Trastuzumab Deruxtecan Plus Pembrolizumab in Advanced/Metastatic Breast or Non–Small Cell Lung Cancer: A Phase 1b Study

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Disclosures

Commercial Interest	Relationship(s)
Millennium	Research support (clinical trials)
Merck	Research support (clinical trials), travel fees
Celgene	Research support (clinical trials), advisory board/consultant
Bristol Myers Squibb	Research support (clinical trials), advisory board/consultant, travel fees
Eli Lilly	Research support (clinical trials), advisory board/consultant, travel fees
Genentech	Advisory board/consultant, travel fees
Pfizer	Advisory board/consultant, honoraria
EMD-Serono	Advisory board/consultant, travel fees
Boehringer Ingelheim	Advisory board/consultant
AstraZeneca	Advisory board/consultant
Novartis	Advisory board/consultant
Genmab	Advisory board/consultant
Regeneron	Advisory board/consultant

Commercial Interest	Relationship(s)
BioNTech	Advisory board/consultant
Cantargia AB	Advisory board/consultant
Amgen	Advisory board/consultant, honoraria, travel fees
AbbVie	Advisory board/consultant
Axiom	Advisory board/consultant
PharmaMar	Advisory board/consultant
Takeda	Advisory board/consultant, data and safety monitoring board
Huya Biosciences	Advisory board/consultant
GLG Pharma	Advisory board/consultant
Daiichi Sankyo	Advisory board/consultant, honoraria
Incyte	Advisory board/consultant, data and safety monitoring board
Sonnet BioTherapeutics	Stockholder
Rgenix	Stockholder

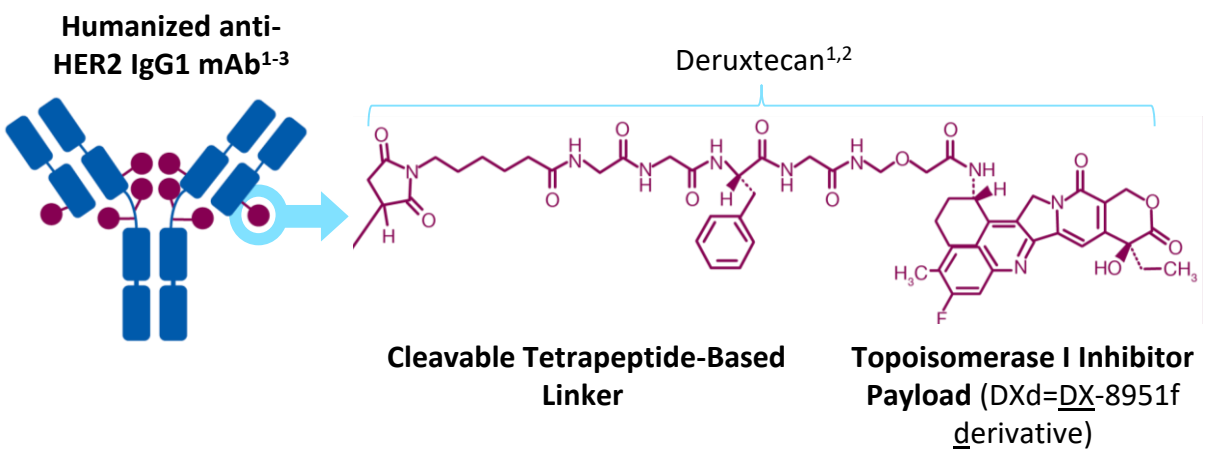
Background: HER2 Alterations in NSCLC and BC

- In NSCLC, HER2 overexpression occurs in an estimated 6% to 35% of cases, with rates as high as 38% in adenocarcinomas, and is associated with a poorer prognosis[1,2]
  - Furthermore, HER2-activating mutations are found in approximately 4% of NSCLC and may be more common in adenocarcinomas and nonsmokers[3,4]
- Similarly, HER2 overexpression (IHC 3+ or ISH-positive) is observed in approximately 15% to 20% of BC and is associated with more aggressive disease[5,6]

BC, breast cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; NSCLC, non–small cell lung cancer.

1. Mazieres J et al. *J Clin Oncol.* 2013;31:1997-2003. 2. Nakamura H et al. *Cancer*. 2005;103:1865-1873. 3. Li C et al. *J Thorac Oncol*. 2012;7:85-89. 4. Stephens P et al. *Nature*. 2004;431:525-526. 5. Howlader N et al. *J Natl Cancer Inst*. 2014;106:dju055. 6. Kohler BA et al. *J Natl Cancer Inst*. 2015;107:djv048.

Background: T-DXd Is a Novel ADC



Conjugation chemistry: The tetrapeptide-based cleavable linker is connected to cysteine residues on the humanized anti-HER2 IgG1 monoclonal antibody, with the same amino acid sequence as trastuzumab.

- Recently, T-DXd (DS-8201) was approved for treating patients with HER2-positive, unresectable or metastatic BC that has progressed on ≥2 lines of HER2-targeted therapy (United States) or after prior chemotherapy (Japan) and HER2-positive, unresectable, advanced/ recurrent gastric cancer that has progressed following chemotherapy (Japan)
- T-DXd is a novel, next-generation, HER2-directed ADC composed of a humanized mAb specifically targeting HER2, a cleavable tetrapeptide-based linker, and a potent topoisomerase I inhibitor payload (DXd); deruxtecan is composed of the topoisomerase I inhibitor and the linker[4]

ADC, antibody–drug conjugate; DXd, DX-8951f derivative; IgG1, immunoglobulin G1; mAb, monoclonal antibody; T-DXd, trastuzumab deruxtecan.

1. Nakada T et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-185. 2. Ogitani Y et al. *Clin Cancer Res*. 2016;22:5097-5108. 3. Trail PA et al. *Pharmacol Ther*. 2018;181:126-142. 4. Ogitani Y et al. *Cancer Sci*. 2016;107:1039-1046.

Background: Clinical Efficacy of T-DXd

The clinical efficacy of T-DXd as a single agent in patients with NSCLC (HER2 expressing and mutated) and those with BC (HER2 positive and low) is summarized below[1-3]

	DS8201-A-J101 NCT02564900			DESTINY-Breast01 NCT03248492
	HER2-expressing (IHC ≥1+ or ISH+) or mutated NSCLC (n = 18)[1]	HER2-mutated NSCLC (n = 11)[1]	HER2-low (IHC 1+ or IHC 2+/IHC−) BC (n = 54)[2]	HER2-positive (IHC 3+ or ISH+) BC (n = 184)[3]
Parameter[a]	6.4 mg/kg q3w	6.4 mg/kg q3w	5.4 or 6.4 mg/kg q3w	5.4 mg/kg q3w
Confirmed ORR, n (%)	10 (55.6)	8 (72.7)	20 (37.0)	113 (61.4)
Confirmed DCR, n (%)	15 (83.3)	10 (90.9)	47 (87.0)	179 (97.3)
DOR, median (95% CI), months	10.7 (6.9-11.5)	9.9 (6.9-11.5)	10.4 (8.8-NE)	20.8 (15.0-NE)
PFS, median (95% CI), months	11.3 (7.2-14.3)	11.3 (8.1-14.3)	11.1 (7.6-NE)	19.4 (14.1-NE)

DCR, disease control rate (complete response [CR] + partial response [PR] + stable disease for ≥6 weeks ±1 week from first dosing date); DOR, duration of response; IHC, immunohistochemistry; ISH, in situ hybridization; NE, not estimable; ORR, objective response rate (CR + PR); PFS, progression-free survival; q3w, every 3 weeks.

[a]By independent central review.

1. Tsurutani J et al. *Cancer Discov*. 2020;10:688-701. 2. Modi S et al. *J Clin Oncol*. 2020;38:1887-1896. 3. Modi S et al. Presented at San Antonio Breast Cancer Symposium. December 8-12, 2020. Abstract PD3-06.

Background: Unmet Need and Objectives of the Study

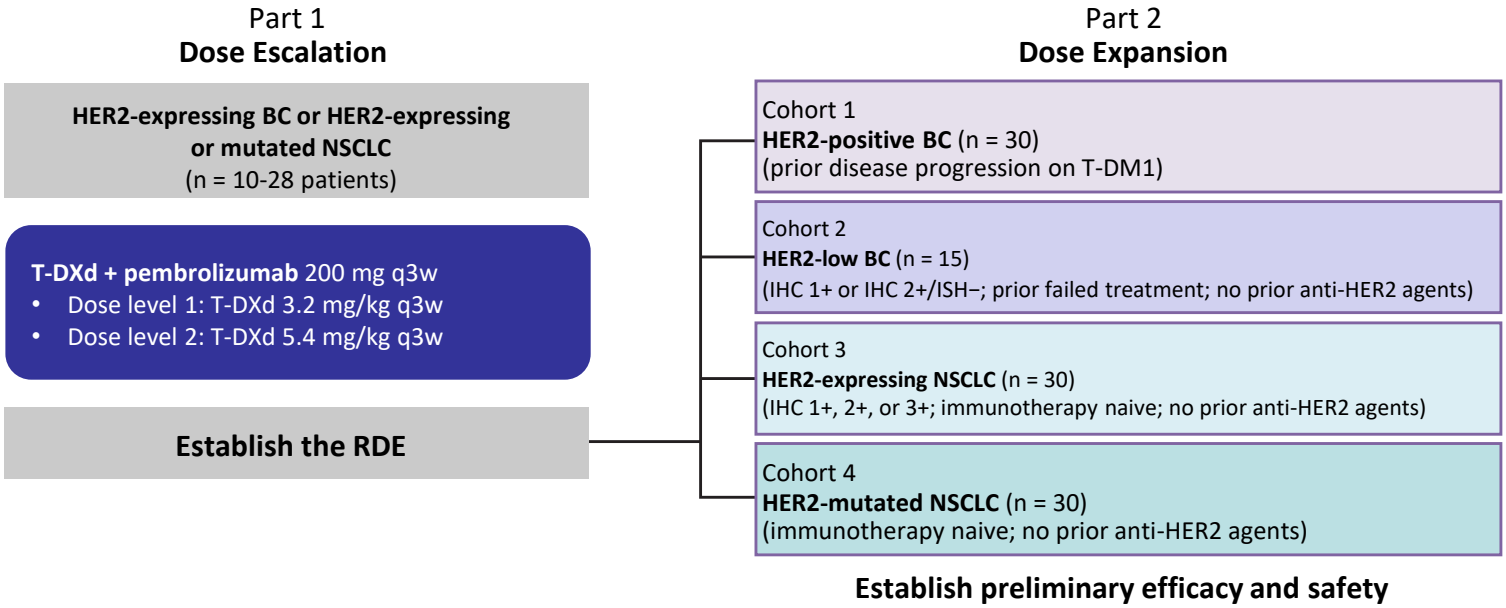
- Currently, there are no approved HER2-targeted treatments for patients with HER2-overexpressing or mutated NSCLC or HER2-low (IHC 1+ or IHC 2+/ISH−) metastatic BC
- Pembrolizumab is a humanized antibody against programmed death 1 (PD-1) approved to treat a variety of cancers, including NSCLC[1]
  - Preclinical animal models demonstrated that T-DXd in combination with an anti–PD-1 antibody had greater antitumor activity than either drug used as monotherapy[2]
- In this study, we will assess T-DXd in combination with pembrolizumab in patients with HER2-expressing or mutated NSCLC or HER2-expressing, advanced/metastatic BC

1. Keytruda (pembrolizumab) [package insert]. Whitehouse Station, NJ, USA: Merck Sharp & Dohme Corp.; 2020. 2. Iwata TN et al. *Mol Cancer Ther*. 2018;17:1494-1503.

Methods: DS8201-A-U106 Trial

- This open-label, multicenter, nonrandomized, 2-part, phase 1b study will assess the efficacy and safety of T-DXd in combination with pembrolizumab in patients with HER2-expressing or mutated NSCLC or HER2-expressing, locally advanced/metastatic BC (NCT04042701; DS8201-A-U106)
- Part 1 of this study is a dose-escalation phase to determine the recommended dose for expansion (RDE)
  - Patients with either HER2-expressing or HER2-mutated, locally advanced/metastatic NSCLC or HER2-expressing, advanced/metastatic BC will initially receive T-DXd 3.2 mg/kg and pembrolizumab 200 mg every 3 weeks
  - Depending on dose-limiting toxicities, the dose of T-DXd will be increased to 5.4 mg/kg every 3 weeks, while the dose of pembrolizumab will remain the same

Methods: Study Design



Approximately 115 patients will be enrolled across 5 sites in part 1 and 25 sites in part 2 in the United States and Europe

T-DM1, trastuzumab emtansine.

Methods: Key Inclusion and Exclusion Criteria

Patients in either part of the study will be enrolled based on key inclusion and exclusion criteria

	Key Inclusion Criteria	Key Exclusion Criteria
All cohorts	• Adults ≥18 years old • ECOG PS 0 or 1 • Presence of ≥1 measurable lesion as assessed by RECIST v1.1 • LVEF ≥50% • Adequate organ function (bone marrow, hepatic, renal, and coagulation)	• Prior pembrolizumab, T-DXd, other anti–PD-1, or anti–PD-L1 treatments • Received prior therapy with an agent directed against another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX40, CD137) and discontinued that therapy because of grade ≥3 immune-related AE • Prior anti-HER2 therapy (cohort 2, 3, or 4) • History of hypersensitivity to mAbs or study drug components • MI ≤6 months before enrollment, history of symptomatic CHF, or troponin levels consistent with MI 28 days before enrollment • QTc prolongation >470 ms (women) or >450 ms (men) • History of (noninfectious) ILD that required steroids, current ILD, or suspected ILD that cannot be ruled out by imaging at screening • Active, known, or suspected autoimmune disease
Cohort-specific criteria[a]	• **Cohort 1**: HER2+, locally advanced/metastatic BC centrally confirmed per ASCO/CAP guidelines that progressed on prior T-DM1 • **Cohort 2**: HER2-low, locally advanced/metastatic centrally confirmed (IHC 1+ or IHC 2+/ISH−) BC for which available standard treatments failed • **Cohort 3**: HER2-expressing, locally advanced/metastatic centrally confirmed (IHC 1+, 2+, or 3+) NSCLC • **Cohort 4**: HER2-mutated, locally advanced/metastatic NSCLC • Patients in cohorts 3 and 4 with mutations in *EGFR* or *ALK*, *BRAF*^{V600E}, or *ROS1* fusion must have progressed on ≥1 genomically targeted therapy, been intolerant of treatment, or refused standard treatment	

AE, adverse event; ALK, anaplastic lymphoma kinase; ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; CHF, congestive heart failure; CTLA-4, cytotoxic T-lymphocyte protein 4; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PD-L1, programmed death ligand 1; QTc, corrected QT interval; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

[a]Patients in part 1 of the study should meet the additional criteria for 1 of the cohorts in part 2.

Methods: Key Study End Points

	End Points	
Primary	• **Part 1: Occurrence of dose-limiting toxicities[a]** • **Part 2: ORR as determined by ICR according to RECIST v1.1**	

Secondary	• Efficacy[b,c]
	  • DOR
	  • DCR
	  • TTR
	  • PFS
	  • OS
		• Safety[d]
		  • TEAEs[e]
		  • Serious AEs
		  • AEs of special interest (ILD/pneumonitis)
		  • LVEF by echocardiogram/MUGA scan

ICR, independent central review; MUGA, multigated acquisition; OS, overall survival; TEAEs, treatment-emergent adverse events; TTR, time to response.
[a]Assessed in all patients who completed 2 cycles of treatment with both study drugs or discontinued due to dose-limiting toxicities. [b]Efficacy assessed in the response-evaluable set (patients who received ≥1 dose of both study drugs and had measurable disease at baseline per independent central review), with the exceptions of OS and PFS, which were assessed in the full analysis set (patients who received ≥1 dose of either study drug). [c]All but OS will be assessed by ICR. [d]Safety was assessed in the full analysis set. [e]AEs will be evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Methods: Statistical Analysis, Enrollment, and Summary

Statistical Analysis

- The primary efficacy end point in part 2 will be summarized by cohort and assessed in all patients who received ≥1 dose of both study drugs and had measurable disease at baseline by independent central imaging review
- Median DOR, PFS, and OS in each cohort will be presented as Kaplan-Meier estimates
- Analyses will also be performed in patients pooled from parts 1 and 2 and grouped by cancer type and HER2 status

Enrollment

- This study started on February 10, 2020, and is currently recruiting patients from approximately 5 sites in part 1 and 25 sites in part 2 in the United States and Europe
  - Part 1 is currently enrolling

Summary

- For more information or to refer a patient for screening, please visit ClinicalTrials.gov (NCT04042701)

Acknowledgments

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- In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo, Inc., for trastuzumab deruxtecan (T-DXd; DS-8201)
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