ONCOLOGY® MAY 2024 VOL 38 NO 5

RECTAL CANCER | THORACIC SURGERY | GYNECOLOGIC MALIGNANCIES

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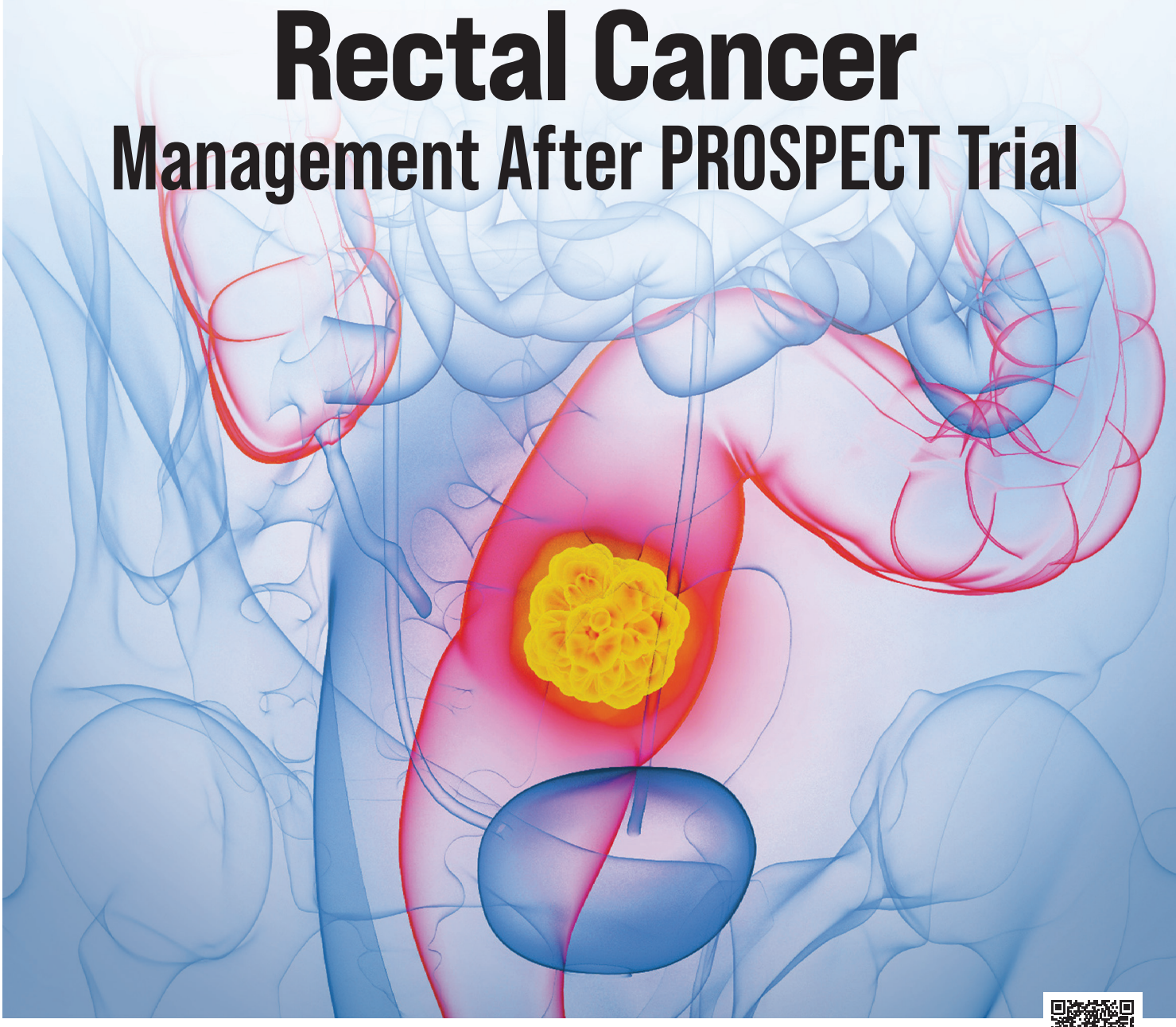
PRACTICAL, PEER-REVIEWED PERSPECTIVES
MAY 2024 | Vol 38 • No 5

Rectal Cancer
Management After PROSPECT Trial



Case Study
Synchronous Well-Differentiated Papillary Mesothelioma and Endometrioid Adenocarcinoma Arising From Endometriosis

Interview
Forging a Path in Thoracic Surgery to Create a Stellar Career

Hot Topics
AI Use for Potential Improvements in Treatments and Patient Care

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EGFR+ mNSCLC WILL FIND THE BACK ROADS

Despite advancements, *EGFR*+ mNSCLC still outmaneuvers today's strategies, leaving patients with limited PFS and at risk of disease progression.[1-8]

Staying ahead of *EGFR*+ mNSCLC is important

25% to 39% of patients with *EGFR*+ mNSCLC never receive 2L therapy, according to multiple studies.[9-11]

Range includes patients who died or discontinued the assigned therapy without receiving 2L therapy during follow-up.

Burden of *EGFR*+ mNSCLC mutations limits survival

Less than **one-fifth of patients** with *EGFR*+ mutations in mNSCLC will survive 5 years, as demonstrated by real-world data.[12]

Based on a real-world analysis of 2,833 adult patients with confirmed *EGFR* mutations treated with a 1st-, 2nd-, and 3rd-generation EGFR TKI in the advanced NSCLC Flatiron registry EHR database between January 1, 2011, and May 21, 2020.[12]

2L, second line; *EGFR*+, mutations in epidermal growth factor receptor; EHR, electronic health records; MET, mesenchymal-epithelial transition; mNSCLC, metastatic non-small cell lung cancer; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Acquired resistance drives disease progression[8]

up to 50%

MET amplification is a common mechanism of off-target acquired resistance to 3rd-generation EGFR TKIs, accounting for **up to 50% of all cases.**[8,13-16]*

*The detection rate of *MET* amplification can differ based on the sensitivity of the employed testing method and the specific cutoff point in each study.

Learn more about the **unmet need in patients with *EGFR*+ mNSCLC** by visiting **EGFRRoutes.com** or **scanning the QR code.**

References: 1. Sequist LV, Yang JC-H, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with *EGFR* mutations. *J Clin Oncol*. 2013;31(27):3327-3334. **2.** Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13(3):239-246. **3.** Wu Y-L, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with *EGFR*-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(11):1454-1466. **4.** Park K, Tan E-H, O'Byrne K, et al. Afatinib versus gefitinib as first-line treatment of patients with *EGFR*-mutation-positive non-small-cell lung cancer (LUX-Lung7): a phase 2B, open-label, randomised, controlled trial. *Lancet Oncol*. 2016;17(5):577-589. **5.** Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated *EGFR*-mutated non-small-cell lung cancer. *N Engl J Med*. 2018;378(2):113-125. **6.** Saito H, Fukuhara T, Furuya N, et al. Erlotinib plus bevacizumab versus erlotinib alone in patients with *EGFR*-positive advanced non-squamous non-small-cell lung cancer (NEJ026): an interim analysis of an open label, randomised, multicentre, phase 3 trial. *Lancet Oncol*. 2019;20(5):625-636. **7.** Nakagawa K, Garon EB, Seto T, et al. Ramucirumab plus erlotinib in patients with untreated, *EGFR*-mutated, advanced, non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol*. 2019;20(12):1655-1669. **8.** Passaro A, Jänne PA, Mok T, Peters S. Overcoming therapy resistance in *EGFR*-mutant lung cancer. *Nat Cancer*. 2021;2(4):377-391. **9.** Nieva J, Kari PS, Okhuoya P, et al. A real-world (rw) observational study of long-term survival (LTS) and treatment patterns after first-line (1L) osimertinib in patients (pts) with epidermal growth factor receptor (EGFR) mutation-positive (m) advanced non-small-cell lung cancer (abstract). *Ann Oncol*. 2023. Abstract 1344P. **10.** Lee JY, Mai V, Garcia M, et al. Treatment patterns and outcomes of first-line osimertinib-treated advanced *EGFR*-mutated NSCLC patients: a real-world study (abstract). Presented at: IASLC 2022 World Lung Conference on Lung Cancer; August 6-9, 2022; Vienna, Austria. Abstract EP08.02-082. **11.** Girard N, Leighl NB, Ohe Y, et al. Mortality among *EGFR*-mutated advanced NSCLC patients after starting first-line osimertinib treatment: a real-world, US attrition analysis. Poster presented at: the European Lung Cancer Congress; March 29-April 1, 2023; Copenhagen, Denmark. **12.** Bazhenova L, Minchom A, Viteri S, et al. Comparative clinical outcomes for patients with advanced NSCLC harboring *EGFR* exon 20 insertion mutations and common *EGFR* mutations. *Lung Cancer*. 2021;162:154-161. **13.** Leonetti A, Sharma S, Minari R, et al. Resistance mechanisms to osimertinib in *EGFR*-mutated non-small-cell lung cancer. *Br J Cancer*. 2019;121(9):725-737. **14.** Yu HA, Kerr K, Rolfo CD, et al. Detection of MET amplification (MET amp) in patients with *EGFR* mutant (m) NSCLC after first-line (1L) osimertinib (abstract). 2023 American Society of Clinical Oncology Annual Meeting. June 2-6, 2023; Chicago, IL. Abstract 9074. **15.** Ramalingam SS, Zhang N, Yu J, et al. Real-world landscape of *EGFR* C797X mutation as a resistance mechanism to osimertinib in non-small-cell lung cancer (abstract). *J Thorac Oncol*. 2022;17(9S):S670S68. Abstract MA07.13. **16.** Besse B, Baik CS, Marmarelis ME, et al. Predictive biomarkers for treatment with amivantamab plus lazertinib among *EGFR*-mutated NSCLC in the post-osimertinib setting: analysis of tissue IHC and ctDNA NGS (abstract). 2023 American Society of Clinical Oncology Annual Meeting. June 2-6, 2023; Chicago, IL. Abstract 9013.

Our Board Members Have Been Busy! Take a look to see what they've been up to.

ONCOLOGY is highlighting 2 editorial advisory board members who have accomplished various achievements in their fields. See how Matthew J. Matasar, MD, MS, and María T. Bourlon, MD, Mac, have beend doing to help advance the field of oncology.

Matthew J. Matasar, MD, MS
Cancer Survivorship Editorial Board Member
Matasar has been given the 2024 Leukemia and Lymphoma Society Quality of Life Award. The award was designed to be given to someone in the medical community, a patient, or caregiver who has supported the community and continues to push the needle forward. Congratulations, Dr. Matasar!

María T. Bourlon, MD, Mac
Genitourinary Cancer Editorial Board Member
Bourlon was the principal author of the article "Envisioning academic global oncologists: proposed competencies for global oncology training from ASCO" published in the Journal of Clinical Oncology. The aim was to help create equitable cancer care by formalizing the training of oncologists across the world.

Call for Reviewers and Papers

ONCOLOGY is seeking to expand its list of ad hoc reviewers to provide constructive feedback on manuscripts that have received initial editorial approval. Comments and criticisms are a necessary and invaluable part of the journal's process, and our need for more willing experts grows in step with the journal.

We are also seeking to expand coverage of original peer-reviewed research articles and are now encouraging authors to submit high-quality original manuscripts about clinical trials and investigations.

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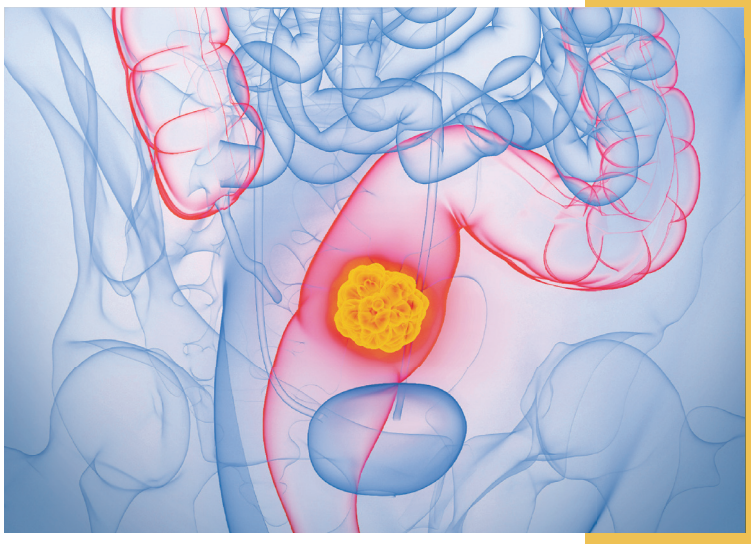

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Complementary and Alternative Medicine in Cancer Care: **Does It Have a Role?**

Julie M. Vose, MD, MBA,
Chief, Hematology/Oncology, Buffett Cancer Center, University of Nebraska Medical Center, Omaha, NE

Frequently patients with cancer ask about alterations in their lifestyle, taking vitamins or supplements, or other treatments or practices that will improve their outcome following a cancer diagnosis. *Complementary and alternative medicine* (CAM) is a term for medical products and/or practices that are not part of standard medical care. However, CAM may be used as an adjunct in cancer care to overcome adverse effects of cancer treatments such as nausea, pain, or fatigue. In addition, CAM may ease the worries about cancer treatments and related stress. Patients often feel they are being an active participant in their cancer care when using CAM treatments.

Other common terms include *integrative* or *complementary medicine*. Both are approaches that combine conventional medicine with CAM approaches that have been shown through science and clinical trials to be safe and effective. Alternative medicine, on the other hand, is the practice of using a treatment or approach instead of standard medical treatments. Types of CAM often fit into 5 categories (**Figure**).[1]

Some CAM therapies have undergone careful evaluation and been found to be generally safe and effective. These include acupuncture, yoga, and meditation.[2] However, others either do not work or are directly harmful, so caution is important. Often CAM therapies might use botanicals or nutritional products that are not FDA approved or used in much higher doses than normal.[3] These need to be monitored for safety and interactions with standard medications and anticancer treatments.

Figure. 5 categories of complimentary and alternative medicine

1. Mind-body therapies: Using tools such as meditation, biofeedback, hypnosis, yoga, tai chi, imagery, or creative outlets such as art, music, or dance.[1]
2. Biologically based practices: Using things found in nature such as vitamins, dietary supplements, botanicals, or special foods or diets.
3. Manipulative and body-based practices: These can include massage therapy, chiropractic therapy, or reflexology.
4. Energy healing: Based on a belief that vital energy flows through the body. The goal is to balance the energy in a patient. Examples are reiki or therapeutic touch.
5. Whole medical systems: Healing systems and beliefs that are used in some parts of the world. Examples are Ayurvedic medicine, traditional Chinese medicine, and naturopathic medicine.

A recent example from my practice was a patient taking turmeric who had liver function tests that were suddenly 5 times normal without any other explanation. Scans and multiple other labs found no reason for the elevated liver function tests, but when the turmeric was stopped, the liver functions rapidly went back to normal. Although this toxicity is rare, it did lead to additional testing, expense, and worry for this patient.

There is an important effort occurring to try to integrate proven complementary approaches to traditional cancer care. The Society for Integrative Oncology has issued evidence-based clinical practice guidelines for health care providers to consider when incorporating complementary health approaches in the care of patients with cancer. An important guideline includes not using unproven methods in place of conventional treatment for the cancer, as this may delay the scientifically-based treatment and reduce the likelihood of a remission or cure.

The bottom line is, first, do no harm. Working with the patient as a team to fight their cancer is of utmost importance. If the patient can use CAM approaches that are safe and found to be effective in clinical trials as a supportive measure, the outcome will hopefully be a positive one for the patient and the medical team. The National Institutes of Health sponsors ongoing studies to evaluate complementary approaches through the National Cancer Institute and the National Center for Complementary and Integrative Health. ■

FOR REFERENCES VISIT
cancernetwork.com/5.24_LTR

Jemperli
(dostarlimab-gxly) Injection 500 mg

The First Immunotherapy Approved in Combination With Carboplatin and Paclitaxel to Treat dMMR/MSI-H Primary Advanced or Recurrent Endometrial Cancer

Learn more about JEMPERLI at JEMPERLIHCP.com

INDICATIONS

- JEMPERLI, in combination with carboplatin and paclitaxel, followed by JEMPERLI as a single agent, is indicated for the treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) that is mismatch repair deficient (dMMR), as determined by an FDA-approved test, or microsatellite instability-high (MSI-H).
- JEMPERLI, as a single agent, is indicated for the treatment of adult patients with dMMR recurrent or advanced EC, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen in any setting and are not candidates for curative surgery or radiation.

IMPORTANT SAFETY INFORMATION

Severe and Fatal Immune-Mediated Adverse Reactions

- Immune-mediated adverse reactions, which can be severe or fatal, can occur in any organ system or tissue and can occur at any time during or after treatment with a PD-1/PD-L1–blocking antibody, including JEMPERLI.
- Monitor closely for signs and symptoms of immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function tests at baseline and periodically during treatment. For suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.
- Based on the severity of the adverse reaction, withhold or permanently discontinue JEMPERLI. In general, if JEMPERLI requires interruption or discontinuation, administer systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until improvement to ≤Grade 1. Upon improvement to ≤Grade 1, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids.

Immune-Mediated Pneumonitis

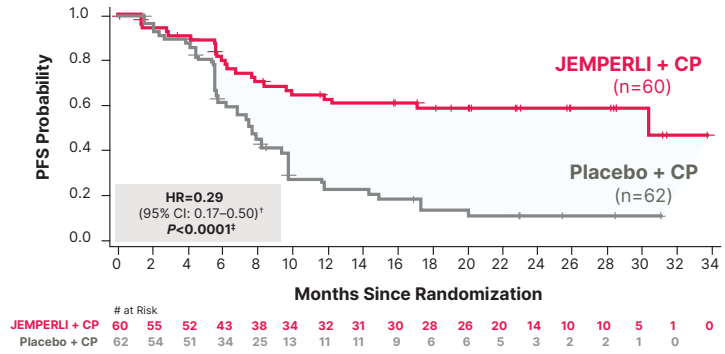
- JEMPERLI can cause immune-mediated pneumonitis, which can be fatal. In patients treated with other PD-1/PD-L1–blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Pneumonitis occurred in 2.3% (14/605) of patients, including Grade 2 (1.3%), Grade 3 (0.8%), and Grade 4 (0.2%) pneumonitis.

RUBY was a randomized, multicenter, double-blind, placebo-controlled clinical trial, with a median efficacy follow-up of 25 months[1,2]

- Patients in the study had primary FIGO Stage III or Stage IV endometrial cancer including patients with aggressive histologies, or first recurrent endometrial cancer with a low potential for cure by radiation therapy or surgery alone or in combination[1]
- Patients were randomized 1:1 into 2 treatment arms. Experimental group received 500 mg of JEMPERLI + CP IV Q3W for 6 doses, followed by 1000 mg of JEMPERLI monotherapy IV Q6W beginning with dose 7. Control group received placebo + CP IV Q3W for 6 doses, followed by placebo IV Q6W beginning with dose 7[1]
  - Treatment with JEMPERLI continued until disease progression, unacceptable toxicity, or a maximum of 3 years[1]
  - The randomization was stratified by MMR/MSI status, prior external pelvic radiotherapy, and disease status[1]
- Efficacy was assessed in a pre-specified subgroup of 122 patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer[1]
- RUBY trial had a major efficacy outcome of PFS* with additional efficacy outcomes of OS, ORR, and DOR in the dMMR/MSI-H EC subgroup[1]

In the dMMR/MSI-H endometrial cancer JEMPERLI + CP arm: Groundbreaking 71% reduction in the risk of progression or death vs CP alone[1]*

Superior PFS with JEMPERLI + CP vs CP alone in the dMMR/MSI-H primary advanced or recurrent endometrial cancer subgroup (n=122)[1]*



Median PFS[1]*‡

30.3 **months with JEMPERLI + CP** (95% CI: 11.8–NR)

7.7 **months with Placebo + CP** (95% CI: 5.6–9.7)

- OS data in this subgroup were immature with 27% deaths[1]

* PFS per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by investigator.[1] † Based on stratified Cox regression model.[1] ‡ One-sided *P*-value based on stratified log-rank test was statistically significant.[1]

CI, confidence interval; **CP**, carboplatin-paclitaxel; **dMMR**, mismatch repair deficient; **DOR**, duration of response; **EC**, endometrial cancer; **HR**, hazard ratio; **IV**, intravenous; **MSI-H**, microsatellite instability-high; **NR**, not reached; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **Q3W**, every 3 weeks; **Q6W**, every 6 weeks.

IMPORTANT SAFETY INFORMATION (CONT'D)

Immune-Mediated Colitis

- Colitis occurred in 1.3% (8/605) of patients, including Grade 2 (0.7%) and Grade 3 (0.7%) adverse reactions. Cytomegalovirus infection/reactivation have occurred in patients with corticosteroid-refractory immune-mediated colitis. In such cases, consider repeating infectious workup to exclude alternative etiologies.

Immune-Mediated Hepatitis

- JEMPERLI can cause immune-mediated hepatitis, which can be fatal. Grade 3 hepatitis occurred in 0.5% (3/605) of patients.

Immune-Mediated Endocrinopathies

- Adrenal Insufficiency
  - Adrenal insufficiency occurred in 1.2% (7/605) of patients, including Grade 2 (0.5%) and Grade 3 (0.7%). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment per institutional guidelines, including hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.
- Hypophysitis
  - JEMPERLI can cause immune-mediated hypophysitis. Grade 3 hypophysitis occurred in 0.4% (1/241) of patients receiving JEMPERLI in combination with carboplatin and paclitaxel. Grade 2 hypophysitis occurred in 0.2% (1/605) of patients receiving JEMPERLI as a single agent. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.

Please see additional Important Safety Information on the following pages.
Please see Brief Summary of Prescribing Information for JEMPERLI on the following pages.

Jemperli (dostarlimab-gxly) Injection 500 mg

JEMPERLI + CP has an established safety profile with over 2 years of efficacy follow-up[1,2]

15% of patients receiving JEMPERLI + CP permanently discontinued JEMPERLI due to ARs[1]

- ARs leading to discontinuation were reported in 8 patients, including 1 case each of rash maculo-papular, fatigue, general physical health deterioration, acute kidney injury, infusion-related reaction, keratitis, muscular weakness, and myelosuppression[1]
- The most common ARs, including laboratory abnormalities (≥20%), were decreased hemoglobin, decreased white blood cell count, decreased platelets, decreased lymphocytes, increased glucose, increased alkaline phosphatase, decreased neutrophils, rash, diarrhea, increased aspartate aminotransferase, increased alanine aminotransferase, decreased sodium, hypothyroidism, and hypertension[1]
- Serious ARs occurred in 13% of patients receiving JEMPERLI + CP; the most common serious AR was sepsis, including urosepsis (6%)[1]
- Fatal ARs occurred in 6% of patients receiving JEMPERLI including septic shock (3.8%) and myelosuppression (1.9%)[1]

AR, adverse reaction; **CP**, carboplatin-paclitaxel.

IMPORTANT SAFETY INFORMATION (CONT'D)

Immune-Mediated Endocrinopathies (cont'd)

- Thyroid Disorders
  - Grade 2 thyroiditis occurred in 0.5% (3/605) of patients. Grade 2 hypothyroidism occurred in 12% (28/241) of patients receiving JEMPERLI in combination with carboplatin and paclitaxel. Grade 2 hypothyroidism occurred in 8% (46/605) of patients receiving JEMPERLI as a single agent. Hyperthyroidism occurred in 3.3% (8/241) of patients receiving JEMPERLI in combination with carboplatin and paclitaxel, including Grade 2 (2.9%) and Grade 3 (0.4%). Hyperthyroidism occurred in 2.3% (14/605) of patients receiving JEMPERLI as a single agent, including Grade 2 (2.1%) and Grade 3 (0.2%). Initiate thyroid hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.
- Type 1 Diabetes Mellitus, Which Can Present with Diabetic Ketoacidosis
  - JEMPERLI can cause type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Grade 3 type 1 diabetes mellitus occurred in 0.4% (1/241) of patients receiving JEMPERLI in combination with carboplatin and paclitaxel. Grade 3 type 1 diabetes mellitus occurred in 0.2% (1/605) of patients receiving JEMPERLI as a single agent. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.

Immune-Mediated Nephritis with Renal Dysfunction

- JEMPERLI can cause immune-mediated nephritis, which can be fatal. Grade 2 nephritis, including tubulointerstitial nephritis, occurred in 0.5% (3/605) of patients.

Immune-Mediated Dermatologic Adverse Reactions

- JEMPERLI can cause immune-mediated rash or dermatitis. Bullous and exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS), have occurred with PD-1/PD-L1–blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes. Withhold or permanently discontinue JEMPERLI depending on severity.

Other Immune-Mediated Adverse Reactions

- The following clinically significant immune-mediated adverse reactions occurred in <1% of the 605 patients treated with JEMPERLI or were reported with the use of other PD-1/PD-L1–blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.
  - *Nervous System:* Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy
  - *Cardiac/Vascular:* Myocarditis, pericarditis, vasculitis

IMPORTANT SAFETY INFORMATION (CONT'D)

Other Immune-Mediated Adverse Reactions (cont'd)

- *Ocular:* Uveitis, iritis, other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur
- *Gastrointestinal:* Pancreatitis, including increases in serum amylase and lipase levels, gastritis, duodenitis
- *Musculoskeletal and Connective Tissue:* Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica
- *Endocrine:* Hypoparathyroidism
- *Other (Hematologic/Immune):* Autoimmune hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenia, solid organ transplant rejection, other transplant (including corneal graft) rejection

Infusion-Related Reactions

- Severe or life-threatening infusion-related reactions have been reported with PD-1/PD-L1–blocking antibodies. Severe infusion-related reactions (Grade 3) occurred in 0.2% (1/605) of patients receiving JEMPERLI. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion or permanently discontinue JEMPERLI based on severity of reaction.

Complications of Allogeneic HSCT

- Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after treatment with a PD-1/PD-L1–blocking antibody, which may occur despite intervening therapy. Monitor patients closely for transplant-related complications and intervene promptly.

Embryo-Fetal Toxicity and Lactation

- Based on its mechanism of action, JEMPERLI can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI and for 4 months after their last dose. Because of the potential for serious adverse reactions from JEMPERLI in a breastfed child, advise women not to breastfeed during treatment with JEMPERLI and for 4 months after their last dose.

Common Adverse Reactions

The most common adverse reactions (≥20%) in patients with dMMR/MSI-H EC who received JEMPERLI in combination with carboplatin and paclitaxel were rash, diarrhea, hypothyroidism, and hypertension. The most common Grade 3 or 4 laboratory abnormalities (≥10%) were decreased neutrophils, decreased hemoglobin, decreased white blood cell count, decreased lymphocytes, increased glucose, decreased sodium, and decreased platelets.

The most common adverse reactions (≥20%) in patients with dMMR EC who received JEMPERLI as a single agent were fatigue/asthenia, anemia, nausea, diarrhea, constipation, vomiting, and rash. The most common Grade 3 or 4 laboratory abnormalities (>2%) were decreased lymphocytes, decreased sodium, increased alanine aminotransferase, increased creatinine, decreased neutrophils, decreased albumin, and increased alkaline phosphatase.

References: 1. JEMPERLI. Prescribing Information. GSK; 2024. **2.** Mirza MR, et al. *N Engl J Med.* 2023;388(23):2145–2158.

Please see additional Important Safety Information on the previous pages.
Please see Brief Summary of Prescribing Information for JEMPERLI on the following pages.

Jemperli
(dostarlimab-gxly) Injection 500 mg

BRIEF SUMMARY

JEMPERLI
(dostarlimab-gxly) injection, for intravenous use

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

1.1 Endometrial Cancer

JEMPERLI, in combination with carboplatin and paclitaxel, followed by JEMPERLI as a single agent, is indicated for the treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) that is mismatch repair deficient (dMMR), as determined by an FDA-approved test, or microsatellite instability-high (MSI-H) *[see Dosage and Administration (2.1) of full prescribing information]*.

JEMPERLI, as a single agent, is indicated for the treatment of adult patients with dMMR recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen in any setting and are not candidates for curative surgery or radiation *[see Dosage and Administration (2.1) of full prescribing information].*

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

JEMPERLI is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance, and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed in WARNINGS AND PRECAUTIONS may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which can be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting a PD-1/PD-L1–blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1–blocking antibodies, they can also manifest after discontinuation of PD-1/PD-L1–blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1–blocking antibodies. Monitor closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function tests at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue JEMPERLI depending on severity *[see Dosage and Administration (2.3) of full prescribing information].* In general, if JEMPERLI requires interruption or discontinuation, administer systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies, dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

JEMPERLI can cause immune-mediated pneumonitis, which can be fatal. In patients treated with other PD-1/PD-L1–blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-mediated pneumonitis occurred in 2.3% (14/605) of patients receiving JEMPERLI, including Grade 2 (1.3%), Grade 3 (0.8%) and Grade 4 (0.2%) pneumonitis. Pneumonitis led to discontinuation of JEMPERLI in 1.3% of patients.

Systemic corticosteroids were required in 79% (11/14) of patients with pneumonitis. Pneumonitis resolved in 11 of the 14 patients. JEMPERLI was withheld for 9 patients. Five patients reinitiated JEMPERLI after symptom improvement; of these, 2 patients had recurrence of pneumonitis.

Immune-Mediated Colitis

JEMPERLI can cause immune-mediated colitis. Cytomegalovirus infection/reactivation have occurred in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1–blocking antibodies. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-mediated colitis occurred in 1.3% (8/605) of patients receiving JEMPERLI, including Grade 2 (0.7%) and Grade 3 (0.7%) adverse reactions. Colitis led to discontinuation of JEMPERLI in 1 (0.2%) patient.

Systemic corticosteroids were required in 75% (6/8) of patients with colitis. Colitis resolved in 5 of the 8 patients. Of the 4 patients in whom JEMPERLI was withheld for colitis, all reinitiated treatment with JEMPERLI; of these, 1 patient had recurrence of colitis.

Immune-Mediated Hepatitis

JEMPERLI can cause immune-mediated hepatitis, which can be fatal.

Immune-mediated hepatitis occurred in 0.5% (3/605) of patients receiving JEMPERLI, all were Grade 3. Hepatitis led to discontinuation of JEMPERLI in 1 (0.2%) patient. Systemic corticosteroids were required in 2 patients with hepatitis and the events resolved in 2 of the 3 patients.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency: JEMPERLI can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment per institutional guidelines, including hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity *[see Dosage and Administration (2.3) of full prescribing information].*

Adrenal insufficiency occurred in 1.2% (7/605) patients receiving JEMPERLI, including Grade 2 (0.5%) and Grade 3 (0.7%).

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5.1 Severe and Fatal Immune-Mediated Adverse Reactions *(cont'd)*

Adrenal insufficiency resulted in discontinuation in 1 (0.2%) patient and resolved in 4 of the 7 patients. Of the 4 patients in whom JEMPERLI was withheld for adrenal insufficiency, all reinitiated treatment with JEMPERLI. Systemic corticosteroids were required in 5 of the 7 patients with adrenal insufficiency.

Hypophysitis: JEMPERLI can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity *[see Dosage and Administration (2.3) of full prescribing information]*.

JEMPERLI in Combination with Carboplatin and Paclitaxel: Hypophysitis (Grade 3) occurred in 0.4% (1/241) of patients receiving JEMPERLI in combination with carboplatin and paclitaxel. Systemic corticosteroids were required and the event resolved. JEMPERLI was withheld and the patient reinitiated treatment.

JEMPERLI as a Single Agent: Hypophysitis (Grade 2) occurred in 0.2% (1/605) of patients receiving JEMPERLI as a single agent. Systemic corticosteroids were required and the event did not resolve. JEMPERLI was withheld and the patient reinitiated treatment.

Thyroid Disorders: JEMPERLI can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate thyroid hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity *[see Dosage and Administration (2.3) of full prescribing information].*

Thyroiditis: Thyroiditis occurred in 0.5% (3/605) of patients receiving JEMPERLI; all were Grade 2. Systemic corticosteroids were required in 1 of 3 patients and anti-thyroid therapy was required for 2 of 3 patients with thyroiditis. JEMPERLI was withheld for 1 patient and the patient reinitiated treatment. None of the events of thyroiditis resolved; there were no discontinuations of JEMPERLI due to thyroiditis.

Hypothyroidism: JEMPERLI in Combination with Carboplatin and Paclitaxel: Hypothyroidism occurred in 12% (28/241) of patients receiving JEMPERLI in combination with carboplatin and paclitaxel, all of which were Grade 2. Hypothyroidism led to discontinuation of JEMPERLI in 1 patient and resolved in 18% (5/28) of patients. JEMPERLI was withheld for 5 patients and all reinitiated treatment with JEMPERLI. Thyroid hormone replacement was required for 26 of the 28 patients with hypothyroidism.

JEMPERLI as a Single Agent: Hypothyroidism occurred in 8% (46/605) of patients receiving JEMPERLI as a single agent, all of which were Grade 2. Hypothyroidism did not lead to discontinuation of JEMPERLI and resolved in 37% (17/46) of patients. JEMPERLI was withheld for 2 patients and both reinitiated treatment. Thyroid hormone replacement therapy was required for 45 of the 46 patients with hypothyroidism.

Hyperthyroidism: JEMPERLI in Combination with Carboplatin and Paclitaxel: Hyperthyroidism occurred in 3.3% (8/241) of patients receiving JEMPERLI in combination with carboplatin and paclitaxel, including Grade 2 (2.9%) and Grade 3 (0.4%). Hyperthyroidism did not lead to discontinuation of JEMPERLI and resolved in 63% (5/8) of patients. JEMPERLI was withheld for 1 patient and the patient reinitiated treatment. Anti-thyroid therapy was required for 2 of the 8 patients while systemic corticosteroids were required for 1 of the 8 patients with hyperthyroidism.

JEMPERLI as a Single Agent: Hyperthyroidism occurred in 2.3% (14/605) of patients receiving JEMPERLI as a single agent, including Grade 2 (2.1%) and Grade 3 (0.2%). Hyperthyroidism did not lead to discontinuation of JEMPERLI and resolved in 71% (10/14) of the 14 patients. JEMPERLI was withheld for 2 patients and both reinitiated treatment. Anti-thyroid therapy was required for 10 of the 14 patients with hyperthyroidism.

Type 1 Diabetes Mellitus, Which Can Present with Diabetic Ketoacidosis: JEMPERLI can cause type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity *[see Dosage and Administration (2.3) of full prescribing information].*

JEMPERLI in Combination with Carboplatin and Paclitaxel: Type 1 diabetes mellitus (Grade 3) occurred in 0.4% (1/241) of patients receiving JEMPERLI in combination with carboplatin and paclitaxel. Type 1 diabetes mellitus led to withholding JEMPERLI; the patient reinitiated treatment and required long-term insulin therapy.

JEMPERLI as a Single Agent: Type 1 diabetes mellitus occurred in 0.2% (1/605) of patients receiving JEMPERLI as a single agent, which was Grade 3. Type 1 diabetes mellitus did not result in treatment discontinuation and did not resolve.

Immune-Mediated Nephritis with Renal Dysfunction

JEMPERLI can cause immune-mediated nephritis, which can be fatal. Nephritis, including tubulointerstitial nephritis, occurred in 0.5% (3/605) of patients receiving JEMPERLI; all were Grade 2. Nephritis led to discontinuation of JEMPERLI in 1 (0.2%) patient and resolved in all patients. JEMPERLI was withheld for 1 patient and the patient reinitiated treatment. Systemic corticosteroids were required in 2 of the 3 patients experiencing nephritis.

Immune-Mediated Dermatologic Adverse Reactions

JEMPERLI can cause immune-mediated rash or dermatitis. Bullous and exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS), have occurred with PD-1/PD-L1–blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes. Withhold or permanently discontinue JEMPERLI depending on severity *[see Dosage and Administration (2.3) of full prescribing information].*

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred in <1% of the 605 patients treated with JEMPERLI or were reported with the use of other PD-1/PD-L1–blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

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5.1 Severe and Fatal Immune-Mediated Adverse Reactions *(cont'd)*

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis.

Ocular: Uveitis, iritis, other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Gastrointestinal: Pancreatitis, including increases in serum amylase and lipase levels, gastritis, duodenitis.

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica.

Endocrine: Hypoparathyroidism.

Other (Hematologic/Immune): Autoimmune hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenia, solid organ transplant rejection, other transplant (including corneal graft) rejection.

5.2 Infusion-Related Reactions

Severe or life-threatening infusion-related reactions have been reported with PD-1/PD-L1–blocking antibodies. Severe infusion-related reactions (Grade 3) occurred in 0.2% (1/605) of patients receiving JEMPERLI. All patients recovered from the infusion-related reactions.

Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion or permanently discontinue JEMPERLI based on severity of reaction *[see Dosage and Administration (2.3) of full prescribing information].*

5.3 Complications of Allogeneic HSCT

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1–blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1–blocking antibody prior to or after an allogeneic HSCT.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, JEMPERLI can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus, resulting in fetal death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI and for 4 months after the last dose *[see Use in Specific Populations (8.1, 8.3)].*

6 ADVERSE REACTIONS

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

- Severe and fatal immune-mediated adverse reactions *[see Warnings and Precautions (5.1)]*
- Infusion-related reactions *[see Warnings and Precautions (5.2)]*

6.1 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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety population described in the *Warnings and Precautions* for use of JEMPERLI in combination with carboplatin and paclitaxel was evaluated in 241 patients with primary advanced or recurrent endometrial cancer (EC) in the randomized, double-blind, active-controlled RUBY trial.

Additionally, the pooled safety population described in *Warnings and Precautions* reflects exposure to JEMPERLI as a single agent in 605 patients with advanced or recurrent solid tumors in the non-randomized, open-label, multicohort GARNET trial that enrolled 314 patients with EC and 291 patients with other solid tumors. JEMPERLI was administered intravenously at doses of 500 mg every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks until disease progression or unacceptable toxicity. Among the 605 patients, 32% were exposed for >1 year and 19% were exposed for >2 years.

Mismatch Repair Deficient (dMMR) or Microsatellite Instability-High (MSI-H) Primary Advanced or Recurrent EC: JEMPERLI in Combination with Carboplatin and Paclitaxel

The safety of JEMPERLI in patients with primary advanced or recurrent dMMR/MSI-H EC was evaluated in RUBY *[see Clinical Studies (14.1) of full prescribing information].* Patients received JEMPERLI 500 mg (n = 52) or placebo (n = 65) in combination with carboplatin and paclitaxel every 3 weeks for 6 doses followed by JEMPERLI 1,000 mg or placebo every 6 weeks until disease progression or unacceptable toxicity. Among the 52 patients, 56% were exposed for >1 year and 31% were exposed for >2 years.

Serious adverse reactions occurred in 13% of patients receiving JEMPERLI in combination with carboplatin and paclitaxel; the most common serious adverse reaction was sepsis, including urosepsis (6%). Fatal adverse reactions occurred in 6% of patients receiving JEMPERLI including septic shock (3.8%), and myelosuppression (1.9%).

In patients receiving JEMPERLI in combination with carboplatin and paclitaxel, JEMPERLI was permanently discontinued due to adverse reactions in 8 patients (15%) including 1 case (1.9%) each of rash maculo-papular, fatigue, general physical health deterioration, acute kidney injury, infusion-related reaction, keratitis, muscular weakness, and myelosuppression.

Dosage interruptions due to an adverse reaction occurred in 35% of patients who received JEMPERLI in combination with carboplatin and paclitaxel. Adverse reactions that required dosage interruption in ≥5% of patients who received JEMPERLI in combination with carboplatin and paclitaxel were anemia, thrombocytopenia, platelet count decreased, peripheral neuropathy, and rash.

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6.1 Clinical Trials Experience *(cont'd)*

The most common adverse reactions, including laboratory abnormalities (≥20%), were decreased hemoglobin, decreased white blood cell count, decreased platelets, decreased lymphocytes, increased glucose, increased alkaline phosphatase, decreased neutrophils, rash, diarrhea, increased aspartate aminotransferase, increased alanine aminotransferase, decreased sodium, hypothyroidism, and hypertension.

Table 1 summarizes the adverse reactions that occurred in ≥10% of patients with primary advanced or recurrent dMMR/MSI-H EC receiving JEMPERLI in combination with carboplatin and paclitaxel in RUBY.

Table 1. Adverse Reactions (≥10%) in Patients with dMMR/MSI-H Endometrial Cancer Who Received JEMPERLI with Carboplatin and Paclitaxel in RUBY

Adverse Reaction	JEMPERLI with Carboplatin and Paclitaxel N = 52		Placebo with Carboplatin and Paclitaxel N = 65	
	All Grades %	Grade 3 or 4 %	All Grades %	Grade 3 or 4 %
Skin and subcutaneous tissue				
Rash[a]	42	8	20	0
Dry skin	12	0	8	0
Gastrointestinal disorders				
Diarrhea	40	1.9	31	0
Endocrine Disorders				
Hypothyroidism[b]	23	0	6	0
Vascular disorders				
Hypertension	21	10	11	6
General and administration site				
Pyrexia	14	0	1.5	0

dMMR = Mismatch Repair Deficient; MSI-H = Microsatellite Instability-High.
Graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.
[a] Includes rash, rash maculo-papular, palmar-plantar erythrodysesthesia syndrome, rash pustular, skin exfoliation, vulvovaginal rash, and dermatitis bullous.
[b] Includes hypothyroidism and immune-mediated hypothyroidism.

Clinically relevant adverse reactions in <10% of patients with primary advanced or recurrent dMMR/MSI-H EC who received JEMPERLI in combination with carboplatin and paclitaxel included:

Endocrine Disorders: Hyperthyroidism, thyroiditis.

Eye Disorders: Keratitis.

Gastrointestinal Disorders: Colitis, pancreatitis.

Metabolism and Nutrition Disorders: Type 1 diabetes mellitus.

Nervous System Disorders: Encephalopathy.

Table 2 summarizes the laboratory abnormalities in patients with primary advanced or recurrent dMMR/MSI-H EC receiving JEMPERLI in combination with carboplatin and paclitaxel in RUBY.

Table 2. Laboratory Abnormalities that Worsened from Baseline to Grade 3 or 4 Occurring in ≥10% of Patients with dMMR/MSI-H Endometrial Cancer Receiving JEMPERLI with Carboplatin and Paclitaxel in RUBY

Laboratory Test	JEMPERLI with Carboplatin and Paclitaxel N = 52		Placebo with Carboplatin and Paclitaxel N = 65	
	All Grades[a] %	Grade 3 or 4[a] %	All Grades[a] %	Grade 3 or 4[a] %
Hematology				
Decreased hemoglobin	77	17	86	25
Decreased platelets	54	10	57	12
Decreased lymphocytes	52	13	51	25
Decreased neutrophils	46	21	58	23
Decreased white blood cell count	73	15	68	14
Chemistry				
Increased glucose	50	13	54	11
Increased alkaline phosphatase[b]	48	6	26	0
Increased aspartate aminotransferase[b]	40	8	25	0
Increased alanine aminotransferase[b]	40	4	26	0
Electrolytes				
Decreased sodium	29	12	26	5

dMMR = Mismatch Repair Deficient; MSI-H = Microsatellite Instability-High.
[a] Consists of new onset of laboratory abnormality or worsening of baseline laboratory abnormality.
[b] Increased alkaline phosphatase, increased aspartate aminotransferase and increased alanine aminotransferase worsened from baseline to Grade 3 or 4 in <10% of patients.

dMMR Recurrent or Advanced EC: JEMPERLI as a Single Agent

The safety of JEMPERLI was evaluated in GARNET in 150 patients with advanced or recurrent dMMR EC who received at least 1 dose of JEMPERLI *[see Clinical Studies (14.1) of full prescribing information]*. Patients received JEMPERLI 500 mg every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks as an intravenous infusion until disease progression or unacceptable toxicity. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Among patients receiving JEMPERLI, 41% were exposed for >1 year and 23% were exposed for >2 years.

A fatal adverse reaction occurred in one patient (0.7%) who received JEMPERLI, due to concurrent immune-mediated encephalitis and urinary tract infection.

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6.1 Clinical Trials Experience *(cont'd)*

Serious adverse reactions occurred in 38% of patients receiving JEMPERLI. Serious adverse reactions in >2% of patients included urinary tract infection (4%), sepsis (3.3%), acute kidney injury (2.7%), and abdominal pain (2.7%).

JEMPERLI was permanently discontinued due to adverse reactions in 15 (10%) patients, including increased transaminases, sepsis, bronchitis, pneumonitis, rash, pruritus, pancreatitis, encephalitis, and nephritis. Dosage interruptions due to an adverse reaction occurred in 28% of patients who received JEMPERLI. Adverse reactions that required dosage interruption in >1% of patients who received JEMPERLI were anemia, diarrhea, asthenia, colitis, sepsis, and pneumonitis.

The most common adverse reactions (≥20%) were fatigue/asthenia, anemia, nausea, diarrhea, constipation, vomiting, and rash.

Table 3 summarizes the adverse reactions that occurred in ≥10% of patients with dMMR EC on JEMPERLI in GARNET.

Table 3. Adverse Reactions (≥10%) in Patients with dMMR Endometrial Cancer Who Received JEMPERLI in GARNET

Adverse Reaction	JEMPERLI N = 150	
	All Grades %	Grade 3 or 4 %
General and administration site		
Fatigue[a]	49	3.3
Pyrexia	13	0
Blood and lymphatic system		
Anemia[b]	35	18
Gastrointestinal		
Nausea	32	0.7
Diarrhea	29	2.7
Constipation	23	0.7
Vomiting	23	0.7
Skin and subcutaneous tissue		
Rash[c]	21	0
Pruritus	19	1.3
Infections		
Urinary tract infection	19	4
Metabolism and nutrition		
Decreased appetite	15	0
Respiratory, thoracic, and mediastinal		
Cough	15	0
Musculoskeletal and connective tissue		
Myalgia	10	0
Investigations		
Increased transaminases[d]	13	4
Endocrine Disorders		
Hypothyroidism	11	0

dMMR = Mismatch Repair Deficient.

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.
[a] Includes fatigue and asthenia.
[b] Includes anemia, decreased hemoglobin, iron deficiency, and iron deficiency anemia.
[c] Includes rash, rash maculo-papular, rash pruritic, erythema, and pemphigoid.
[d] Includes increased alanine aminotransferase, increased aspartate aminotransferase, increased transaminases, and hypertransaminasemia.

Clinically relevant adverse reactions in <10% of patients who received JEMPERLI included:

Endocrine Disorders: Hyperthyroidism, adrenal insufficiency, hypophysitis.

Eye Disorders: Iridocyclitis, uveitis.

Gastrointestinal Disorders: Colitis, pancreatitis, enterocolitis, gastritis.

General Disorders and Administration Site Conditions: Chills.

Musculoskeletal and Connective Tissue Disorders: Immune-mediated myositis, immune-mediated arthritis.

Nervous System Disorders: Encephalitis.

Renal and Urinary Disorders: Nephritis.

Respiratory, Thoracic, and Mediastinal Disorders: Pneumonitis, interstitial lung disease.

Table 4 summarizes laboratory abnormalities worsening from baseline to Grade 3 or 4 in ≥1% of patients with dMMR EC on JEMPERLI in GARNET

Table 4. Laboratory Abnormalities that Worsened from Baseline to Grade 3 or 4 Occurring in ≥1% of Patients with dMMR Endometrial Cancer Receiving JEMPERLI in GARNET

Laboratory Test	JEMPERLI N = 150	
	All Grades[a] %	Grade 3 or 4[a] %
Hematology		
Decreased lymphocytes	46	15
Decreased leukocytes	21	2
Decreased neutrophils	17	2.7
Chemistry		
Decreased albumin	36	2.7
Increased creatinine	33	3.4
Increased alkaline phosphatase	31	2.7
Increased aspartate aminotransferase	31	2
Increased alanine aminotransferase	25	4.7
Electrolytes		
Decreased sodium	29	5
Decreased magnesium	28	2
Decreased potassium	22	2
Increased calcium	8	2

[a] Consists of new onset of laboratory abnormality or worsening of baseline laboratory abnormality.

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, JEMPERLI can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) of full prescribing information].* There are no available data on the use of JEMPERLI in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune mediated rejection of the developing fetus resulting in fetal death *(see Data).* Human IgG4 immunoglobulins (IgG4) are known to cross the placental barrier; therefore, dostarlimab-gxly has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

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.

Data

Animal Data: Animal reproduction studies have not been conducted with JEMPERLI to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering JEMPERLI during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to dostarlimab-gxly may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of dostarlimab-gxly in human milk or its effects on the breastfed child or on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to JEMPERLI are unknown. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment and for 4 months after the last dose of JEMPERLI.

8.3 Females and Males of Reproductive Potential

JEMPERLI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)].*

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating JEMPERLI *[see Use in Specific Populations (8.1)].*

Contraception

Females: Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI and for 4 months after the last dose.

8.5 Geriatric Use

In Combination with Carboplatin and Paclitaxel

Of the 241 patients treated with JEMPERLI in RUBY, 52.3% were younger than 65 years, 36.5% were aged 65 through 75 years, and 11.2% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

As a Single Agent

Of the 605 patients treated with JEMPERLI in GARNET, 51.6% were younger than 65 years, 36.9% were aged 65 through 75 years, and 11.5% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid or other treatment and interruption or discontinuation of JEMPERLI. These reactions may include:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)].*
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.1)].*
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding *[see Warnings and Precautions (5.1)].*
- Immune-mediated endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, thyroiditis, adrenal insufficiency, hypophysitis, or type 1 diabetes mellitus *[see Warnings and Precautions (5.1)].*
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis *[see Warnings and Precautions (5.1)].*
- Severe skin reactions: Advise patients to contact their healthcare provider immediately for any signs or symptoms of severe skin reactions, SJS, TEN, or DRESS *[see Warnings and Precautions (5.1)].*
- Other immune-mediated adverse reactions:
    - Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their healthcare provider immediately for any new signs or symptoms *[see Warnings and Precautions (5.1)].*
    - Advise patients of the risk of solid organ transplant rejection and to contact their healthcare provider immediately for signs or symptoms of organ transplant rejection *[see Warnings and Precautions (5.1)].*

Infusion-Related Reactions

- Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.2)].*

(continued on next page)

17 PATIENT COUNSELING INFORMATION *(cont'd)*

Complications of Allogeneic HSCT

• Advise patients of the risk of post-allogeneic hematopoietic stem cell transplantation complications *[see Warnings and Precautions (5.3)].*

Embryo-Fetal Toxicity

• Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)].*

• Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI and for 4 months after the last dose *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)].*

Lactation

• Advise women not to breastfeed during treatment with JEMPERLI and for 4 months after the last dose *[see Use in Specific Populations (8.2)].*

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RECTAL CANCER

Which Treatment for Which Patient: Rectal Cancer Management After PROSPECT Trial

Seth Felder, MD; Jessica Frakes, MD; Manju George, PhD; Allison Rosen, MS; and Ibrahim Halil Sahin, MD

Over the past decade, enormous collaborative efforts have completed prospective, randomized, multimodality, locally advanced rectal cancer (LARC) trials with long-term oncologic follow-up.[1-3] Long-term overall survival and disease-free survival across a spectrum of patients with LARC treated with neoadjuvant therapy are promising, and patients have several treatment options available, with increasing emphasis on short- and long-term quality of life (QOL) considerations with preservation of oncologic end points.[4] The PROSPECT trial results add important data to this end and expand the complexity of the decision-making process.

Clinical Outcomes of the PROSPECT Trial

The phase 2/3 PROSPECT trial (NCT01515787) randomly assigned patients with lower-risk LARC (ie, no clinical/radiographic T4, N2, threatened radial margins [≤ 3 mm], or expectation that an abdominoperineal resection [APR] would be required) to long course chemoradiation, total mesorectal excision (TME), and adjuvant chemotherapy or 6 cycles of preoperative FOLFOX (leucovorin calcium, fluorouracil, and oxaliplatin) with selective omission of neoadjuvant chemoradiation, TME, and postoperative chemotherapy.[3] The results confirmed the noninferiority of the de-escalation experimental approach in which radiation therapy was omitted from the standard trimodality paradigm of LARC treatment. All patients underwent operative resection, however, within the clinical context of avoiding long-term adverse treatment effects secondary to pelvic radiation. Across this large surgical trial, a negative histologic resection margin (R0) rate was achieved in approximately 98% of the per-protocol population. This impressively high R0 rate likely reflects several factors: (1) highly experienced and skilled surgeons, (2) well-selected patients based on rectal MRI (85% utilization reported), and overall, (3) inherently lower-risk rectal cancers.[5] The notable low local recurrence (LR) rate in the trial (approximately 1%) is concordant with the R0 rate, although it is well recognized that surgical margin status (R0/R1) heavily influences but does not account for all variables responsible for local-regional pelvic recurrence. Along with improvements in surgical technique guided by preoperative MRI, additional tumor-related factors presumably impact LR risk. The excellent local control results reported in PROSPECT treated with neoadjuvant chemotherapy (confirmed > 20% radiographic tumor reduction), TME, and adjuvant chemotherapy for patients with clinically lower-risk LARC is in line with the assertion of Richard J. Heald, MD, decades earlier that a *perfect* mesorectal excision

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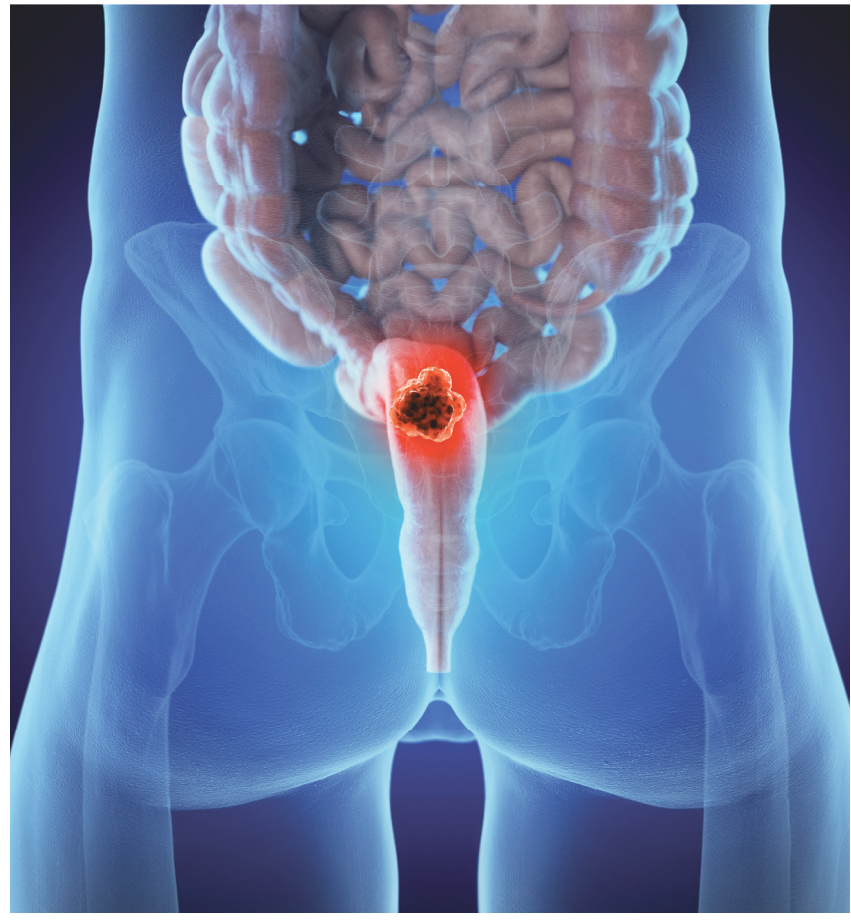
with sharp dissection preserving the parietal and visceral fascia may be all that is necessary for local control.[6]

For context, population studies analyzing the National Cancer Database have reported an approximate 16% rate of pathologically positive radial margin in patients with clinical stage II or stage III disease managed with neoadjuvant chemoradiation (CRT) followed by low anterior resection.[5] The R1 resection rate reported in PROSPECT is notably very low (2%), far lower than most reported rectal cancer surgical trials or observational series. This is likely, in part, due to well-selected "lower risk" tumors as well as highly experienced surgeons. Nonetheless, it is also important to recognize that approximately 5% of patients in the experimental arm had disease that was pathologically T4 and/or N2, and 2% of patients in both arms required APR, highlighting the limitations of rectal MRI and clinical staging. These patients with a pathologically higher-risk LARC, although a minority within the trial, may represent missed opportunities, and they otherwise may have benefited from an alternative approach such as total neoadjuvant treatment (TNT).



Investigators in PROSPECT assessed the de-escalation of therapy, pelvic radiation, within the overarching paradigm of LARC treatment for patients with presumed MRI lower-risk rectal cancers. Pelvic radiation results in short- and long-term adverse effects negatively affecting QOL, including sexual, bowel, and bladder dysfunction, which magnifies the surgically induced functional morbidity associated with a low anterior resection with mesorectal excision.[3] Additionally, pelvic radiation may result in other long-term adverse effects, including increased secondary malignancies, pelvic insufficiency fractures, and reduced bone marrow reserve. The PROSPECT study results proved that patients with lower-risk LARC can omit radiation safely if sphincter-preserving surgery is feasible after a shared decision-making process without an increase in local disease failure. One of the most feared undertreatment outcomes of withholding pelvic radiotherapy is pelvic disease failure, often unsalvageable and associated with significant morbidity and mortality. PROSPECT data indicate that pelvic radiotherapy for patients with low-risk LARC may be overtreatment for those who are willing to undergo low anterior resection following neoadjuvant chemotherapy; the long-term oncologic follow-up shows no statistical difference in local, distant control or survival at 58 months median follow-up.[3]

Clinical Relevance of Patient-Reported Outcomes of PROSPECT: Pros and Cons

PROSPECT investigators also evaluated patient-reported outcomes (PROs) as the secondary end point of the study. Notably, PROs at 12 months post resection revealed improved sexual function, fatigue, and less neuropathy when pelvic radiotherapy was omitted, meeting the PROSPECT trial's prespecified PRO end points.[7] It is important to recognize that, in the PROSPECT trial, 50% of the tumors in both arms were described as palpable, located at a median of 8 cm from the anal verge. This ranged between 2 cm and 25 cm from the anal verge, indicating some patients underwent an ultralow coloanal anastomosis. Secondly, the definition of the upper/proximal rectum vs the distal colon remains imprecise.[8] Since the median tumor height was 8 cm from the anal verge, at least half of the patients had an anatomic extraperitoneal (rather than intraperitoneal) LARC, for which oncologic resection necessitates a TME, rather than a partial or tumor-specific mesorectal excision, which is reserved for proximal rectal cancers. An oncologic proctectomy with TME and sphincter preservation

[SEBASTIAN KAULITZKI] - STOCK.ADOBE.COM

transects the distal rectum at the tapered aspect of the mesorectum approaching the levator floor, resulting in a low pelvic colorectal or coloanal anastomosis.

Arguably, the most significant influence on bowel, urinary, and sexual function in patients with rectal cancer is associated with the pelvic dissection and height of the pelvic anastomosis from the anal verge, with more significant low anterior resection syndrome in patients requiring a low pelvic anastomosis. Low anterior resection syndrome is associated with impaired QOL due to fecal incontinence, urgency, frequency, and incomplete bowel evacuation. Bowel dysfunction at 14 years' follow-up from the Dutch TME trial reported low anterior resection syndrome in 60% of patients, with 25% reporting major low anterior resection syndrome within the upfront TME arm (ie, no pelvic radiation).[9] Even a higher anterior rectal resection for intraperitoneal (upper/proximal) rectal cancer with a tumor-specific mesorectal excision unequivocally results in bowel dysfunction in a substantial proportion of patients. A prospective trial evaluating postoperative bowel and genitourinary dysfunction following sigmoid colectomy for neoplasia reported a 1-year postoperative low anterior resection syndrome rate of 28%, 13% with major low anterior resection syndrome, along with significant urinary and sexual dysfunction.[10] Bowel dysfunction is a strong driver of QOL for patients with rectal cancer, and even in the absence of pelvic radiation following resection for an upper or midrectal cancer, approximately 80% of patients report bowel habit–related QOL impairment.[11]

It cannot be ignored that rectal nonoperative management, also called watch and wait (WW), may represent a therapeutic alternative for many patients and is associated with superior functional outcomes when compared with patients undergoing multimodality treatment(s), including radical resection with mesorectal excision.[12] Rectal organ preservation was achieved in approximately 50% of patients treated with TNT in the phase 2 OPRA trial (NCT02008656), emphasizing the need to account for this possibility in trial design along with a shared decision-making process. In the context of WW, PROSPECT investigators reported a 21.9% pathologic complete response (pCR) following 6 cycles of FOLFOX, similar to the 24% control arm receiving long-course CRT, higher than most rates reported in observational and population trials.[13] A 21.9% pCR rate in the FOLFOX arm is intriguing, generating the question of whether WW may be safe in clinical complete responses to chemotherapy alone, as it has been increasingly practiced following CRT or TNT. Whether induction chemotherapy alone is sufficient to cure or locally control disease in a subgroup of patients with LARC may be further examined in prospective trials.

A significant number of patients with LARC, including those with a presumed lower-risk LARC, may wish to avoid rectal surgery if feasible. Therefore, establishing an individual's treatment goals, almost universally cure with preservation of QOL, is expected to become even more complex. Although sphincter preservation was successfully achieved in the majority of patients in the PROSPECT trial and radiation was omitted, some degree of low anterior resection syndrome is anticipated among most, if not all, of these patients, along with reduced bowel-related QOL. The shared decision-making process should include clear dialogue regarding the advantages and disadvantages of each treatment and approach, aligning each patient's expressed understanding and expectations toward the goals of care.

The PROSPECT trial results create a new treatment alternative for patients with clinically lower-risk LARC. Each component of trimodality treatment for LARC carries the risk of short- and longer-term morbidity and mortality; however, proctectomy with TME remains responsible for the majority of significant long-term effects reducing QOL. Currently endorsed TNT strategies supported by long-term survival data require months of treatments and, therefore, likely risks overtreatment for a substantial proportion of patients without a significant measurable improvement in oncologic outcome. In addition, several patients treated with TNT do not achieve organ preservation due to persistent local or regrowth of disease. Therefore, the PROSPECT trial regimen is a relevant treatment option, in particular for younger patients of reproductive age with long life expectancy hoping to preserve sexual function. Given the increasing incidence of young-onset rectal cancer in Western countries, which is expected to increase over the coming decades by more than 100%, the PROSPECT treatment approach may be ideally suited for this patient subgroup.[14]

Discussion: Balancing Treatment Decisions—Who Decides?

Determining which treatments patients need and which may be safely deferred or avoided, including the historical cornerstone of rectal cancer management, proctectomy with TME, is less clear despite the many successes over the past decades. The "best" treatment approach for a specific patient remains out of reach since efforts to escalate or de-escalate treatment with the intent to cure and preserve a patient's QOL are based on a partial understanding of the biologically heterogeneous behavior and sensitivity to the treatments of rectal cancer.[15] The wide spectrum of tumor response to chemotherapy and radiation across similarly staged LARCs is highly variable, from minimal to complete pathologic regression.[16] Currently, no clinically available tool, test, or biomarker reliably predicts rectal cancer pathologic response to chemotherapy or radiation.[17] As a result, over- and undertreatment, or the ability to truly personalize a treatment strategy by applying escalation or de-escalation considerations, relies largely on MRI rectal staging interpretation. Over the decades, rectal protocoled MRI assessing tumor extent

and reproducible radiographic characteristics reflecting higher risk tumor biology (eg, extramural vascular invasion, tumor deposits, deep mesorectal penetration T3c/d/T4, threatened mesorectal fascia, extramesorectal lymph nodes) has been accepted as a reliable clinical tool to estimate each individual patient's relative risk of local and distant treatment failure following multimodal treatment. However, contemporary clinical risk assessment does not fully depict the biologic variability of rectal cancers to precisely escalate or de-escalate a therapeutic approach, thereby delivering a truly personalized approach, which consequently results in significant clinical and treatment uncertainty.

At this time, the question persists: What should the trade-off be? Treatment escalation in an attempt to potentially preserve the rectum (and de-escalate treatment by deferring radical resection) or, conversely, treatment de-escalation by withholding pelvic radiation to reduce long-term toxicities in presumed lower-risk LARC can complicates management decisions. However, the results of high-quality studies have provided options. Different treatment approaches allow clinicians to better align the expectations, wishes, and concerns of patients to execute an informed, shared-decision treatment plan. This discussion can include objective data from randomized LARC trials to best inform patient decision-making. Nonetheless, it is important to recognize that the increasing complexity of treatment options for patients with LARC may subsequently be more prone to confusion or misunderstanding at the patient and even the clinician levels.

Conclusion

Collectively, the results from the PROSPECT trial support another effective treatment approach for patients with lower-risk LARC. The PROSPECT results are particularly relevant in light of the increasing incidence of early-onset rectal cancer, for which the long-term effects of radiotherapy may negatively impact the QOL for patients with curable disease. With multiple options for sequencing, intensifying, or de-escalating the multimodal treatment paradigm for patients with LARC, clinician and patient discussions weighing relative risks and benefits to best individualize treatments are more complicated, emphasizing the need for high-level multidisciplinary care and explicit clarity when establishing each patient's goals of care. ■

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GYNECOLOGIC MALIGNANCIES

Synchronous Well-Differentiated Papillary Mesothelioma and Endometrioid Adenocarcinoma Arising From Endometriosis

Catherine R. Lewis, MD, PhD; Jocelyn Uchic-Boccella, DO; Jenna Zimmerman, MD; Eirwen Miller, MD; Sharon Liang, MD; Patrick L. Wagner, MD, MPH

ABSTRACT Well-differentiated papillary mesothelioma (WDPM) is a rare mesothelial tumor of uncertain malignant potential. We present a unique case of a woman with synchronous WDPM and well-differentiated endometrioid adenocarcinoma (EA) arising from extraovarian endometriosis. A 56-year-old postmenopausal woman presented with a several-month history of right lower quadrant abdominal pain. She had a history of supracervical hysterectomy and bilateral salpingo-oophorectomy secondary to endometriosis. Imaging reported a mass in the right lower quadrant originating from the distal ileum. At laparotomy, the patient underwent a right colectomy with resection of the terminal ileum and excision of a solitary peritoneal nodule. Pathology was consistent with a diagnosis of well-differentiated EA (arising from extraovarian endometriosis) and WDPM. Further treatment consisted of complete surgical staging/debulking and adjuvant chemotherapy directed toward metastatic well-differentiated EA. Surgeons should be familiar with WDPM as a potential finding in women of reproductive age undergoing abdominal surgery for any indication.

KEYWORDS: endometrioid adenocarcinoma, endometriosis, papillary mesothelioma, WDPM, debulking

Well-differentiated papillary mesothelioma (WDPM) is a rare mesothelial tumor more commonly seen in the peritoneum of women of reproductive age. Extraperitoneal locations are uncommon. An association with mesothelioma has not been definitively established and its cause remains unknown. It is a tumor of uncertain malignant potential, and it is often found incidentally during laparotomy for other benign or malignant reasons.[1-3]

Endometriosis is an estrogen-dependent disease that affects approximately 10% of women of reproductive age. Malignant transformation of endometriosis occurs in approximately 0.7% to 2.5% of women. Up to 25% of endometriosis-associated malignancies (EAMs) are extraovarian and numerous cases have been reported in the intestines.[4,5] Malignant extraovarian endometriosis is more common in women who are obese and postmenopausal who are taking estrogen replacement therapy.[6] To the best of our knowledge, we present the first case of synchronous WDPM with well-differentiated endometrioid adenocarcinoma (EA) arising from extraovarian endometriosis.

Case Presentation

A 56-year-old postmenopausal woman presented with a 1-month history of right lower quadrant abdominal pain. There was associated diarrhea and weight loss of 25 lb over the past 5 months. Past medical history was significant for endometriosis. The patient had a supracervical hysterectomy with bilateral salpingo-oophorectomy 25 years prior for endometriosis. She received hormone replacement therapy (HRT) for 4 years following surgery.

An initial CT scan of the abdomen and pelvis demonstrated a lobulated soft tissue mass in the right mid-pelvis likely originating from the distal ileum. The patient was referred to gastroenterologyfor a

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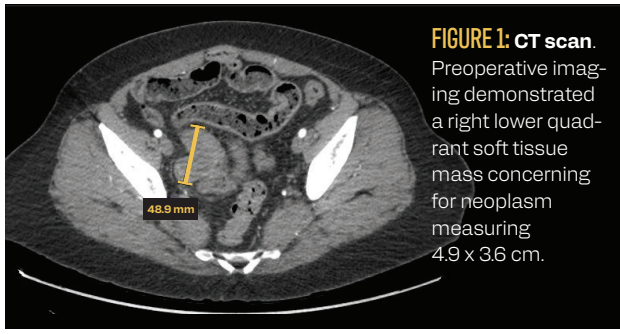

FIGURE 1: CT scan. Preoperative imaging demonstrated a right lower quadrant soft tissue mass concerning for neoplasm measuring 4.9 x 3.6 cm.

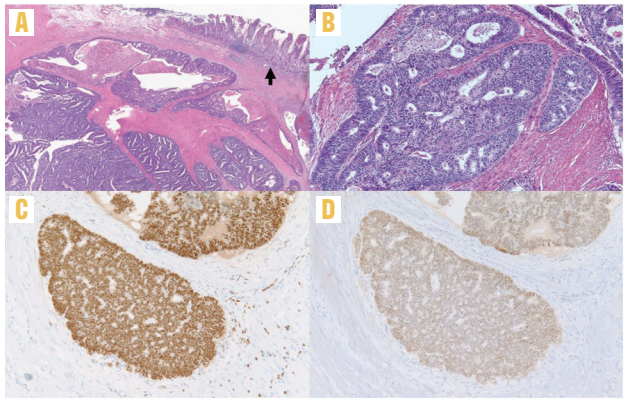

FIGURE 2: Histopathology of right colectomy specimen. (A) The tumor invades the small bowel wall underlying the small intestinal mucosa (arrow). The tumor cells are arranged as back-to-back glands with little to no intervening stroma. There is associated necrosis within some of the tumor nests (×20 magnification) **(B)** The invasive tumor has a cribriform architecture composed of glands lined by columnar cells with round to elongated, pseudostratified nuclei and mild nuclear enlargement (×100 magnification) **(C)** Estrogen receptor is positive in the tumor glands, suggesting endometrioid adenocarcinoma (×100 magnification) **(D)** PAX8 is positive in the tumor glands, which is a marker of Müllerian origin and is positive in endometrioid adenocarcinoma (×100 magnification)

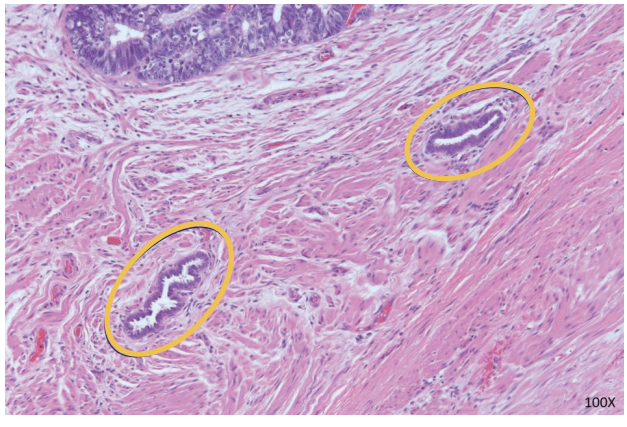

FIGURE 3: Endometriosis focally seen within the ileum and colon. There are focal isolated endometrial glands with pseudostratified nuclei and little to no endometrial stroma. These are dispersed as single glands and do not have the complex architecture of endometrioid adenocarcinoma, such as back-to-back glands with no intervening stroma or a cribriform architecture as is seen at the top of this image. In long-standing endometriosis, the endometrial stroma can become lost or attenuated as seen here. If there is no evidence of endometrioid adenocarcinoma within the uterus or adnexa of this patient, then it can be assumed that this adenocarcinoma arose from the endometriosis involving the bowel wall (100X magnification)

colonoscopy. Before the referral visit, the patient again presented to the emergency department with abdominal pain 1 month later. A repeat CT scan demonstrated a 4.9 × 3.6-cm right lower quadrant mass involving the distal ileum, with the potential for a neoplasm arising from the small bowel or within the right adnexa (**Figure 1**). A colonoscopy was performed and there was no mass noted in the distal ileum. The patient then underwent an exploratory laparotomy, extensive abdominal and pelvic lysis of adhesions, and a right colectomy with resection of the distal terminal ileum with primary anastomosis. An incidental solitary mesenteric implant was noted and was excised.

Histopathology of the right colectomy specimen demonstrated well-differentiated EA involving the wall of the terminal ileum (**Figure 2A**). The mass consisted of neoplastic glandular proliferation with areas of squamoid differentiation (**Figure 2B**). There was no intrinsic mucosal abnormality in the ileum, appendix, or colon. Margins were free of tumor and 15 lymph nodes were negative for metastasis. The tumor stained positive for estrogen receptor and PAX8, with equivocal staining for GATA3, CK7, and CDX2 (**Figures 2C and 2D**). Stains were negative for CK20 and TTF1, consistent with a diagnosis of endometrioid carcinoma. Endometriosis was focally seen embedded within the wall of the ileum and colon, suggesting that the tumor arose in a background of endometriosis (**Figure 3**). The mesenteric implant demonstrated papillary mesothelial proliferation compatible with WDPM (**Figure 4**).

After a multidisciplinary tumor board discussion, a decision was made for surgical reexploration and staging/debulking, as warranted by intraoperative findings. Approximately 3 months after the initial surgery, the patient underwent staging/debulking including trachelectomy, bilateral ureterolysis, bilateral pelvic lymph node dissection, bilateral para-aortic lymph node sampling, partial right colectomy, and omentectomy. No gross residual disease was identified (**Figure 5**). All pathological specimens were negative for residual malignancy. The final stage was IIIC, grade 1 endometrioid carcinoma, best defined as primary peritoneal carcinoma, given that it arose from peritoneal endometriosis with a lack of a primary organ of origin. After surgical recovery, the patient initiated adjuvant systemic chemotherapy including carboplatin and paclitaxel as per standard guidelines for metastatic ovarian and endometrial endometrioid carcinomas.[7] Due to estrogen receptor–positive histology arising from hormonally responsive endometriosis, endocrine maintenance therapy with an aromatase inhibitor is planned upon completion of chemotherapy.

Discussion

Criteria for the pathological diagnosis of an endometriosis-associated tumor were originally defined by John A. Sampson, MD, in 1925.[8] These criteria are (1) evidence of endometriosis near the tumor; (2) invasion from sources other than endometriosis excluded; and (3) the presence of tissue-like endometrial stroma surrounding characteristic epithelial glands. An additional criterion was added in 1953

to include histological evidence of benign endometriosis transitioning into malignant tissue.[6,9,10] These criteria remain as the defining criteria for EAM and were demonstrated on histopathology in our case.

Primary EA is known to occur outside the endometrium, but EA arising from extragonadal endometriosis is rarely reported. Studies involving EAM have primarily focused on endometrioid and clear cell ovarian cancer, as the risk of ovarian cancer in patients with endometriosis is moderately increased.[6,9,11] Malignant extragonadal endometriosis is more common in women who are obese and postmenopausal who are taking estrogen replacement therapy.[6] Although our patient was obese and postmenopausal, she was not currently taking HRT and it is unknown whether she was prescribed combination or estrogen-only HRT after her hysterectomy. In this case, the ovaries were previously resected with no intraoperative evidence of ovarian remnant syndrome, and no normal ovarian tissue was identified on histopathology. Additionally, a trachelectomy was performed to rule out metastatic EA arising from residual lower uterine segment endometrium.

WDPM is an uncommon subtype of epithelioid mesothelioma with a benign course and a good prognosis.[1-3] It is considered a tumor of uncertain malignant potential.[1,12] As in our case, WDPM is pathologically described as a single layer of cuboidal mesothelial cells covered by thin papillary fronds.[2,3] Management of WDPM is not standardized; however, complete surgical cytoreduction is recommended. Adjuvant chemotherapy is not recommended unless there is clear evidence of tumor progression or if complete excision is not possible.[3,13]

Malpica et al demonstrated that endometriosis is associated with WDPM in up to 23% of cases.[1] However, the simultaneous occurrence of WDPM and endometrioid cancer is rare, with only 3 cases reported in the literature.[14-16] WDPM was diffuse and was thought to be peritoneal carcinomatosis in 2 cases.[14,16] One patient presented with abdominal bloating and ascites due to WDPM with endometrioid carcinoma as an incidental finding.[15] To the best of our knowledge, we report the first case of synchronous WDPM and EA arising from extragonadal endometriosis, in this case arising in a patient with a history of a supracervical hysterectomy and bilateral salpingo-oophorectomy.

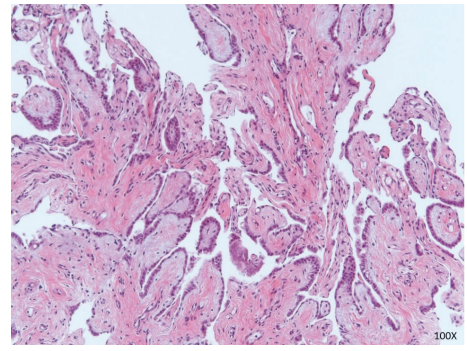

FIGURE 4: **Papillary mesothelial proliferation.** Papillary fronds lined by bland cuboidal mesothelial cells consistent with well-differentiated papillary mesothelioma. This is considered a tumor of uncertain malignant potential (×100 magnification)

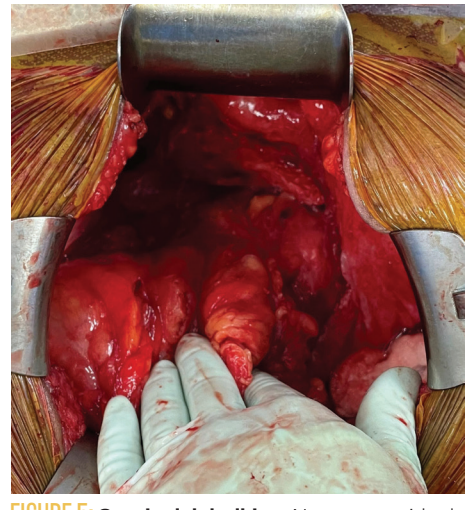

FIGURE 5: **Surgical debulking.** No gross residual disease was identified following a thorough abdominal survey.

Conclusion

We present a unique case of synchronous WDPM and endometrioid adenocarcinoma arising from extraovarian endometriosis. WDPM is a tumor with uncertain malignant potential and its association with endometrioid carcinoma (of any organ site) is rarely reported in the literature. Complete surgical staging and debulking are recommended for both endometrioid adenocarcinoma and WDPM. ■

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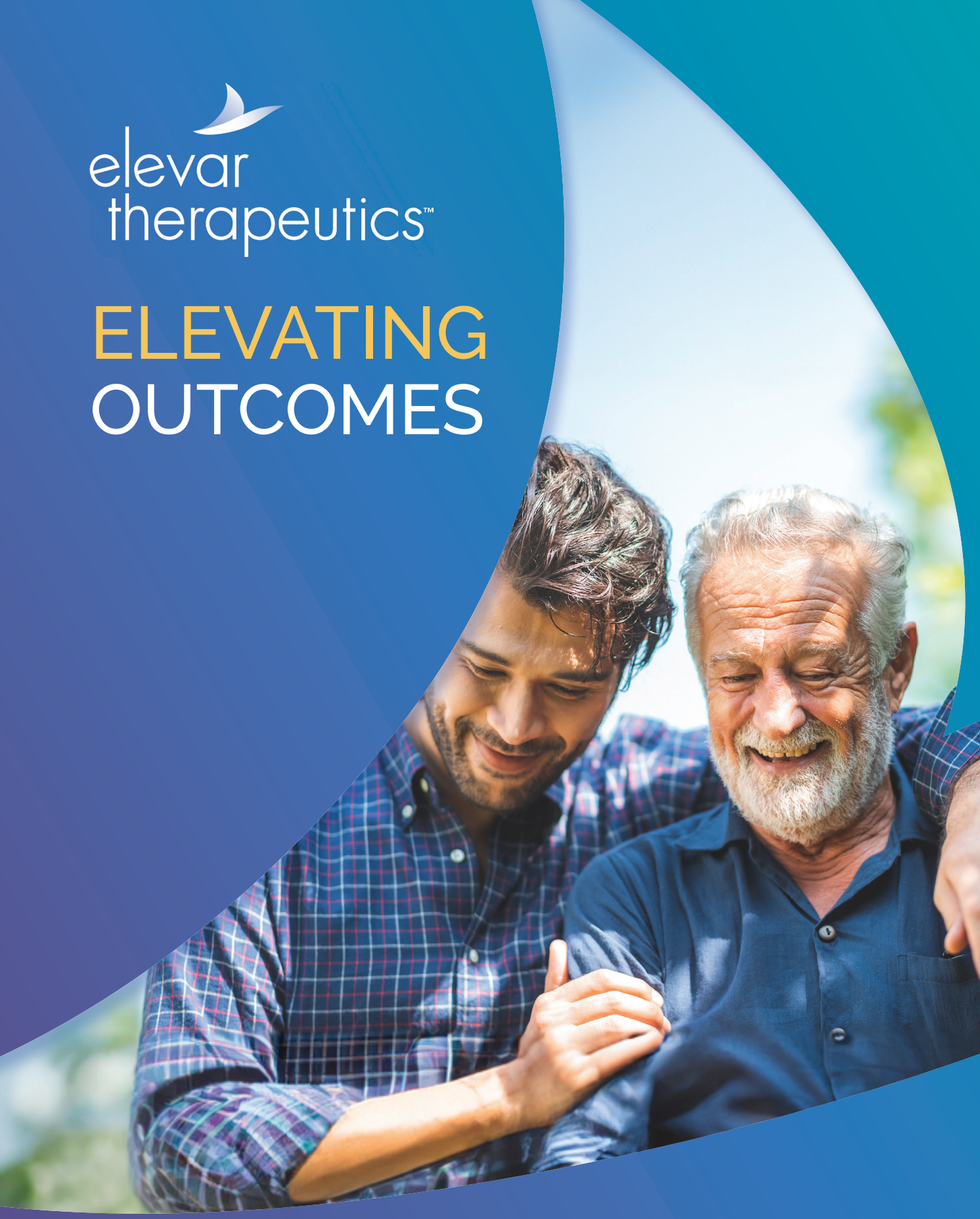

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Forging a Path in Thoracic Surgery to Create a Stellar Career

Rian M. Hasson Charles, MD, MPH, FACS, Inaugural Vice Chair for Diversity, Equity, and Inclusion in the Department of Surgery at Brigham and Women's Hospital

As a Black woman emerging in the field of thoracic surgery, Rian M. Hasson Charles, MD, MPH, FACS, admitted she faced difficulty determining her presence in the oncology field.

"When I was coming into cardiothoracic surgery, there were only 5 Black board-certified surgeons in the nation; now, we're up to about 18. The fact that you can count that on 4 hands is crazy, especially when there are close to 8000 cardiothoracic surgeons in the world."

Hasson began her medical career at the University of California, Berkeley as a psychology major, but she knew medicine would always be in her future. Years later, she is stepping into a new role, the first such one at Brigham and Women's Hospital. She was named the inaugural vice chair for diversity, equity, and inclusion (DEI) in the Department of Surgery. She will also serve as an associate surgeon in the Division of Thoracic Surgery.

As this is a new position, Hasson has a chance to build the program from the ground up, leaving her mark along the way. Her most anticipated projects include focusing on health equity and involving clinicians, residents, and the community in this new initiative.

A Cross-Country Educational Experience

After Hasson completed her undergraduate degree and was thinking about her next steps, a counselor suggested she apply to a postgraduate program, and she was accepted into the Harvard Extension School program. Eventually, she went on to the University of Southern California for medical school.

"I loved it and worked at LA County, which was our main hospital. They [provided] a great experience learning how to be a doctor; working with teams; [and] taking care of the sickest of the sick patients, those who don't have easy access to care, and helping them get the care that they need," Hasson said.

She matched with Brigham and Women's Hospital to complete her general surgery residency and worked under Monica M. Bertagnolli, MD, the 16th director of the National Cancer Institute and the 17th of the National Institutes of Health. Through her time there, her interest in cancer and research understanding grew.

Hasson's first attending job was at Dartmouth Hitchcock Medical Center. When she began her master of public health degree there, the COVID-19 pandemic hit, which increased her curiosity about health equity across various patient populations. During this time, she was able to create a DEI program for the public health school, as well as develop lung cancer screening techniques for patients who are without easy access to care.

"[During my lung screening career, I was looking] at our rural populations and figuring out what the barriers and facilitators are to helping those patients get screened. There is a lot of misinformation. There is a…lack of education and lack of access. When you live 120 miles away from the closest screening center, [you have to] figure out how to get there and make that a priority," she said.

During this time, the inaugural position for vice chair of DEI at Brigham opened, and Hasson jumped at the opportunity because "it's blending everything that I've been working on in separate silos."

An Inaugural Position

As Hasson is the first to hold this position at Brigham, the world is her oyster on how to set up the program. She noted that with the "help" of the COVID-19 pandemic, many eyes were opened on how to integrate health equity not just in oncology, but across health care specialties.

She hopes that through this position, Brigham can bring health equity to the forefront of everything they do. She commends her department for making her feel included during meetings, hearing her voice on accomplishments or concerns, and having conversations on how to create this DEI program.

Although Brigham is an academic center, those who live in the surrounding areas may not have access to care and have significant disparities. To help serve this population, it is important to create a diverse workforce and retain them. Some questions that come to her mind include, "Are we keeping [clinicians] here? If they're not staying here, are they going on to do bigger and better things? Are

practices equitable in terms of who we're hiring and who we're getting to stay here? Are we mentoring correctly?"

She also wants to further enforce cultural sensitivity regarding M&Ms, looking at cases within the institution and surrounding ones to see how Brigham can make improvements.

Most importantly, she is excited about the community connections she can make in this position. "The [cancer] journey is long; it is often multidisciplinary and involves many different steps for you to go from diagnosis to hopefully treatment and cure or treatment and stability. Even if it's in a palliative setting, [we aim to offer treatment] in a humanistic way,…having empathy at the core of that and providing those resources so that patients can travel that journey in a dignified fashion."

A precedent Hasson hopes to set involves making DEI something we think of in our everyday lives. She wants to be able to create equitable care, and work with patients for those who may not have access to or finances for it.

One day, she hopes that this position won't be required for institutions and academic centers.

Paving the Way for Equitable Lung Cancer Screening

At the beginning of her career, Hasson worked with Bertagnolli on the Adenoma Prevention with Celecoxib (APC) trial (NCT00005094). It assessed 2035 patients receiving 200 mg of celecoxib twice daily or 400 mg of celecoxib daily.[1] Working on this trial, she learned that there was the opportunity to change how medicine is practiced, and everything should not always stay within the status quo.

At Dartmouth, she began working with Bill Black, MD, a radiation oncologist. He was one of the key principal investigators for the National Lung Screening Trial (NCT00047385) that compared low-dose helical CT scan with chest radiography in older current or former heavy smokers.[2] They hypothesized that lung cancer treatment would be more effective and the likelihood of death would decrease if cancer was detected through early screening.

Looking at the geographic region that surrounded Dartmouth, Hasson began to question how she could give these patients equitable access to care and still allow them to be screened. She began to create a process to bring mobile lung cancer screening units to these rural populations.

"I was lucky enough to get funding from the National Institutes of Health through a grant for Dartmouth Hitchcock to do this work and help pilot this." However, Hasson was not able to complete this because she accepted the new position at Brigham. She is excited to bring the mobile lung cancer screening idea to Boston and begin working with the surrounding populations.

When asked about the future of lung cancer treatment, Hasson said it is constantly evolving, and the wheel is being reinvented. She cited how lung surgery originally began as a pneumonectomy, then to removing 1 lobe, and finally to being able to sample only lymph nodes.

She believes the field is transitioning to more minimally invasive techniques and patient-specialized care; and the addition of immunotherapy has helped transform lung cancer care overall.

"Even with stage IV disease we are seeing patients [who] are not just living 3 to 6 months, but they're living years. I'm excited. We're always innovating. It's not just in one field, it's in many, and it's at many different stages of the disease process," she said.

Women in Oncology

Hasson noted that being a woman working in the oncology space can feel very lonely at times. She was chief cardiothoracic fellow, and the only woman in her program. "People don't understand the things that you miss out on, [those] conversations that [happen], and then you get to the men's locker room and the conversation continues, but you break off. Small things like that."

As a Black, left-handed woman in cardiothoracic surgery, Hasson noted there was not much else that could impede her progress. She is very grateful for her mentors who looked out for her and guided her.

She noted that she didn't necessarily need to see mentors who looked like her to emulate the type of surgeon and doctor she wanted to be.

For future surgeons, her advice would be to not feel like "you're in a box"—that there are several options and career paths that those practicing medicine can fall into. Nevertheless, students or clinicians just starting should surround themselves with multiple mentors.

Finally, she reminds everyone to cultivate their relationships with their friends and family because they will be the ones who will be with you long after your career is over.

"The world is your oyster. I encourage people to find their focus, find their passion, find the thing that keeps them up at night or that wakes them up in the morning. You can do whatever you set your mind to. With today's resources, there should be nothing that limits you. There may be things that seem like they're discouraging, but you have the power to overcome those and collaborate with people that will help generate success." ■

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mUC

TRODELVY® (sacituzumab govitecan-hziy) is a Trop-2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) who have previously received a platinum-containing chemotherapy and either programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: NEUTROPENIA AND DIARRHEA

- **Severe or life-threatening neutropenia may occur. Withhold TRODELVY for absolute neutrophil count below 1500/mm^3 or neutropenic fever. Monitor blood cell counts periodically during treatment. Consider G-CSF for secondary prophylaxis. Initiate anti-infective treatment in patients with febrile neutropenia without delay.**
- **Severe diarrhea may occur. Monitor patients with diarrhea and give fluid and electrolytes as needed. At the onset of diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤Grade 1 and reduce subsequent doses.**

CONTRAINDICATIONS

- Severe hypersensitivity reaction to TRODELVY.

WARNINGS AND PRECAUTIONS

Neutropenia: Severe, life-threatening, or fatal neutropenia can occur and may require dose modification. Neutropenia occurred in 64% of patients treated with TRODELVY. Grade 3-4 neutropenia occurred in 49% of patients. Febrile neutropenia occurred in 6%. Neutropenic colitis occurred in 1.4%. Withhold TRODELVY for absolute neutrophil count below 1500/mm^3 on Day 1 of any cycle or neutrophil count below 1000/mm^3 on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever. Administer G-CSF as clinically indicated or indicated in Table 1 of USPI.

Diarrhea: Diarrhea occurred in 64% of all patients treated with TRODELVY. Grade 3-4 diarrhea occurred in 11% of patients. One patient had intestinal perforation following diarrhea. Diarrhea that led to dehydration and subsequent acute kidney injury occurred in 0.7% of all patients. Withhold TRODELVY for Grade 3-4 diarrhea and resume when resolved to ≤Grade 1. At onset, evaluate for infectious causes and if negative, promptly initiate loperamide, 4 mg initially followed by 2 mg with every episode of diarrhea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after diarrhea resolves. Additional supportive measures (e.g., fluid and electrolyte substitution) may also be employed as clinically indicated. Patients who exhibit an excessive cholinergic response to treatment can receive appropriate premedication (e.g., atropine) for subsequent treatments.

Hypersensitivity and Infusion-Related Reactions: Serious hypersensitivity reactions including life-threatening anaphylactic reactions have occurred with TRODELVY. Severe signs and symptoms included cardiac arrest, hypotension, wheezing, angioedema, swelling, pneumonitis, and skin reactions. Hypersensitivity reactions within 24 hours of dosing occurred in 35% of patients. Grade 3-4 hypersensitivity occurred in 2% of patients. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 0.2%. The incidence of anaphylactic reactions was 0.2%. Pre-infusion medication is recommended. Have medications and emergency equipment to treat such reactions available for immediate use. Observe patients closely for hypersensitivity and infusion-related reactions during each infusion and for at least 30 minutes after completion of each infusion. Permanently discontinue TRODELVY for Grade 4 infusion-related reactions.

Nausea and Vomiting: Nausea occurred in 64% of all patients treated with TRODELVY and Grade 3-4 nausea occurred in 3% of these patients. Vomiting occurred in 35% of patients and Grade 3-4 vomiting occurred in 2% of these patients. Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK_1 receptor antagonist as well as other drugs as indicated) for prevention of chemotherapy-induced nausea and vomiting (CINV). Withhold TRODELVY doses for Grade 3 nausea or Grade 3-4 vomiting and resume with additional supportive measures when resolved to Grade ≤1. Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for prevention and treatment of nausea and vomiting.

Nearly 30% of patients responded, with ~5% experiencing complete response[1]

TRODELVY®
sacituzumab govitecan-hziy
180 mg for injection

TRODELVY was evaluated in TROPHY, a Phase 2, single-arm, open-label, multicenter study (N=112) in patients with locally advanced or mUC who received prior treatment with a platinum-containing chemotherapy and either PD-1 or PD-L1 inhibitor

ORR*

27.7%

(95% CI: 19.6–36.9)
Complete Response (CR): 5.4%
Partial Response (PR): 22.3%
N=112

Median DOR*

7.2 months (range 1.4+, 13.7)

(95% CI: 4.7–8.6)
Number of responders: 31
+: denotes ongoing

See more data from the TROPHY study at **TRODELVYHCP.com**

*By IRA based on RECIST 1.1.

ADC=antibody-drug conjugate; CI=confidence interval; DOR=Duration of Response; IRA=independent review assessment; ORR=Objective Response Rate; RECIST=Response Evaluation Criteria in Solid Tumors.

Increased Risk of Adverse Reactions in Patients with Reduced UGT1A1 Activity: Patients homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia and may be at increased risk for other adverse reactions with TRODELVY. The incidence of Grade 3-4 neutropenia was 58% in patients homozygous for the UGT1A1*28, 49% in patients heterozygous for the UGT1A1*28 allele, and 43% in patients homozygous for the wild-type allele. The incidence of Grade 3-4 anemia was 21% in patients homozygous for the UGT1A1*28 allele, 10% in patients heterozygous for the UGT1A1*28 allele, and 9% in patients homozygous for the wild-type allele. Closely monitor patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue TRODELVY based on clinical assessment of the onset, duration and severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 function.

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

ADVERSE REACTIONS

In the pooled safety population, the most common (≥25%) adverse reactions including laboratory abnormalities were decreased leukocyte count (84%), decreased neutrophil count (75%), decreased hemoglobin (69%), diarrhea (64%), nausea (64%), decreased lymphocyte count (63%), fatigue (51%), alopecia (45%), constipation (37%), increased glucose (37%), decreased albumin (35%), vomiting (35%), decreased appetite (30%), decreased creatinine clearance (28%), increased alkaline phosphatase (28%), decreased magnesium (27%), decreased potassium (26%), and decreased sodium (26%).

In the TROPHY study, the most common adverse reactions (incidence ≥25%) were diarrhea, fatigue, nausea, any infection, alopecia, decreased appetite, constipation, vomiting, rash, and abdominal pain. The most frequent serious adverse reactions (SAR) (≥5%) were infection (18%), neutropenia (12%, including febrile neutropenia in 10%), acute kidney injury (6%), urinary tract infection (6%), and sepsis or bacteremia (5%). SAR were reported in 44% of patients, and 10% discontinued due to adverse reactions. The most common Grade 3-4 lab abnormalities (incidence ≥25%) in the TROPHY study were reduced neutrophils, leukocytes, and lymphocytes.

DRUG INTERACTIONS

UGT1A1 Inhibitors: Concomitant administration of TRODELVY with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38. Avoid administering UGT1A1 inhibitors with TRODELVY.

UGT1A1 Inducers: Exposure to SN-38 may be reduced in patients concomitantly receiving UGT1A1 enzyme inducers. Avoid administering UGT1A1 inducers with TRODELVY.

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the next page.

Reference: 1. TRODELVY [package insert]. Foster City, CA: Gilead Sciences, Inc.; February 2023.

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Scan the QR code to watch a TROPHY study investigator discuss the data

TRODELVY® (sacituzumab govitecan-hziy) for injection, for intravenous use
Brief Summary of full Prescribing Information. See full Prescribing Information. Rx Only.

WARNING: NEUTROPENIA AND DIARRHEA

- **Severe or life-threatening neutropenia may occur. Withhold TRODELVY for absolute neutrophil count below 1500/mm^3 or neutropenic fever. Monitor blood cell counts periodically during treatment. Consider G-CSF for secondary prophylaxis. Initiate anti-infective treatment in patients with febrile neutropenia without delay.**
- **Severe diarrhea may occur. Monitor patients with diarrhea and give fluid and electrolytes as needed. At the onset of diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤ Grade 1 and reduce subsequent doses.**

[See Warnings and Precautions and Dosage and Administration]

INDICATIONS AND USAGE

*Also see **Clinical Studies***

TRODELVY (sacituzumab govitecan-hziy) is a Trop-2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with:

- Unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.
- Unresectable locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH−) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting.
- Locally advanced or metastatic urothelial cancer (mUC) who have previously received a platinum-containing chemotherapy and either programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

DOSAGE AND ADMINISTRATION

*Also see **Warnings and Precautions***

Do NOT substitute TRODELVY for or use with other drugs containing irinotecan or its active metabolite SN-38.

The recommended dosage of TRODELVY is 10 mg/kg administered as an intravenous infusion once weekly on Days 1 and 8 of 21-day treatment cycles. Continue treatment until disease progression or unacceptable toxicity. Do not administer TRODELVY at doses greater than 10 mg/kg. Administer TRODELVY as an intravenous infusion only. Do not administer as an intravenous push or bolus.

- First infusion: Administer infusion over 3 hours. Observe patients during the infusion and for at least 30 minutes following the initial dose, for signs or symptoms of infusion-related reactions
- Subsequent infusions: Administer infusion over 1 to 2 hours if prior infusions were tolerated. Observe patients during the infusion and for at least 30 minutes after infusion.
- Premedication: Prior to each dose of TRODELVY, premedication for prevention of infusion reactions and prevention of chemotherapy-induced nausea and vomiting (CINV) is recommended. Premedicate with antipyretics, H1 and H2 blockers prior to infusion, and corticosteroids may be used for patients who had prior infusion reactions. Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK_1 receptor antagonist, as well as other drugs as indicated).

Dose Modifications for Infusion-related Reactions: Slow or interrupt the infusion rate of TRODELVY if the patient develops an infusion-related reaction. Permanently discontinue TRODELVY for life-threatening infusion-related reactions.

Dose Modifications for Adverse Reactions: Withhold or discontinue TRODELVY to manage adverse reactions as described below. Do not re-escalate the TRODELVY dose after a dose reduction for adverse reactions has been made.

Severe Neutropenia, defined as Grade 4 neutropenia ≥7 days, OR Grade 3-4 febrile neutropenia, OR at time of scheduled treatment, Grade 3-4 neutropenia which delays dosing by 2 or 3 weeks for recovery to ≤ Grade 1:

- At first occurrence, 25% dose reduction and administer granulocyte-colony stimulating factor (G-CSF). At second occurrence, 50% dose reduction and administer G-CSF. At third occurrence, discontinue TRODELVY and administer G-CSF.
- At time of scheduled treatment, if Grade 3-4 neutropenia occurs which delays dosing beyond 3 weeks for recovery to ≤ Grade 1, discontinue TRODELVY and administer G-CSF at first occurrence.

Severe Non-Neutropenic Toxicity, defined as Grade 4 non-hematologic toxicity of any duration, OR any Grade 3-4 nausea, vomiting or diarrhea due to treatment that is not controlled with antiemetics and anti-diarrheal agents, OR other Grade 3-4 non-hematologic toxicity persisting >48 hours despite optimal medical management, OR at time of scheduled treatment, Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which delays dose by 2 or 3 weeks for recovery to ≤Grade 1:

- At first occurrence, 25% dose reduction. At second occurrence, 50% dose reduction. At third occurrence, discontinue TRODELVY.
- In the event of Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which does not recover to ≤Grade 1 within 3 weeks, discontinue TRODELVY at first occurrence.

CONTRAINDICATIONS

*Also see **Warnings and Precautions***

TRODELVY is contraindicated in patients who have experienced a severe hypersensitivity reaction to TRODELVY.

WARNINGS AND PRECAUTIONS

*Also see **BOXED WARNING, Dosage and Administration, Contraindications, Clinical Pharmacology, Nonclinical Toxicology,** and **Use in Specific Populations***

Neutropenia: Severe, life-threatening, or fatal neutropenia can occur in patients treated with TRODELVY. Neutropenia occurred in 64% of patients treated with TRODELVY. Grade 3-4 neutropenia occurred in 49% of patients. Febrile neutropenia occurred in 6% of patients. The median time to first onset of neutropenia (including febrile neutropenia) was 16 days and has occurred earlier in some patient populations. Neutropenic colitis occurred in 1.4% of patients. Withhold TRODELVY for ANC below 1500/mm^3 on Day 1 of any cycle or neutrophil count below 1000/mm^3 on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever. Dose modifications may be required due to neutropenia. Administer G-CSF as clinically indicated or indicated in Table 1 of full Prescribing Information.

Diarrhea: TRODELVY can cause severe diarrhea. Diarrhea occurred in 64% of all patients treated with TRODELVY. Grade 3-4 diarrhea occurred in 11% of all patients treated with TRODELVY. One patient had intestinal perforation following diarrhea. Diarrhea that led to dehydration and subsequent acute kidney injury occurred in 0.7% of all patients. Withhold TRODELVY for Grade 3-4 diarrhea at the time of scheduled treatment administration and resume when resolved to ≤ Grade 1. At the onset of diarrhea, evaluate for infectious causes and if negative, promptly initiate loperamide, 4 mg initially followed by 2 mg with every episode of diarrhea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after diarrhea resolves. Additional supportive measures (e.g., fluid and electrolyte substitution) may also be employed as clinically indicated. Patients who exhibit an excessive cholinergic response to treatment with TRODELVY (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive appropriate premedication (e.g., atropine) for subsequent treatments.

Hypersensitivity and Infusion-Related Reactions: Serious hypersensitivity reactions including life-threatening anaphylactic reactions have occurred with TRODELVY treatment. Severe signs and symptoms included cardiac arrest, hypotension, wheezing, angioedema, swelling, pneumonitis, and skin reactions. Hypersensitivity reactions within 24 hours of dosing occurred in 35% of patients treated with TRODELVY. Grade 3-4 hypersensitivity occurred in 2% of patients. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 0.2%. The incidence of anaphylactic reactions was 0.2%. Premedication for infusion reactions in patients receiving TRODELVY is recommended. Have medications and emergency equipment to treat infusion-related reactions, including anaphylaxis, available for immediate use when administering TRODELVY. Closely monitor patients for hypersensitivity and infusion-related reactions during each infusion and for at least 30 minutes after completion of each infusion. Permanently discontinue TRODELVY for Grade 4 infusion-related reactions.

Nausea and Vomiting: TRODELVY is emetogenic. Nausea occurred in 64% of all patients treated with TRODELVY. Grade 3-4 nausea occurred in 3% of patients. Vomiting occurred in 35% of patients. Grade 3-4 vomiting occurred in 2% of these patients. Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK_1 receptor antagonist as well as other drugs as indicated) for prevention of CINV. Withhold TRODELVY doses for Grade 3 nausea or Grade 3-4 vomiting and resume with additional supportive measures when resolved to ≤Grade 1. Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for prevention and treatment of nausea and vomiting.

Increased Risk of Adverse Reactions in Patients with Reduced UGT1A1 Activity: Patients homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia and may be at increased risk for other adverse reactions with TRODELVY. The incidence of neutropenia and anemia was analyzed in 948 patients who received TRODELVY and had UGT1A1 genotype results. The incidence of Grade 3-4 neutropenia was 58% in patients homozygous for the UGT1A1*28 allele (n=112), 49% in patients heterozygous for the UGT1A1*28 allele (n=420), and 43% in patients homozygous for the wild-type allele (n=416). The incidence of Grade 3-4 anemia was 21% in patients homozygous for the UGT1A1*28 allele, 10% in patients heterozygous for the UGT1A1*28 allele, and 9% in patients homozygous for the wild-type allele. The median time to first neutropenia including febrile neutropenia was 9 days in patients homozygous for the UGT1A1*28 allele, 15 days in patients heterozygous for the UGT1A1*28 allele, and 20 days in patients homozygous for the wild-type allele. The median time to first anemia was 21 days in patients homozygous for the UGT1A1*28 allele, 25 days in patients heterozygous for the UGT1A1*28 allele, and 28 days in patients homozygous for the wild-type allele. Closely monitor patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue TRODELVY based on onset, duration, and severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 enzyme activity.

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

ADVERSE REACTIONS

*Also see **BOXED WARNING, Warnings and Precautions,** and **Clinical Studies***

The pooled safety population described in the Warnings and Precautions section reflect exposure to TRODELVY in 1063 patients from four studies, IMMU-132-01, ASCENT, TROPiCS-02, and TROPHY which included 366 patients with mTNBC, 322 patients with HR+/HER2- breast cancer, and 180 patients with mUC. Among the 1063 patients treated with TRODELVY, the median duration of treatment was 4.1 months (range: 0 to 63 months). The most common (≥ 25%) adverse reactions including laboratory abnormalities were decreased leukocyte count (84%), decreased neutrophil count (75%), decreased hemoglobin (69%), diarrhea (64%), nausea (64%), decreased lymphocyte count (63%), fatigue (51%), alopecia (45%), constipation (37%), increased glucose (37%), decreased albumin (35%), vomiting (35%), decreased appetite (30%), decreased creatinine clearance (28%), increased alkaline phosphatase (28%), decreased magnesium (27%), decreased potassium (26%), and decreased sodium (26%).

Locally Advanced or Metastatic Triple-Negative Breast Cancer

The safety of TRODELVY was evaluated in a randomized, active-controlled, open-label study (ASCENT) in patients with mTNBC who had previously received a taxane and at least two prior chemotherapies. Patients were randomized (1:1) to receive either TRODELVY (n=258) or single agent chemotherapy (n=224) and were treated until disease progression or unacceptable toxicity. For patients treated with TRODELVY, the median duration of treatment was 4.4 months (range: 0 to 23 months). Serious adverse reactions occurred in 27% of patients, and those in > 1% included neutropenia (7%), diarrhea (4%), and pneumonia (3%). Fatal adverse reactions occurred in 1.2% of patients, including respiratory failure (0.8%) and pneumonia (0.4%). TRODELVY was permanently discontinued for adverse reactions in 5% of patients. These adverse reactions (≥1%) were pneumonia (1%) and fatigue (1%). The most frequent (≥5%) adverse reactions leading to a treatment interruption in 63% of patients were neutropenia (47%), diarrhea (5%), respiratory infection (5%), and leukopenia (5%). The most frequent (>4%) adverse reactions leading to a dose reduction in 22% of patients were neutropenia (11%) and diarrhea (5%). G-CSF was used in 44% of patients who received TRODELVY. The most common (≥25%) adverse reactions including lab abnormalities were decreased hemoglobin (94%), decreased lymphocyte count (88%), decreased leukocyte count (86%), decreased neutrophil count (78%), fatigue (65%), diarrhea (59%), nausea (57%), increased glucose (49%), alopecia (47%), constipation (37%), decreased calcium (36%), vomiting (33%), decreased magnesium (33%), decreased potassium (33%), increased albumin (32%), abdominal pain (30%), decreased appetite (28%), increased aspartate aminotransferase (27%), increased alanine aminotransferase (26%), increased alkaline phosphatase (26%), and decreased phosphate (26%).

Locally Advanced or Metastatic HR-Positive, HER2-Negative Breast Cancer

The safety of TRODELVY was evaluated in a randomized, active-controlled, open-label study (TROPiCS-02) in patients with unresectable locally advanced or metastatic HR+/HER2- breast cancer whose disease has progressed after the following in any setting: a CDK 4/6 inhibitor, endocrine therapy, and a taxane; patients received at least two prior chemotherapies in the metastatic setting (one of which could be in the neoadjuvant or adjuvant setting if progression occurred within 12 months). Patients were randomized (1:1) to receive either TRODELVY (n=268) or single agent chemotherapy (n=249) and were treated until disease progression or unacceptable toxicity. For patients treated with TRODELVY, the median duration of treatment was 4.1 months (range: 0 to 63 months). Serious adverse reactions occurred in 28% of patients, and those in >1% of patients included diarrhea (5%), febrile neutropenia (4%), neutropenia (3%), abdominal pain, colitis, neutropenic colitis, pneumonia, and vomiting (each 2%). Fatal adverse reactions occurred in 2% of patients, including arrhythmia, COVID-19, nervous system disorder, pulmonary embolism, and septic shock (each 0.4%). TRODELVY was permanently discontinued for adverse reactions in 6% of patients. The most frequent (≥0.5%) of these adverse reactions were asthenia, general physical health deterioration, and neutropenia (each 0.7%). The most frequent (≥5%) adverse reaction leading to treatment interruption in 66% of patients was neutropenia (50%). The most frequent (>5%) adverse reactions leading to dose reduction in 33% of patients were neutropenia (16%) and diarrhea (8%). G-CSF was used in 54% of patients who received TRODELVY. The most common (≥25%) adverse reactions including lab abnormalities were decreased leukocyte count (88%), decreased neutrophil count (83%), decreased hemoglobin (73%), and decreased lymphocyte count (65%); diarrhea (62%), fatigue (60%), nausea (59%), alopecia (48%), increased glucose (37%), constipation (34%), and decreased albumin (32%). Other clinically significant adverse reactions in TROPiCS-02 (≤ 10%) include: hypotension (5%), pain (5%), rhinorrhea (5%), hypocalcemia (3%), nasal congestion (3%), skin hyperpigmentation (3%), colitis or neutropenic colitis (2%), hyponatremia (2%), pneumonia (2%), proteinuria (1%), enteritis (0.4%).

Locally Advanced or Metastatic Urothelial Cancer

The safety of TRODELVY was evaluated in a single-arm, open-label study (TROPHY) in patients (n=113) with mUC who had received previous platinum-based and anti-PD-1/PD-L1 therapy. Serious adverse reactions occurred in 44% of patients, and those in >1% included infection (18%), neutropenia (12%, including febrile neutropenia in 10%), acute kidney injury (6%), urinary tract infection (6%), sepsis or bacteremia (5%), diarrhea (4%), anemia, venous thromboembolism, and small intestinal obstruction (3% each), pneumonia, abdominal pain, pyrexia, and thrombocytopenia (2% each). Fatal adverse reactions occurred in 3.6% of patients, including sepsis, respiratory failure, epistaxis, and completed suicide. TRODELVY was permanently discontinued for adverse reactions in 10% of patients. The most frequent of these adverse reactions was neutropenia (4%, including febrile neutropenia in 2%). The most common adverse reactions leading to dose interruption in 52% of patients were neutropenia (27%, including febrile neutropenia in 2%), infection (12%), and acute kidney injury (8%). The most common (>4%) adverse reactions leading to a dose reduction in 42% of patients were neutropenia (13%, including febrile neutropenia in 3%), diarrhea (11%), fatigue (8%), and infection (4%). G-CSF was used in 47% of patients who received TRODELVY. The most common (≥25%) adverse reactions including lab abnormalities were decreased leukocyte count (78%), diarrhea (72%), decreased hemoglobin (71%), decreased lymphocyte count (71%), fatigue (68%), decreased neutrophil count (67%), nausea (66%), increased glucose (59%), decreased albumin (51%), any infection (50%), alopecia (49%), decreased calcium (46%), decreased sodium (43%), decreased appetite (41%), decreased phosphate (41%), increased alkaline phosphatase (36%), constipation (34%), vomiting (34%), increased activated partial thromboplastin time (33%), increased creatinine (32%), rash (32%), decreased magnesium (31%), abdominal pain (31%), increased alanine aminotransferase (28%), increased lactate dehydrogenase (28%), decreased potassium (27%), increased aspartate aminotransferase (26%), and decreased platelet count (25%). Other clinically significant adverse reactions (≤15%) include: peripheral neuropathy (12%), sepsis or bacteremia (9%), and pneumonia (4%).

DRUG INTERACTIONS

*Also see **Warnings and Precautions** and **Clinical Pharmacology***

UGT1A1 Inhibitors: Concomitant administration of TRODELVY with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38. Avoid administering UGT1A1 inhibitors with TRODELVY.

UGT1A1 Inducers: Exposure to SN-38 may be reduced in patients concomitantly receiving UGT1A1 enzyme inducers. Avoid administering UGT1A1 inducers with TRODELVY

USE IN SPECIFIC POPULATIONS

*Also see **Warnings and Precautions, Clinical Pharmacology,** and **Nonclinical Toxicology***

Pregnancy: TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

Lactation: There is no information regarding the presence of sacituzumab govitecan-hziy or SN-38 in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment and for 1 month after the last dose of TRODELVY.

Females and Males of Reproductive Potential: Verify the pregnancy status of females of reproductive potential prior to initiation. TRODELVY can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose.

Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

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

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

Geriatric Use:

Of the 366 patients with TNBC who were treated with TRODELVY, 19% of patients were 65 years and 3% were 75 years and older. No overall differences in safety and effectiveness were observed between patients ≥ 65 years of age and younger patients.

Of the 322 patients with HR+/HER2- breast cancer who were treated with TRODELVY, 26% of patients were ≥ 65 years and 6% were ≥ 75 years. No overall differences in effectiveness were observed between patients ≥ 65 years of age and younger patients. There was a higher discontinuation rate due to adverse reactions in patients aged 65 years or older (14%) compared with younger patients (3%).

Of the 180 patients with UC who were treated with TRODELVY, 59% of patients were ≥ 65 years and 27% were ≥ 75 years. No overall differences in effectiveness were observed between patients ≥ 65 years of age and younger patients. There was a higher discontinuation rate due to adverse reactions in patients aged 65 years or older (14%) compared with younger patients (8%).

Hepatic Impairment: No adjustment to the starting dose is required when administering TRODELVY to patients with mild hepatic impairment. The safety of TRODELVY in patients with moderate or severe hepatic impairment has not been established, and no recommendations can be made for the starting dose in these patients.

761115-GS-007 Feb 2023

GILEAD

TRODELVY®
sacituzumab govitecan-hziy
180 mg for injection

EXPERT COMMENTARY ON THE PRODUCT PROFILE OF

Enfortumab Vedotin Plus Pembrolizumab

ONCOLOGY spoke with Kirollos S. Hanna, PharmD, BCPS, BCOP, FACCC, about the recent approval of enfortumab vedotin plus pembrolizumab. He discussed how the trial has significantly impacted bladder cancer space and the improvement it has made to the standard of care.

PRODUCT PROFILE

DRUG NAMES: Enfortumab vedotin-ejfv (Padcev) plus pembrolizumab (Keytruda)

APPROVAL DATE: December 15, 2023

INITIAL INDICATION: Locally advanced or metastatic urothelial carcinoma

DOSAGE AND ADMINISTRATION: Enfortumab vedotin: Intravenous infusion over 30 minutes at 1.25 mg/kg on days 1 and 8 of a 21-day cycle[1]. Pembrolizumab: 200 mg over 30 minutes on day 1 given 30 minutes after enfortumab vedotin[2]

HOW SUPPLIED: Intravenously

PIVOTAL CLINICAL TRIAL: Phase 3 EV-302 trial (NCT04223856)[3]

Design of the EV-302 Trial

ELIGIBLE PATIENTS
Have not received prior systemic therapy for this indication, can receive cisplatin or carboplatin-containing therapy, ECOG score of 0-2

↓

Intravenous infusion of enfortumab vedotin days 1 and 8 of a 21-day cycle plus intravenous pembrolizumab on day 1 of a 21-day cycle

↓

PRIMARY END POINT
Duration of progression-free survival and duration of overall survival

KEY SECONDARY END POINTS
Objective response rate, time to pain progression, and disease control rate

COMMENTARY

Kirollos S. Hanna, PharmD, BCPS, BCOP, FACCC
Director of Pharmacy at Minnesota Oncology, Assistant Professor of Pharmacy, Mayo Clinic College of Medicine and Science

Q / Can you summarize the recent FDA approval of enfortumab vedotin plus pembrolizumab for patients with locally advanced or metastatic urothelial cancer?

Hanna / For patients with bladder cancer, this was an exciting approval from the FDA. When you look at the numerous advances that we've seen in bladder cancer over the years, we've known that enfortumab vedotin has a role in patients with refractory or relapsed disease. We've also seen pembrolizumab bringing some benefits. The EV-302 study was exciting because it originally provided an accelerated approval for this patient population; there was the phase 1/2 EV-103 data [NCT03288545], and phase 3 EV-302 was the confirmatory study.[4]

Prior to the official FDA approval when the data were presented at the European Society for Medical Oncology [ESMO], this study received a standing ovation.[5] It was exciting just to see the benefit that this

brings to those patients in the frontline [setting] with metastatic bladder cancer because we haven't seen anything in a long time. That has, I would say, displaced standard cytotoxic chemotherapy.

When you look at EV-302, this was a randomized trial, with almost 900 patients. They had no prior systemic therapy, and they were either [randomly assigned] to pembrolizumab with enfortumab vedotin or put on standard cisplatin, platinum-based chemotherapy. We saw a significant benefit in the overall survival for the FDA approval: It was about a 31-and-a-half-month overall survival benefit with the combination [arm] vs only about 16 months in the patients who received platinum-based chemotherapy. This was something very, very significant—a lot of exciting things going on within the space. The National Comprehensive Cancer Network has placed this with some solid recommendations, what we saw come out of ESMO. Now with the FDA having granted accelerated approval, [there are] a lot of exciting things that we've seen with the bladder [cancer] population.

Q / What is the specific patient population that may be treated with this FDA-approved regimen?

Hanna / When you look at the patient population, there's not a unique patient who would benefit more than the other. When you look at the intent-to-treat population, [investigators] looked within the clinical trial based on various stratification criteria, they looked at the degree of PD-L1 expression, they looked at the degree of NECTIN4 expression. Regardless of that, these patients [showed a] benefit, so all-comers will benefit from this combination therapy. When you look at this patient population, a lot of times in that frontline setting, we start to ask ourselves, "Is this patient platinum eligible or platinum ineligible? Could they receive cisplatin? Should they receive carboplatin?" This [approval] takes that out of the equation. Given the combination therapy here, with this particular regimen, there's no particular expression that's needed.

An area where we're still learning a little bit more is those with muscle-invasive bladder cancer. These patients are still being treated with neoadjuvant chemotherapy, things like dose-dense MVAC [methotrexate, vinblastine, doxorubicin, and cisplatin], or a radical cystectomy. In some subsets of patients, they might receive adjuvant nivolumab [Opdivo]. If for some reason I see a unique patient who is on adjuvant nivolumab, in that muscle-invasive setting, and then progresses quickly, that might be a patient I might be a little bit hesitant to treat with the enfortumab vedotin plus pembrolizumab combination. We know they have just progressed on immunotherapy and quickly, so they might not get that maximum benefit from [the combination] therapy. While enfortumab vedotin will still be a very effective agent, that might be a patient I would consider maybe a different approach, depending on how long it's been from their chemotherapy administration.

We've seen a lot of exciting things move in this space as well. Just recently, we had nivolumab approved with combination chemotherapy, but then again, if [the patients] progressed fairly quickly on nivolumab, they wouldn't be an eligible candidate [for this combination treatment].[6]

Q / What are some safety considerations or any adverse effects [AEs] that are associated with this combination?

Hanna / When we look at the safety, we now have 2 therapeutics that are going to come with some shared [adverse] effects in some regard, but also significant differences when you look at enfortumab vedotin; it is cytotoxic in nature, while it is targeting NECTIN4 expression. It is cytotoxic through its payload, so we're going to be considering cytotoxic AEs. When you look at pembrolizumab, it's immunotherapy, and you're going to be worried about those immune-related AEs [iRAEs] that we're all very familiar with. When you talk about enfortumab vedotin, 3 things come to mind around AEs.

We need to be monitoring, and we should be vigilant of neuropathy whether a patient has preexisting neuropathy or not; the MMAE component is known to lead to neuropathy. It's generally sensory, but it does get better with dose reductions and dose modifications. We have to watch that in our patients. No. 2 is that with enfortumab vedotin, some of these patients might experience a rash, and in the clinical studies, about half of the patients experienced a rash. In rare cases, it could be a severe rash. It could be things like Stevens-Johnson syndrome. The reason for that is because we know there is NECTIN4 expression that is on the skin. As these patients are coming in for their infusion, whether you're using enfortumab vedotin for them as monotherapy or in combination with pembrolizumab, because there are some differences in the schedule, these patients will be coming in roughly every week. There's a lot of frequent touch points with these patients. When they are seeing our providers or when they are in the infusion center, we want to make sure that we are looking at their skin and having these evaluations. Don't just look at their extremities: Look at their chest, look at their back, and make sure that that rash, we want to catch it early vs getting to a severe stage. Again, that improves with dose holds and dose modifications, and supportive care as well.

The other thing that comes to mind with enfortumab vedotin is going to be hyperglycemia. Hyperglycemia can sometimes occur with this. We just want to monitor it. If you have a patient who is diabetic, maybe monitor it a little bit more closely. It can exacerbate the neuropathy if it's left uncontrolled, but just something to be cognizant of. Then, just being cytotoxic, you're going to want to watch out for any hematologic AEs as you would with any other cytotoxic

agent. The pembrolizumab is going to [result in] iRAEs. You have your standard iRAEs with the gastrointestinal AEs in your liver with alanine aminotransferase/aspartate aminotransferase elevations, transaminase impact, and skin toxicities.

The biggest thing is that skin AE I mentioned may be an immunotherapy-mediated rash, and you're not sure whether is it due to pembrolizumab or to enfortumab vedotin. Enfortumab vedotin tends to be a little bit more blistering, cracking the skin dry, and very rough vs the [immunotherapy] at a low grade might just be a small rash on the skin that's easy to manage. These are things we want to be cognizant of, the differences between the 2.

Q / How does the efficacy of the combination compare with that of others in the space?

Hanna / This is the very first study that has demonstrated a significant improvement outside of the standard of care for frontline metastatic bladder cancer prior to this study. One thing that does come to mind is the phase 3 JAVELIN Bladder 100 study [NCT02603432].[7] We haven't seen anything exciting in bladder cancer come in that frontline setting that I recall prior to JAVELIN Bladder 100 for a long time. JAVELIN Bladder 100 treated patients with platinum chemotherapy and then put them on avelumab [Bavencio] switch or maintenance therapy. That was one of the very first studies that enhanced the response in the frontline setting where immunotherapy demonstrated an improvement in overall survival over observation or best supportive care. That's what it was compared with.

We can look at EV-302, [where] you have these 2 drugs that have an 11- to 12-month overall survival benefit over platinum-containing chemotherapy. That is huge in terms of an efficacy perspective. We're all also familiar with these agents. We know that they are active in subsequent lines, as well. It was nice to see that combination.

In contrast to that, the FDA approved the combination of nivolumab with cisplatin and gemcitabine. The benefit there, and while I don't want to cross-trial compare, these weren't compared head-to-head, with these regimens, the overall survival benefit that we saw from nivolumab plus cisplatin and gemcitabine wasn't as significant as the difference we saw from pembrolizumab plus enfortumab vedotin. It will be interesting to see how [clinicians] leverage these, but the good thing about that indication is that if you do have that patient, for example, with preexisting neuropathy, and we're concerned about administering [enfortumab vedotin like] we now know, you can add nivolumab to cisplatin and gemcitabine, and then evaluate how your patient is going to be doing on that.

One challenge outside of the EV-302 study is the placement of immunotherapy. If you're [administering] platinum-containing chemotherapy, is it platinum-containing chemotherapy followed by avelumab maintenance a better approach? Or is the combination of nivolumab with platinum-containing chemotherapy a better approach all up front vs some sort of maintenance therapy? It'll be interesting to see how as the data continue to be followed and mature, how that pans out. Over 30 to 40 years, we have not seen something improve upon the overall survival benefit as drastically as we've seen from EV-302.

KEY PRESENTATIONS FROM THE

Society of Gynecologic Oncology Annual Meeting on Women's Cancer

During the 2024 conference, presentations highlighting gynecologic malignancies focused on improving efficacy and safety. There were also negative results reported, which can still help to advance the gynecologic oncology field.

Dostarlimab/Chemo Significantly Improves OS in Advanced Endometrial Cancer

The combination of dostarlimab-gxly (Jemperli) plus carboplatin/paclitaxel demonstrated a 31% improvement in overall survival (OS) compared with placebo/chemotherapy in patients with primary advanced or recurrent endometrial cancer, irrespective of microsatellite instability (MSI) status, according to findings from a second interim analysis of part 1 from the phase 3 ENGOT-EN6-NSGO/GOG-3031/RUBY trial (NCT03981796).

The results showed that the median OS was 44.6 months (95% CI, 32.6-not estimated [NE]) and 28.2 months (95% CI, 22.1-35.6) with dostarlimab and placebo/chemotherapy,

respectively (HR, 0.69; 95% CI, 0.54-0.89; *P* = .002) at 51.2% maturity and a median follow-up of 37.2 months. These data crossed the prespecified stopping boundary for OS (*P* = .01101) and were found to be statistically significant and clinically relevant. The 2- and 3-year OS rates for the dostarlimab arm were 70.1% and 54.9%, respectively; in the placebo arm, these rates were 54.3% and 42.9%, respectively.

At a median follow-up of 36.6 months in patients whose tumors were mismatch repair deficient (dMMR)/ MSI-high (MSI-H), the maturity rate was 39.8%. Here, the median OS was NE (95% CI, NE-NE) with dostarlimab compared with 31.4 months (95% CI, 20.3-NE) for placebo (HR, 0.32; 95% CI, 0.17-0.63), which was a substantial and unprecedented benefit in OS. The 2- and 3-year OS rates were 82.8% and 78.0%, respectively, with dostarlimab and 57.5% and 46.0%, with placebo.

In the proficient mismatch repair (pMMR)/microsatellite stable (MSS) subgroup, the median OS was 34.0 months (95% CI, 28.6-NE) with dostarlimab and 27.0 months (95% CI, 21.5-35.6) with placebo (HR, 0.79; 95% CI, 0.60-1.04) at a median follow-up of 37.5 months. The OS maturity rate was 54.8%. Two- and 3-year OS rates with dostarlimab were 66.5% and 48.6%, respectively; these rates were 53.2% and 41.9%, in the placebo arm.

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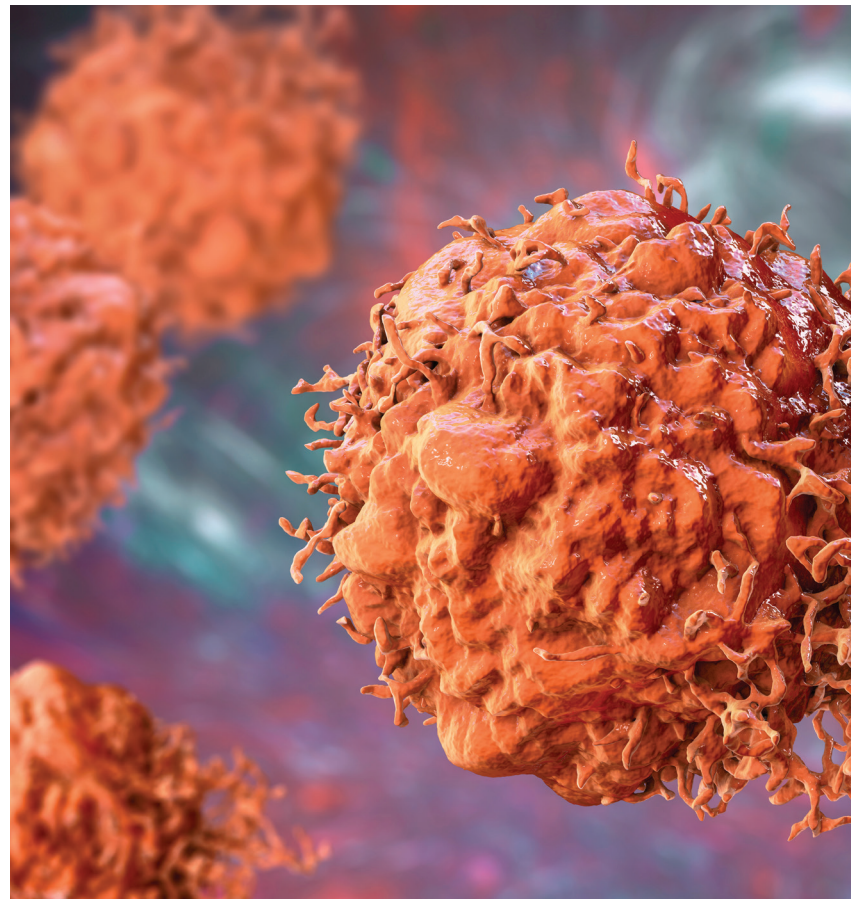

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Pembrolizumab Combo Yields Survival Benefit in Endometrial Cancer

Pembrolizumab (Keytruda) plus chemotherapy yielded a favorable overall survival (OS) benefit for patients with endometrial cancer, according to results from the phase 3 NRG-GY018/KEYNOTE-868 trial (NCT03914612).

During the interim analysis, the OS was immature. For those with mismatch repair proficient (pMMR) status, the median OS was 27.96 months (95% CI, 21.42-not reached [NR]) in the pembrolizumab arm vs 27.37 months (95% CI, 19.52-NR) in the placebo arm (HR, 0.79; 95% CI, 0.53-1.17; *P* = .1157). For those with mismatch repair deficient (dMMR) status, the median OS was not reached in either arm (HR, 0.55; 95% CI, 0.25-1.19; *P* = .0617).

For patients with pMMR disease, via investigator assessment, the median progression-free survival (PFS) was 13.1 months (95% CI, 10.6-19.5) in the pembrolizumab arm and 8.7 months (95% CI, 8.4-11.0) in the placebo arm (HR, 0.57; 95% CI, 0.44-0.74; *P* <.0001). In the blinded independent central review (BICR) assessment, the median PFS was 19.5 months (95% CI, 13.1-28.0) in the pembrolizumab arm and 11.0 months (95% CI, 9.0-11.5) in the placebo arm (HR, 0.64; 95% CI, 0.49-0.85; *P* = .0008).

In the pMMR population, the median PFS for those with a PD-L1 combined positive score (CPS) of 1 or more in the pembrolizumab arm was 13.1 months (95% CI, 9.1-19.8) vs 8.5 months (95% CI, 8.0-10.7) in the placebo arm (HR, 0.59; 95% CI, 0.43-0.80). For those with a PD-L1 CPS of less than 1, the median PFS in the pembrolizumab arm was 15.1 months (95% CI, 11.1-NR) vs 11.0 months (95% CI, 8.3-11.4) in the placebo arm (HR, 0.44; 95% CI, 0.26-0.75).

In patients with dMMR disease, the investigator-assessed median PFS was NR in the pembrolizumab arm (95% CI, 30.7-NR)

and 8.3 months (95% CI, 6.5-12.3) in the placebo group (HR, 0.34; 95% CI, 0.22-0.53; *P* <.0001). When evaluated via BICR, the median PFS was NR in the pembrolizumab arm (95% CI, NR-NR) and 14.1 months (95% CI, 8.5-NR) in the placebo arm (HR, 0.45; 95% CI, 0.27-0.73; *P* = .0005).

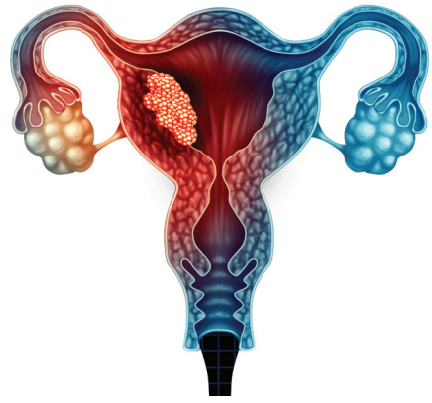
Those with dMMR disease with a PD-L1 CPS of 1 or more had a median PFS that was NR in the pembrolizumab arm (95% CI, NR-NR) and 8.3 months (95% CI, 6.5-14.1) in the placebo arm (HR, 0.27; 95% CI, 0.16-0.47). For those with a CPS of less than 1, the median PFS was 12.0 months (95% CI, 6.5-NR) in the pembrolizumab arm and 4.9 months (95% CI, 4.2-9.9) in the placebo arm (HR, 0.30; 95% CI, 0.11-0.83).

FOR FULL ARTICLE AND REFERENCES VISIT
cancernetwork.com/SGO24_KEYNOTE-868

Lenvatinib Combo Prolongs OS, PFS in Advanced Endometrial Cancer Subgroups

Combining lenvatinib (Lenvima) with pembrolizumab (Keytruda) improved overall survival (OS) and progression-free survival (PFS) compared with chemotherapy across most patients with advanced/recurrent endometrial cancer. However, prespecified statistical criteria for these end points among those with mismatch repair proficient (pMMR) disease were not fulfilled, according to findings from the phase 3 ENGOT-en9/LEAP-001 study (NCT03884101).

Across the prespecified analysis population, the median PFS was 9.6 months (95% CI, 8.2-11.9) with the combination vs 10.2 months (95% CI, 8.4-10.5) with chemotherapy for those with pMMR disease (HR, 0.99; 95%



CI, 0.82-1.21), and the median OS was 30.9 months (95% CI, 25.4-37.7) vs 29.4 months (95% CI, 26.2-35.4) in each arm (HR, 1.02; 95% CI, 0.83-1.26). In the all-comer population, the median PFS in each respective arm was 12.5 months (95% CI, 10.3-15.1) vs 10.2 months (95% CI, 8.4-10.4; HR, 0.91; 95% CI, 0.76-1.09), and the median OS was 37.7 months (95% CI, 32.2-43.6) vs 32.1 months (95% CI, 27.2-35.7; HR, 0.93; 95% CI, 0.77-1.12).

For patients with pMMR disease who received prior neoadjuvant or adjuvant chemotherapy, the median PFS was 12.5 months (95% CI, 6.5-20.3) with lenvatinib plus pembrolizumab vs 8.3 months (95% CI, 6.1-10.2) with chemotherapy (HR, 0.60; 95% CI, 0.37-0.97). The PFS rate in each respective arm was 51.0% vs 25.4% at 12 months and 26.6% vs 8.5% at 24 months. The median PFS was 15.0 months (95% CI, 8.3-21.0) vs 8.3 months (95% CI, 6.2-10.2) in each respective arm across the all-comer population (HR, 0.52; 95% CI, 0.33-0.82). Additionally, the 12-month PFS rate in this population was 56.1% vs 25.1%, and the 24-month rate was 31.8% vs 8.6%.

Among those with pMMR disease and prior receipt of neoadjuvant or adjuvant chemotherapy, the median OS was 34.2 months (95% CI, 22.0-not reached [NR]) in the lenvatinib/pembrolizumab arm vs 21.1 months (95% CI, 15.1-28.1) in the chemotherapy arm (HR, 0.67; 95% CI, 0.41-1.11). The OS rate in each arm was 81.1% vs 80.4% at 12 months and 62.3% vs 45.1% at 24 months. Among all-comers who received prior neoadjuvant or adjuvant chemotherapy, the median OS was 34.2 months (95% CI, 26.6-NR) vs 22.1 months (95% CI, 16.4-35.7) with lenvatinib/pembrolizumab vs chemotherapy, respectively (HR, 0.64; 95% CI, 0.40-1.03). The 12-month and 24-month OS rates in each arm were 84.1% vs 82.8% and 66.7% vs 46.6%, respectively.

In the pMMR population previously treated with adjuvant or neoadjuvant chemotherapy, the objective response rate (ORR) was 60.4% (95% CI, 46.0%-73.5%) with lenvatinib plus pembrolizumab and 43.1% (95% CI, 29.3%-57.8%) with chemotherapy. The median duration of response (DOR) in this population was 16.6 months (range, 2.1+ to 35.2+) vs 8.3 months (range, 2.2+ to 30.6+) across each respective arm. Among all-comers, the ORR was 63.5% (95% CI, 50.4%-75.3%) vs 43.1% (95% CI, 30.2%-56.8%) in each respective arm, and the median DOR was 19.9 months (range, 2.1+ to 35.4+) vs 8.3 months (range, 2.2+ to 30.6+). ■

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EVOLVE YOUR STRATEGY WITH TALVEY® (talquetamab-tgvs)

Learn more

INDICATION AND USAGE

TALVEY® (talquetamab-tgvs) is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

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

IMPORTANT SAFETY INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITY, including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

Cytokine release syndrome (CRS), including life-threatening or fatal reactions, can occur in patients receiving TALVEY®. Initiate TALVEY® treatment with step-up dosing to reduce the risk of CRS. Withhold TALVEY® until CRS resolves or permanently discontinue based on severity.

Neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), and serious and life-threatening or fatal reactions, can occur with TALVEY®. Monitor patients for signs and symptoms of neurologic toxicity including ICANS during treatment and treat promptly. Withhold or permanently discontinue TALVEY® based on severity.

Because of the risk of CRS and neurologic toxicity, including ICANS, TALVEY® is available only through a restricted program called the TECVAYLI® and TALVEY® Risk Evaluation and Mitigation Strategy (REMS).

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS

Cytokine Release Syndrome (CRS): TALVEY® can cause cytokine release syndrome, including life-threatening or fatal reactions. In the clinical trial, CRS occurred in 76% of patients who received TALVEY® at the recommended dosages, with Grade 1 CRS occurring in 57% of patients, Grade 2 in 17%, and Grade 3 in 1.5%. Most events occurred following step-up dose 1 (29%) or step-up dose 2 (44%) at the recommended dosages. Recurrent CRS occurred in 30% of patients. CRS occurred in 33% of patients with step-up dose 3 in the biweekly dosing schedule (N=153). CRS occurred in 30% of patients with the first 0.4 mg/kg treatment dose and in 12% of patients treated with the first 0.8 mg/kg treatment dose. The CRS rate for both dosing schedules combined was less than 3% for each of the remaining doses in Cycle 1 and less than 3% cumulatively from Cycle 2 onward. The median time to onset of CRS was 27 (range: 0.1 to 167) hours from the last dose, and the median duration was 17 (range: 0 to 622) hours. Clinical signs and symptoms of CRS include but are not limited to pyrexia, hypotension, chills, hypoxia, headache, and tachycardia. Potentially life-threatening complications of CRS may include cardiac dysfunction, acute respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation (DIC).

Initiate therapy with step-up dosing and administer pre-treatment medications (corticosteroids, antihistamine, and antipyretics) prior to each dose of TALVEY® in the step-up dosing schedule to reduce the risk of CRS. Monitor patients following administration accordingly. In patients who experience CRS, pre-treatment medications should be administered prior to the next TALVEY® dose.

Counsel patients to seek medical attention should signs or symptoms of CRS occur. At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care based on severity, and consider further management per current practice guidelines. Withhold TALVEY® until CRS resolves or permanently discontinue based on severity.

Neurologic Toxicity including ICANS: TALVEY® can cause serious or life-threatening neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), including fatal reactions. In the clinical trial, neurologic toxicity occurred in 55% of patients who received the recommended dosages, with Grade 3 or 4 neurologic toxicity occurring in 6% of patients. The most frequent neurologic toxicities were headache (20%), encephalopathy (15%), sensory neuropathy (14%), and motor dysfunction (10%).

ICANS was reported in 9% of 265 patients where ICANS was collected and who received the recommended dosages. Recurrent ICANS occurred in 3% of patients. Most patients experienced ICANS following step-up dose 1 (3%), step-up dose 2 (3%), step-up dose 3 of the biweekly dosing schedule (1.8%), or the initial treatment dose of the weekly dosing schedule (2.6%) (N=156) or the biweekly dosing schedule (3.7%) (N=109). The median time to onset of ICANS was 2.5 (range: 1 to 16) days after the most recent dose with a median duration of 2 (range: 1 to 22) days. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Clinical signs and symptoms of ICANS may include but are not limited to confusional state, depressed level of consciousness, disorientation, somnolence, lethargy, and bradyphrenia.

Monitor patients for signs and symptoms of neurologic toxicity during treatment and treat promptly. At the first sign of neurologic toxicity, including ICANS, immediately evaluate the patient and provide supportive care based on severity. Withhold or permanently discontinue TALVEY® based on severity and consider further management per current practice guidelines [see Dosage and Administration (2.5)].

Due to the potential for neurologic toxicity, patients receiving TALVEY® are at risk of depressed level of consciousness. Advise patients to refrain from driving or operating heavy or potentially dangerous machinery during the step-up dosing schedule and for 48 hours after completion of the step-up dosing schedule, and in the event of new onset of any neurological symptoms, until symptoms resolve.

TECVAYLI® and TALVEY® REMS: TALVEY® is available only through a restricted program under a REMS, called the TECVAYLI® and TALVEY® REMS because of the risks of CRS and neurologic toxicity, including ICANS.

Further information about the TECVAYLI® and TALVEY® REMS program is available at www.TEC-TALREMS.com or by telephone at 1-855-810-8064.

TALVEY®
(talquetamab-tgvs) Injection for subcutaneous use
2 mg/mL and 40 mg/mL

Make Your Move

First-in-class GPRC5D × CD3 targeting agent[1,2]

Powerful efficacy demonstrated with TALVEY® monotherapy[1,3,4]

MonumenTAL-1 study design: The efficacy of TALVEY® was evaluated in 219 patients with relapsed or refractory multiple myeloma in the single-arm, open-label, multicenter, phase 1/2 trial. The trial included patients who had received ≥3 prior systemic therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. Efficacy was based on ORR and DOR as assessed by an IRC using IMWG criteria.*

Naïve to T-cell redirection therapy†

- **73.6%** ORR‡ with Q2W dosing (95% CI, 63.0%-82.4%) (n=65/87)
- **73%** ORR‡ with QW dosing (95% CI, 63.2%-81.4%) (n=73/100)

Exposed to T-cell redirection therapy†

- **72%** ORR‡ with QW dosing (95% CI, 53%-86%) (n=23/32)§

Versatile treatment option for patients naïve and exposed to T-cell redirection therapy[1]

The MonumenTAL-1 study included patients who were naïve and exposed to T-cell redirection therapy.†§

Flexible dosing: either Q2W or QW dosing schedule right from the start[1]

Q2W and QW dosing begins after the respective step-up dosing schedule.

Oral Toxicity and Weight Loss: TALVEY® can cause oral toxicities, including dysgeusia, dry mouth, dysphagia, and stomatitis. In the clinical trial, 80% of patients had oral toxicity, with Grade 3 occurring in 2.1% of patients who received the recommended dosages. The most frequent oral toxicities were dysgeusia (49%), dry mouth (34%), dysphagia (23%), and ageusia (18%). The median time to onset of oral toxicity was 15 (range: 1 to 634) days, and the median time to resolution to baseline was 43 (1 to 530) days. Oral toxicity did not resolve to baseline in 65% of patients.

TALVEY® can cause weight loss. In the clinical trial, 62% of patients experienced weight loss of 5% or greater, regardless of having an oral toxicity, including 28% of patients with Grade 2 (10% or greater) weight loss and 2.7% of patients with Grade 3 (20% or greater) weight loss. The median time to onset of Grade 2 or higher weight loss was 67 (range: 6 to 407) days, and the median time to resolution was 50 (range: 1 to 403) days. Weight loss did not resolve in 57% of patients who reported weight loss.

Monitor patients for signs and symptoms of oral toxicity. Counsel patients to seek medical attention should signs or symptoms of oral toxicity occur and provide supportive care as per current clinical practice, including consultation with a nutritionist. Monitor weight regularly during therapy. Evaluate clinically significant weight loss further. Withhold TALVEY® or permanently discontinue based on severity.

Infections: TALVEY® can cause infections, including life-threatening or fatal infections. Serious infections occurred in 16% of patients, with fatal infections in 1.5% of patients. Grade 3 or 4 infections occurred in 17% of patients. The most common serious infections reported were bacterial infection (8%), which included sepsis and COVID-19 (2.7%).

Monitor patients for signs and symptoms of infection prior to and during treatment with TALVEY® and treat appropriately. Administer prophylactic antimicrobials according to local guidelines. Withhold or consider permanent discontinuation of TALVEY® as recommended, based on severity.

Cytopenias: TALVEY® can cause cytopenias, including neutropenia and thrombocytopenia. In the clinical trial, Grade 3 or 4 decreased neutrophils occurred in 35% of patients, and Grade 3 or 4 decreased platelets occurred in 22% of patients who received TALVEY®. The median time to onset for Grade 3 or 4 neutropenia was 22 (range: 1 to 312) days, and the median time to resolution to Grade 2 or lower was 8 (range: 1 to 79) days. The median time to onset for Grade 3 or 4 thrombocytopenia was 12 (range: 2 to 183) days, and the median time to resolution to Grade 2 or lower was 10 (range: 1 to 64) days. Monitor complete blood counts during treatment and withhold TALVEY® as recommended, based on severity.

Skin Toxicity: TALVEY® can cause serious skin reactions, including rash, maculo-papular rash, erythema, and erythematous rash. In the clinical trial, skin reactions occurred in 62% of patients, with grade 3 skin reactions in 0.3%. The median time to onset was 25 (range: 1 to 630) days. The median time to improvement to grade 1 or less was 33 days.

Monitor for skin toxicity, including rash progression. Consider early intervention and treatment to manage skin toxicity. Withhold TALVEY® as recommended based on severity.

Hepatotoxicity: TALVEY® can cause hepatotoxicity. Elevated ALT occurred in 33% of patients, with grade 3 or 4 ALT elevation occurring in 2.7%; elevated AST occurred in 31% of patients, with grade 3 or 4 AST elevation occurring in 3.3%. Grade 3 or 4 elevations of total bilirubin occurred in 0.3% of patients. Liver enzyme elevation can occur with or without concurrent CRS.

Monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated. Withhold TALVEY® or consider permanent discontinuation of TALVEY®, based on severity [see Dosage and Administration (2.5)].

Embryo-Fetal Toxicity: Based on its mechanism of action, TALVEY® may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with TALVEY® and for 3 months after the last dose.

Adverse Reactions: The most common adverse reactions (≥20%) are pyrexia, CRS, dysgeusia, nail disorder, musculoskeletal pain, skin disorder, rash, fatigue, weight decreased, dry mouth, xerosis, dysphagia, upper respiratory tract infection, diarrhea, hypotension, and headache.

The most common Grade 3 or 4 laboratory abnormalities (≥30%) are lymphocyte count decreased, neutrophil count decreased, white blood cell decreased, and hemoglobin decreased.

Please see Brief Summary of full Prescribing Information, including Boxed WARNING for TALVEY®, on adjacent pages.

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*Efficacy results reflect patients who received ≥4 prior lines of therapy.
†T-cell redirection therapy refers to both CAR-T and bispecific antibody therapy.
‡ORR: sCR+CR+VGPR+PR.
§Of 32 patients, 81% had prior CAR-T, 25% had prior bispecific antibody therapy, and 94% had prior BCMA-directed therapy.

BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor-T cell; CD, cluster of differentiation; CI, confidence interval; CR, complete response; DOR, duration of response; GPRC5D, G protein-coupled receptor class C group 5 member D; IMWG, International Myeloma Working Group; IRC, Independent Review Committee; ORR, overall response rate; PR, partial response; QW, once weekly; Q2W, every 2 weeks; sCR, stringent complete response; VGPR, very good partial response.

References: 1. TALVEY® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** U.S. FDA approves TALVEY® (talquetamab-tgvs), a first-in-class bispecific therapy for the treatment of patients with heavily pretreated multiple myeloma. News release. Janssen Biotech, Inc.; August 10, 2023. Accessed January 9, 2024. https://www.janssen.com/fda-approves-talveytm-talquetamab-tgvs-first-class-bispecific-therapy-treatment-patients-heavily **3.** Data on file. Janssen Biotech, Inc. **4.** A study of Talquetamab in participants with relapsed or refractory multiple myeloma. ClinicalTrials.gov identifier: NCT04634552. Updated January 3, 2024. Accessed January 9, 2024. https://clinicaltrials.gov/ct2/show/NCT04634552

Johnson&Johnson

01/24 cp-371120v1

Brief Summary of Prescribing Information for TALVEY™ (talquetamab-tgvs)
TALVEY™ (talquetamab-tgvs) injection, for subcutaneous use

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITY, including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

Cytokine release syndrome (CRS), including life-threatening or fatal reactions, can occur in patients receiving TALVEY. Initiate TALVEY treatment with step-up dosing to reduce the risk of CRS. Withhold TALVEY until CRS resolves or permanently discontinue based on severity *[see Dosage and Administration (2.2, 2.5) in Full Prescribing Information, Warnings and Precautions]*.

Neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), and serious and life threatening or fatal reactions, can occur with TALVEY. Monitor patients for signs and symptoms of neurologic toxicity including ICANS during treatment and treat promptly. Withhold or permanently discontinue TALVEY based on severity *[see Dosage and Administration (2.5) in Full Prescribing Information, Warnings and Precautions]*.

Because of the risk of CRS and neurologic toxicity, including ICANS, TALVEY is available only through a restricted program called the TECVAYLI and TALVEY Risk Evaluation and Mitigation Strategy (REMS) *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

TALVEY is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

This indication is approved under accelerated approval based on response rate and durability of response *[see Clinical Studies (14) in Full Prescribing Information]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Cytokine Release Syndrome (CRS)

TALVEY can cause cytokine release syndrome, including life-threatening or fatal reactions *[see Adverse Reactions]*.

In the clinical trial, CRS occurred in 76% of patients who received TALVEY at the recommended dosages, with Grade 1 CRS occurring in 57% of patients, Grade 2 in 17%, and Grade 3 in 1.5%. Recurrent CRS occurred in 30% of patients. Most events occurred following step-up dose 1 (29%) or step-up dose 2 (44%) at the recommended dosages. CRS occurred in 33% of patients with step-up dose 3 in the biweekly dosing schedule (N=153). CRS occurred in 30% of patients with the first 0.4 mg/kg treatment dose and in 12% of patients treated with the first 0.8 mg/kg treatment dose. The CRS rate for both dosing schedules combined was less than 3% for each of the remaining doses in Cycle 1 and less than 3% cumulatively from Cycle 2 onward. The median time to onset of CRS was 27 (range: 0.1 to 167) hours from the last dose, and the median duration was 17 (range: 0 to 622) hours. Clinical signs and symptoms of CRS include but are not limited to pyrexia, hypotension, chills, hypoxia, headache, and tachycardia. Potentially life-threatening complications of CRS may include cardiac dysfunction, acute respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation (DIC).

Initiate TALVEY therapy with step-up dosing and administer pre-treatment medications (corticosteroids, antihistamine, and antipyretics) prior to each dose of TALVEY in the step-up dosing schedule to reduce the risk of CRS. Monitor patients following administration accordingly. In patients who experience CRS, pre-treatment medications should be administered prior to the next TALVEY dose *[see Dosage and Administration (2.2, 2.3) in Full Prescribing Information]*.

Counsel patients to seek medical attention should signs or symptoms of CRS occur. At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care based on severity and consider further management per current practice guidelines. Withhold TALVEY until CRS resolves or permanently discontinue based on severity *[see Dosage and Administration (2.5) in Full Prescribing Information]*.

TALVEY is available only through a restricted program under a REMS *[see Warnings and Precautions]*.

Neurologic Toxicity including ICANS

TALVEY can cause serious, life-threatening, or fatal neurologic toxicity, including ICANS *[see Adverse Reactions]*.

In the clinical trial, neurologic toxicity, including ICANS, occurred in 55% of patients who received TALVEY at the recommended dosages, with Grade 3 or 4 neurologic toxicity occurring in 6% of patients. The most frequent neurologic toxicities were headache (20%), encephalopathy (15%), sensory neuropathy (14%), and motor dysfunction (10%).

ICANS was reported in 9% of 265 patients where ICANS was collected and who received TALVEY at the recommended dosages *[see Adverse Reactions]*. Recurrent ICANS occurred in 3% of patients. Most patients experienced ICANS following step-up dose 1 (3%), step-up dose 2 (3%), step-up dose 3 of the biweekly dosing schedule (1.8%), or the initial treatment dose of the weekly dosing schedule (2.6%) (N=156) or the biweekly dosing schedule (3.7%) (N=109). The median time to onset of ICANS was 2.5 (range: 1 to 16) days after the most recent dose with a median duration of 2 (range: 1 to 22) days. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Clinical signs and symptoms of ICANS may include but are not limited to confusional state, depressed level of consciousness, disorientation, somnolence, lethargy, and bradyphrenia.

Monitor patients for signs and symptoms of neurologic toxicity during treatment. At the first sign of neurologic toxicity, including ICANS, immediately evaluate the patient and provide supportive care based on severity; withhold or permanently discontinue TALVEY based on severity and consider further management per current practice guidelines *[see Dosage and Administration (2.5) in Full Prescribing Information]*.

Due to the potential for neurologic toxicity, patients receiving TALVEY are at risk of depressed level of consciousness. Advise patients to refrain from driving or operating heavy or potentially dangerous machinery during the step-up dosing schedule and for 48 hours after completion of the step-up dosing schedule *[see Dosage and Administration (2.2) in Full Prescribing Information]* and in the event of new onset of any neurological symptoms, until symptoms resolve.

TALVEY is available only through a restricted program under a REMS *[see Warnings and Precautions]*.

TECVAYLI and TALVEY REMS

TALVEY is available only through a restricted program under a REMS called the TECVAYLI and TALVEY REMS because of the risks of CRS and neurologic toxicity, including ICANS *[see Warnings and Precautions]*.

Notable requirements of the TECVAYLI and TALVEY REMS include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- Prescribers must counsel patients receiving TALVEY about the risk of CRS and neurologic toxicity, including ICANS and provide patients with Patient Wallet Card.
- Pharmacies and healthcare settings that dispense TALVEY must be certified with the TECVAYLI and TALVEY REMS program and must verify prescribers are certified through the TECVAYLI and TALVEY REMS program.
- Wholesalers and distributers must only distribute TALVEY to certified pharmacies.

Further information about the TECVAYLI and TALVEY REMS program is available at www.TEC-TALREMS.com or by telephone at 1-855-810-8064.

Oral Toxicity and Weight Loss

TALVEY can cause oral toxicities, including dysgeusia, dry mouth, dysphagia, and stomatitis *[see Adverse Reactions]*.

In the clinical trial, 80% of patients had oral toxicity, with Grade 3 occurring in 2.1% of patients who received TALVEY at the recommended dosages. The most frequent oral toxicities were dysgeusia (49%), dry mouth (34%), dysphagia (23%), and ageusia (18%). The median time to onset of oral toxicity was 15 (range: 1 to 634) days, and the median time to resolution to baseline was 43 (1 to 530) days. Oral toxicity did not resolve to baseline in 65% of patients.

TALVEY can cause weight loss *[see Adverse Reactions]*. In the clinical trial, 62% of patients experienced weight loss, regardless of having an oral toxicity, including 29% of patients with Grade 2 (10% or greater) weight loss and 2.7% of patients with Grade 3 (20% or greater) weight loss. The median time to onset of Grade 2 or higher weight loss was 67 (range: 6 to 407) days, and the median time to resolution was 50 (range: 1 to 403) days. Weight loss did not resolve in 57% of patients who reported weight loss.

Monitor patients for signs and symptoms of oral toxicity. Counsel patients to seek medical attention should signs or symptoms of oral toxicity occur and provide supportive care as per current clinical practice including consultation with a nutritionist. Monitor weight regularly during therapy. Evaluate clinically significant weight loss further. Withhold TALVEY or permanently discontinue based on severity *[see Dosage and Administration (2.5) in Full Prescribing Information]*.

Infections

TALVEY can cause serious infections, including life-threatening or fatal infections *[see Adverse Reactions]*.

In the clinical trial, serious infections occurred in 16% of patients, with fatal infections in 1.5% of patients. Grade 3 or 4 infections occurred in 17% of patients. The most common serious infections reported were bacterial infection (8%), which included sepsis, and COVID-19 (2.7%).

Monitor patients for signs and symptoms of infection prior to and during treatment with TALVEY and treat appropriately. Administer prophylactic antimicrobials according to local guidelines. Withhold or consider permanent discontinuation of TALVEY as recommended based on severity *[see Dosage and Administration (2.5) in Full Prescribing Information]*.

Cytopenias

TALVEY can cause cytopenias, including neutropenia and thrombocytopenia *[see Adverse Reactions]*.

In the clinical trial, Grade 3 or 4 decreased neutrophils occurred in 35% of patients, and Grade 3 or 4 decreased platelets occurred in 22% of patients who received TALVEY. The median time to onset for Grade 3 or 4 neutropenia was 22 (range: 1 to 312) days, and the median time to resolution to Grade 2 or lower was 8 (range: 1 to 79) days. The median time to onset for Grade 3 or 4 thrombocytopenia was 12 (range: 2 to 183) days, and the median time to resolution to Grade 2 or lower was 10 (range: 1 to 64) days. Monitor complete blood counts during treatment and withhold TALVEY as recommended based on severity *[see Dosage and Administration (2.5) in Full Prescribing Information]*.

Skin Toxicity

TALVEY can cause serious skin reactions, including rash, maculo-papular rash, erythema, and erythematous rash *[see Adverse Reactions]*.

In the clinical trial, skin reactions occurred in 62% of patients, with Grade 3 skin reactions in 0.3%. The median time to onset was 25 (range: 1 to 630) days. The median time to improvement to Grade 1 or less was 33 days.

Monitor for skin toxicity, including rash progression. Consider early intervention and treatment to manage skin toxicity. Withhold TALVEY as recommended based on severity *[see Dosage and Administration (2.5) in Full Prescribing Information]*.

Hepatotoxicity

TALVEY can cause hepatoxicity. In the clinical trial, elevated ALT occurred in 33% of patients, with Grade 3 or 4 ALT elevation occurring in 2.7%; elevated AST occurred in 31% of patients, with Grade 3 or 4 AST elevation occurring in 3.3%. Grade 3 or 4 elevations of total bilirubin occurred in 0.3% of patients *[see Adverse Reactions]*. Liver enzyme elevation can occur with or without concurrent CRS.

Monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated. Withhold TALVEY or consider permanent discontinuation of TALVEY based on severity *[see Dosage and Administration (2.5) in Full Prescribing Information]*.

Embryo-Fetal Toxicity

Based on its mechanism of action, TALVEY may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with TALVEY and for 3 months after the last dose *[see Use in Specific Populations]*.

ADVERSE REACTIONS

The following adverse reactions are also described elsewhere in the labeling:

- Cytokine Release Syndrome *[see Warnings and Precautions]*
- Neurologic Toxicity, including ICANS *[see Warnings and Precautions]*
- Oral Toxicity and Weight Loss *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Cytopenias *[see Warnings and Precautions]*
- Skin Toxicity *[see Warnings and Precautions]*
- Hepatotoxicity *[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.

Relapsed/Refractory Multiple Myeloma

MonumenTAL-1

The safety of TALVEY was evaluated in 339 adult patients with relapsed or refractory multiple myeloma. Patients treated with the weekly dosing schedule received step-up doses of 0.01 mg/kg and 0.06 mg/kg of TALVEY followed by TALVEY 0.4 mg/kg subcutaneously weekly thereafter. Patients treated with the biweekly (every 2 weeks) dosing schedule received step-up doses of 0.01 mg/kg, 0.06 mg/kg, and 0.3 mg/kg (0.75 times the recommended step-up dose 3) followed by TALVEY 0.8 mg/kg subcutaneously every 2 weeks thereafter. The duration of exposure for the 0.4 mg/kg weekly regimen was 5.9 (range: 0.0 to 25.3) months (N=186) and for the 0.8 mg/kg biweekly (every 2 weeks) regimen, it was 3.7 (range: 0.0 to 17.9) months (N=153).

Serious adverse reactions occurred in 47% of patients who received TALVEY. Serious adverse reactions in ≥ 2% of patients included CRS (13%), bacterial infection (8%) including sepsis, pyrexia (4.7%), ICANS (3.8%), COVID-19 (2.7%), neutropenia (2.1%), and upper respiratory tract infection (2.1%).

Fatal adverse reactions occurred in 3.2% of patients who received TALVEY, including COVID-19 (0.6%), dyspnea (0.6%), general physical health deterioration (0.6%), bacterial infection (0.3%) including sepsis, basilar artery occlusion (0.3%), fungal infection (0.3%), infection (0.3%), and pulmonary embolism (0.3%).

Permanent discontinuation of TALVEY due to an adverse reaction occurred in 9% of patients. Adverse reactions which resulted in permanent discontinuation of TALVEY in > 1% of patients included ICANS.

Dosage interruptions of TALVEY due to an adverse reaction occurred in 56% of patients. Adverse reactions which required dosage interruption in > 5% of patients included pyrexia (15%), CRS (12%), upper respiratory tract infection (9%), COVID-19 (9%), bacterial infection (7%) including sepsis, neutropenia (6%), and rash (6%).

The most common adverse reactions (≥ 20%) were pyrexia, CRS, dysgeusia, nail disorder, musculoskeletal pain, skin disorder, rash, fatigue, weight decreased, dry mouth, xerosis, dysphagia, upper respiratory tract infection, diarrhea, hypotension, and headache. The most common Grade 3 or 4 laboratory abnormalities (≥ 30%) were lymphocyte count decreased, neutrophil count decreased, white blood cell decreased, and hemoglobin decreased.

Table 1 summarizes the adverse reactions in MonumenTAL-1.

Table 1: Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Multiple Myeloma Who Received TALVEY in MonumenTAL-1

	TALVEY N=339	
System Organ Class Adverse Reaction	**Any Grade (%)**	**Grade 3 or 4 (%)**
General disorders and administration site conditions		
Pyrexia*	83	4.7†
Fatigue*	37	3.5†
Chills	19	0
Pain*	18	1.8†
Edema*	14	0
Injection site reaction*	13	0
Immune system disorders		
Cytokine release syndrome	76	1.5†
Gastrointestinal disorders		
Dysgeusia[1] ‡	70	0
Dry mouth ‡	34	0
Dysphagia	23	0.9†
Diarrhea	21	0.9†
Stomatitis[2]	18	1.2†
Nausea	18	0
Constipation	16	0
Oral disorder[3]	12	0
Skin and subcutaneous tissue disorders		
Nail disorder[4]	50	0
Skin disorder[5]	41	0.3†
Rash[6]	38	3.5†
Xerosis[7]	30	0
Pruritus	19	0.3†
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain*	43	3.2†
Investigations		
Weight decreased	35	1.5†
Infections and infestations		
Upper respiratory tract infection*	22	2.7†
Bacterial infection including sepsis[8#]	19	9
COVID-19*#	11	2.7
Fungal infection[9#]	10	0.6
Vascular disorders		
Hypotension*	21	2.9
Nervous system disorders		
Headache*	21	0.6†
Encephalopathy[10]	15	1.8†
Sensory neuropathy[11]	14	0
Motor dysfunction[12]	10	0.6†
Metabolism and nutrition disorders		
Decreased appetite	19	1.2†
Respiratory, thoracic and mediastinal disorders		
Cough*	17	0
Dyspnea*#	11	1.8
Hypoxia*	10	1.5†
Cardiac disorders		
Tachycardia*	11	0.6†

Adverse reactions were graded based on CTCAE Version 4.03, with the exception of CRS, which was graded per ASTCT 2019 criteria.

* Includes other related terms.

\# Includes fatal outcome(s): COVID-19 (N=2), dyspnea (N=2), bacterial infection including sepsis (N=1), fungal infection (N=1).

† Only grade 3 adverse reactions occurred.

‡ Per CTCAE v4.03, maximum toxicity grade for dysgeusia is 2 and maximum toxicity grade for dry mouth is 3.

[1] Dysgeusia: ageusia, dysgeusia, hypogeusia and taste disorder.
[2] Stomatitis: cheilitis, glossitis, glossodynia, mouth ulceration, oral discomfort, oral mucosal erythema, oral pain, stomatitis, swollen tongue, tongue discomfort, tongue erythema, tongue edema and tongue ulceration.
[3] Oral disorder: oral disorder, oral dysesthesia, oral mucosal exfoliation, oral toxicity and oropharyngeal pain.
[4] Nail disorder: koilonychia, nail bed disorder, nail cuticle fissure, nail discoloration, nail disorder, nail dystrophy, nail hypertrophy, nail pitting, nail ridging, nail toxicity, onychoclasis, onycholysis and onychomadesis.
[5] Skin disorder: palmar-plantar erythrodysesthesia syndrome, palmoplantar keratoderma, skin discoloration, skin exfoliation and skin fissures.
[6] Rash: dermatitis, dermatitis acneiform, dermatitis contact, dermatitis exfoliative, dermatitis exfoliative generalized, erythema, exfoliative rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular and stasis dermatitis.
[7] Xerosis: dry eye, dry skin and xerosis.
[8] Bacterial infection including sepsis: bacteremia, bacterial prostatitis, carbuncle, cellulitis, citrobacter infection, clostridium difficile colitis, clostridium difficile infection, cystitis escherichia, cystitis klebsiella, diverticulitis, enterobacter bacteremia, escherichia pyelonephritis, escherichia sepsis, folliculitis, gastroenteritis escherichia coli, helicobacter gastritis, human ehrlichiosis, klebsiella bacteremia, klebsiella sepsis, moraxella infection, otitis media acute, pitted keratolysis, pneumococcal sepsis, pneumonia, pneumonia streptococcal, pseudomonal bacteremia, pyuria, renal abscess, salmonella sepsis, sepsis, septic shock, skin infection, staphylococcal bacteremia, staphylococcal infection, staphylococcal sepsis, streptococcal bacteremia, tooth abscess, tooth infection, urinary tract infection enterococcal, and urinary tract infection pseudomonal.
[9] Fungal infection: body tinea, candida infection, ear infection fungal, esophageal candidiasis, fungal infection, fungal sepsis, fungal skin infection, genital candidiasis, onychomycosis, oral candidiasis, oral fungal infection, oropharyngeal candidiasis, tinea pedis, vulvovaginal candidiasis, and vulvovaginal mycotic infection.
[10] Encephalopathy: agitation, altered state of consciousness, amnesia, aphasia, bradyphrenia, confusional state, delirium, depressed level of consciousness, disorientation, encephalopathy, hallucination, lethargy, memory impairment, mood altered, restlessness, sleep disorder and somnolence.
[11] Sensory neuropathy: dysesthesia, hyperesthesia, hypoesthesia, hypoesthesia oral, immune-mediated neuropathy, neuralgia, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, polyneuropathy, sciatica and vestibular neuronitis.
[12] Motor dysfunction: dysarthria, dysgraphia, dysmetria, dysphonia, gait disturbance, muscle atrophy, muscle spasms, muscular weakness and tremor.

Clinically relevant adverse reactions reported in <10% of patients who received TALVEY included ICANS and viral infection.

Table 2 summarizes select laboratory abnormalities in MonumenTAL-1.

Table 2: Select Laboratory Abnormalities (≥30%) That Worsened from Baseline in Patients with Relapsed or Refractory Multiple Myeloma Who Received TALVEY in MonumenTAL-1

	TALVEY[1]	
Laboratory Abnormality	**Any Grade (%)**	**Grade 3 or 4 (%)**
Hematology		
Lymphocyte count decreased	90	80
White blood cell decreased	73	35
Hemoglobin decreased	67	30
Neutrophil count decreased	64	35
Platelet count decreased	62	22
Chemistry		
Albumin decreased	66	2.1
Alkaline phosphatase increased	49	1.5
Phosphate decreased	44	13
Gamma-glutamyl transferase increased	38	7
Alanine aminotransferase increased	33	2.7
Potassium decreased	31	4.4
Sodium decreased	31	6
Aspartate aminotransferase increased	31	3.3

[1] The denominator used to calculate the rate varied from 326 to 338 based on the number of patients with a baseline value and at least one post-treatment value.

Laboratory toxicity grades are derived based on the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.

DRUG INTERACTIONS

For certain cytochrome P450 (CYP) substrates, minimal changes in the substrate concentration may lead to serious adverse reactions. Monitor for toxicity or drug concentrations of such CYP substrates when co-administered with TALVEY.

TALVEY™ (talquetamab-tgvs) injection

Talquetamab-tgvs causes release of cytokines *[see Clinical Pharmacology (12.2) in Full Prescribing Information]* that may suppress activity of CYP enzymes, resulting in increased exposure of CYP substrates. Increased exposure of CYP substrates is more likely to occur from initiation of the TALVEY step-up dosing schedule up to 14 days after the first treatment dose and during and after CRS *[see Warnings and Precautions]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on the mechanism of action, TALVEY may cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) in Full Prescribing Information]*. There are no available data on the use of TALVEY in pregnant women to evaluate for a drug associated risk. No animal reproductive or developmental toxicity studies have been conducted with talquetamab-tgvs.

Talquetamab-tgvs causes T-cell activation and cytokine release; immune activation may compromise pregnancy maintenance. Human immunoglobulin G (IgG) is known to cross the placenta; therefore, TALVEY has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to the fetus.

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

There is no information regarding the presence of talquetamab-tgvs in human milk, the effect on the breastfed child, or the effect on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to TALVEY are unknown. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with TALVEY and for 3 months after the last dose.

Females and Males of Reproductive Potential

TALVEY may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*.

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating TALVEY.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with TALVEY and for 3 months after the last dose.

Pediatric Use

The safety and efficacy of TALVEY have not been established in pediatric patients.

Geriatric Use

There were 339 patients in the clinical trial for relapsed or refractory multiple myeloma. Of the total number of TALVEY-treated patients in the study, 178 (53%) patients were 65 years of age and older, while 57 (17%) patients were 75 years of age and older. No overall differences in safety or effectiveness were observed in patients 65 to less than 74 years of age compared to younger patients. There was a higher rate of fatal adverse reactions in patients 75 years of age or older compared to younger patients *[see Adverse Reactions]*. Clinical studies did not include sufficient numbers of patients 75 years of age or over to determine whether they respond differently from younger patients.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Cytokine Release Syndrome (CRS)

Discuss the signs and symptoms associated with CRS including, but not limited to, pyrexia, hypotension, chills, hypoxia, headache, and tachycardia. Counsel patients to seek medical attention should signs or symptoms of CRS occur. Advise patients that they should be hospitalized for 48 hours after administration of all doses within the TALVEY step-up dosing schedule *[see Dosage and Administration (2.1, 2.5) in Full Prescribing Information, Warnings and Precautions]*.

Neurologic Toxicity, including ICANS

Discuss the signs and symptoms associated with neurologic toxicity, including ICANS including headache, encephalopathy, sensory neuropathy, motor dysfunction, ICANS, confusional state, depressed level of consciousness, disorientation, somnolence, lethargy, and bradyphrenia. Counsel patients to seek medical attention should signs or symptoms of ICANS occur. Advise patients to refrain from driving or operating heavy or potentially dangerous

machinery during the step-up dosing schedule and for 48 hours after completion of the step-up dosing schedule and in the event of new onset of any neurologic toxicity symptoms, until symptoms resolve *[see Dosage and Administration (2.2, 2.5) in Full Prescribing Information, Warnings and Precautions]*.

TECVAYLI and TALVEY REMS

TALVEY is available only through a restricted program called the TECVAYLI and TALVEY REMS. Inform patients that they will be given a Patient Wallet Card that they should carry with them at all times and show to all of their healthcare providers. This card describes signs and symptoms of CRS and neurologic toxicity, including ICANS which, if experienced, should prompt the patient to immediately seek medical attention *[see Warnings and Precautions]*.

Oral Toxicity and Weight Loss

Discuss the signs and symptoms of oral toxicities including dysgeusia, dry mouth, dysphagia, and stomatitis. Counsel patients to seek medical attention should signs or symptoms of oral toxicity occur. Advise patients that they may experience weight loss and to report weight loss. Advise patients that they may be referred to a nutritionist for consultation *[see Dosage and Administration (2.5) in Full Prescribing Information, Warnings and Precautions]*.

Infections

Discuss the signs and symptoms of serious infections *[see Dosage and Administration (2.5) in Full Prescribing Information, Warnings and Precautions]*.

Cytopenias

Discuss the signs and symptoms associated with neutropenia and thrombocytopenia *[see Dosage and Administration (2.5) in Full Prescribing Information, Warnings and Precautions]*.

Skin Toxicity

Discuss the signs and symptoms of skin reactions *[see Dosage and Administration (2.5) in Full Prescribing Information, Warnings and Precautions]*.

Hepatotoxicity

Advise patients that liver enzyme elevations may occur and that they should report symptoms that may indicate liver toxicity, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider if they are pregnant or become pregnant. Advise females of reproductive potential to use effective contraception during treatment with TALVEY and for 3 months after the last dose *[see Warnings and Precautions, Use in Specific Populations]*.

Lactation

Advise women not to breastfeed during treatment with TALVEY and for 3 months after the last dose *[see Use in Specific Populations]*.

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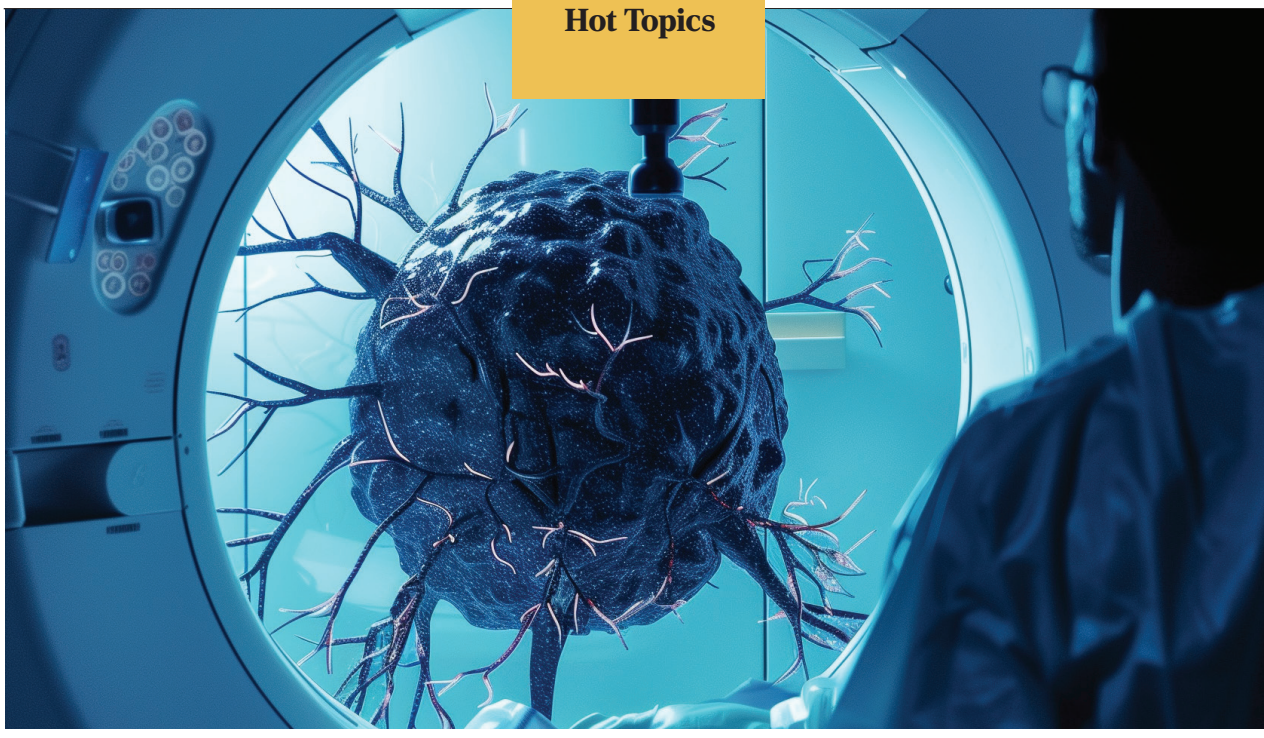

AI Use in Prostate Cancer: Potential Improvements in Treatments and Patient Care

James B. Yu, MD, MHS, FASTRO; Julian C. Hong, MD, MS

Artificial intelligence (AI) generally describes the concept of computers emulating human intelligence. Used synonymously, machine learning (ML) is considered a subset of AI and describes the field where computers can analyze data and interact with users without explicit coding of each potential possibility. For this review, we will use the term *AI*, although it will generally refer to concepts of ML. In recent years, AI increasingly has been applied to medicine, oncology, and prostate cancer.[1] This review will briefly touch upon 4 areas where AI and prostate cancer have overlapped: AI-driven diagnostic image analysis, AI "prediction" of prostate outcomes based on clinical data, AI prediction using multimodal data including histopathology, and AI definition of tumor and normal tissue for radiation oncology treatment planning. After describing each area, we will give practical examples of application. Finally, we will briefly discuss future applications of AI to prostate cancer.

AI-Driven Diagnostic Image Analysis and Radiomics

Image classification is an area where AI has taken large strides, driven by nonclinical work in computer vision. ML architectures such as convolutional neural networks, and newer network architectures such as transformer-based architectures, have improved the ability of AI to correctly identify elements in photographs. These models are similarly being applied to quantitative characteristics of diagnostic images (known as radiomics) for the purpose of detecting clinically significant disease.[2,3] Current published ML models have shown promise but are not able to completely replace radiologist evaluation in real-world situations[4]; however, they may aid less experienced radiologists in distinguishing between cancerous and noncancerous lesions in prostate MRI scans.[5] At the same time, some studies have shown that computer-aided detection (CAD)–assisted mammography may result in reduced sensitivity to non–CAD-identified breast lesions.[6] It is possible that overreliance on AI could morph prostate cancer CAD tools from helpful assistants to a second-rate crutch.

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IMAGE BY BROOKE SPAULDING / MJH LIFE SCIENCES USING AI

AI Predictions of Health Outcomes

ML algorithms have been used to take clinical characteristics and genetic features and predict relevant clinical outcomes such as prostate cancer risk, presence of nodal metastases, response to therapy, and mortality.[7-13] Although these ML algorithms may present predictive performance improvements compared with existing nomograms,[14] their adoption in routine clinical practice likely will require automated integration into existing health care electronic medical records (EMRs), as well as navigation of regulatory frameworks. Also, obstacles to ML implementation in clinical practice include barriers to real-time data extraction and aggregation from multiple commercial EMR sources and information systems.[15] In comparison, a nomogram makes clear the relative contribution of each factor to the intended clinical prediction.

AI Histopathology-Driven Characterization of Prostate Cancer

Evaluation of prostate cancer histopathology is perhaps where the most clinical impact is being made.[16] One example where ML tools are helping pathologists categorize prostate cancer is Paige Prostate (Paige AI), a tool for automatically labeling prostate cancer by Gleason score.[17] Another example is a multimodal deep learning network that incorporates clinical characteristics as well as features extracted from digitized histopathology to predict outcomes from treatment.[18] This model was trained and evaluated in a clinical trials data set to be predictive of androgen deprivation therapy in combination with radiotherapy vs radiotherapy alone.[19] Now commercialized as ArteraAI, the multimodal AI test is approved as a clinical diagnostic laboratory test by the Centers for Medicare & Medicaid Services.

AI-Driven Tumor Definition and Treatment Planning for Radiation Therapy

A rapid area of AI expansion is in aiding radiation oncologists in the automated definition of normal tissue and tumor definition. "Contouring" is the general process whereby radiation oncologists delineate organs at risk for radiation toxicity, as well as define radiation treatment targets. The definition of organs at risk and target volumes is traditionally a time-consuming and technically demanding task. AI models are improving the efficiency of this process through automated contouring and are already commercially available.[20,21] These models will likely continue to improve in accuracy with recent innovations in ML architecture and multimodal imaging data.[22]

Once a target volume is defined, AI can improve treatment planning through improvements in efficiency and optimization of dose.[23-26] These improvements in efficiency are particularly valuable for online adaptive radiotherapy, where treatment plans are adjusted daily based on time-of-treatment cross-sectional images.[27]

"Once a target volume is defined, AI can improve treatment planning through improvements in efficiency and optimization of dose."

Future Applications

With the rise of generative AI in day-to-day life, patients will likely use large language model–based tools to obtain cancer treatment information. Physicians may start using AI to perform routine tasks in symptom management and patient-facing interaction.[28,29] For example, the System for High-Intensity EvaLuation During Radiation Therapy (SHIELD-RT) study (NCT04277650) found that an ML algorithm accurately identified patients at high risk for needing acute care during radiotherapy. These patients were then able to benefit from random assignment to twice-weekly (vs once-weekly) clinical evaluation.[30] It is likely AI will further diffuse into all aspects of health care as a supplemental aid for physicians and patients.[31]

Conclusion

The innovations seen in the application of AI to prostate cancer care mirror those happening throughout health care and information technology. Breakthroughs in image analysis and computer vision have diffused into the classification of prostate diagnostic imaging, pathology, and prediction of treatment outcomes. Radiation oncology has experienced improvements in practice efficiency due to AI tools. Future applications of AI for prostate cancer likely will include improved patient-facing tools.

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Exploring the Benefits and Risks of AI in Oncology

LEARNING OBJECTIVES

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

- Evaluate the potential risks and benefits of incorporating AI technology in health care, considering factors such as patient safety, data privacy, and ethical implications.
- Analyze the potential applications of AI in the oncology setting, including areas such as diagnosis, treatment planning, and patient monitoring.
- Understand the key factors that contribute to clinicians' confidence in the accuracy and reliability of AI tools.

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The history of artificial intelligence (AI) in health care can be traced back to the 1970s when expert systems were developed to assist physicians in decision-making processes.[1] However, it was not until the recent advancements in machine learning, particularly deep learning, that AI began to show significant potential in various medical applications, such as disease diagnosis, drug discovery, and personalized treatment planning.[2] As AI continues to evolve, its integration into health care is expected to revolutionize the way medical services are delivered, enabling more accurate diagnoses, personalized treatments, and improved patient outcomes, while addressing the challenges of increasing health care costs and aging populations.[3]

> **"If done properly, AI could help us overcome current challenges and introduce innovative solutions..."**

While AI has shown promising potential in various medical applications, it is still in a developmental stage, and its implementation in healthcare comes with risks and uncertainties. One major concern is the potential for AI systems to perpetuate or amplify biases present in the data used for training, leading to inaccurate or discriminatory outcomes.[4] Additionally, the complexity of AI models can make it challenging to ensure transparency and interpretability, which are crucial for building trust and accountability in medical decision-making.[5] Regulatory frameworks and ethical guidelines for the safe and responsible use of AI in health care are still evolving, and addressing these concerns will be crucial for the successful integration of AI into clinical practice.[6]

In this article, Ted A. James, MD, MHCM, FACS, chief, breast surgical oncology at Beth Israel Deaconess Medical Center and associate professor of surgery at Harvard Medical School in Boston, Massachusetts, discusses AI's current role in health care, weighing the potential risks and benefits of integrating this technology, and focuses on oncology applications.

Q / Is AI ready for widespread use in health care? If not, what key advancements need to occur before AI can be used in frontline medical settings?

James / AI holds remarkable promise and potential in health care, with numerous pilot studies and test cases showcasing potential advantages and benefits that could transform patient care. However, despite my optimism and enthusiasm for AI, I would say that it is not fully ready for broad application. Several challenges remain, including enhancing AI algorithm accuracy, ensuring data privacy and security, and addressing clinical validation and regulatory considerations before AI can be widely deployed in frontline medicine. Efforts are under way to overcome these hurdles and get AI ready for general adoption.

Q / Can you describe current AI applications in health care and highlight areas of valuable utility?

James / Current applications of AI in health care range from diagnostic assistance to improving operational efficiencies. For example, AI systems are being used to monitor patients following hospital discharge to identify early signs of postoperative or posttreatment complications.

AI is increasingly used to support health care professionals by offering insights for better decision-making and predicting patient outcomes, including preventing potential health issues before they escalate. Several test cases are using AI to automate administrative tasks to alleviate the administrative workload on physicians, allowing more direct face time with patients.

There are also groups exploring AI for drug discovery, which is very exciting. In these ways, AI is starting to improve our understanding and management of care —the applications are very wide-ranging.

Q / Within oncology, what clinical scenarios show promise for impactful AI intervention and decision support?

James / This is an area that I'm very excited about as an oncologist, and I think the field is ripe for AI interventions, especially for precision medicine. Utilizing AI to incorporate tumor characteristics with a patient's genetic profile for prognostic indicators could significantly outperform current prediction models.

AI also shows promise in risk assessment and predictive analytics, allowing us to proactively improve patient outcomes. There are also opportunities to use AI to enhance patient education and engagement.

Q / At its current state, should oncologists explore avenues to pilot and operationalize AI tools in their practice? If so, what specific clinical uses or workflows could benefit most?

James / I'm a strong advocate for oncologists exploring these opportunities within AI. Recognizing this technology as the future direction of medicine, the sooner we engage with AI, the more effectively we can guide its integration to benefit oncology practice and improve patient outcomes.

Some of the most impactful clinical applications involve personalized treatment and streamlining administrative processes in

practice. For example, AI can play a role in personalized patient care by identifying individuals at higher risk of treatment complications or allowing customized care plans tailored to specific patient characteristics.

On the administrative front, AI can help streamline operational workflows. AI is currently being used to predict which patients are most likely to be a no-show. It can then automatically contact these patients to confirm upcoming appointments and, if necessary, quickly fill any gaps by offering available slots to other patients. As oncologists become more familiar with these innovations, the collective experience and knowledge gained will help advance the field. I believe this will lead to better clinical practices and outcomes for patients.

Q / How can clinicians develop confidence in the accuracy and reliability of AI-powered tools? What factors or safeguards allow AI outputs to be deemed trustworthy?

James / One of the challenges with AI in health care is its accuracy. For clinicians to trust AI, they need transparency about how these tools function, supported by validation studies and peer-reviewed research. Explainable AI, which allows us to understand how conclusions are drawn and what data are used, is important in building this trust. Like any medical technology, trust in AI will be built on rigorous testing, reliable data, and adherence to regulatory standards.

Q / Please outline the potential pitfalls of AI, such as vulnerabilities and privacy concerns.

James / Cybersecurity breaches are a significant concern. An emerging threat in this area is the medical deepfake, a situation where AI generates false medical information and integrates it into digital patient records. AI could modify diagnostic imaging tests or lab results. The potential alteration or falsification of data has serious implications for patient safety. This is a concern that goes beyond the typical concerns over privacy breaches.

AI also has a few inherent problems that need to be addressed. The possibility of AI generating fictitious information or "AI hallucinations" is a recognized pitfall. We need safeguards to prevent the spread of inaccurate data. Another pressing issue is AI's potential to perpetuate existing societal biases. Without deliberate efforts to identify and correct these biases, AI systems may inadvertently replicate them in health care settings. Finally, there is the broader risk of dehumanizing patient care if AI is not implemented thoughtfully and with sensitivity. We want to avoid diminishing the personal aspects of patient care.

Q / What strategies would you recommend for clinicians to effectively communicate about AI capabilities and limitations to patients? How should providers address situations where patients have independently used AI for self-diagnosis or treatment guidance?

James / I think clinicians should discuss the capabilities and limitations of AI honestly and openly with their patients. It is important not to oversell or undersell the technology. AI has strengths and weaknesses, and we should be transparent about that. It's also important to emphasize that AI tools are a complement, not replacement, for human clinical judgment. People are inevitably going to turn to AI for information and self-management, but I do not think that we should necessarily be antagonistic about that. Although there are valid concerns about patients using AI directly for self-care, with proper safeguards and validation, AI could become a digital extension of the clinical workforce,

IMAGE BY BROOKE SPAULDING/MJH LIFE SCIENCES USING AI

reaching patients in ways that the current human clinical workforce cannot do on its own.

Again, the more involved we are in the development of this technology, the better positioned we'll be to guarantee that patients have access to credible and reliable information through AI.

Q / How might the integration of medical database information with machine learning models unlock new potential and enhance the capabilities of AI in health care applications?

James / The true power of AI in oncology, and medicine in general, comes from leveraging large medical databases to enhance diagnostic precision and learning algorithms.[7] For example, Google's Med-PaLM 2 is a large language model designed specifically for medical research and care.[8] It has successfully passed the United States Medical Licensing Examination. In the near future, I think we can expect to have expert-level responses from AI when it learns from accurate data.

Another project I'm aware of is I3LUNG, which showcases AI's ability to use big data to tailor cancer treatments.[9] The project focuses on non–small cell lung cancer (NSCLC) and aims to personalize care and enhance outcomes by integrating multiomics data.

Q / Looking ahead, what are the most promising areas or clinical domains where AI could have a transformative impact within health care?

James / The most promising areas, in my opinion, lie in precision medicine, where AI could tailor treatments to individual genetic profiles. I'm fascinated by the idea of using AI to customize treatments based on a person's unique genetic makeup. It has the potential to transform how we approach disease management and therapy. This move toward personalized medicine is something I see having the potential to improve treatment outcomes significantly.

AI could also have a significant impact on patient engagement and self-management. By utilizing AI tools, patients can take a more active role in their health care, which can lead to better health outcomes.

If done properly, AI could help us overcome current challenges and introduce innovative solutions for disease treatment, prevention, and management. Integrating AI into medicine could be a defining moment in the evolution of health care.

Q / Given the litigious nature of the medical field and the potential for AI systems to be infiltrated with malicious information or make errors that negatively impact patient care, who should bear responsibility when something goes wrong due to an AI system being used by health care providers and professionals? How might assigning responsibility shape the future adoption and use of AI in medicine?

James / Addressing who bears responsibility when complications or harm occurs due to AI systems in health care is complex. It's likely there will be shared accountability.

Technology developers need to ensure their AI systems undergo appropriate testing and validation. Health care organizations that use these technologies have the responsibility of implementing cybersecurity measures along with all of the checks and balances associated with introducing a new technology. Physicians using AI will have to exercise due diligence, following guidelines and best practices of using this technology responsibly. Patients also play a role in accountability, through informed engagement, using AI tools in conjunction with professional medical advice, and being careful about the security of their personal health data.

Hopefully, this process of shared accountability will mitigate risks and safeguard against undue harm. It can also promote greater collaboration regarding the safe and effective use of AI in health care. ■

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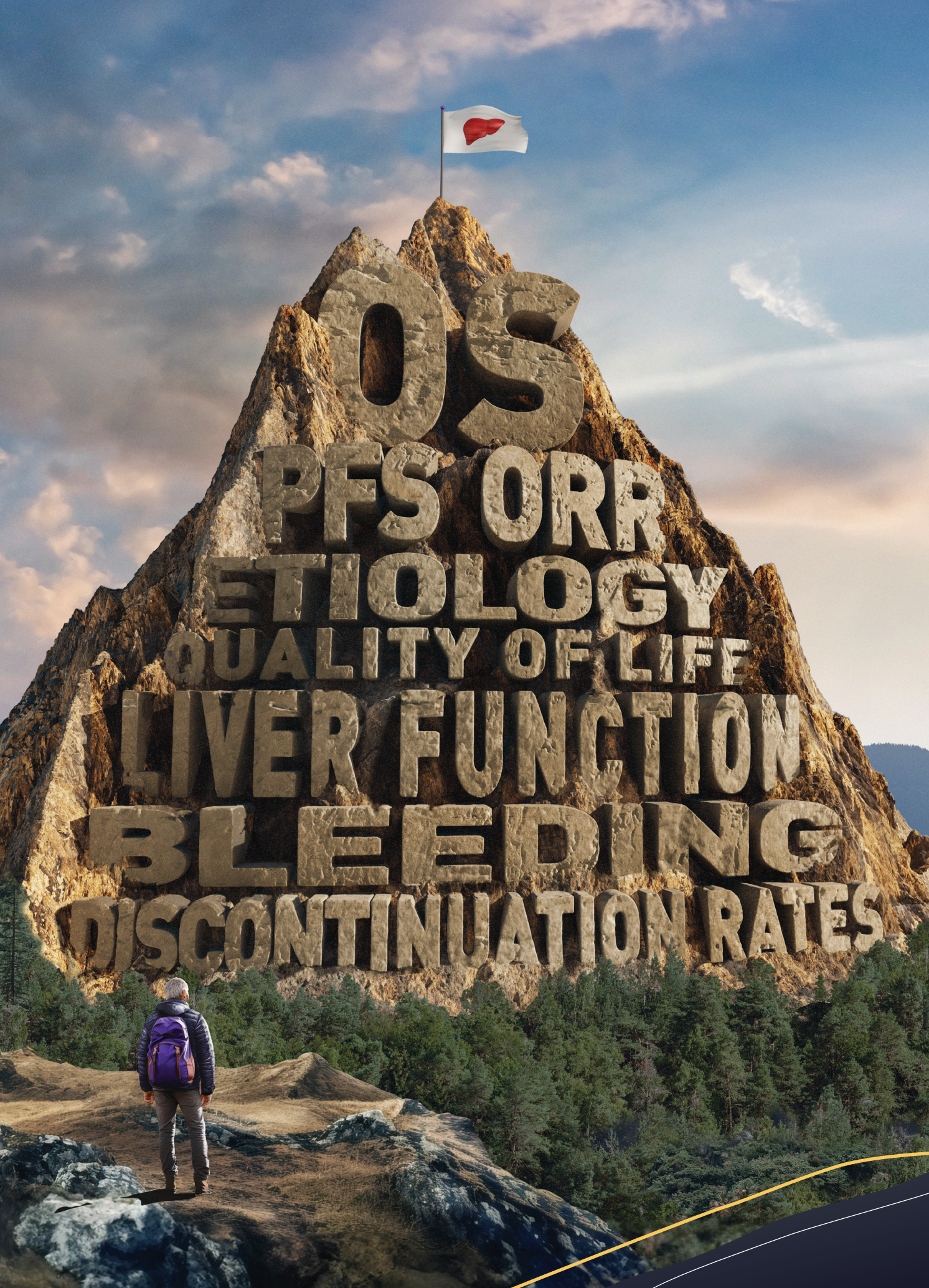
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