MAY 2024

TACOS ONCOLOGY DRUG NEWSLETTER

The Arizona Clinical Oncology Society

FDA APPROVALS

Idecabtagene vicleucel (ide-cel, Abecma)

Idecabtagene vicleucel (ide-cel, Abecma) has been approved by the FDA for the treatment of patients with relapsed or refractory multiple myeloma (RRMM) who have received an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.*1*

Ide-cel showed a 51% reduction in risk of disease progression or death compared with standard of care (SOC), and it is the first and only chimeric antigen receptor T-cell therapy to show superiority over SOC in triple-class exposed RRMM.

"Regarding the primary end point of the study, which was progression-free survival [PFS], with the extended follow-up, ide-cel continued to show a significant improvement in PFS, with a median PFS of 13.8 months vs 4.4 months in the standard regimen arm with a hazard ratio of 0.49. That means a 51% reduction in the risk of progression and death," Paula Rodríguez Otero, MD, PhD, University Clinic of Navarra, Pamplona, Spain, told *Targeted Therapies in Oncology*.

This approval is based on findings from the phase 3 KarMMA-3 study (NCT03651128). In the study, ide-cel demonstrated a clinically meaningful improvement in PFS, the trial's primary end point, compared with SOC at a median follow-up of 18.6 months. The median PFS was 13.3 months (95% CI, 11.8-16.1) with ide-cel compared with 4.4 months (95% CI, 3.4-5.9; HR, 0.49; P < .0001) with SOC.

Moreover, 71% of patients treated with ide-cel achieved a response, and 39% of patients achieved a complete response (CR) or stringent CR. Comparatively, 41% of patients treated with SOC achieved a response, and only 5% achieved a CR or stringent CR. Ide-cel also showed durable response times, with a median duration of response of 14.8 months (95% CI, 12.0-18.6) compared with 9.7 months (95% CI, 5.4-16.3) with SOC.

No new safety signals were observed, and the most common adverse events (AEs) were low-grade cytokine release syndrome (CRS; 88%) and neurotoxicity (15%). Grade 3/4 CRS was observed in 4% of patients, and 1% of patients (n = 2) had a grade 5 CRS AE. Grade 3/4 neurotoxicity was observed in 3% of patients, and there were no incidences of grade 5 neurotoxicity.

In March 2024, the FDA's Oncologic Drug Advisory Committee voted 8 to 3 that the benefits of ide-cel outweighed potential risks in this patient population. In 2021, the FDA approved ide-cel for the treatment of patients with RRMM who had received 4 or more prior lines of therapy.

Mirvetuximab soravtansine-gynx (Elahere)

The FDA has fully approved **mirvetuximab soravtansine-gynx (Elahere)**, a first-in-class

antibody-drug conjugate, for the management of platinum-resistant ovarian cancer with high folate receptor alpha (FRα) expression that has received 1 to 3 prior lines of treatment.[2]

The approval is supported by findings from the confirmatory phase 3 MIRASOL trial (NCT04209855). In the study, mirvetuximab was compared with investigator's choice of chemotherapy in patients with platinum-resistant, advanced epithelial ovarian, primary peritoneal, or fallopian tube cancers with high FRα expression.[3]

The median overall survival observed in the study was 16.5 months (95% CI, 14.5-24.6) among patients in the mirvetuximab soravtansine-gynx arm vs 12.7 months (95% CI, 10.9-14.4) in the chemotherapy arm (HR, 0.67; 95% CI, 0.50-0.88; P = .0046). The median progression-free survival in the mirvetuximab arm was 5.6 months (95% CI, 4.3-5.9) and 4.0 months (95% CI, 2.9-4.5) in the chemotherapy arm (HR, 0.65; 95% CI, 0.52-0.81; P < .0001). Furthermore, the overall response rate was 42% (95% CI, 36-49) vs 16% (95% CI, 12-22; P < .0001), in their respective arms.

"As the first treatment to show a statistically significant overall survival benefit in patients with platinum-resistant ovarian cancer, Elahere provides an effective new option for patients with [FRα]-positive tumors. These patients previously had very limited options, and Elahere changes that," said Kathleen N. Moore, MD, MS, deputy director and associate director of clinical research at the Stephenson Cancer Center of the University of Oklahoma and MIRASOL principal investigator.[4]

Regarding safety, the FDA reported that adverse events occurring in at least 20% of patients "were increased aspartate aminotransferase, fatigue, and increased alanine aminotransferase."[2]

The recommended dose of mirvetuximab soravtansine is 6 mg/kg, ideally adjusted for body weight and administered once every 3 weeks in a 21-day cycle. The agent is given as an intravenous infusion until disease progression or unacceptable toxicity.

Fluorouracil (5-FU, 5-fluorouracil)

Safety label changes for **fluorouracil (5-FU, 5-fluorouracil)** injection products have been approved by the FDA. Additional information regarding the risk of serious adverse events (AEs) in patients with dihydropyrimidine dehydrogenase (DPD) deficiency will now be included.[5]

The initial approval for fluorouracil injection was granted in 1962 for the treatment of colon and rectum adenocarcinoma, breast adenocarcinoma, gastric adenocarcinoma, and pancreatic adenocarcinoma. However, the regulatory agency made changes to the safety label after safety information regarding the risk of serious AEs related to fluorouracil use in patients with DPD deficiency was noted. These new changes align with those made to the prescribing information for capecitabine (Xeloda), which was amended in December 2022. Revisions on the fluorouracil label have been made to the "Warnings and Precautions," "Patient Counseling Information," and "Clinical Pharmacology" sections.[6]

The updated label under the "Warnings and Precautions" sections states that fluorouracil can cause serious and fatal AEs among patients with certain homozygous or compound heterozygous DPYD variants associated with complete or near complete absence of DPD activity. Specifically, the agent is not recommended for patients at elevated risk for acute, early-onset toxicities, which could be serious or fatal, including mucositis, diarrhea, neutropenia, and neurotoxicity. There is also a risk for those with partial DPD deficiency.

If patients treated with fluorouracil injection products have evidence of acute, early-onset, or unusually severe reactions, the agent should be withheld or discontinued, as no fluorouracil dose has been proven safe for patients with complete DPD deficiency. Insufficient data are available to recommend a specific dose in patients with partial DPD deficiency.

There are no specific DPD tests that are currently FDA approved; however, genetic testing may be considered to help determine whether fluorouracil is safe. The updated label also emphasizes the importance of patients being informed about these potential AEs and instructed to report them immediately to their doctor.

The gene *DYPD* encodes an enzyme called DPD, which is responsible for breaking down more than 80% of fluorouracil. Partial DPD deficiency occurs in approximately 3% to 5% of White patients, and complete DPD deficiency is even more rare at around 0.2% in White patients. It is important to note that these rates of DPD deficiency are higher in Black patients. However, there is not enough data to estimate the proportion of DPD deficiency in non-White populations.

Researchers have identified 4 specific genetic variations (c.1905+1G>A [*DPYD**2A], c.1679T>G [*DPYD**13], c.2846A>T, and c.1129-5923C>G [Haplotype B3]) that can reduce DPD activity.

INVESTIGATIONAL NEW DRUG

NST-628

The FDA granted clearance to the investigational new drug application for **NST-628** for the treatment of patients with advanced solid tumors with genetic alterations in the RAS-MAPK pathway. NST-628 is a mechanistically novel, fully brain penetrant, nondegrading pan-RAF/MEK molecular glue, and it works by targeting the RAF and MEK nodes in the RAS-MAPK pathway. In a preclinical trial, NST-628 was given as either a single agent or in combination regimens and demonstrated antitumor activity and tolerability. [7]

With this FDA clearance, a phase 1, open-label, single-arm, 2-part trial (NCT06326411) is designed to evaluate NST-628 in adult patients with RAS-MAPK pathway-mutated/-dependent advanced solid tumors who have no other treatment options. Dosing in the study is expected to begin in the first half of 2024 for patients with advanced solid tumors harboring genetic alterations in the MAPK pathway. The study is assessing the safety, pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy of single-agent NST-628.[8] Part A of the trial is the dose-escalation portion, which will then be followed by part B, the dose-expansion portion.

The primary end points for part A are describing the safety profile of NST-628 and establishing the recommended dose for part B of the study. For part B, the primary end point is to evaluate the objective tumor response rate. Secondary end points for part A and B are to evaluate progression-free survival, overall survival, and PK. For patients with solid tumors other than glioma, they must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and for those with glioma, they must have a Karnofsky score of 70 or greater and an ECOG performance status of 0 or 1. The estimated study completion date is November 2029.

BAT8006

The investigational new drug application for **BAT8006**, an innovative antibody-drug conjugate (ADC) targeting folate receptor α, has been cleared by the FDA for a phase 2 study in platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer. BAT8006 is under development for the treatment of solid tumors, ovarian cancer, endometrial cancer, non–small cell lung cancer, cervical cancer, and breast cancers. The ADC is being developed based on Bio-Thera's ADC platform technology.[9]

Preclinical studies of BAT8006 have shown good stability, safety, and strong antitumor activity. In a phase 1 study

(NCT05378737) that is ongoing in China, BAT8006 elicited responses and had a manageable safety profile when used for the treatment of patients with advanced solid tumors, including ovarian, breast, and cervical cancers.[10]

Among all evaluable patients irrespective of tumor type (n = 29), the objective response rate (ORR) observed was 31.0%. The disease control rate (DCR) in this group was 86.2%. Twelve patients had ovarian cancer with a tumor proportion score more than 25%, and of these patients, the ORR was 58.3% and the DCR was 91.7%. There were 2 partial responses seen in patients with breast cancer and endometrial carcinoma.

PRIORITY REVIEW

Revumenib

The FDA granted priority review to the new drug application (NDA) for **revumenib** in adult and pediatric relapsed or refractory *KMT2A*-rearranged acute leukemia. Revumenib is a first-in-class menin inhibitor. The NDA filing for the agent is currently being reviewed under the FDA's real-time oncology review program, which allows for a more efficient review and engagement between the sponsor and the FDA throughout the submission process. A Prescription Drug User Fee Act date for the agent has been set for September 26, 2024.[11]

Findings from the AUGMENT-101 trial (NCT04065399) of revumenib in adult and pediatric patients with *KMT2A*-rearranged acute myeloid leukemia (AML) and acute lymphoid leukemia support this approval. At the protocol-defined interim analysis, the trial met its primary end point by showing a complete remission (CR) or a CR with a partial hematologic recovery (CRh) rate of 23% (95% CI, 12.7%-35.8%; *P* = .0036).[12] This was seen among the 57 patients who were in the pooled *KMT2Ar* acute leukemia population and were efficacy evaluable.

In both the overall population and among patients with AML, a durable CR/CRh response was observed with a 6.4-month (95% CI, 3.4-not reached) median duration as of the data cutoff on July 24, 2023. At this time, 46% of patients remained in response, and 10 of the 13 patients who achieved CR/CRh had minimal residual disease (MRD) status assessed, and 70% of patients were MRD negative. In the overall cohort of 57 patients, 36 achieved an overall response, 39% (14/36) of whom underwent hematopoietic

stem cell transplant. Additionally, 50% of these patients (7/14) restarted revumenib as a posttransplant maintenance at the time of the data cutoff.

BIOLOGICS LICENSE APPLICATION

Odronextamab (REGN1979)

Two complete response letters have been issued by the FDA for the biologics license application (BLA) for **odronextamab (REGN1979)** in relapsed/refractory follicular lymphoma and in relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after 2 or more lines of systemic therapy. The complete response letters are related to the enrollment status of confirmatory trials that are evaluating the agent. There were no issues regarding the efficacy or safety of odronextamab, as well as no issues regarding trial design, labeling, or manufacturing.[13]

The FDA granted priority review to the BLA seeking the approval of odronextamab in September 2023, supported by findings from the phase 1 ELM-1 (NCT02290951) and phase 2 ELM-2 (NCT03888105) trials. The data from the final analysis of the ELM-2 trial were reported at the 2023 American Society of Hematology Annual Meeting, demonstrating that at a median follow-up of 29.9 months (range, 20.4-32.6) for efficacy, the objective response rate among the 127 patients with relapsed/refractory DLBCL who were naive to chimeric antigen receptor T-cell therapy was 52%. The complete response rate was 31.5%, and the median duration of response was 10.2 months (95% CI, 5.0-17.9).[14]

In addition to this, randomized phase 3 trials of odronextamab in earlier lines of therapy are underway.[13] This includes the OLYMPIA-3 trial (NCT06091865), which is evaluating the agent in patients with previously untreated DLBCL, and the OLYMPIA-4 trial (NCT06230224) in patients who have been previously treated. The FDA has required that both trials include dose-finding and confirmatory portions.

Denileukin diftitox (Lymphir)

The FDA has accepted the resubmission of the biologics license application (BLA) for **denileukin diftitox (Lymphir)** as a potential therapeutic option for patients with relapsed/refractory cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy. The FDA has assigned a Prescription Drug User Fee Act date of August 13, 2024.[15]

On July 28, 2023, Citius Pharmaceuticals, Inc, received a complete response letter (CRL) for the BLA of denileukin diftitox stating additional manufacturing controls and enhanced product testing were needed. In September 2023, the FDA addressed the CRL and gave Citius Pharmaceuticals, Inc, the necessary actions required to support the resubmission of the BLA. The company believes that the enhanced product testing and additional manufacturing controls noted in the letter have been addressed. No safety or efficacy issues were cited, and there is no need for any additional clinical trials.

Denileukin diftitox is an interleukin-2–based immunotherapy with orphan drug designations for peripheral T-cell lymphoma and CTCL. Data from a pivotal phase 3 study (NCT01871727) support the BLA, as no new safety signals were identified when the drug was administered to patients with persistent or recurrent CTCL.[16] A total of 71 patients with stage I to III persistent or recurrent CTCL from the lead-in and main studies were assessed for efficacy, and 69 were included in the primary efficacy analysis set. An overall response rate (ORR) of 36.2% (95% CI, 25.0%-48.7%) was demonstrated in 25 of the 69 patients, and an ORR of 42.3% was seen in 30 of the 71 patients (95% CI, 30.6%-54.6%).

FAST-TRACK DESIGNATION

PT886

The FDA has granted a fast-track designation to **PT886**, a first-in-class native IgG-like bispecific antibody, for metastatic claudin (CLDN)18.2-positive pancreatic adenocarcinoma treatment.[17] The agent works to target CLDN18.2 and CD47 and was created using proprietary bispecific antibody platforms from Phanes Therapeutics, Inc, called PACbody and SPECpair. The agent is undergoing development for the treatment of gastric, gastroesophageal junction, and pancreatic adenocarcinomas.

In 2022, the FDA granted PT886 an orphan drug designation for the treatment of patients with pancreatic cancer, and in the TWINPEAK study (NCT05482893), a multicenter, phase 1 trial, investigators are assessing the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of PT886. Patients with locally advanced or metastatic gastric, gastroesophageal junction, and pancreatic cancers are enrolled in the trial, and it is ongoing.

Enrollment in the phase 1 study is open to patients aged 18 years and older with a histologically or cytologically confirmed diagnosis of locally advanced or metastatic gastric, gastroesophageal junction, and pancreatic cancers. The disease must have progressed after all available standard therapy or for which standard therapy has shown to be ineffective, intolerable, or inappropriate.[18] Patients are required to have measurable disease, including at least 1 lesion amenable to response assessment per RECIST 1.1 criteria, adequate organ function, and an ECOG

performance status of 0 to 1. All acute adverse events that emerged from prior cancer therapies must be resolved to grade 1 or baseline, excluding alopecia or neuropathy.

MVR-T3011

The FDA granted a fast-track designation for **MVR-T3011**, an oncolytic virus product given via intratumoral injection, for the treatment of patients with recurrent or metastatic head and neck squamous cell cancer (HNSCC). Patients evaluated had disease progression following treatment with platinum-based chemotherapy and at least 1 previous line of anti–PD-1/PD-L1 therapy.[19] The goal of the novel genetic engineered agent is to achieve the most favorable profile of attenuated herpes simplex virus type 1 with replication potency in tumor cells and highly restricted replication in normal cells. The product works by incorporating the PD-1 antibody and interleukin-12, which helps to further enhance immune responses in the tumor microenvironment.

Data from 2 trials, including an ongoing phase 1/2a study (NCT05602792) being done in China evaluating MVR-T3011 as monotherapy and a phase 1/2a study (NCT04370587) of the agent as a monotherapy or with pembrolizumab (Keytruda) in the United States, were shared at the 2023 American Society of Clinical Oncology Annual Meeting.[20-22] Findings showed that MVR-T3011 demonstrated clinical efficacy when used alone or as a combination therapy.[20]

The study in China included patients with solid tumors who were given the recommended phase 2 dose of the agent. This included 55 patients who were response evaluable. The confirmed overall response rate (ORR) was 11% and the disease control rate (DCR) was 49%. A total of 12 patients with HNSCC who progressed after treatment with platinum-based chemotherapy and anti–PD-1/PD-L1 therapy had a confirmed ORR of 25% and DCR of 50%. The study showed that among patients with immune-resistant melanoma, the confirmed ORR and DCR were 25.0% and 33.3%, respectively.

ORPHAN DRUG DESIGNATION

P-BCMA-ALLO1

The FDA has granted an orphan drug designation to **P-BCMA-ALLO1**, a novel B-cell maturation antigen (BCMA)–targeted allogeneic, T stem cell memory–rich chimeric antigen receptor (CAR) T-cell therapy for the treatment of relapsed/refractory multiple myeloma.[23] The designation highlights the unmet medical need for this type of treatment and provides potential benefits during development.

In the phase 1 ongoing, multicenter, open-label, dose-escalation study (NCT04960579), 39 patients were enrolled in an intent-to-treat (ITT) population as of the data cutoff of October 23, 2023.[24] A total of 82% of patients (n = 11) in the pooled part 1 and part 2 arms achieved an objective response rate. Among the 6 patients in the part 2 arm, the objective response rate was 83%, and 100% of responding patients had a very good partial response (VGPR) or better. Furthermore, 40% of patients in the part 2 arm achieved a stringent complete response. In the part 1 arm, which consisted of 5 patients, the objective response rate was 80%. Fifty percent of the patients who responded achieved a VGPR. Across both arms, patients who were not previously exposed to a prior BCMA-targeting bispecific antibody (n = 9) achieved an objective response rate of 100%. Patients treated with a previous autologous CAR T-cell BCMA-targeted therapy also had an objective response rate of 100%.

In the ITT population, all patients were given P-BCMA-ALLO1 without the use of bridging chemotherapy or other antimyeloma bridging therapies.[23] According to preliminary safety and efficacy data, P-BCMA-

ALLO1 was well tolerated and had a favorable safety profile with no graft-vs-host disease seen among patients treated at any dose. Data from a subset of recently enrolled patients who are refractory to initial BCMA-targeting therapy are expected to be shared at the 2024 American Association for Cancer Research Annual Meeting. Clinical updates on the P-BCMA-ALLO1 program are planned to be shared at a scientific meeting in the second half of 2024

CHANGES IN LABELED INDICATIONS

Alectinib (Alecensa)

The use of **alectinib (Alecensa)** was associated with severe hepatotoxicity, including drug-induced hepatotoxicity, in patients treated with alectinib. In a pooled safety population, hepatotoxicity occurred in 41% of patients, with 8% experiencing grade 3 or greater hepatotoxicity. In the ALINA study (NCT03456076), hepatotoxicity was observed in 61% of patients, with a grade 3 or greater hepatotoxicity incidence of 4.7%. Most cases of elevated transaminases (72%) occurred within the first 3 months of treatment. Discontinuation of treatment due to hepatotoxicity was reported in 3.6% of patients in the pooled safety population and in 1.6% of patients in the ALINA study.[25]

In the combined safety analysis, the use of alectinib led to interstitial lung disease (ILD) or pneumonitis in 1.3% of patients, with 0.4% encountering grade 3 ILD/pneumonitis. Among these cases, 0.9% of patients discontinued alectinib due to ILD/pneumonitis. The median time until grade 3 or more severe ILD/pneumonitis onset was 2.1 months, with a range of 0.6 to 3.6 months.

Within the combined safety analysis, 12% of patients undergoing alectinib treatment encountered renal impairment, with 1.7% experiencing grade 3 or higher impairment, resulting in fatalities for 0.4% of cases. The median onset time for grade 3 or more severe renal impairment was 3.7 months, spanning from 0.5 to 31.8 months. Dosage modifications due to renal impairment were required in 2.4% of patients.

Alectinib, when given to a pregnant woman, may result in fetal harm. Women of childbearing age should be counseled to use effective contraception throughout treatment and for 5 weeks following the final dose. Assess the pregnancy status of women capable of reproduction before starting treatment.

(Extensive changes; please refer to label for complete information.)

Bendamustine hydrochloride

In the post marketing phase, renal and urinary disorders, such as nephrogenic diabetes insipidus, have been reported for **bendamustine hydrochloride**.[26]

Naxitamab (Danyelza)

Patients with preexisting cardiac conditions who are taking **naxitamab (Danyelza)** should be cautioned that the agent could potentially increase the risk of severe hypotension. Myocarditis has been documented in adolescent patients participating in clinical trials and expanded access programs while receiving naxitamab. The onset of myocarditis typically transpired within days of naxitamab administration, necessitating a temporary halt in drug administration. It is essential to vigilantly observe for indications and symptoms of myocarditis throughout naxitamab therapy. Adjustments such as withholding, dosage reduction, or permanent discontinuation of naxitamab may be necessary depending on the severity of myocarditis.[27]

(Extensive changes; please refer to label for complete information.)

Pralsetinib (Gavreto)

Patients with mild, moderate, or severe hepatic impairment taking **pralsetinib (Gavreto)** do not need dose adjustments.[28]

- Mild hepatic impairment: total bilirubin less than or equal to upper limit of normal (ULN) and aspartate aminotransferase (AST) greater than ULN, or total bilirubin greater than 1 to 1.5 times ULN and any AST.
- Moderate hepatic impairment: total bilirubin greater than 1.5 to 3 times ULN and any AST.
- Severe hepatic impairment: total bilirubin greater than 3 times ULN and any AST.

Lenvatinib (Lenvima)

The safety and effectiveness of **lenvatinib (Lenvima)** alone and in combination were examined in 4 open-label studies (NCT02432274, NCT04154189, NCT04447755, NCT03245151) involving 232 pediatric patients aged 2 to 17 years with recurrent or resistant solid tumors, such as osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, and high-grade glioma. Pediatric patients exhibited a higher incidence of hypothyroidism and pneumothorax compared to adults. However, the PK of lenvatinib in pediatric patients were consistent with those observed in adults at the recommended dose of 24 mg.[29]

The most frequent AEs associated with the use of lenvatinib in combination with everolimus for kidney cancer treatment include fatigue, cough, joint and muscle pain, abdominal pain, decreased appetite, difficulty breathing, vomiting, rash, nausea, weight loss, mouth sores, bleeding, and swelling in the arms and legs.

(For more information, please refer to label for complete information.)

Belumosudil mesylate (Rezurock)

In a new subsection, it's advised to avoid combining **belumosudil mesylate (Rezurock)** with medications metabolized by UGT1A1, P-glycoprotein (P-gp), OATP1B1, and BCRP substrates. Coadministration

may lead to significant changes in drug concentrations, potentially causing severe toxicities. If combining these medications is unavoidable, adjusting the dosage of the affected substrates according to their respective prescribing information is recommended.[30]

Belumosudil mesylate acts as an inhibitor of UGT1A1, P-gp, OATP1B1, and BCRP substrates. When belumosudil mesylate is coadministered with UGT1A1 substrates, it lowers the concentration of glucuronide metabolites in the blood, increasing the risk of AEs. Conversely, coadministration with P-gp, OATP1B1, and BCRP substrates elevates their plasma concentrations, heightening the likelihood of AEs associated with these substrates.

Trametinib (Mekinist)

Other clinically significant AEs observed in less than 10% of patients receiving **trametinib (Mekinist)** in combination with dabrafenib across various studies include cardiac events such as bradycardia, atrioventricular block, and bundle branch block.[31]

In specific studies, such as the BRF113928 trial (NCT01336634), atrioventricular block was observed in less than 20% of patients. In the BRF117019 (NCT02034110) trial, investigators reported decreased ejection fraction (8%), atrioventricular block (2.9%), uveitis (1.9%), and hypersensitivity (1.9%) in less than 20% of patients. Study investigators in the ASCEMBL trial (NCT03106779) documented atrioventricular block in 2.1% of patients (of the total of 48 who received trametinib in combination with dabrafenib). Atrioventricular block (complete), an AE observed

with trametinib monotherapy, requires prompt medical attention.

Trametinib for oral solution can be administered via oral syringe or feeding tube. Contact your health care provider immediately if you experience symptoms of a heart problem, such as palpitations or irregular heartbeat.

Store trametinib for oral solution in its original amber bottle at room temperature and avoid freezing. Keep it in the carton provided, away from moisture and light, and discard any unused solution after the expiration date.

(For more information, please refer to label for complete information.)

Asparaginase erwinia chrysanthemi (Rylaze)

Asparaginase erwinia chrysanthemi (Rylaze) is not recommended for patients with

- A history of severe hypersensitivity reactions to erwinia asparaginase, including anaphylaxis.
- A history of severe pancreatitis during previous asparaginase therapy.
- A history of severe thrombosis during previous asparaginase therapy.
- A history of severe hemorrhagic events during previous asparaginase therapy.
- Severe hepatic impairment.[32]

(Extensive changes; please refer to label for complete information.)

Dabrafenib (Tafinlar)

Atrioventricular block and bundle branch block have been included as AEs associated with **dabrafenib (Tafinlar)** use. In the BRF117019 trial (NCT02034110), clinically relevant AEs observed in less than 20% of patients receiving dabrafenib in combination with trametinib included decreased ejection fraction (8%), atrioventricular block (2.9%), uveitis (1.9%), and hypersensitivity (1.9%).[33]

In the CTMT212X2101 trial (NCT02124772), among 48 patients who received dabrafenib in combination with trametinib, atrioventricular block was a clinically relevant AE observed in less than 20% of patients, specifically at a rate of 2.1%. It is advised to notify your health care provider right away if you have any of the following signs and symptoms of a heart problem such as feeling like your heart is pounding, racing, or beating irregularly, or shortness of breath; swelling of your ankles or feet; and/or lightheadedness.

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