Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer: a plain language summary of the DESTINY-Lung01 study

Smit, E.F.

Future Oncology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ifon20

Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer: a plain language summary of the DESTINY-Lung01 study

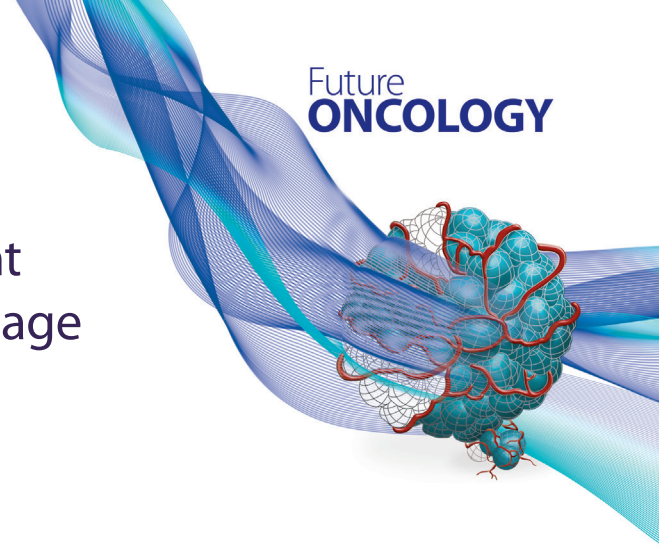
Egbert F. Smit

To cite this article: Egbert F. Smit (2024) Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer: a plain language summary of the DESTINY-Lung01 study, Future Oncology, 20:27, 1961-1971, DOI: 10.1080/14796694.2024.2355724

To link to this article: https://doi.org/10.1080/14796694.2024.2355724

Published online: 16 Jul 2024.

Plain Language Summary of Publication



Future ONCOLOGY

Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer: a plain language summary of the DESTINY-Lung01 study

Egbert F. Smit, M.D., Ph.D.

The Netherlands Cancer Institute, Amsterdam

First draft submitted: 20 October 2023; Accepted for publication: 10 May 2024

Where can I find the original article on which this summary is based?

The full title of the original publication in the *New England Journal of Medicine* is 'Trastuzumab Deruxtecan in HER2-Mutant Non-Small-Cell Lung Cancer'.

You can read the original publication for free at:
https://www.nejm.org/doi/10.1056/NEJMoa2112431

How to say (double click sound icon to play sound)...

- **Trastuzumab:** tras-TOO-zoo-mab
- **Deruxtecan:** der-UHX-teh-can

Summary

What is this summary about?
This is a summary of the publication about the DESTINY-Lung01 study, which was published in the *New England Journal of Medicine* in September 2021. The DESTINY-Lung01 study includes 181 adults with **metastatic** non-small-cell lung cancer (NSCLC) that could not be treated with surgery and who have had previous standard anticancer treatment. The publication includes information and results about 91 of the 181 study participants. These 91 participants had **HER2-mutant** NSCLC. Researchers wanted to learn if the drug trastuzumab deruxtecan (T-DXd) could help treat participants with HER2-mutant NSCLC. At the time of this publication, this study is ongoing.

What are the key takeaways?
Results from the study showed that 55% of participants responded to treatment with T-DXd. The **median** length of time participants continued to respond to T-DXd was 9.3 months.

After receiving T-DXd, 92% of participants had **disease control**. After receiving T-DXd, half of the participants lived for at least 17.8 months. After receiving T-DXd, half of the participants lived for 8.2 months before their cancer got worse.

During the study, 97% of participants had **drug-related adverse events**, with nausea being the most common. There were 20% of participants with serious drug-related adverse events.

What were the main conclusions reported by the researchers?
Based on these results, T-DXd could be a treatment option for people with HER2-mutant NSCLC that has been previously treated.

Metastatic: The cancer has spread in the body from the organ it started in.
HER2-mutant: The HER2 protein on the surface of cells is more 'active'.
Median: The middle number in a list of number organized from lowest to highest.
Disease control: Participants' tumors either completely disappeared, shrank by at least 30%, or remained the same size and did not get worse.
Drug-related adverse events: Medical problems that happened during the study that the doctors reported as being possibly related to T-DXd.

Taylor & Francis
Taylor & Francis Group

This article has been corrected with minor changes. These changes do not impact the academic content of the article.
10.1080/14796694.2024.2355724

ISSN 1744-8301

What is the purpose of this plain language summary?

The purpose of this plain language summary is to help you understand the findings from recent research. T-DXd is used to treat HER2-mutant NSCLC. Approval varies by country; please check with your local provider for more details.

Who should read this article?

This summary may be helpful for patients with HER2-mutant non-small-cell lung cancer (NSCLC) as well as their family members or caregivers. This summary may also be helpful for patient advocates and healthcare professionals. This includes those who are looking for treatment options for patients with HER2-mutant NSCLC.

Who sponsored this study?

Daiichi Sankyo Co., Ltd., and AstraZeneca.

Sponsor: A sponsor is a company organization that oversees and pays for a clinical research study. The sponsor also collects and analyzes the information that was generated during the study.

What is HER2-mutant non-small-cell lung cancer (HER2-mutant NSCLC)?

HER2 human epidermal growth factor receptor 2	**Mutant**	**NSCLC** non-small-cell lung cancer
HER2 is a type of protein found on the surface of some cells that can cause them to grow in an uncontrollable way, forming tumors.	Mutant means that a gene has a change (mutation) in its DNA. A gene is made up of DNA and often provides instructions on how to make a type of protein. The HER2 gene provides instructions on how to make the HER2 protein.	NSCLC is one of two major types of lung cancers. It is called "non-small-cell" because cancer cells appear larger when viewed under a microscope.

People with NSCLC can have HER2 overexpressing NSCLC or HER2-mutant NSCLC.

- HER2 overexpressing means there are high levels of HER2 protein.
- HER2-mutant means the HER2 protein is more "active".

People with HER2-mutant NSCLC are usually treated with chemotherapy and/or immunotherapy. But, their cancer will often stop responding to treatment and become worse quickly. So, researchers are looking for better ways to treat HER2-mutant NSCLC.

At the time this study started, there were no approved treatments specifically for HER2-mutant NSCLC. But since then, T-DXd has been approved as a treatment option for people with metastatic or **unresectable** HER2-mutant NSCLC that has been previously treated.

Unresectable: The cancer cannot be treated with surgery to remove it.

Taylor & Francis
Taylor & Francis Group

What is trastuzumab deruxtecan (T-DXd)?

The study drug, T-DXd, is:

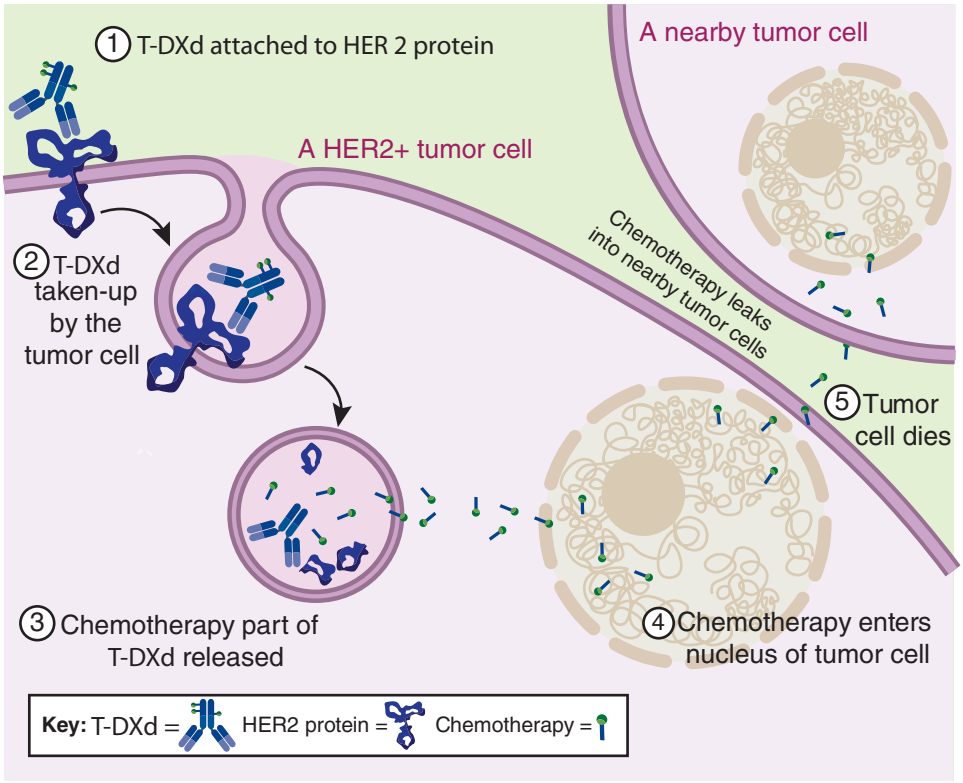
Already approved in several countries to treat **HER2-positive** breast cancer, **HER2-low** breast cancer, and gastric cancer.

Made up of three parts: trastuzumab, a chemotherapy drug called DXd, and a linker that connects them. The trastuzumab part attaches to the HER2 protein on the surface of cancer cells. This allows T-DXd to deliver chemotherapy directly to the cancer cell and kill it.

Given as an injection into a vein (IV infusion).

HER2-positive: The cancer cells collected during a biopsy tested positive for having a high number of HER2 proteins.
HER2-low: The cancer cells have a low number of HER2 proteins.

How T-DXd is designed to work



This graphic was adapted from S Modi. Trastuzumab deruxtecan in previously treated HER2-positive metastatic breast cancer: plain language summary of the DESTINY-Breast01 study. *Future Oncol.*, 17(26), 3415-3424 (2021). https://doi.org/10.2217/fon-2021-0427

About the DESTINY-Lung01 study

Main goals were to learn if T-DXd works and is safe in people with HER2-overexpressing or HER2-mutant NSCLC.

Started in May 2018 and is still ongoing

181 participants

Study treatment
5.4 or 6.4 milligrams per kilogram (mg/kg) of the participants' body weight of T-DXd every 3 weeks

Open-label
all of the participants, researchers, and doctors knew what treatment each participant received

About the DESTINY-Lung01 study participants

90 participants
had **HER2-overexpressing** NSCLC

- 49 of these participants received 6.4 mg/kg of T-DXd.
- 41 of these participants received 5.4 mg/kg of T-DXd.
- The rest of the summary does not include information and results about this group of participants.

91 participants
had **HER2-mutant** NSCLC

- All 91 of these participants received 6.4 mg/kg of T-DXd.
- The rest of the summary discusses information and results about this group of participants only.

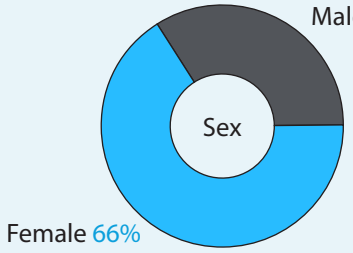
Taylor & Francis
Taylor & Francis Group

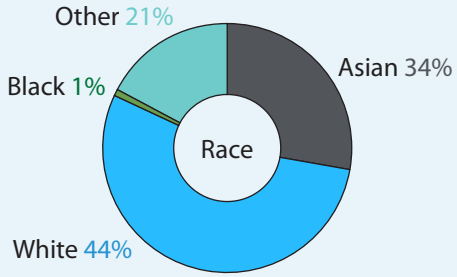
The information below is about the 91 participants with HER2-mutant NSCLC who are included in this summary.

29-88
age range

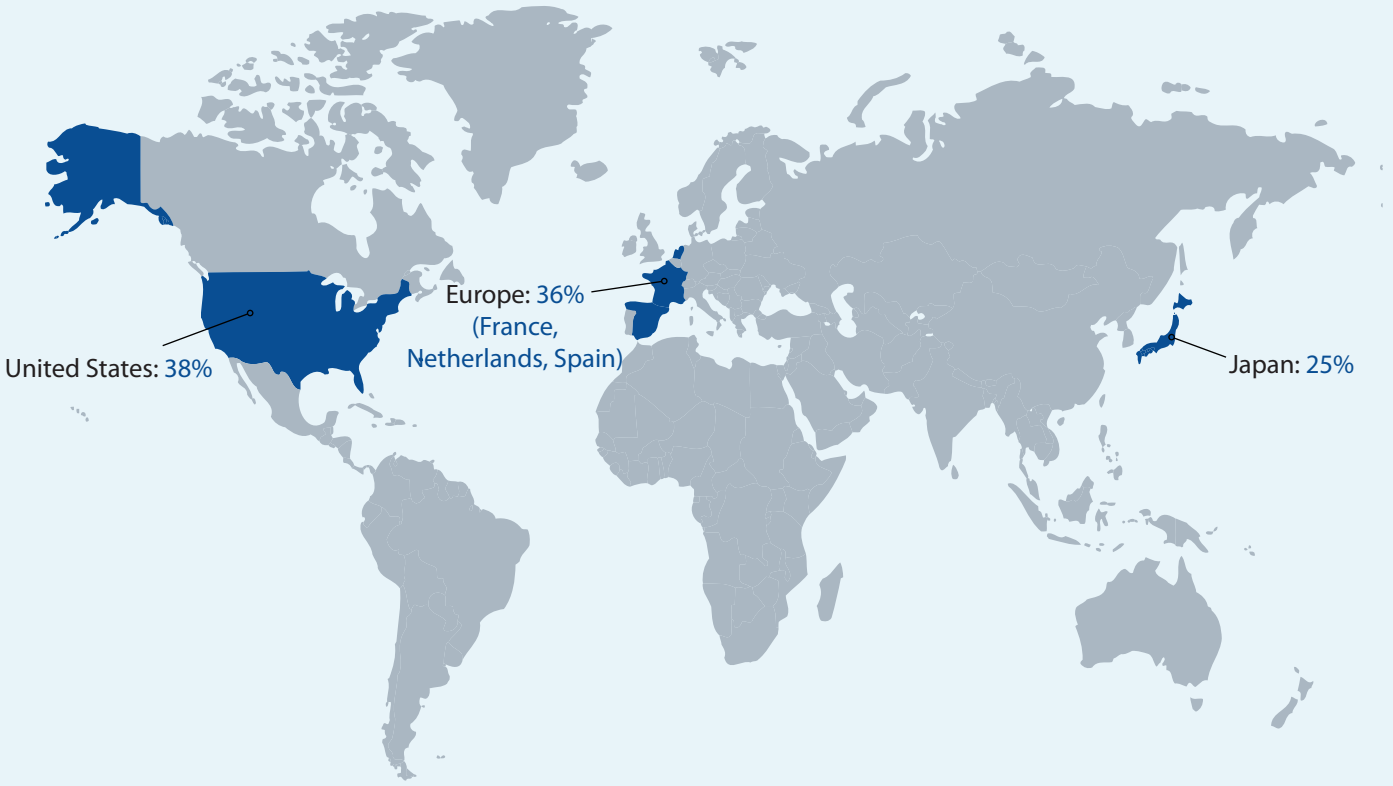
60
median age

The median is the middle number in a list of numbers organized from lowest to highest.





Number of participants per country



All the participants included in this summary **did** have:

- **Metastatic or unresectable NSCLC**
  Metastatic means the cancer has spread in the body from the organ it started in. Unresectable means the cancer cannot be treated with surgery to remove it.
- **HER2 mutation**
  Local laboratories confirm this by taking a sample of the tumor.
- **Standard treatment before the study, but their cancer got worse, or did not have available standard treatment.**
- **A score of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) test**
  The ECOG test measures how much cancer is affecting a patient's ability to complete daily activities. Scores range from 0 to 5, with higher scores meaning higher disability.
- **At least 1 tumor that could be measured using Response Evaluation Criteria in Solid Tumors (RECIST)**
  RECIST is a set of rules or criteria used to analyze the scans of tumors. These rules help define what it means for a tumor to decrease in size (respond), stay the same (stabilize), or increase in size or spread (progress) during treatment.

All the participants included in this summary **did not** have:

- **Prior treatment with most drugs targeting HER2 specifically**
- **Prior or current interstitial lung disease (ILD)**
  ILD is a group of non-infectious lung diseases that can cause scarring and stiffness of the lungs.
- **Prior or current pneumonitis**
  Pneumonitis is inflammation of the lung tissue.
- **Certain heart or lung diseases**

Taylor & Francis
Taylor & Francis Group

What were the results?

A goal of the DESTINY-Lung01 study was to learn if T-DXd could help treat patients with HER2-mutant NSCLC. The researchers wanted to learn the answer to several questions to determine if T-DXd was working. The researchers collected data until May 2021.

For some questions, the researchers used RECIST. RECIST is a set of rules or criteria used to analyze the scans of tumors. These rules help define what it means for a tumor to decrease in size (respond), stay the same (stabilize), or increase in size or spread (progress) during treatment.

Researchers used RECIST to determine if the participants' tumors had:

- completely disappeared. This is called a **complete response**.
- shrank by at least 30%. This is called a **partial response**.
- remained about the same size and did not get worse. This is called **stable disease**.
- grew and got worse. This is called progressive disease or **progressing**.

Question	Answer	How did researchers answer the question?
How many participants responded to T-DXd for at least 4 weeks?	55% 	Researchers analyzed scans of the participants' tumors using RECIST. Then they counted the number of participants who had either a complete or a partial response for at least 4 weeks at some point during the trial. This is also known as the **confirmed objective response rate**.
How long did the participants' response to T-DXd last?	9.3 months	For the participants who had a response to treatment with T-DXd, the researchers monitored these participants' tumors and calculated the median number of months that the participants had no tumor growth. This is also known as **response duration**.
How many participants either responded to T-DXd or had stable disease after receiving T-Dxd?	92% 	Researchers analyzed scans of the participants' tumors using RECIST. Then they counted the number of participants who had a complete response, a partial response, or stable disease. This is also known as **disease control**.
How long did the participants live after receiving T-DXd?	17.8 months	The researchers calculated the median number of months that the participants lived after they started to receive T-DXd. This is also known as **overall survival**.
How long did the participants live without their cancer getting worse after receiving T-DXd?	8.2 months	The researchers calculated the median number of months that the participants lived without their cancer progressing after they started to receive T-DXd. This is also known as **progression-free survival**.

How many participants had drug-related adverse events?

In this summary, medical problems that happened throughout the study are called **adverse events**. An adverse event is considered a **serious adverse event** when it is life-threatening, causes lasting problems, or the participant needs hospital care.

Below are the adverse events that the doctors reported as being **possibly related to the study drug T-DXd**. These are known as "drug-related adverse events."

How many participants had drug-related adverse events?

How many participants had serious drug-related adverse events?

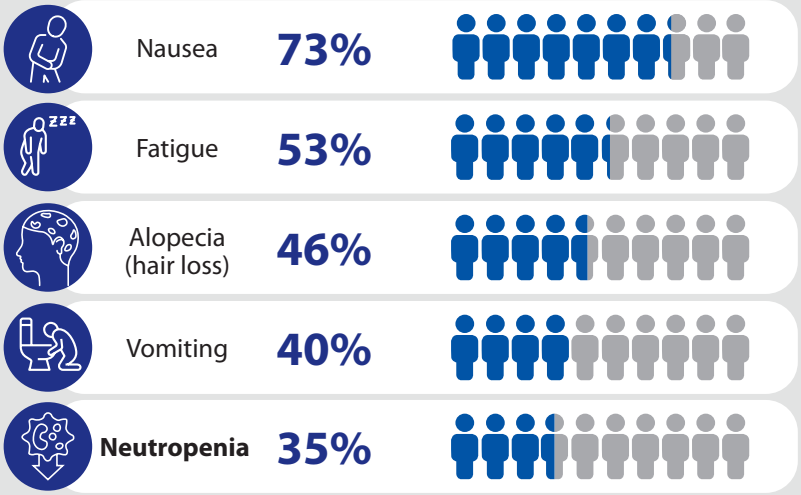
How many participants stopped receiving T-DXd because of drug-related adverse events?

How many participants died because of drug-related adverse events?

There were two participants who died because of a drug-related adverse event. One participant died from inflammation of lung tissue (pneumonitis). One participant died from interstitial lung disease (ILD).

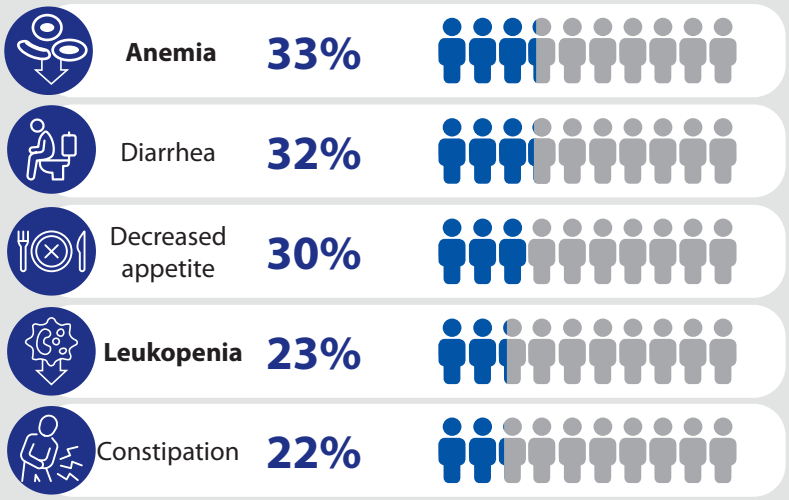
What were the most common drug-related adverse events?

Below are the drug-related adverse events that happened in at least 20% of participants. There were other drug-related adverse events, but those happened in fewer participants. Some participants may have had more than one drug-related adverse event.



Neutropenia: low levels of neutrophils, a type of white blood cell that helps fight infection.

Taylor & Francis
Taylor & Francis Group



Anemia: Low red blood cell counts, which can cause tiredness and pale skin.
Leukopenia: Low levels of white blood cells.

What drug-related adverse events of special interest did the participants have?

In other clinical studies with T-DXd, some participants developed interstitial lung disease (ILD). ILD is a group of non-infectious lung diseases that can cause scarring and stiffness of the lungs. The researchers wanted to learn if the participants in this study also developed ILD.

Scarring of the lungs is also called **fibrosis**. This scarring causes stiffness in the lungs, which can make it difficult to breathe and get oxygen to the bloodstream. ILD can also include pneumonitis, which is when the lungs become inflamed.

During the study, any participants with signs and symptoms of ILD were required to stop receiving T-DXd right away and to be treated with steroids. These signs and symptoms included fever, cough, or shortness of breath.

How many participants had drug-related ILD?

Of the participants who had drug-related ILD, how many had mild or moderate drug-related ILD?

How many participants died because of drug-related ILD?

Of the participants who had drug-related ILD, how many had fully recovered as of May 2021?

What do the results mean?

- A high percentage of participants responded to T-DXd and had disease control after receiving T-DXd.
- There were no unexpected drug-related adverse events. The drug-related adverse events in this study were similar to those in other studies with T-DXd.
- T-DXd may increase the risk for ILD. Patients and their doctors should carefully monitor for the signs and symptoms of ILD and be open to discussing these so it can be found early and be treated.
- T-DXd is now an approved treatment option for people with metastatic or unresectable HER2-mutant NSCLC that has been previously treated.

Where can the readers find more information?

The DESTINY-Lung 01 study started in May 2018. The original publication about the DESTINY-Lung 01 study is called 'Trastuzumab deruxtecan in HER2-mutant non–small-cell lung cancer'.

Li, B. T., Smit, E. F., Goto, Y., Nakagawa, K., Udagawa, H., Mazières, J. & Jänne, P. A. (2022). Trastuzumab deruxtecan in HER2-mutant non–small-cell lung cancer. *New England Journal of Medicine*, 386(3), 241-251.

You can read the original publication for free at: https://www.nejm.org/doi/10.1056/NEJMoa2112431

You can read more about the DESTINY-Lung01 study on the following websites:

- Enter the study number **NCT03505710** into the "Other terms" search field at www.clinicaltrials.gov
- Enter the EudraCT identifier **2017-004781-94** into the search field at www.clinicaltrialsregister.eu

You can read other summaries about other T-DXd clinical trials at:

- https://doi.org/10.2217/fon-2021-0427
- https://doi.org/10.2217/fon-2023-0422
- https://doi.org/10.2217/fon-2023-0245

The DESTNY-Lung02 study is an ongoing study to learn more about T-DXd in more participants with HER2-mutant NSCLC. If you were a study participant and have questions about the results of this study, please speak with the doctor or staff at your study center.

Taylor & Francis
Taylor & Francis Group

Acknowledgments

Daiichi Sankyo and AstraZeneca would like to thank the clinical study participants and their family members and caregivers. They would also like to thank the staff members at the study centers who cared for the participants in the clinical study.

Financial disclosure

Dr. Smit reports research grants paid to his institution, Netherlands Cancer Institute by Novartis Pharma. Daiichi Sankyo Co., Ltd., and AstraZeneca funded this study. The study was designed and led by Daiichi Sankyo Co., Ltd., for data collection and analysis, and was approved by the institutional review board at each partnering site. In March 2019, AstraZeneca entered into a collaboration agreement with Daiichi Sankyo Co., Ltd., for trastuzumab deruxtecan (T-DXd). All authors and sponsors assisted in data interpretation, writing the report, and reviewing the manuscript, and provided final approval to submit the manuscript for publication. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Competing interests disclosure

Dr. Smit has been a consultant for Eli Lilly and Company, and a speaker for AstraZeneca and Bristol Meyers Squibb Company. Dr. Smit has also served on a scientific advisory board for AstraZeneca, Bristol Myers Squibb Company, Daiichi Sankyo Company, Merck, Merck Sharp and Dohme, and Seagen Inc. The author has no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

Medical writing and editorial assistance in the development of this summary were provided by Kim Edwards, PhD, and Scott Finger of the Center for Information & Study on Clinical Research Participation (CISCRP), a non-profit organization focused on educating and informing the public about clinical research participation, and funded by Daiichi Sankyo.