SEPTEMBER 2023

TxSCO ONCOLOGY DRUG NEWSLETTER

FDA APPROVALS

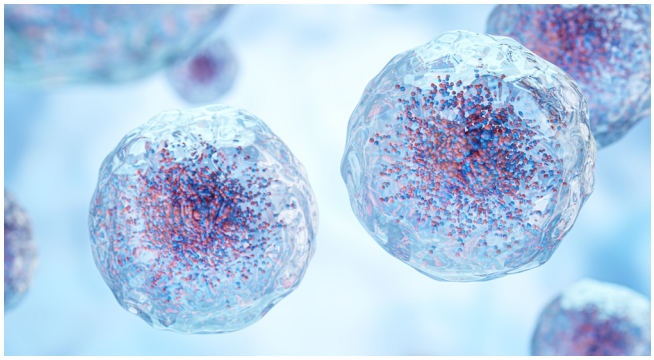
Blinatumomab (Blincyto)

The FDA awarded full approval to **blinatumomab (Blincyto)** for the treatment of adults and pediatric patients with CD19-positive B-cell acute lymphoblastic leukemia (ALL) who had first or second complete remission with minimal residual disease (MRD) of at least 0.1%. "In a phase 2 study, roughly 80% of adult patients treated with blinatumomab experienced a complete MRD response," said principal investigator Elias Jabbour, MD, a professor in the Department of Leukemia, Division of Cancer Medicine, at The University of Texas MD Anderson Cancer Center in Houston, in a news release. "The FDA's decision to grant a full approval for blinatumomab further validates the use of this therapy to treat adults and children with B-cell precursor ALL with MRD present following a remission, which is a strong predictor of relapse in this patient population."

Approval was originally granted based on results from the single-arm BLAST trial (NCT01207388) following an affirmative 8-to-4 vote from the FDA Oncologic Drugs Advisory Committee. Most patients treated with blinatumomab in BLAST achieved a complete MRD response, leading to a significant improvement in relapse-free survival and overall survival, according to published findings. Conversion to full approval results from 2 phase 3 studies, which provided additional data.

Talazoparib (Talzenna)

The FDA has granted approval to the combination of **talazoparib (Talzenna)** plus **enzalutamide (Xtandi)** for the treatment of patients with homologous recombination repair (HRR) gene–mutated metastatic castration-resistant prostate cancer (mCRPC).



Findings from the phase 3 TALAPRO-2 trial (NCT03395197) support the approval. According to data recently presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, the combination achieved statistically significant and clinically meaningful progression-free survival (PFS) improvement as a first-line therapy for patients with mCRPC who have HRR gene–altered disease.

The primary end point of radiographic PFS (rPFS) with a 55% reduced risk of progression of death in patients in the combination arm (n = 200) was achieved in TALAPRO-2, despite a median rPFS that was not reached (NR) in the talazoparib arm (95% CI, 21.9-NR) compared with 13.8 months (95% CI, 11.0-16.7) in the placebo arm (HR, 0.45; 95% CI, 0.33-0.61; P < .0001). Further, the combination showed a 37% lower risk of rPFS in the talazoparib plus enzalutamide arm compared with the placebo plus enzalutamide arm (HR, 0.63; 95% CI, 0.51-0.78; P < .0001

PRIORITY REVIEW

Zolbetuximab (IMAB362)

The FDA has granted priority review to **zolbetuximab (IMAB362)** for its biologics license application (BLA) for the up-front treatment of

patients with locally advanced, unresectable, or metastatic HER2-negative, CLDN18.2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma. Supporting the BLA are results from the phase 3 SPOTLIGHT (NCT03504397) and GLOW (NCT03653507) studies. In both studies, the addition of zolbetuximab to a chemotherapy regimen provided a significant overall survival and progression-free survival benefit in patients with advanced, HER2-negative, CLDN18.2-positive gastric/GEJ cancer. The FDA's Prescription Drug User Fee Act target action date is January 12, 2024.

FAST TRACK DESIGNATION

Paxalisib (GDC-0084)

The FDA has granted fast track designation to the combination of **paxalisib (GDC-0084)** and radiation for the treatment of patients with brain metastases originating from a primary tumor. Concurrent paxalisib with whole-brain radiotherapy is being investigated in a phase 1 study (NCT04192981) of approximately 36 'patient with brain metastases from a solid tumor or those with leptomeningeal metastases harboring PI3K pathway mutations. Data from 12 patients in the study have been reported.

Zenocutuzumab (MCLA-128)

The FDA has granted breakthrough therapy designation to **zenocutuzumab (MCLA-128)** for the treatment of patients with advanced unresectable or metastatic NRG1 fusion–positive pancreatic cancer following disease progression on previous systemic therapy or for whom there are no satisfactory alternatives. Findings from an early access program assessing the safety and antitumor activity of zenocutuzumab (NCT04100694) and the phase 1/2 eNRGy trial (NCT02912949) support the designation.

Zenocutuzumab is an antibody-dependent, cell-mediated, cytotoxicity-enhanced Biclonics antibody. The agent binds to HER2 and potently blocks the interaction of HER3 with its ligand NRG1 or NRG1-fusion proteins. In July 2020, the FDA granted an orphan drug designation to zenocutuzumab for use in patients with pancreatic cancer. In January 2021, the FDA granted the agent fast track status for the treatment of patients with NRG1 fusion–positive metastatic solid tumors that have progressed on standard treatment.

Quaratusugene ozeplasmid (Reqorsa), atezolizumab (Tecentriq)

The FDA has granted fast track designation (FTD) to **quaratusugene ozeplasmid (Reqorsa)** in combination with **atezolizumab (Tecentriq)** for the treatment of patients with extensive-stage small cell lung cancer who did not develop tumor progression after receiving atezolizumab and chemotherapy as initial standard treatment, according to Genprex, Inc. Quaratusugene ozeplasmid targets the TUSC2 gene and is designed to be injected intravenously into tumor cells to interrupt cell signaling pathways and recreate pathways for apoptosis in cancer cells. Quaratusugene ozeplasmid also modulates the immune response against cancer cells and blocks the development of drug resistance. Previously, based on the Acclaim-3 trial (NCT05703971), the FDA has granted 2 FTDs for quaratusugene ozeplasmid, including quaratusugene ozeplasmid in combination with osimertinib (Tagrisso) in patients with late-stage non–small cell lung cancer (NSCLC) whose disease progressed after treatment with osimertinib, and for the combination of quaratusugene ozeplasmid and pembrolizumab (Keytruda) in patients with late-stage NSCLC whose disease progressed after treatment with pembrolizumab.

NEW DRUG APPLICATION

Imetelstat

The FDA has received the submission of a new drug application for **imetelstat**, a novel, first-in-class telomerase inhibitor, for the treatment of transfusion-dependent anemia in adult patients with non-del(5q) lower-risk myelodysplastic syndrome (MDS) that is relapsed or refractory to erythropoiesis-stimulating

agents, according to Geron Corporation. Across key MDS subgroups, including ring sideroblast status, baseline transfusion burden, and International Prognostic Scoring System risk category, statistically significant and clinically meaningful efficacy results were achieved. Moreover, safety data were consistent with what has previously been reported with imetelstat.

ORPHAN DRUG DESIGNATION

VCN-01

The FDA has granted an orphan drug designation to VCN-01 in combination with the standard chemotherapy doublet of gemcitabine and nab-paclitaxel for the frontline treatment of patients with pancreatic ductal adenocarcinoma (PDAC). VCN-01 is a genetically modified adenovirus being developed for the treatment of pancreatic cancer. In preclinical PDAC models, treatment with the oncolytic adenovirus demonstrated direct antitumor efficacy and degraded the tumor stroma, which serves as a barrier to cancer treatment. The agent is under investigation in the phase 2b VIRAGE study (NCT05673811).

KT-253

The FDA has granted an orphan drug designation to KT-253, a novel, highly potent, selective MDM2 degrader, for the treatment of acute myeloid leukemia, according to Kymera Therapeutics. KT-253 targets MDM2, which is a critical regulator of p53. In patients with p53 wild-type disease, the tumor suppressor can modulate cancer cell growth. Small molecule inhibitors aimed at stabilizing and upregulating p53 expression have evolved; however, studies show their potential to cause a feedback loop resulting in elevated MDM2 protein levels, which leads to the repression of p53 and limits their effect.

PROTOCOL AMENDMENT

Uproleselan (GMI-1271)

The FDA has cleared the addition of a protocol amendment for a phase 3 study (NCT03616470) of **uproleselan (GMI-1271)** for relapsed/refractory acute myeloid leukemia. The amendment enables a time-based evaluation of the trial's primary end point and overall survival (OS). The final analysis will occur only if the anticipated 295 survival events required for an event-driven analysis have not been observed.

As part of the protocol amendment, the FDA also cleared the addition of landmark event-free survival and OS analyses as secondary end points. Topline results are expected by the end of the second quarter of 2024.

CHANGES IN LABELED INDICATIONS

Pralsetinib (Gavreto)

Additional update from last month. With the use of Pralsetinib (Gavreto), it has been shown that patients developed a series of adverse events: pneumonitis (12%) including 3.3% with grade 3 or 4, hypertension (35%), serious hepatoxicity (1.5%) including increased aspartate aminotransferase (AST) (49%) with grade 3 or 4 in 7% and increased alanine transaminase (ALT) (37%) with grade 3 or 4 in 4.8%. The median time upon first signs of increased AST ranged from 5 days to 2.5 years and for ALT, 7 days to 3.7 years. Reports of hemorrhagic events also occurred in 4.1% of patients taking pralsetinib.

Patients in the ARROW study (NCT03037385) receiving pralsetinib were 65 years and older, with 7% who were 75 years and older. For patients 65 years and older there is no difference shown in safety, effectiveness, or pharmacokinetics when using pralsetinib. As of now it is not known, if pralsetinib is safe or effective for treating cancers caused by abnormal RET genes or for children with non–small clear cell cancer.

Swelling of the feet, hands, legs, arms and face, cough, and fever are the most common adverse effects, when taking pralsetinib, as well as increased blood levels of alkaline phosphate and potassium. (It is noted to test for bone or liver issues.)

Trifluridine and tipiracil (Lonsurf)

Out of the total of 1114 patients who have taken trifluridine and tipiracil (Lonsurf) as the only agent (NCT04737187), 17% developed anemia, 3 patients (0.3%) developed neutropenic infection (sepsis) and died, and 4% experienced thrombocytopenia. An update of 14% of patients were given granulocyte-colony stimulating factors.

For the elderly patients in this sample size with metastatic colorectal cancer or gastric cancer, 11% were 75 years and older and experienced grade 3 or 4 anemia (20% vs 14%), and grade 3 or 4 thrombocytopenia (6% vs 3%).

When used in combination with bevacizumab (NCT04737187), patients developed a series of adverse events: Grade 3 to 4 of severe or life-threatening myelosuppression with neutropenia (52%), anemia (5%), febrile neutropenia (0.4%), and thrombocytopenia (4%). Two patients (0.8%) died from septic shock and one (0.4%) from abdominal sepsis. Out of the 246 patients, 29% received granulocyte-colony stimulating factors.

For the elderly patients in this sample size, the patients 65 years of age or older had a higher incidence of hematologic laboratory abnormalities: Grade 3 or 4 thrombocytopenia (5% vs 4%) and grade 3 or 4 neutropenia (60% vs 46%).

Patients should not retake a dose if missed or vomited but should continue with their next scheduled dose.

Trifluridine and tipiracil can be taken alone or with bevacizumab to treat colorectal cancer that has spread or after having used certain chemotherapy medicines or at least 2 other types of treatment.

Common adverse events associated with taking trifluridine and tipiracil are as follows: decreased sodium in blood, low blood count, abnormal liver function blood results, diarrhea, fatigue and weakness, nausea, stomach pain, and decreased appetite.

Teclistamab-cqyv (Tecvayli)

The warnings and precautions associated with the use of teclistamab-cqyv (Tecvayli) now also include talquetamab (Talvey) Risk Evaluation and Mitigation Strategy, which has recently been granted approval by the FDA.

REFERENCES

1. FDA grants full approval for Blincyto (Blinatumomab) to treat minimal residual disease-positive b-cell precursor acute lymphoblastic leukemia. News release. June 21, 2023. Accessed June 21, 2023. https://tinyurl.com/2bamekp2
2. Gokbiget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood. 2018;131(14):1522-1531. doi:10.1182/blood-2017-08-798322.
3. Pfizer's TALZENNA in combination with XTANDI receives U.S. FDA approval. News release. Pfizer. June 20, 2023. Accessed June 20, 2023. https://tinyurl.com/y9vahdu3
4. Fizazi K, Azad A, Matsubara N, et al. TALAPRO-2: Phase 3 study of talazoparib (TALA) + enzalutamide (ENZA) versus placebo (PBO) + ENZA as first-line (1L) treatment for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) harboring homologous recombination repair (HRR) gene alterations. J Clin Oncol. 2023;5004(suppl 16). doi:10.1200/JCO.2023.41.16_suppl.5004
5. Astellas announces U.S. FDA grants priority review for zolbetuximab biologics license application. News release. Astellas. July 6, 2023. Accessed July 6, 2023. https://tinyurl.com/yd7d3p5s
6. Shitara K, Lordick F, Bang Y-J, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. Lancet. 2023;401(10389):1655-1668. doi:10.1016/S0140-6736(23)00620-7

7. Xu RH, Shitara K, Ajani JA, et al. Zolbetuximab + CAPOX in 1L claudin-18.2+ (CLDN18.2+)/HER2− locally advanced (LA) or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma: primary phase 3 results from GLOW. Presented at: 2023 March ASCO Plenary Series. Abstract 405736.

8. Astellas announces positive findings from phase 3 glow trial of zolbetuximab during March ASCO Plenary Series. News release. Astellas Pharma Inc. March 21, 2023. Accessed July 6, 2023. https://www.astellas.com/en/news/27481

9. Kazia's paxalisib receives fast track designation from FDA for treatment of solid tumor brain metastases harboring PI3k pathway mutations in combination with radiation therapy. News release. Kazia Therapeutics. July 7, 2023. Accessed July 7, 2023. https://tinyurl.com/4vry53zd

10. GDC-0084 with radiation therapy for people with PIK3CA-mutated solid tumor brain metastases or leptomeningeal metastases. ClinicalTrials.gov. Updated July 3, 2023. Accessed July 7, 2023. https:// clinicaltrials.gov/ct2/show/NCT04192981

11. Yang J, Mann J, Pike L, et al. MMAP-05 phase I study of concurrent paxalisib and radiation therapy in patients with solid tumor brain metastases or leptomeningeal metastases harboring pi3k pathway mutations: results from the dose-escalation cohort. Neurooncol Adv. 2022;4(suppl 1):i15-i16. doi:10.1093/noajnl/vdac078.061

12. Zenocutuzumab (Zeno) granted breakthrough therapy designation by the US Food & Drug Administration for the treatment of NRG1+ pancreatic cancer. News release. Merus NV. June 29, 2023. Accessed July 5, 2023. https://tinyurl.com/2uxeftap

13. Schram AM, Goto K, Kim DW, et al. Efficacy and safety of zenocutuzumab, a HER2 x HER3 bispecific antibody, across advanced NRG1 fusion (NRG1+) cancers. J Clin Oncol. 2022;40(suppl 16):105. doi:10.1200/JCO.2022.40.16_suppl.105

14. Genprex receives U.S. FDA fast track designation for REQORSA immunogene therapy in combination with Tecentriq for the treatment of small cell lung cancer. News release. Genprex Inc. June 28, 2023. Accessed June 29, 2023. https://tinyurl.com/ys5esepp

15. Genprex announces first patient dosed in phase 1/2 Acclaim-1 clinical trial of Reqorsa immunogene therapy in combination with Tagrisso to treat non-small cell lung cancer. News release. Genprex Inc. March 2, 2022. Accessed June 29, 2023. https://bit.ly/35MdYkD

16. Quaratusugene ozeplasmid (Reqorsa) and atezolizumab maintenance therapy in ES-SCLC patients (Acclaim-3). ClinicalTrials.gov. Updated March 24, 2023. Accessed June 29, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT05703971

17. Geron announces submission of new drug application to FDA for first-in-class telomerase inhibitor imetelstat. News release. Geron Corporation. June 20, 2023. Accessed June 21, 2023. https://tinyurl.com/bdzzxnd2

18. Zeidan AM, Platzbecker U, Santini V, et al. IMerge: Results from a phase 3, randomized, double-blind, placebo-controlled study of imetelstat in patients (pts) with heavily transfusion dependent (TD) non-del(5q) lower-risk myelodysplastic syndromes (LR-MDS) relapsed/refractory (R/R) to erythropoiesis stimulating agents (ESA). J Clin Oncol. 2023;41(suppl 16):7004. doi:10.1200/JCO.2023.41.16_suppl.7004

19. Theriva Biologics announces orphan drug designation granted by the U.S. FDA for VCN-01 for the treatment of pancreatic cancer. News release. Theriva Biologics. June 27, 2023. Accessed June 28, 2023. https://tinyurl.com/3vrbx8ak

20. Bazan-Peregrino M, Garcia-Carbonero R, Laquente B, et al. VCN-01 disrupts pancreatic cancer stroma and exerts antitumor effects. J Immunother Cancer. 2021;9(11): e003254. doi:10.1136/jitc-2021-00325

21. Study of nab-paclitaxel and gemcitabine and plus/minus vcn-01 in patients with metastatic pancreatic cancer (VIRAGE). ClincalTrials.gov. Updated June 27, 2023. Accessed June 28, 2023. https://tinyurl.com/mrxmnp7c

22. Kymera Therapeutics receives FDA orphan drug designation for KT-253, a novel, highly potent and selective MDM2 degrader for the treatment of acute myeloid leukemia. News release. Kymera Therapeutics Inc. June 22, 2023. Accessed June 28, 2023. https://tinyurl.com/28tfsk49

23. Safety and clinical activity of KT-253 in adult patients with high grade myeloid malignancies, acute lymphocytic leukemia, lymphoma, solid tumors. ClinicalTrials.gov. Updated June 7, 2023. Accessed June 28, 2023. https://clinicaltrials.gov/study/NCT05775406

24. GlycoMimetics announces U.S. Food and Drug Administration clears addition of time-based final analysis to pivotal phase 3 study of uproleselan in relapsed/refractory acute myeloid leukemia. News release. GlycoMimetics Inc. June 15, 2023. Accessed June 19, 2023. https://tinyurl.com/398e27y5

25. Study to determine the efficacy of uproleselan (GMI-1271) in combination with chemotherapy to treat relapsed/refractory acute myeloid leukemia. ClinicalTrials.gov. Updated April 6, 2023. Accessed June 19, 2023. https://clinicaltrials.gov/ct2/show/NCT03616470 26.