NEWS RELEASE

AstraZeneca advances scientific leadership across multiple cancers with first data from four pivotal Phase III trials at ESMO

10/11/2023

Two highly anticipated Presidential Symposia for TROPION-Lung01 and TROPION-Breast01 will unveil the significance of datopotamab deruxtecan in lung and breast cancers

FLAURA2 data reinforce TAGRISSO® (osimertinib) as the backbone therapy in EGFR-mutated lung cancer and underscore its added benefit of treating brain metastases

DUO-E results for IMFINZI® (durvalumab) plus LYNPARZA® (olaparib) will show the benefit of immunotherapy and PARP inhibitor combinations in endometrial cancer for the first time

First IMFINZI data in gastric cancer from MATTERHORN Phase III trial will highlight the potential of immunotherapy combinations in earlier settings and growing leadership in gastrointestinal cancers

WILMINGTON, Del.--(BUSINESS WIRE)-- AstraZeneca advances its ambition to eliminate cancer as a cause of death with new data across its robust portfolio and pipeline at the European Society for Medical Oncology (ESMO) Congress, October 20-24, 2023.

Nearly 100 abstracts will feature 19 approved and potential new medicines from AstraZeneca including two late-breaking Presidential Symposia and 26 oral presentations. Highlights include:

- TROPION-Lung01 Phase III trial of AstraZeneca and Daiichi Sankyo's datopotamab deruxtecan (Dato-DXd) in

patients with previously treated advanced non-small cell lung cancer (NSCLC) (Presidential Symposium, Monday, October 23).

- TROPION-Breast01 Phase III trial of datopotamab deruxtecan in patients with previously treated inoperable or metastatic hormone receptor (HR)-positive, HER2-low or negative breast cancer (Presidential Symposium, Monday, October 23).
- FLAURA2 Phase III trial of TAGRISSO® (osimertinib) plus chemotherapy in EGFR-mutated (EGFRm) advanced NSCLC including safety and central nervous system metastases outcomes. **Results** were recently presented from the progression-free survival (PFS) primary analysis.
- DUO-E Phase III trial of IMFINZI®(durvalumab) plus platinum-based chemotherapy followed by either IMFINZImonotherapy or IMFINZIplus LYNPARZA® (olaparib) as maintenance therapy in newly diagnosed advanced or recurrent edometrial cancer.
- MATTERHORN Phase III trial of IMFINZI plus neoadjuvant chemotherapy (before surgery) for patients with resectable, early-stage and locally advanced (Stages II, III, IVA) gastric and gastroesophageal junction (GEJ) cancers.
- DESTINY-PanTumor02 Phase II trial of AstraZeneca and Daiichi Sankyo's ENHERTU® (fam-trastuzumab deruxtecan-nxki) in previously treated HER2-expressing advanced solid tumors including PFS and overall survival (OS) data from the primary analysis.
- Three bispecifics: data from several presentations will highlight the Company's robust clinical program of novel immuno-oncology (IO) bispecific antibodies including data for volrustomig in advanced clear cell renal cell carcinoma (MEDI5752, targeting PD-1/CTLA-4), and data for rilvegostomig (AZD2936, targeting PD-1/TIGIT) and sabestomig (AZD7789, targeting PD-1/TIM3) in lung cancer.

Susan Galbraith, Executive Vice President, Oncology R&D, AstraZeneca, said: "At ESMO, we are building on the potential of our antibody drug conjugate portfolio with results from the TROPION-Lung01 and TROPION-Breast01 Phase III trials demonstrating the promise of datopotamab deruxtecan for patients across multiple cancer types in two back-to-back Presidential Symposia. These first pivotal data from our robust clinical program are just the beginning for this TROP2-directed antibody drug conjugate, which we believe could replace conventional chemotherapy for many patients."

Dave Fredrickson, Executive Vice President, Oncology Business Unit, AstraZeneca, said: "Our key data at ESMO demonstrate our commitment to redefining cancer care across a growing number of tumor types with high unmet need. Across lung, breast, gynecologic and gastrointestinal cancers, the first data will be presented from four different pivotal trials which will raise the bar for patients with multiple medicines from our industry-leading portfolio and highlight the power of novel combinations."

Datopotamab deruxtecan takes center stage with promising data in lung and breast cancers

A Presidential Symposium will highlight PFS data from the TROPION-Lung01 Phase III trial evaluating datopotamab deruxtecan in patients with previously treated advanced NSCLC. In **July**, datopotamab deruxtecan became the first antibody drug conjugate to demonstrate a statistically significant improvement in PFS and a trend in improvement for OS compared to docetaxel, the current standard-of-care chemotherapy. Additionally, a mini-oral presentation will feature initial results from the TROPION-Lung05 Phase II trial evaluating datopotamab deruxtecan in patients with heavily pretreated advanced NSCLC with actionable genomic mutations (AGA). There are currently no TROP2-directed antibody drug conjugates approved for the treatment of patients with lung cancer.

Another Presidential Symposium will showcase data from the TROPION-Breast01 Phase III trial of datopotamab deruxtecan in patients with inoperable or metastatic hormone receptor (HR)-positive, HER2-low or negative breast cancer previously treated with endocrine-based therapy and at least one systemic therapy. In **September**, datopotamab deruxtecan demonstrated a statistically significant and clinically meaningful improvement in PFS and a trend in improvement for OS compared to investigator's choice of chemotherapy.

Lastly, a mini-oral presentation will highlight updated safety and efficacy results from the BEGONIA Phase Ib/II trial of datopotamab deruxtecan plus IMFINZI in patients with previously untreated unresectable, locally advanced or metastatic triple-negative breast cancer (TNBC), including duration of response. Early data from the trial **presented previously** demonstrated promising clinical responses in this setting, regardless of PD-L1 expression (low and high tumors).

IMFINZI combinations enter new tumor types and continue delivering in lung and biliary tract cancers

A late-breaking oral presentation will feature PFS data from the DUO-E Phase III trial evaluating treatment with IMFINZI and chemotherapy followed by either IMFINZI plus LYNPARZA or IMFINZIalone as maintenance therapy in patients with newly diagnosed advanced or recurrent endometrial cancer. High-level **results** recently announced showed both regimens demonstrated a statistically significant and clinically meaningful improvement in PFS compared to standard-of-care chemotherapy alone, with greater clinical benefit observed with the combination of IMFINZIand LYNPARZAas maintenance treatment.

Another late-breaking oral presentation will highlight pathologic complete response (pCR) data from the MATTERHORN Phase III trial of IMFINZI added to standard-of-care FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) neoadjuvant chemotherapy for patients with resectable, early-stage and locally advanced gastric and GEJ cancers versus neoadjuvant therapy alone. High-level interim **results** demonstrated a statistically significant and clinically meaningful improvement in the key secondary endpoint of pCR. This is the first global Phase III trial of an immunotherapy and FLOT chemotherapy combination to demonstrate clinical benefit in this setting. The trial is continuing to assess the primary endpoint of event-free survival.

Also in gastrointestinal cancers, two poster presentations of new data from the TOPAZ-1 Phase III trial will further reinforce the benefit of IMFINZI plus chemotherapy as a 1st-line standard-of-care treatment for advanced biliary tract cancer. Results will be shared from an exploratory analysis of an extended cohort of TOPAZ-1 patients enrolled in China. Additionally, results will be shared from an exploratory analysis assessing the impact of prognostic or predictive factors of OS in the trial.

A late-breaking mini-oral presentation in lung cancer will report exploratory analyses from the AEGEAN Phase III trial of IMFINZI-based treatment before and after surgery in patients with resectable NSCLC, evaluating potential associations between circulating tumor DNA (ctDNA) and neoadjuvant treatment responses.

Extending the benefits of ENHERTUacross HER2-expressing tumors

New data from the DESTINY-PanTumor02 and DESTINY-PanTumor01 Phase II trials will underscore the potential of ENHERTU for previously treated patients with HER2-expressing or HER2-mutated advanced solid tumors, respectively, who currently have no targeted treatment options.

A late-breaking mini-oral presentation of primary results from DESTINY-PanTumor02 will highlight efficacy and safety outcomes for ENHERTU in patients with HER2-expressing solid tumors. In **July**, high-level primary analysis results showed ENHERTU demonstrated clinically meaningful PFS and OS, as well as provided robust and durable tumor responses across multiple HER2-expressing solid tumors in the trial. Additionally, a poster presentation will share exploratory biomarker analyses of HER2 expression and gene amplification in tissue and baseline plasma ctDNA.

A further oral presentation will feature the first report of primary results from DESTINY-PanTumor01 in patients with solid tumors that have specific HER2-activating mutations.

A mini-oral presentation will feature post-hoc pooled efficacy and safety analyses of the DESTINY-Lung01 and DESTINY-Lung02 Phase II trials of ENHERTU in patients with HER2-mutated metastatic NSCLC with and without brain metastases.

Several presentations will feature new data from the DESTINY-Breast clinical program for ENHERTU, including its efficacy in patients with brain metastases.

Progressing next-wave treatments including best-in-class bispecifics

Several presentations will share data from AstraZeneca's portfolio of novel IO bispecific antibodies, underscoring

the Company's investment in a robust clinical program for this next wave of IO therapy. These include:

- A mini-oral presentation of data from a Phase Ib trial of volrustomig (MEDI5752), a PD-1/CTLA-4 bispecific antibody, in the 1st-line treatment of patients with advanced clear cell renal cell carcinoma.
- Another mini-oral presentation of safety and preliminary efficacy results from the Phase I/IIa first-in-human trial of sabestomig (AZD7789), a PD-1/TIM-3 bispecific antibody, in patients with Stages IIIb-IV NSCLC resistant to previous anti-PD(L)1 therapy.
- A poster presentation of data from the ARTEMIDE-01 Phase I trial assessing rilvegostomig (AZD2936), a PD-1/TIGIT bispecific antibody, in patients with advanced or metastatic NSCLC.

Collaboration in the scientific community is critical to improving outcomes for patients. AstraZeneca is collaborating with Daiichi Sankyo Company Limited to develop and commercialize ENHERTUand datopotamab deruxtecan, and with Merck & Co., Inc., known as MSD outside the US and Canada, to develop and commercialize LYNPARZA both as a monotherapy and in combination with other potential medicines. Independently, the companies are developing LYNPARZA in combination with their respective PD-L1 and PD-1 medicines, IMFINZI and pembrolizumab, in a number of tumor types.

Key AstraZeneca presentations during ESMO 2023

Lead Author	Abstract Title	Presentation details (CEST)
Antibody drug conjugates		
Datopotamab deruxtecan		
Ahn, M (presented by Lisberg, A)	Datopotamab deruxtecan (Dato-DXd) vs docetaxel in previously treated advanced/metastatic (adv/met) non-small cell lung cancer (NSCLC): Results of the randomized phase 3 study TROPION-Lung01	Abstract #LBA12 Presidential 3 October 23, 2023 04:42 PM
Bardia, A	Datopotamab deruxtecan (Dato-DXd) vs chemotherapy in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer (BC): Primary results from the randomized Phase 3 TROPION-Breast01 trial	Abstract #LBA11 Presidential 3 October 23, 2023 04:30 PM
Paz-Ares, L	TROPION-Lung05: Datopotamab deruxtecan (Dato-DXd) in previously treated non-small cell lung cancer (NSCLC) with actionable genomic alterations (AGAs)	Abstract #1341MO Mini oral session 1 – NSCLC, metastatic October 21, 2023 09:30 AM
Schmid, P	Datopotamab deruxtecan (Dato-DXd) + durvalumab (D) as first-line (1L) treatment for unresectable locally advanced/metastatic triple-negative breast cancer (a/mTNBC): updated results from BEGONIA, a phase 1b/2 study	Abstract #379MO Mini oral session – Breast cancer, metastatic October 22, 2023 08:30 AM
ENHERTU		
Modi, S	Fam-trastuzumab deruxtecan-nxki (T-DXd) Versus Treatment of Physician's Choice (TPC) in patients (pts) With HER2-Low Unresectable and/or Metastatic Breast Cancer (mBC): Updated Survival Results of the Randomized, Phase 3 DESTINY-Breast04 Study	Abstract #376O Proffered Paper session – Breast cancer, metastatic October 21, 2023 10:25 AM

Hurvitz, S	A Pooled Analysis of fam-trastuzumab deruxtecan-nxki (T-DXd) in Patients (pts) With HER2-Positive (HER2+) Metastatic Breast Cancer (Mbc) With Brain Metastases (BMs) from DESTINY-Breast (DB) -01, 02, and -03	Abstract #377O Proffered Paper session – Breast cancer, metastatic October 21, 2023 10:55 AM
Li, B	Efficacy and safety of fam-trastuzumab deruxtecan-nxki (T-DXd) in patients (pts) with solid tumors harboring specific HER2-activating mutations (HER2m): primary results from the international phase 2 DESTINY-PanTumor01 (DPT-01) study	Abstract #654O Proffered Paper session – Developmental therapeutics October 22, 2023 09:20 AM
Li, B	Fam-trastuzumab deruxtecan-nxki (T-DXd) in Patients (pts) With HER2 (ERBB2)-Mutant (HER2m) Metastatic Non–Small Cell Lung Cancer (NSCLC) With and Without Brain Metastases (BMs): Pooled Analyses From DESTINY-Lung01 and DESTINY-Lung02	Abstract #1321MO Mini oral session 2 – NSCLC, metastatic October 22, 2023 0:9:05 AM
Meric-Bernstam, F	Fam-trastuzumab deruxtecan-nxki (T-DXd) for pretreated patients (pts) with HER2-expressing solid tumors: primary analysis from the DESTINY-PanTumor02 (DP-02) study	Abstract #LBA34 Mini oral session – Developmental therapeutics October 23, 2023 04:40 PM
Smit, E	Baseline Circulating Tumor DNA (ctDNA) Biomarker Analysis of Patients With Human Epidermal Growth Factor Receptor 2 (HER2)-Overexpressing Metastatic Non–Small Cell Lung Cancer (NSCLC) Treated With Fam-trastuzumab deruxtecan-nxki (T-DXd)	Abstract #151P e-Poster – Biomarkers (agnostic) October 21, 2023
Tsurutani, J	Subgroup Analysis of Patients (pts) With HER2-Low Metastatic Breast Cancer (mBC) With Brain Metastases (BMs) at Baseline From DESTINY-Breast04, A Randomized Phase 3 Study of Fam-trastuzumab deruxtecan-nxki (T-DXd) vs Treatment of Physicians Choice (TPC)	Abstract #388P e-Poster – Breast cancer, metastatic October 21, 2023
AZD5335		
Meric-Bernstam, F	FONTANA: A Phase 1/2a study of AZD5335 as monotherapy and in combination with anti-cancer agents in patients with solid tumors	Abstract #819TiP e-Poster – Gynecological cancers October 22, 2023
Immuno-oncology		
Westin, S	Durvalumab (durva) plus carboplatin/paclitaxel (CP) followed by maintenance (mtx) durva ± olaparib (ola) as a first line (1L) treatment for newly diagnosed advanced or recurrent endometrial cancer (EC): results from the Phase III DUO-E/GOG-3041/ENGOT-EN10 trial	Abstract #LBA41 Proffered Paper session 2 – Gynecological cancers October 21, 2023 09:15 AM
Janjigian, Y (presented by Al-Batran, S)	Pathological complete response to 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) chemotherapy with or without durvalumab in resectable gastric and gastroesophageal junction cancer (GC/GEJC): Interim results of the phase 3, randomized, double-blind MATTERHORN study	Abstract #LBA73 Proffered Paper session 1 – Gastrointestinal tumors, upper digestive October 20, 2023 02:10 PM
Garassino, M	Durvalumab (durva) after sequential chemoradiotherapy (CRT) in patients (pts) with unresectable Stage III NSCLC: Final analysis from PACIFIC-6	Abstract #LBA61 Mini oral session 2 – Non-metastatic NSCLC and other thoracic malignancies October 23, 2023 03:20 PM
Reck, M	Associations of ctDNA clearance and pathological response with neoadjuvant treatment in patients with resectable NSCLC from the phase 3 AEGEAN trial	Abstract #LBA59 Mini oral session 2 – Non-metastatic NSCLC and other thoracic malignancies October 23, 2023 03:00 PM
Filippi, A	Durvalumab after radiotherapy (RT) in patients with unresectable Stage III NSCLC ineligible for chemotherapy (CT): Primary results from the DUART study	Abstract #LBA62 Mini oral session 2 – Non-metastatic NSCLC and other thoracic malignancies October 23, 2023 03:30 PM
Besse, B	Safety and preliminary efficacy of AZD7789, a bispecific antibody targeting PD-1 and TIM-3, in patients (pts) with stage IIIB-IV non-small cell lung cancer (NSCLC) with previous anti-PD-L(1) therapy	Abstract #1313MO Mini oral session 1 – NSCLC, metastatic October 21, 2023 09:15 AM

Voss, M	MEDI5752 (volrustomig), a novel PD-1/CTLA-4 bispecific antibody, in the first-line (1L) treatment of 65 patients (pts) with advanced clear cell renal carcinoma (aRCC)	Abstract #1883MO Mini oral session – Genitourinary tumors, non-prostate October 22, 2023 11:25 AM
Brandão, M	Preliminary efficacy and safety of rilvegostomig (AZD2936), a bispecific antibody targeting PD-1 and TIGIT, in checkpoint inhibitor (CPI)-pretreated advanced/metastatic non-small-cell lung cancer (NSCLC): ARTEMIDE-01	Abstract #1446P e-Poster – NSCLC, metastatic October 23, 2023
He, A	Potentially prognostic factors of overall survival in advanced biliary tract cancer in the randomized Phase 3 TOPAZ-1 study	Abstract #102P e-Poster – Biliary tract cancer, incl. cholangiocarcinoma October 23, 2023
Qin, S	Efficacy and safety of durvalumab plus gemcitabine and cisplatin in Chinese participants with advanced biliary tract cancer: extension cohort of the Phase 3, randomized, double-blind, placebo-controlled, global TOPAZ-1 study	Abstract #98P e-Poster – Biliary tract cancer, incl. cholangiocarcinoma October 23, 2023
Tumor drivers and resistance		
Jänne, P	Circulating tumor DNA (ctDNA) profiling in patients (pts) with EGFR-mutated (EGFRm) advanced NSCLC receiving osimertinib + chemotherapy vs osimertinib monotherapy: FLAURA2	Abstract #LBA68 Mini oral session 1 – NSCLC, metastatic October 21, 2023 08:30 AM
DNA damage response		
Mehra, N	Efficacy of Olaparib (ola) + abiraterone (abi) vs placebo (pbo) + abi in the non-BRCA mutation (non-BRCAm) subgroup of patients (pts) with metastatic castration-resistant prostate cancer (mCPRC) in the PROpel trial	Abstract #1805P e-Poster – Prostate cancer October 22, 2023

SELECT SAFETY INFORMATION FOR TAGRISSO® (osimertinib)

- There are no contraindications for TAGRISSO
- Interstitial lung disease (ILD)/pneumonitis occurred in patients treated with TAGRISSO, some of which were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening respiratory symptoms. Permanently discontinue if confirmed
- Monitor patients who have a history or predisposition for QTc prolongation or those who are taking medications that are known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia
- Cardiomyopathy occurred in TAGRISSO-treated patients, some of which were fatal. Monitor patients with cardiac risk factors and assess left ventricular ejection fraction in patients who develop symptoms during treatment. Permanently discontinue TAGRISSO in patients with symptomatic congestive heart failure
- Promptly refer patients with signs and symptoms of keratitis to an ophthalmologist
- Withhold TAGRISSO if erythema multiforme major, Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected and permanently discontinue if confirmed
- Withhold TAGRISSO if cutaneous vasculitis is suspected, evaluate for systemic involvement, and consider dermatology consultation. If no other etiology can be identified, consider permanent discontinuation of TAGRISSO based on severity
- Aplastic anemia, including fatal cases, has been reported in patients treated with TAGRISSO. Inform patients of the signs and symptoms of aplastic anemia. If aplastic anemia is suspected, withhold TAGRISSO and obtain

a hematology consultation. If aplastic anemia is confirmed, permanently discontinue TAGRISSO. Perform complete blood count with differential before starting TAGRISSO, periodically throughout treatment, and more frequently if indicated

- Verify pregnancy status of women prior to use. Advise women to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise men to use effective contraception during treatment with TAGRISSO and for 4 months after the final dose
- Most common (≥20%) adverse reactions, including laboratory abnormalities, were leukopenia, lymphopenia, thrombocytopenia, diarrhea, anemia, rash, musculoskeletal pain, nail toxicity, neutropenia, dry skin, stomatitis, fatigue, and cough

INDICATIONS

- TAGRISSO is indicated as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test
- TAGRISSO is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test
- TAGRISSO is indicated for the treatment of adult patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy

Please see complete **Prescribing Information** , including Patient Information for TAGRISSO.

IMPORTANT SAFETY INFORMATION FOR LYNPARZA® (olaparib)

CONTRAINDICATIONS

There are no contraindications for LYNPARZA.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML): Occurred in approximately 1.5% of patients exposed to LYNPARZA monotherapy, and the majority of events had a fatal outcome. The median duration of therapy in patients who developed MDS/AML was 2 years (range: <6 months to >10 years). All of these patients had previous chemotherapy with platinum agents and/or other DNA-damaging agents, including radiotherapy.

Do not start LYNPARZA until patients have recovered from hematological toxicity caused by previous chemotherapy

(≤Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt LYNPARZA and monitor blood count weekly until recovery.

If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. Discontinue LYNPARZA if MDS/AML is confirmed.

Pneumonitis: Occurred in 0.8% of patients exposed to LYNPARZA monotherapy, and some cases were fatal. If patients present with new or worsening respiratory symptoms such as dyspnea, cough, and fever, or a radiological abnormality occurs, interrupt LYNPARZA treatment and initiate prompt investigation. Discontinue LYNPARZA if pneumonitis is confirmed and treat patient appropriately.

Venous Thromboembolism (VTE): Including severe or fatal pulmonary embolism (PE) occurred in patients treated with LYNPARZA. In the combined data of two randomized, placebo-controlled clinical studies (PROfound and PROpel) in patients with metastatic castration-resistant prostate cancer (N=1180), VTE occurred in 8% of patients who received LYNPARZA, including pulmonary embolism in 6%. In the control arms, VTE occurred in 2.5%, including pulmonary embolism in 1.5%. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism, and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animals, LYNPARZA can cause fetal harm. Verify pregnancy status in females of reproductive potential prior to initiating treatment.

Females

Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months following the last dose.

Males

Advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of LYNPARZA and to not donate sperm during this time.

ADVERSE REACTIONS—First-Line Maintenance BRCAm Advanced Ovarian Cancer

Most common adverse reactions (Grades 1-4) in ≥10% of patients who received LYNPARZA in the first-line maintenance setting for SOLO-1 were: nausea (77%), fatigue (67%), abdominal pain (45%), vomiting (40%), anemia (38%), diarrhea (37%), constipation (28%), upper respiratory tract infection/influenza/nasopharyngitis/bronchitis (28%), dysgeusia (26%), decreased appetite (20%), dizziness (20%), neutropenia (17%), dyspepsia (17%), dyspnea (15%), leukopenia (13%), urinary tract infection (13%), thrombocytopenia (11%), and stomatitis (11%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients who received LYNPARZA in the first-line maintenance setting for SOLO-1 were: decrease in hemoglobin (87%), increase in mean corpuscular volume (87%), decrease in leukocytes (70%), decrease in lymphocytes (67%), decrease in absolute neutrophil count (51%), decrease in platelets (35%), and increase in serum creatinine (34%).

ADVERSE REACTIONS—First-Line Maintenance Advanced Ovarian Cancer in Combination with Bevacizumab

Most common adverse reactions (Grades 1-4) in ≥10% of patients treated with LYNPARZA/bevacizumab and at a ≥5% frequency compared to placebo/bevacizumab in the first-line maintenance setting for PAOLA-1 were: nausea (53%), fatigue (including asthenia) (53%), anemia (41%), lymphopenia (24%), vomiting (22%), and leukopenia (18%). In addition, the most common adverse reactions (≥10%) for patients receiving LYNPARZA/bevacizumab irrespective of the frequency compared with the placebo/bevacizumab arm were: diarrhea (18%), neutropenia (18%), urinary tract infection (15%), and headache (14%).

In addition, venous thromboembolism occurred more commonly in patients receiving LYNPARZA/bevacizumab (5%) than in those receiving placebo/bevacizumab (1.9%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients for LYNPARZA in combination with bevacizumab in the first-line maintenance setting for PAOLA-1 were: decrease in hemoglobin (79%), decrease in lymphocytes (63%), increase in serum creatinine (61%), decrease in leukocytes (59%), decrease in absolute neutrophil count (35%), and decrease in platelets (35%).

ADVERSE REACTIONS—Maintenance gBRCAm Recurrent Ovarian Cancer

Most common adverse reactions (Grades 1-4) in ≥20% of patients who received LYNPARZA in the maintenance setting for SOLO-2 were: nausea (76%), fatigue (including asthenia) (66%), anemia (44%), vomiting (37%), nasopharyngitis/upper respiratory tract infection (URI)/influenza (36%), diarrhea (33%), arthralgia/myalgia (30%), dysgeusia (27%), headache (26%), decreased appetite (22%), and stomatitis (20%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients who received LYNPARZA in the maintenance setting for SOLO-2 were: increase in mean corpuscular volume (89%), decrease in hemoglobin (83%), decrease in leukocytes (69%), decrease in lymphocytes (67%), decrease in absolute neutrophil count (51%), increase in serum creatinine (44%), and decrease in platelets (42%).

ADVERSE REACTIONS—Adjuvant Treatment of gBRCAm, HER2-Negative, High-Risk Early Breast Cancer

Most common adverse reactions (Grades 1-4) in ≥10% of patients who received LYNPARZA in the adjuvant setting for OlympiA were: nausea (57%), fatigue (including asthenia) (42%), anemia (24%), vomiting (23%), headache (20%), diarrhea (18%), leukopenia (17%), neutropenia (16%), decreased appetite (13%), dysgeusia (12%), dizziness (11%), and stomatitis (10%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients who received LYNPARZA in the adjuvant setting for OlympiA were: decrease in lymphocytes (77%), increase in mean corpuscular volume (67%), decrease in hemoglobin (65%), decrease in leukocytes (64%), and decrease in absolute neutrophil count (39%).

ADVERSE REACTIONS—gBRCAm, HER2-Negative Metastatic Breast Cancer

Most common adverse reactions (Grades 1-4) in ≥20% of patients who received LYNPARZA in the metastatic setting for OlympiAD were: nausea (58%), anemia (40%), fatigue (including asthenia) (37%), vomiting (30%), neutropenia (27%), respiratory tract infection (27%), leukopenia (25%), diarrhea (21%), and headache (20%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients who received LYNPARZA in the metastatic setting for OlympiAD were: decrease in hemoglobin (82%), decrease in lymphocytes (73%), decrease in leukocytes (71%), increase in mean corpuscular volume (71%), decrease in absolute neutrophil count (46%), and decrease in platelets (33%).

ADVERSE REACTIONS—First-Line Maintenance gBRCAm Metastatic Pancreatic Adenocarcinoma

Most common adverse reactions (Grades 1-4) in ≥10% of patients who received LYNPARZA in the first-line maintenance setting for POLO were: fatigue (60%), nausea (45%), abdominal pain (34%), diarrhea (29%), anemia (27%), decreased appetite (25%), constipation (23%), vomiting (20%), back pain (19%), arthralgia (15%), rash (15%), thrombocytopenia (14%), dyspnea (13%), neutropenia (12%), nasopharyngitis (12%), dysgeusia (11%), and stomatitis (10%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients who received LYNPARZA in the first-line maintenance setting for POLO were: increase in serum creatinine (99%), decrease in hemoglobin (86%), increase in mean corpuscular volume (71%), decrease in lymphocytes (61%), decrease in platelets (56%), decrease in leukocytes (50%), and decrease in absolute neutrophil count (25%).

ADVERSE REACTIONS—HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Most common adverse reactions (Grades 1-4) in ≥10% of patients who received LYNPARZA for PROfound were: anemia (46%), fatigue (including asthenia) (41%), nausea (41%), decreased appetite (30%), diarrhea (21%), vomiting (18%), thrombocytopenia (12%), cough (11%), and dyspnea (10%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients who received LYNPARZA for PROfound were: decrease in hemoglobin (98%), decrease in lymphocytes (62%), decrease in leukocytes (53%), and decrease in absolute neutrophil count (34%).

ADVERSE REACTIONS—Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

Most common adverse reactions (Grades 1-4) in ≥10% of patients who received LYNPARZA/abiraterone with a difference of ≥5% compared to placebo for PROpel were: anemia (48%), fatigue (including asthenia) (38%), nausea (30%), diarrhea (19%), decreased appetite (16%), lymphopenia (14%), dizziness (14%), and abdominal pain (13%).

Most common laboratory abnormalities (Grades 1-4) in ≥20% of patients who received LYNPARZA/abiraterone for PROpel were: decrease in hemoglobin (97%), decrease in lymphocytes (70%), decrease in platelets (23%), and decrease in absolute neutrophil count (23%).

DRUG INTERACTIONS

Anticancer Agents: Clinical studies of LYNPARZA with other myelosuppressive anticancer agents, including DNA-damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

CYP3A Inhibitors: Avoid coadministration of strong or moderate CYP3A inhibitors when using LYNPARZA. If a strong or moderate CYP3A inhibitor must be coadministered, reduce the dose of LYNPARZA. Advise patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during LYNPARZA treatment.

CYP3A Inducers: Avoid coadministration of strong or moderate CYP3A inducers when using LYNPARZA.

USE IN SPECIFIC POPULATIONS

Lactation: No data are available regarding the presence of olaparib in human milk, its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infant, advise a lactating woman not to breastfeed during treatment with LYNPARZA and for 1 month after receiving the final dose.

Pediatric Use: The safety and efficacy of LYNPARZA have not been established in pediatric patients.

Hepatic Impairment: No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

Renal Impairment: No dosage modification is recommended in patients with mild renal impairment (CLcr 51-80 mL/min estimated by Cockcroft-Gault). In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the dose of LYNPARZA to 200 mg twice daily. There are no data in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min).

INDICATIONS

LYNPARZA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated:

First-Line Maintenance BRCAm Advanced Ovarian Cancer

For the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

First-Line Maintenance HRD-Positive Advanced Ovarian Cancer in Combination with Bevacizumab

In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:

- a deleterious or suspected deleterious BRCA mutation, and/or

- genomic instability

Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

Maintenance BRCA-mutated Recurrent Ovarian Cancer

For the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

Adjuvant Treatment of gBRCAm, HER2-Negative, High-Risk Early Breast Cancer

For the adjuvant treatment of adult patients with deleterious or suspected deleterious gBRCAm, human epidermal growth factor receptor 2 (HER2)-negative, high-risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

gBRCAm, HER2-Negative Metastatic Breast Cancer

For the treatment of adult patients with deleterious or suspected deleterious gBRCAm, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

First-Line Maintenance gBRCAm Metastatic Pancreatic Cancer

For the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

For the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an

FDA-approved companion diagnostic for LYNPARZA.

BRCAm Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

In combination with abiraterone and prednisone or prednisolone (abi/pred) for the treatment of adult patients with deleterious or suspected deleterious BRCA-mutated (BRCAm) metastatic castration-resistant prostate cancer (mCRPC). Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

Please see complete **Prescribing Information** , including **Medication Guide** .

IMPORTANT SAFETY INFORMATION FOR IMFINZI® (durvalumab) AND IMJUDO® (tremelimumab-actl)

There are no contraindications for IMFINZI® (durvalumab) or IMJUDO® (tremelimumab-actl).

Severe and Fatal Immune-Mediated Adverse Reactions

Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions. Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment or after discontinuation. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and before each dose. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate. Withhold or permanently discontinue IMFINZI and IMJUDO depending on severity. See USPI Dosing and Administration for specific details. In general, if IMFINZI and IMJUDO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 mg to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Immune-Mediated Pneumonitis

IMFINZI and IMJUDO can cause immune-mediated pneumonitis, which may be fatal. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

- IMFINZI as a Single Agent
    - In patients who did not receive recent prior radiation, the incidence of immune-mediated pneumonitis was 2.4% (34/1414), including fatal (<0.1%), and Grade 3-4 (0.4%) adverse reactions. In patients who received recent prior radiation, the incidence of pneumonitis (including radiation pneumonitis) in patients with unresectable Stage III NSCLC following definitive chemoradiation within 42 days prior to initiation of IMFINZI in PACIFIC was 18.3% (87/475) in patients receiving IMFINZI and 12.8% (30/234) in patients receiving placebo. Of the patients who received IMFINZI (475), 1.1% were fatal and 2.7% were Grade 3 adverse reactions.
    - The frequency and severity of immune-mediated pneumonitis in patients who did not receive definitive chemoradiation prior to IMFINZI were similar in patients who received IMFINZI as a single agent or with ES-SCLC or BTC when given in combination with chemotherapy.
- IMFINZI with IMJUDO
    - Immune-mediated pneumonitis occurred in 1.3% (5/388) of patients receiving IMFINZI and IMJUDO, including fatal (0.3%) and Grade 3 (0.2%) adverse reactions.
- IMFINZI with IMJUDO and Platinum-Based Chemotherapy
    - Immune-mediated pneumonitis occurred in 3.5% (21/596) of patients receiving IMFINZI in combination with IMJUDO and platinum-based chemotherapy, including fatal (0.5%), and Grade 3 (1%) adverse reactions.

Immune-Mediated Colitis

IMFINZI with IMJUDO and platinum-based chemotherapy can cause immune-mediated colitis, which may be fatal.

IMFINZI and IMJUDO can cause immune-mediated colitis that is frequently associated with diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

- IMFINZI as a Single Agent
    - Immune-mediated colitis occurred in 2% (37/1889) of patients receiving IMFINZI, including Grade 4 (<0.1%) and Grade 3 (0.4%) adverse reactions.
- IMFINZI with IMJUDO
    - Immune-mediated colitis or diarrhea occurred in 6% (23/388) of patients receiving IMFINZI and IMJUDO, including Grade 3 (3.6%) adverse reactions. Intestinal perforation has been observed in other studies of IMFINZI and IMJUDO.
- IMFINZI with IMJUDO and Platinum-Based Chemotherapy

- Immune-mediated colitis occurred in 6.5% (39/596) of patients receiving IMFINZI in combination with IMJUDO and platinum-based chemotherapy including fatal (0.2%) and Grade 3 (2.5%) adverse reactions. Intestinal perforation and large intestine perforation were reported in 0.1% of patients.

Immune-Mediated Hepatitis

IMFINZI and IMJUDO can cause immune-mediated hepatitis, which may be fatal.

- IMFINZI as a Single Agent
  - Immune-mediated hepatitis occurred in 2.8% (52/1889) of patients receiving IMFINZI, including fatal (0.2%), Grade 4 (0.3%) and Grade 3 (1.4%) adverse reactions.
- IMFINZI with IMJUDO
  - Immune-mediated hepatitis occurred in 7.5% (29/388) of patients receiving IMFINZI and IMJUDO, including fatal (0.8%), Grade 4 (0.3%) and Grade 3 (4.1%) adverse reactions.
- IMFINZI with IMJUDO and Platinum-Based Chemotherapy
  - Immune-mediated hepatitis occurred in 3.9% (23/596) of patients receiving IMFINZI in combination with IMJUDO and platinum-based chemotherapy, including fatal (0.3%), Grade 4 (0.5%), and Grade 3 (2%) adverse reactions.

Immune-Mediated Endocrinopathies

- Adrenal Insufficiency :IMFINZI and IMJUDO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated.
  - IMFINZI as a Single Agent
    - Immune-mediated adrenal insufficiency occurred in 0.5% (9/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.
  - IMFINZI with IMJUDO
    - Immune-mediated adrenal insufficiency occurred in 1.5% (6/388) of patients receiving IMFINZI and IMJUDO, including Grade 3 (0.3%) adverse reactions.
  - IMFINZI with IMJUDO and Platinum-Based Chemotherapy
    - Immune-mediated adrenal insufficiency occurred in 2.2% (13/596) of patients receiving IMFINZI in combination with IMJUDO and platinum-based chemotherapy, including Grade 3 (0.8%) adverse reactions.
- Hypophysitis :IMFINZI and IMJUDO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts.

Hypophysitis can cause hypopituitarism. Initiate symptomatic treatment including hormone replacement as clinically indicated.

- IMFINZI as a Single Agent
  - Grade 3 hypophysitis/hypopituitarism occurred in <0.1% (1/1889) of patients who received IMFINZI.
- IMFINZI with IMJUDO
  - Immune-mediated hypophysitis/hypopituitarism occurred in 1% (4/388) of patients receiving IMFINZI and IMJUDO.
- IMFINZI with IMJUDO and Platinum-Based Chemotherapy
  - Immune-mediated hypophysitis occurred in 1.3% (8/596) of patients receiving IMFINZI in combination with IMJUDO and platinum-based chemotherapy, including Grade 3 (0.5%) adverse reactions.

- Thyroid Disorders (Thyroiditis, Hyperthyroidism, and Hypothyroidism) :IMFINZI and IMJUDO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement therapy for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated.
  - IMFINZI as a Single Agent
    - Immune-mediated thyroiditis occurred in 0.5% (9/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.
    - Immune-mediated hyperthyroidism occurred in 2.1% (39/1889) of patients receiving IMFINZI.
    - Immune-mediated hypothyroidism occurred in 8.3% (156/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.
  - IMFINZI with IMJUDO
    - Immune-mediated thyroiditis occurred in 1.5% (6/388) of patients receiving IMFINZI and IMJUDO.
    - Immune-mediated hyperthyroidism occurred in 4.6% (18/388) of patients receiving IMFINZI and IMJUDO, including Grade 3 (0.3%) adverse reactions.
    - Immune-mediated hypothyroidism occurred in 11% (42/388) of patients receiving IMFINZI and IMJUDO.
  - IMFINZI with IMJUDO and Platinum-Based Chemotherapy
    - Immune-mediated thyroiditis occurred in 1.2% (7/596) of patients receiving IMFINZI in combination with IMJUDO and platinum-based chemotherapy.
    - Immune-mediated hyperthyroidism occurred in 5% (30/596) of patients receiving IMFINZI in combination with IMJUDO and platinum-based chemotherapy, including Grade 3 (0.2%) adverse reactions.

        - Immune-mediated hypothyroidism occurred in 8.6% (51/596) of patients receiving IMFINZI in combination with IMJUDO and platinum-based chemotherapy, including Grade 3 (0.5%) adverse reactions.

- Type 1 Diabetes Mellitus, which can present with diabetic ketoacidosis : Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated.
    - IMFINZI as a Single Agent
        - Grade 3 immune-mediated Type 1 diabetes mellitus occurred in <0.1% (1/1889) of patients receiving IMFINZI.
    - IMFINZI with IMJUDO
        - Two patients (0.5%, 2/388) had events of hyperglycemia requiring insulin therapy that had not resolved at last follow-up.
    - IMFINZI with IMJUDO and Platinum-Based Chemotherapy
        - Immune-mediated Type 1 diabetes mellitus occurred in 0.5% (3/596) of patients receiving IMFINZI in combination with IMJUDO and platinum-based chemotherapy including Grade 3 (0.3%) adverse reactions.

Immune-Mediated Nephritis with Renal Dysfunction

IMFINZI and IMJUDO can cause immune-mediated nephritis.

- IMFINZI as a Single Agent
    - Immune-mediated nephritis occurred in 0.5% (10/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.
- IMFINZI with IMJUDO
    - Immune-mediated nephritis occurred in 1% (4/388) of patients receiving IMFINZI and IMJUDO, including Grade 3 (0.5%) adverse reactions.
- IMFINZI with IMJUDO and Platinum-Based Chemotherapy
    - Immune-mediated nephritis occurred in 0.7% (4/596) of patients receiving IMFINZI in combination with IMJUDO and platinum-based chemotherapy, including Grade 3 (0.2%) adverse reactions.

Immune-Mediated Dermatology Reactions

IMFINZI and IMJUDO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/L-1 and CTLA-4 blocking antibodies. Topical emollients and/or topical

corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes.

- IMFINZI as a Single Agent
  - Immune-mediated rash or dermatitis occurred in 1.8% (34/1889) of patients receiving IMFINZI, including Grade 3 (0.4%) adverse reactions.
- IMFINZI with IMJUDO
  - Immune-mediated rash or dermatitis occurred in 4.9% (19/388) of patients receiving IMFINZI and IMJUDO, including Grade 4 (0.3%) and Grade 3 (1.5%) adverse reactions.
- IMFINZI with IMJUDO and Platinum-Based Chemotherapy
  - Immune-mediated rash or dermatitis occurred in 7.2% (43/596) of patients receiving IMFINZI in combination with IMJUDO and platinum-based chemotherapy, including Grade 3 (0.3%) adverse reactions.

Immune-Mediated Pancreatitis

IMFINZI in combination with IMJUDO can cause immune-mediated pancreatitis. Immune-mediated pancreatitis occurred in 2.3% (9/388) of patients receiving IMFINZI and IMJUDO, including Grade 4 (0.3%) and Grade 3 (1.5%) adverse reactions.

Other Immune-Mediated Adverse Reactions

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% each in patients who received IMFINZI and IMJUDO or were reported with the use of other immune-checkpoint inhibitors.

- Cardiac/vascular : Myocarditis, pericarditis, vasculitis.
- Nervous system : Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy.
- Ocular : Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.
- Gastrointestinal : Pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis.
- Musculoskeletal and connective tissue disorders : Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatic.
- Endocrine : Hypoparathyroidism.
- Other (hematologic/immune) : Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis),

sarcoidosis, immune thrombocytopenia, solid organ transplant rejection.

Infusion-Related Reactions

IMFINZI and IMJUDO can cause severe or life-threatening infusion-related reactions. Monitor for signs and symptoms of infusion-related reactions. Interrupt, slow the rate of, or permanently discontinue IMFINZI and IMJUDO based on the severity. See USPI Dosing and Administration for specific details. For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses.

- IMFINZI as a Single Agent
  - Infusion-related reactions occurred in 2.2% (42/1889) of patients receiving IMFINZI, including Grade 3 (0.3%) adverse reactions.
- IMFINZI with IMJUDO
  - Infusion-related reactions occurred in 10 (2.6%) patients receiving IMFINZI and IMJUDO.
- IMFINZI with IMJUDO and Platinum-Based Chemotherapy
  - Infusion-related reactions occurred in 2.9% (17/596) of patients receiving IMFINZI in combination with IMJUDO and platinum-based chemotherapy, including Grade 3 (0.3%) adverse reactions.

Complications of Allogeneic HSCT after IMFINZI

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/L-1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/L-1 blockade and allogeneic HSCT. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/L-1 blocking antibody prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity

Based on their mechanism of action and data from animal studies, IMFINZI and IMJUDO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. In females of reproductive potential, verify pregnancy status prior to initiating IMFINZI and IMJUDO and advise them to use effective contraception during treatment with IMFINZI and IMJUDO and for 3 months after the last dose of IMFINZI and IMJUDO.

Lactation

There is no information regarding the presence of IMFINZI and IMJUDO in human milk; however, because of the potential for serious adverse reactions in breastfed infants from IMFINZI and IMJUDO, advise women not to

breastfeed during treatment and for 3 months after the last dose.

Adverse Reactions

- In patients with Stage III NSCLC in the PACIFIC study receiving IMFINZI (n=475), the most common adverse reactions (≥20%) were cough (40%), fatigue (34%), pneumonitis or radiation pneumonitis (34%), upper respiratory tract infections (26%), dyspnea (25%), and rash (23%). The most common Grade 3 or 4 adverse reactions (≥3%) were pneumonia (7%) and pneumonitis/radiation pneumonitis (3.4%).
- In patients with Stage III NSCLC in the PACIFIC study receiving IMFINZI (n=475), discontinuation due to adverse reactions occurred in 15% of patients in the IMFINZI arm. Serious adverse reactions occurred in 29% of patients receiving IMFINZI. The most frequent serious adverse reactions (≥2%) were pneumonitis or radiation pneumonitis (7%) and pneumonia (6%). Fatal pneumonitis or radiation pneumonitis and fatal pneumonia occurred in <2% of patients and were similar across arms.
- In patients with mNSCLC in the POSEIDON study receiving IMFINZI and IMJUDO plus platinum-based chemotherapy (n=330), the most common adverse reactions (occurring in ≥20% of patients) were nausea (42%), fatigue (36%), musculoskeletal pain (29%), decreased appetite (28%), rash (27%), and diarrhea (22%).
- In patients with mNSCLC in the POSEIDON study receiving IMFINZI in combination with IMJUDO and platinum-based chemotherapy (n=330), permanent discontinuation of IMFINZI or IMJUDO due to an adverse reaction occurred in 17% of patients. Serious adverse reactions occurred in 44% of patients, with the most frequent serious adverse reactions reported in at least 2% of patients being pneumonia (11%), anemia (5%), diarrhea (2.4%), thrombocytopenia (2.4%), pyrexia (2.4%), and febrile neutropenia (2.1%). Fatal adverse reactions occurred in a total of 4.2% of patients.
- In patients with extensive-stage SCLC in the CASPIAN study receiving IMFINZI plus chemotherapy (n=265), the most common adverse reactions (≥20%) were nausea (34%), fatigue/asthenia (32%), and alopecia (31%). The most common Grade 3 or 4 adverse reaction (≥3%) was fatigue/asthenia (3.4%).
- In patients with extensive-stage SCLC in the CASPIAN study receiving IMFINZI plus chemotherapy (n=265), IMFINZI was discontinued due to adverse reactions in 7% of the patients receiving IMFINZI plus chemotherapy. Serious adverse reactions occurred in 31% of patients receiving IMFINZI plus chemotherapy. The most frequent serious adverse reactions reported in at least 1% of patients were febrile neutropenia (4.5%), pneumonia (2.3%), anemia (1.9%), pancytopenia (1.5%), pneumonitis (1.1%), and COPD (1.1%). Fatal adverse reactions occurred in 4.9% of patients receiving IMFINZI plus chemotherapy.
- In patients with locally advanced or metastatic BTC in the TOPAZ-1 study receiving IMFINZI (n=338), the most common adverse reactions (occurring in ≥20% of patients) were fatigue (42%), nausea (40%), constipation (32%), decreased appetite (26%), abdominal pain (24%), rash (23%), and pyrexia (20%).
- In patients with locally advanced or metastatic BTC in the TOPAZ-1 study receiving IMFINZI (n=338), discontinuation due to adverse reactions occurred in 6% of the patients receiving IMFINZI plus chemotherapy.

Serious adverse reactions occurred in 47% of patients receiving IMFINZI plus chemotherapy. The most frequent serious adverse reactions reported in at least 2% of patients were cholangitis (7%), pyrexia (3.8%), anemia (3.6%), sepsis (3.3%) and acute kidney injury (2.4%). Fatal adverse reactions occurred in 3.6% of patients receiving IMFINZI plus chemotherapy. These include ischemic or hemorrhagic stroke (4 patients), sepsis (2 patients), and upper gastrointestinal hemorrhage (2 patients).

- In patients with unresectable HCC in the HIMALAYA study receiving IMFINZI and IMJUDO (n=388), the most common adverse reactions (occurring in ≥20% of patients) were rash (32%), diarrhea (27%), fatigue (26%), pruritus (23%), musculoskeletal pain (22%), and abdominal pain (20%).
- In patients with unresectable HCC in the HIMALAYA study receiving IMFINZI and IMJUDO (n=388), serious adverse reactions occurred in 41% of patients. Serious adverse reactions in >1% of patients included hemorrhage (6%), diarrhea (4%), sepsis (2.1%), pneumonia (2.1%), rash (1.5%), vomiting (1.3%), acute kidney injury (1.3%), and anemia (1.3%). Fatal adverse reactions occurred in 8% of patients who received IMJUDO in combination with durvalumab, including death (1%), hemorrhage intracranial (0.5%), cardiac arrest (0.5%), pneumonitis (0.5%), hepatic failure (0.5%), and immune-mediated hepatitis (0.5%). Permanent discontinuation of treatment regimen due to an adverse reaction occurred in 14% of patients.

The safety and effectiveness of IMFINZI and IMJUDO have not been established in pediatric patients.

Indications:

IMFINZI is indicated for the treatment of adult patients with unresectable Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.

IMFINZI, in combination with IMJUDO and platinum-based chemotherapy, is indicated for the treatment of adult patients with metastatic NSCLC with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.

IMFINZI, in combination with etoposide and either carboplatin or cisplatin, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

IMFINZI, in combination with gemcitabine and cisplatin, is indicated for the treatment of adult patients with locally advanced or metastatic biliary tract cancer (BTC).

IMFINZI in combination with IMJUDO is indicated for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC).

Please see Full Prescribing Information including Medication Guide for **IMFINZI** and **IMJUDO** .

IMPORTANT SAFETY INFORMATION FOR ENHERTU® (fam-trastuzumab deruxtecan-nxki)

Indications

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with:

- Unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either:

  – In the metastatic setting, or
  – In the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy

- Unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy

- Unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy

  This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

- Locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms.
- Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.

Contraindications

None.

Warnings and Precautions

Interstitial Lung Disease / Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose one level. Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate systemic corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks.

Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)

In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 1.0% of patients treated with ENHERTU. Median time to first onset was 5 months (range: 0.9 to 23).

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 10% of patients. Median time to first onset was 2.8 months (range: 1.2 to 21).

Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. For Grade 3 neutropenia (Absolute Neutrophil Count [ANC] <1.0 to 0.5 x 109/L), interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC <0.5 x 109/L), interrupt ENHERTU until resolved to Grade 2 or less, then reduce dose by one level. For febrile neutropenia (ANC <1.0 x 109/L and temperature >38.3° C or a sustained temperature of ≥38° C for more than 1 hour), interrupt ENHERTU until resolved, then reduce dose by one level.

Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)

In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 65% of patients. Sixteen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 664). Febrile neutropenia was reported in 1.1% of patients.

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, a decrease in neutrophil count was reported in 72% of patients. Fifty-one percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 16 days (range: 4 to 187). Febrile neutropenia was reported in 4.8% of patients.

Left Ventricular Dysfunction

Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU. Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. When LVEF is >45% and absolute decrease from baseline is 10-20%, continue treatment with ENHERTU. When LVEF is 40-45% and absolute decrease from baseline is <10%, continue treatment with ENHERTU and repeat LVEF assessment within 3 weeks. When LVEF is 40-45% and absolute decrease from baseline is 10-20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose. When LVEF is <40% or absolute decrease from baseline is >20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF of <40% or absolute decrease from baseline of >20% is confirmed, permanently discontinue ENHERTU. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure. Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF <50% prior to initiation of treatment.

Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)

In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 3.6% of patients, of which 0.4% were Grade 3.

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF.

Embryo-Fetal Toxicity

ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a

fetus. Verify the pregnancy status of females of reproductive potential prior to the initiation of ENHERTU. Advise females of reproductive potential to use effective contraception during treatment and for 7 months after the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose of ENHERTU.

Additional Dose Modifications

Thrombocytopenia

For Grade 3 thrombocytopenia (platelets <50 to 25 x 109/L) interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose. For Grade 4 thrombocytopenia (platelets <25 x 109/L) interrupt ENHERTU until resolved to Grade 1 or less, then reduce dose by one level.

Adverse Reactions

Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)

The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 984 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast03, DESTINY-Breast04, and DESTINY-Lung02. Among these patients 65% were exposed for >6 months and 39% were exposed for >1 year. In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (76%), decreased white blood cell count (71%), decreased hemoglobin (66%), decreased neutrophil count (65%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (47%), increased aspartate aminotransferase (48%), vomiting (44%), increased alanine aminotransferase (42%), alopecia (39%), increased blood alkaline phosphatase (39%), constipation (34%), musculoskeletal pain (32%), decreased appetite (32%), hypokalemia (28%), diarrhea (28%), and respiratory infection (24%).

HER2-Positive Metastatic Breast Cancer

DESTINY-Breast03

The safety of ENHERTU was evaluated in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg intravenously every three weeks in DESTINY-Breast03. The median duration of treatment was 14 months (range: 0.7 to 30).

Serious adverse reactions occurred in 19% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were vomiting, interstitial lung disease, pneumonia, pyrexia, and urinary tract infection. Fatalities due to adverse reactions occurred in 0.8% of patients including COVID-19 and sudden death (one patient each).

ENHERTU was permanently discontinued in 14% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 44% of patients treated with ENHERTU. The most frequent

adverse reactions (>2%) associated with dose interruption were neutropenia, leukopenia, anemia, thrombocytopenia, pneumonia, nausea, fatigue, and ILD/pneumonitis. Dose reductions occurred in 21% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were nausea, neutropenia, and fatigue.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (76%), decreased white blood cell count (74%), decreased neutrophil count (70%), increased aspartate aminotransferase (67%), decreased hemoglobin (64%), decreased lymphocyte count (55%), increased alanine aminotransferase (53%), decreased platelet count (52%), fatigue (49%), vomiting (49%), increased blood alkaline phosphatase (49%), alopecia (37%), hypokalemia (35%), constipation (34%), musculoskeletal pain (31%), diarrhea (29%), decreased appetite (29%), respiratory infection (22%), headache (22%), abdominal pain (21%), increased blood bilirubin (20%), and stomatitis (20%).

HER2-Low Metastatic Breast Cancer

DESTINY-Breast04

The safety of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who received ENHERTU 5.4 mg/kg intravenously every 3 weeks in DESTINY-Breast04. The median duration of treatment was 8 months (range: 0.2 to 33) for patients who received ENHERTU.

Serious adverse reactions occurred in 28% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, pneumonia, dyspnea, musculoskeletal pain, sepsis, anemia, febrile neutropenia, hypercalcemia, nausea, pyrexia, and vomiting. Fatalities due to adverse reactions occurred in 4% of patients including ILD/pneumonitis (3 patients); sepsis (2 patients); and ischemic colitis, disseminated intravascular coagulation, dyspnea, febrile neutropenia, general physical health deterioration, pleural effusion, and respiratory failure (1 patient each).

ENHERTU was permanently discontinued in 16% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 39% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, fatigue, anemia, leukopenia, COVID-19, ILD/pneumonitis, increased transaminases, and hyperbilirubinemia. Dose reductions occurred in 23% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, thrombocytopenia, and neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (76%), decreased white blood cell count (70%), decreased hemoglobin (64%), decreased neutrophil count (64%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (44%), alopecia (40%), vomiting (40%), increased aspartate aminotransferase (38%), increased alanine aminotransferase (36%), constipation (34%), increased blood

alkaline phosphatase (34%), decreased appetite (32%), musculoskeletal pain (32%), diarrhea (27%), and hypokalemia (25%).

Unresectable or Metastatic HER2-Mutant NSCLC (5.4 mg/kg)

DESTINY-Lung02 evaluated two dose levels (5.4 mg/kg [n=101] and 6.4 mg/kg [n=50]); however, only the results for the recommended dose of 5.4 mg/kg intravenously every 3 weeks are described below due to increased toxicity observed with the higher dose in patients with NSCLC, including ILD/pneumonitis.

The safety of ENHERTU was evaluated in 101 patients with unresectable or metastatic HER2-mutant NSCLC who received ENHERTU 5.4 mg/kg intravenously every three weeks in DESTINY-Lung02. Nineteen percent of patients were exposed for >6 months.

Serious adverse reactions occurred in 30% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, thrombocytopenia, dyspnea, nausea, pleural effusion, and increased troponin I. Fatality occurred in 1 patient with suspected ILD/pneumonitis (1%).

ENHERTU was permanently discontinued in 8% of patients. Adverse reactions which resulted in permanent discontinuation of ENHERTU were ILD/pneumonitis, diarrhea, hypokalemia, hypomagnesemia, myocarditis, and vomiting. Dose interruptions of ENHERTU due to adverse reactions occurred in 23% of patients. Adverse reactions which required dose interruption (>2%) included neutropenia and ILD/pneumonitis. Dose reductions due to an adverse reaction occurred in 11% of patients.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (61%), decreased white blood cell count (60%), decreased hemoglobin (58%), decreased neutrophil count (52%), decreased lymphocyte count (43%), decreased platelet count (40%), decreased albumin (39%), increased aspartate aminotransferase (35%), increased alanine aminotransferase (34%), fatigue (32%), constipation (31%), decreased appetite (30%), vomiting (26%), increased alkaline phosphatase (22%), and alopecia (21%).

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01. Patients intravenously received at least one dose of either ENHERTU (N=125) 6.4 mg/kg every 3 weeks or either irinotecan (N=55) 150 mg/m2 biweekly or paclitaxel (N=7) 80 mg/m2 weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) for patients who received ENHERTU.

Serious adverse reactions occurred in 44% of patients receiving ENHERTU 6.4 mg/kg. Serious adverse reactions in >2% of patients who received ENHERTU were decreased appetite, ILD, anemia, dehydration, pneumonia, cholestatic

jaundice, pyrexia, and tumor hemorrhage. Fatalities due to adverse reactions occurred in 2.4% of patients: disseminated intravascular coagulation, large intestine perforation, and pneumonia occurred in one patient each (0.8%).

ENHERTU was permanently discontinued in 15% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 62% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, decreased appetite, leukopenia, fatigue, thrombocytopenia, ILD, pneumonia, lymphopenia, upper respiratory tract infection, diarrhea, and hypokalemia. Dose reductions occurred in 32% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia, decreased appetite, fatigue, nausea, and febrile neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased hemoglobin (75%), decreased white blood cell count (74%), decreased neutrophil count (72%), decreased lymphocyte count (70%), decreased platelet count (68%), nausea (63%), decreased appetite (60%), increased aspartate aminotransferase (58%), fatigue (55%), increased blood alkaline phosphatase (54%), increased alanine aminotransferase (47%), diarrhea (32%), hypokalemia (30%), vomiting (26%), constipation (24%), increased blood bilirubin (24%), pyrexia (24%), and alopecia (22%).

Use in Specific Populations

- Pregnancy: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months after the last dose of ENHERTU.
- Lactation: There are no data regarding the presence of ENHERTU in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.
- Females and Males of Reproductive Potential: Pregnancy testing: Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU. Contraception: Females: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for 7 months after the last dose. Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose. Infertility: ENHERTU may impair male reproductive function and fertility.
- Pediatric Use: Safety and effectiveness of ENHERTU have not been established in pediatric patients.
- Geriatric Use: Of the 883 patients with breast cancer treated with ENHERTU 5.4 mg/kg, 22% were ≥65 years and 3.6% were ≥75 years. No overall differences in efficacy within clinical studies were observed between

patients ≥65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged ≥65 years (60%) as compared to younger patients (48%). Of the 101 patients with unresectable or metastatic HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, 40% were ≥65 years and 8% were ≥75 years. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients. Of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were ≥65 years and 14% were ≥75 years. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients.

- Renal Impairment: A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Monitor patients with moderate renal impairment more frequently. The recommended dosage of ENHERTU has not been established for patients with severe renal impairment (CLcr <30 mL/min).
- Hepatic Impairment: In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor. The recommended dosage of ENHERTU has not been established for patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST).

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-FDA-1088 or fda.gov/medwatch.

Please see accompanying full **Prescribing Information** , including Boxed WARNINGS, and **Medication Guide** .

Notes

AstraZeneca in oncology

AstraZeneca is leading a revolution in oncology with the ambition to provide cures for cancer in every form, following the science to understand cancer and all its complexities to discover, develop and deliver life-changing medicines to patients.

The Company’s focus is on some of the most challenging cancers. It is through persistent innovation that AstraZeneca has built one of the most diverse portfolios and pipelines in the industry, with the potential to catalyse changes in the practice of medicine and transform the patient experience.

AstraZeneca has the vision to redefine cancer care and, one day, eliminate cancer as a cause of death.

About AstraZeneca

AstraZeneca is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialization of prescription medicines in Oncology, Rare Diseases and BioPharmaceuticals, including 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 **www.astrazeneca-us.com** and follow us on social media **@AstraZeneca**.

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