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JULY 2020 | Vol 34 • No 7

Emerging Treatments, Better Outcomes

An in-depth look at
the most relevant data
from **ASCO 2020**

Immunotherapy

Immunotherapy in Advanced Lung Cancer

Joy Huang and Karen Reckamp, MD, MS

ASCO ROUNDUP

GU Cancer Phase 3 HERO Trial Results

Hematological Malignancies Promising Results in Indolent Non-Hodgkin Lymphoma

Women's Cancer Mirvetuximab Soravtansine in Ovarian Cancer

GI Cancer Updated Survival Results from BEACON CRC

Lung Cancer Nivolumab/Ipilimumab in Advanced NSCLC

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Forging Ahead in the COVID-19 era

The coronavirus disease 2019 (COVID-19) shows no signs of slowing down or burning out, with cases in the United States reaching daily highs in several locations. Although infectious disease specialists and epidemiologists investigate and discuss the best courses of action for treating and mitigating the effects of this devastating pandemic, medical oncologists around the world continue their own daily fight against cancer.

In this issue of *ONCOLOGY*®, we honor that fight by recapping and reviewing some of the most important posters and presentations from the 2020 American Society of Clinical Oncology Virtual Scientific Program. The virtual format did nothing to dampen the quality of the conference, with several studies reaching practice-influencing conclusions.

The phase 3 HERO trial was one such study, with presented data suggesting that relugolix (Relumina) may become the new standard of care for patients with advanced prostate cancer. Interim and early results from the phase 2 ZUMA-5 trial and phase 1b FORWARD II trial weren't quite as decisive, but nonetheless, patients with indolent B-cell non-Hodgkin lymphoma and patients with ovarian cancer, respectively, were given promising data on new treatments.

Also in this issue, you will read a review of immunotherapy treatments for advanced lung cancer. Despite a recent avalanche of FDA approvals in the lung cancer space, there is an urgent need for reliable biomarkers to best match patients to therapeutics, and questions regarding the proper sequencing and duration of treatment still remain.

For this month's clinical quandary, you will read about the psychological impact of COVID-19 on patients with cancer. How can the field of psycho-oncology contribute to patient care and alleviate some of the issues brought forth by this pandemic? Read on to find out.

Within these pages, you will also find a review of current challenges to cancer clinical trials resulting from the pandemic, and an article discussing the implementation and framework of telemedicine for oncologists.

I hope you find our journal helpful in caring for your patients through what is likely one of the most challenging times in their lives. As always, thank you for reading.

Mike Hennessy Sr

Chairman and founder of *ONCOLOGY's*
parent company, *MJH Life Sciences™*

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The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) and iwCLL Guidelines recommend FISH and molecular genetic testing before CLL treatment^{1,2}

**Del 17p/*TP53*
mutation**

**IGHV
unmutated**

Del 11q

The majority (>50%) of CLL patients have at least one high-risk factor.³⁻⁵

The iwCLL Guidelines now recommend always testing for these important, high-risk prognostic factors²:

IGHV unmutated, del 17p/*TP53* mutation, del 11q

Tests for Prognostic Factors¹

Molecular Analysis
IGHV mutation status

FISH
del 17p
del 11q

Genetic Sequencing
TP53 mutation status

iwCLL recommends testing before you treat

CLL=chronic lymphocytic leukemia, del=deletion, FISH=fluorescent *in situ* hybridization, IGHV=immunoglobulin heavy-chain variable region gene, iwCLL=International Workshop on CLL, NCCN=National Comprehensive Cancer Network, PFS=progression-free survival.

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma V.2.2020. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed October 8, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 2. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131(25):2745-2760. 3. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. *Blood*. 2016;127(2):208-215. 4. Eichhorst B, Fink AM, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol*. 2016;17:928-942. 5. Kröber A, Seiler T, Benner A, et al. *V_H* mutation status, CD38 expression level, genomic aberrations, and survival in chronic lymphocytic leukemia. *Blood*. 2002;100:1410-1416.

LETTER TO THE READERS

COVID-19 Pandemic and Its Effects on Cancer Care, Both Good and Bad

Julie M. Vose, MD, MBA
Chief, Division of Hematology/Oncology
Neumann M. and Mildred E. Professor of Medicine
University of Nebraska Medical Center
Omaha, Nebraska

Now that the world has been dealing with the coronavirus disease 2019 (COVID-19) pandemic for several months, we have learned so much. Some of the modifications we have made have been “good” and will hopefully help oncology care, education, and research going forward. Here are some of the issues and changes that the pandemic engendered:

GOOD

1. Telehealth video visits: We all hope the reimbursements will remain so we can continue to use these when the clinical situation is appropriate.

2. Virtual meetings: These have gone better than expected (except for a few website issues) and in some ways have been very helpful, as you can see more lectures and go through them as time permits. I hope these will be used more in conjunction with future in-person meetings.

3. Meetings, lectures, and tumor boards held by Zoom and WebEx: All have increased the ability of

physicians to attend safely from different locations.

4. Beneficial clinical trial modifications: These include phone or electronic consents, allowing laboratory or radiology testing closer to home, and shipment of investigational oral agents directly to the patient.

5. We’ve seen emergency, record-speed approvals of COVID-19 therapy trials by the FDA, National Cancer Institute, and local institutions.

BAD

1. Decreased cancer screening testing: It was stopped during the pandemic and now, although started again, some patients are afraid to come in to get these tests done. This may ultimately lead to diagnosing cancers at later stages, making them more difficult to treat.

2. Postponing some cancer surgeries: Some patients may have developed disease that is more extensive by the time surgery is performed, which could lead to worse outcomes.

3. Phase 1 clinical trials were stopped in some centers, which may slow down progress in cancer research.

4. Because higher-risk clinical trials were closed during the pandemic, there will be extra administrative work for staff members working within the clinical trials system and institutional review boards when reopening does occur.

5. We’ve had decreased ability to deliver state-of-the-art cancer care to some patients because of capacity issues.

6. Financial stress on the health care system has arisen because of decreases in frequency of standard health care procedures and increased infrastructure costs.

I hope that some of the “good” lessons learned during this difficult time can remain with us going forward into the next phase of oncology care. The COVID-19 pandemic is likely not to be the last pandemic, and we need to learn from our efforts over the past few months. ■

Go to cancernetwork.com/COVID-19_Acalabrutinib to read about a recent study that saw improved clinical outcomes for patients with severe COVID-19 after treatment with acalabrutinib, a selective BTK inhibitor.

1 DAILY DOSE

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Indicated for first-line maintenance treatment of advanced ovarian cancer after response to platinum-based chemotherapy.

THE FIRST AND ONLY ONCE-DAILY ORAL PARP INHIBITOR FOR PLATINUM-RESPONSIVE ADVANCED OVARIAN CANCER¹⁻³

**PROVEN EFFICACY IN 1L MAINTENANCE
REGARDLESS OF BIOMARKER STATUS^{1,4}**

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Indication

ZEJULA is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

Important Safety Information

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including some fatal cases, was reported in 15 patients (0.8%) out of 1785 patients treated with ZEJULA monotherapy in clinical trials. The duration of therapy in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.9 years. These patients had received prior chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

Hematologic adverse reactions (thrombocytopenia, anemia and neutropenia) have been reported in patients receiving ZEJULA. In PRIMA, the overall incidence of Grade ≥ 3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 39%, 31%, and 21% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count, Grade ≥ 3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 22%, 23%, and 15% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients. Do not start ZEJULA until patients have recovered from hematological toxicity caused by prior chemotherapy ($\leq$ Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months, and periodically thereafter. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations.

Hypertension and hypertensive crisis have been reported in patients receiving ZEJULA. In PRIMA, Grade 3-4 hypertension occurred in 6% of patients receiving ZEJULA vs 1% of patients receiving placebo, with no reported discontinuations. Monitor blood

pressure and heart rate at least weekly for the first two months, then monthly for the first year, and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary.

Embryo-Fetal Toxicity and Lactation: Based on its mechanism of action, ZEJULA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months after receiving their final dose of ZEJULA. Because of the potential for serious adverse reactions from ZEJULA in breastfed infants, advise lactating women to not breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.

The most common adverse reactions (Grades 1-4) in $\geq 10\%$ of all patients who received ZEJULA in PRIMA were thrombocytopenia (66%), anemia (64%), nausea (57%), fatigue (51%), neutropenia (42%), constipation (40%), musculoskeletal pain (39%), leukopenia (28%), headache (26%), insomnia (25%), vomiting (22%), dyspnea (22%), decreased appetite (19%), dizziness (19%), cough (18%), hypertension (18%), AST/ALT elevation (14%), and acute kidney injury (12%).

Common lab abnormalities (Grades 1-4) in $\geq 25\%$ of all patients who received ZEJULA in PRIMA included: decreased hemoglobin (87%), decreased platelets (74%), decreased leukocytes (71%), increased glucose (66%), decreased neutrophils (66%), decreased lymphocytes (51%), increased alkaline phosphatase (46%), increased creatinine (40%), decreased magnesium (36%), increased AST (35%) and increased ALT (29%).

Please see Brief Summary on the following pages.

References: 1. ZEJULA (niraparib) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; April 2020. 2. Lynparza (olaparib) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; December 2019. 3. Rubraca (rucaparib) [package insert]. Boulder, CO: Clovis Oncology, Inc; April 2018. 4. González-Martín A, Pothuri B, Vergote I, et al; for the PRIMA/ENGOT-OV26/GOG-3012 Investigators. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2019;381(25):2391-2402.

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1L, first-line; PARP, poly (ADP-ribose) polymerase.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Zejula safely and effectively. See full prescribing information for Zejula available at www.zejula.com.

ZEJULA (niraparib) capsules, for oral use

INDICATIONS AND USAGE

First-Line Maintenance Treatment of Advanced Ovarian Cancer

ZEJULA is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

Maintenance Treatment of Recurrent Ovarian Cancer

ZEJULA is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

Treatment of Advanced Ovarian Cancer after Three or More Chemotherapies

ZEJULA is indicated for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either:

- a deleterious or suspected deleterious *BRCA* mutation, or
- genomic instability and who have progressed more than six months after response to the last platinum-based chemotherapy.

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

DOSAGE AND ADMINISTRATION

Patient Selection for Treatment of Advanced Ovarian Cancer after Three or More Chemotherapies

Select patients for treatment of advanced ovarian cancer after three or more chemotherapy regimens associated with HRD positive status based on either deleterious or suspected deleterious *BRCA* mutation and/or genomic instability score (GIS).

Information on FDA-approved tests for the detection of either deleterious or suspected deleterious *BRCA* mutation or genomic instability for this indication is available at: <http://www.fda.gov/CompanionDiagnostics>.

Recommended Dosage

Continue ZEJULA treatment until disease progression or unacceptable toxicity.

Instruct patients to take their dose of ZEJULA at approximately the same time each day. Advise patients to swallow each capsule whole and not to chew, crush, or split ZEJULA prior to swallowing. ZEJULA may be taken with or without food. Bedtime administration may be a potential method for managing nausea.

In the case of a missed dose of ZEJULA, instruct patients to take their next dose at its regularly scheduled time. If a patient vomits or misses a dose of ZEJULA, an additional dose should not be taken.

First-Line Maintenance Treatment of Advanced Ovarian Cancer

- For patients weighing less than 77 kg (170 lbs) OR with a platelet count of less than 150,000/ μ L, the recommended dose is 200 mg (two 100-mg capsules) taken orally once daily.
- For patients weighing greater than or equal to 77 kg (170 lbs) AND who have a platelet count greater than or equal to 150,000/ μ L, the recommended dose is 300 mg (three 100-mg capsules) taken orally once daily.

For the maintenance treatment of advanced ovarian cancer, patients should start treatment with ZEJULA no later than 12 weeks after their most recent platinum-containing regimen.

Maintenance Treatment of Recurrent Ovarian Cancer

The recommended dose of ZEJULA is 300 mg (three 100-mg capsules) taken orally once daily.

For the maintenance treatment of recurrent ovarian cancer, patients should start treatment with ZEJULA no later than 8 weeks after their most recent platinum-containing regimen.

Treatment of Advanced Ovarian Cancer after Three or More Chemotherapies
The recommended dose of ZEJULA is 300 mg (three 100-mg capsules) taken orally once daily.

Dosage Adjustments for Adverse Reactions

To manage adverse reactions, consider interruption of treatment, dose reduction, or dose discontinuation. The recommended dose modifications for adverse reactions are listed in Tables 1, 2 and 3.

Table 1: Recommended Dose Modifications for Adverse Reactions		
Starting dose level	200 mg	300 mg
First dose reduction	100 mg/day ^a (one 100-mg capsule)	200 mg/day (two 100-mg capsules)
Second dose reduction	Discontinue medication.	100 mg/day ^a (one 100-mg capsule)

^aIf further dose reduction below 100 mg/day is required, discontinue ZEJULA.

Table 2: Dose Modifications for Non-Hematologic Adverse Reactions	
Non-hematologic CTCAE ^a $\geq$ Grade 3 adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	<ul style="list-style-type: none">• Withhold ZEJULA for a maximum of 28 days or until resolution of adverse reaction.• Resume ZEJULA at a reduced dose per Table 1.
CTCAE $\geq$ Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered ZEJULA 100 mg/day	Discontinue medication.

^aCTCAE=Common Terminology Criteria for Adverse Events

Table 3: Dose Modifications for Hematologic Adverse Reactions	
Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment and periodically after this time [see <i>Warnings and Precautions</i>].	
Platelet count $<100,000/\mu$ L	First occurrence: <ul style="list-style-type: none">• Withhold ZEJULA for a maximum of 28 days and monitor blood counts weekly until platelet counts return to $\geq 100,000/\mu$L.• Resume ZEJULA at same or reduced dose per Table 1.• If platelet count is $<75,000/\mu$L, resume at a reduced dose.
	Second occurrence: <ul style="list-style-type: none">• Withhold ZEJULA for a maximum of 28 days and monitor blood counts weekly until platelet counts return to $\geq 100,000/\mu$L.• Resume ZEJULA at a reduced dose per Table 1.• Discontinue ZEJULA if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily.^a
Neutrophil $<1,000/\mu$ L or Hemoglobin <8 g/dL	<ul style="list-style-type: none">• Withhold ZEJULA for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to $\geq 1,500/\mu$L or hemoglobin returns to ≥ 9 g/dL.• Resume ZEJULA at a reduced dose per Table 1.• Discontinue ZEJULA if neutrophils and/or hemoglobin have not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily.^a
Hematologic adverse reaction requiring transfusion	<ul style="list-style-type: none">• For patients with platelet count $\leq 10,000/\mu$L, platelet transfusion should be considered. If there are other risk factors such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count.• Resume ZEJULA at a reduced dose.

^aIf myelodysplastic syndrome or acute myeloid leukemia (MDS/AML) is confirmed, discontinue ZEJULA [see *Warnings and Precautions*].

DOSAGE FORMS AND STRENGTHS

100 mg capsule having a white body with "100 mg" printed in black ink, and a purple cap with "Niraparib" printed in white ink.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received ZEJULA monotherapy in clinical trials. In 1785 patients treated with ZEJULA in clinical trials, MDS/AML occurred in 15 patients (0.8%).

The duration of therapy with ZEJULA in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.9 years. All of these patients had received previous chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

Bone Marrow Suppression

Hematologic adverse reactions (thrombocytopenia, anemia and neutropenia) have been reported in patients treated with ZEJULA.

In PRIMA, the overall incidence of Grade ≥ 3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 39%, 31%, and 21% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count, Grade ≥ 3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 22%, 23%, and 15% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients.

In NOVA, Grade ≥ 3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 29%, 25%, and 20% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 1%, and 2% of patients.

In QUADRA, Grade ≥ 3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 28%, 27%, and 13% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 1% of patients.

Do not start ZEJULA until patients have recovered from hematological toxicity caused by previous chemotherapy ($\leq$ Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time. If hematological toxicities

do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics [see *Dosage and Administration*].

Cardiovascular Effects

Hypertension and hypertensive crisis have been reported in patients treated with ZEJULA.

In PRIMA, Grade 3-4 hypertension occurred in 6% of ZEJULA-treated patients compared to 1% of placebo-treated patients with a median time from first dose to first onset of 43 days (range: 1 to 531 days) and with a median duration of 12 days (range: 1 to 61 days). There were no discontinuations due to hypertension.

In NOVA, Grade 3-4 hypertension occurred in 9% of ZEJULA-treated patients compared to 2% of placebo-treated patients with a median time from first dose to first onset of 77 days (range: 4 to 504 days) and with a median duration of 15 days (range: 1 to 86 days). Discontinuation due to hypertension occurred in $<1\%$ of patients.

In QUADRA, Grade 3-4 hypertension occurred in 5% of ZEJULA-treated patients with a median time from first dose to first onset of 15 days (range: 1 to 316 days) and with a median duration of 7 days (range: 1 to 118 days). Discontinuation due to hypertension occurred in $<0.2\%$ of patients.

Monitor blood pressure and heart rate at least weekly for the first two months, then monthly for the first year and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Medically manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary [see *Dosage and Administration*].

Embryo-Fetal Toxicity

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to a pregnant woman. ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) [see *Warnings and Precautions*]. Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib.

Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of ZEJULA [see *Use in Specific Populations*].

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia [see *Warnings and Precautions*]
- Bone Marrow Suppression [see *Warnings and Precautions*]
- Cardiovascular Effects [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 practice.

The most common adverse reactions of all grades in $>10\%$ of 1314 patients who received ZEJULA in the pooled PRIMA, NOVA and QUADRA trials were nausea (65%), thrombocytopenia (60%), anemia (56%), fatigue (55%), constipation (39%), musculoskeletal pain (36%), abdominal pain (35%), vomiting (33%), neutropenia (31%), decreased appetite (31%), leukopenia (24%), insomnia (23%), headache (23%), dyspnea (22%), rash (21%), diarrhea (18%), hypertension (17%), cough (16%), dizziness (14%), acute kidney injury (13%), urinary tract infection (12%), and hypomagnesemia (11%).

First-Line Maintenance Treatment of Advanced Ovarian Cancer

The safety of ZEJULA for the treatment of patients with advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was studied in the PRIMA trial, a placebo-controlled, double-blind study in which 728 patients received niraparib or placebo. Among patients who received ZEJULA, the median duration of treatment was 11.1 months (range: 0.03 to 29 months).

All Patients Receiving ZEJULA in PRIMA

Serious adverse reactions occurred in 32% of patients receiving ZEJULA. Serious adverse reactions in $>2\%$ of patients were thrombocytopenia (16%), anemia (6%), and small intestinal obstruction (2.9%). Fatal adverse reactions occurred in 0.4% of patients, including intestinal perforation and pleural effusion (one patient each).

Permanent discontinuation due to adverse reactions occurred in 12% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in $>1\%$ of patients who received ZEJULA included thrombocytopenia (3.7%), anemia (1.9%), nausea and neutropenia (1.2% each). Adverse reactions led to dose reduction or interruption in 80% of patients, most frequently from thrombocytopenia (56%), anemia (33%), and neutropenia (20%).

Table 4 and Table 5 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in all patients treated with ZEJULA in the PRIMA study.

Table 4: Adverse Drug Reactions Reported in $\geq 10\%$ of All Patients Receiving ZEJULA in PRIMA ^a				
	Grades 1-4 ^b		Grades 3-4 ^b	
	ZEJULA N=484	Placebo N=244	ZEJULA N=484	Placebo N=244
Blood and Lymphatic System Disorders				
Thrombocytopenia	66	5	39	0.4
Anemia	64	18	31	2
Neutropenia ^c	42	8	21	1
Leukopenia ^d	28	9	5	0.4
Gastrointestinal Disorders				
Nausea	57	28	1	1
Constipation	40	20	1	0.4
Vomiting	22	12	1	1

Table 4: Adverse Drug Reactions Reported in ≥10% of All Patients Receiving ZEJULA in PRIMA ^a (continued)				
	Grades 1-4 ^b		Grades 3-4 ^b	
	ZEJULA N=484 %	Placebo N=244 %	ZEJULA N=484 %	Placebo N=244 %
General Disorders and Administration Site Conditions				
Fatigue	51	41	3	1
Investigations				
AST/ALT elevation	14	7	3	0.8
Metabolism and Nutrition Disorders				
Decreased appetite	19	8	1	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain	39	38	1	0
Nervous System Disorders				
Headache	26	15	0.4	0
Dizziness	19	13	0	0.4
Psychiatric Disorders				
Insomnia	25	15	1	0.4
Renal and Urinary Disorders				
Acute kidney injury ^c	12	5	0.2	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	22	13	0.4	1
Cough	18	15	0	0.4
Vascular Disorders				
Hypertension	18	7	6	1

^aAll adverse reactions in the table consist of grouped preferred terms except for nausea, vomiting, decreased appetite, headache and insomnia, which are single preferred terms.

^bCTCAE=Common Terminology Criteria for Adverse Events version 4.02

^cincludes neutropenia, neutropenic infection, neutropenic sepsis, febrile neutropenia.

^dincludes leukopenia, lymphocyte count decreased, lymphopenia, white blood cell count decreased.

^eincludes blood creatinine increased, blood urea increased, acute kidney injury, renal failure, blood creatine increased.

Table 5: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZEJULA in PRIMA				
	Grades 1-4		Grades 3-4	
	ZEJULA N=484 %	Placebo N=244 %	ZEJULA N=484 %	Placebo N=244 %
Decreased hemoglobin	87	66	29	1
Decreased platelets	74	13	37	0
Decreased leukocytes	71	36	9	0
Increased glucose	66	57	3	3
Decreased neutrophils	66	25	23	1
Decreased lymphocytes	51	29	7	3
Increased alkaline phosphatase	46	21	1	0
Increased creatinine	40	23	0	0
Decreased magnesium	36	34	1	0
Increased aspartate aminotransferase	35	17	1	0.4
Increased alanine aminotransferase	29	17	2	1

Patients Receiving ZEJULA with Dose Based on Baseline Weight or Platelet Count in PRIMA

Among patients who received ZEJULA with the dose based on weight and platelet count, the median duration of treatment was 11.0 months (range: 1 day to 16 months).

Serious adverse reactions occurred in 27% of patients receiving ZEJULA. Serious adverse reactions in > 2% of patients were anemia (8%), and thrombocytopenia (7%). No fatal adverse reactions occurred.

Permanent discontinuation due to adverse reactions occurred in 14% of patients who received ZEJULA. Adverse reactions resulting in permanent

discontinuation in >2% of patients who received ZEJULA included thrombocytopenia and anemia (3.0% each), and nausea (2.4%).

Adverse reactions led to dose reduction or interruption in 72% of patients, most frequently from thrombocytopenia (40%), anemia (23%), and neutropenia (15%).

Table 6 and Table 7 summarize adverse reactions and abnormal laboratory findings in the group of patients who received ZEJULA.

Table 6: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA Based on Baseline Weight or Platelet Count in PRIMA ^a				
	Grades 1-4 ^b		Grades 3-4 ^b	
	ZEJULA N=169 %	Placebo N=86 %	ZEJULA N=169 %	Placebo N=86 %
Blood and Lymphatic System Disorders				
Thrombocytopenia	54	5	21	1
Anemia	50	28	23	1
Neutropenia ^c	36	8	15	1
Leukopenia ^d	28	11	5	0
Gastrointestinal Disorders				
Nausea	53	21	1	0
Constipation	31	15	1	1
Vomiting	17	9	0	1
General Disorders and Administration Site Conditions				
Fatigue	48	36	3	0
Metabolism and Nutrition Disorders				
Decreased appetite	19	5	1	0
Nervous System Disorders				
Headache	22	17	1	0
Dizziness	14	13	0	0
Psychiatric Disorders				
Insomnia	21	14	0	0
Renal and Urinary Disorders				
Acute kidney injury ^e	12	5	1	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	18	10	0	1
Vascular Disorders				
Hypertension	17	9	5	2

^aAll adverse reactions in the table consist of grouped preferred terms except for nausea, vomiting, decreased appetite, headache and insomnia, which are single preferred terms.

^bCTCAE=Common Terminology Criteria for Adverse Events version 4.02

^cincludes neutropenia, neutropenic infection, neutropenic sepsis, febrile neutropenia.

^dincludes leukopenia, lymphocyte count decreased, lymphopenia, white blood cell count decreased.

^eincludes blood creatinine increased, blood urea increased, acute kidney injury, renal failure, blood creatine increased.

Table 7: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZEJULA Based on Baseline Weight or Platelet Count in PRIMA				
	Grades 1-4		Grades 3-4	
	ZEJULA N=169 %	Placebo N=86 %	ZEJULA N=169 %	Placebo N=86 %
Decreased hemoglobin	81	70	21	0
Decreased leukocytes	70	36	6	0
Decreased platelets	63	15	18	0
Increased glucose	63	56	2	1
Decreased neutrophils	60	27	15	0
Decreased lymphocytes	52	30	5	4
Increased alkaline phosphatase	43	17	1	0
Decreased magnesium	44	30	0	0
Increased creatinine	41	22	0	0

Table 7: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZEJULA Based on Baseline Weight or Platelet Count in PRIMA (continued)				
	Grades 1-4		Grades 3-4	
	ZEJULA N=169 %	Placebo N=86 %	ZEJULA N=169 %	Placebo N=86 %
Increased aspartate aminotransferase	31	19	1	0
Increased alanine aminotransferase	28	15	2	2

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of ZEJULA monotherapy 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in the NOVA trial. Adverse reactions in NOVA led to dose reduction or interruption in 69% of patients, most frequently from thrombocytopenia (41%) and anemia (20%). The permanent discontinuation rate due to adverse reactions in NOVA was 15%. The median exposure to ZEJULA in these patients was 250 days.

Table 8 and Table 9 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA in NOVA.

Table 8: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in NOVA				
	Grades 1-4 ^a		Grades 3-4 ^a	
	ZEJULA N=367 %	Placebo N=179 %	ZEJULA N=367 %	Placebo N=179 %
Blood and Lymphatic System Disorders				
Thrombocytopenia	61	5	29	0.6
Anemia	50	7	25	0
Neutropenia ^b	30	6	20	2
Leukopenia	17	8	5	0
Cardiac Disorders				
Palpitations	10	2	0	0
Gastrointestinal Disorders				
Nausea	74	35	3	1
Constipation	40	20	0.8	2
Vomiting	34	16	2	0.6
Mucositis/stomatitis	20	6	0.5	0
Dyspepsia	18	12	0	0
Dry mouth	10	4	0.3	0
General Disorders and Administration Site Conditions				
Fatigue/Asthenia	57	41	8	0.6
Metabolism and Nutrition Disorders				
Decreased appetite	25	15	0.3	0.6
Infections and Infestations				
Urinary tract infection	13	8	0.8	1
Investigations				
AST/ALT elevation	10	5	4	2
Musculoskeletal and Connective Tissue Disorders				
Back pain	18	12	0.8	0
Nervous System Disorders				
Headache	26	11	0.3	0
Dizziness	18	8	0	0
Dysgeusia	10	4	0	0
Psychiatric Disorders				
Insomnia	27	8	0.3	0
Anxiety	11	7	0.3	0.6
Respiratory, Thoracic, and Mediastinal Disorders				
Nasopharyngitis	23	14	0	0
Dyspnea	20	8	1	1
Cough	16	5	0	0
Skin and Subcutaneous Tissue Disorders				
Rash	21	9	0.5	0

Table 8: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in NOVA (continued)				
	Grades 1-4 ^a		Grades 3-4 ^a	
	ZEJULA N=367 %	Placebo N=179 %	ZEJULA N=367 %	Placebo N=179 %
Vascular Disorders				
Hypertension	20	5	9	2

^aCTCAE=Common Terminology Criteria for Adverse Events version 4.02
^bincludes preferred terms of neutropenic infection, neutropenic sepsis, and febrile neutropenia.

Table 9: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA in NOVA				
	Grades 1-4		Grades 3-4	
	ZEJULA N=367 %	Placebo N=179 %	ZEJULA N=367 %	Placebo N=179 %
Decrease in hemoglobin	85	56	25	0.5
Decrease in platelet count	72	21	35	0.5
Decrease in WBC count	66	37	7	0.7
Decrease in absolute neutrophil count	53	25	21	2
Increase in AST	36	23	1	0
Increase in ALT	28	15	1	2

N=number of patients; WBC=white blood cells; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase
The following adverse reactions and laboratory abnormalities have been identified in ≥1 to <10% of the 367 patients receiving ZEJULA in the NOVA trial and not included in the table: tachycardia, peripheral edema, hypokalemia, bronchitis, conjunctivitis, gamma-glutamyl transferase increased, blood creatinine increased, blood alkaline phosphatase increased, weight decreased, depression, epistaxis.
Treatment of Advanced Ovarian Cancer after Three or More Chemotherapies
The safety of ZEJULA monotherapy 300 mg once daily has been studied in QUADRA, a single-arm study in 463 patients with recurrent high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who had been treated with 3 or more prior lines of therapy. The median duration of overall study treatment was 3 months (range: 0.03 to 32 months). For the indicated QUADRA population, the median duration was 4 months (range: 0.1 to 30 months).

Fatal adverse reactions occurred in 2% of patients, including cardiac arrest. Serious adverse reactions occurred in 43% of patients receiving ZEJULA. Serious adverse reactions in >3% of patients were small intestinal obstruction (7%), vomiting (6%), nausea (5%), and abdominal pain (4%). Permanent discontinuation due to adverse reactions (Grade 1-4) occurred in 21% of patients who received ZEJULA.
Adverse reactions led to dose reduction or interruption in 73% of patients receiving ZEJULA. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of ZEJULA were thrombocytopenia (40%), anemia (21%), neutropenia (11%), nausea (13%), vomiting (11%), fatigue (9%), and abdominal pain (5%).
Table 10 and Table 11 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA in QUADRA.

Table 10: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in QUADRA		
	Grades 1-4 ^a N=463 %	Grades 3-4 ^a N=463 %
Blood and Lymphatic System Disorders		
Anemia ^b	51	27
Thrombocytopenia ^c	52	28
Neutropenia ^d	20	13
Gastrointestinal Disorders		
Nausea	67	10
Vomiting	44	8
Constipation	36	5
Abdominal pain	34	7
Diarrhea	17	0.2
General Disorders and Administration Site Conditions		
Fatigue	56	7
Infections and Infestations		
Urinary tract infection	15	2

Table 10: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in QUADRA (continued)		
	Grades 1-4 ^a N=463 %	Grades 3-4 ^a N=463 %
Investigations		
Blood alkaline phosphatase increased	11	2
AST/ALT elevation	11	1
Metabolism and Nutrition Disorders		
Decreased appetite	27	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain	29	3
Nervous System Disorders		
Headache	19	0.4
Dizziness	11	0
Psychiatric Disorders		
Insomnia	21	1
Renal and Urinary Disorders		
Acute kidney injury	17	1
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	22	3
Cough	13	0
Vascular Disorders		
Hypertension	14	5

^aCTCAE=Common Terminology Criteria for Adverse Events version 4.02
^bAnemia includes events with preferred terms of anemia, hemoglobin decreased, anemia macrocytic, aplastic anemia, and normochromic normocytic anemia.
^cThrombocytopenia includes events with preferred terms of thrombocytopenia and platelet count decreased.
^dNeutropenia includes events with preferred terms of neutropenia, neutrophil count decreased, neutropenic infection and neutropenic sepsis.

Table 11: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA in QUADRA		
	Grades 1-4 N=463 %	Grades 3-4 N=463 %
Decreased hemoglobin	83	26
Increased glucose	66	5
Decreased platelets	60	28
Decreased lymphocytes	57	18
Decreased leukocytes	53	9
Decreased magnesium	46	1
Increased alkaline phosphatase	40	4
Increased gamma glutamyl transferase	40	8
Increased creatinine	36	0.4
Decreased sodium	34	6
Decreased neutrophils	34	15
Increased aspartate aminotransferase	29	2
Decreased albumin	27	2

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of ZEJULA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Immune System Disorders: hypersensitivity (including anaphylaxis)
Nervous System Disorders: posterior reversible encephalopathy syndrome (PRES)
Psychiatric Disorders: confusional state/disorientation, hallucination, cognitive impairment
Respiratory, Thoracic, and Mediastinal Disorders: non-infectious pneumonitis
Skin and Subcutaneous Tissue Disorders: photosensitivity
USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
Based on its mechanism of action, ZEJULA can cause fetal harm when administered to pregnant women. There are no data regarding the use of ZEJULA in pregnant women to inform the drug-associated risk. ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) [see *Warnings and Precautions*]. Due to the potential risk to a fetus based on its mechanism of action, animal

developmental and reproductive toxicology studies were not conducted with niraparib. Advise pregnant women of the potential risk to a fetus.
The 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% to 4% and 15% to 20%, respectively.
Lactation
Risk Summary
No data are available regarding the presence of niraparib or its metabolites in human milk, or on its effects on the breastfed infant or milk production. Because of the potential for serious adverse reactions in breastfed infants from ZEJULA, advise a lactating woman not to breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.
Females and Males of Reproductive Potential
Pregnancy Testing
ZEJULA can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations*].
A pregnancy test is recommended for females of reproductive potential prior to initiating ZEJULA treatment.
Contraception
Females
ZEJULA 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 ZEJULA and for at least 6 months following the last dose.
Infertility
Males
Based on animal studies, ZEJULA may impair fertility in males of reproductive potential.
Pediatric Use
Safety and effectiveness of ZEJULA have not been established in pediatric patients.
Geriatric Use
In PRIMA, 39% of patients were aged ≥65 years and 10% were aged ≥75 years. In NOVA, 35% of patients were aged ≥65 years and 8% were aged ≥75 years. No overall differences in safety and effectiveness of ZEJULA were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.
Renal Impairment
No dose adjustment is necessary for patients with mild (CLcr: 60 to 89 mL/min) to moderate (CLcr: 30 to 59 mL/min) renal impairment. The degree of renal impairment was determined by creatinine clearance as estimated by the Cockcroft-Gault equation. The safety of ZEJULA in patients with severe renal impairment or end stage renal disease undergoing hemodialysis is unknown.
Hepatic Impairment
No dose adjustment is needed in patients with mild hepatic impairment according to the National Cancer Institute – Organ Dysfunction Working Group (NCI-ODWG) criteria. The safety of ZEJULA in patients with moderate to severe hepatic impairment is unknown.
OVERDOSAGE
There is no specific treatment in the event of ZEJULA overdose, and symptoms of overdose are not established. In the event of an overdose, healthcare practitioners should follow general supportive measures and should treat symptomatically.

PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information).
MDS/AML
Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts, or a need for blood transfusions. This may be a sign of hematological toxicity or myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) which has been reported in patients treated with ZEJULA [see *Warnings and Precautions*].
Bone Marrow Suppression
Advise patients that periodic monitoring of their blood counts is required. Advise patients to contact their healthcare provider for new onset of bleeding, fever, or symptoms of infection [see *Warnings and Precautions*].
Cardiovascular Effects
Advise patients to undergo blood pressure and heart rate monitoring at least weekly for the first two months, then monthly for the first year of treatment, and then periodically thereafter. Advise patients to contact their healthcare provider if blood pressure is elevated [see *Warnings and Precautions*].
Dosing Instructions
Inform patients on how to take ZEJULA [see *Dosage and Administration*]. ZEJULA should be taken once daily. Instruct patients that if they miss a dose of ZEJULA, not to take an extra dose to make up for the one that they missed. They should take their next dose at the regularly scheduled time. Each capsule should be swallowed whole. ZEJULA may be taken with or without food. Bedtime administration may be a potential method for managing nausea.
Embryo-Fetal Toxicity
Advise females to inform 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 *Warnings and Precautions* and *Use in Specific Populations*].
Contraception
Advise females of reproductive potential to use effective contraception during treatment with ZEJULA and for at least 6 months after receiving the last dose [see *Use in Specific Populations*].
Lactation
Advise patients not to breastfeed while taking ZEJULA and for 1 month after the last dose [see *Use in Specific Populations*].

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AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) 2020 CONFERENCE COVERAGE

COVID-19

Cancer Progression Is Linked to Increased Risk of Death Within 30 Days of COVID-19 Diagnosis

Ryan McDonald

Disease progression and treatment with hydroxychloroquine and azithromycin were associated with increased all-cause 30-day mortality in patients with cancer compared with patients either in remission or with no evidence of disease, according to data presented during a 2020 American Society of Clinical Oncology Virtual Scientific Program press briefing.¹

“The effects of coronavirus disease 2019 [COVID-19] on patients with cancer remain poorly understood,” lead study author Jeremy L. Warner, MD, MS, an associate professor of medicine and biomedical informatics at Vanderbilt University Medical Center, said during a prerecorded presentation. “There are some published reports, but they tend to be on the smaller side, or focused on a specific geographic region.”

As a result, investigators wanted to collect a larger and more representative sample to learn more about the impact COVID-19 has on cancer, anticipating that patients with cancer could be at a greater risk because of several factors, including:

- Overall increased age
- More comorbidities
- More health care contacts
- Decreased immunity
- Decreased performance status

On March 15, 2020, the COVID-19 &

Cancer Consortium (CCC19) was founded; it started receiving reports on March 17. The consortium includes a survey that is designed for real-time reporting as well as for after a course of COVID-19 is complete. Site-level participation includes institutions from the United States and Canada, as well as anonymous reports from individuals in several other countries and regions.

This first analysis includes data from 928 cases. Median age of the patients was 66 years, with 30% of patients aged more than 75 years.

Half of the patients were white, 16% were black or African American, and 16% were Hispanic. Less than half (39%) of the patients were on active treatment and 43% had active cancer. Breast (21%), prostate (16%), and gastrointestinal (12%) cancer were the 3 most common types of cancer in the patient population. More than half (52%) of the patients were never smokers, whereas 37% were former smokers and only 5% were current smokers.

After a median follow-up of 21 days, 13% of the patients have died. Seventy patients aged more than 75 years have died, and 25 deaths have occurred in patients with progressing disease.

Half of the patients were hospitalized; 23% of those patients have died. The investigators also assessed outcomes in the

132 patients who were admitted to the intensive care unit. Of those 132 patients, 38% died, and of those deaths, 54% occurred in patients aged more than 75 years.

Approximately 20% of patients received a combination of hydroxychloroquine and azithromycin, and another 10% received hydroxychloroquine alone. Of note, according to Warner, only 2 patients received the drugs as part of clinical trials. The rest received the drug off label.

Treatment with hydroxychloroquine and azithromycin was associated with a 2.89-fold greater risk of death in patients with cancer and COVID-19, compared with those who were in remission or had no evidence of active disease. However, as Warner noted, hydroxychloroquine alone was not a significant risk factor for death after adjusting for other factors.

“Prospective trials are needed to clarify whether there is a benefit or a risk to these drugs, alone or in combination,” Warner said during the press briefing. “I think what we found is somewhat consistent with *The Lancet* article based also on a retrospective analysis. Our data set is somewhat prospective, some of the reports are retrospective. Even with the prospective reports, they are not being made

For references visit cancernetwork.com/COVID-19_ASCO20

AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) 2020 CONFERENCE COVERAGE

WOMEN'S CANCER

Mirvetuximab Soravtansine Combination Yields Encouraging Response Rates in Ovarian Cancer

Matthew Fowler

Mirvetuximab soravtansine in combination with bevacizumab (Avastin) to treat patients with platinum-agnostic ovarian cancer demonstrated a confirmed 64% overall response rate (ORR), regardless of platinum status, according to study results presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program.

Moreover, the adverse events (AEs) observed with the mirvetuximab soravtansine/bevacizumab combination were manageable and consistent with the AE profiles of each agent.

“With a confirmed 64% ORR, the combination of [mirvetuximab soravtansine] with bevacizumab has promising activity in high [folate receptor alpha] recurrent ovarian cancer, regardless of platinum status, and is encouraging with respect to available therapies reported in similar populations,” study author Lucy Gilbert, MD, MSc, of McGill University Health Center, said in her presentation.

The ORR for the entire cohort of patients was 47%. In a subset analysis of patients with high folate receptor alpha-expressing tumors, the ORR was 64%. The platinum-resistant subset and the platinum-sensitive subset recorded ORRs of 59% and 69%, respectively.

Duration of response and progres-

sion-free survival data are immature because of the median follow-up of 5.5 months.

Overall, 60 patients were included in the analysis (median age, 60 years). The primary cancer diagnoses were epithelial ovarian (n = 41), fallopian tube (n = 15), and primary peritoneal (n = 4). The study's primary objective was to evaluate the safety and tolerability of the mirvetuximab soravtansine combination in these kinds of cancer.

“In this trial, [mirvetuximab soravtansine] was combined with bevacizumab for a broader segment of recurrent ovarian cancer patients, regardless of platinum status,” said Gilbert.

Of the 60 patients in the analysis, 55 (92%) demonstrated tumor burden reduction, with deeper and more durable tumor reduction found in patients with high folate receptor alpha levels.

The most common AEs associated with the combination regimen were diarrhea (68%), blurred vision (63%), fatigue (58%), and nausea (55%); most were low grade. Hypertension and myelosuppression were the most common grade 3/4 AEs, occurring in 12% and 10% of patients, respectively. Thirteen patients (22%) discontinued treatment with bevacizumab and/or mirvetuximab soravtansine because of treatment-related AEs.

“The combination of mirvetuximab soravtansine and bevacizumab may benefit an increasing population of recurrent ovarian cancer patients for whom a non-platinum-based regimen would be appropriate,” explained Gilbert. ■

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Gilbert L, Oaknin A, Matulonis UA, et al. Mirvetuximab soravtansine, a folate receptor alpha (FR α)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients (pts) with platinum-agnostic ovarian cancer. *J Clin Oncol*. 2020;38(suppl15):6004. doi:10.1200/JCO.2020.38.15_suppl.6004

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Ursula A. Matulonis, MD,
on Key Takeaways From
the KEYNOTE-100 Trial in
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AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) 2020 CONFERENCE COVERAGE

PROSTATE CANCER

Phase 3 HERO Trial Finds Relugolix to Be Superior to Leuprolide in Prostate Cancer

Hannah Slater

Results from the phase 3 HERO trial (NCT03085095), presented during the 2020 American Society of Clinical Oncology Virtual Scientific Program, indicated that relugolix (Relumina) demonstrated superiority over leuprolide (Lupron) in sustained testosterone suppression through 48 weeks, fast testosterone recovery after discontinuation, and a 50% reduction in major adverse cardiovascular events (MACE) in patients with advanced prostate cancer.

Moreover, relugolix achieved castration as early as day 4, suggesting the potential for this agent to become a new standard for testosterone suppression in this patient population.

“Relugolix is a novel, oral [gonadotropin-releasing hormone] GnRH receptor antagonist that achieves both [luteinizing hormone] and [follicle-stimulating hormone; FSH] suppression to its direct inhibitory effect on the pituitary GnRH receptors,” Neal D. Shore, MD, of Carolina Urologic Research Center, Myrtle Beach, South Carolina, said in a news release. “This direct inhibition does not result in a testosterone surge.”

The 48-week, global, pivotal phase 3 trial randomized 934 patients with androgen-sensitive advanced prostate cancer in a 2:1 ratio to receive either 120 mg of relugolix orally once daily after a 1-time 360-mg loading dose ($n = 624$) or a 3-month depot injection of leuprolide acetate ($n = 310$). Testosterone recovery was

also evaluated in a subset of 184 patients.

The primary end point was to achieve and maintain serum testosterone suppression to castrate levels (<50 ng/dL) through 48 weeks. Key secondary end points included castration rates at day 4 and day 15, profound castration (<20 ng/dL) rates at days 4 and 15, prostate-specific antigen response rate at day 15, and FSH levels at week 24.

Overall, 96.7% (95% CI, 94.9%-97.9%) of men treated with relugolix achieved and maintained castration through 48 weeks compared with 88.8% on leuprolide. Notably, the difference of 7.9% (95% CI, 4.1%-11.8%) demonstrated noninferiority (margin, -10%) and superiority ($P < .0001$) of relugolix to leuprolide. All key secondary end points also demonstrated superiority over leuprolide ($P < .0001$).

In the subset of patients evaluated for testosterone recovery, median testosterone levels were 270.76 ng/dL in the relugolix group compared with 12.26 ng/dL in the leuprolide group 90 days after discontinuation of therapy.

In a prespecified analysis, the incidence of MACE was found to be lower in the relugolix group than in the leuprolide group (2.9% vs 6.2%, respectively). Otherwise, the safety and tolerability profiles of the 2 agents were generally similar.

Adverse events (AEs) reported for more than 10% of patients treated with relugolix or leuprolide were hot flush

(54.3% vs 51.6%, respectively), fatigue (21.5% vs 18.5%), constipation (12.2% vs 9.7%), diarrhea (12.2% vs 6.8%), arthralgia (12.1% vs 9.1%), and hypertension (7.9% vs 11.7%). Notably, AEs of diarrhea were of grade 1 or 2 and did not result in study discontinuation.

“Relugolix once daily was well tolerated with an adverse event profile consistent with testosterone suppression,” Shore said. “Most notably, the risk of major adverse cardiovascular events was 54% lower in the relugolix group compared with leuprolide.”

“Relugolix is a novel, oral GnRH antagonist that has the potential to become a new standard for androgen deprivation therapy in advanced prostate cancer,” Shore concluded. ■

REFERENCE

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For more great content, check out our website.

Go to cancernetwork.com/Shore_ASC020 to watch Neal D. Shore, MD, discuss the impact and implications of the phase 3 HERO trial.

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LUNG CANCER

Nivolumab/Ipilimumab Combo Yields Durable Efficacy in Advanced NSCLC

Kristie L. Kahl

Frontline treatment with nivolumab (Opdivo) plus ipilimumab (Yervoy) induced durable and long-term efficacy, compared with chemotherapy, in patients with advanced non–small cell lung cancer (NSCLC) and tumor PD-L1 expression greater than 1% or less than 1%, according to updated results from part 1 of the phase 3 CheckMate 227 (NCT02477826) trial presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program.

“Based on these results, we note that the combination of nivolumab and ipilimumab...is a novel chemotherapy-sparing first-line treatment approach for advanced-stage non–small cell lung cancer,” Suresh S. Ramalingam, MD, deputy director, Winship Cancer Institute of Emory University, said during his presentation.

After a median follow-up of 43.1 months, patients with PD-L1 1% or greater had a reduced risk for death when treated with nivolumab plus ipilimumab, compared with chemotherapy (21% reduced risk; HR, 0.79; 95% CI, 0.67-0.93) and nivolumab monotherapy (10% reduced risk; HR, 0.90; 95% CI, 0.77-1.06).

Median overall survival (OS) was 17.1 months in the nivolumab plus ipilimumab arm, compared with 15.7 months in the nivolumab monotherapy arm and 14.9 months in the chemotherapy arm. The 3-year OS rates were 33% with nivolumab plus ipilimumab, 29% with nivolumab monotherapy, and 22% with chemotherapy.

Among patients with a confirmed response, 38% in the nivolumab plus ipilimumab arm, 32% in the nivolumab monotherapy arm, and 4% in the chemotherapy arm remained in response at 3 years. Those with a complete or partial response at 6 months experienced longer subsequent OS with nivolumab plus ipilimumab, compared with chemotherapy. Moreover, those with stable or progressive disease at 6 months had generally similar subsequent OS between treatments.

During the same time period, patients with PD-L1 less than 1% had a 36% and 18%, respectively, reduced risk for death when treated with nivolumab + ipilimumab, compared with chemotherapy (HR, 0.64; 95% CI, 0.51-0.81) and nivolumab monotherapy (HR, 0.82; 95% CI, 0.66-1.03). The 3-year OS rates were 34% with nivolumab + ipilimumab, 20% with nivolumab monotherapy, and 15% with chemotherapy.

Among patients with a confirmed response, 34% in the nivolumab plus ipilimumab arm, 15% in the nivolumab monotherapy arm, and 0% in the chemotherapy arm remained in response at 3 years.

Three-year progression-free survival (PFS) was 18% with nivolumab plus ipilimumab, 12% with nivolumab monotherapy, and 4% with chemotherapy in patients with PD-L1 1% or greater. Three-year PFS was 13% with nivolumab plus ipilimumab, 8% with nivolumab plus chemotherapy, and 2% with chemotherapy

in patients with PD-L1 less than 1%.

Overall response rates were also superior with nivolumab plus ipilimumab (36.4%), compared with nivolumab monotherapy (27.5%) and chemotherapy (30.2%) in patients with PD-L1 1% or greater. This was true also in patients with PD-L1 less than 1% treated with nivolumab + ipilimumab compared with nivolumab plus chemotherapy and chemotherapy alone (27.3% vs 37.9% vs 23.1%, respectively).

In those with PD-L1 1% or greater, treatment with nivolumab plus ipilimumab extended the median duration of response (DOR) (23.2 months; 95% CI, 15.2-32.2), compared with nivolumab alone (15.5 months; 95% CI, 12.7-23.5) and chemotherapy (6.7 months; 95% CI, 5.6-7.6). In those with PD-L1 less than 1%, DOR was also extended with nivolumab plus ipilimumab, compared with nivolumab plus chemotherapy and chemotherapy alone: 18.0 months (95% CI, 12.4-33.2) vs 8.3 months (95% CI, 5.9-9.4) and 4.8 months (95% CI, 3.7-5.8), respectively.

No new safety signals were identified with nivolumab plus ipilimumab with the extended follow-up. ■

REFERENCE

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AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) 2020 CONFERENCE COVERAGE

GI CANCER

Gastrointestinal Cancer Presentations Relevant to Clinical Practice

Mehmet Sitki Copur, MD

The 2020 American Society of Clinical Oncology Virtual Scientific Program delivered many practice-influencing presentations. Here are some of the most notable research results in the field of gastrointestinal cancer that may guide oncologists in their day-to-day work.

Colorectal Cancer

DESTINY-CRC01: Trastuzumab Deruxtecan (T-DXd) in HER2-Expressing Metastatic Colorectal Cancer

Siena et al presented a phase 2, multicenter, open-label study of trastuzumab deruxtecan (Enhertu; T-DXd) in patients with HER2-expressing metastatic colorectal cancer (mCRC).¹ T-DXd is an antibody-drug conjugate composed of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a topoisomerase I inhibitor payload. Results of early studies have shown promising activity in advanced HER2-expressing tumors.

In this study, patients with RAS wild-type and HER2-overexpressing mCRC, who had disease progression after 2 or more prior regimens, were treated with T-DXd at 6.4 mg/kg every 3 weeks in 3 cohorts (A: immunohistochemistry [IHC] score of 3+ or IHC 2+ and positive by fluorescence in situ hybridization [FISH]; B: IHC 2+/FISH-negative; C: IHC 1+).

Median duration of treatment was

3.5 months. The longest duration of treatment occurred in cohort A, with 4.8 months and 38.5% of patients remaining on T-DXd treatment. In this cohort, the confirmed overall response rate (ORR) was 45.3%, including 1 complete response and 23 partial responses. The overall response in patients previously treated with anti-HER2 antibodies was 43.8%. The disease control rate was 83.0%, median progression-free survival (PFS) was 6.9 months, and median overall survival (OS) had not been yet reached in this group. On the contrary, no responses were observed in cohorts B or C.

Grade 3 or higher treatment-emergent adverse events (AEs) were reported in 61.5% of patients. The most common AEs were decreased neutrophil count (21.8%) and anemia (14.1%). Five patients (6.4%) had interstitial lung disease (two grade 2; one grade 3; two grade 5), which accounted for the only drug-related deaths.

Overall, T-DXd at 6.4 mg/kg every 3 weeks demonstrated remarkable activity in patients with HER2-expressing mCRC who are refractory to standard therapies. T-DXd showed activity in patients with previous exposure to anti-HER2 and anti-EGFR antibody therapies; however, the efficacy seems to be limited to IHC 3+ patients. Testing for *HER2* amplification in CRC should be considered standard of care. The trial results did not answer

the question of whether to sequence trastuzumab followed by T-DXd versus up-front therapy with T-DXd, and it did not answer the question of whether RAS-mutated patients would benefit from HER2-targeted therapies. Interstitial lung disease, which caused 2 deaths, necessitates strategies for vigilant recognition and early intervention. The dose of T-DXd may need to be reevaluated.

Updated Survival Results From BEACON CRC

Kopetz et al presented updated survival results from a randomized, 3-arm, phase 3 study of encorafenib (Braftovi) plus cetuximab (Erbix) with binimetinib (Mektovi; triplet therapy) or without binimetinib (doublet therapy) versus investigator's choice of either irinotecan or FOLFIRI plus cetuximab (control) in previously treated patients with *BRCA* V600E-mutated mCRC.²

Primary end points were the OS and objective response rates for patients receiving triplet therapy versus those in the control group. A total of 665 patients were randomized to receive triplet ($n = 224$), doublet ($n = 220$), or control ($n = 221$) therapy.

Median OS was 9.3 months for both the triplet and doublet groups vs 5.9 months for the control group. Confirmed ORR was 26.8% for the triplet, 19.5% for the doublet, and 1.8% for the control groups, respectively. Retrospec-

tive subgroup analyses suggested that some patients may benefit more from triplet than doublet therapy; however, both triplet and doublet therapy showed improved OS compared with control in all subgroups. Grade 3 or higher AEs were experienced by 65.8% of patients receiving triplet therapy, 57.4% of those receiving doublet therapy, and 64.2% of those in the control group.

The updated analysis confirmed that encorafenib + cetuximab with or without binimetinib improved OS and ORR in previously treated patients with *BRAF* V600E-mutated mCRC, compared with standard chemotherapy. To address which patients would benefit from triplet vs doublet therapy will require a study of the subset analysis.

First-Line FOLFOX Plus Panitumumab Versus 5FU Plus Panitumumab in *RAS-BRAF* Wild-Type Metastatic Colorectal Cancer in Elderly Patients

Lonardi et al presented data on first-line FOLFOX plus panitumumab (Vectibix) versus fluorouracil/leucovorin (5FU/LV) plus panitumumab for up to 12 cycles followed by panitumumab maintenance until progressive disease in elderly patients with mCRC, *RAS/BRAF* wild type.³ Although guidelines recommend considering fluoropyrimidine monotherapy as an option for elderly patients, no randomized studies have ever explored the role of the combination with an anti-EGFR agent.

In this prospective, open-label, multicenter phase 2 randomized trial, unresectable and previously untreated patients with *RAS/BRAF* wild type mCRC, 70 years or older, were randomized to receive FOLFOX + panitumumab (arm A) or 5FU/LV + panitumumab (arm B) for up to 12 cycles, followed by panitumumab maintenance until progressive disease. The primary end point was PFS in both arms. Stratification criteria were age (≤ 75 vs > 75 years), ECOG performance status (0-1 vs 2) and geriatric

assessment with G8 score (≤ 14 vs > 14). Median PFS was 9.6 months (95% CI, 8.8-10.9) in arm A compared with 9.1 months (95% CI, 7.7-9.9) in arm B. Response rates were 65% vs 57%, respectively. Grade 3-4 toxicities were neutropenia (9.8% vs 1.1%, respectively), diarrhea (16.3% vs 1.1%), stomatitis (9.8% vs 4.4%), neurotoxicity (3.3% vs 0%), fatigue (6.5% vs 4.4%), and skin rash (25.0% vs 24.2%).

Pancreatic Cancer SWOG S1505: Perioperative Chemotherapy With Modified FOLFIRINOX Versus Gemcitabine/Nab-Paclitaxel for Resectable Pancreatic Ductal Adenocarcinoma

Sohal et al presented data from a randomized phase 2 trial of perioperative chemotherapy with modified FOLFIRINOX (mFOLFIRINOX) versus gemcitabine (gem)/nab-paclitaxel for resectable pancreatic cancer.⁴ Standard of care for resectable pancreatic cancer is surgery followed by adjuvant chemotherapy.

Patients with resectable pancreatic cancer were randomized to 3 months of mFOLFIRINOX followed by surgery followed by 3 months of mFOLFIRINOX versus 3 months of gem/nab-paclitaxel followed by surgery followed by 3 additional months of gem/nab-paclitaxel. About 70% of patients underwent resection; less than 50%, however, were able to complete intended postoperative chemotherapy.

Gem/nab-paclitaxel performed better than expected with pathologic complete response rates of 42% compared with 25% for mFOLFIRINOX. Gem/nab-paclitaxel produced better median disease-free survival with 14.2 months, compared with mFOLFIRINOX at 10.9 months, but the difference did not reach statistical significance ($P = 0.87$). Median OS was 22.4 vs 23.6 months, respectively. OS at 2 years was 41.6% for mFOLFIRINOX arm vs 48.8% for gem/nab-paclitaxel. Neither regimen's 2-year OS estimate was statis-

tically significantly higher than the prior threshold of 40%. The intended target for OS at 2 years was 58%.

Overall, there seems to be little evidence that either regimen improves survival compared with the historical standard.

ESPAC-5F: A Comparison of Immediate Surgery Compared With Neoadjuvant Gemcitabine Plus Capecitabine or FOLFIRINOX or Chemoradiotherapy (CRT) in Patients With Borderline Resectable Pancreatic Cancer

In this study, Ghaneh et al presented data resulting from a 4-arm, prospective, multicenter, phase 2 trial comparing immediate surgery with surgery after 3 different neoadjuvant treatment regimens in patients with borderline resectable pancreatic cancer.⁵ Patients with borderline resectable pancreatic cancer generally have poor survival and low resection rates. Neoadjuvant therapy has been explored to improve the outcomes for these patients.

This trial sought to determine the feasibility and efficacy of immediate surgery; 2 cycles of neoadjuvant gemcitabine plus capecitabine; 4 cycles of neoadjuvant FOLFIRINOX; or 50.4 Gy capecitabine-based neoadjuvant CRT in 28 daily fractions over 5.5 weeks. Resected patients received adjuvant therapy, and follow-up continued for 12 months. Primary end points were recruitment rate and resection rate (R1/R0). Recruitment rate was 20.74%. Resection rate was 62% for immediate surgery and 55% for the 3 neoadjuvant therapy groups ($P = 0.668$). The R0 resection rate on upfront-resected patients was 15%, compared with 23% for the neoadjuvant group ($P = 0.721$). The 1-year survival rate favored neoadjuvant treatment: 40% for immediate surgery vs 77% for neoadjuvant therapy.■

➤ For full list of references visit cancernetwork.com/ASCO-GI-roundup

AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) 2020 CONFERENCE COVERAGE

RENAL CELL CARCINOMA

Final Data Analysis Supports Tivozanib as Superior Treatment for Patients With RCC

Kevin Wright

Tivozanib (Fotivda) significantly improved progression-free survival (PFS), compared with sorafenib (Nexavar), in patients with highly relapsed or refractory metastatic renal cell carcinoma (RCC), according to results from the phase 3 TIVO-3 trial presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program.^{1,2}

“We believe the TIVO-3 data demonstrate a favorable risk/benefit profile for tivozanib in the growing population of patients who have relapsed or become refractory to multiple lines of therapy, including checkpoint inhibitors,” Sumanta Pal, MD, associate clinical professor, Department of Medical Oncology and Therapeutics Research, and codirector, Kidney Cancer Program, at City of Hope Comprehensive Cancer Center, said in a news release.²

The final overall survival (OS) HR was 0.97 (95% CI, 0.75-1.24; $P = .78$). An updated analysis of the data found that with a median follow-up of 38 months for tivozanib and 40 months for sorafenib, median OS was 16.4 months for tivozanib (95% CI, 13.4-22.2) and 19.2 months for sorafenib (95% CI, 15.0-24.2). A subset analysis showed the greatest benefit was derived by the cohort of patients who had received treatment with a prior checkpoint inhibitor and VEGF inhibitor, with an HR of 0.55, or 2 VEGF tyrosine kinase inhibitors (TKIs), with an HR of 0.57.

Previously released data showed an increased median PFS for tivozanib when

compared with sorafenib, (5.6 months vs 3.9 months; HR, 0.73; 95% CI, 0.56-0.94; $P = .016$).

“The lack of clinical data to guide treatment decisions in a robust, evidence-based manner in this setting is a serious and growing unmet medical need,” Pal added. “TIVO-3 provides the first positive superiority study to help guide this important treatment decision and, furthermore, offers this highly refractory patient population a favorable tolerability profile as indicated by fewer dose reductions, interruptions, and discontinuations over a less selective VEGFR TKI in sorafenib.”

The TIVO-3 study was a controlled, multicenter, open-label, phase 3 trial that randomized 350 patients with highly refractory metastatic RCC who had failed ≥ 2 prior regimens, including VEGF-TKI treatment, 1:1 to receive either oral tivozanib or sorafenib. Crossover between arms was not permitted.

Eighteen percent ($n = 31$) of patients in the tivozanib arm achieved partial response, compared with 8% ($n = 14$) of those in the sorafenib arm. The objective response rate was 34% for tivozanib versus 24% for sorafenib.

Treatment with tivozanib was found to be generally well tolerated, and the safety profile was favorable when compared with sorafenib. Treatment-related adverse events (TRAEs) were reported in 84% ($n = 146$) of patients receiving tivozanib and 94% ($n = 160$) of those receiving sorafenib. Serious

TRAEs occurred in 11% ($n = 19$) of patients treated with tivozanib versus 10% ($n = 17$) of patients who received sorafenib.

The most common grade 3 or 4 AE reported in patients receiving tivozanib and sorafenib was hypertension (21% vs 14%, respectively). The most commonly reported any-grade AEs associated with tivozanib were hypertension (38%), diarrhea (33%), fatigue (29%), and decreased appetite (27%).

The investigators reported significantly fewer dose reductions and interruptions due to AEs for tivozanib versus sorafenib (48% vs 63%; $P = .0164$), despite nearly double the average time of cycles initiated for the tivozanib arm (11.9 months vs 6.7 months, respectively). The rates of TRAEs leading to permanent discontinuation were 8% for tivozanib compared with 15% for sorafenib.

“The biggest advantage to tivozanib is tolerability,” Brian Rini, MD, from Vanderbilt-Ingram Cancer Center, said in a recent interview with CancerNetwork®. “Patients, appropriately, always want more options,” he said. “...Having tolerable options, especially in this late-line setting, is a potential advantage to patients. I often describe to patients that we’re just trying to get as many shots on goal as possible....So, I think it adds to our weapons in this disease.” ■

➤ For references, visit cancernetwork.com/TIVO_ASCO20

AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) 2020 CONFERENCE COVERAGE

MYELOMA

Carfilzomib Triplet Fails to Induce Superior PFS in Newly Diagnosed Multiple Myeloma

Jessica Skarzynski

Carfilzomib (Kyprolis) combined with lenalidomide (Revlimid) and dexamethasone (KRd) failed to improve progression-free survival (PFS), compared with the current standard-of-care triplet of bortezomib (Velcade), lenalidomide, and dexamethasone (VRd), in patients with newly diagnosed multiple myeloma (NDMM), according to results of the ENDURANCE trial presented as part of the 2020 American Society of Clinical Oncology Virtual Scientific Program.

Given the higher efficacy of carfilzomib seen in recent phase 2 trials, investigators sought to determine whether carfilzomib could replace bortezomib in the current standard-of-care triplet induction regimen in standard- and intermediate-risk NDMM.

To do so, 1087 patients with NDMM were randomized 1:1 to receive either VRd or KRd for 36 weeks. After this initial period, a second 1:1 randomization was completed, placing patients in 1 of 2 groups: indefinite lenalidomide maintenance therapy or lenalidomide maintenance therapy for only 2 years.

Patients without 17p deletion, t(14;16), t(14;20), plasma cell leukemia, or high-risk GEP70 profile were enrolled in the trial. The median age of all patients was 65 years. The 542 patients in the VRd arm received bortezomib at 1.3 mg/m² on days 1, 4, 8, and 11 (days 1 and 8 for cycles 9-12), lenalidomide at

25 mg on days 1 to 14, and dexamethasone at 40 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of a 3-week cycle for 12 cycles.

The KRd arm of 545 patients received carfilzomib at 36 mg/m² on days 1, 2, 8, 9, 15, and 16 with lenalidomide at 25 mg daily on days 1 to 21 and dexamethasone at 40 mg weekly, in 4-week cycles for 9 cycles. For the maintenance phase, patients received lenalidomide at 15 mg on days 1 to 21 every 4 weeks.

During the second of 3 planned interim analyses, the therapy became ineffective in improving PFS (HR, 1.04; 95% CI, 0.8-1.3; *P* = 0.74).

In the VRd cohort, median PFS was 34.4 months compared with 34.6 months in the KRd arm. The investigators noted that no differences in PFS were seen based on age, the presence or absence of t(4;14), or disease stage.

The randomized phase 3 trial also assessed whether indefinite maintenance with lenalidomide improved overall survival (OS) compared with 2-year maintenance; however, data have yet to mature for this end point.

Three-year OS (95% CI) was also similar in both arms, with 84% in the VRd arm and 86% in the KRd arm.

Patients in the VRd and KRd cohorts were taken off the trial to pursue alternative therapies (18% vs 14%, respectively), or because of adverse events (AEs; 17% vs 9%), withdrawal (7% vs 4%), or disease progression (6% vs 4%).

The most common grade 3 or higher AEs were nonhematological, appearing in 42% of patients in the VRd arm compared with 48% of patients in the KRd arm. Although neuropathy rates were higher with VRd compared with KRd (8% vs 1%, respectively), rates of cardiopulmonary and renal toxicities were higher with KRd (5% vs 16%).■

REFERENCE

JKumar S, Jacobus SJ, Cohen AD, et al. Carfilzomib, lenalidomide, and dexamethasone (KRd) versus bortezomib, lenalidomide, and dexamethasone (VRd) for initial therapy of newly diagnosed multiple myeloma (NDMM): results of ENDURANCE (E1A11) phase III trial. *J Clin Oncol*. 2020;38(suppl 18):LBA3. doi:10.1200/JCO.2020.38.18_suppl.LBA3

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AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) 2020 CONFERENCE COVERAGE

HEMATOLOGICAL MALIGNANCIES

Interim Phase 2 ZUMA-5 Results Show Promise for Axi-Cel in R/R iNHL

Hannah Slater

Results from an interim analysis of the phase 2 ZUMA-5 study showed that axicabtagene ciloleucel (axi-cel; Yescarta) demonstrated significant and durable clinical benefit in patients with relapsed or refractory indolent non-Hodgkin lymphoma, with high overall response rate (ORR) and complete response (CR) rate observed. It also had a manageable safety profile.¹

The results, presented at the 2020 American Society of Clinical Oncology Virtual Scientific Meeting, indicate that axi-cel may be a promising approach to treat this patient population, according to the investigators.

“Advanced-stage indolent B-cell non-Hodgkin lymphomas are largely incurable with conventional therapies, with many patients experiencing multiple relapses over the natural history of their disease and remission shortening with subsequent therapies,” Caron A. Jacobson, MD, of the Dana-Farber Cancer Institute, said during a presentation of the data.

Adults with relapsed or refractory follicular lymphoma (FL) (grades 1-3a) and marginal zone lymphoma (MZL) (nodal or extranodal) with an ECOG status of 0 or 1 were eligible for the study, if they had 2 or more lines of therapy that included an anti-CD20 monoclonal antibody with an alkylating agent. Participants were leukapheresed and received conditioning chemotherapy followed by axi-cel infu-

sion at 2×10^6 chimeric antigen receptor (CAR) T cells/kg.

The primary end point of the study was ORR by central review. Key secondary end points included duration of response (DOR), progression-free survival (PFS), overall survival (OS), safety, and blood levels of cytokines and CAR T cells.

As of December 16, 2019, 140 patients (FL, $n = 124$; MZL, $n = 16$) had received axi-cel with a median follow-up of 15.3 months (range, 1.9-28.8).

In the 96 patients evaluable for efficacy, the ORR was 93% (95% CI, 86%-97%) and the CR rate was 80% (95% CI, 71%-88%). The median time to first response was 1 month (range, 0.8-3.1). Specifically, patients with FL ($n = 80$) had an ORR of 95%, with an 81% CR rate, and those with MZL ($n = 16$) had an ORR of 81%, with a 75% CR rate.

With a median follow-up of 15.3 months, the estimated DOR in all patients was 20.8 months, and 68% of patients with FL had an ongoing response as of the data cutoff. Moreover, the median PFS was 23.5 months (95% CI, 22.8 to not evaluable) in all patients, and the median OS was not reached. However, the 12-month OS rate was 94.3% (95% CI, 86.8%-97.6%) for all patients.

All of the study participants were evaluable for safety, and 119 patients (85%) experienced grade 3 or higher adverse events (AEs). The most commonly observed AEs were neutropenia (34%) and

anemia (22%). Additionally, grade 3 or higher cytokine release syndrome (CRS) and neurologic events occurred in 8% and 17% of patients, respectively. There were only 2 grade 5 AEs, including multisystem organ failure in the context of CRS (related to axi-cel) and aortic dissection (unrelated to axi-cel).

“The safety profile was manageable and reversible, and it appeared to be at least similar to that of axi-cel in aggressive lymphomas,” Jacobson said.

The median time to peak of anti-CD19 CAR T-cell levels after axi-cel infusion was 8 days (range, 8-371). Furthermore, anti-CD19 CAR T cells were detectable at 18 months in most patients with evaluable samples (13 of 15; 87%).

“Axi-cel appears to be a promising therapeutic approach for patients with relapsed and refractory indolent B-cell non-Hodgkin lymphoma,” said Jacobson.

Axi-cel is currently approved by the FDA as a treatment for adult patients with relapsed or refractory large B-cell lymphoma based on findings from the phase 2 ZUMA-1 trial.² The agent is indicated specifically following 2 or more prior therapies for those with diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL transformed from FL.■

➤ For references, visit cancernetwork.com/ZUMA-5_ASCO20

As soon as you diagnose mCSPC or nmCRPC...

START EARLY WITH ERLEADA®

TO PUSH BACK ON PROGRESSION

In the TITAN study*:
33% reduction
in the risk of death¹

(ERLEADA® + ADT vs placebo + ADT; median overall survival was not estimable in either arm; HR=0.67; 95% CI: 0.51, 0.89; P=0.0053)

In the SPARTAN study*:
2-YEAR improvement
in median MFS¹

(ERLEADA® + ADT vs placebo + ADT; 40.5 months vs 16.2 months; HR=0.28; 95% CI: 0.23, 0.35; P<0.0001)

INDICATION

ERLEADA® (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with:

- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration-resistant prostate cancer (nmCRPC)

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Ischemic Cardiovascular Events

In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 3% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 6 patients (0.5%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with current evidence of unstable angina, myocardial infarction, or congestive heart failure within 6 months of randomization were excluded from the SPARTAN and TITAN studies. Ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA®. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA® for Grade 3 and 4 events.

Fractures—In a randomized study (SPARTAN) of patients with nmCRPC, fractures occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 9% of patients treated with ERLEADA® and in 6% of patients treated with placebo. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

Falls—In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA® compared with 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Falls occurred in patients receiving ERLEADA® with increased frequency in the elderly. Evaluate patients for fall risk.

Seizure—In 2 randomized studies (SPARTAN and TITAN), 5 patients (0.4%) treated with ERLEADA® and 1 patient treated with placebo (0.1%) experienced a seizure. Permanently discontinue ERLEADA® in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA®. Advise patients of the risk of developing a seizure while receiving ERLEADA® and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

References: 1. ERLEADA® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. 2. Chi KN, Agarwal N, Bjartell A, et al; for the TITAN Investigators. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2019;381(1):13-24. 3. Smith MR, Saad F, Chowdhury S, et al; for the SPARTAN Investigators. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018;378(15):1408-1418.

Embryo-Fetal Toxicity—The safety and efficacy of ERLEADA® have not been established in females. Based on its mechanism of action, ERLEADA® can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA® [see *Use in Specific Populations* (8.1, 8.3)].

ADVERSE REACTIONS

Adverse Reactions—The most common adverse reactions (≥10%) that occurred more frequently in the ERLEADA®-treated patients (≥2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Laboratory Abnormalities—All Grades (Grade 3-4)

- **Hematology**—In the TITAN study: white blood cell decreased ERLEADA® 27% (0.4%), placebo 19% (0.6%). In the SPARTAN study: anemia ERLEADA® 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA® 47% (0.3%), placebo 29% (0%); lymphopenia ERLEADA® 41% (2%), placebo 21% (2%)
- **Chemistry**—In the TITAN study: hypertriglyceridemia ERLEADA® 17% (3%), placebo 12% (2%). In the SPARTAN study: hypercholesterolemia ERLEADA® 76% (0.1%), placebo 46% (0%); hyperglycemia ERLEADA® 70% (2%), placebo 59% (1%); hypertriglyceridemia ERLEADA® 67% (2%), placebo 49% (0.8%); hyperkalemia ERLEADA® 32% (2%), placebo 22% (0.5%)

Rash—In 2 randomized studies, rash was most commonly described as macular or maculopapular. Adverse reactions of rash were 26% with ERLEADA® vs 8% with placebo. Grade 3 rashes (defined as covering >30% body surface area [BSA]) were reported with ERLEADA® treatment (6%) vs placebo (0.5%).

The onset of rash occurred at a median of 83 days. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA®.

Hypothyroidism—In 2 randomized studies, hypothyroidism was reported for 8% of patients treated with ERLEADA® and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA® and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

ADT = androgen deprivation therapy; AR = androgen receptor; CI = confidence interval; CT = computed tomography; GnRH = gonadotropin-releasing hormone; HR = hazard ratio; mCSPC = metastatic castration-sensitive prostate cancer; MFS = metastasis-free survival; nmCRPC = non-metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival; SPARTAN = Selective Prostate Androgen Receptor Targeting with ARN-509; TITAN = Targeted Investigational Treatment Analysis of Novel Antiandrogens.

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA®—Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, reduce the ERLEADA® dose based on tolerability [see *Dosage and Administration* (2.2)].

Effect of ERLEADA® on Other Drugs—ERLEADA® is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA® with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA® with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA® and evaluate for loss of activity.

P-gp, BCRP, or OATP1B1 Substrates—Apalutamide is a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. Concomitant use of ERLEADA® with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be co-administered with ERLEADA® and evaluate for loss of activity if medication is continued.

Please see Brief Summary of full Prescribing Information for ERLEADA® on subsequent pages.

***Study Design:** TITAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with mCSPC (N=1052). Patients had newly diagnosed mCSPC or relapsed metastatic disease after an initial diagnosis of localized disease. Patients with visceral (ie, liver or lung) metastases as the only sites of metastases were excluded. Patients were randomized 1:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the TITAN trial received a concomitant GnRH analog or had a prior bilateral orchiectomy. The dual primary endpoints were overall survival and rPFS.^{1,2}

¹All patients who enrolled in the TITAN study started ADT for mCSPC ≤6 months prior to randomization.²

***Study Design:** SPARTAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with nmCRPC (N=1207). Patients had a PSA doubling time ≤10 months and serum testosterone levels <50 ng/dL. All patients enrolled were confirmed to be non-metastatic by blinded central imaging review. Patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded. Patients were randomized 2:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the SPARTAN trial received a concomitant GnRH analog or had a bilateral orchiectomy. The primary endpoint was metastasis-free survival (MFS), defined as the time from randomization to the time of first evidence of blinded independent central review-confirmed distant metastasis, defined as new bone or soft tissue lesions or enlarged lymph nodes above the iliac bifurcation, or death due to any cause, whichever occurred first. Secondary endpoints were time to metastasis, progression-free survival, time to symptomatic progression, overall survival, and time to initiation of cytotoxic chemotherapy.^{1,3}

³In the SPARTAN study, conventional imaging (technetium-99m bone scans and CT scans) was used to confirm that patients were non-metastatic at screening for inclusion. Patients with pelvic lymph nodes <2 cm in short axis (N1) located below the iliac bifurcation at screening were allowed in the study. All patients in SPARTAN had a PSA doubling time ≤10 months at study entry.^{1,3}

Brief Summary of Prescribing Information for ERLEADA® (apalutamide)

ERLEADA® (apalutamide) tablets, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

ERLEADA is indicated for the treatment of patients with

- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration-resistant prostate cancer (nmCRPC)

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Ischemic Cardiovascular Events

Ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA for Grade 3 and 4 events.

In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA and 3% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 6 patients (0.5%) treated with ERLEADA and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with current evidence of unstable angina, myocardial infarction, or congestive heart failure within six months of randomization were excluded from the SPARTAN and TITAN studies.

Fractures

Fractures occurred in patients receiving ERLEADA. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

In a randomized study (SPARTAN) of patients with non-metastatic castration-resistant prostate cancer, fractures occurred in 12% of patients treated with ERLEADA and in 7% of patients treated with placebo. Grade 3-4 fractures occurred in 3% of patients treated with ERLEADA and in 1% of patients treated with placebo. The median time to onset of fracture was 314 days (range: 20 to 953 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the SPARTAN study.

In a randomized study (TITAN) of patients with metastatic castration-sensitive prostate cancer, fractures occurred in 9% of patients treated with ERLEADA and in 6% of patients treated with placebo. Grade 3-4 fractures were similar in both arms at 2%. The median time to onset of fracture was 56 days (range: 2 to 111 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the TITAN study.

Falls

Falls occurred in patients receiving ERLEADA with increased frequency in the elderly [See Use in Specific Populations]. Evaluate patients for fall risk.

In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA compared to 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure.

Seizure

Seizure occurred in patients receiving ERLEADA. Permanently discontinue ERLEADA in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA. Advise patients of the risk of developing a seizure while receiving ERLEADA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

In two randomized studies (SPARTAN and TITAN), five patients (0.4%) treated with ERLEADA and one patient treated with placebo (0.1%) experienced a seizure. Seizure occurred from 159 to 650 days after initiation of ERLEADA. Patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded. There is no clinical experience in re-administering ERLEADA to patients who experienced a seizure.

Embryo-Fetal Toxicity

The safety and efficacy of ERLEADA have not been established in females. Based on its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female [see Clinical Pharmacology (12.1) in full Prescribing Information]. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA [see Use in Specific Populations].

ERLEADA® (apalutamide) tablets

ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Ischemic Cardiovascular Events [see Warnings and Precautions].
- Fractures [see Warnings and Precautions].
- Falls [see Warnings and Precautions].
- Seizure [see Warnings and Precautions].

Clinical Trial 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 practice.

The most common adverse reactions ($\geq 10\%$) that occurred more frequently in the ERLEADA-treated patients ($\geq 2\%$ over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Metastatic Castration-sensitive Prostate Cancer (mCSPC)

TITAN, a randomized (1:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had mCSPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or placebo. All patients in the TITAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had prior bilateral orchiectomy. The median duration of exposure was 20 months (range: 0 to 34 months) in patients who received ERLEADA and 18 months (range: 0.1 to 34 months) in patients who received placebo.

Ten patients (2%) who were treated with ERLEADA died from adverse reactions. The reasons for death were ischemic cardiovascular events (n=3), acute kidney injury (n=2), cardio-respiratory arrest (n=1), sudden cardiac death (n=1), respiratory failure (n=1), cerebrovascular accident (n=1), and large intestinal ulcer perforation (n=1). ERLEADA was discontinued due to adverse reactions in 8% of patients, most commonly from rash (2%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 23% of patients; the most frequent ($>1\%$) were rash, fatigue, and hypertension. Serious adverse reactions occurred in 20% of ERLEADA-treated patients and 20% in patients receiving placebo.

Table 1 shows adverse reactions occurring in $\geq 10\%$ on the ERLEADA arm in TITAN that occurred with a $\geq 2\%$ absolute increase in frequency compared to placebo. Table 2 shows laboratory abnormalities that occurred in $\geq 15\%$ of patients, and more frequently ($>5\%$) in the ERLEADA arm compared to placebo.

Table 1: Adverse Reactions in TITAN (mCSPC)

System/Organ Class Adverse reaction	ERLEADA N=524		Placebo N=527	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
General disorders and administration site conditions				
Fatigue ^{1,3}	26	3	25	2
Musculoskeletal and connective tissue disorders				
Arthralgia ³	17	0.4	15	0.9
Skin and subcutaneous tissue disorders				
Rash ²	28	6	9	0.6
Pruritus	11	<1	5	<1
Vascular disorders				
Hot flush	23	0	16	0
Hypertension	18	8	16	9

¹ Includes fatigue and asthenia

² Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular

³ Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3

Additional adverse reactions of interest occurring in 2%, but less than 10% of patients treated with ERLEADA included diarrhea (9% versus 6% on placebo), muscle spasm (3% versus 2% on placebo), dysgeusia (3% versus 1% on placebo), and hypothyroidism (4% versus 1% on placebo).

Table 2: Laboratory Abnormalities Occurring in ≥ 15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% All Grades) in TITAN (mCSPC)

Laboratory Abnormality	ERLEADA N=524		Placebo N=527	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Hematology				
White blood cell decreased	27	0.4	19	0.6
Chemistry				
Hypertriglyceridemia ¹	17	3	12	2

¹ Does not reflect fasting values**Non-metastatic Castration-resistant Prostate Cancer (nmCRPC)**

SPARTAN, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had nmCRPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or a placebo. All patients in the SPARTAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. The median duration of exposure was 16.9 months (range: 0.1 to 42 months) in patients who received ERLEADA and 11.2 months (range: 0.1 to 37 months) in patients who received placebo.

Eight patients (1%) who were treated with ERLEADA died from adverse reactions. The reasons for death were infection (n=4), myocardial infarction (n=3), and cerebral hemorrhage (n=1). One patient (0.3%) treated with placebo died from an adverse reaction of cardiopulmonary arrest (n=1). ERLEADA was discontinued due to adverse reactions in 11% of patients, most commonly from rash (3%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 33% of patients; the most common (>1%) were rash, diarrhea, fatigue, nausea, vomiting, hypertension, and hematuria. Serious adverse reactions occurred in 25% of ERLEADA-treated patients and 23% in patients receiving placebo. The most frequent serious adverse reactions (>2%) were fracture (3%) in the ERLEADA arm and urinary retention (4%) in the placebo arm.

Table 3 shows adverse reactions occurring in ≥10% on the ERLEADA arm in SPARTAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 4 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.

Table 3: Adverse Reactions in SPARTAN (nmCRPC)

System/Organ Class Adverse reaction	ERLEADA N=803		Placebo N=398	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
General disorders and administration site conditions				
Fatigue ^{1,4}	39	1	28	0.3
Musculoskeletal and connective tissue disorders				
Arthralgia ⁴	16	0	8	0
Skin and subcutaneous tissue disorders				
Rash ²	25	5	6	0.3
Metabolism and nutrition disorders				
Decreased appetite ⁵	12	0.1	9	0
Peripheral edema ⁶	11	0	9	0
Injury, poisoning and procedural complications				
Fall ⁴	16	2	9	0.8
Fracture ³	12	3	7	0.8
Investigations				
Weight decreased ⁴	16	1	6	0.3
Vascular disorders				
Hypertension	25	14	20	12
Hot flush	14	0	9	0
Gastrointestinal disorders				
Diarrhea	20	1	15	0.5
Nausea	18	0	16	0

¹ Includes fatigue and asthenia² Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular

³ Includes rib fracture, lumbar vertebral fracture, spinal compression fracture, spinal fracture, foot fracture, hip fracture, humerus fracture, thoracic vertebral fracture, upper limb fracture, fractured sacrum, hand fracture, pubis fracture, acetabulum fracture, ankle fracture, compression fracture, costal cartilage fracture, facial bones fracture, lower limb fracture, osteoporotic fracture, wrist fracture, avulsion fracture, fibula fracture, fractured coccyx, pelvic fracture, radius fracture, sternal fracture, stress fracture, traumatic fracture, cervical vertebral fracture, femoral neck fracture, and tibia fracture

⁴ Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3⁵ Includes appetite disorder, decreased appetite, early satiety, and hypophagia⁶ Includes peripheral edema, generalized edema, edema, edema genital, penile edema, peripheral swelling, scrotal edema, lymphedema, swelling, and localized edema

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ERLEADA included hypothyroidism (8.1% versus 2% on placebo), pruritus (6.2% versus 2% on placebo), and heart failure (2.2% versus 1% on placebo).

Table 4: Laboratory Abnormalities Occurring in ≥ 15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% All Grades) in SPARTAN (nmCRPC)

Laboratory Abnormality	ERLEADA N=803		Placebo N=398	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Hematology				
Anemia	70	0.4	64	0.5
Leukopenia	47	0.3	29	0
Lymphopenia	41	2	21	2
Chemistry				
Hypercholesterolemia ¹	76	0.1	46	0
Hyperglycemia ¹	70	2	59	1
Hypertriglyceridemia ¹	67	2	49	0.8
Hyperkalemia	32	2	22	0.5

¹ Does not reflect fasting values**Rash**

In the combined data of two randomized, placebo-controlled clinical studies, rash associated with ERLEADA was most commonly described as macular or maculo-papular. Adverse reactions of rash were reported for 26% of patients treated with ERLEADA versus 8% of patients treated with placebo. Grade 3 rashes (defined as covering > 30% body surface area [BSA]) were reported with ERLEADA treatment (6%) versus placebo (0.5%).

The onset of rash occurred at a median of 83 days of ERLEADA treatment. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA.

Hypothyroidism

In the combined data of two randomized, placebo-controlled clinical studies, hypothyroidism was reported for 8% of patients treated with ERLEADA and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy was initiated in 5% of patients treated with ERLEADA. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted [see Drug Interactions].

DRUG INTERACTIONS**Effect of Other Drugs on ERLEADA****Strong CYP2C8 or CYP3A4 Inhibitors**

Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl-apalutamide). No initial dose adjustment is necessary however, reduce the ERLEADA dose based on tolerability [see Dosage and Administration (2.2) in full Prescribing Information]. Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.

Effect of ERLEADA on Other Drugs**CYP3A4, CYP2C9, CYP2C19 and UGT Substrates**

ERLEADA is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA and evaluate for loss of activity [see *Clinical Pharmacology (12.3) in full Prescribing Information*].

P-gp, BCRP or OATP1B1 Substrates

Apalutamide was shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. At steady-state, apalutamide reduced the plasma exposure to fexofenadine (a P-gp substrate) and rosuvastatin (a BCRP/OATP1B1 substrate). Concomitant use of ERLEADA with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with ERLEADA and evaluate for loss of activity if medication is continued [see *Clinical Pharmacology (12.3) in full Prescribing Information*].

USE IN SPECIFIC POPULATIONS**Pregnancy****Risk Summary**

The safety and efficacy of ERLEADA have not been established in females. Based on its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy [see *Clinical Pharmacology (12.1) in full Prescribing Information*]. There are no human data on the use of ERLEADA in pregnant women. ERLEADA is not indicated for use in females, so animal embryo-fetal developmental toxicology studies were not conducted with apalutamide.

Lactation**Risk Summary**

The safety and efficacy of ERLEADA have not been established in females. There are no data on the presence of apalutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

Females and Males of Reproductive Potential**Contraception****Males**

Based on the mechanism of action and findings in an animal reproduction study, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. [see *Use in Specific Populations*].

Infertility**Males**

Based on animal studies, ERLEADA may impair fertility in males of reproductive potential [see *Nonclinical Toxicology (13.1) in full Prescribing Information*].

Pediatric Use

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

Geriatric Use

Of the 1327 patients who received ERLEADA in clinical studies, 19% of patients were less than 65 years, 41% of patients were 65 years to 74 years, and 40% were 75 years and over.

No overall differences in effectiveness were observed between older and younger patients.

Of patients treated with ERLEADA (n=1073), Grade 3-4 adverse reactions occurred in 39% of patients younger than 65 years, 41% of patients 65-74 years, and 49% of patients 75 years or older. Falls in patients receiving ERLEADA with androgen deprivation therapy was elevated in the elderly, occurring in 8% of patients younger than 65 years, 10% of patients 65-74 years, and 19% of patients 75 years or older.

OVERDOSAGE

There is no known specific antidote for apalutamide overdose. In the event of an overdose, stop ERLEADA, undertake general supportive measures until clinical toxicity has been diminished or resolved.

PATIENT COUNSELING INFORMATION

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

Ischemic Cardiovascular Events

- Inform patients that ERLEADA has been associated with ischemic cardiovascular events. Advise patients to seek immediate medical attention if any symptoms suggestive of a cardiovascular event occur [see *Warnings and Precautions*].

Falls and Fractures

- Inform patients that ERLEADA is associated with an increased incidence of falls and fractures [see *Warnings and Precautions*].

Seizures

- Inform patients that ERLEADA has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their healthcare provider right away if they experience a seizure [see *Warnings and Precautions*].

Rash

- Inform patients that ERLEADA is associated with rashes and to inform their healthcare provider if they develop a rash [see *Adverse Reactions*].

Dosage and Administration

- Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with ERLEADA.
- Instruct patients to take their dose at the same time each day (once daily). ERLEADA can be taken with or without food. Each tablet should be swallowed whole.
- Inform patients that in the event of a missed daily dose of ERLEADA, they should take their normal dose as soon as possible on the same day with a return to the normal schedule on the following day. The patient should not take extra tablets to make up the missed dose [see *Dosage and Administration (2.1) in full Prescribing Information*].

Embryo-Fetal Toxicity

- Inform patients that ERLEADA can be harmful to a developing fetus. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. Advise male patients to use a condom if having sex with a pregnant woman [see *Warnings and Precautions*].

Infertility

- Advise male patients that ERLEADA may impair fertility and not to donate sperm during therapy and for 3 months following the last dose of ERLEADA [see *Use in Specific Populations*].

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Oncology Clinical Trials During the COVID-19 Pandemic

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KEY POINTS: The coronavirus disease 2019 (COVID-19) pandemic has rapidly spread all over the world in the past several months. No effective treatment for COVID-19 has been established. High transmissibility and considerable mortality rates have forced many national governments to implement quarantine measures. Many patients with cancer rely on clinical trials to receive their oncologic care, but the routine conduct of clinical trials has substantially changed because of the COVID-19 pandemic. The oncology research community should implement formal policies based on the guidance given from regulatory agencies, with the goal of minimizing the risks of COVID-19 infection while maintaining appropriate oncologic treatments for patients during this pandemic.

Introduction

As of June 2020, coronavirus disease 2019 (COVID-19) has affected almost 7 million individuals globally and caused more than 400,000 deaths worldwide.¹ In addition to those lives lost to COVID-19, there have been innumerable consequences to patients who have not contracted the virus but suffer from other serious conditions, such as cancer. Although data published so far have included relatively small numbers of patients, cancer seems to be a risk factor for contracting COVID-19, and patients with cancer could be at a higher risk for poorer outcomes.^{2,3}

Fearing the potentially fatal consequences of COVID-19, patients with cancer, and institutions treating patients with

cancer, have adopted measures to minimize potential exposure within cancer centers and hospitals. Most oncologists have elected for their patients to have, when possible, less intensive treatments; have delayed nonurgent treatments; have moved outpatient consultations away from general hospitals; and have made other tactical decisions to reduce risk. Ultimately, clinical management should be individualized for each patient based on a risk-benefit assessment of the oncology treatment in question, and priority should be given to those therapies offering overall survival gain and/or clear improvement in quality of life.^{4,5}

Clinical trials currently play an essential role in cancer care. This is especially

PERSPECTIVE

Mehmet Sitki Copur, MD,

discusses the current state of clinical trials at cancernetwork.com/Copur_trials

true for patients who do not have access to novel oncology treatment modalities, such as immunotherapy or targeted therapy, or who have exhausted available standard-care options but still have a good performance status.⁶

However, the care of a clinical trial enrollee is much less flexible than that of a patient receiving standard-of-care treatment. For instance, oncology clinical trials may require more in-person hospital visits for safety monitoring, more imaging, and more frequent laboratory testing. These requirements present concerns for patients, institutions, and sponsors alike during this pandemic.⁷

The number of oncology clinical trials that are open for recruitment has significantly decreased over the past months of the pandemic. Between February and May 2020, 920 interventional oncology trials were interrupted because of COVID-19.⁸

We performed a search in clinicaltrials.gov using the keyword *cancer* and filtering for interventional studies (clinical trials) with a recruiting status. We compared the

TABLE. Summary of the US FDA and European Medicines Agency Guidance on the Management of Clinical Trials During the COVID-19 Pandemic.

	FDA ¹⁶	EMA ¹⁵
Clinical trials enrollment	<ul style="list-style-type: none">▪ Sponsors should consider each circumstance, focusing on the safety of trial participants, and modify study conduct accordingly.	<ul style="list-style-type: none">▪ Sponsors should carefully assess the pertinence of enrolling new participants in ongoing clinical trials.
Remote assessment	<ul style="list-style-type: none">▪ Sponsors should consider if remote assessments are appropriate for the clinical data, respecting patients' disabilities/limitations▪ Document whether the assessment was in person or remote, and any patient limitations	<ul style="list-style-type: none">▪ Telemedicine/phone calls can be used if per-protocol physical visits are reduced or postponed
Remote monitoring	<ul style="list-style-type: none">▪ Remote monitoring can be performed▪ Documentation should be the same as that of onsite monitoring	<ul style="list-style-type: none">▪ Remote monitoring should focus only on the most critical information▪ Data are likely to require remonitoring
Distribution of investigational products	<ul style="list-style-type: none">▪ Home delivery of investigational products could be adopted if no additional risks are implied	<ul style="list-style-type: none">▪ If a patient's supply of drugs runs out, distributors can deliver the drugs directly to the patient, if the conduct of the trial will not be compromised
Protocol deviations	<ul style="list-style-type: none">▪ Changes in the protocol may be implemented to protect patients' safety without IRB approval▪ Communicate with the IRB/IEC about such changes as soon as possible▪ Consider protocol deviations when locking the trial's database	<ul style="list-style-type: none">▪ Periodically analyze any protocol deviations and evaluate any need for protocol amendments▪ Deviations should be reported in the clinical study report
Other relevant issues	<ul style="list-style-type: none">▪ Sponsors should record the participants who were affected by the trial's interruption because of COVID-19▪ Contingency measures and protocol deviations that were experienced should be described in the clinical study report▪ Procedures in accordance with the regional/national policies for prevention and control of COVID-19 should be adopted▪ Protocol amendment is not necessary if screening for COVID-19 was performed because of the policy of a health care system	<ul style="list-style-type: none">▪ Contingency measures and protocol deviations that were experienced should be described in the clinical study report▪ Consider alternative study sites and study assessments (labs and imaging studies) nearer to the patients' locations▪ Avoid in-person visits dedicated only to consent documentation; use other means▪ Procedures in accordance with the regional/national policies for prevention and control of COVID-19 should be adopted▪ The sponsor should cover unexpected expenses

COVID-19, coronavirus disease 2019; EMA, European Medicines Agency; IRB, institutional review board; IEC, independent ethics committee.

number of recruiting cancer trials in 2 periods: January to May 2019, and January to May 2020. From January 1, 2020, to May 31, 2020, we found 817 clinical trials involving cancer, compared with 1405 during the same period last year. This represents a 41.8% reduction of the recruiting clinical trials in oncology (Figure 1).

In this review, we will discuss the main aspects of cancer clinical trial activities that have changed during COVID-19 pandemic, along with recommendations from regulatory agencies. The Table summarizes the US FDA and the European Medicines Agency (EMA) guidance on the management of clinical trials during this time.

Challenges to Clinical Oncology Trials During the Pandemic

The difficulties faced in keeping all phases of cancer clinical trials active are undeniable. For example, Tarantino et al described

the new routine of phase 1 studies at the European Institute of Oncology in Milan; Italy has been among the countries most affected by COVID-19. A major priority to maintain patient safety has involved decisions around the accrual of new patients, continuation (or not) of treatment for patients already enrolled, and alternate ways of monitoring. Additional training was provided to staff. Only the most necessary in-person activities were allowed at the hospital. Because of quarantine, patient access to the main trial site was also largely prohibited. In accord with the sponsors, it was decided to move radiological and biochemical studies to facilities nearer to patients' homes, with central review of the scans. Furthermore, optional biopsies were temporarily withheld, and oral drugs were delivered to patients' homes.⁹

Also recently published was an account of the multicenter, phase 3 ASCOLT trial, con-

ducted largely in Asia. The trial is evaluating aspirin vs placebo after standard adjuvant therapy for high-risk colorectal cancer, and the approach during the COVID-19 pandemic varied among centers in different countries. In some nations, recruitment was suspended, but the patients who were already enrolled continued taking the drug, with adaptations in safety monitoring, such as virtual visits by telephone. However, in Hong Kong, for instance, the study center pharmacy stopped delivering oral research treatments. Differences in the management of different patients enrolled in clinical trials during the pandemic raises the inevitable question of how the study's final results will be affected.¹⁰

Similarly, it is difficult to compare the conduct of clinical trials in different countries and regions, because the epidemiology of COVID-19 varies considerably.¹ Although regulatory agencies have published

guidance for sponsors and study sites, institutional differences must always be taken into consideration when analyzing the potential changes in clinical trials.¹¹

The American Society of Clinical Oncology (ASCO) conducted a survey to better understand the situation in 64 different American research programs. A total of 32 surveys were adequately answered and included in the analysis; 18 (56.25%) of them were nonacademic research centers. Of note, 20 (64.52%) institutions answered that a formal policy was developed for their own ongoing trials.¹²

Important Topics Involving Research Addressed by Regulatory Agencies During the COVID-19 Pandemic

ENROLLMENT IN ONCOLOGY CLINICAL TRIALS

Numerous research centers have chosen to halt patient enrollment, and oncology has been among the most affected areas in terms of suspending, postponing, or making other changes in conducting clinical trials. A GlobalData report showed that as of April 8, 2020, 28% of 389 disrupted clinical trials were in oncology. Of note, more than 50% of the disrupted oncology trials were focused on lung cancer, breast cancer, multiple myeloma, myelodysplastic syndrome, and prostate cancer.¹³

Screening and/or enrollment on any oncology clinical trial was halted in approximately 25% of US research centers. Priority for continued enrollment has been given to trials with lower risk and higher safety profiles, such as those with shorter infusion times, easier schedules, and less pharmacokinetic testing.¹²

Another analysis combined results from a survey of 36 investigators conducting oncology clinical trials worldwide, and data from IQVIA and clinicaltrials.gov; these results were consistent with previously published data. Only about 20% of institutions in the United States and about 14% of those in Europe were pursuing active normal trial enrollment. In Asia, 60% of institutions had active enrollment at the time of the survey; this relatively

FIGURE 1. Effect of COVID-19 on Recruiting Oncology Clinical Trials.

COVID-19, coronavirus disease-2019.

high number was presumably attributable to the decline, at the time, of the number of COVID-19 cases locally. Key factors involved in the decision to enroll patients in clinical trials were patient care and therapy type, but the institutions also considered such other important factors as line of treatment, patient performance status, and indication of treatment. These factors will also be considered in future clinical trials, according to the survey.¹⁴

Sponsors should carefully evaluate the feasibility of enrolling patients into ongoing clinical trials and of beginning new clinical trials. Risk vs benefit of new or continued accruals should be discussed with the staffs at investigational sites.¹⁵

REMOTE METHODS IN CLINICAL TRIALS

The regulatory agencies have addressed and offered guidance regarding the use of remote methods in clinical trials. The EMA notes that onsite monitoring visits could be canceled or postponed. Remote monitoring and source data verification should be reserved for crisis periods. Telemedicine could be used for checking adverse events, for instance. Importantly, in-person patient visits should be restricted to urgent situations when there are no good alternatives. Visits with the sole purpose of obtaining reconsent should be avoided; this should be accomplished remotely.¹⁵

The US FDA recognizes that alternative ways of monitoring could result in delayed identification of protocol deviations or could impair compliance with the Good Clinical Practice standard. While the FDA acknowledged that remote methods can be used both with patients and sponsors to optimize clinical trials and minimize possible exposure to coronavirus,¹⁶ they also pointed out that access to remote technologies differs among patients, and patients' disabilities must be considered when planning telemedicine consultations. Other regulatory agencies have also recommended remote patients' safety evaluations and remote site monitoring during the COVID-19 pandemic.^{11,17}

Approximately 90% of the American research centers that participated in the ASCO survey were adopting remote patient review of symptoms, and 75% of study staff members were also working remotely. In more than 60% of the centers, remote methods were used as well for site initiation visits, sponsor monitoring, and/or other clinical research activities. Interestingly, most of these measures were initiated by the research site. A challenge of remote communication in clinical trials was the time spent preparing for and conducting the telehealth visits. Nevertheless, the majority of the institutions will consider telehealth visits, remote site initiation visits, and remote monitoring as suitable

FIGURE 2. Oncology Clinical Trials During COVID-19 Pandemic.

IRB, institutional review board; IEC, independent ethics committee; SIV, site initiation visits.

alternatives for clinical trials in the future, post COVID-19.¹²

In addition, of 22 investigators interviewed on this topic in a recent Nature Reviews paper, the overwhelming majority (82%) also stated that telemedicine is or will be an important strategy to be utilized in clinical trials during this pandemic.¹⁴

Any use of new remote technologies in conducting trials must consider patients' rights to privacy and data confidentiality. In addition, virtual consultations should be as complete as possible and, when imaging or laboratory studies are performed in other than the usual facilities—ie, those nearer patients' homes—it is crucial to review the results carefully to assure patients' continued safety.¹⁸

DISTRIBUTION OF INVESTIGATIONAL PRODUCTS

Depending on where a patient resides, traveling to a research center for an investigational therapy may be a challenge. Therefore, regulatory agencies have allowed new delivery methods for some drugs, such as ones distributed for self-administration. The FDA has also mentioned planning for alternative administration for drugs that are normally administered in a health care facility, utilizing visiting nurse services, for instance, or even creating al-

ternate sites run by nonstudy staff.¹⁶

In addressing drug supply, the EMA has stated that distributors can deliver drugs directly to a patient if their supply runs out. However, this shipment should be described in a contract between the distributor and the sponsor. The investigator must explain the procedures to trial participants and obtain their verbal consent, which is then documented in the patient's medical record. These procedures should not compromise trials' blinding and compliance with randomization.¹⁵

In all cases, safety must be ensured. If necessary, trial participants, and/or their caregivers, must be trained in handling their medications.

PROTOCOL DEVIATIONS

A higher probability of protocol deviations exists during this pandemic. Almost 40% of the institutions surveyed by ASCO considered protocol compliance to be a challenge,¹² and several ethics committees are currently focusing on protocol deviations.¹⁴ Investigators are concerned that protocol deviations would cause unsolved queries.

The EMA recommends that sponsors periodically analyze interim trial results for possible deviations, and evaluate

whether protocol amendments are needed. Every deviation should be included in the clinical study report.¹⁵

Normally, protocol amendments would go through institutional review board (IRB)/independent ethics committee (IEC) review. However, sometimes this process may not be possible because of the pandemic. The FDA allows changes in the protocol without IRB approval to protect the life and well-being of trial participants, but in such situations, communicating with the IRB/IEC must be done as soon as possible. Any protocol deviations should be taken into account prior to locking a trial's database.¹⁶ Because many activities of an IRB may be currently focused on clinical trials related to COVID-19, it is crucial that a constant channel exists to discuss protocol deviations in other trials. In many institutions, this has been or will be accomplished by teleconferencing (**Figure 2**).

OTHER RELEVANT ISSUES

Additional training and safety. With fewer staff members working onsite at research centers, those research staff and physician investigators who are present may need to take on additional responsibilities. They must receive adequate training, if necessary, to ensure patients' safety.¹⁸

If possible, a study center should have a low-risk area specifically for patients participating in clinical trials, in which personal protective equipment must be worn and all safety measures are consistently enforced for every person (patient or staff member) involved in the clinical trial process. Screening of staff for COVID-19 symptoms should be considered.¹⁹

Patient education. The investigator should inform participants about any changes on clinical trials that could affect their care and scheduling during the study. Moreover, the study staff should adopt all procedures in accordance with regional or national policies to prevent and control COVID-19, and discuss these measures with patients.^{15,16}

Expenses. Unexpected trial expenses may accrue for a trial participant in this

current scenario, and the EMA recommends that sponsors cover them as soon as possible.¹⁵

Screening for COVID-19. Screening for COVID-19 may become mandatory (by action of the health care system or the government) during the clinical trial. Should that happen, protocol amendment is not necessary, according to the FDA, unless these tests become a part of the research objective.¹⁶

Clinical study report. According to the regulatory agencies, the clinical study report must describe all contingency measures taken and all protocol deviations, and it must list all participants affected by COVID-19 and the severity of their illness during the trial.^{15,16}

Oncology Clinical Trials During the COVID-19 Pandemic: The Experience of a Referral Oncologic Center In Brazil

Brazil is still experiencing the continuous rise of both number of new cases and deaths from COVID-19. As of June 8, 2020, 691,758 cases and 36,455 deaths had been recorded.^{20,21} Like the FDA and EMA, Brazil's regulatory agency, ANVISA, has published recommendations regarding the conduct of clinical trials during this pandemic, highlighting the importance of good clinical practice and patients' safety. ANVISA's main points include¹⁷:

- The sponsors, along with investigators and the IRB/IEC, may decide whether a participant should remain in a clinical trial, based on potential risks and benefits to the participant.
- Remote methods can be used for safety evaluations and monitoring.
- ANVISA need not be notified of COVID-19 screening procedures as

a protocol amendment, unless these tests will be part of the research objectives.

- ANVISA need not be notified of protocol amendments made as a consequence of COVID-19, but the amendments will need to be described in the annual clinical research report.
- Delivery of investigational products directly to patients' homes, with adequate patient training, is allowed.
- Protocol deviations should be considered before locking a trial's database. If there is any chance that the deviations could affect final results, the sponsors must communicate with ANVISA.

In March 2020, our institution, Hospital Sírio Libanês, located in São Paulo, Brazil, created specific guidance for clinical trials conducted during this pandemic, mostly based on ANVISA's guidance. Recommendations were made such that investigators, along with sponsors, could decide whether a protocol should be interrupted when there is no direct benefit to a trial's participants, adding the risk of coronavirus exposure. Trials that bring direct benefit to participants should be continued, and remote technologies should be employed as much as possible in such trials. Discussions about specific methods to minimize patients' exposure should include remote technology for patient evaluation, delivery of oral drugs at patients' homes, and any others that would be applicable. All such measures and protocol deviations should be reported to the hospital's ethics committee in the annual research report. Suspension of the enrollment of new patients in clinical trials should be discussed. The clinical research staff should also discuss ways of minimizing their own exposure,

such as working remotely.²²

Currently, most oncology clinical trials in our hospital have put recruitment on hold. Trials with a set start date were postponed. Research teams have been working remotely, for the most part, but patients who continue on clinical trials are still making in-person visits. We remain active in planning for the future, with feasibility studies ongoing for future trials. Regulatory staff are focusing on reviewing budgets and pending contracts. Teleconferences have been widely used in research meetings and, importantly, we have used this period to plan improvements in our research program.

Conclusions

COVID-19 has changed the international health care system in every single way. Consequently, oncology clinical trials have suffered, with a high rate of disruption. For the trials that continue, ensuring participants' security is crucial. Regulatory agencies have formalized recommendations to help guide the research community. Research institutions ultimately should write their own guidance materials, considering their site's COVID-19 epidemiology and access of staff and patients to technologies, and discussions with their trials' sponsors and their IRB/IEC should be ongoing. ■

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➤ For references, visit cancernetwork.com/COVID19_trials

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COVID-19 and Malpractice: New Risks to Watch For

It remains to be seen how the pandemic will specifically affect medical liability; so many aspects of health care are changing rapidly as a result of this world-shaking event. But physicians can take steps to protect themselves from these new risks. *Medical Economics*® recently sat down with Sean P. Byrne, JD, a medical malpractice defense lawyer, to talk through these strategies and to explain how physicians can best protect themselves from getting sued in this new normal.

Q: Can you discuss how the unprecedented coronavirus disease 2019 (COVID-19) pandemic has affected medical malpractice liability?

BYRNE: Of course. The diversion of health care resources into treating the pandemic has affected us in the medical liability world significantly. Our health care practitioner clients and experts have been quite unavailable to participate in our active, ongoing cases. And the court system has put [just about] everything on hold, [too]. So, some active cases are slowing down and coming to a halt, and we're seeing how the pandemic might affect new cases as well.

Q: Something many physicians are wondering about is increased liability related to the pandemic. Can you provide some facts about how this pandemic is specifically impacting a physician's chance of facing a lawsuit?

BYRNE: In medical liability cases, the test

is always: "Did you comply with the standard of care? So, did you act like a reasonably prudent provider would act under the same or similar circumstances?" But never in the era of modern medicine have we faced the same or similar circumstances with a novel virus and a pandemic. So, what the law will ultimately define as reasonable health care services that met the standard of care is going to be evolving.

We've seen a couple of responses across the country, state by state, to try to address [that question]. A number of states, either by executive action or by legislative change, have put immunity provisions into place to protect health care professionals from liability claims that may arise in this era. A number of those state laws will say that you cannot be sued for simple negligence, which just means a mistake or careless error, in this era for claims related to COVID-19. Those [laws] vary widely across the country, in terms of how nimble [they are], what the politics are, and what people have done. A number of [the laws] are limited to that you can't be sued for COVID-19-related claims [when the damage was] caused by a lack of resources. And resources can mean PPE, staffing, intensive care unit beds.

A number of states have also said, "We're going to give you some protection from lawsuits if you practice somewhat outside your scope of practice, but within your license." So, when we see resources being diverted from one area of hospital to another to fight waves of pandemic

patients, state laws have given some protection in those cases.

The big issue to think about is standard of care. Are you acting reasonably under the circumstances, following directives? You should know you have some legal immunity and protections, and it's helpful to know what [those protections] are in your state, as you make decisions at a health care professional level. Another topic that arises is, "What do we say to our patients? How do we deal with the disclosure of risk?"

Q: What does disclosure of risk mean, exactly? What do doctors need to communicate to their patients, and in what way?

BYRNE: Start with just the fundamentals. We've always got an obligation to give our patients advice about risks, benefits, alternatives. [Still, in this time of COVID-19,] folks are wondering, "What do I have to disclose to the patient? And can I protect myself from a lawsuit?"

We deal with these questions in a couple of ways. Many providers have drafted, with the assistance of their lawyer and their risk management teams, COVID-19-specific programs. These would include protocols you have in place in your office for infection control, patient monitoring, and screening employees and patients. It would also include some COVID-specific screening that goes into the patient's medical chart about international travel, symptoms, and exposure. And then there should be a disclaimer or at least a discussion

in your informed consent paperwork, in which the patient acknowledges that they're aware that by being present in the health care environment, they're assuming some risk of contracting the virus despite the best efforts of the provider. We're dealing with those [changes] on a number of fronts, and I've seen practices pivot really quickly to manage that risk.

Q: Physicians ask, "If I get a patient to sign something that says that they're assuming risk, does that essentially wipe away my liability?" Can you talk through some of the nuances of that?

BYRNE: Typically, it's not that simple. Most states have a public policy principle that says, [in essence,] We ought not let people waive negligence. [That's why] the back of your ticket to a ballgame or the documents you sign before surgery will include some broad language acknowledging the risk you're undergoing, but typically, though, you can't waive negligence claims. So those disclaimers and informed consent documents are helpful; [ignoring them] can be damaging. They can help you prove that you did disclose the risks and discuss them with the patient.

Ultimately, though, the test is usually going to be, "Did you act reasonably?" I think it's advisable to include some language about COVID-19 in your discussions with your patients and in your documentation, but doing so is not blanket protection against a lawsuit. Interestingly, immunity provisions have come into play in a number of states that do provide some protection.

What's not crystal clear is this: What about the downstream issues of preventative care screening for, say, breast cancer, for colon cancer, for other significant conditions? What about the other health care that's being delayed? And given both lack of resources and reduced numbers of patients seeking care, how will our immunity protections and the standard of care address that in the future? So

This pandemic has fast-forwarded the thinking both from a business perspective and also from a regulatory and insurance perspective.

those will be evolving considerations that, unfortunately, will keep lawyers like me busy in the years to come.

Q: Many physicians are now using telehealth to treat patients. What unique malpractice risks does telehealth present? Should physicians take anything specific into account?

BYRNE: We have some really important considerations. Many of the medical malpractice insurance carriers who had very specific rules about telehealth have lessened or adjusted them to accommodate the shift in delivery models and the prolific use of telehealth on such short notice during the pandemic. So, it's a good idea for a provider or practice group to look and see what their insurance carrier is saying about that. Have they acknowledged that it's within the scope of your malpractice policy?

Similarly, state regulations that impose some requirements on how and when you can do telehealth have been broadened in many cases. Some of the regulatory hurdles have been set to the side so that providers have easier access to telehealth. So the legal environment for telehealth has changed. This pandemic has fast-forwarded the thinking from a business perspective as well as from a regulatory and insurance perspective.

Q: What about patients who have pre-existing serious health issues or new serious situations developing, and aren't getting in-person care because of the pandemic? Or, because of the pandemic, new barriers to care

now exist. What should a physician be thinking about to proactively manage both pandemic risks and the downstream risks you mentioned?

BYRNE: The advice we often give as medical liability defense attorneys is that your documentation can be your best friend. [Let's say] a claim or lawsuit develops a couple of years from now, and we have to prove what you were thinking, your analysis, your careful reaction and your adjustment to the limitations that were being imposed on you and your practice by COVID-19. Good documentation of that, in the chart, is helpful. So, if certain patients are receiving routine follow-up or screening or maintenance care, and those appointments are being missed or discontinued or postponed, good documentation of your follow-up efforts will be really helpful. I see people sometimes fall short when they make phone calls to patients to follow up on abnormal lab results or imaging studies, or missed appointments, but they don't document those efforts. That makes it hard for me to prove you were doing it. Your documentation becomes really important to help you out in these uncertain times.

Q: In terms of physician malpractice policy, in general, should we expect some policy situations to change going forward? Will there be new policy riders that physicians should think about purchasing? Or are there any other ways that you should change your approach to coverage?

BYRNE: Great question. There might be a couple of things to think about, including

when quarantine rules took effect. Everybody went into lockdown, businesses shut down, and the courts shut down, too. And so the deadlines for filing lawsuits, which are usually matters of state law—in which a patient has a hard and fast deadline of a year or 2 years or 5 years to file a claim—changed. Often, insurance policies follow alongside those deadlines in terms of the scope and duration of your coverage. As a result of COVID-19, those deadlines have been extended in various states.

So, in Virginia, for example, there was no real access to the courts for 3 or 4 months, and the deadlines for filing lawsuits got extended for months at a time. Providers [should think] about that when they're looking at the business side and their insurance policies and claims. If they're using different delivery models in terms of telehealth and they're practicing in other locations, they want to make sure that those locations are accessible. If their policy discusses their scope of practice in a defined way, and they're now exceeding that scope of practice, they want to make sure they remain covered. The insurance carriers that I've seen and worked with have been very responsive in trying to figure out how to be there, as partners, for their health care providers.

Q: What topics are you hearing about from your physician clients? How do you address their concerns?

BYRNE: It varies widely by practice area, right? Our gastroenterologists, orthopedic surgeons, people that do elective procedures, were sidelined and saw their patient volumes dramatically decrease. Our dental practices were essentially closed for more than a month. So those folks have had to figure out how to sustain themselves economically and [figure out what things should] look like when they return. Urgent care, emergency medicine, most providers really, have shifted their focus into testing, preven-

tative measures, and being prepared for COVID-19. So, it's affected each practice area a little differently. We get calls for risk management and compliance advice in all these areas. And people are thoughtful about when they can reopen. Also, the state governments imposed restrictions on elective procedures, [so] there's debate about whether a particular procedure is elective or medically necessary. It probably depends on your perspective: whether it's you or your loved one, or your practice or someone else's practice. So, we've had some debate about that. We've seen a few complaints with unsatisfied patients saying, "Hey, my procedure was postponed as elective and it shouldn't have been, and I want to move forward." I think the medical boards won't have a lot of sympathy for patients who make those complaints, when they know the providers are doing the best they can.

Q: Is there anything else that you think it's important for physicians to know?

BYRNE: The really interesting thing to me is that, ultimately, malpractice cases come down to convincing the jury that you are reasonable. The cases in which we clearly made a mistake get settled. Cases that are frivolous nonsense, we fight to the death. The cases in the middle, though, come down to jury perception on your good name as a physician, working hard to do the best you could for the patient under the circumstances.

And so, in this era of health care heroes, it'll be interesting to see how juries respond to medical malpractice cases. A lot of plaintiff attorneys who are well regarded and very selective in their cases, case management, and decisions have said publicly, "I don't want to take COVID-19 cases, when I understand the crunch that the providers are under." So, whether the future brings more medical liability lawsuits raising out of COVID-19, or fewer, and how it affects

jury perception, is a real unknown.

I think what providers can continue to do is focus on good charting, good relationships, and staying up to speed on the developments. Then, hopefully, they will stay in the medical facility and out of the courtroom. ■

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Emotional Distress During the COVID-19 Pandemic: Psycho-Oncology Perspective

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The Quandary

The headline “U.S. Deaths Near 100,000, an Incalculable Loss” ran across the front page of the *New York Times* on May 24, 2020, reflecting the ongoing coronavirus disease 2019 (COVID-19) pandemic and the biggest global health crisis faced in our lifetimes. The first symptoms were noted among a group of individuals in China in December 2019,¹ with similar cases rapidly appearing in succession throughout the world. On March 11, 2020, the World Health Organization declared COVID-19 to be a pandemic, a crisis that has fundamentally changed the way we live and interact with others, as well as the care we provide for those who are ill.²

Patients with cancer represent a vulnerable population and are at greater risk of developing serious complications as a result of a COVID-19 infection.³⁻⁵ In response, oncology societies around the world have proposed changes to their standards of care. These changes have helped guide health care providers in prioritizing clinical management of patients with cancer: identifying situations in which urgent intervention is needed and those that can be triaged until the risk of infection has lessened.

Notably, while these precautions are necessary to protect our patients, COVID-19 has also dramatically affected the way in which patients and caregivers perceive their own health status; increased their feelings of fear, panic, vulnerability and loss of control; and isolated them

from family, friends, and health care providers. Social relations play a critical role in mental health and emotional well-being; indeed, loneliness has been recognized as a risk factor for all causes of morbidity and mortality.⁶⁻⁷ Unfortunately, the psychosocial needs among patients with cancer and COVID-19 remain poorly documented.

Patients fear not only the possibility of contracting COVID-19, but the potential that this pandemic may affect their ability to receive timely care and their ability to access important sources of social and professional support. The pandemic has drastically affected cancer care. Patients are socially isolated and restricted with regard to their ability to access informal and formal sources of support. These dramatic changes have resulted in fewer patients being enrolled in clinical trials; in more clinic visits and treatments delayed or canceled out of caution; and in many patients hospitalized, or at the end of their life, being alone and isolated. Patients are

even experiencing some changes in the way they must report their symptoms, considering that they are presenting less to the hospital.

These changes, and the vulnerability and isolation they have brought with them, will have an enduring impact on those with conditions that place them at higher risk of contracting COVID-19. As a result, psycho-oncology must seek alternative ways in which to identify patients in need, to whom we can provide our services during these unprecedented times and beyond. Clinics around the world have been forced to rapidly reengineer how they support their patients and help them manage their emotional well-being. In view of this current reality, how can the field of psycho-oncology contribute to patient care during this pandemic?

Virtual Screening

For more than 20 years, psycho-oncology experts have advocated for distress screening programs to be integrated into routine

In view of this current reality, how can the field of psycho-oncology contribute to patient care during this pandemic?

- A. Virtual screening
- B. Remote care
- C. Routine follow-up
- D. All of the above

➔ **TURN TO PAGE 271** for the answer and a discussion of this case by experts.

CORRECT ANSWER: D. All of the Above

Continued from page 270

oncology care, enabling unmet needs to be identified and treated.⁸ This simple strategy has enabled health care providers to identify the prevalence of distress and most common associated domains (eg, physical, practical, social/familiar) among patients and caregivers during the continuum of cancer care, and to develop psychosocial interventions and programs to mitigate some of these symptoms. However, these programs and support services have often been built around in-person clinic visits and in-person counseling; they need to rapidly adapt to our current circumstances.

Remote screening must now be adopted to identify patients in need of help. Yet barriers exist to such planning; not all programs are electronically based and easily convertible to remote screening, and many patients lack access to the internet or to appropriate devices. Still, many studies have demonstrated the benefit of using electronic devices, phone apps, or internet-based programs to access these patients remotely. The implementation of remote screening can be an integral part of high-quality care, used as a strategy for automated algorithms that can systematize care pathways in real time, facilitating symptom management, and optimizing resources available in each institution and within communities.⁹⁻¹¹

Many studies have demonstrated the benefit of using electronic devices, phone apps, or internet-based programs to access these patients remotely.

Remote Care

Furthermore, we must develop new interventions appropriate to the COVID-19 era and utilize existing online behavioral interventions to the greatest degree possible. The current literature includes resources that potentially could be adapted in these circumstances, including mindfulness programs and those focused on reducing fears of cancer recurrence/progression.¹²⁻¹⁴ Some

of these programs are available without cost during the COVID-19 pandemic, including, for example, the Am Mindfulness app (<https://www.midigitaltherapeutics.com/am-mindfulness.html>) and the guided meditation and yoga videos offered by the Integrative Medicine department at Memorial Sloan Kettering Cancer Center in New York, New York.¹⁵ Also, beyond finding ways to assist our patients during this time of isolation and fear, we must also prepare for an influx of mental health care needs that are likely to arise once health care services are able to resume some degree

of normalcy and the true impact of this pandemic is fully realized.

Routine Follow-up

Given the current state of oncologic care, routine follow-up discussions and efficient communication among patients,

caregivers, and health care professionals are critical in easing concerns and anxiety. Psycho-oncologists can be integral to these broader relationships, helping to address barriers to care, exploring alternatives to attenuate biopsychosocial distress, addressing patient needs, and ensuring that patients feel heard by and connected to their care team during this stressful time. Further, through routine follow-up, psycho-oncologists can help ensure that patients and caregivers understand and communicate their treatment preferences. They can offer tips on managing general distress, including fear and uncertainty, and contribute to shared decision-making during this pandemic. ■

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➤ **For references, visit**
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Immunotherapy in Advanced Lung Cancer

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ABSTRACT: Historically, platinum-based chemotherapy was the standard of care for metastatic lung cancer. However, since the success of immune checkpoint inhibitors (ICIs) in melanoma, PD-1/PD-L1 and CTLA-4 immune checkpoint pathways have been established as effective therapies to manage advanced non-small cell lung cancer (NSCLC) and extensive-stage (ES) small cell lung cancer (SCLC). Multiple large-scale randomized clinical trials have analyzed the effects of ICIs in NSCLC, and results of these trials have since translated to the approval of single-agent PD-1/PD-L1 inhibitors, and the combination of PD-1 inhibitors with platinum-based chemotherapy has become the new standard of care for patients with advanced NSCLC. Furthermore, in ES SCLC, in which chemotherapy or chemoradiation has been the standard of care for decades, 2 anti-PD-1/PD-L1 agents have been approved for use in the frontline setting for ES SCLC, in combination with chemotherapy. Despite progressive integration of immunotherapy into treatment regimens, there remains a need for reliable biomarkers to precisely determine therapy candidates.

Immune Checkpoint Inhibitors

Tumor cells can usurp immune checkpoint signals—CD28/B7 activating signal and CTLA-4 and PD-1/PD-L1 inhibitory signals—to dampen effector T-cell responses to promote tumor cell survival and cancer progression.¹ The T-cell costimulation model proposes that T cells require 2 signals in order to be fully activated.² The first signal provides specificity to the immune reaction through class I major histocompatibility complex (MHC I) and T-cell receptor binding. The second signal is an antigen-independent costimulatory signal to promote T-cell clonal expansion and adequate immune response. Altered interactions between antigen-presenting

cells (APCs) and T cells can stifle the second costimulatory signal, hinder T-cell activation, and prevent adequate immune response.³ Cancer cells are able to exploit these pathways to evade the immune system and proliferate.³ By introducing immune checkpoint inhibitors (ICIs) to target disrupted checkpoint signaling, APC and T-cell interactions can be restored to elicit a lasting antitumor immune response.

PD-1 and PD-L1/PD-L2 Targeted Therapies

The primary function of cytotoxic T cells is to recognize MHC I to induce apoptosis in virus-infected and malignant cells.⁴ PD-1 is a transmembrane inhibitory receptor that

can be found on T cells, B cells, activated monocytes, and dendritic cells.³ It has 2 ligands, PD-L1 and PD-L2. PD-L1 is commonly overexpressed in tumor cells and APC, and PD-L2 is primarily expressed on macrophages and dendritic cells. The binding of PD-L1 and PD-L2 to PD-1 on cytotoxic T cells suppresses the immune system. Therefore, the overexpression of PD-L1 enables cancer cells to impede cytotoxic T-cell function, bypass host antitumor immune response, and proliferate. The goal of anti-PD-1/PD-L1 ICI is to reinstate downregulated T cells and resume normal immune response.

CTLA-4 Targeted Therapies

CTLA-4 is an inhibitory surface receptor expressed on activated dendritic cells and cytotoxic and helper T cells.⁵ Under normal circumstances, B7 ligands expressed on APCs bind to CD28 surface proteins found on T cells to initiate an immune response against “nonself” cells and avoid autoimmune attack. However, CTLA-4, which has a 10-fold higher affinity for B7, competes with CD28 for B7 binding to curtail CD28/B7 interactions.⁶ The reduced CD28/B7 activating signal decreases T-cell stimulation and IL-2 secretion to repress immune response.⁷ Competition for B7 binding between CTLA-4 and CD28 downregulates T-cell activation, allowing tumor cells to circumvent detection. Antibodies that target CTLA-4 can interrupt CTLA-4/B7 binding to restore baseline CD28/B7 interactions and anti-

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tumor activity.

First-Line Immune Checkpoint Inhibition

First-Line Single-Agent Inhibition

Pembrolizumab (Keytruda), an immunoglobulin (Ig) G4 monoclonal anti-PD-1 agent, has shown survival benefit in the frontline setting for patients with metastatic NSCLC as a single-agent monotherapy and with platinum-based agents in combination therapy. KEYNOTE-001, a large phase 1 study, assessed the safety and efficacy of pembrolizumab in locally advanced carcinoma and melanoma, with multiple cohorts of patients with NSCLC.⁸ This was the first study to evaluate the association of PD-L1 levels with patient outcomes in ICI-treated patients. PD-L1 expression was quantified based on immunohistochemical (IHC) assay results, which reported the percentage of cells with PD-L1 in patient tumor samples, known as tumor proportion score (TPS). KEYNOTE-001 trial results exhibited a positive correlation between PD-L1 expression and patient outcomes and differences in treatment response based on the line of therapy.⁸ In the cohort of treatment-naïve patients with NSCLC, the median overall survival (OS), progression-free survival (PFS), and response rate (RR) were 22.3 months, 6.0 months, and 24.8%, respectively. When analyzing RR by smoking status, smokers were more responsive to therapy than nonsmokers (current/former smokers, 22.5%, vs nonsmokers, 10.3%). The 5-year follow-up revealed that patients who received 2 or more years of pembrolizumab ($n = 60$) with a TPS 50% or greater had an estimated 5-year survival of greater than 25%.⁹ The median OS for patients with TPS $\geq 50\%$ was 34.5 months; for patients with TPS 1%-49%, it was 19.5 months. KEYNOTE-001 largely illustrates the potential for long-term OS benefits and antitumor responses with pembrolizumab in treatment-naïve and previously treated advanced patients with advanced NSCLC. Furthermore, the IHC assay and study results introduced the pos-

sibility of outcome advantages owing to high PD-L1 tumor expression.

KEYNOTE-024, an open-label, randomized phase 3 study, compared the effects of pembrolizumab versus platinum-based chemotherapy in treatment-naïve patients with advanced NSCLC with PD-L1 expression 50% or greater.¹⁰ At the 3-year follow-up, patients on pembrolizumab had significantly longer median OS (30.0 vs 14.2 months for the chemotherapy arm) despite sizable crossover from the chemotherapy arm.¹¹ KEYNOTE-024 reported higher estimated 3-year OS rates (43.7% vs 24.9%, respectively) and longer treatment duration (11.1 vs 4.4 months) in addition to having fewer treatment-related adverse events (AEs) in the pembrolizumab arm. The findings suggest that patients with advanced NSCLC and PD-L1 TPS 50% or greater can receive significantly greater benefit and longer responses with single-agent immunotherapy over chemotherapy as frontline treatment.

Previous trial results indicate that first-line pembrolizumab monotherapy improves OS and PFS in patients with PD-L1 TPS 50% or greater. KEYNOTE-042, a phase 3, randomized trial, investigated OS of first-line, single-agent pembrolizumab monotherapy versus traditional platinum-based chemotherapy for patients with locally advanced or metastatic NSCLC and PD-L1 TPS 1% or greater (**Table 1**).^{10-13, 16, 18, 20, 22-25, 28, 33, 36, 50} Trial results found that all TPS populations reached their primary end point. There was improved median OS in the experimental arm: pembrolizumab, 20.0 months (PD-L1 TPS $\geq 50\%$), 17.7 months (PD-L1 TPS $\geq 20\%$), and 16.7 months (PD-L1 TPS $\geq 1\%$) vs chemotherapy: 10.8 months (PD-L1 TPS $\geq 50\%$), 8.3 months (PD-L1 TPS $\geq 20\%$), and 8.3 months (PD-L1 TPS $\geq 1\%$). When evaluating PFS, only patients with TPS 50% or greater in the pembrolizumab arm showed benefit over chemotherapy. Patients with higher PD-L1 expression experienced higher RR regardless of therapy. Duration of response (DOR) with pembrolizumab was consistent across all PD-

L1 cohorts (PD-L1 TPS $\geq 1\%$, $\geq 20\%$, and $\geq 50\%$) and superior over chemotherapy. However, upon conducting further survival analysis, pembrolizumab failed to show benefit for patients with TPS 1% to 49%. This finding questions the impact of pembrolizumab monotherapy in patients with PD-L1 TPS less than 50%. The data from KEYNOTE-042 are consistent with those of previous trials and support pembrolizumab monotherapy for patients with PD-L1 expression 50% or greater, with survival results from TPS populations 1% or greater or 20% or greater largely driven by patients with PD-L1 expression 50% or greater.

IMpower110, a randomized phase 3 trial, evaluated the effects of atezolizumab (Tecentriq) with platinum-based chemotherapy.¹³ This study used the Ventana SP142 IHC assay to quantify PD-L1 expression both in immune cells (ICs) and tumor cells (TCs). The study found that atezolizumab monotherapy significantly improved OS for TC3 (TCs with PD-L1 $\geq 50\%$) or IC3 (ICs with PD-L1 $\geq 10\%$) over chemotherapy (median OS, 20.2 vs 13.1 months, respectively) in the frontline setting.^{13,14} The FDA approved atezolizumab monotherapy for first-line treatment of NSCLC for patients with high PD-L1 expression in May 2020, based on IMpower110 trial results.¹⁵

Nivolumab (Opdivo), an anti-PD-1 ICI, has also been studied in the frontline setting. CheckMate 026, a randomized phase 3 trial, evaluated frontline nivolumab vs chemotherapy in patients with stage IV or recurrent advanced NSCLC with PD-L1 expression 5% or greater. Nivolumab was not found to be superior over chemotherapy in PFS and RR, nor did it significantly increase OS (PFS, 4.2 vs 5.9 months, respectively; RR, 26% vs 33%; OS, 14.4 vs 13.2 months).¹⁶ However, despite unremarkable PFS and RR, the DOR for patients treated with nivolumab was more than twice as long as for those in the chemotherapy arm (12.1 vs 5.7 months, respectively).

The trial acknowledged several imbal-

ances between patient characteristics: The percentage of patients with disease characteristics associated with better prognosis, PD-L1 expression 50% or greater and high tumor mutational burden (TMB), may have disadvantaged the nivolumab arm and favored chemotherapy. TMB subset analysis was motivated by findings from Rizvi and colleagues, who used whole exome sequencing to determine TMB and reported an association between high TMB and improved immunotherapy treatment response.¹⁷ In CheckMate 026, the analysis indicated that patients with high TMB (≥ 243 somatic missense mutations) in the nivolumab arm had increased RR and longer PFS than patients on chemotherapy (RR, 47% vs 28%, respectively; PFS, 9.7 vs 5.8 months).¹⁶ Moreover, high-TMB patients treated with nivolumab also experienced notable benefit in OS and 1-year survival rates (>18 months and 64%, respectively). These TMB subset analysis data agree with the proposed hypothesis that immunotherapy responses may be augmented in patients with high TMB.

Combination Anti-PD-1/PD-L1 and Chemotherapy

Various immunotherapy plus chemotherapy combination trials have demonstrated encouraging results for patients with advanced NSCLC. KEYNOTE-189 and KEYNOTE-407 assessed the effects of pembrolizumab in combination with chemotherapy vs chemotherapy alone in untreated metastatic nonsquamous (KEYNOTE-189) and squamous NSCLC (KEYNOTE-407).^{18,19} In KEYNOTE-189, RR, PFS, and OS were significantly superior in the pembrolizumab/chemotherapy arm vs the placebo/chemotherapy arm, with benefit in OS seen across all TPS subgroups (OS, 22.0 vs 10.7 months, respectively; PFS, 9.0 vs 4.9 months; RR, 47.6% vs 18.9%).¹⁸ The 2-year follow-up concluded that the pembrolizumab/chemotherapy patient arm continued to display OS benefit in 2-year OS rate (46% vs 30% for placebo/chemotherapy) despite 54% of placebo/chemotherapy patients crossing

TABLE 1. First-Line Immune Monotherapy and Combination Therapy vs Chemotherapy

Comparison	RR	Median PFS	Median OS
KEYNOTE-024¹¹			
Pembrolizumab	44.8%	10.3 mo (HR, 0.5; $P < .0001$)	30.0 mo (HR, 0.63; $P = .002$)
Chemotherapy	27.8%	6.0 mo	14.2 mo
KEYNOTE-042¹²			
Pembrolizumab	TPS $\geq 50\%$: 39% TPS $\geq 20\%$: 33% TPS $\geq 1\%$: 27	TPS $\geq 50\%$: 7.1 mo (HR, 0.81; $P = .017$) TPS $\geq 20\%$: 6.2 mo (HR, 0.94) TPS $\geq 1\%$: 5.4 (HR, 1.07)	TPS $\geq 50\%$: 20.0 mo (HR, 0.69; $P = .0003$) TPS $\geq 20\%$: 17.7 mo (HR, 0.77; $P = .002$) TPS $\geq 1\%$: 16.7 mo (HR, 0.81; $P = .0018$)
Chemotherapy	TPS $\geq 50\%$: 32% TPS $\geq 20\%$: 29% TPS $\geq 1\%$: 27%	TPS $\geq 50\%$: 6.4 mo TPS $\geq 20\%$: 6.6 mo TPS $\geq 1\%$: 6.5 mo	TPS $\geq 50\%$: 12.2 mo TPS $\geq 20\%$: 13.0 mo TPS $\geq 1\%$: 12.2 mo
KEYNOTE-189^{18,20}			
Pembrolizumab + chemotherapy	57.9%	6.4 mo (HR, 0.56; $P < .001$)	15.9 mo (HR, 0.64; $P < .001$)
Placebo + chemotherapy	38.4%	4.8 mo	11.3 mo
IMpower110¹³			
Atezolizumab	TC3 or IC3: 38.3%	8.1 mo (HR, 0.63; $P = .0070$)	TC3 or IC3: 20.2 mo (HR, 0.595; $P = .0106$)
Chemotherapy	TC3 or IC3: 28.6%	5.0 mo	TC3 or IC3: 13.1 mo
IMpower130²¹			
Atezolizumab + CnP	49.2%	7.0 mo (HR, 0.64; $P < .0001$)	18.6 mo (HR, 0.79; $P = .033$)
CnP	31.9%	5.5 m	13.9 m
IMpower150²²			
Atezolizumab + chemotherapy + bevacizumab	63.5%	Overall: 8.3 mo (HR, 0.62; $P < .001$) PD-L1 $\geq 50\%$: 12.6 mo (HR, 0.39) PD-L1 $< 50\%$: 8.0 mo (HR, 0.68) EGFR or ALK: 9.7 mo (HR, 0.59)	19.2 mo
Chemotherapy	48.0%	Overall: 6.8 mo PD-L1 $\geq 50\%$: 6.8 mo PD-L1 $< 50\%$: 6.8 mo EGFR or ALK: 6.1 mo	14.7 mo
CheckMate 026¹⁶			
Nivolumab	26%	4.2 mo (HR, 1.15; $P = .25$)	14.4 mo (HR, 1.02)
Chemotherapy	33%	5.9 mo	13.2 mo
CheckMate 227²⁸			
Nivolumab + ipilimumab +	High TMB: 45.3% (HR, 0.57; $P < .001$)	Overall: 4.9 mo High TMB: 7.2 mo (HR, 0.58; $P < .001$)	17.1 mo
Placebo + chemotherapy	High TMB: 26.9%	Overall: 5.5 mo High TMB: 5.5 mo	14.9 mo
CheckMate 9LA³³			
Nivolumab + ipilimumab + chemotherapy	38%	6.7 mo (HR, 0.68)	15.6 mo (HR, 0.66)
Chemotherapy	25%	5.0 mo	10.9 mo

CnP, carboplatin and nab-paclitaxel; IC, immune cell; OS, overall survival; PFS, progression-free survival; RR, response rate; TC, tumor cell; TMB, tumor mutation burden; TPS, tumor proportion score.

TABLE 2. Second-Line Immunotherapy vs Chemotherapy

Comparison	RR	Median PFS	Median OS
KEYNOTE-010^{25,50}			
Pembrolizumab 2 mg/kg	Overall: 18% TPS ≥50%: 30% (<i>P</i> < .0001)	Overall: 3.9 mo (HR, 0.88; <i>P</i> = .08) TPS ≥50%: 5.0 mo (HR, 0.53; <i>P</i> < .00001)	Overall: 10.4 mo (HR, 0.71; <i>P</i> = .0008) TPS ≥50%: 14.9 mo (HR, 0.54; <i>P</i> = .0002)
Pembrolizumab 10 mg/kg	Overall: 18% TPS ≥50%: 29% (<i>P</i> < .0001)	Overall: 4.0 mo (HR, 0.69; <i>P</i> < .0001) TPS ≥50%: 5.2 mo (HR, 0.59; <i>P</i> < .0001)	Overall: 12.7 mo (HR, 0.61; <i>P</i> < .0001) TPS ≥50%: 17.3 mo (HR, 0.5; <i>P</i> < .0001)
Docetaxel	Overall: 9% TPS ≥50%: 8%	Overall: 4.0 mo TPS ≥50%: 4.1 mo	Overall: 8.5 mo TPS ≥50%: 8.2 mo
CheckMate 017³³			
Nivolumab	20% (<i>P</i> = .008)	3.5 mo (HR, 0.62; <i>P</i> < .001)	9.2 mo (HR, 0.59; <i>P</i> < .001)
Docetaxel	9%	2.8 mo	6.0 mo
CheckMate 057²⁴			
Nivolumab	19% (<i>P</i> = .02)	2.3 mo (HR, 0.92; <i>P</i> = .39)	12.2 mo (HR, 0.73; <i>P</i> = .002)
Docetaxel	12%	4.3 mo	9.4 mo
OAK^{23,36}			
Atezolizumab	ITT850: 14.6%	ITT850: 2.8 mo (HR, 0.93)	ITT850: 13.8 mo (HR, 0.75; <i>P</i> = .00006) TC1/2/3 or IC1/2/3: 15.7 mo (HR, 0.74; <i>P</i> = .0102)
	ITT1225: 13.7%	ITT1225: 2.7 mo (HR, 0.96)	ITT1225: 13.3 mo (HR, 0.80; <i>P</i> = .0012) TC1/2/3 or IC1/2/3: 14.3 mo (HR, 0.77; <i>P</i> = .0045)
Docetaxel	ITT850: 13.4%	ITT850: 4.0 mo	ITT850: 9.6 mo TC1/2/3 or IC1/2/3: 10.3 mo
	ITT1225: 11.8%	ITT1225: 3.8 mo	ITT1225: 9.8 mo TC1/2/3 or IC1/2/3: 10.8 mo

IC, immune cells; ITT, intention to treat; OS, overall survival; PFS, progression-free survival; RR, response rate; TC, tumor cells; TPS, tumor proportion score.

over to anti-PD-1/PD-L1 therapy.²⁰ In KEYNOTE-407, patients who received pembrolizumab/chemotherapy experienced greater survival benefit than those who received placebo/chemotherapy (OS, 15.9 vs 11.3 months, respectively; PFS, 6.4 vs 4.8 months; RR, 57.9% vs 38.4%).¹⁹ In both studies, subgroup statistical analysis of varying PD-L1 expression (TPS ≤1%, TPS ≥1%, TPS ≥50%) pointed toward pembrolizumab combination therapy as the superior treatment regardless of PD-L1 status. Clinical trials KEYNOTE-189 and KEYNOTE-407 support the role of pembrolizumab in the first-line setting for

metastatic NSCLC regardless of histology or PD-L1 expression, contrary to the findings of previous trials.^{18,19}

IMpower130, a randomized phase 3 trial, evaluated the effects of carboplatin and nab-paclitaxel (CnP) with or without atezolizumab in advanced nonsquamous NSCLC.²¹ Atezolizumab provided significant improvement in median OS and PFS across all PD-L1 subgroups and prognostic subgroups except in patients with liver metastases and those harboring *EGFR* or *ALK* mutations (OS, 18.6 vs 13.9 months, respectively; PFS, 7.0 vs 5.5 months). The ORR and percentage of grade 3/4 AEs

were higher for the atezolizumab plus CnP arm (ORR, 49.2% vs 31.9%, respectively; grade 3/4 AEs, 72.3% vs 60.3%).

IMpower150, a randomized, phase 3 clinical trial, investigated immunotherapy plus chemotherapy and bevacizumab in the frontline setting for patients with advanced NSCLC (Table 1).^{11-13, 16, 18, 20, 22-25, 28, 33, 36, 50} Patients with advanced non-squamous NSCLC were randomized to 1 of 3 arms: atezolizumab (a human IgG1 monoclonal antibody to PD-L1) with carboplatin plus paclitaxel; atezolizumab and bevacizumab with carboplatin plus paclitaxel (ABCP); or placebo with bevacizumab and chemotherapy (BCP). Typically, studies exclude patients with *EGFR*- and *ALK*-activating alterations; however, IMpower150 enrolled patients harboring *EGFR*- and *ALK*-activating mutations following first-line tyrosine kinase therapy. The RR for the ABCP arm was 63.5%, exceeding the BCP treatment group's RR of 48.0%. A significant OS benefit, as well as improvement in PFS regardless of PD-L1 expression, presence of liver metastases, and sensitization for *EGFR* or *ALK* mutations, was observed in the ABCP vs the BCP treatment arm (OS, 19.2 vs 14.7 months, respectively; PFS, 8.3 vs 6.8 months). Historically, trials of second-line or greater treatment have shown that patients with *EGFR* genetics do not benefit from checkpoint inhibition.²³⁻²⁵ IMpower150 was a pivotal study in that it was the first trial to report a benefit from ICI therapy for patients with *EGFR*- and *ALK*-altered NSCLC.

Combination CTLA-4 and Chemotherapy

Ipilimumab (Yervoy) is an anti-CTLA-4 monoclonal antibody that first showed survival benefit in melanoma.²⁶ A phase 2 clinical trial compared the effects of paclitaxel and carboplatin with placebo or ipilimumab as first-line therapy for patients with advanced NSCLC.²⁷ Patients were randomly assigned 1:1:1 to each treatment arm and received concurrent dosing (4 doses of 10-mg/kg ipilimumab with paclitaxel and car-

boplatin followed by 2 doses of paclitaxel and carboplatin), phased dosing (2 doses of paclitaxel and carboplatin followed by 4 doses of ipilimumab in combination with paclitaxel and carboplatin), or control (up to 6 cycles of paclitaxel and carboplatin). Immune-related PFS was improved with phased therapy over placebo (5.7 vs 4.6 months, respectively). When comparing OS and RR among phased dosing, concurrent dosing, and chemotherapy, both phased and concurrent dosing reached statistically insignificant numerical outcomes favorable over control (OS, 12.2 vs 9.7 vs 8.3 months, respectively; RR, 32%, 21%, and 14%). Furthermore, the addition of ipilimumab produced an increase in grade 3/4 AEs (6%, 20%, and 15% for control, concurrent, and phased arms, respectively). Despite unremarkable findings of ipilimumab plus chemotherapy combination treatment in NSCLC compared with PD-1/PD-L1 ICIs, ongoing ipilimumab trials have since focused attention on the benefit of ipilimumab in combination with nivolumab and other immune-modulating therapies.

Combination Immunotherapy

The advantages of anti-PD-1/PD-L1 monotherapy, and of anti-PD-1/PD-L1 plus chemotherapy, over traditional platinum-based therapy have inspired trials to study the effects of anti-PD-1/PD-L1 agents in combination with anti-CTLA-4 agents. By combining therapies of 2 independent pathways, the treatments can hopefully complement each other therapeutically to enhance RR and survival outcomes.²⁸

CheckMate 227, a phase 3 randomized study, evaluated the effects of nivolumab plus ipilimumab in patients with advanced NSCLC as first-line therapy. Patients with PD-L1 1% or greater were randomly assigned to receive nivolumab + ipilimumab, nivolumab monotherapy, or chemotherapy.²⁹ Patients with PD-L1 less than 1% were randomly assigned to nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy, and did not have a statistical end point included. PD-L1 expression and TMB were used to assess outcomes in

TABLE 3. **Durvalumab vs Placebo, Post Chemoradiation**

Comparison	RR	Median PFS	Median OS
Impower133³⁶			
Atezolizumab	60.2%	5.2 mo (HR, 0.77; <i>P</i> = .02)	12.3 mo (HR, 0.70; <i>P</i> = .007)
Chemotherapy	64.4%	4.3 mo	10.3 mo
CASPIAN³⁵			
Durvalumab	79%	5.1 mo (HR, 0.78)	13.0 mo (HR, 0.73; <i>P</i> = .0047)
Placebo	70%	5.4 mo	10.3 mo
KEYNOTE-604³⁷			
Pembrolizumab + platinum + etoposide	71%	4.5 mo (HR, 0.75; <i>P</i> = .0023)	10.8 mo (HR, 0.80; <i>P</i> = .0164)
Placebo + platinum + etoposide	62%	4.3 mo	9.7 mo

OS, overall survival; PFS, progression-free survival.

patient subgroups (Table 1).³⁰ Contrary to the results of previous immunotherapy trials,⁹⁻¹¹ CheckMate 227 reported higher median OS and 2-year ongoing RR in patients who received ipilimumab plus nivolumab than in patients treated with chemotherapy alone, regardless of PD-L1 expression (median OS, 17.1 vs 14.9 months, respectively; 2-year rate of ongoing response: 49% vs 11%).²⁸ Median PFS was also improved with nivolumab + ipilimumab over chemotherapy for all patients regardless of PD-L1 expression, but it was numerically higher for patients with PD-L1 expression less than 1%. Initial reports also indicated that patients with high TMB (TMB ≥10 mut/MB) across PD-L1 ≥1% and <1% subgroups saw improved PFS when treated with nivolumab + ipilimumab over chemotherapy.²⁹ Investigators expected to see an association between TMB and treatment response based on the results from CheckMate 568.³¹ However, upon performing a further subset analysis based on TMB, the data revealed consistent median OS regardless of TMB. These findings prompted the approval of nivolumab plus ipilimumab as a first-line treatment for patients with NSCLC with PD-L1 expression 1% or greater.³¹ CheckMate 227 highlights the reality that ICI and TMB biomarkers used to predict patient response remain

elusive and warrant further investigation and validation.

Building off CheckMate 227, CheckMate 9LA, a randomized phase 3 trial, compared nivolumab plus ipilimumab plus 2 cycles of chemotherapy vs 4 cycles of chemotherapy alone.³² At the 12.7-month follow-up, regardless of PD-L1 expression, patients treated with nivolumab and ipilimumab with limited-course chemotherapy saw significantly improved median OS (15.6 vs 10.9 months, respectively) and higher percentage of patients with grade 3/4 AEs (47% vs 38%, respectively).

Immune Checkpoint Inhibition as Subsequent Therapy

KEYNOTE-001 evaluated pembrolizumab in both treatment-naïve and previously treated patients.⁸ Previously treated patients had a 18% RR compared with the observed 45.2% RR for patients with PD-L1 TPS 50% or greater. At the 5-year follow up, previously treated patients with TPS 50% or greater had a median OS of 15.4 months versus 8.5 months for those with TPS 1% to 49% and 8.6 months for those with TPS less than 1% (estimated 5-year survival rates were 25% vs 12.6% vs 3.5%, respectively).⁹

KEYNOTE-010 also compared pembrolizumab (2 mg/kg or 10 mg/kg) with docetaxel for previously treated patients

TABLE 4. ICI Plus Chemotherapy vs Chemotherapy, ES SCLC

Comparison	RR	Median PFS	Median OS	Median time to death or metastasis
PACIFIC ³²⁻³⁴				
Durvalumab	28.4%	17.2 mo (HR, 0.52; P <.0001)	12-mo OS rate: 83.1% 24-mo OS rate: 66.3%	Not reached (HR, 0.69)
Placebo	16.0%	6.0 mo	12-mo OS rate: 75.3% 24-mo OS rate: 55.6%	29.1 mo

ES SCLC, extensive-stage small cell lung cancer; OS, overall survival; PFS, progression-free survival; RR, response rate.

with NSCLC with PD-L1 TPS 1% or greater.²⁵ There was no significant difference in overall PFS across treatments, but when taking TPS into account, PFS was significantly higher in patients who were administered pembrolizumab vs docetaxel. The median OS of patients with TPS ≥1% was 10.4 months with 2-mg/kg pembrolizumab, 12.7 months with 10-mg/kg pembrolizumab, and 8.4 months with docetaxel. For patients with TPS 50% or greater, the median OS was significantly higher with 2-mg/kg and 10-mg/kg doses of pembrolizumab: 14.9 and 17.3 months, respectively. The long-term outcomes of KEYNOTE-001 and KEYNOTE-010 illuminate the success of pembrolizumab monotherapy in the frontline setting and the association of high PD-L1 expression with favorable treatment response.

CheckMate 017 and CheckMate 057, both randomized phase 3 trials, evaluated the effects of nivolumab vs docetaxel in patients with advanced squamous (CheckMate 017) and nonsquamous (CheckMate 057) NSCLC (Table 2).^{24,33,34} The results of CheckMate 017 indicated a 20% RR with nivolumab vs a 9% RR with docetaxel, and significantly longer PFS and OS with nivolumab over docetaxel (PFS, 3.5 vs 2.8 months, respectively; OS, 9.2 vs 6.0 months).³³ From the results, no predictive association could be concluded upon evaluating PD-L1 expression with treatment efficacy. In CheckMate 057, patients on nivolumab experienced significantly improved OS versus those on docetaxel (12.2 vs 9.4 months, respectively), improved RR (19% vs 12%), and shorter PFS (2.3 vs 4.2

months).²⁴ Contrary to CheckMate 017, CheckMate 057 identified a correlation between high PD-L1 expression and improved response. At the 5-year follow-up for CheckMate 017/CheckMate 057, nivolumab continued to show long-term OS and PFS benefit over docetaxel for both squamous and nonsquamous NSCLC, with 5-year OS rates of 15% vs 3% and 5-year PFS rates of 8% vs 0%, respectively.³⁴

OAK, a randomized phase 3 study, compared atezolizumab with docetaxel in previously treated, advanced NSCLC. Atezolizumab displayed a better safety and survival profile vs docetaxel in the intention-to-treat group regardless of PD-L1 expression (OS, 13.8 vs 9.6 months, respectively) or histology.²³ When quantifying for PD-L1 expression, median OS and PFS improved in higher PD-L1 expression groups.³⁵

Immune Checkpoint Inhibition for Locally Advanced NSCLC

Durvalumab (Imfinzi) is a PD-L1 inhibitor that acts to disrupt PD-L1 binding to PD-1 and CD80. This differs from pembrolizumab and nivolumab, because binding to PD-L1 inhibits PD-1/PD-L1 binding, whereas anti-PD-1 therapy interrupts PD-1/PD-L1 and PD-1/PD-L2 interactions.³⁶ The PACIFIC trial evaluated consolidation durvalumab and placebo for 12 months following concurrent chemoradiation for patients with unresectable stage III NSCLC (Table 3). Significant improvement in 12- and 24-month OS rate, PFS, and RR was seen for patients on durvalumab vs those on placebo (12-month OS rate,

83.1% vs 75.3%, respectively; 24-month OS rate: 66.3% vs 55.6%; PFS, 17.2 vs 5.6 months; RR, 28.4% vs 16.0%), regardless of PD-L1 expression.^{36,37} At the 3-year follow-up, median OS in the placebo arm was 29.1 months while median OS was still unreached in the durvalumab arm.³⁸ Findings from the PACIFIC trial and the 3-year follow-up reinforces the use of consolidation durvalumab as the standard of care for unresectable stage III NSCLC. In earlier-stage NSCLC, ongoing trials continue to address the integration of perioperative immunotherapy to improve survival and quality of life for more patients with lung cancer.

Immune Checkpoint Inhibition in Extensive-Stage SCLC

First-line treatment for patients with extensive-stage small cell lung cancer (ES SCLC) is platinum-based chemotherapy with or without radiation; this has been the standard of care for more than 3 decades.³⁹ Although patients with SCLC initially respond to chemotherapy, relapse is common and the number of available second-line treatments is limited. Given the effectiveness of immunotherapy in NSCLC and high TMB SCLC, ongoing trials are exploring how immune-based modalities can be incorporated into new treatment regimens for ES SCLC.

IMpower133, a randomized phase 3 trial, compared carboplatin and etoposide with or without atezolizumab in patients with untreated ES SCLC (Table 4).⁴⁰ IMpower133 was the first trial to demonstrate significant improvement in median OS and PFS with an immunotherapy-based regimen. The median OS and PFS for patients with atezolizumab were 12.3 and 5.2 months, respectively, versus 10.3 and 4.3 months for placebo (survival results were consistent across TMB subgroups).

CASPIAN, a large, randomized, open-label phase 3 trial, evaluated platinum plus etoposide with or without durvalumab as a first-line treatment for ES SCLC.³⁹ Durvalumab plus platinum/etoposide was associated with manageable immune-related

AEs, improved median OS with durvalumab over no durvalumab (13.0 vs 10.3 months, respectively), and an improved median 18-month OS rate (34% vs 25%). Similar to the IMpower133 results, survival results were consistent across TMB subgroups. The strong and promising efficacy and safety data gathered from the IMpower133 and CASPIAN trials have resulted in FDA approval of atezolizumab and durvalumab as optional additions to the standard of care when treating ES SCLC.

KEYNOTE-604, a randomized phase 3 trial, evaluated pembrolizumab plus platinum plus etoposide versus placebo plus platinum plus etoposide in patients with untreated ES SCLC.⁴¹ Pembrolizumab + platinum + etoposide significantly improved 12-month PFS estimates (13.6% vs 3.1% for placebo) and showed no unexpected toxicities. While median OS with pembrolizumab did not reach statistically significant improvement over placebo, the study results support the benefit and safety of pembrolizumab plus platinum plus etoposide for untreated ES SCLC.

Biomarkers for Immunotherapy

Despite the progress that has been made with immunotherapy, the vast majority of patients with lung cancer do not respond to ICI. Accurate and consistent biomarkers and assays are critical to improve patient sensitivity to ICI treatment. Previous clinical trials have demonstrated some association between PD-L1 and TMB and treatment response. However, both measures have shown inconsistencies across trials in their ability to predict treatment response.

8-10,18,19,28,30

Multiple antibody-staining PD-L1 IHC assays have been approved as companion diagnostics for ICIs, and high TMB was approved in June 2020 as a diagnostic for pembrolizumab across tumor types.⁴² The FDA has approved the PD-L1 IHC 22C3 and 28-8 assays; these use 223C and 28-8 antibodies, respectively, to stain patient tumor samples and determine the percentage of cells with membranous PD-L1.⁴³ The percentage of stained cells is

the patient's TPS for the IHC 22C3 assay, which is used to identify individuals eligible for pembrolizumab.⁴⁴ The PD-L1 IHC 28-8 assay quantifies PD-L1 expression to identify patients who are suitable for second-line nivolumab for nonsquamous NSCLC and first-line nivolumab plus ipilimumab in NSCLC patients.⁴⁵ Meanwhile, the Ventana SP142 IHC assay quantifies PD-L1 expression of IC and TC. Depending on the percentage of stained ICs and TCs, PD-L1 expression will be scored as TC1, 2, or 3 (TC1: PD-L1 $\geq 1\%$; TC2: PD-L1 $\geq 5\%$; TC3: PD-L1 $\geq 50\%$) and IC1, 2, or 3 (IC1: PD-L1 $\geq 1\%$; IC2: PD-L1 $\geq 5\%$; IC3: PD-L1 $\geq 10\%$). Based on IMpower110 study results, the Ventana SP142 IHC assay has been approved as a companion diagnostic for first-line atezolizumab monotherapy.¹⁵

Because of the nature of high tumor heterogeneity in advanced NSCLC and ES SCLC, determining PD-L1 expression and TMB has been challenging. Both tests require adequate tissue biopsies, which may not always be feasible or accessible; moreover, even if tissue is available, test results may not be indicative of the tumor microenvironment because of tumor heterogeneity.⁴⁶⁻⁴⁸ The obstacles faced with tissue biopsies have instigated research and validation to use blood samples and blood TMB (bTMB).⁴⁹ bTMB is determined through next-generation sequencing (NGS) of circulating-tumor DNA (ctDNA), pieces of DNA shed by the tumor in its surrounding microenvironment. By using NGS on ctDNA, the number of mutations in ctDNA can be calculated to determine bTMB. Analyses performed on POPLAR and OAK blood samples found that bTMB 16 or greater mutations per megabase is a clinically meaningful predictor of PFS for NSCLC atezolizumab patients.⁴⁶ The analysis also observed improved OS with bTMB with the POPLAR study, but the OAK trial was unable to validate those results, which Gandara et al attributed to superior OS benefit in the biomarker-evaluable population relative to the intention-to-treat population.

Although bTMB is a noninvasive test, its success depends on the tumor shedding

DNA and on the blood samples to contain ctDNA; if no DNA is shed or found, the blood sample is insufficient and cannot determine bTMB. Despite the limitations inherent in each method—tTMB, bTMB, and PD-L1 IHC assays—these are the best predictors available until more suitable biomarkers and assays are validated.

Conclusions

Understanding anti-PD-1/PD-L1 and anti-CTLA-4 immunomodulators has dramatically altered the treatment approach to lung cancer. In advanced NSCLC, the effective, durable, and manageable toxicity profiles of ICI over chemotherapy have culminated in FDA approvals for multiple agents in all treatment lines and have even become the new standard of care. In ES SCLC, checkpoint inhibitors are being incorporated into therapies, and their inclusion to the standard of care shows promise. As ongoing trials explore the utility of various single-agent and combination therapies, the need for reliable biomarkers remains. Although PD-L1 expression remains the primary FDA approved biomarker, TMB is developing as a biomarker to identify patients suitable for immunotherapy. Because of the survival benefit and durable responses immunotherapy provides, studies continue to evaluate novel immune-modulating combinations to resume innate antitumor activity and improve long-term survival for all patients with lung cancer. ■

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➤ For full reference list, visit cancernetwork.com/lungcancer_review

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Telemedicine Use in Oncology Practices

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ABSTRACT: Telemedicine (TM) will play an increasingly significant role in practices that diagnose cancers and treat patients. Although only a small percentage of oncologists currently use TM, many more will embrace this technology in the near future. Although TM has been available for several decades, it was the coronavirus disease 2019 pandemic that highlighted how useful the concept was for connecting and communicating not only with patients who live a significant distance away from their oncologist's brick-and-mortar office, but with those who are homebound, for whatever reason. For instance, patients who have tested positive for coronavirus but who are not significantly symptomatic can be safely treated while they remain at home. One barrier to the widespread implementation of TM was lack of compensation for the time spent communicating with patients using audio-visual technology. As of March 2020, however, CMS has mandated that TM virtual visits and face-to-face visits have financial parity. This article will explore the process of implementing TM into an oncology practice with minimal time, energy, effort, and expense, as well as the concepts and the trends behind using TM to provide care for patients with cancer.

KEYWORDS: telemedicine, telehealth, synchronous video conferencing, oncology care

Introduction

Whether they know it or not, most oncology professionals have already practiced some form of telemedicine (TM) (perhaps without the video component). TM can include taking after-hours phone calls from patients asking for medication refills, for instance. In such cases, an oncologist has the choice of calling in a refill to a pharmacy or denying the request and mandating that the patient make an appointment to receive a new prescription. The latter action, understandably, will probably not endear the oncologist to the patient, but on the other hand, providers have been aware that if they acquiesce to patients' phone requests to have

prescriptions filled—or to give medical advice by phone outside of a proscribed visit—they have been ineligible for any compensation. Now, the legal landscape and reimbursement regulations are rapidly changing, and adopting a formal TM policy may seem prudent.

Before doing so, it is important to consult with a health care attorney who understands the TM technology and state-by-state regulatory and reimbursement challenges. Oncologists are held legally responsible for any advice and medications they provide to patients, even when communicating by phone or another electronic medium. It's still true that caring for patients who intentionally call their

oncologist for advice or medication refills without making or keeping appointments isn't, overall, a sound practice: Patients may well continue to seek free medical advice if they can get away with it. However, providing care without documentation does not make for good medical practice. That's where TM comes in—as an important adjunct to a high-functioning oncology practice. With a TM plan, oncologists can be compensated for text, phone, and video interactions with patients while practicing good medicine, as an electronic record of interactions will be generated and there will be a seamless method of billing the patient or their insurance company for the virtual visit.

TABLE. Oncology Scenarios in Which Patients Might Be Seen Using Telemedicine

- Routine office follow-up visits
- Monitoring for chemotherapy treatment toxicity
- Consultations (second opinions)
- Access to national and international cancer experts
- Participation in new cancer treatments
- Tele-rounds for hospital patients
- Remote chemotherapy supervision
- Access to clinical trials
- Remote emergency department visits (using digital devices to conduct heart and lung exams)
- Melanoma screenings
- Remote patient monitoring
- Evaluating patient in the home and deciding whether an office visit, emergency department visit, or hospitalization is required
- Comfort, support, reassurance: virtual check-in
- Post bone marrow transplantation (used at Memorial Sloan Kettering Cancer Center)
- Wound care, symptom management, palliative care
- Bundled care: oncologist, surgeon, cytopathologist, radiologist
- New patient: Given the coronavirus disease 2019 pandemic, CMS has agreed not to audit introductory telemedicine visits to ensure prior relationship with providers

Oncologists must recognize and embrace the improvements in technology that have changed the landscape of the entire health care industry—to make our practices more appealing to our patients, for 1 reason. Also, the proper use of TM will lower the cost of health care for both patients with cancer and their providers.¹ The oncology professionals who harness TM will magnify their competitive advantage exponentially, as they'll be better able to connect with existing patients as well as potential new ones. Using TM, oncologists will be able to reach and attract patients in a larger geographic area, limited much less by traditionally measured distances.

Several decades ago, TM's best use was for rural areas where there were few physicians, especially oncologists, and in that scenario, reimbursement was available.² Now, more urban medical practices are

embracing TM. Results of a Kaiser Permanente report showed that between 2011 and 2016, telehealth service use nationally increased substantially: growth was 629% and 960% in urban and rural areas, respectively.³

Even before the pandemic, Boston-based American Well (known also as Amwell), a TM company that connects patients with doctors over secure video, estimated that by 2022, between 341,000 and 591,000 physicians would be using telehealth to see patients.⁴ The American Society of Clinical Oncology has projected that between 2016 and 2026, the number of cancer survivors will rise from 15.5 million to 20.3 million.⁵ This increased survivorship, combined with increasing rates of new cancer in the aging population, is expected to result in a 40% increase in cancer care demand. This increase will coincide with an es-

timated shortage of 2200 oncologists, many of whom will be aging out of the workforce.⁶

Benefits of TM to Oncologists

Like other health care providers, oncologists have begun to recognize the benefit of using TM in patient care. The number of physicians using TM has been increasing by about 20% per year, coinciding with growth in TM patient visits, which increased annually 261% between 2015 and 2017.⁷

As proposed by Berwick et al, improving the US health care system requires simultaneous pursuit of 3 aims: improving the experience of care, improving the health of populations, and reducing per capita costs of health care. This Triple Aim concept can be applied specifically to TM as well.⁸

Because of its efficiency, TM can reduce the expenses of caring for patients with cancer. A TM program can be begun with minimal or no start-up costs. An oncologist needs only a laptop computer, smartphone, or tablet—no purchase of additional hardware or software is necessary.

TM can enhance traditional face-to-face interactions between the patient and the oncologist. A strong doctor-patient relationship almost always begins with a face-to-face encounter. Although TM should not replace this traditional method of care delivery, TM can support it. With TM, providers can provide flexible, convenient care appointments for follow-up visits and checkups, and for patient education.

For some patients, TM can be even more appealing than in-person visits. Although still engaging in real-time visits, patients with busy schedules of any kind, whether due to workforce participation or providing care to children or elderly relatives, can appreciate the benefits of no travel or waiting-room time. Most patients, in fact, seek more convenient ways of accessing their health care providers and receiving immediate care.

On the provider side, more physicians than in previous decades are retiring early or experiencing burnout, because the

TM can improve job satisfaction by making it easier for oncologists to interact with patients and also to balance their work and family life.

health care profession is so challenging and stressful. Unfortunately, oncologists have one of the highest burnout rates of all physician specialties,⁹ and, to boot, more than 50% of practicing oncologists are more than 55 years of age and nearing retirement.¹⁰ With the aging patient population, the demand for oncology care is increasing, putting pressure on oncologists to see more patients and spend less time with each. TM can help by bridging the gap between physician supply and patient demand.¹¹

TM can improve job satisfaction by making it easier for oncologists to interact with patients and also to balance their work and family life. This could well decrease the rate of physician burnout, which is now at an epidemic proportion, affecting 52% of all physicians.¹²

Cancer therapies are, of course, quite expensive, and among oncologists' challenges are to help control health care costs. Nationally, the health care budget consumes nearly 18% of the gross domestic product, exceeding \$3 trillion annually; of that, 8.6% can be attributed to physician expenses.¹³ Strikingly, in one report, 93% of consumers who used TM said that it lowered their health care costs.¹⁴ Lower health care costs ultimately improve the image of oncologists with our patients and the public.

Oncology Patients: TM Candidates

TM was first embraced by primary care physicians, dermatologists, and radiologists, and now specialists—even obstetricians and surgeons—use TM as well.¹⁵ Many of the potentially appropriate uses of TM in patients with cancer are shown in the **Table**. Providing care for a new patient is a special case: In the past, caring

for a new patient without establishing rapport, face-to-face, was not recommended. However, because of coronavirus disease 2019 (COVID-19), CMS has relaxed Health Insurance Portability and Accountability Act restrictions and decided that they will not audit practices and/or doctors who use TM to provide initial care.

Here's an example of an patient with cancer who is amenable to TM management: A middle-aged, otherwise healthy woman with stage IV lung cancer was previously treated with surgery and radiation therapy and is currently receiving chemotherapy on a clinical trial protocol from Memorial Sloan Kettering Cancer Center. It was not convenient or prudent for the patient to travel from her Texas home to New York for a consultation and possible infusion of chemotherapy. Also, she was significantly immunocompromised, and going to her oncologist's office would place her at risk of contracting COVID-19. Instead, she remained at home, and a local physician assistant from an oncology office went to the patient's home and conducted a virtual visit with her oncologist and surgeon in New York. Prior to the patient's virtual visit, she was seen at home by a phlebotomist who drew and submitted the blood for the panel that was required by the trial protocol. The physician assistant performed a physical exam on the patient, including a pulmonary assessment, and reported the results to the Sloan Kettering oncologist during the TM visit. Thus the patient could remain at home and avoid COVID-19 and other communicable diseases, yet still meet with both her surgeon and oncologist. The decision was made to withhold her infusion because of an abnormal white blood cell count and

platelet count. Take-home message: For many cancer patients, having to travel a great distance every month for follow-up visits is expensive and unnecessary. Once the treatment protocol is established, many patients can be easily, safely, and effectively monitored from home.

Patients with Cancer: Not TM Candidates

In general, scenarios that are not suitable for TM involve those in which a patient has a serious/severe issue and/or those in which a physical examination, protocol-driven procedures, and aggressive interventions are or could be necessary. Other patients for whom TM is not suitable include some patients with cognitive disorders or language barriers, intoxicated patients, patients in emergency situations that warrant an office visit or a visit to the emergency department, and patients who do not have access to the technology to conduct a virtual visit.

Conclusions

TM has been available for several decades, but now the COVID-19 pandemic has changed the playing field. TM enables communication with our patients with cancer when face-to-face visits or in-person examinations are not required. The moment of mass adoption of TM has arrived, and soon more and more patients will be requesting virtual visits with their oncologists. ■

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CONTINUING MEDICAL EDUCATION (CME)

Updates in CAR T Therapy for Multiple Myeloma

FACULTY

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LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:

- Analyze the mechanistic properties of CAR T-cell therapies, including design characteristics that impact efficacy and safety
- Evaluate clinical trial data regarding applications of CAR T-cell therapy in multiple myeloma management
- Summarize the role of CAR T-cell therapy in multiple myeloma across existing indications and potential future indications

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Multiple myeloma (MM) is a hematological malignancy characterized by uncontrolled proliferation of plasma cells that ultimately leads to end-organ damage.¹ With 30,000 individuals diagnosed each year in the United States, MM accounts for approximately 1% of all cancers.² Although MM remains largely incurable, significant therapeutic advances have been made in the last 2 decades resulting in substantial improvements in overall survival for patients. Despite this, 12,000 deaths are attributable to MM each year in the United States. The current standard of care for the treatment of MM based on National Comprehensive Cancer Network guidelines consists of multidrug regimens that include chemotherapy and dexamethasone combined with bortezomib in the first-line setting and either bortezomib, daratumumab, or elotuzumab in subsequent-line settings, with the goal of eligible patients proceeding to allogeneic hematopoietic cell transplantation (HCT).³

Chimeric antigen receptor (CAR) T-cell therapy is an emerging therapeutic strategy currently undergoing clinical evaluation for the treatment of patients with MM.⁴ The use of CAR T therapy has already demonstrated substantial clinical benefit for the treatment of other hematologic malignancies including diffuse large B-cell lymphoma, acute lymphoblastic leukemia (ALL), and chronic lymphocytic leukemia.⁵⁻⁸ The process of CAR T therapy begins with

T cells collected from the patient.⁹ The autologous T cells are then expanded *in vitro* and transduced with the CAR gene using a retroviral vector. Finally, the CAR-modified T cells are infused back into the patient. The therapeutic value of CARs arises from the ability to incorporate binding domains for tumor-specific targets, such as the B cell maturation antigen (BCMA) expressed on myeloma cells.¹⁰ Upon antigen binding, the CAR sends an internal activation signal to induce T cell response.

There are currently 2 FDA-approved CAR T cell therapies. Tisagenlecleucel is indicated for the treatment of select patients with B-cell precursor ALL that is refractory or in the second or later relapse and in patients with relapsed or refractory large B-cell lymphoma.¹¹ Axicabtagene ciloleucel is indicated for the treatment of adults with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy.¹² Both of these CAR T therapies have black box warnings for cytokine release syndrome (CRS) and neurological toxicities.¹¹⁻¹²

Sagar Lonial, MD, reviews recent data from clinical trials investigating CAR-T therapies for the treatment of MM and the potential impact of CAR-T therapy on the clinical management of patients with MM in the near future.

Q: What is the rationale for using CAR T-cell therapy as a treatment strategy for MM?

LONIAL: It is clear that in the

context of refractory myeloma, new treatment approaches and targets are needed. Many of the available treatments have worked for a long time but are no longer effective in these patients. The idea of using the patient's immune cells as a way to target myeloma is an attractive therapeutic strategy in this situation. CAR T cells allow the patient to use their own immune system, with some help, to attack the myeloma. I think this is an exciting treatment approach for MM, especially in the refractory setting.

Q: What are the advantages of using a CAR for targeting myeloma cells compared to its native T-cell receptor counterpart for the treatment of MM?

LONIAL: We know that there may be host anti-myeloma T cells, but many of those T cells are either suppressed or eliminated as the disease grows. What is unique about the CAR T-cell construct is that BCMA, for instance, which is currently the most common CAR T-cell target that we use, is unique to plasma cells and represents a good, selective target.¹⁰ While there may be host immune cells, including T cells, that do have some anti-myeloma effects, they are either eliminated or not available. This makes something like BCMA-targeted T cells far more effective.

Q: What are the key criteria that determine whether a patient with MM is eligible

to receive CAR T therapy?

LONIAL: Many of the trials that use CAR T cells have varying eligibility criteria. The easiest trials to get into right now are those enrolling patients with refractory myeloma who have progressed on anti-CD38 antibodies and proteasome inhibitors and do not have another available treatment option.³ There are certainly several trials that are looking at first relapse and second relapse that are currently ongoing (**Table 1**). If we are fortunate to have an approval of a CAR T-cell therapy in myeloma in this year, it will likely be in the setting of refractory myeloma with a median of 4 to 5 prior lines of therapy; those are the trials that are furthest along and have been reported to date.

Q: What are some of the latest key findings from clinical trials investigating CAR T-cell therapy for patients with MM?

LONIAL: One of the key pieces of information that is beginning to come out now with longer follow-up is that patients who achieve deep responses, whether it is early complete remission (ie, within 30 days) or minimal residual disease (MRD)-negative complete remission between 3 and 6 months following treatment, seem to have very long durations of remission. It appears at least from early data that the median progression-free survival (PFS) is somewhere between 9 and 12 months, depending upon which product you look at, which will proba-

TABLE 1. Select Investigational BCMA-Targeted CAR T-Cell Therapies for MM

Investigational agent	Clinical trial identifier	Key eligibility criteria	Preliminary efficacy	Preliminary safety
Bb2121 ¹⁶	NCT02658929	R/R MM following ≥3 prior lines of therapy	N = 33 ORR, 85% CR, 45%	Grade ≥3 AEs: neutropenia (85%), leukopenia (58%), anemia (45%), thrombocytopenia (45%).
	NCT03651128 (phase 3 KarMMa-3 study)	R/R MM	NR	NR
LCAR-B38M ^{13,17}	NCT03090659 phase 1/2	R/R MM	N = 17 ORR, 88% CR, 76%	Grade ≥3 AEs: fever (47%), elevated AST (24%)
	NCT03758417 phase 2	R/R MM	N = 57 ORR, 88% CR, 74%	Grade ≥3 AEs: leukopenia (30%), thrombocytopenia (23%), elevated AST (21%), CRS (7%)
	NCT04133636 phase 2	Newly-diagnosed and R/R MM	NR	NR
Orvacabtagene autoleucel ¹⁸ (formerly JCARH125)	NCT03430011 (phase 1/2 EVOLVE study)	R/R MM	N = 44 ORR, 91% CR, 39%	Grade ≥3 AEs: neutropenia (55%), thrombocytopenia (44%), anemia (21%)

AE, adverse event; AST, aspartate aminotransferase; CR, complete response; NR, not reported; ORR, overall response rate; R/R, relapsed or refractory.

bly be relatively stable. In fact, interim data from an ongoing study evaluating LCAR-B38M in China reported that patients achieving MRD-negative complete remission have ongoing remission durations of greater than 2 years.¹³ Essentially, not only can we achieve responses with CAR T cells, but trying to figure out how to increase the fraction of patients that achieve MRD-negative complete remission between 3 and 6 months is likely to help patients have better long-term outcomes.

Q: In patients with MM who relapse after initially responding to CAR T therapy, which factors would you consider in determining the most appropriate subsequent therapy?

LONIAL: If patients relapse post-CAR T-cell therapy, the first question I have in my mind is, are there still CAR T cells present in the blood? And if there are, is there a way to turn on those CAR T cells that may have been “put to sleep,” if you will, or exhausted through antitumor mechanisms that exist within the body? And in that situation, we will think about using PD-1 inhibition or immunomodulatory agents. There have been case reports, and we have had patients who have re-responded when we take that approach in the context of relapse post-CAR T-cell therapy. If a patient does not have CAR T cells present in the blood, then we are looking for a different target, perhaps something new, in a phase 1 or phase 2 study, or another way to target BCMA. One of

the things that is somewhat unique in myeloma and different from ALL is that most CAR T cell failures do not lose expression of BCMA, whereas many patients with progressing ALL lose CD19 expression.¹⁴ Using a BCMA-targeted approach from another treatment, whether it’s an antibody-drug conjugate or it’s a bio-specific, may be a different option in that situation.

Q: What are some clinical best practices in mitigating CRS and neurotoxicity in patients receiving CAR T therapy?

LONIAL: One of the first things to note is that the incidence of severe CRS and severe neurotoxicity in patients with MM and patients receiving BCMA-directed CAR T cells

is much lower than in the CD19 experience that we have seen in ALL and large-cell lymphoma. While it is an issue, there is certainly a much lower frequency of severe toxicities than for those other diseases. However, the keys are early and quick intervention. There does not appear to be a downside to giving tocilizumab early in patients who have grade 1 or 2 CRS. Patients who develop neurotoxicity, while it is a rare event, can also respond to early intervention. Whether it is using steroids or other immunomodulators, intervening early is the best way to prevent severe grades of CRS and neurotoxicity.

Q: What is the rationale for key emerging targets of novel CAR-T therapies that are being

evaluated in early-phase clinical trials for the treatment of MM?

LONIAL: Other targets are being evaluated as CAR T-cell targets in addition to BCMA. Some of them are traditional myeloma targets like SLAMF7, CD38, or CD138.⁴ The disadvantages that those 3 have is that their expression is not unique to plasma cells, which makes it possible to have on-target, off-tumor effects if those CAR T cells were highly effective. While they may not be the optimal targets, they are being evaluated by a number of different groups around the world. A new and emerging target that many groups are interested in is known as GPRC5D (also called SCRHS).¹⁵ This target is relatively specific to plasma cells and may represent a dual-targeting strategy together with BCMA or a highly effective single target for MM. They are in very early stages of identifying immune targets for MM beyond BCMA.

Q: Which patients with MM would you consider recommending clinical trial enrollment for CAR-T therapy?

LONIAL: In our center, we evaluate clinical trial eligibility for every patient that walks in the door, no matter what stage of treatment or disease they have. But currently, the patients that are probably best-suited for a CAR T-cell trial are those that are triple-class refractory. Recognizing that we do have trials in first relapse, second relapse, and third relapse comparing more standard

approaches with CAR T cells in the hopes that earlier use of CAR T cells may translate into better complete response rates and longer durations of remission. But that is something we have to test and has not yet been clearly proven.

Q: In what ways do you anticipate CAR T therapy being integrated into the standard of care for MM? Can CAR T therapy potentially replace HCT?

LONIAL: I think that CAR T cells being brought earlier and earlier into the disease course makes sense, especially since, being a live immune therapy, there is the potential to induce a group of memory T cells that might last longer than the life of that original CAR T cell. This induction might lead to longer-term surveillance and suppression of myeloma than with many traditional therapies, where once the treatment is stopped, the myeloma has an opportunity to grow again. The ideal situations to use this kind of treatment are still being defined. For instance, in a patient with low-level disease positivity, trying to wipe that out with a CAR T cell certainly makes a lot of sense. Ongoing trials are comparing induction therapy and transplant versus CAR T-cell therapy as consolidation with a short period of maintenance for both. Those trials will help answer the question about the optimal time and place for a CAR T cell. It is our hope that the earlier use of CAR T cells will result in longer remission because the

health of the T cells from the donor may be better earlier in the disease course, but this remains unknown. The only way to answer those questions is through well-designed trials to see whether CAR T cells can, in fact, be more effective earlier in the disease course and ultimately replace HCT. ■

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➤ For full reference list, visit <https://www.gotoper.com/go/cart20mm-print>

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