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ONCOLOGY
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Our Board Members Have Been Busy!

Take a look to see what they've been up to.

Kelley A. Rone, DNP, RN, AGNP-c

ONCOLOGY would like to welcome the newest editorial advisory board member, Kelley A. Rone, DNP, RN, AGNP-c. Rone is an advanced practice nurse who specializes in gastrointestinal oncology at Mayo Clinic in Phoenix, Arizona. Specifically, Rone focuses on toxicity management and end-of-life discussions. She recently spoke with *ONCOLOGY* regarding approaching these discussions, incorporating them into multidisciplinary care, and how she combats burnout. To read the full interview, stay tuned for the December issue of *ONCOLOGY* and check out our website, cancernetwork.com.

Call for Reviewers and Papers

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

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Gender Equity in Hematology/Oncology
Have We Made Any Progress?

There has been growth in the representation of women in many areas of medicine. For example, in 2017, for the first time, more women than men matriculated into United States medical schools.[1] However, women remain underrepresented in academic medicine as well as leadership positions in academic medicine.[2] The theory has been that it just takes time for women to go through the ranks and they can gain representation as time goes on. Although this has happened to some degree, with the major increase in women going through medical training, more representation would be expected at this point.

In hematology/oncology, this trend is evident, with slow improvements over the past several decades. For example, of the 59 presidents of the American Society of Clinical Oncology (ASCO), only 9 have been women. However, 4 of the past 10 have been women. Such slow improvement is evident at every level of academic oncology, especially over the past decade. Another example is the exceptionally low level of representation of women on editorial boards of major medical journals, and the near total lack of women as editors-in-chief for major oncology journals.[3] The lack of women in these positions is multifactorial and individual for each situation. However, the modifiable determinants should be addressed on an individual basis. When positions become available, a broad net should be cast for applicants, with specific outreach to qualified candidates in underrepresented categories.

In some exceptional circumstances, traditional expectations need to be modernized to meet candidates' needs. This could include flexible hours, improved clinical or administrative support, or a modified career plan timeline considering family and personal needs. The one-size-fits-all academic and clinical entity approach does not work well for the diversification of physicians or the growth of the hematology/oncology specialty. It is incumbent on the few women in leadership positions in hematology/oncology to change the trajectory for the future of women in the field. ■

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Uterine Transposition Surgery Offers QOL Improvement Through Fertility Preservation

John Paul Diaz, MD, Chief of Gynecologic Oncology, Director of Robotic Surgery, Director of the Center of Excellence in Minimally Invasive Gynecologic Surgery at Baptist Health, and Lead Physician for Clinical Trials in Gynecologic Oncology at Miami Cancer Institute

The new surgical technique of uterine transposition allows women undergoing radiation therapy directed to the pelvic field to attempt to preserve their fertility. John Paul Diaz, MD, spoke about this new technique and how this could be a pivotal operation to protect quality of life.

Diaz, chief of gynecologic oncology, director of robotic surgery, director of the Center of Excellence in Minimally Invasive Gynecologic Surgery at Baptist Health, and lead physician for Clinical Trials in Gynecologic Oncology at Miami Cancer Institute, highlighted that this surgery can be for any patients with colorectal or gynecologic cancers who may be receiving radiation to the affected areas.

The surgery, which moves the uterus into the abdominal wall away from the affected radiation area, is one way that surgeons are beginning to think outside the box, according to Diaz.

CancerNetwork / What are the specific surgical techniques involved in uterine transposition, including the methods used to temporarily relocate and secure the uterus?

Diaz / The surgical techniques used for uterine transposition are quite simple and very similar to a hysterectomy. The idea is to begin by opening the retroperitoneum. We want to make sure that we avoid touching any of the blood supply to the uterus, like the infundibulopelvic ligament. That's what's going to preserve the uterus after the fact. The difference here is we're going to preserve the uterus, as opposed to removing it during a hysterectomy. Once we get down to the main blood supply of the uterus, the uterine arteries are ligated, and the uterus and cervix are released from the vagina. We then mobilize the uterus up into the abdomen, and then stitch it up to the anterior abdominal wall, thereby taking it out of the radiation field so patients can safely receive the radiation they need to treat their pelvic tumor but preserve their fertility and hopefully carry a future pregnancy.

Q / This surgery occurred with the collaboration of Memorial Sloan Kettering (MSK) Cancer Center; how did this come about?

Diaz / At Baptist Health, South Florida, we're part of the MSK Cancer Alliance. I trained at MSK and continued to keep in close contact with a lot of the physicians and surgeons there, including my friend and mentor, Dr Mario Leitao, who has the largest series in the United States performing uterine transpositions. When I had a patient who would be a candidate for this, I discussed the case with Leitao and went up to MSK to observe the technique in the operating room. When it came for us to do our first procedure, Leitao came down to South Florida and observed us in the operating room. This collaboration has been great to help expand the number of patients who could benefit from this surgical technique.

Q / What are the outcomes you saw with the 2 patients who underwent this procedure?

Diaz / We've had 2 patients who have undergone this procedure here in South Florida. Our first patient has completed her adjuvant radiation therapy, and we completed phase 2 of the procedure, which is now to move the uterus and the ovaries back into the pelvis, and reanastomosis to the vagina. That was a very successful procedure. The patient is currently 3 months [post operation] and is doing very well, and now we're eagerly awaiting the opportunity for her to become pregnant in

the future. Our second patient is currently receiving her radiation therapy, and the plan is for later this year to proceed with stage 2 of the procedure.

Q / What sets uterine transposition apart from other fertility preservation methods and gynecologic care?

Diaz / For some time, we've been looking at how we can treat these cancers for women and preserve their fertility. [There are] different things that we've tried in the past, but when [patients are] going to receive pelvic radiation, we would mobilize the ovaries out of the radiation field, and now at least try to preserve the ovaries so they can contain their estrogen production and possibly allow them for a genetic child in the future with a surrogate carrier.

We've also done other techniques, such as a radical trachelectomy described in the first series over 15 years ago. We continue to try to adapt our treatments for these young patients, where we can successfully treat their cancers but preserve fertility. The interesting part about this technique is we're preserving the entire uterus. These patients can receive their pelvic radiation and then be able to carry a child in the future. There's no radiation technique now that can safely be performed to preserve this uterus function. This is an exciting and big change in the treatment of [patients with] these cancers.

Q / How can you best identify candidates for this procedure and which cancer types or stages is it most useful for?

Diaz / Candidates for this procedure are women who have some pelvic tumor, either colorectal cancer or vaginal cancer, in which they're going to require pelvic radiation, which would otherwise sterilize the uterus, and [they may be] unable to carry a pregnancy in the future. These tend to be younger women who still want to preserve their fertility. There are cancers that can be potentially treated and cured with a combination of pelvic radiation. We're going to mobilize this uterus out of that radiation field and safely allow them to get the cancer treatment they need, and then bring the uterus back into its natural [home] in the pelvis so they can hopefully carry a pregnancy in the future.

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Q / Were there any challenges encountered during the development or implementation of this procedure, and how did you overcome them?

Diaz / One of the biggest challenges with this procedure, or any of these procedures, is just thinking outside the box. As surgical oncologists, our priority has always been, and rightfully so, to treat the cancer. When we first did this, the idea was a radical surgery; the more tissue around the tumor you got that was negative, the better oncologic outcomes. We've learned over time that we can continue to keep great oncologic outcomes but tailor our techniques to improve outcomes for women. We saw this in the evolution of the management of breast cancers, from these very radical

surgeries now to lumpectomies with sentinel lymph nodes. This has been patient driven. The patients have been forcing us surgeons to come up with better techniques where we can treat the disease but also give them a better quality of life afterward. This is no different. The procedure itself, as I said, surgically, is very simple. It's something we all would feel comfortable performing. It's just a matter of thinking about it in this way, and once you see it done, you realize that this can be done, and hopefully can be applied to many women to preserve their future fertility.

Q / How effective is this procedure in preserving fertility, and are there any limitations that may impact the success of future pregnancies?

Diaz / This is a novel technique. There have only been a handful of cases that have been done around the world, so our experience continues to grow. In the initial experience in Brazil, about 75% of their surgeries were successful. In other words, the uterus was preserved and was functioning. That number has now improved as we continue to collaborate with our partners around the world and share our surgical techniques; in that initial collaboration, we saw 3 of the 4 women who attempted fertility to have a successful pregnancy, and so that's encouraging.

We also have to remember we're dealing with cancer here. We're dealing with a novel surgical technique. Some of these patients, unfortunately, may not have a successful treatment of their cancer, so fertility then may become secondary as they go on to treat this progressing disease. When removing the uterus from the normal area, the blood supply can sometimes be compromised. We're starting to learn more and more, but success rates have continued to improve with greater experience.

Q / What are some key short- and long-term outcomes for patients who undergo this procedure?

Diaz / One of the short-term things that we're looking for immediately in the operating room is the uterus perfusing well. We use a dye called indocyanine green that we inject, and we see the uterus absorb the dye and become green. That's an indication that it's perfusing well. In the short term, you want to see again, if there are no postoperative complications that we continue to see, good perfusion, good outcomes of this uterus, and the successful treatment of the prescribed cancer treatment that these patients are undergoing. We can then go back and reimplant the uterus back into its normal anatomical position. Obviously, the ultimate long-term success is for the patient to be cured of their disease and to go on to have a successful live birth. That takes time and patience for both the patient and us, but this is what we're looking for, and [we're] excited about granting this opportunity to future patients.

One of the challenges is that providers out there need to be aware that this is even an option.

Q / Have you experienced any challenges trying to raise awareness for this procedure?

Diaz / One of the challenges is that providers out there need to be aware that this is even an option. We're going to those providers who are seeing these patients. We're going to our colorectal surgeons, our colleagues in rectal cancer and colon cancer to make them aware that this may be an option for their young patients because they're the ones who need to identify these patients and ultimately refer them to someone like us. We're also working to share knowledge about this procedure, and hopefully, more surgeons around the United States, can offer this to their patients and their colleagues, and that's been the biggest challenge. How do we get this word out? How do we educate the providers who are first seeing these patients so they can be referred to someone who feels comfortable performing this procedure?

Q / What are the next steps for this procedure?

Diaz / Some of the next steps with this procedure are to expand access to patients and to let other doctors know that this is even an option. This is still novel, although the first description of it was almost 10 years ago. We're only starting to now hear about this in the United States, so we are spreading that information to physicians who are first seeing patients with these pelvic tumors. They can educate these patients about this fertility option before they initiate their cancer treatments, and then continue to work and develop new and novel techniques. Some of these are great advances, like radical trachelectomy to preserve the uterus or the uterine transposition. This was again focused on improving patients' postcancer diagnosis so they could retain their fertility.

Q / Is there anything else you would like to highlight?

Diaz / It's just exciting that we're thinking outside the box, that we're moving a reproductive organ outside of the field of radiation so women can preserve fertility. We're doing this successfully. This is something that a few years ago, we wouldn't have even thought about, and so it's exciting to see this. We're seeing better outcomes for patients, especially at a time when we're seeing more and more young women who are being diagnosed with pelvic tumors.

MULTIPLE MYELOMA

The Hidden Danger
Unveiling the Connection Between Multiple Myeloma and Pleural Effusion

ABSTRACT We present a 65-year-old man with multiple myeloma who developed a rare complication of pleural effusion. Initial laboratory results showed elevated creatinine, calcium, and protein electrophoresis with an M spike. A bone marrow biopsy confirmed 80% plasma cells. Despite the rarity of pleural effusion in patients with multiple myeloma, our patient demonstrated significant improvement with targeted therapy and palliative care. This case highlights the importance of early recognition and management of pleural effusion in patients with multiple myeloma and underscores the need for further research into optimal management strategies and underlying mechanisms.

Introduction

Multiple myeloma is a cancer of plasma cells that produces monoclonal proteins (M protein). The term *multiple myeloma* originates from the Greek words *myelos*, meaning "marrow," and *oma*, meaning "tumor."[1] This refers to the tumors that develop in the bone marrow due to the malignant plasma cell proliferation, leading to bone destruction, anemia, and immune dysfunction.

Multiple myeloma is the second most common hematologic malignancy, accounting for approximately 1% of all cancers and 10% of hematologic malignancies.[2] Pleural effusion in multiple myeloma is a rare manifestation occurring in less than 1% of patients and termed as myelomatous pleural effusion as a direct result of multiple myeloma.[3] Despite advances in treatment, multiple myeloma remains a significant clinical challenge, with a median survival rate of 5 to 7 years.[4]

Case Presentation

A 65-year-old man presented with fatigue, weight loss, bone pain, and shortness of breath. On examination the patient looked pale and had yellowish sclera and generalized bone tenderness. Chest auscultation revealed reduced breath sounds on the right side and an abdominal examination showed a tender right upper quadrant with hepatomegaly. Investigations revealed the following:

- normocytic anemia with hemoglobin of 10.5 g/dL;
- hypercalcemia with calcium levels at 14.5 mg/dL; and
- creatinine levels at 1.5 mg/dL.

Table 1[2-4] indicates the laboratory findings of the patient. A chest x-ray confirmed pulmonary effusion, as shown in **Figure 1**.

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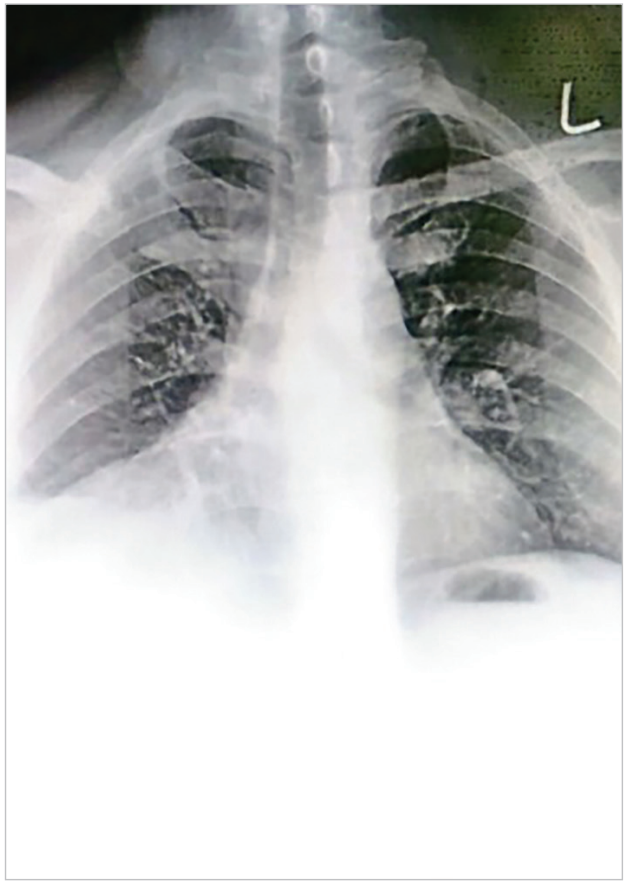


FIGURE 1. Chest Anteroposterior X-Ray of the Patient Showing Bilateral Pleural Effusion

Table 2 indicates the pleural fluid analysis of the patient. Urine protein electrophoresis showed the presence of M protein. Additionally, serum protein electrophoresis and immunofixation electrophoresis detected M proteins. These findings were consistent with a diagnosis of multiple myeloma. Therapeutic and diagnostic pleural tap showed exudative effusion with atypical cells with increased count and raised lactate dehydrogenase levels. A bone marrow biopsy confirmed plasma cell infiltration in 60% of total cells. **Figures 2** and **3** show the bone marrow biopsy and indicate the abnormal myeloma cells.

The patient was treated with bortezomib, lenalidomide, and dexamethasone and underwent thoracentesis for pleural effusion management. Despite the rarity of pleural effusion in patients with multiple myeloma, limited research exists on optimal management strategies, highlighting the need for further investigation to improve patient outcomes. Additionally, the underlying mechanisms driving pleural effusion development in patients with multiple myeloma remain poorly understood, warranting further study.

Discussion

Multiple myeloma is a complex and multifactorial disease and its pathophysiology is not fully understood. However, research has made significant progress in recent years, shedding light on the molecular mechanisms underlying multiple myeloma. For instance, studies have identified genetic mutations, such as translocations and deletions, that contribute to the development and progression of multiple myeloma.[5] Additionally, the role of the bone marrow microenvironment in supporting multiple myeloma cell growth and survival has been elucidated.[6]

Multiple myeloma is characterized by a range of clinical features, including bone destruction, anemia, and immune dysfunction. The disease can also manifest in rare ways, such as pleural effusion,

TABLE 1. Laboratory Findings of the Patient[2-4]

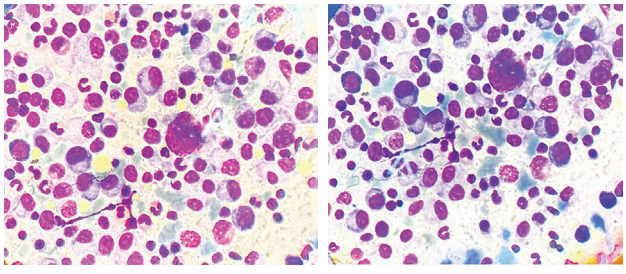
S.NO	LABORATORY TEST	NORMAL VALUE	PATIENT FINDINGS
1.	WBC (U/µL)	4500-11000	6440
2.	Hemoglobin (g/dL)	11.5-17.5	10.5
3.	Platelets (U/µL)	150,000-450,000	200,000
4.	C-reactive protein (mg/dL)	<0.5	5.50
5.	Ferritin (ng/mL)	30-400	1944
6.	ESR mm/hr	0-15	102
7.	ALP (U/L)	40-129	308
8.	Serum creatinine (mg/dL)	0.64-1.2	1.5
9.	Serum calcium (mg/dL)	8.0-10.0	14.5
10.	Serum LDH (U/L)	80-235	509

ALP, alkaline phosphatase; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; WBC, white blood cell.

TABLE 2. Pleural Fluid Analysis of the Patient[2-4]

S.NO	LABORATORY TEST	TRANSUDATIVE	EXUDATIVE	PATIENT FINDINGS
1.	Cell type	Varies	Varies	Atypical
2.	Cell count (cells/μL)	<1000	>1000	5250/cm
3.	Pleural fluid LDH %	<60%	>60%	>60%
4.	Serum to pleural fluid ratio	<0.5	>0.5	0.9
5.	Pleural fluid protein (g/dL)	<2.5	>3	5

LDH, lactate dehydrogenase.



FIGURES 2 AND 3. Abnormal Plasma Cells Confirmed by Bone Marrow Biopsy

reported in less than 1% of cases.[7] This highlights the importance of considering multiple myeloma in the differential diagnosis of patients presenting with unusual clinical features. Furthermore, the identification of genetic mutations and molecular mechanisms underlying multiple myeloma has led to the development of targeted therapies, improving treatment options for patients.[4]

Malignant effusions in patients with multiple myeloma are associated with poor prognosis. Affected patients are usually resistant to treatment and often relapse despite aggressive chemotherapy necessitating pleurodesis.[8] Therefore, continued research is essential to improve our understanding of multiple myeloma and develop effective therapeutic strategies. This includes exploring new targets for therapy, such as the bone marrow microenvironment, and identifying biomarkers to predict treatment response. By advancing our knowledge of multiple myeloma, we can improve patient outcomes and quality of life. New studies are underway to enhance the treatment of pleural effusion in multiple myeloma.

Conclusion

This case highlights the rare complication of pleural effusion in multiple myeloma and the importance of early recognition and management. Despite the challenges, our patient showed significant improvement with targeted therapy and palliative care. This case underscores the need for further research into the optimal management of pleural effusion in patients with multiple myeloma and the underlying mechanisms driving this complication. ■

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CONSENT

Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review from the editorial team of this journal on request.

AUTHOR CONTRIBUTION

The conceptualization was done by MHG and FF. The literature and drafting of the manuscript were conducted by FA and NS. The editing and supervision were performed by ABW and MZ. All authors have read and agreed to the final version of the manuscript.

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MULTIPLE MYELOMA

Quadruplet Therapy Shows Benefit for Newly Diagnosed Multiple Myeloma

CancerNetwork® spoke with Thomas G. Martin, MD, a clinical professor of medicine at the Adult Leukemia and Bone Marrow Transplantation Program and associate director of the myeloma program at the University of California, San Francisco; and coleader of the Cancer Immunology & Immunotherapy Program at the Helen Diller Family Comprehensive Cancer Center. The conversation followed the recent FDA approval of isatuximab-irfc (Sarclisa) in combination with lenalidomide (Revlimid), bortezomib (Velcade), and dexamethasone, known as Isa-VRd, in patients with transplant-ineligible, newly diagnosed multiple myeloma (NDMM).[1]

Martin briefly outlined results from the phase 3 IMROZ trial (NCT03319667), which portrayed enhanced efficacy and similar safety for quadruplet therapy vs VRd.[2,3] He emphasized the quadruplet therapy's higher minimal residual disease (MRD) negativity rate, significantly improved 60-month progression-free survival (PFS) rate, and promising interim overall survival (OS) data, indicating a benefit for patients with transplant-ineligible NDMM.

Martin additionally stressed that infection rates, adverse effects, and toxicity incidences were similar across treatment groups, particularly when accounting for treatment duration. He concluded by disclosing other multiple myeloma developments that he believes may impact clinical practice, including an additional trial evaluating quadruplet vs triplet therapy with bortezomib as the investigational agent, and recent approvals for the use of B cell maturation antigen–bispecific antibodies in earlier lines of therapy.

Thomas G. Martin, MD, Helen Diller Family Comprehensive Cancer Center

Q / What does the FDA approval of Isa-VRd in patients with newly diagnosed multiple myeloma mean for this population?

Martin / The recent FDA approval based on the IMROZ trial is in a patient population who do not intend to go to bone marrow transplant. These patients receive induction therapy, and then it evolves into consolidation therapy, and this is a big advantage for them now to be able to get a 4-drug induction therapy. This combination of Isa-VRd provides deep and durable responses in this patient population, and we know that it increases the PFS vs the VRd triplet. It likely will improve the OS, and it certainly improves the ability for patients to achieve what is considered MRD negativity, which is our gold standard these days, for a complete response in multiple myeloma. This is a great regimen and a nice win for patients who have NDMM who are transplant ineligible.

Q / The supporting data for the approval in this indication came from the phase 3 IMROZ trial. What is your impression of the findings?

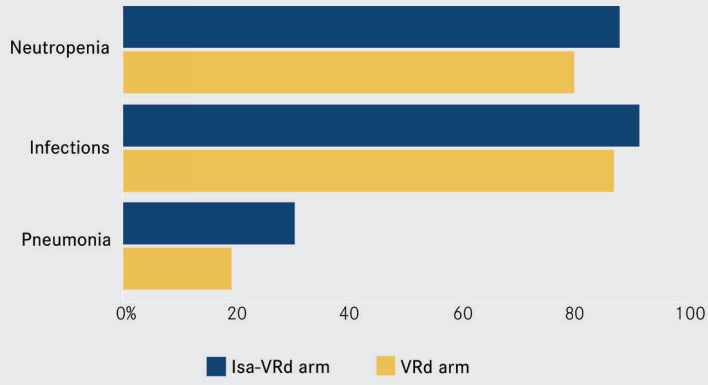
Martin / The phase 3 IMROZ trial did compare the quadruplet of Isa-VRd to VRd. Patients were randomly assigned to 4-drug induction vs 3-drug [induction] and then they received that essentially for 8 to 9 months' worth of therapy. Then [patients] continued on maintenance-based therapy, [including] isatuximab, lenalidomide, and dexamethasone vs what is standard, which is lenalidomide and dexamethasone. It is continuous therapy, and these patients tolerated the therapy quite well.

In fact, there was not a significant safety signal [found with] 4 drugs vs 3 drugs. The quadruplet is quite safe and it is easy to add isatuximab to what we consider a VRd backbone. The patient population was quite large: Over 250 patients received Isa-VRd and 180 patients received VRD. The median age for this group was 72 years. Approximately 10% of them had high-risk disease, and that is what is typical for this older patient population.

When patients were followed for the events of PFS, there was a marked advantage in the quadruplet [Isa-VRd] vs the triplet [VRD arm], where the 60-month PFS in the isatuximab arm was 63% and the 60 month PFS in the VRD arm was 45%, a marked difference. That 63% at 60 months is the longest PFS that we have seen—the longest remission duration of an up-front, newly diagnosed multiple myeloma trial in this transplant-ineligible patient population that has ever

STATS AT A GLANCE

Any-grade treatment-emergent adverse effects



PFS

Not reached: Isa-RVd arm
54.34 months: VRd arm

60-month PFS rates

63.2% Isa-VRd arm

45.2% VRd arm

Isa-VRd, isatuximab, bortezomib, lenalidomide, and dexamethasone
VRd, bortezomib, lenalidomide, and dexamethasone

been published or presented.

This means that patients are going to go more than, on average, 5 years—perhaps it will end up being 6 or 7 years—of remission duration or longer with this combination. That is a huge advantage of this quadruplet vs what we were doing in the past, which was a triplet. It typically was a CD38 plus lenalidomide as a triplet in the past as our standard. This, in my mind, is the new standard based on this high PFS rate.

The investigators of the study did multiple subgroup analyses looking at age and ECOG performance status and whether they had extramedullary disease at the start, what their revised [International Staging System] stage was, or their cytogenetics. In fact, every subgroup that received this therapy benefited from receiving the quadruplet vs receiving the triplet. It is [intended] for all patients who can tolerate a 4-drug regimen [who have] transplant-ineligible multiple myeloma.

The MRD rates were [55%] MRD negative in the quadruplet vs 44% in the VRd arm, a statistically significant advantage. Then the sustained MRD advantage of more than 12 months was 47% vs 24%. [Isatuximab] doubled the sustained MRD results, demonstrating the potency of this quadruplet regimen. Although the OS data are premature, there seems to be, right around the 5-year mark, a separation of the curves. I suspect there will be a survival advantage. It just [indicates] that we should be using powerful combinations like this quadruplet in the front line for patients who have transplant-ineligible NDMM.

Q / What unmet need does this approval help to reduce?

Martin / It is great because in the present, with multiple myeloma, we have so many new drugs and so many novel combinations, but the true unmet need is getting smaller and smaller. One of the unmet needs is the patients who have an early progression from frontline therapy. Because this quadruplet is so potent, we are seeing fewer patients who have early relapse or early progression. It is capturing patients and inducing deep and durable remissions right from the beginning.

The previous combination of the CD38 [antibody plus] lenalidomide and dexamethasone, that triplet was our standard triplet prior to these data on the quadruplet, and that triplet did quite a good job. It had a median PFS of about 60 months. [The quadruplet] is going to eclipse that. Some of the people who would have relapsed even on our most powerful previous triplet will still be in remission on this quadruplet therapy.

The unmet need in the front line is to try to keep people in remission for longer and to induce a deeper and more durable remission. This also enhances the level of patients achieving MRD negativity. In terms of the unmet need for front line, it is deeper and more durable remissions. This checks both those boxes.

Q / How might you see the combination therapy being implemented into clinical practice?

Martin / These data stand out and speak for themselves, especially the safety component of the data. The addition of isatuximab to VRD does not add a significant amount of toxicity, which is great. That means that adding this CD38 antibody to what many people use as their induction regimen is easy, in my mind. It is very

well tolerated. It is not going to enhance significant cytopenia or other [adverse] effects that need to be mitigated. What it is going to do is provide a more beneficial antimyeloma effect.

People will see the safety data as well as the response data and say there is no reason why I should not give this particular patient a quadruplet over a triplet. We just had a myeloma meeting in Brazil, and there was much to do about that discussion of who can tolerate a triplet vs a quadruplet. Many multiple myeloma physicians like myself support the fact that these quadruplet regiments are so well tolerated that, essentially, there are few patients who are frail that we would start with perhaps a doublet or a triplet and try to get to the quadruplet. For most patients—and this involved patients up to age 80—certainly can tolerate this. In my practice, I use it in patients who are over age 80, especially if they are in good shape.

Q / Are there any toxicities or adverse effects associated with the combination therapy that stands out to you?

Martin / In general, if we look at grade 3 treatment-related adverse events [TRAEs], they were very similar in both arms. If we specifically look at the grade 3 events, there was slightly higher grade 3 neutropenia, which we know when [a CD38 antibody] combines with [immunomodulatory drugs], we do see a slightly higher rate of that, but there was not an increased risk of febrile neutropenia.

If we look at overall infections, rates were similar between the 2 arms. If we look specifically at pneumonia, there was a slightly higher risk of grade 3 pneumonia in the Isa-VRd arm vs the VRd arm. Other AEs—neuropathy, and gastrointestinal AEs—are all similar. There was no change in the incidence of secondary malignancies. If you look at events like infections per patient-year— because patients who are on the quadruplet are on therapy longer than the triplet—if you look at infections, and you do it over time, the infection rate in both arms is exactly similar.

There were [slightly] more infections in the quadruplet arm, but patients were on therapy for longer, and the infections can happen anytime while they are on therapy. If you look at, over time, how many infections per week or month, etc, [both arms were] similar. There is no toxicity…that limits the use of these drugs in this population. There are none. It is great. That is the nice signal here.

Q / Beyond this approval, what other developments in multiple myeloma have the potential to change clinical practice?

Martin / That is a big question. I will start with a few. One of the developments is in another isatuximab-based trial. It was the phase 3 BENEFIT trial (NCT04751877) [compared] Isa-VRd vs isatuximab lenalidomide and dexamethasone (Isa-Rd).[4]

This [trial] was the first time we had quadruplet vs triplet [regimens], where the only drug that changed was bortezomib—whether to leave bortezomib out, not leave CD38 out, like all the [other trials evaluating] quadruplets vs triplets. The other advantage was that bortezomib was given in a weekly administration. It was given [subcutaneously 3] out of 4 weeks for the first 12 cycles, and then it was every other week for the next 6 cycles. Bortezomib continued for 18 months.

This is also the first trial where bortezomib continued for this long as induction-based therapy. Usually, bortezomib is completed by the first 8 to 10 months, mostly because of neuropathy. This was to do it weekly to see better. I was anticipating that there would not be much difference between the quadruplet vs the triplet, but that is why we do the trials. The surprising result was that the quadruplet of Isa-VRd vs Isa-Rd showed a significant advantage for the primary end point [which] was MRD negativity. There was a deeper and more durable response based on MRD negativity in the Isa-VRd arm vs the Isa-Rd arm.

The bortezomib, maybe even at weekly dosing, 3 out of 4 weeks for the first 12 months, showed a significant advantage and that trial only has 24 months of follow-up. We are not close to the median PFS just yet. The median PFS, with these regimens, looks like it is going to be over 60 months, which is amazing. We are going to need 2 or 3 more years of follow-up to see what the difference in the PFS is in those 2 arms. That changed my practice because now I use [a CD38 antibody] plus bortezomib weekly, 3 out of 4 weeks, plus lenalidomide and dexamethasone.

Q / Is there anything else related to the FDA approval or the IMROZ trial that you would like to highlight?

Martin / For people who are practicing out there, and they are going to choose their next regimen, a quadruplet regimen is tolerable for the far majority of patients with multiple myeloma, whether they are transplant eligible or ineligible. The combination of Isa-VRd, especially with bortezomib given on the weekly 3-out-of-4-week dosing regimen, is well tolerated and has the ability to produce deep and durable remissions.

There [are not] many exclusionary comorbidities that prevent patients from getting these therapies. Potentially, they have diabetes, they have bad baseline neuropathy, or they have a bad cardiopulmonary reserve—for those patients you might want to start on a doublet or a triplet and add in a medicine, as they are tolerating it. Again, for the far majority, the data from trials like IMROZ prove that quadruplets are the way to go. ■

FOR REFERENCES, VISIT
cancernetwork.com/11.24_Martin

Assessing NP Roles in Talquetamab Treatment for Multiple Myeloma

Samantha Shenoy, MSN, NP
Nurse Practitioner, University of California San Francisco Health

CancerNetwork spoke with Samantha Shenoy, MSN, NP, a nurse practitioner at University of California San Francisco (UCSF) Health, about the role she plays when treating a patient with multiple myeloma who is undergoing treatment with talquetamab-tgvs (Talvey).

Shenoy outlined the importance nurses play in communicating to providers the presence of adverse effects (AEs) related to talquetamab treatment, as well as having responsibility for helping patients manage symptoms. She identified common treatment-related AEs and touched upon cytokine release syndrome (CRS) treatment and preventive measures. Additionally, Shenoy emphasized educating patients on AE management before starting talquetamab to foster awareness.

Furthermore, guidelines for monitoring patients were discussed, with an emphasis on weight loss and taste changes. She subsequently gave her opinion on the future of talquetamab, particularly as a combination therapy. Shenoy concluded by highlighting how AEs can be mitigated, including decreasing the frequency of the drug once patients have achieved a response to therapy.

Q / What is the role of the oncology nurse during talquetamab treatment? Why is this patient-nurse-provider communication so essential during this treatment process?

Shenoy / There is the inpatient component and outpatient component. The patients first receive step-up dosing in the hospital, and during that time, the bedside nurses are critical in monitoring these patients for signs and symptoms of CRS or potential neurotoxicity. They are critical in that regard. Then with talquetamab specifically, because we know it has these very unique GPRC5D-related AEs, nurses can be essential in identifying patients who might be at a higher risk of weight loss.

For example, in my experience, patients can begin to have dry mouth and taste changes even during step-up dosing in the hospital. Nurses can play a key role in communicating to a provider, "Hey, this would be a patient who would benefit from seeing [a dietitian]." [Nurses] are right there at the bedside. I have a handout that I made for our patients. Nurses can help go over that handout with patients. One of the things that we like to do at UCSF is educate patients before AEs happen before they are admitted, or while they are in the hospital having step-up dosing.

If they have not [received] that education, nurses are crucial in spending time with them, talking about the different ways they can manage some of the AEs. In terms of communication with the provider, [nurses relay] if they have CRS, any signs of neurotoxicity, and anything related to GPRC5D-associated AEs. In the same way [nurses help for] inpatient, they can do that for outpatient, too. Our nurses are fantastic, and they bring to the provider awareness about patients who are struggling with some of the taste changes or swallowing.

Q / What are some of the AEs most associated with talquetamab treatment, and how are they managed?

Shenoy / Talquetamab [AEs can be] branched into 2 categories: oral and dermatologic. In terms of oral AEs, there are taste changes, dry mouth, and sometimes difficulty swallowing. Due to these oral AEs, patients may experience weight loss. Patients may voice, especially in the first cycle, that their mouth is sore, and so things like spicy food or citrus can irritate it.

In terms of dermatologic AEs, some of the main things we can see are skin rashes—usually that is in the first cycle—and palmar-plantar desquamation. [There] can be extreme peeling of the palms, the hands, and the soles of the feet. Then [there are] nail changes. Patients can have nail ridging or fragility—most patients' nails do fall off at some point. There can be separation of the nail plate from the nail bed—onychomadesis—where you can imagine if your nail is starting to separate as you are trying to comb your hair or wearing a wool sweater, your nails are getting caught on that. That can be challenging for patients as well.

Those are the main [AEs] that [come to mind] with talquetamab. Of all those AEs, the ones that are the most challenging in terms of quality of life are the taste changes. It is a broad spectrum. Some patients completely lose their taste. Some

patients can only taste sweet things, or for some patients, everything tastes bitter or salty. It is challenging, and it can last for several weeks. I mentioned dry mouth as well. That can be a big one that people do not always talk about, but that can be difficult for patients, especially at night when they are trying to sleep. I have had patients who have had trouble sleeping because their mouth is so dry.

Q / How is CRS managed, and what protocols does your institution have to prevent or treat severe CRS?

Shenoy / We have a protocol that we created for bispecific antibodies specifically at our institution, that we follow for management grade 1 to 4 CRS. We have different interventions. The first sign of CRS is generally fever, but it can manifest in different ways. We give acetaminophen [Tylenol] and tocilizumab [Actemra] with the first fever. If a patient has a second fever, we will give them steroids, like dexamethasone. We like to address it quickly. If someone is having associated hypotension, we will give them fluids and other supportive care for any other signs or symptoms of CRS.

We follow our CRS management algorithm closely. It will outline, "If it is grade 2 [or grade 3, etc], what are interventions?" We nip it in the bud quickly. Usually, it is not an issue.

Q / Are there any neurological effects that are associated with treatment?

Shenoy / There can be neurotoxicity associated with bispecific antibody therapy, but it is rare and it occurs in a small percentage of patients. We, at our institution, do [immune effector cell encephalopathy (ICE)] scores every 12 hours. That is another role that nurses play… doing those ICE scores with patients and watching them closely. Yes, it can occur. Is it an issue? Generally, not with bispecifics. A small percentage of patients experience neurotoxicity.

Q / Are there any guidelines or monitoring parameters that patients and clinicians should abide by when receiving this treatment?

Shenoy / We are generally, as with any other bispecific, looking at laboratory values and vital signs. We are keeping an eye out for any cytopenias, which generally, if we do see that, are going to be in the first few cycles, and then over time it gets better. I would say the biggest difference with talquetamab that we are looking out for, that is different from other bispecifics, is the unique oral and skin AEs we see with the drug. That is where I would say it is very different from teclistamab-cqyv (Tecvayli) or elranatamab-bcmm (Elrexfio).

At every visit, I check in with my patients about how much they are eating and I also monitor their weight. The other dermatologic AEs are manageable. Where we want to be careful is to make sure someone is not having profound weight loss. That is the [main] parameter for [talquetamab]. People might have taste changes, but the question for me is always, "Are you losing weight; is it getting to the point where it is a concerning amount of weight loss?"

Q / Some clinicians have tried different methods of how to overcome taste changes. Have you tried any methods, or do you have any methods for addressing taste changes?

Shenoy / I've been working with patients who have been receiving talquetamab for about 4 years now. I had great dietitians who worked with my patients and gave me a lot of the tips that are now in my handout. Within our institution specifically, we worked with patients to find different techniques to address different taste changes or dry mouth.

For example, if a patient was saying something tastes too salty or sweet, we have different recommendations for each patient's specific taste alterations. [What] I learned throughout this process is we have to address dry mouth because, without saliva, you are not going to be able to taste very well. Some interventions for dry mouth are lozenges, tart candies such

General Lifestyle Recommendations for Patients Receiving Talquetamab

Through years of experience, Samatha Shenoy, NP, MSN, has curated a sheet dedicated to improving the quality of life for patients with multiple myeloma who are receiving talquetamab-tgvs (Talvey). Each section is divided into specifically what the patient may be experiencing and measures on how to overcome it.

These strategies have been tried by patients and recommended by colleagues such as dietitians, dermatologists, and other health care providers. Trying one of these lifestyle recommendations may improve the treatment experience.

Shenoy would like to note that this is not an all-encompassing list and is updated frequently based on feedback from patients and colleagues on what works best.

Taste Adverse Effects

Management Strategies for Taste Alteration (Dysgeusia, Ageusia, Hypogeusia)

- Practice good oral hygiene such as brushing your teeth 2 times per day with a gentle toothbrush and see your dentist at least 2 times per year.
- Use baking soda and salt rinses before and after eating to clear taste buds.
  - Recipe: 1 tsp of baking soda and 1 tsp of kosher salt per quart of water
- Refer to Rebecca Katz's FASS (fat, acid, salt, sweet) formula to balance flavors (Rebeccakatz.com).
- Eat smaller portions on a small plate; also think about food presentation.
  - Food that is presented in a visually pleasing manner can stimulate saliva and appetite.
- If taste alteration is not better despite following these recommendations, and the multiple myeloma is responding to treatment, discuss further with your medical team as they may consider modifying the dose of talquetamab.

- **AVOID: If the mouth, tongue, or throat is sore, avoid adding types of vinegar, citrus, pickled foods, hot spices, alcohol, or tomato-based foods to your diet.**

If foods taste metallic or bitter:

- Metallic
  - Add olive oil, lemon, and maple syrup.
    - These can be combined to use as much as needed.
  - Tart foods can mask a metallic taste; try adding vinegar, citrus, or pickles to meals.
  - If meat tastes metallic, try alternative protein-rich foods such as nuts, nut butter, tuna/egg salad, white flaky fish, protein shakes, yogurt, cottage cheese, beans, or tofu.
- Bitter
  - Add sweet fruits, honey, or syrup to foods and drinks.
  - Add fresh or dried herbs (rosemary, thyme, basil, oregano, tarragon, cilantro, mint, and dill), onion, garlic, and spices (cinnamon, cumin, paprika, chili powder, and turmeric).
- Either taste
  - Eat foods cold or at room temperature.
  - Suck on sugar-free lemon drops, mints, or gum.

- **AVOID: Metal utensils and canned foods/drinks.**

If foods taste blunted, bland, or like cardboard:

- Add lemon, a pinch of sea salt, and a few drops of maple syrup.
  - These can be combined to use as much as needed.
- Add citrus (lemon or lime), vinegar, herbs, spices, or pickled items.
- Marinate foods in wine, Italian dressing, lemon juice, or soy sauce.
- Marinate meats or fish in sweet juices, fruits, wine, acidic dressings, lemon juice, soy sauce, or teriyaki sauce.
  - After marinating and cooking, add parsley, olive oil, sea salt, garlic, and lemon.
- Use sea salt instead of iodized salt.
- Blend fruit into shakes, ice cream, or yogurt.
- Try frozen fruits such as whole grapes, mandarin oranges, watermelon, or cantaloupe.
- Add a few drops of honey or maple syrup to sweet foods.
- Add texture by including chopped nuts for crunch, nut butter, or olive oil for a creamier texture.

If foods taste too sweet:

- Season foods with tart flavors such as lemon, citrus, vinegar, and pickled items.
  - Add a squeeze of lemon to fruit juice.
- Add plain yogurt or buttermilk to decrease the sweetness or increase the tartness.
- Add coffee or unused finely ground decaffeinated coffee to sweeter oral supplements, such as Boost or Ensure.
- Dilute beverages with either water, ice, milk, or unsweetened plant milk.
  - Plant milk will help to add calories.

Management Strategies for Dry Mouth (Xerostomia)

- Stay well hydrated. This loosens thick saliva and keeps the mouth moist. Sip on clear, hydrating beverages throughout the day.
  - Sage Toothette Oral Care Mouth Moisturizer is helpful to use at night because you can coat the oral mucosa/tongue/lips.
- Stimulate saliva production by squeezing lemon/lime in water or eating an orange slice before meals. Tart foods/drinks like lemonade or cranberry juice also increase saliva.
  - Try mouth lozenges
    - XyliMelts: helpful at night, adhere to the gumline and keep the mouth moist
    - Biotene
    - TheraBreath, or ACT (dry mouth lozenges)
  - Saliva substitute sprays (Biotene)
  - Biotene toothpaste
- Sugarless gum or sugar-free hard candies (citrus-flavored candies work best)
- Soft, bland-tasting foods that are cold or room temperature such as fruits and vegetables that have been blended; well-cooked, tender beef, chicken, or fish; and thin, moist cereals
  - Add broth, soup, or gravy sauces to moisten foods.
  - Dip or soak food in liquid.
- Suck on frozen fruit pops, ice chips, or sorbets.
- Oral care: Baking soda/saltwater rinses 3 to 5 times per day; use a soft brush plus toothpaste after each meal.
- Swish and spit with club soda or lemon-lime soda to help loosen and remove dry or thick saliva.
- Use a cool-mist humidifier to moisten air, especially at night.

- **AVOID**
  - **Caffeinated and alcoholic beverages**
  - **Smoking and chewing tobacco**
  - **Alcohol-based oral rinse**

Management Strategies for Difficulty Swallowing due to Dry Mouth (Dysphagia)

- Cut foods into bite-sized pieces.
- Consume small, frequent meals/snacks to get enough calories.

- Eat soft foods or foods that can be cooked until tender.
  - Mashed potatoes, squash, ground beef/turkey, soups, smoothies
- Eat soft foods that are rich in protein.
  - Cottage cheese, yogurt, milk, cheese, custard, eggs, ground chicken/turkey/beef, tofu, beans/peas/lentils, nuts/nut butter
- Add foods high in calories.
  - Drizzle oil into soup, add creamy nut butter to hot cereals/smoothies, add avocados; high-calorie liquids like gravy, milk, or broth instead of water.
- Use a blender or food processor to puree food.
- Add sauce, gravy, or oil to meals to make swallowing easier and add calories.
- Drink liquids through a straw; sit upright while eating, sip liquids with solids.

Nutrition

Management Strategies for Weight Loss

- Consume small, frequent meals/snacks at least every 2 to 3 hours to get enough calories.
  - Carry snacks with you at all times.
- Drink liquids *after* meals to avoid fullness with meals.
- Consume nutritious liquids.
  - Smoothies, supplement drinks, milk, or 100% juice
  - Limit foods and beverages low in calories.
- Consume protein, plant or animal, with each meal/snack.
  - Eat fatty fish (salmon, sardines, black cod) 2 to 3 times a week.
- Choose nutrient-dense food or liquids; calorie-boosting food with each meal.
  - Olive oil, avocado, nut butter, or hummus
- Try oral nutrition supplements.
  - Kate Farms: Organic Plant-Based Nutrition
  - Order through Amazon or Kate Farms website: https://www.katefarms.com
- Movement and physical activity may help to stimulate appetite.
- Discuss with your medical team whether the degree of weight loss warrants changes in medications affected by weight loss (hypertension, diabetes, thyroid disorder).
  - Discuss introducing an appetite stimulant with your medical team.
  - Your medical team may consult nutrition experts to help with methods to combat weight loss.

Dermatology

Management Strategies for Skin Toxicities

- Apply heavy moisturizers such as CeraVe, Vanicream, Eucerin, or Cetaphil within minutes of getting out of the shower every day.
  - Take lukewarm or cold showers.
- For skin peeling, use AmLactin (ammonium lactate 12%) plus heavy moisturizers and topical steroids 2 times per day.
  - Try triamcinolone and then clobetasol if you need a stronger steroid.
- For significant dryness, apply Aquaphor/Vaseline to hands, feet, anywhere needed.
  - Wear cotton gloves/socks at least 15 to 30 minutes after applying to maximize absorption (overnight is best).

Management for Rash

- For a rash, topical steroids can be used or you may need oral steroids for more severe rash. Discuss first with your provider.
- For itchy skin, manage with proper moisturization and use heavy moisturizers listed above.
  - Topical steroids 2 times per day for itchiness
  - Should not be used for face/folds/beyond 3 months without further dermatology evaluation given the risk of striae/atrophy
  - Sarna for more diffuse itchiness; keep refrigerated to maximize effect
  - Oral antihistamines for itchiness can be found over the counter; discuss with provider.
  - Colloidal oatmeal baths for itching/rash/dry skin
- Fissures on hands/feet: super glue to close skin
- For sloughing skin/pain: a small amount of Voltaren gel and Epsom salt baths
- Good hydration with water and noncaffeinated, nonalcoholic beverages
- Your medical team may consult with the dermatology department if concern for infection or if interventions are not helpful.

- **AVOID: Soaps with perfumes/dyes**

Management Strategies for Nail Toxicities

- Clear nail polish or nail hardeners
  - Try OPI Nail Envy or Mavala
- Cuticle oil/vitamin E oil to keep cuticles from drying out. Frequent application of ointments/balms like Vaseline/Aquaphor
- Keep nails short and clean
  - File to smooth the edges and corners of the nail plates
  - Wear Band-Aids to prevent loose nails from catching
- Wear nail gloves/finger cots
  - Sold on Amazon.com
  - Consider full hand gloves when washing hair
- Monitor for infection
  - Symptoms include pain, swelling, and tenderness around the nail; report to your medical team.
- Topical steroids for peeling around nails
- Biotin may be helpful in strengthening nails.

- **AVOID:**
  - **Tight shoes; wear soft socks**
  - **Frequent/long durations of water immersion**
  - **Activities that can create or worsen nail damage (that put pressure/force on nails)**

The creation of this guide was a collaborative effort. Special thanks to my dermatology and dietitian colleagues at UCSF for helping to curate this list.

as lemon/citrus, and good hydration. There [are many] dry mouth lozenges like XyliMelts.

Colleagues have asked me if they should be consulting nutrition for every patient receiving talquetamab. I don't think that is necessary, but it is important to consult nutrition for patients who are at high risk of weight loss. I do think these patients specifically should be teamed up with a nutritionist from the very beginning.

In the handout that I made, one of the recommendations is if something tastes like cardboard, have certain spices, etc, at hand when you are eating at the table, or things you can add to it. Alternatively, if something tastes metallic or bitter there are recommendations for that. By having this handout, patients can have tools and options at their disposal, so then when taste changes occur, they will be ready to address some of the challenges that are associated with this treatment. That helps empower patients.

If you can educate patients before they have even started, then they will have the tools they need. I spend time going through the handout with them and I try to tease out what the taste alteration is.

I spoke with a woman named Rebecca Katz, a culinary translator and an expert on the role of food in supporting optimal health, who has worked for years with patients with cancer who have had taste alterations. Something that I learned from her was focusing on food presentation. We often miss how important that can be. When I go to a restaurant and something looks good, my mouth starts to water. I want to eat it because it is plated well; it looks beautiful. One of the things she said was, "I talked to patients about making each meal an event." Choosing your nicest dishes, laying it out, making it an event, putting garnishes on the side, doing things that make you want to eat the food.

Also, when you do not want to eat and do not have an appetite, do not put a big plate of food in front of you. Do small amounts so that it does not feel overwhelming. Another cool tip I learned from her is when you cannot taste as well, texture takes on a whole new level of importance. For example, think about adding nuts, so even if you cannot taste as well, if things taste crunchy, that can bring some satisfaction to the eating experience. If you cannot taste as well, texture can add some enjoyment. There are all these little tips that can help with the whole eating experience.

Q / What characteristics do these patients have that put them at risk for significant weight loss?

Shenoy / I would say patients who have a low body mass index [BMI], or who have struggled with gaining weight, or who do not have a great appetite to start with. If I know that weight has been an issue with them in the past already, those are the patients I would think about.

Q / Where do you see this agent headed?

Shenoy / Talquetamab is an excellent agent. What I try to tell patients from the beginning is about the efficacy of the drug, because it is impressive. On trial, [many] of these patients already had BCMA-targeted agents. They had several lines of therapy already. I had a patient who had been living with multiple myeloma for 20 years, and she has now been on this drug for about 3 years. When you think about it, that is impressive.

Combinations are the wave of the future with talquetamab. Multiple myeloma is all about combining drugs. One of the trials that I was on, specifically, was the phase 1 TRIMM-2 trial [NCT04108195], where you combine talquetamab with daratumumab [Darzalex]. That is the best way to use these drugs as combination therapies.

Q / Is there anything else that you would want to highlight from our discussion, or maybe something we did not touch on?

Shenoy / I have seen patients who have had many lines of therapy with limited options left and are now achieving deep and durable responses with talquetamab. I feel passionately about educating patients on management of AEs so that they have a better quality of life. I can imagine how frustrating it is not to be able to taste, to have dry mouth, and to have the skin/nail toxicities associated with talquetamab. The toxicities are manageable for most patients with the interventions I have shared, and I encourage patients to hang in there as their symptoms/AEs will improve over time. ■

Reference
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BREAST CANCER

Implementing a Multidisciplinary Lifestyle Medicine Clinic for Cancer Survivorship

ABSTRACT

Background: Lifestyle medicine (LM) is increasingly recognized in cancer survivorship guidelines. The 6 LM pillars are physical activity, a predominantly plant diet, restorative sleep, stress management, avoiding risky substance use, and social connections. Through a multidisciplinary LM clinic in oncology, we describe 2 illustrative cases and the implications for broader implementation and dissemination of this clinic model.

Methods: In the multidisciplinary LM clinic in oncology, patients meet with an American College of Lifestyle Medicine (ACLM) board-certified physician or nurse practitioner, a registered dietitian, and, as needed, a clinical psychologist, a psychiatrist, an obesity medicine physician, a physical therapist, and/or a rehabilitation medicine physician.

Results: Patient 1 met with the physician, the registered dietitian, the psychologist, and an affiliated cancer center psychiatrist. Patient 2 met with the nurse practitioner and the registered dietitian. The 2 cases presented illustrate the diversity of LM pillars and strategies to increase health and well-being post cancer treatment.

Conclusion: This paper details the model of implementation of a novel oncology-focused multidisciplinary LM clinic and the clinical focuses of 2 diverse patients. The LM needs of cancer survivors seeking lifestyle consultation are growing, and awareness of the benefits of LM for this population can enhance the quality of life for patients who are survivors of cancer.

Keywords: lifestyle medicine, cancer, survivorship, clinical program, case studies

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There are currently over 18 million cancer survivors in the US, with this population projected to increase to 26 million by 2040.[1,2] As the US population ages and cancer survival rates increase, there is a growing need to address the complex care needs of this population.[2] Cancer survivorship is often a time of heightened worry about ending treatment, fear of cancer recurrence, and concerns about the health consequences of treatment.[3] Awareness of the critical importance of healthy lifestyle behaviors in the survivorship period has grown such that authoritative bodies such as the American Society of Clinical Oncology (ASCO), the American Cancer Society (ACS), the NCCN, the CDC, and the American College of Lifestyle Medicine (ACLM) now recommend incorporating lifestyle medicine (LM) education and practice into the continuum of cancer care.[4-8] ACLM defines the field of LM as the "therapeutic use of evidence-based lifestyle interventions to treat and prevent lifestyle-related diseases in a clinical setting."[8] The 6 pillars of LM are physical activity, a plant-predominant diet, restorative sleep, stress management, avoidance of risky substances, and social connections, all of which are important components of cancer survivorship.[7,9-13]

Guidance around each LM pillar for cancer survivors is as follows:

1. **Physical activity:** Engage in 150 to 300 minutes per week of at least moderate-intensity, aerobic activity and incorporate strength training.[5]
2. **Nutrition:** Eat a whole-food, predominantly plant diet, with a variety of fruits, vegetables, and whole grains, and limit consumption of red meats and processed meats.[5]
3. **Sleep:** Focus on achieving quality, restorative sleep and implement strategies to address sleep disturbance and insomnia.[14]
4. **Stress management:** Learn strategies such as eliciting the relaxation response and mindfulness-based stress reduction.[10,11]
5. **Avoidance of risky substances:** This includes tobacco, alcohol, and other substances.[10]
6. **Social support:** Build and enhance social connections to improve outcomes for this population.[15]

Addressing these 6 pillars in the survivorship period can improve quality of life and physical functioning and, in many cases, reduce the risk of recurrence and the development of additional cancers.[7,9-13]

Though awareness and access have grown, few clinics have been established to address the LM needs of people in cancer survivorship.[16] Accordingly, our team of oncologists and supportive oncology clinicians developed a multidisciplinary LM clinic for cancer survivors. The development of this clinic, the first known of its kind within supportive oncology, has been previously documented.[17] The present case studies and discussion are based on patients seen in the multidisciplinary longitudinal clinic within the past year (2023-2024).

Methods

The present multidisciplinary clinic is conducted within the cancer center of an academic medical center in a major US metropolitan area. The clinic operates virtually via Health Insurance Portability and Accountability Act–compliant Zoom. The structure has evolved since its launch in 2020 from a single-day, in-person consult clinic to an insurance-billed, electronic medical record–integrated longitudinal clinic.[17] Patients can be referred through a member of their oncology care team or a primary care provider, or be self-referred. Patients can be anywhere in their cancer trajectory, and all types of cancer diagnoses are seen.

The first appointment is with the ACLM-certified physician or nurse practitioner. During this visit, a comprehensive medical history is taken and patients are screened for limitations on physical activity using the Physical Activity Readiness Questionnaire.[4,17] The 6 pillars of LM are used as a foundational structure for the initial visits. Patients are encouraged to identify the topics within LM most important to them as a focus of the consultation (eg, exercise limitations or recommendations). Patients may follow up with the physician or nurse practitioner on a semiregular basis or as needed. Currently, there is no deadline or prescribed end point to the follow-up visits, although this may come about if clinic volume continues to increase.

Patients can then be referred to other members of the LM team or various programs or specialists in the hospital system as appropriate. Most commonly, patients are referred to an oncology-registered dietitian for a comprehensive nutrition assessment and personalized recommendations. Nutrition follow-up can be further scheduled if the patient has specific nutrition-related goals. Follow-ups are scheduled as needed following the initial nutrition consultation. If psychosocial concerns, stressors, or difficulty with behavior change planning are identified, a referral is placed to the clinical psychologist who sees patients for short-term cognitive/behavioral therapy (eg, 3-16 sessions). Additional referrals to obesity medicine, stress management groups, psychiatry, physiatry, and physical therapy are made as needed, based on the needs and goals identified in the visit. A 6-session virtual group visit program based on the 6 pillars of LM was developed by members of this team to offer ongoing education and skills for lifestyle education and behavior change skills. The virtual group visits offer a structured, longitudinal LM model to increase access for patients seeking more general LM support and education, as a separate resource, beyond the individual consultation visits. The curriculum for the group visits is based on the established PAVING The Path to Wellness curriculum,[18,19] to which patients with breast cancer can also be referred. The groups are offered on a rolling basis, and participants are encouraged to attend all 6 visits.

This article will present 2 cases seen by members of our multidisciplinary team, demonstrating the range of lifestyle medicine interventions that can improve health and quality of life for survivors of diverse cancers.

CASE 1

Young man with diagnoses of seminoma, alcohol use disorder, obesity, neuropathy, OCD, and ADHD

LM specialists involved: LM physician, psychologist, dietitian, psychiatrist

Background: The patient is a 33-year-old, single, White man who lives alone, has a bachelor's degree, and works in the field of art/music production. He initially presented to a local emergency department (approximately 30 miles from our hospital: Mass General Brigham) but transferred due to needing specialty care unavailable at his community hospital. He ultimately presented to our hospital's emergency department with paraplegia and bladder/bowel incontinence and he was found on imaging to have evidence of spinal cord compression secondary to an epidural tumor at T10-12. The patient underwent a thorough workup and was diagnosed with stage IIIC seminoma. The patient proceeded with aggressive treatment for curative intent, with a left orchiectomy and 4 cycles of chemotherapy (bleomycin, etoposide, and cisplatin). Following the completion of therapy, he had no evidence of disease. He was subsequently referred to the multidisciplinary cancer center LM program to address further strategies to optimize his health and outcome.

Following an initial assessment with the team physician, who focused on the 6 pillars of LM outlined above, the patient revealed that he had alcohol use disorder, untreated attention-deficit/hyperactivity disorder (ADHD, inattentive type), and obsessive-compulsive disorder (OCD). His body mass index at the time of diagnosis was in the obese range and he described difficulty with healthy meal planning and regular exercise. After his LM consultation, he was referred to our team's psychologist and oncology-registered dietitian to address these health challenges. As he progressed through his recovery, he was able to better engage with healthy lifestyle medicine practices, including improving his dietary habits, losing weight, and increasing exercise, while remaining sober.

Pillars 1 and 2 of behavioral therapy: physical activity and nutrition. Following his cancer treatment, the patient was unable to engage in his preferred physical activities due to peripheral neuropathy in his feet. This symptom was reviewed by his oncology team. The neuropathy symptoms diminished over time with increased physical activity and no additional medical intervention. Using a cognitive behavioral therapy approach with the team's psychologist, he explored much about his cancer journey, including its impacts on his values of working vs having time to pursue his creative activities. Over time, he decided to cut back on his work hours, which allowed him to engage more in physical activity and healthy eating. During the 1 year of monthly therapy sessions, specific, measurable, achievable, relevant, and time-bound (SMART) goals were set around his physical activity (eg, skateboarding, working at a physically demanding job, reducing sedentary time). During the later stages of his time in the clinic, he met with the team's registered dietitian. He was counseled about cutting back on processed and convenience foods and increasing fruits, vegetables, and water intake. He reported making all these changes without major barriers and was pleased with his progress.

Pillars 3 and 4 of behavioral therapy: avoiding risky substances and stress reduction. Regarding his alcohol use, at initial intake, he was drinking 4 to 6 beers per night, often socially, to help fuel his music/art production and to mitigate underlying anxiety symptoms. He had quit smoking cannabis during his cancer diagnosis but continued to use cannabis edibles several nights per week. He felt that alcohol use was impacting his sleep, weight, motivation, and cognition. Further, he came to the clinic with diagnoses of OCD and ADHD, neither of which was being treated with medications or therapy at the time. Therapy began to focus on the benefits of abstaining from substance use from a motivational interviewing standpoint, as well as considerations for engaging with psychiatry for medication management of his mental health conditions. After 4 months of therapy, he was amenable to speaking with our cancer center psychiatrist. She helped him start an anxiolytic and a stimulant, which are still being used to excellent effect.

Pillars 5 and 6: sleep and social connections. Though these were not primary areas of concern for this patient, these topics were discussed during therapy. His sleep was disrupted because of his alcohol use and he reported difficulty waking up for work. Upon abstaining from alcohol, his sleep improved dramatically, impacting his energy and work functioning. He has strong family support and a large circle of friends; however, his social life largely surrounded drinking alcohol. Upon his sobriety, he has been able to uncouple socializing from drinking.

Outcomes: The patient has been abstinent from alcohol for the past 7 months, with appreciable improvement in sleep and energy and without experiencing cravings (new diagnosis: alcohol use disorder, mild to moderate, in early remission). He minimizes socialization built around alcohol and finds intoxication undesirable to be around. He continues to use cannabis edibles several nights per week. He continues to find satisfaction with his consolidated part-time work hours, with improved financial and mental (stress) outcomes, and he pursues his art and music with great motivation. He has lost 50 lb since abstaining from alcohol, which he attributes to reduced fluid retention, his adoption of an active lifestyle, and decreased intake of processed foods. His OCD symptoms are greatly reduced, to the point of resolution, and he can find meaning and direction in his work and creative activities: "I wake up looking forward to the day."

CASE 2

Middle-aged female survivor of breast cancer and, with impaired lifestyle health behaviors

LM specialists involved: LM nurse practitioner, dietitian, physical therapist

Background: This patient is a single, 46-year-old, White woman who is single, has her master's degree, and works doing freelance work, with a prior history of localized melanoma and a recent diagnosis of early-stage estrogen receptor–positive, HER2-positive invasive ductal carcinoma of the breast. She also carries a *PALB2* mutation. The patient underwent lumpectomy followed by adjuvant chemotherapy with paclitaxel plus trastuzumab followed by radiation, and she then completed a full year of trastuzumab therapy. She was prescribed adjuvant endocrine therapy with tamoxifen.

At the time of her breast cancer diagnosis, she noted work-related stress: She was finishing a book manuscript and the time required to do so led to a reduction in her self-care practices, which included regular exercise (eg, marathon training) and an overall healthy diet. To save time, she ordered takeout food 3 days a week, skipped meals, worked late, slept less, decreased her physical activity, and experienced increased stress. Her diagnosis of breast cancer and subsequent treatment added to her stress levels and she also experienced fatigue, which further stalled her return to her healthy lifestyle behaviors. Her oncology social worker referred her to the multidisciplinary cancer center LM program to help her learn strategies to aid in her recovery, and provide a comprehensive discussion about healthy lifestyle behaviors.

In her initial visit, she met with an oncology advanced practice provider (APP) who is ACLM certified as an LM practitioner. At the time of the visit, the patient had been undergoing radiation therapy but had begun to feel better after completion of adjuvant chemotherapy and had been taking some steps to improve her health habits. The LM plan included goal setting in each of the 6 LM pillars.

Pillars 1 and 2: physical activity and nutrition. The patient reported starting to increase her exercise activities, though she noted some discomfort and tightness in the shoulder and chest wall likely related to her surgery. The LM APP referred the patient to physical therapy to address postsurgical pain and tightness. The ACS exercise guidelines for survivors of cancer were discussed. She set an exercise goal to build up to and maintain a weekly exercise regimen of at least 3 days of moderate to vigorous physical activity per week and to return to a weekly yoga class. She was also referred to an oncology-registered dietitian for a comprehensive nutrition evaluation and counseling. They worked together to help her learn how to prepare healthy meals and resume a more regular eating pattern that suited her energy and nutrient needs.

Pillars 3 and 4: avoiding risky substances and stress reduction. This patient reported a history of depression, but her mood was stable at the time she was seen in the clinic. She was followed by an outside therapist and an oncology social worker. She chose to incorporate short meditation and breathing practices into her daily routine to further reduce stress. She reported rare alcohol use, no tobacco use, and occasional cannabidiol (CBD) use. Given the questions she had about CBD, she was referred to a cannabis therapeutics physician to further explore the safety and use of CBD/cannabis for symptom management.

Pillars 5 and 6: sleep and social connections. The patient had begun taking steps to improve sleep hygiene practices to reduce the use of cannabis as a sleep aid. She reported difficulty "sometimes" falling asleep but did not meet the criteria for insomnia. She aimed to return to her previously effective sleep hygiene regimen with a goal to reduce screen use at bedtime. For social support, she reported close friendships, though her family did not live close by. She acknowledged some challenges maintaining certain friendships while undergoing treatment but overall, noted she was navigating this well with helpful input from her oncology social worker. This pillar was not a focus of her work in the LM clinic.

Outcomes: Over time, the patient set a goal to resume distance running. To reinforce her knowledge about the importance of a healthy lifestyle after cancer, motivation, and peer support, she was referred to the LM Group Visit Program and completed all 6 shared medical visits. Fifteen months after her initial LM consultation and completion of the LM Group Visit Program, she has resumed running 3 days per week without pain, has improved and maintained healthy sleep habits, and is practicing stress reduction with meditation on most days. She has transitioned to a whole-food, plant-based diet and plans to train for another marathon within the next year. In reflection, she noted the power of the diversity of LM interventions making the biggest impact. She reflected on her improved well-being from a holistic perspective: "Cancer is a complicated web of factors, and you can't sharp-shoot [1 single pillar of LM] to mitigate your risk."

Discussion

The 2 patient cases presented here demonstrate the benefits of incorporating broad and diverse LM tools in oncology supportive care. Both patients benefited from a multidisciplinary approach with a focus on education about the 6 pillars of LM and coaching to help them with behavior change. Case 1 focused on a 33-year-old man with stage IIIC seminoma. At the conclusion of his aggressive treatment, he had no evidence of disease. However, he had numerous other medical issues that needed to be addressed in the survivorship phase of his care to reduce his risk of future health complications. His referral to the LM

clinic enabled him to access a multidisciplinary team that offered expertise in behavioral health so he could address his alcohol use disorder, weight, neuropathy, OCD, and ADHD.

Case 2 focused on a 46-year-old woman with a history of early-stage, estrogen receptor–positive, HER2-positive breast cancer and localized melanoma. Due to the demands of treatment for her breast cancer, and other stressors, she had moved away from her prior commitment to a healthy diet and regular physical activity, and she noted severe fatigue and difficulty readopting healthy lifestyle behaviors. Her referral to the LM clinic enabled her to access a different scope of the multidisciplinary team, which included expertise in nutrition and physical therapy, as well as the LM Group Visit Program, so she could develop her own SMART goals and improve her health behaviors.

These case studies illustrate the benefits of enhancing care for cancer survivors by incorporating multiple tools from LM. Both patients derived great benefits from an initial individualized assessment in our LM clinic and were referred to programs and specialists within our hospital system/cancer center. These referrals included treatment with an oncology registered dietitian, a psychologist with expertise in behavior change, a physical therapist, a psychiatrist, a social worker, and other specialists. Our program also facilitates referrals to obesity medicine, stress management groups, and physiatry, among others.

Key elements of survivorship care include monitoring for disease recurrence, addressing the medical and psychosocial consequences of cancer treatment, and promoting health with lifestyle interventions that may improve quality of life, reduce the risk of other chronic diseases, and decrease the risk of cancer recurrence in this growing population.[2] Addressing lifestyle factors from the time of diagnosis, during treatment, and beyond is a challenging but essential component of comprehensive care for individuals with a diagnosis of cancer. Recent studies have demonstrated the rising burden of cardiovascular disease in cancer survivors[20] due to cardiometabolic risk factors and treatment toxicity, as well as the role of obesity, poor diet, and metabolic health in worsening outcomes after a cancer diagnosis/treatment.[21] Thus, it is imperative that survivors of cancer receive comprehensive, whole-person care to improve their quality of life and physical functioning and, in many cases, reduce the risk of cancer recurrence and the development of other chronic diseases.[7,9,22-26]

Despite the growing evidence of benefits, there are many barriers to the implementation of LM in oncology care. In 2014, ASCO made "Obesity and Cancer" a core initiative, a key component of which was to increase oncologists' knowledge about nutrition, physical activity, and weight management and to ensure that these topics were being addressed in the oncology clinic. ASCO conducted a survey of its members to assess knowledge about the role of obesity and the role of nutrition and physical activity.[27] This study reported survey data from nearly 1000 practicing oncology health care providers and noted that most respondents frequently assessed their patients' body weight, physical activity level, and diet habits. However, the rate of referral of patients to weight management or physical activity programs was much lower.

Barriers to implementation included (1) lack of education on these topics for the oncology team members, (2) lack of time during a clinic visit, and (3) lack of programs for cancer patients to focus on weight management and physical activity. New initiatives are needed to support oncology health care providers' comfort and ease of referral and counseling. ASCO subsequently conducted an online survey of survivors of cancer to assess what weight-management education was provided during clinic visits.[28] The study, as well as a health behavior survey conducted within the present clinic,[17] found that most respondents are not meeting diet or physical activity recommendations.

Further, weight management was addressed in only a quarter of visits. Importantly, in those instances where an oncology health care provider addressed the role of diet and/or physical activity, the respondents were more likely to adopt changes in these behaviors compared with those respondents who did not receive this type of counseling. These findings highlight the important role that members of the oncology health care team play in terms of health promotion and ensuring that cancer survivors incorporate healthy lifestyle behaviors as a part of their survivorship care. There is a need to educate oncology health care providers about tools from LM and to develop multidisciplinary clinics that can address the needs of our patients.

Based on guidelines from all major authoritative bodies, LM tools should be incorporated into the continuum of cancer care to improve the quality of life, physical functioning, and downstream health outcomes of cancer survivors.[4-7,9,22-26] Despite these benefits, few clinics have been established to address the LM needs of this population.[16] The development of our LM clinic model, the first known of its kind within supportive oncology,[17] has great potential to enhance the care and quality of life of cancer survivors. ■

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RYBREVANT® (amivantamab-vmjw)
Injection for IV Use | 350 mg/7 mL (50 mg/mL)

LAZCLUZE™ (lazertinib)
Tablets | 240 mg/80 mg

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RYBREVANT® + LAZCLUZE™ form the **first and only multitargeted combination** to show statistically significant mPFS improvement vs osimertinib[1,2]

The most common adverse reactions (≥20%) were rash, nail toxicity, infusion-related reaction, musculoskeletal pain, stomatitis, edema, VTE, paresthesia, fatigue, diarrhea, constipation, COVID-19, hemorrhage, dry skin, decreased appetite, pruritus, nausea, and ocular toxicity.[1]

INDICATION

RYBREVANT® (amivantamab-vmjw) is indicated:

- in combination with LAZCLUZE™ (lazertinib) for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

RYBREVANT® can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting. The median time to IRR onset is approximately 1 hour.

RYBREVANT® with LAZCLUZE™

RYBREVANT® in combination with LAZCLUZE™ can cause infusion-related reactions. In MARIPOSA (n=421), IRRs occurred in 63% of patients treated with RYBREVANT® in combination with LAZCLUZE™, including Grade 3 in 5% and Grade 4 in 1% of patients. The incidence of infusion modifications due to IRR was 54% of patients, and IRRs leading to dose reduction of RYBREVANT® occurred in 0.7% of patients. Infusion-related reactions leading to permanent discontinuation of RYBREVANT® occurred in 4.5% of patients receiving RYBREVANT® in combination with LAZCLUZE™.

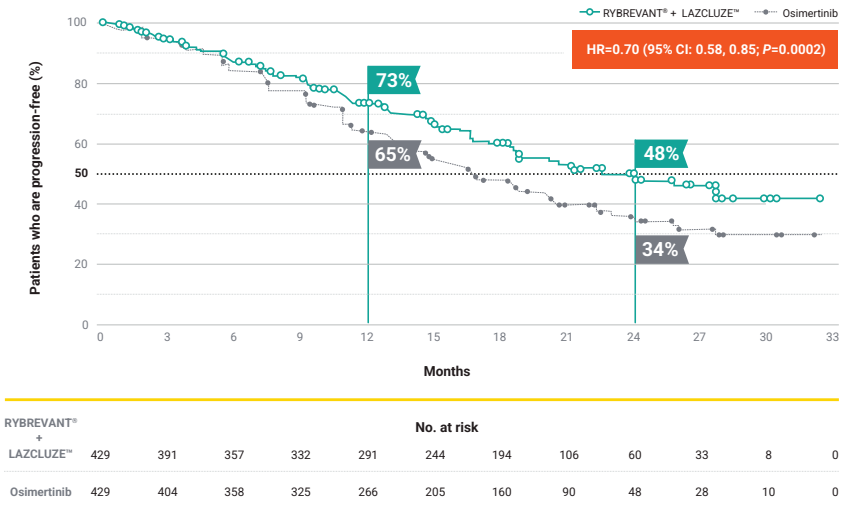
Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT® as recommended. Administer RYBREVANT® via a peripheral line on Week 1 and Week 2 to reduce the risk of infusion-related reactions. Monitor patients for signs and symptoms of infusion reactions during RYBREVANT® infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT® based on severity.

Johnson&Johnson

7.1 MONTH IMPROVEMENT IN MEDIAN PFS

23.7 months (95% CI: 19.1, 27.7) for RYBREVANT® + LAZCLUZE™ vs **16.6 months** (95% CI: 14.8, 18.5) for osimertinib; (HR=0.70 [95% CI: 0.58, 0.85]; *P*=0.0002)[1]

RYBREVANT® + LAZCLUZE™ demonstrated a statistically significant reduction in the risk of progression or death by 30% vs osimertinib[1,3]



Study Design

MARIPOSA was a randomized, active-controlled, multicenter Phase 3 trial assessing the efficacy of RYBREVANT® in combination with LAZCLUZE™. Eligible patients were required to have untreated locally advanced or metastatic NSCLC with either exon 19 deletions or exon 21 L858R substitution *EGFR* mutations identified by local testing, not amenable to curative therapy. Patients with asymptomatic or previously treated and stable intracranial metastases were eligible to enroll. Patients were randomized (2:2:1) to receive RYBREVANT® in combination with LAZCLUZE™ (N=429), osimertinib monotherapy (N=429), or LAZCLUZE™ monotherapy (an unapproved regimen for NSCLC) until disease progression or unacceptable toxicity. The evaluation of efficacy for the treatment of untreated metastatic NSCLC relied upon comparison between RYBREVANT® in combination with LAZCLUZE™, and osimertinib. The primary efficacy endpoint was PFS according to RECIST 1.1 as evaluated by BICR.[1,3]

In the non-registrational LAZCLUZE™ arm, median PFS was 18.5 months (95% CI: 14.8, 20.1)[3]

BICR, blinded independent central review; CI, confidence interval; EGFR; epidermal growth factor receptor; HR, hazard ratio; mNSCLC, metastatic non–small cell lung cancer; mPFS, median progression-free survival; NSCLC, non–small cell lung cancer; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; VTE, venous thromboembolism.

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IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Interstitial Lung Disease/Pneumonitis

RYBREVANT® can cause severe and fatal interstitial lung disease (ILD)/pneumonitis.

RYBREVANT® with LAZCLUZE™

In MARIPOSA, ILD/pneumonitis occurred in 3.1% of patients treated with RYBREVANT® in combination with LAZCLUZE™, including Grade 3 in 1.0% and Grade 4 in 0.2% of patients. There was one fatal case (0.2%) of ILD/pneumonitis and 2.9% of patients permanently discontinued RYBREVANT® and LAZCLUZE™ due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). For patients receiving RYBREVANT® in combination with LAZCLUZE™, immediately withhold both drugs in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed.

Venous Thromboembolic (VTE) Events with Concomitant Use of RYBREVANT® and LAZCLUZE™

RYBREVANT® in combination with LAZCLUZE™ can cause serious and fatal venous thromboembolic (VTEs) events, including deep vein thrombosis and pulmonary embolism. The majority of these events occurred during the first four months of therapy.

In MARIPOSA, VTEs occurred in 36% of patients receiving RYBREVANT® in combination with LAZCLUZE™, including Grade 3 in 10% and Grade 4 in 0.5% of patients. On-study VTEs occurred in 1.2% of patients (n=5) while receiving anticoagulation therapy. There were two fatal cases of VTE (0.5%), 9% of patients had VTE leading to dose interruptions of RYBREVANT®, and 7% of patients had VTE leading to dose interruptions of LAZCLUZE™; 1% of patients had VTE leading to dose reductions of RYBREVANT®, and 0.5% of patients had VTE leading to dose reductions of LAZCLUZE™; 3.1% of patients had VTE leading to permanent discontinuation of RYBREVANT®, and 1.9% of patients had VTE leading to permanent discontinuation of LAZCLUZE™. The median time to onset of VTEs was 84 days (range: 6 to 777).

Administer prophylactic anticoagulation for the first four months of treatment. The use of Vitamin K antagonists is not recommended. Monitor for signs and symptoms of VTE events and treat as medically appropriate.

Please see Brief Summaries of full Prescribing Information for RYBREVANT® and LAZCLUZE™ on subsequent pages.

IMPORTANT SAFETY INFORMATION (cont'd)
WARNINGS AND PRECAUTIONS (cont'd)

Withhold RYBREVANT® and LAZCLUZE™ based on severity. Once anticoagulant treatment has been initiated, resume RYBREVANT® and LAZCLUZE™ at the same dose level at the discretion of the healthcare provider. In the event of VTE recurrence despite therapeutic anticoagulation, permanently discontinue RYBREVANT® and continue treatment with LAZCLUZE™ at the same dose level at the discretion of the healthcare provider.

Dermatologic Adverse Reactions

RYBREVANT® can cause severe rash including toxic epidermal necrolysis (TEN), dermatitis acneiform, pruritus, and dry skin.

RYBREVANT® with LAZCLUZE™

In MARIPOSA, rash occurred in 86% of patients treated with RYBREVANT® in combination with LAZCLUZE™, including Grade 3 in 26% of patients. The median time to onset of rash was 14 days (range: 1 to 556 days). Rash leading to dose interruptions occurred in 37% of patients for RYBREVANT® and 30% for LAZCLUZE™, rash leading to dose reductions occurred in 23% of patients for RYBREVANT® and 19% for LAZCLUZE™, and rash leading to permanent discontinuation occurred in 5% of patients for RYBREVANT® and 1.7% for LAZCLUZE™.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT® or LAZCLUZE™ in combination with RYBREVANT®. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free (e.g., isopropanol-free, ethanol-free) emollient cream is recommended for dry skin.

When initiating RYBREVANT® treatment with or without LAZCLUZE™, administer alcohol-free emollient cream to reduce the risk of dermatologic adverse reactions. Consider prophylactic measures (e.g. use of oral antibiotics) to reduce the risk of dermatologic reactions. If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. For patients receiving RYBREVANT® in combination with LAZCLUZE™, withhold, dose reduce or permanently discontinue both drugs based on severity.

Ocular Toxicity

RYBREVANT® can cause ocular toxicity including keratitis, blepharitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, eye pruritus, and uveitis.

RYBREVANT® with LAZCLUZE™

In MARIPOSA, ocular toxicity occurred in 16% of patients treated with RYBREVANT® in combination with LAZCLUZE™, including Grade 3 or 4 ocular toxicity in 0.7% of patients. Withhold, reduce the dose, or permanently discontinue RYBREVANT® and continue LAZCLUZE™ based on severity.

Promptly refer patients with new or worsening eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT® based on severity.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal models, RYBREVANT® and LAZCLUZE™ can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential of the potential risk to the fetus.

Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of RYBREVANT®.

Advise females of reproductive potential to use effective contraception during treatment with LAZCLUZE™ and for 3 weeks after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with LAZCLUZE™ and for 3 weeks after the last dose.

Adverse Reactions

RYBREVANT® with LAZCLUZE™

For the 421 patients in the MARIPOSA clinical trial who received RYBREVANT® in combination with LAZCLUZE™, the most common adverse reactions (≥20%) were rash (86%), nail toxicity (71%), infusion-related reactions (RYBREVANT®, 63%), musculoskeletal pain (47%), stomatitis (43%), edema (43%), VTE (36%), paresthesia (35%), fatigue (32%), diarrhea (31%), constipation (29%), COVID-19 (26%), hemorrhage (25%), dry skin (25%), decreased appetite (24%), pruritus (24%), nausea (21%), and ocular toxicity (16%). The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased albumin (8%), decreased sodium (7%), increased ALT (7%), decreased potassium (5%), decreased hemoglobin (3.8%), increased AST (3.8%), increased GGT (2.6%), and increased magnesium (2.6%).

Serious adverse reactions occurred in 49% of patients who received RYBREVANT® in combination with LAZCLUZE™. Serious adverse reactions occurring in ≥2% of patients included VTE (11%), pneumonia (4%), ILD/pneumonitis and rash (2.9% each), COVID-19 (2.4%) and pleural effusion and infusion-related reaction (RYBREVANT®) (2.1% each). Fatal adverse reactions occurred in 7% of patients who received RYBREVANT® in combination with LAZCLUZE™ due to death not otherwise specified (1.2%); sepsis and respiratory failure (1% each); pneumonia, myocardial infarction, and sudden death (0.7% each); cerebral infarction, pulmonary embolism (PE), and COVID-19 infection (0.5% each); and ILD/pneumonitis, acute respiratory distress syndrome (ARDS), and cardiopulmonary arrest (0.2% each).

LAZCLUZE™ Drug Interactions

Avoid concomitant use of LAZCLUZE™ with strong and moderate CYP3A4 inducers. Consider an alternate concomitant medication with no potential to induce CYP3A4.

Monitor for adverse reactions associated with a CYP3A4 or BCRP substrate where minimal concentration changes may lead to serious adverse reactions, as recommended in the approved product labeling for the CYP3A4 or BCRP substrate.

Please read accompanying full Prescribing Information for RYBREVANT®.

Please read accompanying full Prescribing Information for LAZCLUZE™.

cp-464671v1

References: 1. RYBREVANT® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** RYBREVANT® (amivantamab-vmjw) plus LAZCLUZE™ (lazertinib) approved in the U.S. as a first-line chemotherapy-free treatment for patients with EGFR-mutated advanced lung cancer. Press release. Johnson & Johnson. August 20, 2024. Accessed August 20, 2024. https://www.prnewswire.com/news-releases/rybrevant-amivantamab-vmjw-plus-lazcluze-lazertinib-approved-in-the-us-as-a-first-line-chemotherapy-free-treatment-for-patients-with-egfr-mutated-advanced-lung-cancer-302226047.html **3.** Cho BC, Lu S, Felip E, et al; MARIPOSA Investigators. Amivantamab plus lazertinib in previously untreated EGFR-mutated advanced NSCLC. *N Engl J Med*. 2024. doi:10.1056/NEJMoa2403614

Johnson&Johnson

RYBREVANT® + LAZCLUZE™

(amivantamab-vmjw) Injection for IV Use | 350 mg/7 mL (50 mg/mL)

(lazertinib) Tablets | 240 mg/80 mg

RYBREVANT® (amivantamab-vmjw) injection, for intravenous use
Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

First-Line Treatment of NSCLC with *EGFR* Exon 19 Deletions or Exon 21 L858R Substitution Mutations

RYBREVANT, in combination with lazertinib, is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test *[see Dosage and Administration (2.2) in Full Prescribing Information]*.

Previously Treated NSCLC with *EGFR* Exon 19 Deletions or Exon 21 L858R Substitution Mutations

RYBREVANT, in combination with carboplatin and pemetrexed, is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with an EGFR tyrosine kinase inhibitor *[see Dosage and Administration (2.2) in Full Prescribing Information]*.

First-Line Treatment of NSCLC with *EGFR* Exon 20 Insertion Mutations

RYBREVANT, in combination with carboplatin and pemetrexed, is indicated for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test *[see Dosage and Administration (2.2) in Full Prescribing Information]*.

Previously Treated NSCLC with *EGFR* Exon 20 Insertion Mutations

RYBREVANT is indicated as a single agent for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test *[see Dosage and Administration (2.2) in Full Prescribing Information]*, whose disease has progressed on or after platinum-based chemotherapy.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

RYBREVANT can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting. The median time to IRR onset is approximately 1 hour.

RYBREVANT with Lazertinib

RYBREVANT in combination with lazertinib can cause infusion-related reactions. In MARIPOSA, *[see Adverse Reactions]*, IRRs occurred in 63% of patients treated with RYBREVANT in combination with lazertinib, including Grade 3 in 5% and Grade 4 in 1% of patients. The incidence of infusion modifications due to IRR was 54%, and IRRs leading to dose reduction of RYBREVANT occurred in 0.7% of patients. Infusion-related reactions leading to permanent discontinuation of RYBREVANT occurred in 4.5% of patients receiving RYBREVANT in combination with lazertinib.

RYBREVANT with Carboplatin and Pemetrexed

Based on the pooled safety population *[see Adverse Reactions]*, IRR occurred in 50% of patients treated with RYBREVANT in combination with carboplatin and pemetrexed, including Grade 3 (3.2%) adverse reactions. The incidence of infusion modifications due to IRR was 46%, and 2.8% of patients permanently discontinued RYBREVANT due to IRR.

RYBREVANT as a Single Agent

In CHRYSALIS, *[see Adverse Reactions]*, IRR occurred in 66% of patients treated with RYBREVANT as a single agent. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62%, and 1.3% of patients permanently discontinued RYBREVANT due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT as recommended *[see Dosage and Administration (2.5) in Full Prescribing Information]*. Administer RYBREVANT via a peripheral line on Week 1 and Week 2 to reduce the risk of infusion-related reactions *[see Dosage and Administration (2.8) in Full Prescribing Information]*.

Monitor patients for signs and symptoms of infusion reactions during RYBREVANT infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT based on severity *[see Dosage and Administration (2.6) in Full Prescribing Information]*.

Interstitial Lung Disease/Pneumonitis

RYBREVANT can cause severe and fatal interstitial lung disease (ILD)/pneumonitis.

RYBREVANT with Lazertinib

In MARIPOSA *[see Adverse Reactions]*, ILD/pneumonitis occurred in 3.1% of patients treated with RYBREVANT in combination with lazertinib, including Grade 3 in 1% and Grade 4 in 0.2% of patients. There was one fatal case of ILD/pneumonitis and 2.9% of patients permanently discontinued RYBREVANT and lazertinib due to ILD/pneumonitis *[see Adverse Reactions]*.

RYBREVANT with Carboplatin and Pemetrexed

Based on the pooled safety population *[see Adverse Reactions]*, ILD/pneumonitis occurred in 2.1% treated with RYBREVANT in combination with carboplatin and pemetrexed with 1.8% of patients experiencing Grade 3 ILD/pneumonitis. 2.1% discontinued RYBREVANT due to ILD/pneumonitis

RYBREVANT as a Single Agent

In CHRYSALIS, *[see Adverse Reactions]*, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT as a single agent, with 0.7 % of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) permanently discontinued RYBREVANT due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed *[see Dosage and Administration (2.6) in Full Prescribing Information]*.

Venous Thromboembolic (VTE) Events with Concomitant Use of RYBREVANT and Lazertinib

RYBREVANT in combination with lazertinib can cause serious and fatal venous thromboembolic (VTE) events, including deep vein thrombosis and pulmonary embolism. The majority of these events occurred during the first four months of therapy *[see Adverse Reactions]*.

In MARIPOSA *[see Adverse Reactions]*, VTEs occurred in 36% of patients receiving RYBREVANT in combination with lazertinib, including Grade 3 in 10% and Grade 4 in 0.5% of patients. On-study VTEs occurred in 1.2% of patients (n=5) while receiving anticoagulation therapy. There were two fatal cases of VTE (0.5%), 9% of patients had VTE leading to dose interruptions of RYBREVANT, 1% of patients had VTE leading to dose reductions of RYBREVANT, and 3.1% of patients had VTE leading to permanent discontinuation of RYBREVANT. The median time to onset of VTEs was 84 days (range: 6 to 777). Administer prophylactic anticoagulation for the first four months of treatment *[see Dosage and Administration (2.4) in Full Prescribing Information]*. The use of Vitamin K antagonists is not recommended. Monitor for signs and symptoms of VTE events and treat as medically appropriate.

Withhold RYBREVANT and lazertinib based on severity *[see Dosage and Administration (2.6) in Full Prescribing Information]*. Once anticoagulant treatment has been initiated, resume RYBREVANT and lazertinib at the same dose level at the discretion of the healthcare provider *[see Dosage and Administration (2.4) in Full Prescribing Information]*. In the event of VTE recurrence despite therapeutic anticoagulation, permanently discontinue RYBREVANT. Treatment can continue with lazertinib at the same dose level at the discretion of the healthcare provider *[see Dosage and Administration (2.6) in Full Prescribing Information]*. Refer to the lazertinib prescribing information for recommended lazertinib dosage modification.

Dermatologic Adverse Reactions

RYBREVANT can cause severe rash including toxic epidermal necrolysis (TEN), dermatitis acneiform, pruritus, and dry skin.

RYBREVANT with Lazertinib

In MARIPOSA, *[see Adverse Reactions]*, rash occurred in 86% of patients treated with RYBREVANT in combination with lazertinib, including Grade 3 in 26% of patients. The median time to onset of rash was 14 days (range: 1 to 556 days). Rash leading to dose interruptions of RYBREVANT occurred in 37% of patients, rash leading to dose reductions of RYBREVANT occurred in 23% of patients, and rash leading to permanent discontinuation of RYBREVANT occurred in 5% of patients.

RYBREVANT with Carboplatin and Pemetrexed

Based on the pooled safety population *[see Adverse Reactions]*, rash occurred in 82% of patients treated with RYBREVANT in combination with carboplatin and pemetrexed, including Grade 3 (15%) adverse reactions. Rash leading to dose reductions occurred in 14% of patients, and 2.5% permanently discontinued RYBREVANT and 3.1% discontinued pemetrexed.

RYBREVANT as a Single Agent

In CHRYSALIS, *[see Adverse Reactions]*, rash occurred in 74% of patients treated with RYBREVANT as a single agent, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT was permanently discontinued due to rash in 0.7% of patients *[see Adverse Reactions]*.

Toxic epidermal necrolysis (TEN) occurred in one patient (0.3%) treated with RYBREVANT as a single agent.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free (e.g., isopropanol-free, ethanol-free) emollient cream is recommended for dry skin.

When initiating treatment with RYBREVANT, administer alcohol-free (e.g., isopropanol-free, ethanol-free) emollient cream to reduce the risk of dermatologic adverse reactions. Consider prophylactic measures (e.g., use of oral antibiotics) to reduce the risk of dermatologic adverse reactions. If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, reduce the dose, or permanently discontinue RYBREVANT based on severity *[see Dosage and Administration (2.6) in Full Prescribing Information]*.

Ocular Toxicity
RYBREVANT can cause ocular toxicity including keratitis, blepharitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, eye pruritus, and uveitis.

RYBREVANT with Lazertinib
In MARIPOSA *[see Adverse Reactions]*, ocular toxicity occurred in 16% of patients treated with RYBREVANT in combination with lazertinib, including Grade 3 or 4 ocular toxicity in 0.7% of patients. Withhold, reduce the dose, or permanently discontinue RYBREVANT and continue lazertinib based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

RYBREVANT with Carboplatin and Pemetrexed
Based on the pooled safety population *[see Adverse Reactions]*, ocular toxicity occurred in 16% of patients treated with RYBREVANT in combination with carboplatin and pemetrexed. All events were Grade 1 or 2.

RYBREVANT as a Single Agent
In CHRYSALIS, *[see Adverse Reactions]*, keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVANT. All events were Grade 1-2.

Promptly refer patients with new or worsening eye symptoms to an ophthalmologist. Withhold, reduce the dose, or permanently discontinue RYBREVANT based on severity *[see Dosage and Administration (2.6) in Full Prescribing Information]*.

Embryo-Fetal Toxicity
Based on its mechanism of action and findings from animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. Administration of other EGFR inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo-fetal development, embryo lethality, and abortion. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of RYBREVANT. *[see Use in Specific Populations]*.

ADVERSE REACTIONS
The following adverse reactions are discussed elsewhere in the labeling:

- Infusion-Related Reactions *[see Warnings and Precautions]*
- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions]*
- Venous Thromboembolic Events *[see Warnings and Precautions]*
- Dermatologic Adverse Reactions *[see Warnings and Precautions]*
- Ocular Toxicity *[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.

RYBREVANT in Combination with Lazertinib
The data described in the WARNINGS AND PRECAUTIONS reflect exposure to RYBREVANT in combination with lazertinib in the MARIPOSA study in 421 patients with previously untreated locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R substitution mutation *[see Clinical Studies (14.1) in Full Prescribing Information]*. Patients received RYBREVANT intravenously at 1,050 mg (for patients < 80 kg) or 1,400 mg (for patients ≥ 80 kg) once weekly for 4 weeks, then every 2 weeks thereafter starting at week 5 in combination with lazertinib, 240 mg orally once daily, until disease progression or unacceptable toxicity. Among 421 patients who received RYBREVANT in combination with lazertinib, 73% were exposed for 6 months or longer and 59% were exposed for greater than one year. The most common adverse reactions (≥ 20%) were rash, nail toxicity, infusion-related reaction, edema, musculoskeletal pain, stomatitis, VTE, paresthesia, fatigue, diarrhea, constipation, COVID-19, dry skin, hemorrhage, decreased appetite, pruritus, nausea, and ocular toxicity. The most common Grade 3 or 4 laboratory abnormalities (≥ 2%) were decreased albumin, increased ALT, decreased sodium, decreased hemoglobin, increased AST, increased GGT and increased magnesium.

RYBREVANT in Combination with Carboplatin and Pemetrexed
The pooled safety population described in the WARNINGS AND PRECAUTIONS also reflect exposure to RYBREVANT in combination with carboplatin and pemetrexed in 281 patients in two studies:

- MARIPOSA-2 *[see Clinical Studies (14.2) in Full Prescribing Information]* in 130 patients with previously treated locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations whose disease has progressed on or after treatment with osimertinib.
- PAPILLON *[see Clinical Studies (14.3) in Full Prescribing Information]* in 151 patients with previously untreated, locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations.

Patients received RYBREVANT intravenously at 1,400 mg (for patients < 80 kg) or 1,750 mg (for patients ≥ 80 kg) once weekly through 4 weeks, then every 3 weeks with a dose of 1,750 mg (for patients < 80 kg) or 2,100 mg (for patients ≥ 80 kg) starting at Week 7 until disease progression or unacceptable toxicity, in combination with carboplatin at area under the curve AUC 5 once every 3 weeks, for up to 12 weeks, and pemetrexed at 500 mg/m^2 once every 3 weeks until disease progression or unacceptable toxicity. Among 281 patients who received RYBREVANT in combination with carboplatin and pemetrexed, 65% were exposed for 6 months or longer and 24% were exposed for greater than one year. In the safety population, the most common (≥ 20%) adverse reactions were rash, nail toxicity, infusion-related reaction, fatigue, nausea, stomatitis, constipation, edema, decreased appetite, musculoskeletal pain, vomiting, and COVID-19. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased neutrophils, decreased leukocytes, decreased platelets, decreased hemoglobin, decreased potassium, decreased sodium, increased alanine aminotransferase, increased gamma-glutamyl transferase, and decreased albumin.

RYBREVANT as a Single Agent
The data in the WARNINGS AND PRECAUTIONS also reflect exposure to RYBREVANT as a single agent in CHRYSALIS *[see Clinical Studies (14.4) in Full Prescribing Information]* in 302 patients with locally advanced or metastatic NSCLC. Patients received RYBREVANT at 1,050 mg (for patient baseline body weight < 80 kg) or 1,400 mg (for patient baseline body weight ≥ 80 kg) once weekly for 4 weeks, then every 2 weeks thereafter until disease progression or unacceptable toxicity. Among 302 patients who received RYBREVANT as a single agent, 36% were exposed for 6 months or longer and 12% were exposed for greater than one year. In the safety population, the most common (≥ 20%) adverse reactions were rash, infusion-related reaction, paronychia, musculoskeletal pain, dyspnea, nausea, edema, cough, fatigue, stomatitis, constipation, vomiting and pruritus. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were increased gamma glutamyl transference, decreased sodium, decreased potassium and increased alkaline phosphatase.

First-line Treatment of NSCLC with Exon 19 deletions or Exon 21 L858R substitution mutations

The safety data described below reflect exposure to RYBREVANT in combination with lazertinib in 421 previously untreated patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R substitution mutation in the MARIPOSA *[see Clinical Studies (14.1) in Full Prescribing Information]*. Patients received RYBREVANT intravenously at 1,050 mg (for patients < 80 kg) or 1,400 mg (for patients ≥ 80 kg) once weekly for 4 weeks, then every 2 weeks thereafter starting at week 5 in combination with lazertinib, 240 mg orally once daily. Among the 421 patients who received RYBREVANT in combination with lazertinib, 73% were exposed to RYBREVANT for ≥ 6 months and 59% were exposed to RYBREVANT for > 1 year.

The median age of patients who received RYBREVANT in combination with lazertinib was 64 years (range: 25 to 88); 64% were female; 59% were Asian, 38% were White, 1.7% were American Indian or Alaska Native, 0.7% were Black or African American, 1% were of unknown or other races; and 13% were Hispanic or Latino, 67% had Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1, 33% had ECOG PS of 0, 60% had EGFR exon 19 deletions, and 40% had EGFR exon 21 L858R substitution mutations.

Serious adverse reactions occurred in 49% of patients who received RYBREVANT in combination with lazertinib. Serious adverse reactions occurring in ≥ 2% of patients included VTE (11%), pneumonia (4%), rash, and ILD/pneumonitis (2.9% each), COVID-19 (2.4%), pleural effusion and infusion-related reaction (2.1% each). Fatal adverse reactions occurred in 7% of patients who received RYBREVANT in combination with lazertinib due to death not otherwise specified (1.2%); sepsis and respiratory failure (1% each); pneumonia, myocardial infarction and sudden death (0.7% each); cerebral infarction, pulmonary embolism (PE), and COVID-19 infection (0.5% each); and ILD/pneumonitis, acute respiratory distress syndrome (ARDS), and cardiopulmonary arrest (0.2% each).

Permanent discontinuation of RYBREVANT due to an adverse reaction occurred in 34% of patients. Adverse reactions which resulted in permanent discontinuation in ≥ 1% of patients included rash, infusion-related reactions, nail toxicity, VTE, ILD/pneumonitis, pneumonia, edema, hypoalbuminemia, fatigue, paresthesia and dyspnea.

Dosage interruption of RYBREVANT due to an adverse reaction occurred in 88% of patients. Adverse reactions which required dosage interruption in ≥ 5% of patients were infusion-related reactions, rash, nail toxicity, COVID-19, VTE, increased ALT, edema, and hypoalbuminemia.

Dose reductions of RYBREVANT due to an adverse reaction occurred in 46% of patients. Adverse reactions requiring dose reductions in ≥ 5% of patients were rash and nail toxicity.

The most common adverse reactions (≥ 20%) were rash, nail toxicity, infusion-related reaction, musculoskeletal pain, stomatitis, edema, VTE, paresthesia, fatigue, diarrhea, constipation, COVID-19, hemorrhage, dry skin, decreased appetite, pruritus, and nausea. The most common Grade 3 or 4 laboratory abnormalities (≥ 2%) were decreased albumin, decreased sodium, increased ALT, decreased potassium, decreased hemoglobin, increased AST, increased GGT, and increased magnesium.

Table 1 summarizes the adverse reactions (≥ 10%) in MARIPOSA.

Table 1: Adverse Reactions (≥ 10%) in Patients with NSCLC with Exon 19 Deletion or Exon 21 L858R Substitution Mutations in MARIPOSA

Adverse Reaction	RYBREVANT in combination with lazertinib (N=421)		Osimertinib (N=428)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders				
Rash*	86	26	48	1.2
Nail toxicity*	71	11	34	0.7
Dry skin*	25	1	18	0.2
Pruritus	24	0.5	17	0.2
Injury, poisoning and procedural complications				
Infusion-related reaction+	63	6	0	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	47	2.1	39	1.9
Gastrointestinal disorders				
Stomatitis*	43	2.4	27	0.5
Diarrhea*	31	2.6	45	0.9
Constipation	29	0	13	0
Nausea	21	1.2	14	0.2
Vomiting	12	0.5	5	0
Abdominal pain*	11	0	10	0
Hemorrhoids	10	0.2	2.1	0.2
General disorders and administration site conditions				
Edema*	43	2.6	8	0
Fatigue*	32	3.8	20	1.9
Pyrexia	12	0	9	0
Vascular disorders				
Venous thromboembolism*	36	11	8	2.8
Hemorrhage*	25	1	13	1.2
Nervous system disorders				
Paresthesia*	35	1.7	10	0.2
Dizziness*	14	0	10	0
Headache*	13	0.2	13	0
Infections and infestations				
COVID-19	26	1.7	24	1.4
Conjunctivitis	11	0.2	1.6	0
Metabolism and nutrition disorders				
Decreased appetite	24	1	18	1.4
Respiratory, thoracic, and mediastinal disorders				
Cough*	19	0	23	0
Dyspnea*	14	1.7	17	3.5
Eye disorders				
Ocular toxicity*	16	0.7	7	0
Psychiatric disorders				
Insomnia	10	0	11	0

* Grouped terms
\+ Applicable for RYBREVANT only

Clinically relevant adverse reactions in < 10% of patients who received RYBREVANT in combination with lazertinib included ILD/pneumonitis (3.1%).

Table 2 summarizes the laboratory abnormalities in MARIPOSA.

Table 2: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with NSCLC with EGFR Exon 19 Deletion or Exon 21 L858R Substitution Mutations in MARIPOSA+

Laboratory Abnormality	RYBREVANT in combination with lazertinib (N=421)		Osimertinib (N=428)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Decreased albumin	89	8	22	0.2
Increased ALT	65	7	29	2.6
Increased AST	52	3.8	36	1.9
Increased alkaline phosphatase	45	0.5	15	0.5
Decreased calcium (corrected)	41	1.4	27	0.7
Increased GGT	39	2.6	24	1.9
Decreased sodium	38	7	35	5
Decreased potassium	30	5	15	1.2
Increased creatinine	26	0.7	35	0.7
Decreased magnesium	25	0.7	10	0.2
Increased magnesium	12	2.6	20	4.8

RYBREVANT® (amivantamab-vmjw) injection

Table 2: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with NSCLC with EGFR Exon 19 Deletion or Exon 21 L858R Substitution Mutations in MARIPOSA+ (continued)

Laboratory Abnormality	RYBREVANT in combination with lazertinib (N=421)		Osimertinib (N=428)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Decreased platelet count	52	0.7	57	1.4
Decreased hemoglobin	47	3.8	56	1.9
Decreased white blood cell	38	1	66	0.7
Decreased neutrophils	15	1.4	33	1.4

\+ The denominator used to calculate the rate is the number of patients with a baseline value and at least one post-treatment value for the specific lab test.

Previously Treated Non-Small Cell Lung Cancer (NSCLC) with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations

The safety data described below reflect exposure to RYBREVANT in combination with carboplatin and pemetrexed was evaluated in MARIPOSA-2 *[see Clinical Studies (14.2) in Full Prescribing Information]*. Eligible patients had locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations with progressive disease on or after treatment with osimertinib. Patients with asymptomatic or previously treated and stable intracranial metastases were eligible. Patients received RYBREVANT intravenously at 1,400 mg (for patients < 80 kg) or 1,750 mg (for patients ≥ 80 kg) once weekly through 4 weeks, then every 3 weeks with a dose of 1,750 mg (for patients < 80 kg) or 2,100 mg (for patients ≥ 80 kg) starting at Week 7 until disease progression or unacceptable toxicity, in combination with carboplatin at area under the curve AUC 5 once every 3 weeks, for up to 12 weeks, and pemetrexed at 500 mg/m^2 once every 3 weeks until disease progression or unacceptable toxicity. Among patients who received RYBREVANT (n=130), 52% were exposed for 6 months or longer and 7% were exposed for greater than one year. The median treatment duration was 6.3 months (range: 0 to 14.7 months).

The median age was 62 years (range: 36 to 84 years); 62% were female; 48% were Asian, 46% were White, 2.3% Black or African American, 1.5% race not reported, 1.5% race unknown, 0.8% Alaska native; 7% were Hispanic or Latino; and 87% had baseline body weight < 80 kg.

Serious adverse reactions occurred in 32% of patients who received RYBREVANT in combination with carboplatin and pemetrexed. Serious adverse reactions in > 2% of patients included dyspnea (3.1%), thrombocytopenia (3.1%), sepsis (2.3%), and pulmonary embolism (2.3%). Fatal adverse reactions occurred in 2.3% of patients who received RYBREVANT in combination with carboplatin and pemetrexed; these included respiratory failure, sepsis, and ventricular fibrillation (0.8% each).

Permanent discontinuation of RYBREVANT due to adverse reactions occurred in 11% of patients. The most frequent adverse reactions leading to discontinuation of RYBREVANT in ≥ 5% of patients were infusion-related reactions.

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 60% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 52% of patients. Adverse reactions requiring dose interruption in ≥ 5% of patients included infusion-related reaction, rash and fatigue.

Dose reductions of RYBREVANT due to an adverse reaction occurred in 17% of patients. Adverse reactions requiring dose reductions in ≥ 2% of patients included rash.

The most common adverse reactions ≥ 20% were rash, infusion-related reactions, fatigue, nail toxicity, nausea, constipation, edema, stomatitis, decreased appetite, musculoskeletal pain, vomiting, and COVID-19.

Table 3 summarizes the adverse reactions in MARIPOSA-2.

Table 3: Adverse Reactions (≥ 10%) in Previously Treated Patients with NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations Treated with RYBREVANT in Combination with Carboplatin and Pemetrexed in MARIPOSA-2

Adverse Reaction	RYBREVANT + Carboplatin + Pemetrexed (N=130)		Carboplatin + Pemetrexed (N=243)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders				
Rash*	72	11	12	0
Nail toxicity*	45	2.3	0.4	0
Pruritus	15	0	7	0
Dry skin*	15	0	2.5	0
General disorders and administration site conditions				
Infusion-related reaction	59	5.4	0.4	0
Fatigue*	51	3.8	35	3.7
Edema*	36	1.5	11	0.4
Pyrexia	12	0	10	0

Table 3: Adverse Reactions (≥ 10%) in Previously Treated Patients with NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations Treated with RYBREVANT in Combination with Carboplatin and Pemetrexed in MARIPOSA-2 (continued)

Adverse Reaction	RYBREVANT + Carboplatin + Pemetrexed (N=130)		Carboplatin + Pemetrexed (N=243)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Nausea	45	0.8	37	0.8
Constipation	39	0.8	30	0
Stomatitis*	35	2.3	11	0
Vomiting	25	0.8	17	0.4
Diarrhea*	15	1.5	7	0.8
Metabolism and nutrition disorders				
Decreased appetite	31	0	21	1.2
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	30	3.1	19	0.8
Infections and infestations				
COVID-19	21	1.5	10	0
Eye disorders				
Ocular toxicity*	17	0	3.7	0
Vascular disorders				
Hemorrhage*	14	0.8	4.9	0
Venous Thromboembolism* (VTE)	10	2.3	4.5	2.9
Respiratory, thoracic, and mediastinal disorders				
Cough*	14	0	16	0.4
Dyspnea*	13	1.5	8	1.2

* Grouped term

Clinically relevant adverse reactions in < 10% of patients who received RYBREVANT in combination with carboplatin and pemetrexed include: abdominal pain, hemorrhoids, dizziness, visual impairment, trichomegaly, keratitis, and interstitial lung disease.

Table 4 summarizes the laboratory abnormalities in MARIPOSA-2.

Table 4: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations Treated with RYBREVANT in Combination with Carboplatin and Pemetrexed in MARIPOSA-2

Laboratory Abnormality	RYBREVANT + Carboplatin + Pemetrexed (N=130)		Carboplatin + Pemetrexed (N=243)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Decreased white blood cells	91	42	85	19
Decreased neutrophils	74	49	64	25
Decreased platelets	74	17	58	9
Decreased hemoglobin	71	12	77	9
Decreased lymphocytes	69	28	58	18
Chemistry				
Decreased albumin	73	3.8	26	0.4
Decreased sodium	49	11	30	6
Increased aspartate aminotransferase	47	0.8	52	0.9
Increased alkaline phosphatase	42	0	29	0.4
Increased alanine aminotransferase	39	3.9	56	6
Decreased magnesium	38	0.8	17	0.4
Decreased potassium	37	11	12	3.4
Increased gamma-glutamyl transferase	30	3.1	41	1.3
Decreased calcium (corrected)	25	0	11	0.9

First-line Treatment of Non-Small Cell Lung Cancer (NSCLC) with Exon 20 Insertion Mutations

The safety data described below reflect exposure to RYBREVANT in combination with carboplatin and pemetrexed at the recommended dosage in the PAPILLON trial *[see Clinical Studies (14.3) in Full Prescribing Information]* in 151 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations. Among patients who received RYBREVANT in combination with carboplatin and pemetrexed the median exposure was 9.7 months (range: 0.0 to 26.9 months). In patients that received carboplatin and pemetrexed alone, the median exposure was 6.7 months (range 0.0 to 25.3).

The median age was 61 years (range: 27 to 86 years); 56% were female; 64% were Asian, 32% were White, 1.3% were Black or African American, race was not reported in 1.3% of patients; 89% were not Hispanic or Latino; 86% had baseline body weight < 80 kg.

Serious adverse reactions occurred in 37% of patients who received RYBREVANT in combination with carboplatin and pemetrexed. Serious adverse reactions in ≥ 2% of patients included rash, pneumonia, interstitial lung disease (ILD), pulmonary embolism, vomiting, and COVID-19. Fatal adverse reactions occurred in 7 patients (4.6%) due to pneumonia, cerebrovascular accident, cardio-respiratory arrest, COVID-19, sepsis, and death not otherwise specified.

Permanent discontinuation of RYBREVANT due to an adverse reaction occurred in 11% of patients. Adverse reactions resulting in permanent discontinuation of RYBREVANT in ≥ 1% of patients were rash and ILD.

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 64% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 38% of patients. Adverse reactions requiring dose interruption in ≥ 5% of patients included rash and nail toxicity.

Dose reductions of RYBREVANT due to an adverse reaction occurred in 36% of patients. Adverse reactions requiring dose reductions in ≥ 5% of patients included rash and nail toxicity.

The most common adverse reactions (≥ 20%) were rash, nail toxicity, stomatitis, infusion-related reaction, fatigue, edema, constipation, decreased appetite, nausea, COVID-19, diarrhea, and vomiting. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased albumin, increased alanine aminotransferase, increased gamma-glutamyl transferase, decreased sodium, decreased potassium, decreased magnesium, and decreases in white blood cells, hemoglobin, neutrophils, platelets, and lymphocytes.

Table 5 summarizes the adverse reactions in PAPILLON.

Table 5: Adverse Reactions (≥ 10%) in Patients with Metastatic NSCLC with Exon 20 Insertion Mutations Who Received RYBREVANT in Combination with Carboplatin and Pemetrexed in PAPILLON

Adverse Reaction[1]	RYBREVANT in Combination with Carboplatin and Pemetrexed (n=151)		Carboplatin and Pemetrexed (n=155)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders				
Rash[2]	90	19	19	0
Nail toxicity[2]	62	7	3	0
Dry skin[2]	17	0	6	0
Gastrointestinal disorders				
Stomatitis[2]	43	4	11	0
Constipation	40	0	30	0.7
Nausea	36	0.7	42	0
Vomiting	21	3.3	19	0.7
Diarrhea	21	3	13	1.3
Hemorrhoids	12	1	1.3	0
Abdominal pain[2]	11	0.7	8	0
General disorders and administration site conditions				
Infusion-related reaction	42	1.3	1.3	0
Fatigue[2]	42	6	45	3.9
Edema[2]	40	1.3	19	0
Pyrexia[2]	17	0	6	0
Metabolism and nutrition disorders				
Decreased appetite	36	2.6	28	1.3
Infections and infestations				
COVID-19	24	2	14	0.6
Pneumonia[2]	13	5	6	1.9
Vascular disorders				
Hemorrhage[2]	18	0.7	11	1.9
Respiratory, thoracic, and mediastinal disorders				
Cough[2]	17	0	16	0
Dyspnea[2]	11	1.3	16	3.2
Investigations				
Weight decreased	14	0.7	8	0
Nervous system disorders				
Dizziness[2]	11	0	12	0
Psychiatric disorders				
Insomnia	11	0	13	0

[1] Adverse reactions were graded using CTCAE version 5.0
[2] Grouped Term

Clinically relevant adverse reactions in < 10% of patients who received RYBREVANT in combination with carboplatin and pemetrexed included pulmonary embolism, deep vein thrombosis, skin ulcer, conjunctivitis, and interstitial lung disease (ILD)/pneumonitis.

Table 6 summarizes the laboratory abnormalities in PAPILLON.

Table 6: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with Metastatic NSCLC with EGFR Exon 20 Insertion Mutations Who Received RYBREVANT in Combination with Carboplatin and Pemetrexed in PAPILLON

Laboratory Abnormality[1]	RYBREVANT in Combination with Carboplatin and Pemetrexed[2]		Carboplatin in Combination with Pemetrexed[3]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Decreased white blood cells	89	17	76	10
Decreased hemoglobin	79	11	85	13
Decreased neutrophils	76	36	61	23
Decreased platelets	70	10	54	12
Decreased lymphocytes	61	11	49	13
Chemistry				
Decreased albumin	87	7	34	1
Increased aspartate aminotransferase	60	1	61	1
Increased alanine aminotransferase	57	4	54	1
Decreased sodium	55	7	39	4
Increased alkaline phosphatase	51	1	28	0
Decreased potassium	44	11	17	1
Decreased magnesium	39	2	30	1
Increased gamma-glutamyl transferase	38	4	43	4
Decreased calcium (corrected)	27	1	18	1

[1] Adverse reactions were graded using CTCAE version 5.0
[2] The denominator used to calculate the rate varied from 113 to 150 based on the number of patients with a baseline value and at least one post-treatment value.
[3] The denominator used to calculate the rate varied from 119 to 154 based on the number of patients with a baseline value and at least one post-treatment value.

Previously Treated NSCLC Exon 20 Insertion Mutations

The safety data described below reflect exposure to RYBREVANT at the recommended dosage in 129 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations in the CHRYSALIS trial *[see Clinical Studies (14.4) in Full Prescribing Information]*, whose disease had progressed on or after platinum-based chemotherapy. Among patients who received RYBREVANT, 44% were exposed for 6 months or longer and 12% were exposed for greater than one year.

The median age was 62 years (range: 36 to 84 years); 61% were female; 55% were Asian, 35% were White, and 2.3% were Black; and 82% had baseline body weight < 80 kg.

Serious adverse reactions occurred in 30% of patients who received RYBREVANT. Serious adverse reactions in ≥ 2% of patients included pulmonary embolism, pneumonitis/ILD, dyspnea, musculoskeletal pain, pneumonia, and muscular weakness. Fatal adverse reactions occurred in 2 patients (1.5%) due to pneumonia and 1 patient (0.8%) due to sudden death.

Permanent discontinuation of RYBREVANT due to an adverse reaction occurred in 11% of patients. Adverse reactions resulting in permanent discontinuation of RYBREVANT in ≥ 1% of patients were pneumonia, IRR, pneumonitis/ILD, dyspnea, pleural effusion, and rash.

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 78% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 59% of patients. Adverse reactions requiring dose interruption in ≥ 5% of patients included dyspnea, nausea, rash, vomiting, fatigue, and diarrhea.

Dose reductions of RYBREVANT due to an adverse reaction occurred in 15% of patients. Adverse reactions requiring dose reductions in ≥ 2% of patients included rash and paronychia.

The most common adverse reactions (≥ 20%) were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased albumin, decreased phosphate, decreased potassium, increased glucose, increased alkaline phosphatase, increased gamma-glutamyl transferase, and decreased sodium.

Table 7 summarizes the adverse reactions in CHRYSALIS.

Table 7: Adverse Reactions (≥ 10%) in Patients with NSCLC with Exon 20 Insertion Mutations Whose Disease Has Progressed on or after Platinum-based Chemotherapy and Received RYBREVANT in CHRYSALIS

Adverse Reactions	RYBREVANT[1] (N=129)	
	All Grades (%)	Grades 3 or 4 (%)
Skin and subcutaneous tissue disorders		
Rash*	84	3.9
Pruritus	18	0
Dry skin	14	0
General disorders and administration site conditions		
Infusion-related reaction	64	3.1
Fatigue*	33	2.3
Edema*	27	0.8
Pyrexia	13	0
Infections and infestations		
Paronychia	50	3.1
Pneumonia*	10	0.8
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain*	47	0
Respiratory, thoracic, and mediastinal disorders		
Dyspnea*	37	2.3
Cough*	25	0
Gastrointestinal disorders		
Nausea	36	0
Stomatitis*	26	0.8
Constipation	23	0
Vomiting	22	0
Diarrhea	16	3.1
Abdominal Pain*	11	0.8
Vascular disorders		
Hemorrhage*	19	0
Metabolism and nutrition disorders		
Decreased appetite	15	0
Nervous system disorders		
Peripheral neuropathy*	13	0
Dizziness	12	0.8
Headache*	10	0.8

* Grouped term
[1] Adverse reactions were graded using CTCAE version 4.03

Clinically relevant adverse reactions in < 10% of patients who received RYBREVANT included ocular toxicity, ILD/pneumonitis, and toxic epidermal necrolysis (TEN).

Table 8 summarizes the laboratory abnormalities in CHRYSALIS.

Table 8: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients With Metastatic NSCLC with EGFR Exon 20 Insertion Mutations Whose Disease Has Progressed on or After Platinum-based Chemotherapy and Who Received RYBREVANT in CHRYSALIS

Laboratory Abnormality	RYBREVANT+ (N=129)	
	All Grades (%)	Grades 3 or 4 (%)
Chemistry		
Decreased albumin	79	8
Increased glucose	56	4
Increased alkaline phosphatase	53	4.8
Increased creatinine	46	0
Increased alanine aminotransferase	38	1.6
Decreased phosphate	33	8
Increased aspartate aminotransferase	33	0
Decreased magnesium	27	0
Increased gamma-glutamyl transferase	27	4
Decreased sodium	27	4
Decreased potassium	26	6
Hematology		
Decreased lymphocytes	36	8

+ The denominator used to calculate the rate was 126 based on the number of patients with a baseline value and at least one post-treatment value.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on the mechanism of action and findings in animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. There are no available data on the use of RYBREVANT in pregnant women or animal data to assess the risk of RYBREVANT in pregnancy. Disruption or depletion of EGFR in animal models resulted in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development. The absence of EGFR or MET signaling has resulted in embryo lethality, malformations, and post-natal death in animals *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

No animal studies have been conducted to evaluate the effects of amivantamab-vmjw on reproduction and fetal development; however, based on its mechanism of action, RYBREVANT can cause fetal harm or developmental anomalies. In mice, EGFR is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-fetal/postnatal survival and development. Reduction or elimination of embryo-fetal or maternal EGFR signaling can prevent implantation, can cause embryo-fetal loss during various stages of gestation (through effects on placental development) and can cause developmental anomalies and early death in surviving fetuses. Adverse developmental outcomes were observed in multiple organs in embryos/neonates of mice with disrupted EGFR signaling. Similarly, knock out of MET or its ligand HGF was embryonic lethal due to severe defects in placental development, and fetuses displayed defects in muscle development in multiple organs. Human IgG1 is known to cross the placenta; therefore, amivantamab-vmjw has the potential to be transmitted from the mother to the developing fetus.

Lactation

Risk Summary

There are no data on the presence of amivantamab-vmjw in human milk, the effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions from RYBREVANT in breast-fed children, advise women not to breastfeed during treatment with RYBREVANT and for 3 months after the last dose.

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

Females

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

Pediatric Use

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

Geriatric Use

- Of the 421 patients with locally advanced or metastatic NSCLC treated with RYBREVANT in combination with lazertinib in the MARIPOSA study, 45% were ≥ 65 years of age and 12% were ≥ 75 years of age.
- Of the 130 patients with locally advanced or metastatic NSCLC treated with RYBREVANT in combination with carboplatin and pemetrexed in the MARIPOSA-2 study, 40% were ≥ 65 years of age and 10% were ≥ 75 years of age.
- Of the 151 patients with locally advanced or metastatic NSCLC treated with RYBREVANT in combination with carboplatin and pemetrexed in the PAPILLON study, 37% were ≥ 65 years of age and 8% were ≥ 75 years of age.
- Of the 302 patients with locally advanced or metastatic NSCLC treated with RYBREVANT as a single agent in the CHRYSALIS study, 39% were ≥ 65 years of age and 11% were ≥ 75 years of age.

No clinically important differences in safety or efficacy were observed between patients who were ≥ 65 years of age and younger patients.

PATIENT COUNSELING INFORMATION

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

Infusion-Related Reactions

Advise patients that RYBREVANT can cause infusion-related reactions, the majority of which may occur with the first infusion. Advise patients to alert their healthcare provider immediately for any signs or symptoms of infusion-related reactions *[see Warnings and Precautions]*.

RYBREVANT® (amivantamab-vmjw) injection

Interstitial Lung Disease/Pneumonitis

Advise patients of the risks of interstitial lung disease (ILD)/pneumonitis. Advise patients to immediately contact their healthcare provider for new or worsening respiratory symptoms *[see Warnings and Precautions]*.

Venous Thromboembolic Events with Concomitant Use with Lazertinib

When RYBREVANT is used in combination with lazertinib, advise patients of the risks of serious and life threatening venous thromboembolic (VTE) events, including deep venous thrombosis and pulmonary embolism. Advise patients that prophylactic anticoagulants are recommended to be used for the first four months of treatment. Advise patients to immediately contact their healthcare provider for signs and symptoms of venous thromboembolism *[see Warnings and Precautions]*.

Dermatologic Adverse Reactions

Advise patients of the risk of dermatologic adverse reactions. Advise patients to apply alcohol-free (e.g., isopropanol-free, ethanol-free) emollient cream to reduce the risk of skin reactions. Consider prophylactic measures (e.g., use of oral antibiotics) to reduce the risk of dermatologic adverse reactions. Advise patients to limit direct sun exposure during and for 2 months after treatment, to use broad-spectrum UVA/UVB sunscreen, and to wear protective clothing during treatment with RYBREVANT *[see Warnings and Precautions]*.

Ocular Toxicity

Advise patients of the risk of ocular toxicity. Advise patients to contact their ophthalmologist if they develop eye symptoms and advise discontinuation of contact lenses until symptoms are evaluated *[see Warnings and Precautions]*.

Paronychia/Nail Toxicity

Advise patients of the risk of paronychia. Advise patients to contact their healthcare provider for signs or symptoms of paronychia *[see Adverse Reactions]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment with RYBREVANT and for 3 months after the last dose, and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions, Use in Specific Populations]*.

Lactation

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

Product of Ireland

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

For patent information: www.janssenpatents.com

cp-213278v5

LAZCLUZE™ (lazertinib) tablets, for oral use
Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

LAZCLUZE is indicated in combination with amivantamab for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test *[see Dosage and Administration (2.1) in Full Prescribing Information]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Venous Thromboembolic Events

LAZCLUZE in combination with amivantamab can cause serious and fatal venous thromboembolic events (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE). The majority of these events occurred during the first four months of therapy *[see Adverse Reactions]*.

In MARIPOSA *[see Adverse Reactions]*, VTE occurred in 36% of patients receiving LAZCLUZE in combination with amivantamab, including Grade 3 in 10% and Grade 4 in 0.5% of patients. On-study VTEs occurred in 1.2% of patients (n=5) while receiving anticoagulation therapy. There were two fatal cases of VTE (0.5%), 7% of patients had VTE leading to dose interruptions of LAZCLUZE, 0.5% of patients had VTE leading to dose reductions of LAZCLUZE, and 1.9% of patients permanently discontinued LAZCLUZE due to VTE. The median time to onset of VTEs was 84 days (range: 6 to 777).

Administer prophylactic anticoagulation for the first four months of treatment *[see Dosage and Administration (2.3) in Full Prescribing Information]*. The use of Vitamin K antagonists is not recommended. Monitor for signs and symptoms of VTE and treat as medically appropriate.

Withhold LAZCLUZE and amivantamab based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*. Once anticoagulant treatment has been initiated, resume LAZCLUZE and amivantamab at the same dose level at the discretion of the healthcare provider. In the event of VTE recurrence despite therapeutic anticoagulation, permanently discontinue amivantamab. Continue treatment with LAZCLUZE at the same dose level at the discretion of the healthcare provider *[see Dosage and Administration (2.4) in Full Prescribing Information]*. Refer to the amivantamab prescribing information for recommended amivantamab dosage modification.

Interstitial Lung Disease (ILD)/Pneumonitis

LAZCLUZE in combination with amivantamab can cause interstitial lung disease (ILD)/pneumonitis.

In MARIPOSA *[see Adverse Reactions]*, ILD/pneumonitis occurred in 3.1% of patients treated with LAZCLUZE in combination with amivantamab, including Grade 3 in 1.0% and Grade 4 in 0.2% of patients. There was one fatal case (0.2%) of ILD/pneumonitis and 2.9% of patients permanently discontinued LAZCLUZE and amivantamab due to ILD/pneumonitis *[see Adverse Reactions]*.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold LAZCLUZE and amivantamab in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Dermatologic Adverse Reactions

LAZCLUZE in combination with amivantamab can cause severe rash including dermatitis acneiform, pruritus and dry skin.

In MARIPOSA *[see Adverse Reactions]*, rash occurred in 86% of patients treated with LAZCLUZE in combination with amivantamab, including Grade 3 in 26% of patients. The median time to onset of rash was 14 days (range: 1 to 556 days). Rash leading to dose reduction of LAZCLUZE occurred in 19% of patients, rash leading to dose interruption of LAZCLUZE occurred in 30% of patients, and LAZCLUZE was permanently discontinued due to rash in 1.7% of patients *[see Adverse Reactions]*.

When initiating treatment with LAZCLUZE in combination with amivantamab, administer alcohol-free (e.g., isopropanol-free, ethanol-free) emollient cream to reduce the risk of dermatologic adverse reactions *[see Dosage and Administration (2.3) in Full Prescribing Information]*. Instruct patients to limit sun exposure during and for 2 months after treatment with LAZCLUZE in combination with amivantamab. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen.

Consider prophylactic measures (e.g., use of oral antibiotics) to reduce the risk of dermatologic adverse reactions. If skin reactions develop, administer topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, administer oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, reduce the dose or permanently discontinue LAZCLUZE and amivantamab based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Ocular Toxicity

LAZCLUZE, in combination with amivantamab, can cause ocular toxicity, including keratitis.

In MARIPOSA *[see Adverse Reactions]*, ocular toxicity occurred in 16% of patients treated with LAZCLUZE in combination with amivantamab, including Grade 3 or 4 ocular toxicity in 0.7% of patients. Promptly refer patients presenting with new or worsening eye symptoms to an ophthalmologist. Withhold, reduce the dose or permanently discontinue amivantamab and continue LAZCLUZE based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, LAZCLUZE can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of lazertinib to pregnant animals during the period of organogenesis resulted in reduced embryo-fetal survival and fetal body weight in rats and malformations in rabbits at exposures approximately 4 and 0.5 times, respectively, the human exposure at the recommended dose of 240 mg/day based on AUC.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LAZCLUZE and for 3 weeks after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with LAZCLUZE and for 3 weeks after the last dose *[see Use in Specific Populations]*.

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Venous Thromboembolic Events *[see Warnings and Precautions]*
- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions]*
- Dermatologic Adverse Reactions *[see Warnings and Precautions]*
- Ocular Toxicity *[see Warnings and Precautions]*

Clinical Trials Experience

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

The data described in WARNINGS AND PRECAUTIONS and below reflect exposure to LAZCLUZE in combination with amivantamab in 421 previously untreated patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R substitution mutations in MARIPOSA *[see Clinical Studies (14) in Full Prescribing Information]*. Patients received LAZCLUZE 240 mg orally once daily in combination with amivantamab intravenously at 1,050 mg (for patients < 80 kg) or 1,400 mg (for patients ≥ 80 kg) once weekly for 4 weeks, then every 2 weeks thereafter starting at week 5. Among the 421 patients who received LAZCLUZE in combination with amivantamab, 84% were exposed to LAZCLUZE for ≥ 6 months and 73% were exposed to LAZCLUZE for > 1 year.

The median age of patients who received LAZCLUZE in combination with amivantamab was 64 years (25 to 88); 64% were female; 59% were Asian, 38% were White, 1.7% were American Indian or Alaska Native, 0.7% were Black or African American, 1% were of unknown or other races; 13% were Hispanic or Latino; 67% had Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1, 33% had ECOG PS of 0; 60% had EGFR exon 19 deletions, and 40% had EGFR exon 21 L858R substitution mutations.

Serious adverse reactions occurred in 49% of patients who received LAZCLUZE in combination with amivantamab. Serious adverse reactions occurring in ≥ 2% of patients included VTE (11%), pneumonia (4%), rash and ILD/pneumonitis (2.9% each), COVID-19 (2.4%), and pleural effusion and infusion-related reaction (amivantamab) (2.1% each). Fatal adverse reactions occurred in 7% of patients who received LAZCLUZE in combination with amivantamab due to death not otherwise specified (1.2%); sepsis and respiratory failure (1% each); pneumonia, myocardial infarction, and sudden death (0.7% each); cerebral infarction, pulmonary embolism (PE), and COVID-19 infection (0.5% each); and ILD/pneumonitis, acute respiratory distress syndrome (ARDS), and cardiopulmonary arrest (0.2% each).

Permanent discontinuation of LAZCLUZE due to an adverse reaction occurred in 21% of patients. Adverse reactions which resulted in permanent discontinuation of LAZCLUZE in ≥ 1% of patients included ILD/pneumonitis, pneumonia, VTE, rash, respiratory failure, and sudden death.

Dosage interruption of LAZCLUZE due to an adverse reaction occurred in 72% of patients. Adverse reactions which required dosage interruption in ≥ 5% of patients were rash, nail toxicity, COVID-19, VTE, increased ALT, and increased AST.

Dose reductions of LAZCLUZE due to an adverse reaction occurred in 42% of patients. Adverse reactions requiring LAZCLUZE dose reductions in ≥ 5% of patients were rash and nail toxicity.

The most common adverse reactions (≥ 20%) were rash, nail toxicity, infusion-related reaction (amivantamab), musculoskeletal pain, edema, stomatitis, VTE, paresthesia, fatigue, diarrhea, constipation, COVID-19, hemorrhage, dry skin, decreased appetite, pruritus, nausea, and ocular toxicity. The most common Grade 3 or 4 laboratory abnormalities (≥ 2%) were decreased albumin, decreased sodium, increased ALT, decreased potassium, decreased hemoglobin, increased AST, increased GGT, and increased magnesium.

Table 1 summarizes the adverse reactions (≥ 10%) in MARIPOSA.

Table 1: Adverse Reactions (≥ 10%) in Patients with NSCLC with Exon 19 Deletion or Exon 21 L858R Substitution Mutations in MARIPOSA

Adverse Reaction	LAZCLUZE in combination with amivantamab (N=421)		Osimertinib (N=428)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders				
Rash*	86	26	48	1.2
Nail toxicity*	71	11	34	0.7
Dry skin*	25	1	18	0.2
Pruritus	24	0.5	17	0.2
Injury, poisoning and procedural complications				
Infusion-related reaction†	63	6	0	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	47	2.1	39	1.9
Gastrointestinal disorders				
Stomatitis*	43	2.4	27	0.5
Diarrhea*	31	2.6	45	0.9
Constipation	29	0	13	0
Nausea	21	1.2	14	0.2
Vomiting	12	0.5	5	0
Abdominal pain*	11	0	10	0
Hemorrhoids	10	0.2	2.1	0.2
General disorders and administration site conditions				
Edema*	43	2.6	8	0
Fatigue*	32	3.8	20	1.9
Pyrexia	12	0	9	0
Vascular disorders				
Venous thromboembolism*	36	11	8	2.8
Hemorrhage*	25	1	13	1.2
Nervous system disorders				
Paresthesia*	35	1.7	10	0.2
Dizziness*	14	0	10	0
Headache*	13	0.2	13	0
Infections and infestations				
COVID-19	26	1.7	24	1.4
Conjunctivitis	11	0.2	1.6	0
Metabolism and nutrition disorders				
Decreased appetite	24	1	18	1.4
Respiratory, thoracic and mediastinal disorders				
Cough*	19	0	23	0
Dyspnea*	14	1.7	17	3.5
Eye disorders				
Ocular toxicity*	16	0.7	7	0
Psychiatric disorders				
Insomnia	10	0	11	0

* Grouped terms
† Applicable only to amivantamab

Clinically relevant adverse reactions occurring in < 10% of patients who received LAZCLUZE in combination with amivantamab included ILD/pneumonitis (3.1%).

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Table 2 summarizes the laboratory abnormalities in MARIPOSA.

Table 2: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with NSCLC with EGFR Exon 19 Deletion or Exon 21 L858R Substitution Mutations in MARIPOSA+

Laboratory Abnormality	LAZCLUZE in combination with amivantamab (N=421)		Osimertinib (N=428)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Decreased albumin	89	8	22	0.2
Increased ALT	65	7	29	2.6
Increased AST	52	3.8	36	1.9
Increased alkaline phosphatase	45	0.5	15	0.5
Decreased calcium (corrected)	41	1.4	27	0.7
Increased GGT	39	2.6	24	1.9
Decreased sodium	38	7	35	5
Decreased potassium	30	5	15	1.2
Increased creatinine	26	0.7	35	0.7
Decreased magnesium	25	0.7	10	0.2
Increased magnesium	12	2.6	20	4.8
Hematology				
Decreased platelet count	52	0.7	57	1.4
Decreased hemoglobin	47	3.8	56	1.9
Decreased white blood cell	38	1.0	66	0.7
Decreased neutrophils	15	1.4	33	1.4

+ The denominator used to calculate the rate is the number of patients with a baseline value and at least one post-treatment value for the specific lab test.

DRUG INTERACTIONS

Effect of Other Drugs on LAZCLUZE

CYP3A4 Inducers

Avoid concomitant use of LAZCLUZE with strong and moderate CYP3A4 inducers. Consider an alternate concomitant medication with no potential to induce CYP3A4.

Lazertinib is a CYP3A4 substrate. Concomitant use with a strong or moderate CYP3A4 inducer decreased lazertinib concentrations *[see Clinical Pharmacology (12.3) in Full Prescribing Information],* which may reduce the efficacy of lazertinib.

Effect of LAZCLUZE on Other Drugs

Certain CYP3A4 Substrates

Monitor for adverse reactions associated with a CYP3A4 substrate where minimal concentration changes may lead to serious adverse reactions, as recommended in the approved product labeling for the CYP3A4 substrate.

Lazertinib is a weak CYP3A4 inhibitor. Concomitant use of LAZCLUZE increased concentrations of CYP3A4 substrates *[see Clinical Pharmacology (12.3) in Full Prescribing Information],* which may increase the risk of adverse reactions related to these substrates.

Certain BCRP Substrates

Monitor for adverse reactions associated with a BCRP substrate where minimal concentration changes may lead to serious adverse reactions, as recommended in the approved product labeling for the BCRP substrate.

Lazertinib is a BCRP inhibitor. Concomitant use of LAZCLUZE increased concentrations of BCRP substrates *[see Clinical Pharmacology (12.3) in Full Prescribing Information],* which may increase the risk of adverse reactions related to these substrates.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1) in Full Prescribing Information],* LAZCLUZE can cause fetal harm when administered to a pregnant woman. There are no available data on the use of LAZCLUZE in pregnant women to inform a drug-associated risk. Oral administration of lazertinib to pregnant animals

during the period of organogenesis resulted in reduced embryo-fetal survival and fetal body weight in rats and malformations in rabbits at exposures approximately 4 and 0.5 times, respectively, the human exposure at the recommended dose of 240 mg/day based on AUC *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study, pregnant rats received oral doses of 7.5, 30, or 60 mg/kg/day of lazertinib during the period of organogenesis (gestation day 6 to 17). Lazertinib decreased fetal body weights in association with maternal toxicity at 60 mg/kg/day (approximately 4 times the human exposure at the recommended dose of 240 mg/day based on AUC). In a dose range-finding embryo-fetal development study, oral administration of a higher dose of lazertinib (75 mg/kg/day) to pregnant rats during the period of organogenesis resulted in increased post-implantation loss. In an embryo-fetal development study in rabbits, pregnant animals received oral doses of 5, 25, or 45 mg/kg/day of lazertinib during the period of organogenesis (gestation day 7 to 19). Lazertinib caused maternal toxicity (reduced body weight and food consumption leading to moribund condition and early termination) and an increase in the incidence of skeletal malformations in the vertebra and skull (fused maxillary process/zygomatic arch) at 45 mg/kg/day (approximately 0.5 times the human exposure at the recommended dose of 240 mg/day based on AUC).

Lactation

Risk Summary

There are no data on the presence of lazertinib or its metabolites in human milk or their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with LAZCLUZE and for 3 weeks after the last dose. Refer to the amivantamab prescribing information for lactation information during treatment with amivantamab.

Females and Males of Reproductive Potential

Based on animal data and its mechanism of action, LAZCLUZE can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating LAZCLUZE.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with LAZCLUZE and for 3 weeks after the last dose. Refer to the amivantamab prescribing information for recommended duration of contraception during treatment with amivantamab.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with LAZCLUZE and for 3 weeks after the last dose.

Infertility

Based on findings in animals, LAZCLUZE may impair fertility in females and males of reproductive potential. The effects on female fertility were reversible. The effects on male testes in animal studies were not reversible within a 2-week recovery period *[see Nonclinical Toxicology (13.1) in Full Prescribing Information]*.

Pediatric Use

The safety and effectiveness of LAZCLUZE in pediatric patients have not been established.

Geriatric Use

Of the 421 patients with locally advanced or metastatic NSCLC treated with LAZCLUZE in combination with amivantamab in MARIPOSA, 45% were 65 years and older and 12% were 75 years and older. No overall differences in safety or effectiveness were observed between patients aged 65 and older and younger patients.

Renal Impairment

No dose adjustment is recommended in patients with mild or moderate renal impairment (eGFR 30 – 89 mL/min) *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

LAZCLUZE has not been studied in patients with severe renal impairment or end-stage renal disease (eGFR < 30 mL/min).

Hepatic Impairment

No dose adjustment is recommended in patients with mild (total bilirubin ≤ ULN and AST > ULN or total bilirubin ≤ 1.5×ULN and any AST) or moderate (total bilirubin ≤ 1.5 to 3×ULN and any AST) hepatic impairment *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

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LAZCLUZE has not been studied in patients with severe hepatic impairment (total bilirubin > 3×ULN and any AST).

PATIENT COUNSELING INFORMATION

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

Venous Thromboembolic Events

Advise patients of the risks of serious and life threatening venous thromboembolic events (VTE), including deep venous thrombosis and pulmonary embolism. Advise patients that prophylactic anticoagulants are recommended to be used for the first four months of treatment. Advise patients to immediately contact their healthcare provider for signs and symptoms of venous thromboembolism *[see Warnings and Precautions]*.

Interstitial Lung Disease/Pneumonitis

Advise patients of the risks of interstitial lung disease (ILD)/pneumonitis. Advise patients to immediately contact their healthcare provider for new or worsening respiratory symptoms *[see Warnings and Precautions]*.

Dermatologic Adverse Reactions

Advise patients of the risk of dermatologic adverse reactions. Advise patients to apply alcohol-free (e.g., isopropanol-free, ethanol-free) emollient cream to reduce the risk of dermatologic adverse reactions. Advise patients to limit direct sun exposure during and for 2 months after treatment, to use broad-spectrum UVA/UVB sunscreen, and to wear protective clothing during treatment with LAZCLUZE. Consider prophylactic measures (e.g., use of oral antibiotics) to reduce the risk of dermatologic adverse reactions *[see Warnings and Precautions]*.

Ocular Toxicity

Advise patients of the risk of ocular adverse reactions. Advise patients to contact their ophthalmologist if they develop eye symptoms. Advise discontinuation of contact lenses until symptoms are evaluated *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment with LAZCLUZE and for 3 weeks after the last dose, and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions, Use in Specific Populations]*. Refer to the amivantamab prescribing information for recommended duration of contraception during treatment with amivantamab.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with LAZCLUZE and for 3 weeks after the last dose *[see Use in Specific Populations]*.

Lactation

Advise women not to breastfeed during treatment with LAZCLUZE and for 3 weeks after the last dose *[see Use in Specific Populations]*. Refer to the amivantamab prescribing information for lactation information during treatment with amivantamab.

Infertility

Advise males and females of reproductive potential of the potential risk for impaired fertility with LAZCLUZE *[see Nonclinical Toxicology (13.1) in Full Prescribing Information]*.

Product of Belgium

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Follow-Up VISIT from PER®

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3 Things You Should Know About Biomarkers in DLBCL

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LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:
- Identify current and emerging biomarkers that can inform clinical decision-making in patients with DLBCL
- Describe how results of biomarker testing can be used to determine targeted treatments for patients with DLBCL

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Diffuse large-B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma, comprising up to 40% of all newly diagnosed cases.[1] DLBCL is a genetically heterogeneous malignancy with multiple subtypes and recent investigations based on molecular profiles have opened the possibility for personalized therapy in this disease space. Here are 3 things you should know about the use of biomarkers in DLBCL.

1 Biological heterogeneity appears to drive outcomes associated with standard treatment.

The 2 largest cell-of-origin (COO) subtypes arising from different stages of lymphoid differentiation, activated B cell (ABC) and germinal center B cell (GCB), comprise 50% and 30% of DLBCL cases, respectively.[1] Although combination rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) therapy is curative in approximately 60% of patients, those who do not respond to R-CHOP often have dismal outcomes.[2] Patients with the ABC subtype tend to be among those who experience poor outcomes, with a 3-year progression-free survival (PFS) following R-CHOP of 40% vs 75% in patients with GCB DLBCL ($P < .001$).[3]

Timely identification of patients' COO subtypes can enable the creation of individualized treatment plans to promote optimal patient outcomes. With that goal in mind, the Lymphoma/Leukemia Molecular Profiling Project developed the Lymph2Cx assay, a digital gene expression (NanoString)–based test to assign COO using immunohistochemistry on formalin-fixed paraffin-embedded tissue.[4] This protocol uses less expensive tests on more readily available material than previous assays. Validation of the Lymph2Cx assay against the gold-standard gene expression profiling methods using a cohort of 20 genes resulted in Lymph2Cx correctly designating 57 of 58 cases (98%) as ABC, GCB, or unclassified (5%-7% of cases). COO classification using the Lymph2Cx method correlated strongly with patient outcomes. Patients with ABC DLBCL were more likely to experience disease progression than those with the GCB subtype (relative risk [RR], 3.6; 95% CI, 1.6-8.4; $P < .001$). When the same participants were classified according to the gold standard, the correlation was less strong (RR, 2.6; 95% CI, 1.1-6.3; $P = .01$).

Although the ABC and GCB subtypes share some targetable oncogenic pathways, they each also have unique genetic alterations that might indicate better efficacy of a drug in one subtype over the other (**Figure**).[2] In a subgroup analysis of the phase 3 POLARIX trial (NCT03274492), the antibody-drug conjugate (ADC) polatuzumab vedotin combined with rituximab, cyclophosphamide, doxorubicin, and prednisone (pola-R-CHP) yielded better outcomes vs R-CHOP in patients with ABC DLBCL but not in patients with GCB DLBCL.[5,6] In the overall population, the 2-year PFS rate was 76.7% (95% CI, 72.7%-80.8%) with pola-R-CHP vs 70.2% (95% CI, 65.8%-74.6%) with R-CHOP.[5] However, the HR for disease progression, relapse, or death for pola-R-CHP vs R-CHOP was 0.34 (95% CI, 0.13-0.85) in the ABC subgroup vs 1.18 (95% CI, 0.75-1.84) in the GCB subgroup.[6] Although the safety profiles of the 2 regimens were generally similar, the incidence of febrile neutropenia was higher among patients receiving pola-R-CHP vs R-CHOP (13.8% vs 8.0%). Therefore, R-CHOP might be the preferred regimen for patients with GCB DLBCL who appear to receive no benefit from pola-R-CHP.

2 Outcomes of patients with double-hit DLBCL are worse than for those with a single *MYC* or *BCL2* aberration.

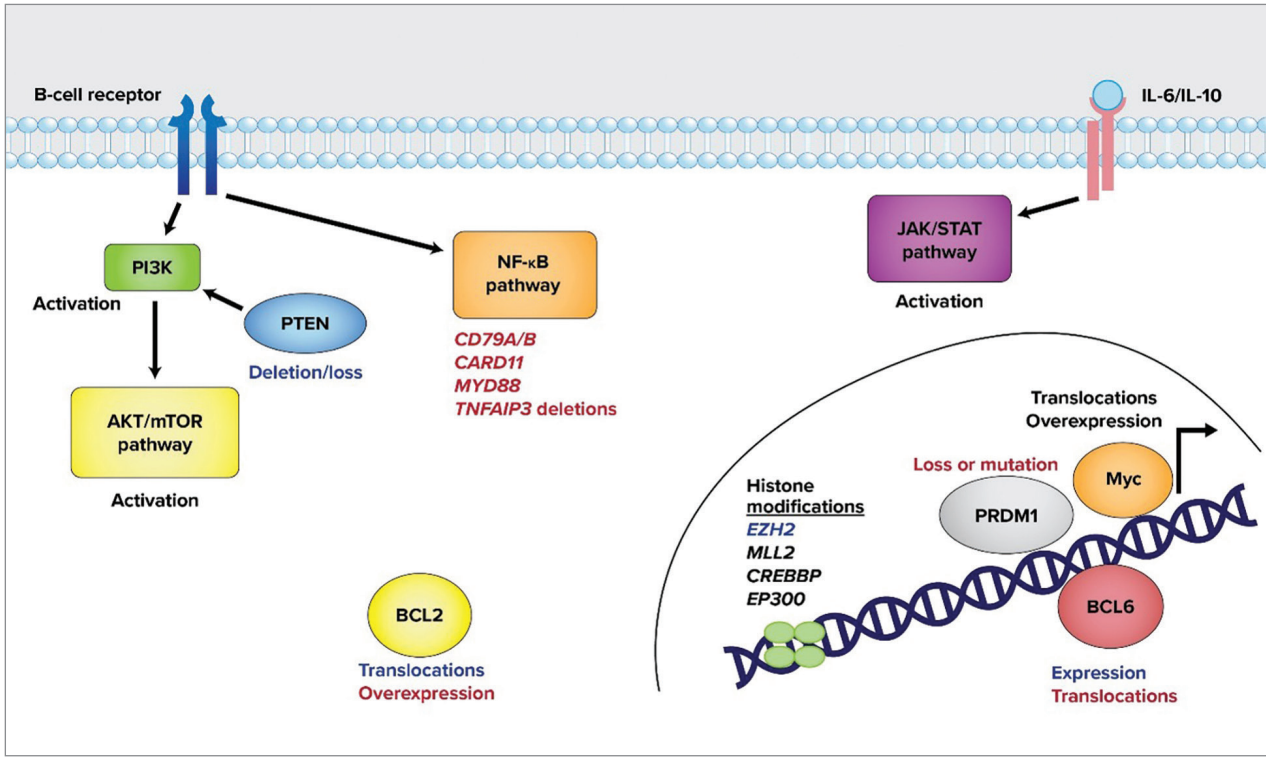
A minority of patients with DLBCL (10%) harbor both *MYC* gene rearrangements, and approximately half of them also harbor rearrangements in *BCL2*, *BCL6,* or both, conditions termed double-hit DLBCL (DHL) and triple-hit DLBCL (THL), respectively.[1] These cases arise largely in the GCB subtype. Multiple retrospective studies suggest that patients with DHL have poorer outcomes with standard therapy. One analysis of 167 patients with DLBCL demonstrated that, relative to the overall population, those with DHL had reduced overall survival (OS) (HR, 3.2; $P = .001$).[7]

Higher-intensity chemoimmunotherapy may provide better outcomes than R-CHOP for patients with DHL. A single-arm, phase 2 study (NCT01092182) enrolled 53 patients with DLBCL, including 19 with *MYC* rearrangements and 24 with DHL to receive dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R).[8] The 48-month event-free survival (EFS) was 71.0% (95% CI, 56.5%-81.4%), and the 48-month OS was 76.7% (95% CI, 62.6%-86.1%). Grade 4 adverse events included neutropenia (53%) and thrombocytopenia (13%). Febrile neutropenia of any grade was reported in 19% of patients. Treatment-related death due to infection occurred in 3 patients. As a result of this study, DA-EPOCH-R became the preferred treatment for patients with DHL.

A subsequent retrospective study of 6412 patients with DLBCL, including 304 with DHL or THL, demonstrated that patients with DHL/THL who received R-EPOCH as first-line treatment (n=131) had significantly improved OS (median not reached [NR]) vs those who received R-CHOP in the first line (n=97; median OS, 20.2 months; 95% CI, 14.8 months to NR).[9] Treatment with R-EPOCH resulted in a 50% lower risk of death (HR, 0.50; 95% CI, 0.33-0.77). There were no significant survival benefits for either regimen in patients without DHL/THL.

Based on the presence of *BCL2* rearrangements in patients with DHL, the Alliance A051701 phase 2/3 study (NCT03984448) investigated the benefit of adding venetoclax to DA-EPOCH-R.[10] There was no benefit to response rates, PFS, or OS with the

FIGURE. Common Signaling Pathway Alterations in DLBCL[2]



ABC, activated B cell; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B cell.
Alterations shown in black are found in all types of DLBCL. Alterations shown in blue are more common to GCB DLBCL. Alterations shown in red are more common to ABC DLBCL.

addition of venetoclax compared with patients receiving only DA-EPOCH-R. Furthermore, 6 patients (17%) receiving venetoclax plus DA-EPOCH-R died during treatment due to sepsis (n=4) or cardiac arrest (n=2) vs 1 patient (3%) in the DA-EPOCH-R–only arm (due to *Pneumocystis jirovecii* pneumonia).

An alternative drug combination of cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate with ifosfamide, etoposide, high-dose cytarabine and rituximab (CODOX-M/IVAC-R) was compared with DA-EPOCH-R in a retrospective analysis of 113 patients younger than 60 years who had DHL/THL.[11] Complete response was achieved by 80% of the 49 patients receiving CODOX-M/IVAC-R vs 58% of the 64 patients receiving DA-EPOCH-R. Additionally, treatment with CODOX-M/IVAC-R was associated with improved EFS vs DA-EPOCH-R (HR, 0.54; 95% CI, 0.31-0.97). However, there was no OS benefit.

3 ADCs may represent new options for patients with R/R DLBCL.

Outcomes tend to be dismal for patients with relapsed/refractory (R/R) DLBCL. The ECHELON-3 trial (NCT04404283) investigated whether adding the anti-CD30 ADC brentuximab vedotin (BV) to lenalidomide plus rituximab (R^2) could improve outcomes for patients with R/R DLBCL who were ineligible for transplant or chimeric antigen receptor (CAR) T-cell therapy.[12] Results are outlined in the **Table**.[12] Benefit with BV plus R^2 was even seen in patients without high expression of CD30.

The search is ongoing for a curative therapy for patients who do not respond to R-CHOP; however, outcomes are steadily improving with novel therapy combinations. ■

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FOR FULL LIST OF REFERENCES, VISIT
https://www.gotoper.com/bdlbcl24etdio-postref

TABLE. Addition of Brentuximab Vedotin to Lenalidomide and Rituximab in R/R DLBCL[12]

OVERALL	ORR, % (95% CI)	CR, %	MEDIAN OS, MO (95% CI)	MEDIAN PFS, MO (95% CI)
BV + R²	64.3 (54.7%-73.1%)	40.2	13.8 (10.3-18.8)	4.2 (2.9-7.1)
Placebo + R²	41.5 (32.5%-51.0%)	18.6	8.5 (5.4-11.7)	2.6 (1.4-3.1)
HR (95% CI)	*P* = .0006	-	0.629 (0.446-0.891) *P* = .0085	0.527 (0.380-0.729) *P* < .0001
BV + R² Subgroups				
CD30+	72.2	38.9	-	-
CD30–	60.5	40.8	-	-

BV, brentuximab vedotin; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R², lenalidomide plus rituximab; R/R, relapsed/refractory.

1 In studies investigating polatuzumab vedotin plus R-CHP versus R-CHOP alone for newly diagnosed or relapsed/refractory DLBCL, which cell of origin subtype appears to benefit most in terms of PFS from polatuzumab vedotin?

A. Activated B-cell like only
B. Germinal center B-cell like only
C. Both activated B-cell like and germinal center B-cell like

2 In the phase 3 ECHELON-3 study, what was the apparent impact of CD30 positivity overall survival with the addition of brentuximab vedotin to lenalidomide plus rituximab for patients with relapsed/refractory DLBCL?

A. There was no clear difference in survival.
B. CD30+ disease was associated with longer survival than CD30– disease.
C. CD30– disease was associated with longer survival than CD30+ disease.

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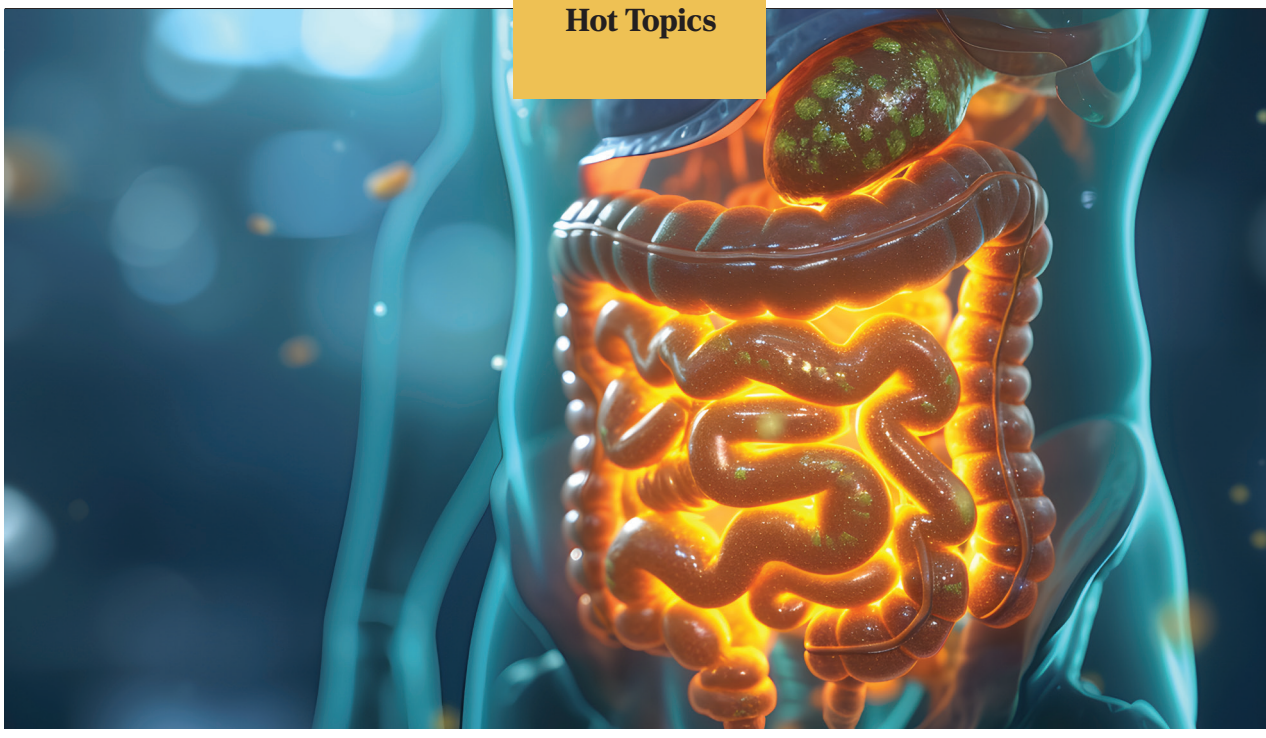

Casting a Wide NET: When Is the Optimal Time for ^{177}Lu-Dotatate Treatment?

Natasha Bahri, MD, MS; Christiana Crook, MS; and Daneng Li, MD

The incidence of neuroendocrine tumors (NETs) in the US is rising, with 8.3 cases per 100,000 individuals diagnosed in 2018 compared with 6.98 cases per 100,000 individuals diagnosed in 2012.[1,2] Most patients with NETs are diagnosed with metastatic disease, at which point curative surgery is no longer a treatment option.[3] Prior to 2017, available treatments for advanced NETs included somatostatin analogues (lanreotide [Somatuline] and octreotide [Sandostatin]), targeted therapy (everolimus [Afinitor] and sunitinib [Sutent]), and chemotherapy.[4-7] In 2017, the World Health Organization added a classification for well-differentiated grade 3 NETs (Ki67 > 20% and ≤ 55%).[8] Previously these tumors were placed under the umbrella of poorly differentiated neuroendocrine carcinomas. Given that well-differentiated grade 3 NETs are relatively new, standard-of-care treatment options are undefined.

NETTER-1 Trial

The international, randomized phase 3 NETTER-1 trial (NCT01578239) evaluated a novel radioligand therapy in patients with inoperable, locally advanced or metastatic, grade 1/2 midgut NETs who had progressed on octreotide long-acting repeatable (LAR). Patients were randomly assigned to either lutetium 177 dotatate (^{177}Lu-dotatate; Lutathera) with standard-dose octreotide (n=111) or high-dose octreotide alone (n=110).[9] ^{177}Lu-dotatate significantly prolonged progression-free survival (PFS) vs high-dose octreotide, with an HR of 0.18 (95% CI, 0.11-0.29; $P < .0001$). The median overall survival (OS) was 48.0 months in the ^{177}Lu-dotatate group and 36.3 months in the control group (HR, 0.84; 95% CI, 0.60-1.17; 2-sided $P = .30$).

Importantly, 2 (2%) of 111 patients given ^{177}Lu-dotatate developed myelodysplastic syndrome (MDS), 1 of whom died 33 months after randomization (the only reported ^{177}Lu-dotatate–related death). Data from NETTER-1 and the single-center retrospective ERASMUS trial, a single-center retrospective study of ^{177}Lu-dotatate in patients with gastroenteropancreatic NETS, led to the FDA approval of ^{177}Lu-dotatate in patients with somatostatin receptor–positive grade 1 and 2 gastroenteropancreatic NETs.[10,11]

NETTER-2 Trial

NETTER-2 (NCT03972488) is a phase 3 international, randomized study of patients with locally advanced or metastatic, well-differentiated, somatostatin receptor–positive, high grade 2 (Ki67 ≥ 10% and ≤ 20%) or grade 3 (Ki67 > 20% and ≤ 55%) gastroenteropancreatic NETs.[12] Patients were randomly assigned to either 4 cycles of ^{177}Lu-dotatate plus intramuscular octreotide 30 mg LAR then octreotide 30 mg LAR every 4 weeks (^{177}Lu-dotatate,

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n=151) or high-dose octreotide 60 mg LAR every 4 weeks (control, n=75). The primary end point was PFS; secondary end points included objective response rate (ORR), disease control rate (DCR), quality of life (QOL), OS, and safety.

The median PFS was 22.8 months (95% CI, 19.4-not estimated) in the ^{177}Lu-dotatate group and 8.5 months (95% CI, 7.7-13.8) in the control group. Response rates were higher in the ^{177}Lu-dotatate group (ORR, 43.0%; DCR, 90.7%) compared with the control group (ORR, 9.3%; DCR, 66.7%). There was no significant difference in QOL measurements between groups. OS data are immature; median OS had not yet been reached for either arm.

The most common any-grade adverse effects were nausea (27% vs 18%), diarrhea (26% vs 34%), and abdominal pain (18% vs 27%) in the ^{177}Lu-dotatate and control groups, respectively. Grade 3 or higher hematologic toxicities were reported in 20 patients (14%) in the ^{177}Lu-dotatate arm and 1 patient (1%) in the control arm. One patient in the ^{177}Lu-dotatate arm developed MDS. There were no study drug-related deaths during the treatment period.

QOL Considerations in NETTER-2

Though the PFS data from NETTER-2 are promising, there are several reasons to proceed with caution in applying these results to all patients with high grade 2 and grade 3 NETs in the frontline setting. Patients with NETs have previously emphasized the importance of maintaining QOL during and after treatment. A cross-sectional survey study asked patients with advanced NETs starting a new line of systemic therapy about treatment goals and preferences.[13] A majority of patients (70%) indicated that their primary goal of treatment was not survival, selecting maintenance of QOL and reduction in pain/symptoms as more important. Additionally, patients stated that they valued the quantity as well as the quality of their life in both the present (ie, during treatment) and the future (both short term [1 year from now] and long term [5 years from now]). Given that there was no difference in QOL between the ^{177}Lu-dotatate and control arms in NETTER-2, it is difficult to recommend ^{177}Lu-dotatate as a first-line therapy for all-comers.

In addition to the lack of improvement in QOL, the hematologic toxicities and risk of MDS are important. When extrapolated to a broader population, the 2% of patients in NETTER-1 who developed MDS could correlate to roughly 188 individuals (2% of US patients with advanced midgut grade 3 NETs) who could potentially develop this serious adverse effect.[14-16]

Regarding Efficacy and Looking Ahead

Despite significant improvements in PFS among patients treated with ^{177}Lu-Dotatate from both NETTER trials, this has not resulted in any significant improvements in OS, suggesting that subsequent lines of therapy are potentially impactful. In patients with well-differentiated grade 3 NETs, a median OS of 33.8 months has been reported, implying that this patient population may have the opportunity to receive multiple lines of therapy.[17] Therefore, the true impact of ^{177}Lu-dotatate in the frontline setting compared with later lines of therapy requires additional investigation.

Though the PFS data from NETTER-2 are promising, there are several reasons to proceed with caution in applying these results to all patients with high grade 2 and grade 3 NETs in the frontline setting.

Without a clear OS advantage and no improvement in QOL, we would be hesitant to unnecessarily expose patients to the risk of MDS or acute leukemias in the first-line setting.

Looking forward, it will be pertinent to see long-term data for OS, QOL, and safety in NETTER-2 before ^{177}Lu-dotatate can be fully considered for use in the first-line setting for patients with high grade 2 and grade 3 NETs.

NETTER-2 provides intriguing results in the management of patients with high grade 2 and grade 3 NETs. However, many major questions remain in terms of ideal patient selection for use in the first-line setting. Given the absence of OS and QOL advantage, in addition to the risk of MDS and acute leukemias, studies evaluating ideal sequencing of therapies to better characterize the optimal timing for ^{177}Lu-Dotatate treatment are needed. ■

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Precision Medicine in NSCLC
The Power of Molecular Testing

RELEASE DATE: November 1, 2024
EXPIRATION DATE: November 1, 2025

LEARNING OBJECTIVES

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

- Apply molecular testing strategies effectively to identify targetable mutations in clinical practice
- Apply results of molecular profiling of NSCLC to individualized treatment plans for patients
- Implement practices to facilitate real-time updates and adjustments to treatment plans based on evolving biomarker status.

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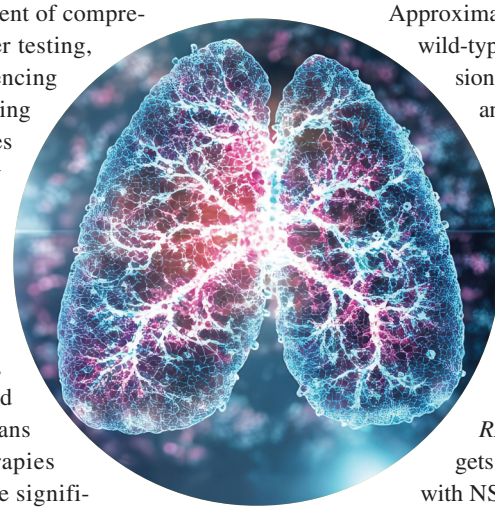
Evolution of Personalized Therapy via Biomarker Testing

Personalized therapy for non–small cell lung cancer (NSCLC) has evolved significantly with the advent of comprehensive molecular testing.[1] Biomarker testing, specifically via next-generation sequencing (NGS), has become crucial for identifying driver mutations. These testing strategies facilitate timely and precise delivery of targeted therapy, which has shown meaningful improvements in overall survival (OS) in NSCLC.[2]



Biomarker testing allows the identification of actionable mutations to guide treatment decisions, avoid unnecessary chemotherapy, and implement individualized treatment plans based on molecular profiling.[3] Therapies targeted to biomarkers identified have significantly extended progression-free survival (PFS) and overall response rates (ORRs).[3] Therapy selection relies on accurate molecular profiling to determine the most effective targeted therapy.[3]

Managing NSCLC With *MET* Mutations

MET alterations, including *MET* exon 14 skipping mutations and amplifications, are significant therapeutic targets in NSCLC.[3] Approximately 3% to 4% of patients with NSCLC will harbor *MET* exon 14 skipping mutations.[4] The MET tyrosine kinase inhibitors crizotinib, capmatinib, and tepotinib have demonstrated efficacy in patients with these mutations.[5-7]

In the PROFILE 1001 (NCT00585195) trial, crizotinib use was studied in patients with *MET* exon 14 skipping mutations.[5] Results showed an ORR of 32% with a median duration of response (mDOR) of 9.1 months and a median PFS (mPFS) of 7.3 months. Common treatment-related adverse events (TRAEs) included edema (51%), vision disorder (45%), nausea (41%), diarrhea (39%), and vomiting (29%).

Capmatinib demonstrated efficacy in the GEOMETRY Mono-1 trial (NCT02414139) in the first-line setting (ORR, 67%; mDOR, 12.6 months; PFS, 12.3 months; OS, 20.8 months) and the second-line setting (ORR, 44%; mDOR, 9.7 months; and PFS, 5.5 months).[6] Grade 3/4 TRAEs occurred in 68.5% of patients.

Tepotinib showed substantial activity in *MET* exon 14 skipping mutation–positive NSCLC in the VISION trial (NCT02864992).[7] The trial reported an ORR of 54% in treatment-naive patients and of 44% in previously treated patients (second line or more) with an mDOR of 11.1 months. The mPFS was 10.4 and 11.0 months in the first line and second line and beyond, respectively. Peripheral edema was the most common TRAE of at least grade 3, occurring in 7% of patients.

Approximately one quarter of patients with *EGFR* wild-type NSCLC have c-Met protein overexpression.[8] Telisotuzumab vedotin, a c-Met–directed antibody-drug conjugate, resulted in ORRs of 34.6% and 22.95% in patients with high and intermediate expression, respectively, in patients who had received 2 or fewer prior lines of therapy. The ORR was 28.6%. Grade 5 interstitial lung disease and respiratory failure occurred in 2 patients.

RET Fusion–Targeted Therapy

RET fusions represent key therapeutic targets in NSCLC, with 1% to 2% of all patients with NSCLC harboring *RET* fusions.[9] In general, *RET* fusions do not occur concurrently with alterations in *EGFR*, *ALK*, *ROS1*, *BRAF*, or *KRAS*.[10] Use of the selective RET inhibitors selpercatinib and pralsetinib demonstrated significant efficacy in clinical trials.

Outcomes of the LIBRETTO-001 trial (NCT03157128) showed that use of selpercatinib resulted in an ORR of 84% in treatment-naive patients and of 61% in those previously treated with platinum-based chemotherapy.[11] The mPFS when the drug was used in the first or second lines was 22.0 vs 24.9 months, respectively.

When compared with chemotherapy plus pembrolizumab, first-line selpercatinib resulted in improved PFS (24.8 vs 11.2 months; HR, 0.46; $P<.001$), ORR (84% vs 65%), and DOR (24.2 vs 11.5 months) in a phase 3 LIBRETTO-431 trial (NCT04194944).[12]

In the ARROW trial (NCT03037385), pralsetinib demonstrated an ORR of 72% in treatment-naive patients and 59% in patients previously treated with platinum-based chemotherapy.[13,14] The mDOR was not reached in treatment-naive patients and was 22.3 months in previously treated patients.

The ongoing, phase 3 AcceleRET Lung trial (NCT04222972) is assessing pralsetinib vs standard-of-care therapy for *RET* fusion–positive NSCLC in the first-line setting.[15] PFS is the primary end point, and the estimated completion date is June 2025.

In perioperative trials, such as the LIBRETTO-432 (NCT04819100) and NAUTIKA1 (NCT04302025) studies, the role of selpercatinib and other targeted therapy in stage II to III NSCLC is being explored.[16,17]

Targeting *KRAS* Mutations

KRAS mutations, particularly *KRAS* G12C, represent a common

and challenging target in NSCLC. The development of the selective KRAS G12C inhibitors sotorasib and adagrasib has marked a significant advancement in the management of these mutations.

Sotorasib resulted in an ORR of 37.1% (including a 3.2% complete response rate) with a median PFS and OS of 6.8 and 12.5 months, respectively, in the phase 2 CodeBreaK 100 trial (NCT03600883) in patients previously treated with platinum-based chemotherapy and PD-L1 inhibitors.[18]

In the phase 3 CodeBreaK 200 trial (NCT04303780), sotorasib was compared with docetaxel in previously treated patients with *KRAS* G12C–mutated NSCLC.[19] Sotorasib demonstrated a superior ORR of 28% compared with 13% with use of docetaxel. The mPFS was longer with sotorasib (5.6 vs 4.5 months, respectively; HR, 0.66; $P = .0017$). Patients treated with sotorasib experienced fewer grade TRAEs of at least grade 3 (18% vs 34%).

> **Approximately one-quarter of patients with *EGFR* wild-type NSCLC have c-Met protein overexpression.**

In the phase 1/2 KRYSTAL-1 trial (NCT03785249), adagrasib was evaluated in previously treated patients with *KRAS* G12C–mutated NSCLC.[20] Adagrasib demonstrated an ORR of 42.9% with an mPFS of 6.5 months. Additionally, the mDOR was 8.2 months. Follow-up data revealed an OS of 12.6 months. Notably, the intracranial ORR was 33.3%. TRAEs of at least grade 3 occurred in 44.8% of patients, with 6.9% of patients discontinuing treatment based on AEs.

Further expanding on the results of KRYSTAL-1, adagrasib was compared with docetaxel in patients with *KRAS* G12C–mutated NSCLC in the KRYSTAL-12 trial (NCT04685135).[21] Primary results showed a significantly longer PFS (5.49 vs 3.84 months; HR, 0.58; $P < .0001$) and higher ORR (32% vs 9%; OR 4.68; $P < .0001$) with adagrasib than with docetaxel. The mDOR was also longer in the adagrasib group (8.3 vs 5.4 months, respectively). Rates of TRAEs of grade 3 or more were similar in both groups (47.0% vs 45.7%). AEs led to treatment discontinuation in 7.7% and 14.3% of patients treated with adagrasib and docetaxel, respectively. ■

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IMPORTANT SAFETY INFORMATION (cont'd)

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

Immune-Mediated Pneumonitis

- OPDIVO and YERVOY can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-Mediated Colitis

- OPDIVO and YERVOY can cause immune-mediated colitis, which may be fatal. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-Mediated Hepatitis and Hepatotoxicity

- OPDIVO and YERVOY can cause immune-mediated hepatitis.

Immune-Mediated Endocrinopathies

- OPDIVO and YERVOY can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated.

Immune-Mediated Nephritis with Renal Dysfunction

- OPDIVO and YERVOY can cause immune-mediated nephritis.

Immune-Mediated Dermatologic Adverse Reactions

- OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.
- YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, SJS, TEN, and DRESS. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes.
- Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

Other Immune-Mediated Adverse Reactions

- The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO monotherapy or OPDIVO in combination with YERVOY or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *cardiac/vascular:* myocarditis, pericarditis, vasculitis; *nervous system:* meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *ocular:* uveitis, iritis, and other ocular inflammatory toxicities can occur; *gastrointestinal:* pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis; *musculoskeletal and connective tissue:* myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica; *endocrine:* hypoparathyroidism; *other (hematologic/immune):* hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft)

Other Immune-Mediated Adverse Reactions (cont'd)

- In addition to the immune-mediated adverse reactions listed above, across clinical trials of YERVOY monotherapy or in combination with OPDIVO, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified: *nervous system:* autoimmune neuropathy (2%), myasthenic syndrome/myasthenia gravis, motor dysfunction; *cardiovascular:* angiopathy, temporal arteritis; *ocular:* blepharitis, episcleritis, orbital myositis, scleritis; *gastrointestinal:* pancreatitis (1.3%); *other (hematologic/immune):* conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, hypersensitivity vasculitis, neurosensory hypoacusis, psoriasis.

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

- Some ocular IMAR cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, which has been observed in patients receiving OPDIVO and YERVOY, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

Infusion-Related Reactions

- OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation

- Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with OPDIVO or YERVOY. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between OPDIVO or YERVOY and allogeneic HSCT.
- Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with OPDIVO and YERVOY prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity

- Based on its mechanism of action and findings from animal studies, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. The effects of YERVOY are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and YERVOY and for at least 5 months after the last dose.

Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone

- In randomized clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Lactation

- There are no data on the presence of OPDIVO or YERVOY in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 5 months after the last dose.

Serious Adverse Reactions

- In Checkmate 9LA, serious adverse reactions occurred in 57% of patients (n=358). The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia.

Common Adverse Reactions

- In Checkmate 9LA, the most common (>20%) adverse reactions were fatigue (49%), musculoskeletal pain (39%), nausea (32%), diarrhea (31%), rash (30%), decreased appetite (28%), constipation (21%), and pruritus (21%).

Please see Brief Summary of Prescribing information for **OPDIVO** and **YERVOY** on the following pages.

Study design: Checkmate 9LA was a randomized, open-label phase 3 study of OPDIVO 360 mg q3w in combination with YERVOY 1 mg/kg q6w and 2 cycles of histology-based chemotherapy versus 4 cycles of platinum-doublet chemotherapy as a first-line treatment in patients with metastatic or recurrent NSCLC regardless of histology or PD-L1 status. Treatment continued until disease progression, unacceptable toxicity, or for up to 2 years. The primary endpoint was OS.[1]

References: 1. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. **2.** Reck M, Ciuleanu TE, Schenker M, et al. Five-year outcomes with first-line nivolumab plus ipilimumab with chemotherapy vs chemotherapy in patients with metastatic NSCLC in CheckMate 9LA. Poster presentation at ASCO 2024. Abstract 8560. **3.** Reck M, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone (four cycles) in advanced non-small-cell lung cancer: CheckMate 9LA 2-year update. *ESMO Open*. 2021;6(5):100273. **4.** YERVOY [package insert]. Princeton, NJ: Bristol-Myers Squibb Company.

OPDIVO® (nivolumab) INJECTION FOR INTRAVENOUS USE 10 mg/mL + YERVOY® (ipilimumab) Injection for intravenous use 5 mg/mL

Please also see Brief Summary for YERVOY® (ipilimumab) following OPDIVO® (nivolumab).

OPDIVO® (nivolumab) injection, for intravenous use

℞ ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

- OPDIVO (nivolumab), in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.

DOSAGE AND ADMINISTRATION

Patient Selection

Select patients with metastatic NSCLC for treatment with OPDIVO in combination with ipilimumab based on PD-L1 expression *[see Clinical Studies (14.4) in full Prescribing Information]*. Information on FDA-approved tests for the determination of PD-L1 expression in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS

Severe and Fatal Immune-Mediated Adverse Reactions

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

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

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

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

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

Immune-Mediated Pneumonitis

OPDIVO can cause immune-mediated pneumonitis, which is defined as requiring use of steroids and no clear alternate etiology. In patients treated with other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

In NSCLC, immune-mediated pneumonitis occurred in 9% (50/576) of patients receiving OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks, including Grade 4 (0.5%), Grade 3 (3.5%), and Grade 2 (4.0%) immune-mediated pneumonitis. Four patients (0.7%) died due to pneumonitis. Immune-mediated pneumonitis led to permanent discontinuation of OPDIVO with ipilimumab in 5% of patients and withholding of OPDIVO with ipilimumab in 3.6% of patients.

Systemic corticosteroids were required in 100% of patients with pneumonitis. Pneumonitis resolved in 72% of the patients. Approximately 13% (2/16) of patients had recurrence of pneumonitis after reinitiation of OPDIVO with ipilimumab.

Immune-Mediated Colitis

OPDIVO can cause immune-mediated colitis, defined as requiring use of corticosteroids and no clear alternate etiology. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-Mediated Hepatitis and Hepatotoxicity

OPDIVO can cause immune-mediated hepatitis, defined as requiring the use of corticosteroids and no clear alternate etiology.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

OPDIVO can cause primary or secondary adrenal insufficiency. For grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold OPDIVO depending on severity *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Hypophysitis

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

Thyroid Disorders

OPDIVO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management as clinically indicated. Withhold or permanently discontinue OPDIVO depending on severity *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold OPDIVO depending on severity *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Immune-Mediated Nephritis with Renal Dysfunction

OPDIVO can cause immune-mediated nephritis, which is defined as requiring use of steroids and no clear alternate etiology.

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash or dermatitis, defined as requiring the use of steroids and no clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson Syndrome, toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) has occurred with PD-1/L-1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue OPDIVO depending on severity *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO or OPDIVO in combination with ipilimumab, or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy

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

Gastrointestinal: Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis

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

Endocrine: Hypoparathyroidism

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

Infusion-Related Reactions

OPDIVO (nivolumab) can cause severe infusion-related reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1 receptor blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause) *[see Adverse Reactions]*. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1 receptor blocking antibody prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months after the last dose *[see Use in Specific Populations]*.

Increased Mortality in Patients with Multiple Myeloma when OPDIVO Is Added to a Thalidomide Analogue and Dexamethasone

In randomized clinical trials in patients with multiple myeloma, the addition of a PD-1 blocking antibody, including OPDIVO, to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling *[see Warnings and Precautions]*: Severe and Fatal Immune-Mediated Adverse Reactions, Infusion-Related Reactions, Complications of Allogeneic HSCT.

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 data in WARNINGS AND PRECAUTIONS reflect exposure to OPDIVO as a single agent in 1994 patients enrolled in CHECKMATE-037, CHECKMATE-017, CHECKMATE-057, CHECKMATE-066, CHECKMATE-025, CHECKMATE-067, CHECKMATE-205, CHECKMATE-039 or a single-arm trial in NSCLC (n=117); OPDIVO 1 mg/kg with ipilimumab 3 mg/kg in patients enrolled in CHECKMATE-067 (n=313), CHECKMATE-040 (n=49), or another randomized trial (n=94); OPDIVO 3 mg/kg administered with ipilimumab 1 mg/kg (n=666) in patients enrolled in CHECKMATE-214 or CHECKMATE-142; OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks in patients enrolled in CHECKMATE-227 (n=576) or CHECKMATE-743 (n=300); and OPDIVO 360 mg with ipilimumab 1 mg/kg and 2 cycles of platinum-doublet chemotherapy in CHECKMATE-9LA (n=361); and OPDIVO 240 mg with cabozantinib 40 mg in patients enrolled in CHECKMATE-9ER (n=320).

First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Ipilimumab and Platinum-Doublet Chemotherapy

The safety of OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was evaluated in CHECKMATE-9LA *[see Clinical Studies (14.4) in full Prescribing Information]*. Patients received either OPDIVO 360 mg administered every 3 weeks in combination with ipilimumab 1 mg/kg administered every 6 weeks and platinum-doublet chemotherapy administered every 3 weeks for 2 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 4 cycles. The median duration of therapy in OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was 6 months (range: 1 day to 19 months): 50% of patients received OPDIVO and ipilimumab for >6 months and 13% of patients received OPDIVO and ipilimumab for >1 year.

Serious adverse reactions occurred in 57% of patients who were treated with OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy. The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia.

Study therapy with OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was permanently discontinued for adverse reactions in 24% of patients and 56% had at least one treatment withheld for an adverse reaction. The most common (>20%) adverse reactions were fatigue, musculoskeletal pain, nausea, diarrhea, rash, decreased appetite, constipation, and pruritus.

Tables 1 and 2 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9LA.

Table 1: Adverse Reactions in >10% of Patients Receiving OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Adverse Reaction	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	49	5	40	4.9
Pyrexia	14	0.6	10	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[b]	39	4.5	27	2.0
Gastrointestinal				
Nausea	32	1.7	41	0.9
Diarrhea[c]	31	6	18	1.7
Constipation	21	0.6	23	0.6
Vomiting	18	2.0	17	1.4
Abdominal pain[d]	12	0.6	11	0.9
Skin and Subcutaneous Tissue				
Rash[e]	30	4.7	10	0.3
Pruritus[f]	21	0.8	2.9	0
Alopecia	11	0.8	10	0.6
Metabolism and Nutrition				
Decreased appetite	28	2.0	22	1.7

(Continued)

Table 1: Adverse Reactions in >10% of Patients Receiving OPDIVO (nivolumab) and Ipilimumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA *(Continued)*

Adverse Reaction	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Respiratory, Thoracic and Mediastinal				
Cough[g]	19	0.6	15	0.9
Dyspnea[h]	18	4.7	14	3.2
Endocrine				
Hypothyroidism[i]	19	0.3	3.4	0
Nervous System				
Headache	11	0.6	7	0
Dizziness[j]	11	0.6	6	0

Toxicity was graded per NCI CTCAE v4.
[a] Includes fatigue and asthenia
[b] Includes myalgia, back pain, pain in extremity, musculoskeletal pain, bone pain, flank pain, muscle spasms, musculoskeletal chest pain, musculoskeletal disorder, osteitis, musculoskeletal stiffness, non-cardiac chest pain, arthralgia, arthritis, arthropathy, joint effusion, psoriatic arthropathy, synovitis
[c] Includes colitis, ulcerative colitis, diarrhea, and enterocolitis
[d] Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, and gastrointestinal pain
[e] Includes acne, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, generalized exfoliative dermatitis, eczema, keratoderma blenorrhagica, palmar-plantar erythrodysaesthesia syndrome, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, morbilliform rash, papular rash, pruritic rash, skin exfoliation, skin reaction, skin toxicity, Stevens-Johnson syndrome, urticaria
[f] Includes pruritus and generalized pruritus
[g] Includes cough, productive cough, and upper-airway cough syndrome
[h] Includes dyspnea, dyspnea at rest, and exertional dyspnea
[i] Includes autoimmune thyroiditis, increased blood thyroid stimulating hormone, hypothyroidism, thyroiditis, and decreased free tri-iodothyronine
[j] Includes dizziness, vertigo and positional vertigo

Table 2: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Laboratory Abnormality	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy		Platinum-Doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	70	9	74	16
Lymphopenia	41	6	40	11
Neutropenia	40	15	42	15
Leukopenia	36	10	40	9
Thrombocytopenia	23	4.3	24	5
Chemistry				
Hyperglycemia	45	7	42	2.6
Hyponatremia	37	10	27	7
Increased ALT	34	4.3	24	1.2
Increased lipase	31	12	10	2.2
Increased alkaline phosphatase	31	1.2	26	0.3
Increased amylase	30	7	19	1.3
Increased AST	30	3.5	22	0.3
Hypomagnesemia	29	1.2	33	0.6
Hypocalcemia	26	1.4	22	1.8
Increased creatinine	26	1.2	23	0.6
Hyperkalemia	22	1.7	21	2.1

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab and platinum-doublet chemotherapy group (range: 197 to 347 patients) and platinum-doublet chemotherapy group (range: 191 to 335 patients).

Immunogenicity

As with all therapeutic proteins, there is a 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 incidence of antibodies to OPDIVO with the incidences of antibodies to other products may be misleading.

Of the patients with NSCLC who were treated with OPDIVO 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and platinum-doublet chemotherapy, and were evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 34% (104/308); the incidence of neutralizing antibodies against nivolumab was 2.6% (8/308).

There was no evidence of increased incidence of infusion-related reactions with anti-nivolumab antibody development.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of OPDIVO. 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. *Eye:* Vogt-Koyanagi-Harada (VKH) syndrome; *Complications of OPDIVO Treatment After Allogeneic HSCT:* Treatment refractory, severe acute and chronic GVHD; *Blood and lymphatic system disorders:* hemophagocytic lymphohistiocytosis (HLH) (including fatal cases), autoimmune hemolytic anemia (including fatal cases).

USE IN SPECIFIC POPULATIONS

PREGNANCY

Risk Summary

Based on data from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1) in full Prescribing Information]*, OPDIVO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death *(see Data)*. Human IgG4 is known to cross the placental barrier and nivolumab is an immunoglobulin G4 (IgG4); therefore, nivolumab has the potential to be transmitted from the mother to the developing fetus. The effects of OPDIVO are likely to be greater during the second and third trimesters of pregnancy. There are no available data on OPDIVO use in pregnant women to evaluate a drug-associated risk. Advise pregnant women of the potential risk to a fetus.

The background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to increase fetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis through delivery, at exposure levels of between 9 and 42 times higher than those observed at the clinical dose of 3 mg/kg (based on AUC). Nivolumab administration resulted in a non-dose-related increase in spontaneous abortion and increased neonatal death. Based on its mechanism of action, fetal exposure to nivolumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice. In surviving infants (18 of 32 compared to 11 of 16 vehicle-exposed infants) of cynomolgus monkeys treated with nivolumab, there were no apparent malformations and no effects on neurobehavioral, immunological, or clinical pathology parameters throughout the 6-month postnatal period.

Lactation

Risk Summary

There are no data on the presence of nivolumab in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment and for 5 months after the last dose of OPDIVO (nivolumab).

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating OPDIVO *[see Use in Specific Populations–Pregnancy]*.

Contraception

OPDIVO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations–Pregnancy]*. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose.

Pediatric Use

The safety and effectiveness of OPDIVO and YERVOY (ipilimumab) have not been established in pediatric patients less than 18 years old with NSCLC *[see Indications and Usage]*.

Geriatric Use

Of the 361 patients with NSCLC who were randomized to OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy, 51% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (43%) relative to all patients who received OPDIVO with ipilimumab and chemotherapy (24%). For patients aged 75 years or older who received chemotherapy only, the discontinuation rate due to adverse reactions was 16% relative to all patients who had a discontinuation rate of 13%. Based on an updated analysis for overall survival, of the 361 patients randomized to OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy, the hazard ratio for overall survival was 0.61 (95% CI: 0.47, 0.80) in the 176 patients younger than 65 years compared to 0.73 (95% CI: 0.56, 0.95) in the 185 patients 65 years or older *[see Clinical Studies (14.4) in full Prescribing Information]*.

PATIENT COUNSELING INFORMATION

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

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and withholding or discontinuation of OPDIVO, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions]*
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions]*
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions]*
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus *[see Warnings and Precautions]*
- Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction *[see Warnings and Precautions]*
- Skin Adverse Reactions: Advise patients to contact their healthcare provider immediately for rash *[see Warnings and Precautions]*.

Infusion-Related Reactions

- Advise patients of the potential risk of infusion-related reactions *[see Warnings and Precautions]*.

Complications of Allogeneic HSCT

- Advise patients of potential risk of post-transplant complications *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions, Use in Specific Populations]*.
- Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose *[see Use in Specific Populations]*.

Lactation

- Advise women not to breastfeed during treatment with OPDIVO and for 5 months after the last dose *[see Use in Specific Populations]*.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
U.S. License No. 1713

Revised: March 2024

YERVOY® (ipilimumab) injection, for intravenous use

℞ ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

- YERVOY (ipilimumab), in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations.

DOSAGE AND ADMINISTRATION

Patient Selection

Select patients with metastatic NSCLC for treatment with YERVOY in combination with nivolumab based on PD-L1 expression *[see Clinical Studies (14.6) in full Prescribing Information]*. Information on FDA-approved tests for the determination of PD-L1 expression in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS

Severe and Fatal Immune-Mediated Adverse Reactions

YERVOY is a fully human monoclonal antibody that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, thereby removing inhibition of the immune response with the potential for induction of immune-mediated adverse reactions. Immune-mediated adverse reactions listed herein may not be inclusive of all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting YERVOY (ipilimumab). While immune-mediated adverse reactions usually manifest during treatment, immune-mediated adverse reactions can also manifest after discontinuation of YERVOY.

Early identification and management are essential to ensure safe use of YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and before each dose. Institute medical management promptly, including specialty consultation as appropriate.

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

Immune-Mediated Colitis

YERVOY can cause immune-mediated colitis, which may be fatal. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-Mediated Dermatologic Adverse Reactions

YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, Stevens Johnson Syndrome, toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms). Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes. Withhold or permanently discontinue YERVOY depending on severity *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Immune-Mediated Endocrinopathies

Hypophysitis:

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

Immune-Mediated Pneumonitis

In NSCLC, immune-mediated pneumonitis occurred in 9% (50/576) of patients receiving YERVOY 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks, including Grade 4 (0.5%), Grade 3 (3.5%), and Grade 2 (4.0%) immune-mediated pneumonitis. Four patients (0.7%) died due to pneumonitis. The median duration was 1.5 months (range: 5 days to 25+ months). Immune-mediated pneumonitis led to permanent discontinuation of YERVOY with nivolumab in 5% of patients and withholding of YERVOY with nivolumab in 3.6% of patients.

Systemic corticosteroids were required in 100% of patients with pneumonitis followed by a corticosteroid taper. Pneumonitis resolved in 72% of the patients. Approximately 13% (2/16) of patients had recurrence of pneumonitis after re-initiation of YERVOY with nivolumab.

Other Immune-Mediated Adverse Reactions

Across clinical trials of YERVOY administered as a single agent or in combination with nivolumab, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified, as shown below:

Nervous System: Autoimmune neuropathy (2%), meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, nerve paresis, motor dysfunction

Cardiovascular: Angiopathy, myocarditis, pericarditis, temporal arteritis, vasculitis

Ocular: Blepharitis, episcleritis, iritis, orbital myositis, scleritis, uveitis. Some cases can be associated with retinal detachment. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving YERVOY and may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

Gastrointestinal: Duodenitis, gastritis, pancreatitis (1.3%)

Musculoskeletal and Connective Tissue: Arthritis, myositis, polymyalgia rheumatica, polymyositis, rhabdomyolysis

Other (hematologic/immune): Aplastic anemia, conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), hypersensitivity vasculitis, meningitis, neurosensory hypoacusis, psoriasis, sarcoidosis, systemic inflammatory response syndrome

Infusion-Related Reactions

Severe infusion-related reactions can occur with YERVOY. Discontinue YERVOY in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Complications of Allogeneic Hematopoietic Stem Cell Transplant after YERVOY

Fatal or serious graft-versus-host disease (GVHD) can occur in patients who receive YERVOY either before or after allogeneic hematopoietic stem cell transplantation (HSCT). These complications may occur despite intervening therapy between CTLA-4 receptor blocking antibody and allogeneic HSCT.

Follow patients closely for evidence of GVHD and intervene promptly *[see Adverse Reactions]*. Consider the benefit versus risks of treatment with YERVOY after allogeneic HSCT.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, YERVOY can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ipilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner. The effects of ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with YERVOY and for 3 months after the last dose *[see Use in Specific Populations]*.

Risks Associated When Administered in Combination with Nivolumab

When YERVOY is administered in combination with nivolumab, refer to the nivolumab Full Prescribing Information for additional risk information that applies to the combination use treatment.

ADVERSE REACTIONS

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

- Severe and fatal immune-mediated adverse reactions *[see Warnings and Precautions]*.
- Infusion-related reactions *[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 with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described in the Warnings and Precautions section reflect exposure to YERVOY 1 mg/kg, administered in combination with nivolumab and platinum-doublet chemotherapy in CHECKMATE-9LA, an open-label, multicenter, randomized trial in adult patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations.

First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Nivolumab and Platinum-Doublet Chemotherapy

The safety of YERVOY in combination with nivolumab and platinum-doublet chemotherapy was evaluated in CHECKMATE-9LA *[see Clinical Studies (14.6) in full Prescribing Information]*. Patients received either YERVOY 1 mg/kg administered every 6 weeks in combination with nivolumab 360 mg administered every 3 weeks and platinum-doublet chemotherapy administered every 3 weeks for 2 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 4 cycles. The median duration of therapy in YERVOY in combination with nivolumab and platinum-doublet chemotherapy was 6 months (range: 1 day to 19 months): 50% of patients received YERVOY and nivolumab for >6 months and 13% of patients received YERVOY and nivolumab for >1 year.

Serious adverse reactions occurred in 57% of patients who were treated with YERVOY in combination with nivolumab and platinum-doublet chemotherapy. The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia.

Study therapy with YERVOY (ipilimumab) in combination with nivolumab and platinum-doublet chemotherapy was permanently discontinued for adverse reactions in 24% of patients and 56% had at least one treatment withheld for an adverse reaction. The most common (>20%) adverse reactions were fatigue, musculoskeletal pain, nausea, diarrhea, rash, decreased appetite, constipation, and pruritus.

Tables 1 and 2 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9LA.

Table 1: Adverse Reactions in >10% of Patients Receiving YERVOY and Nivolumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Adverse Reaction	YERVOY and Nivolumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	49	5	40	4.9
Pyrexia	14	0.6	10	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[b]	39	4.5	27	2.0
Gastrointestinal				
Nausea	32	1.7	41	0.9
Diarrhea[c]	31	6	18	1.7
Constipation	21	0.6	23	0.6
Vomiting	18	2.0	17	1.4
Abdominal pain[d]	12	0.6	11	0.9
Skin and Subcutaneous Tissue				
Rash[e]	30	4.7	10	0.3
Pruritus[f]	21	0.8	2.9	0
Alopecia	11	0.8	10	0.6
Metabolism and Nutrition				
Decreased appetite	28	2.0	22	1.7
Respiratory, Thoracic and Mediastinal				
Cough[g]	19	0.6	15	0.9
Dyspnea[h]	18	4.7	14	3.2
Endocrine				
Hypothyroidism[i]	19	0.3	3.4	0
Nervous System				
Headache	11	0.6	7	0
Dizziness[j]	11	0.6	6	0

Toxicity was graded per NCI CTCAE v4.
[a] Includes fatigue and asthenia
[b] Includes myalgia, back pain, pain in extremity, musculoskeletal pain, bone pain, flank pain, muscle spasms, musculoskeletal chest pain, musculoskeletal disorder, osteitis, musculoskeletal stiffness, non-cardiac chest pain, arthralgia, arthritis, arthropathy, joint effusion, psoriatic arthropathy, synovitis
[c] Includes colitis, ulcerative colitis, diarrhea, and enterocolitis
[d] Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, and gastrointestinal pain
[e] Includes acne, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, generalized exfoliative dermatitis, eczema, keratoderma blenorrhagica, palmar-plantar erythrodysaesthesia syndrome, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, morbilliform rash, papular rash, pruritic rash, skin exfoliation, skin reaction, skin toxicity, Stevens-Johnson syndrome, urticaria
[f] Includes pruritus and generalized pruritus
[g] Includes cough, productive cough, and upper-airway cough syndrome
[h] Includes dyspnea, dyspnea at rest, and exertional dyspnea
[i] Includes autoimmune thyroiditis, increased blood thyroid stimulating hormone, hypothyroidism, thyroiditis, and decreased free tri-iodothyronine
[j] Includes dizziness, vertigo and positional vertigo

Table 2: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on YERVOY and Nivolumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Laboratory Abnormality	YERVOY and Nivolumab and Platinum-Doublet Chemotherapy		Platinum-Doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	70	9	74	16
Lymphopenia	41	6	40	11
Neutropenia	40	15	42	15
Leukopenia	36	10	40	9
Thrombocytopenia	23	4.3	24	5
Chemistry				
Hyperglycemia	45	7	42	2.6
Hyponatremia	37	10	27	7
Increased ALT	34	4.3	24	1.2
Increased lipase	31	12	10	2.2
Increased alkaline phosphatase	31	1.2	26	0.3
Increased amylase	30	7	19	1.3
Increased AST	30	3.5	22	0.3
Hypomagnesemia	29	1.2	33	0.6
Hypocalcemia	26	1.4	22	1.8
Increased creatinine	26	1.2	23	0.6
Hyperkalemia	22	1.7	21	2.1

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: YERVOY and nivolumab and platinum-doublet chemotherapy group (range: 197 to 347 patients) and platinum-doublet chemotherapy group (range: 191 to 335 patients).

Immunogenicity

As with all therapeutic proteins, there is a 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 incidences of antibodies to other studies or to other products may be misleading.

Of 305 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-9LA, 8% were positive for anti-ipilimumab antibodies and 1.6% were positive for anti-ipilimumab neutralizing antibodies. There was no evidence of increased incidence of infusion reactions to YERVOY in patients with anti-ipilimumab antibodies. Of 308 patients evaluable for anti-nivolumab antibodies in CHECKMATE-9LA, 34% were positive for anti-nivolumab antibodies and 2.6% had neutralizing antibodies against nivolumab.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of YERVOY (ipilimumab). 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.

Blood and lymphatic system disorders: hemophagocytic lymphohistiocytosis (HLH)

Immune System: graft-versus-host disease, solid organ transplant rejection

Skin and Subcutaneous Tissue: Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1) in full Prescribing Information]*, YERVOY can cause fetal harm when administered to a pregnant woman. There is insufficient human data for YERVOY exposure in pregnant women. In animal reproduction studies, administration of ipilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner *[see Data]*. The effects of ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Human IgG1 is known to cross the placental barrier and ipilimumab is an IgG1; therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus. Advise pregnant women of the potential risk to a fetus. Report pregnancies to Bristol-Myers Squibb at 1-844-593-7869.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In a combined study of embryo-fetal and peri-postnatal development, pregnant cynomolgus monkeys received ipilimumab every 3 weeks from the onset of organogenesis in the first trimester through parturition. No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, administration of ipilimumab at doses resulting in exposures approximately 2.6 to 7.2 times the human exposure at a dose of 3 mg/kg resulted in dose-related increases in abortion, stillbirth, premature delivery (with corresponding lower birth weight), and an increased incidence of infant mortality. In addition, developmental abnormalities were identified in the urogenital system of 2 infant monkeys exposed in utero to 30 mg/kg of ipilimumab (7.2 times the human exposure based on area under the curve at a dose of 3 mg/kg). One female infant monkey had unilateral renal agenesis of the left kidney and ureter, and 1 male infant monkey had an imperforate urethra with associated urinary obstruction and subcutaneous scrotal edema.

Genetically engineered mice heterozygous for CTLA-4 (CTLA-4^{+}/–), the target for ipilimumab, appeared healthy and gave birth to healthy CTLA-4+/– heterozygous offspring. Mated CTLA-4+/– heterozygous mice also produced offspring deficient in CTLA-4 (homozygous negative, CTLA-4–/–). The CTLA-4–/– homozygous negative offspring appeared healthy at birth, exhibited signs of multiorgan lymphoproliferative disease by 2 weeks of age, and all died by 3 to 4 weeks of age with massive lymphoproliferation and multiorgan tissue destruction.

Lactation

Risk Summary

There are no data on the presence of YERVOY in human milk or its effects on the breastfed child or milk production. In monkeys, ipilimumab was present in milk *(see Data)*. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with YERVOY and for 3 months following the last dose.

Data

In monkeys treated at dose levels resulting in exposures 2.6 and 7.2 times higher than those in humans at a 3 mg/kg dose, ipilimumab was present in milk at concentrations of 0.1 mcg/mL and 0.4 mcg/mL, representing a ratio of up to 0.3% of the steady-state serum concentration of the drug.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating YERVOY *[see Use in Specific Populations–Pregnancy]*.

Contraception

YERVOY can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations–Pregnancy]*. Advise females of reproductive potential to use effective contraception during treatment with YERVOY and for 3 months following the last dose.

Pediatric Use

The safety and effectiveness of OPDIVO (nivolumab) and YERVOY (ipilimumab) have not been established in pediatric patients less than 18 years old with NSCLC.

Geriatric Use

Of the 361 patients randomized to YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 360 mg every 3 weeks and platinum-doublet chemotherapy every 3 weeks (for 2 cycles) in CHECKMATE-9LA (NSCLC), 51% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (43%) relative to all patients who received YERVOY with nivolumab and chemotherapy (24%). For patients aged 75 years or older who received chemotherapy only, the discontinuation rate due to adverse reactions was 16% relative to all patients who had a discontinuation rate of 13%. Based on an updated analysis for overall survival, of the 361 patients randomized to YERVOY in combination with nivolumab and platinum-doublet chemotherapy in CHECKMATE-9LA, the hazard ratio for overall survival was 0.61 (95% CI: 0.47, 0.80) in the 176 patients younger than 65 years compared to 0.73 (95% CI: 0.56, 0.95) in the 185 patients 65 years or older.

PATIENT COUNSELING INFORMATION

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

Immune-Mediated Adverse Reactions

Advise patients that YERVOY can cause immune-mediated adverse reactions including the following *[see Warnings and Precautions]*:

- Immune-Mediated Diarrhea or Colitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of diarrhea or colitis.
- Immune-Mediated Hepatitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatitis.
- Immune-Mediated Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately if they develop a new rash.
- Immune-Mediated Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus
- Immune-Mediated Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening symptoms of pneumonitis.
- Immune-Mediated Nephritis with Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis.

Infusion-Related Reactions

Advise patients who are receiving YERVOY of the potential risk of an infusion-related reaction *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions and Use in Specific Populations]*.
- Advise females of reproductive potential to use effective contraception during treatment with YERVOY and for 3 months after the last dose *[see Use in Specific Populations]*.
- Advise patients who may have been exposed to YERVOY during pregnancy to contact Bristol-Myers Squibb at 1-844-593-7869 *[see Use in Specific Populations]*.

Lactation

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

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
U.S. License No. 1713

Revised: May 2022

7356-US-2400507 09/24

Bristol Myers Squibb®

NOW WITH 5-YEAR DATA

OPDIVO® (nivolumab) INJECTION FOR INTRAVENOUS USE 10 mg/mL + YERVOY® (ipilimumab) Injection for intravenous use 5 mg/mL

and 2 cycles of chemo*

FOR PATIENTS WITH 1L METASTATIC NSCLC[1†]

THEIR **PD-L1** <1% DESERVES YOUR 100%

Reevaluate your current treatment approach.

Give patients with **PD-L1 <1%** a chance for long-term, durable survival with OPDIVO® + YERVOY® and 2 cycles of chemo.[1,2a]

- At the initial pre-specified interim analysis in the ITT population with an 8.1-month minimum follow-up, median OS was 14.1 months (95% CI: 13.2–16.2) with OPDIVO + YERVOY with chemo and 10.7 months (95% CI: 9.5–12.5) with chemo alone; HR=0.69 (96.71% CI: 0.55–0.87); *P*=0.0006[1,3]
- Median OS at the 57.3-month minimum follow-up analysis was 15.8 months (95% CI: 13.9–19.7) with OPDIVO + YERVOY with chemo and 11.0 months (95% CI: 9.5–12.7) with chemo; HR=0.73 (95% CI: 0.62–0.85)[2]
- At the 57.3-month minimum follow-up analysis in patients expressing PD-L1 <1%, 22% were still alive in the OPDIVO + YERVOY with chemo arm (median OS of 17.7 months [95% CI: 13.7–20.3]) compared with 8% in the chemo arm (median OS of 9.8 months [95% CI: 7.7–13.5]); HR=0.63 (95% CI: 0.49–0.83)[2]
- At the 5-year extended follow-up analysis, OS in the ITT population was 18% with OPDIVO + YERVOY with chemo and 11% with chemo alone[2]

[a]Exploratory analysis: Study was not powered for comparison. Minimum/median follow-up for OS: 57.3/64.5 months.[2]

Are you 100% satisfied with your treatment strategy for patients with PD-L1 <1%?

Scan the QR code to see long-term follow-up data

OPDIVO (10 mg/mL) and YERVOY (5 mg/mL) are injections for intravenous use.[1,4]
*Platinum-doublet chemotherapy.[1] †Without *EGFR* or *ALK* aberrations.[1]
1L=first line; ALK=anaplastic lymphoma kinase; CI=confidence interval; EGFR=epidermal growth factor receptor; HR=hazard ratio; ITT=intent to treat; NSCLC=non-small cell lung cancer; OS=overall survival; PD-L1=programmed death ligand 1.

INDICATION

- OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab) and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.

IMPORTANT SAFETY INFORMATION

Severe and Fatal Immune-Mediated Adverse Reactions

- Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune-mediated adverse reactions.
- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO or YERVOY. Early identification and management are essential to ensure safe use of OPDIVO and YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and periodically during treatment with OPDIVO and before each dose of YERVOY. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Severe and Fatal Immune-Mediated Adverse Reactions

- Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO or YERVOY interruption or discontinuation is required, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

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

Your trusted partners in helping to cure patients with ***complex cancers***.

Home to the leading-edge Bone Marrow and Stem Cell Transplant Program, Indiana University Health Medical Center offers a specialized multidisciplinary approach to care in order to achieve the best possible outcomes.

Making history with almost 30 years of breakthroughs in complex cancer treatment.

IU Health Medical Center is at the forefront of helping cure patients through innovative protocols and advanced cellular therapy. As a partner to the only NCI designated comprehensive cancer center in Indiana, we have the long-standing skill and expertise to treat the unique challenges of complex cancers.

SIGNIFICANT CLINICAL AND ACADEMIC ADVANCEMENTS

- **Ensuring patients have access to stem cell transplant early** in the treatment of their disease to help achieve longer remissions.
- **Introducing stem cell transplantation** with high dose carboplatin and etoposide for metastatic germ cell tumors curing 80% of patients.
- **Initiating the use of a novel treatment** to reduce acute graft-versus-host-disease following stem cell transplant.
- **One of the first sites in the country** to access CAR T-cell therapies in achieving long-term remission in lymphoma and leukemia subtypes and are creating new CAR T-cell therapies to help additional patients where no cellular therapy options were available.
- **Pioneering umbilical cord blood transportation** to treat cancer and immune disorders.

NATIONALLY-RECOGNIZED LEADERS

- **A Core Institute** of the Blood and Marrow Transplant Clinical Trials Network, improving your patients outcomes through access to promising therapeutic approaches in large, multi-institutional clinical trials.
- **Accredited by the Foundation for the Accreditation of Cellular Therapy**, providing assurance that your patients are always receiving high quality patient care.
- **Indiana University Medical Center is ranked #1 in Indiana** according to *U.S. News & World Report,* ensuring your patients receive the best care when they need it the most.

ADVANCEMENTS IN CELLULAR THERAPY

We are leading the science in immunotherapy and moving this into first-in-human clinical trials to bring new treatments and therapeutic approaches to the bedside.

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- **Evolving** multiple myeloma treatment protocols
- **CAR T-cell therapy for multiple cancers** and other diseases
- **Experimental peptides** to block or activate immune cells
- **Monoclonal antibodies** to target specific tumors
- **Continuing leadership** in germ-cell tumor protocols for testicular cancer

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