EU Risk Management Plan for Enhertu (Trastuzumab Deruxtecan/T-DXd)

RMP version to be assessed as part of this application:

Data lock point for this RMP	19 Dec 2022	RMP version number	7.0
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Rationale for submitting an updated RMP:

New indication.

Summary of significant changes in this RMP:

Part I and Part VI: New indication included. Study DESTINY-Lung04 added to Table Part IV.1 and Section II.C.1

QPPV name:

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PART I PRODUCT(S) OVERVIEW

Table Part I.1: Product Overview

Active substance(s) (INN or common name):	Trastuzumab deruxtecan (T-DXd)
Pharmacotherapeutic group(s) (ATC Code):	L01FD04
Marketing Authorisation Holder:	Daiichi Sankyo Europe GmbH
Medicinal products to which this RMP refers:	Trastuzumab deruxtecan (T-DXd)
Invented name(s) in the European Economic Area (EEA):	Enhertu
Marketing authorisation procedure:	Centralised
Brief description of the product:	Chemical class: Human epidermal growth factor receptor 2 (HER2)-targeted antibody and topoisomerase I inhibitor conjugate
	Summary of mode of action: Trastuzumab deruxtecan, hereafter referred to as T-DXd, is an antibody-drug conjugate (ADC) composed of 3 components: 1) a humanised anti-HER2 immunoglobulin G1 (IgG1) monoclonal antibody (mAb) with the same amino acid sequence as trastuzumab, covalently linked to 2) a topoisomerase I inhibitor, DXd, an exatecan derivative, via 3) a tetrapeptide-based cleavable linker. Deruxtecan is composed of the linker and the topoisomerase I inhibitor.
	Important information about its composition: White to yellowish-white lyophilised powder in a single-dose vial for reconstitution and further dilution. The monoclonal antibody intermediate used in T-DXd is a humanized IgG1 mAb produced by mammalian (Chinese hamster ovary) cell culture.
Hyperlink to the Product Information:	Summary of Product Characteristics (SmPC)

Table Part I.1: Product Overview (Continued)

Indication(s) in the EEA:	Current: Enhertu as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer (BC) who have received one or more prior anti-HER2-based regimens. Enhertu as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low BC who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Enhertu as monotherapy for the treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen. Enhertu as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum based chemotherapy with or without immunotherapy.
Dosage in the EEA	Current: Metastatic BC and NSCLC: 5.4 mg/kg given as an intravenous (IV) infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. Advanced gastric cancer (GC): 6.4 mg/kg given as an IV infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.
Pharmaceutical form(s) and strengths	Current: 100 mg of T-DXd as a white to yellowish- white lyophilized powder for concentrate for solution for infusion in a single-dose vial. Must be reconstituted and diluted by a healthcare professional and administered as an IV infusion. T-DXd must not be administered as an IV push or bolus.
Is/will the product be subject to additional monitoring in the EU?	Yes

EU = European Union; HER2 = human epidermal growth factor receptor 2; INN = International Nonproprietary Name; RMP = Risk Management Plan

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

SI.1. HER2-positive Breast Cancer

SI1.1. Incidence and Prevalence

Approximately 11.7% of all new cancers are female BC, which has an annual incidence rate of 47.8 per 100,000 persons worldwide. Australia/New Zealand, Europe, and North America have the highest incidence by region.[1]

BC is the most common cancer in women, accounting for 2.3 million new cases worldwide in 2020. In 2020, there were an estimated 7,790,717 women living with BC diagnosed in the last 5 years worldwide, with a 5-year prevalence proportion of 201.6 per 100,000.[1]

Approximately 20% of patients with BC globally have HER2-positive tumours.[2] HER2 positivity is associated with more aggressive disease. HER2-positive BC is also associated with negative hormone receptor (HR) status and a younger patient population.[3,4] Among all BC cases in the Cortet study , 6.3% were HR-positive/HER2-positive and 3.7% were HR-negative/HER2-positive.[5]

Crude and world- and Europe-standardised incidence rates for HER2-positive BC are compared to overall BC incidence rates in Table Part II: Module SI.1.[5]

Table Part II: Module SI.1: Incidence Rates for HER2-positive Breast Cancer Compared to Overall Breast Cancer

	Year of Diagnosis					
	2007	**2008**	**2009**	**2010**	**2011**	**2012**
Crude incidence rate						
Overall	170.99	166.88	159.45	177.99	170.83	171.37
HER2-positive/HR-positive	9.59	11.10	10.36	11.41	9.38	13.00
HER2-positive/HR-negative	5.65	5.28	5.65	6.75	6.59	6.45
World standardized incidence rate						
Overall	116.84	113.77	109.67	119.35	114.59	113.89
HER2-positive/HR-positive	6.70	8.26	8.37	8.74	7.26	10.03
HER2-positive/HR-negative	4.10	4.08	4.53	5.00	4.94	4.48
Europe standardized incidence rate						
Overall	154.27	149.78	142.02	157.86	150.87	149.10
HER2-positive/HR-positive	8.37	10.65	10.20	11.18	9.32	11.88
HER2-positive/HR-negative	4.90	4.99	5.35	6.33	6.09	5.61

Source: Cortet 2018[5]
HER2 = human epidermal growth factor receptor 2; HR = hormone receptor

European Union (EU):

In the 27 members of the EU (EU-27), 355,457 new cases of female BC were diagnosed in 2020, comprising approximately 12.1% of all cancers. The estimated annual age-standardised (worldwide) incidence rate of BC is 82.46 per 100,000 in the EU. In 2020, there were an estimated 1,457,608 women living with BC in the EU who were diagnosed in the last 5 years, providing a 5-year prevalence proportion of 640.6 per 100,000.[1]

Among patients with metastatic BC, HER2 overexpression varies from 22% (France) to 34% (Italy). For Germany, Spain, and the United Kingdom (UK), the numbers were 32.4%, 26.3% and 28.4%, respectively. The study population comprised a total of 152,311 patients with metastatic BC in the UK, Germany, France, Spain, and Italy (EU-5) countries. HER2-positive/HR-negative BC was the least prevalent in France (9%) and most prevalent in Italy (13.5%). The proportion of HER2-positive/HR-positive patients ranged from 13.1% in France to 20.7% in Italy.[6]

Breast cancer patients tested IHC 1+ or IHC 2+ without HER2 gene amplification are defined as HER2-low. An estimated 45% to 55% of all primary BC patients are HER2-low.[7] The majority (65% to 83%) of the HER2-low BC patients have HR-positive tumours, which are mostly luminal subtype. The rest of the HER2-low BC patients are HR negative and are predominantly basal-like subtype. For the therapeutic purpose, patients with HER2-low BC are currently considered to have HER2-negative BC.[8]

SI1.2. Demographics of the Population in the Proposed Indication and Risk Factors for the Disease

Sex: Breast cancer is mainly a disease in females, with 1% of cases occurring in males.[9]

Age: In the EU-27, approximately 11.4% of BCs occur in women younger than 45 years of age. BCs are most commonly (47%) diagnosed among women 55 years to 75 years of age in the EU.[3] Worldwide, 48% of the newly diagnosed patients with BC are 45 years to 64 years of age. BC incidence is much higher among adults and increases with age, with the highest incidence rate among those 65 years and older.[1]

Among patients with metastatic BC, those with HER2-positive tumours are younger than those with HER2-negative tumours (including HER2-low). The youngest among a metastatic BC EU-5 population seemed to be those with HER2-positive HR-negative tumours, where 28% were younger than 50 years of age.[6]

Race and/or Ethnicity: According to the Surveillance, Epidemiology, and End Results (SEER) cancer query system, age-adjusted incidence of BC is highest in White females (104.1 per 100,000). Incidence of BC in Black and Asian/Pacific Islander females is 99.2 and 85.4 per 100,000, respectively. BC risk is lower in Hispanic females, with an age-adjusted incidence rate of 80.3 per 100,000.[10]

Family history: Women with a family history, especially a mother, sister, or daughter who has or had BC, have a higher risk of having BC. In western countries, genetic predisposition is the cause of up to 10% of BC cases. The most common inherited causes are mutation in the *BRCA1* and *BRCA2* genes.[11]

Reproductive factors: Women who have early menarche (before age 12) or late menopause (after age 55) have a higher risk of developing BC.[11,12] Nulliparous women and women who are over age 30 at their first birth may have a greater chance of developing BC.[12]

Obesity: Obesity increases the risk of BC (possibly through an increase in oestrogen levels) in postmenopausal women. In premenopausal women, obesity is associated with a reduced incidence of BC.[13]

Previous benign breast disease: Women with atypical epithelial hyperplasia have a higher risk (4 to 5 times) of developing BC.[14]

Birth control pills: Oral contraceptive use may slightly increase the risk of developing BC. The risk decreases once the pills are stopped. Ten years after cessation of the oral contraceptive agent, there is no significantly increased risk of having BC.[15]

Combined postmenopausal hormone therapy: Women who use combined hormone therapy after menopause have an increased risk of developing BC. There is a dose-response relationship, with larger risks corresponding with longer durations of combined hormonal therapy use.[16]

Radiation exposure**: Children or young adults exposed to radiation therapy to the chest area have a** significantly increased risk of developing BC later in life.[17]

SI1.3. The Main Existing Treatment Options

Although HER2-targeted drugs have been developed as molecularly targeted therapies, locally advanced and metastatic tumours invariably relapse with time.[2]

HER2-positive Metastatic Breast Cancer

The first targeted agent for HER2 therapy, trastuzumab (HERCEPTIN®), is a humanized mAb directed against the extracellular domain of HER2. Other HER2-targeting agents have subsequently been approved, including the ADC KADCYLA® (T-DM1); the tyrosine kinase inhibitor NERLYNX® (neratinib) as monotherapy in early-stage BC and in combination with capecitabine in metastatic BC; the mAbs PERJETA® (pertuzumab) and MARGENZA® (margetuximab), and the tyrosine kinase inhibitors TYKERB® (lapatinib) and TUKYSA (tucatinib)[18] each in combination with other chemotherapeutic agents. Although anti-HER2 targeted therapies have improved outcomes, they are not curative in the metastatic setting. The ADC T-DXd (Enhertu®) monotherapy was approved as a new treatment option in the United States (US), EU, Japan and a few other countries for patients with HER2-positive unresectable or metastatic BC who have received one or more prior anti-HER2-based regimens.

The current standard of care (SoC) for newly diagnosed HER2-positive metastatic BC in Europe is a combination of pertuzumab, trastuzumab, and taxane, per the European Society for Medical Oncology (ESMO),[19] based on results from the CLEOPATRA[20] study. T-DXd has been established as the standard of care for subsequent-line anti-HER2 therapy. [19]

Tucatinib was approved based on the results from the HER2CLIMB study,[21] in which subjects previously treated with trastuzumab, pertuzumab, and T-DM1 were randomised to receive trastuzumab plus capecitabine with or without tucatinib.

HER2-low Metastatic Breast Cancer

Current therapeutic guidelines for patients with BC exhibiting HER2-low expression are the same as those for patients with HER2-negative BC.[19,22] For patients with metastatic HER2-negative BC, treatment recommendations from the National Comprehensive Cancer Network,[22] ESMO,[23] and the Japanese Breast Cancer Society[24] clinical practice guidelines are based on tumour HR status, presence or absence of visceral crisis, and menopausal status.

HER2-low Hormone Receptor-Positive Metastatic Breast Cancer

In the first-line metastatic setting, in the absence of a visceral crisis, the SoC for patients with HER2-/HR+ BC is endocrine therapy (ET) with or without a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor.[19,22,24]

In the second- and subsequent-line metastatic setting, preferred regimens include, but are not limited to, fulvestrant in combination with a CDK4/6 inhibitor if a CDK4/6 inhibitor was not previously used, ET plus everolimus, a nonsteroidal aromatase inhibitor, a steroidal aromatase inactivator, fulvestrant, and selective estrogen receptor modulators.[19,22,24] For PIK3CA-mutated tumours, another option includes fulvestrant plus targeted therapy with alpelisib. Patients with deleterious or suspected deleterious germline BRCA mutations can be treated with poly adenosine diphosphate-ribose polymerase inhibitors.

Once tumours are refractory to ET, therapeutic guidelines recommend the use of sequential systemic single-agent chemotherapy.[19,22,24] Preferred single-agent regimens in this setting include the anthracyclines doxorubicin and liposomal doxorubicin, the antimetabolites capecitabine and gemcitabine, the microtubule inhibitors vinorelbine and eribulin, and the taxane paclitaxel.[22,25] Other recommended single agents are the taxanes docetaxel and nanoparticle albumin-bound (nab)-paclitaxel, the anthracycline epirubicin, and ixabepilone. Single-agent chemotherapy is preferred over combination therapy in this setting.[22]

The most recent approved treatment for patients with HR-positive tumours refractory to ET who have received at least one prior line of chemotherapy is the CDK4/6 inhibitor abemaciclib, and the ADC sacituzumab govitecan. T-DXd is the first HER2-targeted therapy to demonstrate statistically significant and clinically meaningful improvement in PFS and OS over commonly used chemotherapeutic agents in adult patients with unresectable or metastatic HER2-low BC who have received a prior systemic therapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.[26]

HER2-negative Hormone Receptor-negative (Triple Negative) Breast Cancer

For patients with metastatic triple-negative breast cancer (TNBC), the treatment in the first-line metastatic setting is sequential single-agent chemotherapy, with the same preferred chemotherapeutic options as those for patients with HER2-/HR+ BCs who are refractory to ET.[19,22] Regardless of BRCA status, for patients with TNBC previously treated with anthracyclines and taxanes in the adjuvant or neoadjuvant setting, platinum agents are the preferred option.[22] For patients with BRCA1/2 mutations, the recommendation is to use poly adenosine diphosphate -ribose polymerase inhibitors (olaparib or talazoparib) or platinum agents.[22]

For patients with metastatic TNBC with programmed death-ligand 1-positive disease, the preferred therapeutic option in the first-line setting is a programmed cell death protein 1-blocking antibody (pembrolizumab) in combination with chemotherapy.[22,27]

For patients with TNBC who have received at least 2 previous regimens, including at least 1 of the treatment regimens in the metastatic setting, the ADC sacituzumab govitecan is approved.[28]

Positive results from a small cohort of subjects with HR- BC led to approval of T-DXd as another targeted-therapy option for this segment of patients with a poor prognosis.[29]

SI1.4. Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

- According to Globocan data, approximately 684,996 women died from BC worldwide in 2020, with a 5-year age-adjusted mortality rate of 13.6 per 100,000.[1] Data from

279 population-based cancer registries from 67 countries showed that the 5-year survival from BC is increasing in most developed countries.[30]

- Metastatic BC is the third most common cause of death in Europeans after lung and colorectal cancer. The estimated number of deaths from BC in the EU was 91,826 in 2020.[1] Overall, BC mortality rates in the EU declined by 15%, from 17.9% in 2002 to 15.2% per 100,000 in 2012. The mortality rate increased with increasing age and was highest among the oldest age group (70 years to 79 years).[31] Triple negative and HER2-positive subtypes have the worst survival outcome.
- The 5-year relative survival rate for patients with BC in the US is 90.3%. Survival is higher among White patients than African American patients in all age groups. Survival also differs by cancer stage at diagnosis, with localised disease having a survival rate up to 99.0% and metastatic disease having a survival rate up to 29.0%. Overall, the 5-year relative survival for BC has been increasing from 74.5% in 1975 to 92.2% in 2019. In 2021, there were an estimated 43,600 deaths among patients with BC in the US. The mortality rate has been estimated to be 20.1 deaths per 100,000 persons per year based on the 2015 to 2019 data. The median age at death was 69 years.[32]
- In 2020, Japan had an estimated 17,081 deaths due to BC, with a 5-year mortality rate of 9.9 per 100,000.[1]
- Metastatic HER2-positive BC remains an incurable disease that is ultimately fatal. Although treatment with anti-HER2 therapies has improved the disease outcomes for patients with unresectable or metastatic HER2-positive BC, the disease invariably progresses, with median survival being 2 to 4 years.

Events that Occur Frequently in Subjects with Metastatic Breast Cancer

Events that occur frequently in subjects with metastatic BC are described below. These include events associated with the disease or with therapies.

Bone metastases: Among patients with BC who had distant metastases, bone is the most common site for metastasis.[33] The risk of developing bone metastases within 10 years after diagnosis was 7% to 9% according to a Canadian study.[34] A retrospective study on 35,912 Danish patients with BC found that 4.2% of patients with BC develop bone metastasis within 5 years of diagnosis. Among patients with BC who had bone metastases, 47.7% developed skeletal-related events (SREs) defined as pathological fractures, spinal cord compression, bone pain requiring palliative radiotherapy, and orthopedic surgery.[35]

Brain metastases: Brain metastasis (BM) was found in 5.1% of patients with BC.[36,37] The symptoms most commonly associated with BM were headache (35%), vomiting (26%), nausea (23%), hemiparesis (22%), visual changes (13%), seizures (12%) and altered mental status (7%).[38] In a retrospective study of clinical data of German patients with BC who had BM, median overall survival (OS) time after BM development was reported as 7.4 months, with a one-year survival rate of 37.7%. Patients with HER2-positive tumours had the longest median OS of 11.6 months (95% confidence interval: 10.0, 13.4) and those who received anti-HER2 therapy had a longer median OS (17.1 months).[39]

Cardiotoxicity: Anthracyclines (eg, doxorubicin and epirubicin) used in the treatment of BC cause a dose-dependent, cumulative, progressive cardiac dysfunction that may ultimately lead to symptomatic congestive heart failure (CHF).[40] Cardinale et al reported that in 1344 patients with BC receiving anthracycline-based therapy, the incidence of cardiac toxicity was 9.7% at a median follow-up of 5.2 years.[41]

Trastuzumab treatment in patients with HER2-positive BC was associated with cardiac toxicity with heart failure incidence up to 4.7%[42] and asymptomatic decline in left ventricular ejection fraction (LVEF) up to 20.6%.[43]

Radiation exposure in patients with BC is associated with increased risk of ischemic heart disease with a magnitude of the risk of 7.4% per gray. There was no apparent threshold below which there was no risk. The risk was dose-dependent with a lag time of up to 20 years.[44]

Hepatoxicity/Liver metastases: Liver metastases develop in approximately half of the women with metastatic BC and represent a frequent cause of mortality among these patients.[33] According to a UK study, the risk of developing liver metastasis in 6 years after BC diagnosis is 5.2%.[45] Liver metastases were present in only 1.4% of overall patients with BC and 3.3% of patients with HER2-positive BC at the time of the initial BC diagnosis and are typically associated with metastases at other sites.[46] In 78.6% of cases, the liver metastases were asymptomatic at the time of metastatic diagnosis. The remainder were symptomatic, presenting with epigastric pain or fullness (21.4%), palpable hepatomegaly (27.3%) and ascites (6.2%).[47]

Pulmonary toxicity/Pulmonary metastases: In a systematic literature review of pneumonitis associated with BC therapy, the authors reported that most of the currently used BC treatments may induce pneumonitis with an incidence of 1% to 3%.[48]

Approximately 31% of metastatic patients with BC suffer lung metastasis.[33] Metastasis to the lung is associated with poor prognosis, with patients presenting with clinical symptoms such as pain, cough, haemoptysis, pleural effusion, and pulmonary dysfunction.[49]

SI1.5. Important Comorbidities

Patients with BC who have comorbidities have overall higher mortality compared to patients without comorbidities.

Multiple registry studies have shown a correlation between the presence of comorbidities and higher mortality. A nationwide population-based cohort study of 9329 patients with BC of all ages in Denmark, a nationally representative cancer registry in Sweden including 42,646 patients with BC from 1992 to 2008, and a Dutch registry-based study of 9123 patients with BC all included similar proportions of patients with at least 1 comorbidity (22%, 13%, and 28%, respectively). In each of these studies, patients with at least 1 comorbid condition had a higher mortality rate than patients with no comorbidities.[50,51,52]

In the US, a retrospective cohort study (N = 5186) in an elderly BC population found 22% of patients had at least 1 comorbidity at the time of BC diagnosis. Patients with comorbidities had a significantly higher mortality rate (risk ratio [RR] = 1.4 for patients with a single comorbidity and RR = 2.0 for patients with 2 or more comorbidities) compared to patients without any comorbidities.[53]

A systematic review of 18 studies on BC survival and comorbid conditions demonstrated that the presence of comorbidities at baseline was an important independent prognostic factor and was associated with poorer BC survival. In this review population, hypertension was the most common comorbidity. Other reported common comorbid conditions were cardiovascular disease, diabetes, previous cancer, cerebrovascular disease, and pulmonary disease.[54,55,56,57,58,59,60]

Among patients in a study of 5 European countries, the majority of patients with HER2-positive BC had no comorbidities (Table Part II: Module SI.2).[6]

Table Part II: Module SI.2: Summary of Important Comorbidities

	Number and Percentage of Patients					
	Metastatic BC (N = 152,311)		**HER2-positive/ HR-positive (N = 27,159)**		**HER2-positive/ HR-negative (N = 16,870)**	
Cardiac dysfunction	20,080	13.2	3164	11.7	1385	8.2
COPD	11,054	7.3	1605	5.9	816	4.8
Diabetes	22,690	14.9	3372	12.4	1442	8.5
None	108,295	71.1	20,530	75.6	13,477	79.9

BC = breast cancer; COPD = chronic obstructive pulmonary disease; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; UK = United Kingdom
Includes patients from UK, Germany, France, Spain and Italy
Source: DeKoven 2012[6]

SI.2. HER2-positive Gastric Cancer

As there are limited epidemiological data in the literature for the HER2-positive GC population, data herein are presented on general GC, with HER2-positive GC data included where available.

SI.2.1. Incidence and Prevalence of HER2-positive Gastric Cancer Population

GC is the fifth most common cancer, accounting for 1.09 million new cases worldwide in 2020. Approximately 5.6% of all new cancers are GC, with an annual incidence rate of 11.1 per 100,000 persons worldwide. In 2020, there were an estimated 1,805,968 persons worldwide living with GC that had been diagnosed in last 5 years, with a 5-year prevalence proportion of 23.2 per 100,000. Almost 75.3% of new GC cases occur in Asia. [1,61]

Overexpression of HER2 can be found in 8.2% to 29.5% of patients with GC. HER2 expression in GC varies based on the site of the primary tumour (gastric versus GEJ) and histological types.[62] Reports of the relationship between HER2 overexpression and disease prognosis in patients with GC are inconsistent: some studies found HER2 positivity to be associated with more aggressive disease, with significantly shortened disease-free survival and OS, while other studies did not demonstrate such an association.[63,64,65,66,67]

European Union: In the EU-27, approximately 75,443 new cases of GC were diagnosed in 2020, comprising approximately 3% of all cancers.[68] The estimated annual incidence rate of GC was 6.8 per 100,000 persons in the EU. The incidence rate per 100,000 persons was highest in Lithuania (13.4), Estonia (12.6), and Latvia (12.1), and lowest in Sweden (3.3), Finland (3.8), and Denmark (4.4).[68] In 2020, there were an estimated 119,887 patients in the EU living with GC that had been diagnosed in previous 5 years, with a 5-year prevalence proportion of 26.9 per 100,000.[1]

SI.2.2. Demographics of the Population in the Proposed Indication and Risk Factors for the Disease

Sex: GC is more prevalent in males than females, with nearly two-thirds of all new GC cases occurring in males. The worldwide age-standardized incidence of GC in males is 15.8 per 100,000 compared with 7.0 per 100,000 among females.[61] In the EU-27, incidence (ASR-World) of GC in males and females are 22.4 and 10.6 per 100,000 respectively.[68]

Age: According to SEER 2014-2018 data, the median age at diagnosis in the US was 68 years, with 71.6% of patients diagnosed at 55 years to 84 years of age.[69] A similar age distribution of patients with GC was found in the EU-27, with 73.9% of patients diagnosed at 55 years to 84 years of age.[68]

Race and/or Ethnicity: According to SEER 2018 age-adjusted data, GC was most common in persons of Hispanic ethnicity (10.4 per 100,000), the Asian/Pacific Islander population (10.1 per 100,000), and the Black population (10.0 per 100,000). The incidence was significantly lower in the non-Hispanic White population (5.6 per 100,000).[10]

***Helicobacter pylori* (*H. pylori*) infection**: *H. pylori* infection is the main risk factor of GC, with a 3-fold to 6-fold increased risk in persons with *H. pylori* infection compared to persons without *H. pylori* infection.[70] Approximately 65% to 80% (660,000 new cases) of all GC cases are caused by *H. pylori*.[71]

Obesity: Increased body mass index (BMI) is associated with an increased risk of cardia GC. Compared to individuals with a BMI of <25, individuals with a BMI of 30 to 35 have a 2-fold higher risk of GC and those with a BMI of >40 have a 3-fold risk.[71]

Smoking: Smoking was found to be associated with higher risk of cardia GC, with male smokers having a higher risk of GC compared to female smokers.[70,71,72] Approximately 11% of GC cases globally and 17% of GC cases in Europe were attributed to smoking.[72]

Pernicious anaemia: A person with pernicious anaemia has a 6.9% chance of developing GC, particularly non-cardia cancer.[72]

Diet: People who have a diet rich in salt and pickled foods exhibit higher rates of GC. Consuming preserved meats also increase the risk of GC. [70,71] Higher intake of fruits and vegetables was associated with a 37% lower risk of GC.[72]

Socioeconomic status: Socioeconomic status is inversely associated with GC risk, with higher status reported to be associated with lower GC risk.[71,72]

Genetics: CDH1 germline mutations were found in 25% of families with hereditary diffuse GC. Mutation in the adenomatous polyposis coli (APC) gene was linked to familial adenomatous polyposis, which involves development of different tumours, including GC.[70,71,72]

Gastroesophageal reflux disease (GERD): Several studies have reported a significant association between GERD and cardia GC. GERD also increases the risk of oesophageal adenocarcinoma by 5- to 7-fold.[71]

SI.2.3. The Main Existing Treatment Options

Systemic chemotherapy has been shown to improve survival and quality of life compared to best supportive care alone in patients with locally advanced or metastatic disease with adequate performance status.[73,74]

- For patients with locally advanced or metastatic HER2-positive GC, the current SoC in the first-line setting in the US,[73] Europe,[74] and Japan[75] is a combination of chemotherapy with a fluoropyrimidine agent (fluorouracil or capecitabine or S-1 in Japan) and a platinum agent (oxaliplatin or cisplatin), plus the anti-HER2 trastuzumab. As an alternative to platinum-based therapy, irinotecan plus leucovorin and infusional 5-FU (FOLFIRI) was shown to be efficacious and well tolerated regardless of HER2 expression and may be considered for selected patients. [74, 75] In the US, the combination of pembrolizumab in combination with trastuzumab and fluoropyrimidine- and

platinum-containing chemotherapy is approved in first-line setting.[76] After progression in the first-line therapy, response rates and median survival are low.

- In the US and EU, T-DXd is approved as a second-line treatment option, and in Japan as a third-line treatment option, for HER2-positive gastric or gastroesophageal junction adenocarcinoma patients who had received prior trastuzumab based therapy.[73,74,75]
- Other recommended treatment options for second and further-lines of chemotherapy include taxane (docetaxel, paclitaxel), or irinotecan, or ramucirumab as single agent or in combination with paclitaxel dependent on Performance Status (PS).[74]
- Regimens recommended for the third-line and later therapy regardless of HER2 expression include irinotecan, taxanes, pembrolizumab (if programmed cell death-ligand 1 expression by combined positive score ≥1), and the trifluridine/tipiracil- regimen. The programmed cell death protein-1-blocking antibody nivolumab is approved in Japan for use in the third-line- or later setting. Survival outcomes in the third-line metastatic setting and beyond are poor (approximately 6 months).[77,78]

SI.2.4. Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

- According to Globocan data, approximately 502,788 men and 266,005 women worldwide died from GC in 2020, with a 5-year age-adjusted mortality rate of 7.7 per 100,000.[1]
- In the EU-27, an estimated 32,143 men and 19,942 women are expected to die from GC in 2020.[68]
- Metastatic HER2-positive GC remains an incurable disease that is ultimately fatal. Although treatment with anti-HER2 therapies has improved the disease outcomes for patients with unresectable or metastatic HER2-positive GC, the disease invariably progresses, with a 5-year relative survival rate of 32.4% in the US, while Stage IV GC has a 5-year survival rate of 5.5%, per the SEER 2011-2017 data.[69]

Events that Occur Frequently in Subjects with Metastatic Gastric Cancer

Events that occur frequently in subjects with metastatic GC are described below. These include events associated with the disease or with therapies.

Bleeding: Approximately 2% to 8% of all upper gastrointestinal (GI) bleeding events are attributed to GI malignancies.[79] The majority (58%) of cases of malignancy-related bleeding are caused by GC.[79] In a population-based study in the UK, 62 (21%) of the 300 patients with previously undiagnosed GC presented with hematemesis/melena.[80]

Malignant obstruction: Patients with advanced GC may develop malignant gastric outlet obstruction, which eventually leads to associated symptoms, including nausea, vomiting, abdominal pain, dehydration, malnutrition, and weight loss.[81]

Nausea and **vomiting**: In a population-based study in the UK, 35% of the 300 patients with previously undiagnosed GC presented with vomiting.[80] In advanced GC, pyloric stenosis may cause persistent vomiting.[82]

Dumping syndrome: Approximately 68% of patients with GC experience early dumping syndrome after gastrectomy, which usually appears within 30 minutes after a meal. The most frequently experienced symptoms include abdominal pain or fullness (46.6%), diarrhoea (37.5%), nausea or vomiting (20.3%), palpitations (16.3%), cold sweats (13.2%), and flushing (8.2%). In contrast, 38.4% of patients experienced late dumping syndrome that usually appears

2 hours to 3 hours after a meal, with hunger (20.7%) and faintness (20.7%), followed by dizziness (13.5%), cold sweats (10.2%), tremors (10.1%), and loss of consciousness (2.2%) as the most common symptoms.[83]

SI.2.5. Important Comorbidities

Comorbidities play an important role in cancer treatment choice and patient survival.[84] Multiple population-based studies in the Netherlands have found that 60% to 70% of patients with newly diagnosed GC also present with at least 1 comorbid condition.[85,86] Hypertension (27.9%), cardiac disease (27.3%), digestive tract disease (18.2%), diabetes (16.6%), and previous malignancies (13.9%) are the most common comorbid conditions found in patients with stomach cancer.[85]

Using the SEER-Medicare database, a US retrospective cohort study of 12,612 elderly patients with GC found that 61.3% of patients had at least 1 comorbidity. The prevalence at or before the index date and the 12-month incidence of most comorbid conditions were higher among the patients with GC compared to a cancer-free matched comparator group. The 12-month incidence of acute comorbid conditions (eg, anaemia, electrolyte disorder, and infection) was higher in patients with GC compared to the comparator group, which was thought likely to be related to treatment side effects and disease sequelae.[84] Another retrospective cohort study using the Nationwide Inpatient Sample database from 2001 to 2011 identified all hospitalizations associated with GC. Hypertension (40.3%), anaemia (23.8%), and diabetes without complications (15.5%) were found to be the most common comorbidities associated with GC-related hospitalization. Obesity (odds ratio 2.0, 95% confidence interval [CI]: 1.6, 2.6) was significantly associated with increased risk of mortality in this patient population.[87]

A population-based study in Japan found peptic ulcer (26%), diabetes without chronic complications (10%), other cancer (8%), and liver diseases (5%) to be the most common comorbidities in patients with GC. The adjusted hazard ratio for all-cause mortality for a single-point elevation in the Charlson Comorbidity Index score was 1.12 (95% CI: 1.02, 1.23) for GC.[88]

SI.3. HER2-mutant Non-small Cell Lung Cancer

As there are limited epidemiological data in the literature for the HER2-mutant NSCLC population, data herein are presented on general lung cancer (LC) and NSCLC, with HER2-mutant NSCLC data included where available.

SI.3.1. Incidence and Prevalence

Lung cancer is the second most common cancer worldwide, accounting for 2.2 million new cases in 2020. Approximately 11.4% of all new cancers are LC, which has an annual incidence rate of 22.4 per 100,000 worldwide. Micronesia/Polynesia (36.7), Eastern Asia (34.4), Western Europe (32.7) and Northern America (32.6) have the highest incidence rate by region. In 2020, there were an estimated 2,604,791 men and women living with LC diagnosed in the last 5 years around the globe, with a 5-year prevalence proportion of 33.4 per 100,000.[1]

Approximately 80% to 85% of LC patients have NSCLC according to the American Cancer Society.[89] The HER2 mutation is reported to be found in 1.7% to 4.2% of NSCLC cases.[90,91,92]

EU:

In the 27 member states of the EU (ie, the EU-27), 318,327 new cases of LC were diagnosed in 2020, comprising approximately 11.9% of all cancers.[68] The estimated annual age-standardised

(worldwide) incidence rate of LC is 31.2 per 100,000 in the EU.[68] In 2020, there were an estimated 394,704 people living with LC in the EU-27 who were diagnosed in the last 5 years, providing a 5-year prevalence proportion of 88.6 per 100,000.[1]

US:

In the US, an estimated 236,740 new cases of LC cases were diagnosed in 2022, comprising approximately 12.3% of all new cancer cases.[93] The lifetime risk of developing LC is approximately 6%.[93] The age-standardised (worldwide) incidence rate of LC was estimated to be 33.1 per 100,000 in the US.[1] In 2020, there were an estimated 295,263 people living with LC in the US who were diagnosed in the last 5 years, providing a 5-year prevalence proportion of 89.2 per 100,000.[1]

Japan:

In Japan, 138,532 new cases of LC were diagnosed in 2020, comprising approximately 13.5% of all new cancer cases.[1] The age-standardised (worldwide) incidence rate of LC was estimated to be 32.1 per 100,000 in Japan.[1] In 2020, there were an estimated 216,629 people living with LC in Japan who were diagnosed in the last 5 years, providing a 5-year prevalence proportion of 171.28 per 100,000.[1]

SI.3.2. Demographics of the Non-small Cell Lung Cancer Population and Risk Factors for the Disease

Sex: LC is more common in males than females. The worldwide age-standardised incidence of LC in males and females is 31.5 and 14.6 per 100,000, respectively.[1] In the EU, the lifetime risk of developing LC is 1 in 19 for males and 1 in 37 for females.[68] Nonsquamous NSCLCs with HER2 mutations are more associated with females than NSCLC without HER2 mutations.[94]

Age: According to Globocan, only 2.4% of LCs in the world occur in people younger than 45 years.[1] In the EU, 99% of LCs occur at or after 45 years of age.[68] The median age at diagnosis of LC is 71 years in the US.[93] Nonsquamous NSCLCs with HER2 mutations are more associated with younger age than NSCLC without HER2 mutations.[94]

Race and/or ethnicity: According to SEER, the age-adjusted incidence of LC is highest in Black males, with 71.6 per 100,000 in the US.[93] Among women, LC incidence is highest in White females, with 54.3 per 100,000.[93]

Smoking: Smoking is, by far, the leading risk factor for LC. Each year, an estimated 80% of LC cases in men and 50% in women are caused by smoking.[95]

Secondhand smoke (smoke from other people's cigarettes, pipes, or cigars) also can cause LC. According to the American Cancer Society, secondhand smoke is the cause of more than 7,000 LC deaths each year.[96]

Nonsquamous NSCLCs with HER2 mutations are more associated with never-smokers than NSCLC without HER2 mutations.[94]

Radon: Radon is the second most common cause of LC and the most common cause among never-smokers. In Europe, the risk of LC increases by 16% with exposure to each 100 Bq/m^3 increase in indoor radon.[97] In the US, the risk of LC increases by 11% with each 100 Bq/m^3 increase in residential radon.[98]

Occupational carcinogen exposure: Increased LC is associated with exposure to asbestos, arsenic, cadmium, chromium, beryllium, and nickel.[99] Occupational exposure to asbestos (odds ratio: 1.76; 95% CI: 1.42, 2.18), crystalline silica (odds ratio: 1.31; 95% CI: 1.00, 1.71), and

nickel–chromium (odds ratio: 1.18; 95% CI: 0.90, 1.53) is associated with increased risk of LC, even at a low exposure level.[100]

Air pollution: The risk of LC is higher among urban people in comparison to rural people. Increase in the level of particulate matter 2.5 in the air increases the risk of LC. Indoor coal burning produces gas emissions that are carcinogenic to humans.[101]

Familial: First-degree relatives of patients with LC have a 1.51-fold (95% CI: 1.39, 1.63) increased risk of developing LC.[102]

Previous radiation therapy: According to the Centers for Disease Control, patients who had radiation therapy to the chest for prior cancers are at higher risk of LC.[103]

SI.3.3. The Main Existing Treatment Options

Clinical guidelines from National Comprehensive Cancer Network (NCCN)[104] and European Society for Medical Oncology (ESMO)[105] for patients with metastatic NSCLC without an actionable oncogenic driver irrespective of programmed cell death ligand 1 (PD-L1) status are presented below.

In the first-line metastatic setting, the SoC is a combination of platinum-based chemotherapy and pembrolizumab (KEYTRUDA®) irrespective of PD-L1 expression.[104,105] Other approved treatment options based on demonstrated OS improvement over other regimens are combination regimens that include atezolizumab or nivolumab.

In the second-line metastatic setting, the current SoC irrespective of PD-L1 expression for patients who have progressed on or after platinum-based chemotherapy and have not received prior PD-L1 therapy is anti-programmed cell death protein 1/PD-L1 agents.[104,105] Other therapeutic options include docetaxel with or without ramucirumab. Clinical outcomes with currently approved treatment options for patients without an actionable oncogenic driver in the second-line metastatic setting are generally limited (Table Part II: Module SI.3).

Table Part II: Module SI.3: Disease Outcomes with Currently Approved Therapies in the First and Second-line Metastatic NSCLC Setting

Therapy	Objective Response Rate % (95% CI)	Median Duration of Response Months (Range)	Median Progression-free Survival Months (95% CI)	Median Overall Survival Months (95% CI)
Nivolumab[106]	19 (15, 24)	17.2 (1.8, 22.6+)	2.3 (2.2, 3.3)	12.2 (9.7, 15.0)
Pembrolizumab[107] [PD-L1 TPS ≥50% group]	33.1 (27.7, 38.8)	68.4 (2.0+, 71.7+)	5.3 (4.2, 6.5)	16.9 (12.3, 21.4)
Atezolizumab[108]	13.7 (11.1, 16.7)	23.9 (12.8, NE)	2.7 (2.4, 2.9)	13.3 (11.3, 14.9)
Docetaxel[109]	5.5 (1.1, 15.1)	Not reported	Not reported	7.5 (5.5, 12.8)
Ramucirumab plus docetaxel[110]	22.9 (19.7, 26.4)	Not reported	4.5 (4.2, 5.4)	10.5 (9.5, 11.2)
versus				
Placebo plus docetaxel	13.6 (11.0, 16.5)		3.0 (2.8, 3.9)	9.1 (8.4, 10.0)

CI = confidence interval; NE = not estimable; NSCLC = non-small cell lung cancer; TPS = tumor proportion score

Targeted Therapy (ADC) with Activity Against HER2 Mutations

T-DXd has been approved in the US on 11 Aug 2022 as a therapy for patients with previously treated HER2-mutant metastatic NSCLC. The use of T-DXd in metastatic HER2-mutant NSCLC is also recommended by NCCN.[104] In addition, NCCN recommends the HER2-targeting ADC T-DM1 as a treatment option for patients with metastatic NSCLC and HER2 mutations based on a Phase 2 basket study.[104,111]

SI.3.4. Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

Patients with LC have a dismal prognosis with the highest mortality rate among all cancers. Surgical resection is an option in only one-third of patients with LC due to the late detection of the disease. The 5-year OS rate of treatment-naïve Stage IV NSCLC is only 6%.[112]

According to Globocan data, LC caused approximately 1,796,144 deaths worldwide in 2020, with an age-adjusted mortality rate of 18.0 per 100,000.[1]

LC is the most common cause of cancer death in the EU-27. The estimated number of deaths from LC in the EU was 257,293 in 2020.[1] Overall, LC mortality rates in the EU declined in many countries. According to 2000 to 2007 data, 5-year survival of LC is highest in Austria, Germany, and Belgium and lowest in Bulgaria, Lithuania, and Denmark among EU countries.[68]

Mutations in the gene-encoding HER2 (ERBB2) drive approximately 3% of nonsquamous NSCLCs and are associated with female sex, never-smoking history, and a poor prognosis, as well as with a slightly younger age and higher incidence of brain metastases than NSCLC without HER2 mutations or with other mutations.[94]

Events That Occur Frequently in Patients with Lung Cancer

Events that occur frequently in patients with LC are described below. These include events associated with the disease or with therapies.

Dysgeusia with weight loss: Patients with LC commonly suffer from taste and smell alterations. Among patients with LC, 35% to 38% suffer from dysgeusia,[113] and 53.4% of patients have significant weight loss.[114]

Pneumonia: At baseline, 15.9% of patients with NSCLC present with pneumonia.[115] During the course of LC, 50% to 70% of patients suffer from serious lung infections, including pneumonia.[116]

Bone metastases: Bone is the most common site for metastasis in patients with LC. At diagnosis, 57.5% of patients with LC present with bone metastasis. Among patients with LC who had bone metastases, 57.7% developed skeletal related events, defined as bone pain requiring palliative radiotherapy (71.4%), pathological fractures (16.3%), spinal cord compression (6%), and orthopaedic surgery (3.3%). Patients with LC have a median OS of 9.5 months after bone metastasis diagnosis.[117]

Brain metastases (BM): An estimated 7.4% of patients with NSCLC present with BM at diagnosis, and 25% to 30% of patients develop BM during their illness. NSCLC patients with BM have a poor prognosis, with a median survival of 3.4 months.[118]

Cough: Although cough is very common in LC, few robust data have been reported about its incidence in patients before treatment. In a single-institution cross-sectional study conducted in the UK, cough was reported by 57% of patients with LC.[119]

Fatigue: In a study involving consecutive outpatients with Stage IV LC, fatigue was reported by 40% of patients.[120] Fatigue can be caused by the disease, the treatment, or psychological distress. The prevalence of fatigue is 57% in surgically treated early-stage LC and 70% among LC survivors.[121]

Hemoptysis: Hemoptysis is one of the most frequent clinical manifestations of LC. An estimated 10% to 30% of patients with LC in the US suffer from hemoptysis during their disease course. Massive hemoptysis can be found in 10% of these patients.[122,123]

SI.3.5. Important Comorbidities

Most frequent comorbidities in patients with LC are usually smoking-related illnesses. This includes cardiovascular and respiratory diseases. Diabetes and its complications also share common risk factors with LC and frequently present in these patients.[124]

A nationwide population-based cohort study of 10,378 patients with NSCLC of all ages in Denmark showed that 53% of patients have at least 1 comorbidity. NSCLC patients with comorbidities (hazard ratio: 1.12 for single disorder and 1.27 for multiple disorder) have overall higher mortality compared to patients without comorbidities. In Cox regression analysis, hazard ratio was significantly higher in patients with cardiovascular disorder (hazard ratio: 1.30, CI: 1.13, 1.49), chronic obstructive pulmonary disease (hazard ratio: 1.2, CI: 1.10, 1.31), diabetes (hazard ratio: 1.19, CI: 1.02, 1.39), and cerebrovascular disorders (hazard ratio 1.18, CI: 1.05, 1.33).[125]

In a population-based cohort study from French cancer registries, 55% of the 1130 patients with NSCLC presented with at least 1 comorbidity. Chronic obstructive pulmonary disease, peripheral vascular disease, and congestive heart failure were the most frequent comorbidities. Even though observed and net survival rates decreased for Charlson Comorbidity Index Grade ≥3 for NSCLC, after adjustment for sex, age group, stage, and diagnostic mode, Charlson Comorbidity Index grades were no longer associated with lower survival rates.[126]

In the US, a retrospective cohort study (N = 6662) in the LC population found 51% of patients had at least 1 comorbidity and 18% had at least 4 comorbidities at the time of cancer diagnosis. Chronic lung disease (43%), peripheral vascular disease (24%), renal disease (21%), diabetes with (15%) or without (9%) complications, prior cancer or metastatic carcinoma (15%), cerebrovascular disease (12%), myocardial infarction (11%), and heart failure (11%) were the most frequent comorbid conditions among the study population. Patients in comorbidity class 1 had significantly higher survival compared to the patients in other classes (2 to 5).[127]

Some studies also suggest that the presence of comorbidity in patients with LC had led to a higher frequency of physician visits and was associated with early diagnosis of LC.[128,129]

PART II: MODULE SII NONCLINICAL PART OF THE SAFETY SPECIFICATION

The nonclinical safety profile of T-DXd has been characterised using both in vitro and in vivo pharmacological, pharmacokinetic (PK), and toxicological studies in rats and monkeys.

Findings are discussed within the dose ranges specified in Table Part II: Module SII.1.

Table Part II: Module SII.1: Human-Equivalent Doses of Trastuzumab Deruxtecan and Released Drug Studied in the Nonclinical Development Programme

Rats				Monkeys			
Trastuzumab Deruxtecan		Released Drug		Trastuzumab Deruxtecan		Released Drug	
Dose Studied (mg/kg)	HED (mg/kg)	Dose Studied (mg/kg)	HED (mg/kg)	Dose Studied (mg/kg)	HED (mg/kg)	Dose Studied (mg/kg)	HED (mg/kg)
20	3.2	3	0.48	3	0.96	1	0.32
60	9.7	10	1.6	10	3.2	3	0.97
197	31.8	30	4.8	30	9.7	12	3.9
-	-	-	-	78.8	25.4	-	-

FDA = Food and Drug Administration; HED = human equivalent dose
Conversion factors for rats and monkeys to estimate HED are per Appendix B Table 3 in the FDA Guidance for Industry[130]

Information on key safety findings from the nonclinical studies with T-DXd and released drug (the drug component of T-DXd, a derivative of exatecan, a topoisomerase I inhibitor) and their relevance to human usage is presented in Table Part II: Module SII.2.

Table Part II: Module SII.2: Summary of Nonclinical Findings for Trastuzumab Deruxtecan

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Toxicity	
Intestinal toxicity: Trastuzumab deruxtecan: In monkeys given 78.8 mg/kg of T-DXd (dosing once every 3 weeks [q3w] for 6 weeks), diarrhoea was noted. T-DXd -treated rats and monkeys had very slight single-cell necrosis of the crypt epithelium in the small and large intestines at low doses (rat: ≥20 mg/kg; monkey: ≥3 mg/kg). These changes showed reversibility after a recovery period in both rats and monkeys. Released drug: The intestinal toxicity caused by T-DXd also occurred in the 4-week intermittent dose study (once-weekly dosing) of the released drug in rats and monkeys (rat: ≥3 mg/kg; monkey: 12 mg/kg).	Nonclinical studies in rats and monkeys indicated a potential for GI effects, such as diarrhoea, with T-DXd and released drug. Several GI events are considered identified risks for T-DXd; however, these events can be adequately managed through labelling and are not considered important risks for inclusion in the RMP (Section SVII.3).

Table Part II: Module SII.2: Summary of Nonclinical Findings for Trastuzumab Deruxtecan (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Lymphatic/haematopoietic toxicity: Trastuzumab deruxtecan: In the rat 6-week intermittent-dose (q3w dosing) toxicity study of T-DXd, a decrease in reticulocyte ratio at ≥20 mg/kg and decreases in white blood cell parameters (lymphocyte, eosinophil, basophil, and neutrophil counts) at ≥60 mg/kg were observed. The haematological changes in rats seemed to be associated with the following histopathological changes: decreased erythroblasts, single-cell necrosis of lymphocytes in the thymus, atrophy of follicles in the submandibular lymph nodes, and Peyer's patches at ≥60 mg/kg and decreased myelocytes in the bone marrow and atrophy in the thymus at 197 mg/kg. In the monkey 3-month intermittent dose (q3w dosing) toxicity study of T-DXd, a decrease in reticulocyte ratio associated with decreased erythroblasts in the bone marrow was observed at 30 mg/kg. At the higher dose of 78.8 mg/kg in the 6-week intermittent dose toxicity study, decreased peripheral erythroid parameters (erythrocytes, haemoglobin, haematocrit, and reticulocyte ratio) were also observed. Released drug: The lymphatic/hematopoietic organ toxicity observed with T-DXd also occurred in the 4-week intermittent dose (once-weekly dosing) study of the released drug in rats and monkeys (rat: ≥3 mg/kg; monkey: ≥1 mg/kg).	Haematological findings with T-DXd and released drug, including decreased haematopoietic cells (ie, red blood cells, white blood cells, and platelets) and reversible histopathological changes in lymphoid organs, were seen in nonclinical studies with rats and monkeys. Similarly, haematological laboratory abnormalities were observed in clinical studies. Anaemia, thrombocytopenia and neutropenia, including febrile neutropenia, are considered identified risks for T-DXd; however, they are not considered important risks for inclusion in the RMP as they can be managed through standard clinical practice (Section SVII.1.1).

Table Part II: Module SII.2: Summary of Nonclinical Findings for Trastuzumab Deruxtecan (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Pulmonary toxicity: Trastuzumab deruxtecan: T-DXd caused pulmonary toxicity in monkeys at ≥30 mg/kg, and no pulmonary toxicity was observed in rats. In the 6-week monkey intermittent dose (q3w dosing, 3 animals/sex/group) toxicity study of T-DXd, 1 male given 78.8 mg/kg showed aggregation of foamy macrophages in the alveolus, focal interstitial inflammation, alveolar oedema, and anisokaryosis of the alveolar and bronchiolar epithelium at the end of the dosing period. Similar histopathological changes were found in 1 male and 2 females in the 78.8 mg/kg recovery group (2 animals/sex). In contrast, no changes in the lungs were noted in all monkeys in the 30 mg/kg group at the end of the dosing period (3 animals/sex), and very slight changes that were not accompanied by alveolar oedema were found in 1 of 4 monkeys at the end of the recovery period (2 animals/sex). The incidence and severity of the lesions were dose dependent. In the monkey 3-month study of T-DXd, similar lesions in the lungs were observed in the 30 mg/kg group (the highest dose) at the end of the dosing period. An extended dosing period did not increase the severity of lesions, and the pulmonary finding in monkeys observed at 30 mg/kg showed reversibility after the 3-month recovery period. Released drug: No pulmonary toxicity was observed in studies of the released drug in rats or monkeys.	Nonclinical studies in monkeys suggested T-DXd could potentially lead to pulmonary toxicity, with an associated dose dependency in incidence and severity. Events of dose-dependent ILD have been observed in clinical studies, with fatal outcomes reported. ILD/pneumonitis is considered an important identified risk for inclusion in this RMP (Section SVII.3).

Table Part II: Module SII.2: Summary of Nonclinical Findings for Trastuzumab Deruxtecan (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Renal toxicity: Trastuzumab deruxtecan: In the rat 6-week study of T-DXd (q3w dosing), abnormalities in renal function were observed. Urinalysis revealed proteinuria at ≥60 mg/kg. Blood chemistry indicated increases in urea nitrogen, inorganic phosphorus, creatinine, and potassium and decreases in sodium and chloride at 197 mg/kg. Histopathological changes such as tubular basophilia and hyaline casts in the kidney were noted at ≥60 mg/kg. All findings in rats resolved after a 9-week recovery period. In the monkey 3-month study with T-DXd (q3w dosing), while anisokaryosis in the proximal tubules in the kidney was observed at 30 mg/kg at the end of dosing and the 3-month recovery periods, no findings suggestive of abnormalities in renal function were observed in urinalysis or blood chemistry. Released drug: No renal toxicity was observed in studies of the released drug in rats or monkeys.	Abnormal renal function was seen in rats but not in monkeys in nonclinical studies with T-DXd. Histopathological changes at only supratherapeutic doses of T-DXd were observed in both rats and monkeys. No renal toxicity was observed with the released drug. No safety concern with renal function from clinical studies with T-DXd has been identified. However, TEAEs of Blood creatinine increased were observed with a higher incidence (4.3% vs 1.1%) in the T-DXd arm than in the T-DM1 comparator arm in Study DS8201-A-U302 and, therefore, Blood creatinine increased is listed as an ADR in the SmPC. Based on the histopathological changes found in rats and monkeys as well as renal toxicity observed in rats, renal toxicity is a potential risk, but is not considered an important potential risk for inclusion in the RMP (Section SVII.1.1).
Skin toxicity: Trastuzumab deruxtecan: In the rat 6-week intermittent-dose (q3w dosing) toxicity study of T-DXd, trauma and/or crust at ≥20 mg/kg and sparse fur and/or loss of fur at 197 mg/kg were observed. In histopathological examinations, single-cell necrosis in the hair follicles, ulcer, crust, epidermal thickening, and/or fibrosis and inflammatory cell infiltration in the dermis were observed at ≥60 mg/kg. All the findings in the skin in rats resolved after a 9-week recovery period. In the monkey 3-month study with T-DXd (q3w dosing), single-cell necrosis in the hair follicles in the skin at ≥10 mg/kg and epidermal pigmentation at ≥30 mg/kg were noted. At the end of the 3-month recovery period, single-cell necrosis in the hair follicles resolved, whereas epidermal pigmentation persisted. Released drug: No skin toxicity was observed in studies of the released drug in rats or monkeys.	Nonclinical findings related to skin toxicity such as changes in the hair follicles and epidermis were seen in studies with rats and monkeys. The changes in the hair follicles seen in nonclinical studies may be associated with the alopecia observed in clinical studies. Rash (which includes rash, rash pustular and rash maculopapular) and hyperpigmentation are considered identified risks for T-DXd; however, they are not considered important risks for inclusion in the RMP (Section SVII.1.1).

Table Part II: Module SII.2: Summary of Nonclinical Findings for Trastuzumab Deruxtecan (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Hepatotoxicity: Trastuzumab deruxtecan: In the 6-week intermittent IV dose (q3w dosing) toxicity study of T-DXd in monkeys, transient increases in AST and ALT at ≥10 mg/kg were observed, while no histopathological findings were observed in the liver. In the 3-month monkey study (q3w dosing), elevations of enzymes (AST, lactate dehydrogenase, and creatine kinase) that did not accompany histopathological changes in the liver were observed in monkeys receiving 30 mg/kg T-DXd. These increases in the enzymes were not considered to be significant toxicological changes. Released drug: In the 4-week intermittent dose (once-weekly dosing) study of the released drug in monkeys, single-cell necrosis in hepatocytes accompanied by increases in AST and ALT were observed at the highest dose (12 mg/kg).	Nonclinical studies in monkeys suggested transient increases in ALT and AST without histopathological changes in the liver with T-DXd and released drug. Increases in ALT and AST have been observed in clinical studies, with no confirmed case of Hy's law. AST increased and ALT increased are considered identified risks for T-DXd but are not considered important for inclusion in this RMP (Section SVII.1.1).

Table Part II: Module SII.2: Summary of Nonclinical Findings for Trastuzumab Deruxtecan (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Cardiotoxicity: Trastuzumab deruxtecan: A 6-week or 3-month administration of T-DXd caused no histopathological changes in the heart in rats and monkeys. In the 6-week intermittent IV dose (q3w dosing; 3 animals/sex/group to 5 animals/sex/group) study of T-DXd in monkeys, ECG parameter changes (slight QTc prolongation; a change of approximately 14%) were found in 1 animal in the 78.8 mg/kg group (5 animals/sex). No abnormalities in ECG parameters, cardiac function tests (LVEF, etc), or cardiac troponin I levels were found in the 3-month intermittent dosing study in monkeys. In the safety pharmacology study, T-DXd had no effect on the cardiovascular parameters (blood pressure, heart rate, or ECG) at doses of up to 78.8 mg/kg when a single IV dose was administered to male monkeys. Released drug: In the 4-week intermittent-dose (once-weekly dosing) study of the released drug in rats and monkeys, myocardial cell degeneration/necrosis was observed in a moribund cynomolgus monkey at a dose level of 12 mg/kg. In hERG studies, the released drug did not show inhibition of the hERG channel current.	Nonclinical studies suggested a potential effect on QT interval with T-DXd and released drug. QT was routinely monitored through ECG in clinical studies with T-DXd. A study to evaluate the effect of T-DXd 6.4 mg/kg on QTc confirmed no clinically meaningful impact on the QTc interval. Therefore, QT prolongation is not considered a risk for inclusion in this RMP.
Ocular toxicity: Trastuzumab deruxtecan: In the intermittent IV dosing studies of T-DXd (q3w dosing for 6 weeks or 3 months), ocular toxicity was not found at doses up to the highest dose (78.8 mg/kg in cynomolgus monkeys, 197 mg/kg in rats). Released drug: In the 4-week intermittent-dose (once-weekly dosing) study of the released drug in rats and monkeys, single-cell necrosis in the corneal epithelium was seen at ≥3 mg/kg in rats and at 12 mg/kg in monkeys. The finding resolved after the 4-week recovery period.	Nonclinical studies suggested a potential for adverse corneal effects with only the released drug. Vision blurred is an identified risk for T-DXd but is not considered an important risk. Keratitis is a potential risk for T-DXd but is not considered an important risk for inclusion in this RMP (Section SVII.1.1).

Table Part II: Module SII.2: Summary of Nonclinical Findings for Trastuzumab Deruxtecan (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Reproductive/developmental toxicity and genotoxicity: Since embryo-foetal developmental toxicity studies are not warranted for drugs that are genotoxic and target rapidly dividing cells, embryo-foetal developmental toxicity studies were not conducted in accordance with the ICH S9.[131] Trastuzumab deruxtecan: In the 6-week intermittent-dose study of T-DXd in rats, small-sized testes and epididymides that accompanied reduced organ weights were observed at 197 mg/kg. Histopathological findings in rats included spermatid retention at 20 mg/kg and 60 mg/kg, and tubular degeneration/atrophy in the testes accompanying secondary changes of luminal cell debris and reduced sperm in the epididymis at 197 mg/kg. The changes produced at 197 mg/kg did not recover by the end of the 9-week recovery period. In the 6-week and 3-month intermittent-dose studies of T-DXd in cynomolgus monkeys, decreased numbers of round spermatids in the Stage V to VI seminiferous tubule in the testes was observed at ≥30 mg/kg. These changes in the testes of monkeys showed reversibility. Released drug: There was no testicular toxicity in studies in rats and monkeys with the released drug. In vitro genotoxicity studies of the released drug indicated that this drug had no potential to induce gene mutation in bacteria but had the potential to induce structural chromosome aberrations in mammalian cultured cells. An in vivo micronucleus study in bone marrow of rats indicated that the released drug had the potential to induce micronuclei.	Reproductive studies in rats and monkeys indicate changes to the reproductive organs of males. Postmarketing AE reports for trastuzumab showed that treatment during pregnancy has resulted in oligohydramnios, manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. DXd, the released drug was genotoxic in an in vitro chromosome aberration study with mammalian cultured cells and an in vivo micronucleus study in rats. The characteristics of trastuzumab and released drug indicate that T-DXd can potentially cause foetal harm when administered to a pregnant woman. Embryo-foetal toxicity is considered an important potential risk for inclusion in this RMP (Section SVII.1.2). Testicular toxicity is a potential risk based on the findings in animal studies, however it is not considered an important potential risk for inclusion in the RMP (Section SVII.1.1).
Carcinogenicity: No carcinogenicity studies have been conducted in accordance with ICH S9.	T-DXd is being studied for the treatment of cancer.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram; GI = gastrointestinal; hERG = human ether-à-go-go-related gene; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; ILD = interstitial lung disease; IV = intravenous; LVEF = left ventricular ejection fraction; q3w = every 3 weeks; QTc = corrected QT interval; RMP = Risk Management Plan; T-DXd = trastuzumab deruxtecan

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

The exposure data presented in this Risk Management Plan (RMP) focus exclusively on subjects in Daiichi Sankyo-sponsored studies and do not include subjects in investigator-sponsored studies.

Cumulatively, 2145 subjects were exposed to ≥5.4 mg/kg T-DXd in the following 9 pooled studies (Studies DS8201-A-J101, DS8201-A-U201, DS8201-A-J202, DS8201-A-U204, DS8201-A-U205, DS8201-A-U206, DS8201-A-U301, DS8201-A-U302, and DS8201-A-U303). An outline of these 9 studies in terms of design, exposure, and data cut-off dates is provided below (Module 5.3.5.3 SCS SAP Version 2.0):

- Study DS8201-A-J101, hereafter referred to as Study J101, was a Phase 1, 2-part, multicentre, nonrandomised, open-label, multiple-dose first-in-human study in subjects with advanced solid malignant tumours (280 treated subjects; data cut-off date: 01 Aug 2019).
- Study DS8201-A-U201, hereafter referred to as Study U201, was a Phase 2, multicentre, open-label study in subjects with HER2-positive, unresectable and/or metastatic breast cancer previously treated with T-DM1 (253 subjects treated; data cut-off date: 08 Jun 2020).
- Study DS8201-A-J202, hereafter referred to as Study J202, was a Phase 2, multicentre, open-label study in subjects with HER2-expressing advanced gastric or GEJ adenocarcinoma (169 subjects treated; data cut-off date: 03 Jun 2020).
- Study DS8201-A-U204, hereafter referred to as Study U204, was a Phase 2, multicentre, open-label, 2-cohort study for HER2-overexpressing or HER2-mutated, unresectable and/or metastatic non-small cell lung cancer (NSCLC) (181 subjects treated; data cut-off date: 03 Dec 2021).
- Study DS8201-A-U205, hereafter referred to as Study U205, was a Phase 2, open-label, single-arm study in HER2-positive, unresectable or metastatic gastric or GEJ adenocarcinoma subjects who have progressed on or after a trastuzumab-containing regimen (79 subjects treated; data cut-off date: 08 Nov 2021).
- Study DS8201-A-U206, hereafter referred to as Study U206, is a Phase 2, multicentre, randomised, 2-arm study in HER2-mutant NSCLC subjects who had disease recurrence or progression during/after at least 1 regimen of prior anticancer therapy (second-line or later) that must have contained a platinum-based chemotherapy drug in the metastatic/locally advanced setting (151 subjects, of whom 101 were treated with 5.4 mg/kg T-DXd and 50 were treated with 6.4 mg/kg T-DXd; interim analysis data cut-off date: 24 Mar 2022).
- Study DS8201-A-U301, hereafter referred to as Study U301, was a Phase 3, multicenter, open-label, active-controlled study for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with T-DM1 (608 subjects, of whom 404 subjects were treated with 5.4 mg/kg T-DXd; data-cut-off date: 30 Jun 2022).

- Study DS8201-A-U302, hereafter referred to as Study U302, was a Phase 3, multicentre, open-label, active-controlled study in subjects with HER2-positive, unresectable and/or metastatic breast cancer previously treated with trastuzumab and taxane (518 subjects, of whom 257 were treated with T-DXd; data cut-off date: 25 Jul 2022).
- Study DS8201-A-U303, hereafter referred to as Study U303, was a Phase 3, multicentre, open-label, active-controlled study for HER2-low, unresectable and/or metastatic breast cancer subjects (543 subjects, of whom 371 subjects were treated with T-DXd; data cut-off date: 11 Apr 2022).

The median duration of exposure among subjects within these 9 studies split into 5 pools (ie, 5.4 mg/kg [BC]; 5.4 mg/kg [NSCLC]; 5.4 mg/kg [ATT]; 6.4 mg/kg [GC]; 6.4 mg/kg [ATT]) is presented in Table Part II: Module SIII.1.

For the purpose of this RMP, the overall pool of 2145 subjects treated with ≥5.4 mg/kg in the variety of tumour types (ie, the All Tumour Types [ATT] ≥5.4 mg/kg Pool) is referred to as "ATT ≥5.4 mg/kg Pool". The number of subjects split by age group and sex across the 5 pools is presented in Table Part II: Module SIII.2 and Table Part II: Module SIII.3, while the number of subjects split by ethnic origin, race, and geographic distribution is presented in Table Part II: Module SIII.4.

Table Part II: Module SIII.1: Duration of Exposure to Trastuzumab Deruxtecan (Safety Analysis Set)

Duration of Exposure (months)[a]		Number (%) of Subjects in Pool			
	BC 5.4 mg/kg (N = 1287)	**HER2-mut NSCLC 5.4 mg/kg (N=101)**	**5.4 mg/kg All Tumour Types (N = 1449)**	**HER2-pos GC 6.4 mg/kg (N = 229)**	**6.4 mg/kg All Tumour Types (N = 669)**
0 to ≤3	161 (12.5)	39 (38.6)	225 (15.5)	81 (35.4)	203 (30.3)
>3 to ≤6	196 (15.2)	43 (42.6)	252 (17.4)	64 (27.9)	165 (24.7)
>6 to ≤9	204 (15.9)	12 (11.9)	225 (15.5)	39 (17.0)	111 (16.6)
>9 to ≤12	149 (11.6)	7 (6.9)	162 (11.2)	16 (7.0)	50 (7.5)
>12 to ≤18	188 (14.6)	0	195 (13.5)	23 (10.0)	75 (11.2)
>18 to ≤24	192 (14.9)	0	192 (13.3)	3 (1.3)	32 (4.8)
>24	197 (15.3)	0	198 (13.7)	3 (1.3)	33 (4.9)
Median duration of exposure (months)	10.48	3.71	9.59	4.60	5.52
Total patient-years [b]	1426.0	35.24	1493.9	115.1	431.78

BC = breast cancer; GC = gastro/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; mut = mutant; N = total number of subjects in the pool; NSCLC = non-small cell lung cancer;.
Percentages were calculated by using the number of subjects in the Safety Analysis Set as the denominator.
BC 5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-U302, DS8201-A-U301, DS8201-A-U201, and DS8201-A-J101.
HER2-mut NSCLC 5.4 mg/kg Data: Study DS8201-A-U206.
All Tumour Types 5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-U302, DS8201-A-U301, DS8201-A-U201, DS8201-A-J101, DS8201-A-U204, and DS8201-A-U206.
HER2-Positive GC 6.4 mg/kg Pooled Data: Studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
All Tumour Types 6.4 mg/kg Pooled Data: Studies DS8201-A-U201, DS8201-A-J101, DS8201-A-J202, DS8201-A-U204, DS8201-A-U205, and DS8201-A-U206.
[a] Duration of treatment (months) = (date of the last dose – date of the first dose + 21)/30.44.
[b] Patient-years of exposure = sum (duration of exposure [months])/12.
Data cut-off dates: 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 08 Nov 2021 for Study U205, 25 Jul 2022 for Study U302, 11 Jan 2022 for Study U303, and 30 Jun 2022 for U301.
Source: Module 5.3.5.3 SCS Table 14.1.3.1 (NSCLC), Module 5.3.5.3 SCS Table 1.1.3 (GC), Module 5.3.5.3 SCS Table 1.1.3 (U301).

Table Part II: Module SIII.2: Age Group and Sex of Subjects Receiving Trastuzumab Deruxtecan (Safety Analysis Set)

Age Group[a]	All Tumour Types 5.4 mg/kg (N = 1449)				BC 5.4 mg/kg (N = 1287)				HER2 mut NSCLC 5.4 mg/kg (N = 101)			
	Number (%) of Subjects		Patient-Years of Exposure[b]		Number (%) of Subjects		Patient-years of Exposure [b]		Number (%) of Subjects		Patient-years of Exposure [b]	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
<65 years	47 (3.2)	1052 (72.6)	19.6	1147.9	5 (0.4)	1000 (77.7)	4.1	1127.2	23 (22.8)	38 (37.6)	7.5	13.3
65-74 years	24 (1.7)	263 (18.2)	11.5	261.6	2 (0.2)	231 (17.9)	2.2	248.1	9 (8.9)	23 (22.8)	3.3	8.9
75-85years	6 (0.4)	51 (3.5)	2.3	48.3	0	43 (3.3)	0	41.7	4 (4.0)	4 (4.0)	1.4	0.9
≥85 years	0	6 (0.4)	0	2.8	0	6 (0.5)	0	2.8	0	0	0.0	0.0

BC = breast cancer; N = total number of subjects in the pool; NSCLC = non-small cell lung cancer..
Percentages were calculated by using the number of subjects in the Safety Analysis Set as the denominator.
BC 5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-U302, DS8201-A-U301, DS8201-A-U201, and DS8201-A-J101.
HER2-mut NSCLC 5.4 mg/kg Data: Study DS8201-A-U206
All Tumour Types 5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-U302, DS8201-A-U301, DS8201-A-U201, DS8201-A-J101, DS8201-A-U204, and DS8201-A-U206.
[a] Age in years was calculated by using the informed consent date and the birth date.
[b] Patient-years = sum (duration of exposure [months])/12.
Data cut-off dates: 01 Aug 2019 for Study J101, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 25 Jul 2022 for Study U302, 11 Jan 2022 for U303, and 30 Jun 2022 for U301.
Source: Module 5.3.5.3 EU RMP Table 2 and Table 3 (U301), Module 5.3.5.3 EU RMP Table 3 (NSCLC).

Table Part II: Module SIII.3: Age Group and Sex of Subjects Receiving Trastuzumab Deruxtecan (Safety Analysis Set)

Age Group[a]	HER2-positive GC 6.4 mg/kg (N = 229)				All Tumour Types 6.4 mg/kg (N = 669)			
	Number (%) of Subjects		Patient-Years of Exposure[b]		Number (%) of Subjects		Patient-Years of Exposure[b]	
	Male	Female	Male	Female	Male	Female	Male	Female
<65 years	88 (38.4)	21 (9.2)	42.3	11.1	175 (26.2)	232 (34.7)	97.7	186.1
65-74 years	67 (29.3)	29 (12.7)	36.3	11.2	111 (16.6)	100 (14.9)	53.5	67.2
75-84 years	17 (7.4)	7 (3.1)	11.7	2.5	24 (3.6)	24 (3.6)	13.8	11.7
≥85 years	0	0	0	0	1 (0.1)	2 (0.3)	1.0	0.7

GC = gastro/gastrooesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; N = total number of subjects in the pool; T-DXd = trastuzumab deruxtecan.

Percentages were calculated by using the number of subjects in the Safety Analysis Set as the denominator.

HER2-positive GC 6.4 mg/kg Pooled Data: Studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205

All Tumour Types 6.4 mg/kg Pooled Data: Studies DS8201-A-U201, DS8201-A-J101, DS8201-A-J202, DS8201-A-U204, and DS8201-A-U205.

[a] Age in years was calculated by using the informed consent date and the birth date.

[b] Patient-years = sum (duration of exposure [months])/12.

Data cut-off dates: 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 08 Nov 2021 for Study U205.

Source : Module 5.3.5.3 EU RMP Table 4 (NSCLC), Module 5.3.5.3 EU RMP Table 3 (2L BC).

Table Part II: Module SIII.4: Ethnic Origin, Race, and Geographical Distribution of Subjects Receiving Trastuzumab Deruxtecan (Safety Analysis Set)

Parameter	Number (%) of Subjects				
	BC 5.4 mg/kg (N = 1287)	HER2-mut NSCLC T-DXd 5.4 mg/kg (N=101)	All Tumour Types 5.4 mg/kg (N = 1449)	HER2-positive GC 6.4 mg/kg (N = 229)	All Tumour Types 6.4 mg/kg (N = 669)
Ethnicity[a] – n (%)					
Hispanic/Latino	107 (8.3)	1 (1.0)	109 (7.5)	5 (2.2)	19 (2.8)
Not Hispanic/Non-Latino	1023 (79.5)	88 (87.1)	1152 (79.5)	70 (30.6)	316 (47.2)
Unknown	21 (1.6)	12 (11.9)	33 (2.3)	4 (1.7)	306 (45.7)
Not applicable[b]	109 (8.5)	-	109 (7.5)	0	28 (4.2)
Not reported	0	-	4 (0.3)	0	-
Missing	27 (2.1)	-	42 (2.9)	150 (65.5)	-
Race					
White	633 (49.2)	23 (22.8)	692 (47.8)	69 (30.1)	212 (31.7)
Black or African American	34 (2.6)	-	36 (2.5)	1 (0.4)	-
Asian	525 (40.8)	64 (63.4)	607 (41.9)	154 (67.2)	401 (59.9)
American Indian or Alaska Native	4 (0.3)	-	5 (0.3)	0	-
Native Hawaiian or Other Pacific Islander	2 (0.2)	-	2 (0.1)	1 (0.4)	-
Multiple	2 (0.2)	-	2 (0.1)	0	0
Other	83 (6.4)	14 (13.9)	101 (7.0)	3 (1.3)	54 (8.1)
Missing	4 (0.3)	-	4 (0.3)	1 (0.4)	2 (0.3)
Region[c]					
Asia	494 (38.4)	62 (61.4)	-	150 (65.5)	381 (57.0)
North America	214 (16.6)	4 (4.0)	-	34 (14.8)	162 (24.2)
Europe	425 (33.0)	33 (32.7)	299 (31.7)[d]	45 (19.7)	125 (18.7)[d]
Rest of World	154 (12.0)	2 (2.0)	-	0	1 (0.1)
Country of Origin					
US	-	-	186 (19.7)	34 (14.8)	-
Japan	193 (15.0)	37 (36.6)	166 (17.6)	124 (54.1)	324 (48.4)

Parameter	Number (%) of Subjects				
	BC 5.4 mg/kg (N = 1287)	**HER2-mut NSCLC T-DXd 5.4 mg/kg (N=101)**	**All Tumour Types 5.4 mg/kg (N = 1449)**	**HER2-positive GC 6.4 mg/kg (N = 229)**	**All Tumour Types 6.4 mg/kg (N = 669)**
Not Japan	1094 (85.0)	64 (63.4)	-	-	345 (51.6)
Korea	-	-	107 (11.3)	26 (11.4)	-

BC = breast cancer; GC = gastro/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; N = total number of subjects in the pool; NSCLC = non-small cell lung cancer; US = United States

Note: Percentages were calculated by using the number of subjects in the Safety Analysis Set as the denominator.

BC 5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-U302, DS8201-A-U201, and DS8201-A-J101.

HER2-mut NSCLC 5.4 mg/kg Data: Study DS8201-A-U206

All Tumour Types 5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-U302, DS8201-A-U301, DS8201-A-U201, DS8201-A-J101, DS8201-A-U204, and DS8201-A-U206.

HER2-positive GC 6.4 mg/kg Pooled Data: Studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.

All Tumour Types 6.4 mg/kg Pooled Data: Studies DS8201-A-U201, DS8201-A-J101, DS8201-A-J202, DS8201-A-U204, DS8201-A-U205, and DS8201-A-U206.

[a] Ethnicity was not required to be collected in all countries.

[b] Subjects of Japanese origin in Study DS8201-A-J101 were instructed to respond with “Not Applicable” upon enrolment. This option was removed for later studies.

[c] Regional and country of origin information is collected differently for each data pool. Therefore, data are not available for all categories in each data pool.

[d] Subjects were enrolled from Austria, Belgium, France, Greece, Hungary, Italy, Portugal, Russia, Spain, Sweden, Switzerland, the United Kingdom, and the Netherlands.

Data cut-off dates: 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 08 Nov 2021 for Study U205, 25 Jul 2022 for Study U302, and 11 Jan 2022 for Study U303.

Source : Module 5.3.5.3 EU RMP Table 14.1.2.1 (NSCLC), Module 5.3.5.3 EU RMP Table 4 (2L BC), Module 5.3.5.3 SCS Table 1.1.2 (U301).

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

The following were key exclusion criteria from the 9 pooled studies in the ATT ≥5.4 mg/kg Pool:

Age less than the years of maturity (eg, <18 years in the US and EU, <20 years in Japan and Korea)

Reason for exclusion:

Conditions under study are rare in paediatric patients and therefore not relevant to study.

Is it considered to be included as missing information?

No

Rationale:

These patients are not relevant for the current proposed indications.

Eastern Cooperative Oncology Group performance status ≥2

Reason for exclusion:

Cancer patients with poor performance status are excluded before safety and efficacy of a product are confirmed in patients with good PS. The inclusion criterion was limited to Eastern Cooperative Oncology Group PS 0 or 1 in order to monitor whether the drug has a negative effect on PS.

Is it considered to be included as missing information?

No

Rationale:

There is no evidence to suggest that the safety profile in these patients is different from that of the population intended for treatment.

Known human immunodeficiency virus (HIV) infection or active hepatitis B or C infection

Reason for exclusion:

To maximise subject safety during the conduct of these studies, subjects with known HIV or active Hepatitis B or C infection were excluded from participation in the clinical programme because of the potential for drug-drug interactions with concomitant medications.

Is it considered to be included as missing information?

No

Rationale:

There was no clinically meaningful drug-drug interaction with ritonavir or itraconazole in Study DS8201-A-A104 in subjects with HER2-expressing advanced solid malignant tumours (ie, minimal increase in exposure and no change in the safety profile). No differences are expected between subjects with HER2+ and HER2-low BC with respect to drug-drug interactions. No additional safety concerns are anticipated if the product is used in these patient populations. Therefore, the use of T-DXd in patients with pre-existing HIV or active Hepatitis B/C is not considered missing information.

Pre-existing severe renal impairment (creatinine clearance [CrCL] <30 mL/min)

Reason for exclusion:

Subjects with severe renal impairment were excluded from participation in the clinical programme before the safety profile was established in subjects without severe renal impairment. One subject in Study J101 and 1 subject in Study U204 met the CrCL criteria for severe renal impairment on the first day of the first cycle prior to dosing; however, the subject was enrolled meeting the CrCL criteria for moderate renal impairment at screening. Another subject in Study U204 was enrolled meeting the CrCL criteria for severe renal impairment at screening and CrCL values remained on the same level over the course of 20 cycles of treatment. In Study U303, 1 subject meeting the CrCL criteria for severe renal impairment was enrolled at screening and discontinued study drug after the first cycle because of worsening hepatic failure while severe renal impairment persisted.

Is it considered to be included as missing information?

No

Rationale:

The major excretion pathway of T-DXd, as observed in a rat study, was primarily through faeces via the biliary route with minimal renal excretion. In addition, based on the population PK analysis for mild and moderate renal impairment and data from nonclinical studies, a different safety profile is not expected in patients with severe renal impairment.

Pre-existing moderate hepatic impairment

Reason for exclusion:

A potential effect of impaired hepatic function on T-DXd elimination and exposure is possible. The inclusion criteria related to hepatic impairment were not identical among the 9 studies but allowed for inclusion of subjects with baseline moderate hepatic impairment, which occurred in 8 subjects.

Is it considered to be included as missing information?

Yes

Pre-existing severe hepatic impairment (defined as total bilirubin >3.0 × upper limit of normal [ULN] and any AST regardless of Gilbert Syndrome)

Reason for exclusion:

A potential effect of impaired hepatic function on T-DXd elimination and exposure is possible. This patient population was excluded before safety and efficacy data were established in patients without severe hepatic impairment.

Is it considered to be included as missing information?

Yes

History of myocardial infarction (MI), recent troponin levels consistent with MI, or recent unstable angina

Reason for exclusion:

Cardiotoxicity has been observed with anti-HER2 drugs, including trastuzumab, which has a warning for cardiomyopathy. A nonclinical study in monkeys has shown myocardial cell degeneration/necrosis at supratherapeutic doses (not tested in humans) with the released drug of T-DXd.

Is it considered to be included as missing information?

No

Rationale:

Clinical data do not support an association between T-DXd and cardiotoxicity manifesting as ischemic cardiac events such as MI. This lack of cardiac liability suggests that the safety profile in this population would not be different from that of the indicated population and it is, therefore, not relevant for inclusion as missing information.

Left ventricular ejection fraction <50% or recent symptomatic congestive heart failure

Reason for exclusion:

Cardiotoxicity has been observed with anti-HER2 drugs, including trastuzumab, which has a warning for cardiomyopathy. A nonclinical study in monkeys with T-DXd did not show an abnormality in cardiac function tests (including LVEF).

Is it considered to be included as missing information?

No

Rationale:

Left ventricular dysfunction is an important identified risk for T-DXd as described in SmPC Section 4.4 and 4.8. Additional information on this risk is included in Section SVII.3.

QTcF >470 msec (female) or >450 msec (male) or recent serious cardiac arrhythmia requiring treatment

Reason for exclusion:

A nonclinical study in monkeys has shown a slight corrected QT interval using Fridericia's formula (QTcF) prolongation at supratherapeutic doses of T-DXd (not tested in humans).

Is it considered to be included as missing information?

No

Rationale:

No clinically meaningful association between QT prolongation and the use of T-DXd was observed in a study to evaluate QT effects (Study DS8201-A-J102). This result is consistent with the clinical data from the 9 completed studies. As there is no signal of QT liability with T-DXd, there is no evidence to suggest the safety profile in this population is different from that of the general target population.

History of Interstitial Lung Disease (ILD) requiring steroid treatment or active or suspected ILD

Reason for exclusion:

Nonclinical studies in monkeys have shown changes in the lung, such as focal interstitial inflammation and alveolar oedema, at supratherapeutic doses of T-DXd (not tested in humans). Patients with a history of ILD may be at an increased risk of recurrence and, therefore, may be associated with worse outcomes. In order to minimise the potential risk to patients in the clinical programme, these patients were excluded.

Is it considered to be included as missing information?

No

Rationale:

ILD/pneumonitis is an important identified risk for T-DXd and is described in SmPC Section 4.2, SmPC Section 4.4 and SmPC Section 4.8. Additional information on this risk is included in Section SVII.3.

Use of OATP1B inhibitors or strong CYP3A4 inhibitors

Reason for exclusion:

In an in vitro study, cytochrome P450 (CYP)3A4 was identified as the primary CYP enzyme in the metabolism of the released drug of T-DXd. The released drug is also a substrate for organic anion transporting polypeptide (OATP)1B.

Is it considered to be included as missing information?

No

Rationale:

Based on a drug-drug interaction study (Study DS8201-A-A104), concomitant use of OATP1B inhibitors or strong CYP3A4 inhibitors with T-DXd resulted in a small increase in area under the curve that was not considered to be clinically meaningful.

Clinically significant corneal disease (Study U201 only)

Reason for exclusion:

In a nonclinical study of the released drug of T-DXd, single-cell necrosis in the corneal epithelium was observed in rats and monkeys at supratherapeutic doses (not tested in humans).

Is it considered to be included as missing information?

No

Rationale:

Corneal events observed in clinical studies with T-DXd were primarily keratitis. The majority of keratitis events in the All Tumour Types ≥5.4 mg/kg Pool were Grade 1 or Grade 2 in severity; 2 (0.1%) of the subjects experienced Grade 3 keratitis and 1 (0.1%) of the subjects experienced Grade 3 ulcerative keratitis. Dose reduction was required in 1 (0.1%) subject who had Grade 3 keratitis. None of the events was associated with drug discontinuation, and all events could be managed through standard clinical practice. Keratitis is classified as a potential risk for T-DXd; however, it is not considered important. There is no evidence to suggest that the safety profile in subjects with corneal disease would differ from that of the general indicated population and it is therefore not relevant for inclusion as missing information.

Pregnant or lactating women and women and men of reproductive/childbearing potential who do not use a highly effective form of contraception or abstinence

Reason for exclusion:

Trastuzumab, a HER2 receptor antagonist, has postmarketing case reports of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death during pregnancy. Additionally, based on nonclinical findings from reproductive/developmental and genotoxicity studies of T-DXd in rats and monkeys and its mechanism of action as a topoisomerase I inhibitor, the released drug of T-DXd may cause embryo-foetal harm when administered to a pregnant woman (SmPC Section 4.4 and SmPC Section 4.6).

Is it considered to be included as missing information?

No

Rationale:

Embryo-foetal toxicity is considered an important potential risk and testicular toxicity is considered a potential risk for T-DXd. Additional information on the risk of embryo-foetal toxicity is included in Section SVII.3.

SmPC Section 4.6 advises that women of childbearing potential and men with female partners of childbearing potential should use effective contraception during and after treatment and that women should discontinue breastfeeding prior to initiating treatment. Exposure in these

populations is therefore not expected, and so they are not relevant for inclusion as missing information.

Clinically active brain metastases (symptomatic and untreated or requiring treatment)

Reason for exclusion:

This population was excluded from the T-DXd clinical development programme based on concerns of poor functional status and shortened life expectancy.

Is it considered to be included as missing information?

No

Rationale:

This population was excluded to avoid factors that may confound understanding of the safety profile and efficacy of T-DXd and to ensure appropriate interpretation of the safety data. There is no evidence to suggest that the safety profile in this population would be different from that of the general indicated population and it is therefore not relevant for inclusion as missing information.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programme

The clinical development programme for T-DXd is unlikely to detect certain types of adverse reactions, such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

With 2145 subjects in the ATT ≥5.4 mg/kg Pool, there is at least a 99.9% chance of observing Aes with a true incidence rate of 1% or higher.

SIV.3 Limitations in Respect to Populations Typically Under-represented in the Clinical Trial Development Programme

The number of subjects with a variety of tumour types that were exposed to T-DXd doses of 5.4 mg/kg and higher is presented in Table Part II: Module SIV.3.1.

Table Part II: Module SIV.3.1: Exposure of Special Populations Included or Not in Clinical Trial Development Programme (Safety Analysis Set)

Type of Special Population	Number of Subjects in Pool			
	BC 5.4 mg/kg Pool (N = 1287)	HER2-positive GC 6.4 mg/kg Pool (N = 229)	All Tumour Types ≥5.4 mg/kg Pool (N = 2145)	HER2 mut NSCLC 5.4 mg/kg Pool (N = 101)
Pregnant or breastfeeding women	Not included in the clinical development programme			
Paediatric	Not included in the clinical development programme[a]			
Elderly				
≥65 years	282 (21.9)	120 (52.4)	621 (29.0)	40 (39.6)
≥75 years	49 (3.8)	24 (10.5)	114 (5.3)	8 (7.9)
≥85 years	6 (0.5)	0	9 (0.4)	0
Subjects with relevant comorbidities (baseline)				
Subjects with renal impairment (all grades)				
Severe impairment (creatinine clearance ≥15, <30 mL/min)	2 (0.2)	0	4 (0.2)[b]	0
Moderate impairment (creatinine clearance ≥30, <60 mL/min)	136 (10.6)	56 (24.5)	306 (14.3)	22 (21.8)
Mild impairment (creatinine clearance ≥60, <90 mL/min)	448 (34.8)	91 (39.7)	795 (37.1)	40 (39.6)
Subjects with hepatic impairment (all grades) [c]				
Severe impairment	0	0	0	0
Moderate impairment	7 (0.5)	1 (0.4)	8 (0.4)	0
Mild impairment	561 (43.6)	57 (24.9)	788 (36.7)	25 (24.8)
Subjects with cardiovascular impairment	Subjects with LVEF <50% or recent symptomatic CHF were excluded from the clinical development programme			

AST = aspartate aminotransferase; BC = breast cancer; CHF = congestive heart failure; EMA = European Medicines Agency; GC = gastro/gastrooesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; N = total number of subjects in the pool; NSCLC = non-small cell lung cancer; T-DXd = trastuzumab deruxtecan; TBL = total bilirubin; ULN = upper limit of normal

All Tumour Types ≥5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-J101, DS8201-A-J202, DS8201-A-U201, DS8201-A-U204, DS8201-A-U205, DS8201-A-U301, and DS8201-A-U302

HER2-mut NSCLC 5.4 mg/kg Data: Study DS8201-A-U206

BC T-DXd 5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-J101, DS8201-A-U201, and DS8201-A-U302

HER2-positive GC 6.4 mg/kg Pooled Data: Studies DS8201-A-J101, DS8201-A-J202, DS8201-A-U205, and DS8201-A-U206.

[a] EMA has waived the obligation to conduct clinical studies in the paediatric population for the intended indication.

[b] For details on subjects with severe renal impairment please refer to Section SIV.1.

[c] Hepatic impairment: Severe impairment = TBL >3.0 × ULN and any AST regardless of Gilbert Syndrome; Moderate impairment = (TBL >1.5 × ULN and ≤3.0 × ULN) and any AST regardless of Gilbert Syndrome; Mild impairment = (TBL >ULN and ≤1.5 × ULN) and any AST except for subjects with Gilbert Syndrome; (TBL >ULN and ≤3.0 × ULN) and AST >ULN for subjects with Gilbert Syndrome; or (TBL ≤ULN and AST >ULN) regardless of Gilbert Syndrome.

Sources : Module 5.3.5.3 EU RMP Table 4 (U301), Module 5.3.5.3 SCS Table 14.1.2 .1 (NSCLC), Module 5.3.5.3 SCS Table 1.1.2 (GC).

PART II: MODULE SV POSTAUTHORISATION EXPERIENCE

SV.1 Postauthorisation Exposure

T-DXd was approved for marketing in the US on 20 Dec 2019; it was first made available to patients on 31 Dec 2019. It was also approved by the Japan Ministry of Health, Labor, and Welfare (MHLW) on 25 Mar 2020 and since 18 Jan 2021 in the EU. Furthermore, T-DXd is also approved in over 40 countries.

SV.1.1 Method Used to Calculate Exposure

The postmarketing patient exposure in patient-years was estimated by (a) counting numbers of vials sold by MAH warehouses (b) further assuming average adult bodyweight in the approved country (eg. 4.3 vials are used in 1 infusion in US, 3.4 vials per infusion in Japan), and (c) multiplying the number of infusions by 21 days, divided by 365 days/year, to account for the administration of an infusion once every 3 weeks (21-day cycle).

SV.1.2 Exposure

Cumulatively, since the first approval of T-DXd on 20 Dec 2019 through 19 Dec 2022, there were [redacted] vials of T-DXd sold from MAH warehouses worldwide. Based on the average body weight of adults in the countries where the product is marketed, it is estimated that [redacted] infusions were administered. Considering that an infusion of T-DXd is administered once every 3 weeks (21-day cycle) and 17.3 cycles per year, the estimated cumulative patient exposure through 19 Dec 2022 was 17,108.3 patient-years.

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for transmission of infectious agents

The risk of transmission of infectious agents by this product is considered negligible based on product design, manufacturing process, facility design and controls, and current testing programmes. European Pharmacopoeia standards have been met.

Potential for misuse for illegal purposes

T-DXd does not contain any substances that have the potential for misuse for illegal purposes.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

The safety concerns presented are supported by pooled data of the 9 completed studies.

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

SVII.1.1.1 Identified Risks

Adverse reactions with clinical consequences, even serious, but considered to be acceptable in relation to the severity of the treated indication include the following: gastrointestinal (GI) adverse drug reactions (ADRs), rash, alopecia, cough, dizziness, dry eye, dyspnoea, epistaxis, fatigue, headache, infusion-related reaction, upper respiratory tract infection, AST increased, ALT increased, hypokalaemia, anaemia, thrombocytopenia, leukopenia, lymphopenia, and neutropenia including febrile neutropenia (see individual descriptions below). All these events are recognized ADRs for T-DXd and are included in SmPC Section 4.8.

Identified Risk: Gastrointestinal ADRs

Preferred terms in the identified risk of gastrointestinal ADRs were reported at the following frequencies in the HER2-positive BC 5.4 mg/kg Pool: nausea (187 [79.9%] subjects), vomiting (114 [48.7%]), constipation (84 [35.9%]), decreased appetite (81 [34.6%]), diarrhoea (72 [30.8%]), abdominal pain (46 [19.7%]), stomatitis (35 [15.0%]), and dyspepsia (33 [14.1%]). The highest frequency of drug interruption and dose reduction due to a GI event was from nausea: 4 (1.7%) subjects and 8 (3.4%) subjects, respectively. Only 1 subject had a GI event (diarrhoea) that led to drug discontinuation. Although frequent, GI events were generally nonserious and generally Grade 1 to 2 in severity.

Identified Risk: Rash

Events of rash (grouped term that includes preferred terms [PTs] of rash, rash pustular, and rash maculo-papular) were reported in 30 (12.8%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, events of rash were all nonserious and generally Grade 1 in severity, leading to drug interruption in 1 subject and to no dose reduction or drug discontinuation.

Identified Risk: Alopecia

Events of alopecia were reported in 108 (46.2%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, events of alopecia were nonserious and generally Grade 1 in severity, with no drug interruption, dose reduction, or drug discontinuation.

Identified Risk: Cough

Events of cough were reported in 50 (21.4%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, events of cough were nonserious and generally Grade 1 in severity, leading to drug interruption in 1 (0.4%) subject and to discontinuation of study drug in 1 (0.4%) subject, with no dose reductions.

Identified Risk: Dizziness

Events of dizziness were reported in 25 (10.7%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, events of dizziness were nonserious and generally Grade 1 in severity, with no drug interruption, dose reduction, or drug discontinuation.

Identified Risk: Dry Eye

Events of dry eye were reported in 27 (11.5%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, events of dry eye were generally nonserious and Grade 1 in severity, except in 1 subject who had a Grade 4 event that improved to Grade 1 without requiring intervention and did not recur. No event of dry eye led to drug interruption, dose reduction, or drug discontinuation.

Identified Risk: Dyspnoea

Events of dyspnoea were reported in 34 (14.5%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, events of dyspnoea were generally nonserious (1 subject had dyspnoea reported as a serious AE (SAE) and generally Grade 1 to 2 in severity, leading to no dose reduction, to drug interruption in 2 (0.9%) subjects (both with dyspnoea) and to drug discontinuation in 1 subject who had drug discontinued due to concurrent dyspnoea and pneumonitis.

Identified Risk: Epistaxis

Events of epistaxis were reported in 33 (14.1%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, events of epistaxis were all nonserious and generally Grade 1 in severity, with no drug interruption, dose reduction or drug discontinuation.

Identified Risk: Fatigue

Events of fatigue (grouped term that includes PTs of fatigue and asthenia) were reported in 141 (60.3%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, all events of fatigue were nonserious and generally Grade 1 to 2 in severity. Dose was reduced in 9 (3.8%) subjects and drug was interrupted in 5 (2.1%) subjects. No events of fatigue led to drug discontinuation.

Identified Risk: Headache

Events of headache (grouped term that includes PTs of headache, sinus headache, and migraine) were reported in 47 (20.1%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, events of headache were all nonserious and Grade 1 or 2 in severity. No event led to drug interruption, dose reduction, or drug discontinuation in any subject.

Identified Risk: Infusion-related Reaction

Events of infusion-related reaction (a grouped term comprising 14 PTs, including infusion-related reaction [4 events], flushing [1 event], and hypersensitivity [1 event]) were reported in 6 (2.6%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Events of infusion-related reaction were generally nonserious (1 subject had hypersensitivity reported as an SAE), and all were Grade 2 in severity, leading to no dose reduction or drug discontinuation in any subject and to drug interruption in 1 subject (PT of infusion-related reaction).

Identified Risk: Upper Respiratory Tract Infection

Events of upper respiratory tract infection (grouped term that includes PTs of influenza, influenza-like illness, and upper respiratory tract infection) were reported in 43 (18.4%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, all events of upper respiratory

tract infection were nonserious, and generally Grade 1 to 2 in severity, leading to no dose reduction or drug discontinuation in any subject and to drug interruption in 7 (3.0%) subjects.

Identified Risk: Aspartate Aminotransferase Increased and Alanine Aminotransferase Increased

Events of AST increased were reported in 35 (15.0%) subjects and events of ALT increased were reported in 25 (10.7%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, events of AST increased and ALT increased are consistent with laboratory-based increases in AST and ALT, all events were nonserious, and events were generally Grade 1 in severity, transient, and reversible, and did not lead to drug discontinuation. One (0.4%) subject had drug interruption due to ALT increase; 1 (0.4%) subject had dose reduction due to ALT increased and 1 (0.4%) due to AST increased. One subject had values that met the biochemical criteria for potential Hy's Law (ALT or AST ≥3 x ULN and total bilirubin >2 x ULN). This case of potential Hy's Law was determined not to be causally associated with study drug due to alternative aetiology (acute hepatitis B ongoing from baseline) at the time of occurrence of the event.

Identified Risk: Hypokalaemia

Events of hypokalaemia were reported in 30 (12.8%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Events of hypokalaemia were consistent with laboratory-based decreases in potassium. Although frequent, events of hypokalaemia were reported as Grade 1 in 21 (9.0%) subjects, Grade 2 in 1 (0.4%) subject, and Grade 3 in 8 (3.4%) subjects; with 3 (1.3%) subjects having hypokalaemia reported as an SAE. Two (0.9%) subjects had drug interruption due to hypokalaemia, with no subjects having dose reduction or drug discontinuation.

Identified Risk: Anaemia

Events of anaemia (grouped term that includes PTs of anaemia, haemoglobin decreased, red blood cell count decreased, and haematocrit decreased) were reported in 79 (33.8%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Events of anaemia were consistent with laboratory-based decreases in haemoglobin count. Although frequent, events in only 2 (0.9%) subjects were reported as SAEs. The majority of events were Grade 1 to 2 in severity, with 21 (9.0%) subjects reported as having anaemia events ≥Grade 3. Events led to drug interruption in 8 (3.4%) subjects and dose reduction in 1 (0.4%) subject, with no drug discontinuation in any subject.

Identified Risk: Thrombocytopenia

Events of thrombocytopenia (grouped term that includes PTs of platelet count decreased and thrombocytopenia) were reported in 54 (23.1%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Events of thrombocytopenia were consistent with laboratory-based decreases in platelet count. Although frequent, events were generally Grade 1 to 2 in severity, with 10 (4.3%) subjects reported as having thrombocytopenia events of Grade 3. Events led to drug interruption in 6 (2.6%) subjects, dose reduction in 2 (0.9%) subjects, and drug discontinuation in 2 (0.9%)

subjects. One (0.4%) subject had an event reported as an SAE. No event was associated with major bleeding.

Identified Risk: Leukopenia

Events of leukopenia (grouped term that includes PTs of white blood cell (WBC) count decreased and leukopenia) were reported in 48 (20.5%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Events of white blood cell count decrease were consistent with laboratory-based decreases in WBC count. Although frequent, events were all nonserious and generally Grade 1 to 2 in severity, leading to drug interruption in 7 (0.3%) subjects and dose reduction in 1 (0.4%) subject, with no drug discontinuation in any subject.

Identified Risk: Lymphopenia

Events of lymphopenia (grouped term that includes PTs of lymphocyte count decreased and lymphopenia) were reported in 26 (11.1%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Events of lymphopenia were consistent with laboratory-based decreases. Although frequent, events were all nonserious and generally Grade 1 to 2 in severity, leading to dose reduction in 1 (0.4%) subject, with no drug discontinuation or interruption in any subject.

Identified Risk: Neutropenia, Including Febrile Neutropenia

Events of neutropenia (grouped term) were reported in 76 (32.5%) subjects (observed in the HER2-positive BC 5.4 mg/kg Pool; however, these events were generally nonserious (1 [0.4%] subject had an SAE), did not require drug discontinuation, and were not associated with fatal outcomes. Laboratory data were consistent with the reported Aes of neutropenia (grouped term).

Febrile neutropenia was reported in 4 (1.7%) subjects in the HER2-positive BC 5.4 mg/kg Pool, did not require drug discontinuation, and was not associated with fatal outcomes.

One subject had PTs of Grade 3 neutrophil count decrease and Grade 3 febrile neutropenia reported concurrently with a serious event of Grade 4 sepsis. The event of sepsis resolved following treatment with antibiotics. No other subjects with an event of Grade ≥3 neutropenia (grouped term) or Grade ≥3 febrile neutropenia had a concurrent serious infection.

Neutropenia, including febrile neutropenia, is generally manageable through standard clinical practice and following dose modification guidelines (SmPC Section 4.2).

SVII.1.1.2 Potential Risks

Risks With Minimal Clinical Impact on Patients: Keratitis

Corneal toxicity was observed in a nonclinical study of the released drug of T-DXd and has been seen in drugs in similar class. The mechanism for corneal toxicity with T-DXd remains unclear; however, it is known that HER2 is expressed in corneal epithelia.[132] Keratitis was observed in clinical studies with T-DXd. In the HER2-positive BC 5.4 mg/kg Pool, keratitis was reported in 6 (2.6%) subjects, punctate keratitis in 2 (0.9%) subjects, and ulcerative keratitis in 1 (0.4%) subject. All events of keratitis were nonserious and either Grade 1 or 2 in severity, leading to drug interruption in 1 (0.4%) subject and to no dose reduction or drug discontinuation.

Risks With Minimal Clinical Impact on Patients: Testicular Toxicity

Reproductive studies in rats and monkeys indicate changes to the reproductive organs of males (eg, spermatid retention, small-sized testes and epididymides accompanying reduced organ weights; tubular degeneration/atrophy in the testes, luminal cell debris and reduced sperm in the epididymides) with T-DXd. It is not known whether T-DXd or its metabolites are found in seminal fluid. The potential risk for male patients is further minimized by statements in SmPC Section 4.6 advising male patients to seek counselling on sperm storage before starting treatment and male patients must not freeze or donate sperm throughout the treatment period, and for at least 4 months after the final dose of T-DXd.

Risks With Minimal Clinical Impact on Patients: Renal Toxicity

In nonclinical studies with T-DXd abnormal renal function was seen in rats but not in monkeys. In the rat 6-week study of T-DXd (q3w dosing), abnormalities in renal function were observed. At a supratherapeutic dose urinalysis revealed proteinuria and blood chemistry indicated increases in urea nitrogen, inorganic phosphorus, creatinine, and potassium and decreases in sodium and chloride. Supratherapeutic doses of T-DXd were observed in both rats and monkeys. At supratherapeutic doses, histopathological changes such as tubular basophilia and hyaline casts in the kidney were noted and all findings in rats resolved after a 9-week recovery period. In the monkey 3-month study while anisokaryosis in the proximal tubules in the kidney was observed at 30 mg/kg at the end of dosing and the 3-month recovery periods, no findings suggestive of abnormalities in renal function were observed in urinalysis or blood chemistry. No renal toxicity was observed in studies of the released drug in rats or monkeys.

In the HER2-positive BC 5.4 mg/kg Pool, no clinically meaningful shifts to worse creatinine values were observed. 2 (0.9%) subjects reported a TEAE of blood creatinine increase in the HER2-positive BC 5.4 mg/kg Pool. No subject in the pool had ≥Grade 3 serum creatinine increase, except for 1 subject [redacted] who had fatal events of acute hepatic failure and acute renal injury 34 days after last study drug dose. Both events were assessed by the investigator as being due to disease progression (liver metastases). Overall, no safety concern with renal function from clinical studies or during postmarketing period with T-DXd has been identified.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important identified risks are: ILD/pneumonitis and left ventricular dysfunction. Important potential risks include embryo-foetal toxicity and product confusion-related medication errors.

SVII.1.2.1 Important Identified Risks

Important Identified Risk: Interstitial Lung Disease/Pneumonitis

Benefit-risk impact:

All data presented in this section are for "adjudicated drug-related ILD," which is defined as events that were adjudicated as ILD and as related to trastuzumab deruxtecan (regardless of the determination made by the investigator) by an independent, multidisciplinary Adjudication Committee (AC).

The incidence of adjudicated ILD in the HER2-positive BC 5.4 mg/kg Pool was 32 (13.7%) subjects, with 12 (5.1%) subjects having events reported as serious.

Events of ILD were adjudicated to be Grade 1 in 6 (2.6%) subjects, Grade 2 in 19 (8.1%), Grade 3 in 1 (0.4%), Grade 4 in 0 (%), and Grade 5 in 6 (2.6%). These 6 Grade 5 events were adjudicated as ILD associated with a fatal outcome (including 4 subjects from the EU).

Drug was interrupted in 6 (2.6%) subjects, dose was reduced in 4 (1.7%), and drug was discontinued in 22 (9.4%) subjects. Among the 32 subjects with adjudicated drug-related ILD events, the reported outcome was resolved in 8 (25.0%) subjects, recovered with sequelae in 1 (3.1%), recovering in 2 (6.3%), not recovered in 13 (40.6%), fatal in 6 (18.8%), and missing/unknown in 2 (6.3%).

ILD/pneumonitis requires appropriate monitoring and management to mitigate the risk of Grade 4 or Grade 5 events, which have the potential to impact the benefit-risk for the patient. The risk of ILD/pneumonitis is further characterised in Section SVII.3.1.

Important Identified Risk: Left Ventricular Dysfunction

Benefit-risk impact:

The incidence of the PT of Ejection fraction decreased in the HER2-positive BC 5.4 mg/kg Pool was 3 (1.3%) subjects, with no events reported as serious. The events were Grade 2 in 2 (0.9%) subjects and Grade 3 in 1 (0.4%) subject.

Study drug was interrupted in all 3 (1.3%) subjects, with no dose reductions or discontinuations of study drug due to ejection fraction decreased.

Left ventricular dysfunction is characterised in Section SVII.3.1.

Because the lack of a control group in available clinical data does not allow to rule out completely a causal association with T-DXd, and cardiac failure has been reported for drugs in similar class, left ventricular dysfunction is considered an important identified risk. Appropriate monitoring and management is required to mitigate the risk of left ventricular dysfunction, which has the potential to impact the benefit-risk for the patient.

SVII.1.2.2 Important Potential Risks

Important Potential Risk: Embryo-Foetal Toxicity

Benefit-risk impact:

Nonclinical reproductive and developmental toxicity data for T-DXd are described in Section Part II: Module SII.

No clinical data on the effect of T-DXd on embryo-foetal toxicity potential are available. However, in postmarketing reports, the use of trastuzumab, a HER2 receptor antagonist, during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on findings in animals and its mechanism of action, the released drug of T-DXd can also cause embryo-foetal harm when administered to a pregnant woman (SmPC Section 4.4 and SmPC Section 4.6). Appropriate contraception as described in the SmPC is required to mitigate the risk of pregnancy, which could impact the benefit-risk of the drug.

Important Potential Risk: Product confusion-related medication errors

Benefit-risk impact:

With the availability of other trastuzumab-containing products and the HER2-targeted ADC trastuzumab emtansine (KADCYLA), prescribers could potentially mix up trastuzumab-containing products if they do not use the tradename. There is a potential for serious clinical consequences (eg, lack of efficacy) by inadvertently substituting one trastuzumab containing product for another.

For T-DXd there have been no reports of product confusion-related medication errors in clinical trials or since marketing of the product in the US and Japan.

Missing Information: Use in Patients with Moderate or Severe Hepatic Impairment

No dedicated hepatic impairment study was conducted. While patients with moderate hepatic impairment were generally excluded from the clinical programme, up to a maximum of 10 patients with moderate hepatic impairment were eligible for enrolment into Study U201. However, only 1 patient meeting these criteria was enrolled. Patients with severe hepatic impairment were excluded from the clinical programme.

Based on the elimination of trastuzumab via hepatic metabolism, it is unknown whether moderate or severe hepatic impairment has an effect on trastuzumab deruxtecan elimination and exposure in humans, as well as whether patients with moderate or severe hepatic impairment have a safety profile different from that of the general indicated population. A warning statement is included in Section 4.4 of the SmPC that administration of trastuzumab deruxtecan should be undertaken with caution in patients with moderate to severe hepatic impairment.

Collection of PK and safety data from at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies with trastuzumab deruxtecan is planned.

Missing Information: Long-term Safety

The median treatment duration (defined as date of last dose – date of first dose + 21) in the HER2-positive BC 5.4 mg/kg Pool (N = 234) was 9.82 months (range: 0.7 to 37.1). A total of 164/234 (70.1%) subjects had been treated for >6 months, 127/234 (54.3%) for >9 months, 69/234 (29.5%) for >12 months, and 5/234 (2.1%) for >24 months.

With continuation of currently ongoing Phase 3 studies (Studies DS8201-A-U301 and DS8201-A-U302), more long-term safety data will become available, which will be used to further characterise cumulative toxicity and the overall safety profile of trastuzumab deruxtecan.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

There was no new safety concern identified for T-DXd.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Interstitial lung disease/Pneumonitis

Potential mechanisms:

The exact underlying mechanism of drug-induced ILD/pneumonitis with T-DXd is unknown. In drugs of similar class for which ILD/pneumonitis has been identified as a risk, 2 types of mechanisms have been proposed: chemotherapy that could lead to dose-dependent toxicity via an increase in the level of inflammatory cytokines, oxidative stress, and direct cytotoxic damage and monoclonal antibodies that could lead to an immune-mediated allergic lung injury.[133]

Evidence source(s) and strength of evidence:

Dose-dependent changes in the lung were seen in nonclinical data. An independent AC adjudicated all potential events of ILD. Although T-DXd is associated with a risk of ILD/pneumonitis and cases with fatal outcomes have been reported, most events have been Grade 1 or 2 in severity and manageable following clinical treatment guidelines, which include close monitoring signs and symptoms of potential ILD/pneumonitis (eg, cough, fever, and dyspnoea) and proactive management with dose modification (dose reduction or interruption), and use of steroid treatment and (for moderate, severe or life-threatening ILD/pneumonitis) discontinuation of T-DXd.

Characterisation of the risk:

ILD data collected in the clinical programme are based on events that the independent ILD AC adjudicated as being ILD and as related to T-DXd (regardless of the determination made by the investigator).

ILD in the ATT ≥5.4 mg/kg Pool is summarized by event category and grade in Table Part II: Module SVII.3.1, which includes 3 ILD events in Study J101 that occurred >28 days after the last dose (TEAE definition), per investigator-reported onset dates.

Among the 307 of 2145 (14.9%) subjects who had an adjudicated ILD event, 296 (13.8%) subjects had events that were adjudicated as drug-related ILD at the following grades: 78 (3.6%) Grade 1, 166 (7.7%) Grade 2, 22 (1.0%) Grade 3, 1 (0.0%) Grade 4, and 29 (1.4%) Grade 5 (Module 5.3.5.3 SCS Table 1.2.5.1 [U301]).

Median time to onset date of the first adjudicated drug-related ILD event was 167.0 days (range: 0 to 960) (Module 5.3.5.3 SCS Table 1.2.5.4 [U301]).

Table Part II: Module SVII.3.1: Number and Percentage of Adjudicated Drug-related ILD Events by Indication, Category, and Grade (Safety Analysis Set)

Pool	Outcome of Adjudication	Number (%) of Subjects by CTCAE Grade (as Graded by ILD Adjudication Committee					
		1	2	3	4	5	Total
All Tumour Types ≥5.4 mg/kg [95% CI] (N = 2145)	Adjudicated as drug-related ILD	78 (3.6) (2.9, 4.5)	166 (7.7) (6.6, 9.0)	22 (1.0) (0.6, 1.5)	1 (0.05) (0.0, 0.3)	29 (1.4) (0.9, 1.9)	296 (13.8) (12.4, 15.3)
HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)	Adjudicated as drug-related ILD	6 (2.6)	15 (6.6)	2 (0.9)	1 (0.4)	1 (0.4)	25 (10.9)
All BC 5.4 mg/kg (N = 1287)	Adjudicated as drug-related ILD	43 (3.3)	98 (7.6)	11 (0.9)	0	13 (1.0)	165 (12.8)
HER2-mut NSCLC 5.4 mg/kg (N=101)	Adjudicated as drug-related ILD	3 (3.0)	2 (2.0)	1 (1.0)	0	0	6 (5.9)

AC = Adjudication Committee; BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events; GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; N = total number of subjects in the pool; NSCLC = non-small cell lung cancer; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event
Percentages were calculated by using the number of subjects in the Safety Analysis Set as the denominator.
The 95% confidence interval for the ILD rate is based on the exact (Clopper-Pearson) method for binomial distribution.
This table includes all events that were adjudicated and considered drug-related events by the AC.
If a subject had multiple ILD events, the CTCAE grade is shown for the event with the worst grade. If a subject has both missing and nonmissing CTCAE grades for an event, the worst CTCAE grade is based on the nonmissing grade.
The pooled analysis group is based on tumour type and first dose received for subjects in each study.
All Tumour Types T-DXd ≥5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-J101, DS8201-A-J202, DS8201-A-U201, DS8201-A-U204, DS8201-A-U205, DS8201-A-U206, DS8201-A-U301, and DS8201-A-U302. HER2-positive GC T-DXd 6.4 mg/kg Pooled Data: Studies DS8201-A-J101, and DS8201-A-U205, DS8201-A-U206; BC 5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-J101, DS8201-A-U201, and DS8201-A-U302.
Sources: Module 5.3.5.3 EU RMP Table 10 (U301), Module 5.3.5.3 SCS Table 1.2.5.1 (GC), Module 5.3.5.3 Table 2.16 (NSCLC), Module 5.3.5.3 SCS Table 1.2.5.1 (U301)

Table Part II: Module SVII.3.2: Summary of Adjudicated Drug-related ILD in the All Tumour Types ≥5.4 mg/kg Pool (Safety Analysis Set)

Adverse Event Category	Number (%) of Subjects With Adjudicated Drug-related ILD
	All Tumour Types ≥5.4 mg/kg Pool (N = 2145)
Adjudicated Drug-related ILD	296 (13.8)
Worst CTCAE Grade ≥3	52 (2.4)
Serious AE	91 (4.2)
Associated with drug discontinuation	220 (10.3)
Associated with dose reduction	14 (0.7)
Associated with drug interruption	62 (2.9)
Associated with Grade 5 events	29 (1.4)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ILD = interstitial lung disease; N = total number of subjects in the pool
All Tumour Types ≥5.4 mg/kg Pooled Data: Studies DS8201-A-J101, DS8201-A-J202, DS8201-A-U201, DS8201-A-U204, DS8201-A-U205, DS8201-A-U206, DS8201-A-U301, DS8201-A-U302, and DS8201-A-U303.
Sources: Module 5.3.5.3 SCS (U301) Table 1.2.4.1, Table 1.2.4.2, Table 1.2.4.3, Table 1.2.4.4, Table 1.2.4.5, Table 1.2.4.6, and Table 1.2.5.1.

Among the 296 (13.8%) subjects with events adjudicated as drug-related ILD in the ATT ≥5.4 mg/kg Pool, per the investigator, 137 (46.3%) recovered, 13 (4.4%) recovered with sequelae, 22 (7.4%) were recovering, 95 (32.1%) were not recovered, 21 (7.1%) had a fatal outcome, 1 (0.3%) had an event that was ongoing, and 7 (2.4%) were missing outcome information (Module 5.3.5.3 SCS Table 1.2.5.4 [U301]).

The median time to first onset of ILD event was 167 days, and the median duration of the first ILD event (as reported by the Investigator) was 47.5 days. In the ATT ≥5.4 mg/kg Pool, a higher incidence of adjudicated drug-related ILD was reported in subjects from Japan (121 [20.6%] subjects) compared with the subjects from other countries (175 [11.2%] subjects), and in subjects with mild/moderate renal impairment at baseline (172 [15.6%] subjects) compared with subject who had normal renal function (120 [11.8%] subjects). This difference was mainly driven by a higher number of subjects with Grade 1 and Grade 2 events in subjects with moderate renal impairment at baseline (Grade 1: 46 [4.2%] subjects and Grade 2: 96 [8.7%] subjects) (Module 5.3.5.3 SCS Table 1.4.13 [U301]).

Spontaneous data from the global safety database up to data lock point (19 Dec 2022):

The following group of MedDRA PTs have been used to define T-DXd-related ILD in the postmarketing setting: Pneumonitis, Interstitial lung disease, Organising pneumonia, and Acute interstitial pneumonitis. By using this approach, a total of 945 cases were identified cumulatively. Of the 945 cases, 107 had a fatal outcome related to ILD, 427 met other seriousness criteria, and for 410 cases, ILD was classified as nonserious. Ages ranged from 27 years to 90 years (median: 64.0 years) with 68.1% female patients and 16.9% male patients (for remaining patients, sex was not reported). Indications for T-DXd were BC in 64.4% of cases,

GC in 17.4% of cases, and the remaining cases derived from other cancer types (1.5%) and unknown indications (14.3%).

In the majority of cases (68.9%), T-DXd was withdrawn due to the ILD event. Outcomes primarily improved with appropriate ILD management (recovered 25.8%, recovering 20.1%, and recovered with sequelae 0.9%). Reporting rates are different between regions; in particular, the ILD reporting rate in Japan is higher because of more intensified reporting in ongoing ILD-directed surveys. Overall, evidence from post-marketing, spontaneous cases does not alter the risk of ILD/pneumonitis as observed in clinical studies.

Risk factors and risk groups:

A stepwise multivariate Cox regression model evaluating the association of baseline factors with the time to occurrence of any grade of adjudicated drug-related ILD was conducted among 1150 subjects who received at least 1 dose of T-DXd (5.4, 6.4, 7.4, or 8.0 mg/kg) in 9 phase 1 or 2 studies across multiple tumour types.[134]

Seven baseline factors were potentially associated with increased ILD risk:

- Patients treated in Japan vs non-Japan
- Dose of >6.4 mg/kg vs ≤6.4 mg/kg
- Baseline oxygen saturation <95% vs ≥95%
- Moderate/severe renal impairment at baseline vs no impairment
- Presence of lung comorbidities (yes vs no; asthma, chronic obstructive pulmonary disease, prior ILD/pneumonitis, pulmonary fibrosis, pulmonary emphysema, or radiation pneumonitis)
- Time since initial diagnosis of >4 years vs ≤4 years
- Age <65 years vs. ≥65 years

Given the limitations of this analysis (extensive prior treatment, differences in treatment durations, preselection of thresholds for Cox multivariate regression based on clinical judgement, and heterogeneity of the patient population), the potential clinical risk factors remain to be confirmed with future data in a larger, more homogenous patient population.

Preventability:

- While the occurrence of some events of ILD/pneumonitis is not completely preventable, steps can be taken to prevent events from progressing to a more serious outcome.
- Patients should be advised to immediately report cough, dyspnoea, fever, and/or any new or worsening respiratory symptoms.
- Patients should be monitored for signs and symptoms of ILD/pneumonitis (SmPC Section 4.4).
- Evidence of ILD/pneumonitis should be promptly investigated and patients with suspected ILD/pneumonitis should be evaluated by radiographic imaging. Consultation with a pulmonologist should be considered.

- For asymptomatic (Grade 1) ILD/pneumonitis
  - Corticosteroid treatment (eg, ≥0.5 mg/kg/day prednisolone or equivalent) should be considered.
  - T-DXd should be withheld until recovery to Grade 0 and may be resumed according to instructions in Table 2 of the SmPC Section 4.2.
- For symptomatic ILD/pneumonitis (Grade 2 or greater)
  - Corticosteroid treatment (eg, ≥1 mg/kg/day prednisolone or equivalent) should be promptly initiated and continued for at least 14 days and then gradually tapered for at least 4 weeks).
  - T-DXd should be permanently discontinued in patients who are diagnosed with any symptomatic (Grade 2 or greater) ILD/pneumonitis (SmPC Section 4.2).

Patients with a history of ILD/pneumonitis may be at increased risk of developing ILD/pneumonitis (SmPC Section 4.4). Patients with moderate or severe renal impairment should be monitored carefully because a higher incidence of Grade 1 and 2 ILD has been observed in these patients.

Additional risk minimisation measures that will be implemented will include a Health Care Professional (HCP) Guide and a Patient Card (PC) to reinforce early detection of and intervention for ILD/pneumonitis cases in clinical practice and thus minimise the occurrence of more serious ILD/pneumonitis cases.

Impact on the risk-benefit balance of the product:

Although T-DXd is associated with a risk of ILD/pneumonitis and cases with fatal outcomes have been reported, most events have been Grade 1 or 2 in severity and manageable following clinical treatment guidelines, which include close monitoring for signs and symptoms of potential ILD/pneumonitis (eg, cough, fever, and dyspnoea) and proactively managing events with dose modification (reduction or interruption), use of steroid treatment, and (for moderate, severe or life-threatening ILD/pneumonitis) discontinuing use of T-DXd. Appropriate monitoring and management is required to mitigate the risk of Grade 4 or Grade 5 ILD/pneumonitis, which has the potential to impact the benefit-risk for the patient.

Public health impact:

There is no potential public health impact beyond the treated population.

Important Identified Risk: Left Ventricular Dysfunction

Potential mechanisms:

The exact mechanism of potential cardiotoxicity manifesting as left ventricular dysfunction remains unknown for T-DXd. HER2 receptors expressed in the membranes of adult cardiomyocytes have an important role in transmitting growth and survival signals. Specifically, neuregulin (NRG)-HER2 signalling is involved in cardiac development and physiology, and it is suggested that blocking the NRG-1-mediated activation of HER2 reduces fundamental intracellular mechanisms that support cardiomyocyte contractility. This is a possible mechanism for anti-HER2 agent mediated cardiotoxicity; however, different mechanisms of action of HER2-

targeted therapies contribute to the variable risks of cardiotoxicity across these agents. Notably, the mAb trastuzumab is associated with mostly asymptomatic, reversible cardiac dysfunction, whereas the ADC T-DM1 allows intracellular drug delivery that is specific to HER2-overexpressing cells and is thereby associated with a lower rate of cardiac dysfunction.[135,136,137]

Evidence source(s) and strength of evidence:

Cardiotoxicity has been observed with anti-HER2 drugs, including single-agent trastuzumab, which has a warning for cardiomyopathy. A nonclinical study in monkeys with T-DXd did not show an abnormality in cardiac function tests (including LVEF).

Ejection fraction decreases have been reported with T-DXd. However, available clinical data show that the reported ejection fraction decreases are of low frequency and severity and are often asymptomatic in nature.

Characterisation of the risk:

Table Part II: Module SVII.3.3: Summary of LV Dysfunction in the All Tumour Types ≥5.4 mg/kg Pool (Safety Analysis Set)

Adverse Event Category	Number (%) of Subjects with LV Dysfunction[a] (N = 2145)
Treatment-emergent AE with any grade	69 (3.2)
CTCAE Grade ≥3	10 (0.5)
Serious AE	3 (0.1)
Associated with drug discontinuation	8 (0.4)
Associated with dose reduction	1 (0.0)
Associated with drug interruption	23 (1.1)
Associated with an outcome of death	0

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; LV = left ventricular; PT = preferred term

All Tumour Types T-DXd ≥5.4 mg/kg Pooled Data: Studies DS8201-A-J101, DS8201-A-J202, DS8201-A-U201, DS8201-A-U204, DS8201-A-U205, DS8201-A-U206, DS8201-A-U301, DS8201-A-U302, and DS8201-A-U303.

[a] LV dysfunction includes PTs of Acute left ventricular failure, Acute right ventricular failure, Cardiac failure, Cardiac failure acute, Cardiac failure chronic, Cardiac failure congestive, Chronic left ventricular failure, Chronic right ventricular failure, Ejection fraction decreased, Left ventricular failure, Right ventricular failure, Ventricular failure, and Left ventricular dysfunction.

Sources: Module 5.3.5.3 SCS (U301) Table 1.2.6.1, Table 1.2.6.2, Table 1.2.6.3, Table 1.2.6.4, Table 1.2.6.5, and Table 1.2.6.6

LV dysfunction was reported infrequently. Specifically, 11 (0.5%) subjects experienced Grade 1 events, 48 (2.2%) subjects experienced Grade 2 events, and 10 (0.5%) subjects experienced Grade 3 events. Observed frequency of LVEF decreased on the basis of TEAEs and laboratory parameters (echocardiogram or multigated acquisition [MUGA] scanning) was 318 (14.8%), the majority (290/2145 [13.5%]) being Grade 2 and 23 of 2145 (1.1%) being Grade 3 (Module 5.3.4.3 EU RMP Table 5 (U301). Notably, in Study U302 similar proportions of subjects in the T-DXd and T-DM1 arms showed Grade 2 and Grade 3 LVEF measurements (see Module 5.3.4.3 SCS Table 1.2.6.8 [HER2-low BC]). In addition, the maximum LVEF decrease and increase

from baseline were similar in the T-DXd arm. The LVEF events were generally nonserious, asymptomatic, and resolved. Dose reduction or drug discontinuation was only required in few subjects. Temporary LVEF decreases <40% was measured in 6 subjects in the ATT ≥5.4 mg/kg Pool (details below) (see Module 5.3.5.3 SCS Table 1.2.6.8 [U301]).

The most frequent PT used for LV dysfunction was PT of Ejection fraction decreased (63/69). Seven additional subjects in the ATT ≥5.4 mg/kg Pool had events of PTs other than Ejection fraction decreased, including

- SAE of Grade 2 cardiac failure congestive that was associated with study drug discontinuation and resolved (LVEF value of 63% at baseline and 66% to 70% during the study).
- SAE of Grade 2 cardiac failure that was associated with study drug interruption and resolved (LVEF value of 52% at baseline and 39% to 64% during the study).
- Nonserious Grade 3 cardiac failure (LVEF value of 45%) that was associated with study drug discontinuation and resolved (LVEF value of 60% at baseline). Grade 2 ejection fraction decreased was also reported and was not resolved at the data cut-off date (LVEF value of 55%).
- Grade 1 cardiac failure on Day 1 after the first dose that was not resolved at the data cut-off date (LVEF value of 52% at baseline and 57% to 60% during the study).
- Grade 2 left ventricular dysfunction (LVEF value of 58% at baseline and 36% at Day 85) associated with study drug discontinuation; subject was recovering (LVEF value of 47%) 1 month later.
- Grade 1 left ventricular dysfunction that recovered without dose change.
- Grade 1 left ventricular dysfunction (LVEF value of 45%) at Cycle 9 that recovered within 35 days after drug interruption.

Spontaneous data from the global safety database up to data lock point (19 Dec 2022):

The SMQ Cardiac failure (Narrow Scope+PT left ventricular dysfunction) was used to define left ventricular dysfunction in the post-marketing setting. This approach yielded 49 cases cumulatively, 33 reporting ejection fraction (EF) decrease (4 of them accompanied by cardiac disorder, cardiomyopathy, cardiotoxicity, and acute myocardial infarction, respectively), 11 cardiac failure, 1 cardiopulmonary failure, 3 pulmonary edema, and 1 left ventricular dysfunction. Of the 49 cases, 24 cases were serious (mainly cases of cardiac failure, cardiomyopathy, cardiotoxicity, and EF decreased), and 25 cases were nonserious (mainly cases of EF decreased). Cases were often confounded by underlying cardiac/cardiovascular comorbidities and/or disease progression. For 4 cases (2 cardiac failure, 1 cardiopulmonary failure with pneumonitis, and 1 EF decrease with pneumonitis), a fatal outcome was reported; however, death was primarily associated with progression of the underlying disease.

The indication for T-DXd was breast cancer in 57.1% of the cases, gastric cancer in 18.4%, and lung cancer in 2%, with the remaining cases derived from other cancers (4.1%) and unknown indication (18.4%).

When information was provided, EF decrease was reported to be mild, including isolated cases with EF decrease to 30%. Dose reduction in line with the scheme provided in T-DXd label led to improvement of EF decrease in most case, where information was available.

Risk factors and risk groups:

No risk factors or risk groups have been associated with LVEF decrease.

Anthracycline therapies are known to cause cardiotoxicity and have been shown to have a synergistic effect of cardiotoxicity with trastuzumab, a HER2 receptor antagonist. In the ATT T-DXd ≥5.4 mg/kg Pool, approximately 35% subjects received prior therapy of doxorubicin and epirubicin.

Preventability:

Standard cardiac function testing (echocardiogram or MUGA scanning) should be performed to assess LVEF prior to the initiation of T-DXd and at regular intervals during treatment, as clinically indicated (SmPC Section 4.4). LVEF decrease should be managed through treatment interruption or discontinuation (SmPC Section 4.2, 4.4). Treatment with T-DXd has not been studied in patients with LVEF <50% prior to the initiation of treatment (SmPC Section 4.4).

Impact on the benefit-risk balance of the product:

If not identified and managed appropriately, left ventricular dysfunction has the potential to lead to serious consequences such as cardiac failure with a reduction in the benefit-risk for the patient.

Potential public health impact:

There is no potential public health impact beyond the treated population.

Important Potential Risk: Embryo-Foetal Toxicity

Potential mechanisms:

Based on results from general animal toxicity studies, T-DXd and its topoisomerase I inhibitor component (DXd) were toxic to rapidly dividing cells (lymphatic/hematopoietic organs, intestine, or testes), and DXd was genotoxic, suggesting the potential for embryotoxicity and teratogenicity (SmPC Section 5.3).

Evidence source(s) and strength of evidence:

Findings from nonclinical data, the potential mechanism of action of the released drug of T-DXd, and known effects of anti-HER2 agents on embryo-foetal toxicity suggest that T-DXd may potentially cause foetal harm.

Characterisation of the risk:

No pregnancy has occurred among women of childbearing potential who were subjects in or female partners of male subjects in clinical studies with T-DXd.

No clinical data on the effect of T-DXd on fertility are available.

Risk factors and risk groups:

No risk factors or risk groups have been associated with embryo-foetal toxicity.

Preventability:

Contraception guidelines for both women of childbearing potential and men with female partners of childbearing potential are provided in SmPC Section 4.4 and SmPC Section 4.6. The pregnancy status of females of childbearing potential should be verified prior to the initiation of T-DXd. Females of childbearing potential and male patients with female partners of childbearing potential should be advised to use highly effective contraception.

Impact on the benefit-risk balance of the product:

It is possible that exposure to T-DXd during pregnancy may cause foetal harm.

Potential public health impact:

There is no potential public health impact beyond the treated population.

Important Potential Risk: Product confusion-related medication errors

Potential mechanisms:

With the availability of other trastuzumab-containing products and the HER2-targeted ADC trastuzumab emtansine (KADCYLA) prescribers could potentially mix up trastuzumab containing product if they would not use the tradename. Pharmacists reconstituting the infusion could potentially mix up trastuzumab-containing products if there are no specific distinguishing features regarding livery and cap colour of the vial to differentiate between trastuzumab-containing products.

Evidence source(s) and strength of evidence:

For trastuzumab emtansine (KADCYLA) 4 cases due to a confusion between trastuzumab emtansine and trastuzumab were reported in clinical trials[138] and 2 spontaneous cases are evident for KADCYLA in the Eudravigilance database (data lock point 19 Dec 2022) reporting PT ‘Wrong drug administered’ or ‘Product name confusion’. Both cases involve two trastuzumab-containing products and both cases were not associated with an adverse event.

As of 19 Dec 2022, there have been no case reports of product confusion-related medication errors associated with T-DXd.

Characterisation of the risk:

There is a potential for serious clinical consequences (eg, lack of efficacy) by inadvertently substituting one trastuzumab-containing product for another considering different dosing schedules apply for each product.

Risk factors and risk groups:

Not determinable.

Preventability:

To minimise the potential risk of product confusion-related medication errors with other trastuzumab-containing products, the vials and packages of T-DXd have distinctly different

designs. Additionally, the SmPC (SmPC Sections 4.2, 4.4, and 6.6) contains clear instructions for the health care professional regarding correct administration of T-DXd and differentiation from other trastuzumab-containing products, which is expected to further reduce the risk of medication errors with -DXd.

Furthermore, T-DXd will only be prescribed by a physician and administered under the supervision of a healthcare professional who is experienced in the treatment of cancer patients which will further reduce the risk of such medication error. The use of the trade name (ENHERTU), rather than the International Nonproprietary Name (trastuzumab deruxtecan) can also minimise this risk of product confusion-related medication errors.

Potential public health impact:

There is no potential public health impact beyond the treated population.

Missing Information: Use in Patients with Moderate and Severe Hepatic Impairment

Evidence source:

The safety profile of T-DXd may be different in subjects with moderate or severe hepatic impairment as the drug is primarily hepatically metabolised.

Population in need of further characterisation:

Patients with metastatic BC, GC, or NSCLC who have moderate or severe hepatic impairment.

Data from ongoing studies will be reviewed to further characterise the safety profile of T-DXd in this patient population.

Missing Information: Long-term Safety

Evidence source:

T-DXd is intended for long-term treatment and to date, long-term safety is considered missing information

Population in need of further characterisation:

Patients with metastatic BC, GC, or NSCLC. Long-term safety will be further characterised through Phase 3 clinical studies.

PART II: MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

Table Part II: Module SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Interstitial lung disease/Pneumonitis • Left ventricular dysfunction
Important potential risks	• Embryo-foetal toxicity • Product confusion-related medication errors
Missing information	• Use in patients with moderate or severe hepatic impairment • Long-term safety

PART III PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for ILD/Pneumonitis and LV dysfunction:

- **ILD/Pneumonitis:** Follow-up questionnaire for spontaneous ILD/pneumonitis events that captures additional details, including clinical course and presentation, relevant medical history, concomitant medications, laboratory data, and imaging data as available for enhanced safety surveillance and monitoring of this important identified risk in the postmarketing setting.
- **LV dysfunction:** Follow-up questionnaire for spontaneous LVEF decrease (including cardiac failure) events that captures additional details, including clinical presentation, relevant medical history, concomitant medications, and laboratory data as available for enhanced safety surveillance and monitoring of this important identified risk for any new safety signal in the postmarketing setting.

Batch related activities:

- T-DXd will be administered by a health care professional via IV infusion once every 3 weeks.
- The Marketing Authorisation Holder (MAH) will implement a process to systematically follow-up each postmarketing AE reported for T-DXd to obtain information on batch number(s) in the EU. If provided by the reporter, batch information for T-DXd will be included in the global safety database.
- Signal detection activities will include analysis for regional/batch-specific safety concerns.

III.2 Additional Pharmacovigilance Activities

A prescriber survey is implemented to measure effectiveness of an HCP Guide pertaining to the important identified risk of ILD/pneumonitis (details provided in Annex 6).

Furthermore, the collection of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies with T-DXd is planned to provide an overall assessment of these 10 subjects with moderate hepatic impairment.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.3.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study: **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation: None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances: None				
Category 3 – Required additional pharmacovigilance activities				
Prescriber Survey preparations ongoing	EU survey of relevant healthcare professionals on understanding of key risk minimization measures pertaining to ILD/pneumonitis	ILD	Final Report	Q2 2024
Phase 2 or 3 studies preparations ongoing	Collection of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies	Use in patients with moderate or severe hepatic impairment	Final report (for 10 subjects)	Q4 2023

EU = European Union; ILD = interstitial lung disease

PART IV PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

The MAH is currently conducting 2 Phase 3 clinical trials:

- Study DS8201-A-U306 is a confirmatory study expected to provide comprehensive evidence of the clinical benefit of T-DXd treatment in subjects with HER2-positive metastatic and/or unresectable gastric or gastro-esophageal junction (GEJ) adenocarcinoma.
- Study D967SC00001 (DESTINY-Lung04) is a confirmatory study expected to provide evidence of the clinical benefit of T-DXd as first-line treatment in subjects with unresectable, locally advanced, or metastatic NSCLC harboring HER2 exon 19 or 20 mutations.

For protocol details, please see Annex 5.

Table Part IV.1: Efficacy Studies which are Conditions of the Marketing Authorisation

Study: Status	Summary of objectives	Efficacy uncertainty addressed	Milestones	Due dates
DS-8201-A-U306: A Phase 3, multicenter, 2-arm randomized, open-label study of trastuzumab deruxtecan in subjects with HER2-positive metastatic and/or unresectable gastric or gastro-esophageal junction (GEJ) adenocarcinoma subjects who have progressed on or after a trastuzumab-containing regimen Ongoing	To examine the efficacy and safety of T-DXd, compared with subjects who received Ram + PTX for treatment of HER2-positive, gastric or gastro-esophageal junction adenocarcinoma	Overall efficacy and safety	Submission of results	Q4 2025
DESTINY-Lung04: An open-label, randomized, multicenter, Phase 3 study to assess the efficacy and safety of trastuzumab deruxtecan as first-line treatment of unresectable, locally advanced, or metastatic NSCLC harboring HER2 exon 19 or 20 mutations Ongoing	To assess the efficacy of T-DXd relative to platinum with pemetrexed plus pembrolizumab by assessment of PFS by BICR in participants with unresectable, locally advanced, or metastatic NSCLC harboring HER2 exon 19 or 20 mutations	Overall efficacy and safety	Submission of results	Q4 2025

BICR = blinded independent central review; HER2 = human epidermal growth factor receptor 2; NSCLC = non-small cell lung cancer; PFS = progression-free survival; PTX = paclitaxel; Ram = ramucirumab; T-DXd = trastuzumab deruxtecan

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

For the important identified risk of ILD/pneumonitis and for the important potential risk of product confusion-related medication errors, additional risk minimisation measures are proposed by the Applicant.

V.1 Routine Risk Minimisation Measures

Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Important Identified Risks	
Interstitial lung disease/Pneumonitis	Routine risk communication : SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Patient Information Leaflet Section 2 Patient Information Leaflet Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for ILD/pneumonitis monitoring and detecting early signs and symptoms of ILD/pneumonitis are included in SmPC Section 4.4. The use of corticosteroid treatment in ILD/pneumonitis is included in SmPC Section 4.2. Dose modification guidance for managing the risk of ILD/pneumonitis is included in SmPC Section 4.2. Recommendation for careful monitoring of patients with moderate or severe renal impairment is included in SmPC Section 4.2. Other routine risk minimisation measures beyond the Product Information: Legal status: T-DXd is subject to medical prescription.

Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern (Continued)

Safety Concern	Routine Risk Minimisation Activities
Important Identified Risks	
Left ventricular dysfunction	Routine risk communication : SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Patient Information Leaflet Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for monitoring of LVEF decrease are included in SmPC Section 4.4. Dose modification guidance for managing the risk of LVEF decrease is included in SmPC Section 4.2. Other routine risk minimisation measures beyond the Product Information: Legal status: T-DXd is subject to medical prescription.
Important Potential Risks	
Embryo-foetal toxicity	Routine risk communication : SmPC Section 4.4 SmPC Section 4.6 Patient Information Leaflet Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for pregnancy monitoring and contraception usage are included in SmPC Section 4.4 and SmPC Section 4.6. Other routine risk minimisation measures beyond the Product Information: Legal status: T-DXd is subject to medical prescription
Product confusion-related Medication error	Routine risk communication : SmPC Section 4.2 SmPC Section 4.4 SmPC Section 6.6 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Legal status: T-DXd is subject to medical prescription.

Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern (Continued)

Safety Concern	Routine Risk Minimisation Activities
Missing Information	
Use in patients with moderate or severe hepatic impairment	Routine risk communication : SmPC Section 4.2 SmPC Section 4.4 SmPC Section 5.2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Legal status: T-DXd is subject to medical prescription
Long-term safety	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: T-DXd is subject to medical prescription.

ILD = interstitial lung disease; LVEF = left ventricular ejection fraction; SmPC = Summary of Product Characteristics; T-DXd = trastuzumab deruxtecan

V.2 Additional Risk Minimisation Measures

For the important identified risk of ILD/pneumonitis, an HCP Guide and a Patient Card are additional risk minimisation measures.

For the important potential risk of product confusion-related medication errors, an HCP Guide is an additional risk minimisation measure.

The proposed draft key messages of the additional risk minimisation activities are provided in Annex 6.

Additional risk minimisation 1: Healthcare Professional Guide (ILD/Pneumonitis)

Objectives:

The objective of the HCP Guide is to ensure early recognition and diagnosis of ILD/pneumonitis, to allow prompt and appropriate treatment and minimise serious outcomes.

Rationale for the additional risk minimisation activity:

The HCP Guide improves HCP awareness of the risk of ILD/pneumonitis and management options, which may lead to early detection of and intervention for ILD/pneumonitis cases in clinical practice and thus potentially minimises the occurrence of more serious ILD/pneumonitis cases. The guide also improves the adherence to the key risk minimisation measures for ILD/pneumonitis defined in the T-DXd SmPC.

Target audience and planned distribution path:

Where T-DXd is supplied, all HCPs are provided with the HCP Guide to use as a reminder/quick reference material before the administration of T-DXd.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The Applicant verifies distribution of the HCP Guide and tests the understanding and knowledge of the key messages by the HCPs and evaluates the effectiveness using a survey.

The frequency of all ILD/pneumonitis including ILD/pneumonitis cases with a fatal outcome in the postmarketing setting will be evaluated periodically and are presented in each Periodic Safety Update Report.

Additional risk minimisation 2: Patient Card

Objectives:

The objective of the PC is to remind the patient of the risk of ILD/pneumonitis as well as its signs and symptoms and to encourage the patients to consult with the treating physician if they develop any relevant clinical signs/symptoms. The wallet-size Patient Card is intended as a convenient way to keep patients aware of the ILD/pneumonitis risk.

Rationale for the additional risk minimisation activity:

Being reminded about the signs and symptoms of ILD/pneumonitis increases the likelihood that patients will seek attention from an HCP for early detection and treatment of ILD/pneumonitis.

Target audience and planned distribution path:

The HCP provides the PC to the patient before initial administration of T-DXd. The PC has a compact design for portability.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The MAH verifies distribution of the PC in the prescriber survey.

The frequency of all ILD/pneumonitis including ILD/pneumonitis cases with a fatal outcome in the postmarketing setting are evaluated periodically and are presented in each Periodic Safety Update Report.

Additional risk minimisation 3: Healthcare Professional Guide for prevention of product confusion-related medication errors

Objectives:

The objective of the HCP Guide is to ensure that the medicinal product being prescribed, prepared and administered is T-DXd and not other trastuzumab-containing products or the HER2-targeted ADC trastuzumab emtansine (KADCYLA).

Rationale for the additional risk minimisation activity:

The HCP Guide improves HCP awareness of the potential risk for product confusion-related medication errors due to the availability of multiple trastuzumab-containing products and trastuzumab emtansine. The HCP Guide ensures the adherence to labelled language during the prescription, preparation and administration processes with T-DXd.

Target audience and planned distribution path:

Where T-DXd is supplied, all HCPs are provided with the HCP Guide for prevention of medication errors to use as a reminder/quick reference material before the administration of T-DXd.

Plans to evaluate the effectiveness of the interventions and criteria for success:

All cases representing potential product confusion-related medication errors in the postmarketing setting are evaluated periodically in terms of frequency, involved drugs, root causes (if available) as well as clinical outcomes and are presented in each Periodic Safety Update Report.

V.3 Summary of Risk Minimisation Measures

Table Part V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Interstitial Lung Disease/Pneumonitis	Routine risk minimisation measures : SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Patient Information Leaflet Section 2 Patient Information Leaflet Section 4 Recommendations for ILD/pneumonitis monitoring and detecting early signs and symptoms of ILD/pneumonitis are included in SmPC Section 4.4. Dose modification guidance and recommendation for corticosteroid treatment for managing the risk of ILD/pneumonitis are included in SmPC Section 4.2. Recommendation for careful monitoring of patients with moderate or severe renal impairment is included in SmPC Section 4.2. Additional risk minimisation activities: HCP Guide and Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire Additional pharmacovigilance activities: Prescriber survey
Left ventricular dysfunction	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Patient Information Leaflet Section 2 Recommendations for monitoring of left ventricular dysfunction are included in SmPC Section 4.4. Dose modification guidance for managing the risk of left ventricular dysfunction is included in SmPC Section 4.2. Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire Additional pharmacovigilance activities: None

Table Part V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern (Continued)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risks		
Embryo-foetal toxicity	Routine risk minimisation measures: SmPC Section 4.4 SmPC Section 4.6 Patient Information Leaflet Section 2 Recommendations for pregnancy monitoring and contraception usage are included in SmPC Section 4.4 and SmPC Section 4.6. Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Product confusion-related medication error	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 6.6 Pack and vials: specific livery for ENHERTU on the packaging and specific colours for vial cap and bottle to distinguish from other trastuzumab containing products Additional risk minimisation activities: HCP Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing Information		
Use in patients with moderate or severe hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 5.2 Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Review of data from ongoing clinical studies Additional pharmacovigilance activities: Analysis of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies

Table Part V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern (Continued)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing Information		
Long-term safety	Routine risk minimisation measures: None Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

HCP = healthcare professional; ILD = interstitial lung disease; PK = pharmacokinetic; SmPC = Summary of Product Characteristics

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR ENHERTU

This is a summary of the RMP for T-DXd. The RMP details important risks of T-DXd, how these risks can be minimised, and how more information will be obtained about T-DXd's risks and uncertainties (missing information).

The SmPC and package leaflet for T-DXd give essential information to HCPs and patients on how T-DXd should be used.

This summary of the RMP for T-DXd should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which will be part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of T-DXd's RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

Trastuzumab deruxtecan is indicated:

- As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.
- As monotherapy for the treatment of adult patients with advanced HER2-positive gastric or GEJ adenocarcinoma who have received a prior trastuzumab-based regimen.

- As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.
- As monotherapy for the treatment of adult patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum based chemotherapy with or without immunotherapy.

Further information about the evaluation of T-DXd's benefits be found in T-DXd's EPAR (https://www.ema.europa.eu/en/medicines/human/EPAR/enhertu), including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERIZE THE RISKS

Important risks of T-DXd, together with measures to minimise such risks, are outlined below.

- Measures to minimise the risks identified for medicinal products can be the following:
  - Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
  - Important advice on the medicine's packaging.
  - The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
  - The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of T-DXd, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks below.

In addition to these measures, information about adverse reactions is continuously collected and regularly analysed, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of is not yet available for T-DXd, it is listed under "missing information" below.

II.A List of Important Risks and Missing Information

Important risks of T-DXd are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of T-DXd. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this

association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table Part VI Module II.1: Lists of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	• Interstitial Lung Disease/Pneumonitis • Left Ventricular Dysfunction
Important potential risks	• Embryo-foetal Toxicity • Product confusion-related medication errors
Missing information	• Use in Patients with Moderate or Severe Hepatic Impairment • Long-term safety

II.B Summary of Important Risks

Important identified risks with T-DXd include ILD/pneumonitis and left ventricular dysfunction as outlined below.

Important Identified Risk 1: Interstitial Lung Disease/Pneumonitis	
Evidence for linking the risk to the medicine	Dose-dependent changes in the lung were seen in nonclinical data (Section Part II: Module SII). ILD/pneumonitis was reported in clinical studies with T-DXd, including fatal outcomes. An independent Adjudication Committee adjudicated all potential events of ILD.
Risk factors and risk groups	Seven baseline factors of interest were identified: age <65 vs ≥65 years; patients treated in Japan vs non-Japan; dose of >6.4 vs ≤6.4 mg/kg; baseline oxygen saturation <95% vs ≥95%; moderate/severe renal impairment at baseline vs no impairment; presence of lung comorbidities (yes vs no; asthma, chronic obstructive pulmonary disease, prior ILD/pneumonitis, pulmonary fibrosis, pulmonary emphysema, or radiation pneumonitis); and time since initial diagnosis of >4 vs ≤4 years.
Risk minimisation measures	Routine risk communication: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Routine risk minimisation measures: Recommendation for ILD/pneumonitis monitoring and detecting early signs and symptoms of ILD/pneumonitis are included in SmPC Section 4.4. The use of corticosteroid treatment in ILD/pneumonitis is included in SmPC Section 4.2. Dose modification guidance for managing the risk of ILD/pneumonitis is included in SmPC Section 4.2. Recommendation for careful monitoring of patients with moderate or severe renal impairment is included in SmPC Section 4.2. Additional risk minimisation measures: Healthcare Professional Guide and Patient Card
Additional pharmacovigilance activities	Prescriber survey

ILD = interstitial lung disease; SmPC = Summary of Product Characteristics

Important Identified Risk 2: Left Ventricular Dysfunction	
Evidence for linking the risk to the medicine	Cardiotoxicity has been observed with anti-HER2 drugs, including single-agent trastuzumab, which has a warning for cardiomyopathy. LVEF decreases have been observed infrequently in clinical studies with T-DXd.
Risk factors and risk groups	None
Risk minimisation measures	Routine risk communication: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for monitoring of LVEF decrease are included in SmPC Section 4.4. Dose modification guidance for managing the risk of LVEF decrease is included in SmPC Section 4.2. Additional risk minimisation measures: None

HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; SmPC = Summary of Product Characteristics; T-DXd = trastuzumab deruxtecan

Important potential risks considered important for inclusion in the list of safety concerns include embryo-foetal toxicity and product confusion-related medication errors, as outlined below.

Important Potential Risk 1: Embryo-foetal Toxicity	
Evidence for linking the risk to the medicine	Findings from nonclinical data, the potential mechanism of the released drug of T-DXd and known effects of anti-HER2 agents on embryo-foetal toxicity suggest that T-DXd may potentially cause foetal harm.
Risk factors and risk groups	None
Risk minimisation measures	Routine risk communication: SmPC Section 4.4 SmPC Section 4.6 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for pregnancy monitoring and contraception usage are included in SmPC Section 4.4 and SmPC Section 4.6. Additional risk minimisation measures: None

HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; SmPC = Summary of Product Characteristics

Important Potential Risk 2: Product confusion-related medication errors	
Evidence for linking the risk to the medicine	Medication errors between trastuzumab (ie, Herceptin) and trastuzumab emtansine (ie, KADCYLA) have been reported. Potential for medication errors due to product confusion of T-DXd with trastuzumab and trastuzumab emtansine indicated for breast cancer treatment is considered.
Risk factors and risk groups	None
Risk minimisation measures	Routine risk communication: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 6.6 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Additional risk minimisation measures: Healthcare Professional Guide

SmPC = Summary of Product Characteristics; T-DXd = trastuzumab deruxtecan

Missing information with T-DXd includes use in patients with moderate or severe hepatic impairment, as outlined below.

Missing Information 1: Use in Patients With Moderate or Severe Hepatic Impairment	
Evidence for linking the risk to the medicine	T-DXd has not been studied in subjects with severe hepatic impairment. A maximum of 10 subjects with moderate hepatic impairment were eligible for inclusion in Study U201; however, only 2 subjects in the All Tumour Types ≥5.4 mg/kg Pool had moderate hepatic impairment at baseline. Based on a population PK analysis, the clearance of the released drug of T-DXd decreases with increasing AST and increasing total bilirubin.
Risk minimisation measures	Routine risk communication: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 5.2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Additional risk minimisation activities: None
Additional pharmacovigilance activities	Analysis of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies.

AST = aspartate aminotransaminase; BC = breast cancer; HER2 = human epidermal growth factor receptor 2; PK = pharmacokinetic; SmPC = Summary of Product Characteristics; T-DXd = trastuzumab deruxtecan

Missing Information 2: Long-term Safety	
Evidence for linking the risk to the medicine	The median treatment duration (defined as: date of last dose − date of first dose + 21) in the HER2-positive BC 5.4 mg/kg Pool (N = 234) was 9.82 months (range: 0.7 to 37.1). A total of 164/234 (70.1%) subjects had been treated for >6 months, 127/234 (54.3%) for >9 months, 69/234 (29.5%) for >12 months, and 5/234 (2.1%) for >24 months.
Risk minimisation measures	Routine risk minimisation communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Additional risk minimisation activities: None

BC = breast cancer; HER2 = human epidermal growth factor receptor 2

II.C Postauthorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

The Phase 3 clinical trials DS8201-A-U306 and DESTINY-Lung04 serve as the confirmatory trials (see also RMP Part IV). Details are provided in the table below.

DS8201-A-U306	
Short title	A Phase 3, multicenter, 2-arm randomized, open-label study of trastuzumab deruxtecan in subjects with HER2-positive metastatic and/or unresectable gastric or gastro esophageal junction (GEJ) adenocarcinoma subjects who have progressed on or after a trastuzumab containing regimen
Purpose of the study	Primary objective: To compare Overall Survival in HER2-positive (defined as IHC 3+ or IHC 2+/ISH+) gastric cancer (GC) and GEJ adenocarcinoma subjects treated with T-DXd vs. Ram + PTX. Key secondary objective: To compare Progression Free Survival in HER2-positive GC and GEJ adenocarcinoma subjects treated with T DXd or Ram + PTX. Other secondary Objectives: • To evaluate the safety of T-DXd compared to Ram + PTX • To compare the clinical efficacy of T DXd and Ram + PTX by ORR based on investigator assessment • To compare the clinical efficacy of T-DXd and Ram + PTX by DoR.To compare the clinical efficacy of T-DXd and Ram + PTX by disease control rate (DCR) • To evaluate the PK of T-DXd • To evaluate immunogenicity of T DXd Safety concern addressed: overall safety

DESTINY-Lung04	
Short title	Phase 3 study of the efficacy and safety of trastuzumab deruxtecan as first-line treatment for NSCLC with HER2 exon 19 or exon 20 mutations.
Purpose of the study	Primary objective: To assess the efficacy of T-DXd relative to platinum with pemetrexed plus pembrolizumab by assessment of PFS by BICR in participants with unresectable, locally advanced, or metastatic NSCLC harboring HER2 exon 19 or 20 mutations. Secondary objectives: • To assess the efficacy of T-DXd relative to platinum with pemetrexed plus pembrolizumab by assessment of OS. • To further assess the efficacy of T-DXd relative to platinum with pemetrexed plus pembrolizumab in terms of PFS by investigator assessment, ORR, DoR, PFS2, and landmark analysis of PFS12 and OS24. • To assess the efficacy of T-DXd relative to platinum with pemetrexed plus pembrolizumab by assessment of CNS-PFS (per RECIST 1.1). • To assess the safety and tolerability of T-DXd as compared to platinum with pemetrexed plus pembrolizumab. • To assess the PK of T-DXd, total anti-HER2 antibody and DXd in serum. • To investigate the immunogenicity of T-DXd. • To assess the benefit of T-DXd relative to platinum with pemetrexed plus pembrolizumab with patient-reported pulmonary symptoms associated with NSCLC. • To describe patient-reported tolerability of T-DXd as compared to platinum with pemetrexed plus pembrolizumab. Safety concern addressed: overall safety

BICR = blinded independent central review; CNS-PFS = progression-free survival in central nervous system; DoR = duration of response; DXd = deruxtecan; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = in situ hybridization; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; OS24 = proportion of participants alive at 24 months; PFS = progression-free survival; PFS12 = proportion of participants alive and progression-free at 12 months; PFS2; time to second progression or death; PK = pharmacokinetics; PTX = paclitaxel; Ram = ramucirumab; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; T-DXd = trastuzumab deruxtecan

II.C.2 Other Studies in Postauthorisation Development Plan

Prescriber survey	
Short title	EU survey of relevant healthcare professionals on understanding of key risk minimization measures pertaining to ILD/pneumonitis
Purpose of the study	The primary objective is to evaluate the effectiveness of proposed educational material as risk minimization measures by: Evaluating the level of knowledge of educational materials by HCPs of risks, early recognition, diagnosis and management of ILD/pneumonitis. Evaluating the extent to which HCPs receive the HCP guide and distribute the PC to patients. Safety concern addressed: risk minimization for ILD/pneumonitis.

EU = European Union; HCP = healthcare professional; ILD = interstitial lung disease; PC = Patient Card

PK and safety data analysis in patients with moderate hepatic impairment	
Short title	Collection and analysis of PK and safety data in subjects with moderate hepatic impairment from ongoing clinical studies
Purpose of the study	Overall assessment of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies. Safety concern addressed: Missing information: Use in patients with moderate or severe hepatic impairment.

PK = pharmacokinetic

PART VII ANNEXES

LIST OF ANNEXES

ANNEX 1 EUDRAVIGILANCE INTERFACE

Available in electronic format only and is electronically submitted as per guidelines.

ANNEX 2 TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

Table Part VII.1: Planned and Ongoing Studies/Pharmacovigilance Activities

Study/Activity	Summary of Objectives	Safety Concerns Addressed	Milestones
Prescriber survey	EU survey of relevant healthcare professionals on understanding of additional risk minimisation measures pertaining to ILD/pneumonitis	ILD/pneumonitis	Final report, Q2 2024
Ongoing Phase 2 or 3 studies	Collection of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing clinical studies	Use in patients with moderate or severe hepatic impairment	Final assessment report (for 10 subjects), Q4 2023

EU = European Union; ILD = interstitial lung disease; PK = pharmacokinetic

ANNEX 3 PROTOCOLS FOR PROPOSED, ONGOING, AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

Prescriber Survey on understanding of key risk minimization measures related to ILD/pneumonitis with Trastuzumab Deruxtecan treatment

Milestones and timelines

Milestone	Timeline (Quarter/Year)
T-DXd approval	Q1 2021
Protocol submission to PRAC	Q2 2021
Registration in the ENCePP EU PAS register	After approval of the protocol and before start of data collection
Study initiation	1 year after launch of the product in each participating country

Background and Rationale

In January 2021, the European Commission has granted T-DXd a conditional approval for use as a monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens.

ILD and/or pneumonitis have been identified as important risks for patients treated with T-DXd, and fatal outcomes have been observed.

To prevent/minimize the occurrence of severe ILD/pneumonitis, the MAH Daiichi-Sankyo Europe (DSE) proposed additional risk minimisation measures (aRMM) for ILD/pneumonitis and developed educational material (EM), which includes:

- An HCP Guide and
- A PC.

A prescriber survey will be performed in the EU Member States where T-DXd is marketed to evaluate effectiveness of these key risk minimisation measures for ILD/pneumonitis.

Research question and objectives

The aim of this study is to evaluate the effectiveness of T-DXd's aRMMs for the important identified risk of ILD/pneumonitis by assessing their correct implementation among physicians expected to have prescribed or will potentially prescribe Enhertu (T-DXd). Physicians' awareness, knowledge and implementation pertaining the key messages of the aRMMs distributed by DSE will be evaluated.

The primary objective for this study is:

- To assess physicians' awareness, knowledge, and implementation of additional risk minimisation measures related to the risk, early detection, diagnosis, and management of ILD/pneumonitis.

The secondary objectives for this study are:

- To measure physician's awareness of the ILD/pneumonitis risk and its related minimisation measures.
- To assess the extent to which physicians are aware of having received the educational material (HCP guide and PC).
- To measure physician's knowledge on the requirement for treatment modifications in case of suspected ILD/pneumonitis.
- To measure physicians' knowledge on the requirement to monitor specific signs and symptoms that allow early detection of ILD/pneumonitis.
- To assess whether physicians implement the recommended talking points to patients at the recommended frequency.
- To assess the extent to which physicians implement the distribution of the patient card to their patients.

Methods

Study design

This is a cross-sectional, multinational survey conducted among physicians who are prescribers or potential prescribers of T-DXd in a selection of European countries where T-DXd is marketed.

Data source

The survey is a primary data collection of the responses provided by physicians via a web-based questionnaire.

Physicians from the distribution list of the EM will be contacted in a random order.

Population selection

The survey will be conducted among office and hospital-based physicians in European countries approximately 12 months after the distribution of EM for T-DXd. According to the launch sequence of T-DXd in European countries planned for 2021-2022, the following 7 countries will be included in the survey: Austria, Denmark, France, Germany, Sweden, Spain, and UK.

The population to be surveyed in the selected countries will comprise physicians from the distribution list for the EM who are prescribers or potential prescribers of T-DXd. Physicians will be further selected on the basis that they treat patients for their breast cancer and that they are aware of T-DXd.

Inclusion criteria:

Physicians of the relevant specialties (ie, either oncologists or gynaecologists) must meet all of the following inclusion criteria:

- Physicians on the distribution list for the EM.

Exclusion criteria:

- Physicians who may have conflicts of interest with the survey (ie, physicians employed by pharmaceutical industry or contracted by regulatory bodies, eg, EMA).
- Physicians who are not actively treating patients for their breast cancer.
- Physicians who are not aware of T-DXd.

Study variables

Variables related to physician characteristics, practice information, their awareness of the important identified risk of ILD/pneumonitis, and clinical actions related to the identified risk will be collected. Physicians will be asked to indicate their knowledge of the requirement to monitor specific signs and symptoms for early detection of ILD/pneumonitis, their management, and the implementation of proposed risk mitigation measures. In addition, physicians' opinions on the usefulness of EM (HCP guideline) will be sought.

Survey size

The survey aims to recruit 262 physicians from different European countries in the project. The target is to collect responses from at least 165 prescribers of T-DXd and up to 97 potential prescribers.

Based on the number of physicians on the distribution list of the education material, it is assumed that approximately 78 physicians will complete the survey.

Statistical methods

The statistical analysis will be done descriptively and conducted using the software SAS® V9.3 or higher.

The statistical results of the physician survey data will be presented in one report, by country, and combined.

In addition, analyses will be stratified by physicians' prescribing status (prescriber vs. potential prescriber) and, if applicable, by specialty.

Analysis of submitted questionnaires will be performed for 3 domains:

- Awareness questions.
- Knowledge questions.
- Implementation questions.

For the protocol synopsis of the two ongoing Phase 3 studies please see Annex 5 of the RMP as both belong to the category of postauthorisation efficacy studies.

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ENHERTU® Potential Interstitial Lung Disease (ILD) Event Follow-up Questionnaire

ENHERTU® Potential Left Ventricular Ejection Fraction (LVEF) Follow-up Questionnaire

ENHERTU® Potential Interstitial Lung Disease (ILD) Event Follow-up Questionnaire

Report Information			
Daiichi Sankyo ARGUS #:			
Patient Information			
Initials:		Date of birth (dd/mm/yyyy) or age:	
Gender:		Race/Ethnicity:	
Weight (units):		Height (units):	
BMI (units):		Occupation:	
ILD Adverse Event Details *Please provide start date and details of the ILD adverse event.*			
Start date (dd/mm/yyyy):			
ILD adverse event details			
Signs/Symptoms *Please provide start and stop date(s) and details of the following relevant signs/symptoms, if applicable.*			
Relevant Signs/Symptoms	**Start and Stop Date(s) (dd/mm/yyyy)**	**Details**	
☐ Fever			
☐ Dyspnea (shortness of breath)			
☐ Cough			
☐ Pleural effusion			
☐ Other(s)			

Laboratory Tests *Please provide details of the following relevant lab tests, if applicable.*				
Relevant Lab Tests	**Maximum Value (units)/ Reference Range**	**Date of Maximum Value (dd/mm/yyyy)**	**Most Recent Value (units)/ Reference Range**	**Date of Most Recent Value (dd/mm/yyyy)**
Eosinophils				
Neutrophils				
Other:				
Other:				
Other:				

Diagnostic Tests *Please provide date(s) and results of the following relevant diagnostic tests, if applicable.*		
Relevant Diagnostic Tests	**Date(s) (dd/mm/yyyy)**	**Results**
☐ Chest X-ray		
☐ Computed tomography (CT)		
☐ High-resolution computed tomography (HRCT)		
☐ Bronchoscopy		
☐ Bronchoalveolar lavage (BAL)		
☐ Culture(s)		Type(s):
☐ Arterial blood gas (ABG) including PO2 (oxygen saturation)		
☐ ILD serum biomarkers (eg, KL-6, SP-D)		
☐ Pulmonary function tests		FEV1: FEV1/FVC: TLC: RV: FVC:
☐ Diffusing capacity of the lungs for carbon monoxide (DLCO)		
☐ Lung biopsy		Type:
☐ Other(s) (eg, rapid influenza diagnostic, CMV antigen, pneumococcal urinary antigen, beta D-glucan, BNP, NT-proBNP)		

Pulmonary Consultation	
Was a pulmonary specialist consulted?	☐ Yes ☐ No If yes, consultation notes:
Primary Cancer History	
Date of initial diagnosis (dd/mm/yyyy):	
Did the patient have prior chest radiation?	☐ Yes ☐ No Details (eg, date [dd/mm/yyyy], dose, fraction, location):

Prior Cancer Therapy	
Number of prior cancer therapies:	
Did the patient receive prior cancer therapy known to cause ILD?	☐ Yes ☐ No Details (eg, drug/regimen name, indication, dose, frequency, start/stop dates [dd/mm/yyyy]):
Social History	
☐ Smoker	☐ Yes (☐ Current ☐Past) ☐ No If yes, number of years: If yes, packs per year:
☐ Any e-cigarette/vaping (nicotine, THC) use in the past 30 days?	☐ Yes ☐ No If yes, what type of product?: ☐ Tobacco containing nicotine ☐ THC only ☐ Nicotine and THC ☐ Others Number of years: Frequency of use: ☐ Daily ☐ >3-5 times a week ☐ Occasionally ☐ Only for recreational purposes
☐ Occupational/environmental exposure	☐ Yes ☐ No If yes, details:
☐ Recreational exposure (other than THC products)	☐ Yes ☐ No If yes, details:

Relevant Medical History *Please provide date(s)/diagnosis date and details of the following relevant past medical history, if applicable.*		
Relevant Medical History	**Start Date/Diagnosis Date (dd/mm/yyyy)**	**Details**
☐ Previous ILD		If yes, did patient receive steroid treatment? ☐ Yes ☐ No
☐ Lung metastases or pulmonary malignancy (eg, Lymphangitis Carcinomatosis)	☐ Past ☐ Present	
☐ Prior lung surgery		Location:
☐ Asthma		
☐ Chronic obstructive pulmonary disease (COPD)		
☐ Radiation pneumonitis		
☐ Respiratory infection (eg, pneumonia)		
☐ Renal impairment		
☐ Other(s) (eg, bronchiolitis obliterans organizing pneumonia, cryptogenic organizing pneumonia)		

Treatment(s)				
Did patient receive any treatment for ILD? ☐ Yes ☐ No Choose treatment(s) and specify details below: ☐ Corticosteroid(s) ☐ Immunosuppressant(s) ☐ Antibiotic(s) ☐ Other(s)				
Drug	Indication	Dose/Route/Frequency	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)
Action Taken				
ENHERTU discontinued due to ILD event?	☐ Yes ☐ No If yes, date of suspect drug discontinuation (dd/mm/yyyy):			
Event resolved after drug discontinued?	☐ Yes ☐ No ☐ N/A If yes, date (dd/mm/yyyy) of resolution:			
ENHERTU restarted?	☐ Yes ☐ No ☐ N/A If yes, date of suspect drug restarted (dd/mm/yyyy):			
ILD reoccurred after drug restarted?	☐ Yes ☐ No ☐ N/A If yes, date of suspect drug restarted (dd/mm/yyyy):			

Is ILD event possibly related to ENHERTU?	☐Yes ☐No ☐UNK	Explanation:
Event Outcome *Please select all that apply.*		
☐ Recovered without sequelae	☐ Recovered with sequelae Details:	☐ Recovered after treatment Treatment details:
☐ Recovering	☐ Not recovered	☐ Worsened Details:
☐ Unknown	☐ Fatal (please provide copy of post-mortem report)	

Suspect Drug *Please complete if reported ILD event was due to* ENHERTU.			
Suspect drug name:			
Lot number:		Indication:	
Dose:		Frequency:	
Start dates (dd/mm/yyyy):		Stop dates (dd/mm/yyyy):	
Suspect Drug *Please complete if reported ILD event was due to any other suspect drug besides* ENHERTU.			
Suspect drug name:			
Lot number:		Indication:	
Dose:		Frequency:	
Start dates (dd/mm/yyyy):		Stop dates (dd/mm/yyyy):	

Concomitant Medications
(Prescription, illicit drug use, over the counter, nutritional supplements, herbals)

Drug	Indication	Dose/Route/Frequency	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)

Other	
Are there any other contributing factors to the adverse event?	☐ Yes ☐ No If yes, details:
Reporter Information	
Information provided by:	
Date of Report (dd/mm/yyyy)**:**	**Reporter Signature:**

ENHERTU® Potential Left Ventricular Ejection Fraction (LVEF) Follow-up Questionnaire

Report Information			
Daiichi Sankyo ARGUS #: :			
Patient Information			
Initials:		Date of Birth (dd/mm/yyyy) or age:	
Gender:		Race/Ethnicity:	
Weight (units):		Height (units):	
LVEF Adverse Event Details			
Start date of event: (dd/mm/yyyy)		Stop date of event: (dd/mm/yyyy)	
Treatment with Enhertu discontinued due to LVEF event?	☐ Yes / ☐ No	Date of the drug discontinuation	
Event resolved after discontinuation?	☐ Yes / ☐ No	Treatment with Enhertu restarted?	☐ Yes / ☐ No If yes ☐ Dose unchanged ☐ Dose reduced to mg/kg
Date of treatment with Enhertu restarted		LVEF Event reoccurred?	☐ Yes / ☐ No
Causality between Enhertu and Event	☐ Yes ☐ No ☐ unknown	Further LVEF adverse event details:	
Event Outcome			
☐ Recovered	☐ Recovered with Sequelae If sequelae, please specify	☐ Recovering	
☐ Not Recovered	☐ Fatal (if conducted, please provide copy of post-mortem report)	☐ Unknown	
Signs/Symptoms *Please circle all that apply.*			
Dyspnea or orthopnea (shortness of breath)/Fatigue/Palpitations/Chest pain/Peripheral edema/Hepatomegaly (enlarged liver)/Other (s)			
Cardiac Consultation			

Was a cardiac specialist consulted?	☐ Yes ☐ No If yes, consultation notes:

New York Heart Association (NYHA) Classification

Please provide severity of heart failure (at the time of adverse event), if applicable.

Class	Definition	Yes or No	Date of Classification (dd/mm/yyyy)
NYHA I	No limitation: ordinary physical exercise does not cause undue fatigue, dyspnoea, or palpitations	☐ Yes ☐ No	
NYHA II	Slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue, palpitations, or dyspnoea	☐ Yes ☐ No	
NYHA III	Marked limitation of physical activity: comfortable at rest but less than ordinary activity results in symptoms	☐ Yes ☐ No	
NYHA IV	Unable to carry out any physical activity without discomfort: symptoms of heart failure are present even at rest with increased discomfort with any physical activity	☐ Yes ☐ No	

Diagnostic/Laboratory Tests

Please provide date(s) and results of the following relevant diagnostic/laboratory tests, if applicable.

Relevant Diagnostic/Laboratory Tests	Date(s) (dd/mm/yyyy)	Results
☐ Echocardiography (ECHO) / Radionuclide ventriculography (MUGA)		% LVEF:
☐ Chest X-ray		
☐ Cardiac magnetic resonance imaging (MRI) / positron emission tomography (PET)		
☐ Electrocardiography (ECG)		
☐ Troponin test		
☐ Natriuretic peptides (eg, BNP, NT-proBNP)		
☐ Creatine kinase-muscle/brain (CK-MB)		
☐ Other(s)		

Primary Cancer History

Specification of primary cancer:	Date of initial diagnosis (dd/mm/yyyy):
Did the patient have prior chest radiation?	☐ Yes ☐ No Details (eg, date [dd/mm/yyyy], dose, fraction, location):

Prior Cancer Therapy	
Number of prior cancer therapies:	
Did the patient receive prior cancer therapy known to cause cardiotoxicity (eg, anthracycline [doxorubicin])?	☐ Yes ☐ No Details (eg, drug/regimen name, indication, dose, frequency, start/stop dates [dd/mm/yyyy]):

Relevant Medical History

Please provide date(s)/diagnosis date and details of the following relevant past medical history, if applicable.

	Start Date/Diagnosis Date (dd/mm/yyyy)	**Details**
☐ Previous heart failure		NYHA class:
☐ Prior heart surgery		Location:
☐ Acute coronary syndrome (eg, myocardial infarction [heart attack])		
☐ Arrhythmia (irregular heart beat)		If yes, on treatment?: ☐ Yes ☐ No
☐ Hypertension (high blood pressure)		If yes, on treatment?: ☐ Yes ☐ No
☐ Dyslipidemia (high cholesterol)		If yes, on treatment?: ☐ Yes ☐ No
☐ Diabetes		If yes, on treatment?: ☐ Yes ☐ No
☐ Pulmonary condition(s)		If yes, on treatment?: ☐ Yes ☐ No
☐ Other(s) cardiac condition (eg, Ischemic heart disease, Valvular heart disease, Cardiomyopathy)		If yes, on treatment?: ☐ Yes ☐ No
☐ Smoker		
☐ Alcohol use		
☐ Others (eg, Occupational/environmental exposure), please specify		

Other	
Are there any other contributing factors to the adverse event?	☐ Yes ☐ No If yes, details:

Suspect Drug

Please complete if reported LVEF event was due to ENHERTU

Suspect drug name:			
Lot number:		Indication:	

Dose:		Frequency:	
Start dates (dd/mm/yyyy):		Stop dates (dd/mm/yyyy):	

Concomitant Medications
(Prescription, illicit drug use, over the counter, nutritional supplements, herbals)

Drug	Indication	Dose/Route/Frequency	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)

Treatment

Did the patient receive any treatment for heart failure? ☐ Yes ☐ No
Choose treatment(s) and specify details below:
☐ Beta-blocker ☐ Diuretic ☐ Angiotensin-converting enzyme (ACE) inhibitor ☐ Angiotensin II receptor blocker (ARB)
☐Aldosterone receptor antagonist ☐ Cardiac glycoside (eg, digoxin) ☐ Other(s)

Drug	Indication	Dose/Route/Frequency	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)

Reporter Information

Information provided by:

HCP ☐ Yes / ☐ No If no, please specify

Date of Report (dd/mm/yyyy)**:**	**Reporter Signature:**

ANNEX 5 PROTOCOLS FOR PROPOSED AND ONGOING STUDIES IN RMP PART IV

Protocol synopsis of Study DS8201-A-U306.

Protocol synopsis of Study DESTINY-Lung04.

PROTOCOL SYNOPSIS STUDY DS8201-A-U306

Protocol Title
A Phase 3, Multicenter, 2-Arm Randomized, Open-Label Study of Trastuzumab Deruxtecan in Subjects with HER2-Positive Metastatic and/or Unresectable Gastric or Gastro-Esophageal Junction (GEJ) Adenocarcinoma Subjects who have Progressed on or After a Trastuzumab-Containing Regimen (DESTINY-Gastric04)
Protocol Short Title
Trastuzumab Deruxtecan for Subjects with HER2-Positive Gastric Cancer or Gastro-Esophageal Junction Adenocarcinoma after Progression on or After a Trastuzumab-Containing Regimen
Protocol Number
DS8201-A-U306
Sponsor/Collaborators
Sponsor: Daiichi Sankyo, Inc. Collaborators: AstraZeneca and Syneos Health
Registry Identification(s)
EudraCT Number: 2020-004559-34
IND Number
136179
Study Phase
Phase 3
Planned Geographical Coverage, Study Sites, and Location
Approximately 148 study sites in Asia-Pacific, Europe, and Latin America
Study Population
Subjects with human epidermal growth factor receptor 2 (HER2)-positive metastatic gastric or GEJ adenocarcinoma who have progressed on or after a trastuzumab-containing regimen.
Study Objectives/Outcome Measures and Endpoints
The table below lists primary and secondary study objectives and endpoints that have outcome measures.

Objectives	Outcome Measures	Endpoints	Category
Primary			
To compare OS in HER2-positive (defined as IHC 3+ or IHC 2+/ISH+) GC and GEJ adenocarcinoma subjects treated with T-DXd vs. Ram + PTX.	**Title:** OS **Description:** Time from randomization to death **Time frame:** After at least 237 (70%) OS events are recorded for interim analysis and 339 OS events are recorded for final analysis	The primary efficacy endpoint is OS, defined as the time from date of randomization until death from any cause.	Efficacy
Secondary			
To compare PFS in HER2-positive GC and GEJ adenocarcinoma subjects treated with T-DXd or Ram + PTX.	**Title:** PFS **Description:** Time from randomization until objective disease progression or death **Time frame:** At the time of interim analysis and final analysis	PFS, defined as the time from date of randomization until first objective radiographic tumor progression or death from any cause, based on investigator assessment.	Efficacy
To compare the clinical efficacy of T-DXd and Ram + PTX by ORR based on investigator assessment	**Title:** ORR by investigator assessment **Description:** The proportion of subjects with CR or PR assessed by investigator assessment **Time frame:** At the time of interim analysis and final analysis	ORR is defined as the proportion of subjects who achieve a best response of CR or PR using the RECIST version 1.1 criteria as assessed by investigator. Confirmation of CR and PR is required by a subsequent assessment.	Efficacy
To compare the clinical efficacy of T-DXd and Ram + PTX by DoR	**Title:** DoR **Description:** Time from CR or PR to disease progression or death **Time frame:** At the time of primary analysis	DoR, defined as time from the initial response (CR or PR) until documented tumor progression or death from any cause and based on investigator assessment.	Efficacy

To compare the clinical efficacy of T-DXd and Ram + PTX by DCR	**Title:** DCR **Description:** The sum of CR, PR, and SD **Time frame:** At the time of primary analysis	DCR, defined as the proportion of subjects who achieved CR, PR, or SD for a minimum of 6 weeks during study treatment, based on investigator assessment.	Efficacy
To evaluate the safety of T-DXd compared to Ram + PTX	**Title:** TEAEs and other safety parameters during the study **Description:** Descriptive statistics of safety endpoints **Time frame:** Continuous monitoring and reported at the time of the primary analysis	AEs, including SAEs, TEAEs, and AESIs, will be graded according to the NCI-CTCAE Version 5.0. Physical examination findings including ECOG PS, vital sign measurements, ophthalmologic findings, standard clinical laboratory parameters, ECG parameters, ECHO/MUGA findings.	Safety
To evaluate the PK of T-DXd	**Title:** PK profile **Description:** Serum concentrations of T-DXd, total anti-HER2 antibody, and MAAA-1181a **Time frame:** At the time of primary analysis	The PK endpoints include serum concentrations of T-DXd, total anti-HER2 antibody, and MAAA-1181a.	PK
To evaluate immunogenicity of T-DXd	**Title:** Immunogenicity **Description:** Incidence of ADA and NAb. **Time frame:** At the time of primary analysis	The immunogenicity endpoint includes incidence of ADA and NAbs.	Immunogenicity
Exploratory			
To assess symptoms, functioning, and HRQoL in subjects treated with T-DXd vs. Ram + PTX	**Title:** PROs **Description:** Changes from baseline/time to deterioration in	• FACT-Ga – Change from baseline in FACT-Ga scale scores – Time to	PROs

using PROs	FACT-Ga, PGIS, PGIC, PGI-TT, and EQ-5D-5L **Time frame:** At the time of primary analysis	deterioration in FACT-Ga scores • Global Anchors (PGIS, PGIC, PGI-TT) • EQ-5D-5L – VAS scores & health state utility index from EQ-5D-5L	
To assess correlations between biomarker status and efficacy and/or safety	Not applicable	Identification of candidate predictive/resistance biomarkers using platforms such as RNAseq, DNAseq, MS analysis, digital pathology. These exploratory analyses may be conducted using recently obtained tumor biopsy samples (mandatory), archival tumor samples (strongly recommended), on-treatment and end-of-treatment tumor samples (optional), and blood samples (cfDNA analysis, etc).	Efficacy/Safety
To evaluate the clinical efficacy of T-DXd and Ram + PTX based on baseline HER2 amplification status assessed in cfDNA	Not applicable	Assess the correlation between HER2 amplification status and clinical efficacy endpoints (eg, OS, PFS, and ORR).	Biomarker
To evaluate TTR and best percent change in the sum of the diameters for all target lesions	Not applicable	TTR, defined as the time from the date of randomization to the date of the first documentation of objective response (CR or PR), based on investigator assessment. Best percent change from baseline in the sum of the diameters for all	Efficacy

		target lesions based on investigator assessment.	

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; cfDNA = cell-free deoxyribonucleic acid; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DNAseq = deoxyribonucleic acid sequencing; DoR = duration of response; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EQ-5D-5L = EuroQol-5 dimensions-5 levels of severity; FACT-Ga = Functional Assessment of Cancer Therapy-Gastric; GC = gastric cancer; GEJ = gastro-esophageal junction; HEOR = Health Economics and Outcomes Research; HER2 = human epidermal growth factor receptor 2; HRQoL = health-related quality of life; IHC = immunohistochemistry; ISH = in situ hybridization; MAAA-1181a = released drug; MS = mass spectrometry; MUGA = multigated acquisition; NAb = neutralizing antibodies; NCI = National Cancer Institute; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PGIC = Patient Global Impression-Change; PGIS = Patient Global Impression-Severity; PGI-TT = Patient Global Impression-Treatment Tolerability; PK = pharmacokinetics; PR = partial response; PRO = patient reported outcome; PTX = paclitaxel; Ram = ramucirumab; RECIST = Response Evaluation Criteria in Solid Tumors; RNAseq = ribonucleic acid sequencing; SAE = serious adverse event; SD = stable disease; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TTR = time to response; VAS = visual analogue scale.

Study Design

This is a global, multicenter, 2-arm, randomized, open-label Phase 3 study of subjects with HER2-positive (defined as immunohistochemistry [IHC] 3+ or IHC 2+/in situ hybridization [ISH]+) gastric or GEJ adenocarcinoma (based on [American Society of Clinical Oncology (ASCO) College of American Pathologists (CAP) guidelines and confirmed by central assessment of tumor tissue]) and who have received 1 prior line of a trastuzumab-containing regimen in the advanced or metastatic setting. This study is designed to evaluate the efficacy and safety of trastuzumab deruxtecan (T-DXd) compared with ramucirumab (Ram) + paclitaxel (PTX).

Subjects will be randomized to 1 of 2 arms in a 1:1 ratio to receive either T-DXd or Ram + PTX. Randomization will be stratified by the following factors: HER2 status (IHC 3+ vs. IHC 2+/ISH+), geography (Asia [excluding mainland China] vs. Western Europe vs. mainland China/rest of the world), and time to progression on first-line therapy (<6 months vs. ≥6 months).

The study will be divided into 4 periods: Tissue Screening, Main Screening, Treatment, and Follow-up (which includes Long-Term Follow-Up [LTFU]). The Tissue Screening Period will start on the day of obtaining a signed and dated written Tissue Screening informed consent form (ICF) from the subject prior to collecting tissue. (A tumor tissue biopsy after the confirmation of the progression on the prior treatment and before randomization is mandatory. If the tumor tissue provided for HER2 status testing was collected after progression on the prior treatment, an additional tumor tissue sample is not required.) To determine eligibility, subjects must have gastric or GEJ adenocarcinoma that is confirmed for HER2-positive status as evaluated at a central laboratory.

The Screening Period will start on the day of signing the Main ICF and will comprise a maximum duration of 28 days. Re-screening is permitted one time during this phase after consultation with the Sponsor if the subject fails initial Screening. Eligible subjects will be randomized and enter the Treatment Period.

The Treatment Period starts on Day 1 of Cycle 1 and subjects will receive assigned study drug (T-DXd or Ram + PTX) until the subject meets 1 of the discontinuation criteria. The first dose at Cycle 1 Day 1 should occur within 3 days after the date the subject is randomized. No crossover to the other treatment arm is allowed. Subjects will undergo radiographic assessment of the disease status every 6 weeks (±1 week) from randomization until disease progression.

The Follow-up Period will start upon permanent discontinuation of T-DXd or Ram + PTX at any time. Subjects will be followed 40 days (+7 days) after the last study treatment administration or before starting new anticancer treatment, whichever comes first. After completion of the 40-day (+7 days) safety follow-up visit, subsequent LTFU visits should occur at the following frequencies to assess survival and collect information on anti-cancer treatments: every 2 months (±2 weeks) until death, withdrawal of consent, or loss of follow-up, whichever comes first.

The **primary completion date** is the date when the pre-specified number of 339 OS events have been documented in the clinical database. This date is used as the cut-off date for the analysis of the primary efficacy endpoints of the study. All subjects still on treatment and continuing to derive benefit from study drug at the primary completion date will continue to follow the study's Schedule of Events until the **overall End of Study (EOS)** is reached or an alternative option for continuing study drug is available (eg, rollover study).

Overall EOS will occur when:

- All subjects have discontinued treatment and discontinued long-term survival follow-up or have died.
- An alternative study becomes available for subjects continuing to derive benefit from treatment with T-DXd, where the study drug is offered to these subjects.
- The study is discontinued by the Sponsor for other reasons (administrative, program-level, or class related).

The subject's EOS is the date of their last study visit/contact. For clinical studies conducted in the European Union (EU) and under the EU Clinical Trial Registry, if the EOS in the last EU Member State occurs before the EOS in the last global country, the clinical study results summary will be submitted within 12 months (6 months for pediatrics) after the EOS in the final global country (ie, in such a situation, the submission will not be based on the EOS in the last EU Member State). Holding the submission until the study is complete globally is justified, because in situations where the clinical study is still ongoing in other countries and data from these other countries are not available, the full statistical analysis planned for the study is not feasible, and incomplete results are uninterpretable.

Study Duration

The Tissue Screening Period will start on the day of obtaining a signed and dated written Tissue Screening ICF from the subject prior to collecting tissue. The Screening Period will start on the day of signing the Main ICF and will have a maximum duration of 28 days.

The study start date is the date when the first subject has signed the Main ICF. A subject is eligible to be enrolled into the interventional phase of the study when the investigator or designee has obtained written informed consent (ie, Main ICF), has confirmed all eligibility criteria have been met by the subject, and all screening procedures have been completed. Anticipated total duration of the study is approximately 36 months. The study will continue until the primary endpoint is achieved. The EOS is defined as the date of completion of the last visit or procedure shown in the Schedule of Events in the study globally.

Eligibility Criteria

Inclusion Criteria:

1. Sign and date the Tissue Screening and Main ICFs, prior to the start of any study-specific qualification procedures.
2. Adults (according to local regulation) and able to provide informed consent for study participation.
3. Pathologically documented gastric and GEJ adenocarcinoma that has been previously treated in the metastatic setting (unresectable, locally advanced, or metastatic disease).

4. Progression on or after first-line therapy with a trastuzumab or approved trastuzumab biosimilar-containing regimen.

   Note: Prior neoadjuvant or adjuvant therapy with a trastuzumab-containing regimen can be counted as a line of therapy if the subject progressed on or within 6 months of completing neoadjuvant or adjuvant therapy. Prior neoadjuvant or adjuvant therapy that does not include trastuzumab will not be counted as a line of therapy, regardless of the progression status of the subject.
5. Is willing and able to provide an adequate tumor sample for tissue screening to confirm HER2 status by Central Laboratory.
6. Centrally confirmed HER2-positive (IHC 3+ or IHC 2+ and evidence of HER2 amplification by ISH) as classified by ASCO-CAP on a tumor biopsy obtained after progression on or after a first-line trastuzumab or approved trastuzumab biosimilar-containing regimen.
7. Eastern Cooperative Oncology Group performance status of 0 or 1 at Screening.
8. Adequate laboratory parameters as evidenced by all the following blood counts within 14 days of randomization:

Parameter	**Laboratory value**
Adequate bone marrow function	
Platelet count	≥100,000 cells/μL (Platelet transfusion is not allowed within 7 days prior to screening assessment.)
Hemoglobin	≥8.0 g/dL (Red blood cell transfusion is not allowed within 7 days prior to screening assessment.)
Absolute neutrophil count (ANC)	≥1500/mm^3 (Granulocyte colony-stimulating factor administration is not allowed within 7 days prior to screening assessment.)
Adequate renal function	
Serum creatinine	Creatinine clearance ≥30 mL/min as calculated using the Cockcroft-Gault equation
Adequate hepatic function	
Alanine aminotransferase (ALT), Aspartate aminotransferase (AST)	≤5× upper limit of normal (ULN)
Total bilirubin	≤1.5× ULN if no liver metastases or <3× ULN in the presence of documented Gilbert syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline Note: biliary drainage is allowed for biliary obstruction
Serum albumin	≥2.5 g/dL
Adequate blood clotting function	

International normalized ratio (INR)/prothrombin time (PT) and either partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT)	≤1.5× ULN

9. Has adequate treatment washout period before randomization/enrollment, defined as

Treatment	**Washout Period**
Major surgery	≥4 weeks
Radiation therapy, including palliative stereotactic radiation to chest	≥4 weeks
Palliative stereotactic radiation therapy to other anatomic areas	≥2 weeks
Anti-cancer (immunotherapy [non-antibody-based therapy]), retinoid therapy	≥3 weeks
Targeted agents and small molecules	≥2 weeks or 5 half-lives, whichever is longer
Nitrosoureas or mitomycin C	≥6 weeks
Antibody-based anti-cancer therapy	≥4 weeks
Chloroquine/hydroxychloroquine	>14 days
Cell-free and concentrated ascites reinfusion therapy, peritoneal shunt or drainage of pleural effusion, ascites or pericardial effusion	≥2 weeks prior to the screening assessment

10. Left ventricular ejection fraction ≥50% within 28 days before randomization per echocardiogram or multigated acquisition scan.
11. Recovered from the effects of any prior surgery or radiotherapy.
12. Males and females of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 7 months for female subjects and 4 months for male subjects after the last dose of study drug. For subjects receiving Ram + PTX, sites should follow the locally approved label.
    - If the subject is a female of childbearing potential, she must have a negative serum or urine pregnancy test at Screening before the first dose of study drug and must be willing to use highly effective birth control method upon randomization, during the Treatment Period, and for 7 months following the last dose of study drug. A woman is considered of childbearing potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months) unless permanently sterile (undergone a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).
    - If male, the subject must be surgically sterile or willing to use highly effective birth control method upon randomization, during the Treatment Period, and for 4 months following the last dose of study drug.
13. Male subjects must not freeze or donate sperm starting from randomization and throughout the study period, and at least 4 months after the final study drug administration. Preservation of sperm

should be considered prior to randomization in this study. For Ram + PTX, sites should follow local label or institutional guidelines.

14. Female subjects must not donate, or retrieve for their own use, ova from the time of randomization and throughout the study Treatment Period, and for at least 7 months after the final study drug administration. Preservation of ova may be considered prior to randomization in this study. For Ram + PTX, sites should follow local label or institutional guidelines.
15. Is willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.

Exclusion Criteria:

Subjects who meet any of the following criteria will be disqualified from entering the study:

1. Use of anticancer therapy after trastuzumab-containing treatment.
2. Medical history of myocardial infarction (MI) within 6 months before randomization/enrollment, symptomatic congestive heart failure (New York Heart Association Class II to IV). Subjects with troponin levels above ULN at screening (as defined by the manufacturer), and without any MI related symptoms should have a cardiologic consultation before enrollment to rule out MI.
3. Has a QT interval corrected by Fridericia's formula (QTcF) prolongation to >470 msec (female subjects) or >450 msec (male subjects) based on average of the Screening triplicate12-lead electrocardiogram.
4. Criterion removed.
5. Has a history of (non-infectious) interstitial lung disease (ILD/pneumonitis) that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at Screening.
6. Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disease (eg, pulmonary emboli within the previous 3 months of the study randomization, severe asthma, severe chronic obstructive pulmonary disease, restrictive lung disease, pleural effusion, etc.).
7. Any autoimmune, connective tissue or inflammatory disorders (eg, rheumatoid arthritis, Sjögren syndrome, sarcoidosis, etc.) where there is documented (or a suspicion of) pulmonary involvement at the time of Screening. Full details of the disorder should be recorded in the electronic case report form for patients who are included in the study.
8. Prior complete pneumonectomy.
9. Spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms.
    a. Subjects with clinically inactive brain metastases may be included in the study.
    b. Subjects with brain metastases who were treated and are no longer symptomatic, and subjects who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy (WBRT) and randomization/study enrollment.
10. Has multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, other solid tumors curatively treated.
11. History of severe hypersensitivity reactions to either the T-DXd or inactive ingredients in T-DXd.
12. History of severe hypersensitivity reactions to other monoclonal antibodies, including ramucirumab or any of its excipients.

13. Known allergy or hypersensitivity to paclitaxel or any components used in the paclitaxel preparation or other contraindication for taxane therapy.
14. Current uncontrolled infection requiring antibiotics, antivirals, or antifungals or an unexplained fever >38.0°C during Screening visits or on the first scheduled day of dosing (at the discretion of the investigator, subjects with tumor fever may be enrolled), which in the investigator's opinion might compromise the subject's participation in the study or affect the study outcome
15. Substance abuse or any other medical conditions such as clinically significant cardiac or pulmonary diseases or psychological conditions, that may, in the opinion of the investigator, interfere with the subject's participation in the clinical study or evaluation of the clinical study results
16. Social, familial, or geographical factors that would interfere with study participation or follow-up
17. Known human immunodeficiency virus (HIV) infection or active hepatitis B or C infection, such as those with serologic evidence of viral infection within 28 days of Cycle 1 Day 1. Subjects with past or resolved hepatitis B virus infection are eligible if hepatitis B virus surface antigen(-) and anti- hepatitis B core(+). Subjects positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Subjects should be tested for HIV prior to randomization/enrollment if required by local regulations or institutional review board (IRB)/independent ethics committee (IEC).
18. Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤1 or baseline. Note: Subjects may be enrolled with chronic, stable, Grade 2 toxicities (defined as not worsening to >Grade 2 for at least 3 months prior to randomization and managed with standard-of-care treatment) that the investigator deems related to previous anticancer therapy, such as the following:
    - Chemotherapy-induced neuropathy
    - Fatigue
    - Residual toxicities from prior immuno-oncology treatment: Grade 1 or Grade 2 endocrinopathies, which may include the following:
        - Hypothyroidism/hyperthyroidism
        - Type I diabetes
        - Hyperglycemia
        - Adrenal insufficiency
        - Adrenalitis
        - Skin hypopigmentation (vitiligo)
19. Prior treatment with an antibody-drug conjugate (ADC) consisting of an exatecan derivative that is a topoisomerase I inhibitor
20. Pregnant, breastfeeding, or planning to become pregnant. In addition, for subjects enrolled in the study, breastfeeding should not commence until at least 7 months after the last dose of study drug.
21. Subjects who, in the opinion of the investigator, have symptoms or signs suggestive of clinically unacceptable deterioration of the primary disease at the time of Screening or otherwise considered inappropriate for the study by the investigator
22. Clinically significant gastrointestinal disorder (eg, including hepatic disorders, bleeding, inflammation, occlusion, ileus, diarrhea Grade >1, jaundice, intestinal paralysis, malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, or partial bowel obstruction) in the

opinion of investigator
Investigational Medicinal Product, Dose, and Mode of Administration
➢ T-DXd drug product (T-DXd for injection 100 mg) will be supplied as Lyo-DP. Lyo-DP is a sterile lyophilized powder provided in an amber glass vial for intravenous (IV) infusion. Each glass vial contains 100 mg of T-DXd. Each vial is designed for single use and is not to be used to treat more than 1 subject. Lyo-DP is reconstituted with 5 mL of water for injection to provide a solution with a concentration of 20 mg/mL of T-DXd in a buffer containing L-histidine, L-histidine hydrochloride monohydrate, sucrose, and polysorbate 80. The starting dose of 6.4 mg/kg is based on body weight taken at the Screening visit (baseline). If during the course of treatment the subject's weight changes by ±10% of the baseline weight, the subject's dose will be recalculated based on the subject's updated weight. For weight changes <10%, dose-calculation adjustments should follow local guidelines. ➢ Ramucirumab and paclitaxel will be supplied by the clinical site unless prohibited by country or institutional regulations, in which case they will be supplied by the Sponsor: – Ramucirumab 8 mg/kg IV on Days 1 and 15 of each 28-day cycle – Paclitaxel 80 mg/m^2 IV on Days 1, 8, and 15 of each 28-day cycle Refer to the package insert or appropriate local labeling for a detailed description of administration.
Active Ingredient(s)/INN
T-DXd (also known as trastuzumab deruxtecan) is a novel HER2-targeting antibody-drug conjugate (ADC) composed of an antibody component, MAAL-9001, covalently conjugated to a drug component, MAAA-1181a, through an enzyme-cleavable maleimide tetrapeptide linker, MAAA-1162a. The antibody component, MAAL-9001, is a recombinant humanized anti-human HER2 immunoglobulin G1 monoclonal antibody with the same amino acid sequence as trastuzumab. The drug component, MAAA-1181a, an exatecan derivative, is a novel topoisomerase I inhibitor permeable to the cell membrane and more potent than SN-38, the active metabolite of irinotecan. T-DXd has a high drug-to-antibody ratio (approximately 8) when compared with trastuzumab emtansine.
Planned Sample Size
The study is planned with a group sequential design, which includes an interim assessment for OS using the Lan-DeMets alpha-spending function with an O'Brien-Fleming stopping boundary. Assuming a median OS of 10.8 months in the Ram + PTX arm based on the results of the RAINBOW study, it is hypothesized that treatment with T-DXd will result in a hazard ratio (HR) of 0.7, a 30% reduction in the hazard rate of OS that would correspond to a 43% improvement in median OS from 10.8 months in the Ram + PTX arm to 15.4 months in the T-DXd arm under the exponential model assumption. A total of approximately 490 subjects will be randomized in a 1:1 ratio (245 subjects to T-DXd and 245 subjects to Ram + PTX). An interim analysis that allows the study to declare superiority of the primary efficacy endpoint is planned after completion of enrollment and at least 237 (70%) of the targeted OS events are documented. The final OS analysis will occur after approximately 339 OS events have been documented, if superiority is not demonstrated at the interim analysis. With 339 OS events, the study will have approximately 90% power to detect an HR of 0.70 in OS at an overall 2-sided significance level of 0.05 to reject the null hypothesis (HR =1) using a log-rank test and a 2-look group sequential design with Lan-DeMets alpha-spending function with O'Brien-Fleming efficacy boundary. East version 6.5 was used for sample size/power computation. The primary efficacy analysis will be based on the data from the Full Analysis Set (FAS).

The primary endpoint, OS is defined as the time from the date of randomization to the date of death due to any cause. OS will be calculated on the FAS.

An interim and a final analysis for OS are planned in this study. The overall two-sided alpha is to be controlled at 0.05 for the interim OS analysis and final OS analysis using the Lan-DeMets alpha-spending function with an O'Brien-Fleming boundary. The primary efficacy analysis will be the comparison of the distribution of OS between the 2 treatment groups using a stratified log-rank test, with strata being the same as the randomization stratification factors from the Interactive Response Technology (IRT) system, at an overall two-sided significance level of 0.05. The survival distribution of OS will be estimated using the Kaplan-Meier (K-M) method for each treatment group and the results will be presented graphically by treatment group.

The median OS time and the two-sided 95% confidence intervals (CIs) using Brookmeyer and Crowley method will be provided for each treatment group. In addition, K-M estimates of OS rates at fixed time points (eg, 3, 6, 9, 12 months) and the two-sided 95% CIs will be provided for each treatment group.

PFS, is defined as the interval from randomization to the date of objective disease progression or death due to any cause, based on the investigator assessment review of tumor scan data using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. PFS analysis would be similar to OS analysis. The treatment effect HR of PFS and its two-sided 95% CI will be estimated using stratified Cox proportional hazards regression model with the same stratification factors as the randomization stratification factors taken from IRT.

ORR, based on investigator assessment using RECIST version 1.1.

Cochran-Mantel-Haenszel tests stratified by the randomization stratification factors will be used to compare ORR (based on investigator assessment) between the treatment groups. ORR (based on investigator assessment) will be summarized by treatment group along with their 2-sided 95% CIs using Clopper-Pearson methods.

Duration of response (based on investigator assessment) will be summarized with median event time and its 2-sided 95% CIs using Brookmeyer and Crowley method for each treatment group. In addition, K-M estimates at each fixed time point (eg, 3, 6, 9, 12 months) along with their 2-sided 95% CIs will be provided for each treatment group.

PROTOCOL SYNOPSIS STUDY DESTINY-Lung04

Protocol Title: An Open-label, Randomized, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Trastuzumab Deruxtecan as First-line Treatment of Unresectable, Locally Advanced, or Metastatic NSCLC Harboring HER2 Exon 19 or 20 Mutations (DESTINY-Lung04).

Short Title: Phase 3 study of the Efficacy and Safety of Trastuzumab Deruxtecan as First-line Treatment for NSCLC with HER2 Exon 19 or Exon 20 Mutations.

Rationale:

Lung cancer remains the leading cause of cancer-related mortality worldwide accounting for approximately 18% of all cancer deaths globally in 2018 (Bray et al 2018). The standard of care treatment for patients with metastatic NSCLC is currently based on molecular characterization and matched targeted therapy for specific driver-mutated subsets (Heigener et al 2019). For metastatic NSCLC patients without EGFR or ALK genomic tumor aberrations, platinum doublet chemotherapy with anti-PD-1 and/or PD-L1 targeting immunotherapy (including pembrolizumab) is the current SoC based on results from KEYNOTE189 (Gandhi et al 2018).

There are several driver mutations for which targeted therapies have been approved, including EGFR, MET, ALK fusions, BRAF, MEK, ROS1, NTRK, RET fusions, EGFR exon 20 insertion, and KRAS G12C (Mazieres et al 2013, NCCN 2021). Although HER2 alterations have been widely studied as a predictive biomarker in breast cancer, with multiple approved therapeutic options, there are no approved therapies (targeted or not) to date for HER2 alterations in metastatic NSCLC.

HER2 mutations have been identified in approximately 2% to 4% of NSCLC (Arcila et al 2012, Mazieres et al 2013, Tomizawa et al 2011, Wei et al 2020). The most common HER2 mutations are exon 20 insertions found in the tyrosine kinase domain; their frequency, as a group, has been reported to range from 35% to 70% of all HER2 mutations in NSCLC (Ou et al 2019, Singh et al 2020, Wei et al 2020). More rarely, HER2 mutations are observed in the extracellular domain (eg, S310F, S310Y in exon 8), outside of exon 20 in the tyrosine kinase domain (eg, L755P in exon 19), and in the transmembrane domain, representing approximately 25%, 16%, and 10% of HER2 mutations, respectively (Robichaux et al 2019).

In general, HER2-mutated NSCLC is more commonly associated with female patients, non-smokers, and adenocarcinoma histology (Arcila et al 2012). HER2 mutations and other driver mutations are reported to be mutually exclusive (Mazieres et al 2013, Pillai et al 2017), although rare cases of non-tyrosine kinase domain HER2 mutations have been observed with concurrent EGFR mutations (Ou et al 2019, Wei et al 2020). The TP53 mutation has been described as a frequent co-mutation and other mutations including KEAP1, STK11, and KRAS have also been observed (Wei et al 2020). HER2 co-amplification has been described in approximately 5% to 15% of HER2-mutated NSCLC (Ou et al 2019, Singh et al 2020).

There are currently no approved therapies (targeted or not) for patients with HER2-mutated NSCLC, and these patients receive the same SoC treatment as NSCLC patients without actionable molecular markers, typically platinum doublet chemotherapy with anti-PD-L1 targeting immunotherapy. HER2 activating mutations have been included in guidelines as an emerging potentially targetable biomarker in NSCLC (NCCN 2021). Available data suggest that

therapies may result in poorer clinical outcomes in patients with HER2-mutated NSCLC compared to NSCLC patients without driver mutation (see Section 2.2.3).

HER2 ADCs are recognized as a promising therapeutic option (NCCN 2021). Activity of HER2-directed ADCs in HER2 mutated tumors has been demonstrated in cell line experiments, and a proposed mechanism of action for targeted apoptotic cell death is increased receptor and ADC internalization for HER2-mutated tumors compared to wild-type tumors.

Furthermore, studies have shown that radionuclide-tagged trastuzumab accumulates in HER2-mutated and amplified lung cancer patients on PET imaging, suggesting that HER2-mutated tumors selectively accumulate HER2 targeting agents (Li et al 2020).

In a Phase 2 clinical study, T-DM1 showed activity in patients with NSCLC and HER2 mutations. Trastuzumab emtansine demonstrated an ORR of 50% (14/28, 95% CI: 31, 69) amongst patients with HER2 mutation and 50% (5/10, 95% CI: 19, 81) amongst patients with concurrent HER2 mutation and amplification. Amongst the HER2 mutation or amplification population, ORR was 51% (25/49, 95% CI: 36, 66), median duration of response was 4.4 months (95% CI not reported), and median PFS was 5.0 months (95% CI: 3.5, 5.9) (Li et al 2020).

Study DS8201 A U204 (DESTINY Lung01; [NCT03505710]; hereinafter referred to as Study U204) (Smit et al 2020) provided encouraging preliminary clinical efficacy data for T-DXd in the setting of heavily pre-treated NSCLC patients with HER2 mutations, and T-DXd response durability appears improved over that of T-DM1 from non-clinical and clinical data. When taken together, the non-clinical and clinical findings suggest that T-DXd may have clinically meaningful benefit over SoC therapy in treatment-naïve patients with

HER2-mutated NSCLC and warrant further investigation in this population.

Considering there is no targeted therapy currently approved for HER2-mutated NSCLC and recognizing this unmet medical need and based on T-DXd non-clinical and clinical data, DESTINY-Lung04 is proposed as an opportunity to bring a novel HER2-targeted therapy to this patient population.

Objectives and Endpoints

Objectives	Estimand description/Endpoints
Primary	
To assess the efficacy of T-DXd relative to platinum with pemetrexed plus pembrolizumab by assessment of PFS by BICR in participants with unresectable, locally advanced, or metastatic NSCLC harboring HER2 exon 19 or 20 mutations. Note: The study population will not be repeated in each row below but is understood to apply.	PFS is defined as time from randomization until progression per RECIST 1.1 as assessed by BICR, or death due to any cause. The analysis will include all randomized participants, regardless of whether the participant withdraws from randomized therapy or receives another anticancer therapy. The measure of interest is the HR of PFS.

Objectives	Estimand description/Endpoints
Secondary	
To assess the efficacy of T-DXd relative to platinum with pemetrexed plus pembrolizumab by assessment of OS.	OS is defined as time from randomization until the date of death due to any cause. The comparison will include all randomized participants, regardless of whether the participant withdraws from randomized therapy or receives another anticancer therapy. The measure of interest is the HR of OS.
To further assess the efficacy of T-DXd relative to platinum with pemetrexed plus pembrolizumab in terms of PFS by investigator assessment, ORR, DoR, PFS2, and landmark analysis of PFS12 and OS24.	PFS by investigator assessment is defined as time from randomization until progression per RECIST 1.1 as assessed by the investigator, or death due to any cause. The analysis will include all randomized participants, regardless of whether the participant withdraws from randomized therapy or receives another anticancer therapy. The measure of interest is the HR of PFS.
	ORR as assessed by BICR and investigator according to RECIST 1.1. ORR is defined as the proportion of participants who have a CR or PR. The analysis will include all randomized participants. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the participant withdraws from randomized therapy. Participants who go off treatment without a response or progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR. The measure of interest is the odds ratio for ORR.
	DoR as assessed by BICR and investigator assessment according to RECIST 1.1. DoR is defined as the time from the date of first documented response until date of documented progression. The measure of interest is the median of DoR.

Objectives	Estimand description/Endpoints
	PFS2 will be identified using assessments conducted per local standard clinical practice. PFS2 is defined as the time from randomization until second progression on next-line of treatment as assessed by investigator at the local site, or death due to any cause. The comparison will include all randomized participants as randomized regardless of whether the participant withdraws from subsequent therapy and regardless of missed visits. The measure of interest is the HR of PFS2.
	PFS12 is the landmark of PFS which is defined as proportion of participants alive and progression-free at 12 months, as assessed by BICR and investigator.
	OS24 is the landmark of OS which is defined as proportion of participants alive at 24 months.
To assess the efficacy of T-DXd relative to platinum with pemetrexed plus pembrolizumab by assessment of CNS-PFS (per RECIST 1.1).	CNS-PFS is defined as time from randomization until CNS progression per RECIST 1.1 as assessed by BICR or death due to any cause in the absence of CNS progression. The analysis will include all randomized participants, regardless of whether the participant withdraws from randomized therapy or receives another anticancer therapy. The measure of interest is the HR of CNS-PFS (per RECIST 1.1).
To assess the safety and tolerability of T-DXd as compared to platinum with pemetrexed plus pembrolizumab.	Assessed by the occurrence of AEs, SAEs, and changes from baseline in laboratory parameters, vital signs, ECG, and ECHO/MUGA scan results. The safety analysis includes all participants who received at least one dose of study intervention.
To assess the PK of T-DXd, total anti-HER2 antibody and DXd in serum.	Serum concentration of T-DXd, total anti-HER2 antibody and DXd. PK analysis includes all participants who received at least one dose of T-DXd and have at least one post-dose evaluable PK data point for T-DXd.
To investigate the immunogenicity of T-DXd.	Presence of ADAs for T-DXd. ADA analysis includes all participants who received at least one dose of T-DXd and have a non-missing baseline ADA T-DXd result and at least one post-baseline ADA T-DXd result.
To assess the benefit of T-DXd relative to platinum with pemetrexed plus pembrolizumab with patient-reported pulmonary symptoms associated with NSCLC.	Time to sustained deterioration in pulmonary symptoms (cough, dyspnea, chest pain) while on treatment using the NSCLC-SAQ. This analysis will include all participants, as randomized. Sustained worsening is defined as a meaningful worsening at 2

Objectives	Estimand description/Endpoints
	or more consecutive post-baseline assessments.
To describe patient-reported tolerability of T-DXd as compared to platinum with pemetrexed plus pembrolizumab.	Patient-reported tolerability will be described among participants, as treated, using the following outcomes: Symptomatic AEs: Descriptive summary of the proportion of participants reporting symptomatic AEs while on treatment, as assessed by the PRO-CTCAE and items from the EORTC Item Library. Overall side-effect bother: Descriptive summary of the proportion of participants reporting overall side-effect bother on the PGI-TT while on treatment. Physical Function: The proportion of participants with maintained or improved physical function while on treatment, based on the EORTC-QLQ-C30 physical functioning scale.

ADA, anti-drug antibody; AE, adverse event; BICR, blinded independent central review; CNS, central nervous system; CNS-PFS, progression-free survival in central nervous system; DoR, duration of response; DXd, deruxtecan; ECG, electrocardiogram; ECHO, echocardiogram; EOTRC, European Organisation for Research and Treatment of Cancer; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; MUGA, multiple gated acquisition scanning; NSCLC, non-small cell lung cancer; NSCLC-SAQ, Non-small Cell Lung Cancer Symptom Assessment Questionnaire; ORR, objective response rate; OS, overall survival; OS24, proportion of participants alive at 24 months; PFS, progression-free survival; PFS2; time to second progression or death; PFS12; proportion of participants alive and progression-free at 12 months; PGI-TT, Patient's Global Impression of Treatment Tolerability; PK, pharmacokinetic(s); PRO-CTCAE, Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; RECIST 1.1, Response Evaluation Criteria in Solid Tumors Version 1.1; SAE, serious adverse event; SAF safety analysis set; T-DXd, trastuzumab deruxtecan.

For exploratory objectives and outcome measures, see Section 3 of the CSP.

Overall Design

Disclosure Statement: This is a Phase 3, randomized, open-label, 2-arm, multicenter, international study assessing the efficacy and safety of T-DXd compared with SoC (platinum-based chemotherapy with pemetrexed in combination with pembrolizumab) in patients with NSCLC harboring HER2 exon 19 or 20 mutations.

Patient Population:

The target population of interest in this study is participants with unresectable, locally advanced, or metastatic NSCLC with HER2 exon 19 or 20 mutations. Participants must be ≥ 18 years of age, have at least one (RECIST 1.1) measurable lesion, and have a WHO/ECOG PS of 0 or 1 at enrollment. Participants must be treatment-naïve for palliative intent systemic therapy for locally advanced or metastatic disease.

HER2 mutation for eligibility will be based on either an existing prior (qualifying) HER2 mutation result or by central assessment. Retrospective central confirmation will be performed for those enrolled based on existing local HER2 mutation(s) results. Note: In addition,

mandatory archival (preferred; or newly collected) biopsy tissue samples are required for central testing.

Number of Participants:

Approximately 5500 participants with non-squamous NSCLC will be screened in order to randomize approximately 264 participants from around 150 sites across 21 countries globally.

Note: Participants will be enrolled into the study after signing either the pre-screening ICF and/or the main ICF. Participants who fail to meet the eligibility criteria (including pre-screening assessment) will be termed “screen failures”.

Intervention Groups and Duration

Participants will be randomized in a 1:1 ratio to one of the following interventions: T-DXd (Arm 1) or platinum (cisplatin or carboplatin; up to 4 cycles) with pemetrexed plus pembrolizumab Q3W (Arm 2). Randomization will be stratified by smoking history and presence of brain metastasis at baseline.

- Participants in Arm 1 (T-DXd) will receive 5.4 mg/kg of T-DXd as an IV infusion Q3W until RECIST 1.1-defined progression by investigator, until unacceptable toxicity, withdrawal of consent, or other discontinuation criteria. or other discontinuation criteria (with the exception of CNS-PD; see note below).

  Participants in Arm 2 (active comparator arm) will receive platinum chemotherapy (cisplatin or carboplatin) with pemetrexed and pembrolizumab Q3W. Note: Investigator choice of cisplatin or carboplatin (switch from cisplatin to carboplatin during the treatment period is permitted). Platinum chemotherapy will be administered for up to 4 cycles. Pembrolizumab and pemetrexed will be administered until RECIST 1.1-defined progression by investigator, until unacceptable toxicity, withdrawal of consent, or other discontinuation criteria (with the exception of CNS-PD; see note below).

- Note: In both arms, participants with objective radiological CNS-PD (based on RECIST 1.1), who in the investigator’s opinion, continue to receive benefit from their assigned treatment and meet the criteria for treatment in the setting of CNS-PD may continue to receive therapy on trial for as long as they are gaining clinical benefit and are without any discontinuation criteria, until one of the criteria Section 6.1.1.2 is met.

Tumor evaluation scans will be performed at screening (as baseline) with follow-ups at Week 6 (± 1)-week intervals from the date of randomization for 54 weeks, and then Q9W ± 1 week [starting at Week 63] until RECIST 1.1-defined radiological PD per investigator assessment (plus one additional follow-up scan [4 weeks later], if clinically feasible). For the brain, images from MRI (preferred, unless contraindicated) will be collected for all participants at baseline and EoT, and for participants with brain metastases at regular intervals during study intervention. In the case of CNS-PD, participants continuing to receive study intervention should follow the on-treatment data collection schedule, including RECIST 1.1 tumor assessments, until a second progression (CNS or body; plus one additional follow-up scan [4 weeks later], if clinically feasible) see Section 6.1.1.2).

Follow-up of participants post discontinuation of study intervention:

After study intervention discontinuation, all participants will undergo an EoT visit (within 7 days of discontinuation) and will be followed-up for safety assessments 40 (+ 7) days after their last dose of study intervention (ie, the safety follow-up visit).

Participants who have discontinued study intervention in the absence of RECIST 1.1-defined PD confirmed by investigator will be followed up with tumor assessments according to Table 1 until RECIST 1.1-defined radiological PD per investigator assessment (including one additional follow-up scan, if clinically feasible) or death regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

All participants will be followed up after intervention discontinuation every 3 months (± 14 days) from the date of the safety follow-up until death, withdrawal of consent, or the end of the study, as per Table 1.

In addition, participants will be followed up for PFS2, defined as time from randomization to second progression (the earliest of the progression event subsequent to first subsequent therapy) or death. The occurrence of PFS2 will be identified using assessments conducted per local standard clinical practice. Following discontinuation of study intervention due to disease progression, as determined by the investigator according to RECIST 1.1 assessment, participants who started on subsequent cancer therapy post-progression will continue to be followed at the 40-day (+ 7 days) follow-up visit, and every 3 months (± 14 days) thereafter for documentation of progression on subsequent anticancer therapy. Participants who continue study intervention following CNS-PD progression will be censored at the time of that progression in the analysis of PFS2, since they will not initiate subsequent cancer therapy.

See Sections 6.7 and 8 for a description of assessments following the PFS and OS FA DCOs**.**

Independent Data Monitoring Committee:

An IDMC comprised of independent experts will be convened to review unblinded safety data and make recommendations to continue, amend, or stop the study based on safety findings.

For the PFS IA, the IDMC will review unblinded efficacy data and inform AstraZeneca whether the interim boundaries specified in Section 9.6 are met. Full details of the IDMC procedures, processes, and interim analyses can be found in the IDMC Charter. Ad hoc IDMC meetings may also be scheduled as needed.

Statistical methods:

The primary endpoint of this study is PFS by BICR according to RECIST 1.1 in the FAS (ITT population). The key secondary efficacy endpoint is OS in the FAS.

PFS by BICR will be tested at one IA and one FA as described below:

- The PFS IA will be performed when PFS reaches approximately 58% maturity or approximately 80% information fraction (152 events), which is estimated to occur 31 months after the first participant is randomized (5 months after randomization is completed), assuming a non-uniform accrual of participants within a duration of 26 months.

- The PFS FA will be performed when PFS reaches approximately 72% maturity (189 events). This is estimated to occur 38 months after the first participant is randomized (12 months after randomization is completed).

OS in the FAS population will be tested at 2 IAs and one FA, as well as an administrative OS IA (Williams et al 1993) as described below:

- An administrative OS IA will be conducted at the time of the PFS IA. There will be no formal hypothesis testing.
- The first OS IA is planned to be performed at the time of the final PFS analysis. It is expected that approximately 114 OS events (43% maturity or 62% information fraction) will have been observed. If the PFS FA is not performed, the first OS IA will occur when approximately 114 OS events have occurred.
- The second OS IA will occur when approximately 154 OS events have been observed (58% maturity or 84% information fraction). This is anticipated to occur approximately 50 months after the first participant is randomized (24 months after randomization is completed).
- The final OS analysis will be performed when approximately 184 OS events have been observed (70% maturity), which is expected to occur approximately 63 months after the first participant is randomized (37 months after randomization is completed).

To strongly control the family wise error rate at 5% in terms of the primary endpoint and the key secondary endpoint, a fixed sequence multiple testing procedure will be employed. PFS will be tested first and 5% alpha will be distributed between the IA and FA using the Haybittle-Peto spending function (Haybittle 1971, Peto et al 1976), ie, a 2-sided alpha of 0.006 will be spent at PFS IA. Overall survival will be formally tested only if the PFS null hypothesis is rejected. The administrative OS IA will be performed at the time of PFS IA with an alpha-spending of 0.001 and there is no formal hypothesis testing planned. For the testing of the OS hypothesis, the 4.9% alpha will be distributed between the 2 IAs and FA using the Lan DeMets spending function that approximates the O'Brien-Fleming alpha-spending approach (Lan and DeMets 1983).

Under the O'Brien-Fleming alpha-spending approach procedure, the significance levels are determined by the information fraction available at the time of analysis (ie, exact number events observed), giving greater weight to analyses performed at the end of the study than those performed earlier.

For the primary endpoint, PFS per BICR will be compared between T-DXd and SoC (platinum with pemetrexed plus pembrolizumab) Q3W, using a stratified log-rank test with treatment as fixed effect adjusting for stratification, ie, baseline brain metastases (yes vs no) and smoking status (ever smoker vs never smoker). The stratification variables in the statistical modeling will be based on the values entered in IRT. If there are insufficient events per stratum, the strata will be pooled following a pooling strategy that will be prespecified. The HR and its corresponding CI will be estimated from a stratified Cox proportional hazards model with strata being the same as the stratification variables from IRT.

Analysis of OS will be performed to compare T-DXd vs SoC in the FAS using the same methodology as for the PFS primary endpoint.

Safety data will be summarized descriptively and will not be formally analyzed unless otherwise specified.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Prior to the launch of trastuzumab deruxtecan in each member state, the Marketing Authorisation Holder (MAH) must agree on the content and format of the educational programme (Healthcare Professional [HCP] Guide, Patient Card for ILD/pneumonitis and HCP Guide for product confusion-related medication errors), including communication media, distribution modalities, and other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at:

I) ensuring early recognition of interstitial lung disease (ILD)/pneumonitis, to allow prompt appropriate treatment and to mitigate worsening of the condition

II) improving HCP awareness of the potential risk for product confusion-related medication errors due to the availability of multiple trastuzumab-containing products and trastuzumab emtansine

The MAH will ensure that each member state where trastuzumab deruxtecan is marketed, all HCPs and patients who are expected to administer/be administered trastuzumab deruxtecan are provided with the educational material.

I) **Healthcare Professional (HCP) Guide for ILD/pneumonitis**

The HCP Guide will contain the following key elements:

- Summary of important findings of trastuzumab deruxtecan-induced ILD/pneumonitis (eg, frequency, grade, time to onset) observed in the clinical trial setting
- Description of the appropriate monitoring and evaluation of ILD/pneumonitis in patients receiving trastuzumab deruxtecan
- Detailed description of management of ILD/pneumonitis in patients treated with trastuzumab deruxtecan including guidance on drug interruption, reduction and treatment discontinuation for ILD/pneumonitis
- Reminder to HCP that they should repeat the information about signs and symptoms of ILD/pneumonitis at each patient visit, including when the patient should seek attention from an HCP (eg, the symptoms to watch for; the importance to adhere to scheduled appointments)
- Reminder to HCP to provide the patient with the Patient Card (PC), including advice that the PC should be kept with the patient at all times

Patient Card

The Patient Card will contain the following key elements:

- Description of the important risks of ILD/pneumonitis associated with the use of trastuzumab deruxtecan
- Description of key signs and symptoms of ILD/pneumonitis and guidance on when to seek attention from an HCP
- Contact details of the trastuzumab deruxtecan prescriber

- Cross-reference to Patient Information Leaflet

II) **Healthcare Professional Guide for prevention of medication errors**

The HCP Guide will contain the following key elements:

- Alert to HCPs about a potential risk of confusion between TRADENAME (trastuzumab deruxtecan) and other trastuzumab-containing products and the HER2-targeted ADC KADCYLA® (trastuzumab emtansine)
- Mitigation measures for prescribing errors due to similarities in active ingredient names and measures to avoid errors during prescription phase by physicians
- Comparison of commercial appearance between TRADENAME (trastuzumab deruxtecan) and other trastuzumab-containing products and the HER2-targeted ADC KADCYLA® (trastuzumab emtansine)
- Potential mitigation strategies to avoid errors during preparation phase by pharmacists
- Detailed Information about the dosage, method of administration and preparation as well as instructions to avoid medication errors during administration phase by nurses

ANNEX 7 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

List of References

1. Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer; 2020 [cited 10 Aug 2021]. Available from: https://gco.iarc.fr/today.
2. Santa-Maria CA, Nye L, Mutonga MB, et al. Management of metastatic HER2-positive breast cancer: where are we and where do we go from here? Oncology. 2016; 30(2):148-55.
3. Mitri Z, Constantine T, O'Regan R. The HER2 receptor in breast cancer: pathophysiology, clinical use, and new advances in therapy. Chemother Res Pract. 2012; 743193.
4. Taucher S, Rudas M, Mader RM, et al. Do we need HER-2/neu testing for all patients with primary breast carcinoma? Cancer Dec. 2003; 98:2547-53.
5. Cortet M, Bertaut A, Molinié F, et al. Trends in molecular subtypes of breast cancer: description of incidence rates between 2007 and 2012 from three French registries. BMC Cancer. 2018; 18(1):161.
6. DeKoven M, Bonthapally V, Jiao X, et al. Treatment pattern by hormone receptors and HER2 status in patients with metastatic breast cancer in the UK, Germany, France, Spain and Italy (EU-5): results from a physician survey. J Comp Eff Res. 2012; 1(5):453-63.
7. Gampenrieder SP, Rinnerthaler G, Tinchon C et al. Landscape of HER2-low metastatic breast cancer (MBC): results from the Austrian AGMT_MBC-Registry. Breast Cancer Res. 2021; 23:112. Available from: https://doi.org/10.1186/s13058-021-01492-x.
8. Zhang H, Katerji H, Turner BM et al. HER2-low breast cancers: incidence, HER2 staining patterns, clinicopathologic features, MammaPrint and BluePrint genomic profiles. Mod Pathol. 2022. Available from: https://doi.org/10.1038/s41379-022-01019-5.
9. Ottini L, Capalbo C, Rizzolo P, et al. HER2-positive male breast cancer: an update. Breast Cancer (Dove Med Press). 2010; 2:45-58.
10. Surveillance, Epidemiology, and End Results (SEER) Program [Internet]. SEER*stat database: incidence - SEER 21 regs research data + Hurricane Katrina impacted Louisiana cases, Nov 2020 Sub (2000-2018). National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2021, based on the November 2020 submission [cited 12 Oct 2021]. Available from: https://seer.cancer.gov/.
11. Bilimoria M, Morrow M. The woman at increased risk for breast cancer: evaluation and management strategies. CA Cancer J Clin. 1995; 45:263–78.
12. Kelsey JL, Gammon MD, John EM. Reproductive and hormonal risk factors. Reproductive Factors. 1993; 15(1):36-47.
13. Munsell MF, Sprague BL, Berry DA, et al. Body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status. Epidemiol Rev. 2014; 36:114–36.

14. McPherson K, Steel CM, Dixon JM. ABC of breast diseases: Breast cancer—epidemiology, risk factors, and genetics. British Med J. 2000; 321(Sep):624-28.
15. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. Lancet. 1996; 347:1713-27.
16. Shah NR, Borenstein J, Dubois RW. Postmenopausal hormone therapy and breast cancer: a systematic review and meta-analysis. Menopause. 2005; 12(6):668–78.
17. Ronckers CM, Erdmann CA, Land CE. Radiation and breast cancer: a review of current evidence. Breast Cancer Res. 2005; 7:21-32.
18. TUKYSA® (tucatinib). Full Prescribing Information. Revised: 04/2020 (United States) [cited Jan 2021]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213411s000lbl.pdf.
19. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021. Available from: doi.org/10/1016/j.annonc.2021.09.019
20. Baselga J, Cortés J, Kim S, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012; 366(2):109-19.
21. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med. 2020; 382(7):597-609.
22. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) - Breast Cancer (Version 2.2022 –24 Nov 2021). [cited 15 Dec 2021]. Available from: NCCN.org.
23. Giuliani S, Ciniselli CM, Leonardi E, et al. In a cohort of breast cancer screened patients the proportion of HER2 positive cases in lower than that earlier reported and pathological characteristics differ between HER2 3+ and HER2 2+/HER2 amplified cases. Virchows Arch. 2016; 469(1):45-50.
24. Shimoi T, Nagai SE, Yoshinami T, et al. The Japanese Breast Cancer Society Clinical Practice Guidelines for systemic treatment of breast cancer, 2018 edition. Breast Cancer. 2020; 27(3):322-31.
25. Cortazar P, Justice R, Johnson J, et al. US Food and Drug Administration approval overview in metastatic breast cancer. J Clin Oncol. 2012; 30(14):1705-11.
26. Dickler MN, Tolaney SR, Rugo HS, et al. MONARCH 1, a phase 2 study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2-metastatic breast cancer. Clin Cancer Res. 2017; 23(17):5218-24.
27. Cortes J, Cescon DW, Rogo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomized, placebo-controlled, double-blind, phase 3 clinical trial. Lancet. 2020; 396(10265):1817-28.
28. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab govitecan in metastatic triple negative breast cancer. N Engl J Med. 2021; 384(16):1529-41.

29. Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-low advance breast cancer. N Engl J Med. 2022; DOI: 10.1056/NEJMoa2203690
30. Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet. 2015; 385:977-1010.
31. Carioli G, Malvezzi M, Rodriguez T, et al. Trends and predictions to 2020 in breast cancer mortality in Europe. The Breast. 2017; 36:89-95.
32. SEER Cancer Stat Facts: Female Breast Cancer. National Cancer Institute, Bethesda, MD [cited 13 Oct 2021]. Available from: https://seer.cancer.gov/statfacts/html/breast.html.
33. Savci-Heijink CD, Halfwerk H, Hooijer GKJ, et al. Retrospective analysis of metastatic behavior of breast cancer subtypes. Breast Cancer Res Treat. 2015;150:547-57.
34. Dent R, Hanna WM, Trudeau M, et al. Pattern of metastatic spread in triple-negative breast cancer. Breast Cancer Res Treat. 2009; 115:423-8.
35. Jensen AO, Jacobsen JB, Norgaard M, et al. Incidence of bone metastases and skeletal-related events in breast cancer patients: a population-based cohort study in Denmark. BMC Cancer. 2011; 11:29.
36. Barnholtz-Sloan JS, Sloan AE, Davis FG, et al. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. J Clin Oncol. 2004; 22(14):2865-72.
37. Pestalozzi BC, Zahrieh D, Price KN, et al for the International Breast Cancer Study Group. Identifying breast cancer patients at risk for central nervous system (CNS) metastases in trials of the International Breast Cancer Study Group (IBCSG). Ann Oncol. 2006; 17:935-44.
38. Rostami R, Mittal S, Rostami P, et al. Brain metastasis in breast cancer: a comprehensive literature review. J Neurooncol. 2016; 127:407-14.
39. Witzel I, Laakmann E, Weide R, et al. Treatment and outcomes of patients in the brain metastases in Breast Cancer Network Registry. Eur J Cancer. 2018; 102:1-9.
40. Jones LW, Haykowsky MJ, Swartz JJ, et al. Early breast cancer therapy and cardiovascular injury. J Am Coll Cardiol. 2007; 50:1435-41.
41. Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015; 131:1981-8.
42. Balduzzi S, Mantarro S, Guarneri V, et al. Trastuzumab-containing regimens for metastatic breast cancer (review). Cochrane Database Syst Rev. 2014; 2014(6):CD006242.
43. Matos E, Jug B, Bagus R, et al. A prospective cohort study on cardiotoxicity of adjuvant trastuzumab therapy in breast cancer patients. Arq Bras Cardiol. 2016; 107(1):40-7.
44. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013; 368(11):987-98.
45. Hoe AL, Royle GT, Taylor I. Breast liver metastases – incidence, diagnosis and outcome. J R Soc Med. 1991; 84(12):714-6.

46. Xie J, Xu Z. A population-based study on liver metastases in women with newly diagnosed breast cancer. Cancer Epidemiol Biomarkers Prev. 2019; 28(2):283-92.
47. Wyld L, Gutteridge E, Pinder SE, et al. Prognostic factors for patients with hepatic metastases from breast cancer. Br J Cancer. 2003; 89(2):284-90.
48. Omarini C, Thanopoulou E, Johnston SRD. Pneumonitis and pulmonary fibrosis associated with breast cancer treatments. Breast Cancer Res Treat. 2014; 146:245-58.
49. Jin L, Han B, Siegel E, et al. Breast cancer lung metastasis: molecular biology and therapeutic implications. Cancer Biol Ther. 2018; 19(10):858-68.
50. Ording AG, Cronin-Fenton DP, Jacobsen JB, et al. Comorbidity and survival of Danish breast cancer patients from 2000–2011: a population-based cohort study. Clin Epidemiol. 2013;5: 39-46.
51. Berglund A, Wigertz A, Adolfsson J, et al. Impact of comorbidity on management and mortality in women diagnosed with breast cancer. Breast Cancer Res Treat. 2012; 135:281-9.
52. Louwman WJ, Janssen-Heijnen MLG, Houterman S, et al. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: a population-based study. Eur J Cancer. 2005; 41:779-85.
53. McPherson CP, Swenson KK, Lee MW. The effects of mammographic detection and comorbidity on the survival of older women with breast cancer. J Am Geriatr Soc. 2002; 50:1061-8.
54. Land LH, Dalton SO, Jørgensen TL, et al. Comorbidity and survival after early breast cancer. A review. Crit Rev Oncol/Hemat. 2012; 81:196-205.
55. Yancik R, Wesley MN, Ries LAG, et al. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. J Am Med Assoc. 2001;285(7):885-92.
56. Houterman S, Janssen-Heijnen MLG, Verheij CDGW, et al. Comorbidity has negligible impact on treatment and complications but influences survival in breast cancer patients. Br J Cancer. 2004; 90:2332-7.
57. Braithwaite D, Moore DH, Satariano WA, et al. Prognostic impact of comorbidity among long-term breast cancer survivors: results from the LACE study. Cancer Epidemiol Biomark Prev. 2012; 21(7):1115-25.
58. Mehta LS, Watson KE, Barac A, et al. Cardiovascular disease and breast cancer: where these entities intersect a scientific statement from the American Heart Association. Circulation. 2018; 137:e30-66.
59. Janssen-Heijnen MLG, Houterman S, Lemmens VEPP, et al. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. Crit Rev Oncol/Hemat. 2005; 55:231-40.
60. Ording AG, Garne JP, Nyström PMW, et al. Comorbid diseases interact with breast cancer to affect mortality in the first year after diagnosis—a Danish nationwide matched cohort study. PLOS ONE. 2013; 8(10):e76013.

61. Ferlay J, Ervik M, Lam F,et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer [cited 13 Oct 2021]. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/7-Stomach-fact-sheet.pdf.
62. Boku N. HER2-positive gastric cancer. Gastric Cancer. 2014; 17:1-12.
63. Chua TC, Merrett ND. Clinicopathologic factors associated with HER2-positive gastric cancer and its impact on survival outcomes-a systematic review. Int J Cancer. 2012; 130(12):2845-56.
64. Gomez-Martin C, Garralda E, Echarri MJ, et al. HER2/*neu* testing for anti-HER2-based therapies in patients with unresectable and/or metastatic gastric cancer. J Clin Pathol. 2012; 65(8):751-7.
65. Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol. 2008; 19(9):1523-9.
66. Jorgensen JT, Hersom M. HER2 as a prognostic marker in gastric cancer - a systematic analysis of data from the literature. J Cancer. 2012; 3:137-44.
67. Cho JH, Lim JY, Cho JY. Survival analysis based on human epidermal growth factor 2 status in stage II-III gastric cancer. World J Gastroenterol. 2017; 23(41):7407-14.
68. European Cancer Information System [cited 02 Dec 2020]. Available from: https://ecis.jrc.ec.europa.eu/.
69. SEER Cancer Stat Facts: Stomach Cancer. National Cancer Institute, Bethesda, MD [cited 13 Oct 2021]. Available from: https://seer.cancer.gov/statfacts/html/stomach.html.
70. Zali H, Rezaei-Tavirani M, Azodi M. Gastric cancer: prevention, risk factors and treatment. Gastroenterol Hepatol Bed Bench. 2011; 4(4):175-85.
71. Karimi P, Islami F, Anandasabapathy S, et al. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiol Biomarkers Prev. 2014; 23(5):700-13.
72. Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. Gastroenterol Rev. 2019; 14(1):26-38.
73. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Gastric cancer (Version 2.2022); 2022 [cited 11 Jan 2022]. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1434.
74. Lordick F, Carneiro F, Cascinu S, et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022; 33(10):1005-20. .
75. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2021. 6th ed. November 2022. Gastric Cancer. 2023; 26:1-25.
76. KEYTRUDA (pembrolizumab). Highlights of Prescribing Information. Revised: January 2020 (United States) [cited 20 Sep 2021]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125514s066lbl.pdf.

77. Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer. Phase 2 Clinical KEYNOTE-059 trial. JAMA Oncol. 2018; 4(5):e180013.

78. Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2018; 19:1437-48.

79. Kawabata H, Hitomi M, Motoi S. Management of bleeding from unresectable gastric cancer. Biomedicines. 2019; 7(3):54. Available from: https://doi.org/10.3390/biomedicines7030054.

80. Blackshaw GR, Stephens MR, Lewis WG, et al. Prognostic significance of acute presentation with emergency complications of gastric cancer. Gastric Cancer. 2004; 7:91-6.

81. Miyazaki Y, Takiguchi S, Takahashi T, et al. Treatment of gastric outlet obstruction that results from unresectable gastric cancer: current evidence. World J Gastrointest Endosc. 2016; 8(3):165-72.

82. Correa P. Gastric cancer: overview. Gastroenterol Clin North Am. 2013; 42(2):211-17.

83. Mine S, Sano T, Tsutsumi K, et al. Large-scale investigation into dumping syndrome after gastrectomy for gastric cancer. J Am Coll Surg. 2010; 211:628-36.

84. Lowe KA, Danese MD, Gleeson ML, et al. Racial and ethnic variability in the prevalence and incidence of comorbidities associated with gastric cancer in the United States. J Gastrointest Canc. 2016; 47:168-81.

85. van Gestel Y, Lemmens V, deHingh I, et al. Influence of comorbidity and age on 1-, 2-, and 3-month postoperative mortality rates in gastrointestinal cancer patients. An Surg Oncol. 2013; 20:371-80.

86. Coebergh JWW, Janssen-Heijnen MLG, Razenberg PPA. Prevalence of co-morbidity in newly diagnosed patients with cancer: a population-based study. Crit Rev Oncol Hematol. 1998; 27:97-100.

87. Solanki S, Chakinala RC, Haq KF, et al. Inpatient burden of gastric cancer in the United States. Ann Transl Med. 2019; 7(23):772.

88. Morishima T, Matsumoto Y, Koeda N, et al. Impact of comorbidities on survival in gastric, colorectal, and lung cancer patients. J Epidemiol. 2019; 29(3):110-15.

89. Wang T, Nelson RA, Bogardus A, et al. Five-year lung cancer survival: which advanced stage nonsmall cell lung cancer patients attain long-term survival? Cancer. 2010; 116(6):1518-25.

90. Mazières J, Peters S, Lepage B, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol. 2013;31(16):1997-2003.

91. Tomizawa K, Suda K, Onozato R, et al. Prognostic and predictive implications of HER2/ERBB2/neu gene mutations in lung cancers. Lung Cancer. 2011;74(1):139-44.

92. Stephens P, Hunter C, Bignell G, et al. Lung cancer: intragenic ERBB2 kinase mutations in tumours. Nature. 2004;431(7008):525-6.

93. SEER Cancer Stat Facts: Lung and Bronchus Cancer. National Cancer Institute. Bethesda, MD, [cited 08 Jul 2022] Available from https://seer.cancer.gov/statfacts/html/lungb.html.

94. 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.

95. Mao Y, Yang D, He J, et al. Epidemiology of lung cancer. Surg Oncol Clin N Am. 2016; 25(3):439-45.

96. American Cancer Society: Lung Cancer Risk Factors [cited 22 Jul 2022] Available from: https://www.cancer.org/cancer/lung-cancer/causes-risks-prevention/risk-factors.html.

97. Darby S, Hill D, Auvinen A, et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ. 2005;330(7485):223.

98. Krewski D, Lubin JH, Zielinski JM, et al. Residential radon and risk of lung cancer: a combined analysis of 7 North American case-control studies. Epidemiology. 2005;16(2):137-45.

99. National Cancer Institute. Lung Cancer Prevention (PDQ®) – Health Professional Version. Updated 22 Apr 2022. [cited 08 Jul 2022] Available from: https://www.cancer.gov/types/lung/hp/lung-prevention-pdq.

100. De Matteis S, Consonni D, Lubin JH, et al. Impact of occupational carcinogens on lung cancer risk in a general population. Int J Epidemiol. 2012;41(3):711–21.

101. Shankar A, Dubey A, Saini D, et al. Environmental and occupational determinants of lung cancer. Transl Lung Cancer Res. 2019;8(Suppl 1):S31-49.

102. Coté ML, Liu M, Bonassi S, et al. Increased risk of lung cancer in individuals with a family history of the disease: a pooled analysis from the International Lung Cancer Consortium. Eur J Cancer. 2012;48(13):1957–68.

103. Centers for Disease Control and Prevention. What are the risk factors for lung cancer? Division of Cancer Prevention and Control, Centers for Disease Control and Prevention. Reviewed 18 Oct 2021. [cited 08 Jul 2022] Available from: https://www.cdc.gov/cancer/lung/basic_info/risk_factors.htm.

104. Ettinger DS, Wood DE, Aisner DL, et al. Non-small cell lung cancer, version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022;20(5):497-530.

105. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018; 29(Suppl 4):iv192-237.

106. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373(17):1627-39.

107. Herbst RS, Garon EB, Kim D-W, et al. Five year survival update from KEYNOTE-010: pembrolizumab versus docetaxel for previously treated, programmed death-ligand 1-positive advanced NSCLC. J Thorac Oncol. 2021; 16(10): 1718-32.

108. Fehrenbacher L, von Pawel J, Park K, et al. Updated efficacy analysis including secondary population results for OAK: a randomized Phase III study of atezolizumab versus docetaxel in patients with previously treated advanced non-small cell lung cancer. J Thorac Oncol. 2018; 13(8):1156-70.

109. TAXOTERE® (docetaxel). Full prescribing information. Revised: 05/2020 (United States). [cited: February 2021]. Available from: www.accessdata.fda.gov/drugsatfda_docs/label/2020/020449s084lbl.pdf.

110. CYRAMZA® (ramucirumab). EPAR - product information. Last updated: 04/08/2022 (European Union). [cited: February 2021]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/cyramza#product-information-section.

111. Li BT, Shen R, Buonocore D, et al. Ado-trastuzumab emtansine for patients with HER2 mutant lung cancers: results from a phase II basket trial. J Clin Oncol. 2018;36(24):2532-7.

112. Raz DJ, Zell JA, Ou SI, et al. Natural history of stage I non-small cell lung cancer: implications for early detection. Chest. 2007;132(1):193-9.

113. Spencer AS, da Silva Dias D, Capelas ML, et al. Managing severe dysgeusia and dysosmia in lung cancer patients: a scoping systematic review. Front Oncol. 2021;11:774081.

114. Morel H, Raynard B, d'Arlhac M, et al. Prediagnosis weight loss, a stronger factor than BMI, to predict survival in patients with lung cancer. Lung Cancer. 2018;126:55-63.

115. Kocher F, Hilbe W, Seeber A, et al. Longitudinal analysis of 2293 NSCLC patients: A comprehensive study from the TYROL registry. Lung Cancer. 2015;87(2):193-200.

116. Akinosoglou KS, Karkoulias K, Marangos M. Infectious complications in patients with lung cancer. Eur Rev Med Pharmacol Sci. 2013;17(1):8-18.

117. Santini D, Barni S, Intagliata S, et al. Natural history of non-small-cell lung cancer with bone metastases. Sci Rep. 2015;5:18670.

118. Owen S, Souhami L. The management of brain metastases in non-small cell lung cancer. Front Oncol. 2014;4(248).

119. Harle A, Molassiotis A, Buffin O, et al. A cross sectional study to determine the prevalence of cough and its impact in patients with lung cancer: a patient unmet need. BMC Cancer. 2020;20:9.

120. Sung MR, Patel MV, Djalalov S, et al. Evolution of symptom burden of advanced lung cancer over a decade. Clin Lung Cancer. 2017;18(3):274-80.

121. Carnio S, Di Stefano RF, Novello S. Fatigue in lung cancer patients: symptom burden and management of challenges. Lung Cancer (Auckl). 2016;7:73-82.

122. Gershman E, Guthrie R, Swiatek K, et al. Management of hemoptysis in patients with lung cancer. Ann Transl Med. 2019;7(15):358.

123. Park HS, Kim YI, Kim HY, et al. Bronchial artery and systemic artery embolization in the management of primary lung cancer patients with hemoptysis. Cardiovasc Intervent Radiol. 2007;30:638-43.

124. Leduc C, Antoni D, Charloux A, et al. Comorbidities in the management of patients with lung cancer. Eur Respir J. 2017;49(3):1601721.

125. Iachina M, Jakobsen E, Møller H, et al. The effect of different comorbidities on survival of non-small cells lung cancer patients. Lung. 2015;193(2):291-7.

126. Seigneurin A, Delafosse P, Trétarre B, et al. Are comorbidities associated with long-term survival of lung cancer? A population-based cohort study from French cancer registries. BMC Cancer. 2018;18:1091.

127. Gould MK, Munoz-Plaza CE, Hahn EE, et al. Comorbidity profiles and their effect on treatment selection and survival among patients with lung cancer. Ann Am Thorac Soc. 2017;14(10):1571-80.

128. Dima S, Chen KH, Wang KJ, et al. Effect of comorbidity on lung cancer diagnosis timing and mortality: a nationwide population-based cohort study in Taiwan. Biomed Res Int. 2018;1252897.

129. Janssen-Heijnen ML, Schipper RM, Razenberg PP, et al. Prevalence of co-morbidity in lung cancer patients and its relationship with treatment: a population-based study. Lung Cancer.1998;21(2):105-13.

130. Guidance for industry: estimating the maximum safety starting dose in initial clinical trials for therapeutics in adult healthy volunteers. Rockville, MD: US Food and Drug Administration, Center for Drug Evaluation and Research, Pharmacology and Toxicology; July 2005.

131. S9 Nonclinical Evaluation for Anticancer Pharmaceuticals. Rockville, MD: US Food and Drug Administration, Center for Biologics Evaluation and Research; 2018.

132. Liu Z, Carvajal M, Carraway CA, et al. Expression of the receptor tyrosine kinases, epidermal growth factor receptor, ErbB2 and ErbB3 in human ocular surface epithelia. Cornea. 2001; 20(1):81-5.

133. Matsuno O. Drug-induced interstitial lung disease: mechanisms and best diagnostic approaches. Respir Res. 2012; 13(1):39.

134. Powell CA, Modi S, Iwata H, et al. Pooled analysis of drug-related ILD in 8 single-arm T-DXd studies [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2021; 2021 Apr 10-15 and May 17-21; Philadelphia, PA.

135. Kondapalli L. Cardiotoxicity: an unexpected consequence of HER2-targeted therapies. American College of Cardiology; 2016 [cited 17 Mar 2020]. Available from: https://www.acc.org/latest-in-cardiology/articles/2016/06/06/09/32/cardiotoxicity.

136. Mohan N, Jiang J, Dokmanovic M, et al. Trastuzumab-mediated cardiotoxicity: current understanding, challenges, and frontiers. Antib Ther. 2018; 1(1):13-7.

137. Florido R, Smith KL, Cuomo KK, et al. Cardiotoxicity from human epidermal growth factor receptor-2 (HER 2) targeted therapies. J Am Heart Assoc. 2017; 6(9):e006915.

138. European Medicines Agency. Kadcyla: EPAR Public Assessment Report. EMA/CHMP/641539/2013; 2013 [cited 04 Nov 2021]. Available from: https://www.ema.europa.eu/en/documents/assessment-report/kadcyla-epar-public-assessment-report_en.pdf.

ANNEX 8 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Table Part VII.2: Summary of Change to the Risk Management Plan Over Time

Version	Approval Date Procedure	Change
1.0	18 Jan 2021 Marketing authorisation application EMEA/H/C/005124/0000	Not applicable - initial version of RMP
2.0	13 Jul 2022 EMEA/H/C/005124/II/0014	Safety concerns: Update of characterisation for important risks based on pooled data Outcome of EMEA/H/C/005124/MEA/003: Annex 3 amended to align with final protocol language Change of date for final study report
3.0	12 Dec 2022 EMEA/H/C/005124/II/0012	Safety concerns: Update of characterisation for important risks based on pooled data Outcome of EMEA/H/C/005124/II/0019: Part IV amended to change date for final study results (DS8201-A-U301) Condition of EMEA/H/C/005124/II/0012: Study DS-8201-A-U306 added in Table Part IV.1 and Section II.C.1
4.0	24 Jan 2023 EMEA/H/C/005124/II/0022	Safety concerns: Update of characterisation for important risks based on pooled data
6.0	06 Jul 2023 EMEA/H/C/005124/II/0031	Safety concerns: Update of characterisation for important risks based on pooled data. Condition of EMEA/H/C/005124/0000: Study DS-8201-A-U301 removed from Table Part IV.1 and Section II.C.1.
7.0	NA EMEA/H/C/005124/II/0027	New indication: NSCLC included in Part I and Part VI. Condition of EMEA/H/C/005124/0027: Study DESTINY-Lung04 added to Table Part IV.1 and Section II.C.1.