FEBRUARY 2024

NCOA ONCOLOGY DRUG NEWSLETTER

NORTH CAROLINA Oncology Association

FDA APPROVALS

Enfortumab Vedotin-Ejfv (Padcev) and Pembrolizumab (Keytruda)

The FDA has granted approval to the combination of **enfortumab vedotin-ejfv (Padcev)** and **pembrolizumab (Keytruda)** for the treatment of patients with locally advanced or metastatic urothelial cancer who are not eligible to receive cisplatin-containing chemotherapy.[1] The approval is supported by efficacy and safety data from the phase 3 EV-302/KN-A39 trial (NCT04223856), in which investigators evaluated the combination of enfortumab vedotin and pembrolizumab in this patient population.[2]

Findings from the EV-302/KN-A39 study were presented at the European Society for Medical Oncology Congress 2023 and published in *Annals of Oncology*.[2] In all, 886 patients were randomly assigned 1:1 to receive enfortumab vedotin plus pembrolizumab or chemotherapy. The median follow-up was 17.2 months. The confirmed overall response rate was 67.7% in the enfortumab vedotin/pembrolizumab arm compared with 44.4% in the chemotherapy arm.

Use of enfortumab vedotin/pembrolizumab provided encouraging safety and efficacy. Significant improvements in overall survival (OS) and progression-free survival (PFS) were demonstrated for enfortumab vedotin/pembrolizumab compared with platinum-based chemotherapy. Median OS was 31.5 months (95% CI, 25.4 months to not estimable) for patients who received enfortumab vedotin/pembrolizumab and 16.1 months (95% CI, 13.9-18.3 months) for those given platinum-based chemotherapy (HR, 0.47; 95% CI, 0.38-0.58; *P*<.0001). Median PFS was 12.5 months (95% CI, 10.4-16.6 months) for patients who received enfortumab vedotin/pembrolizumab vs 6.3 months (95% CI, 6.2-6.5 months) for those given platinum-based chemotherapy (HR, 0.45; 95% CI, 0.38-0.54 months; *P*<.0001).

Grade 3 or greater treatment-related adverse events (TRAEs) occurred in 55.9% of patients in the enfortumab vedotin/pembrolizumab arm and 69.5% of those in the chemotherapy arm. The most common TRAEs in the enfortumab vedotin/pembrolizumab arm were maculopapular rash (7.7%), hyperglycemia (5.0%), and neutropenia (4.8%) and in the chemotherapy arm were anemia (31.4%), neutropenia (30%), and thrombocytopenia (19.4%).

Belzutifan (Welireg)

The FDA approved **belzutifan (Welireg)** for the treatment of adult patients with advanced renal cell carcinoma (RCC) whose disease progressed following PD-1/PD-L1 and VEGF tyrosine kinase inhibitor treatment.[3] This regulatory decision is supported by data from the phase 3 LITESPARK-005 study (NCT04195750) in which the coprimary end point of progression-free survival (PFS) was met.[3]

In this open-label, randomized, phase 3 study, 746 patients with advanced RCC whose disease progressed after treatment with anti–PD-1/PD-L1 and VEGF-targeted therapies were randomly assigned to receive either belzutifan, 120 mg, orally once daily or everolimus (Afinitor), 10 mg, orally once daily.[4,5]

Investigators evaluated the coprimary end points of PFS and overall survival (OS).[6] Secondary end points of the trial included overall response rate (ORR), duration of response (DOR), number of patients experiencing 1 or more adverse events (AEs) and who discontinued study treatment as a result, time to deterioration (TTD) of health-related quality of life (HRQOL), and TTD in physical functioning and disease symptoms. In addition, investigators noted changes from baseline in HRQOL per the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) score for items 29 and 30 and in physical functioning based on the score for items 1 through 5, in disease symptoms according to the Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index-Disease Related Symptoms score for items 1 through 9, and in health utility score from baseline for the European Quality of Life 5 Dimensions 5-level Questionnaire.[4]

Patients with unresectable, locally advanced, or metastatic disease who had received no more than 3 prior systemic agents for locally advanced or metastatic RCC and had adequate organ function were enrolled. At the landmark 18-month analysis, a significant and clinical meaningful improvement in PFS was noted with use of belzutifan as compared with everolimus treatment (Afinitor) (22.5% vs 9%, respectively; HR, 0.74; 95% CI, 0.63-0.88). Belzutifan demonstrated a significant improvement in PFS compared with everolimus (HR, 0.75; 95% CI, 0.63-0.90; 1-sided *P*=.0008). Kaplan-Meier analysis indicated nonproportional hazards with similar median PFS estimates (belzutifan, 5.6 months [95% CI, 3.9-7.0 months]; everolimus, 5.6 months [95% CI, 4.8-5.8 months]).

To date, there have been no significant OS benefits seen with belzutifan compared with everolimus (55.2% vs 50.6%, respectively), although there is a signal for OS benefit (HR, 0.88; 95% CI, 0.73-1.07; *P*=.099). A complete response was observed in 3.5% of those treated with belzutifan vs 0.0% of patients given everolimus. Patients showed a similar median time to response (3.7 vs 3.8 months), but the median DOR was longer with belzutifan than with everolimus (19.5 vs 13.7 months). A significant improvement in the key secondary end point of ORR was also observed with belzutifan vs everolimus (22.7% vs 3.5%).

For safety, both arms had similar grade 3 or worse AEs, but AEs leading to treatment discontinuation were seen in 6% of patients given belzutifan vs 15% of those given everolimus. The most common AEs included anemia and fatigue. Approximately 30% of patients in the belzutifan arm had grade 3 or worse anemia.

Eflornithine (Iwilfin)

Eflornithine (Iwilfin) has been granted FDA approval for use in adult and pediatric patients with high-risk neuroblastoma (HRNB) who have had at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy to reduce the risk of relapse.[7] This regulatory decision was based on findings from a controlled trial comparing outcomes from Study NMTRC003B (NCT02395666; investigational arm) and Study ANBL0032 (NCT00026312; clinical trial-derived external control arm). In October 2023, the FDA's Oncologic Drug Advisory Committee voted 14 to 6 that there was sufficient evidence that eflornithine therapy reduced the risk of relapse in pediatric patients with HRBN who were in remission and who had completed multiagent, multimodality therapy.[8,9]

The multicenter, open-label, nonrandomized, phase 2 Study NMTRC003B included 2 cohorts. In the first cohort, 105 eligible patients with HRNB were given eflornithine orally twice daily at a dosage based on body surface area until disease progression or unacceptable toxicity occurred or until therapy was given for a maximum of 2 years.[7]

The external control arm consisted of 1241 patients on the experimental arm of the multicenter, open-label, randomized, phase 3 Study NMTRC003B. Investigators evaluated use of dinutuximab (Unituxin), granulocyte-macrophage colony-stimulating factor, interleukin-2, and cis-retinoic acid compared with cis-retinoic acid alone in pediatric patients with HRNB.

Patients were matched 1:3 using propensity scores if they met the criteria for the comparative analysis of Study NMTRC003B and Study ANBL0032. A total of 90 patients were included in the matched efficacy populations for the primary analysis and 270 control patients were included from Study ANBL0032.

Investigators evaluated event-free survival (EFS) (defined as disease progression, relapse, secondary cancer, or death due to any cause) and other end points of overall survival (OS) (defined as death due to any cause). The HR for EFS was 0.48 (95% CI, 0.27-0.85) and for OS was 0.32 (95% CI, 0.15-0.70). Further, the EFS HR ranged from 0.43 (95% CI, 0.23-0.79) to 0.59 (95% CI, 0.28-1.27), and the OS HR ranged from 0.29 (95% CI, 0.11-0.72) to 0.45 (95% CI, 0.21-0.98). For safety, the most common AES, which were seen in 5% or more of patients in Study NMTRC003B, consisted of otitis media, diarrhea, and cough.

INVESTIGATIONAL NEW DRUG

VIPER-101

The FDA has cleared the investigational new drug application for **VIPER-101** for the treatment of patients with T-cell lymphoma. With this clearance, a first-in-human phase 1 trial will be initiated.[10] VIPER-101 is a gene-edited, autologous, chimeric antigen receptor (CAR) T-cell therapy for the potential treatment of patients with relapsed or refractory T-cell lymphoma. The CD5-deleted CAR T-cell therapy was made using the proprietary cell therapy engineering and manufacturing platform Senza5.[10]

VIPER-101 is engineered to avoid fratricide and unlock the benefit of circumventing the inhibitory CD5 signaling pathway. As VIPER-101 is made using a proprietary 5-day process to preserve cell stemness, it synergizes to maximize potency, safety, and manufacturing efficiency. Across distinct tumor models, VIPER-101 has shown enhanced antitumor efficacy and broad utility of the proprietary Senza5 cell therapy engineering and manufacturing platform, which acts on the fundamental biology of T cells and which can be used to improve the efficacy of engineered T-cell therapies. Further, data from the upcoming phase 1 trial of VIPER-101 in patients with relapsed/refractory T-cell lymphoma are expected in early 2025.[10]

CT071

The FDA has cleared an investigational new drug application for **CT071** for the treatment of patients with relapsed/refractory (R/R) multiple myeloma (MM) or R/R primary plasma cell leukemia (PCL), according to CARsgen Therapeutics Holdings Limited.[11] An ongoing phase 1 clinical trial (NCT05838131) in China is evaluating the safety and efficacy of CT071 for the treatment of patients with R/R MM or R/R PCL.[12]

CT071 is an autologous chimeric antigen receptor (CAR) T-cell therapy candidate that incorporates a fully human single-chain variable fragment. The therapy works by targeting GPRC5D. There is overexpression of GPRC5D on the surface of malignant plasma cells and limited presence of GPRC5D on normal tissues, making this CAR T-cell therapy an ideal candidate for the treatment of R/R MM and R/R PCL.

Manufactured with CARsgen's proprietary CARcelerate platform in less than 2 days, CT071 yields younger, healthier, and possibly more potent CAR T cells than does conventional manufacturing. This platform also enhances supply capacity, reduces manufacturing costs, and expedites availability of the product and delivery to the patient.

PRIORITY REVIEW

Tarlatamab

The FDA has accepted and granted priority review for the biologics license application (BLA) for **tarlatamab** for use in patients with advanced small cell lung cancer (SCLC) with disease progression during or after platinum-based chemotherapy.[13] This BLA was based on results from the phase 2 DeLLphi-301 trial (NCT05060016) showing antitumor activity, a durable response, and encouraging survival outcomes among patients with previously treated SCLC who were given tarlatamab. The safety profile observed in the phase 2 study was in line with findings reported from the phase 1 DeLLphi-300 trial (NCT03319940). A Prescription Drug User Fee Act date for tarlatamab has been set for June 12, 2024.[13]

Tarlatamab is a potential first-in-class, investigational DLL3-targeting agent. This bispecific T-cell engager therapy is being developed to treat adult patients with advanced SCLC with disease progression during or after platinum-based chemotherapy. In the DeLLphi-301 trial, investigators evaluated the antitumor activity and safety of 10 mg or 100 mg of tarlatamab given every 2 weeks via intravenous infusion to patients with previously treated SCLC.[14] The primary end point was objective response as assessed by blinded independent central review according to RECIST v1.1. The median progression-free survival was 4.9 months (95% CI, 2.9-6.7 months) among patients treated at the 10-mg dose vs 3.9 months (95% CI, 2.6-4.4 months) among those given the 100-mg dose; the overall survival estimates at 9 months were 68% vs 66%, respectively.

Mirvetuximab Soravtansine-Gynx (Elahere)

The supplemental biologics license application for **mirvetuximab soravtansine-gynx (Elahere)** in FRα-positive, platinum-resistant ovarian cancer has been granted priority review by the FDA.[15] The review is supported by findings from the phase 3 MIRASOL trial (NCT04209855), and the FDA has set a Prescription Drug User Fee Act target action date of April 5, 2024.[15]

Mirvetuximab soravtansine is a first-in-class antibody-drug conjugate that is composed of an FRα-binding antibody, cleavable linker, and a tubulin inhibitor. In November

2022, the agent was granted accelerated approval from the FDA for FRα-high, platinum-resistant ovarian cancer.

Data from the MIRASOL study showed improvements in progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) in this patient population. In patients who previously received a PARP inhibitor, the PFS HR was 0.58 (95% CI, 0.43-0.78; *P*=.0002). The ORR among those given mirvetuximab soravtansine was 45% (95% CI, 36%-54%) including 7 CRs; among patients given the investigator's choice chemotherapy, the ORR was 17% (95% CI, 11%-25%) with no CRs (*P*<.0001). In the group not previously given a PARP inhibitor, the ORR among patients given mirvetuximab soravtansine was 40% (95% CI, 30%-51%) including 5 CRs; in the chemotherapy arm, the ORR was 14% (95% CI, 8%-23%) with no CRs (*P*<.0001). In patients given prior PARP inhibition, the HR for OS was 0.48 (95% CI, 0.33-0.71; p=.0002). Among those who were PARP inhibitor–naïve, however, the OS HR was 0.90 (95% CI, 0.590-1.38, P=.6319).[15,16]

The MIRASOL trial has an enrollment of 453 patients and an estimated study completion date of April 2024.[17]

Nivolumab (Opdivo)

Nivolumab (Opdivo) plus cisplatin-based chemotherapy has been granted priority review by the FDA in treatment-naive unresectable or metastatic urothelial carcinoma.[18] The filing is supported by results from the phase 3 CheckMate901 study (NCT03036098); the FDA has set a Prescription Drug User Fee Act target action date of April 5, 2024.[18]

According to findings published in the *New England Journal of Medicine* and presented at the European Society for Medical Oncology Congress 2023, overall survival (OS) (HR, 0.78; 95% CI, 0.63-0.96; *P*=.02) and progression-free survival (PFS) (HR, 0.72; 95% CI, 0.59-0.88; *P*=.001) were improved with nivolumab/chemotherapy compared with gemcitabine/cisplatin alone.[19] At a median follow-up of 33.6 months, the median OS was 21.7 months (95% CI, 18.6-26.4) in the nivolumab combination arm vs 18.9 months (95% CI, 15.7-22.4) in the chemotherapy arm. PFS at 12 months was 34.2% vs 21.8% (median PFS, 7.9 vs 7.6 months).[19]

Objective response rate (ORR) was 57.6% in the nivolumab combination arm and 43.1% in the arm given chemotherapy alone; the complete response (CR) rate 21.7% vs 11.8%, respectively. The median duration of response was 37.1 vs 13.2 months.

FAST TRACK DESIGNATION

Cretostimogene Grenadenorepvec (CG 0070)

A breakthrough therapy designation and fast track designation were granted by the FDA to the oncolytic immunotherapy **cretostimogene grenadenorepvec (CG 0070)** for the treatment of patients with high-risk, bacillus Calmette-Guerin–unresponsive, non–muscle invasive bladder cancer with carcinoma in situ with or without Ta or T1 (papillary) tumors.[20]

Findings from the phase 3 BOND-003 trial (NCT04452591) support this regulatory decision. In the study, 75.7% (95% CI, 63%-85%) of patients given cretostimogene grenadenorepvec had a complete response (CR) at any time point, and responses were durable. A CR was reported in 45 patients (68.2%) at 3 months and in 42 patients (63.6%) at 6 months. Additionally, 74.4% of the CRs lasted for a minimum of 6 months.[21]

Data from the interim analysis also showed that 31% of patients who did not respond to their first course of treatment were salvaged with reinduction. In the safety population, which included 112 patients, most adverse events (AEs) were grade 1 or 2 with the most common treatment-related AEs being bladder spasm (20.5%), pollakiuria (16.1%), dysuria (14.3%), micturition urgency (11.6%), and hematuria (10.7%).

BREAKTHROUGH THERAPY DESIGNATION

TAR-200 (JNJ-63723283)

TAR-200 (JNJ-63723283) has received a breakthrough therapy designation (BTD) from the FDA in BCG-unresponsive, high-risk, non–muscle invasive bladder cancer that is not amenable to radical cystectomy. The BTD is supported by findings from the phase 2 SunRISe-1 trial (NCT04640623).[22]

TAR-200 is an investigational agent that can deliver a targeted, sustained release of gemcitabine into the bladder for weeks at a time. The agent is being further investigated in individuals with NMIBC in the phase 3 SunRISe-3 trial (NCT05714202) and in patients with muscle-invasive bladder cancer in the phase 3 SunRISe-2 (NCT04658862) and phase 2 SunRISe-4 (NCT04919512) studies.

In the SunRISe-1 trial, use of TAR-200 plus cetrelimab (JNJ-63723283) is being compared with each agent given alone in patients with carcinoma in situ with or without concomitant high-grade Ta or T1 papillary disease.[23] The primary end points are overall complete response and disease-free survival. The secondary end points are duration of response, overall survival, gemcitabine concentrations in urine and plasma, serum concentrations of anti-cetrelimab antibodies, number of patients with anti-cetrelimab antibodies, change from baseline in quality of life, and number of patients who experience adverse events.

CHANGES IN LABELED INDICATIONS

Enasidenib Mesylate (Idhifa)

Female patients using **enasidenib mesylate (Idhifa)** use a *nonhormonal* contraceptive device during treatment and for 2 months after the last dose. This also applies to female partners of male patients taking enasidenib mesylate due to the embryofetal toxicity associated with this drug.[24]

Tablets should be swallowed whole with water and not crushed, tampered with, or chewed.

Use of certain CYP1A2 substrates with enasidenib mesylate should be avoided unless otherwise recommended in the prescribing information. Caffeine intake should be reduced due to potential amplification of its effects. Enasidenib, a CYP1A2 inhibitor, increases exposure to CYP1A2 substrates, elevating the risk of adverse events (AEs).

Enasidenib, a CYP2C19 inhibitor, raises the exposure of CYP2C19 substrates, increasing the risk of related AEs.

Concomitant use of certain CYP3A substrates with enasidenib mesylate should be avoided unless otherwise advised in the prescribing information. Enasidenib should not be given with CYP3A substrate antifungal agents; as a CYP3A inducer, enasidenib decreases the exposure of CYP3A substrates, potentially reducing their efficacy.

Coadministration of certain OATP1B1, OATP1B3, and BCRP substrates with enasidenib mesylate should be avoided, if possible. If not, consider decreasing the dosage of these substrates. Use of enasidenib—an OATP1B1, OATP1B3, and BCRP transporter inhibitor—increases exposure to these substrates and raises the risk of AEs.

Recommended prescribing information for P-glycoprotein (P-gp) substrates should be followed, and patients should be monitored more frequently when receiving P-gp substrates with enasidenib mesylate. Enasidenib is a P-gp transporter inhibitor.

Durvalumab (Imfinzi)

Numbness, tingling, or weakness in the legs or arms was added as a possible sign or symptom of immune system issues during **durvalumab (Imfinzi)** therapy. Patients are instructed to inform their health care provider if this occurs.[25]

Pembrolizumab (Keytruda)

The safety profile of **pembrolizumab (Keytruda)** was assessed in the KEYNOTE-394 study (NCT03062358) involving patients with hepatocellular carcinoma who received prior treatment.[26]

Patients were randomly assigned 2:1 to receive either pembrolizumab or placebo. Overall, 299 patients were given 200 mg of pembrolizumab intravenously, and 153 patients were given placebo every 3 weeks. Patients in the pembrolizumab group received up to 35 cycles of therapy, whereas those in the placebo arm received treatment for an average of 2.2 months (range, 1 day to 15.5 months).

Pembrolizumab administration was halted in 13% of patients due to adverse events (AEs). Permanent discontinuation of pembrolizumab was most frequently caused by ascites (2.3%). In 26% of patients, an AE occurred that necessitated pembrolizumab interruption. The primary AEs or laboratory abnormalities prompting interruption of pembrolizumab (affecting ≥ 2% of participants) were elevated blood bilirubin levels (9%), elevated aspartate aminotransferase levels (5%), and elevated alanine aminotransferase levels (2%).

Erdafitinib (Balversa)

Regarding safety, 22% of patients receiving **erdafitinib (Balversa)** experienced central serous retinopathy (CSR)/retinal pigment epithelial detachment (median time to first onset, 46 days). Among 104 patients with CSR, 40% needed dose interruptions, 56% required dose reductions, and 2.9% needed permanent dose discontinuation. Of 24 patients who continued therapy after dose interruption, 67% experienced worsened CSR. Of the 104 patients, 41% had ongoing CSR at the last evaluation. Withholding of therapy or permanent discontinuation of treatment was based on severity and/or ophthalmology examination findings.[27]

Increased phosphate levels occurred in 73% of patients receiving erdafitinib at the median onset time of 16 days. In all, 24% of patients received phosphate binders, and 0.2% experienced vascular calcification. Patients were given dietary restrictions to avoid increased serum phosphate levels. It is advised that an oral phosphate binder be given until phosphate levels return to less than 7.0 mg/dL.

If a moderate CYP2CP inhibitor or strong CYP3A4 inhibitor is used with erdafitinib, monitor closely for adverse reactions and consider dose modification. If a moderate CYP2CP inhibitor or strong CYP3A4 inhibitor discontinued, the erdafitinib dose should be resumed before dose modifications if there is no drug-related toxicity. Strong CYP3A4 inducers decrease the plasma concentrations of erdafitinib significantly; coadministration should be avoided. Moderate CYP3A4 inducers cause a decrease in erdafitinib plasma concentrations and possible decreased activity of the drug; if coadministration is necessary when initiating erdafitinib therapy, 9 mg/d of erdafitinib should be given. If a moderate CYP3A4 inducer is being discontinued, erdafitinib should be continued at the same dose if no drug-related toxicity has occurred.

Regarding reproductive updates, erdafitinib can cause fetal harm; verification for pregnancy status is necessary. Erdafitinib could impair Infertility.

Regarding the use of erdafitinib in geriatric patients, among the 479 patients receiving erdafitinib, 40% of patients were 65 years or younger, 40% were aged 65 to 75 years, and 20% were 75 years or older. Discontinuation of therapy due to adverse effects was more common among older patients than younger patients (age: < 65 years, 10%; 65-74 years, 20%; ≥ 75 years, 35%). However, overall efficacy did not differ between age groups.

Alpelisib (Piqray)

Consideration of metformin use for premedication along with individual patient risk factors (eg, hyperglycemia, gastrointestinal tolerance, and overall clinical circumstances) is advisable before beginning use of **alpelisib (Piqray)** and fulvestrant. Findings from the METALLICA study (NCT04300790) suggested that initiating metformin 7 days before starting alpelisib

may mitigate both the frequency and intensity of hyperglycemic events. Importantly, however, this approach seems to correlate with a higher occurrence and severity of nausea, vomiting, and diarrhea.[28]

Eye disorders such as uveitis have been identified when using alpelisib. Patients are advised to inform their health care provider if signs of uveitis occur.

Use of CYP3A4 inducers should be avoided when taking alpelisib; however, if use is unavoidable, close monitoring is advised. Dose adjustments are not required when using alpelisib with CYP3A4, CYP2C8, CYP2C9, CYP2C19, and CYP2B6 substrates.

Bendamustine Hydrochloride (Treanda)

During postmarketing experience, urinary and renal disorders (eg, nephrogenic diabetes insipidus) have been reported with use of **bendamustine hydrochloride (Treanda)**.[29]

Tremelimumab-ACTL (Imjudo)

It is important for patients taking **tremelimumab-ACTL (Imjudo)** to inform their health care provider if they experience tingling, numbness, or weakness in their legs or arms *or* persistent or severe muscle pain or weakness, muscle cramps, or joint pain, stiffness, or swelling.[30]

Pazopanib Hydrochloride (Votrient)

Use of **pazopanib hydrochloride (Votrient)** is not indicated in patients younger than 2 years; based on the drug's mechanism of action, severe effects on organ growth and maturation may occur.[31]

Administration of pazopanib hydrochloride to juvenile rats younger than 21 days led to harmful effects on the lungs, liver, heart, and kidneys, resulting in fatalities

at doses significantly lower than those recommended clinically or tolerated by older animals.

The safety and effectiveness of pazopanib hydrochloride or an unapproved pazopanib formulation were explored but not confirmed in 2 open-label investigations. One study (NCT00929903) involved 37 pediatric patients (age, 2 to <17 years) with recurrent or resistant solid tumors, and the other study (NCT01956669) involved 46 pediatric patients (age, 1 year to <17 years) with resistant solid tumors, including sarcoma. These studies did not demonstrate substantial antitumor activity.

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