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SCOS ONCOLOGY DRUG NEWSLETTER

FDA APPROVALS

Pirtobrutinib (Jaypirca)

The FDA has approved **pirtobrutinib (Jaypirca)** in relapsed or refractory chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) based on findings from the phase 1/2 BRUIN trial (NCT03740529).[1,2]

The overall response rate (ORR) was 72% (95% CI, 63%-80%), and the median duration of response (DOR) was 12.2 months (95% CI, 9.3-14.7). All responses were partial responses.[1] The approved dose is 200 mg orally once daily until disease progression or unacceptable toxicity.

Further findings from the BRUIN trial presented at the International Workshop on Chronic Lymphocytic Leukemia 2023, held virtually and in Boston, Massachusetts, demonstrated an 80% ORR (95% CI, 65.7%-89.8%) in patients with CLL who had experienced disease progression on pirtobrutinib, and retreatment with pirtobrutinib showed a clearance of Bruton tyrosine kinase (BTK) C481 clones and development of non-C481 clones.[3] The open-label, international, single-arm, multicohort trial assessed pirtobrutinib in 108 patients with CLL or SLL who had previously received treatment with a BTK or B-cell lymphoma 2 inhibitor. The primary phase 2 end point was ORR. The secondary end points for phase 2 included DOR, progression-free survival, overall survival, safety, pharmacokinetics, symptomatic response, and functional response.

For safety, common adverse events (AEs; 20% or greater) included fatigue, bruising, and cough. The grade 3 or 4 AEs observed in more than 10% of

patients included decreased neutrophil counts, anemia, and decreased platelet counts. A total of 32% of patients experienced serious infections, and 10% of patients died from infection.[1]

Nirogacestat (Ogsiveo)

The FDA has granted approval to **nirogacestat (Ogsiveo)** for the treatment of adult patients with desmoid tumors.[4] Findings from the phase 3 DeFi trial (NCT03785964) support this approval. In the study findings, nirogacestat reduced the risk of disease progression or death by 71% among patients with desmoid tumors when compared with patients who were given placebo (HR, 0.29; 95% CI, 0.15-0.55; P = .001).[5]

Among those given nirogacestat (n = 70), the Kaplan-Meier–estimated median progression-free survival (PFS) was not estimable, and patients treated with placebo (n = 72) had a median PFS of 15.1 months (95% CI, 8.4-not estimable). The likelihood of being event free at 1 year was higher among patients treated with nirogacestat vs placebo at 85% (95% CI, 73%-92%) and 53% (95% CI, 40%-64%), respectively.[4]

Event-free survival rates at 2 years were 76% (95% CI, 61%-87%) with nirogacestat and 44% (95% CI, 32%-

56%) with placebo. The confirmed objective response rate was 41% with nirogacestat vs 8% with placebo (P = .001), and the complete response rates were 7% and 0%, respectively.

The median time to confirm first response was 5.6 months and 11.1 months for the investigative vs control arm, respectively, and the median best percent change in target tumor size was -27.1% (range, -100% to 37%) vs 2.3% (range, -100% to 47%). Any-grade adverse events (AEs) were observed in 100% of patients in the nirogacestat arm compared with 96% in the placebo arm, with grade 3 or greater AEs observed in 55% vs 17% of patients in the nirogacestat vs placebo arms, respectively.

POSTAPPROVAL INVESTIGATIONS

CAR T-Cell Immunotherapies

The FDA is investigating risks following reports of secondary T-cell malignant tumors arising in patients who received **B-cell maturation agent (BCMA)-** or **CD19-directed autologous chimeric antigen receptor (CAR) T-cell immunotherapies.**[6]

The risk of T-cell malignant tumors, including CAR-positive lymphoma, applies to the following currently approved BCMA- and CD19-directed CAR T-cell therapies: **idecabtagene vicleucel (Abecma), lisocabtagene maraleucel (liso-cel; Breyanzi), ciltacabtagene autoleucel (cilta-cel; Carvykti), tisagenlecleucel (tisa-cel; Kymriah), brexucabtagene autoleucel (Tecartus), and axicabtagene ciloleucel (axi-cel; Yescarta).**

A total of 12 T-cell lymphoma cases have been reported through the FDA Adverse Event Reporting System. This includes 7 patients who received tisa-cel, 3 patients who received axi-cel, 1 patient who received cilta-cel, and 1 patient who received liso-cel.[7] "Although the overall benefits of these products continue to outweigh their potential risks for their approved uses, [the] FDA is investigating the identified risk of T-cell malignancy with serious outcomes, including hospitalization and death, and is evaluating the need for regulatory action," the FDA said in its announcement.[6]

The risk of developing secondary malignant tumors is a class warning for the previously mentioned therapies, as it is for all gene therapy agents with lentiviral or retroviral vectors. The approvals of these agents were also contingent on 15-year observational safety follow-up, including assessing for the risk of secondary malignant tumors. Tisa-cel, the first CAR T-cell therapy to be approved in the United States, was only approved in 2017.[8]

The FDA has not yet issued any recalls or advisory council meetings. The FDA recommends lifelong monitoring for new malignant tumors in patients who have been treated with CAR T-cell therapy.[1]

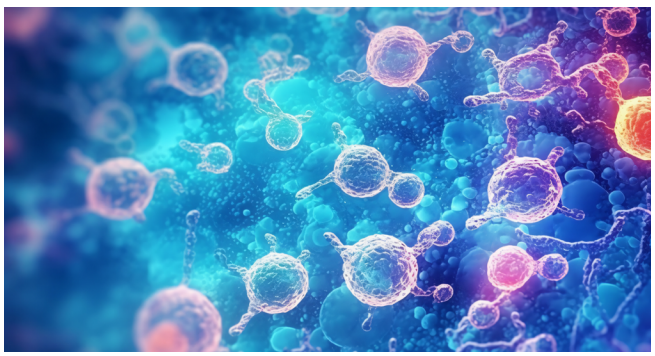
INVESTIGATIONAL NEW DRUG

KSQ-001EX

The FDA has approved an investigational new drug application for a phase 1/2 study (NCT05240898) of **KSQ-001EX**, an engineered tumor-infiltrating lymphocyte (TIL) program, according to a news release from KSQ Therapeutics.[9]

The phase 1/2 study will be initiated at the University of Texas MD Anderson Cancer Center in Houston, Texas, and is an open-label, safety lead-in study for patients with melanoma, head and neck squamous cell carcinoma, and non–small cell lung cancer. Phase 1 will evaluate KSQ-001EX's safety and tolerability. Patients in the safety lead-in portion will be initially dosed without IL-2. Phase 2 will evaluate the antitumor activity of KSQ-001EX in indication-specific cohorts.

KSQ-001EX is composed of TILs where clustered, regularly interspaced, short palindromic repeats (CRISPR)/CRISPR-associated protein 9 gene editing inhibits SOCS1. Investigators identified SOCS1 as a key gene that regulates the antitumor potency and persistence of TIL and provides KSQ-001EX with the best potential to manage solid tumors.



CT-0525

The FDA has cleared the investigational new drug application for **CT-0525**, an ex vivo gene-modified autologous chimeric antigen receptor (CAR)-monocyte cellular therapy for the management of HER2-overexpressing solid tumors.[10]

With this notification given by the FDA, a study may proceed. A phase 1 study (NCT04660929) is set to begin in the coming months, with the first patient expected to be treated in the first half of 2024. With the CAR-monocyte manufacturing platform, there is the ability to manufacture up to 10 billion cells from a single apheresis. It uses a rapid, single-day manufacturing process that can reduce the cost of goods and manufacturing turnaround time associated with this autologous cell therapy.

TCB-008 (OmnImmune)

The FDA has cleared the investigational new drug application for the phase 1b ACHIEVE study (NCT05358808) of **TCB-008 (OmnImmune)**, an allogeneic unmodified cell therapy consisting of activated and expanded γδ T cells (GDTs) in relapsed/refractory acute myeloid leukemia (AML).[11] TCB-008 is made of GDT cells from healthy donors that are expanded and activated in large numbers prior to being purified and formulated for infusion into patients. The therapeutic is a frozen and thawed product and comes from donor-derived cells.

The ACHIEVE2 trial is planned to be an open-label, multicenter, phase 1b study evaluating 9 patients with AML. The study will include a dose-escalation portion to measure safety and a dose-expansion portion to evaluate TCB-008. Persistence, expansion, and the preliminary efficacy of single and multiple doses of TCB-008 given to patients with AML or myelodysplastic syndrome/AML via intravenous infusion will be evaluated in addition to safety.[12]

BIOLOGICS LICENSE APPLICATION

Enfortumab Vedotin (Padcev)/ Pembrolizumab (Keytruda)

The FDA has accepted for priority review a supplemental biologics license application for the combination of **enfortumab vedotin (Padcev)** and **pembrolizumab (Keytruda)** for the treatment of adult patients with locally advanced or metastatic urothelial cancer (UC). Findings from the phase 3 EV-302 trial (NCT04223856) support this regulatory decision because the combination led to improved rates of overall survival and progression-free survival among patients with previously unmanaged locally advanced or metastatic UC compared with platinum-containing chemotherapy. No new safety issues were identified. A Prescription Drug User Fee Act target action date has been set for May 9, 2024, by the FDA.[13]

EV-302, an open-label, randomized, controlled, phase 3 study, included 886 patients with previously unmanaged locally advanced or metastatic UC. Patients were required to have an ECOG performance status of 2 or less and be eligible for cisplatin- or carboplatin-containing chemotherapy. Once enrolled, patients were randomly assigned to receive standard-of-care chemotherapy for a maximum of 6 cycles (n = 444) or enfortumab vedotin at a dose of 1.25 mg/kg via intravenous (IV) infusion on days 1 and 8 and 200 mg of pembrolizumab via IV infusion on day 1 of 3-week cycles (n = 442). The maximum number of pembrolizumab cycles allowed was 35, and there was no maximum number of cycles for enfortumab vedotin.

Obecabtagene Autoleucel (Obe-Cel; AUTO1)

The FDA has received a biologics license application (BLA) seeking the approval of **obecabtagene autoleucel (obe-cel; AUTO1)** as a potential therapeutic option in adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL), according to Autolus Therapeutics.[14]

Findings from the phase 2 FELIX trial (NCT04404660) were presented at the 2023 American Society of Clinical Oncology Annual

Meeting in Chicago, Illinois, and support this BLA submission. At a median follow-up of 9.5 months (range, 1.9-19.0), 94 patients with B-ALL were treated with an infusion of obe-cel; an overall response rate of 76% (95% CI, 66%-84%; P = .0001) was achieved. Among these patients, the complete response (CR) rate was 54.3% and the CR rate with incomplete count recovery rate was 21.3%.[15] Additionally, 97% of patients who responded had minimal residual disease–negative results at the 10-4 level via flow cytometry.

Obe-cel is an investigational CAR T-cell therapy that has a fast target binding off-rate. The agent works to reduce excessive activation of the programmed T cells, which leads to less toxicity and T-cell exhaustion, enhanced persistence, and high levels of durable remissions in this patient population.

FAST TRACK DESIGNATION

Zotatifin (eFT226) Combination

The FDA has granted a fast-track designation to the combination of **zotatifin (eFT226), fulvestrant (Faslodex),** and **abemaciclib (Verzenio)** as a second- or third-line treatment for adult patients with estrogen receptor–positive (ER+)/HER2-negative (HER2-) advanced or metastatic breast cancer with disease progression following treatment with endocrine therapy and a CDK4/6 inhibitor.[16]

Zotatifin, a potent and sequence-selective small-molecule inhibitor of the RNA helicase eukaryotic initiation factor-4A, is currently undergoing evaluation in an ongoing phase 1/2 dose-escalation and dose-expansion clinical trial (NCT04092673) in patients with ER+/HER2- metastatic breast cancer. The agent works by suppressing expression of a network of cancer-driving proteins, including cyclins D and E, CDK2, CDK4, CDK6, select receptor tyrosine kinases, and KRAS. This regulatory decision follows FDA review of preclinical and clinical data for zotatifin as well as recent safety and efficacy data for the triplet therapy.

In the phase 1/2 dose-escalation and dose-expansion study in ER+/HER2- breast cancer, experts are evaluating the safety, pharmacokinetics,

pharmacodynamics, and antitumor activity of the zotatifin combination. Several cohorts were included, including one that was presented at the 2023 American Society of Clinical Oncology Annual Meeting in Chicago, Illinois, that enrolled 38 patients with metastatic or locoregionally recurrent ER+ breast cancer.[17]

Olvimulogene Nanivacirepvec (Olvi-Vec)

The FDA has granted fast-track designation to **olvimulogene nanivacirepvec (olvi-vec)** in platinum-refractory/platinum-resistant ovarian cancer, according to a news release from Genelux.[18]

Olvi-vec is an oncolytic viral-based immunotherapy. The phase 2 trial (NCT02759588) met its primary end point of overall response rate. With a median follow-up of 47 months (95% CI, 35.9-not reached), the overall response rate was 54% (95% CI, 33%-74%) and the duration of response was 7.6 months (95% CI, 3.7-9.6). The disease control rate was 88%, and 86% of patients had tumor shrinkage.[19]

The median progression-free survival (PFS) by RECIST v1.1 criteria was 11 months (95% CI, 6.7-13.0). In the platinum-resistant and platinum-refractory groups, PFS was 10 months (95% CI, 6.4-not reached) and 11.4 months (95% CI, 4.3-13.2), respectively. The 6-month PFS rate was 77% overall. For overall survival (OS), the median OS was 18.5 months (95% CI, 11.3-23.8) in the platinum-resistant group and 14.7 months (95% CI, 10.8-33.6) in the platinum-refractory group. The median OS for all patients was 15.7 months (95% CI, 12.3-23.8). The phase 3 OnPrime/GOG-3076

study (NCT05281471) is evaluating olvi-vec followed by platinum-based doublet chemotherapy and bevacizumab (Avastin) compared with platinum-based doublet chemotherapy and bevacizumab alone.[20]

BREAKTHROUGH THERAPY DESIGNATION

Epcoritamab (Epkinly)

Epcoritamab (Epkinly), an investigational T-cell–engaging bispecific antibody, has received a breakthrough therapy designation (BTD) from the FDA in relapsed or refractory (R/R) follicular lymphoma. The BTD is supported by findings from the phase 1/2 EPCORE NHL-1 trial (NCT03625037).[21]

The phase 1/2 study is a global, multicenter, open-label safety and efficacy trial of epcoritamab in patients with a documented CD20-positive mature B-cell neoplasm.[22] The trial has an estimated enrollment of 786 patients with R/R disease following treatment with an anti-CD20 monoclonal antibody.

The primary end points for the dose-escalation portion are dose-limiting toxicities and incidence of adverse events. The primary end point for the dose-expansion portion is objective response rate (ORR). The primary end points for the dose-optimization portion are number of patients with cytokine release syndrome (CRS) and percentage of patients with grade 2 or higher CRS events. Secondary end points include ORR, partial response rate, complete response rate, time to response, duration of response, progression-free survival, and overall survival.

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