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TACOS ONCOLOGY DRUG NEWSLETTER

The Arizona Clinical Oncology Society

FDA APPROVALS

Motixafortide (Aphexda)

The FDA has granted approval to **motixafortide (Aphexda)** used in combination with filgrastim granulocyte-colony stimulating factor (G-CSF). This compound therapy is intended to mobilize hematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with multiple myeloma.[1]

The approval was granted based on findings from the phase 3 GENESIS study (NCT03246529), in which 122 patients were enrolled to receive G-CSF plus either motixafortide or placebo.[1,2] In the double-blind, placebo-controlled, multicenter study, patients were randomly assigned 2:1 to receive motixafortide/G-CSF or placebo/G-CSF. Results by central laboratory assessment showed that 67.5% of patients in the motixafortide/G-CSF arm achieved the stem cell collection goal of at least 6 × 10^6 CD34-positive cells/kg within 2 sessions compared with 9.5% in the placebo/G-CSF arm. Further, 92.5% of patients in the motixafortide/G-CSF arm reached the stem cell collection goal in up to 2 apheresis sessions vs 21.4% in the arm given placebo.

The primary end point of the GENESIS study was the percentage of participants mobilizing at least 6.0 × 10^6 CD34-positive cells/kg within up to 2 apheresis sessions. Secondary end points included the rate of patients who collected at least 2.0 × 10^6 CD34-positive cells/kg in 1 apheresis session, the rate of patients who collected at least 6.0 × 10^6 CD34-positive cells/kg in 1 apheresis session, time to neutrophil engraftment, time to platelet engraftment, and graft durability at 100 days postengraftment.

Luspatercept-aamt (Reblozyl)

The FDA has granted approval to luspatercept-aamt (Reblozyl) for the treatment of anemia without previous erythropoiesis-stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions, according to an announcement by Bristol Myers Squibb. This approval expands the use of luspatercept to the frontline setting.[3]

The approval was granted based on findings from the phase 3 COMMANDS study (NCT03682536), in which use of luspatercept led to superior concurrent RBC transfusion independence (RBC-TI) and hemoglobin (Hb) level increase compared with epoetin alfa (Epogen, Procrit), regardless of ring sideroblast status. Overall, 86 of 147 patients (58.5%) who received luspatercept vs 48 of 154 patients (31.2%) given epoetin alfa achieved the primary end point of RBC-TI of at least 12 weeks with a mean Hb level increase of at least 1.5 g/dL within the first 24 weeks (common risk difference on response rate, 26.6; 95% CI, 15.8-37.4; P < .0001).[3,4]

In the phase 3, open-label, randomized COMMANDS study, investigators evaluated the efficacy and safety

of luspatercept compared with epoetin alfa for the treatment of patients with anemia due to very low-, low-, or intermediate-risk MDS who were RBC transfusion dependent and ESA naïve.[5]

The primary end point of the study was RBC-TI for 12 weeks with a mean Hb level increase of 1.5 g/dL or greater. Secondary end points were RBC-TI for 24 weeks, RBC-TI of 12 weeks or more, and erythroid response of at least 8 weeks during weeks 1 through 24 of the study. Other secondary end points explored in the study were mean change in Hb level over 24 weeks, hematologic improvement, time to first RBC transfusion, RBC transfusion burden on treatment, safety, pharmacokinetics, frequency of antidrug antibodies, number and percentage of participants progressing to acute myeloid leukemia (AML), time to AML progression, and overall survival.

Melphalan/Hepatic Delivery System (Hepzato Kit)

The FDA has granted approval to the **melphalan/ Hepatic Delivery System (HDS) (Hepzato Kit)**. This liver-directed treatment is intended for use in adult patients with metastatic uveal melanoma with unresectable hepatic metastases affecting less than 50% of the liver and no extrahepatic disease or extrahepatic disease limited to the bone, lymph nodes, subcutaneous tissues, or lung that is amenable to resection or radiation.[6]

Results from the phase 3 FOCUS study (NCT02678572) supported the FDA's decision. In the study, melphalan (Hepzato) was administered using the HDS during a percutaneous hepatic perfusion procedure. In 91 patients with hepatic and extrahepatic lesions who were treated every 6 to 8 weeks for up to 6 treatments, melphalan delivered by HDS led to an objective response rate of 36.3% (95% CI, 26.4%-47.0%). Responses included complete response in 7.7% and partial response rate in 28.6%. The median duration of response was 14 months (95% CI, 8.3-17.7 months), and the disease control rate was 73.6% (95% CI, 63.3%-82.3%).[7]

FOCUS is a phase 3, single-arm, multicenter, open label study. Patients included in the study had either hepatic or extrahepatic lesions. Some of the patients were naïve to cancer treatment (56.0%), and others were previously treated (44.0%).

To be included in the study, patients must have been 18 years or older; weighed 35 kg or greater; had measurable disease in the liver; had evidence of limited extrahepatic disease; had not received chemotherapy, radiotherapy, or chemoembolization within 30 days of treatment; and had an ECOG performance status of 0 to 1 at screening. Patients with a history of clinically significant pulmonary disease, active bacterial infections, a latex allergy, or prior Whipple procedure were not eligible to participate.

FoundationOne CDx

The FDA has granted approval for **FoundationOne CDx**, which is indicated for use as a companion diagnostic (CDx) for the niraparib and abiraterone acetate dual-action tablet (Akeega). More than 30 indications have been granted for the FoundationOne CDx. The assay can detect more than 300 cancer-related genes. Foundation Medicine Inc, the developer of the FoundationOne CDx, has also developed more than 60% of the next-generation sequencing–based assays approved in the United States, according to a press release.[8]

The niraparib and abiraterone acetate dual-action tablet is newly FDA approved for the treatment of adult patients with deleterious or suspected, deleterious, BRCA-mutated, metastatic, castration-resistant prostate cancer (mCRPC). Findings from the phase 3 MAGNITUDE study (NCT03748641) served as the basis for the approval.[9,10]

In the MAGNITUDE study, all 765 patients with mCRPC were screened prospectively for homologous recombination repair gene alterations, including ATM,

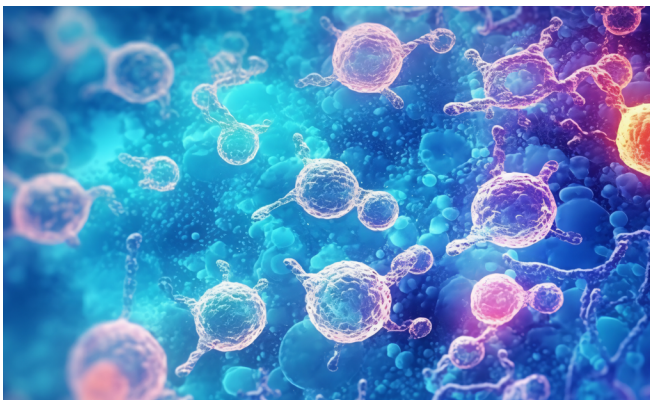
BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, and PALB2. To conduct this molecular testing, the FoundationOne CDx was used, along with the Resolution HRD liquid biopsy assay and AmoyDx blood and tissue assays. Using FoundationOne CDx, 225 patients with BRCA1/2 mutations were identified in the study.

The results ultimately showed clinically significant improvement in radiographic progression-free survival when the dual-action tablet was added to prednisone compared with abiraterone acetate and prednisone alone in BRCA-positive mCRPC, which underscored the importance of molecular testing.

Erdafitinib (Balversa)

The FDA has received a supplemental New Drug Application (sNDA) seeking full approval of **erdafitinib (Balversa)** for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma with susceptible FGFR3 genetic alterations that has progressed during or after at least 1 line of a PD-1 or PD-L1 inhibitor has been given in the locally advanced or metastatic setting or within 12 months of neoadjuvant or adjuvant therapy.[11]

Data from cohort 1 of the phase 3 THOR study (NCT03390504) support the sNDA submission for erdafitinib. In the randomized, controlled, open-label, multicenter trial, investigators assessed the efficacy and safety of erdafitinib and determined that the primary end point of overall survival (OS) was met, as patients treated with erdafitinib had a median OS of more than 1 year at the prespecified interim analysis data cutoff.[12]



Confirmatory data from cohort 1 demonstrated a 36% reduction in the risk of death in patients treated with erdafitinib compared with chemotherapy. The safety profile of erdafitinib in the THOR study was also consistent with what has been reported.

Two cohorts were evaluated in the study. In cohort 1, patients were given erdafitinib or standard of care chemotherapy using either docetaxel or vinflunine after they received at least 1 line of treatment including an anti–PD-L1 agent; in cohort 2, patients were given erdafitinib or pembrolizumab (Keytruda) after receiving 1 prior treatment not containing an anti–PD-L1 agent.

BIOLOGICS LICENSE APPLICATION

Denileukin diftitox (Lymphir)

The FDA has provided additional guidance for the planned resubmission of the Biologics License Application (BLA) for **denileukin diftitox (Lymphir)** for the treatment of patients with relapsed or refractory cutaneous T-cell lymphoma after at least 1 prior systemic therapy.[13]

According to a press release by Citius Pharmaceuticals, the FDA has agreed with plans to address the requirements outlined in the complete response letter (CRL) received for the agent on July 28, 2023. No clinical safety or efficacy issues were raised with the product or the proposed prescribing information.

Under the CRL, the FDA has required incorporation of enhanced product testing and additional controls as per an agreement between Citius and the FDA during the marketing application review.[14] With this guidance, a clear path and necessary actions have been provided to support the resubmission of the BLA for denileukin diftitox. Further, the FDA did not request any additional clinical efficacy or safety trials for the resubmission.

Amivantamab-vmjw (Rybrevant)

A supplemental Biologics License Application (sBLA) has been submitted to the FDA for **amivantamab-vmjw (Rybrevant)** used in combination with carboplatin and pemetrexed for the treatment of patients with locally advanced or metastatic non–small

cell lung cancer (NSCLC) with EGFR exon 20 insertion (EGFR ex20ins) mutations in the frontline setting.[15]

The efficacy and safety of amivantamab plus chemotherapy, which support the sBLA, were demonstrated in the phase 3 PAPILLON study (NCT04538664). PAPILLON is a confirmatory study that solidifies another indication for the agent—the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR ex20ins mutations whose disease has progressed on or after platinum-based chemotherapy. It is the first randomized study evaluating patients with newly diagnosed NSCLC with EGFR ex20ins mutations to demonstrate clinically meaningful results.[15,16]

In PAPILLON, treatment with amivantamab plus carboplatin and pemetrexed in patients with newly diagnosed advanced or metastatic NSCLC characterized by EGFR ex20ins mutations showed a statistically significant and clinically meaningful improvement in progression-free survival, meeting the primary end point of the study. The combination also had a safety profile consistent with the safety profile of each drug alone. Full results from the study are expected to be presented at an upcoming scientific meeting.[17]

ORPHAN DRUG DESIGNATION

INT230-6

The FDA has granted an Orphan Drug designation to the 3 active components of INT230-6—cisplatin, vinblastine sulfate, and the diffusion enhancer SHAO-FA (8-((2-hydroxybenzoyl) amino) octanoate)—for the treatment of patients with soft tissue sarcoma (STS).[18]

Clinical data were provided to the FDA, including immune activation results in patients with sarcoma, based on findings from a phase 1/2 clinical study (IT-01; NCT03058289) of INT230-6. These findings were presented during the 2023 American Society of Clinical Oncology Annual Meeting (ASCO 2023). Data showed that the median overall survival (mOS) observed with the agent in patients with refractory STS was extended by approximately 450 days compared with findings in a synthetic control group. Investigators also noted favorable safety over what would have been expected

for the patient population. Results also reported at ASCO 2023 showed that when delivered locally, INT230-6 led to a systemic immune response in several sarcoma subtypes that are nonimmunogenic cancers.[19]

Additional findings from the study showed that the mOS among 15 patients treated with INT230-6 alone was 649 days vs not reached in the combination arm with more than 1 year of median follow-up. INT230-6 dosed at a volume/total tumor burden ratio of 40% or greater resulted in an mOS of 715 days. Patients in the all-treated population who were given at least 1 dose of INT230-6 had a disease control rate of 93% for monotherapy and of 86% with the combination.

CHANGES IN LABELED INDICATIONS

Copanlisib dihydrochloride (Aliqopa)

An update to the warning and precautions of this drug includes a grade 1 or 2 cytomegalovirus (CMV) reactivation or infection reported in 0.97% of patients receiving this monotherapy. Physicians should monitor for CMV infection through the course of treatment of patients with a history of CMV infection. If infection or viremia is active, hold treatment until it is resolved, and then administer the previous dose while testing with a polymerase chain reaction or antigen test monthly or more frequently[20]

Patients with liver issues or hypertension are encouraged to inform their physician before starting treatment and to report symptoms (eg, intense heart palpitations, headache, dizziness, and passing out) of these conditions.

Avelumab (Bavencio)

Infusion-related reactions have been updated to 0.5% of patients experiencing grade 3/4 reactions. Overall, 15% of patients experienced reactions from avelumab injection. [21]

In the JAVELIN Bladder 100 trial (NCT02603432), the safety for avelumab treatment was evaluated. In all, 204 patients received 10 mg/kg of avelumab or 800 mg of the drug every 2 weeks by intravenous injection until intolerable toxicity occurred or the disease progressed. The median duration of therapy was 4.1 months. Of 204 patients included in this trial, 78% were 65 years or older, and 43% were 75 years or older. There were no safety differences between young and older patient groups.[22]

In all, 52% of patients experienced serious adverse events (AEs). The most common AEs (seen in 2% or more of patients) included a decline in general physical health, acute kidney injury, anemia, abdominal pain, severe infections, hyponatremia, and reactions during infusion.

About 27% of patients discontinued treatment. The most frequent reasons for discontinuation were infusion-related reactions, anemia, and increased alanine aminotransferase (ALT) and aspartate aminotransferase liver enzymes levels.

About 29%of patients had to temporarily discontinue treatment due to AES, not including those caused by reactions during infusion. The most common AEs requiring dosage interruption were nasopharyngitis, anemia, diarrhea, lung infections, and elevated ALT levels.

The most reported AEs included fatigue, musculoskeletal pain, infusion-related reactions, skin rash, nausea, constipation, diarrhea, and cough (all ≥ 20%). Other AEs included headache, dizziness, increased transaminase level, tubulointerstitial nephritis, and increased creatine and phosphokinase levels (all 10%).

It is important for patients to report whether they have diabetes before taking this treatment.

Cabozantinib S-malate (Cometriq)

Updates to label changes include a risk of hypertension and hypertensive crisis; further, patients with musculoskeletal and connective tissue disorders can experience pain in their extremities during therapy. Patients are advised that use of this drug can lower calcium levels; patients should be monitored throughout treatment and report any symptoms or signs of hypocalcemia.[23]

Before taking this drug, patients should report whether they have a healing or open wound hypocalcemia. Female patients able to become pregnant should take effective birth control throughout treatment; female patients should report whether they are pregnant before using this drug.

Patients should avoid taking supplements that contain grapefruit or St John's wort while taking this drug. They should inform their doctor it they experience persistent severe pain in the stomach area, node bleeds, severe headaches, confusion or tiredness, changes in vision, breathing trouble, chest pain, blood in urine, irregular heartbeat, or jaw-related issues (eg, sore gums, jaw pain, toothache). Use of this drug can lower calcium levels in the blood; it is important to report the occurrence of seizures, numbness or tingling in (or around) fingers or toes, muscle stiffness or muscle spasms, sudden weight gain, or swelling of the arms, hands, legs, mouth, or ankles.

Docetaxel (Docefrez)

Genetic toxicity findings noted during animal testing has revealed that this drug is harmful if given during pregnancy. Female patients should use effective birth control during and for 2 months after their last dose.

Male patients with female partners for should use effective birth control for 4 months after taking the last dose.[24]

Mobocertinib succinate (Exkivity)

Patients with severe renal impairment should be monitored with increased frequency, because mobocertinib plasma concentrations are higher in such patients and could result in adverse events (AEs). As a safety measure, use a lower dosage for patients with severe renal impairment, particularly when their estimated glomerular filtration rate (eGFR) is below 30 mL/min/1.73 m2 according to the Modification of Diet in Renal Disease equation. For patients with mild to moderate renal impairment (eGFR, 30-89 mL/min/1.73 m2), no dosage reduction is needed.[25]

Patients with mild to severe hepatic impairment (ranging from total bilirubin levels at or slightly above the upper limit of normal [ULN] to total bilirubin levels > 3 times the ULN along with any elevation in aspartate aminotransferase level) do not require a dosage adjustment.

Embryofetal toxicity may occur with use of this drug.

Palbociclib (Ibrance)

Postmarketing experience of skin and subcutaneous tissue disease (palmer-planter erythrodysesthesia syndrome) has been reported when taking this drug.[26]

Olaparib (Lynparza)

This drug has a restricted use for maintenance therapy of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in adults who have a complete or partial response to platinum-based chemotherapy only if they are found to harbor a BRCA mutation. Patients should be selected according to results of testing with a companion FDA-approved diagnostic for olaparib.[27] The health care provider is instructed to order a test to ensure that the drug is ideal for each patient.[28]

Trametinib dimethyl sulfoxide (Mekinist)

The label change involves the management of BRAF V600E mutation–positive, unresectable or metastatic solid tumors and low-grade glioma in pediatric

patients. The safety and efficacy of using this drug with dabrafenib (Tafinlar) has been established for pediatric patients 1 year or older. For younger patients, safety and efficacy has not established.[29]

Dabrafenib mesylate (Tafinlar)

As above, the label change involves use in pediatric patients to manage BRAF V600E mutation¬–positive, unresectable or metastatic solid tumors and low-grade glioma. Safety and efficacy of this drug used with trametinib (Mekinist) has been established for pediatric patients 1 year or older. For younger patients, safety and efficacy has not established.[30]

Temozolomide (Temodar)

This update includes extensive changes; physicians are directed to refer to the label directly[31]

Filgrastim-aafi (Nivestym)

The update to this label involves postmarketing experiences that now include extramedullary hematopoiesis.[32]

Filgrastim-ayow (Releuko)

As above, the update to this label involves postmarketing experiences that now include extramedullary hematopoiesis.[33]

Palbociclib (Ibrance)

Indications for this drug now include inflammatory myofibroblastic tumor disease (IMT) in pediatric patients, IMT in adults when a defect in the ALK gene has returned or the tumor cannot be removed surgically or is no longer responsive to treatment, and non–small cell lung cancer that has spread due to a defect in the ALK or the ROS1 gene in adults. It

remains unknown whether use of this drug is safe for older adults with anaplastic large cell lymphoma.[34]

The dosage instructions have also been updated. Patients are advised to swallow the capsules whole. Capsules should not be crushed, chewed, or split. Patients should drink enough water to ensure that the capsules are swallowed. The medication is available as capsules and oral pellets.

Patients using the oral pellets should pour them directly into the mouth from the shell, a spoon, or medicine cup. However, the shell should not be swallowed, and the pellets should not be crushed or chewed. Blood cell counts should be monitored weekly throughout the first month of treatment and monthly thereafter. The oral uncoated pellets contain the inactive ingredients of poloxamer and stearyl alcohol; the film coating contains glyceryl, hypromellose, medium chain triglycerides, glyceryl monostearate, polyethylene, talc, sucrose, and glycol/macrogol.

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