AstraZeneca

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Enhertu continues to demonstrate durable responses with new data from DESTINY-Breast01 in HER2-positive metastatic breast cancer

Median duration of response exceeded 20 months

Update shows encouraging landmark survival in exploratory analysis with an estimated three out of four patients alive at 18 months

Updated results from the positive DESTINY-Breast01 Phase II trial showed AstraZeneca and Daiichi Sankyo Company, Limited (Daiichi Sankyo)'s *Enhertu* (trastuzumab deruxtecan) continued to demonstrate impressive efficacy and durable responses in patients with HER2-positive metastatic breast cancer following two or more prior HER2-based regimens.

The updated data were presented in a Spotlight Poster Discussion at the 2020 San Antonio Breast Cancer Symposium (SABCS).

With a median duration of follow-up of 20.5 months, patients treated with *Enhertu* (5.4 mg/kg) achieved an objective response rate (ORR) of 61.4% and a median duration of response (DoR) of 20.8 months. The median progression-free survival (PFS) was 19.4 months. In an exploratory landmark analysis of overall survival (OS), evaluated at 35% maturity, an estimated 74% of patients remained alive at 18 months.

In the previous analysis at 11.1 months of follow-up, an ORR of 60.9% was seen with a median DoR of 14.8 months and median PFS of 16.4 months. Additional trials are ongoing to confirm the results seen in DESTINY-Breast01.

Approximately one in five patients with breast cancer are considered HER2 positive, which is associated with aggressive disease, high recurrence rate, and increased mortality. [1,2]

Shanu Modi, MD, Breast Medical Oncologist, Memorial Sloan Kettering Cancer Center and principal investigator in the DESTINY-Breast01 trial, said: "These longer-term data from the DESTINY-Breast01 trial further highlight the role that this treatment optionmay have in changing clinical outcomes for patients with previously treated HER2-positive metastatic breast cancer. It is important that we are able to offer patients therapy like this which provides a meaningful clinical benefit, as historically there have been few therapies that were able to do that in this patient population."

José Baselga, Executive Vice President, Oncology R&D, said: "These results reinforce the transformational potential of *Enhertu* in patients with previously treated HER2-positive metastatic breast cancer. With a median duration of response of greater than twenty months, the updated results of DESTINY-Breast01 are unprecedented. We look forward to further confirming the DESTINY-Breast01 findings with results from our Phase III development

programme for *Enhertu*."

Antoine Yver, Executive Vice President and Global Head, Oncology R&D, Daiichi Sankyo, said: "The updated findings illustrate the practice-changing potential for *Enhertu* to become a long-term treatment option for patients with previously treated HER2-positive metastatic breast cancer. The duration of response and long-term safety profile further validate that our proprietary DXd antibody drug conjugate technology delivers effective and durable treatment."

Summary of updated efficacy results from DESTINY-Breast01

	As of 1 Aug 2019 (n=184)[i]	**As of 8 Jun 2020 (n=184)[ii]**
Median duration of follow-up	11.1 months (0.7-19.9)	20.5 months (0.7-31.4)
Patients remaining on treatment	42.9% (n=79)	20.1% (n=37)
Confirmed ORR by ICR[95% CI][iii,iv]	60.9% [53.4-68.0] (n=112)	61.4% [54.0-68.5] (n=113)
Complete response	6.0% (n=11)	6.5% (n=12)
Partial response	54.9% (n=101)	54.9% (n=101)
Stable disease	36.4% (n=67)	35.9% (n=66)
Progressive disease	1.6% (n=3)	1.6% (n=3)
Median duration of response (95% CI)	14.8 months (13.8-16.9)	20.8 months (15.0-NE)[v]
Median PFS (95% CI)[vi]	16.4 months (12.7-NE)	19.4 months (14.1-NE)
Median OS (95% CI)[vii]	NE (NE-NE)	24.6 months (23.1-NE)
Estimated OS at 12 months (95% CI)	86.2% (79.8-90.7)	85% (79-90)
Estimated OS at 18 months (95% CI)	--	74% (67-80)

i Data from the 1 August 2019 cut-off were presented at the 2019 SABCS and published in The New England Journal of Medicine

ii As of data cut-off, 20.1% of patients remained on treatment with *Enhertu*

iii ICR, independent central review

iv CI, confidence interval

v NE, not estimable

vi 114 patients (62.0%) were censored at time of analysis

vii OS was estimated at 35% maturity, with 119 patients (64.7%) censored and only 17 patients at risk at 24 months; additional follow-up is required for more mature OS data

The overall safety and tolerability profiles of Enhertu were consistent with what has been previously reported, with few additional treatment discontinuations due to adverse events with longer treatment duration. In the updated analysis, 18.5% of patients discontinued treatment due to adverse events compared to 15.2% in the previous analysis. Most cases of interstitial lung disease (ILD) or pneumonitis occurred during the first 12 months of treatment and the results suggest the risk of developing ILD or pneumonitis toxicity is not related to cumulative treatment with Enhertu. There were three new cases of treatment-related ILD reported, as determined by an independent adjudication committee, including one Grade 1, one Grade 2 and one death (Grade 5). Two potential cases were pending adjudication at data cut-off. Continued attention to monitoring to identify pulmonary symptoms and ensure early intervention is warranted.

Enhertu was approved in the US and Japan for the treatment of HER2-positive, unresectable or metastatic breast cancer following two or more prior anti-HER2 based regimens in the metastatic setting based on the earlier results from the DESTINY-Breast01 trial. In the US, *Enhertu* was approved under FDA Accelerated Approval and confirmatory trials are underway.

Several ongoing randomised Phase III trials are further testing *Enhertu* in patients with HER2-expressing metastatic breast cancer. These include DESTINY-Breast02, which is evaluating *Enhertu* as a 3rd-line treatment for patients with HER2-positive metastatic breast cancer and DESTINY-Breast03, which is testing *Enhertu* as a 2nd-line treatment for these patients. DESTINY-

Breast04 is investigating *Enhertu* in patients with metastatic breast cancer and low expression of HER2.

HER2-positive breast cancer

In women, breast cancer is the most common cancer and one of the most common causes of cancer mortality worldwide; there were an estimated 2.1 million new cases of female breast cancer diagnosed in 2018. [3,4] Breast cancer occurs mainly in women, but in rare cases it occurs in men too.[5]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumours, including gastric, breast and lung cancers. HER2 overexpression is associated with a specific HER2 gene alteration known as HER2 amplification and is often associated with aggressive disease and poorer prognosis. [6] Approximately one in five patients with breast cancer are considered HER2 positive.[2]

DESTINY-Breast01

DESTINY-Breast01 is a pivotal Phase II, single-arm, open-label, global, multicentre, two-part trial evaluating the safety and efficacy of *Enhertu*in patients with HER2-positive unresectable and/or metastatic breast cancer previously treated with trastuzumab emtansine. The primary endpoint of the trial is ORR, as determined by ICR. Secondary objectives include DoR, disease control rate, clinical benefit rate, PFS and OS.

Enhertu

Enhertu is a HER2-directed antibody drug conjugate (ADC). *Enhertu* is the lead ADC in the oncology portfolio of Daiichi Sankyo and the most advanced programme in AstraZeneca's ADC scientific platform.

ADCs are targeted cancer medicines that deliver cytotoxic chemotherapy ('payload') to cancer cells via a linker attached to a monoclonal antibody that binds to a specific target expressed on cancer cells. *Enhertu* is comprised of a HER2 monoclonal antibody attached to a topoisomerase I inhibitor payload by a tetrapeptide-based linker.

Enhertu (5.4mg/kg) is approvedin the US and Japan 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 in the metastatic setting based on the DESTINY-Breast01 trial.*Enhertu* (6.4mg/kg) is approved in Japan for patients with HER2-positive unresectable advanced or recurrent gastric cancer that progressed after chemotherapy.

_Enhertu_clinical development

A comprehensive development program is underway globally, with nine registrational trials evaluating the efficacy and safety of trastuzumab deruxtecan monotherapy across multiple HER2 cancers, including breast, gastric and lung cancers. Trials in combination with other anticancer treatments, such as immunotherapy, are also underway.

In October 2020, *Enhertu* was granted Priority Review from the US Food and Drug Administration for the treatment of patients with HER2-positive metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma. In May 2020, *Enhertu* received a Breakthrough Therapy Designation (BTD) and Orphan Drug Designation (ODD) for gastric cancer, including GEJ adenocarcinoma.

In July 2020, The European Medicines Agency's Committee for Medicinal Products for Human Use granted accelerated assessment for the treatment of adults with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens.

In May 2020, *Enhertu* also received a BTD for the treatment of patients with metastatic non-small cell lung cancer whose tumours have a HER2 mutation and with disease progression on or after platinum-based therapy.

Collaboration between AstraZeneca and Daiichi Sankyo

Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialise trastuzumab deruxtecan (a HER2-directed ADC) in March 2019, and datopotamab deruxtecan (DS-1062; a TROP2-directed ADC) in July 2020, except in Japan where Daiichi Sankyo maintains exclusive rights. Daiichi Sankyo is responsible for manufacturing and supply of trastuzumab

deruxtecan and datopotamab deruxtecan.

AstraZeneca in breast cancer

Driven by a growing understanding of breast cancer biology, AstraZeneca is starting to challenge, and redefine, the current clinical paradigm for how breast cancer is classified and treated to deliver even more effective treatments to patients in need – with the bold ambition to one day eliminate breast cancer as a cause of death.

AstraZeneca has a comprehensive portfolio of approved and promising compounds in development that leverage different mechanisms of action to address the biologically diverse breast cancer tumour environment. AstraZeneca aims to continue to transform outcomes for HR-positive breast cancer with foundational medicines *Faslodex* (fulvestrant) and *Zoladex* (goserelin) and the next-generation SERD and potential new medicine AZD9833. PARP inhibitor, *Lynparza* (olaparib) is a targeted treatment option for metastatic breast cancer patients with an inherited BRCA mutation. AstraZeneca with MSD (Merck & Co., Inc. in the US and Canada) continue to research *Lynparza* in metastatic breast cancer patients with an inherited BRCA mutation and are exploring new opportunities to treat these patients earlier in their disease state. Building on the first approval of *Enhertu,* a HER2-directed antibody-drug conjugate*,* in previously treated HER2-positive metastatic breast cancer, AstraZeneca and Daiichi Sankyo are exploring its potential in earlier lines of treatment and in new breast cancer settings. To bring much needed treatment options to patients with triple-negative breast cancer, an aggressive form of breast cancer, AstraZeneca is testing immunotherapy durvalumabin combination with other oncology medicines, including *Lynparza* and *Enhertu*, investigating the potential of AKT kinase inhibitor, capivasertib, in combination with chemotherapy, and collaborating with Daiichi Sankyo to explore the potential of TROP2-directed ADC, datopotamab deruxtecan (DS-1062).

AstraZeneca in oncology

AstraZeneca has a deep-rooted heritage in oncology and offers a quickly growing portfolio of new medicines that has the potential to transform patients' lives and the Company's future. With seven new medicines launched between 2014 and 2020, and a broad pipeline of small molecules and

biologics in development, the Company is committed to advance oncology as a key growth driver for AstraZeneca focused on lung, ovarian, breast and blood cancers.

By harnessing the power of six scientific platforms – Immuno-Oncology, Tumour Drivers and Resistance, DNA Damage Response, Antibody Drug Conjugates, Epigenetics, and Cell Therapies – and by championing the development of personalised combinations, AstraZeneca has the vision to redefine cancer treatment and, one day, eliminate cancer as a cause of death.

AstraZeneca

AstraZeneca (LSE/STO/Nasdaq: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of diseases in three therapy areas - Oncology, Cardiovascular, Renal & Metabolism, and Respiratory & Immunology. Based in Cambridge, UK, AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on Twitter @AstraZeneca.

Contacts

For details on how to contact the Investor Relations Team, please click here. For Media contacts, click here.

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Dr. Modi has provided consulting/advisory services for Daiichi Sankyo.

Om AstraZeneca

AstraZeneca är ett globalt, innovationsdrivet bioläkemedelsföretag med fokus på forskning, utveckling och marknadsföring av receptbelagda läkemedel, primärt för behandling av sjukdomar inom tre huvudsakliga terapiområden: cancer, kardiovaskulära sjukdomar, njursjukdomar och metabola sjukdomar och sjukdomar i andningsvägarna. AstraZeneca bedriver verksamhet i över 100 länder och dess innovativa läkemedel används av miljontals patienter över hela världen.

Mer information finns på: www.astrazeneca.com och www.astrazeneca.se. Du kan även följa oss på twitter https://twitter.com/AstraZenecaSE

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