The Prognostic Significance of Peripheral Blood Biomarkers in Patients With Advanced Non–Small Cell Lung Cancer Treated With Pembrolizumab: A Clinical Study

Matulonis Provides Overview of Gynecologic Treatment Landscape Advances

Thymoma: Original Research The Effect of Prior Cancer on Survival of Patients With Thymoma

Prostate Cancer: Case Study Successful Diagnosis and Treatment of Occult Prostate Cancer Despite Multiple Negative Prostate Biopsies and Negative Prostate MRIs

Pancreatic Cancer: CME Single-Agent PARP Inhibitors and Combination Therapies for Pancreatic Cancer
**LETTER TO THE READERS**

**The Emerging Value of ctDNA in Colon Cancer Adjuvant Therapy Decisions**

Howard S. Hochster, MD

A ll our cells die, and then they release DNA strands into the blood stream, which today we can detect as cell-free DNA (cfDNA). A small proportion of this cfDNA is due to death and turnover of tumor cells. This circulating tumor DNA (ctDNA) can be measured and identified using deep sequencing technology. Some ctDNA tests use specific exome sequences linked with known tumor-associated antigens, while others use whole-exome sequencing of the tumor tissue to develop “personalized” probes. Many tests are said to detect minimal residual disease, as it is a molecular indicator of disease persistence, akin to measuring presence of Philadelphia chromosome in the bone marrow of patients with chronic myeloid leukemia that is in remission.

One of the most interesting abstracts presented at the recent 2022 Gastrointestinal Cancers Symposium came from the investigators of the CIRCULATE-Japan clinical trial (jRCT1031200006), who are studying adjuvant therapy in colon cancer using the Signatera ctDNA test. Being accrued to the trial are 5200 patients, some of whom are assigned to therapeutic arms. The data presented at the symposium pertained to the 1500+ patients enrolled in the observational arm, entitled the GALAXY study. About 500 patients were excluded either because they were enrolled in the therapeutic trials or had incomplete data; 1040 were evaluable with a week 4 postsurgical blood test for ctDNA (Signatera) and follow-up data. Of the patients in this data set, 8% had stage I disease, 30% stage II, 38% stage III, and 24% stage IV.

Overall, the ctDNA positivity rate at the 4-week time-point was 18%, which increased with stage (stage I, 2%; II, 8%; III, 23%; IV, 31%). Additionally, reduced incidence of 4-week ctDNA positivity was associated with \( \text{BRAF} \) mutation and microsatellite instability—high status. Using this one test point, the 12-month disease-free survival (DFS) rates were 93% vs 48% (HR, 10.9; \( P < .001 \)) for ctDNA negative vs positive status in the entire sample, respectively, and 95% vs 56% for patients with stage II/III only (n = 712; HR, 13.3; \( P < .001 \)). The expected DFS rates for this group (including about 40% stage II and 60% stage III) would be 70% to 75%, so clearly the ctDNA is an improved prognostic marker compared with standard pathologic staging.

In multivariate analysis, the ctDNA positivity had greatest prognostic ability for recurrence with ctDNA positive status at 4 weeks (HR, 15.3), and other significant factors including \( \text{BRAF} \) (HR, 5.2) and \( \text{RAS} \) mutations (HR, 1.8). T stage and N stage were not prognostic; therefore, ctDNA positivity at 4 weeks is a more powerful prognostic tool than is stage. Additionally, for patients converting from positive status at 4 weeks to negative at 12 weeks, the recurrence rate was very low—similar to those negative at 4 weeks—compared with a rate of 50% to 60% for those remaining or converting to positive at 12 weeks.

Another important observation in this study pertained to the benefit of adjuvant chemotherapy. Patients were chosen by the physician to receive treatment or not, so there was some imbalance in factors (96 with adjuvant therapy and 87 without). In the adjuvant treatment group, there was significantly more stage III disease but approximately similar high-risk stage II patients vs no adjuvant therapy. The patients who received adjuvant triplet (folinic acid, fluorouracil, and oxaliplatin) or doublet (capecitabine plus oxaliplatin) therapy had a ctDNA clearance rate of 68%, compared with 10% in those who did not receive adjuvant therapy. The multivariate analysis for recurrence in stage II to IV disease with adjuvant therapy showed a hazard ratio of 5.6 (\( P < .001 \)) with all other factors not significant except \( \text{RAS} \) mutations (HR, 2.0). And perhaps even more interesting for the 531 patients who were ctDNA negative at 4 weeks, 214 were given adjuvant chemotherapy and 317 not treated (with imbalance by stage); yet there was no difference in the 12-week DFS rates between these groups (96% vs 95%; HR, 1.3). However, this is an observational cohort without randomization, so these results are certainly not definitive.

In conclusion, large nonrandomized observational studies suggest that, first, adjuvant chemotherapy may result in ctDNA clearance in 65% to 70% of patients at 4 weeks post surgery, and second, those with negative ctDNA at 4 weeks do not seem to benefit from chemotherapy. These studies are not sufficient to establish the predictive value of ctDNA testing, but they are suggestive. Randomized studies addressing this question are required and, in fact, are ongoing, with the COBRA trial for low-risk stage II colon cancer (NCT04068103) and the CIRCULATE-US trial for stage III disease, which will open soon (NCT05174169). I encourage all our readers to participate in these important studies.

**REFERENCE**


CANCERNETWORK.COM ONCOLOGY® 143
LETTER TO READERS
143 The Emerging Value of ctDNA in Colon Cancer Adjuvant Therapy Decisions
Howard S. Hochster, MD

PUBLISHERS NOTE
146 Considerations for Treating Thoracic Malignancies
Mike Hennessy Jr

GYNECOLOGIC CANCERS: Interview
154 Matulonis Provides Overview of Gynecologic Treatment Landscape Advances

THYMOMA: Original Research
172 The Effect of Prior Cancer on Survival of Patients With Thymoma
ShiHong Wu, MD; Junhua Fang, MB; Ling Ji, MD; HaiPeng Liu, MD; JiuFei Li, MD; WenFa Jiang, MD; and ChenYang Xu, MD

PROSTATE CANCER: Case Study
178 Successful Diagnosis and Treatment of Occult Prostate Cancer Despite Multiple Negative Prostate Biopsies and Negative Prostate MRIs
Kostantinos E. Morris, BS; Dominic C. Grimberg, MD; Rajan T. Gupta, MD; Avani A. Pendse, MD, PhD; and Judd W. Moul, MD

PROSTATE CANCER: Clinical Consult
184 Treatment Options in Metastatic Castration-Sensitive Prostate Cancer

LUNG CANCER: Product Profile
186 Expert Commentary on the Product Profile of Amivantamab-vmjw

MULTIPLE MYELOMA: CME
188 Single-Agent PARP Inhibitors and Combination Therapies for Pancreatic Cancer

CHECK OUT CONTINUING EDUCATION ACTIVITIES from our partners at Physicians’ Education Resource® (PER®), LLC.
We’ve picked this one especially for our ONCOLOGY® readers. Go to: https://bit.ly/3bGWNAI

ONCOLOGY® (ISSN 0890-9091) is published monthly by MultiMedia Healthcare LLC, 2 Clarke Drive, Suite 100 Cranbury, NJ 08512. Annual subscription rates: US, $237 and Canada, $261; students and nurses, $96; international, $296. Single copies: $20 each. Institutional US, $299; Canada, $329; international, $375. Periodicals postage paid at Trenton, NJ and at additional mailing offices. POSTMASTER: Please send address changes to Oncology PO Box 457, Cranbury NJ 08512-0457, USA. Publications Mail Agreement No 40612608. Return Undeliverable Canadian Addresses to: IMEX Global Solutions, PO Box 25542 London ON N6C 6B2. Canadian G.S.T number: R-124213133RT001. Printed in U.S.A.
For address changes, please notify the Circulation Department by visiting www.surveymonkey.com/s/subscriptions, or by mail to ONCOLOGY®, © 2022 MJH Life Sciences®, PO Box 457, Cranbury NJ 08512-0457. Send old address, new address and attach a copy of mail label, if possible.
ONCOLOGY® and its website, CancerNetwork.com, provide oncologists with the practical, timely, clinical information they need to deliver the highest level of care to their patients. Expert authors and peer review ensure the quality of ONCOLOGY® and CancerNetwork.com’s articles and features. Focused discussions capture key clinical take-aways for application in today’s time-constrained practice environment.

**EDITORIAL ADVISORY BOARD**

**MISSION STATEMENT**

**EDITORS-IN-CHIEF**

Julie M. Vose, MD, MBA
Omaha, NE

Howard S. Hochster, MD
New Brunswick, NJ

**EDITORIAL BOARD**

**TUMOR CHAIRS**

**BREAST CANCER**
Sara A. Hurvitz, MD, Los Angeles, CA

**GENITOURINARY CANCER**
Robert A. Figlin, MD, Los Angeles, CA

**GASTROINTESTINAL CANCER**
Tanios S. Bekaii-Saab, MD, Phoenix, AZ

**HEAD AND NECK CANCER**
Eric J. Sherman, MD, New York, NY

**HEMATOLOGIC MALIGNANCIES**
C. Ola Landgren, MD, PhD, Miami, FL

**THORACIC MALIGNANCIES**
Hossein Borghaei, DO, MS, Philadelphia, PA

**INTERESTED IN SUBMITTING TO ONCOLOGY®?**
Please contact CancerNetwork@mjhlifesciences.com for submission guidelines.

**BOARD MEMBERS**

**BREAST CANCER**
William J. Gradishar, MD, FACP, Chicago, IL

Tari King, MD, Boston, MA

Stephen M. Schleicher, MD, MBA, Lebanon, TN

Vered Stearns, MD, Baltimore, MD

Melinda L. TeLLi, MD, Palm Alto, CA

**CANCER SURVIVORSHIP**
Matthew J. Matasar, MD, MS, New York, NY

**COLORECTAL/GASTROINTESTINAL CANCER**
Edward Chu, MD, Pittsburgh, PA

Mehmet Sbiti Copur, MD, FACP, Omaha, NE

Daniel Haller, MD, Philadelphia, PA

John L. Marshall, MD, Washington, DC

Shubham Pant, MD, Houston, TX

Matthew B. Yurgelun, MD, Boston, MA

**GENITOURINARY CANCER**
L. Michael Glodé, MD, FACP, Denver, CO

Paul Mathew, MD, Boston, MA

Elisabeth Heath, MD, FACP, Detroit, MI

Bobby Liaw, MD, New York, NY

**GYNECOLOGIC ONCOLOGY**
Mario M. Leitao Jr, MD, New York, NY

Ritu Salani, MD, Los Angeles, CA

**HEALTH ECONOMICS**
Nora Janjan, MD, MPSA, MBA, Dallas, TX

**HEMATOLOGIC MALIGNANCIES**
Danielle M. Brander, MD, Durham, NC

Christopher R. Flowers, MD, Houston, TX

Steven T. Rosen, MD, Duarte, CA

Naval G. Davor, MD, Houston, TX

Ehab L. Aaesth, MD, Milwaukee, WI

**INFECTIOUS DISEASE**
Genoveta Papanicolaou, MD, New York, NY

**INTEGRATIVE ONCOLOGY**
Ting Bao, MD, New York, NY

Linda Carlson, PhD, RPsych, Calgary, Alberta, Canada

**LUNG CANCER**
David S. Ettinger, MD, Baltimore, MD

James L. Mulshine, MD, Chicago, IL

Edward S. Kim, MD, Duarte, CA

Jennifer W. Carlisle, MD, Atlanta, GA

**NEURO-ONCOLOGY**
David A. Reardon, MD, Boston, MA

Stuart A. Grossman, MD, Baltimore, MD

Nicole A. Shonka, MD, Omaha, NE

**PEDIATRIC ONCOLOGY**
David G. Poplack, MD, Houston, TX

Richard A. Drachtman, MD, New Brunswick, NJ

**PROSTATE CANCER**
Tomasz M. Beer, MD, Portland, OR

E. David Crawford, MD, Denver, CO

Judd W. Moul, MD, FACS, Durham, NC

**PSYCHO-ONCOLOGY**
Daniel C. McFarland, DO, New York, NY

Michelle Riba, MD, Los Angeles, CA

**RADIATION ONCOLOGY**
Louis Potters, MD, FACR, Hempstead, NY

James B. Yu, MD, MHS, New Haven, CT

**SARCOMA**
Kenneth Cardona, MD, FACS, Atlanta, GA

**SUPPORTIVE AND PALLIATIVE CARE**
Thomas J. Smith, MD, FACP, Baltimore, MD

**SURGICAL ONCOLOGY**
Burton L. Eisenberg, MD, Newport Beach, CA
Considerations for Treating Thoracic Malignancies

In this issue of ONCOCOLOGY®, contributors focus on the treatment of thoracic malignancies. Original research by Kira MacDougall, MD, of the Department of Hematology & Medical Oncology at the Oklahoma University of Health Sciences in Oklahoma City, and colleagues explored the significance of peripheral blood biomarkers for non–small cell lung cancer (NSCLC) treated with pembrolizumab (Keytruda).

In the manuscript (see pages 156-161), the investigators looked at baseline levels of absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) plus the ANC/ALC ratio to determine those levels’ effects on survival in the indicated patient population. The team determined that a certain threshold of levels was consistent with response to PD-1 inhibitor therapy, with results supported by further comparison with data from a metanalysis. These data are important to the space for many reasons, most important of which is the inconsistent effect of the drug class on the greater NSCLC population.

“Given the significant immune-related AEs that can occur with these drugs, along with their financial toxicity, there is a need to individualize treatment for every single patient. Tumor PD-L1 immunohistochemical testing is often used as a predictor of response, but it has limitations. Complete blood count measures and differential testing are inexpensive and should be routinely performed before the initiation of immunotherapy and before every treatment cycle,” wrote MacDougall et al.

In another original research contribution, investigators led by Shilong Wu, MD, aimed to determine effects of prior cancer on patients with thymoma to uncover the potential impact this history could have on clinical trial populations (see pages 172-177). They determined that although survival was worse for the patients with a history of cancer, the results were not generalizable to the whole group; certain subgroups, they concluded, should be considered for study. “A prior cancer history has variable impact on the survival of patients with thymoma, depending upon age and treatment method. [Prior cancer history] is associated with worse survival for patients who were younger and treated with chemoradiotherapy,” the authors wrote.

As always, keep up with the latest issues of our journal for more on this and other important news and literature.
INDICATIONS

GAVRETO is indicated for the treatment of:

- Adult patients with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer as detected by an FDA approved test
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

SELECT SAFETY INFORMATION

Interstitial Lung Disease (ILD)/Pneumonitis occurred in 10% of patients who received GAVRETO, including 2.7% with Grade 3/4, and 0.5% with fatal reactions. Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold GAVRETO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD.

Hypertension occurred in 29% of patients, including Grade 3 hypertension in 14% of patients. Overall, 7% had their dose interrupted and 3.2% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating GAVRETO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue GAVRETO based on the severity.

Please see additional Select Safety Information throughout and Brief Summary of the full Prescribing Information for GAVRETO on adjacent pages.
GAVRETO demonstrated robust and durable response in RET fusion+ mNSCLC.

Efficacy and safety with GAVRETO (400 mg once daily) was evaluated in patients with RET fusion+ mNSCLC, advanced or metastatic RET-mutant medullary thyroid cancer (MTC) and advanced or metastatic RET fusion+ thyroid cancer in the ARROW study, a phase 1/2, nonrandomized, open-label, single-arm, multicohort, multicenter clinical trial. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DoR), as assessed by a blinded independent central review (BICR) according to RECIST v1.1. All patients must have had a non-resectable RET-altered solid tumor or MTC per local assessment of tumor tissue and/or blood. All patients must also have had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1.1,2

RECIST=Response Evaluation Criteria in Solid Tumors.

### Efficacy and safety results with GAVRETO in RET fusion+ mNSCLC 1,3

#### TREATMENT-NAÏVE PATIENTS

- **ORR:** 70% (95% CI: 50%-86%)
- **PR:** 59% (n=27)
- **CR:** 11%

Median DoR (n=19) was 9.0 months (6.3 months-NE)

- 58% of patients continued to respond to treatment at 6 months*
- Median time to first response was 1.9 months (range: 1.4-5.6 months)3

#### PREVIOUSLY PLATINUM-TREATED PATIENTS

- **ORR:** 57% (95% CI: 46%-69%)
- **PR:** 5.2% (n=87)
- **CR:** 5.7%

Median DoR (n=50) was NE (15.2 months-NE)

- 80% of patients continued to respond to treatment at 6 months*
- Median time to first response was 1.8 months (range: 1.3-9.1 months)3

*Calculated using the proportion of responders with an observed duration of response at least 6 months or greater. CI=confidence interval; CR=complete response; NE=not estimable; PR=partial response.

### SELECT SAFETY INFORMATION (cont’d)

**Hepatotoxicity:** Serious hepatic adverse reactions occurred in 2.1% of patients treated with GAVRETO. Increased aspartate aminotransferase (AST) occurred in 69% of patients, including Grade 3/4 in 5% and increased alanine aminotransferase (ALT) occurred in 46% of patients, including Grade 3/4 in 6%. The median time to first onset for increased AST was 15 days (range: 5 days to 1.5 years) and increased ALT was 22 days (range: 7 days to 1.7 years). Monitor AST and ALT prior to initiating GAVRETO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue GAVRETO based on severity.

Grade ≥ 3 hemorrhagic events occurred in 2.5% of patients treated with GAVRETO including one patient with a fatal hemorrhagic event. Permanently discontinue GAVRETO in patients with severe or life-threatening hemorrhage.

**Tumor Lysis Syndrome (TLS):** Cases of TLS have been reported in patients with medullary thyroid carcinoma receiving GAVRETO. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

**Impaired wound healing** can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, GAVRETO has the potential to adversely affect wound healing. Withhold GAVRETO for at least 5 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of GAVRETO after resolution of wound healing complications has not been established.

Please see additional Select Safety Information throughout and Brief Summary of the full Prescribing Information for GAVRETO on adjacent pages.
Efficacy results with GAVRETO in advanced or metastatic RET-mutant MTC

**CABOZANTINIB AND VANDETANIB-NAÏVE**

<table>
<thead>
<tr>
<th>ORR</th>
<th>CR: 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>66%</td>
<td>(n=29)</td>
</tr>
<tr>
<td>95% CI: 46%-82%</td>
<td></td>
</tr>
</tbody>
</table>

> 84% of patients continued to respond to treatment at 6 months*  
> Median time to first response was 3.7 months (range: 1.7-11.1 months)*

**Efficacy results with GAVRETO in advanced or metastatic RET fusion+ thyroid cancer**

<table>
<thead>
<tr>
<th>ORR</th>
<th>CR: 1.8%</th>
</tr>
</thead>
<tbody>
<tr>
<td>60%</td>
<td>(n=55)</td>
</tr>
<tr>
<td>95% CI: 46%-73%</td>
<td></td>
</tr>
</tbody>
</table>

> 79% of patients continued to respond to treatment at 6 months*  
> Median time to first response was 3.7 months (range: 1.8-12.9 months)*

**Adverse reactions (≥15%) in RET-altered thyroid cancer patients (n=138)**

- The most common adverse reactions (≥15%) were musculoskeletal pain (42%), constipation (41%), hypertension (40%), fatigue (38%), diarrhea (34%), edema (29%), cough (27%), headache (24%), rash (24%), dyspnea (22%), pyrexia (22%), peripheral neuropathy (20%), dizziness (19%), abdominal pain (17%), dry mouth (17%), dysgeusia (17%), nausea (17%), stomatitis (17%), and decreased appetite (15%).

*Calculated using the proportion of responders with an observed duration of response at least 6 months or greater. NR=not reached.

**SELECT SAFETY INFORMATION (cont’d)**

Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the final dose. Advise women not to breastfeed during treatment with GAVRETO and for 1 week after the final dose.

**Common adverse reactions (≥25%)** were constipation, hypertension, fatigue, musculoskeletal pain and diarrhea. Common Grade 3/4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased phosphate, decreased calcium (corrected), decreased sodium, increased AST, increased ALT, decreased platelets and increased alkaline phosphatase.

Avoid coadministration of GAVRETO with **strong CYP3A inhibitors or combined P-gp and strong CYP3A inhibitors**. If coadministration cannot be avoided, reduce the GAVRETO dose. Avoid coadministration of GAVRETO with **strong CYP3A inducers**. If coadministration cannot be avoided, increase the GAVRETO dose.

Please see Brief Summary of the full Prescribing Information for GAVRETO on adjacent pages.


GAVRETO, Blueprint Medicines, and associated logos are trademarks of Blueprint Medicines Corporation. The Genentech logo is a registered trademark of Genentech, Inc. © 2021 Blueprint Medicines Corporation and Genentech, Inc. All rights reserved. M-US-00010439v10j
INDICATIONS AND USAGE
Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer
GAVRETO is indicated for the treatment of adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.

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

RET-Mutant Medullary Thyroid Cancer
GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy.

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

RET Fusion-Positive Thyroid Cancer
GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

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

WARNINGS AND PRECAUTIONS
Interstitial Lung Disease/Pneumonitis
Severe, life-threatening, and fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with GAVRETO. Pneumonitis occurred in 10% of patients who received GAVRETO, including 2.7% with Grade 3-4, and 0.5% with fatal reactions. Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold GAVRETO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD.

Hypertension
Hypertension occurred in 29% of patients, including Grade 3 hypertension in 14% of patients. Overall, 7% had their dose interrupted and 3.2% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating GAVRETO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue GAVRETO based on the severity.

Hepatotoxicity
Serious hepatic adverse reactions occurred in 2.1% of patients treated for GAVRETO. Increased AST occurred in 69% of patients, including Grade 3 or 4 in 5% and increased ALT occurred in 46% of patients, including Grade 3 or 4 in 6%. The median time to first onset for increased AST was 15 days (range: 5 days to 1.5 years) and increased ALT was 22 days (range: 7 days to 1.7 years). Monitor AST and ALT prior to initiating GAVRETO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue GAVRETO based on severity.

Hemorrhagic Events
Serious, including fatal, hemorrhagic events can occur with GAVRETO. Grade ≥3 hemorrhagic events occurred in 2.5% of patients treated with GAVRETO including one patient with a fatal hemorrhagic event. Permanently discontinue GAVRETO in patients with severe or life-threatening hemorrhage.

Tumor Lysis Syndrome
Cases of tumor lysis syndrome (TLS) have been reported in patients with medullary thyroid carcinoma receiving GAVRETO. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

Risk of Impaired Wound Healing
Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, GAVRETO has the potential to adversely affect wound healing. Withhold GAVRETO for at least 5 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of GAVRETO after resolution of wound healing complications has not been established.

Embryo-Fetal Toxicity
Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. Oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in malformations and embryolethality at maternal exposures below the human exposure at the clinical dose of 400 mg once daily. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the final dose.

ADVERSE REACTIONS
The following clinically significant adverse reactions are described above:

- Interstitial Lung Disease/Pneumonitis
- Hypertension
- Hepatotoxicity
- Hemorrhagic Events
- Tumor Lysis Syndrome
- Risk of Impaired Wound Healing

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

The pooled safety population in the WARNINGS AND PRECAUTIONS reflect exposure to GAVRETO as a single agent at 400 mg orally once daily in 438 patients with RET-altered solid tumors, including with RET fusion-positive NSCLC (n=220), and RET-altered thyroid cancer (n=138), in ARROW. Among 438 patients who received GAVRETO, 47% were exposed for 6 months or longer and 23% were exposed for greater than one year.

The most common adverse reactions (≥25%) were constipation, hypertension, fatigue, musculoskeletal pain.
and diarrhea. The most common Grade 3-4 laboratory abnormalities (≥22%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased phosphate, decreased calcium (corrected), decreased sodium, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), decreased platelets, and increased alkaline phosphatase.

**RET Fusion-Positive Non-Small Cell Lung Cancer**

The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 220 patients with metastatic rearranged during transfection (RET fusion-positive) non-small cell lung cancer (NSCLC) in ARROW. Among the 220 patients who received GAVRETO, 42% were exposed for 6 months or longer and 19% were exposed for greater than one year. The median age was 60 years (range: 26 to 87 years); 52% were female, 50% were White, 41% were Asian, and 4% were Hispanic/Latino.

Serious adverse reactions occurred in 45% of patients who received GAVRETO. The most frequent serious adverse reaction (in ≥2% of patients) was pneumonia, pneumonitis, sepsis, urinary tract infection, and pyrexia. Fatal adverse reaction occurred in 5% of patients; fatal adverse reaction which occurred in > 1 patient included pneumonia (n = 3) and sepsis (n = 2).

Permanent discontinuation due to an adverse reaction occurred in 15% of patients who received GAVRETO. Adverse reactions resulting in permanent discontinuation which occurred in > 1 patient included pneumonitis (1.8%), pneumonia (1.8%), and sepsis (1%).

Dosage interruptions due to an adverse reaction occurred in 66% of patients who received GAVRETO. Adverse reactions requiring dosage interruption in ≥2% of patients included neuropenia, pneumonitis, anemia, hypertension, pneumonia, pyrexia, increased aspartate aminotransferase (AST), increased blood creatine phosphokinese, fatigue, leukopenia, thrombocytopenia, vomiting, increased alanine aminotransferase (ALT), sepsis, and dyspnea.

Dose reductions due to adverse reactions occurred in 36% of patients who received GAVRETO. Adverse reactions requiring dosage reductions in ≥2% of patients included neutropenia, anemia, pneumonitis, neutrophil count decreased, fatigue, hypertension, pneumonia, and leukopenia.

**Adverse Reactions (≥15%) in RET Fusion-Positive NSCLC Patients Who Received GAVRETO in ARROW**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>GAVRETO N=220</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue†</td>
<td>35</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20</td>
</tr>
<tr>
<td>Edema‡</td>
<td>20</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>35</td>
</tr>
<tr>
<td>Diarrhea†</td>
<td>24</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>16</td>
</tr>
<tr>
<td><strong>Musculoskeletal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain*</td>
<td>32</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension†</td>
<td>28</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal</strong></td>
<td></td>
</tr>
<tr>
<td>Cough‡</td>
<td>23</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
</tr>
<tr>
<td>Pneumonia‡</td>
<td>17</td>
</tr>
</tbody>
</table>

**SELECTED LABORATORY ABNORMALITIES (≥20%) WORSENING FROM BASELINE IN RET Fusion-Positive NSCLC Patients Who Received GAVRETO in ARROW**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>GAVRETO N=220</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>74</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>49</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>42</td>
</tr>
<tr>
<td>Decreased calcium (corrected)</td>
<td>39</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>36</td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>35</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>33</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>29</td>
</tr>
<tr>
<td>Increased potassium</td>
<td>26</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>61</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>58</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>56</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>27</td>
</tr>
</tbody>
</table>

Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 216 to 218 patients.

Clinically relevant laboratory abnormalities (≥20%) of patients who received GAVRETO included increased phosphate (10%).

**RET-altered Thyroid Cancer**

The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 138 patients with RET-altered Thyroid Cancer in ARROW. Among the 138 patients who received GAVRETO, 68% were exposed for 6 months or longer, and 40% were exposed for greater than one year. The median age was 59 years (range: 18 to 83 years); 36% were female, 74% were White, 17% were Asian, and 6% were Hispanic/Latino.

Serious adverse reactions occurred in 39% of patients who received GAVRETO. The most frequent serious adverse reactions (in ≥2% of patients) were pneumonia, pneumonitis, urinary tract infection, pyrexia, fatigue, diarrhea, dizziness, anemia, hyponatremia, and ascites. Fatal adverse reactions occurred in 2.2% of patients; fatal adverse reactions that occurred in > 1 patient included pneumonia (n=2).

Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received GAVRETO. Adverse reactions resulting in permanent discontinuation which occurred in > 1 patient included fatigue, pneumonia, and anemia.

Dosage interruptions due to an adverse reaction occurred in 67% of patients who received GAVRETO. Adverse reactions requiring dosage interruption in ≥2% of patients included neutropenia, hypertension, diarrhea, fatigue, pneumonitis, anemia, increased blood creatine phosphokinese, pneumonia, urinary tract infection, musculoskeletal pain, vomiting.
pyrexia, increased AST, dyspnea, hypocalcemia, cough, thrombocytopenia, abdominal pain, increased blood creatinine, dizziness, headache, decreased lymphocyte count, stomatitis, and syncope.

Dose reductions due to adverse reactions occurred in 44% of patients who received GAVRETO. Adverse reactions requiring dosage reductions in ≥2% of patients included neutropenia, anemia, hypertension, increased blood creatine phosphokinase, decreased lymphocyte count, pneumonitis, fatigue and thrombocytopenia.

**Adverse Reactions (≥15%) in RET-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>GAVRETO N=138</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscleoskeletal</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>42 (0.7*)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>41 (0.7*)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34 (5*)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>17 (0.7*)</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>17 (0.7*)</td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (0.7*)</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>40 (21*)</td>
</tr>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>38 (6*)</td>
</tr>
<tr>
<td>Edema</td>
<td>29 (0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22 (2.2*)</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>24 (0)</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>20 (0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19 (0.7*)</td>
</tr>
<tr>
<td>Dyseusia</td>
<td>17 (0)</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>27 (1.4*)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22 (2.2*)</td>
</tr>
<tr>
<td>Skin and Subcutaneous</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>24 (0)</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>15 (0)</td>
</tr>
</tbody>
</table>

1 Musculoskeletal Pain includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain
2 Diarrhea includes colitis, diarrhea
3 Abdominal Pain includes abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness, epigastric discomfort
4 Stomatitis includes mucosal inflammation, stomatitis, tongue ulceration
5 Fatigue includes asthenia, fatigue
6 Edema includes eyelid edema, face edema, edema, edema peripheral, periorbital edema
7 Headache includes headache, migraine
8 Peripheral neuropathy includes dysesthesia, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy, polyneuropathy
9 Dizziness includes dizziness, dizziness postural, vertigo
10 Dyseusia includes aegusa, dysgeusia
11 Cough includes cough, productive cough, upper-airway cough syndrome
12 Dyspnea includes dyspnea, dyspnea exertional
13 Rash includes dermatitis, dermatitis acneiform, eczema, palmoplantar, erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular

* Only includes a Grade 3 adverse reaction

Clinically relevant adverse reactions in <15% of patients who received GAVRETO included tumor lysis syndrome and increased creatine phosphokinase.

**Select Laboratory Abnormalities (≥20%) Worsening from Baseline in RET-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>GAVRETO N=138</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Decreased calcium (corrected)</td>
<td>70 (9)</td>
</tr>
<tr>
<td>Increased AST</td>
<td>69 (4.3)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>43 (3.6)</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>41 (1.5)</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>41 (0)</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>28 (2.2)</td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>28 (8)</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>27 (0.7)</td>
</tr>
<tr>
<td>Increased potassium</td>
<td>26 (1.4)</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>24 (1.4)</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>22 (1.4)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>67 (27)</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>63 (13)</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>59 (16)</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>31 (2.9)</td>
</tr>
</tbody>
</table>

Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 135 to 138 patients.

**DRUG INTERACTIONS**

**Effects of Other Drugs on GAVRETO**

**Strong CYP3A Inhibitors**

Avoid coadministration with strong CYP3A inhibitors. Coadministration of GAVRETO with a strong CYP3A inhibitor increases pralsetinib exposure, which may increase the incidence and severity of adverse reactions of GAVRETO.

Avoid coadministration of GAVRETO with combined P-gp and strong CYP3A inhibitors. If coadministration with a combined P-gp and strong CYP3A inhibitor cannot be avoided, reduce the GAVRETO dose.

**Strong CYP3A Inducers**

Coadministration of GAVRETO with a strong CYP3A inducer decreases pralsetinib exposure, which may decrease efficacy of GAVRETO. Avoid coadministration of GAVRETO with strong CYP3A inducers. If coadministration of GAVRETO with strong CYP3A inducers cannot be avoided, increase the GAVRETO dose.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. There are no available data on GAVRETO use in pregnant women to inform drug-associated risk. Oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in malformations and embryolethality at maternal exposures below the human exposure at the clinical dose of 400 mg once daily. Advise pregnant 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 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal development study, once daily oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in 100% post-implantation loss at dose levels ≥20 mg/kg (approximately 1.8 times the human exposure based on area under the curve [AUC] at the clinical dose of 400 mg). Post-implantation loss also occurred at the 10 mg/kg dose level (approximately 0.6 times the human exposure based on AUC at the clinical dose of 400 mg). Once daily oral administration of pralsetinib at dose levels ≥5 mg/kg (approximately 0.2 times the human AUC at the clinical dose of 400 mg) resulted in an increase in visceral malformations and variations (absent or small kidney and ureter, absent ureteral horn, malpositioned kidney or testis, retroesophageal aortic arch) and skeletal malformations and variations (vertebral and rib anomalies and reduced ossification).

Lactation

Risk Summary

There are no data on the presence of pralsetinib or its metabolites in human milk or their effects on either the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with GAVRETO and for 1 week after the final dose.

Females and Males of Reproductive Potential

Based on animal data, GAVRETO can cause embryolethality and malformations at doses resulting in exposures below the human exposure at the clinical dose of 400 mg daily.

Pregnancy Testing

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

Contraception

GAVRETO can cause fetal harm when administered to a pregnant woman.

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. GAVRETO may render hormonal contraceptives ineffective.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the final dose.

Infertility

Based on histopathological findings in the reproductive tissues of male and female rats and a dedicated fertility study in which animals of both sexes were treated and mated to each other, GAVRETO may impair fertility.

Pediatric Use

The safety and effectiveness of GAVRETO have been established in pediatric patients aged 12 years and older for RET-mutant MTC and RET-fusion thyroid cancer. Use of GAVRETO in this age group is supported by evidence from an adequate and well-controlled study of GAVRETO in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the pharmacokinetics of pralsetinib, that the exposure of pralsetinib is expected to be similar between adults and pediatric patients aged 12 years and older, and that the course of RET-mutant MTC and RET-fusion thyroid cancer is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients.

The safety and effectiveness of GAVRETO have not been established in pediatric patients with RET fusion-positive NSCLC or in pediatric patients younger than 12 years old with RET-mutant MTC or RET-fusion thyroid cancer.

Animal Toxicity Data

In a 4-week repeat-dose toxicity study in non-human primates, phyesal dysplasia in the femur occurred at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. In rats there were findings of increased phyesal thickness in the femur and sternum as well as tooth (incisor) abnormalities (fractures, dentin matrix alteration, ameloblast/odontoblast degeneration, necrosis) in both 4- and 13-week studies at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. Recovery was not assessed in the 13-week toxicity study, but increased phyesal thickness in the femur and incisor degeneration did not show evidence of complete recovery in the 28-day rat study.

Monitor growth plates in adolescent patients with open growth plates. Consider interrupting or discontinuing therapy based on the severity of any growth plate abnormalities and based on an individual risk-benefit assessment.

Hepatic Impairment

GAVRETO has not been studied in patients with moderate hepatic impairment (total bilirubin >1.5 to 3.0 × upper limit of normal [ULN] and any aspartate aminotransferase [AST]) or severe hepatic impairment (total bilirubin >3.0 × ULN and any AST). No dose adjustment is required for patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5 times ULN and any AST).

Manufactured for:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

Jointly marketed by: Genentech USA, Inc. and Blueprint Medicines Corporation

© 2021 Blueprint Medicines Corporation and Genentech, Inc. All rights reserved. M-US-00012419(v1.0)

For more information, go to www.GAVRETO-hcp.com or call 1-888-835-2555.

Revised: 04/2021

GAVRETO
pralsetinib
Matulonis Provides Overview of Gynecologic Treatment Landscape Advances

“Team science is important for being open-minded [and] thinking outside of the box.”

The landscape of gynecologic oncology continues to evolve quickly, with the FDA approving multiple treatments for ovarian, endometrial, and uterine cancer in the last few years. Moreover, investigators continue to explore new treatment combinations to provide patients with more options and help improve survival.

In an interview with ONCOLOGY®, Ursula A. Matulonis, MD, discussed clinical trials that have significantly impacted the standard of care (SOC), as well as ongoing studies that have practice-changing potential. She also spoke about several trials that will be presented at the upcoming Society of Gynecologic Oncology (SGO) conference.

Matulonis detailed what made her change her own practice and described trends observed throughout the community. She even touched upon advice she gives to new faculty who are beginning their work in clinical trials.

Q: Can you give a brief overview of the recent gynecologic treatment landscape?

A: The top billing goes to cervical cancer because of what has happened over the past year, with immuno-oncology (IO) agents becoming available for patients with newly diagnosed advanced or recurrent cervical cancer. Testing and introduction of IO agents into SOC treatment for cervical cancer was recently published [KEYNOTE-826; NCT03635567] in the New England Journal of Medicine with the addition of pembrolizumab [Keytruda] to carboplatin and paclitaxel plus or minus bevacizumab [Avastin].1

In uterine cancer, the SOC now is single-agent IO drugs, specifically pembrolizumab and dostarlimab [Jemperli], which got an FDA accelerated approval in 2021 for microsatellite instability or mismatch repair–deficient endometrial cancer.2 Pembrolizumab is approved as a single agent for TMB [tumor mutational burden]–high (ie, greater than 10 mutations per megabase) [disease] and for microsatellite-deficient disease as well.3,4 That is a viable option post chemotherapy for those patients with recurrent endometrial cancer. KEYNOTE-775 [NCT03517449], which was published in the New England Journal of Medicine, also investigated and showed benefit of pembrolizumab and lenvatinib [Lenvima] vs chemotherapy for microsatellite-proficient recurrent uterine cancer that has progressed through at least 1 round of platinum [chemotherapy].5

Ovarian cancers are a different story, and the only approval of an IO agent in ovarian cancer is...
pembrolizumab for microsatellite instability or high TMB (tumor-agnostic indications), but IO does not have any formal indications right now. Additionally, new therapies are being tested, specifically antibody-drug conjugates [ADCs].

Finally, there is a trend of targeting specific drugs to specific tumors with ADCs. All IOs, to a certain extent, have targets with either microsatellite instability or stability as a biomarker. ADCs like tisotumab vedotin don’t have a marker, but the FDA approval doesn’t indicate that there must be tissue factor present. Other ADCs, namely nirvetuximab, that require a biomarker are being tested.

Q: What biomarkers for, if any, should be explored in clinical research?
A: Basket trials are good if there is a true target. If a target is being considered—for example, [targeting] HER2 with DS-8201a [trastuzumab deruxtecan; T-DXd], which is an anti-HER2 ADC—investigators can get a sense of what the level of expression of HER2 has to be [to see efficacy].

Some tumors in gynecologic cancers have RAS mutations, such as low-grade serous mucinous cancers of the ovary and endometrioid cancers of the uterus, but they are not targetable. [Gynecologic] cancers can have [RAS] G12D and G12V mutations, and they’re not targetable by known inhibitors quite yet. If we had a drug that could potentially target those mutations, then we could line up the different gynecologic cancers that have those RAS mutations. Basket trials are a neat way of not having to conduct 10 different phase 2 studies, but package them all into one trial.

Q: What role do you think PARP inhibitors play? Are any practice-changing trends on the horizon?
A: Three PARP inhibitors are approved in the United States for newly diagnosed advanced-stage cancer. One is based on the SOLO-1 trial [NCT01844986], with 2 years of maintenance olaparib [Lynparza] for patients who have BRCA1/2-mutated cancer after response to chemotherapy. SOLO-1 has certainly been a practice-changing trial since that initial presentation a few years ago at the [European Society for Medical Oncology] Congress. My practice immediately changed because the progression-free survival improvement was dramatically better in SOLO-1 vs placebo.

The second trial is PRIMA [NCT02655016], using niraparib [Zejula] maintenance for about 3 years, which expands to high-grade serous [cancer] with no BRCA mutation regardless of homologous recombination deficiency [HRD] status. Then, the PAOLA-1 trial [NCT02477644], adds olaparib to bevacizumab [Avastin] as maintenance for patients who receive some bevacizumab for at least 3 cycles during their upfront carboplatin or paclitaxel chemotherapy. Olaparib received approval for cancers with HRD. If the tumor is deemed [homologous recombination proficient] per an FDA-approved assay, then olaparib [maintenance is not indicated].

Rucaparib [Rubraca] then came along for either BRCA-mutated or HRD platinum-sensitive [disease]; you can use it in that setting as well and then as maintenance treatment.

Q: Should clinicians be aware of other agents?
A: The drug adavosertib in recurrent uterine serous cancers is a Wee1 inhibitor. The concept is that the whole genome is under stress from different mechanisms, with loss of p53 allowing the agent to work. There’s cyclin E amplification, MEK amplification, and HER2 overexpression. These data were published in the Journal of Clinical Oncology, which showed a 29% response rate with single-agent adavosertib in recurrent uterine serous cancers. This has led to a larger trial called ADAGIO [NCT04590248]; it’s closed for the moment, but it will reopen.

Additionally, the [combination of] CDK4/6 inhibitor abemaciclib [Verzenio] plus letrozole has data that are being presented at the SGO Annual Meeting on Women’s Cancer in [mid-March]. This is a phase 2 trial [NCT03675893] in recurrent estrogen receptor–positive endometrial trials. Another trial of DS-8201a plus olaparib, a [National Cancer Institute]–sponsored trial [NCT04585958] for HER2-positive gynecologic cancers, is mostly [looking at] endometrial serous cancers.

Yet another trial is looking at nirvetuximab, which is an ADC against the folate receptor α, plus pembrolizumab in recurrent uterine serous cancers. About 30% of uterine serous cancers are folate receptor α–positive, and we prescreened those patients [beforehand].

Q: What advice do you have for new clinicians?
A: They must understand the patient they’re treating to gain ideas about what should be done. Currently, per year in the United States, there are fewer than 13,000 cases of cervical cancer, about 20,000 ovarian, and 66,000 uterine. [These clinicians must] become experts. [They begin by] writing it up [a trial] and presenting it at a meeting. [When working on this], everybody needs to be incorporated, from surgeons to medical oncologists, radiation oncologists, pathologists, and basic scientists, depending upon the project that you want to start. Team science is important for being open-minded and thinking outside of the box.

For references visit cancernetwork.com/Matulonis_3.22
The Prognostic Significance of Peripheral Blood Biomarkers in Patients With Advanced Non–Small Cell Lung Cancer Treated With Pembrolizumab: A Clinical Study

Kira MacDougall, MD; Muhammad Rafay Khan Niazi, MD; Jeff Hosry MD; Sylvester Homsy, MD; Alexander Bershadsky, MD

ABSTRACT

INTRODUCTION: Systemic inflammation has long been associated with poor outcomes in many types of solid tumors. Peripheral blood biomarkers, such as absolute lymphocyte count (ALC) and the ratio of absolute neutrophil count to absolute lymphocyte count (ANC/ALC), have been shown to be immune-inflammatory parameters highlighting an individual’s immune status. The prognostic role of ALC and ANC/ALC on overall survival (OS) was examined in patients with advanced non–small cell lung carcinoma (NSCLC) receiving pembrolizumab.

Of a total of 239 patients, 52% were male, with a median age of 67 years (interquartile range [IQR], 59-73). Most patients had a diagnosis of adenocarcinoma (76%), with stage IV disease (82%). PD-L1 expression was >50% in 44% of the patients. The median time on treatment with pembrolizumab was 5.8 months (IQR, 2.9-12.7).

An ANC/ALC <5 was associated with improved OS at initiation of pembrolizumab ($P = .002$), whereas an ALC >1.4 deciliter (dL) trended toward improved OS compared with ALC <1.4 dL ($P = .053$). After adjusting for potential cofounders with a multivariate analysis, a baseline ANC/ALC of 5 or higher was associated with a significantly increased risk of death (HR, 1.93; 95% CI, 1.27-2.93; $P = .002$).

An ANC/ALC <5 at the time of initiation of treatment with pembrolizumab was associated with improved OS in patients with advanced NSCLC. The median ALC and ANC/ALC were significantly lower after 6 weeks of treatment with pembrolizumab.

KEYWORDS: pembrolizumab; non–small cell lung cancer; absolute lymphocyte count; absolute neutrophil count to absolute lymphocyte count ratio; immunotherapy; peripheral blood counts; anti–PD-1
Introduction
Lung cancer is the most common cause of cancer-related deaths, both in the United States and internationally. Non–small cell lung cancer (NSCLC) accounts for approximately 80% to 85% of these cases. The discovery of immune checkpoint inhibitor therapy has led to significant improvement in both overall survival (OS) and progression-free survival (PFS) and represents a paradigm shift in treatment of NSCLC. In 2019, 2 anti–PD-1 antibodies, pembrolizumab (Keytruda) and nivolumab (Opdivo), and 1 anti–PD-L1 antibody, atezolizumab, were approved by the FDA for the treatment of metastatic NSCLC. PD-1 is an immune checkpoint transmembrane protein that is expressed on macrophages, dendritic cells, and T and B lymphocytes. When PD-1 binds to one of its ligands that are expressed on human cancer cells—PD-L1 or PD-L2—it inhibits cytotoxic T-cell response and evades the body’s immune surveillance system.

While PD-L1 receptor positivity in tumor cells has been shown to predict the responsiveness of the cancer to these agents, it has its limitations. Several small studies have been performed to assess the utility of hematologic biomarkers in predicting the effectiveness of immunotherapy. However, these studies have been small retrospective studies with small sample sizes. These peripheral markers include absolute neutrophil count (ANC), absolute lymphocyte count (ALC), the ratio of absolute neutrophil count to absolute lymphocyte count (ANC/ALC), absolute eosinophil count, and absolute monocyte count (AMC). These biomarkers have been shown to be immune-inflammatory parameters highlighting an individual’s immune status. Aggressive cancers are associated with an increased systemic inflammatory state, creating a microenvironment that promotes angiogenesis, survival of malignant cells, and metastasis. The response to immunotherapy in these cases is poor. Therefore, this question has arisen: Can these peripheral blood biomarkers predict patient outcomes in patients treated with immunotherapy?

The aim of this study is to investigate ALC and ANC/ALC in patients with advanced NSCLC receiving pembrolizumab and to determine if a correlation exists between these key biomarkers and OS. To our knowledge, of studies investigating this relationship, this is the largest in terms of number of patients with NSCLC treated with pembrolizumab.

Methods
Patient Selection
This retrospective observational study was approved by the Northwell Health Institutional Review Board, which waived the requirement for informed consent. Data for all patients with advanced NSCLC treated with pembrolizumab between September 2016 and May 2020 at Northwell Health hospital sites were collected by reviewing their electronic medical records. Patients treated with immunotherapy other than pembrolizumab were excluded. This helped to minimize heterogeneity related to different immunotherapy treatments.

Data Collection
All records were reviewed retrospectively and organized in the REDCap database. Parameters such as age at diagnosis, sex, histologic type, tumor PD-L1 status, stage of disease, line of treatment, history of radiation to the tumor, presence or absence of central nervous system (CNS) disease, and ECOG performance status were defined and adjusted for confounding. Peripheral blood counts including ALC, ANC, and AMC were examined at initiation of pembrolizumab and at 6 weeks on treatment. Patients without follow-up blood counts at 6 weeks were excluded.

Statistical Analysis
Based on literature review and previous studies that investigated this relationship, ANC/ALC cut-off values were ≥5 and <5, and ALC cut-off values were ≥1.4 dL and <1.4 dL. The primary outcome was OS, as defined as date of first dose of pembrolizumab to death or last follow-up. Patients discontinued their immunotherapy due to disease progression or death, or because they experienced adverse events (AEs). Descriptive statistics were used to present patient characteristics. Chi-square or Fisher’s exact test were used to compare categorical variables, and the Wilcoxon-Mann-Whitney test was used to compare continuous variables. OS rates were plotted on Kaplan-Meier curves and differences were evaluated with the log-rank test. A multivariable Cox regression model was used to determine the effect of baseline ANC/ALC on the risk of death after adjusting for potential confounders. All statistical tests were 2-sided and conducted using SPSS version 25.0 (IBM). P < .05 was considered statistically significant.

Results
Patient Characteristics
A total of 239 patients with advanced NSCLC treated with pembrolizumab at Northwell Health hospital centers were included. Baseline characteristics are presented in Table 1. Median age at diagnosis was 67 years (interquartile range [IQR], 59-73). Of all patients, 52% were male and most (76%) had a diagnosis of adenocarcinoma, with stage IV disease (82%). The majority (52%) of the included
### TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of patients (%) or median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis, years</strong></td>
<td>67 (59-73)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>124 (52)</td>
</tr>
<tr>
<td>Female</td>
<td>115 (48)</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>182 (76)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>52 (22)</td>
</tr>
<tr>
<td>Adenosquamous cell carcinoma</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Sarcomatoid carcinoma</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>43 (18)</td>
</tr>
<tr>
<td>IV</td>
<td>196 (82)</td>
</tr>
<tr>
<td><strong>PD-L1 expression</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;1%</td>
<td>65 (27)</td>
</tr>
<tr>
<td>1%-4%</td>
<td>17 (7)</td>
</tr>
<tr>
<td>5%-49%</td>
<td>41 (18)</td>
</tr>
<tr>
<td>³50%</td>
<td>105 (44)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>11 (5)</td>
</tr>
<tr>
<td><strong>Smoking history</strong></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>43 (18)</td>
</tr>
<tr>
<td>Former</td>
<td>123 (52)</td>
</tr>
<tr>
<td>Current</td>
<td>73 (30)</td>
</tr>
<tr>
<td><strong>Line of therapy</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>157 (65)</td>
</tr>
<tr>
<td>2</td>
<td>59 (25)</td>
</tr>
<tr>
<td>3</td>
<td>12 (5)</td>
</tr>
<tr>
<td>4</td>
<td>7 (3)</td>
</tr>
<tr>
<td>5</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>6</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>49 (20)</td>
</tr>
<tr>
<td>1</td>
<td>120 (50)</td>
</tr>
<tr>
<td>2</td>
<td>53 (22)</td>
</tr>
<tr>
<td>3</td>
<td>16 (7)</td>
</tr>
<tr>
<td><strong>CNS disease</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>68 (28)</td>
</tr>
<tr>
<td>No</td>
<td>171 (72)</td>
</tr>
<tr>
<td><strong>Radiation therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>48 (20)</td>
</tr>
<tr>
<td>No</td>
<td>191 (80)</td>
</tr>
<tr>
<td><strong>Concurrent chemotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab alone</td>
<td>119 (50)</td>
</tr>
<tr>
<td>Pembrolizumab plus platinum-based chemotherapy</td>
<td>120 (50)</td>
</tr>
<tr>
<td><strong>Peripheral blood biomarkers at initiation of pembrolizumab</strong></td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>9.6 (7.3-12.2)</td>
</tr>
<tr>
<td>ANC</td>
<td>6.6 (4.8-9.5)</td>
</tr>
<tr>
<td>ALC</td>
<td>1.4 (1.0-2.0)</td>
</tr>
<tr>
<td><strong>Peripheral blood biomarkers at 6 weeks</strong></td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>7.4 (5.5-9.9)</td>
</tr>
<tr>
<td>ANC</td>
<td>4.8 (3.3-6.8)</td>
</tr>
<tr>
<td>ALC</td>
<td>1.3 (0.9-1.7)</td>
</tr>
</tbody>
</table>

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CNS, central nervous system; IQR, interquartile range; WBC, white blood cell count.
patients were former smokers. PD-L1 expression was >50% in 44% of the patients. ECOG performance status was 0 or 1 in 70% of patients. Radiographic evidence of CNS disease at the time of pembrolizumab therapy was present in 28% of patients, and 20% had received radiation therapy to the tumor prior to the initiation of pembrolizumab. Pembrolizumab was first-line therapy in 65% of patients. Pembrolizumab monotherapy was being used for treatment in 119 patients (50%), whereas 120 patients (50%) received a combination of pembrolizumab plus platinum-based chemotherapy.

Comparison of Peripheral Blood Biomarkers at Baseline and at 6 Weeks of Treatment
The median ALC and ANC/ALC ratio were significantly lower after 6 weeks of pembrolizumab therapy compared with the start date of treatment (1.3 dL [IQR, 0.9-1.7] vs 1.4 dL [IQR, 1.0-2.0]; P < .001, and 3.6 [IQR, 2.1-6.1] vs 4.6 [IQR, 2.8-7.0] respectively; P = .002).

Comparison of OS Based on Baseline Peripheral Blood Biomarkers
Median OS was 10.8 months (IQR, 4.9-17.4) and overall time on treatment was 5.8 months (IQR, 2.9-12.7). An ALC of ≥1.4 dL trended toward improved OS compared with ALC <1.4 dL (P = .053) (Figure A). Patients with a baseline ANC/ALC of ≥5 had a worse median OS rate compared with those with ANC/ALC <5, at 8.8 months (IQR, 3.98-15.65) vs 11.75 months (IQR, 6.68-20.51; P = .02) (Figure B), and after adjusting for potential cofounders in multivariate analysis (HR, 1.93; 95% CI, 1.27-2.93; P = .002) (Table 2). There was no difference in OS in patients who received pembrolizumab monotherapy compared with those who received pembrolizumab plus platinum-based chemotherapy (HR, 1.51; 95% CI, 0.92-2.47; P = .11).

Discussion
This is the largest study analyzing the effect of the baseline serum levels of ANC and ALC, and of the ANC/ALC ratio, on the OS of patients treated with pembrolizumab for NSCLC. We show here that patients with an ALC of ≥1.4 dL and an ANC/ALC ratio <5 at the initiation of pembrolizumab therapy had an improved OS compared with their respective counterparts. After adjusting for potential cofounders, we found that patients with baseline ANC/ALC ratio of ≥5 treated with pembrolizumab had almost 2 times increased risk of death (all-cause mortality) (HR, 1.93; 95% CI, 1.27-2.93), compared with those with a baseline ANC/ALC <5.

Our findings are consistent with those of previous studies on peripheral blood biomarkers in patients being treated with anti–PD-1 antibodies. In a metanalysis of 16 studies that included 1700 patients, a high blood neutrophil-to-lymphocyte ratio (NLR) or ANC/ALC was found to be associated with shorter OS and PFS in patients getting treatment with PD-1/PD-L1 inhibitors for NSCLC. In a retrospective study of 22 patients with NSCLC treated with nivolumab, baseline ALC levels and ANC/ALC ratios were

| Table 2. Multivariable Cox Regression Analysis for Association of Baseline Peripheral Blood Biomarkers With Overall Survival |
|-------------------|---|---|---|
| Age (<60 vs ≥60 years) | 1.15 | 0.72-1.86 | .56 |
| Adenocarcinoma vs other histology | 0.57 | 0.36-0.90 | .02 |
| ECOG performance status (2-3 vs 0-1) | 2.11 | 1.36-3.26 | <.01 |
| PD-L1 expression (≥50% vs <50%) | 0.45 | 0.27-0.74 | <.01 |
| CNS involvement (yes vs no) | 0.64 | 0.39-1.06 | .08 |
| ANC/ALC (≥5 vs <5) | 1.93 | 1.27-2.93 | <.01 |
| Pembrolizumab monotherapy vs pembrolizumab plus platinum-based chemotherapy | 1.51 | 0.92-2.47 | .11 |

The columns in bold show statistically significant difference in the OS of that particular baseline characteristic. ANC/ALC, absolute neutrophil count to absolute lymphocyte count ratio; CNS, central nervous system.
positively and negatively correlated, respectively, with OS on nivolumab. Another study of 109 patients with advanced NSCLC treated with nivolumab found that posttreatment ANC/ALC ≥5 after 2 cycles of nivolumab was associated with poor OS. Soyano et al studied this effect in patients treated with nivolumab (n = 146) and pembrolizumab (n = 11), finding that a baseline ANC/ALC ratio of 5.9 or more was associated with a significantly increased risk of death (HR, 1.94; 95% CI, 1.24-3.03; P = .004). Hasegawa et al demonstrated that high NLR (>4.55) at the pretreatment stage was significantly associated with shorter PFS and OS in a study of 51 patients with NSCLC who had a tumor proportion score >49%. Unlike our study, this was studied solely in patients who received pembrolizumab monotherapy. Zer et al studied these peripheral biomarkers in correlation with OS, disease control rate, and time to progression, and they found improved outcomes in patients with NLR of ≤4, in the patients with NSCLC who were under treatment with PD-1/PD-L1 for NSCLC.

The results of several studies have shown that tumor-related neutrophils are predictive of a poor prognosis in patients with malignancies. These neutrophils are attracted by cytokines such as interleukin-8 (IL-8), which further promotes the angiogenesis, local invasion of vessels, and growth factor release that causes metastatic spread of disease, leading to poor outcomes. One study demonstrated that lung carcinomas release IL-6 and granulocyte monocyte colony-stimulating factor that leads to increased peripheral leukocyte count, predicting ominous outcomes. PD-1/PD-L1 inhibitors act by blocking the interaction of negative regulators of T-cells that increase the antitumor immunity and decreases the antitumor immune tolerance, and it is plausible that these changes alter the count of peripheral neutrophils and lymphocytes. Increased peripheral neutrophil count correlates with reduced CD8-positive T-lymphocyte counts in NSCLC, and lymphopenia reflects impaired cellular immune response. Conversely, high lymphocyte counts have been considered a positive prognostic factor due to an improved antigen-driven immune response. The exact mechanism by which NLR affects immunotherapy or checkpoint blockade is not known, but it has

---

**FIGURE.** Kaplan-Meier Survival Estimates Between Groups With Different ANC/ALC Ratio and ALC Ratio at the Start Date of Pembrolizumab

A

<table>
<thead>
<tr>
<th>ALC</th>
<th>Cumulative survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.4</td>
<td>1.0</td>
</tr>
<tr>
<td>≥1.4</td>
<td>0.8</td>
</tr>
</tbody>
</table>

P = .053

B

<table>
<thead>
<tr>
<th>ANC/ALC</th>
<th>Cumulative survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥5</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;5</td>
<td>0.8</td>
</tr>
</tbody>
</table>

P = .002

ANC/ALC, ratio of absolute neutrophil count to absolute lymphocyte count; OS, overall survival.
been repeatedly shown to be associated with better outcomes in malignancies and other systemic diseases.

The use of PD-1 and PD-L1 inhibitors have revolutionized cancer immunotherapy and have led to improvement in patient outcomes. Their effect, however, seems to be limited to certain patient subgroups. Given the significant immune-related AEs that can occur with these drugs, along with their financial toxicity, there is a need to individualize treatment for every single patient. Tumor PD-L1 immunohistochemical testing is often used as a predictor of response, but it has limitations. Complete blood count measures and differential testing are inexpensive and routinely performed before the initiation of immunotherapy and before every treatment cycle.

Limitations

This study sought to determine the usefulness of hematologic biomarkers in predicting patient outcomes. However, it did have limitations due to its retrospective study design. Concurrent inflammatory states and use of immunomodulatory agents or steroids could not be ruled out; these could alter the cell counts. Furthermore, the ANC/ALC could not be assessed separately at the tumor site and could differ from that of the peripheral blood. Future studies should be designed to address these issues.

Conclusions

An ANC/ALC <5 at the time of initiation of treatment with pembrolizumab was associated with improved OS in patients with advanced NSCLC. However, further prospective studies are warranted to establish if ANC/ALC can be reliably used as a predictive biomarker in patients with advanced NSCLC who are treated with immunotherapy.

AUTHOR AFFILIATIONS:
1. Department of Hematology & Medical Oncology, Oklahoma University of Health Sciences, Oklahoma City, OK, USA
2. Department of Internal Medicine, Zucker School of Medicine at Hofstra/Northwell at Staten Island University Hospital, Staten Island, NY, USA
3. Department of Hematology & Medical Oncology, SUNY Downstate Medical Center, Brooklyn, NY, USA
4. Division of Hematology & Medical Oncology, Zucker School of Medicine at Hofstra/Northwell at Staten Island University Hospital, New York, NY, USA

REFERENCES
In the treatment of newly diagnosed, transplant-ineligible multiple myeloma:

ADD TO THE MOMENTUM
WITH DARZALEX® + Rd IN FRONTLINE

Reach for a treatment that significantly extended progression-free survival vs Rd alone in a clinical trial1-3

IMPORTANT SAFETY INFORMATION
DARZALEX® AND DARZALEX FASPRO®:
CONTRAINDICATIONS

DARZALEX® and DARZALEX FASPRO® are contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase (for DARZALEX FASPRO®), or any of the components of the formulations.

DARZALEX®: Infusion-Related Reactions

DARZALEX® can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening, and fatal outcomes have been reported. In clinical trials (monotherapy and combination: N=2066), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX®. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, pulmonary edema, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma.

Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting, and nausea. Less common signs and symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension, and blurred vision.

When DARZALEX® dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX®, the incidence of infusion-related reactions was 11% for the first infusion following ASCT. Infusion-related reactions occurring at re-initiation of DARZALEX® following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4: <1%) with those reported in previous studies at Week 2 or subsequent infusions. In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days, ie, 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX® infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX® therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE
• Powerful efficacy to start the treatment journey.1,4
After a median ~30 months* of follow-up, mPFS was not reached with DARZALEX + Rd vs 31.9 months with Rd alone.1,4
• 70.6% of patients had not progressed with DRd vs 55.6% of patients in the Rd group (DRd: 95% CI, 65.0–75.4; Rd: 95% CI, 49.5–61.3)¹

44% reduction in the risk of disease progression or death with DRd vs Rd alone (HR=0.56; 95% CI, 0.43–0.73; P<0.0001)

• Demonstrated safety profile
(median treatment duration of 25.3 months)¹
- The most common adverse reactions (≥20%) were upper respiratory infection, neutropenia, IRRs, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia.
- Serious adverse reactions with a 2% greater incidence in the DRd arm compared with the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%), and dehydration (DRd 2% vs Rd <1%)

MAIA Study Design: A phase 3 global, randomized, open-label study, compared treatment with DRd (n=368) to Rd (n=369) in adult patients with newly diagnosed, transplant-ineligible multiple myeloma. Treatment was continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was PFS.²

With an ~3 to 5 minute subcutaneous injection, DARZALEX FASPRO can be administered substantially faster than intravenous daratumumab.³⁴

See the latest data rolling out. Visit FrontlineMomentum.com

Efficacy results in long-term follow-up.²³
At median ~5 years (56 months)² of follow-up, mPFS was not reached with DRd vs 34.4 months with Rd alone.²
• 53% of patients had not progressed after ~5 years of treatment with DRd vs 29% with Rd alone (DRd: 95% CI, 47–58; Rd: 95% CI, 23–35)¹

47% reduction in the risk of disease progression or death with DRd vs Rd alone (HR=0.53; 95% CI, 0.43–0.66)

These ~5-year analyses were not adjusted for multiplicity and are not included in the current Prescribing Information.

Safety results in long-term follow-up (median treatment duration of 47.5 months)²
At median ~5 years of follow-up²³:
- Most frequent TEAEs ≥30% were diarrhea, neutropenia, fatigue, constipation, peripheral edema, anemia, back pain, asthma, nausea, bronchitis, cough, dyspnea, insomnia, weight decreased, peripheral sensory neuropathy, pneumonia, and muscle spasms.
- Grade 3/4 infections were 41% for DRd vs 29% for Rd.
- Grade 3/4 TEAEs ≥10% were neutropenia (54% for DRd vs 37% for Rd), pneumonia (19% vs 11%), anemia (17% vs 22%), lymphopenia (16% vs 11%), hypokalemia (13% vs 10%), leukopenia (12% vs 6%), and cataract (11% vs 11%)

These ~5-year analyses are not included in the current Prescribing Information.

Appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.
To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX infusions.
Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.
Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with DARZALEX infusion. If ocular symptoms occur, interrupt DARZALEX infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX.

DARZALEX FASPRO: Hypersensitivity and Other Administration Reactions
Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX FASPRO.
Systemic Reactions
In a pooled safety population of 898 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO as monotherapy or in combination, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.2%; Grade 3: 1%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.3% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 140 systemic administration-related reactions that occurred in 77 patients, 121 (86%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.
Severe reactions included hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.
Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO. Consider administering

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE
corticosteroids and other medications after the administration of DARZALEX® FASPRO® depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliovitreal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms develop, interrupt DARZALEX® or FASPRO® and seek immediate ophthalmologic evaluation prior to restarting DARZALEX® FASPRO®.

**Local Reactions**

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.7%. The most frequent (>1%) injection-site reaction was injection-site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX® FASPRO®. Monitor for local reactions and consider symptomatic management.

**Daratumumab** and DARZALEX® FASPRO®: Neutropenia and Thrombocytopenia

Daratumumab and DARZALEX® FASPRO® may increase neutropenia and thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX® or DARZALEX FASPRO® until recovery of neutrophils or for recovery of platelets. In lower body weight patients receiving DARZALEX® FASPRO®, higher rates of Grade 3-4 neutropenia were observed.

**DARZALEX® and DARZALEX FASPRO®: Interference With Serological Testing**

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum. The determination of a patient’s ABO and Rh blood type are not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX® and DARZALEX® FASPRO®, type and screen patients prior to starting DARZALEX® and DARZALEX FASPRO®.

**DARZALEX® and DARZALEX FASPRO®: Interference With Determination of Complete Response**

Daratumumab is a human immunoglobulin G (IgG) kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

**DARZALEX® and DARZALEX FASPRO®: Embryo-Fetal Toxicity**

Based on the mechanism of action, DARZALEX® and DARZALEX FASPRO® can cause fetal harm when administered to a pregnant woman. DARZALEX® and DARZALEX FASPRO® may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX® or DARZALEX FASPRO® and for 3 months after the last dose.

The combination of DARZALEX® or DARZALEX FASPRO® with lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

**DARZALEX®: Adverse Reactions**

The most frequently reported adverse reactions (incidence ≥20%) were upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX® are neutropenia, lymphopenia, thrombocytopenia, leukopenia, and anemia.

**DARZALEX FASPRO®: Adverse Reactions**

In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX FASPRO® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, headache, pyrexia, cough, muscle spasms, back pain, vomiting, hypertension, upper respiratory tract infection, peripheral sensory neuropathy, constipation, pneumonia, and peripheral edema. The most common hematology laboratory abnormalities (≥40%) with DARZALEX FASPRO® are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

**INDICATIONS**

DARZALEX® (daratumumab) is indicated for the treatment of adult patients with multiple myeloma:

- In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
- In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with carfilzomib and dexamethasone in patients who have received at least one prior therapy
- In combination with carfilzomib and dexamethasone in patients who have relapsed or refractory multiple myeloma who have received one to three prior lines of therapy
- In combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI)
- As monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent DARZALEX FASPRO® (daratumumab and hyaluronidase-fihp) is indicated for the treatment of adult patients with multiple myeloma:
  - In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
  - In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
  - In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
  - In combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor (PI)
  - In combination with carfilzomib and dexamethasone in patients who have relapsed or refractory multiple myeloma who have received one to three prior lines of therapy
  - In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
  - As monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

**Please see Brief Summary of full Prescribing Information for DARZALEX® and DARZALEX FASPRO® on adjacent pages.**

© Janssen Biotech, Inc. 2022
All rights reserved. 02/22 cp-233641v4


**INDICATIONS AND USAGE**

**DARZALEX** is indicated for the treatment of adult patients with multiple myeloma:

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

**CONTRAINDICATIONS**

**DARZALEX** is contraindicated in patients with a history of severe hypersensitivity (e.g., anaphylactic reactions) to daratumumab or any of the components of the formulation [see Warnings and Precautions].

**WARNINGS AND PRECAUTIONS**

**Infusion-Related Reactions**

**DARZALEX** can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening and fatal outcomes have been reported [see Adverse Reactions].

In clinical trials (monotherapy and combination: N=2,068), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 (16 mg/kg) infusion, and 0% with the Week 2 (16 mg/kg) infusion. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). The incidence of infusion modification due to reactions was 36%. Median durations of 18 mg/kg infusions for the Week 1, Week 2, and subsequent infusions were approximately 2, 2, and 3 hours, respectively.

Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion-related reactions occurred up to 48 hours after infusion. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypotension, hypoglycemia, bradycardia, laryngeal edema, pulmonary edema, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common signs and symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension, and blurred vision [see Adverse Reactions].

When DARZALEX dosing was interrupted in the setting of AST/ACS (AASSPEA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX, the incidence of infusion-related reactions was 11% for the first infusion following AST. Infusion rate/dilution volume used upon re-initiation was that used for the last DARZALEX infusion prior to interruption for AST. Infusion-related reactions occurring at re-initiation of DARZALEX following AST were consistent in terms of symptoms and severity (Grade 3 or 4:<1%) with those reported in prior studies at Week 5 or subsequent infusions. In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 hours for Week 1-Day 1, 4.2 hours for Week 1-Day 2, and 3.4 hours for the subsequent infusions. Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion [see Dosage and Administration (2.3) in Full Prescribing Information]. Interrupt DARZALEX infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX therapy if an anaphylactic reaction occurs. If grade 4 reaction occurs and institute appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion [see Dosage and Administration (2.4) in Full Prescribing Information].

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following Daratumumab infusions [see Dosage and Administration (2.3) in Full Prescribing Information]. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease [see Dosage and Administration (2.3) in Full Prescribing Information].

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciclochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with DARZALEX infusion. If acute symptoms occur, interrupt DARZALEX infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX.

**Interference with Serological Testing**

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum [see References]. The determination of a patient’s ABO and Rh blood type are not impacted [see Drug Interactions].

Notify blood transfusion centers of this interference with serological testing and inform blood bankers that a patient has received DARZALEX. Type and screen patients prior to starting DARZALEX [see Dosage and Administration (2.1) in Full Prescribing Information].

**Neutropenia**

DARZALEX may increase neutropenia induced by background therapy [see Adverse Reactions].

Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with a history of neutropenia for signs of infection. Consider withholding DARZALEX until recovery of neutrophils.

**Thrombocytopenia**

DARZALEX may increase thrombocytopenia induced by background therapy [see Adverse Reactions].

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Consider withholding DARZALEX until recovery of platelets.

**Interference with Determination of Complete Response**

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum and plasma samples. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

**Embryo-Fetal Toxicity**

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

The combination of DARZALEX with lenalidomide, pomalidomide, or thalidomide contraindicated in pregnant women, because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

**ADVERSE REACTIONS**

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

- Infusion-related reactions [see Warning and Precautions].
- Neutropenia [see Warning and Precautions].
- Thrombocytopenia [see Warning and Precautions].

**Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety data described below reflects exposure to DARZALEX (16 mg/kg) in 2,459 patients with multiple myeloma including 2,303 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy. In this pooled safety population, the most common adverse reactions (≥20%) were upper respiratory infection, decreased appetite, and cough. Common adverse reactions (10-19%) included headache, pyrexia, fatigue, and diarrhea. Adverse events of special interest included infusion-related reactions occurring up to 48 hours after treatment, neutropenia, thrombocytopenia, anemia, peripheral neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia.

**Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant**

**Combination Treatment with Lenalidomide and Dexamethasone (DRd)**

The safety of DARZALEX in combination with lenalidomide and dexamethasone was evaluated in MAIA [see Clinical Studies (14.1) in Full Prescribing Information]. Adverse reactions described in Table 1 reflect exposure to DARZALEX for a median treatment duration of 25.3 months (range: 0.1 to 40.44 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 21.3 months (range: 0.03 to 40.64 months) for lenalidomide-dexamethasone (RD). Serious adverse reactions with a 2% greater incidence in the DRd arm compared to the RD arm were pneumonia (DRd 15% vs RD 8%), bronchitis (DRd 4% vs RD 2%) and dehydration (DRd 2% vs RD 1%).
Table 1: Adverse Reactions Reported in ≥10% of Patients and With At Least a 5% Greater Frequency in the DRd Arm in MAIA

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>DRd (N=306)</th>
<th>Rd (N=305)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td>577</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>458</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td>430</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>321</td>
<td>1</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td>352</td>
<td>2</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td></td>
<td>265</td>
<td>2</td>
</tr>
<tr>
<td>Bronchitis</td>
<td></td>
<td>423</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td>308</td>
<td>1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td></td>
<td>182</td>
<td>0</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>412</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td></td>
<td>352</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>412</td>
<td>1</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td></td>
<td>321</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td></td>
<td>232</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td></td>
<td>135</td>
<td>0</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td></td>
<td>313</td>
<td>3</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td></td>
<td>334</td>
<td>1</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td>303</td>
<td>1</td>
</tr>
<tr>
<td>Cough</td>
<td></td>
<td>303</td>
<td>1</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td>128</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td></td>
<td>128</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>135</td>
<td>1</td>
</tr>
<tr>
<td>Paresthesia</td>
<td></td>
<td>165</td>
<td>0</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td></td>
<td>128</td>
<td>1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td></td>
<td>154</td>
<td>1</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td></td>
<td>148</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>135</td>
<td>1</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td>102</td>
<td>0</td>
</tr>
<tr>
<td>Key: D=daratumumab, Rd=lenalidomide-dexamethasone.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRd (N=306)</th>
<th>Rd (N=305)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>90</td>
<td>30</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>84</td>
<td>11</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>47</td>
<td>13</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

Table 3: Adverse Reactions Reported in ≥10% of Patients and With At Least a 5% Greater Frequency in the DRd Arm in POLLUX

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRd (N=283)</th>
<th>Rd (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td>65</td>
<td>6</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>48</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>35</td>
<td>6</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>43</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>Cough</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

Laboratory abnormalities worsening during treatment from baseline listed in Table 2.
Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

<table>
<thead>
<tr>
<th></th>
<th>DRd (N=283)</th>
<th>Rd (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>95</td>
<td>42</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>99</td>
<td>36</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>73</td>
<td>17</td>
</tr>
<tr>
<td>Anemia</td>
<td>52</td>
<td>13</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

Herpes Zoster Virus Reactivation

Pharyngitis for Herpes Zoster Virus reactivation was recommended for patients in some clinical trials of DARZALEX. In monotherapy studies, herpes zoster was reported in 3% of patients. In the combination therapy studies, herpes zoster was reported in 2-5% of patients receiving DARZALEX.

Infections

Grades 3 or 4 infections were reported as follows:

- Relapsed/refractory patient studies: DvD: 21% vs. Vd: 19%; DRd: 28% vs. Rd: 23%; DvD: 28%; Dk+DvD: 37%; Kd+: 29%; DvD: 21%.
- Where carfilzomib 20/56 mg/m² was administered twice-weekly.

Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. In active controlled studies, discontinuations from treatment due to infections occurred in 1-4% of patients.

Fatal infections (Grade 5) were reported as follows:

- Relapsed/refractory patient studies: DvD: 1%; Vd: 2%; DRd: 2%; Rd: 1%; DpD: 2%; DkD: 5%; Kd+: 3%; DkD+: 0%.
- Where carfilzomib 20/56 mg/m² was administered twice-weekly.
- Where carfilzomib 20/70 mg/m² was administered once-weekly.
- Newly diagnosed patient studies: D-VMP: 1%; VMP: 1%; DRd: 2%; Rd: 2%; DRd: 0%; Vd: 0%.

Fetal and Neonatal Adverse Reactions

Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus reactivation has been reported in less than 1% of patients (including fatal cases) treated with DARZALEX in clinical trials.

Other Clinical Trials Experience

The following adverse reactions have been reported following administration of daratumumab and hyaluronidase for subcutaneous injection:

Nervous System disorders: Syncope

Immunogenicity

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

In clinical trials of patients with multiple myeloma treated with DARZALEX as monotherapy or as combination therapies, none of the 111 evaluable monotherapy patients, and 2 of the 1,399 evaluable combination therapy patients, tested positive for anti-daratumumab antibodies. One patient administered DARZALEX as combination therapy, developed transient neutralizing antibodies against daratumumab. However, this assay has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab; therefore, the incidence of antibody development might not have been reliably determined.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of daratumumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System disorders: Anaphylactic reaction, IRR (including deaths)

Gastrointestinal disorders: Pancreatitis

Infections: Cytomegalovirus, Listeriosis

DARZALEX® (daratumumab) injection

Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

<table>
<thead>
<tr>
<th></th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>95</td>
<td>42</td>
<td>10</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>99</td>
<td>36</td>
<td>17</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>73</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Anemia</td>
<td>52</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Interfering antibodies are not removed by heat. False positive tests may occur for patients with IgG kappa myeloma protein impacting initial assessment of red blood cell (RBC) compatibility. Daratumumab interference may cause falsely low or non-reactive antibody titers. Daratumumab interference may cause falsely low or non-reactive antibody titers.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Interference with protein electrophoresis (SPE) and immunofixation (IFE) tests for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete response by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from other remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

DARZALEX can cause fetal harm when administered to a pregnant woman. The risk associated with daratumumab is unknown. The potential for harm to the fetus outweighs the potential benefit to the mother. The use of daratumumab is contraindicated in pregnant women, because lenalidomide, pomalidomide, and thalidomide may cause birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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.

The combination of DARZALEX and lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women, because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Lenalidomide, pomalidomide, and thalidomide are only available through a REMS program. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX may cause depletion of fetal CD38 positive immune cells and decreased bone density. Refer administering live vaccines to neonates and infants exposed to DARZALEX in utero until a hematologic evaluation is completed.

Data

Fetal Data

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in regulating humoral immune responses (mice), fetal-maternal immune tolerance (mice), and early embryonic development (frogs).

Lactation

Risk Summary

There is no data on the presence of daratumumab in human milk, the effects on the breastfed child, or the effects on milk production. Although immunoglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX is administered with lenalidomide, pomalidomide, or thalidomide, advise women not to breastfeed during treatment with DARZALEX. Refer to lenalidomide, pomalidomide, or thalidomide prescribing information for additional information.

Females and Males of Reproductive Potential

DARZALEX can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations].

Pregnancy Testing

With the combination of DARZALEX with lenalidomide, pomalidomide, or thalidomide, refer to the lenalidomide, pomalidomide, or thalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.
**DARZALEX® (daratumumab) injection**

**Contraception**
Advise females of reproductive potential to use effective contraception during treatment with DARZALEX and for 3 months after the last dose. Additionally, refer to the lenalidomide, pomalidomide, or thalidomide labeling for additional recommendations for contraception.

**Pediatric Use**
Safety and effectiveness of DARZALEX in pediatric patients have not been established.

**Geriatric Use**
Of the 2,459 patients who received DARZALEX at the recommended dose, 38% were 65 to 74 years of age, and 15% were 75 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. The incidence of serious adverse reactions was higher in older than in younger patients [see Adverse Reactions]. Among patients with relapsed and refractory multiple myeloma (n=1,213), the serious adverse reactions that occurred more frequently in patients 65 years and older were pneumonia and sepsis. Within the DkD group in CANDOR, fatal adverse reactions occurred in 14% of patients 65 years and older compared to 6% of patients less than 65 years. Among patients with newly diagnosed multiple myeloma who were ineligible for autologous stem cell transplant (n=710), the serious adverse reaction that occurred more frequently in patients 75 years and older was pneumonia.

**REFERENCES**

**PATIENT COUNSELING INFORMATION**
Advertise the patient to read the FDA-approved patient labeling (Patient Information).

**Infusion-Related Reactions**
Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion-related reactions: itchy, runny or blocked nose; fever, chills, nausea, vomiting, throat irritation, cough, headache, dizziness or lightheadedness, tachycardia, chest discomfort, wheezing, shortness of breath or difficulty breathing, itching, and blurred vision [see Warnings and Precautions].

**Neutropenia**
Advise patients to contact their healthcare provider if they have a fever [see Warnings and Precautions].

**Thrombocytopenia**
Advise patients to contact their healthcare provider if they notice signs of bruising or bleeding [see Warnings and Precautions].

**Interference with Laboratory Tests**
Advise patients to inform their healthcare providers, including personnel at blood transfusion centers that they are taking DARZALEX, in the event of a planned transfusion [see Warnings and Precautions].

Advise patients that DARZALEX can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response [see Warnings and Precautions].

**Hepatitis B Virus (HBV) Reactivation**
Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX could cause hepatitis B virus to become active again [see Adverse Reactions].

**Embryo-Fetal Toxicity**
Advise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions, Use in Specific Populations].

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX and for 3 months after the last dose [see Use in Specific Populations].

Advise patients that lenalidomide, pomalidomide, or thalidomide has the potential to cause fetal harm and has specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide, pomalidomide, and thalidomide are only available through a REMS program [see Use in Specific Populations].

**Hereditary Fructose Intolerance (HFI)**
DARZALEX contains sorbitol. Advise patients with HFI of the risks related to sorbitol [see Description (11) in Full Prescribing Information].

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044
U.S. License Number 1864

© 2015-2021 Janssen Pharmaceutical Companies

cp-271935v2
DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE
DARZALEX FASPRO is indicated for the treatment of adult patients with multiple myeloma:
- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

CONTRAINDICATIONS
DARZALEX FASPRO is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation (see Warnings and Precautions and Adverse Reactions).

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions
Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX FASPRO (see Adverse Reactions).

Systemic Reactions
In a pooled safety population of 888 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=183) who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 9% of patients experienced a systemic administration-related reaction (Grade 2-3, Grade 3-4). Systemic administration-related reactions occurred in 6% of patients with the first injection, 0.3% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 1144 administration-related reactions that occurred in 77 patients, 121 (88%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions include hypoxia, dyspnea, hypertension, and tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, and hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids (see Dosage and Administration (2.5) in Full Prescribing Information). Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO, depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions (see Dosage and Administration (2.5) in Full Prescribing Information).

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber, and choroidal effusions, with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX FASPRO and seek immediate ophthalmologic evaluation prior to restarting DARZALEX FASPRO.

Local Reactions
In a pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.7%. The most frequent (>1%) injection-site reaction was injection-site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX FASPRO. Monitor for local reactions and consider symptomatic management.

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis
Serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received DARZALEX FASPRO in combination with bortezomib, cyclophosphamide and dexamethasone (see Adverse Reactions). Serious cardiac disorders occurred in 16% and fatal cardiac disorders occurred in 10% of patients. Patients with NYHA Class IIIa or Mayo Stage IIIa disease may be at greater risk. Patients with NYHA Class IIIb or IV disease were not studied.

Monitor patients with cardiac involvement of light chain (AL) amyloidosis more frequently for cardiac adverse reactions and administer supportive care as appropriate.

Neutropenia
Daratumumab may increase neutropenia induced by background therapy (see Adverse Reactions).

Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX FASPRO until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO, higher rates of Grade 3-4 neutropenia were observed.

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

Thrombocytopenia
Daratumumab may increase thrombocytopenia induced by background therapy (see Adverse Reactions).

Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX FASPRO until recovery of platelets.

Embryo-Fetal Toxicity
Based on the mechanism of action, DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose (see Use in Specific Populations).

Thrombocytopenia
Daratumumab binds to CD33 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum (see References (19)).

Thrombocytopenia
Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein (see Drug Interactions). This interference can impact the determination of complete response and of disease progression in some DARZALEX FASPRO-treated patients with IgG kappa myeloma protein.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:
- Hypersensitivity and Other Administration Reactions (see Warnings and Precautions).
- Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis (see Warnings and Precautions).
- Neutropenia (see Warnings and Precautions).
- Thrombocytopenia (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
In Combination with Lenalidomide and Dexamethasone
The safety of DARZALEX FASPRO with lenalidomide and dexamethasone was evaluated in a single-arm cohort of PLEADES (see Clinical Studies (14.2) in Full Prescribing Information). Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity (N=65) in combination with lenalidomide and dexamethasone. Among these patients, 92% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Serious adverse reactions occurred in 48% of patients who received DARZALEX FASPRO. Serious adverse reactions in ≥5% of patients included pneumonia, infection and diarrhea. Fatal adverse reactions occurred in 3.1% of patients.

Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 11% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient were pneumonia and anemia.

Dosage interruptions due to an adverse reaction occurred in 83% of patients who received DARZALEX FASPRO. Adverse reactions resulting in dosage interruptions in ≥5% of patients included neutropenia, pneumonia, upper respiratory tract infection, influenza, dyspnea, and blood creatinine increased. The most common adverse reactions (≥20%) were fatigue, diarrhea, upper respiratory tract infection, musculoskeletal pain, constipation, pyrexia, pneumonia, and dyspnea.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO in PLEADES.
Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>52</td>
<td>5*</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
<td>2*</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>18</td>
<td>3*</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45</td>
<td>5*</td>
</tr>
<tr>
<td>Constipation</td>
<td>26</td>
<td>2*</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection*</td>
<td>43</td>
<td>3*</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Bronchitis*</td>
<td>14</td>
<td>2*</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>31</td>
<td>2*</td>
</tr>
<tr>
<td>Back pain</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea*</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Peripheral sensory neuropathy</td>
<td>17</td>
<td>2*</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>17</td>
<td>5*</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>12</td>
<td>9*</td>
</tr>
<tr>
<td>Hypocalemia</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

* Denominator is based on the safety population treated with DARZALEX FASPRO-Rd (N=65).

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihij) injection

Table 2: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>94</td>
<td>34</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>82</td>
<td>56</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>86</td>
<td>8</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>89</td>
<td>52</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>45</td>
<td>8</td>
</tr>
</tbody>
</table>

* Denominator is based on the safety population treated with DARZALEX FASPRO-Rd (N=65).

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

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, less than 1% of 819 patients developed treatment-emergent anti-daratumumab antibodies.

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 7% of 812 patients developed treatment-emergent anti–HvPh20 antibodies. The anti–HvPh20 antibodies did not appear to affect daratumumab exposure. None of the patients who tested positive for anti–HvPh20 antibodies tested positive for neutralizing antibodies.

Postmarketing Experience
The following adverse reactions have been identified with post-approval use of daratumumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal: Pancreatitis
Infections: Cytomegalovirus, Listeriosis

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)
Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with diisobutylketone (DTK) to disrupt daratumumab binding (see References) or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, administer non-cross-matched ABO/Rh-compatible RBCs per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests
Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In DARZALEX FASPRO-treated patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient’s serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
DarZALEX FASPRO® can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout animal models (see Data). There are no available data on the use of DARZALEX FASPRO in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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.

The combination of DARZALEX FASPRO and lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women, because lenalidomide, thalidomide and pomalidomide may cause birth defects and death of the unborn child. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information on use during pregnancy.
Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX FASPRO may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to daratumumab in utero until a hematologic evaluation is completed.

Data

Animal Data

DARZALEX FASPRO for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously during organogenesis, which is 45 times higher than the human dose.

There were no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Lactation

Risk Summary

There is no data on the presence of daratumumab and hyaluronidase in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX FASPRO is administered with lenalidomide, thalidomide or pomalidomide, advise women not to breastfeed during treatment with DARZALEX FASPRO. Refer to lenalidomide, thalidomide or pomalidomide prescribing information for additional information.

Data

Analytical Data

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during lactation with 990,000 U/kg hyaluronidase subcutaneously which is 134 times higher than the human doses.

Females and Males of Reproductive Potential

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations].

Pregnancy Testing

With the combination of DARZALEX FASPRO with lenalidomide, thalidomide or pomalidomide, refer to the lenalidomide, thalidomide or pomalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose. Additionally, refer to the lenalidomide, thalidomide or pomalidomide labeling for additional recommendations for contraception.

Pediatric Use

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

Geriatric Use

Of the 291 patients who received DARZALEX FASPRO as monotherapy for relapsed and refractory multiple myeloma, 37% were 65 to <75 years of age, and 18% were 75 years of age or older. No overall differences in effectiveness of DARZALEX FASPRO have been observed between patients ≥65 years of age and younger patients. Adverse reactions that occurred at a higher frequency (≥5% difference) in patients ≥65 years of age included fatigue, pyrexia, peripheral edema, urinary tract infection, diaphoresis, constipation, vomiting, dyspepsia, cough, and hyperglycemia. Serious adverse reactions occurring at a higher frequency (≥2% difference) in patients ≥65 years of age included neutropenia, thrombocytopenia, diarrhea, anemia, COVID-19, ischemic colitis, deep vein thrombosis, general physical health deterioration, pulmonary embolism, and urinary tract infection.

Of the 193 patients who received DARZALEX FASPRO as part of a combination therapy for light chain (AL) amyloidosis, 35% were 65 to <75 years of age, and 10% were 75 years of age or older. Clinical studies of DARZALEX FASPRO as part of a combination therapy for patients with light chain (AL) amyloidosis did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs from that of younger patients. Adverse reactions that occurred at a higher frequency in patients ≥65 years of age were peripheral edema, anemia, pneumonia and hypotension.

No clinically meaningful differences in the pharmacokinetics of daratumumab were observed in geriatric patients compared to younger adult patients [see Clinical Pharmacology (12.3) in Full Prescribing Information].

REFERENCES


PATIENT COUNSELING INFORMATION

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

Hypersensitivity and Other Administration Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of systemic administration-related reactions: itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing, and blurred vision [see Warnings and Precautions].

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Advise patients to immediately contact their healthcare provider if they have signs or symptoms of cardiac adverse reactions [see Warnings and Precautions].

Neutropenia

Advise patients to contact their healthcare provider if they have a fever [see Warnings and Precautions].

Thrombocytopenia

Advise patients to contact their healthcare provider if they have bruising or bleeding [see Warnings and Precautions].

Embryo-Fetal Toxicity

Advise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions]. Use in Specific Populations.

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX FASPRO and for 3 months after the last dose [see Use in Specific Populations].

Advise patients that lenalidomide, thalidomide and pomalidomide have the potential to cause fetal harm and have specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program [see Use in Specific Populations].

Interference with Laboratory Tests

Advise patients to inform their healthcare provider, including personnel at blood transfusion centers, that they are taking DARZALEX FASPRO, in the event of a planned transfusion [see Warnings and Precautions].

Advise patients that DARZALEX FASPRO may affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response [see Warnings and Precautions].

Hepatitis B Virus (HBV) Reactivation

Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX FASPRO could cause hepatitis B virus to become active again [see Adverse Reactions].

Product of Switzerland

Manufactured by:

Janssen Biotech, Inc.

Horsham, PA 19044

U.S. License Number 1864

© 2021 Janssen Pharmaceutical Companies

cp-267681v2
The Effect of Prior Cancer on Survival of Patients With Thymoma

Shilong Wu, MD1#; Junhua Fang, MB1#; Ling Ji, MD1; Haipeng Liu, MD1; Jiufei Li, MD1; Wenfa Jiang, MD1*#; and Chenyang Xu, MD1*#

ABSTRACT

BACKGROUND: Thymoma is an uncommon intrathoracic malignant tumor and has a long natural history, with overall survival (OS) in these patients lasting decades. It is uncertain whether the survival of a patient with thymoma is affected by their prior cancer history (PCH). Finding out the impact of PCH on thymoma survival has important implications for both decision-making and research.

METHODS: The Surveillance, Epidemiology, and End Results database was queried for patients with thymoma diagnosed between 1975 and 2015. Kaplan-Meier methods and the Cox proportional hazards model were used to analyze OS across a variety of stages, ages, and treatment methods, in patients both with and without PCH.

RESULTS: A total of 3604 patients with thymoma were identified, including 507 (14.1%) with a PCH. The 10-year survival rate of patients with a PCH (53.8%) was worse than that of those without a PCH (40.32%; 95% CI, 35.24%-45.33%; \( P < .0001 \)). However, adjusted analyses showed that the impact of a PCH was heterogenous across ages and treatment methods. In subset analyses, PCH was associated with worse survival among patients who were treated with chemoradiotherapy (HR, 2.80; 95% CI, 1.51-5.20; \( P = .001 \)) and among those who were \( \leq 65 \) years (HR, 1.33; 95% CI, 1.02-1.73; \( P = .036 \)).

CONCLUSIONS: PCH provides an inferior OS for patients with thymoma. However, it does not worsen the survival in some subgroups, and these patients with thymoma may be eligible for study.

KEYWORDS: prior cancer history, thymoma, survival, SEER database, clinical trial.

Background

Thymoma is a rare tumor deriving from the epithelial cells of the thymus, although it is the most common primary tumor in the anterior mediastinum. The prevalence of thymoma has been reported as 0.13 per 100,000 person-years in the United States. Unlike most other cancers, thymoma has a long natural history and the overall survival (OS) of patients with thymoma can regularly be measured in decades. Nonetheless, patients with thymoma and multiple primary cancers are still worthy of study. Some studies have found that patients with thymoma had a broadly increased risk for future cancers; certain patients even experience worse survival. Still, the full impact of prior malignancy on thymoma outcomes remains unknown.

Clinical trials play a pivotal role in improving the survival of patients with cancer. However, cancer history is a commonly used exclusion criterion in oncology clinical trials, due to concerns that previous treatment and survival impact could interfere with clinical results. Still, the exclusion of patients with a personal cancer history may be problematic, because it is common for clinical trials to struggle to recruit enough patients with thymoma. What’s more, no data exist to clearly support the hypothesis that prior cancer history (PCH) impacts the survival of patients with thymoma. Further, it is uncertain whether the results...
**TABLE. Baseline Characteristics of Patients With Thymoma in Each Cohort**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Full cohort; N = 3604 (%)</th>
<th>First primary cohort; n = 3097 (%)</th>
<th>Prior cancer history; n = 507 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>58.12 (15.05)</td>
<td>56.72 (14.97)</td>
<td>66.83 (12.55)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1739 (48.3%)</td>
<td>1478 (47.7%)</td>
<td>261 (51.5%)</td>
<td>.12</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2455 (68.1%)</td>
<td>2062 (66.6%)</td>
<td>393 (77.5%)</td>
<td>.01</td>
</tr>
<tr>
<td>Black</td>
<td>531 (14.7%)</td>
<td>468 (15.1%)</td>
<td>63 (12.4%)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>618 (17.1%)</td>
<td>567 (18.3%)</td>
<td>51 (10.1%)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Married</td>
<td>2178 (60.4%)</td>
<td>1857 (60.0%)</td>
<td>321 (63.3%)</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>585 (16.2%)</td>
<td>529 (17.1%)</td>
<td>56 (11.0%)</td>
<td></td>
</tr>
<tr>
<td>Separated/divorced/widowed</td>
<td>684 (19.0%)</td>
<td>576 (18.6%)</td>
<td>108 (21.3%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>157 (4.4%)</td>
<td>135 (4.4%)</td>
<td>22 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>1975-1988</td>
<td>370 (10.3%)</td>
<td>343 (11.1%)</td>
<td>27 (5.3%)</td>
<td></td>
</tr>
<tr>
<td>1989-2002</td>
<td>1005 (27.9%)</td>
<td>890 (28.7%)</td>
<td>115 (22.7%)</td>
<td></td>
</tr>
<tr>
<td>2003-2015</td>
<td>2229 (61.8%)</td>
<td>1864 (60.2%)</td>
<td>365 (72.0%)</td>
<td></td>
</tr>
<tr>
<td>Masaoka-Koga stage</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>I/IIA</td>
<td>298 (8.3%)</td>
<td>257 (8.3%)</td>
<td>41 (8.1%)</td>
<td></td>
</tr>
<tr>
<td>II B</td>
<td>749 (20.8%)</td>
<td>680 (22.0%)</td>
<td>69 (13.6%)</td>
<td></td>
</tr>
<tr>
<td>III/IV</td>
<td>308 (8.5%)</td>
<td>278 (9.0%)</td>
<td>30 (5.9%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2249 (62.4%)</td>
<td>1882 (60.8%)</td>
<td>367 (72.4%)</td>
<td></td>
</tr>
<tr>
<td>WHO type</td>
<td></td>
<td></td>
<td></td>
<td>.03</td>
</tr>
<tr>
<td>A</td>
<td>232 (6.4%)</td>
<td>195 (6.3%)</td>
<td>37 (7.3%)</td>
<td></td>
</tr>
<tr>
<td>AB</td>
<td>433 (12.0%)</td>
<td>382 (11.7%)</td>
<td>71 (13.0%)</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>345 (9.6%)</td>
<td>290 (9.4%)</td>
<td>55 (10.9%)</td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>350 (9.7%)</td>
<td>298 (9.6%)</td>
<td>52 (10.3%)</td>
<td></td>
</tr>
<tr>
<td>B3</td>
<td>476 (13.2%)</td>
<td>397 (12.9%)</td>
<td>79 (15.6%)</td>
<td></td>
</tr>
<tr>
<td>NOS</td>
<td>1768 (49.1%)</td>
<td>1555 (50.2%)</td>
<td>213 (42.0%)</td>
<td></td>
</tr>
<tr>
<td>Size (mm), mean (SD)</td>
<td>75.50 (60.75)</td>
<td>76.49 (60.44)</td>
<td>69.61 (62.30)</td>
<td>.04</td>
</tr>
<tr>
<td>Surgery</td>
<td>2782 (77.2%)</td>
<td>2399 (77.5%)</td>
<td>383 (75.5%)</td>
<td>.34</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>1046 (29.0%)</td>
<td>856 (27.6%)</td>
<td>190 (37.5%)</td>
<td></td>
</tr>
<tr>
<td>Surgery plus adjuvant therapy</td>
<td>1736 (48.2%)</td>
<td>1543 (49.8%)</td>
<td>193 (38.1%)</td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td>177 (4.9%)</td>
<td>154 (5.0%)</td>
<td>23 (4.5%)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>196 (5.4%)</td>
<td>174 (5.6%)</td>
<td>22 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>Radiation plus chemotherapy</td>
<td>195 (5.4%)</td>
<td>166 (5.4%)</td>
<td>29 (5.7%)</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>254 (7.0%)</td>
<td>204 (6.6%)</td>
<td>50 (9.9%)</td>
<td></td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Alive</td>
<td>1823 (50.6%)</td>
<td>1600 (51.7%)</td>
<td>223 (44.0%)</td>
<td></td>
</tr>
<tr>
<td>Cancer death</td>
<td>730 (20.3%)</td>
<td>730 (23.6%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Noncancer death</td>
<td>1051 (29.2%)</td>
<td>767 (24.8%)</td>
<td>284 (56.0%)</td>
<td></td>
</tr>
</tbody>
</table>

NOS, not otherwise specified; WHO, World Health Organization.
of clinical trials that excluded patients with PCH could then apply equally to patients with such history. Therefore, determining the impact of PCH on thymoma survival is important for both patients and the oncology community.

Until recently, no study has specifically evaluated the impact of PCH on thymoma outcomes, and we know little about the features of patients with thymoma with PCH. In this study, we aimed to identify the relationship between cancer history—in patients with thymoma who had such history—and the prognosis for their thymoma. Mortality risk of thymoma, as it related to a patient’s PCH, was evaluated using a cohort of patients with thymoma in the Surveillance, Epidemiology, and End Results (SEER) database.

Methods

Data Source and Study Population

All data were extracted from the SEER database through SEER*Stat Software version 8.3.6. We searched all records of patients diagnosed with thymoma between 1975 and 2015. A diagnosis of any thymoma, excluding thymic carcinoma, was identified by histology and primary site (tumor site code). The SEER sequence number variable represented the order of reportable tumors diagnosed in a lifetime and was used to determine the prevalence of prior cancer.

The patients with thymoma were divided into 2 cohorts based on whether or not they had a PCH. The PCH cohort included patients who had a cancer diagnosis before the thymoma diagnosis, and the first primary (FP) cohort included those patients for whom thymoma represented their first and only malignancy. All patients must have been diagnosed with microscopic confirmation by cytology or histology. Patients were excluded if: (1) they had only death certificates or autopsy records, with no cytological or histological confirmation by cytology or histology. Patients were further divided into 6 subgroups based on the thymoma treatment they received: surgery only, surgery and chemotherapy, and no treatment.

Data Elements

Extracted from the SEER database were demographic and clinicopathological characteristics, including age, sex, race, marital status, year of diagnosis, histological subtype, stage, and surgery, chemotherapy, and radiotherapy records. Survival data were calculated in months, and any survival times of 0 months were recorded as 0.5 months. Masaoka-Koga staging was estimated using an approach modeled which was proposed by Fernandes et al. Briefly, patients were categorized into 4 groups: stage IIA (“invasive tumor confined to gland of origin” or “localized, not otherwise specified”), stage IIB (“adjacent connective tissue”), stage III/IV (“adjacent organs/structures” or “further contiguous extension” or “any positive lymph nodes”), and unknown (unknown extent of disease).

Statistical Analysis

Data were presented as mean values, using standard deviations for continuous variables and percentages for categorical variables. Continuous variables were compared using t tests; categorical variables were analyzed using the Pearson χ² test. Survival curves were plotted by using the Kaplan-Meier method and compared by using the log-rank test. Cox proportional hazards regression models were adjusted for demographic and clinicopathological characteristics. Survival time was calculated as months from diagnosis to death or end of follow-up. The primary end point of this study was OS, and the cutoff date for follow-up was December 31, 2016. All P values were 2-tailed, and P values < .05 were considered statistically significant. Statistical analysis was performed using Stata 16.0 (StataCorp).

Results

Patient Characteristics

A total of 3604 patients with thymoma who met the inclusion criteria were collected from the SEER database, including 507 (14.1%) with PCH. The baseline patient characteristics are shown in the Table. The median (SD) age was 58 (15) years and 1739 (48.3%) patients were female. A total of 1239 patients (34.4%) with thymoma were older than 65 years. The prevalence of patients with PCH was concentrated between 2003 and 2015 (72%). None of the patients in the PCH cohort were seen to have died of thymoma. In general, the PCH cohort had more elderly patients, more deaths, and smaller tumors compared with the FP cohort. Patients were further divided into 6 subgroups based on the thymoma treatment they received: surgery only, surgery and adjuvant therapy, radiation only, chemotherapy only, radiation and chemotherapy, and no treatment.

Unadjusted Survival Comparisons

With a median follow-up of 68 months (range, 0-468), as shown in Figure 1A, the 10-year OS rate of the FP cohort (53.8%; 95% CI, 51.7%-55.86%; P < .0001) was better than that of the PCH cohort (40.32%; 95% CI, 35.24%-45.33%; P < .0001). Figures 1B-D depict stratified Kaplan-Meier survival curves by stage. Patients with PCH with thymoma of stages I to IV exhibited worse survival than those in the FP cohort; however, the difference was statistically different only for those patients with stage II disease (P = .005). Among patients with stage II thymoma, the 10-year OS rate for the FP and PCH cohorts, respectively, were 48.24% (95% CI, 44.42%-51.95%) and 37.68% (95% CI, 26.4%-48.91%). Figures 2A-B present stratified Kaplan-Meier curves by age. Patients with PCH displayed worse survival if they were age < 18 years; or (3) had incomplete follow-up information or survival data.
The survival curve of patients with prior cancer history compared with those in whom the thymoma represented their first and only malignancy as well stratified by Masaoka-Koga stage (A, all stage; B, Stage I/IIA; C, stage IIB; D, stage III/IV).

**FIGURE 1. Kaplan-Meier Survival Plots for Different Stage**

Time (months) Survival probability

log-rank: \( P = .005 \)

log-rank: \( P = .08 \)

log-rank: \( P = .0001 \)

log-rank: \( P = .15 \)

≤65 years (\( P = .004 \)), while patients aged >65 years with PCH showed survival similar to that of the FP cohort.

**Adjusted Survival Comparisons**

Cox proportional hazard models were adjusted for patient demographics and stratified by treatment. As shown in Figure 3, PCH was associated with worse survival for 5.4% of patients with thymoma, but the impact of PCH was not statistically significant for 94.6% of those patients. The patients treated with radiation and chemotherapy in the PCH cohort had worse OS compared with the FP cohort (HR, 2.80; 95% CI, 1.51-5.20; \( P = .001 \)). For the patients with PCH who were treated with other methods, having PCH made no statistical difference. Multivariate Cox proportional hazard model analysis showed that PCH was not associated with significantly worse survival for stage II thymoma (HR, 1.03; 95% CI, 0.72-1.46; \( P = .889 \)) but was associated with worse survival for patients ≤65 years (HR, 1.33; 95% CI, 1.02-1.73; \( P = .036 \)).

**Discussion**

To our knowledge, this is the first study to analyze the impact of PCH on outcomes in thymoma. Our study results indicate that PCH had a significant but heterogenous effect on the survival of patients with thymoma. To some degree, the unadjusted survival analyses for thymoma show that PCH is associated with worse OS vs FP (Figure 1A). PCH was seen to have an adverse effect on OS in patients younger than 65 years. For patients with stage II thymoma, patients with PCH showed worse survival than those in the FP cohort (Figure 1C) but had no statistical difference in survival after multivariate Cox proportional hazard model analysis.

Patients may have competing priorities to make treatment decisions, and treatment modalities may have implications for survival. The adjusted survival analyses were stratified by treatment modalities for further analysis, which revealed that the chemoradiotherapy subgroup of the PCH cohort had significantly worse survival than members of the other subgroups.
The cancer survivor population has been growing rapidly in the United States over the past 30 years, largely driven by the aging population, the improvement of treatment, and expanding cancer screening efforts. These factors have led to an increased prevalence of multiple primary cancers. In our study, 20% of older patients (> 65 years) and more than 10% of younger patients (≤ 65 years) who were diagnosed with thymoma had PCH. As shown in Figure 2A, the patients in the younger adult subgroup with PCH had significantly worse prognosis than those in the corresponding FP subgroup.

A study conducted by Andrew et al found that PCH did not adversely affect clinical outcomes in patients with thymoma. The authors also suggested that patients with PCH should not be excluded from clinical trials recruiting patients with advanced lung cancer. They argued that older patients were more likely to die from the progression of cancer and comorbidities; therefore, PCH had less impact, relatively. Younger patients with thymoma tend to have a better prognosis than older patients and are more likely to be cured. On the other hand, prior cancer treatment could increase the risks of treatment intolerance, thus worsen the survival of younger patients with thymoma.

Although several staging systems exist, the Masaoka-Koga staging classification system is the most extensively used and is a reliable predictor for the prognosis of thymoma. The 5-year OS rate was approximately 85% in the patients with stage I to III thymoma and 65% in those with stage IV thymoma.

For stage I and stage II thymoma, complete surgical resection is the recommended standard treatment. What’s more, postoperative radiotherapy is suggested in incompletely resected or high-risk stage II thymomas. Adjuvant radiotherapy can reduce local recurrence rates, and completely resected stage II tumors may benefit from adjuvant radiotherapy, but this seems to have no impact on OS. It is not yet clear whether patients with a PCH and stage II thymoma could benefit from postoperative radiotherapy. In our work, we found that patients with PCH didn’t display significantly worse OS than those without PCH, when patients had stage II thymoma.

Thymomas are representative of slow-growing tumors that can spread locally. Metastases are usually restricted to the pericardium, diaphragm, or pleura, and extrathoracic regional metastases are uncommon. Because of their rarity, various studies are necessary to explore and improve current therapeutic standards. Surgery is the cornerstone of the multimodal treatment strategy for thymoma. Complete removal of the tumor and total thymectomy are recommended for most resectable tumors. Incompletely resected tumors or tumors with a positive resection margin are generally treated with radiotherapy. Chemotherapy combined with radiotherapy is recommended in unresectable thymomas or advanced thymomas. As seen in Figure 3, the patients in the PCH cohort who received radiation and chemotherapy experienced worse OS compared with the FP cohort. Intriguingly, our results showed that the impact of PCH was not statistically significant for most patients with advanced thymomas. Nonetheless, prior cancer treatment increased the toxicity and intolerance of chemoradiotherapy prescribed to treat thymoma, and patients with unresectable thymoma with PCH tended to have more complex conditions than their FP counterparts.
The current study suggested that PCH have a variable impact on the selection of retrospective study and clinical trial. We suggest including PCH as a stratification or covariate variable when PCH is known to modify the effect of 1 or more independent variables. The relationship between OS and PCH most probably reflects interactions among (1) the recurrence or lethality of prior cancer, (2) the recurrence or lethality of the newly diagnosed thymoma, and (3) the personal circumstances of patients.

Limitations
Undeniably, the present study has several limitations. Firstly, we confirmed a PCH according to the sequence number only, without detailed prior cancer characteristics. Therefore, we could not distinguish whether the index thymoma was from local recurrence. Secondly, the current study focused on PCH in general, without description of the specific prior cancer type. Prior cancer type could affect results, as the previously diagnosed cancer could be “likely lethal” or “likely irrelevant” to prognosis. Thirdly, the SEER database lacked detailed information on therapeutic regimens for chemotherapy and radiotherapy or toxicity, as well as on comorbidities and adverse events. In addition, the data acquired from the SEER database cover approximately 34.6% of the population in the United States. Further studies are required to confirm the generalizability of our findings.

Conclusions
A prior cancer history has variable impact on the survival of patients with thymoma, depending upon age and treatment method. PCH is associated with worse survival for patients who were younger and treated with chemoradiotherapy. However, further studies are required for confirmation.

FIGURE 3. Multivariate Cox Proportional Hazards of Patients, Stratified by Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>1.17(0.87-1.57)</td>
<td>0.292</td>
</tr>
<tr>
<td>Surgery plus adjuvant therapy</td>
<td>1.26(0.98-1.62)</td>
<td>0.072</td>
</tr>
<tr>
<td>Radiation</td>
<td>1.44(0.73-2.85)</td>
<td>0.292</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0.85(0.42-1.73)</td>
<td>0.661</td>
</tr>
<tr>
<td>Radiation plus chemotherapy</td>
<td>2.80(1.51-5.20)</td>
<td>0.001</td>
</tr>
<tr>
<td>No Treatment</td>
<td>1.27(0.69-2.34)</td>
<td>0.437</td>
</tr>
</tbody>
</table>

Analysis of the impact of prior cancer history on overall survival by treatment. The model is adjusted for Masaoka-Koga stage, race, WHO type, size, marital status, age, and year of diagnosis.
Successful Diagnosis and Treatment of Occult Prostate Cancer Despite Multiple Negative Prostate Biopsies and Negative Prostate MRIs

Kostantinos E. Morris, BS1; Dominic C. Grimberg, MD1; Rajan T. Gupta, MD1,2,3; Avani A. Pendse, MD, PhD4; and Judd W. Moul, MD1,3

ABSTRACT: Prostate-specific antigen (PSA) values above 100 ng/mL often suggest metastatic prostate cancer. We present the case of a patient with a PSA of 110 ng/mL, 4 negative prostate biopsies, and 4 negative prostate MRIs. After his fifth MRI revealed a PI-RADS 5 lesion, he underwent his fifth transrectal biopsy; this revealed Gleason 3 + 4 = 7. He was found to have organ-confined pT2 disease on subsequent radical prostatectomy pathology. This case highlights that there may be no PSA for which one can assume metastatic disease with certainty. Depending on life expectancy, patients with extremely elevated PSA may still warrant a full staging workup.

KEY WORDS: prostate, prostate cancer, mpMRI, radical prostatectomy, PSA, PHI, Exosome, delayed diagnosis, surgical pathology

Introduction And Initial Presentation
A man, aged 73 years, presented to our care in early 2021 with a prostate-specific antigen (PSA) of 110 ng/mL after 4 negative prostate biopsies and 4 negative prostate MRIs. His journey had begun in 2002 when his PSA was 3 ng/mL. Two years later, in 2004, at a PSA level of 3.8 ng/mL, he had his first transrectal ultrasound-guided (TRUS) biopsy. All 6 cores were negative. His PSA continued to oscillate between 3 and 10 ng/mL for the next 5 years, warranting 12-core TRUS biopsies in 2007 and 2009. These were negative, and his prostate size of 40 grams was thus cited as the cause of his PSA elevation.

In 2010, as his PSA rose above 10 ng/mL, he had the first of 4 prostate MRIs; it did not reveal suspicious lesions. It was followed by a negative 12-core TRUS biopsy in 2011. His PSA rose from 65 ng/mL to about 100 ng/mL from 2014 to 2019, and repeat MRIs in 2014 and 2017 did not demonstrate any suspicious lesions. However, a mix of stromal and hyperplastic nodules in the transition zone (TZ) of the prostate were exhibited. Prostate MRI in 2019, at an outside academic center, again did not demonstrate a suspicious prostatic lesion. His prostate exam remained benign, with hypertrophy of the gland to 60 grams. In late 2020, his PSA measured above 100 ng/mL and he was referred to us for care.

Assessment
At presentation to our clinic in early 2021, the patient’s PSA was 110 ng/mL, with minimal lower urinary tract symptoms and a negative review of systems. His prostate was 60 grams and smooth. An Exosome Dx urine test (EXO Dx; Exosome Diagnostics/Bio-Techne) revealed an extremely elevated score of 69 (normal is below 15.6). His Prostate Health Index (PHI; Beckman Coulter) was 259, and his percent free PSA was 7.5%. These prompted his fifth and final MRI.
Diagnosis And Management
A PI-RADS 5 lesion was identified in the left anterior TZ (Figures 1A-1D), and an 18-core TRUS fusion biopsy shortly thereafter revealed 2 cores of Gleason 3 + 4 = 7, Gleason grade (GG) 2 disease (Figure 2A). After metastatic staging with a negative CT and nuclear medicine bone scan, he underwent open radical prostatectomy (RP) in May 2021. Final pathology revealed a 66-gram prostate, Gleason 4 + 3 = 7, GG3, organ-confined disease with negative lymph nodes, pT2N0Mx (Figure 2B).

Discussion
We used several novel secondary screening tests in this case: the PHI and the EXO Dx.1,2 Many contemporary patients are skeptical and reluctant to undergo an invasive prostate biopsy based only on total elevated PSA. Tutrone et al showed that compliance in following through on a biopsy using PSA alone was 39% vs 72% for men who also had an abnormal EXO Dx test to consider.3 Our patient was reluctant to have further invasive testing considering his prior negative work-up.

Although his high total PSA was outside the labeled indication for both tests, we felt the tests were useful in this most unusual case.

While infectious etiologies such as prostatitis, prostate abscess, and even tuberculosis can be considered, studies have shown that a PSA elevation due to an inflammatory prostatic process is often to a level much lower than what was seen with our patient.4 PSA values above 100 ng/ml do often suggest metastatic prostate cancer. In 1993, Stamey et al presented 3 similar patients with TZ lesions, PSA between 150 and
456 ng/mL, and Gleason 4 + 3 = 7. All were found to have organ-confined disease. TZ lesions have been shown to have higher PSA density than their peripheral zone (PZ) counterparts, and while large tumor volumes may be observed in the TZ, they are more likely to have favorable pathologic features and lower biochemical recurrence (BCR) rates. A more recent study in 2015 by Lee et al showed similar findings, with higher preoperative PSA values and larger tumor volume in TZ lesions compared with PZ lesions. Furthermore, they showed decreased odds of seminal vesicle invasion, extracapsular extension, and hazard of tumor recurrence. Additional study is needed to verify if the capsule around the TZ could be restricting tumor spread.

While a high PSA may be an excellent predictor, it is not perfect. A 2020 Swedish study of 8850 men with PSA above 100 ng/mL found that 71% had metastatic prostate cancer, and among men with PSA of above 500 ng/mL, the rate of metastases still ranged from 50% to 94%. Even if the disease is localized at the time of treatment, BCR is significantly higher for patients with PSA above 100 ng/mL who have undergone RP. BCR-free survival is only 29% at 10 years for PSA above 100 ng/mL for these patients.

Q&A With Key Investigators

Q: Dr Moul, did you believe this patient had cancer when he presented to you? How did his past 4 MRIs and 4 biopsies impact your approach?

A: I do not recall seeing a prior patient with such a prolonged work-up and a PSA this elevated who did not have prostate cancer. When the PSA is above 100 ng/mL, the chance of finding prostate cancer is at least 75%.

I am very fortunate to be at a major center with multidisciplinary care where we have access to secondary screening tests such as PHI and EXO Dx urine testing. When the EXO Dx returned at 69, I knew there was a high probability not only of cancer, but of Gleason 7 or higher. While the EXO Dx test is officially marketed for use in men with a total PSA between 2 and 10 ng/ml, I ordered the test to help convince this patient, who had already endured so much and felt well, to have another MRI and possibly another biopsy. Although the PHI is not approved for use in men with a total PSA of above 20, I also ordered this test, for similar reasons. In the end, we were able to identify what we believe...
Thursday, March 31
3:00 PM – 7:00 PM EST

Business Training for Physicians
- Coding & Reimbursement
- Concierge Medicine
- Remote Patient Monitoring
- Tax Planning for Physicians

Maximize your time and your earning potential
Industry experts will guide you through four business-focused sessions that will help you reach your full profit potential.

REGISTER FOR FREE!
Scan or visit: onclive.com/springbootcamp

Sponsored by:
to have been occult disease, and not interval cancer development, as anterior lesions can be missed in up to 46% of 12-core biopsies.\textsuperscript{11}

**Q:** Dr Moul, had his repeat MRI not shown a lesion, what would your next step have been?

A: That is a great question. With total PSA, EXO Dx urine, free PSA, and PHI pointing to previously missed occult prostate cancer, I would likely have pushed the patient toward another biopsy. I would likely have recommended a saturation biopsy with special attention to anterior cores. The patient was understandably hesitant about more invasive testing and I believe it may have been challenging to convince him to do more testing, given that he felt perfectly fine. Fortunately, MRI did find the lesion that had been eluding his caregivers for [so long].

**Q:** Dr Moul, did you immediately consider surgery? What was your biggest concern in offering surgery?

A: I am very careful about offering RP to men 70 years and older due to concern for increased sexual and urinary morbidity in the group aged 70 to 79 years. However, this gentleman was enjoying excellent health and had a normal body mass index so I was a bit less concerned about incontinence. I did explain to him that age alone made him less likely to regain potency even with a bilateral nerve-sparing technique. I estimated his nerve-sparing technique. I estimated his likelihood of regaining erections firm enough for intercourse, either spontaneously or with the help of oral medications, was about 20% to 25%. I also told him that he faced a 5% to 10% chance of still requiring a pad for stress incontinence at 1 year post surgery even though the risk of total incontinence was 1% or less in my series. Only RP pathologic assessment could help us understand why his cancer had been so elusive over the past 18 years. I did have the patient consult with radiation oncology as part of our multidisciplinary program and would have supported his decision for local therapy.\textsuperscript{12}

**Q:** Dr Moul, what clinical pearls can we take away from this case from the perspective of a urologist?

A: Don’t give up in healthy men who have elevated and rising PSA. This is an extreme and prolonged example of occult prostate cancer eluding multiple diagnostic and imaging efforts. I do not recall, in my 30-plus years of practice, ever seeing a patient with a PSA above 100 ng/mL who did not have prostate cancer. I think we were able to utilize the latest in technological advancements—those that did not exist 18 years ago when this patient first presented with an elevated PSA. Finally, this case had a happy ending with organ-confined disease and at his 3-month follow up visit, the patient had a PSA less than 0.1 ng/mL and only mild stress incontinence (1 pad per 24 hours).

**Q:** Dr Gupta, what makes reading these MRI images so difficult?

A: A Prostate MRI is a challenging imaging study to interpret, especially in the TZ. The TZ is challenging because of the overlap in imaging appearance of certain types of benign prostatic hyperplasia nodules with malignancy. Specifically, the degree of restricted diffusion and contrast enhancement can overlap with stromal and hyperplastic nodules, respectively. That said, there are morphologic features of anterior TZ lesions that are critical to recognize. Specifically, T2 weighted imaging is the dominant imaging sequence used to diagnose and characterize TZ lesions and these are characterized by an “erased charcoal” appearance, as in this case. Also, these lesions should have markedly restricted diffusion as evidenced by low signal on apparent diffusion coefficient (ADC) maps and high signal on high b-value diffusion weighted imaging (DWI).

**Q:** Dr Gupta, do you believe the 4 MRIs the patient had (2010, 2014, 2017, 2019) were all warranted? At what interval do you usually view meaningful changes in an MRI read?

A: This question really comes down to suspicion of clinically significant cancer. Clearly the patient had a PSA that was persistently elevated without imaging or biopsy findings to explain this. To that end, I think that repeat MRIs can be warranted. That said, it is critical to ensure high-quality MRI, with interpretation performed by radiologists with significant experience in prostate MRI. As for the interval during which we see meaningful changes on MRI, we can take some guidance from imaging performed as part of active surveillance protocols. In these cases, imaging can be helpful every 1 to 2 years, looking for changes in a lesion that would suggest that it is suspicious for clinically significant disease. This would include increase in size and/or increased restricted diffusion, as evidenced by lower signal on ADC maps and high signal on high b-value DWI.

**Q:** Dr Gupta, what imaging pearls can we take away from this case from a radiologist’s perspective?

A: This case has some key takeaways. First, knowledge of the existence and prevalence of anterior TZ lesions is key to accurate diagnosis of these lesions. Radiologists are uniquely able to add value to patient care in this setting as these lesions are frequently missed on
systematic biopsy due to their anterior location. Finally, when performing prostate MRI, even though PI-RADS states that decisions on lesion categorization should be made based on imaging findings only, in my opinion, prostate MRI cannot be read in a vacuum. That is, clinical information such as rising PSA must be considered when reading prostate MRI, especially when multiple exams have been performed.

Q: Dr Pendse, is there anything particular about this patient’s tumor that ties together the PSA above 100 ng/mL and organ-confined disease?
A: High levels of total PSA have been shown to correlate with a larger volume of cancer, a high Gleason score (7 or higher), and capsular penetration in RP specimens. Also, the low percent free PSA levels were correlated with high Gleason score (7 or higher), and larger tumor volume. Our patient—with a very high total PSA level and a relatively low percent free PSA level of 7.5%, measured in 2021—had preoperative factors predicting a high Gleason score (7 or higher), larger tumor volume, and a higher chance of capsular penetration into the extraprostatic tissue. Additionally, the high PSA level also increased the preoperative probability of regional lymph node involvement.

This case demonstrates that the accurate prediction of tumor burden and stage in a single individual can still prove to be tricky. As expected, the Gleason score was high at 4 + 3 = 7. The negative resection margins were surprising, though. A possible explanation for high PSA levels and organ-confined disease may be the presence of significant disease burden in the anterior prostate. Higher PSA levels have been seen in anterior tumors. These tumors usually represent an extension of the more common posterior tumor and are often part of larger tumor foci. The tumor distribution in our patient with a high PSA involved the entirety of the left prostate including a significant amount of tumor in the anterior quadrant.

Q: Dr Pendse, can you describe the salient features of the pathology images (Figure 2)?
A: The RP specimen showed a dominant larger focus of prostatic acinar adenocarcinoma in the left prostate, extending from apex to base including both anterior and posterior quadrants (Figure 2B). The tumor showed a Gleason score of 4 + 3 = 7 with 70% pattern 4 and cribriform pattern 4. The striking feature on histopathology was the very compact arrangement of tumor cells compared with most cancer cases that I have seen, with very scant intervening stroma. I speculate that high tumor cell density contributed to the very high PSA level.

The final prostate biopsies showed prostatic adenocarcinoma in 5 of 18 cores. The lesion demonstrated on the MRI in the left anterior prostate showed prostatic adenocarcinoma 3 + 4 = 7, involving 7% of the tissue (Figure 2A; 100× magnification, hematoxylin and eosin stain). This finding of a much higher than expected tumor volume in the RP compared with prior biopsies is rather puzzling. Interestingly, Stein et al have shown that in patients with repeat false negative biopsies, there is a statistically nonsignificant tendency toward a higher Gleason score and tumor stage in tumors detected via fourth or fifth biopsies compared with tumors detected via second set of biopsies.

Q: Dr Pendse, what pearls can we take away from this case from a pathologist’s perspective?
A: In a vast majority of cases, there is a high concordance level among tumor grade, volume, and distribution on biopsy and RP specimens. PSA levels are also correlative of tumor volume. In this patient, the tumor grade and volume were higher than expected based on multiple prior biopsies. The higher PSA level suggested a high tumor volume, which was confirmed on the prostatectomy. Organ-confined disease was somewhat unexpected. Every case is unique and can have surprising findings. Given their inherent uniqueness and profound implications on patient treatment and prognosis, it is important to practice with vigilance to not miss subtle diagnostic findings.

Conclusions
Ultimately, our case highlights that there may be no PSA for which one can assume metastatic disease with certainty and that using tumor location could help stratify patient risk. Depending on life expectancy, these patients may still warrant full staging workup. Considering the continuing controversy surrounding prostate cancer screening with PSA, some might argue that this is much ado about nothing. The patient was aged more than 70 years and clinically well. Ultimately, he had organ-confined disease that may have never seriously harmed him. In retrospect, this patient could have possibly lived his allotted life expectancy based on the fact that his disease was organ confined. However, we contend that the management was appropriate and justified and could have been a medico-legal risk if not addressed.

AUTHOR AFFILIATIONS:
1. Division of Urology, Department of Surgery, Duke Cancer Institute, Duke University Medical Center, Durham, NC
2. Department of Radiology, Duke University Medical Center, Durham, NC
3. OCM Center for Prostate and Urologic Cancers, Duke Cancer Institute, Duke University Medical Center, Durham, NC
4. Department of Pathology, Duke University Medical Center, Durham, NC

FUNDING SUPPORT: This research received no outside funding

For references visit cancernetwork.com/Morris_3.21
Treatment Options in Metastatic Castration-Sensitive Prostate Cancer

During a Clinical Consult presentation, Atish D. Choudhury, MD, PhD, spoke with CancerNetwork® about long-term safety and efficacy data for agents related to metastatic castration-sensitive prostate cancer (mCSPC) as well as several unmet needs for this patient population.

“We have been seeing an increase in men who are presenting initially with metastatic disease,” explained Choudhury, co-director of the Prostate Cancer Center at the Dana-Farber/Brigham and Women’s Cancer Center and assistant professor of medicine at Harvard Medical School. “It means that more men are presenting in a space and we’re getting some increasing data around how to optimally manage them.”

Choudhury expanded on those unmet needs for patients with mCSPC and the various treatment options that are considered for each individual patient.

Clinical Research Supporting Treatment Options for mCSPC

“The backbone of all treatment is androgen deprivation therapy [ADT]. These medications suppress the level of testosterone in the body, since testosterone is the fuel for prostate cancer to grow and spread,” Choudhury explained.

Although ADT remains a key component of treating patients with mCSPC, Choudhury emphasized that ADT alone works only for a few patients. He explained that intensifying ADT with different treatment modalities has been linked with prolonged survival.

Specifically, Choudhury mentioned docetaxel chemotherapy; androgen receptor (AR)–targeted agents, including abiraterone acetate (Zytiga), apalutamide (Erleada), and enzalutamide (Xtandi); and radiation as viable modalities to intensify therapy.

“It’s not clear from [completed] studies that any one of those agents is superior to any other in terms of overall survival,” Choudhury explained. “We can conclude only that they are all superior to ADT alone.”

Choudhury mentioned 2 studies—ARCHES (NCT02677896), examining enzalutamide plus ADT, and TITAN (NCT02489318), of apalutamide plus ADT—as research that confirmed positive survival data with these drugs in mCSPC.1,2 Additionally, both trials led to FDA approvals of their respective agents for patients in this setting.3,4

ARCHES built on previously reported results from the phase 3 ENZAMET trial (NCT02446405), which investigated enzalutamide for metastatic prostate cancer. A significant reduction in the risk of death or progression was noted in the ARCHES cohort of patients who received...
enzalutamide plus ADT compared with placebo plus ADT (HR, 0.39; 95% CI, 0.30-0.50; \( P < .001 \)). In TITAN, the combination of apalutamide plus ADT reduced the risk of death by 35% compared with matched placebo (HR, 0.65; 95% CI, 0.53-0.79; \( P < .0001 \)) and by 48% after adjusting for treatment crossover (HR, 0.52; 95% CI, 0.42-0.64; \( P < .0001 \)).

“These data confirm findings from previous studies that all demonstrated a prolongation of overall survival when adding an AR pathway inhibitor to initial ADT,” Choudhury explained.

Further, triplet therapies—with abiraterone plus docetaxel/ADT in the PEACE-1 trial (NCT01957436) and darolutamide (Nubeqa) plus docetaxel/ADT in the ARASENS trial (NCT02799602)—have shown a benefit over docetaxel plus ADT alone for patients with mCSPC.

“It’s clear from the studies presented [to date] that even patients with low-volume metastatic disease benefit from intensification of treatment,” Choudhury explained. “Quality-of-life [QOL] data from these studies also suggest that patients will benefit from earlier treatment with [androgen deprivation therapy].”

Choudhury said, “The QOL with these agents is superior [to that of] patients who are treated with ADT alone.” Overall, Choudhury emphasized the importance of starting therapy earlier in the process. Unless a contraindication exists for patients, he suggested that the survival and QOL data support the early integration of intensified therapy into mCSPC treatment.

“There’s no cancer-related or QOL reason to not consider these agents earlier in the process,” Choudhury said.

**Unmet Needs for mCSPC**

“There are a variety of unmet needs to understand how to best manage each individual patient,” Choudhury acknowledged. These include determining optimal treatment for patients with localized disease; the role of androgen receptor therapy intensification for patients treated in the neoadjuvant or adjuvant setting; using molecular diagnostics to determine if a patient should escalate or deescalate treatment; and who should receive salvage radiation and when it should be initiated. Of note, Choudhury mentioned that the US Preventive Services Task Force recommendations in 2012 played a key role in changing the diagnosis and management of patients with mCSPC and specifically cited decreased prostate-specific antigen (PSA) screenings in this setting.

“Where novel imaging comes into play is unclear,” Choudhury explained. “Should all patients who have a PSA less than 0.2 get a [prostate-specific membrane antigen]/PET scan as part of the radiation planning? I don’t think that answer has been developed yet.”

**Concluding Thoughts**

“So many advances have been made in hormone-sensitive prostate cancer that survival has been prolonged quite a bit,” Choudhury explained. “Some patients may discontinue treatment and still retain benefit. It’s a constantly changing space and we need to be adaptive on a patient-to-patient [basis] and make sure that our recommendations are individualized.”

Despite the evident need to individualize treatment, Choudhury said the benefit of intensification is clear. “[That] all patients would benefit from some form of intensification is the most important lesson that we’ve learned over the past year,” he said. “The data that have been presented recently justify that patients’ QOL is better with the addition of these other agents, even though many providers are concerned about their toxicities.”

**REFERENCES**


EXPERT COMMENTARY ON THE PRODUCT PROFILE OF Amivantamab-vmjw

Product Profile

Drug name: amivantamab-vmjw (Rybrevant)

Date of approval: May 21, 2021

Initial indication: adult patients with locally or advanced metastatic non–small cell lung cancer (NSCLC) who have EGFR exon 20 insertion mutations that have been detected by an FDA-approved test, and whose disease has progressed on or after a platinum-based therapy.¹

Dosage and administration: if patient’s weight is less than 80 kg, the recommended dose is 1050 mg; if 80 kg or more, the recommended dose is 1400 mg.

How supplied: given intravenously

Pivotal clinical trial: phase 1 CHRYSALIS trial (NCT02609776)²

Trial Design of the Pivotal Phase 1 CHRYSALIS

ELIGIBLE PATIENTS

• Histologically confirmed NSCLC that is metastatic or unresectable
• Progressed after prior SOC for metastatic disease or are ineligible or refused current treatment options
• ECOG score of 0 or 1

PART 1

• EGFR exon 19 deletion or L858R activating mutation
• Either treatment-naïve for metastatic disease without access to third generation TKI in frontline setting; progressed after first- or second-line TKI; or were treated with third-generation TKI
• Have evaluable disease

• Intravenous infusion of amivantamab as monotherapy or in combination with lazertinib or carboplatin/pemetrexed
• Starting dose of amivantamab at 140 mg with dose escalation 3 + 3 design administered over 28-day cycles

Primary end point
Rate of dose-limiting toxicities

Key secondary end points
PFS, TTF, OS, pharmacokinetics, pharmacodynamics

PART 2

• EGFR-mutated disease with evidence of resistance to available EGFR inhibitors.
• Previous treatment with platinum-based chemotherapy
• Have measurable disease per RECIST 1.1

• Intravenous amivantamab as monotherapy or combination with lazertinib at the recommended phase 2 dose determined in phase 1

Primary end points
Rate of AEs or SAEs, ORR, DOR, CBR, trough serum concentration, and AUCtau

AEs, adverse events; AUCtau, area under the curve from time zero to end of dosing interval; CBR, clinical benefit rate; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SAEs, serious AEs; SOC, standard of care; TKI, tyrosine kinase inhibitor; TTF, time to treatment failure.
Q: What are the biggest concerns with the toxicity profile? Have any additional concerns arisen with its use in the real-world setting?

The safety and efficacy of amivantamab were evaluated in the phase 1 open-label CHRYSALIS trial. The most common [all-grade] treatment-related adverse effects [AEs] were rash and infusion-related reactions, which occurred in about 86% and 66% of patients, respectively. More than 96% of these AEs were grade 1 or 2. Several AEs related to EGFR inhibition were not surprising, including paronychia in 45% of patients, stomatitis in 21%, pruritus in 17%, and diarrhea in 12%. Some AEs related to MET inhibition [occurred] that were also not surprising, including hypoalbuminemia in 27% of patients and peripheral edema in 18%.

Rash and edema do continue to be concerns in clinical practice, and infusion-related reactions are also something we need to look out for closely. This is reflected in the extensive premedication regimen and complex infusion schedule of amivantamab. These infusion reactions could be happening because amivantamab is a monoclonal antibody, but it could also be due to its formulation with polysorbate 80, which is a surfactant used in several other oncology products that carries its own risk for hypersensitivity reactions. The vast majority of infusion reactions in the CHRYSALIS trial were low grade and occurred almost exclusively during the first cycle. [In fact], of those reactions, [most] occurred on the first day of administration. That initial period is where we need to practice increased vigilance and make sure our colleagues are well educated on the signs and symptoms so they can intervene if a reaction occurs.

Q: Are dosing modifications common with this agent?

The dosing of amivantamab is unique in that it’s [given as] a flat dose but is also dependent on baseline body weight. The labeled dose for patients with a baseline body weight of less than 80 kg is 1050 mg. For patients with a weight of 80 kg or higher, the dose is 1400 mg. The package insert specifically states that you don’t have to dose-adjust [for] subsequent body weight changes. It’s all about that baseline body weight. This difference in dosing was based on pharmacokinetic data evaluating systemic exposure and volume of distribution. The labeled doses produced similar systemic exposures for patients above and below 80 kg so we would expect them to have similar efficacy.

In the CHRYSALIS trial, dose reductions due to AEs occurred in 13% of patients, with rash being the most common cause for a dose reduction. Specific dose reductions are recommended in the package insert, which correspond to vial sizes to avoid wasting product, which I think is appropriate for a monoclonal antibody product. Only 4% of patients discontinued amivantamab due to AEs, which included rash, infusion-related reactions, and paronychia.

Q: Should clinicians be aware of any drug interactions?

Since amivantamab is an immunoglobulin antibody and is primarily eliminated through proteolytic degradation, it doesn’t use hepatic drug-metabolizing enzymes for metabolism. Therefore, there are no drug interactions to watch for with this product.
Single-Agent PARP Inhibitors and Combination Therapies for Pancreatic Cancer

LEARNING OBJECTIVES

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

- Review study data on the immune-related genes and gene expression associated with pancreatic cancer subtypes
- Outline the role of single-agent PARP inhibitors and combination therapies for pancreatic cancer
- Discuss the clinical impact of the development of resistance to PARP inhibitors

RELEASE DATE: March 1, 2022
EXPIRATION DATE: March 1, 2023

INSTRUCTIONS FOR PARTICIPATION / HOW TO RECEIVE CREDIT

1. Read this activity in its entirety.
2. Go to https://www.gotoper.com/sa22parp-ref to access and complete the posttest.
3. Answer the evaluation questions.
4. Request credit using the drop-down menu.

You may immediately download your certificate.

FACULTY, STAFF, AND PLANNERS’ DISCLOSURES

In accordance with ACCME Guidelines, PER® has identified and resolved all COI for faculty, staff, and planners prior to the start of this activity by using a multistep process.

Disclosures (Dr Saif): Wasif M. Saif, MD, MBBS, has no relevant financial relationships with ineligible companies.

The staff of PER® have no relevant financial relationships with commercial interests to disclose.

OFF-LABEL DISCLOSURE AND DISCLAIMER

This activity may or may not discuss investigational, unapproved, or off-label use of drugs. Learners are advised to consult prescribing information for any products discussed. The information provided in this activity is for accredited continuing education purposes only and is not meant to substitute for the independent clinical judgment of a healthcare professional relative to diagnostic, treatment, or management options for a specific patient’s medical condition. The opinions expressed in the content are solely those of the individual faculty members, and do not reflect those of PER® or any of the companies that provided commercial support for this activity.

This activity is funded by PER®.

ACCREDITATION/CREDIT DESIGNATION

Physicians’ Education Resource®, LLC, is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide accredited continuing medical education for physicians. Physicians’ Education Resource®, LLC, designates this enduring material for a maximum of 0.5 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
Pancreatic cancer is the third leading cause of death in the United States, with only a 10% five-year survival rate. Unfortunately, due to a lack of diagnostic tools and nonspecific symptoms, patients are typically diagnosed in the advanced or metastatic stages when patients’ response to current chemotherapy is very limited, as is their survival benefit. A promising new angle to treating pancreatic cancer is studying its underlying genetics and using this information to develop new therapies. Pancreatic cancer is a heterogeneous disease, with subtypes that are defined by distinct driver mutations. Some of these subtypes present with actionable mutations that can be targeted with currently available therapeutic agents. In a study using a targeted genomic profile analysis of 3954 samples from patients with pancreatic ductal adenocarcinoma (PDAC), actionable mutations were identified in 17% of the samples. Actionable mutations in homologous recombination repair (HRR) genes have been identified, including BRCA1, BRCA2, and PALB2. A class of drugs that inhibits poly ADP-ribose polymerase (PARP) is now available to treat some patients with pancreatic cancer, based on their genetic profile. Studies show that in pancreatic cancer cells with mutations in HRR genes, PARP inhibition leads to cell death via synthetic lethality caused by the accumulation of double-strand DNA breaks. 

Wasif Saif, MD, reviews the role of genetic testing in patients with pancreatic cancer, and of using the identification of genetic mutations to help guide treatment selection, focusing on the use of PARP inhibitors. He also examines evidence from clinical trials on how targeted therapy may help to improve outcomes in patients with pancreatic cancer.

Q: Which patients with pancreatic cancer should have genetic testing to see if they fit into a subtype of patients with identifiable genetic mutations? Dr. Saif: Germline testing should be considered for any patient with pancreatic cancer. The National Comprehensive Cancer Network guideline recommends this as well. Genetic testing not only has therapeutic implications but may also offer benefit to the patient’s family, identifying carriers of mutations. I recommend performing genetic testing at the time of diagnosis of pancreatic cancer, irrespective of the stage, particularly in patients with a personal or family history or clinical suspicion.

1. Know the tumor
2. Know the patient
3. Know the cancer drug

Q: What is the impact of BRCA mutations on overall survival in patients with pancreatic cancer? Dr. Saif: Studies have demonstrated a survival advantage in patients with pancreatic cancer who have BRCA mutations when their treatment includes the addition of a DNA cross-linking agent, such as platinum added to a standard chemotherapy backbone. Additionally, PARP inhibitors may play a role. For example, olaparib was approved in 2019 for use as a first-line maintenance treatment of germline BRCA-mutated metastatic PDAC (mPDAC), based on findings from the pivotal POLO trial.

Q: How do the results of genetic testing currently influence treatment or clinical trial decisions in patients with pancreatic cancer? Dr. Saif: The results of a germline or somatic test may influence the treatment plan for pancreatic cancer, because certain genetic mutations affect how pancreatic cancer responds to specific treatments. For instance, researchers have demonstrated that platinum-based chemotherapy might best suit people with pancreatic cancer who test positive for germline or somatic mutations in DNA repair genes. The BRCA1, BRCA2, and PALB2 genes are 3 examples of DNA repair genes. Similarly, patients with microsatellite instability–high or NTRK-1 mutations can benefit from targeted therapy.

Q: Please outline the immunosuppressive microenvironment of mPDAC. Dr. Saif: Pancreatic cancer features a highly immunosuppressive tumor microenvironment (TME). The interaction between the tumor cells and TME components facilitates tumorigenesis and tumor progression. The immunosuppressive TME is characterized by:

• Dense desmoplastic stroma. This hinders blood flow, impedes drug delivery, and depresses antitumor immune response, leading to tumor progression.
• Upregulation of cells. Myeloid-derived suppressor cells, tumor-associated macrophages, regulatory T cells, fibroblasts, and mast cells are upregulated in the TME, providing protection to tumor cells from the effect of the immune system.2,5
• Downregulation of cells. Natural killer (NK) cells and CD8+ T cells are downregulated; hence, they are unable to kill tumor cells.2
• Hypoxic environment, acidic extracellular pH, and high interstitial fluid pressure in the TME also abet both carcinogenesis and cancer progression.4

**Q:** How does the tumor microenvironment influence treatment efficacy?
**DR. SAIF:** Pancreatic cancer represents a paradigmatic instance of the complexity and impact of possible tumor-stroma interactions; these interactions are believed responsible for pancreatic cancer’s refractoriness to novel immunotherapies.1 Researchers have suggested that the low immunogenicity and antigenicity of pancreatic cancer is mediated by complex mechanisms that regulate the interplay of myeloid, lymphoid, and stromal cellular compartments.2,5 But at the same time, this scenario underlines the significance of developing sophisticated therapeutic strategies to overcome these tumor stroma-related interactions. Moreover, efforts to overcome the desmoplastic reaction have been underway for the last decade.

**Q:** What is the mechanism of action of PARP inhibitors?
**DR. SAIF:** PARP enzymes primarily repair single-strand DNA breaks and play crucial roles in DNA damage repair (DDR).7 PARP inhibitors are small molecules that trap PARP enzymes on DNA and prevent the process of DDR.5,7 Accumulation of single-strand DNA breaks in the presence of PARP inhibitors results in the formation of double-strand breaks, which require homologous recombination to repair. Cancer cells that harbor mutations in DNA repair genes such as _BRCA1/_BRCA2_ are unable to utilize DNA repair via homologous recombination, and they accumulate double-strand DNA breaks over time, resulting in cell death.5,7

**Q:** How has POLO changed the landscape of pancreatic cancer research?
**DR. SAIF:** POLO has changed the research landscape by showing that a PARP inhibitor was definitively active in _BRCA_-related PDAC.9 Remaining issues include:
• whether these agents will work in other settings (neoadjuvant, adjuvant);
• improving PARP inhibitors’ activity and adding other agents to PARP inhibitors; and
• expanding the population for whom the strategy might be effective.

**Q:** What other PARP inhibitors are being studied in patients with pancreatic cancer?
**DR. SAIF:** Many PARP inhibitors, notably olaparib, veliparib and rucaparib, have been published in clinical trials in patients with pancreatic cancer.7,11-15

**Q:** How does resistance to PARP inhibitors occur?
**DR. SAIF:** Patients who initially respond to PARP inhibitors will unfortunately develop resistance to them, which leads to restoration of homologous DNA repair or reestablishment of replication fork stability. Several mechanisms for PARP inhibitor resistance have been reported, such as16,17:
• epigenetic regulation of DNA splicing;
• alternative mRNA splicing;
• regulation by microRNAs; and
• restoration of an open reading frame to form a nearly full-length _BRCA_ by reversion mutations.
Q: Can resistance to PARP inhibitors be prevented?
DR. SAIF: Molecular studies of PARP inhibitor resistance have shown that most of these tumors have a hyperactivated ATR/CHK1 pathway.\(^1\) PARP inhibition in BRCA-mutated cancer cells causes increased reliance on the ATR/CHK1 pathway for genome stability.\(^1\) To test this hypothesis, researchers are testing inhibiting PARP and ATR/CHK1 simultaneously.

Q: What questions remain about PARP inhibitors?
DR. SAIF: Studies need to address some important aspects of PARP inhibitors in pancreatic cancer. These include:  
- efficacy in patients with somatic mutations;  
- whether platinum-based therapy should be prioritized for all DDR mutations;  
- prospective studies that incorporate molecular testing; and  
- determining what role PARP/ATR/ATM and other DDR inhibitors play in DDR-mutant tumors.

Q: What clinical trials still need to be done regarding the use of PARP inhibitors in patients with pancreatic cancer?
DR. SAIF: Differences in outcomes with the use of different PARP inhibitors have raised some potential explanations for the development of resistance to these agents. More importantly, high rates of pretreatment with platinum agents as well as rates of earlier disease progression on platinum-based regimens have suggested a high level of platinum resistance in this study population, which may in turn lead to PARP inhibitor resistance.\(^7\) This is a plausible explanation, given the known association between platinum sensitivity and PARP inhibitor sensitivity seen in ovarian cancer. That association needs to be confirmed in this disease as well.

Q: Please outline the most important trends in pancreatic cancer research: Where is the field moving?
DR. SAIF: Let me say this first: There is no doubt that we’re moving in the right direction in the treatment of pancreas cancer. For decades, we were stuck at a 5-year survival rate of up to 5%, but we have doubled it with the recent development of novel regimens and more drugs available to treat these patients. This increase may not sound big, but to me, this is definitely dramatic, at least in a disease like pancreatic cancer. We need to continue to improve our understanding about the disease and develop novel strategies to overcome the resistance challenges presented by the TME, including immune response against cancer cells. Artificial intelligence is becoming an integral part of cancer research, and it needs to be incorporated into both diagnostic and predictive tasks in pancreatic cancer. Lastly, we desperately need an effective screening test for earlier detection of pancreatic cancer to diagnose more patients at an earlier and curable stage.

Q: Would you like to make any additional points regarding the role of PARP inhibitors in the treatment of pancreatic cancer?
DR. SAIF: The genomic instability and increased total mutational load of BRCA-mutated and other homologous recombinant deficient tumors result in neoantigens that may increase efficacy of immunotherapy in these tumors, supporting the potential role for PARP inhibitors with immunotherapy.\(^5,7\) Talazoparib, a PARP inhibitor, has been shown to increased infiltration by immune cells and enhanced functionality of CD8 T cells and NK cells in animal studies.\(^18\) Moreover, in vivo studies have also shown that the use of PARP inhibitors led to upregulation of PD-L1.\(^19\) Based on these data, multiple phase 2 clinical trials are investigating combinations of PARP inhibitors with immune checkpoint blockers in pancreatic cancer.\(^20\)

KEY REFERENCES

For full reference list, visit https://www.gotoper.com/sa22parp-ref
Redefining the landscape of prostate cancer diagnosis, evaluation and clinical management

We are applying our leadership in PET radiopharmaceutical innovation to explore promising new compounds with the goal of changing the future of prostate cancer care.

Learn more at www.ProstateCancer-BlueEarthDx.com