoimmunotherapy holds a therapeutic advantage. The combination of T-DXd and pembrolizumab will be investigated in a phase Ib study in patients with locally advanced and metastatic *HER2*-positive breast and

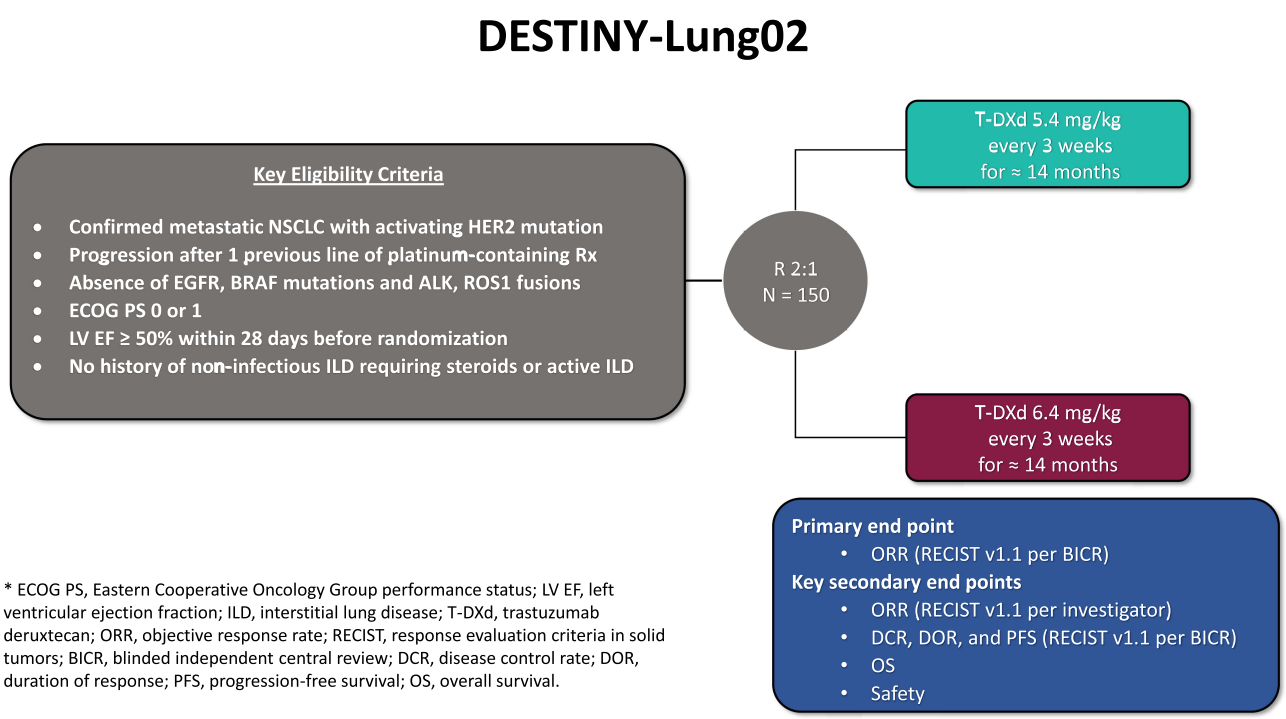

Figure 4 Schema for DESTINY-Lung02. Additional details can be found at: https://clinicaltrials.gov/ct2/show/NCT04644237.
Abbreviations: *ECOG PS, Eastern Cooperative Oncology Group performance status; LV EF, left ventricular ejection fraction; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; ORR, objective response rate; RECIST, response evaluation criteria in solid tumors; BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; PFS, progression-free survival; OS, overall survival.

NSCLC who did not receive prior PD-1, PD-L1 or *HER2*-targeted therapy. In part 1 (dose-escalation phase), T-DXd will be administered at a dose of 3.2 or 5.4 mg/kg. The recommended dose for part 2 (expansion phase) will be determined in the dose-escalation part. *HER2*-mutant or *HER2*-expressing (IHC ≥ 1+) NSCLC patients will be enrolled. The first patient enrolled on February 10th, 2020. Dose-limiting toxicity and confirmed ORR are the primary outcomes in dose-escalation and expansion parts, respectively.[60] Similarly, the HUDSON trial (NCT03334617), an umbrella phase II trial, is ongoing to evaluate the combination of durvalumab with other classes of drugs, including T-DXd. Multiple arms of treatment are under evaluation, including NSCLC patients who have progressed to PD-1/PD-L1 inhibition. T-DXd will be administered at a dose of 5.4 mg/kg with primary endpoint being objective response rate. DESTINY-Lung03, a phase 1b trial, evaluating the safety of T-DXd combined with immuno- and cytotoxic therapy is also underway. Patients with treatment-naïve *HER2*-overexpressing (IHC 3+ or 2+) NSCLC will be included. Initially, at least six patients will receive T-DXd plus durvalumab for safe run-in. This is followed by dose–escalation, where patients will be treated with T-DXd plus durvalumab and cytotoxic therapy (either cisplatin, carboplatin, or pemetrexed). Optional dose-expansion will be conducted depending on data from the dose-escalation phase. In addition to safety evaluation, determination of an appropriate phase II dose is the primary endpoint.[61] The safety profile of combination therapy, particularly the potential for developing pneumonitis, will be critical to the fate of these combinations.

While the response rate of T-DXd in *HER2*-overexpressing NSCLC was less impressive (ORR 24.5%), the patients treated had a median of 3 previous lines of therapy. After progression to platinum- and checkpoint inhibitor-based therapies, the current options for adenocarcinoma of the lung consist of single-agent chemotherapy (docetaxel, pemetrexed, gemcitabine). The addition of ramucirumab to docetaxel only improves survival by 1.4 months.[62] As such, T-DXd might cement a place as an attractive option in subsequent lines of therapy. The efficacy and tolerability of T-DXd at a dose of 5.4 mg/kg in *HER2*-amplified solid tumors is under evaluation in the phase II basket (HERALD) trial. Guardant360 cfDNA analysis will be utilized to identify *HER2* amplification. In addition, predictive biomarkers are

evaluated using serial collection of tumor tissue and cfDNA.[63]

Novel *HER2* TKIs Under Investigation

Besides T-DXd, targeted *HER2* treatment of NSCLC is currently under investigation utilizing 3 different tyrosine kinase inhibitors. Poziotinib showed high potency in preclinical studies of *EGFR* exon 20 mutation.[64] Poziotinib was investigated in a phase II clinical trial in patients with previously treated, *EGFR*-mutated or exon 20 *HER2*-mutant NSCLC. Although the initial clinical activity was demonstrated with ORR and DCR of 50% and 83%, respectively, in the *HER2* exon 20 mutation cohort,[65] more mature data presented at AACR 2020 showed a disappointing RR of 27.8%.[66] Preclinical studies have demonstrated antitumor activity of poziotinib in combination with T-DM1 in NSCLC with exon 20 *HER2* mutation. By upregulating mutant *HER2* in tumor cells, poziotinib enhances the clinical activity of T-DM1, leading to complete regression.[67] Clinical trials of this combination could be considered. Tarloxotinib is a hypoxia-activated prodrug of a pan-ErbB kinase inhibitor that releases a potent irreversible active metabolite (tarloxotinib-E) to preferentially target tumor tissues. Tarloxotinib has demonstrated preclinical efficacy in *EGFR* exon 20 and *HER2*-mutant NSCLC, as well as other oncogenic alterations in the ERBB gene family such as NRG1 fusions. First reports from the Rain-701 trial showed a PR of 22% (2/9), SD of 44% (4/9), and PD of 33% (3/9).[68] Mobocertinib is a first-in-class TKI designed to target *EGFR* and *HER2* exon 20 insertions. While results for *EGFR* exon 20 insertions from the EXCLAIM trial were reported at WCLC 2020, accrual for *HER2* exon 20 insertions has closed (personal communication).

Conclusion

T-DXd holds significant promise in *HER2*-mutated NSCLC and, to a lesser-degree, in *HER2*-overexpressing NSCLC. The optimal strategy of using T-DXd in NSCLC is not yet well established. To this end, combination therapy utilizing T-DXd with checkpoint inhibitors and chemoimmunotherapy is under current investigation. Despite targeting *HER2* mutated lung cells, pneumonitis and ILD remain a serious challenge. The identification of patients likely to develop this adverse event requires further investigation.

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