APRIL 2024

NCOA ONCOLOGY DRUG NEWSLETTER

NORTH CAROLINA Oncology Association

FDA APPROVALS

Nivolumab (Opdivo)

Nivolumab (Opdivo) plus cisplatin-based chemotherapy has been approved by the FDA for the treatment of patients with treatment-naive unresectable or metastatic urothelial carcinoma (UC).[1]

This regulatory decision is supported by results from the phase 3 CheckMate901 study (NCT03036098) as published in the New England Journal of Medicine and presented at the European Society for Medical Oncology Congress 2023. Use of the combination led to longer overall survival (OS) (HR for death, 0.78; 95% CI, 0.63-0.96; P=.02) and progression-free survival (PFS) (HR for progression or death, 0.72; 95% CI, 0.59-0.88; P=.001) compared with gemcitabine/cisplatin alone.

At a median follow-up of approximately 33.6 months, nivolumab plus cisplatin-based chemotherapy produced a median OS of 21.7 months (95% CI, 18.6-26.4 months) vs 18.9 months (95% CI, 15.7-22.4 months) with chemotherapy. At 12 and 24 months, the OS rates in the nivolumab combination arm were 70.2% and 46.9%, respectively, compared with 62.7% and 40.7% in the active comparator arm.[2]

PFS was 34.2% in the combination arm versus 21.8% in the chemotherapy arm at 12 months, 23.5% vs 9.6% at 24 months, and the median PFS was 7.9 months vs 7.6 months, respectively (HR, 0.72; 95% CI, 0.59-0.88; P=.0012). The overall objective response rate was 57.6% in the nivolumab combination arm and 43.1% with chemotherapy alone. Further, the complete response (CR) rate in the nivolumab combination arm was 21.7% versus 11.8% with chemotherapy alone, and the median duration of response was 37.1 months versus 13.2 months, respectively.

Grade 3 or higher adverse events (AEs) were observed in 61.8% of patients in the nivolumab combination arm and 51.7% in the chemotherapy arm; however, no new safety concerns were identified.[2,3]

In this open-label, multinational study, 608 patients were randomly assigned to receive either nivolumab in combination with ipilimumab (Yervoy) or cisplatin-based chemotherapy followed by nivolumab monotherapy or standard-of-care chemotherapy alone.[1,2] To be eligible for enrollment, patients need to have histological or cytological evidence of metastatic or inoperable UC, not receive any prior systemic chemotherapy for UC, have an ECOG performance status of 0 or 1, and follow specific methods of contraception, if applicable. Patients were not eligible to enroll if they had disease that was suitable for local therapy, any uncontrolled medical disorder, or prior treatment with an anti–PD-1, anti–PD-L1, anti–PD-L2, anti-CD137, or anti–CTLA-4 antibody.[3,4]

The primary end points of the study were OS in cisplatin-ineligible patients, OS in PD-L1–positive patients, PFS in cisplatin-eligible patients with previously untreated UC, and OS in cisplatin-eligible patients with previously untreated UC. The secondary end points were PFS in cisplatin-ineligible patients, PFS in PD-L1–positive patients, PFS in all patients, European Organisation for Research and

Treatment of Cancer (EORTC) Global Health Status score, EORTC Global Health Status score in cisplatin-eligible and previously untreated UC, PFS by PD-L1 expression, and OS by PD-L1 expression.

Amivantamab-vmjw (Rybrevant)

The FDA has approved **amivantamab-vmjw (Rybrevant)** with carboplatin and pemetrexed as a first-line treatment in patients with EGFR exon 20 insertion mutation–positive non–small cell lung cancer (NSCLC).[5]

This approval is supported by findings from the phase 3 PAPILLON study (NCT04538664), which showed that combined use of amivantamab, carboplatin, and pemetrexed (Alimta) resulted in a progression-free survival (PFS) of 11.4 months (95% CI, 9.8-13.7 months) versus 6.7 months (95% CI, 5.6-7.3 months) for carboplatin and pemetrexed (HR, 0.40; 95% CI, 0.30-0.53; P < .0001).5 For the secondary end point of overall survival (OS), findings were immature at the time of the current analysis. Further, 44% of prespecified deaths for the final analysis were reported, and there was no trend toward a detriment seen.

For safety, the most common adverse events (AEs) observed in patients receiving the combination were rash, nail toxicity, stomatitis, infusion-related reaction, fatigue, edema, constipation, decreased appetite, nausea, COVID-19, diarrhea, and vomiting.

In addition, the FDA granted traditional approval to amivantamab 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, whose disease has progressed on or after platinum-based chemotherapy.

In the PAPILLON trial, 308 patients with EGFR exon 20–insertion mutations were randomly assigned to receive either amivantamab with carboplatin and pemetrexed or chemotherapy alone. The primary end point was PFS assessed by blinded independent central review. OS was the key secondary end point.[5] Other secondary end points included objective response rate, duration of response, PFS after first subsequent therapy, time to symptomatic progression, intracranial PFS, and incidence and severity of AEs.[6]

Patients were eligible to enroll in the trial if they had histologically or cytologically confirmed, locally advanced or metastatic NSCLC with primary EGFR exon 20 insertion–activating mutation, and an ECOG performance status of 0 or 1 and agreed to genetic characterization of tumor status. Women of childbearing potential must have had a negative pregnancy test within 72 hours of the first study dose and agreed to further serum or urine pregnancy tests during the study.

Patients were ineligible for enrollment if they had evidence of synchronous NSCLC disease, untreated brain metastases, history of spinal cord compression or interstitial lung disease, contraindication to carboplatin or pemetrexed, or a hypersensitivity to cobalamin or folic acid.

According to the press release from the FDA, the recommended dose of amivantamab is based on body weight.[5]

APPROVAL WITHDRAWALS

Melphalan flufenamide (melflufen) (Pepaxto)

The FDA has withdrawn its approval of **melphalan flufenamide (melflufen) (Pepaxto)** for use in combination with dexamethasone for the treatment of patients with multiple myeloma (MM), as grounds for withdrawal were met.[7]

The basis for withdrawal was results of the confirmatory OCEAN trial (NCT03151811), which did not prove the clinical benefit of melflufen; further, available evidence demonstrated that the agent was not shown to be safe or effective under its conditions of use.[7,8]

The ultimate decision was issued by Peter Marks, MD, PhD, acting as the commissioner's representative for the FDA's

Center for Biologics Evaluation and Research. This decision took effect immediately.

The FDA intends to release a notice in the Federal Register to announce the decision and remove melflufen from the Approved Drug Products With Therapeutic Equivalence Evaluations (commonly known as the Orange Book).[7] The manufacturer, Oncopeptides AB, will "thoroughly assess the decision," which it had appealed in 2023.[9,10]

In February 2021, the FDA granted accelerated approval to melflufen in combination with dexamethasone for the treatment of patients with relapsed/refractory MM who have received 4 or more prior lines of therapy and whose disease is refractory to at least 1 proteasome inhibitor, 1 immunomodulatory drug, and 1 CD38-directed monoclonal antibody.

Findings from the single-arm, multicenter, phase 2 HORIZON trial (NCT02963493) supported this FDA decision.[11] Among those treated with melflufen, the overall response rate was 29% (95% CI 22%-37%) in the overall population and 26% (95% CI, 18%-35%) in the triple-class refractory population.[11] Responses included 1 stringent CR, 17 very good partial responses (VGPRs), 28 partial responses (PRs), and 25 minimal responses for a clinical benefit rate (CBR) of 45% (95% CI, 37%-53%) in the overall population versus 13 VGPRs, 18 PRs, and 16 minimal responses in patients with triple-class refractory disease, which equated to a CBR of 39% (95% CI, 31%-49%).[12]

The median duration of response was 5.5 months in the all-treated population (95% CI, 3.9-7.6 months) and 4.4 months (95% CI, 3.4-7.6 months) in the triple-class refractory population.

In July 2021, the FDA requested a partial clinical hold on studies of melflufen, as the combination of melflufen and dexamethasone led to an increased risk of death in the phase 3 OCEAN trial.[11] Although the study results met the primary end point of improved PFS (HR, 0.792; 95% CI, 0.640-0.979, P = .0311), the key secondary end point of improved OS greatly differed across the prespecified subgroups treated with either melflufen plus dexamethasone or pomalidomide (Pomalyst) plus dexamethasone (HR, 1.104; 95% CI, 0.846-1.441).

The Oncologic Drugs Advisory Committee met in September 2022 to discuss the results of OCEAN. In a 14 to 2 vote, the committee decided that the benefit-risk profile of melphalan flufenamide was not favorable for the indicated patient population based on the results of the trial. In December 2022, the FDA requested that the company withdraw the US marketing authorization for melflufen based on the results of the OCEAN trial.[12] The marketing of the agent was halted in the United States on October 22, 2021, based on the FDA's request.

INVESTIGATIONAL NEW DRUG

JAB-30300

The FDA has granted an investigational new drug (IND) application to **JAB-30300**, a drug developed for the treatment of patients with advanced solid tumors.[13] With this IND, there are plans to initiate a phase 1/2a clinical trial for the treatment of advanced solid tumors. The safety and efficacy of JAB-30300 will be assessed across a variety of advanced solid tumors.

JAB-30300 activates p53 in patients harboring a TP53 Y220C mutation. TP53 is the most frequently altered gene observed in cancers in humans, with mutations present in approximately 50% of all invasive tumors. Currently, there is only one phase 1 program studying an activator of the p53 Y220C–mutant protein globally. The orally bioavailable small-molecule activator JAB-30300 is currently undergoing investigation in trials for the treatment of patients with solid tumors with TP53 Y220C mutations.[14] Prior studies have shown JAB-30300 to have high binding affinity to p53 Y220C–mutant proteins; use of the agent resulted in tumor regression in multiple cancer models, including gastric cancer, ovarian cancer, breast cancer, and lung cancer.[13]

IMC001

The investigational new drug application of **IMC001**, an autologous chimeric antigen receptor (CAR) T-cell therapy for infusion that targets the EpCAM protein, has been accepted by the FDA for the treatment of patients with EpCAM-positive advanced gastrointestinal tumors, including gastric cancer and gastroesophageal junction adenocarcinoma.[15] The agent is the first CAR T-cell therapy to aim to cure solid tumors by treating them as hematologic malignancies.

The phase 1, first-in-human, open-label trial (NCT05028933) involved 2 separate, single-site trials, both of which followed a 3+3 design with a dose escalation of 0.3-million, 1-million, or 3-million CAR T cells/kg following lymphodepletion chemotherapy.15 Patients with EpCAM-positive cancers were eligible for enrollment in the study if they had no further standard treatment options and had an ECOG performance status of 0 or 1. Investigators assessed the safety, the pharmacokinetic and pharmacodynamic profile, and the preliminary efficacy of IMC001. Prior trial data showed that the agent had an acceptable safety profile and produced promising efficacy data.[16]

In the investigator-initiated clinical trial that included patients with advanced gastric cancer, 2 of 5 patients achieved a partial remission (PR), and the OS rate was 40% as of January 31, 2024. Among those with a PR, 1 patient underwent a successful radical surgery for gastric cancer 30 weeks after a single infusion of IMC001. This patient is still alive 85 weeks after IMC001 treatment. Another patient with a PR had a 48% reduction in tumor size by week 16.

PRIORITY REVIEW

Epcoritamab-bysp (Epkinly)

The FDA has granted priority review of the supplemental biologics license application for **epcoritamab-bysp (Epkinly)** for the treatment of adult relapsed or refractory (R/R) follicular lymphoma (FL) after at least 2 lines of therapy.[17]

Findings from the phase 1/2 EPCORE NHL-1 trial (NCT03625037) support this regulatory decision, as subcutaneous use of epcoritamab led to deep and durable responses and demonstrated high overall and CRs among patients with R/R FL.18 Results from a cohort of 128 adult patients revealed that at a median follow-up of 17.4 months, the study's primary end point of overall response rate

was 82%, and the CR rate was 63%. The median times to response and to CR were 1.4 and 1.5 months, respectively.[18]

Among prespecified high-risk subgroups, including patients refractory to prior treatments, the overall response rate and CR rates remained generally consistent with those of the overall study population. Importantly, the median durations of response and of CR were not yet reached, and an estimated 85% and 74% of patients who achieved a CR remained responsive to treatment at 12 and 18 months, respectively.

No new safety signals emerged in this cohort, providing reassurance regarding the agent's tolerability. The most common treatment-emergent AE was cytokine release syndrome, which was observed in 67% of patients at varying grades of severity. Notably, no cases of immune effector cell–associated neurotoxicity syndrome were reported.[18]

BIOLOGICS LICENSE APPLICATION

Tislelizumab (Tevimbra)

The FDA has accepted the biologics license application of **tislelizumab (Tevimbra)**, an anti–PD-1 monoclonal antibody, when combined with fluoropyrimidine- and platinum-containing chemotherapy for the treatment of patients locally advanced, unresectable or metastatic gastric and gastroesophageal junction adenocarcinoma.[19] A Prescription Drug User Fee Act target action date of December 2024 is anticipated.

The application is based on findings from the global phase 3 RATIONALE 305 trial (NCT03777657), which met its primary end point of OS.19 The OS was 15.0 months for patients treated with tislelizumab plus chemotherapy

vs 12.9 months for patients treated with placebo plus chemotherapy (HR, 0.80; 95% CI, 0.70-0.92; P = .0011).

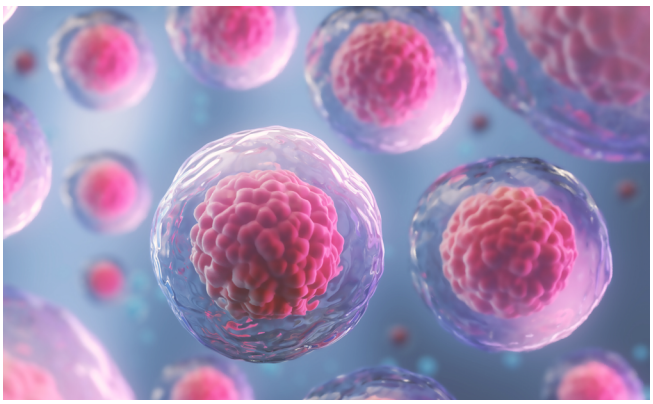
Tislelizumab plus chemotherapy also demonstrated a higher objective response rate (47.3% vs 40.5%) and median duration of response (8.6 months vs 7.2 months) compared with placebo plus chemotherapy.19 Further, the median PFS was 6.9 months in the tislelizumab arm versus 6.2 months in the placebo arm (HR, 0.78; 95% CI, 0.67-0.90).20 The safety profile of the drug combination was manageable and in line with what has been previously reported with use of the individual agents.

FAST TRACK DESIGNATION

IDP-023

IDP-023 has been granted a fast track designation by the FDA for the treatment of non-Hodgkin lymphoma (NHL) and MM.21 IDP-023 is a natural killer cell therapy that is currently in a phase 1/2 trial (NCT06119685). Patients either receive IDP-023 as a monotherapy or in combination with rituximab or daratumumab (Darzalex).[22] The trial has an estimated enrollment of 128 patients; investigators currently are recruiting patients at centers in Minnesota, New York, Oregon, Texas, and Virginia.

The primary end points of the dose-escalation period are incidence of AEs and incidence and nature of dose-limiting toxicities (DLTs) with IDP-023 monotherapy, incidence and nature of DLTs seen with the combination of IDP-023 and rituximab or daratumumab, and maximum tolerated dose. The primary end points of the expansion period in MM are objective response rate (ORR), complete response rate, stringent complete response, very good partial response, and partial response. ORR is the primary end point for NHL in the expansion period. Secondary end points include pharmacokinetics, ORR, and incidence of AEs.



Patients are eligible for study enrollment if they have an ECOG performance status of 0 or 1 and a life expectancy of 12 weeks or longer. Patients with MM must have relapsed or refractory disease after 3 or more lines of therapy, and patients with NHL must have experienced failure of 2 or more lines of chemotherapy. Patients are excluded from the trial if they have impaired cardiac function, a history of significant cardiac disease; HIV, hepatitis C, or active hepatitis B or SARS-CoV-2 infection; or untreated central nervous system, epidural tumor, or brain metastasis. Initial findings from the study are expected to be reported in the second half of this year.[21]

9MW2821

The FDA has granted a fast track designation to **9MW2821**, an antibody-drug conjugate (ADC) targeting Nectin-4, as a potential treatment option for patients with advanced, recurrent, or metastatic esophageal squamous cell carcinoma.[23]

9MW2821 is a novel Nectin-4–targeting ADC developed using a unique linker technology and a streamlined conjugation process, 9MW2821 precisely modifies antibodies, enabling them to target and bind to Nectin-4. Once injected, 9MW2821 is taken up by the targeted cells, where it releases a cell-killing agent and triggers programmed cell death, eliminating the tumor cells.

Data from a phase 2 study (NCT05216965) showed that as of February 20, 2024, 9MW2821 led to an overall response rate of 30% and a disease control rate of 73.3%.[23] These findings come from 30 patients with advanced esophageal cancer who were treated with 1.25 mg/kg of 9MW2821and completed at least 1 tumor assessment. Among the 30 patients enrolled and treated with 9MW2821, 28 patients have undergone chemotherapy and immunotherapy.

CLINICAL HOLD UPDATE

LN-145

The FDA has announced it will lift the partial clinical hold on the IOV-LUN-202 trial (NCT04614103) investigating the tumor-infiltrating lymphocyte cell therapy **LN-145** for the treatment of NSCLC following collaboration with the FDA and an independent data monitoring committee to

develop additional safety and monitoring measures.[24] In December 2023, the FDA placed the IOV-LUN-202 trial on a partial clinical hold following a patient death potentially related to the nonmyeloablative lymphodepletion preconditioning regimen.[25]

Investigators working on the IOV-LUN-202 trial are studying LN-145 for the treatment of patients with advanced unresectable or metastatic NSCLC without EGFR, ROS, or ALK mutations. Patients must have been previously treated with chemotherapy, an anti–PD-1 agent, and at least 1 additional line of targeted therapy for those with actionable genetic mutations. The enrollment of approximately 120 patients is expected to be completed by 2025.[24]

Initial findings were released in July 2023 and showed an overall response rate of 26.1%, consisting of 1 complete response and 5 partial responses. The disease control rate (DCR) was 82.6%. The median duration of response (DOR) was not reached (range, 1.4-9.7 months).[25,26] Updated findings from November 2023 showed that 71% of confirmed responders had ongoing responses and confirmed DORs of more than 6 months.[24] The study's primary end point is ORR, and the secondary end points include complete response rate, DOR, DCR, PFS, OS, incidence of AEs, and core biopsies.[27]

BREAKTHROUGH THERAPY DESIGNATION

BAY 2927088

The FDA has granted a breakthrough therapy designation to **BAY 2927088** in non–small cell lung cancer with HER2-activating mutations.[28] BAY 2927088 is an oral, small-molecule tyrosine kinase inhibitor with the potential to inhibit mutant HER2 receptors, including in tumors harboring HER2 exon 20 insertions, HER2 point mutations, and EGFR mutations.

The designation is supported by findings from a phase 1 study (NCT05099172).[28] The study's primary end points are incidence of treatment-emergent AEs, treatment-emergent serious AEs, severity of AEs, number of patients who discontinue treatment due to an AE, maximum tolerated dose, dose-limiting toxicities, overall response rate, and pharmacokinetics.[29] Secondary end points include recommended phase 2 dose, disease control rate, duration of response, PFS, and OS.

Patients in the dose-escalation portion of the study are receiving doses of BAY 2927088 that are increased in a stepwise fashion until the maximum tolerated dose is reached. The dose-expansion portion is initiated after the dose-escalation portion, and the dose-extension portion begins once all ongoing participants in the expansion cohort have received at least 12 weeks of treatment.

CHANGES IN LABELED INDICATIONS

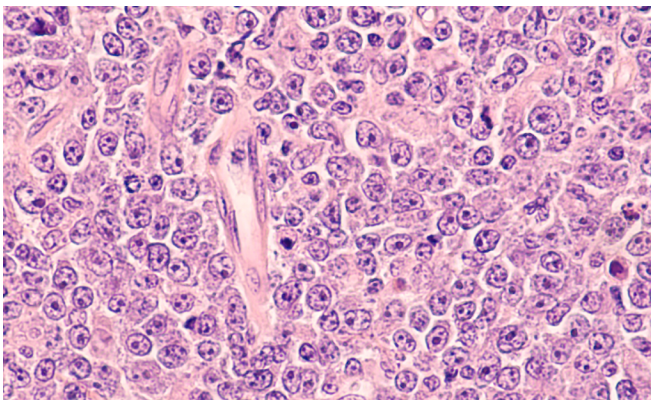
Avelumab (Bavencio)

The severe and fatal immune-mediated AEs section of the drug label for **avelumab (Bavencio)** now includes other transplant (including corneal graft) rejection.[30]

Inotuzumab ozogamicin (Besponsa)

Inotuzumab ozogamicin (Besponsa) used in adult patients for acute lymphoblastic leukemia (ALL) can induce hepatotoxicity, including veno-occlusive disease (VOD). In the INO-VATE ALL trial (NCT01564784), hepatotoxicity including severe, life-threatening, and sometimes fatal hepatic VOD occurred in 14% of patients treated with inotuzumab ozogamicin, with 3% experiencing VOD during study therapy or in follow-up without intervening hematopoietic stem cell transplant (HSCT).[31] Among those proceeding to HSCT, VOD incidence rose to 23%.[31]

In pediatric trials, such as the WI203581 study (ITCC-059; NCT03677596), the VOD rate was 15% among patients given inotuzumab ozogamicin monotherapy; it rose to 19% among those who underwent HSCT.31 Liver test abnormalities were common, with 4% and 5% of patients experiencing grade 3 or 4 elevations in aspartate aminotransferase, alanine aminotransferase, and bilirubin



levels, respectively, in adult trials; in pediatric trials, 21%, 21%, and 9% of patients, respectively, experienced these elevated findings.

Due to these risks, dose adjustments or discontinuation may be necessary. Post-HSCT nonrelapse mortality rates were higher with use of inotuzumab ozogamicin than in patients given the investigator's choice of chemotherapy, particularly in pediatric patients, highlighting the need for careful monitoring and consideration of treatment decisions.

(Significant modifications have been made; please consult the label for details.)

Blinatumomab (Blincyto)

Blinatumomab (Blincyto), used in treating certain cancers, poses a risk of severe, life-threatening, or fatal neurologic toxicity including immune effector cell–associated neurotoxicity syndrome (ICANS). The incidence of neurologic toxicities was approximately 65%, with 7.5% of patients experiencing signs and symptoms of ICANS. Onset of ICANS may occur concurrently with cytokine release syndrome (CRS), after CRS resolution, or independently.[32]

Patients should be aware of potential symptoms such as convulsions, speech difficulties, and confusion and instructed to promptly report these to health care providers. Due to the risk of neurologic events, patients should avoid activities like driving or operating heavy machinery while receiving blinatumomab.

Vandetanib (Caprelsa)

Vandetanib (Caprelsa) is a medication with risks of fetal harm based on animal studies and should not be used during pregnancy. It can adversely affect female fertility, embryofetal development, and postnatal development in animals at exposures equivalent to or lower than those expected at typical clinical doses. Patients, especially females of reproductive potential, should be advised to use effective contraception during vandetanib treatment and for 4 months after its discontinuation. Males with female partners of reproductive potential should also use contraception during treatment and for 4 months afterward.[33]

If experiencing symptoms like faintness, lightheadedness,

or irregular heartbeat, patients should contact their health care provider promptly, as these may be related to heart rhythm abnormalities (eg, QT prolongation).

Vandetanib is accessible only through the restricted Caprelsa risk evaluation and mitigation strategy program. For more information, please call 1-800-817-2722 or go to www.caprelsa.com.

Patients should inform their health care provider about all medications they take, including over the counter drugs and herbal supplements, as interactions with vandetanib may occur. Specifically, use of St John's wort should be avoided during vandetanib treatment. Patients should consult their health care provider or pharmacist before taking any new medications (specifically cardiac medications) while on vandetanib.

Trastuzumab deruxtecan (Enhertu)

Among patients receiving 5.4 mg/kg of **trastuzumab deruxtecan (Enhertu)** for metastatic breast cancer and HER2-mutant NSCLC, interstitial lung disease (ILD) occurred in 12% of patients. Fatal outcomes attributed to ILD and/or pneumonitis were reported in 1.0% of patients. The median time to the first onset of ILD was 6 months (range, 0.9-32 months).[34]

Among patients with metastatic breast cancer and HER2-mutant NSCLC receiving 5.4 mg/kg of trastuzumab, 3.9% experienced a decrease in left ventricular ejection fraction, with 0.4% being grade 3.

In patients with metastatic breast cancer and HER2-mutant NSCLC receiving 5.4 mg/kg of trastuzumab, 65% experienced a decrease in neutrophil count (grade 3 or 4, 16%). The median time to the first onset of decreased

neutrophil count was 22 days (range, 2-939 days). Febrile neutropenia was reported in 0.9% of patients.

Among 1287 breast cancer patients receiving 5.4 mg/kg of trastuzumab, 22% were 65 years or older, and 3.8% were 75 years or older. Efficacy differences were not observed between patients 65 years and older compared to younger patients. However, a higher incidence of grade 3 or 4 AEs was noted in patients 65 years or older (59%) compared to younger patients (49%).

(Significant modifications have been made; please consult the label for details.)

Ibrutinib (Imbruvica)

Fatal and nonfatal infections (including bacterial, viral, or fungal infections) have been reported with **ibrutinib (Imbruvica)** therapy. In clinical trials, grade 3 or greater infections occurred in 21% of 1476 patients with B-cell malignancies who received ibrutinib.[35]

Hypertension was observed in 19% of 1476 patients with B-cell malignancies who received ibrutinib, with grade 3 or greater hypertension occurring in 8% of patients. The median time to onset was 5.9 months, with a cumulative increase in the rate of hypertension over time, as evidenced by results of a long-term safety analysis over 5 years.

Of the 1476 patients with B-cell malignancies who received ibrutinib, 10% developed other malignancies that included non-skin carcinomas (3.9%).

Based on the results of animal studies, ibrutinib can cause fetal harm when given to pregnant women. Administration of ibrutinib to pregnant rats and rabbits during organogenesis caused embryofetal toxicity, including malformations, at exposures 3 to 20 times higher than those reported in patients with hematologic malignancies.

(Significant modifications have been made; please consult the label for details.)

Dostarlimab-gxly (Jemperli)

Additions to AEs associated with taking **dostarlimab-gxly (Jemperli)** now include other transplant rejection (including corneal graft).[36]

Cemiplimab-rwlc (Libtayo)

Additions to AEs associated with taking **cemiplimab-rwlc (Libtayo)** now include other transplant rejection (including corneal graft).[37]

Trametinib (Mekinist)

An addition to AEs observed in less than 10% of 559 patients given **trametinib (Mekinist)** in combination with dabrafenib (Tafinlar) was photosensitivity regarding skin and subcutaneous tissue.[38]

Ixazomib citrate (Ninlaro)

Stevens-Johnson syndrome and toxic epidermal necrolysis, including fatal occurrences, have been reported with use of **ixazomib citrate (Ninlaro)**. If either of these severe skin reactions is suspected, discontinuation of ixazomib citrate that is followed by appropriate clinical management is recommended.[39]

A new subsection has been added to address AEs identified during postapproval use of ixazomib citrate. Among these, toxic epidermal necrolysis has been reported. As these AEs are voluntarily reported and come from a population of uncertain size, the frequency and causal relationship to drug exposure may not always be reliably estimated.

Pegaspargase (Oncaspar)

Use of **pegaspargase (Oncaspar)** in combination with standard chemotherapy has been associated with hepatotoxicity, including severe, life-threatening, and potentially fatal cases of hepatic VOD. Administration of pegaspargase is inadvisable in patients with severe hepatic impairment. Prior to each dose of pegaspargase and at

least weekly during treatment cycles involving the drug, monitor bilirubin and transaminase levels.[40]

Monitoring for signs and symptoms of hepatic VOD (eg, rapid weight gain, ascites, painful hepatomegaly, elevated bilirubin) is recommended. More frequent monitoring for liver test abnormalities and signs and symptoms of VOD is advised in patients who develop abnormal liver test results following pegaspargase administration. In cases of severe liver toxicity, including VOD, discontinuation of pegaspargase treatment and provision of appropriate supportive care are warranted. Patients should be informed about the potential for liver problems and should be instructed to promptly report any symptoms suggestive of liver issues (eg, jaundice, rapid weight gain, abdominal swelling, right upper abdominal pain or tenderness) to their health care provider for immediate evaluation and management.

(Significant modifications have been made; please consult the label for details.)

Nivolumab (Opdivo)

Of 304 patients with urothelial carcinoma who were given **nivolumab (Opdivo)** in combination with gemcitabine and platinum-doublet chemotherapy, 40% were 65 years or older, with 11% being 75 years or older. No overall differences were observed in safety or effectiveness between patients 65 years and older and younger patients (there were insufficient numbers of patients aged 75 years and over to determine potential differences in safety and effectiveness compared with younger patients).[41]

Nivolumab may be used in combination with chemotherapy involving cisplatin and gemcitabine for initial treatment for metastatic urinary tract cancer or when the cancer cannot be surgically removed.

For urinary tract cancer that has spread or cannot be surgically removed, nivolumab given in combination with cisplatin and gemcitabine is administered every 3 weeks for up to 6 cycles. Chemotherapy is administered on the same day. Thereafter, nivolumab alone is given every 2 or 4 weeks, depending on the prescribed dosage.

(Significant modifications have been made; please consult the label for details.)

Nivolumab and relatlimab-rmbw (Opdualag)

Additions to AEs associated with taking nivolumab and **relatlimab-rmbw (Opdualag)** now include other transplant rejection (including corneal graft).[42]

Entrectinib (Rozlytrek)

The health care provider will order tests to monitor heart function before and during treatment with **entrectinib (Rozlytrek).**[43]

Amivantamab-vmjw (Rybrevant)

Amivantamab-vmjw (Rybrevant) given in combination with carboplatin and pemetrexed (Alimta) can lead to infusion-related reactions (IRRs). Among patients treated with this combination, IRRs occurred in 42%; these included grade 3 reactions in 1.3% of cases. Infusion modifications due to IRRs were needed in 40% of patients; permanent discontinuation of the drug was required in 0.7% of patients. Additionally, dermatologic AEs, such as rash were observed in 89% of patients, with 19% experiencing grade 3 reactions.[44]

Use of amivantamab-vmjw monotherapy resulted in IRRs in 66% of patients and rash in 74%. Toxic epidermal necrolysis (TEN) occurred in 1 patient (0.3%).

When combined with carboplatin and pemetrexed, use of amivantamab-vmjw may cause ocular toxicity with events such as blepharitis, dry eye, conjunctival redness, blurred vision, and eye pruritus being reported. All occurrences were grade 1 to 2.

Results of the PAPILLON study (NCT04538664) revealed that 37% of patients treated with amivantamab-vmjw in combination with carboplatin and pemetrexed were 65 years or older, and 8% were at least 75 years old.[44] In

the CHRYSALIS study (NCT02609776), 39% of patients receiving amivantamab-vmjw as a single agent were 65 years or older, and 11% were at least 75 years old.[44]

Amivantamab-vmjw is prescribed to treat adults with NSCLC that has metastasized or that cannot be surgically removed; it is used with carboplatin and pemetrexed as a first-line treatment in patients who possess certain abnormal EGFR genes and is used alone in patients with certain abnormal EGFR genes whose disease has worsened on or after platinum-based chemotherapy. The most common AEs when used in combination with carboplatin and pemetrexed include rash, constipation, paronychia, and infusion-related reactions. The most common AEs noted during monotherapy include rash; swelling of the hands, ankles, feet, face, or entire body; and infusion-site reactions.

Patients should be advised of the risk of paronychia and instructed to contact their health care provider if signs or symptoms occur.

Dabrafenib (Tafinlar)

Among 586 patients treated with **dabrafenib (Tafinlar)** monotherapy, additional important AEs observed in less than 10% of cases included photosensitivity. [45]

Across 559 patients treated during the COMBI-d (NCT01584648) and COMBI-v (NCT01597908) studies, other AEs that were observed in less than 10% of patients given dabrafenib with trametinib included panniculitis and photosensitivity.[45]

Osimertinib (Tagrisso)

Among 1813 patients receiving **osimertinib (Tagrisso)**, interstitial lung disease (ILD)/pneumonitis occurred in 4% of cases, with a fatal outcome noted among 0.4% of patients. In the FLAURA2 study (NCT04035486), ILD/pneumonitis was observed in 3.3% of patients treated with osimertinib in combination with pemetrexed (Alimta) and platinum-based chemotherapy, with 0.4% of cases being fatal.[46]

Use of osimertinib monotherapy is associated with heart rate–corrected QTc interval prolongation. Cardiomyopathy occurred in 9% of patients treated with osimertinib in combination with pemetrexed and

platinum-based chemotherapy, with 1.1% of cases being fatal. Additionally, 8% of 262 patients given that combination therapy experienced decreases in left ventricular ejection fraction of at least 10 percentage points and a drop to less than 50%. Please consult FLAURA2 study data for further updates.

Keratitis was reported in 0.6% of 1813 patients treated with osimertinib monotherapy. Aplastic anemia has been reported in clinical trials and postmarketing surveillance.

Among 1813 patients treated with osimertinib monotherapy, 770 patients were 65 years or older, and 207 patients were 75 years or older. For patients receiving osimertinib in combination with chemotherapy, 104 patients were 65 years or older, and 23 patients were 75 years or older. Result of an exploratory analysis suggested that higher incidences of grade 3 or higher AEs and more frequent dosage modifications for AEs occurred in older patients compared with younger ones. However, no overall differences in safety or effectiveness were observed between older and younger patients.

For patients receiving the drug via nasogastric tube (NG), osimertinib tablets should be mixed with 15 mL of water in a container with use of carbonated water or other liquids avoided. The mixture should be stirred until the tablets break into small pieces without completely dissolving. Crushing, heating, or use of ultrasound should be avoided. Another 15 mL of water should be added to ensure that no tablet fragments remain. The mixture should be given via an NG tube within 30 minutes as directed by the NG tube manufacturer. An additional 30 mL of water should be used to flush the tube and ensure that the full dose is delivered.

When osimertinib is used in combination with pemetrexed

and platinum-based chemotherapy, common AEs may include low white blood cell counts, changes in nails (eg, redness, tenderness, pain, inflammation, brittleness, separation from the nailbed, and shedding), dry skin, low platelet counts, increased levels of creatinine in the blood, rash, diarrhea, and mouth sores. These AEs may occur during treatment, and they should be monitored by health care providers.

(Significant modifications have been made; please consult the label for details.)

Nilotinib (Tasigna)

Musculoskeletal and connective tissue disorders such as osteonecrosis have been noted during postmarketing experience in patients receiving **nilotinib hydrochloride mononitrate (Tasigna)**.[47]

Tepotinib (Tepmetko)

ILD)/pneumonitis, grade 3 hepatotoxicity, and grade 3 and 4 pancreatic toxicity have been added to the Warnings and Precautions section for **tepotinib (Tepmetko)**.[48]

Patients should be informed about the need for regular laboratory tests to monitor pancreatic function. They should be advised to promptly report any signs or symptoms of pancreatitis to their health care provider. Additionally, patients should disclose any history of pancreatic problems to their health care provider. Tepotinib may cause elevations in blood amylase and lipase levels, indicating potential pancreatic issues. Health care providers will conduct blood tests to assess pancreatic function before and during treatment. Patients should immediately report any signs or symptoms of pancreas problems, including upper abdominal pain, nausea, vomiting, and unexplained weight loss.

Updates regarding the most common AEs associated with tepotinib use include loss of appetite, rash, and alterations in the results of certain blood tests. These AEs should be monitored closely during treatment with tepotinib.

(Significant modifications have been made; please consult the label for details.)

Bendamustine (Vivimusta)

Renal and urinary disorders such as nephrogenic diabetes insipidus have been documented in patients given **bendamustine (Vivimusta)** during postmarketing experience.[49]

Pegfilgrastim-bmez (Ziextenzo)

The observed incidence of antidrug antibodies is heavily influenced by the sensitivity and specificity of the assay used. Meaningful comparisons of antidrug-antibody incidence across studies, including those involving pegfilgrastim, may not be possible due to differences in assay methodologies.[50]

Pegfilgrastim is used to enhance survival in pediatric patients exposed to myelosuppressive doses of radiation. This usage is supported by the agent's approval as a biosimilar to pegfilgrastim and evidence from efficacy studies conducted in animals.

Clinical data also support the efficacy of pegfilgrastim in cancer patients undergoing myelosuppressive chemotherapy. Efficacy studies of pegfilgrastim in humans with acute radiation syndrome were not feasible due to ethical considerations. Outcomes from population modeling and simulation suggest that 2 doses of pegfilgrastim administered 1 week apart offer pediatric patients exposure comparable to that of adults receiving the standard 2 doses of 6 mg given 1 week apart.

Patients exposed to myelosuppressive doses of radiation, specifically those with hematopoietic subsyndrome of acute radiation syndrome, should be informed that efficacy studies of pegfilgrastim for this indication were not feasible in humans due to ethical and logistical constraints. Approval for this use was primarily based on efficacy studies conducted in animals.

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