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LUNG CANCER | CASE STUDY

# Neoadjuvant Capecitabine Plus Temozolomide in Atypical Lung NETs

INTERVIEW: **Sister Study Cohorts Show Association Between Genital Talc Use and Ovarian Cancer**

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**Joshua Richter, MD**
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During the 2024 European Hematology Association Congress, the International Myeloma Working Group hosted a meet-up for its members. During one of the events, the Plasma Cells performed. Richter joined the band playing guitar with his colleagues. Check out a picture of the band here: https://tinyurl.com/yf6fxue6

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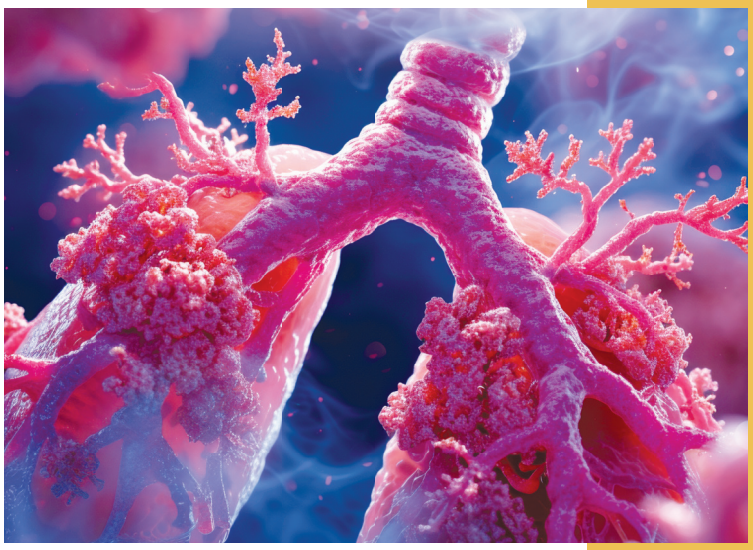








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# Highlights and Updates From ASCO 2024

The American Society of Clinical Oncology (ASCO) Annual Meeting always stirs much anticipation for the presentation of the latest oncology research, meeting old and new colleagues, and looking toward the future of oncology treatment. This year was no exception with the theme of "The Art and Science of Cancer Care: From Comfort to Cure," which was selected by the 2023-2024 ASCO president, Lynn M. Schuchter, MD, FASCO. Her focus was on enhancing patient care while improving survivorship and outcomes. The theme was infused throughout the meeting in the presentations and educational activities.

The opening session included Schuchter's presidential address, which discussed clinical trials she has been involved within the area of melanoma research as well as the lessons she has learned from patients she has treated. Other impressive talks in the opening session included those by W. Kimryn Rathmell, MD, PhD, National Cancer Institute director, and Lillian L. Siu, MD, FRCPC, who was recognized with the 2024 David Karnofsky Memorial Award for her work on drug development and early-phase clinical trials.

The plenary session featured 5 abstracts, as follows, which were chosen from the thousands submitted for this year's meeting[1-5]:

- **LBA1**: Prospective randomized multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (ESOPEC trial). First author: Jens Hoeppner, MD, University of Bielefeld, Bielefeld, Germany.
- **LBA2**: Neoadjuvant nivolumab plus ipilimumab versus adjuvant nivolumab in macroscopic, resectable stage III melanoma: the phase 3 NADINA trial. First author: Christian U. Blank, MD, Netherlands Cancer Institute (NKI-AVL), Amsterdam, Netherlands.
- **LBA3**: Comparative effectiveness trial of early palliative care delivered via telehealth versus in person among patients with advanced lung cancer. First author: Joseph A. Greer, PhD, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.
- **LBA4**: Osimertinib (osi) after definitive chemoradiotherapy (CRT) in patients (pts) with unresectable stage (stg) III epidermal growth factor receptor-mutated (EGFRm) NSCLC: primary results of the phase 3 LAURA study. First author: Suresh S. Ramalingam, MD, Emory University School of Medicine, Winship Cancer Institute, Atlanta, Georgia.
- **LBA5**: ADRIATIC: durvalumab (D) as consolidation treatment (tx) for patients (pts) with limited-stage small-cell lung cancer (LS-SCLC). First author: David R. Spigel, MD, Sarah Cannon Research Institute, Nashville, Tennessee.

One additional structural change was the inclusion of rapid oral presentations, which allowed discussions focusing on many of the different malignancies. Presenter diversity was enhanced with this structure, and there were improvements in the dispersion of new knowledge to the ASCO community. Every year the ASCO staff and committees improve the infrastructure and educational offerings and the international oncology community looks forward to continuous improvement at future ASCO meetings. ■

**Julie M. Vose, MD, MBA**
Chief, Division of Hematology/Oncology, University of Nebraska Medical Center/Buffett Cancer Center, Omaha, NE 68198-6840

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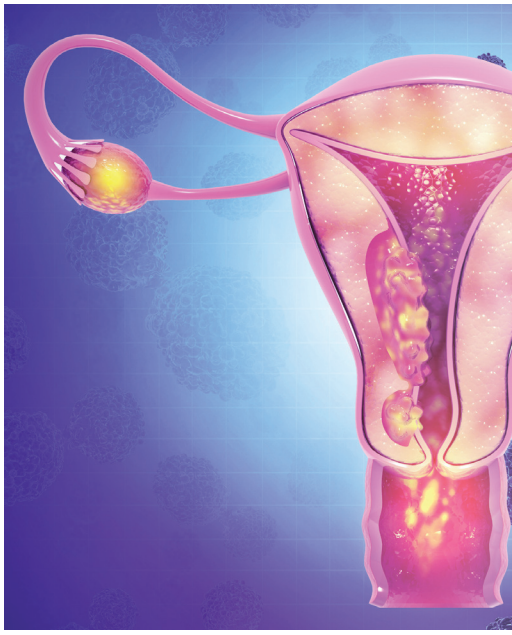
# Sister Study Cohorts Show Association Between Genital Talc Use and Ovarian Cancer

**Fumiko Chino, MD,** Assistant Attending Radiation Oncologist, Memorial Sloan Kettering Cancer Center; New York, NY



A recent study published in the *Journal of Clinical Oncology* highlighted the association between ovarian cancer and talcum powder (talc) use.[1] The findings published were from an extensive analysis of the Sister Study cohort.[2]

CancerNetwork spoke with Fumiko Chino, MD, assistant attending radiation oncologist at Memorial Sloan Kettering Cancer Center and the American Society of Clinical Oncology (ASCO) expert who was quoted in the news release of the findings. She shared her expertise on why having a cohort population study like this one is so important in enhancing cancer outcomes.

The investigators found that of the 50,884 women enrolled, there was a positive correlation between ovarian cancer and genital talc use (HR, 1.17-3.34). Overall, data were collected on 41% to 64% of patients who douched and 35% to 56% of patients who used genital talc.

**Q / What is the importance of these findings to the association between talc use and ovarian cancer?**

**Chino /** This research backs up some information that's been known for a while, but mostly from retrospective data at a population level. This research provides a little bit more of a nuanced view of it, and the information was collected prospectively. What it shows is that there seems to be an association between these feminine hygiene products, their use, and things like ovarian cancer. That's important because hygiene products are often sold as a self-care item, something that's going to improve how you feel about yourself, or your overall investment in yourself. The fact that these products may be inadvertently associated with harm for patients is an important takeaway message. It aligns with some of the information that's coming out, which is that the female genital system is quite good at cleaning itself. We probably don't need to be putting a lot of extra products down there, and that may be harming us.

**Q / Were there any limitations that should be highlighted?**

**Chino /** Even though the data were collected prospectively, [they are] still somewhat susceptible to recall bias, because people have to report their use. It is a population that is enriched for female cancers because it's via the Sister Study project, which is essentially the healthy sister of someone who had breast cancer. The female cancers can read together, so maybe this is a slightly higher-risk population. All of that needs to be accounted for. Overall, though, I was encouraged by how large the sample was and the longitudinal nature of the follow-up, meaning, how often they got information from this population, and how

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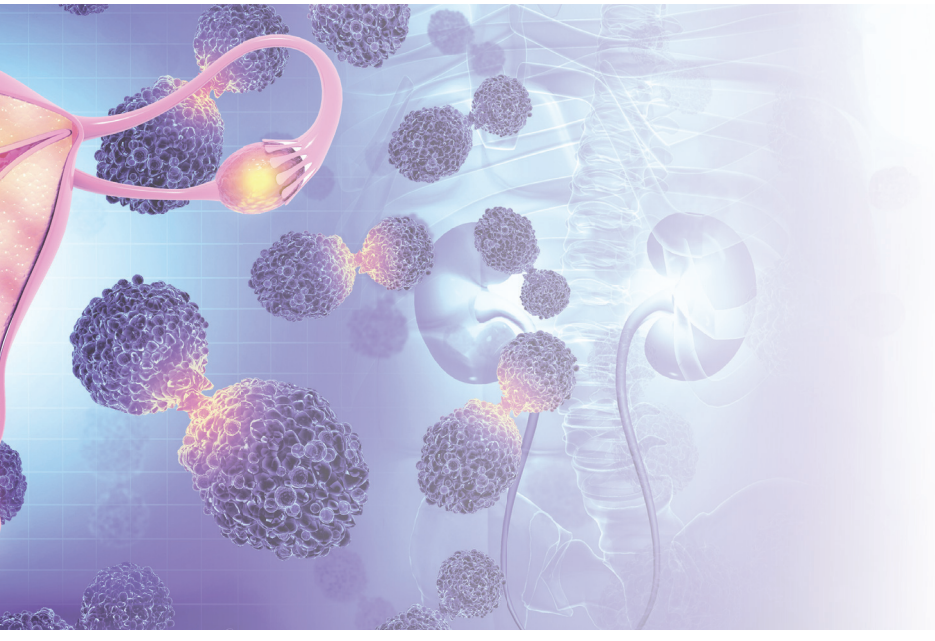
much they tried to account for an analysis for things like confounders.

**Q / Those involved in the Sister Study were the population for these findings. How do cohort studies like this help advance the field?**

**Chino /** In general, we think about trying to answer important questions. If I'm trying to translate a drug, it makes sense.



You find a population of people who have the disease, and you get this driver or that drug, and try to see what happens [in the long run]. If you're trying to measure things like exposure and long-term risk, these studies are much harder to do, because it requires enrolling a sample of healthy [patients] and seeing what happens to them over the long run. These types of studies require a lot of effort and require a lot of time and dedication from the volunteers who are enrolled. My main message when we get good information from a study like this cohort study is that it is my profound gratitude for the women who enrolled on the study and did these sequential surveys. They gave a lot of themselves, sharing some of their personal information to try to help the larger good.

**Q / What are the next steps for further developing these findings?**

**Chino /** There [have] been some efforts, for example, the [Johnson & Johnson] lawsuits, to try to define who was potentially harmed by some of these products and to try to find the best way of making sure that we're getting the right population [for these studies]. We're screening them early, meaning trying to catch long-term harm early, making sure they have the right treatment for the cancers that do develop. [We also make sure] that they do have things like restitution, and they have proper and adequate care for cancers, if it wasn't related to harm from a consumer product.

**Q / As a radiation oncologist, how does this fit into the treatment plans for ovarian cancer?**

**Chino /** In general, radiation is used sparingly with ovarian cancer. My specific research is on access, affordability, and equity. For some feminine hygiene products, this is more of an equity issue in that there has been a disproportionate role of these products in certain populations. Those populations are also the ones most at risk for health care disparities or gaps. In terms of actual radiation, radiation is used for things like isolated reoccurrences for ovarian cancer, or for symptomatic disease that could benefit from radiation, meaning [for] something that's causing pain or something that's bleeding, radiation is quite effective for those patients.

**Q / Is there anything you presented from the ASCO Annual Meeting that you would like to highlight?**

**Chino /** I'm involved in a couple of different projects that we're very excited about. They're having to do primarily with access to care and also obstructions to care, which is the flip side of the coin for access. I presented research on prior authorization and about how prioritization and denial of pain medications specifically for [patients] with cancer led to some negative downstream effects, meaning things like hospitalization. That is a pressing issue right now because prior authorization has proliferated in the modern era. We also have some research typically looking at high-deductible health care plans, plans that require a big payout up front before paying anything out for things like a cancer diagnosis. Overall, we found that these plans are associated with just worse outcomes, as you would expect, because people are [not incentivized] to get proper care. ■

**REFERENCES**

**1.** Study finds association between genital talc use and increased risk of ovarian cancer. News release. American Society of Clinical Oncology. May 15, 2024. Accessed May 20, 2024. https://shorturl.at/boATU

**2.** The Sister Study. National Institute of Environmental Health Sciences. Accessed May 20, 2024. https://shorturl.at/glnD8

LUNG CANCER

# Neoadjuvant Capecitabine Plus Temozolomide in Atypical Lung NETs

Georgios Evangelou, MD, MSc; Ioannis Vamvakaris, MD, PhD, MSc; Irene Konstantopoulou, PhD; and Konstantinos Syrigos, PhD

ABSTRACT Neoadjuvant and adjuvant treatment in lung neuroendocrine tumors (NETs) is a field that has not been explored in-depth, with little information on the impact on disease-free survival. This case study highlights the effectiveness of neoadjuvant treatment with capecitabine plus temozolomide (CAPTEM) in a woman with well-differentiated atypical carcinoid. The patient was asymptomatic at diagnosis and was referred to the outpatient NET clinic at Sotiria Hospital in Athens, following an incidental finding on a chest x-ray. $^{18}$F-fluorodeoxyglucose (FDG) PET/CT and $^{68}$Ga-Dotatoc PET/CT revealed another mass in the pancreas, with avidity in both imaging studies. The patient underwent treatment for 6 months with CAPTEM with a response in the lung NET and mediastinal lymph nodes. However, the mass in the pancreas slightly increased and was removed with a central pancreatectomy. The patient continued treatment with CAPTEM for 6 more months. There was further response according to RECIST 1.1 criteria (partial response in the mediastinal lymph nodes and a 21% regression in the primary tumor size). Pathology report after lobectomy with lymph node dissection showed a pathologic complete response in the mediastinal lymph nodes. Twenty-four months after surgery, the patient remains disease-free and has a good quality of life. Although large clinical trials are needed, this case study underlines the value of preoperative chemotherapy in atypical carcinoids.

## Background

Lung neuroendocrine tumors (NETs) are rare malignancies, accounting for 1% to 2% of all lung cancers.[1] They are sporadic tumors with an unclear association with smoking, and a minority are related to *MEN1* pathogenic variants.[2] There is a paucity of evidence for managing different clinical scenarios in patients diagnosed with these tumors, including the indications for adjuvant and neoadjuvant treatment. Surgery is the recommended approach in the local/locally advanced stage without generally accepted criteria defining what constitutes a resectable disease. In this case report, a woman with *MEN1* pathogenic variant, an atypical lung NET in the lower lobe of her left lung with confirmed metastases to mediastinal lymph nodes with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) biopsy, and a synchronous primary grade 2 NET in the body of the pancreas underwent treatment with capecitabine plus temozolomide (CAPTEM). After 6 months of treatment, the pancreatic NET (panNET) was removed with a central pancreatectomy. The patient continued treatment with CAPTEM for another 6 months and underwent lobectomy with lymph node dissection (including stations 12, 11, 10, 9, 8, and 7); there was complete pathologic remission in the mediastinal lymph nodes, with a primary tumor shrinkage of approximately 21%.

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## Case Presentation

A 62-year-old White woman with a known history of hypercalcemia treated with parathyroidectomy 8 years ago presented with fever and productive cough to her general practitioner (GP). She was a never-smoker and had a history of dyslipidemia on treatment with a statin. Her GP ordered a chest x-ray, revealing a mass in the left lower lobe. The GP prescribed antibiotics and referred the patient to the outpatient NET clinic of Sotiria General Hospital of Thoracic Diseases in Athens, Greece, to manage the lung mass. There was no family history of cancer; her older son received a diagnosis of hypercalcemia at age 30 years. At the outpatient clinic, the patient appeared in good general health; symptoms from the recent infection had subsided, and she was anxious about the mass in the chest x-ray. There was no stridor on auscultation, and respiratory sounds were normal in both lungs. She reported no changes in her ability to manage everyday tasks or weight loss over the past year. She had no breathlessness, pain, or other symptoms over the previous year besides coughing and fever in the first days of the infection, which had resolved.

### Imaging and Laboratory Results

- A chest CT scan showed a mass of 3.8 x 3.2 cm in the left lower lobe and enlarged subcarinal lymph nodes (2.4 x 1.9 cm). Bronchoscopic biopsy of the mass revealed atypical bronchial NET.
- Ki-67 of 20%
- Thyroid transcription factor-1 negative
- Orthopedia homeobox protein (OTP) negative
- Somatostatin receptor subtype 2 + 3 (**Figure 1**)
- EBUS-TBNA confirmed metastasis of the NET to lymph nodes in station 7.

An $^{18}$F-fluorodeoxyglucose (FDG) PET/CT scan confirmed the findings and, in addition, showed an FDG-avid mass in the body of the pancreas, 1.2 x 1 cm (**Figures 2 and 3**). The cytology from the endoscopic ultrasound–guided fine-needle aspiration biopsy of the pancreatic mass showed a NET. However, because of inadequate material, there was no further characterization of the tumor's primary origin and grade. A $^{68}$Ga-PET/CT scan revealed avidity in the mass of the left lower lobe, subcarinal lymph nodes, and pancreatic mass (**Figures 4 and 5**).

## Treatment

The patient was referred to a geneticist due to a family history of hypercalcemia and NET diagnosis. The genetic assessment revealed 4 members in the genealogic tree with early-onset hyperparathyroidism, and genetic testing in the patient confirmed a pathologic

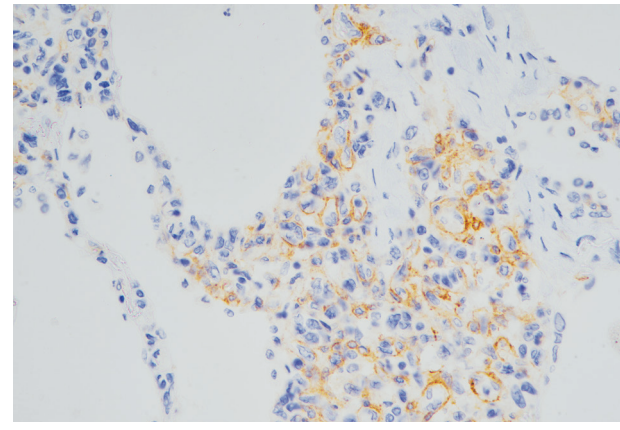

FIGURE 1. SSTR2 staining of surgical biopsy tissue 40x[50].

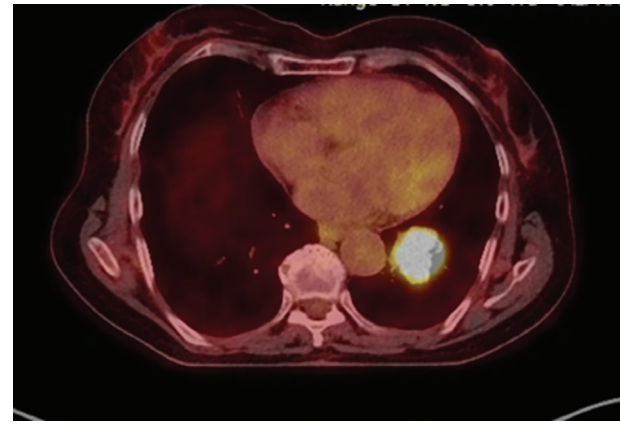

FIGURE 2. $^{18}$FDG PET-CT showing avidity of the primary tumor in the left lower lobe (standard uptake value 24.1).

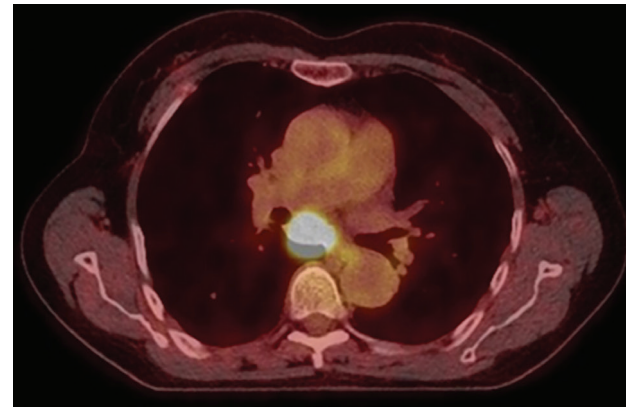

FIGURE 3. $^{18}$FDG PET-CT showing avidity in mediastinal lymph nodes (station 7; standard uptake value 25.1).

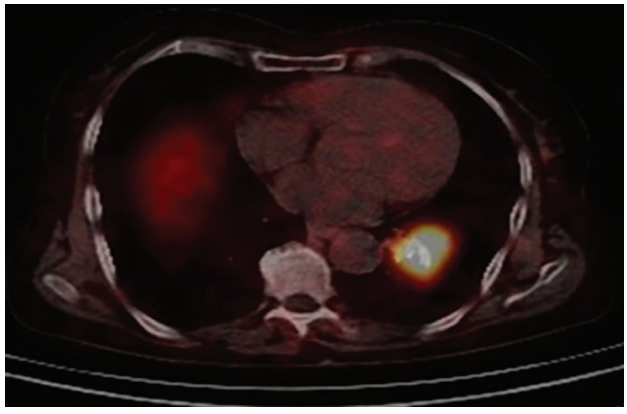

FIGURE 4. Dotatoc PET-CT showing avidity of the primary tumor in the left lower lobe (standard uptake value 15.9).

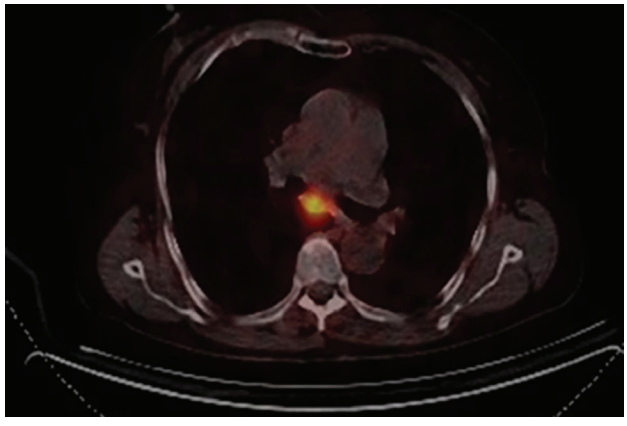

FIGURE 5. Dotatoc PET-CT showing avidity in mediastinal lymph nodes (station 7; standard uptake value 8.8).

variant in *MEN1* gene c.959C>G (p.Pro320Arg) in exon 7 (**Figure 6**). Consequently, members of her family tree were informed and screened for the same variant, although some refused to undergo the test. Her older son, was also a carrier of the pathogenic variant, and further investigations revealed no signs of *MEN1* syndrome manifestations. Even though surgical treatment was an option for both lung and pancreatic lesions at this point, a stepwise approach was considered more appropriate. The investigators decided to start treatment with CAPTEM and observe the responsiveness of the disease and its biological behavior. If there was disease progression following 3 to 6 months of treatment with CAPTEM, the risk-benefit ratio of surgical resection of both the lung and the pancreatic lesions would be of dubious value for the patient based on data extrapolated from other neoplasms such as oligometastatic non–small cell lung cancer (NSCLC) and colon cancer liver metastases.[3,4]

On the contrary, disease control or tumor shrinkage with CAPTEM would render surgical resection a more favorable option with possibly better chances for prolonged disease-free survival. The patient tolerated CAPTEM well, with main complaints of nausea and exhaustion on the days the 2 drugs were taken together. There was also grade 1 leukopenia and anemia that did not require medical intervention. Following 6 months of treatment, there was a minor volume reduction of the mass in the left lower lobe from 3.8 x 3.2 cm to 3.7 x 3.0 cm and subcarinal lymph node from 2.4 x 1.9 cm to 2.2 x 1.8 cm but an increase in the size of the pancreatic mass from 1.2 x 1 cm to 1.4 x 1 cm. Treatment with CAPTEM was discontinued for 1 month, and the mass was excised with a central pancreatectomy. Pathology reported a grade 2 panNET, islet cell antibody positive, 2 to 3 mitoses per $mm^2$, Ki-67 of 3%, without lymph node metastases. The patient recovered without complications and continued treatment with CAPTEM for 6 weeks after the operation. After another 6 months of treatment with CAPTEM, a further reduction was observed in the mass size in left lower lobe from 3.7 x 3.0 cm to 3.1 x 3.0 cm and in the subcarinal lymph node from 2.2 x 1.8 cm to 2.0 x 1.6 cm. Because of the response to treatment, the patient underwent left lower lobe resection with hilar and mediastinal lymph node excision. The pathology report confirmed the initial diagnosis of atypical carcinoid, Ki-67 of 20%, OTP negative, 4 mitoses per 2 $mm^2$, and no cancer cells identified in the subcarinal lymph nodes.

## Outcomes and Follow-Up

The patient recovered with no significant complications. However, returning to her usual activities took 5 to 6 months. She lost 7% of her weight in the first 4 months and has been stable ever since. FDG PET/CT and $^{68}$Ga PET/CT scans post surgery showed no avid lesions. The patient is on follow-up with CT scans every 6 months with no signs of recurrence 24 months following the lobectomy. The patient reports occasional pain in the area around the surgical wound, which she correlates with weather changes. Regarding her older son, an MRI of the pituitary gland showed an enlarged gland (1.8 x 1.5 x 1.7 cm) with no definite indications of a lesion with a mild shift of the stalk of the gland. He remains asymptomatic and has regular follow-ups according to published guidelines by the neurosurgeon and in the NET clinic.[5]

## Discussion

The case study highlights the efficacy of neoadjuvant treatment in a patient with atypical carcinoid, which can significantly affect the management of these tumors. There are limited prospective data for the effectiveness of neoadjuvant or adjuvant treatment for these rare tumors, and therefore clinical management relies on consensus guidelines and published case series. In addition, *MEN1* pathogenic variants are rare findings in patients with atypical carcinoids, and this report contributes to a better understanding of the biological behavior of these rare cases.

In the study by Daddi et al, a retrospective analysis of 247 patients with atypical carcinoids, only 1 patient had the *MEN1* pathogenic variant (0.4%), indicating that these tumors are mostly

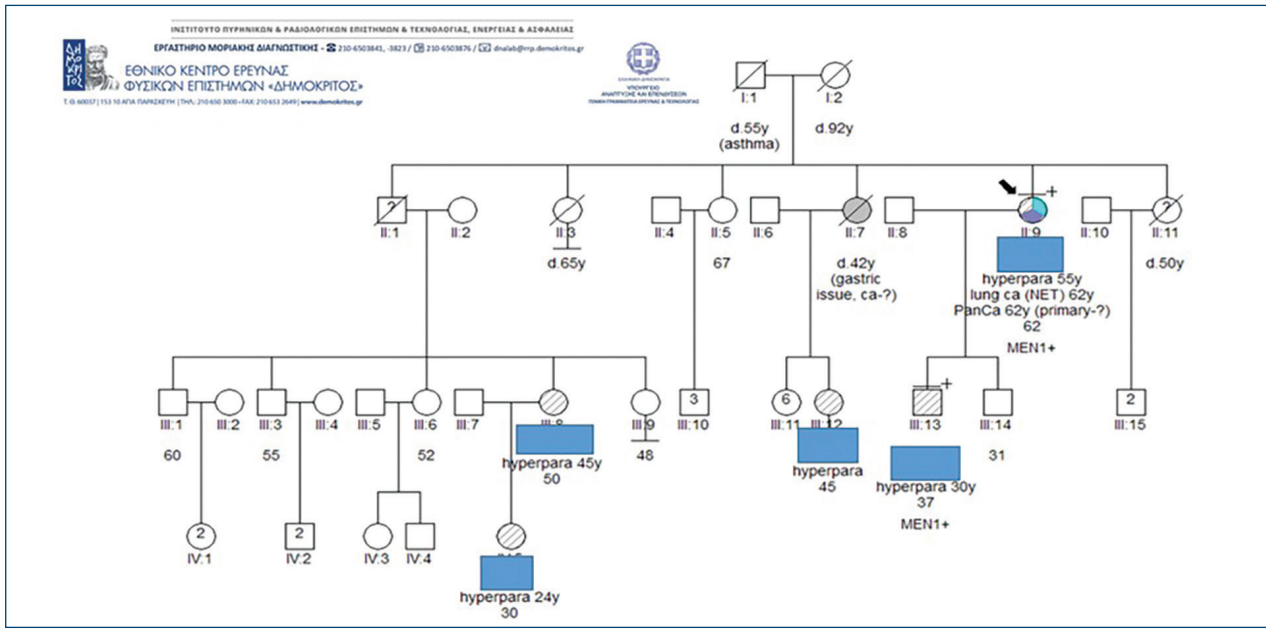


FIGURE 6. Patients' genealogic tree. The patient's older son was diagnosed with hypercalcemia at 30 years old. Both he and the patient are carriers of the pathologic variant in *MEN1* gene c.959CG (p.Pro320Arg) in exo.

sporadic.[6] Neoadjuvant chemotherapy was chosen as a treatment plan in 6 of 247 patients (2.8%), reflecting the clinicians' lack of confidence in the effectiveness of neoadjuvant treatment. On the contrary, adjuvant therapy with either chemotherapy, radiotherapy, or both was chosen in 27% of patients, with nodal metastasis being the main selection criterion. This analysis illustrates the bias in decision-making for managing these tumors mostly from practices used in NSCLC or SCLC.

Neoadjuvant chemotherapy has been evaluated in retrospective studies, mostly locally advanced and oligometastatic gastroenteropancreatic NETs (GEP-NETs). In 662 patients with GEP-NETs treated in European and Asian centers, chemotherapy was administered in the neoadjuvant setting in 1.4% of the patients,[6] while in another series, this percentage was 4%.[7,8] Different regimens were tested in the preoperative setting with no head-to-head comparison of their effectiveness. Results of a study by Dumont et al showed improved rates of R0 resection and higher rates of tumor downstaging following neoadjuvant treatment, which led to surgical resection in low to intermediate panNETs.[9] Contrary to these results, other studies showed no significant downstaging in localized panNETs with preoperative treatment when different regimens were used.[10,11] Besides tumor shrinkage, a recent study by Xie et al investigated the use of neoadjuvant therapy in the largest group of patients with pancreatic neuroendocrine neoplasms (pNENs).[12] The study included 4892 patients who underwent surgery with the intent of curing their cancer. The researchers found no significant improvement in overall survival, even in patients with grade 1 and 2 pNENs. These findings suggest that neoadjuvant therapy should be used with caution in patients with pNENs, as there is a lack of conclusive evidence to support its use.

Limited evidence exists on the effectiveness of preoperative chemotherapy in lung NETs. In a series of 45 patients with typical and atypical carcinoids, 2 patients underwent neoadjuvant treatment with fluorouracil, cisplatin, and streptozocin, and both patients had good response and tumor downstaging.[13] Peptide receptor radionuclide therapy (PRRT) has also been evaluated in the preoperative setting in patients with midgut and lung NETs with moderate response rates.[14-16] In a meta-analysis of 468 patients with pNENs, both PRRT and chemotherapy showed efficacy in tumor shrinkage, with PRRT having a significant advantage over chemotherapy regarding overall response rate.[17] In patients with lung NETs, tumor shrinkage was significantly less than in those with panNETs.

CAPTEM is a chemotherapy regimen with a moderate toxicity profile and response rates ranging from 21% to 44%.[18-20] It is effective both in typical and atypical carcinoids as well as GEP-NETs and can be used in first or later lines of treatment.[21] In a study where CAPTEM was used in the preoperative setting in patients with panNETs, 43% of patients had a partial response and 54% had stable disease.[22] These patients had a median progression-free survival of 28.2 months and 5-year overall survival of 63%.

The results of most studies show that adjuvant chemotherapy has no clear benefit in typical and atypical carcinoids, even in confirmed nodal metastasis.[23,24] These results should be interpreted cautiously because of their retrospective nature and considering that many variables could affect the findings, such as staging with both FDG PET/CT and [$^{68}$Ga]- PET/CT, type of chemotherapy administered, criteria for patient selection, and type of surgical resection. These variables can vary significantly between studies, considerably influencing the results.

A case report published in 2021 underlies the effectiveness of CAPTEM in a patient with unresectable atypical carcinoid tumor of the mediastinum.[25] The patient underwent treatment for

6 months before the tumor was considered resectable. Although the authors report that the tumor was primarily mediastinal and not a lung carcinoid, this case shows successful tumor shrinkage due to neoadjuvant chemotherapy. Downstaging was achieved following 6 months of treatment, indicating that results appear after prolonged preoperative treatment administration, as in the patient with the atypical carcinoid we present, and not after 3 months, as, for example, in patients with NSCLC. Although there are no accepted protocols for response reevaluation in lung NETs on treatment with chemotherapy, reevaluation should be performed every 6 months along with a resectability assessment of the disease, given that the treatment is well tolerated during this period.

The possibility of disagreement between preoperative biopsy diagnosis and the final surgical specimen adds to the difficulty in decision-making for patients with advanced lung NETs. It is estimated that discordance can be as frequent as 57% of patients with resectable disease, and thus bronchoscopic biopsies should be interpreted cautiously when forming treatment plans.[26] Considering the findings from both FDG PET/CT and [$^{68}$Ga]- PET/CT helps to increase accuracy in the staging of the disease and alleviate, to some degree, the bronchoscopic biopsy shortcomings.[27] The decision for neoadjuvant treatment in lung NETs should employ FDG PET/CT and [$^{68}$Ga]- PET/CT and not rely entirely on the pathology report of the bronchoscopic biopsy and CT scans.

The preferred treatment for lung NETs is lobectomy with systematic nodal dissection in both typical and atypical carcinoids, although parenchyma-sparing approaches might be considered for the former. A common challenge in clinical practice is the extent of lung parenchyma removal when these tumors are centrally located. A bronchoplasty is often employed, and when this procedure is not indicated, a sleeve resection can be performed to avoid pneumonectomy.[28] Tumor downstaging may offer fewer ablative surgical excisions in these tumors and possibly improve survival and R0 resections, although clinical trials will answer these questions.

Another issue that must be addressed in lung NETs is the resectability criteria. Clinicians might be prejudiced by the recommended practice in NSCLC, where N2 disease is often considered a relative resection contraindication unless neoadjuvant treatment leads to tumor downstaging. In 2019, Yoon et al published their paper on the prognostic significance of TNM staging in lung NETs.[29] Prognosis in the advanced T or N stages is considerably better in lung NETS than in NSCLC Based on these findings, resectability criteria should be broader in typical and atypical carcinoids, and clinicians should not follow the paradigm of NSCLC management.

The limitation of this case study is the fact that this is not a sporadic atypical carcinoid case since the patient is a carrier of a known pathologic variance in the *MEN1* gene. In addition, there are no guidelines to describe the pathology findings of neoadjuvant treatment in these tumors, and only imaging criteria are presented for response in the primary tumor. With these limitations, it is a case study showing that preoperative treatment can benefit selected patients with lung carcinoids when tumor burden reduction is the primary goal.

In conclusion, typical and atypical carcinoids can often be very challenging to manage because the prognosis is considerably better than either NSCLC or SCLC, and the impact of medical interventions must be weighed carefully against the immediate or late adverse effects. There are limited data for managing different clinical scenarios, and clinicians often base their decisions on extrapolating evidence from either NSCLC or SCLC and GEP-NETs. A typical scenario is a need for downstaging when tumors are centrally located and lobectomy is not an option, or when adjacent structures are invaded. Neoadjuvant treatment with CAPTEM with reevaluation every 6 months can be proposed in such a scenario, as in our case study. There might also be a benefit in survival, although large clinical trials will answer this question.

## Patient's Perspective

The patient's primary concern during the treatment was whether the benefit/risk ratio would be favorable for her in the long run, despite the initial discomfort and recovery period. She tolerated treatment with CAPTEM well without significant adverse effects (grade 3/4) and did not have to change her daily activities. She describes that her mood changes during the treatment oscillated between hope and fear that the treatment might not be sufficient or might have adverse effects. Twenty-four months following the lobectomy, she finds that the fear of recurrence affects her daily life, particularly when experiencing occasional pain in any area of her body. She is under periodic surveillance by a clinic psychiatrist and is not taking any medication for anxiety or depression. She is also concerned about the possibility of her older son developing *MEN1*-related diseases and how this will affect the rest of his life. She is satisfied that both operations did not affect her quality of life in the long term and that she is 2 years disease-free. ■


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### DECLARATION OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

### PATIENT CONSENT

Written informed consent has been obtained from the patient for publication of the submitted article and accompanying images.

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COLORECTAL CANCER

# Expert Commentary on the Product Profile of Fruquintinib in Metastatic CRC

*ONCOLOGY* spoke with Jagoda Misniakiewicz, PharmD, about the recent approval of fruquintinib for patients with metastatic colorectal cancer. The conversation focused on the mechanism of action of the agent and how it compares with other available treatment options in the space.

## PRODUCT PROFILE

**DRUG NAME:** Fruquintinib (Fruzaqla)

**DATE OF APPROVAL:** November 8, 2023[1]

**INITIAL INDICATION:** Patients with metastatic colorectal cancer who received prior fluoropyrimidine-, oxaliplatin-, and an irinotecan-based chemotherapy; an anti-VEGF therapy; and, if *RAS* wild-type and medically appropriate, an anti-EGFR therapy.

**DOSAGE AND ADMINISTRATION:** 5 mg orally each day for 21 days of each 28-day cycle plus best supportive care[2]

**HOW SUPPLIED:** Orally with or without food

**PIVOTAL CLINICAL TRIAL:** Phase 3 FRESCO-2 trial (NCT04322539)[3]

## DESIGN OF THE PIVOTAL FRESCO-2 TRIAL

**ELIGIBLE PATIENTS**
Progressed or been intolerant to treatment with either TAS-102 or regorafenib, have microsatellite instability–high or DNA mismatch repair–deficient tumors, and have been treated with prior immune checkpoint inhibitors, and weigh 40 kg or more.

↓

**END POINTS**
**Primary:** Overall survival
**Secondary:** Progression-free survival, objective response rate, and disease control rate

COMMENTARY
Jagoda Misniakiewicz, PharmD
Clinical Pharmacy Specialist, Medical University of South Carolina

**Q / What is the mechanism of action of fruquintinib?**

**Misniakiewicz /** Fruquintinib is a highly selective and potent oral small-molecule kinase inhibitor of VEGFR-1, -2, and -3, which are key regulators of angiogenesis associated with tumor growth and metastasis. Fruquintinib inhibits VEGF-mediated endothelial cell proliferation, tubular formation, VEGF receptor phosphorylation, and tumor growth. Fruquintinib prevents VEGF receptor structural change and dimerization, therefore preventing the phosphorylation of the intracellular kinase domain that impacts downstream signaling cascades. It directly affects tumor cell function by inhibiting new blood vessel growth and results in vascular regression, normalization, and construction. It's known that angiogenesis inhibition has been proven to be an effective treatment strategy throughout the continuum of care in metastatic colorectal cancer, which led to the [approval] of fruquintinib in this setting. Notably, fruquintinib is a weak inhibitor of RET, FGFR1, and CK kinases, which contributes to decrease in tumor growth.

**Q / Are there any specific biomarkers or tumor characteristics that might help identify patients who are most likely to benefit from fruquintinib?**

**Misniakiewicz /** Today, little is known about the pattern of response to fruquintinib. In the FRESCO-2 study, the subgroup analysis showed consistent results having a benefit in the majority of the prespecified subgroups, which had previously used TAS-102 [trifluridine, tipiracil, and hydrochloride; Lonsurf], regorafenib [Stivarga], *RAS* status, and duration of metastatic disease. It showed a benefit for patients who had liver metastases; however, it would be helpful to have more data on patients with lung metastases. Right now, anyone who has progressed on prior lines of therapy would ideally benefit from fruquintinib therapy. There just needs to be more research into what is that specific [patient population] that could show more benefit.

The data that came out of FRESCO-2 were exciting. The forest plot was something that everyone was excited by.

There is some literature looking at the efficacy of fruquintinib in patients who may have become resistant to bevacizumab [Avastin]. That would be an interesting population. Right now, there are no specific biomarkers or tumor characteristics that we are looking at. Most patients would be appropriate candidates, and we would expect them to receive some benefit from fruquintinib therapy. The only exception to that would be patients whose [diseases] express DNA mismatch repair or are microsatellite instability-high [MSI–high], as they would receive benefit from immunotherapy first, but that probably isn't even relevant at this time since fruquintinib is used in later settings.

**Q / How significant was the progression-free survival (PFS) improvement in the FRESCO-2 trial compared with other treatment options available for this population?**

**Misniakiewicz /** The data that came out of FRESCO-2 were exciting. The forest plot was something that everyone was excited by; it showed a novel treatment for patients with relapsed/refractory colorectal cancer. When we look at what the PFS is compared with the agents that we would be grouping it with, so regorafenib and TAS-102, there is a difference. There are no head-to-head studies looking at that but there is a meta-analysis of 5 clinical trials that showed no difference in the efficacy analysis of overall survival and that fruquintinib was superior in PFS compared with TAS-102.[4] Overall, I would say that this is significant when we look at this improvement, and it does show a promising treatment option for patients with refractory colorectal cancer.

**Q / Were there any common or significant adverse effects (AEs) associated with this treatment? How do they compare with other agents in the space?**

**Misniakiewicz /** According to the results from FRESCO-2 and the package insert, the most common AEs of fruquintinib are hypertension and asthenia, which makes sense based on its mechanism of action. It is comparable with what we would expect with other tyrosine kinase inhibitors (TKIs) used for colorectal cancer and that specific TKI is regorafenib.

Clinically, we can see some differences in AEs. Fatigue has been very significant in our patients who are treated with fruquintinib. This may be associated with the significant and rapid change in their thyroid function tests that we're seeing. Within 2 weeks of starting therapy, patients are expressing rapid changes in their thyroid-stimulating hormone, and that could be contributing to the fatigue that they're feeling. We're seeing a lot of voice changes in hoarseness, which is also to be expected with regorafenib.

Due to fruquintinib's mechanism of action, one would expect AEs related to the VEGF pathway, so hypertension, proteinuria, bleeding, impaired wound healing, and arterial thromboembolism. Those are the same AEs that I would be on the lookout for in patients treated with regorafenib. The big difference that we see is that patients treated with regorafenib experience more hand-foot syndrome and diarrhea than we have seen in patients with fruquintinib. Hand-foot syndrome has a high incidence in the FRESCO-2 trial; we just are not seeing as much as we see in patients who have been treated with regorafenib.

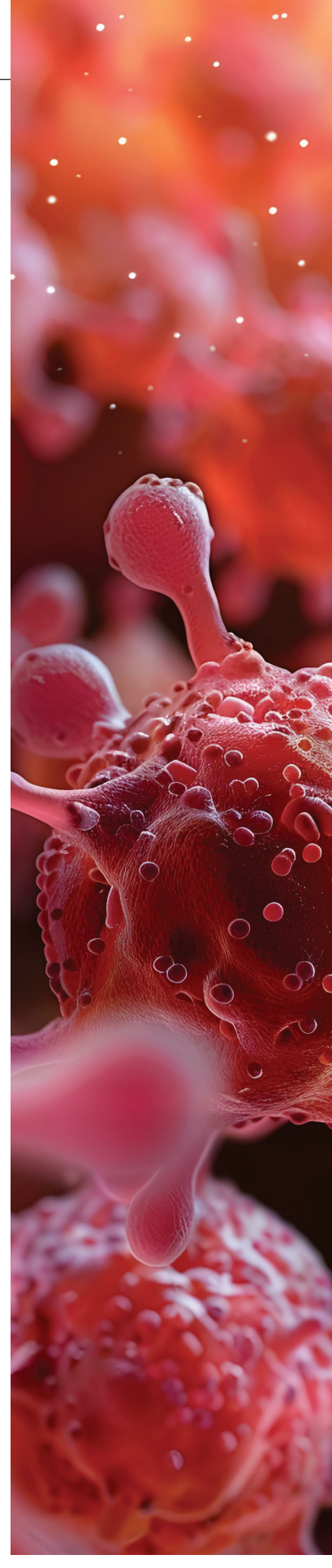
**Q / What are some known potential resistance mechanisms associated with fruquintinib?**

**Misniakiewicz /** The mechanisms of resistance to anti-VEGF therapies are not exactly clear. To date, there are 3 main theorized mechanisms that include activation of compensatory pathways, redundancy and angiogenic pathways, and MET upregulation and hepatocyte growth factor/c-MET activation. It's also important to consider that factors such

as hypoxia and limited blood supply can decrease drug delivery leading to resistance. Interestingly, some strategies have been explored to overcome these potential resistance mechanisms, including targeting alternative angiogenic pathways and combining VEGF targets with PD-1 and MET. It will be interesting to see if fruquintinib has a role in patients who may develop resistance to bevacizumab therapies and then differentiate what is the known resistance mechanism to bevacizumab. How does that compare with fruquintinib, especially since we'll be using it in later lines?

**Q / Where do you see this agent headed?**

**Misniakiewicz /** There are currently a lot of clinical trials looking at fruquintinib in combination with chemotherapy. That will be an avenue to be explored. It's being studied with chemotherapy as well as other targeted agents and immunotherapy. Seeing the outcomes of these trials will be interesting and then seeing it navigate its place in the treatment algorithm will also be interesting to see what comes of that. I can see fruquintinib making its way into other gastrointestinal malignancies. There's some studies in the gastric cancer setting, and we will see if it will make its way into those guidelines in the coming years. Then we will see if fruquintinib will continue to move its way up in terms of lines of treatment. The FRESCO-2 trial studied it as a fourth- or fifth-line setting. Right now, in the guidelines, it could be a third-line treatment option. There are some clinical trials looking at fruquintinib in combination with FOLFOX [leucovorin calcium, fluorouracil, and oxaliplatin] in the first-line setting, so I'm interested to see what will come of that.



**Q / Is there anything else you want to highlight?**

**Misniakiewicz /** Treatment options for metastatic colorectal cancer are limited, and the approval of fruquintinib will hopefully bridge that gap a little bit. Oral agents have changed the landscape of treatment for patients with cancer. Furthermore, targeted agents allow us to tailor therapy with the goal of improving clinical outcomes while minimizing off-target toxicities. Fruquintinib hopefully allows us to do this and for patients with metastatic colorectal cancer, oral anticancer therapies are an area where we oncology pharmacists can play a big role in patient care. There's a lot of opportunities to help with AE management and help with being able to keep these patients on therapy longer, helping patients have access to therapies, and then being able to provide patients with a therapy where they don't need to come into the clinic for long treatment days and trying to optimize their quality of life. Fruquintinib's approval has been very exciting in this space, and I hope to continue to see great outcomes with it as we have more patients started on it. It's a big area for oncology pharmacists to help manage these toxicities. ■

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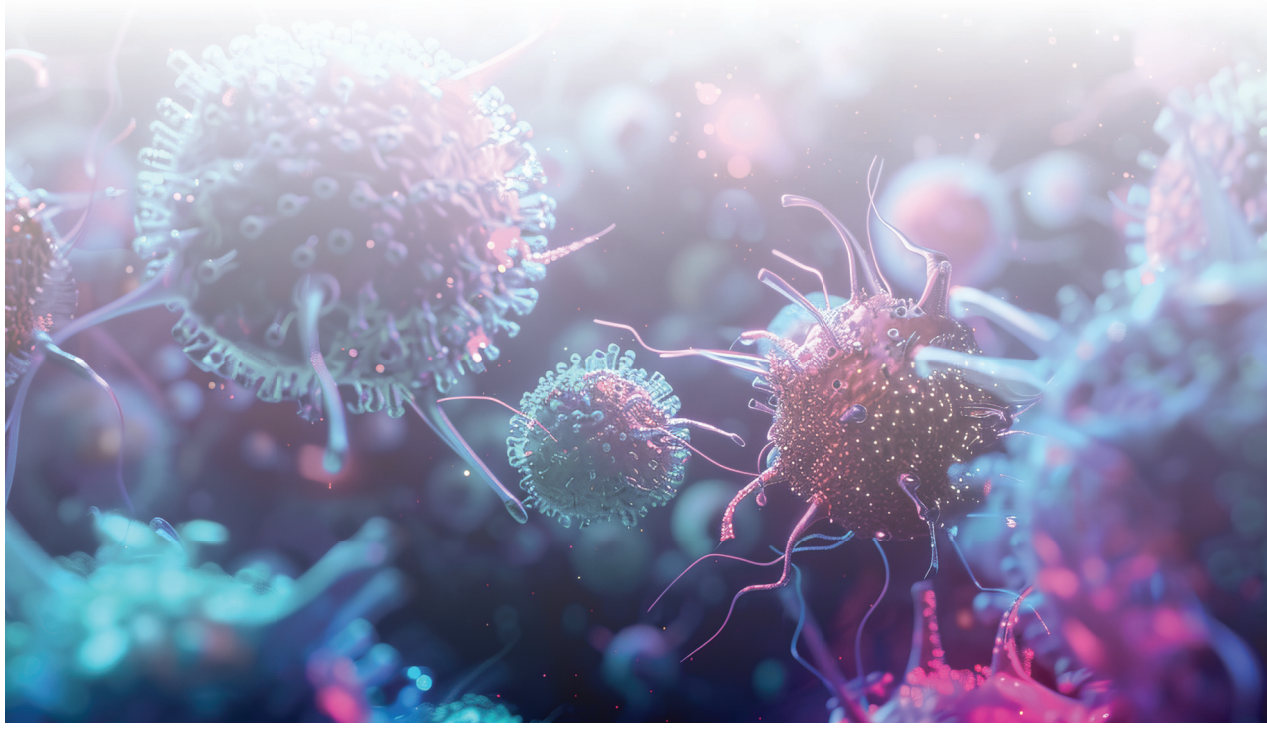


# Liso-Cel in Relapsed/Refractory Mantle Cell Lymphoma

In May 2024, lisocabtagene maraleucel (liso-cel; Breyanzi) was approved by the FDA for patients with relapsed/refractory mantle cell lymphoma (MCL) who have received 2 prior lines of systemic therapy including a Bruton tyrosine kinase inhibitor (BTKi).[1] Data from the approval were based on results from the phase 1 TRANSCEND NHL 001 trial (NCT02631044).[2]

Most notable was the objective response rate (ORR) of 85.3% (95% CI, 74.6%-92.7%) observed in 83 patients. The complete response (CR) rate was 67.6% (95% CI, 55.2%-78.5%). The median follow-up was 22.8 months (95% CI, 16.7%-23.0%), and the median duration of response was 15.7 months (95% CI, 6.2-24.0)

The progression-free survival was 15.3 months (95% CI, 6.6-24.9), and the overall survival (OS) was 18.2 months (95% CI, 12.9-36.3). For patients who achieved a CR, the median OS was 36.3 months (95% CI, 15.7-not reached).

*ONCOLOGY* spoke with Michael Wang, MD, Puddin Clarke Endowed Professor in the Lymphoma Service at The University of Texas MD Anderson Cancer Center, and lead author of the TRANSCEND trial, regarding the approval and how it will be used in the space.

**Q / What were the results that led to the approval of liso-cel in patients with relapsed/refractory MCL?**

**Wang /** This approval was exciting, not only because the ORR was high at around 85%. The CR was also high at 67%. Most importantly, the toxicities are not as bad as [previously reported]. Low rates of cytokine release syndrome [CRS; were observed], and low rates of neurotoxicity, making this [agent] a [viable option] for patients who are older and [frail]. Patients who are older and [frail] are those who cannot tolerate intensive CAR T-cell therapy like brexucabtagene autoleucel [brexu-cel; Tecartus] and could be considered for liso-cel therapy. I think this is a great addition to the CAR T-cell therapy options that our patients with MCL have.

**Q / Were there any significant adverse effects (AEs) experienced during the trial?**

**Wang /** For liso-cel, the CRS was grade 3/4 and it was low, about 1% to 3%. The neurotoxicity was grade 3/4 and was also low, about 9%. Those numbers are even lower than some of the bispecific antibody-induced CRS and, and neurotoxicities. This is a milder form of CAR T-cell therapy because the CAR T-cell therapy utilizes 4-1BB as a costimulator instead of a CD28 costimulator. The intensity is not as high, so the CRS and the neurotoxicity are relatively low. It is well tolerated by older patients in this setting.

**Q / How does the efficacy compare with that of other agents in the space?**

**Wang /** The ORR was 85% with a CR of 67%. This is the newly approved liso-cel compared with the already approved brexu-cel.[3] The brexu-cel ORR was 93% with a CR that was 68%. Although the overall response rate is a little higher, the CR rate is 68% vs 67%. They are very comparable in terms of efficacy, especially in the complete remission rate.

However, the toxicity is very different. Because the costimulation factor is CD28 for brexu-cel, which makes the CRS high, the CRS for grades 3/4 is about 15% and the neurotoxicity in grade 3/4 is about 31%. You cannot compare trial to trial, but we at least put the data into historical context. The CRS for the newly approved liso-cel is less than 3% and neurotoxicity grade 3/4 is also quite low, around or less than 9%.

The newly approved product has good efficacy and a much lower toxicity level, making this liso-cel better tolerated in the older or frail population. The second approval for CAR T-cell therapy is a welcome addition to the CAR T-cell therapy list.

**Q / What are the next steps for liso-cel in this population?**

**Wang /** In the future, liso-cel needs to combine with different therapies such as the BTKis. Also, liso-cel could be approved with a new construct in the future to modify the microenvironment and make the CAR T-cell therapy work even better. ■

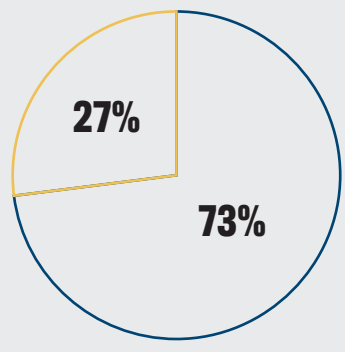
## STATS AT A GLANCE

**85**
**patients received liso-cel infusion**

**85.3%**
**Overall response rate**

**67.6%**
**Complete response rate**

**Patient Ages**

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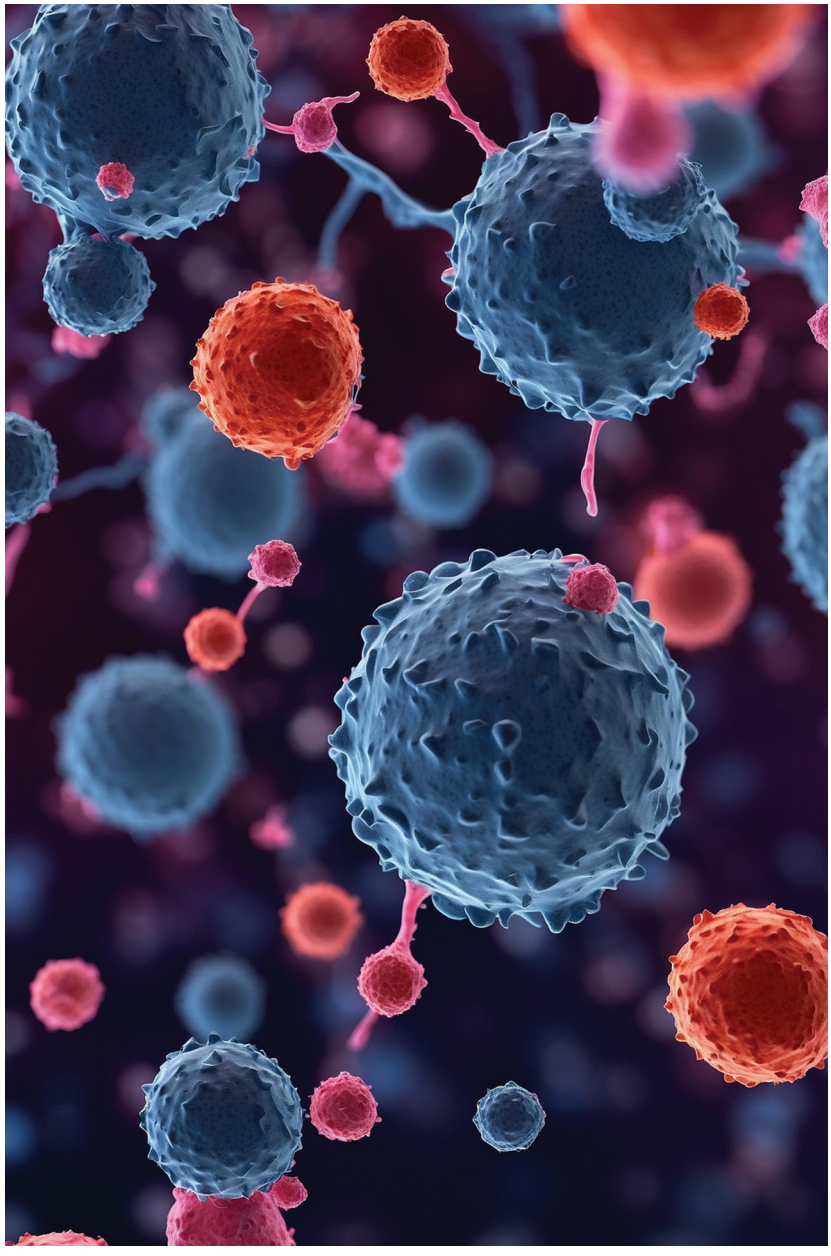
# Oncology Care

*ONCOLOGY* reviews trial results presented during the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting. Highlights include advancements in treatments for various diseases that can be translated into clinical practice.



Genitourinary Cancers

## Delays in All Organ Tumor Progression Observed in Lenvatinib/ Pembrolizumab in Advanced RCC

Comparing lenvatinib (Lenvima) plus pembrolizumab (Keytruda) vs sunitinib (Sutent) found delays in tumor progression in all organs for patients with advanced renal cell carcinoma (RCC), according to findings from an analysis of the phase 3 CLEAR trial (NCT02811861).

Findings from the analysis showed that the time to disease progression was favorable for patients who received the combination vs sunitinib among those with tumors of the bone (HR, 0.40; 95% CI, 0.25-0.63), central nervous system (CNS; HR, 0.47; 95% CI, 0.19-1.19), kidney (HR, 0.65; 95% CI, 0.37-1.14), liver (HR, 0.52; 95% CI, 0.32-0.84), lung (HR, 0.48; 95% CI, 0.36-0.62), and lymph nodes (HR, 0.63; 95% CI, 0.46-0.85). The median time to disease progression was not estimable (NE; 95% CI, NE-NE) in both arms of the bone, CNS, kidney, and liver tumor organ groups. In the lung tumor group, the median time to disease progression was 47.9 months (95% CI, 43.3-NE) in the combination arm vs 16.6 months (95% CI, 11.1-24.0) in the sunitinib arm; in the lymph node tumor subgroup, the median time to disease progression was NE (95% CI, 41.6-NE) vs NE (95% CI, 24.0-NE), respectively.

Data from the final prespecified overall survival (OS) analysis of

CLEAR demonstrated that the median OS in the lenvatinib plus pembrolizumab arm was 53.7 months (95% CI, 48.7-NE) vs 54.3 months (95% CI, 40.9-NE) in the sunitinib arm (HR, 0.79; 95% CI, 0.63-0.99; nominal $P = .0424$). The median progression-free survival was 23.9 months (95% CI, 20.8-27.7) vs 9.2 months (95% CI, 6.0-11.0), respectively (HR, 0.47; 95% CI, 0.38-0.57; $P < .0001$). The overall response rates were 71.3% (95% CI, 66.6%-76.0%) vs 36.7% (95% CI, 31.7%-41.7%), respectively, including respective complete response rates of 18.3% vs 4.8%.

Additional findings from the patterns of progression analysis demonstrated that the median change in sums of targeted lesions vs baseline in all patients who received lenvatinib plus pembrolizumab (n = 355) and sunitinib (n = 357) was –48.1% vs –17.4%, respectively. At baseline, the median sum of target lesions was 56.7 mm for those who received the combination vs 56.7 mm for those who received sunitinib. At progression, the median sum of target lesions was 29.8 mm vs 42.8 mm, respectively.

**For full article + references visit**
cancernetwork.com/CLEAR_ASCO24

## Lenvatinib Combo Improves Clinical Benefit in Clear Cell RCC Subgroups

Combining lenvatinib (Lenvima) with pembrolizumab (Keytruda) improved clinical benefits compared with sunitinib (Sutent) in patients with advanced clear cell renal cell carcinoma (RCC) regardless of biomarker subtypes, according to data from the phase 3 CLEAR trial (NCT02811861).

Findings revealed that progression-free survival (PFS) consistently favored lenvatinib plus pembrolizumab vs sunitinib regardless of mutation status of RCC driver genes. A PFS benefit was observed in patients with mutated *VHL* (HR, 0.48; 95% CI, 0.39-0.58), *PBRM1* (HR, 0.51; 95% CI, 0.34-0.78), *SETD2* (HR, 0.58; 95% CI, 0.34-1.01), *BAP1* (HR, 0.47; 95% CI, 0.26-0.86), and *KDM5C* (HR, 0.48; 95% CI, 0.24-0.98), which were the most frequently mutated genes.

Additionally, patients with wild-type disease also experienced a PFS benefit with the combination vs sunitinib, including those with wild-type *VHL* (HR, 0.53; 95% CI, 0.34-0.82), *PBRM1* (HR, 0.48; 95% CI, 0.34-0.67), *SETD2* (HR, 0.46; 95% CI, 0.34-0.62), *BAP1* (HR, 0.48; 95% CI, 0.35-0.64), and *KDM5C* (HR, 0.49; 95% CI, 0.37-0.65).

Additionally, gene signature scores were not associated with PFS outcomes for the lenvatinib plus pembrolizumab arm.

PFS by gene signature scores in each treatment arm were examined by 1 T-cell inflamed (GEP), 2 immuno-oncology (monocytic myeloid-derived suppressor cells and granulocytic myeloid-derived suppressor cells), 3 angiogenesis (angiogenesis, microvessel density, and Angio36), and 7 pan-cancer signatures. The signatures for pan-cancer were proliferation, MYC, RAS, WNT, stroma/epithelial-mesenchymal transition/TBFβ, glycolysis, and hypoxia.

Patients treated with the combination of lenvatinib plus pembrolizumab also experienced a longer PFS vs sunitinib regardless of having a high or low signature. The most prominent benefit was reported in the angiogenesis-low (HR, 0.39; 95% CI, 0.27-0.57), GEP-low (HR, 0.41; 95% CI, 0.24-0.68), MYC-high (HR, 0.42; 95% CI, 0.30-0.60), Angio36-low (HR, 0.44; 95% CI, 0.31-0.63), RAS -low (HR, 0.44; 95% CI, 0.30-0.64), and hypoxia-low (HR, 0.44; 95% CI, 0.30-0.65) subgroups.

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### Hematologic Malignancies

## Asciminib Improves Efficacy vs TKIs in Ph+ Chronic Myeloid Leukemia

Compared with standard tyrosine kinase inhibitors (TKIs), significant improvements in efficacy were reported with frontline asciminib (Scemblix) for patients with newly diagnosed Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML), according to data from the phase 3 ASC4FIRST trial (NCT04971226).

Primary results shared during a news briefing showed that at a data cutoff of November 28, 2023, patients with Ph+ chronic phase CML who received asciminib (n = 201) achieved a 48-week major molecular response rate of 67.7% (95% CI, 60.7%-74.1%) compared with 49.0% (95% CI, 42.0%-56.1%) among patients who were treated with an investigator-selected TKI (n = 204); this represented an 18.9% improvement (95% CI, 9.6%-28.2%; $P < .001$).

Additional findings from ASC4FIRST showed that more patients who received asciminib experienced deep molecular responses compared with those treated with investigator-selected TKIs. The MR4 rates at week 48 were 38.8% vs 20.6%, respectively, and the 48-week MR4.5 rates were 16.9% vs 8.8%, respectively.

In terms of safety, the most common nonhematologic any-grade adverse effects (AEs) observed among all patients treated with asciminib (n = 200) were diarrhea (15.5%), fatigue (14.0%), and headache (13.5%). Patients who received imatinib (n = 99) experienced diarrhea (26.3%), nausea (21.2%), and periorbital/face edema (20.2%) most frequently. Any-grade AEs in the second-generation TKI group (n = 102) included diarrhea (25.5%), headache (21.6%), and rash (21.6%).

**For full article + references visit**
cancernetwork.com/ASC4FIRST_ASCO24

## Pelabresib/Ruxolitinib Reduces Splenomegaly in MPN

A reduced tumor symptom score (TSS) from baseline, a durable reduction in splenomegaly, and improved anemia and bone marrow fibrosis at week 24 were observed with the combination of pelabresib and ruxolitinib (Jakafi) vs ruxolitinib alone in patients with Janus kinase inhibitor–naive myelofibrosis, according to results from the phase 3 MANIFEST-2 study (NCT04603495).

As previously presented, the trial met its primary end point when a higher percentage of those who received the doublet (n=214) experienced a 35% or greater reduction in spleen volume (SVR35) at week 24 vs those given ruxolitinib alone (n=216), at 65.9% and 35.2%, respectively (difference, 30.4; 95% CI, 21.6-39.3; *P*<.001). The mean percentage change in spleen volume at week 24 in the pelabresib/ruxolitinib arm was –50.6% (95% CI, –53.2% to –48.0%) vs –30.6% (95% CI, –33.7% to –27.5%) in the ruxolitinib-alone arm.

Among all responders who achieved SVR35 response, the proportion who lost response at any point in the pelabresib/ruxolitinib arm was 13.4% and more than double in the ruxolitinib-alone arm, at 27.8%. In an examination of the criteria of loss of SVR35 response plus a spleen volume increase greater than 25% from nadir, this occurred in 9.3% and 14.8% of patients, respectively. Notably, SVR35 response was consistently higher with the doublet vs the monotherapy across all predefined subgroups and hematologic subgroups.

A strong trend for numerical decrease in absolute change in TSS from baseline at week 24 was observed with the doublet vs the monotherapy, at –15.99 and –14.05, translating to a mean difference of –1.94 points (95% CI, –3.92 to 0.04; *P*=.0545). A higher proportion of patients who received the combination vs ruxolitinib alone achieved a 50% reduction in TSS (TSS50), at 52.3% vs 46.3% (difference, 6.0; 95% CI, –3.5 to 15.5; *P*=.216); this difference did not reach statistical significance. A 2-fold increase in patients who achieved both SVR35 and TSS50 responses was observed with pelabresib plus ruxolitinib vs ruxolitinib alone, at 40.2% and 18.5%, respectively.

**For full article + references visit**
cancernetwork.com/MANIFEST-2_ASCO24

## Tucidinostat/R-CHOP Combo Appears Effective, Safe in DLBCL Subtype

Treatment with tucidinostat plus R-CHOP (rituximab [Rituxan], cyclophosphamide, doxorubicin, vincristine, and prednisone) appeared to be efficacious and well tolerated among patients with previously untreated diffuse large B-cell lymphoma (DLBCL) expressing MYC and BCL2, or double-expression lymphoma, according to an interim analysis of the phase 3 DEB study (NCT04231448).

Further, the 24-month event-free survival (EFS) rate with tucidinostat was 58.9% (95% CI, 48.9%-67.6%), compared with 46.2% (95% CI, 35.7%-56.1%) with placebo. The prespecified subgroup analysis also showed a benefit in favor of tucidinostat use in combination with R-CHOP.

The complete response rate with the tucidinostat combination was 73.0% (95% CI, 66.6%-78.5%) vs 61.8% (95% CI, 55.1%-68.1%) with the placebo regimen, with an adjusted difference of 11.1% (95% CI, 2.3%-20.0%; *P* = .014). The prespecified subgroup analysis also favored tucidinostat.

Median progression-free survival (PFS) was not reached in either group; however, it showed a potential prolongation trend. In total, 43 EFS events occurred in the tucidinostat group, compared with 56 in the placebo arm (HR, 0.72; 95% CI, 0.49-1.08; *P* = .110). Further, the 24-month PFS rates were 67.3% (95% CI, 56.2%-76.2%) and 57.0% (95% CI, 44.2%-68.0%), respectively.

As of the cutoff date, overall survival (OS) events were limited, and trends could not be determined. Overall, 27 OS events occurred in the tucidinostat combination arm, compared with 31 events in the placebo arm (HR, 0.84; 95% CI, 0.50-1.40; *P*=.500), with 24-month OS rates of 82.8% (95% CI, 75.1-88.3%) and 76.5% (95% CI, 66.4%-84.0%), respectively.

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cancernetwork.com/DEB_ASCO24

## Safety Profile of Oral Azacitidine Remains Consistent in Lower-Risk MDS

The safety of oral azacitidine (Onureg) following a decreased dosing schedule remained consistent with the previously known safety profile of the agent in lower- to intermediate-risk myelodysplastic syndrome (MDS), according to findings from the phase 2/3 ASTREON trial (NCT05469737).

Regarding adverse effects (AEs), patients in both treatment arms experienced similar rates. Twenty-three patients (96%) in the 200-mg arm and 20 patients (87%) in the 300-mg arm reported having at least 1 treatment-related (TRAE) or treatment-emergent AE.

Serious TRAEs occurred in 1 patient from the 200-mg arm and 3 patients from the 300-mg arm, researchers noted. Two deaths occurred in the 300-mg arm, which were treatment-related and treatment-emergent, respectively. No patients from the 200-mg arm experienced grade 5 AEs.

Of note, the rates of TRAEs of all grades leading to treatment discontinuation or dose reduction were higher in the 300-mg arm. Four patients (17%) in the 200-mg arm

discontinued treatment due to disease progression. Three patients (13%) in the 300-mg arm discontinued treatment due to TRAEs.

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cancernetwork.com/ASTREON_ASCO24

## Belantamab Mafodotin Combo Shows PFS Improvement in R/R Multiple Myeloma

Combining belantamab mafodotin-blmf (Blenrep) with pomalidomide (Pomalyst) and dexamethasone (BPd) conferred a significant progression-free survival (PFS) improvement compared with bortezomib (Velcade) plus pomalidomide/dexamethasone (PVd) in those with relapsed/refractory multiple myeloma, according to data from the phase 3 DREAMM-8 study (NCT04484623).

The median PFS was not reached (NR; 95% CI, 20.6 months to NR) in the BPd arm compared with 12.7 months (95% CI, 9.1-18.5) in the PVd arm (HR, 0.52; 95% CI, 0.37-0.73; $P < .001$). At 12 months, the PFS rate was 71% and 51% in each respective arm. Findings also highlighted that treatment with BPd reduced the risk of progression or death in difficult-to-treat subgroups, which included patients with cytogenic or functional high-risk disease, refractory disease following lenalidomide (Revlimid), and previous treatment with anti-CD38 therapy.

The overall response rate with BPd was 77% (95% CI, 70.0%-83.7%) vs 72% (95% CI, 64.1%-79.2%) with PVd, with complete responses (CRs) reported in 40% (95% CI, 32.2%-48.2%) and 16% (95% CI, 10.7%-23.3%) of patients, respectively. In each respective arm, minimal residual disease negativity was observed in 23.9% (95% CI, 17.4%-31.4%) and 4.8% (95% CI, 1.9%-9.6%) of those with a CR or stringent CR, and in 32.3% (95% CI, 25.0%-40.2%) and 5.4% (95% CI, 2.4%-10.4%) of patients with a CR, stringent CR, or very good partial response. Additionally, the median duration of response was NR (95% CI, 24.9 months to NR) vs 17.5 months (95% CI, 12.1-26.4), respectively.

Data showed a median PFS2 of NR (95% CI, 33.0 months to NR) in the BPd arm vs 22.4 months (95% CI, 13.8-NR) in the PVd arm (HR, 0.61; 95% CI, 0.43-0.86). The median overall survival (OS) was NR with both the belantamab mafodotin triplet (95% CI, 33.0 months to NR) and bortezomib-based therapy (95% CI, 25.2 months to NR; HR, 0.77; 95% CI, 0.53-1.15; $P = .095$). Investigators will continue to follow up with patients for additional OS data for future prespecified analyses.

**For full article + references visit**
cancernetwork.com/DREAMM-8_ASCO24

## Daratumumab Retreatment Yields Sustained Response in R/R Multiple Myeloma

Patients with relapsed/refractory multiple myeloma who are refractory to daratumumab (Darzalex) may have additional responses when being retreated with daratumumab.

The overall response rate in the initial daratumumab-based therapy arm (D1) was 52% vs 54% for the retreatment (D2) arm. Additional results in the D1 arm included 36% of patients having a partial response (PR), 13% having a very good PR (VGPR), and 3% having a stringent complete response (sCR)/CR. In the D2 arm, 35% of patients had a PR, 13% had a VGPR, and 6% had a sCR/CR.

The median progression-free survival (PFS) following daratumumab retreatment was 10.8 months (95% CI, 8.48-16.5), and the median follow-up was 53.9 months (95% CI, 48.3-60.1). The median overall survival was 47.4 months (95% CI, 41.5-not reached).

Subgroup analyses occurred for patients given 4 or fewer lines of therapy (n=101) or more than 4 lines (n=56) in the D2 arm. The median PFS was 16.53 months (95% CI, 9.66-23.3) vs 7.62 months (95% CI, 4.10-11.3) in patients who received fewer than 4 lines or more than 4 lines of therapy, respectively ($P = .004$).

For those with a retreatment interval of no more than 180 days, the median PFS was 16.1 months (95% CI, 9.03-29.4) vs 9.46 months (95% CI, 6.93-14.3) for more than 180 days ($P = .11$).

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cancernetwork.com/Daratumumab_ASCO24

## Step-Up Teclistamab Dosing Produces Responses in R/R Multiple Myeloma

A step-up dose of teclistamab-cqyv (Tecvayli) plus prophylactic tocilizumab (Actemra) elicited evaluable responses in a small cohort of patients with relapsed/refractory multiple myeloma, according to results from the phase 2 OPTec trial (NCT05972135).

Of the 11 patients enrolled, 5 had responses after 2 cycles of therapy, with 3 patients having a partial response (PR) and 2 having a very good PR (VGPR). After 4 lines of therapy, 1 patient had a PR, and 4 had VGPRs.

Regarding safety, the first 11 patients did not meet the stopping criteria for grade 3 or higher cytokine release syndrome or neurotoxicity. The most common adverse effects included headache (n= 5), nausea (n=5), neutropenia (n=4), and injection site reactions (n=4). During treatment with tocilizumab or teclistamab, no patient required hospitalization. Grade 2 infection of the upper respiratory tract and urinary tract was noted in 1 patient, and 2 patients had either grade 2 *Candida* infection or grade 2 viral upper respiratory tract infection.

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cancernetwork.com/OPTec_ASCO24

## Daratumumab Combo Yields MRD-Negative Status in Transplant-Eligible Myeloma

Improvements in minimal residual disease (MRD) negativity occurred among patients with newly diagnosed transplant-eligible multiple myeloma who received daratumumab (Darzalex) plus bortezomib (Velcade), lenalidomide (Revlimid) and dexamethasone (D-VRd) followed by maintenance daratumumab and lenalidomide (D-R), according to findings from the phase 3 PERSEUS trial (NCT03710603).

Findings showed that 47.3% of patients treated in the D-VRd arm (n=355) experienced MRD negativity at a $10^{-6}$ sensitivity for 12 months or more compared with 18.6% of patients in the VRd arm (n=354). At a $10^{-5}$ sensitivity, these rates were 64.8% and 29.7%, respectively. Additionally, MRD negativity at a $10^{-6}$ sensitivity was sustained for at least 18 months in 42.0% of patients given D-VRd vs 15.0% of those treated with VRd. At a $10^{-5}$ sensitivity, these respective rates were 59.4% and 25.1%.

Additional data showed that responses deepened over time in both arms with a higher rate of improvement in the D-VRd group. In the experimental arm, the complete response or better rates at the end of induction, at the end of autologous stem cell transplantation, at the end of consolidation, and overall were 22.5%, 27.9%, 44.5%, and 87.9%, respectively. These respective rates in the VRd arm were 21.2%, 23.4%, 34.7%, and 70.1%.

Furthermore, rates of MRD negativity deepened over time from the start of treatment, with a greater increase observed in the experimental arm. At a $10^{-6}$ sensitivity, the MRD-negative rates in the D-VRd arm at the end of consolidation, up to 12 months, up to 24 months, and up to 36 months were 34.4%, 43.9%, 57.7%, and 63.9%, respectively. These respective rates were 16.1%, 20.9%, 27.4%, and 30.8% for the VRd arm.

At a $10^{-5}$ sensitivity, the MRD-negative rates for the D-VRd arm were 57.5% at the end of consolidation, 65.1% at up to 12 months, 72.1% at up to 24 months, and 74.6% at up to 36 months. In the VRd arm, these rates were 32.5%, 38.7%, 44.9%, and 46.9%, respectively.

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cancernetwork.com/PERSEUS_ASCO24

### Gynecologic Cancers

## Lymphadenectomy Does Not Improve PFS/OS in Advanced Ovarian Cancer

Progression-free survival (PFS) and overall survival (OS) were not improved when retroperitoneal lymphadenectomy was added to cytoreductive surgery during primary surgery or after neoadjuvant chemotherapy for patients with advanced ovarian cancer, according to results from the phase 3 CARACO trial (NCT01218490).

The median PFS for those who did not receive retroperitoneal lymphadenectomy was 14.8 months vs 18.6 months for those who did (HR, 0.96; 95% CI, 0.77-1.20; *P*=.712). The median OS was 48.9 months for those who did not receive retroperitoneal lymphadenectomy vs 58.8 months for those who did (HR, 0.92; 95% CI, 0.72-1.17; *P*=.489).

Among patients who received retroperitoneal lymphadenectomy, the median number of resected lymph nodes was 28. Additionally, 43% of patients had 1 or more involved lymph nodes.

Within 30 days of surgery, 29.7% of patients in the non–retroperitoneal lymphadenectomy arm had a transfusion or blood loss compared with 39.3% of patients who had the retroperitoneal lymphadenectomy (*P*=.049). Reintervention was noted in 3.1% vs 8.3% of patients (*P*=.031), and urinary injury was also highlighted in 0.0% vs 3.8% (*P*=.006), respectively. A digestive fistula was observed in 1.1% vs 2.2%, a pulmonary embolism in 3.7% vs 1.6%, and death in 0.5% vs 1.1%, respectively.

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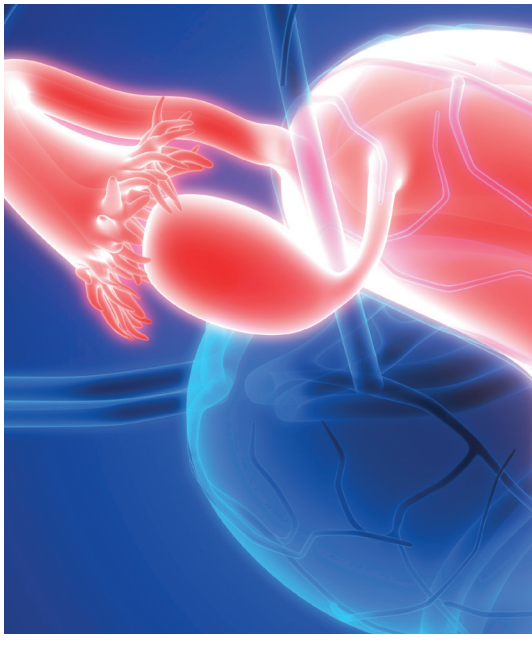
cancernetwork.com/CARACO_ASCO24

## Nivolumab/Ipilimumab Improves Responses in Ovarian/Gynecologic Clear Cell Carcinoma

The combination of nivolumab (Opdivo) plus ipilimumab (Yervoy) produced greater responses and survival outcomes vs nivolumab monotherapy for patients with ovarian or gynecologic clear cell carcinoma, according to results from the phase 2 BrUOG 354 trial (NCT03355976).

In the combination arm, a complete response (CR) was noted in 16.7% of patients vs 0% in the monotherapy arm, and a partial response (PR) occurred in



16.7% vs 14.3%. The combined CR and PR rate was 33.3% vs 14.3%, respectively. Additionally, stable disease was observed in 33.3% vs 35.7%, disease progression in 33.3% vs 50%, and the median duration of response was 22.4 months (± 11.8 months) vs 30.6 months (± 4.5 months), respectively.

The median progression-free survival in the combination arm was 5.6 months (95% CI, 1.6-29.1) vs 2.2 months (95% CI, 1.2-3.4) in the monotherapy arm. The median overall survival was 24.7 months (95% CI, 5.9-not reached) vs 17.3 months (95% CI, 2.1-42.7), respectively.

In the combination arm, all-grade adverse effects (AEs) included fatigue (22.5%), pruritus (26.7%), and hypothyroidism (20.0%). Grade 3 or 4 AEs included elevated amylase (5.0% vs 2.5%) and elevated lipase (5.0% vs 7.5%).

In the monotherapy arm, all-grade AEs included hypothyroidism (35.7%) and maculopapular rash (14.2%). Grade 3 AEs included thromboembolism (7.1%) and diarrhea (7.1%).

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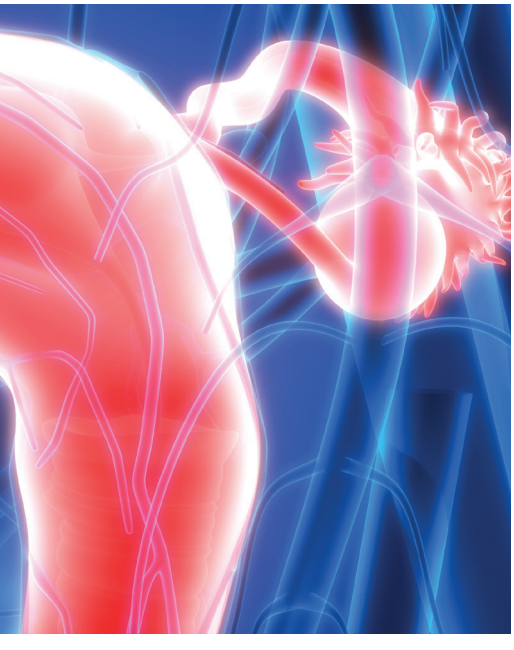
cancernetwork.com/BrUOG_ASCO24



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## No Benefit to Adding Atezolizumab to Chemo/Bevacizumab for Ovarian Cancer

The addition of atezolizumab (Tecentriq) to single-agent non–platinum-based chemotherapy and bevacizumab (Avastin) did not provide any additional benefits for patients with recurrent ovarian cancer, according to the final analysis of the phase 3 AGO-OVAR 2.29/ENGOT-ov34 study (NCT03353831).

The median progression-free survival was 6.4 months (95% CI, 6.1-7.5) with the addition of atezolizumab to chemotherapy and bevacizumab compared with a median of 6.7 months (95% CI, 6.2-8.1) with placebo plus chemotherapy and bevacizumab (HR, 0.87; 95% CI, 0.73-1.04; $P = .12$). The median overall survival was 14.2 months (95% CI, 13.0-16.1) with the atezolizumab combination compared with 13.0 months (95% CI, 11.9-15.1) with placebo (HR, 0.83; 95% CI, 0.68-1.01; $P = .06$). An improvement in outcomes was also not observed in those with PD-L1–positive disease, although a hypothesis-generating improvement was seen in patients who received prior bevacizumab and those who received paclitaxel.

The objective response rate (ORR) in the atezolizumab arm was 39.6% (95% CI, 33.6%-45.6%), with 4.3% of patients experiencing a complete response (CR) and 35.3% having a partial response (PR). In the placebo arm, the ORR was 43.5% (95% CI, 37.4%-49.7%), with 2.4% having a CR and 41.1% having a PR. The median duration of response with atezolizumab was 8.6 months (95% CI, 6.9-10.4) compared with 6.1 months (95% CI, 5.3-7.2) in the placebo group.

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cancernetwork.com/ENGOT-ov34_ASCO244

Thoracic Malignancies

## Adjuvant Atezolizumab Sustains Survival vs BSC in Stage IB to IIIA NSCLC

After 5 years of follow-up in the phase 3 IMpower010 trial (NCT02486718), disease-free survival (DFS) results remained consistent, showing positive overall survival (OS) outcomes with adjuvant atezolizumab (Tecentriq) vs best supportive care (BSC) for patients with resected stage IB to IIIA non–small cell lung cancer.

The rate of DFS events in the atezolizumab arm was 47.1% vs 52.2% in the BSC arm for patients in the intent-to-treat (ITT) population. Additionally, DFS events in the stage II to IIIA population affected 49.5% and 54.5%, respectively.

In the ITT population, the boundary for DFS was not crossed (stratified HR, 0.85; 95% CI, 0.71-1.01; $P$=.07). The median DFS was 65.6 months vs 47.8 months in the atezolizumab and BSC arms, respectively. The 3-year DFS rates were 61.4% vs 55.5%, and the 5-year DFS rates were 52.0% and 46.5%, respectively.

For the stage II to IIIA population, the stratified DFS HR was 0.83 (95% CI, 0.69-1.00). The median DFS was 57.4 months in the atezolizumab arm and 40.8 months in the BSC arm. At 3 years, the DFS rates were 59.3% and 52.6%, while the 5-year DFS rates were 49.3% and 44.4%, respectively.

In the stage II to IIIA PD-L1 tumor cell (TC) of at least 1% of the population, the median DFS in the atezolizumab arm was 68.5 months vs 37.3 months (HR, 0.70; 95% CI, 0.55-0.91). The DFS rate at 3 years was 62.7% vs 52.1%, and at 5 years, it was 53.2% vs 42.7%.

For the ITT population, the 3-year OS rates were 79.3% vs 81.1%, and the 5-year rates were 70.9% vs 69.8%. For the stage II to IIIA population, the 3- and 5-year rates were 78.7% vs 79.7% and 69.8% vs

68.6%, respectively.

The median OS for the stage II to IIIA PD-L1 TC of 1% or more population was not estimable in the atezolizumab arm and 87.1 months in the BSC arm (HR, 0.77; 95% CI, 0.56-1.06). The 3-year OS rates were 82.1% vs 78.9%, and the 5-year OS rates were 74.8% vs 66.3%.

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cancernetwork.com/IMpower010_ASCO24

## Durable EFS Noted in Nivolumab/Chemo in Resectable NSCLC

The 4-year update from the phase 3 CheckMate 816 study (NCT02998528) found neoadjuvant nivolumab (Opdivo) plus chemotherapy had durable event-free survival (EFS) with an improvement toward overall survival (OS) in patients with resectable non–small cell lung cancer.

The findings showed that the median EFS with nivolumab plus chemotherapy (n=179) was 43.8 months (95% CI, 30.6-not reached [NR]) vs 18.4 months (95% CI, 14.0-26.7) with chemotherapy alone (n=179), with an HR of 0.66 (95% CI, 0.49-0.90). The 48-month respective Kaplan Meier–estimated EFS rates were 49% (95% CI, 41%-57%) and 38% (95% CI, 30%-46%), respectively.

The median OS was NR in both arms with an HR of 0.71 (98.36% CI, 0.47-1.07; unstratified HR, 0.69; 95% CI, 0.49-0.97). The significance boundary for OS, which had a *P* value of .0164, has not been met yet (*P*=.0451). The respective Kaplan Meier–estimated 48-month OS rates were 71% (95% CI, 63%-77%) and 58% (95% CI, 50%-65%). The median lung cancer–specific survival was also NR in both arms (unstratified HR, 0.62; 95% CI, 0.41-0.93), with respective Kaplan Meier–estimated 48-month rates of 79% (95% CI, 72%-84%) and 66% (95% CI, 58%-72%).

The safety profile of neoadjuvant nivolumab plus chemotherapy was consistent with what has previously been reported with the regimen.

In the nivolumab/chemotherapy arm (n=176), any-grade adverse effects (AEs) occurred in 94% of patients, with 43% of events being grade 3 or 4. Any-grade serious AEs occurred in 17% of patients, with 11% of effects grade 3 or 4 in severity.

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cancernetwork.com/CheckMate816_ASCO24

## EFS Improvement Observed With Perioperative Nivolumab in Stage III N2/Non-N2 NSCLC

Patients with stage III N2 and stage III non-N2 non–small cell lung cancer treated with neoadjuvant nivolumab (Opdivo) plus chemotherapy saw an improvement in event-free survival (EFS), according to results from the phase 3 CheckMate 77T trial (NCT04025879).

Data showed that in patients with stage III N2 disease, the median EFS was 30.2 months (95% CI, 26.9-not reached [NR]) with nivolumab (n=91) compared with 10.0 months (95% CI, 8.1-15.1) with placebo (n=90), leading to a 54% improvement in EFS with the nivolumab regimen (HR, 0.46; 95% CI, 0.30-0.70). The 12-month EFS rates were 70% (95% CI, 58%-78%) and 45% (95% CI, 34%-55%), respectively.

For those with stage III non-N2 disease, the median EFS from randomization was NR (95% CI, 24.2-NR) with nivolumab (n=55) compared with 17.0 months (95% CI, 10.6-NR) with placebo (n=57; HR, 0.60; 95% CI, 0.33-1.08). The 12-month EFS rates were 74% (95% CI, 60%-84%) and 62% (95% CI, 48%-74%), respectively.

Additional results showed that the pathologic complete response (pCR) rate in patients with stage III N2 disease was 22.0% (95% CI, 14.0%-31.9%) compared with 5.6% (95% CI, 1.8%-12.5%) in the placebo arm. In those with stage III non-N2 disease, the pCR rates were 25.5% (95% CI, 14.7%-39.0%) and 5.3% (95% CI, 1.1%-14.6%), respectively.

Findings also showed that patients with stage N2 disease had similar rates of surgical feasibility as patients with non-N2 disease following neoadjuvant nivolumab and chemotherapy. In the stage III N2 subgroup, 77% of nivolumab-treated patients underwent surgery vs 73% of those on placebo. pCR rates in this group were 28.6% (95% CI, 18.4%-40.6%) vs 7.6% (95% CI, 2.5%-16.8%) with nivolumab vs placebo, respectively. Resection results were similar in the stage III non-N2 subgroup; 82% of those on nivolumab and 79% of those on placebo underwent resection, with pCR rates of 31.1% (95% CI, 18.2%-46.6%) and 6.7% (95% CI, 1.4%-18.3%), respectively.

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cancernetwork.com/CheckMate77T_ASCO24

### Breast Cancer

## Pembrolizumab/Sacituzumab Govitecan Does Not Statistically Improve PFS in HR+ Breast Cancer

There was a numerical but not statistically significant improvement in progression-free survival (PFS) when pembrolizumab (Keytruda) plus sacituzumab govitecan-hziy (Trodelvy) was combined to treat patients with hormone receptor–positive, HER2-negative metastatic breast cancer unselected by PD-L1 status, according to data from the phase 2 SACI-IO HR+ study (NCT04448886).

The doublet (n=52) led to a median PFS of 8.12 months (95%

CI, 4.51-11.12) vs 6.22 months (95% CI, 3.85-8.68) with the monotherapy (n = 52), equating to difference of 1.9 months (HR, 0.81; 95% CI, 0.51-1.28; *P* = .37). Although immature, at a median follow-up of 12.5 months, overall survival (OS) was not significantly improved in those who received the doublet vs the monotherapy, at a median of 18.52 months (95% CI, 16.55-not applicable [NA]) and 17.96 months (95% CI, 12.50-NA), respectively (HR, 0.65; 95% CI, 0.33-1.28; *P* = .21).

Moreover, in patients with PD-L1 positivity, defined as a combined positive score of 1 or higher, a nonsignificant trend toward improved PFS and OS was observed in favor of the combination regimen.

OS data were not mature, but in patients who were PD-L1 positive, the median OS with the doublet was 18.52 months (95% CI, 16.88-NA) vs 12.50 months (95% CI, 11.97-NA) with the monotherapy (HR, 0.61; 95% CI, 0.18-2.04; *P* = .42). In the PD-L1–negative patients, the median OS in the respective arms was 16.55 months (95% CI, 14.64-NA) and 18.03 months (95% CI, 17.34-NA; HR, 0.68; 95% CI, 0.29-1.59; *P* = .38).

The objective response rate achieved with pembrolizumab plus sacituzumab govitecan was 21.2% vs 17.3% with sacituzumab govitecan alone (*P* = .80). The median time to overall response with the doublet was 2.3 months (95% CI, 1.8-8.7) vs 4.1 months (95% CI, 2.0-10.2) with the monotherapy (*P* = .68); the median duration of response was 12.9 months (95% CI, 4.4-NA) vs 4.5 months (95% CI, 4.5-NA), respectively (*P* = .31). The respective clinical benefit rates were 50.0% (95% CI, 35.8%-64.2%) and 46.2% (95% CI, 32.2%-60.5%; *P* = .84).

**For full article + references visit**
cancernetwork.com/SACIO-IOHR_ASCO24

## Inavolisib Combo Reduces Time to Subsequent Treatment in Breast Cancer

The time to next treatment and the risk of disease progression or death was reduced following treatment with inavolisib plus palbociclib (Ibrance) and fulvestrant (Faslodex) among those with hormone receptor–positive, HER2-negative advanced or metastatic breast cancer harboring *PIK3CA* mutations, according to data from the phase 2/3 INAVO120 trial (NCT04191499).

The time from randomization to end of next-line treatment (progression-free survival 2 proxy) was 24.0 months with the addition of inavolisib compared with 15.1 months for palbociclib and fulvestrant alone (HR, 0.54; 95% CI, 0.38-0.77). The time to first chemotherapy was not yet reached with the addition of inavolisib compared with 15.0 months with placebo (unstratified HR, 0.54; 95% CI, 0.37-0.78).

At a median follow-up of 21.3 months, treatment had been discontinued for 57.8% of those in the inavolisib arm compared with 70.1% in the placebo group. There had been 12 deaths in the inavolisib arm (7.5%) compared with 19 in the placebo group (11.6%). Overall survival findings were not yet mature.

**For full article + references visit**
cancernetwork.com/INAVO120_ASCO24

## T-DXd Boosts PFS vs Chemo in HR+, HER2-Low Metastatic Breast Cancer

Significant improvements in progression-free survival (PFS) were observed in patients with HER2-low/HER2-ultralow hormone receptor–positive metastatic breast cancer with trastuzumab deruxtecan (T-DXd; Enhertu), according to the phase 3 DESTINY-Breast06 trial (NCT04494425).

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Findings showed that patients with HER2-low disease treated with the antibody-drug conjugate (n = 359) experienced a median PFS of 13.2 months per blinded independent central review assessment compared with 8.1 months for those given investigator's choice of chemotherapy (n = 354; HR, 0.62; 95% CI, 0.51-0.74; *P* < .0001).

In the intention-to-treat population comprising patients with HER2-low and -ultralow disease, the median PFS was 13.2 months for T-DXd (n=436) vs 8.1 months for chemotherapy (n=430; HR, 0.63; 95% CI, 0.53-0.75; *P*<.0001). Patients with HER2-ultralow disease

treated with T-DXd (n=76) achieved a median PFS of 13.2 months compared with 8.3 months for those given chemotherapy (n=76; HR, 0.78; 95% CI, 0.50-1.21).

At data cutoff, overall survival (OS) data were only 40% mature. Second interim and final OS analyses will be performed at approximately 56% and 74% maturity, respectively.

**For full article + references visit**
cancernetwork.com/DESTINY-Breast06_ASCO24

Gastrointestinal Cancers

## OS Prolonged With Perioperative Chemo vs Neoadjuvant CRT in Esophageal Cancer

An overall survival (OS) benefit was observed when patients with resectable esophageal cancer were given perioperative chemotherapy with docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil (FLOT) vs neoadjuvant chemoradiation (CROSS), according to results from the phase 3 ESOPEC trial (NCT02509286).

At a median follow-up of 55 months, patients in the intention-to-treat population who received the FLOT protocol (n=221) achieved a median OS of 66 months (95% CI, 36-not evaluable [NE]) compared with 37 months (95% CI, 28-43) among those who were treated with the CROSS protocol (n=217; HR, 0.70; 95% CI, 0.53-0.92; *P*=.012). The 3-year OS rates were 57.4% vs 50.7%, respectively, and the 5-year OS rates were 50.6% vs 38.7%, respectively.

Additionally, the median progression-free survival (PFS) was 38 months (95% CI, 21-NE) in the FLOT arm compared with 16 months (95% CI, 12-22) in the CROSS arm (HR, 0.66; 95% CI, 0.51-0.85; *P*=.001). The 3-year PFS rates were 51.6% vs 35.0%, respectively, and the 5-year PFS rates were 44.4% vs 30.9%, respectively.

Additional findings from ESOPEC showed that the pathological complete remission rate among patients who underwent surgery in the FLOT arm was 16.8% compared with 10.0% in the CROSS arm. In both arms, complete regression (18.3% vs 13.3%) or near complete regression (25.1% vs 39.4%) was observed. Most patients across both arms underwent an R0 resection (94.2% vs 95.0%).

Patients in the predefined protocol population in the FLOT (n=207) and CROSS (n=196) arms achieved a median OS of 66 months (95% CI, 38-NE) vs 39 months (95% CI, 29-45), respectively (HR, 0.72; 95% CI, 0.54-0.96; *P*=.023). The 3-year OS rates were 58.1% vs 52.6%, respectively, and the 5-year OS rates were 51.8% vs 40.5%, respectively.

**For full article + references visit**
cancernetwork.com/ESOPEC_ASCO24

## Sustained Responses Achieved With Zanidatamab in HER2+ Biliary Tract Cancer

Patients with previously treated advanced, unresectable, or metastatic HER2-amplified biliary tract cancer continued to derive benefit from treatment with zanidatamab in the phase 2b HERIZON-BTC-01 trial (NCT04466891).

Results showed that the confirmed objective response rate with zanidatamab was 41.3% and the disease control rate was 68.8%, which was maintained from the study's primary analysis. One additional patient achieved a complete response (CR), marking 2 CRs in the study thus far. Furthermore, the median duration of response increased to 14.9 months (95% CI, 7.4-not reached).

The median overall survival (OS) in the cohort of patients with immunohistochemistry (IHC) 2+ or 3+ was 15.5 months (95% CI, 10.4-18.5), and the 6- and 12-month OS rates were 80.3% (95% CI, 69.4%-87.6%) and 56.2% (95% CI, 44.3%-66.5%), respectively.

OS data within cohort 1 showed that in patients with IHC 2+, the median OS was 5.2 months (95% CI, 3.1-10.2); the 6-month OS rate was 41.7% (95% CI, 17.5%-64.4%); and the 12-month OS rate was 20.8% (95% CI, 5.1%-43.7%). In those with IHC 3+, the median OS was 18.1 months (95% CI, 12.2-23.2), and the 6- and 12-month OS rates were 90.1% (95% CI, 79.2%-95.4%) and 65.0% (95% CI, 51.6%-75.6%), respectively.

**For full article + references visit**
cancernetwork.com/HERIZON-BTC-01_ASCO24

## Multipeptide Vaccine Combo Shows Tolerability in Metastatic MSS CRC

Administering PolyPEPI1018, an off-the-shelf multipeptide vaccine, in combination with atezolizumab (Tecentriq) demonstrated tolerability and induced immune responses across a small cohort of patients with relapsed/

refractory microsatellite-stable (MSS) metastatic colorectal cancer (CRC), according to findings from the phase 2 Oberto-301 study (NCT05243862).

Data showed no serious adverse effects (AEs) during study treatment. Overall, 18 patients had 58 mild AEs, and 18 moderate AEs were reported in 8 patients; no severe toxicities occurred. Common mild events included injection site reactions (n = 21), fatigue (n = 7), and headache (n = 4). The most frequent moderate AEs were blood alkaline phosphate increases (n = 2), nausea (n = 2), and pyrexia (n = 2).

The median progression-free survival across the overall population was 12 weeks (95% CI, 7-18), and the median overall survival (OS) was 55 weeks (95% CI, 38-not evaluable [NE]). Regarding median OS, investigators reported no significant differences in outcomes between patients with liver metastases (37 months; 95% CI, 14-NE) and those without metastases (71 months; 95% CI, 47-NE; HR, 0.58; 95% CI, 0.18-1.90; *P* = .36). A longer median OS was highlighted in those who had a robust T-cell response (NE; 95% CI, 71 months-NE) compared with those who had a weak immune response (47 months; 95% CI, 14-NE; HR, 0.13; 95% CI, 0.02-1.02).

The treatment yielded an objective response rate of 0% and a disease control rate of 61%.

Findings highlighted a significant increase in tumor-infiltrating lymphocyte density based on posttreatment biopsies as well as a significant expansion of PD-L1 expression. Additionally, ex vivo analysis indicated CD8 and CD4 responses and antigen-specific humoral responses were also observed.

**For full article + references visit**
cancernetwork.com/Oberto-301_ASCO24

Melanoma

## Encorafenib Regimen Shows No PFS Improvement in Metastatic *BRAF*+ Melanoma

A progression-free survival (PFS) improvement did not occur when adding encorafenib (Braftovi) and binimetinib (Mektovi) to nivolumab (Opdivo)/ipilimumab (Yervoy) before subsequent nivolumab monotherapy in those with metastatic or unresectable *BRAF* V600E/K–mutated melanoma, according to data from the phase 2 EBIN trial (NCT03235245).

Findings showed that patients treated in the encorafenib/binimetinib arm (n=136) experienced a median PFS of 9 months (95% CI, 7-13) and 9 months (95% CI, 5-14) for those given nivolumab/ipilimumab alone (n=135; HR, 0.87; 90% CI, 0.67-1.12; stratified log-rank *P*=.360). The 12-week, 6-month, and 24-month PFS rates in the encorafenib/binimetinib arm were 99% (95% CI, 95%-100%), 62% (95% CI, 53%-70%), and 29% (95% CI, 20%-38%), respectively. Those respective rates in the control arm were 73% (95% CI, 64%-80%), 56% (95% CI, 47%-64%), and 35% (95% CI, 26%-44%).

PFS events in the intention-to-treat population included metastasis in the lymph node, skin, or other soft tissue only (experimental arm, n=10; control arm, n=10); metastasis in the lung and not in the visceral area or central nervous system (CNS; n=9; n=3); metastasis in the visceral area but not the CNS (n=17; n=24); CNS metastasis (n=34; n=11); progression without new reported metastases (n=18; n=33); and death without progression (n=2; n=2).

Patients treated with encorafenib/binimetinib experienced an objective response rate (ORR) of 53%, including a complete response (CR) rate of 12% and a partial response (PR) rate of 41%. In the control arm, the ORR was 45% with CR and PR rates of 10% and 36%, respectively.

An exploratory analysis showed that the 2-year overall survival rates were 68% (95% CI, 57%-77%) for patients treated with encorafenib/binimetinib induction compared with 74% (95% CI, 64%-82%) for those who started with nivolumab/ipilimumab.

**For full article + references visit**
cancernetwork.com/EBIN_ASCO24

## Nivolumab Combo Improves EFS in Stage III Melanoma

Event-free survival (EFS) was improved when combining neoadjuvant nivolumab (Opdivo) with ipilimumab (Yervoy) prior to therapeutic lymph node dissection plus adjuvant therapy in patients with macroscopic stage III node-positive melanoma, according to data from the phase 3 NADINA study (NCT04949113).

At the first interim analysis conducted after a median 9.9 months of follow-up, the estimated 12-month EFS rate with the neoadjuvant combination of nivolumab and ipilimumab plus response-driven adjuvant therapy was 83.7% compared with 57.2% for adjuvant therapy alone (HR, 0.32; 99.9% CI, 0.15-0.66; *P*<.0001). This benefit remained consistent across key subgroups, and a correlation was seen between pathologic complete response rates and EFS.

For those with *BRAF*-mutant melanoma, the EFS rate was 83.5% with neoadjuvant nivolumab/ipilimumab compared with 52.1% for those treated with adjuvant therapy alone (HR, 0.29; 99% CI, 0.13-0.63; *P*<.0001). In the *BRAF* wild-type group, the EFS with neoadjuvant nivolumab/ipilimumab was 83.9% compared with 62.4% with adjuvant therapy alone (HR, 0.35; 99% CI, 0.15-0.82; *P* = .0014).

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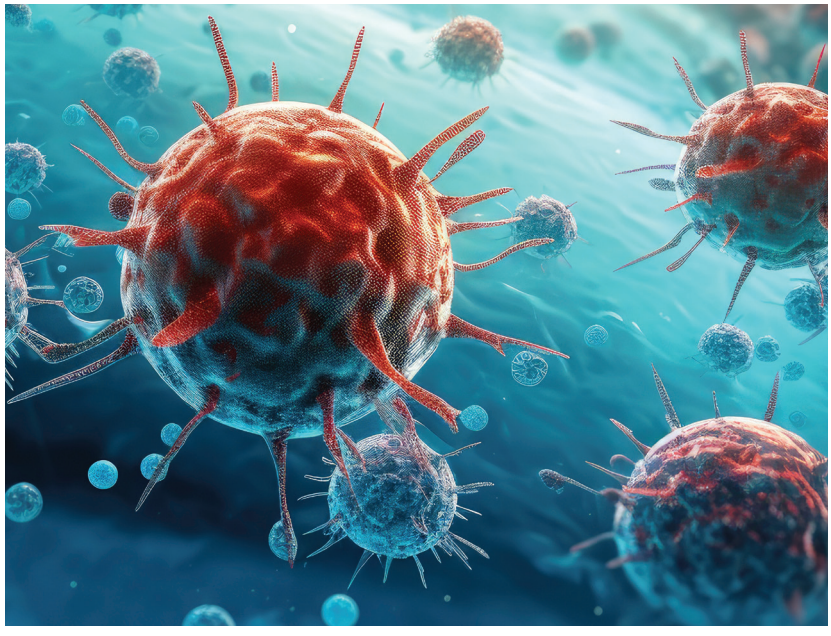
cancernetwork.com/NADINA_ASCO24

HEMATOLOGIC MALIGNANCIES

*ONCOLOGY* reviews trials from the 2024 European Hematology Association (EHA) Congress. Advances across the hematology space were made with various updates provided.



## Lower Tumor Burden, Basal Inflammation Confer PFS With Ide-Cel in Myeloma

Characteristics such as lower tumor burden and lower basal inflammation appear to correlate with improved progression-free survival (PFS) among patients with relapsed/refractory multiple myeloma who receive treatment with idecabtagene vicleucel (ide-cel; Abecma), according to correlative analysis findings from the phase 3 KarMMa-3 trial (NCT03651128).

Those with a lower tumor burden based on reduced soluble B-cell maturation antigen levels had a higher likelihood of experiencing a longer PFS ($P$<.00002). Lower concentrations of inflammatory factors such as tumor necrosis factor-α ($P$<.00001) and interleukin-10 ($P$<.00001) also correlated with longer PFS. Clinical parameters that conferred longer PFS included lower levels of β-2 microglobulin ($P$=.00005), lactate dehydrogenase ($P$=.0001), ferritin ($P$=.002), and C-reactive protein ($P$=.02).

At 6 months following infusion, 87% of patients with longer PFS, defined as more than 15.7 months, had minimal residual disease (MRD) negativity at a sensitivity of $10^{-5}$ compared with 41% of those with a PFS of 15.7 months or shorter. The rates of MRD negativity in each respective group were 78% vs 14% after 6 months at a sensitivity of $10^{-6}$ and 53% vs 6% after at least 8 months at a sensitivity of $10^{-5}$.

The overall response rate (ORR) was 97% among patients with longer PFS, which included a stringent complete response (sCR) or CR rate of 76%, a very good partial response (VGPR) rate of 18%, and a PR rate of 3%. The ORR for those with a shorter PFS was 65%, with reports of sCRs or CRs in 25%, VGPRs in 22%, and PRs in 19%.

Patients with longer PFS also tended to have higher cellular expansion, while PFS appeared to overlap between patients with and without detectable transgene levels. Additionally, 100% of patients with longer PFS had a completely cleared serum-free light chain compared with 54.5% of those who achieved a shorter PFS. Serum-free light chain clearance tended to last longer for patients with a longer PFS vs those with a shorter PFS ($P$=.00025).

**For full article + references visit**
cancernetwork.com/KarMMa-3_EHA24

## MCL Subgroup Analysis Finds Liso-Cel May Be More Effective in Earlier LOT

A post hoc subgroup analysis of the phase 1 TRANSCEND NHL 001 trial (NCT02631044) assessing the number of previous systemic therapy lines given before a Bruton tyrosine kinase inhibitor for those on lisocabtagene maraleucel (liso-cel; Breyanzi) for relapsed/refractory mantle cell lymphoma (MCL) found clinically meaningful activity across all subgroups.

Patients who received fewer than 5 prior lines of therapy had

numerically higher median duration of response (DOR), progression-free survival (PFS), and overall survival (OS). After 5 or more prior lines of therapy, the median DOR was 6.7 months (95% CI, 2.4-15.8), the median PFS was 7.4 months (95% CI, 3.3-12.3), and the median OS was 13.5 months (95% CI, 9.5-17.1). The respective values for patients with 3 or 4 prior lines were 17.5 months (95% CI, 3.3-not reached [NR]), 16.6 months (95% CI, 2.6-NR), and 18.4 months (95% CI, 6.7-NR).

For patients who had disease that was not refractory, the median DOR was 24.0 months (95% CI, 7.6-NR) vs 5.3 months (95% CI, 2.3-15.8) in those who had refractory disease. The median PFS was 24.0 months (95% CI, 8.6-NR) vs 6.1 months (95% CI, 3.1-16.5), and the median OS was 36.3 months (95% CI, 15.3-NR) vs 11.1 months (95% CI, 6.1-17.1).

For patients who received 5 or more prior lines of therapy, the overall response rate (ORR) was 81% (95% CI, 60.6%-93.4%), and the complete response (CR) rate was 65% (95% CI, 44.3%-82.8%). Among patients with 3 or prior lines of therapy, the ORR and CR rates, respectively, were 86% (95% CI, 68.3%-96.1%) and 72% (95% CI, 52.8%-87.3%).

For those who were not refractory, the ORR was 91% (95% CI, 76.9%-98.2%), and the CR rate was 80% (95% CI, 63.1%-91.6%). For those who were refractory, the ORR was 76% (95% CI, 60.5%-87.1%), and the CR rate was 64% (95% CI, 48.8%-78.1%).

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cancernetwork.com/TRANSCENDNHL001_EHA24

## Englumafusp Alfa Combo Yields Activity in B-Cell Non-Hodgkin Lymphoma

Early responses and tolerability were reported in patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma following therapy with englumafusp alfa plus glofitamab-gxbm (Columvi), according to data from the phase 1b BP41072 study (NCT04077723).

Results showed that of 83 patients in the second-line and beyond setting, the best overall response with the combination was 67.0% and the complete response rate was 57.0%. In the third-line and beyond setting, these rates were 65.7% and 52.8%, respectively.

Regarding safety in the entire population (n=134), any adverse effect (AE) was reported in most patients (97.8%) and any infections in more than half (58.2%); grade 3 and grade 5 infections occurred in 16.4% and 5.2% of patients, respectively. Additional AEs included cytokine release syndrome (CRS; 55.2%), anemia (32.1%), COVID-19 (26.9%), neutropenia (25.4%), diarrhea (23.9%), and pyrexia (20.9%). Any serious AEs occurred in 61.2% of patients, comprising CRS (23.9%), COVID-19 (8.2%), COVID-19–related pneumonia (6.0%), and pyrexia (5.2%). Any treatment-related AEs (TRAEs) occurred in 89.6% of all patients; 73.1% were related only to glofitamab, 53.0% were related to both agents, and 11.9% were related to englumafusp alfa only. Four patients (3.0%) had any TRAE that led to drug withdrawal, and 3 patients (2.2%) died due to TRAEs, which included 1 dose-limiting toxicity of *Pneumocystis jirovecii* pneumonia.

**For full article + references visit**
cancernetwork.com/BP41072_EHA24

## Blinatumomab Improves MRD Clearance vs Chemotherapy in B-ALL Subtype

Patients with Down syndrome B-precursor acute lymphoblastic leukemia (B-ALL) had higher rates of undetectable minimal residual disease (MRD) following consolidation treatment with blinatumomab (Blincyto) vs chemotherapy, according to findings from the ALLTogether1 study (NCT04307576).

At the end of cycle 1, the undetectable MRD rate with blinatumomab was 91% (95% CI, 79.8%-99.3%) in evaluable patients (n=33), which proved to be significantly higher than the 61% observed in historical controls treated with chemotherapy in the UKALL 2011 study (EudraCT/CTIS: 2010-020924-22; n=22), meeting the trial's primary end point.

With regard to secondary end points, at a median follow-up of 15 months in the entire cohort, no deaths, relapses, or secondary cancers have been observed; as such, the event-free survival and overall survival rates were 100%.

Moreover, a lower rate of adverse effects (AEs) has been reported with blinatumomab vs historical controls who received chemotherapy in the same period. Of the 22 controls treated with 2 cycles of chemotherapy consolidation, 77.3% experienced a grade 3 or 4 AE vs 39.4% of those given blinatumomab ($P$=.0057). However, a trend for a higher rate of seizures was observed in patients over 10 years of age, at 18.2% in the blinatumomab arm and 4.5% in the historical chemotherapy arm ($P$=.14).

**For full article + references visit**
cancernetwork.com/ALLTogether1DS_EHA24

## Glofitamab With Gemcitabine/Oxaliplatin Improves Survival in Transplant-Ineligible R/R DLBCL

Updated data from the phase 3 STARGLO study (NCT04408638) demonstrated that fixed-duration glofitamab-gxbm (Columvi) plus gemcitabine/oxaliplatin significantly improved both progression-free and overall survival

(PFS; OS) compared with rituximab (Rituxan) plus gemcitabine/oxaliplatin in patients with relapsed/refractory diffuse large B-cell lymphoma, specifically those who are ineligible for autologous stem cell transplant.

Results showed that the median OS with the glofitamab regimen (n=183) was 25.5 months (95% CI, 18.3-not evaluable) vs 12.9 months (95% CI, 7.9-18.5) with the rituximab regimen (n=91), translating to a 38% reduction in the risk of death (HR, 0.62; 95% CI, 0.43-0.88; *P*=.006) at a median follow-up of 20.7 months. The 24-month OS rates in the glofitamab and rituximab arms were 52.8% (95% CI, 44.8%-60.7%) and 33.5% (95% CI, 22.2%-44.9%), respectively.

At a median follow-up of 16.1 months, the median PFS with glofitamab plus gemcitabine/oxaliplatin was 13.8 months (95% CI, 8.7-20.5) by independent review committee assessment vs 3.6 months (95% CI, 2.5-7.1) with rituximab plus gemcitabine/oxaliplatin, translating to a 60% reduction in the risk of disease progression or death (HR, 0.40; 95% CI, 0.28-0.57; *P*<.000001). The respective 12-month PFS rates were 51.7% (95% CI, 44.0%-59.4%) and 25.2% (95% CI, 13.6%-36.9%).

Additional data from the updated analysis showed that the objective response rate achieved with glofitamab plus gemcitabine/oxaliplatin was 68.3% vs 40.7% with rituximab plus gemcitabine/oxaliplatin. The complete response rate in the glofitamab arm was 58.5% vs 25.3% in the rituximab arm, translating to a statistically significant 33.2% difference between the arms (95% CI, 19.7-44.5; *P*< .0001).

**For full article + references visit**
cancernetwork.com/STARGLO_EHA24

## Ide-Cel Continues to Yield Deep Responses in High-Risk Multiple Myeloma

Frequent, deep, and durable responses were observed when idecabtagene vicleucel (ide-cel; Abecma) was used to treat patients with high-risk multiple myeloma who experienced an early relapse within 18 months of frontline therapy, according to results from cohort 2B of the phase 2 KarMMa-2 trial (NCT03601078).

The overall response rate in those who had a response but were treated in the frontline setting was 80.6% (95% CI, 62.5%-92.5%) vs 93.5% (95% CI, 78.6%-99.2%) in those with responses to ide-cel. Between both groups, the complete response (CR) rate was 3.2% (95% CI, 0.1%-16.7%) vs 71.0% (95% CI, 52.0%-85.8%).

Minimal residual disease (MRD) was assessed between 3 and 36 months following treatment with ide-cel. At 3 months, 11% of patients were MRD positive, 11% were MRD intermediate, and 79% were MRD negative. Subsequently, at 6 months, MRD rates showed 18% were MRD positive and 82% were MRD negative; 19% vs 81% at 12 months; 20% vs 80% at 18 months; 18% vs 82% at 24 months; and 25% vs 75% at 36 months.

The rate of ongoing responses at 24 months was 65.3% in patients with a response vs 75.7% in patients with a CR or better. The progression-free survival (PFS) rate at 12 months was 70.0%; at 24 months, it was 63.3%. The overall survival (OS) rate at 12 months was 89.9% vs 78.9% at 24 months.

The investigators noted that the median PFS was not reached, and at data cutoff, the median OS was not reached.

**For full article + references visit**
cancernetwork.com/KarMMa-2_EHA24

## Lower Tumor Burden Increases Liso-Cel Response Likelihood in R/R CLL/SLL

Factors associated with a lower disease burden, such as absence of bulky disease, conferred a higher probability of response to lisocabtagene maraleucel (liso-cel; Breyanzi) among those with relapsed/refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), according to exploratory analysis findings from the phase 1/2 TRANSCEND CLL 004 trial (NCT03331198).

The overall response rate (ORR) was 54.5% (95% CI, 32.2%-75.6%) among patients with a maximum of 3 prior lines of therapy (n = 22) compared with 44.6% (95% CI, 32.3%-57.5%) in those who received more than 3 prior lines (n = 65; OR, 1.49; 95% CI, 0.56-3.93).

The ORR for patients without bulky disease (n = 38) was 63.2% (95% CI, 46.0%-78.2%) vs 31.7% (95% CI, 18.1%-48.1%) in those with bulky disease (n = 41; OR, 3.69; 95% CI, 1.46-9.37). Additionally, the mean sum of the product of perpendicular diameters (SPD) was 24.1 $cm^2$ (95% CI, 19.8-29.2) in those with a response (n = 37) compared with 52.7 $cm^2$ (95% CI, 41.7-66.6) among patients without a response (n = 42). The mean lactate dehydrogenase level prior to lymphodepletion chemotherapy was 226.2 U/L (95% CI, 200.6-255.0) in patients with a response (n = 40) vs 298.9 U/L (95% CI, 259.0-344.9) in those without a response.

A complete response (CR) occurred in 29.7% (95% CI, 15.9%-47.0%) of patients with Rai stage 0 to II disease (n = 37) compared with 11.4% (95% CI, 3.8%-24.6%) of those with stage III to IV disease (n = 44; OR, 3.30; 95% CI, 1.03-10.61). The mean SPD was 21.5 U/L (95% CI, 15.6-29.7) in patients with a CR (n = 14) vs 40.9 U/L (95% CI, 34.1-49.1) in those without (n = 65). Additionally, the mean β-2 microglobulin level was 3.4 U/L (95% CI, 2.8-4.2) in patients who had a CR (n = 14) vs 5.4 U/L (95% CI, 4.5-6.5) in those without (n = 61).

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# Continuing Medical Education

# An Embarrassment of Riches
## Treatment Sequencing in Gastrointestinal Cancers


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This activity was written by PER® editorial staff under faculty guidance and review. The Q&A portion of the activity was transcribed from a recorded interview with the faculty and edited by faculty and PER editorial staff for clarity.

### LEARNING OBJECTIVES

*Upon successful completion of this activity, you should be better prepared to:*
- Discuss current state of affairs and future directions of treatment sequencing in GI cancers
- Describe challenges in addressing unmet needs in treatment sequencing in GI cancers

**RELEASE DATE:** July 1, 2024 **EXPIRATION DATE:** July 1, 2025

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Treatment options have expanded over the past few decades across many cancer types. Although these advances provide new opportunities for patients, they also pose new challenges for treatment sequencing for providers. In this article, Laura Goff, MD, MSCI, MMHC, discusses the current state and future directions of treatment sequencing in lower gastrointestinal (GI) cancers.

**Q/ How has the question of treatment sequencing in GI cancers evolved over the past 10 years, and what is at stake when choosing a sequence of therapy for an individual patient?**

**Goff** / There is more attention being paid to the question of sequencing our treatments.[1,2] Thankfully, we have a lot more treatments, and they are more effective. We are seeing patients live longer, and we oncologists are charged with caring for patients over the course of their entire life. So we are thinking: How will this first-line therapy affect what options may be open to them down the road? How long will they live overall?

In addition, one of the more important factors when thinking about sequencing therapies is how patients will tolerate their therapy now and down the road. For example, we do not want to give a lot of therapy that will cause severe neuropathy early on in the course of a patient's disease, because they may end up with neuropathy for the rest of their lives.[3] Are there ways we could time that better, or space out therapies to minimize long-term toxicity? Are there ways to think about de-escalation to maintenance therapy, again, to prolong the quality of life for a patient while not sacrificing overall survival?

> **Some of the interesting questions that we will be looking at over the next few years will be: Is there a value to continuing immunotherapy beyond the first line with chemotherapy? Is there a value in combining targeted therapy with chemotherapy, with immunotherapy, and in what order?**

**Q/ What are the barriers to addressing the issue of treatment sequencing?**

**Goff** / There are several barriers to addressing treatment sequencing. One may be a relative lack of data. It is hard to collect data over a long period of time, or subsequent lines of therapy, due to the nature of how clinical trials are conducted. Patients move around, and may change centers, so it may be hard to keep track of all of the data longitudinally. Especially now that patients are living longer, it may take many years to ascertain: What impact does the choice of the first-line therapy have on how long a patient lives?

Other barriers, notably in some of the GI cancers, are that the standards of care can change, which is a wonderful thing.[1] But it changes our understanding of what to do next, when the frontline therapy has changed.

## Biliary Tract Cancer

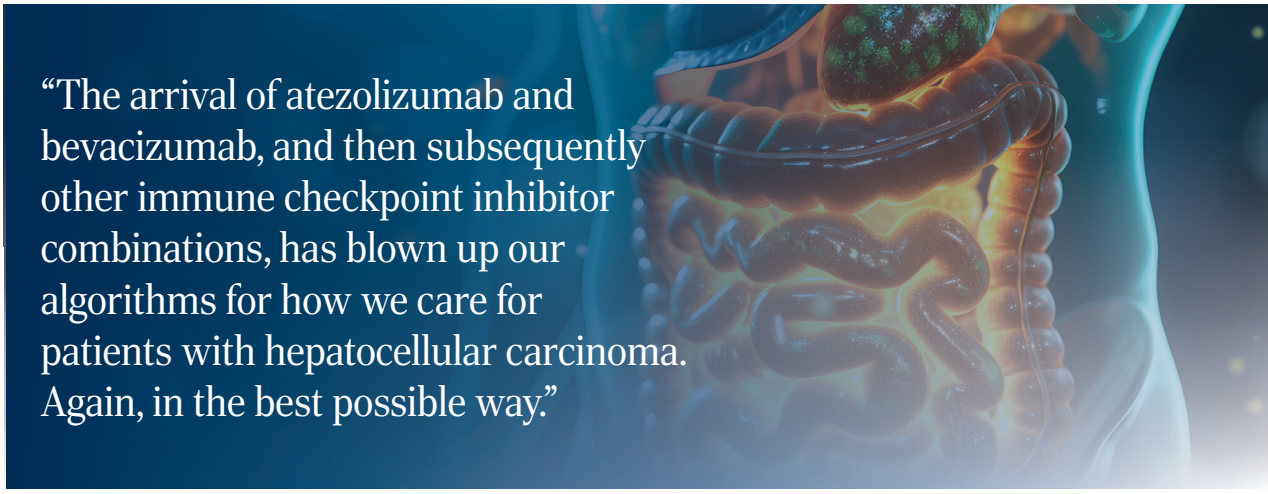
**Q/ In broad strokes, how are therapies currently sequenced in biliary tract cancer?**

**Goff** / In the advanced setting, the current frontline standard involves gemcitabine and cisplatin chemotherapy combined with immunotherapy, either durvalumab or pembrolizumab.[4] Following that, we have a few options, and that is where things become more of an art than a science. Tailoring the subsequent therapies to the individual patient becomes critically important. We may need to make some decisions based on whether they have abnormal liver function tests or elevated bilirubin. Obviously, if they have a driver gene alteration, that is going to affect our choices.[5] We also need to evaluate other potential overlapping toxicities. For example, if patients have preexisting neuropathy, oxaliplatin may not be a particularly good choice.[2] As additional lines of therapy are being considered, the likelihood of benefit gets smaller, which makes an in-depth discussion on the patient's goals and wishes critically important.

All patients with biliary tract cancers should have molecular testing done on their tumors, if at all possible.[6] Right now, molecularly targeted therapy is primarily standard in the second line and beyond. There are ongoing clinical trials looking at moving up molecularly selected treatments to the earlier lines of therapy.[2] Patients who have a driver gene alteration in 1 of several pathways would typically receive that targeted therapy in the second line. If no molecular alteration is found for a patient, then there are a couple of different chemotherapy options, either FOLFOX chemotherapy, or 5-fluorouracil with nanoliposomal irinotecan.

**Q/ What are some of the greatest unmet needs regarding treatment sequencing in biliary tract cancer?**

**Goff** / Always we would like more therapies and more effective therapies in order to treat patients well. Some of the interesting




questions that we will be looking at over the next few years will be: Is there a value to continuing immunotherapy beyond the first line with chemotherapy?[2] Certainly, there is the question of whether targeted therapy is going to supplant first-line chemoimmunotherapy. Is there a value in combining targeted therapy with chemotherapy, with immunotherapy, and in what order? Are we best serving our patients for their overall survival?

## Hepatocellular Carcinoma

### Q/ What percentage of patients have an actionable mutation in this disease state? Who should have gene testing?

**Goff** / Actionable alterations in pure hepatocellular carcinoma (HCC) are rare.[1] Patients should continue to undergo next-generation sequencing if they are fit for therapy, because what we are finding is that we may still identify patients who have a mixed phenotype, the combined hepatocellular carcinoma and cholangiocarcinoma. We will intermittently find patients who have a classic cholangiocarcinoma driver alteration—an *FGFR* fusion, for example.[7] This is likely due to the fact that they come from a common progenitor cell.

### Q/ How has the introduction of immune checkpoint inhibitors as first-line therapy disrupted treatment sequencing algorithms for subsequent therapies that were based on first-line sorafenib?

**Goff** / The arrival of atezolizumab and bevacizumab, and then subsequently other immune checkpoint inhibitor combinations, has blown up our algorithms for how we care for patients with hepatocellular carcinoma.[1] Again, in the best possible way. We are thrilled to have this problem of questioning which of our effective regimens do we need to use first and are our subsequent therapies still active following our new immunotherapy combination doublets.

### Q/ What other factors are shaping the discussion of treatment sequencing in HCC?

**Goff** / Whenever we are taking care of patients with hepatocellular carcinoma, we have to be mindful that many of them have background comorbidities, particularly cirrhosis.[1] So, we are oftentimes dealing with 2 diseases: hepatocellular carcinoma and cirrhosis. This can affect the options that patients are able to tolerate. In HCC, we have 2 pathways that we are targeting when we treat. We target the immune system with immunotherapy, and we target the VEGF pathway, sometimes with additional targets.

Does it make sense to use those 2 classes of drugs up front? Or is it better to space those out? Are there some patients for whom targeting VEGF is really off the table? Specifically, patients with cirrhosis may not be candidates for VEGF inhibition if they have large varices or background significant cardiovascular disease, which is now a growing risk factor for metabolic-associated hepatotoxicity.[8]

### Q/ What are some of the greatest unmet needs regarding treatment sequencing in HCC?

**Goff** / We have a couple of critical questions to answer in the treatment of hepatocellular carcinoma in the near future. First, is there a best first-line regimen? As of ASCO 2024, we have 3 doublet regimens that have all been standard frontline tyrosine kinase inhibitors (TKIs). We have atezolizumab and bevacizumab, durvalumab and tremelimumab, and now nivolumab and ipilimumab, all of which showed improvement in overall survival compared with frontline TKIs.[9-11] We do not know if 1 of those 3 regimens is better than the others to start.

We do not know if there is a benefit to starting with lower dose immunotherapy, or atezolizumab and bevacizumab, and saving the ability to escalate to nivolumab and ipilimumab. Or is it better to maximize our immunotherapy up front, and get a high response rate? Will that put patients at the highest likelihood of really prolonged overall survival? It is hard to say at the moment what the right first-line regimen is.

Additionally, we would like to know [the answer to] a question similar to those with biliary tract cancer: Is there value in extending immunotherapy beyond the first line, either in combination with an alternative VEGF targeting agent, or in escalating therapy from a single to a doublet, or in the case of the MONTBLANC study (NCT05844046), from a doublet to a triplet in the second line?[12]

Our preliminary suggestions from a couple of small prospective studies are that single-agent TKIs do seem to perform about the same in the second-line regimen following immune checkpoint inhibitor–containing regimens as they did following frontline sorafenib.[1] It is still a modest response, but quite similar. But again, we have a lot of questions. Does it matter what you do first? Does it matter what you do second? I think we still have a lot to figure out.

## Colorectal Cancer

### Q/ How does the conversation around treatment sequencing differ in colorectal cancer vs other GI cancers?

**Goff /** Patients with colorectal cancer have historically lived longer than patients with hepatobiliary cancers.[13] We have known from the care of patients with colorectal cancer that thinking about the course of their life possibly over many years makes it really, really important to incorporate considerations about toxicity and long-term adverse effects of therapy in the decision-making when planning the sequence.

Because colorectal cancer is more common, some of the sequencing questions are a little bit farther along. At ASCO, we saw data about the combination of nivolumab and ipilimumab in patients with microsatellite instability (MSI)–high colorectal cancer.[14] One of the most interesting components was seeing that even PFS-2 was improved for patients who had gotten first-line nivo-ipi.[15] We were able to start to see how even in the second line, the choice of first-line therapy was continuing to have an impact.

The other interesting hint we get from colorectal cancer sequencing is in the area of HER2-positive colorectal cancer. HER2 positivity happens in biliary tract cancers as well, but because colorectal cancer is more common, we have been able to see a little bit about how the sequencing of targeted therapies may be developed.[16] For HER2 colorectal cancer, tucatinib plus trastuzumab is often used as the first HER2 therapy, following frontline chemotherapy.[17] Trastuzumab deruxtecan works in patients who have received other HER2-directed therapy, but it may have some higher rates of adverse effects.[18] Therefore, the treatment algorithm is evolving where tucatinib plus trastuzumab may be sequenced first, then utilizing trastuzumab-deruxtecan upon progression.[17] These data points are things we hope to eventually have for the treatment of other hepatobiliary cancers.

## Looking Forward

### Q/ Have any exciting data regarding treatment sequencing clinical trials recently been presented, or is there anything you're looking forward to?

**Goff /** The study of regorafenib plus pembrolizumab following progression in hepatocellular carcinoma that was presented at ASCO is quite important in our understanding of historical response rates for patients following progression on immune checkpoint inhibitor-containing regimens.[19] Although the response rates are low, this prospective data is foundational to our understanding for future studies. This is coupled with the recent publication of the outcomes of cabozantinib following the frontline treatment with an immune checkpoint inhibitor, also in hepatocellular carcinoma.[20] Again, there was a low response rate of about 6.4%, but still on par with the responses we were seeing from cabozantinib following progression on frontline TKI.

We are all eagerly awaiting the results of the IMbrave251 study (NCT04770896), which will really look at the question of continuation of immune checkpoint inhibitor therapy beyond the first line.[21] For patients who had progressed on atezolizumab plus bevacizumab, this is a randomized trial of continued immune checkpoint inhibitor with TKI vs TKI alone. That should give us more robust data to determine the role of continuation of immune checkpoint inhibitor therapy in the second line. ■

**KEY REFERENCES**

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DARZALEX® (daratumumab) injection for intravenous infusion 100 mg/5 mL, 400 mg/20 mL | DARZALEX *Faspro*® (daratumumab and hyaluronidase-fihj) Injection for subcutaneous use | 1,800mg/30,000units

### In the treatment of newly diagnosed, transplant-ineligible multiple myeloma[1]:

# ADVANCE THE FRONTLINE MOMENTUM WITH DARZALEX® + Rd

**Help your patients live longer than Rd alone with DRd, an established frontline treatment proven to significantly extend overall survival[1]**


**After 56 months: 32% reduction in the risk of death with DRd vs Rd alone in the MAIA trial**
(HR=0.68; 95% CI: 0.53, 0.86; *P*=0.0013; mOS not reached in either arm).*[1]

*Median follow-up was 56 months in the DRd group (range: 53.0-60.1 months) and in the Rd group (range: 52.5-59.4 months)[1,2]

CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio; mOS=median overall survival; Rd=lenalidomide (R) + dexamethasone (d).

## 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 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.

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

**IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶**

**MAIA Study Design:** A phase 3 global, randomized, open-label study, compared treatment with DARZALEX® (daratumumab) + Rd (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 progression-free survival (PFS) and OS was a secondary endpoint.[1]

## Powerful efficacy to start the treatment journey[1,3]

At follow-up of 28 months, **median progression-free survival (mPFS) was not reached** with DARZALEX® + Rd vs 31.9 months (95% CI, 28.9 to not reached) with Rd alone*

- **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)†

**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)

## Efficacy results in long-term follow-up[1,4]

After 64 months of follow-up, the median PFS was 61.9 months (95% CI: 54.8, not evaluable) in the DRd arm and 34.4 months (95% CI: 29.6, 39.2) in the Rd arm

**45%** **reduction in the risk of disease progression or death** with DARZALEX® + Rd vs Rd alone (HR=0.55; 95% CI, 0.45-0.67)

## Secondary endpoint of overall survival (OS)[1,2]
After 56 months of follow-up:

- 66% of patients were still alive with DRd vs 53% with Rd alone (DRd: 95% CI, 60.8-71.3; Rd: 95% CI, 47.2-58.6)†
- Median OS was not reached for either arm

**32%** **reduction in the risk of death** in patients treated in the DRd arm vs Rd alone (HR=0.68; 95% CI: 0.53, 0.86; *P*=0.0013)

## Demonstrated safety profile
(median treatment duration of 25.3 months)[1]

- The most common adverse reactions (≥20%) for DRd were diarrhea, constipation, nausea, upper respiratory tract infection, bronchitis, pneumonia, infusion-related reactions, peripheral edema, fatigue, asthenia, pyrexia, back pain, muscle spasms, dyspnea, cough, peripheral sensory neuropathy, and decreased appetite
- 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%)

## Safety results in long-term follow-up
(median follow-up of 64.5 months)[4]

**This information is not included in the current Prescribing Information and has not been evaluated by the FDA.**

- Most frequent TEAEs for DRd occurring in ≥30% of patients were diarrhea, neutropenia, fatigue, constipation, peripheral edema, anemia, back pain, asthenia, nausea, bronchitis, cough, dyspnea, insomnia, weight decreased, peripheral sensory neuropathy, pneumonia, and muscle spasms‡
- Grade 3/4 infections were 43% for DRd vs 30% for Rd‡
- Grade 3/4 TEAEs occurring in ≥10% of patients were neutropenia (54% for DRd vs 37% for Rd), pneumonia (20% vs 11%), and anemia (17% vs 22%)‡

**Treatment-emergent adverse events are reported as observed. These analyses have not been adjusted for multiple comparisons and no conclusions should be drawn.**

CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); FDA=U.S. Food and Drug Administration; HR=hazard ratio; OS=overall survival; Rd=lenalidomide (R) + dexamethasone (d); TEAE=treatment-emergent adverse event.
*Range: 0.0-41.4 months.[1,3]
†Kaplan-Meier estimate.[3]
‡Safety analysis set. TEAEs are defined as any adverse event (AE) that occurs after the start of the first study treatment through 30 days after the last study treatment; or the day prior to start of subsequent antimyeloma therapy, whichever is earlier; or any AE that is considered related (very likely, probably, or possibly related) regardless of the start date of the event; or any AE that is present at baseline but worsens in toxicity grade or is subsequently considered drug related by the investigator.

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### IMPORTANT SAFETY INFORMATION (CONTINUED)

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*® (daratumumab and hyaluronidase-fihj): 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 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.

**IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE▶**

## IMPORTANT SAFETY INFORMATION (CONTINUED)

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 daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX *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.

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

DARZALEX® 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 hematologic 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 and dexamethasone in patients who have received at least one prior therapy
- In combination with carfilzomib and dexamethasone in patients with 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-fihj) 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 with 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.**

cp-248517v3

**References: 1.** DARZALEX® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Facon T, Kumar SK, Plesner T, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2021;22(11):1582-1596. doi:10.1016/s1470-2045(21)00466-6 **3.** Facon T, Kumar S, Plesner T, et al; the MAIA Trial Investigators. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med.* 2019;380(22):2104-2115. doi:10.1056/NEJMoa1817249 **4.** Kumar SK, Moreau P, Bahlis N, et al. Daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) alone in transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM): updated analysis of the phase 3 MAIA study. Poster presented at: 64th American Society of Hematology (ASH) Annual Meeting & Exposition; December 10-13, 2022; New Orleans, LA.


07/23 cp-352216v2

janssen Oncology
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

**DARZALEX® (daratumumab) injection, for intravenous use**
**Brief Summary of Full Prescribing Information**

## 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=2,066), 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). The incidence of infusion modification due to reactions was 36%. Median durations of 16 mg/kg infusions for the Week 1, Week 2, and subsequent infusions were approximately 7, 4, 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, 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 *[see Adverse Reactions]*.

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 rate/dilution volume used upon re-initiation was that used for the last DARZALEX infusion prior to interruption for 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 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 or life-threatening (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 DARZALEX 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 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.

### 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 banks 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 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 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 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 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 and for 3 months after the last dose *[see Use in Specific Populations]*.

The combination of DARZALEX 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.

## 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, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory 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**

| Body System<br>Adverse Reaction | DRd (N=364) | | | Rd (N=365) | | |
|---|---|---|---|---|---|---|
| | All Grades (%) | Grade 3 (%) | Grade 4 (%) | All Grades (%) | Grade 3 (%) | Grade 4 (%) |
| **Gastrointestinal disorders** | | | | | | |
| Diarrhea | 57 | 7 | 0 | 46 | 4 | 0 |
| Constipation | 41 | 1 | <1 | 36 | <1 | 0 |
| Nausea | 32 | 1 | 0 | 23 | 1 | 0 |
| Vomiting | 17 | 1 | 0 | 12 | <1 | 0 |
| **Infections** | | | | | | |
| Upper respiratory tract infection[a] | 52 | 2 | <1 | 36 | 2 | <1 |
| Bronchitis[b] | 29 | 3 | 0 | 21 | 1 | 0 |
| Pneumonia[c] | 26 | 14 | 1 | 14 | 7 | 1 |
| Urinary tract infection | 18 | 2 | 0 | 10 | 2 | 0 |
| **General disorders and administration site conditions** | | | | | | |
| Infusion-related reactions[d] | 41 | 2 | <1 | 0 | 0 | 0 |
| Peripheral edema[e] | 41 | 2 | 0 | 33 | 1 | 0 |
| Fatigue | 40 | 8 | 0 | 28 | 4 | 0 |
| Asthenia | 32 | 4 | 0 | 25 | 3 | <1 |
| Pyrexia | 23 | 2 | 0 | 18 | 2 | 0 |
| Chills | 13 | 0 | 0 | 2 | 0 | 0 |
| **Musculoskeletal and connective tissue disorders** | | | | | | |
| Back pain | 34 | 3 | <1 | 26 | 3 | <1 |
| Muscle spasms | 29 | 1 | 0 | 22 | 1 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | | | | | | |
| Dyspnea[f] | 32 | 3 | <1 | 20 | 1 | 0 |
| Cough[g] | 30 | <1 | 0 | 18 | 0 | 0 |
| **Nervous system disorders** | | | | | | |
| Peripheral sensory neuropathy | 24 | 1 | 0 | 15 | 0 | 0 |
| Headache | 19 | 1 | 0 | 11 | 0 | 0 |
| Paresthesia | 16 | 0 | 0 | 8 | 0 | 0 |
| **Metabolism and nutrition disorders** | | | | | | |
| Decreased appetite | 22 | 1 | 0 | 15 | <1 | <1 |
| Hyperglycemia | 14 | 6 | 1 | 8 | 3 | 1 |
| Hypocalcemia | 14 | 1 | <1 | 9 | 1 | 1 |
| **Vascular disorders** | | | | | | |
| Hypertension[h] | 13 | 6 | <1 | 7 | 4 | 0 |

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

[a] Acute sinusitis, Bacterial rhinitis, Laryngitis, Metapneumovirus infection, Nasopharyngitis, Oropharyngeal candidiasis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinusitis, Tonsillitis, Tracheitis, Upper respiratory tract infection, Viral pharyngitis, Viral rhinitis, Viral upper respiratory tract infection

[b] Bronchiolitis, Bronchitis, Bronchitis viral, Respiratory syncytial virus bronchiolitis, Tracheobronchitis

[c] Atypical pneumonia, Bronchopulmonary aspergillosis, Lung infection, Pneumocystis jirovecii infection, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia aspiration, Pneumonia pneumococcal, Pneumonia viral, Pulmonary mycosis

[d] Infusion-related reaction includes terms determined by investigators to be related to infusion

[e] Generalized edema, Gravitational edema, Edema, Peripheral edema, Peripheral swelling

[f] Dyspnea, Dyspnea exertional

[g] Cough, Productive cough

[h] Blood pressure increased, Hypertension

**DARZALEX®** (daratumumab) injection

Laboratory abnormalities worsening during treatment from baseline listed in Table 2.

**Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA**

| | DRd (N=364) | | | Rd (N=365) | | |
|---|---|---|---|---|---|---|
| | All Grades (%) | Grade 3 (%) | Grade 4 (%) | All Grades (%) | Grade 3 (%) | Grade 4 (%) |
| Leukopenia | 90 | 30 | 5 | 82 | 20 | 4 |
| Neutropenia | 91 | 39 | 17 | 77 | 28 | 11 |
| Lymphopenia | 84 | 41 | 11 | 75 | 36 | 6 |
| Thrombocytopenia | 67 | 6 | 3 | 58 | 7 | 4 |
| Anemia | 47 | 13 | 0 | 57 | 24 | 0 |

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

Relapsed/Refractory Multiple Myeloma

*Combination Treatment with Lenalidomide and Dexamethasone*

The safety of DARZALEX in combination with lenalidomide and dexamethasone was evaluated in POLLUX *[see Clinical Studies (14.2) in Full Prescribing Information]*. Adverse reactions described in Table 3 reflect exposure to DARZALEX for a median treatment duration of 13.1 months (range: 0 to 20.7 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 12.3 months (range: 0.2 to 20.1 months) for lenalidomide-dexamethasone (Rd).

Serious adverse reactions occurred in 49% of patients in the DRd arm compared with 42% in the Rd arm. Serious adverse reactions with at least a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 12% vs Rd 10%), upper respiratory tract infection (DRd 7% vs Rd 4%), influenza and pyrexia (DRd 3% vs Rd 1% for each).

Adverse reactions resulted in discontinuations for 7% (n=19) of patients in the DRd arm versus 8% (n=22) in the Rd arm.

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

| Adverse Reaction | DRd (N=283) | | | Rd (N=281) | | |
|---|---|---|---|---|---|---|
| | All Grades (%) | Grade 3 (%) | Grade 4 (%) | All Grades (%) | Grade 3 (%) | Grade 4 (%) |
| **Infections** | | | | | | |
| Upper respiratory tract infection[a] | 65 | 6 | < 1 | 51 | 4 | 0 |
| **General disorders and administration site conditions** | | | | | | |
| Infusion-related reactions[b] | 48 | 5 | 0 | 0 | 0 | 0 |
| Fatigue | 35 | 6 | < 1 | 28 | 2 | 0 |
| Pyrexia | 20 | 2 | 0 | 11 | 1 | 0 |
| **Gastrointestinal disorders** | | | | | | |
| Diarrhea | 43 | 5 | 0 | 25 | 3 | 0 |
| Nausea | 24 | 1 | 0 | 14 | 0 | 0 |
| Vomiting | 17 | 1 | 0 | 5 | 1 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | | | | | | |
| Cough[c] | 30 | 0 | 0 | 15 | 0 | 0 |
| Dyspnea[d] | 21 | 3 | < 1 | 12 | 1 | 0 |
| **Musculoskeletal and connective tissue disorders** | | | | | | |
| Muscle spasms | 26 | 1 | 0 | 19 | 2 | 0 |
| **Nervous system disorders** | | | | | | |
| Headache | 13 | 0 | 0 | 7 | 0 | 0 |

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

[a] upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection

[b] Infusion-related reaction includes terms determined by investigators to be related to infusion

[c] cough, productive cough, allergic cough

[d] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment from baseline listed in Table 4.

**Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX**

| | DRd (N=283) | | | Rd (N=281) | | |
|---|---|---|---|---|---|---|
| | All Grades (%) | Grade 3 (%) | Grade 4 (%) | All Grades (%) | Grade 3 (%) | Grade 4 (%) |
| Lymphopenia | 95 | 42 | 10 | 87 | 32 | 6 |
| Neutropenia | 92 | 36 | 17 | 87 | 32 | 8 |
| Thrombocytopenia | 73 | 7 | 6 | 67 | 10 | 5 |
| Anemia | 52 | 13 | 0 | 57 | 19 | 0 |

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

Herpes Zoster Virus Reactivation

Prophylaxis 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

Grade 3 or 4 infections were reported as follows:

- Relapsed/refractory patient studies: DVd: 21% vs. Vd: 19%; DRd: 28% vs. Rd: 23%; DPd: 28%; DKd[a]: 37%, Kd[a]: 29%; DKd[b]: 21%
  - [a] where carfilzomib 20/56 mg/m$^2$ was administered twice-weekly
  - [b] where carfilzomib 20/70 mg/m$^2$ was administered once-weekly
- Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%; DVTd: 22%; VTd: 20%.

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[a]: 5%, Kd[a]: 3%; DKd[b]: 0%
  - [a] where carfilzomib 20/56 mg/m$^2$ was administered twice-weekly
  - [b] where carfilzomib 20/70 mg/m$^2$ was administered once-weekly
- Newly diagnosed patient studies: D-VMP: 1%, VMP: 1%; DRd: 2%, Rd: 2%; DVTd: 0%, VTd: 0%.

Fatal infections were generally infrequent and balanced between the DARZALEX containing regimens and active control arms. Fatal infections were primarily due to pneumonia and sepsis.

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, 0.35% (6/1,713) of patients developed treatment-emergent anti-daratumumab antibodies. Of those, 4 patients tested positive for neutralizing antibodies.

**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

## 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 dithiothreitol (DTT) 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/RhD-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 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 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 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 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. Defer administering live vaccines to neonates and infants exposed to DARZALEX *in utero* until a hematology evaluation is completed.

Data

*Animal 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), feto-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. 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 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.

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 are 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**

1. Chapuy, CI, RT Nicholson, MD Aguad, et al., 2015, Resolving the daratumumab interference with blood compatibility testing, Transfusion, 55:1545-1554 (accessible at http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf).

**PATIENT COUNSELING INFORMATION**

Advise 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, USA
U.S. License Number 1864

For patent information: www.janssenpatents.com



cp-271933v4

**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 898 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.2%, 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 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, nausea, 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 angle due to ciliochoroidal 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 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.

### 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.



### 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].*

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

### 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 *[see References (15)].* 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 banks that a patient has received DARZALEX FASPRO. Type and screen patients prior to starting DARZALEX FASPRO *[see Dosage and Administration (2.1) in Full Prescribing Information].*

### Interference with Determination of Complete Response

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 PLEIADES *[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, influenza 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 63% of patients who received DARZALEX FASPRO. Adverse reactions requiring 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, muscle spasms, constipation, pyrexia, pneumonia, and dyspnea.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO in PLEIADES.

**Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES**

| Adverse Reaction | DARZALEX FASPRO with Lenalidomide and Dexamethasone (N=65) | |
|---|---|---|
| | All Grades (%) | Grades ≥3 (%) |
| **General disorders and administration site conditions** | | |
| Fatigue[a] | 52 | 5# |
| Pyrexia | 23 | 2# |
| Edema peripheral | 18 | 3# |
| **Gastrointestinal disorders** | | |
| Diarrhea | 45 | 5# |
| Constipation | 26 | 2# |
| Nausea | 12 | 0 |
| Vomiting | 11 | 0 |
| **Infections** | | |
| Upper respiratory tract infection[b] | 43 | 3# |
| Pneumonia[c] | 23 | 17 |
| Bronchitis[d] | 14 | 2# |
| Urinary tract infection | 11 | 0 |
| **Musculoskeletal and connective tissue disorders** | | |
| Muscle spasms | 31 | 2# |
| Back pain | 14 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Dyspnea[e] | 22 | 3 |
| Cough[f] | 14 | 0 |
| **Nervous system disorders** | | |
| Peripheral sensory neuropathy | 17 | 2# |
| **Psychiatric disorders** | | |
| Insomnia | 17 | 5# |
| **Metabolism and nutrition disorders** | | |
| Hyperglycemia | 12 | 9# |
| Hypocalcemia | 11 | 0 |

[a] Fatigue includes asthenia, and fatigue.
[b] Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection viral, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.
[c] Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia.
[d] Bronchitis includes bronchitis, and bronchitis viral.
[e] Dyspnea includes dyspnea, and dyspnea exertional.
[f] Cough includes cough, and productive cough.
[#] Only Grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with lenalidomide and dexamethasone included:

- **Musculoskeletal and connective tissue disorders:** arthralgia, musculoskeletal chest pain
- **Nervous system disorders:** dizziness, headache, paresthesia
- **Skin and subcutaneous tissue disorders:** rash, pruritus
- **Gastrointestinal disorders:** abdominal pain
- **Infections:** influenza, sepsis, herpes zoster
- **Metabolism and nutrition disorders:** decreased appetite
- **Cardiac disorders:** atrial fibrillation
- **General disorders and administration site conditions:** chills, infusion reaction, injection site reaction
- **Vascular disorders:** hypotension, hypertension

Table 2 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO in PLEIADES.

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

| Laboratory Abnormality | DARZALEX FASPRO with Lenalidomide and Dexamethasone[a] | |
|---|---|---|
| | All Grades (%) | Grades 3-4 (%) |
| Decreased leukocytes | 94 | 34 |
| Decreased lymphocytes | 82 | 58 |
| Decreased platelets | 86 | 9 |
| Decreased neutrophils | 89 | 52 |
| Decreased hemoglobin | 45 | 8 |

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

**DARZALEX FASPRO®** (daratumumab and hyaluronidase-fihj) injection

**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-rHuPH20 antibodies. The anti-rHuPH20 antibodies did not appear to affect daratumumab exposure. None of the patients who tested positive for anti-rHuPH20 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.

*Immune System:* Anaphylactic reaction, Systemic administration reactions (including death)

*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 dithiothreitol (DTT) 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/RhD-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 hematology 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 daily 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

*Animal 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 19% 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 upper respiratory tract infection, urinary tract infection, dizziness, cough, dyspnea, diarrhea, nausea, fatigue, and peripheral edema. Serious adverse reactions that occurred at a higher frequency (≥2% difference) in patients ≥65 years of age included pneumonia.

Of the 214 patients who received DARZALEX FASPRO as combination therapy with pomalidomide and dexamethasone or DARZALEX FASPRO as combination therapy with lenalidomide and low-dose dexamethasone for relapsed and refractory multiple myeloma, 43% were 65 to <75 years of age, and 18% were 75 years of age or older. No overall differences in effectiveness were observed between patients ≥65 years (n=131) and <65 years (n=85). Adverse reactions occurring at a higher frequency (≥5% difference) in patients ≥65 years of age included fatigue, pyrexia, peripheral edema, urinary tract infection, diarrhea, constipation, vomiting, dyspnea, 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, asthenia, 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**

1. Chapuy, CI, RT Nicholson, MD Aguad, et al., 2015, Resolving the daratumumab interference with blood compatibility testing, Transfusion, 55:1545-1554 (accessible at http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf).

**PATIENT COUNSELING INFORMATION**

Advise the patient 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 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 FASPRO could cause hepatitis B virus to become active again *[see Adverse Reactions]*.

Manufactured by:
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U.S. License Number 1864

For patent information: www.janssenpatents.com



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