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A SPECIAL MEETING REVIEW EDITION

Highlights in Metastatic Breast Cancer From the 2020 San Antonio Breast Cancer Symposium

A Review of Selected Presentations From the 2020 SABCS Virtual Symposium • December 8-11, 2020

Special Reporting on:

- Biomarker Evaluation in the Phase 3 ASCENT Study of Sacituzumab Govitecan Versus Chemotherapy in Patients With Metastatic Triple-Negative Breast Cancer
- Double-Blind Placebo-Controlled Randomized Phase 3 Trial Evaluating First-Line Ipatasertib Combined With Paclitaxel for *PIK3CA/AKT1/PTEN*-Altered Locally Advanced Unresectable or Metastatic Triple-Negative Breast Cancer: Primary Results From IPATunity130 Cohort A
- Delivery and Activity of SN-38 by Sacituzumab Govitecan in Breast Cancer Brain Metastases
- Results From CONTESSA: A Phase 3 Study of Tesetaxel Plus a Reduced Dose of Capecitabine Versus Capecitabine Alone in Patients With HER2–, Hormone Receptor+ Metastatic Breast Cancer Who Have Previously Received a Taxane
- Additional Efficacy Endpoints From the Phase 3 KEYNOTE-355 Study of Pembrolizumab Plus Chemotherapy vs Placebo Plus Chemotherapy as First-Line Therapy for Locally Recurrent Inoperable or Metastatic Triple-Negative Breast Cancer
- E2112: Randomized Phase 3 Trial of Endocrine Therapy Plus Entinostat/Placebo in Patients With Hormone Receptor-Positive Advanced Breast Cancer. A Trial of the ECOG-ACRIN Cancer Research Group
- Correlative Biomarker Analysis of Intrinsic Subtypes and Efficacy Across the MONALEESA Phase III Studies
- Clinical Utility of Repeated Circulating Tumor Cell Enumeration as Early Treatment Monitoring Tool in Metastatic Breast Cancer—A Global Pooled Analysis With Individual Patient Data
- Safety and Efficacy of Veliparib Plus Carboplatin/Paclitaxel in Patients With HER2-Negative Metastatic or Locally Advanced Breast Cancer: A Subgroup Analysis of Germline *BRCA1* or *BRCA2* Mutations From the Phase 3 BROCADE3 Trial
- Continued Efficacy of Neratinib in Patients With HER2-Positive Early-Stage Breast Cancer: Final Overall Survival Analysis From the Randomized Phase 3 ExteNET Trial

With Expert Commentary by:

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ON THE WEB:
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(PubMed/MEDLINE), PubMed Central (PMC), and EMBASE

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

Biomarker Evaluation in the Phase 3 ASCENT Study of Sacituzumab Govitecan vs Chemotherapy in Patients With Metastatic Triple-Negative Breast Cancer

Sacituzumab govitecan-hziy is the first antibody-drug conjugate (ADC) directed against Trop-2, an antigen expressed in all breast cancer subtypes and linked to poor prognosis.[1,2] This ADC differs from others in its high degree of specificity for Trop-2 as well as its high drug-to-antibody ratio.[3,4]

The FDA granted sacituzumab govitecan-hziy accelerated approval for metastatic triple-negative breast cancer (TNBC) in April 2020 on the basis of a single-arm, multicenter study of 108 patients.[5] The phase 3 confirmatory study, ASCENT, compared sacituzumab govitecan-hziy with physician's choice of treatment in patients with metastatic TNBC who had received at least 2 prior chemotherapy regimens for advanced disease. The primary endpoint was progression-free survival (PFS). The secondary endpoints included PFS for all patients, including those with or without brain metastases, along with overall survival (OS), overall response rate (ORR), time to response, duration of response, and safety.

The trial was stopped early because of the efficacy of the experimental drug.[5] A total of 529 patients were enrolled in the study, with 267 randomized to the experimental arm and 262 randomized to the standard treatment arm. Standard treatment consisted of one of the following: eribulin, vinorelbine, gemcitabine, or capecitabine.[6] The median PFS was 5.6 months (range, 4.3-6.3) among the patients receiving sacituzumab govitecan-hziy and 1.7 months (range, 1.5-2.6) among those receiving physician's choice of treatment. OS was also significantly improved among the patients taking the experimental drug: 12.1 months with sacituzumab govitecan-hziy (range, 10.7–14.0) vs 6.7 months with standard treatment (range, 5.8-7.7).

The ORR among patients who were negative for brain metastases was 7 times greater among those who received sacituzumab govitecan-hziy vs those who received chemotherapy: 35% (82 patients) vs 5% (11 patients). Of these patients, 10 in the experimental arm achieved a complete response vs 2 in the control arm; 72 vs 9, respectively, achieved a partial response.

Adverse events proved to be manageable in the ASCENT trial. Those that reached grade 3 or higher in the 2 arms included neutropenia (46% in the experimental arm and 27% in the control arm), diarrhea (10% and <1%, respectively), and leukopenia (10% and 5%, respectively). None of the patients taking sacituzumab govitecan-hziy experienced grade 2 or higher neuropathy or grade 3 or higher interstitial lung disease, and no treatment-related deaths occurred in this arm.

On the basis of these primary results, an international group of researchers conducted a biomarker evaluation.[7] They wanted to investigate whether the outcomes of treatment with sacituzumab govitecan-hziy were associated with Trop-2 expression or with germline *BRCA1/2* mutation status.

Of the 149 patients who did not have brain metastases and who were evaluated for *BRCA1/2* mutational status, 16 had a *BRCA1/2* mutation and 133 did not. Among the 151 patients evaluated for Trop-2 expression scores, 27 patients had a low score, 39 had an intermediate score, and 85 had a high score.

According to the results, among the patients who had either high or intermediate Trop-2 expression, median OS was longer in those treated with sacituzumab govitecan-hziy than in those receiving chemotherapy: 14.2 vs 6.9 months, respectively, for high Trop-2 expression and 14.9 vs 6.9 months, respectively, for intermediate Trop-2 expression (Figure 1). Median OS among patients with low Trop-2 expression was slightly better in the experimental arm than in the chemotherapy arm: 9.3 vs 7.6 months, respectively. Median PFS followed the same pattern: 6.9 vs 2.5 months, 5.6 vs 2.2 months, and 2.7 vs 1.6 months for treatment with sacituzumab govitecan-hziy vs chemotherapy in the patients with high, intermediate, and low Trop-2 expression, respectively.

Among the 16 patients receiving the experimental treatment who had a *BRCA1/2* mutation, the ORR was 19%. By comparison, among the 18 patients in the control arm who had a *BRCA1/2* mutation, the ORR was 6%. The ORRs among the *BRCA1/2*-negative patients followed suit: 33% in the experimental arm (n=133) vs 6% in the control arm (n=125). The median OS was 15.6 vs 4.4 months among *BRCA1/2*-positive patients, and the median PFS was 4.6 vs 2.5 months in this group (Figure 2). Among the *BRCA1/2*-negative patients, the median OS was 10.9 vs 7 months, and the median PFS was 4.9 vs 1.6 months. The incidence of adverse events did not change when they were correlated with Trop-2 expression levels.

The trial investigators concluded that the clinical benefit seen with sacituzumab govitecan-hziy in the ASCENT trial did not depend on the level of Trop-2 expression or the *BRCA1/2* mutation status. At the SABCS presentation, lead researcher Sara Hurvitz, of the University of California Los Angeles, noted that caution should be exercised when interpreting these data because of the small sample sizes in both the group with low Trop-2 expression and the group with a *BRCA1/2* mutation.

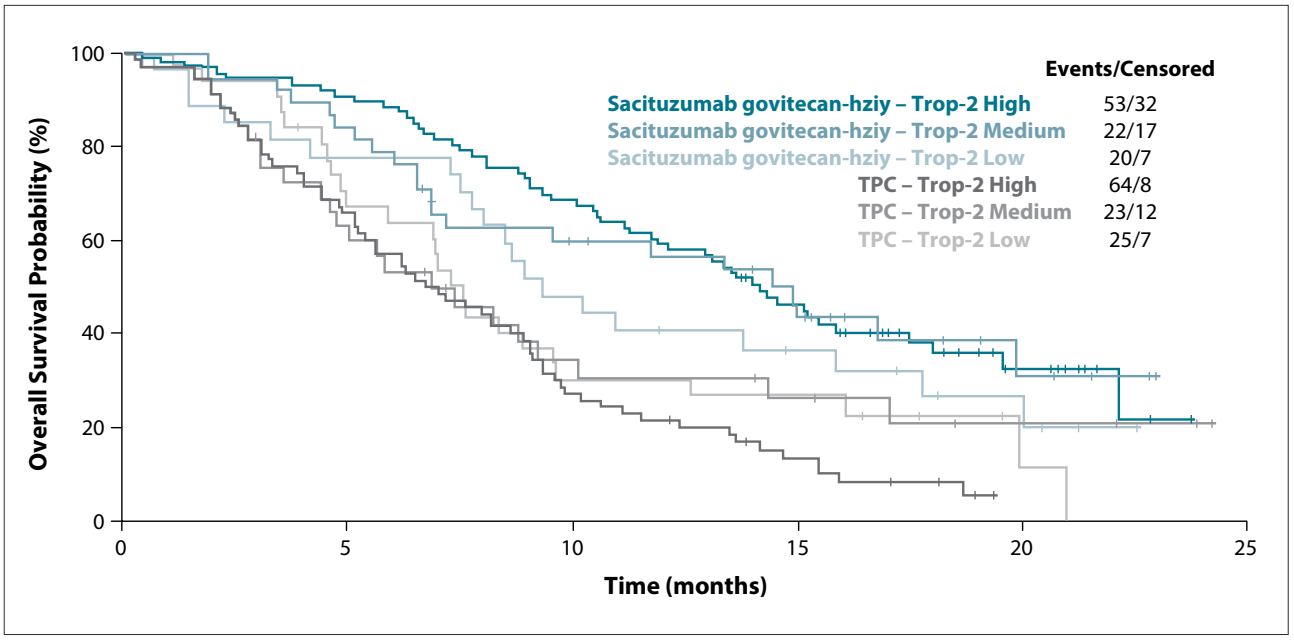

Figure 1. Overall survival in the phase 3 ASCENT trial according to Trop-2 expression. TPC, treatment of physician's choice. Adapted from Hurvitz S et al. SABCS abstract GS3-06. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[7]

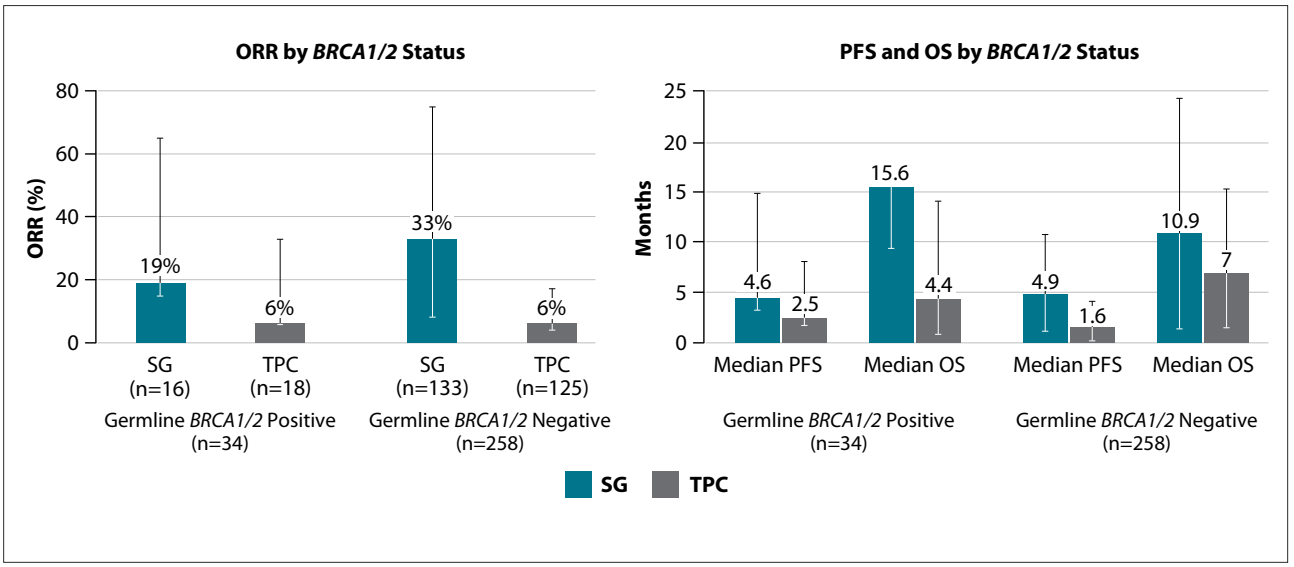

Figure 2. Summary of efficacy in the ASCENT trial according to germline *BRCA1/2* status. ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan-hziy; TPC, treatment of physician's choice. Adapted from Hurvitz S et al. SABCS abstract GS3-06. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[7]

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Double-Blind Placebo-Controlled Randomized Phase III Trial Evaluating First-Line Ipatasertib Combined With Paclitaxel for *PIK3CA/AKT1/PTEN*-Altered Locally Advanced Unresectable or Metastatic Triple-Negative Breast Cancer: Primary Results From IPATunity130 Cohort A

Ipatasertib is a highly selective AKT inhibitor. In LOTUS, a randomized phase 2 trial, first-line treatment with the combination of ipatasertib plus paclitaxel was associated with a longer PFS than paclitaxel alone in patients with locally advanced or metastatic TNBC.[1] Patients whose tumors had alterations of *PIK3CA/AKT1/PTEN*, all key regulators of the AKT pathway, derived a greater benefit. OS data showed a trend favoring the experimental arm.

The IPATunity cohort A study evaluated the addition of ipatasertib to first-line paclitaxel in patients with TNBC with alterations in *PIK3CA/AKT1/PTEN*. These patients either had never been treated for TNBC or had not received chemotherapy for at least 12 months.[2] A total of 255 patients were enrolled, and no crossover between treatment arms was permitted. The primary endpoint was investigator-assessed PFS.

The findings differed from those of the LOTUS trial and the PAKT study, which investigated capivasertib. Both of these trials showed a benefit for the experimental agents. Here, the median PFS was 7.4 months for the experimental arm and 6.1 months for the control arm, a difference that was not statistically significant (Figure 3). The ORR was 39% for the experimental arm vs 35% for the control arm, and the clinical benefit rates were 47% and 45%, respectively. The investigators did not identify a subgroup that appeared to benefit from the addition of ipatasertib to paclitaxel. Toxicities were similar in the 2 arms, although the rate of diarrhea was higher in the experimental arm.

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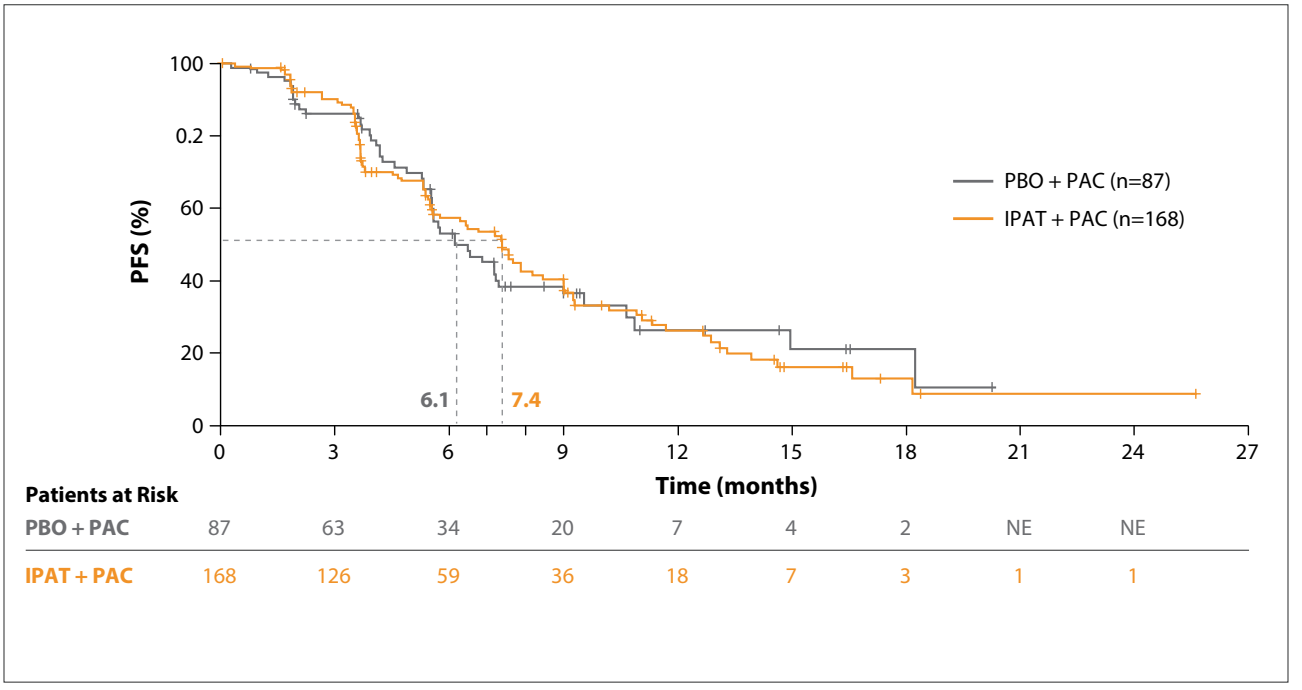

Figure 3. Progression-free survival in cohort A of the IPATunity study, which evaluated the addition of ipatasertib to first-line paclitaxel in patients with *PIK3CA/AKT1/PTEN*-altered locally advanced unresectable or metastatic triple-negative breast cancer. IPAT, ipatasertib; PAC, paclitaxel; PBO, placebo; PFS, progression-free survival. Adapted from Dent R et al. SABCS abstract GS3-04. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[2]

Delivery and Activity of SN-38 by Sacituzumab Govitecan in Breast Cancer Brain Metastases

Sacituzumab govitecan-hziy delivers SN-38, the active metabolite of irinotecan, to tumors. With other ADCs, vasculature disruption may be necessary before tumor antigens can be reached across the blood-brain barrier. By contrast, sacituzumab govitecan-hziy may release SN-38 within the vasculature because release is triggered by the reduced pH of the tumor microenvironment. Theoretically, free SN-38 is then able to accumulate in tumors across the blood-brain barrier. Preclinical research lends support to this notion.[1,2]

In a phase 1/2 basket trial of sacituzumab govitecan-hziy in patients with previously treated, hormone receptor (HR)–positive, HER2-negative metastatic breast cancer (MBC), those treated with sacituzumab govitecan-hziy had an ORR of 31.5%, a median duration of response of 8.7 months, a median PFS of 5.5 months, and a median OS of 12 months. Adverse events were manageable.[3]

Researchers conducted a single-center nonrandomized phase 0 study to evaluate whether sacituzumab govitecan-hziy can access tumor tissue in brain metastases. They also examined median PFS, median OS, and safety.[4] Administration of sacituzumab govitecan-hziy was followed by craniotomy and brain tumor resection or biopsy in patients with a diagnosis of either glioblastoma multiforme (GBM) or breast cancer that had metastasized to the brain (BCBM). The researchers tested for free SN-38 (which can cross the blood-brain barrier), SN-38G and total SN-38 in tumor tissue, cerebrospinal fluid (depending on tumor location) and whole blood (serum) in order to assess the degree to which this metabolite was reaching tumor tissue.

The first cohort enrolled 11 patients with BCBM. Among the 4 patients whose disease progressed during the study, the mean total concentration in tumors of SN-38 was 455 nM (range, 174-1160) and the mean concentration of free SN-38 was 73 nM (range, 15-198). Among the 6 of the 13 enrolled patients with GBM whose disease progressed, the mean total concentration of SN-38 in tumor tissue was 270 nM (range, 93-687) and the mean concentration of free SN-38 was 46 nM (range, 20-90). (Laboratory closures during the Covid-19 pandemic delayed the analysis of 14 additional tumor samples.)

Of 10 evaluable patients with BCBM, 8 completed at least 1 cycle of treatment following surgery, and 6 of the 8 had measurable disease. All had active residual disease. Five patients had no disease progression at days 274, 248, 50, 31, and 3. Four patients progressed at days 329, 240, 238 and 198. The last of the 10 patients withdrew with a partial response at day 266. Of the 13 patients in the GBM group, 10 completed at least 1 treatment cycle following surgery. A partial response occurred in 2 patients, and 5 remained progression free at days 384, 223, 103, 76, and 7. Four patients progressed at days 225, 99, 98 and 45.

The findings showed that total SN-38 levels were 150-fold higher than the mean half maximal inhibitory concentration (IC_{50}) in the patients with BCBM and 40-folder higher than the IC_{50} in the patients with GBM. The fact that patients in both cohorts had partial responses indicates that sacituzumab govitecan-hziy is active in tumors of the central nervous system. The value of sacituzumab govitecan-hziy in this patient population will be further elucidated in 2 ongoing trials.

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Results From CONTESSA: A Phase 3 Study of Tesetaxel Plus a Reduced Dose of Capecitabine Versus Capecitabine Alone in Patients With HER2–, Hormone Receptor+ Metastatic Breast Cancer Who Have Previously Received a Taxane

Tesetaxel is a novel oral taxane taken once every 3 weeks. Unlike docetaxel and paclitaxel, tesetaxel does not undergo efflux by the P-glycoprotein pump and is therefore intrinsically orally bioavailable.[1,2] It is also more soluble than docetaxel and paclitaxel, and has a longer half-life.[3,4] Because of these characteristics, tesetaxel may be administered orally as 2 to 5 capsules taken once every 3 weeks.

CONTESSA, a phase 3 study, investigated tesetaxel plus a reduced dose of capecitabine vs capecitabine

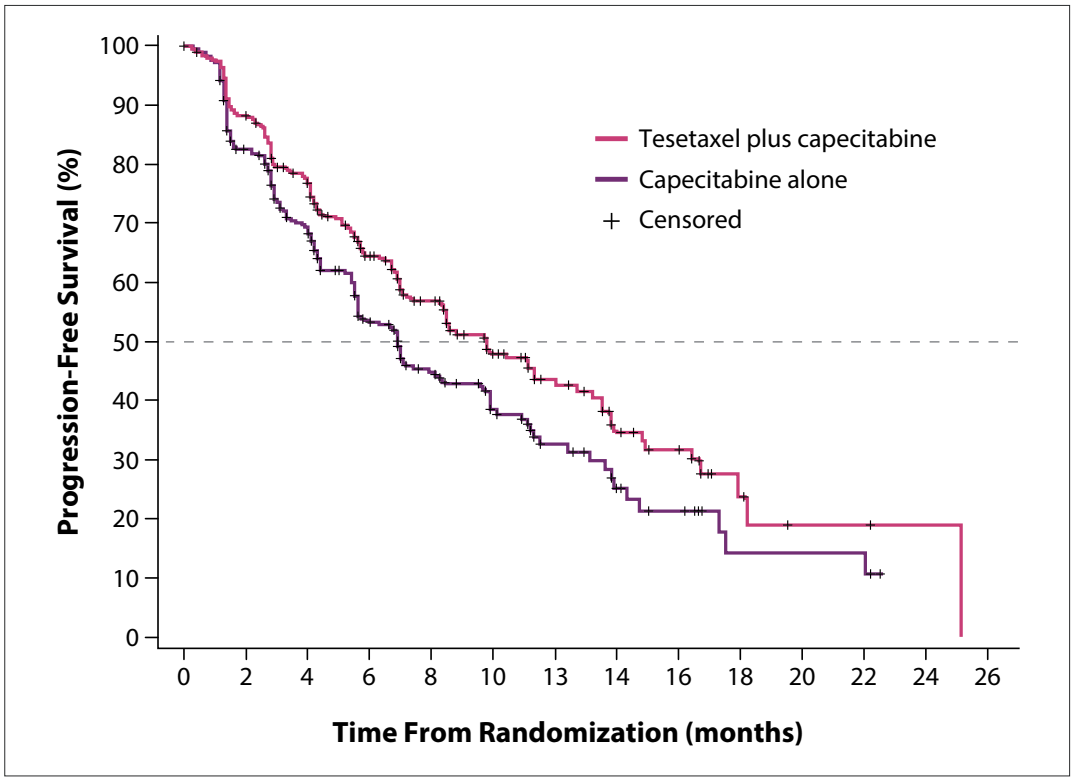

Figure 4.
Progression-free survival among patients treated with tesetaxel plus a reduced dose of capecitabine vs capecitabine alone in the phase 3 CONTESSA trial. Adapted from O'Shaughnessy J et al. SABCS abstract GS4-01. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[5]

alone in patients with MBC who were HR-positive and HER2-negative and who had received 1 prior taxane in the neoadjuvant or adjuvant setting. Patients were randomized to receive either (1) tesetaxel at a dose of 27 mg/m^2 orally on day 1 of a 21-day cycle plus daily capecitabine at a dose of 1650 mg/m^2 orally for 14 days of the 21-day cycle (343 patients) or (2) daily capecitabine at a dose of 2500 mg/m^2 orally, also for 14 days of the 21-day cycle (342 patients). The primary endpoint was PFS, with secondary endpoints of OS, ORR, and disease control rate.

At a median follow-up of 13.9 months, median PFS was 9.8 months in the experimental arm vs 6.9 months in the control arm, a statistically significant difference, with a hazard ratio of 0.716 (Figure 4).[5] The benefit was similar across subgroups, including patients who had or had not previously been disease-free for more than 24 months and those who had or had not previously received a CDK 4/6 inhibitor.

The ORR was 57% among the 274 evaluable patients who received tesetaxel plus capecitabine and 41% among the 283 evaluable patients in the capecitabine-alone arm. The corresponding disease control rates at 24 weeks were 67% and 50%. OS survival data were not available at the time of the presentation.

The most common adverse events seen among the 337 evaluable patients in the experimental arm were neutropenia (76.9%), nausea (62.6%) and diarrhea (61.1%). Among the 337 evaluable patients in the control arm, the most common issues were hand-foot syndrome (66.2%), diarrhea (46.9%), and nausea (42.1%). Aside from neutropenia, adverse events were mostly grade 1 or 2. Neutropenia was the most common grade 3 event in the experimental arm, and hand-foot syndrome was the most common grade 3 event in the control arm. Very few patients experienced grade 3 or 4 neuropathy, and no treatment-related hypersensitivity reactions occurred.

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Additional Efficacy Endpoints From the Phase 3 KEYNOTE-355 Study of Pembrolizumab Plus Chemotherapy vs Placebo Plus Chemotherapy as First-Line Therapy for Locally Recurrent Inoperable or Metastatic Triple-Negative Breast Cancer

Pembrolizumab is a humanized monoclonal anti–programmed death 1 (anti-PD1) antibody.[1] KEYNOTE-355 is a phase 3 study comparing pembrolizumab plus chemotherapy with chemotherapy alone. The study enrolled patients who had previously untreated TNBC that was either locally recurrent and inoperable or metastatic. Patients were randomized in a 2:1 ratio to the experimental arm or chemotherapy alone; chemotherapy options included paclitaxel, nab-paclitaxel, and gemcitabine, at the choice of the physician.

The study had 2 primary endpoints: PFS and OS in patients with programmed death ligand 1 (PD-L1)–positive tumors. Secondary endpoints included the objective response rate, disease control rate, and duration of response. As an exploratory endpoint, the researchers also examined consistency of the treatment effect in all patients and in those with PD-L1–positive tumors according to the on-study chemotherapy partner.

The SABCS 2020 virtual meeting included a report on PFS outcomes for each type of chemotherapy as well as key secondary efficacy endpoints from the KEYNOTE-355 study.[2] A total of 847 patients from 29 countries were randomized to the 2 arms: 566 to pembrolizumab plus chemotherapy and 281 to placebo plus chemotherapy. For the chemotherapy regimens, about 32% of patients received nab-paclitaxel, 13% received paclitaxel, and 55% received gemcitabine/carboplatin. In each arm, about 30% of the patients had de novo metastasis at baseline. An estimated 22% in the experimental arm and 18% in the control arm had a disease-free interval of less than 12 months at baseline, and 48% in the experimental arm and 52% in the control arm had a disease-free interval of 12 months or more at baseline.

Among the patients with a PD-L1 combined positive score (CPS) of 1 or higher, median PFS was 7.6 months in the experimental group and 5.6 months in the control group, with 68% in the experimental group and 77% in the control group experiencing disease progression or death, outcomes that were not statistically significantly different. These measures were roughly the same in the intent-to-treat (ITT) group. The hazard ratio for disease progression or death was 0.82, and statistical significance was not tested in this population. Overall, the hazard ratio for PFS favored pembrolizumab

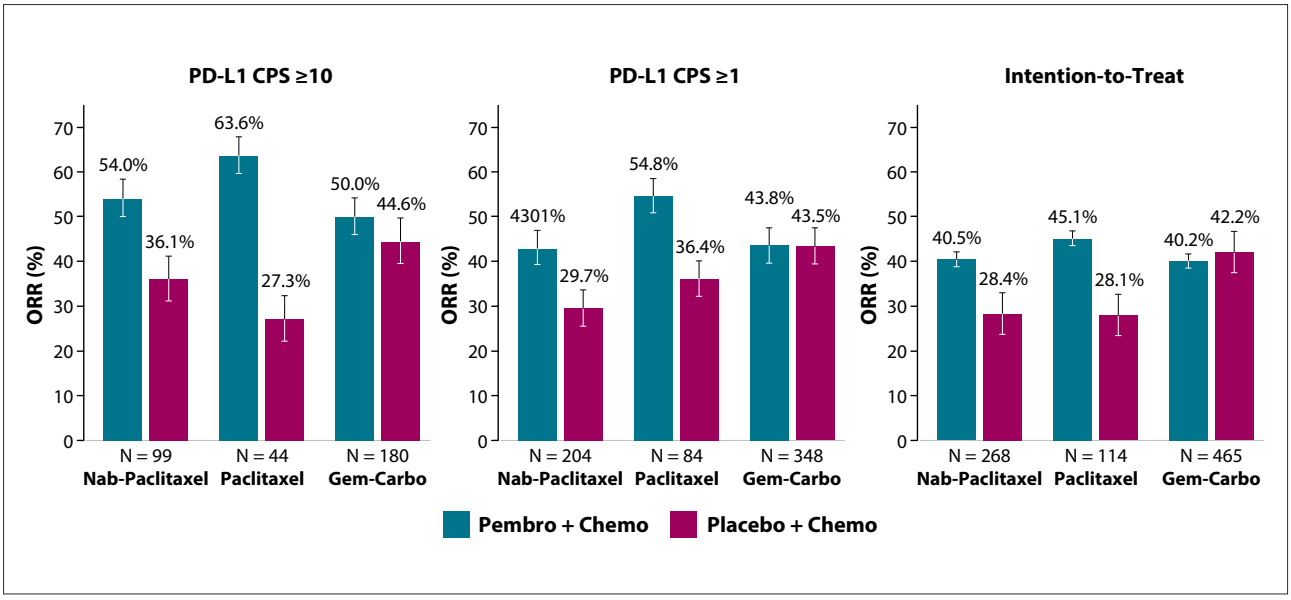

Figure 5. Response rates according to subgroups in the phase 3 KEYNOTE-355 study, which evaluated pembrolizumab plus chemotherapy vs placebo plus chemotherapy as first-line therapy. Carbo, carboplatin; CPS, combined positive score; Gem, gemcitabine; ORR, overall response rate; PD-L1, programmed death ligand 1; Pembro, pembrolizumab. Adapted from Rugo HS et al. SABCS abstract GS3-01. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[2]

plus chemotherapy regardless of which chemotherapy agent was given or the CPS value. The trial design did not include an analysis to determine which chemotherapy drug paired best with pembrolizumab.

Response rates showed a similar trend (Figure 5). In the group with a PD-L1 CPS of 10 or higher (220 patients in the experimental arm and 103 patients in the control arm), the response rate was 53% in the experimental arm and 40% in the control arm. In those with a PD-L1 CPS of 1 or higher (425 patients in the experimental arm and 211 patients in the control arm), the response rates were 45% and 38%, respectively. In the ITT group (566 in the experimental arm and 281 patients in the control arm), the response rates were 41% and 36%, respectively. The difference between the disease control rates of the 2 treatment groups was less stark, although the experimental arm was still favored. The median duration of response was longer in the experimental arm than in the control arm, with greater proportions of patients in the experimental treatment group having a duration of response of 12 months or longer and of 6 months or longer.

The results of this study led to accelerated approval by the US Food and Drug Administration of pembrolizumab in combination with chemotherapy for locally recurrent inoperable or metastatic TNBC with PD-L1 expression.

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E2112: Randomized Phase 3 Trial of Endocrine Therapy Plus Entinostat/Placebo in Patients With Hormone Receptor-Positive Advanced Breast Cancer. A Trial of the ECOG-ACRIN Cancer Research Group

Resistance to endocrine therapy is an ongoing problem in the treatment of breast cancer. One of the various agents currently being investigated to overcome this issue is the oral agent entinostat, a potent and selective inhibitor of class I and class IV HDACs.

In the phase 2 ENCORE 301 study, entinostat plus exemestane improved PFS and OS compared with exemestane plus placebo in patients who had endocrine therapy–resistant advanced breast cancer.[1] In that study, the median OS was 28 months in the experimental arm, compared with 20 months in the control arm. The trial investigators also observed that extensions in PFS among patients receiving entinostat were associated with protein lysine acetylation.

Following these results, a multicenter double-blind randomized phase 3 study, E2112, was launched to investigate whether entinostat plus exemestane would benefit patients with breast cancer who had previously been treated with a nonsteroidal aromatase inhibitor. A total of 600 patients were randomized to receive either oral exemestane at a dose of 25 mg daily plus oral entinostat at a dose of 5 mg weekly or to receive exemestane at the same dose plus placebo. Blood samples were taken at baseline and at day 15 to evaluate for lysine acetylation. The primary endpoints of the study were PFS and OS.

Roisin Connolly, of University College Cork, presented the final results at the SABCS 2020 virtual meeting.[2] A total of 305 patients were randomized to the experimental arm and 303 patients to the control arm. Two-thirds had visceral disease, one-quarter had received prior therapy for metastatic disease, and one-third had received a prior CDK inhibitor. Grade 3/4 adverse events in the experimental arm included neutropenia (19%), hypophosphatemia (13%), and anemia (7%). A reduction in the dose of entinostat was required for 30% of patients in the experimental arm, and 4 treatment-related deaths occurred, 3 of which were attributed to entinostat.

The median PFS was similar in the 2 arms: 3.3 months in the 180 evaluable patients in the experimental arm and 3.1 months in the 180 evaluable patients in the control arm, with a hazard ratio of 0.87. The difference was not statistically significant. The ORR was low for all patients: 4.6% in the experimental arm and 4.3% in the control arm. OS was also similar in the 2 arms: 23.4 months for the 305 patients in the entinostat arm and 21.7 months for the 303 patients in the placebo arm, a difference that was not statistically significant (Figure 6). Subgroup analyses did not reveal any distinctive differences from the general study population.

The experimental arm showed a significantly higher increase in lysine acetylation, indicating that the drug was inhibiting the target, but the increase did not correlate with an accompanying extension in median PFS. This result differed from the

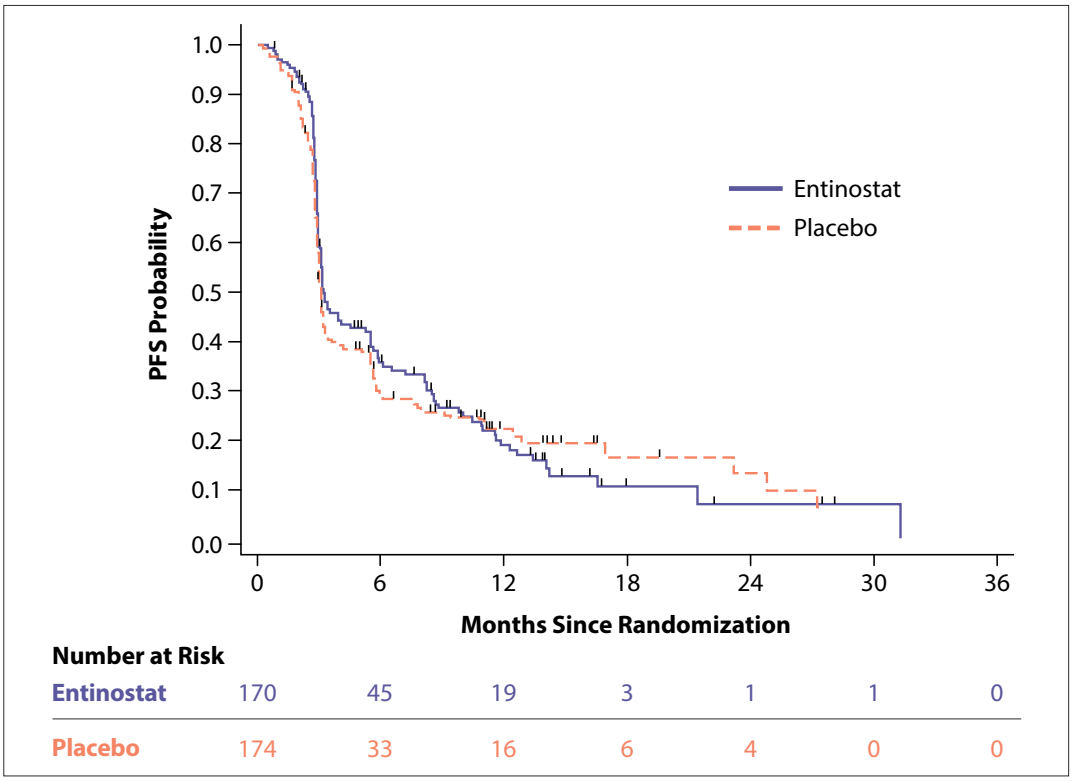

Figure 6.
Progression-free survival among patients in the phase 3 E2112 trial, which evaluated the addition of entinostat to exemestane. PFS, progression-free survival. Adapted from Connolly RM et al. SABCS abstract GS4-02. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[2]

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Correlative Biomarker Analysis of Intrinsic Subtypes and Efficacy Across the MONALEESA Phase 3 Studies

The phase 3 studies known as MONALEESA-2, -3, and -7 found a meaningful extension of PFS in patients with HR-positive, HER2-negative advanced breast cancer treated with ribociclib and endocrine therapy vs those who received placebo.[1-3] However, the prognostic and predictive value of luminal A, luminal B, HER2-enriched, and basal-like—the four main intrinsic subtypes of breast cancer—with this treatment approach is unknown.

A research team led by Aleix Prat, of Hospital Clinic Barcelona, evaluated the association between these subtypes and PFS and ORR to assess whether a subtype analysis is of any prognostic or predictive value in this treatment approach. Findings were presented at the SABCS 2020 virtual meeting.[4] Gene expression and subtype profiling were conducted in a total of 1303 tumor samples from the MONALEESA trials, with 1160 samples eligible for the analysis.

The luminal A subtype accounted for about 47%, luminal B for about 24%, HER2-enriched for about 13%, and basal-like for about 3% of the tumor samples. An estimated 14% of the samples were classified as normal. The analysis revealed a link between intrinsic subtype and PFS in both arms of the trials. For luminal A (222 patients), the median PFS among those in the ribociclib arm was 30 months vs 20 months among those in the placebo arm. For luminal B (124 patients), the median PFS was 22 months with ribociclib vs 13 months with placebo. For basal-like (13 patients), this outcome was 4 months with both ribociclib and placebo. For HER2-enriched, PFS was 16 months with ribociclib vs 6 months

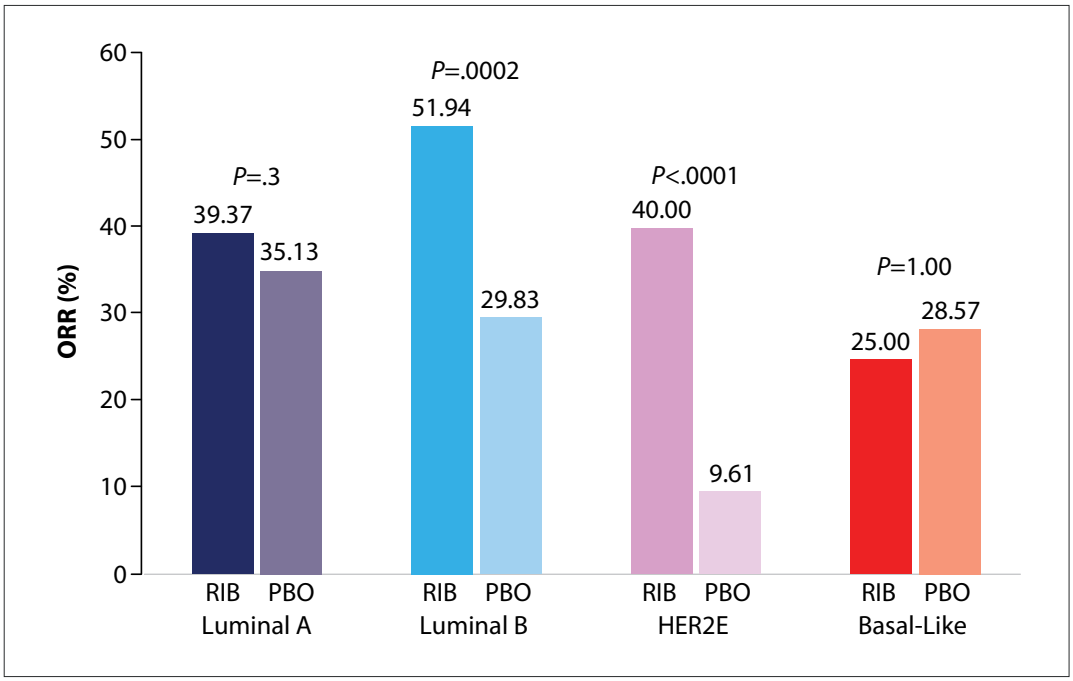

Figure 7. Overall response according to molecular subgroups among patients in the phase 3 MONALEESA trials, which compared ribociclib vs placebo. HER2E, human epidermal growth factor receptor 2 enriched; ORR, overall response rate; PBO, placebo; RIB, ribociclib. Adapted from Prat A et al. SABCS abstract GS1-04. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[4]

with placebo.

Among the patients in the ribociclib arm, the risk for tumor progression was higher in those with luminal B, HER2-enriched, and basal-like subtypes than in those with the luminal A subtype. Patients with the HER2-enriched, luminal A, and luminal B subtypes all had a longer PFS in response to ribociclib treatment than did those with the basal-like subtype, with the first group showing the greatest relative reduction in the risk for progression or death.

The ORRs were roughly equivalent in the 2 trial arms among patients with the luminal A and basal-like subtypes (Figure 7). Among patients with the luminal B subtype, the ORR was 52% in the experimental arm vs 30% in the control arm, and among patients with the HER2-enriched subtype, the ORR was 40% in the experimental arm and 10% in the control arm. Both of these differences were statistically significant. The results confirm the prognostic value of these subtypes in patients receiving endocrine therapy and in those receiving endocrine therapy plus ribociclib.

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Clinical Utility of Repeated Circulating Tumor Cell Enumeration as Early Treatment Monitoring Tool in Metastatic Breast Cancer - A Global Pooled Analysis With Individual Patient Data

Circulating tumor cell (CTC) enumeration is a useful means for assessing response status in patients with MBC.[1] Wolfgang Janni, of Ulm University, and colleagues conducted a comprehensive pooled analysis to obtain additional insights regarding the role of CTC enumeration in monitoring treatment for patients with MBC.[2] In particular, they focused on the power of this measurement to predict OS in an array of breast cancer subtypes.

The researchers gathered peer-reviewed studies that included data from repeated CTC assessments in patients with MBC and asked investigators to provide individual patient

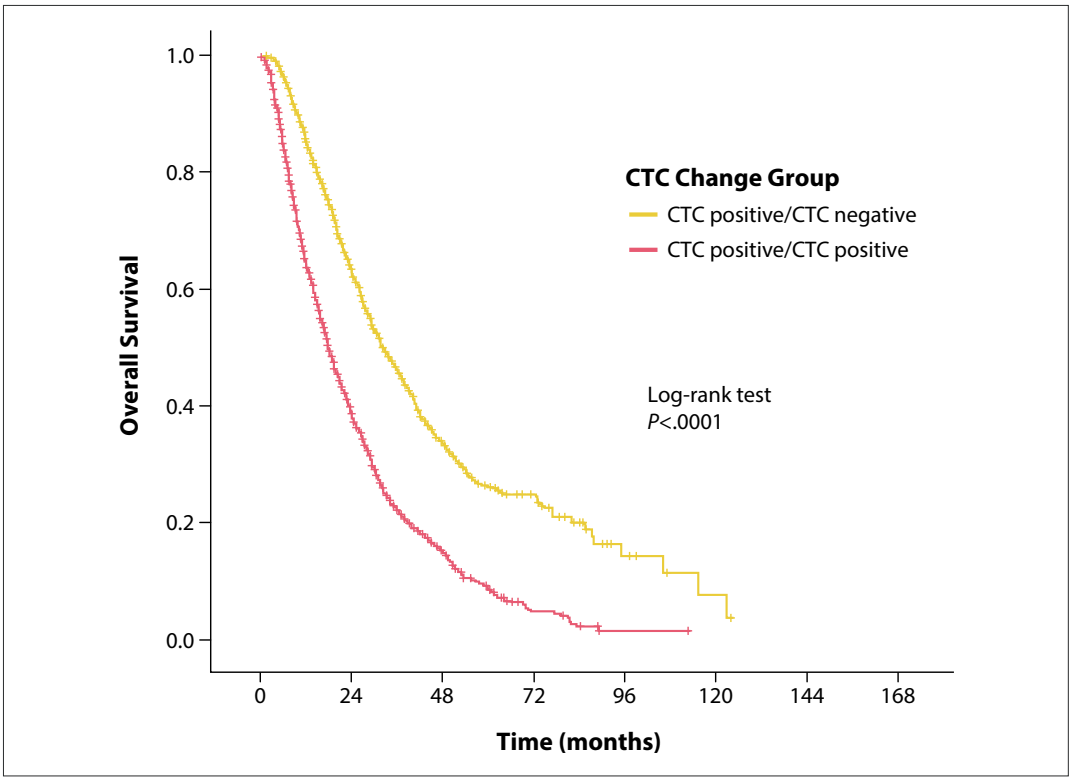

Figure 8. Overall survival according to change in circulating tumor cell status from baseline to first follow-up among patients with metastatic breast cancer in a global pooled analysis. Adapted from Janni W et al. SABCS abstract GS4-08. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[2]

data. After accruing data for a total of 4079 patients from the United States, Europe, and Asia, they used log rank tests and Cox regressions to uncover possible associations between CTC counts and OS in both the full patient population and certain subgroups. The percentage of patients who were CTC-positive at the first follow-up was considerably lower than the percentage at baseline, likely as a consequence of treatment. The percentage was lower regardless of the CTC positivity threshold.

At the SABCS 2020 virtual meeting, the researchers presented data showing OS according to CTC number at baseline (Figure 8). A higher count at baseline was statistically significantly associated with worse OS. They then looked more closely at 2 subgroups: (1) patients who were CTC-positive at baseline and remained so (n=1765) and (2) patients were CTC-positive at baseline and became CTC-negative during treatment (n=1054). The former group had an OS of 18 months, and the latter group had an OS of 32 months.

The researchers also investigated whether categorizing the patient population by intrinsic subtype would yield any insights. In patients with the luminal-like subtype, OS followed the same pattern seen among the general patient population. In patients with HER2-subtype tumors, the separation was less clear. Patients with triple-negative tumors had the least favorable OS outcomes across all CTC categories.

At a median of 29 days following the start of treatment, the CTC counts predicted OS. OS was significantly increased in the patients whose CTC count had decreased during this interval. The results suggest that early monitoring of the CTC count can predict OS for all subtypes. The findings provide evidence to support early monitoring of the CTC count as a means of assessing response to treatment in advanced breast cancer.

References

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Safety and Efficacy of Veliparib Plus Carboplatin/Paclitaxel in Patients With HER2-Negative Metastatic or Locally Advanced Breast Cancer: A Subgroup Analysis of Germline *BRCA1* or *BRCA2* Mutations From the Phase 3 BROCADE 3 Trial

This study was a preplanned subgroup analysis to compare the safety and efficacy of veliparib in patients with *BRCA1* vs *BRCA2* mutations.[1] The investigation was based on the fact that previous data had found greater hematologic toxicity following chemotherapy in patients with *BRCA1* mutations vs those with *BRCA2* mutations or wild-type *BRCA1/2*.

A total of 509 patients with confirmed *BRCA1* (n=256) or *BRCA2* (n=243) mutations were randomized in the BROCADE 3 study, with 10 patients excluded from the subgroup analysis. Most of the patients with *BRCA1* mutations had TNBC, and most of the patients with *BRCA2* mutations had HR-positive disease.

Whether a patient harbored a *BRCA1* or *BRCA2* mutation did not influence the efficacy of veliparib plus carboplatin/paclitaxel or placebo plus

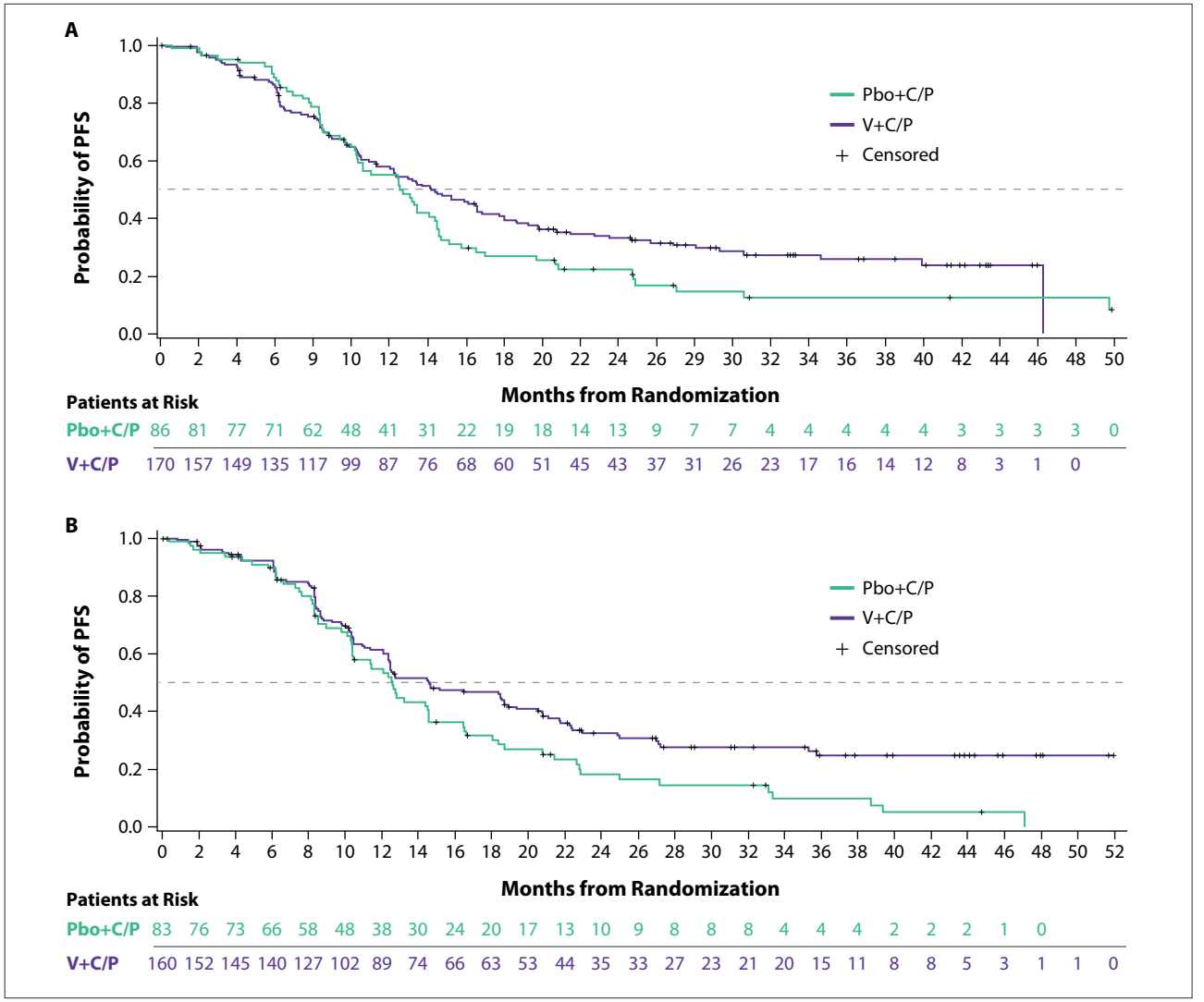

Figure 9. Progression-free survival according to *BRCA1* (A) or *BRCA2* (B) mutation status among patients treated with veliparib plus carboplatin/paclitaxel or carboplatin/paclitaxel alone in the phase 3 BROCADE 3 trial. C/P, carboplatin/paclitaxel; Pbo, placebo; PFS, progression-free survival; V, veliparib. Adapted from Wildiers H et al. SABCS abstract PS11-03. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[1]

carboplatin/paclitaxel (Figure 9). The addition of veliparib improved PFS for both groups compared with placebo. Furthermore, the 2 subgroups showed no relevant differences in toxicity. Adverse events reflected what was observed among the general study population. Thrombocytopenia and anemia were more common in the experimental arm, regardless of the *BRCA* mutation subgroup.

Reference

1. Wildiers H, Ayoub JP, Friedlander M, et al. Safety and efficacy of veliparib plus carboplatin/paclitaxel in patients with HER2-negative metastatic or locally advanced breast cancer: a subgroup analysis of germline BRCA1 or BRCA2 mutations from the phase 3 BROCADE3 trial. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract PS11-03.

Continued Efficacy of Neratinib in Patients With HER2-Positive Early-Stage Breast Cancer: Final Overall Survival Analysis From the Randomized Phase 3 ExteNET Trial

The ExteNET trial compared neratinib with placebo in the ITT population. A final analysis of OS included data for subgroups of interest.[1] In the ITT population, 127 of the 1420 patients in the neratinib group had died at the analysis cut-off date, compared with 137 of the 1420 patients in the placebo group. The estimated 8-year OS rates were 90.1% for the experimental group and 90.2% for the placebo group. In the subgroup of patients with HR-positive disease, 8-year OS rates were 91.6% with neratinib and 90.1% with placebo (Figure 10). Among patients with HR-negative disease, the rates were 88.1% and 90.3%, respectively.

Among patients with HR-positive disease who had completed trastuzumab-based treatment within a year of this study, deaths at the last analysis were reported in 53 of the 670 patients receiving neratinib (7.9%) and 68 of the 664 patients receiving placebo (10.2%). Therefore, the experimental approach may have a survival benefit for patients with HR-positive disease. The authors also observed a trend toward improved CNS outcomes in patients with early-stage HER2-positive disease receiving neratinib, who had consistently fewer CNS events compared with the patients receiving placebo across all subgroups.

Reference

1. Holmes FA, Moy B, Delaloge S, et al. Continued efficacy of neratinib in patients with HER2-positive early-stage breast cancer: final overall survival analysis from the randomized phase 3 ExteNET trial. Presented at: the 2020 San Antonio Breast Cancer Symposium Virtual Meeting; December 8-11, 2020. SABCS abstract PD3-03.[1]

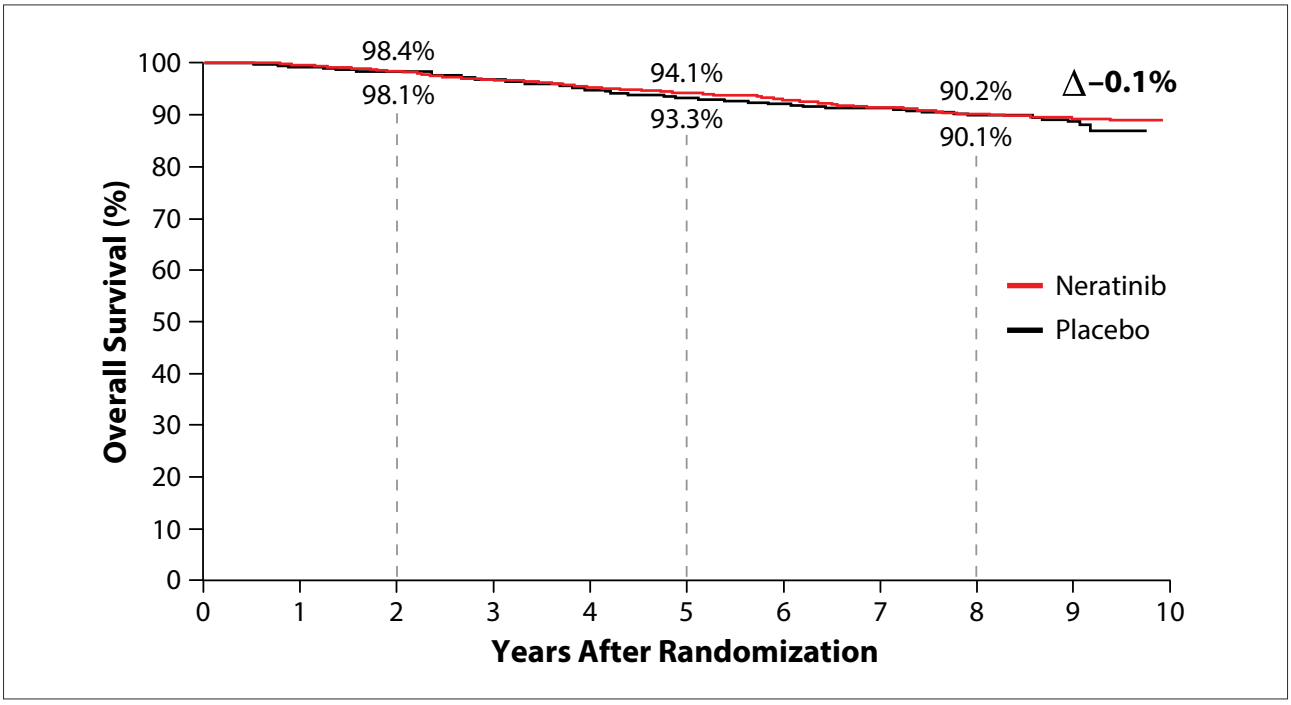

Figure 10. Overall survival in the intention-to-treat population of patients with HER2-positive early-stage breast cancer in the phase 3 ExteNET trial, which compared neratinib vs placebo. Adapted from Holmes FA et al. SABCS abstract PD3-03. HER, human epidermal growth factor receptor 2. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[1]

Highlights in Metastatic Breast Cancer From the 2020 San Antonio Breast Cancer Symposium: Commentary

Hope S. Rugo, MD

The 2020 San Antonio Breast Cancer Symposium (SABCS), which took place virtually in early December 2020, included many significant advances in metastatic breast cancer. What follows are only a small sample of the key presentations.

Sacituzumab govitecan-hziy is a first-in-class antibody-drug conjugate (ADC) directed against human trophoblast cell surface antigen (Trop-2), which is highly expressed on most cancers. The antibody is linked to SN-38, the active component of irinotecan, with a high drug-to-antibody ratio in the conjugate. Based on encouraging data from a phase 2 trial, sacituzumab govitecan-hziy received accelerated approval by the FDA for the treatment of patients with heavily re-treated metastatic, triple-negative breast cancer (TNBC) in the spring of 2020. Data from the ASCENT trial, first presented at the European Society for Medical Oncology Virtual Congress 2020, demonstrated that in patients with metastatic TNBC who had received at least 2 prior chemotherapy regimens, sacituzumab govitecan-hziy significantly extended both progression-free survival (PFS) and overall survival (OS) compared with those randomized to receive physician's choice of treatment. Given these encouraging results, there has been significant interest in understanding whether additional predictive factors may be important.

At the SABCS, Sara Hurvitz presented data on Trop-2 expression in tumor samples from the ASCENT study in order to clarify the impact of tumor Trop-2 expression on the efficacy of sacituzumab govitecan-hziy. The majority of patients had high to moderate expression of Trop-2. Sacituzumab govitecan-hziy was more effective than treatment of physicians choice regardless of Trop-2 expression, although there were very few patients with low to no expression. These data indicate that patients with metastatic, triple-negative breast cancer can be treated with sacituzumab govitecan-hziy regardless of Trop-2 status, and at present, there is no need to evaluate Trop-2 expression in the tumors from patients being considered for this therapy.

Data from the subset of patients enrolled in ASCENT with stable brain metastases was presented by Véronique Diéras. In this very small dataset, sacituzumab govitecan-hziy appeared numerically more effective than treatment of physician choice for tumor response and PFS, but overall the prognosis was poor, as expected. Further evaluation of sacituzumab govitecan-hziy in patients having surgery for breast cancer metastatic to brain or glioblastoma multiforme was presented by Andrew Brenner, demonstrating SN-38 in brain tissue 18 hours after infusion with some evidence of response. Prospective trials are planned in both tumor types.

On behalf of my colleagues, I presented results from an important study on the toxicity of sacituzumab govitecan-hziy. Neutropenia, diarrhea and nausea are the most common side effects, but they can be very well controlled with dose reductions and the use of antiemetics and antidiarrheal medications, without impacting efficacy. Patients with the *UGT1A1* homozygous *28/*28 genotype were at modestly higher risk for neutropenia and diarrhea with sacituzumab govitecan-hziy; given this low risk and incidence, routine testing is not recommended. Hair loss is also common, and it is important to inform patients about this side effect. Studies so far have shown no incidence of clinically significant interstitial lung disease (also known as pneumonitis), neuropathy, or cardiotoxicity with sacituzumab govitecan-hziy.

Presentations at the SABCS included important data on several other agents as well. A report on the phase 3 IPATunity trial, which evaluated the AKT inhibitor ipatasertib plus paclitaxel for the first-line treatment of metastatic TNBC, followed on from phase 2 results that indicated a benefit in PFS and possibly also OS with the combination of ipatasertib plus paclitaxel vs paclitaxel alone, but only in tumors with alterations in the PI3K pathway. The phase 2 study and other investigations of AKT inhibitors had generated excitement regarding the potential of this class of drugs. However, IPATunity found no benefit from the addition of ipatasertib to paclitaxel as first-line therapy for metastatic TNBC with alterations in the PI3K pathways. There is an ongoing trial with capivasertib combined with paclitaxel in patients with metastatic TNBC, and we await this data. There is also excitement about the potential for these two AKT inhibitors in hormone receptor–positive metastatic breast cancer in combination with endocrine therapy, with multiple ongoing trials.

A great deal of interest is being shown in oral taxanes. Data from the CONTESSA trial, a phase 3 study of tesetaxel plus capecitabine vs capecitabine alone, presented by Joyce O'Shaughnessy, offered significant progress in this area of research. The study was limited to patients with hormone receptor–positive metastatic breast cancer who had received a prior

taxane for early-stage disease. Tesetaxel is given once every 3 weeks. The CONTESSA study reached its primary endpoint of improved PFS in the experimental arm, with toxicities including nausea, diarrhea, neutropenia and neuropathy, but only modest hair loss. Oral chemotherapy offers an obvious advantage over intravenous medication, and the toxicities seen in this trial could generally be managed with dose reductions and supportive medications. One concern about this data was the use of combination therapy, with correspondingly greater toxicity than sequential single agent chemotherapy. With regulatory approval possibly in 2021, it is likely that tesetaxel will be used either briefly in combination followed by single agent therapy, or as an upfront, single agent. Updated data on a second oral taxane combination, oral paclitaxel and encequidar, compared to every-3-week paclitaxel was also presented. This trial met its primary endpoint of improved overall response rates (ORRs), with toxicity including nausea, diarrhea, and neutropenia. This oral taxane, which is given for 3 sequential days every week, requires fasting both before and after dosing.

We presented subset analyses from KEYNOTE-355, a randomized phase 3 study of pembrolizumab plus chemotherapy vs placebo plus chemotherapy as first-line therapy for patients with metastatic TNBC, with chemotherapy including weekly paclitaxel, nab-paclitaxel or gemcitabine and carboplatin. We had earlier reported that pembrolizumab was associated with an improved PFS of about 4.1 months in patients with PD-L1 positive disease, defined as a combined positive score using the antibody 22C3 of 10 or more, which led to accelerated approval of this drug in combination with chemotherapy in November 2020. This data was published recently in the *Lancet* by Javier Cortes. The follow-up data presented at SABCS demonstrated that pembrolizumab maintained its benefit regardless of which chemotherapy was given alongside it. The duration of response was a particularly striking finding: 7 months for those receiving placebo plus chemotherapy vs 19 months for those receiving pembrolizumab plus chemotherapy. However, only about 40% of patients have PD-L1–positive disease using the combined positive score assay and can potentially benefit from this therapy. Research is ongoing to evaluate combinations that might enhance the effectiveness of checkpoint inhibitors like this one in patients with triple-negative disease, and intriguing efficacy has been seen with both pembrolizumab and atezolizumab in the neoadjuvant setting.

Initial data with entinostat, a histone deacetylase (HDAC) inhibitor, in combination with exemestane in patients with metastatic disease looked encouraging and led to a phase 3 trial with a similar study design. However, E2112 was presented at SABCS and found no benefit for entinostat compared to placebo in combination with exemestane in patients with hormone receptor–positive disease. This drug is also being evaluated in other malignancies, and in combination with immunotherapy.

The MONALEESA trials evaluated the cyclin dependent kinase (CDK) 4/6 inhibitor ribociclib in combination with endocrine therapy in metastatic disease. Aleix Prat presented intriguing data from a pooled analysis of biomarkers that yielded some intriguing results. In particular, this agent was associated with a benefit among patients whose tumors are classified by intrinsic subtyping as "HER2-enriched" but who do not have HER2-positive disease using defined testing. For these patients, the ORR was 40% for those receiving ribociclib vs 10% for those receiving placebo. PFS was similarly increased more for this subset than others. The only subset without apparent benefit were those with basal-like intrinsic subtyping, which had generally been correlated with hormone resistance.

Shanu Modi presented updated data from the phase 2 DESTINY-Breast01 study of trastuzumab deruxtecan, which received accelerated approval for the treatment of patients with previously treated HER2-positive, metastatic breast cancer. This nonrandomized, phase 2 expansion trial found that the already impressive PFS had increased since the original publication from about 16 months to more than 19 months. The current findings demonstrated that trastuzumab deruxtecan can overcome mechanisms of resistance to HER2-targeted therapy with durable responses compared to what would be expected in the third-line or greater setting. Toxicity is a concern, particularly interstitial lung disease which can be fatal, and therefore early identification and management is critical. We await phase 3 trials comparing trastuzumab deruxtecan to trastuzumab emtansine as well as other studies, including in HER2-low disease.

Although it is always rewarding to present results in person, because the 2020 SABCS was a virtual meeting, people from all over the world were able to attend. Still, we hope that in 2021 a return to in-person discussions will be possible as the exciting progress of research into the treatment and understanding of metastatic breast cancer continues.

Disclosure

Dr Rugo has received research support for clinical trials through the University of California from Pfizer, Novartis, Lilly, Merck, Genentech/Roche, Odonate, Daiichi, AstraZeneca, MacroGenics, Seattle Genetics, Sermonix, Immunomedics, Polyphor, and Boehringer Ingelheim. She has received travel support from Daiichi, Mylan, Pfizer, Merck, AstraZeneca, Novartis, and Puma. She has received honoraria/consulting fees from PUMA and Samsung.