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A SPECIAL MEETING REVIEW EDITION

Highlights in Metastatic Breast Cancer From the European Society for Medical Oncology Virtual Congress 2020

A Review of Selected Presentations From the ESMO Virtual Congress 2020

Special Reporting on:

- ASCENT: A Randomized Phase 3 Study of Sacituzumab Govitecan vs Treatment of Physician's Choice in Patients With Previously Treated Metastatic Triple-Negative Breast Cancer
- IMpassion130: Final OS Analysis From the Pivotal Phase III Study of Atezolizumab + Nab-Paclitaxel vs Placebo + Nab-Paclitaxel in Previously Untreated Locally Advanced or Metastatic Triple-Negative Breast Cancer
- Primary Results From Impassion131, a Double-Blind Placebo-Controlled Randomized Phase 3 Trial of First-Line Paclitaxel +/– Atezolizumab for Unresectable Locally Advanced/Metastatic Triple-Negative Breast Cancer
- Ipatasertib + Paclitaxel for *PIK3CA/AKT1/PTEN*-Altered Hormone Receptor–Positive, HER2-Negative Advanced Breast Cancer: Primary Results From Cohort B of the IPATunity130 Randomised Phase III Trial
- Rucaparib + Sacituzumab Govitecan: Initial Data From the Phase Ib/II SEASTAR Study
- GEICAM/2014-12 (FLIPPER) Study: First Analysis From a Randomized Phase II Trial of Fulvestrant/Palbociclib Versus Fulvestrant/Placebo as First-Line Therapy in Postmenopausal Women With HR+/HER2– Endocrine-Sensitive Advanced Breast Cancer
- Overall Survival Results From SOLAR-1, a Phase 3 Study of Alpelisib + Fulvestrant for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer
- Vandetanib Plus Fulvestrant Versus Placebo Plus Fulvestrant After Relapse or Progression on an Aromatase Inhibitor in Metastatic ER-Positive Breast Cancer (FURVA): A Randomised, Double-Blind, Placebo-Controlled, Phase II Trial

PLUS Meeting Abstract Summaries

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THE **FIRST AND ONLY** ADC FDA APPROVED FOR ADULT PATIENTS WITH mTNBC WHO HAVE RECEIVED AT LEAST 2 PRIOR THERAPIES FOR METASTATIC DISEASE

33.3%

OVERALL RESPONSE RATE (n=36/108; CR+PR)

(95% CI: 24.6; 43.1)

7.7 MEDIAN MONTHS

DURATION OF RESPONSE (range: 1.9, 30.4)

(95% CI: 4.9; 10.8)

Based on investigator assessment.

TRODELVY was evaluated in an open-label, uncontrolled, single-arm phase 1/2 trial of 108 patients with mTNBC who had received at least 2 prior treatments for metastatic disease. TRODELVY was administered intravenously at a dose of 10 mg/kg on Days 1 and 8 of continuous 21-day treatment cycles, and patients were treated until disease progression or unacceptable toxicity. Major efficacy outcome measures were investigator-assessed overall response rate (ORR) using RECIST 1.1 and duration of response.

CI=confidence interval; CR=complete response; PR=partial response.

INDICATION

TRODELVY™ (sacituzumab govitecan-hziy) is indicated for the treatment of adult patients with metastatic triple-negative breast cancer (mTNBC) who have received at least 2 prior therapies for metastatic disease.

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

IMPORTANT SAFETY INFORMATION

WARNING: NEUTROPENIA AND DIARRHEA

TRODELVY can cause severe or life-threatening neutropenia. Withhold TRODELVY for absolute neutrophil count (ANC) below 1500/mm^3 on Day 1 of any cycle or ANC below 1000/mm^3 on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever.

Monitor blood cell counts periodically during treatment. Consider Granulocyte Colony-Stimulating Factor (G-CSF) for secondary prophylaxis. Initiate anti-infective treatment in patients with febrile neutropenia without delay.

- Dose modifications may be required due to neutropenia. Febrile neutropenia occurred in 6% (24/408) of patients treated with TRODELVY, including 8% (9/108) of patients with mTNBC after at least 2 prior therapies. Less than 1% (1/408) of patients had febrile neutropenia leading to permanent discontinuation. The incidence of Grade 1-4 neutropenia was 64% in patients with mTNBC (n=108). In all patients treated with TRODELVY (n=408), the incidence of Grade 1-4 neutropenia was 54%; Grade 4 neutropenia occurred in 13%. Less than 1% (2/408) of patients permanently discontinued treatment due to neutropenia.

Severe diarrhea may occur. Monitor patients with diarrhea and give fluid and electrolytes as needed. Administer atropine, if not contraindicated, for early diarrhea of any severity. At the onset of late diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤ Grade 1 and reduce subsequent doses.

- Diarrhea occurred in 63% (68/108) of patients with mTNBC and 62% (254/408) of all patients treated with TRODELVY. In each population, events of Grade 3-4 occurred in 9% (10/108) of mTNBC patients and 9% (36/408) of all patients treated with TRODELVY. Four out of 408 patients (<1%) discontinued treatment because of diarrhea. Neutropenic colitis was observed in 2% (2/108) of patients in the mTNBC cohort and 1% of all patients treated with TRODELVY

Contraindications: Severe hypersensitivity reaction to TRODELVY.

Hypersensitivity

- TRODELVY can cause severe and life-threatening hypersensitivity, including anaphylactic reactions. Hypersensitivity reactions occurred within 24 hours of dosing in 37% (151/408) and Grade 3-4 hypersensitivity occurred in 1% (6/408) of all patients treated with TRODELVY (n=408). The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 1% (3/408).
- Pre-infusion medication for patients receiving TRODELVY is recommended. Observe patients closely for infusion-related reactions during each TRODELVY infusion and for at least 30 minutes after completion of each infusion. Medication to treat such reactions, as well as emergency equipment, should be available for immediate use.

Nausea and Vomiting

- TRODELVY is emetogenic. Nausea occurred in 69% (74/108) of patients with mTNBC and 69% (281/408) of all patients treated with TRODELVY. Grade 3 nausea occurred in 6% (7/108) and 5% (22/408) of these populations, respectively. Vomiting occurred in 49% (53/108) of patients with mTNBC and 45% (183/408) of all patients treated with TRODELVY. Grade 3 vomiting occurred in 6% (7/108) and 4% (16/408) of these patients, respectively.

Immunomedics

2020-US-TROT-00023

For patients with mTNBC who have received at least 2 prior therapies for metastatic disease

A WAY IN WITH TRODELVY

TRODELVY attacks **metastatic triple-negative breast cancer** (mTNBC) with an antibody-drug conjugate (ADC) that binds to Trop-2

Based on pre-clinical data. May not correlate with clinical outcomes.

- Premedicate with a 2- or 3-drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK-1 receptor antagonist as well as other drugs as indicated) for prevention of chemotherapy-induced nausea and vomiting (CINV).
- Withhold TRODELVY doses for Grade 3 nausea or Grade 3-4 vomiting at the time of scheduled treatment administration and resume with additional supportive measures when resolved to Grade ≤ 1. Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for prevention and treatment of nausea and vomiting.

Use in Patients with Reduced UGT1A1 Activity

- Individuals who are homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia and may be at increased risk for other adverse events following initiation of TRODELVY treatment. Closely monitor patients with reduced UGT1A1 activity for severe neutropenia. The appropriate dose for patients who are homozygous for UGT1A1*28 is not known and should be considered based on individual patient tolerance to treatment.
- In 84% (343/408) of patients who received TRODELVY (up to 10 mg/kg on Days 1 and 8 of a 21-day cycle) and had retrospective UGT1A1 genotype results available, the incidence of Grade 4 neutropenia was 26% (10/39) in patients homozygous for the UGT1A1*28 allele, 13% (20/155) in patients heterozygous for the UGT1A1*28 allele, and 11% (16/149) in patients homozygous for the wild-type allele.

Embryo-Fetal Toxicity

- TRODELVY contains a genotoxic component and can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.
- Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months following the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

Lactation

Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment and for 1 month after the last dose of TRODELVY.

Adverse Reactions

Most common adverse reactions (incidence >25%) in patients with mTNBC are nausea (69%), neutropenia (64%), diarrhea (63%), fatigue (57%), anemia (52%), vomiting (49%), alopecia (38%), constipation (34%), rash (31%), decreased appetite (30%), abdominal pain (26%), and respiratory infection (26%).

Please see the Brief Summary of full Prescribing Information, including boxed Warning, on the pages that follow.

Efficacy. Directed.

TRODELVY™

sacituzumab govitecan-hziy

180 mg for injection

VISIT TRODELVY.COM TO LEARN MORE.

Brief Summary of Prescribing Information

TRODELVY™ (sacituzumab govitecan-hziy) for injection, for intravenous use

See package insert for full Prescribing Information.

INDICATIONS AND USAGE

TRODELVY is indicated for the treatment of adult patients with metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease.

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

WARNING: NEUTROPENIA AND DIARRHEA

- **Severe neutropenia may occur. Withhold TRODELVY for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment. Consider G-CSF for secondary prophylaxis. Initiate anti-infective treatment in patients with febrile neutropenia without delay *[see Warnings and Precautions]*.**
- **Severe diarrhea may occur. Monitor patients with diarrhea and give fluid and electrolytes as needed. Administer atropine, if not contraindicated, for early diarrhea of any severity. At the onset of late diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide *[see Warnings and Precautions]*. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤ Grade 1 and reduce subsequent doses.**

CONTRAINDICATIONS

TRODELVY is contraindicated in patients who have experienced a severe hypersensitivity reaction to TRODELVY *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Neutropenia

TRODELVY can cause severe or life-threatening neutropenia. Withhold TRODELVY for absolute neutrophil count below 1500/mm³ on Day 1 of any cycle or neutrophil count below 1000/mm³ on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever. Dose modifications may be required due to neutropenia.

Febrile neutropenia occurred in 6% (24/408) patients treated with TRODELVY, including 8% (9/108) patients with mTNBC after at least two prior therapies. Less than 1% (1/408) of patients had febrile neutropenia leading to permanent discontinuation.

The incidence of Grade 1-4 neutropenia was 64% in patients with mTNBC (n=108). In all patients treated with TRODELVY (n=408), the incidence of Grade1-4 neutropenia was 54%; Grade 4 neutropenia occurred in 13%. Less than 1% (2/408) of patients permanently discontinued treatment due to neutropenia.

Diarrhea

TRODELVY can cause severe diarrhea. Withhold TRODELVY for Grade 3-4 diarrhea at the time of scheduled treatment administration and resume when resolved to ≤ Grade 1.

At the onset of diarrhea, evaluate for infectious causes and if negative, promptly initiate loperamide, 4 mg initially followed by 2 mg with every episode of diarrhea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after diarrhea resolves. Additional supportive measures (e.g. fluid and electrolyte substitution) may also be employed as clinically indicated.

Patients who exhibit an excessive cholinergic response to treatment with TRODELVY (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive appropriate premedication (e.g., atropine) for subsequent treatments.

Diarrhea occurred in 63% (68/108) of patients with mTNBC and 62% (254/408) of all patients treated with TRODELVY. In each population, events of Grade 3-4 occurred in 9% (10/108) of mTNBC patients and 9% (36/408) of all patients treated with TRODELVY. Four out of 408 patients (<1%) discontinued treatment because of diarrhea. Neutropenic colitis was observed in 2% (2/108) of patients in the mTNBC cohort and 1% of all patients treated with TRODELVY.

Hypersensitivity

TRODELVY can cause severe and life-threatening hypersensitivity. Anaphylactic reactions have been observed in clinical trials with TRODELVY.

Hypersensitivity reactions within 24 hours of dosing occurred in 37% (151/408) of patients treated with TRODELVY. Grade 3-4 hypersensitivity occurred in 1% (6/408) of patients treated with TRODELVY. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 1% (3/408).

Pre-infusion medication for patients receiving TRODELVY is recommended. Observe patients closely for infusion-related reactions during each TRODELVY infusion and for at least 30 minutes after completion of each infusion. Medication to treat such reactions, as well as emergency equipment, should be available for immediate use.

Nausea and Vomiting

TRODELVY is emetogenic. Nausea occurred in 69% (74/108) of patients with mTNBC and 69% (281/408) of all patients treated with TRODELVY. Grade 3 nausea occurred in 6% (7/108) and 5% (22/408) of these populations, respectively.

Vomiting occurred in 49% (53/108) of patients with mTNBC and 45% (183/408) of all patients treated with TRODELVY. Grade 3 vomiting occurred in 6% (7/108) and 4% (16/408) of these patients, respectively.

Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK-1 receptor antagonist as well as other drugs as indicated) for prevention of chemotherapy-induced nausea and vomiting (CINV).

Withhold TRODELVY doses for Grade 3 nausea or Grade 3-4 vomiting at the time of scheduled treatment administration and resume with additional supportive measures when resolved to Grade ≤ 1.

Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for prevention and treatment of nausea and vomiting.

Use in Patients with Reduced UGT1A1 Activity

Individuals who are homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia and may be at increased risk for other adverse reactions following initiation of TRODELVY treatment.

In 84% (343/408) of patients who received TRODELVY (up to 10 mg/kg on Days 1 and 8 of a 21-day cycle) and had retrospective UGT1A1 genotype results available, the incidence of Grade 4 neutropenia was 26% (10/39) in patients homozygous for the UGT1A1*28 allele, 13% (20/155) in patients heterozygous for the UGT1A1*28 allele and 11% (16/149) in patients homozygous for the wild-type allele.

Closely monitor patients with reduced UGT1A1 activity for severe neutropenia. The appropriate dose for patients who are homozygous for UGT1A1*28 is not known and should be considered based on individual patient tolerance to treatment.

Embryo-Fetal Toxicity

Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. TRODELVY contains a genotoxic component, SN-38, and targets rapidly dividing cells. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose *[see Use in Specific Populations]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Neutropenia *[see Warnings and Precautions]*
- Diarrhea *[see Warnings and Precautions]*
- Hypersensitivity *[see Warnings and Precautions]*
- Nausea and Vomiting *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described in the Warnings and Precautions section reflect exposure to TRODELVY as a single agent in a single-arm, open-label study (IMMU-132-01) in 408 patients with mTNBC and other malignancies who had received prior systemic therapeutic regimen for advanced disease. TRODELVY was administered as an intravenous infusion once weekly on Days 1 and 8 of 21-day treatment cycles at doses up to 10 mg/kg until disease progression or unacceptable toxicity.

The data in Table 2 reflect exposure to TRODELVY in a subset of 108 patients with mTNBC who had received at least two prior treatments for metastatic disease in study (IMMU-132-01). Patients received TRODELVY 10 mg/kg via intravenous infusion on Days 1 and 8 of 21-day treatment cycles until disease progression or unacceptable toxicity. The median treatment duration in these 108 patients was 5.1 months (range: 0-51 months).

Serious adverse reactions were reported in 31% of the patients. The most frequent serious adverse reactions (reported in >1%) of the patients receiving TRODELVY were febrile neutropenia (6%) vomiting (5%), nausea (3%), dyspnea (3%), diarrhea (4%), anemia (2%), pleural effusion, neutropenia, pneumonia, dehydration (each 2%).

TRODELVY was permanently discontinued for adverse reactions in 2% of patients. Adverse reactions leading to discontinuation were anaphylaxis, anorexia/fatigue, and headache (each <1%, 1 patient for each event). Forty-five percent (45%) of patients experienced an adverse reaction leading to treatment interruption. The most common adverse reaction leading to treatment interruption was neutropenia (33%). Adverse reactions leading to dose reduction occurred in 33% of patients treated with TRODELVY, with 24% having one dose reduction and 9% with two dose reductions. The most common adverse reaction leading to dose reductions was neutropenia/febrile neutropenia.

Adverse reactions occurring in ≥10% of patients with mTNBC in the IMMU-132-01 study are summarized in Table 2.

Table 2: Adverse Reactions in ≥ 10% of Patients with mTNBC in IMMU-132-01

Adverse Reaction	TRODELVY (n=108)	
	Grade 1-4 (%)	Grade 3-4 (%)
Any adverse reaction	100	71
Gastrointestinal disorders	95	21
Nausea	69	6
Diarrhea	63	9
Vomiting	49	6
Constipation	34	1
Abdominal pain[i]	26	1
Mucositis[ii]	14	1
General disorders and administration site conditions	77	9
Fatigue[iii]	57	8
Edema[iv]	19	0
Pyrexia	14	0
Blood and lymphatic system disorders	74	37
Neutropenia	64	43
Anemia	52	12
Thrombocytopenia	14	3
Metabolism and nutrition disorders	68	22
Decreased appetite	30	1
Hyperglycemia	24	4
Hypomagnesemia	21	1
Hypokalemia	19	2
Hypophosphatemia	16	9
Dehydration	13	5
Skin and subcutaneous tissue disorders	63	4
Alopecia	38	0
Rash[v]	31	3
Pruritus	17	0
Dry Skin	15	0
Nervous system disorders	56	4
Headache	23	1
Dizziness	22	0
Neuropathy[vi]	24	0
Dysgeusia	11	0
Infections and infestations	55	12
Urinary Tract Infection	21	3
Respiratory Infection[vii]	26	3
Musculoskeletal and connective tissue disorders	54	1
Back pain	23	0
Arthralgia	17	0
Pain in extremity	11	0

Immunomedics

Table 2: Adverse Reactions in ≥ 10% of Patients with mTNBC in IMMU-132-01 *(cont'd)*

Respiratory, thoracic and mediastinal disorders	54	5
Cough[viii]	22	0
Dyspnea[ix]	21	3
Psychiatric disorders	26	1
Insomnia	13	0

Graded per NCI CTCAE v. 4.0
[i] Including abdominal pain, distention, pain (upper), discomfort, tenderness
[ii] Including stomatitis, esophagitis, and mucosal inflammation
[iii] Including fatigue and asthenia
[iv] Including edema; and peripheral, localized, and periorbital edema
[v] Including rash; maculopapular, erythematous, generalized rash; dermatitis acneiform; skin disorder, irritation, and exfoliation
[vi] Including gait disturbance, hypoesthesia, muscular weakness, paresthesia, peripheral and sensory neuropathy
[vii] Including lower and upper respiratory tract infection, pneumonia, influenza, viral upper respiratory infection, bronchitis and respiratory syncytial virus infection
[viii] Includes cough and productive cough
[ix] Includes dyspnea and exertional dyspnea

Table 3: Laboratory Abnormalities observed in >10% of Patients while receiving TRODELVY

Laboratory Abnormality	TRODELVY (n=108)	
	All Grades (%)	Grade 3-4 (%)
Hematology		
Decreased hemoglobin	93	6
Decreased leukocytes	91	26
Decreased neutrophils	82	32
Increased activated partial thromboplastin time	60	12
Decreased platelets	30	3
Chemistry		
Increased alkaline phosphatase	57	2
Decreased magnesium	51	3
Decreased calcium	49	3
Increased glucose	48	3
Increased aspartate aminotransferase	45	3
Decreased albumin	39	1
Increased alanine aminotransferase	35	2
Decreased potassium	30	3
Decreased phosphate	29	5
Decreased sodium	25	4.7
Increased magnesium	24	4
Decreased glucose	19	2

Immunogenicity
As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other sacituzumab govitecan products may be misleading.

The analysis of immunogenicity of TRODELVY in serum samples from 106 patients with mTNBC was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-sacituzumab govitecan-hziy antibodies. Detection of the anti-sacituzumab govitecan-hziy antibodies was done using a 3-tier approach: screen, confirm, and titer. Persistent anti-sacituzumab govitecan-hziy antibodies developed in 2% (2/106) of patients.

DRUG INTERACTIONS

Effect of Other Drugs on TRODELVY

UGT1A1 Inhibitors

Concomitant administration of TRODELVY with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38 *[see Warning and Precaution]*. Avoid administering UGT1A1 inhibitors with TRODELVY.

UGT1A1 Inducers

Exposure to SN-38 may be substantially reduced in patients concomitantly receiving UGT1A1 enzyme inducers *[see Warning and Precaution]*. Avoid administering UGT1A1 inducers with TRODELVY.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. TRODELVY contains a genotoxic component, SN-38, and is toxic to rapidly dividing cells. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 – 4% and 15 – 20%, respectively.

Data

Animal data

There were no reproductive and developmental toxicology studies conducted with sacituzumab govitecan-hziy.

Lactation

Risk Summary

There is no information regarding the presence of sacituzumab govitecan-hziy or SN-38 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 and for 1 month after the last dose of TRODELVY.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of TRODELVY.

Contraception

Females

TRODELVY can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose.

Males

Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

Infertility

Females

Based on findings in animals, TRODELVY may impair fertility in females of reproductive potential.

Pediatric Use

Safety and effectiveness of TRODELVY have not been established in pediatric patients.

Geriatric Use

Of the patients who received TRODELVY, 19/108 (18%) patients with mTNBC and 144/408 (35%) of all patients were ≥ 65 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.

Hepatic Impairment

No adjustment to the starting dose is required when administering TRODELVY to patients with mild hepatic impairment (bilirubin less than or equal to 1.5 ULN and AST/ALT < 3 ULN).

The exposure of TRODELVY in patients with mild hepatic impairment (bilirubin less than or equal to ULN and AST greater than ULN, or bilirubin greater than 1.0 to 1.5 ULN and AST of any level; n=12) was similar to patients with normal hepatic function (bilirubin or AST less than ULN; n=45).

The safety of TRODELVY in patients with moderate or severe hepatic impairment has not been established. TRODELVY has not been tested in patients with serum bilirubin > 1.5 ULN, or AST and ALT > 3 ULN, or AST and ALT > 5 ULN and associated with liver metastases.

No dedicated trial was performed to investigate the tolerability of TRODELVY in patients with moderate or severe hepatic impairment. No recommendations can be made for the starting dose in these patients.

OVERDOSAGE

In a clinical trial, planned doses of up to 18 mg/kg (approximately 1.8 times the maximum recommended dose of 10 mg/kg) of TRODELVY were administered. In these patients, a higher incidence of severe neutropenia was observed.

Pharmacogenomics

SN-38 is metabolized via UGT1A1. Genetic variants of the UGT1A1 gene such as the UGT1A1*28 allele lead to reduced UGT1A1 enzyme activity. Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia from TRODELVY *[see Warnings and Precautions]*. Approximately 20% of the Black or African American population, 10% of the White population, and 2% of the East Asian population are homozygous for the UGT1A1*28 allele. Decreased function alleles other than UGT1A1*28 may be present in certain populations.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information)

Neutropenia

Advise patients of the risk of neutropenia. Instruct patients to immediately contact their healthcare provider if they experience fever, chills, or other signs of infection *[see Warnings and Precautions]*.

Diarrhea

Advise patients of the risk of diarrhea. Instruct patients to immediately contact their healthcare provider if they experience diarrhea for the first time during treatment; black or bloody stools; symptoms of dehydration such as lightheadedness, dizziness, or faintness; inability to take fluids by mouth due to nausea or vomiting; or inability to get diarrhea under control within 24 hours *[see Warnings and Precautions]*.

Hypersensitivity

Inform patients of the risk of serious infusion reactions and anaphylaxis. Instruct patients to immediately contact their healthcare provider if they experience facial, lip, tongue, or throat swelling, urticaria, difficulty breathing, lightheadedness, dizziness, chills, rigors, wheezing, pruritus, flushing, rash, hypotension or fever, that occur during or within 24 hours following the infusion *[see Warnings and Precautions]*.

Nausea/Vomiting

Advise patients of the risk of nausea and vomiting. Premedication according to established guidelines with a two or three drug regimen for prevention of chemotherapy-induced nausea and vomiting (CINV) is also recommended. Additional antiemetics, sedatives, and other supportive measures may also be employed as clinically indicated. All patients should receive take-home medications for preventing and treating delayed nausea and vomiting, with clear instructions. Instruct patients to immediately contact their healthcare provider if they experience uncontrolled nausea or vomiting *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

Advise female patients to contact their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy *[see Use in Specific Populations]*.

Contraception

Advise female patients of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of TRODELVY *[see Use in Specific Populations]*.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of TRODELVY *[see Use in Specific Populations]*.

Lactation

Advise women not to breastfeed during treatment and for 1 month after the last dose of TRODELVY *[see Use in Specific Populations]*.

Infertility

Advise females of reproductive potential that TRODELVY may impair fertility *[see Use in Specific Populations]*.

Manufactured by:
Immunomedics, Inc.
300 The American Road
Morris Plains, NJ 07950, USA U.S. License No. 1737

TRODELVY™
sacituzumab govitecan-hziy
180 mg for injection

ASCENT: A Randomized Phase 3 Study of Sacituzumab Govitecan vs Treatment of Physician's Choice in Patients With Previously Treated Metastatic Triple-Negative Breast Cancer

Sacituzumab govitecan-hziy is a novel antibody-drug conjugate.[1] The antibody component targets the trophoblast cell-surface antigen 2 (Trop-2), which is highly expressed in breast cancer and associated with a poor prognosis.[1-3] A hydrolysable linker attaches the antibody to the drug payload, SN-38, which is more potent than its parent compound, irinotecan.[1] Sacituzumab govitecan-hziy has several other unique properties, including a high drug-to-antibody ratio, the ability to liberate SN-38 without the need for internalization and enzymatic cleavage by the tumor cell, and the ability to liberate SN-38 extracellularly in the tumor microenvironment, thus inducing a bystander effect.[1,4-6]

Bardia and colleagues investigated the efficacy and safety of sacituzumab govitecan-hziy among patients with metastatic triple-negative breast cancer (TNBC) in the confirmatory ASCENT trial.[7] This international, multicenter, phase 3 study enrolled patients treated with at least 2 prior standard chemotherapies for advanced disease. Patients with brain metastases were included, but the number was capped at 15% of the study population.

Patients were randomly assigned to receive sacituzumab govitecan-hziy administered intravenously at a dose of 10 mg/kg on days 1 and 8 of a 21-day cycle (n=237) or the physician's choice of single-agent chemotherapy (either eribulin, vinorelbine, gemcitabine, or capecitabine; n=262).[7] The predefined primary endpoint was progression-free survival (PFS) measured by blinded independent central review in patients without brain metastases. This prespecified primary endpoint, approved by regulatory authorities, allowed for investigation of the clinical benefit of the interventions without the confounding effects of brain metastasis, a poor prognostic factor. In March 2020, a unanimous data safety monitoring committee halted the ASCENT trial early based on compelling evidence of efficacy. Bardia and colleagues completed the primary analysis from ASCENT, which included PFS and overall survival (OS).

Overall, the patient demographics

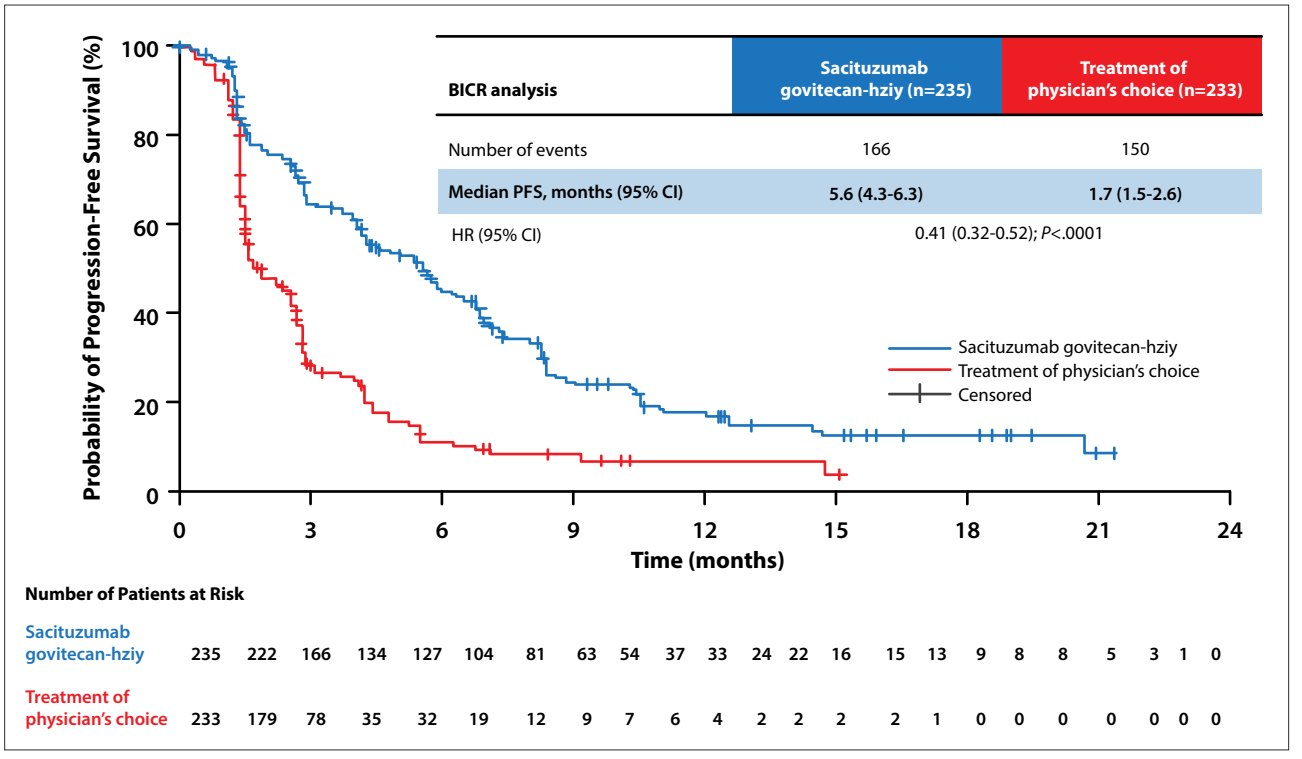

Figure 1. Progression-free survival in the ASCENT trial of sacituzumab govitecan-hziy vs treatment of physician's choice in patients with previously treated metastatic triple-negative breast cancer without brain metastases. BICR, blinded independent central review; HR, hazard ratio; PFS, progression-free survival. Adapted from Bardia A et al. ESMO abstract LBA17. *Ann Oncol.* 2020;31(suppl 4):S1149-S1150.[7]

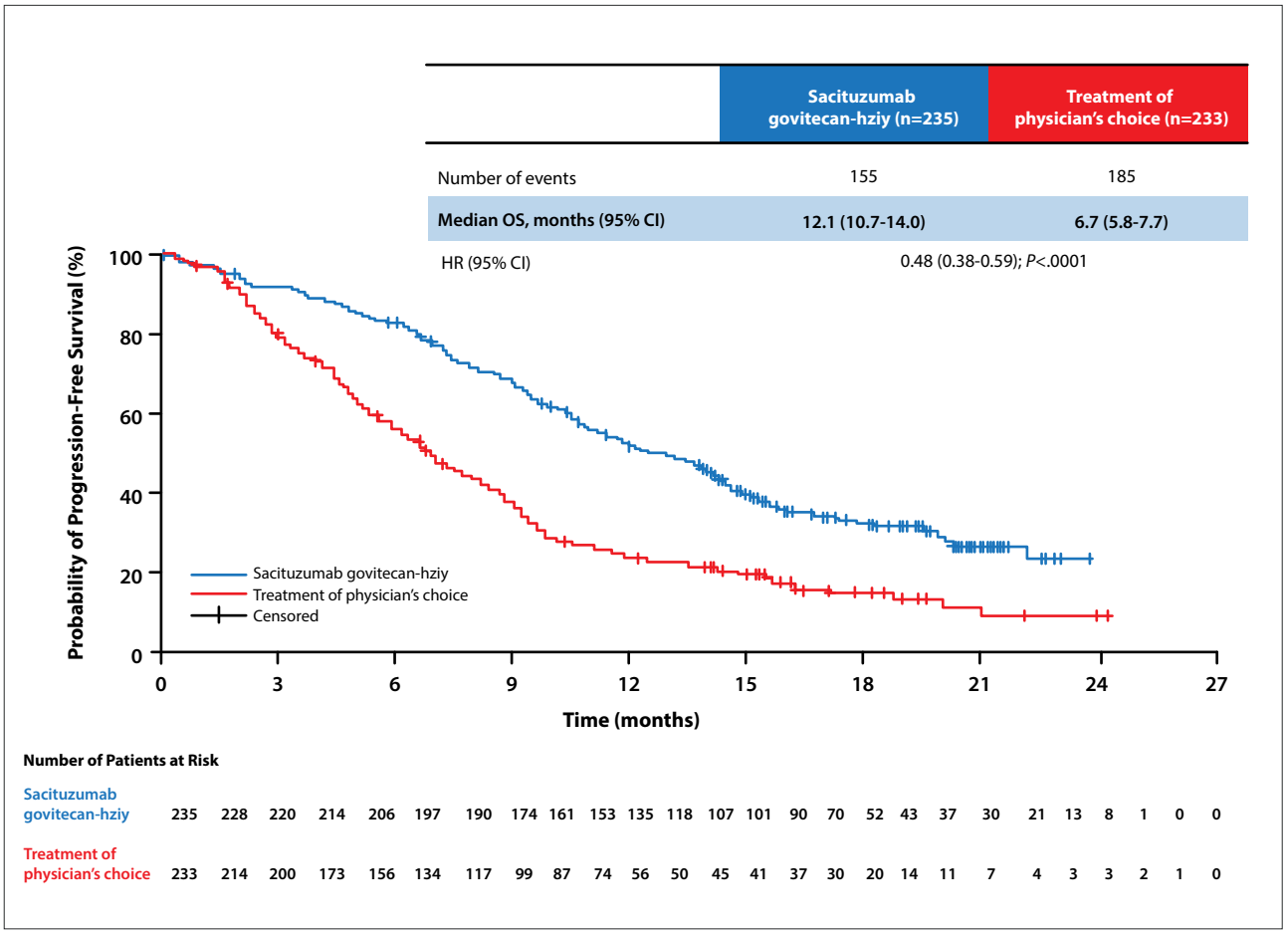

Figure 2. Overall survival in the ASCENT trial of sacituzumab govitecan-hziy vs treatment of physician's choice in patients with previously treated metastatic triple-negative breast cancer without brain metastases. HR, hazard ratio; OS, overall survival. Adapted from Bardia A et al. ESMO abstract LBA17. *Ann Oncol.* 2020;31(suppl 4):S1149-S1150.[7]

at baseline were well balanced between the treatment arms.[7] Most patients were women, and the median age was 54 years. Patients had received a median of 4 previous anticancer regimens. All patients had received prior chemotherapy with a taxane, and approximately 30% of patients in each arm had received a prior checkpoint inhibitor.

The ASCENT study met the primary endpoint of PFS in patients without brain metastases.[7] The median PFS was 5.6 months with sacituzumab govitecan-hziy compared with 1.7 months with standard chemotherapy (hazard ratio [HR], 0.41; 95% CI, 0.32-0.52; *P*<.0001; Figure 1). Sacituzumab govitecan-hziy reduced the risk for progression by 59%, with a clear separation of the PFS curves noticeable within 3 months after treatment was initiated. Similar findings were reported for the investigator-assessed median PFS, as well as median PFS in the full population (including patients with brain metastases). Furthermore, the PFS benefit with sacituzumab govitecan-hziy was consistent across all prespecified subgroups, including those based on age, race, prior chemotherapy, geographic region, prior checkpoint inhibitor use, and presence of liver metastases.

In addition, a significant improvement in OS was observed with sacituzumab govitecan-hziy compared with standard chemotherapy.[7] The median OS was 12.1 months with sacituzumab govitecan-hziy vs 6.7 months with chemotherapy, which corresponded to a 52% reduction in the risk for death (HR, 0.48; 95% CI, 0.38-0.59; *P*<.0001; Figure 2). Similar to the PFS curves in the primary analysis, there was a clear separation of the OS curves within 3 months of initiating treatment, and this separation was maintained over time.

The objective response rate (ORR) was 35% with sacituzumab govitecan-hziy vs 5% with chemotherapy (*P*<.0001).[7] Most of the responses were partial (reported in 31% of the sacituzumab govitecan-hziy arm vs 4% of the control arm). Changes in tumor size from baseline are shown in Figure 3. The clinical benefit rate—defined as the proportion of patients achieving a complete response, a partial

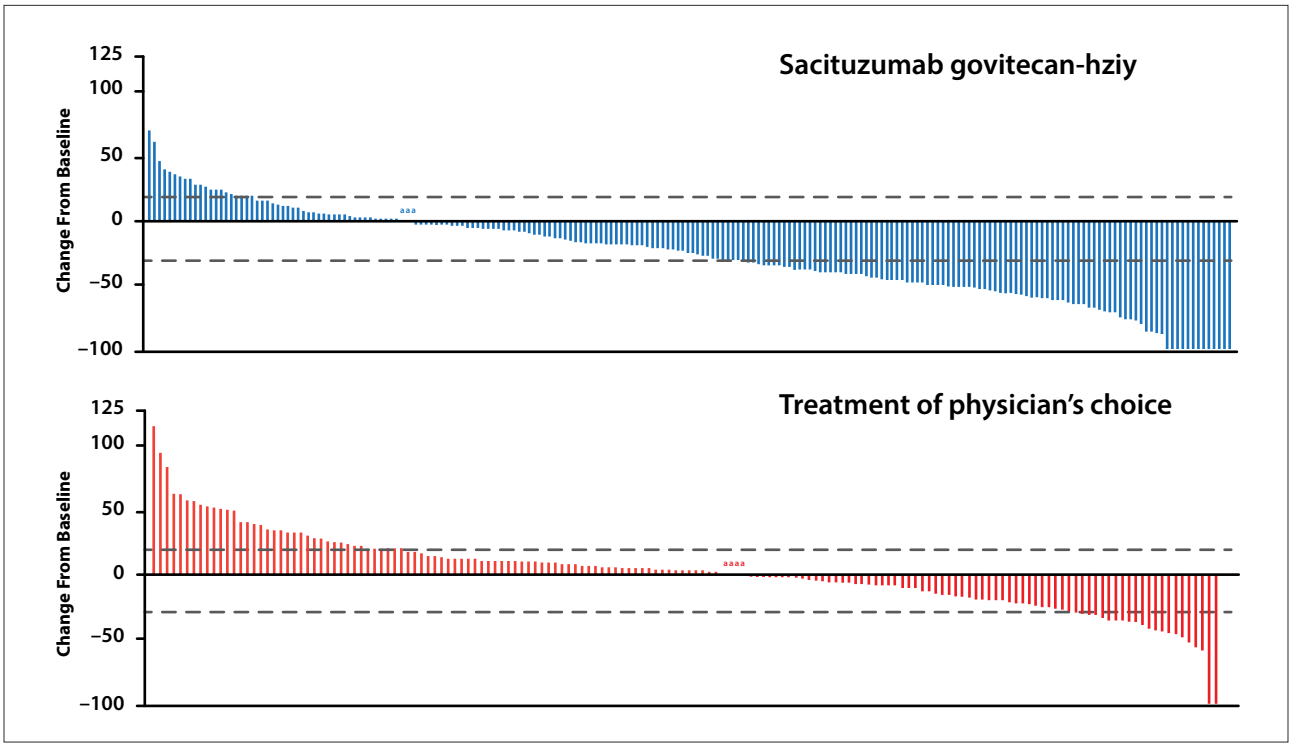

Figure 3. Best percent change from baseline in tumor size in the ASCENT trial of sacituzumab govitecan-hziy vs treatment of physician's choice in patients with previously treated metastatic triple-negative breast cancer. [a]Denotes patients who had a 0% change from baseline in tumor size. Adapted from Bardia A et al. ESMO abstract LBA17. *Ann Oncol.* 2020;31(suppl 4):S1149-S1150.[7]

response, or stable disease for at least 6 months—was 45% in the sacituzumab govitecan-hziy arm vs 9% in the chemotherapy arm (P<.0001). The median duration of response was 6.3 months (95% CI, 5.5-9.0) in the sacituzumab govitecan-hziy arm and 3.6 months (95% CI, 2.8 to not evaluable) in the chemotherapy arm (P=.057). Patients received a median of 7 treatment cycles of sacituzumab govitecan-hziy, with a median treatment duration of 4.4 months (range, 0.03-22.9).

The most common treatment-related adverse events of any grade that occurred with greater frequency with sacituzumab govitecan-hziy compared with chemotherapy were neutropenia (63% vs 43%), diarrhea (59% vs 12%), nausea (57% vs 26%), alopecia (46% vs 16%), fatigue (45% vs 30%), and anemia (34% vs 24%). Key grade 3 or higher treatment-related adverse events included neutropenia (51% vs 33%), diarrhea (10% vs <1%), leukopenia (10% vs 5%), anemia (8% vs 5%), and febrile neutropenia (6% vs 2%).

Neutropenia was managed with dose reduction and/or dose delays, as well as the use of growth factor support from day 2, as needed. Use of granulocyte-colony stimulating factor was required by 49% of patients in the sacituzumab govitecan-hziy arm vs 23% of those in the chemotherapy arm. Adverse events leading to treatment discontinuation were reported in 4.7% of the sacituzumab govitecan-hziy arm and 5.4% of the chemotherapy arm. Among patients treated with sacituzumab govitecan-hziy, there were no cases of severe cardiovascular toxicity, neuropathy above grade 2, or interstitial lung disease above grade 3. There were no deaths attributable to treatment in the sacituzumab govitecan-hziy arm. There was 1 treatment-related fatal event of neutropenic sepsis in the chemotherapy arm.

The investigators concluded that the clinical benefit observed with sacituzumab govitecan-hziy in the ASCENT study confirms the use of this agent as a new standard of care for patients who have received prior treatment for metastatic TNBC.[7] Compared with physician's choice of chemotherapy, the use of sacituzumab govitecan-hziy leads to significant improvements in PFS, OS, and ORR overall and across all subgroups. Sacituzumab govitecan-hziy is well tolerated, has a manageable safety profile, and is associated with a low rate of treatment discontinuation related to adverse events. The US Food and Drug Administration granted accelerated approval to sacituzumab govitecan-hziy for the treatment of metastatic triple-negative breast cancer in patients who had received at least 2 prior lines of therapy for metastatic disease.

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IMpassion130: Final OS Analysis From the Pivotal Phase III Study of Atezolizumab + Nab-Paclitaxel vs Placebo + Nab-Paclitaxel in Previously Untreated Locally Advanced or Metastatic Triple-Negative Breast Cancer

Metastatic TNBC is associated with a poor prognosis compared with other subtypes.[1,2] The phase 3 IMpassion130 trial evaluated the efficacy and safety of first-line atezolizumab plus nab-paclitaxel in previously untreated patients with inoperable, locally advanced, or metastatic TNBC.[3,4] IMpassion130 was a global, randomized, double-blind trial that enrolled 902 patients. The co–primary endpoints, PFS and OS, were hierarchically tested in the intention-to-treat (ITT) population and among patients with tumors that expressed programmed death ligand 1 (PD-L1) on immune cells.

The primary PFS analysis of the IMpassion130 trial demonstrated a statistically significant benefit with the addition of atezolizumab to nab-paclitaxel relative to placebo plus nab-paclitaxel in both the ITT and PD-L1 immune cell–positive patient populations. In the first and second interim OS analyses, a clinically meaningful improvement in OS was observed specifically in the population of patients whose tumors expressed PD-L1 on immune cells, although this was not formally tested owing to the prespecified hierarchical statistical analysis plan.

Based on the primary analysis and interim OS analyses of the IMPassion130 trial, international guidelines now recommend use of the combination of atezolizumab plus nab-paclitaxel as first-line therapy in patients with metastatic TNBC whose tumors express PD-L1 on tumor-infiltrating immune cells.[5,6]

Emens and colleagues reported on data for the final OS analysis for the IMpassion130 trial.[7] The key eligibility criteria included histologically documented metastatic or inoperable, locally advanced TNBC. Patients had received no prior therapy for advanced disease. However, prior chemotherapy, including taxanes, was permitted in the curative setting, provided that the treatment-free interval was at least 12 months. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, were eligible for taxane monotherapy, and had an available tumor sample for PD-L1 testing. Stratification factors included the presence or absence of liver metastases, prior taxane exposure, and PD-L1 immune cell status.

Patients were randomly assigned to receive atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel (n=451 in each group).[7] Atezolizumab at 840 mg was administered intravenously on days 1 and 15 of a 28-day cycle, and nab-paclitaxel at 100 mg/m^2 was administered intravenously

ABSTRACT SUMMARY Abraxane Plus Cisplatin Compared With Gemcitabine Plus Cisplatin as First-Line Treatment in Patients With Metastatic Triple-Negative Breast Cancer (GAP): A Multicenter, Randomized, Open-Label, Phase III Trial

Cisplatin has been associated with clinical benefit in metastatic TNBC and is listed as first-line treatment, in combination with gemcitabine, in several clinical practice guidelines. However, the optimal partner for cisplatin remains to be determined. Hu and colleagues conducted the multicenter phase 3 GAP trial to compare the efficacy and safety of nab-paclitaxel plus cisplatin vs gemcitabine plus cisplatin in women with metastatic TNBC who had not received chemotherapy or targeted therapy in the metastatic setting (Abstract 282MO). Combining nab-paclitaxel with cisplatin significantly improved median PFS compared with the combination of gemcitabine plus cisplatin (9.9 vs 7.5 months; *P*=.004). ORR was also significantly higher with nab-paclitaxel than gemcitabine (81% vs 56%; *P*<.001). Adverse events were tolerable and consistent with the known safety profiles of each agent. Grade 3 or 4 neuropathy was more common in the nab-paclitaxel arm (18% vs 0%), whereas thrombocytopenia was more common in the gemcitabine arm (4% vs 29%).

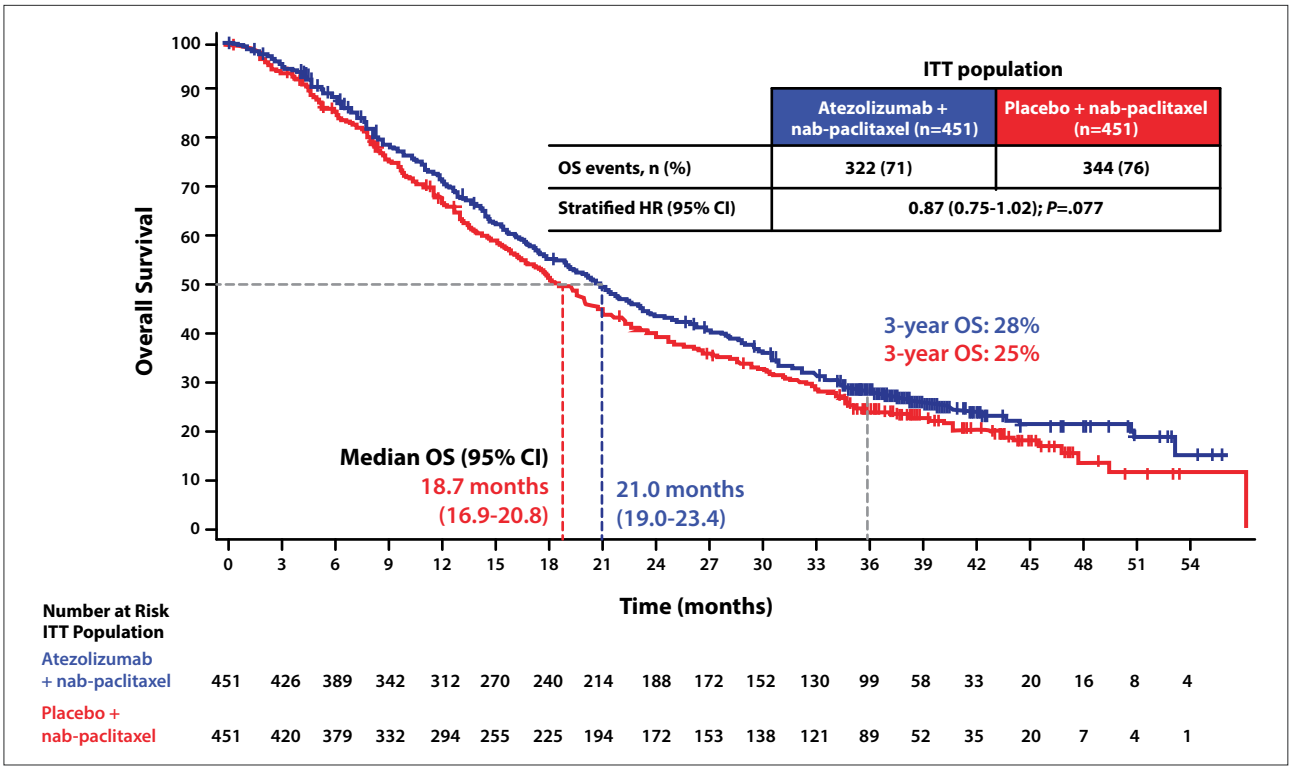

Figure 4. Overall survival among the ITT population in the IMpassion130 trial, which evaluated first-line atezolizumab plus nab-paclitaxel in previously untreated patients with inoperable, locally advanced, or metastatic triple-negative breast cancer. ITT, intention-to-treat. Adapted from Emens LA et al. ESMO abstract LBA16. *Ann Oncol.* 2020;31(suppl 4):S1148.[7]

on cycle days 1, 8, and 15. Patients received their assigned treatment until disease progression or unacceptable toxicity.

The patients' median age was 55 years (range, 20-82) in the atezolizumab group and 56 years (range, 26-86) in the control group.[7] Approximately 90% of patients in each group had metastatic disease at baseline, 41% were PD-L1 immune cell–positive, and 51% had prior taxane exposure.

The median duration of follow-up was 19.7 months in the atezolizumab arm and 18.0 months in the control arm.[7] At the final analysis, there were 27 patients (6%) alive and receiving treatment in the atezolizumab arm vs 8 patients (2%) in the control arm.

In the ITT population, there were 322 (71%) OS events in the atezolizumab arm compared with 344 (76%) in the control arm.[7] The addition of atezolizumab to nab-paclitaxel extended the median OS from 18.7 months to 21.0 months (stratified HR, 0.87; 95% CI, 0.75-1.02; *P*=.077; Figure 4), corresponding to a 13% reduction in the risk for death. The 3-year OS rates were 28% in the atezolizumab arm and 25% in the control arm.

The between-group differences were more apparent among patients with expression of PD-L1 immune cells (≥1%).[7] Among these patients, there were 120 (65%) OS events in the atezolizumab arm compared with 139 (76%) in the control arm. The median OS was 17.9 months vs 25.4 months, respectively, and the 3-year OS rates were 36% vs 22%. The addition of atezolizumab to nab-paclitaxel reduced the risk for death by 33%, and this clinical benefit appeared to be limited to the PD-L1 immune cell–positive population.

The investigators also examined OS across major clinical subgroups.[7] Similar clinical benefits were observed across all subgroups in the ITT population, with the exception of the PD-L1 immune cell–positive group, which derived greater clinical benefit.

Patients in the atezolizumab arm had more exposure to treatment than patients in the control arm.[7] Treatment exposure up to 24 months was reported in 13% of patients receiving atezolizumab compared with 4% of patients receiving placebo. Exposure beyond 24 months occurred in 8% vs 1% of patients, respectively.

The investigators concluded that no new safety signals were identified in the additional follow-up.[7] Most patients experienced an adverse event of any grade. In both treatment arms, the most common adverse events were alopecia, fatigue, nausea, and diarrhea. These adverse events were essentially driven by the chemotherapy component of the treatment. Grade 3 or 4 adverse events were seen in 51% of the atezolizumab arm vs 43% of the control arm.[7] Serious adverse events

occurred in 24% vs 19%, respectively. Adverse events leading to discontinuation were reported in 19% vs 8% of patients, and grade 3/4 adverse events of special interest occurred in 9% vs 5%.

Overall, treatment withdrawal was related to nab-paclitaxel and driven by neuropathy. The group treated with atezolizumab plus nab-paclitaxel had more cases of immune-related adverse events; however, most cases were low grade, easily managed, and did not require treatment discontinuation.

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Primary Results From Impassion131, a Double-Blind Placebo-Controlled Randomized Phase 3 Trial of First-Line Paclitaxel +/– Atezolizumab for Unresectable Locally Advanced/Metastatic Triple-Negative Breast Cancer

The IMpassion130 study established the anti–PD-L1 monoclonal antibody atezolizumab as a new standard of care for patients with metastatic TNBC that is positive for expression of PD-L1.[1-3] The addition of atezolizumab to nab-paclitaxel prolonged PFS and led to a clinically meaningful improvement in OS in these patients. IMpassion131 is an ongoing, randomized, double-blind, placebo-controlled, phase 3 trial that is evaluating atezolizumab in combination with first-line paclitaxel.

Miles and colleagues presented the primary analysis of the IMpassion131 trial.[4] Eligible patients had metastatic or unresectable, locally advanced TNBC. Patients had not received prior chemotherapy or targeted therapy for advanced TNBC, and they had completed previous treatment for early breast cancer at least 1 year before randomization. Patients were eligible for treatment with taxanes, had measurable disease, and had an ECOG performance status of 0 or 1.

Patients were randomly assigned to treatment with atezolizumab plus paclitaxel (n=431) or placebo plus paclitaxel (n=220).[4] Atezolizumab at 840 mg was administered on days 1 and 15 of a 28-day cycle, and paclitaxel 80 mg/m^2 was administered on cycle days 1, 8, and 15. Patients also received dexamethasone at 8 mg to 10 mg for at least 2 infusions as a premedication strategy for paclitaxel.

The hierarchical statistical analysis plan was informed by the results of the IMpassion130 study.[4] The primary endpoint was PFS as assessed by the investigators, with the primary analysis performed in the PD-L1 positive population. If this difference was significant, then PFS would be tested in the ITT population.

The patients' median age was approximately 54 years, and 45% of patients were PD-L1–positive (defined as at least 1% of the tumor area stained for tumor-infiltrating immune cells).[4] Approximately one-quarter of patients had liver metastases, 50% had received treatment with a prior taxane, 50% had received a prior anthracycline, and 30% had de novo metastatic disease at baseline.

The investigators reported no significant improvement in PFS in the PD-L1–positive population.[4] The median PFS was 6.0 months in the atezolizumab arm and 5.7 months in the control arm (stratified HR, 0.82; 95% CI, 0.60-1.12; log-rank *P*=.20; Figure 5). Similarly, in the ITT population, the median PFS was similar between the treatment arms (5.7 vs 5.6 months, respectively). Since the primary endpoint was not met, no statistical analyses were performed on subsequent endpoints.

There appeared to be a trend toward an improvement in investigator-assessed ORR with the addition of atezolizumab.[4] In the ITT population, the ORR was 54% in the atezolizumab arm vs 48% in the control arm. In the PD-L1 positive population, ORR was 63% vs 55%, respectively.

The first interim OS analysis was performed after deaths occurred in 27% of the ITT population.[4] However, there were some concerns that

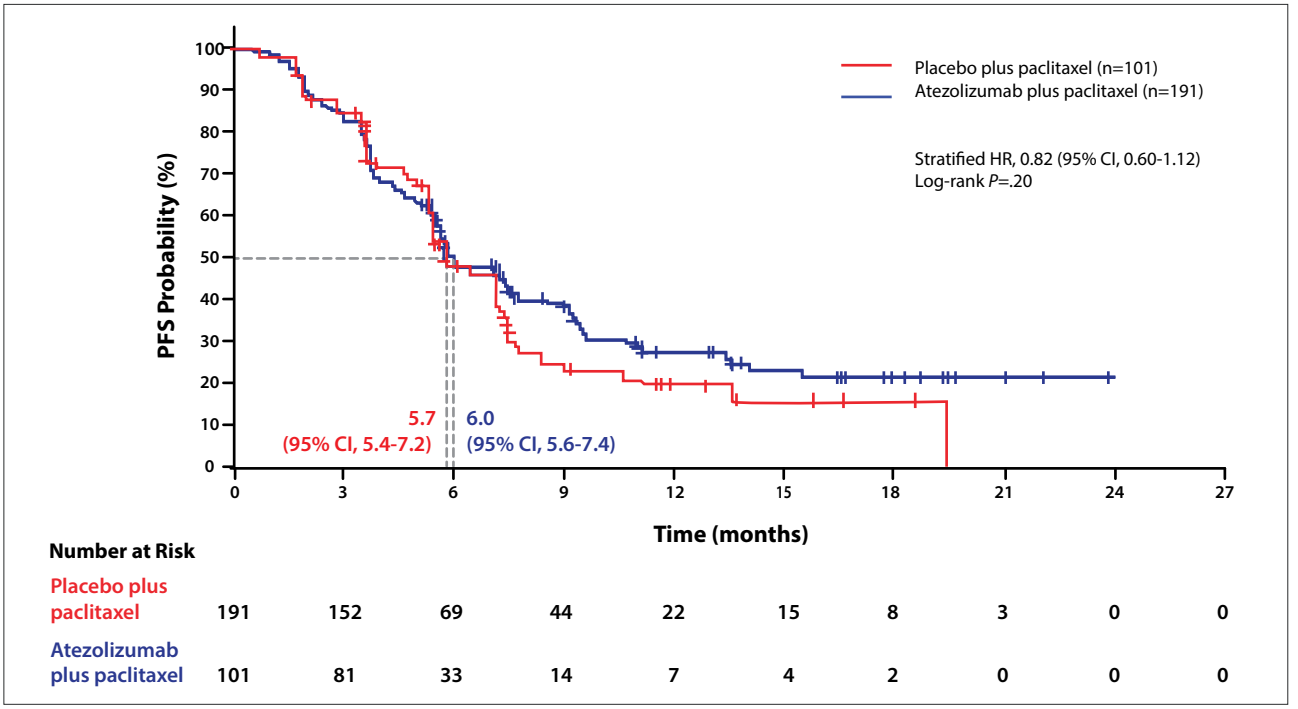

Figure 5. Progression-free survival in the IMpassion131 trial, which evaluated atezolizumab plus paclitaxel as first-line treatment in patients with unresectable locally advanced/metastatic triple-negative breast cancer. Adapted from Miles DW et al. ESMO abstract LBA15. *Ann Oncol.* 2020;31(suppl 4):S1147-S1148.[4]

there might be a trend toward better survival in the control group. In a subsequent interim analysis performed after deaths occurred in 47% of the ITT population, the median OS was 19.2 months in the atezolizumab arm vs 22.8 months in the control arm (HR, 1.11). The median OS was 22.1 months vs 28.3 months, respectively, in the PD-L1 positive population (HR, 1.12). The 2-year OS rates were similar between the treatment arms in both the ITT (42% vs 45%) and PD-L1–positive (49% vs 51%) populations. These data provided some confidence that treatment with atezolizumab did not confer an adverse effect. However, the investigators noted that further follow-up is warranted.

Treatment exposure was similar in the 2 treatment arms.[4] Patients in the atezolizumab arm received a median of 5 cycles, while patients in the control arm received a median of 6 cycles. The median dose intensity exceeded 99% in the atezolizumab arm and 100% in the control arm.

The safety profile of the combination of atezolizumab plus paclitaxel was consistent with the known effects of each drug.[4] The most common adverse events of alopecia, anemia, and peripheral neuropathy occurred at similar rates in both treatment arms, and they were attributable to the chemotherapy backbone. Adverse events with fatal outcomes occurred in 2% of each treatment arm, with 4 cases (<1%) attributed to treatment in the atezolizumab arm and none in the control arm.[4] Grade 3/4 adverse events of special interest occurred in 42 patients (10%) in the atezolizumab arm compared with 11 patients (5%) in the control arm. The incidence of grade 3/4 immune-mediated adverse events was low in both treatment arms.

The investigators observed that the lack of PFS and OS benefit contrasts with the benefit observed with atezolizumab and nab-paclitaxel in the IMpassion130 trial.[4] Further exploration is needed to explain these differences.

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Ipatasertib + Paclitaxel for *PIK3CA/AKT1/PTEN*-Altered Hormone Receptor–Positive, HER2-Negative Advanced Breast Cancer: Primary Results From Cohort B of the IPATunity130 Randomised Phase III Trial

Previous research and data from clinical trials have shown that the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway plays a critical role in patients with hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer.[1] AKT activation has been implicated in the development of resistance to endocrine therapy. Ipatasertib is an oral ATP-selective inhibitor of AKT1 to 3, the central node of the PI3K/AKT pathway.[2-6] In the phase 2 LOTUS trial in metastatic TNBC, adding ipatasertib to paclitaxel improved PFS and OS, particularly among patients with *PIK3CA/AKT1/PTEN*-altered tumors.[7,8]

Turner and colleagues reported results from cohort B of the phase 2/3 IPATunity130 trial.[9,10] The study evaluated treatment with ipatasertib in patients with hormone receptor–positive, HER2-negative measurable advanced breast cancer with *PIK3CA/AKT1/PTEN* alterations. All patients were candidates for treatment with chemotherapy. The study excluded patients who had received prior chemotherapy for advanced breast cancer or who had relapsed within a year of neoadjuvant or adjuvant chemotherapy.

Cohort B of the IPATunity130 study enrolled 222 patients between January 2018 and May 2019, with 50% of participants coming from European sites and 26% from sites in the Asia-Pacific region.[9] Patients were randomly assigned to ipatasertib plus paclitaxel or placebo plus paclitaxel administered during 28-day cycles. Ipatasertib 400 mg was given orally once daily for the first 21 days of each cycle, and paclitaxel was administered intravenously at a dose of 80 mg/m^2 on days 1, 8, and 15. Patients received treatment until progression or unacceptable toxicity. The primary endpoint was investigator-assessed PFS.

PIK3CA/AKT1-activating mutations were present in 88% of the ipatasertib arm and 81% of the control arm (81%).[9] The remainder of patients in each of the treatment arms had PTEN alterations without *PIK3CA/AKT1*-activating mutations.

After a median follow-up of 12.9 months, the median PFS as assessed by the investigators was 9.3 months in both treatment arms (stratified HR, 1.0; 95% CI, 0.71-1.40; *P*=.9965; Figure 6).[9] In both arms, the ORR was 47% and the median duration of response was 9.2 months. At the time of the primary analysis, the median OS was not estimable in the ipatasertib arm vs 21 months in the control arm (HR, 0.72).

The mean duration of treatment with ipatasertib or placebo was 8.4 months in the ipatasertib arm vs 8.7 months in the control arm.[9] The mean duration of treatment with paclitaxel was 7.8 months vs 8.5 months, respectively. Among patients treated with ipatasertib plus paclitaxel, 11% discontinued treatment owing to adverse

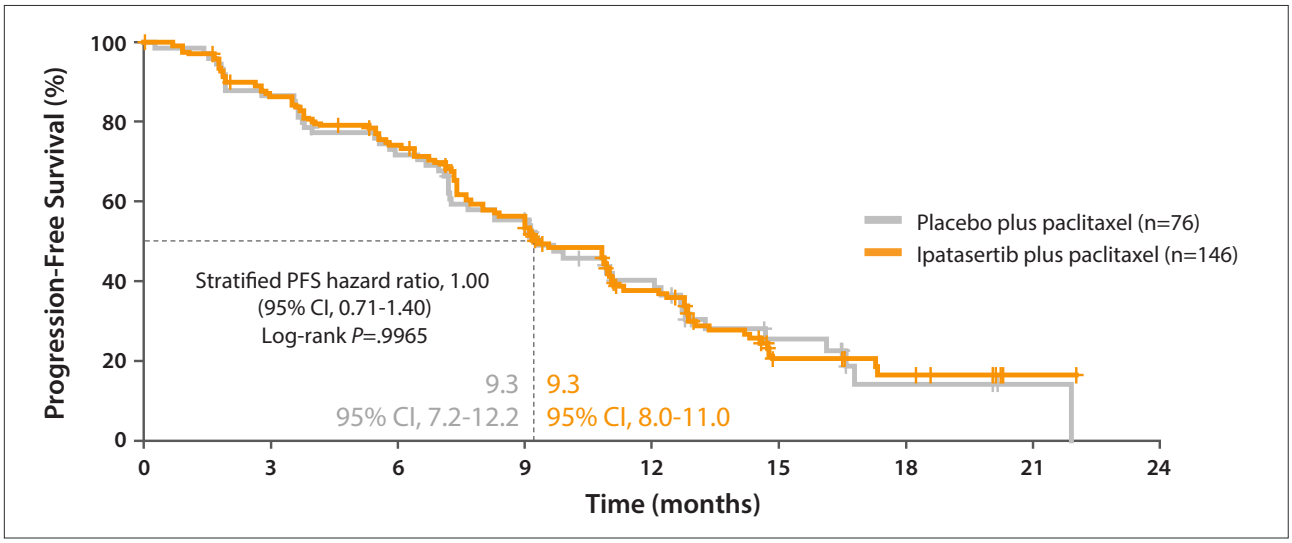

Figure 6. Progression-free survival in the IPATunity130 trial, which evaluated ipatasertib plus paclitaxel in patients with *PIK3CA/AKT1/PTEN*-altered, hormone receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer. Adapted from Turner N et al. ESMO abstract 283MO. *Ann Oncol.* 2020;31(suppl 4):S354-S355.[9]

events associated with ipatasertib. In the control arm, 4% of patients discontinued treatment owing to adverse events associated with the placebo. Adverse events related to paclitaxel led to treatment discontinuation in 26% of the ipatasertib arm and 13% of the control arm.

The most common adverse event was diarrhea, occurring in 85% of the ipatasertib arm vs 37% of the control arm.[9] Other common adverse events included alopecia (50% vs 59%) and nausea (41% vs 20%). Among patients receiving ipatasertib, diarrhea resolved in 94% over a median of 15 days, while nausea resolved in 87% over a median of 22.5 days. The investigators also looked at potential AKT adverse events. They found a minor increase in rash with ipatasertib, but no clear increase in hyperglycemia.

The investigators concluded that the addition of ipatasertib to paclitaxel among patients with *PIK3CA/AKT1/PTEN*-altered, hormone receptor–positive, HER2-negative advanced breast cancer did not improve PFS or ORR.[9] In contrast, combining an AKT inhibitor with fulvestrant improved PFS in the phase 2 FAKTION trial,[11] suggesting that endocrine blockade is critical to the activity of AKT inhibitors in hormone receptor–positive, HER2-negative advanced breast cancer.

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Rucaparib + Sacituzumab Govitecan: Initial Data From the Phase Ib/II SEASTAR Study

The combination of poly(ADP-ribose) polymerase (PARP) inhibitors and DNA topoisomerase (TOP1) inhibitors exhibited highly synergistic antitumor effects in preclinical studies, and overlapping toxicities in clinical trials.[1-5] Tumor-targeted delivery of a TOP1 inhibitor, such as with the antibody-drug conjugate sacituzumab govitecan-hziy, may overcome issues related to systemic toxicity.[6]

Yap and colleagues evaluated the safety, tolerability, and preliminary efficacy of rucaparib plus sacituzumab govitecan-hziy in the SEASTAR study, an open-label, parallel-arm, phase 1b trial.[7] Eligible patients had metastatic TNBC, urothelial carcinoma, platinum-resistant ovarian cancer, or another solid tumor with an identified deleterious mutation in a homologous recombination repair (HRR) gene, such as *BRCA1/2*. The trial enrolled patients who had received a prior PARP inhibitor, but excluded those previously treated with TOP1 inhibitors, such as irinotecan and topotecan.

Three patients were enrolled in cohort 1 and a further 3 patients in cohort 2.[7] The starting dose regimen in cohort 1 was rucaparib at 300 mg orally twice daily plus sacituzumab govitecan-hziy at 6 mg/kg administered intravenously on days 1 and 8 of a 21-day cycle. In cohort 2, the starting dose of rucaparib was reduced to 300 mg once daily, whereas the sacituzumab govitecan-hziy dose remained unchanged.

Two patients in cohort 1 experienced dose-limiting grade 4 neutropenia during cycle 1.[7] One was a 56-year-old woman with metastatic granulosa cell ovarian cancer with no *HRR* gene mutation detected, while the other patient was a 63-year-old man with metastatic transitional cell urothelial carcinoma and a *BRCA2* gene mutation.

In contrast, none of the patients in cohort 2 experienced dose-limiting grade 4 treatment-emergent adverse events.[7] All patients in cohort 2 were women ages 50 years or older. Two patients had metastatic TNBC (invasive ductal carcinoma) and had received at least 6 prior anticancer regimens. One of these patients had no known deleterious *HRR* gene mutations, whereas the other had not been tested. However, all patients in cohort 2 experienced either grade 3 or 4 neutropenia that delayed the start of the second cycle by 1 to 2 weeks.

Despite the early toxicities, all 6

patients in the SEASTAR study continued treatment for at least 12 weeks.[7] The treatment-emergent adverse events were managed through interruption of the treatment, dose reduction, and/or use of hematopoietic growth factor.

All patients had a best response of stable disease or better.[7] Three patients who had a confirmed partial response had been previously treated with a PARP inhibitor. One of these cases was a patient in cohort 2 who had metastatic TNBC, had no known *HRR* gene mutation, and had received prior veliparib.

The investigators concluded that initial encouraging signs of antitumor activity were seen with the combination of rucaparib and sacituzumab govitecan-hziy among patients with advanced solid tumors.[7] These findings were observed in patients with exposure to a prior PARP inhibitor and in patients without a deleterious *HRR* gene mutation.

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GEICAM/2014-12 (FLIPPER) Study: First Analysis From a Randomized Phase II Trial of Fulvestrant/Palbociclib Versus Fulvestrant/Placebo as First-Line Therapy in Postmenopausal Women With HR+/HER2– Endocrine-Sensitive Advanced Breast Cancer

Palbociclib combined with fulvestrant is standard-of-care treatment for patients with hormone receptor–positive, HER2-negative metastatic breast cancer who progressed or relapsed on previous endocrine therapy. The phase 3 PALOMA-3 trial demonstrated a significant increase in the median PFS from 4.6 months with placebo plus fulvestrant to 9.5 months with palbociclib plus fulvestrant (P<.0001).[1] However, patients with endocrine-sensitive metastatic breast cancer were excluded from PALOMA-3.

Albanell and colleagues presented the first analysis from the randomized phase 2 FLIPPER study, which compared the efficacy and safety of palbociclib plus fulvestrant vs fulvestrant plus placebo among postmenopausal women diagnosed with endocrine-sensitive, hormone receptor–positive, HER2-negative metastatic breast cancer.[2] The study investigators defined endocrine-sensitive disease as a relapse that occurred after adjuvant endocrine therapy of more than 5 years and a disease-free interval exceeding 12 months, or de novo metastatic disease.[2] Patients were randomly assigned to palbociclib in combination with fulvestrant or placebo plus fulvestrant. Stratification factors included the presence of visceral or nonvisceral metastases, and de novo metastatic or recurrent disease presentation at study entry. The treatment was administered in 28-day cycles. Oral palbociclib at

ABSTRACT SUMMARY Sacituzumab Govitecan in Combination With the PARP Inhibitor Talazoparib in Metastatic Triple-Negative Breast Cancer

Bardia and colleagues presented the design of a phase 1b/2 open-label study of the novel antibody-drug conjugate sacituzumab govitecan-hziy in combination with talazoparib in men and women with metastatic TNBC (NCT04039230; Abstract 358 TiP). The study comprises a dose-escalation phase to assess dose-limiting toxicity and the maximum tolerated dose of sacituzumab govitecan-hziy in combination with talazoparib, followed by a dose-expansion phase to assess the efficacy (response rates and survival outcomes) of this combination at the recommended phase 2 dose. By September 2020, the study had enrolled 20 patients with histologically or cytologically confirmed metastatic TNBC. Patients had received no more than 1 prior therapy for metastatic disease during the dose-expansion phase. (There was no limit on prior therapy during the dose-escalation phase.) The eligibility criteria include premenopausal and postmenopausal women, men, patients with an ECOG performance status of 0 or 1, and patients with stable central nervous system metastatic disease. The trial is expected to enroll between 15 and 30 patients in phase 1b and 35 patients in phase 2.

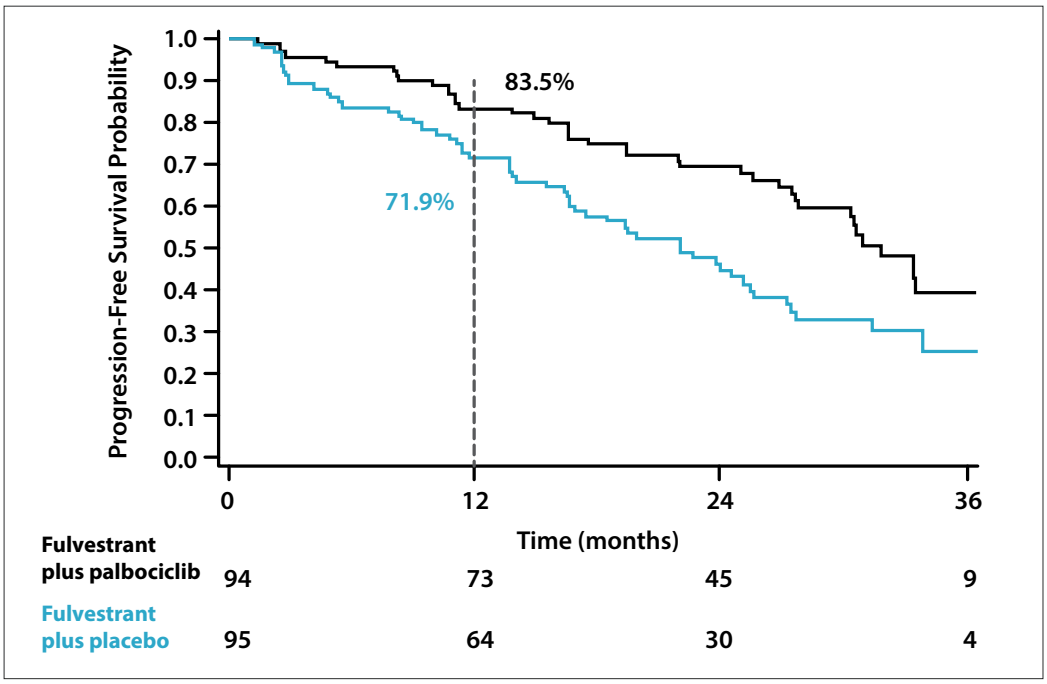

Figure 7. Progression-free survival in the phase 2 GEICAM/2014-12 (FLIPPER) study, which evaluated palbociclib plus fulvestrant as first-line therapy in postmenopausal women with hormone receptor–positive/human epidermal growth factor receptor 2–negative endocrine-sensitive advanced breast cancer. Adapted from Abanell J et al. ESMO abstract LBA19. *Ann Oncol.* 2020;31(suppl 4):S1151.[2]

125 mg was administered once daily for 3 weeks and then halted for the final week in each cycle. Fulvestrant was administered intramuscularly at a dose of 500 mg on days 1 and 15 of the first 28-day cycle, then once every 28 days during subsequent cycles. The primary analysis of PFS rate at 1 year was performed when all patients had at least 12 months of follow-up.

The median age of all patients was 64 years, and approximately 97% had an ECOG performance status of 0 or 1.[2] The analysis included 94 patients in the palbociclib arm and 95 patients in the control arm. Similar rates of de novo metastatic disease (47% vs 44%) and visceral disease (61% vs 60%) were observed between the treatment arms.

After a median follow-up of 28.6 months, the PFS rate at 1 year was 83.5% in the palbociclib arm and 71.9% in the control arm (Figure 7).[2] This difference produced a hazard ratio of 0.55 (*P*=.064), which was considered statistically significant based on the statistical parameters established for this phase 2 study. The addition of palbociclib significantly prolonged median PFS from 22 months in the control arm to 32 months (*P*=.002) in the palbociclib arm.

An exploratory analysis of the PFS rate at 1 year examined the differences by site of metastases (visceral or nonvisceral) and disease presentation at study entry (de novo metastatic or recurrent).[2] Compared with the control arm, the addition of palbociclib to fulvestrant significantly increased the 1-year PFS rate in patients with visceral disease (82% vs 70%) and de novo metastatic disease (91% vs 60%).

Measurable disease was reported in 63 patients in the palbociclib arm and 64 patients in the control arm.[2] Among these patients, the ORR was 68% vs 42%, respectively (*P*=.004). The clinical benefit rate was 90% in the palbociclib arm vs 80% in the control arm (*P*=.048).

Treatment-related serious adverse events were reported in 3% of the palbociclib arm and 2% of the control arm.[2] All of these events led patients to discontinue treatment. Treatment-related grade 3 or 4 adverse events were more common in the palbociclib arm. These events were as expected and included neutropenia (68% vs 0%), leukopenia (27% vs 0%), and lymphopenia (15% vs 2%). There were no reports of febrile neutropenia or cases of treatment-related mortality. Among the nonhematologic adverse events observed, grade 2 fatigue was reported in 12% of the palbociclib arm vs 5% of the control arm.

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Overall Survival Results From SOLAR-1, a Phase 3 Study of Alpelisib + Fulvestrant for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer

Approximately 40% of patients with hormone receptor–positive, HER2-negative advanced breast cancer have mutations in the *PIK3CA* gene.[1,2] These mutations lead to hyperactivation of the PI3K pathway and have been associated with poor outcomes, including reduced survival.[3,4]

Alpelisib is an α-selective inhibitor of PI3K that was evaluated in the phase 3 SOLAR-1 trial. SOLAR-1 enrolled men and postmenopausal women with hormone receptor–positive, HER2-negative advanced breast cancer. The patients had not received prior treatment with chemotherapy, and they developed disease progression during or after treatment with an aromatase inhibitor.[5] Patients were randomly assigned to receive alpelisib in combination with fulvestrant or placebo plus fulvestrant. Stratification factors included the presence of lung and/or liver metastases and prior treatment with cyclin-dependent kinase 4/6 inhibitors. Alpelisib was administered at 300 mg once daily, and fulvestrant was administered intramuscularly at a dose of 500 mg on days 1 and 15 of the first 28-day cycle, then on day 1 of subsequent 28-day cycles.

In the primary efficacy analysis of SOLAR-1, the median PFS was 11.0 months in the alpelisib arm vs 5.7 months in the control arm (*P*=.00065).[5] Among patients with *PIK3CA* mutations, PFS was improved in the alpelisib arm vs the control arm. Since the study met its primary endpoint, the planned analysis of the key secondary endpoint, OS, could be conducted. However, the first interim OS data were immature at the time of the primary efficacy analysis.

André and colleagues presented the results of the final OS analysis in 341 patients with *PIK3CA* mutations in SOLAR-1.[6] The analysis was performed after 181 deaths were reported, and was based on a median follow-up of 42.4 months. The median OS was prolonged from 31.4 months in the control arm to 39.3 months in the alpelisib arm (HR, 0.86; 95% CI, 0.64-1.15; Figure 8). The addition of alpelisib to fulvestrant increased OS by 7.9 months (*P*=.15); however, this difference did not cross the prespecified efficacy boundary.

Among the subgroup of patients who had liver and/or lung metastases, the median OS was 37.2 months

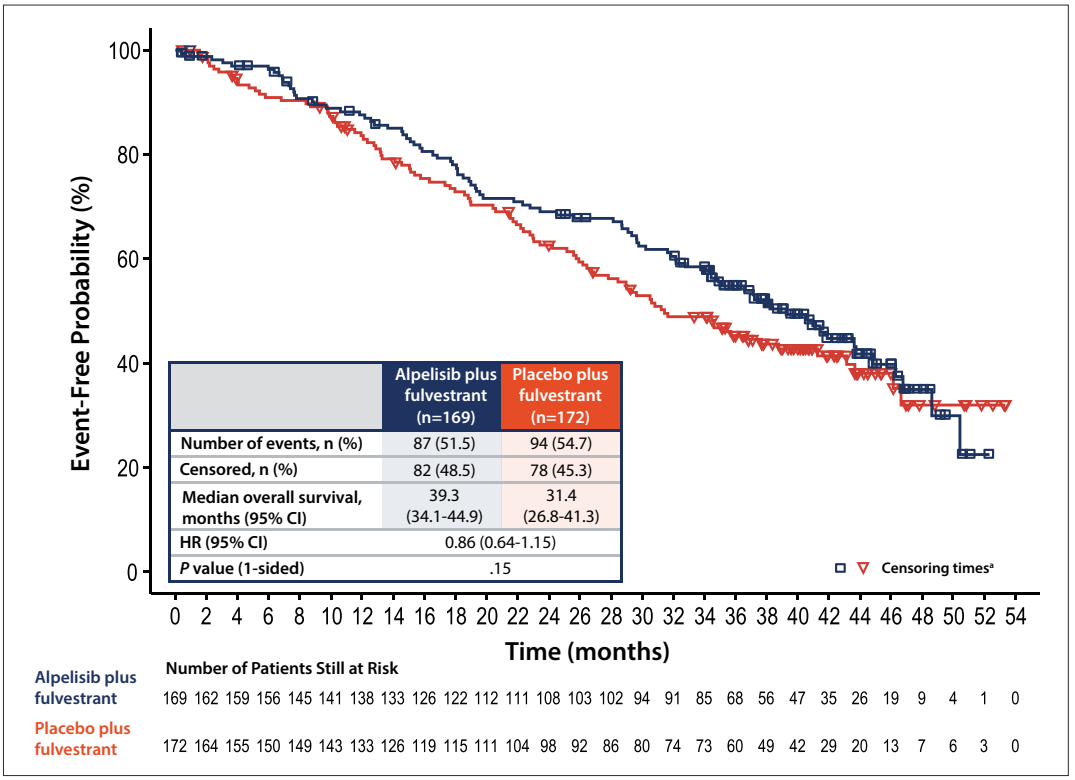

Figure 8. Overall survival in the phase 3 SOLAR-1 trial, which evaluated alpelisib plus fulvestrant in patients with hormone receptor–positive, human epidermal growth factor receptor 2–negative, advanced breast cancer. [a]Date of censoring was defined as the last contact date for overall survival. Adapted from André F et al. ESMO abstract LBA18. *Ann Oncol.* 2020;31(suppl 4):S1150-S1151.[6]

with alpelisib plus fulvestrant vs 22.8 months with placebo plus fulvestrant.[6] This subgroup analysis demonstrated that the addition of alpelisib to fulvestrant prolonged median OS by 14.4 months in patients with liver and/or lung metastases. Patients who received alpelisib and fulvestrant were also able to delay the start of chemotherapy by 8.5 months (from 14.8 months with placebo and fulvestrant to 23.3 months with alpelisib and fulvestrant).

The safety profile of alpelisib was consistent with that reported in the primary analysis.[6] An adverse event of any grade was reported in 99% of the alpelisib arm and in 93% of the control arm; the majority of these events were grade 1 or 2 in severity. The most frequent adverse events with alpelisib plus fulvestrant were hyperglycemia, occurring in 65%, and diarrhea, occurring in 60%. The most frequent adverse events with placebo plus fulvestrant were nausea, occurring in 22%, and fatigue, occurring in 18%.

Among cases of diarrhea in the alpelisib arm, 33% were grade 3 and 4% were grade 4.[6] Among patients in the control arm, less than 1% experienced grade 3/4 diarrhea. Special adverse events of interest were also investigated. Rash was observed in 54% of patients in the alpelisib arm compared with 9% of patients in the control arm. Most cases were grade 1 or 2 in severity.

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Vandetanib Plus Fulvestrant Versus Placebo Plus Fulvestrant After Relapse or Progression on an Aromatase Inhibitor in Metastatic ER-Positive Breast Cancer (FURVA): A Randomised, Double-Blind, Placebo-Controlled, Phase II Trial

Fulvestrant is a selective estrogen receptor downregulator and a therapeutic option for patients with estrogen receptor–positive breast cancer who have developed resistance to an aromatase inhibitor or tamoxifen.[1] Resistance mechanisms include upregulation of epidermal growth factor receptor and RET-receptor tyrosine kinase–signaling pathways.[2,3] Vandetanib is a multikinase inhibitor that predominantly inhibits RET and vascular endothelial growth factor receptors and has been shown to increase antitumor activity when added to endocrine therapy in preclinical endocrine-sensitive and endocrine-resistant breast cancer models.[4,5]

Jones and colleagues presented results of the FURVA study, an investigator-led, double-blind, placebo-controlled, randomized phase 2 trial.[6] The FURVA trial enrolled postmeno-

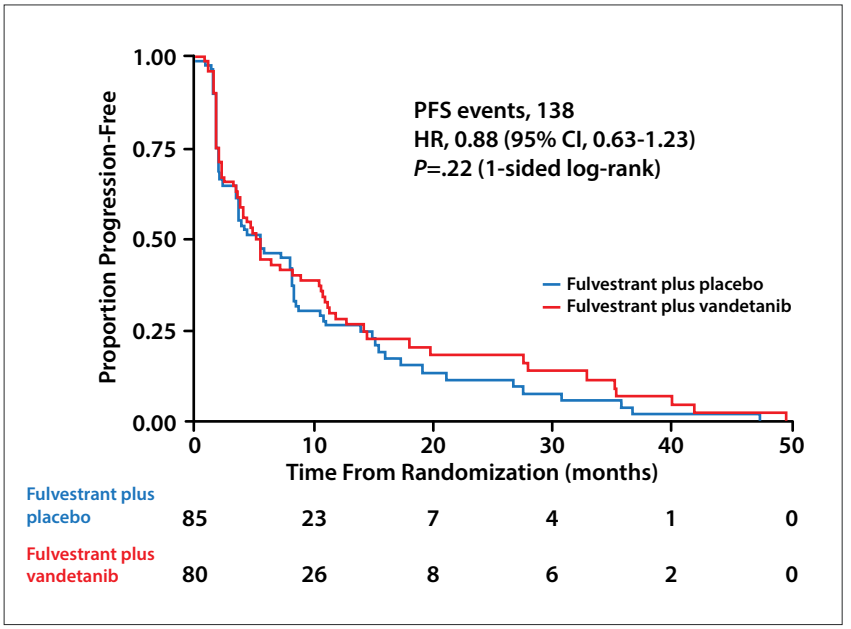

Figure 9. Progression-free survival in the FURVA trial, which evaluated vandetanib in patients with metastatic, estrogen receptor–positive breast cancer. Adapted from Jones A et al. ESMO abstract LBA20. *Ann Oncol.* 2020;31(suppl 4):S1151.[6]

pausal women with estrogen receptor–positive, HER2-negative metastatic or locally advanced aromatase inhibitor–resistant breast cancer from 19 UK sites. Patients were randomly assigned to fulvestrant at 500 mg (days 1 and 15 of cycle 1, followed by day 1 only of subsequent 28-day cycles) with either vandetanib at 300 mg daily or placebo. Treatment was administered until disease progression, unacceptable toxicity, or withdrawal of consent.

The patients' median age was 65 years.[6] In both arms, similar proportions of patients had visceral disease (78% in the vandetanib arm vs 75% in the control arm), bone-only disease (20% vs 22%), and resistance to secondary aromatase inhibitors (85% vs 84%).

The addition of vandetanib to fulvestrant did not significantly improve PFS or OS in the ITT population.[6] After 138 events, the median PFS was 5.5 months in both treatment arms (HR, 0.88; *P*=.22; Figure 9). The median OS analyzed after 86 deaths was 19.5 months in the vandetanib arm and 19.9 months in the control arm (HR, 0.92; *P*=.71).

A prespecified analysis assessed the correlation between total RET protein expression and patient outcomes.[6] The investigators performed immunostaining with a heat-mediated antigen-retrieval method, using an assay developed for the trial, on formalin-fixed, paraffin-embedded specimens (n=115). Tumor epithelial cells were scored for staining using the H-score method, and high RET expression was defined as an H-score higher than 166.

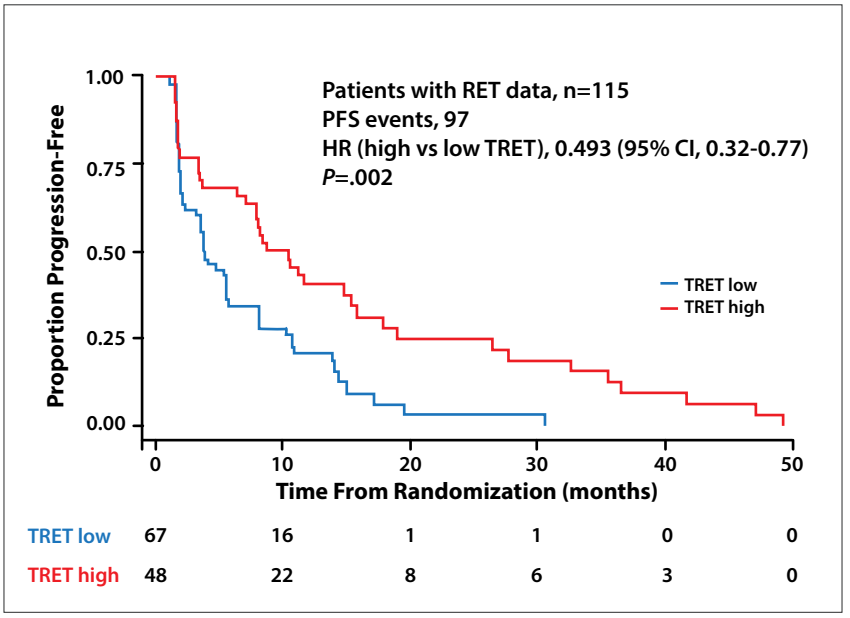

Figure 10. Progression-free survival according to RET expression in the FURVA trial, which evaluated vandetanib in patients with metastatic, estrogen receptor–positive breast cancer. HR, hazard ratio; TRET, total RET. Adapted from Jones A et al. ESMO abstract LBA20. *Ann Oncol.* 2020;31(suppl 4):S1151.[6]

Unexpectedly, high total RET protein expression was associated with a significant PFS advantage (HR, 0.493; *P*=.002; Figure 10), which was supported by an OS advantage (HR, 0.58; *P*=.051).[6] These correlations were observed in both treatment arms. In a post-hoc regression analysis, high total RET expression was associated with a shorter interval between the date of relapse and trial entry, decreasing by more than 6 points for every year since diagnosis.

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Highlights in Metastatic Breast Cancer From the European Society for Medical Oncology Virtual Congress 2020: Commentary

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Several presentations at the European Society for Medical Oncology (ESMO) Virtual Congress 2020 provided important insights into the management of metastatic breast cancer. Studies provided new data for several novel therapies, including sacituzumab govitecan-hziy, atezolizumab, alpelisib, and the AKT inhibitors ipatasertib and capivasertib.

Sacituzumab Govitecan-hziy

The ASCENT study was a randomized phase 3 trial of sacituzumab govitecan-hziy vs treatment of physician's choice in patients with metastatic triple-negative breast cancer.[1] Triple-negative breast cancer is an aggressive form of breast cancer that has a higher predilection for young women and African Americans.[2] This subtype is associated with a high risk for recurrence, visceral metastases, and poor prognosis. Clinically, there is an unmet need for patients with metastatic triple-negative breast cancer. Sacituzumab govitecan-hziy is a first-in-class antibody-drug conjugate directed against trophoblast cell surface antigen 2 (Trop-2). Trop-2 is expressed in a majority of triple-negative breast cancers.[3] A hydrolysable linker attaches the antibody to SN-38, the drug payload. Sacituzumab govitecan-hziy has 3 unique properties as an antibody-drug conjugate.[4-7] First, it is highly specific for Trop-2. Second, it has a high drug-to-antibody ratio. Third, it exerts a bystander effect. Internalization and enzymatic cleavage by tumor cells are not required for liberation of SN-38 from the antibody. Hydrolysis of the linker also releases the SN-38 cytotoxic agent extracellularly in the tumor microenvironment, providing a bystander effect.

We were involved with the phase 1/2 basket clinical trial of sacituzumab govitecan-hziy in patients with advanced epithelial cancers.[8] Among the 108 patients with relapsed/refractory metastatic triple-negative breast cancer, the objective response rate was 33%, which is more than double that expected from standard chemotherapy in this setting. These results led the US Food and Drug Administration (FDA) to grant accelerated approval to sacituzumab govitecan-hziy for the treatment of metastatic triple-negative breast cancer in patients who had received at least 2 prior lines of therapy for metastatic disease.[9] The ASCENT trial was a confirmatory randomized phase 3 trial that compared sacituzumab govitecan-hziy vs standard chemotherapy in patients with metastatic triple-negative breast cancer who had received at least 2 prior lines of chemotherapy for advanced disease.[1] The trial randomly assigned 529 patients to sacituzumab govitecan-hziy or treatment of their physician's choice (eribulin, vinorelbine, gemcitabine, or capecitabine; TPC). The primary endpoint was progression-free survival (PFS); the secondary endpoints were overall survival, objective response rate, and safety. Stratification factors included the number of prior chemotherapies, the geographic region, and the presence or absence of brain metastases.

The ASCENT trial was halted early based on compelling evidence of efficacy, per a unanimous recommendation from the data safety monitoring committee. At the ESMO Virtual Congress 2020, on behalf of the team, I presented the primary results for PFS, overall survival, and other outcomes.[1] In terms of statistical consideration, the primary endpoint was PFS based on central assessment among patients without brain metastases, using a stratified log-ranked test. The trial protocol predefined a maximum 15% cap for patients with brain metastases. Assuming a hazard ratio of 0.667, a sample size of at least 488 patients provided 95% power to detect statistically significant improvement in PFS, with 315 defined PFS events. The safety population included all patients, with or without brain metastases, who received at least 1 dose of study treatment. The data cutoff was March 11, 2020.

The treatment arms were well balanced in terms of age, race, performance status per the Eastern Cooperative Oncology Group, triple-negative breast cancer at the initial diagnosis, prior anticancer regimens, and sites of metastases. All patients had received prior taxanes, and most had received anthracyclines and platinum. Approximately one-third of the patients had

received prior checkpoint inhibitors.

The ASCENT study met its primary endpoint of improvement in PFS.[1] The median PFS was 5.6 months in the sacituzumab govitecan-hziy arm vs 1.7 months in the TPC arm. This difference corresponded to a hazard ratio of 0.41, which was highly statistically significant (P<.0001). A benefit with sacituzumab govitecan-hziy was seen in all subgroups, including those based on age (<65 years vs ≥65 years), race, number of prior lines of therapy, geographic region, prior use of programmed death ligand 1 (PD-L1) or programmed death 1 (PD-1) inhibitors, and presence of liver metastases. Overall survival was also improved among patients treated with sacituzumab govitecan-hziy. The median overall survival was 12.1 months with sacituzumab govitecan-hziy vs 6.7 months with TPC. This difference corresponded to a hazard ratio of 0.48, which was highly statistically significant (P<.0001). The objective response rate was 35% with sacituzumab govitecan-hziy vs 5% with TPC (P<.0001).

The key grade 3 treatment-related adverse events associated with sacituzumab govitecan-hziy included neutropenia, diarrhea, anemia, and febrile neutropenia.[1] The incidence of febrile neutropenia was 6%. Use of granulocyte colony–stimulating factor was reported in 49% of the sacituzumab govitecan-hziy arm vs 23% of the physician's choice arm. Dose reductions owing to adverse events were similar in both treatment arms. Among patients treated with sacituzumab govitecan-hziy, there were no reports of severe cardiovascular toxicity. All episodes of neuropathy were grade 2 or lower, and all cases of interstitial lung disease were grade 3 or lower. There were no treatment-related deaths in the sacituzumab govitecan-hziy arm. The rate of adverse events leading to treatment discontinuation was low for both arms, at 4.7% with sacituzumab govitecan-hziy and 5.4% with treatment of the physician's choice.

In conclusion, ASCENT is the first phase 3 trial of an antibody-drug conjugate to demonstrate a significant improvement compared with standard chemotherapy in pretreated metastatic triple-negative breast cancer.[1] Sacituzumab govitecan-hziy improved PFS, overall survival, and the objective response rate. Benefits were seen across all patient subgroups. Sacituzumab govitecan-hziy was well tolerated, with a manageable safety profile that was consistent with previous reports. The rate of adverse events leading to treatment discontinuation was low. The results of this randomized, phase 3 study confirmed that sacituzumab govitecan-hziy should be considered a new standard of care in patients with pretreated metastatic triple-negative breast cancer. Ongoing studies are evaluating sacituzumab govitecan-hziy in earlier lines of therapy, including the neoadjuvant (NEOSTAR)[10] and adjuvant (SASCIA)[11] settings, in combination with other targeted agents, and in patients with hormone receptor–positive metastatic breast cancer.

In terms of combinatorial treatment regimens, my institution has initiated a phase 1b/2 study combining sacituzumab govitecan-hziy with a poly(ADP-ribose) polymerase (PARP) inhibitor. This study was presented as a Trial in Progress poster at the ESMO Virtual Congress 2020.[12] The rationale behind the study is the synergy between sacituzumab govitecan-hziy, a topoisomerase 1 isomerase inhibitor, and a PARP inhibitor. The topoisomerase 1 isomerase induces double-stranded DNA breaks. The PARP enzyme is responsible not only for clearance of the cleavage (the topoisomerase 1 cleavage complex), but also for repair of DNA. Preclinical data suggest that the combination of a PARP inhibitor with sacituzumab govitecan-hziy has synthetic lethality.[13] The phase 1b portion of the clinical trial follows a 3-plus-3 design. The primary objective of the phase 1b component is to determine the recommended phase 2 dose. As of August 30, 2020, the trial enrolled 20 patients. Once the phase 1b portion is complete, the study will enter a phase 2 portion to evaluate the combination of sacituzumab govitecan-hziy and the PARP inhibitor.

In the setting of hormone receptor–positive metastatic breast cancer, the randomized phase 3 TROPiCS-02 trial is comparing sacituzumab govitecan-hziy vs standard chemotherapy in patients with metastatic or locally recurrent inoperable hormone receptor–positive, human epidermal growth factor receptor 2 [HER2]-negative metastatic breast cancer previously treated with 2 to 4 chemotherapy regimens.[14] The phase 2 NEOSTAR trial is evaluating sacituzumab govitecan-hziy as neoadjuvant therapy.[10] The study aims to determine whether treatment with sacituzumab govitecan-hziy can improve rates of pathologic complete response, a known surrogate marker for disease-free survival.

Atezolizumab

The double-blind, placebo-controlled randomized phase 3 trials IMpassion130 and IMpassion131 evaluated immunotherapy with atezolizumab in patients with untreated metastatic triple-negative breast cancer.[15,16] IMpassion131 evaluated paclitaxel with or without atezolizumab.[15] IMpassion130 utilized nab-paclitaxel, rather than paclitaxel, as the chemotherapy backbone.[16] Results from the IMpassion130 trial led the FDA to grant accelerated approval to atezolizumab in combination with nab-paclitaxel for the treatment of patients with PD-L1–positive metastatic triple-negative breast cancer.[17] In the trial, the immunotherapy-based combination improved both PFS and overall survival as compared with nab-paclitaxel without immunotherapy in these patients.

Dr Leisha Emens provided final overall survival results for IMpassion130 at the ESMO Virtual Congress 2020.[18] The combination of nab-paclitaxel plus atezolizumab was

superior to atezolizumab plus placebo for PD-L1–positive metastatic triple-negative breast cancer. Results from IMpassion131 were more surprising.[16] This study had a similar population as IMpassion130, with the same inclusion/exclusion criteria. The study design was also similar. The only difference was that the chemotherapy backbone was paclitaxel instead of nab-paclitaxel. IMpassion131 showed no difference in PFS or overall survival between the 2 treatment arms, whether for all-comers or the PD-L1 subgroup.

There has been ongoing discussion regarding why one study was positive and the other negative. There are 3 potential explanations. The first possibility is that the negative results might be a fluke (due to chance). The second possibility is related to the chemotherapy backbone in IMpassion131. Paclitaxel is generally administered with corticosteroids, which can decrease the immune response. In the IMpassion131 trial, the use of corticosteroids might have impacted the response to atezolizumab. Overall, the rate of immune-related adverse events appeared to be lower with paclitaxel in IMpassion131 vs nab-paclitaxel in IMpassion130, possibly owing to the use of corticosteroids. A third possibility is that the dose of the chemotherapy partner, whether nab-paclitaxel or paclitaxel, had an impact on the response to atezolizumab. In IMpassion131, the dose of paclitaxel was 90 mg/m^2, given on days 1, 8, and 15. This dose is higher than that typically used in the United States, which is 80 mg/m^2. In contrast, the dose of nab-paclitaxel in IMpassion130, at 100 mg/m^2 IV on days 1, 8, and 15, was lower than that typically used in the United States. It is possible that (a) the higher dose of paclitaxel led to higher efficacy in the control arm and (b) the higher dose of paclitaxel led to more lymphopenia and suppression of the immune system, which in turn lowered the efficacy of atezolizumab and therefore blunted the difference between the arms in IMpassion131. Additional biomarker and hypothesis-driven analyses are needed to understand the contribution of these factors to the differential outcomes.

To conclude, results from these trials do not change the current treatment strategy. At this time, nab-paclitaxel plus atezolizumab is the standard of care for patients with PD-L1–positive metastatic triple-negative breast cancer. Based on the results from IMpassion130, this combination will remain the standard of care.[15] Practitioners should not replace nab-paclitaxel with paclitaxel, at least according to the current data.

Alpelisib

The phase 3 SOLAR-1 trial compared the phosphoinositide 3-kinase (PI3K) inhibitor alpelisib plus fulvestrant vs fulvestrant alone in patients with advanced hormone receptor–positive breast cancer.[19] The study enrolled patients with or without the *PIK3CA* mutation. Positive results were previously reported at the 2018 ESMO meeting, showing an improvement in the primary endpoint, PFS, among patients treated with alpelisib.[20] These data led to the FDA approval of alpelisib for patients with *PIK3CA*-mutant, hormone receptor–positive metastatic breast cancer.[21]

At the ESMO Virtual Congress 2020, Dr Fabrice André presented the overall survival results from SOLAR-1.[19] Overall survival was a key secondary endpoint. The median overall survival was 39.3 months with alpelisib plus fulvestrant vs 31.4 months with fulvestrant alone, a difference that was not statistically significant (1-sided P=.15). The adverse events were similar to those previously reported. The most common adverse events included diarrhea, rash, and hyperglycemia. Early recognition and management of adverse events is critical to ensure that patients can remain on treatment. The use of alpelisib will continue according to the FDA approval: in combination with fulvestrant to treat hormone receptor–positive/HER2-negative, *PIK3CA*-mutated, advanced or metastatic breast cancer (as detected by an FDA-approved test) following progression during or after treatment with an endocrine-based regimen.[21]

AKT Inhibitors

The phase 3 IPATunity130 trial compared ipatasertib plus paclitaxel vs paclitaxel alone among patients with *PI3K/AKT/PTEN*-altered, hormone receptor–positive, HER2-negative, advanced breast cancer.[22] Ipatasertib is a pan-AKT inhibitor. Nearly 50% of hormone receptor–positive breast cancers have alterations in the *PI3K/AKT* pathway. The study was designed to test the efficacy of ipatasertib with a taxane backbone in patients with *PI3K/AKT*-altered, hormone receptor–positive metastatic breast cancer.

Overall, the study demonstrated no difference in the median PFS between the 2 arms.[22] More research is needed to determine why the addition of ipatasertib failed to improve outcome. Although speculative, one possible explanation is that the trial did not allow patients to receive endocrine therapy. Research suggests that inhibition of the PI3K pathway can—because of crosstalk—activate the estrogen receptor pathway.[23] The estrogen receptor pathway might have served as an escape mechanism that led to disease progression, thus blunting the difference in PFS between the treatment arms.

This theory is also consistent with results from the BEECH study.[24] This study compared another AKT inhibitor, capivasertib, vs placebo among patients receiving a taxane. The study was also negative, showing no difference in median PFS between the treatment arms. The BEECH trial also did not allow patients to receive endocrine therapy. Future research should focus on the combination of endocrine therapy with AKT inhibitors. Clinical trials are ongoing. For example,

the ongoing phase 3 CAPItello trial is evaluating endocrine therapy plus the AKT inhibitor capivasertib in patients with hormone receptor–positive metastatic breast cancer.[25] It will be interesting to learn whether endocrine therapy plus an AKT inhibitor can improve PFS in patients with hormone receptor–positive metastatic breast cancer, particularly those with an altered PI3K/AKT pathway.

Disclosure

Dr Bardia has performed consulting for and/or is a member of the advisory boards of Pfizer, Novartis, Genentech, Merck, Radius Health, Immunomedics/Gilead, Taiho, Sanofi, Daiichi Sankyo/AstraZeneca, Puma, Biotheranostics, Phillips, Eli Lilly, and Foundation Medicine. He has received contracted research/grant support (directed to his institution) from Genentech, Novartis, Pfizer, Merck, Sanofi, Radius Health, Immunomedics, and Daiichi Sankyo/AstraZeneca.

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