JULY 2024

TACOS ONCOLOGY DRUG NEWSLETTER

The Arizona Clinical Oncology Society

FDA APPROVALS

Lisocabtagene maraleucel (liso-cel; Breyanzi)

The FDA has approved the chimeric antigen receptor (CAR) T-cell therapy **lisocabtagene maraleucel (liso-cel; Breyanzi)** for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after treatment with 2 or more lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor.[1]

The approval is supported by findings from the MCL cohort of the phase 1 TRANSCEND-NHL-001 study (NCT02631044). Enrolled patients were adults with relapsed or refractory MCL who had previously received at least 2 or more prior lines of therapy, including a BTK inhibitor. Of the 68 patients treated with liso-cel and evaluated for efficacy, 85.3% (95% CI, 74.6%-92.7%) responded to treatment, and 67.6% (95% CI, 55.2%-78.5%) achieved a complete response (CR). Responses were rapid and durable with a median time to response of 1 month (range, 0.7-3).[1]

At a median follow-up of 22.2 months (95% CI, 16.7-22.8), the median duration of response was 13.3 months (95% CI, 6.0-23.3). A total of 51.4% of those who responded (95% CI, 37.5%-63.7%) continued to have a response at 12 months, and 38.8% (95% CI, 25%-52.4%) remained in response at 18 months.[1]

Findings from the primary analysis were published in the Journal of Clinical Oncology and showed an overall response rate (ORR) of 83.1% (95% CI, 73.3%-90.5%) and a CR rate of 72.3% (95% CI, 61.4%-81.6%) at the time of the analysis.[2] Here, the median duration of response was 15.7 months (95% CI, 6.2-24.0).

Additionally, findings from a subgroup analysis of the TRANSCEND-NHL-001 study showed a progression-free survival (PFS) of 15.3 months (95% CI, 6.6-24.9) in patients with Ki-67 of 30% or higher, 24.0 months (95% CI, 2.4-not reached [NR]) in patients with Ki-67 under 30%, 7.4 months (95% CI, 3.3-NR) in patients with a TP53 mutation, and 7.8 months (95% CI, 3.1-NR) for patients with blastoid morphology. These data were presented at the 2024 Tandem Meetings on Transplantation & Cellular Therapy in February.[3]

Safety findings were presented at the 17th International Congress on Malignant Lymphoma in June 2024.[4] The most common treatment-emergent adverse events (TEAEs) of grade 3 or higher were neutropenia (56%), anemia (37.5%), thrombocytopenia (25%), and hypophosphatemia (9%). For all-grade TEAEs, cytokine release syndrome (61%), neutropenia (59%), anemia (44%), and fatigue (35%) were the most common.

The maximum tolerated dose was not reached, and 31 dose-limiting toxicities (DLTs) were observed. Two patients experienced DLTs at dose level 2. Additionally, 4 patients experienced a grade 5 adverse event (AE), and 3 were considered related to liso-cel.[4]

TRANSCEND-NHL-001 is an open-label study determining the safety, pharmacokinetics, and antitumor activity of liso-cel in patients with various non-Hodgkin lymphomas, including MCL.[5] The primary end points are incidence of treatment-related AEs, DLTs, and ORR. Secondary end points include CR rate, duration of response, PFS, overall survival (OS), health-related quality of life, and pharmacokinetics. Patients received either 1 or 2 intravenous injections of liso-cel following lymphodepletion therapy.

Liso-cel is a CD19-directed CAR T-cell therapy for the treatment of patients with large B-cell lymphomas (LBCL).[6] Liso-cel is recommended by the National Comprehensive Cancer Network for patients with LBCL whose disease is relapsed or refractory after 12 or more months regardless of transplant eligibility and patients who are transplant ineligible regardless of time to relapse.

In March 2024, liso-cel was approved by the FDA for the treatment of patients with chronic lymphocytic leukemia and small lymphocytic lymphoma based on findings from the phase 1/2 TRANSCEND-CLL-004 study (NCT03331198). In May 2024, liso-cel was approved for the treatment of patients with follicular lymphoma.[6]

Selpercatinib (Retevmo)

Selpercatinib (Retevmo) has received accelerated approval from the FDA for the treatment of pediatric patients 2 years and older with advanced or metastatic medullary thyroid cancer with a RET mutation, advanced or metastatic thyroid cancer with a RET fusion, or locally advanced or metastatic solid tumors with a RET gene fusion.[7] This marks the first approved targeted therapy for pediatric patients with RET gene alterations.

Selpercatinib's efficacy was verified in the phase 1/2 LIBRETTO-121 study (NCT03899792). In the trial, patients received 92 mg/m^2 of oral selpercatinib twice daily until disease progression, unacceptable toxicity, or other reason for treatment discontinuation. The study enrolled patients aged 2 to 20 years with RET-activated locally advanced or metastatic solid tumors that were nonresponsive to available therapies or did not have standard systemic treatments available.[7]

The confirmed ORR was 48% (95% CI, 28%-69%) as confirmed by a blinded independent central review. The median duration of response (DOR) was not reached (95% CI, not evaluable [NE]-NE), and 92% of responders were still in response at 12 months.[7]

In patients with RET-mutant medullary thyroid cancer (n = 14), the ORR was 43% (95% CI, 18%-71%), and among those with RET fusion-positive thyroid cancer, the ORR was 60% (95% CI, 26%-88%).[7]

Regarding safety, the most common AEs (25% or greater) were musculoskeletal pain, diarrhea, headache, vomiting, COVID-19 infection, abdominal pain, fatigue, pyrexia, and hemorrhage. Grade 3 or 4 laboratory abnormalities observed in at least 5% of patients were decreased calcium, decreased hemoglobin, and decreased neutrophils.[7]

The primary end points of phase 2 of LIBRETTO-121 are ORR and ORR based on response assessment in neuro-oncology.[8] Secondary end points included pharmacokinetics, investigator-assessed ORR, DOR, PFS, OS, clinical benefit rate, and incidence of AEs.

Patients with a Karnofsky Performance Scale or Lansky Play-Performance Scale score of at least 50, adequate laboratory levels, and evidence of an activating RET alteration were eligible for enrollment in the study. Individuals with uncontrolled cardiovascular disease, uncontrolled systemic infection, uncontrolled hyperthyroidism or hypothyroidism, or active malabsorption syndrome were not eligible for participation.[8]

Afuresertib (LAE002) plus LAE001

The FDA has approved the phase 3 trial protocol of **afuresertib (LAE002)** plus the CYP17A1/CYP11B2 dual inhibitor LAE001 (LAE201) for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who have received standard-of-care treatment.[9]

The phase 2, open-label, dose-escalation, and dose-expansion trial (NCT04060394) evaluated LAE201 in the US in June 2021 and in South Korea in September 2022. Investigators sought to assess the efficacy and safety of the combination for the treatment of patients with mCRPC.[9]

As of November 21, 2023, 40 patients who had progressed on 1 to 3 lines of standard treatments, including at least 1 line of abiraterone acetate (Zytiga) or the second generation of androgen receptor antagonists, were enrolled in the group receiving the recommended phase 2 dose of LAE201. Findings showed that the median radiographic progression-free survival (rPFS) was 8.1 months, which was a significant improvement compared with the median rPFS of 2 to 4 months historically seen for patients with mCRPC under standard-of-care treatments.[9]

Of the 12 patients who had measurable lesions at baseline based on RECIST 1.1, there were 2 confirmed partial responses (PRs) and 2 unconfirmed PRs observed.[10] In terms of safety, the combination was generally well-tolerated, with manageable treatment-emergent adverse events.

Afuresertib, a potent AKT inhibitor, has shown promise compared with other AKT inhibitors. The agent, which is 1 of the 2 AKT inhibitors that are in or have completed the pivotal-stage clinical development for anticancer treatment worldwide, inhibits AKT1, AKT2, and AKT3.[9]

LAE001 is an androgen synthesis inhibitor. The agent inhibits CYP17A1 and CYP11B2, and according to the agent's manufacturer, Laekna Inc, it is the only dual CYP17A1/CYP11B2 inhibitor currently being studied in clinical trials for the treatment of prostate cancer globally.[10]

LAE102 is Laekna's first internally discovered antibody that has received an FDA investigational new drug application.[10]

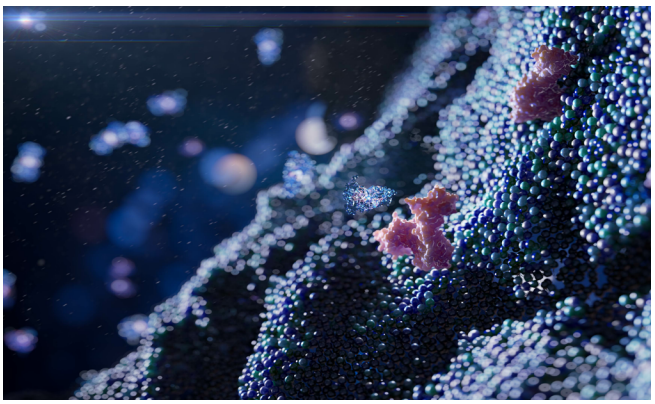
Tarlatamab-dlle (Imdeltra)

The FDA granted accelerated approval to **tarlatamab-dlle (Imdeltra)** for the treatment of patients with small cell lung cancer (SCLC) that has progressed on or after platinum-based chemotherapy, making it the first bispecific T-cell engager approved for a major solid tumor and the first therapeutic option for the third-line treatment of advanced SCLC.[11]

The approval is supported by data from the phase 2 DeLLphi-301 trial (NCT05060016) that were published in The New England Journal of Medicine and presented at the 2023 European Society of Medical Oncology (ESMO) Congress. The objective response rate for patients treated with 10 mg of tarlatamab was 40 % (97.5% CI, 29%-52%) vs 32% (97.5% CI, 21%-44%) with the 100-mg dose. At the time of data cutoff, ongoing objective responses were observed in 55% of patients in the 10-mg group and in 57% of patients in the 100-mg group.[12]

The median progression-free survival was 4.9 months (95% CI, 2.9-6.7) for the 10-mg group and 3.9 months (95% CI, 2.6-4.4) for the 100-mg group, and the median OS was 14.3 months (95% CI, 10.8-not estimable [NE]) and NE (95% CI, 12.4-NE), respectively. Although OS data were not mature, at the last follow-up, 57% of patients in the 10-mg group and 51% of those in the 100-mg group were still alive.

The most common TEAE was cytokine release syndrome (CRS), which occurred in 49% of patients



in the 10-mg group and 61% in the 100-mg group. CRS primarily occurred during the first cycle and was mostly grade 1 or 2. Grade 3 CRS was seen in 5.7% of patients treated with the 100-mg dose. TEAEs that led to either dose interruption or reduction were reported in 14% of patients treated with the 10-mg dose and 29% in those treated with the 100-mg dose.

In December 2023, the FDA granted priority review to the biologics license application of tarlatamab. In October 2023, tarlatamab was granted breakthrough therapy designation.[13]

"Tarlatamab represents a new immunotherapeutic approach for small cell lung cancer, a tumor type that is characterized by an immunosuppressive microenvironment," the researchers wrote in The New England Journal of Medicine, which was simultaneously published with the ESMO presentation.[14]

Lisocabtagene maraleucel (liso-cel; Breyanzi)

The FDA has granted accelerated approval to **lisocabtagene maraleucel (liso-cel; Breyanzi)** for relapsed/refractory (R/R) follicular lymphoma (FL) based on findings from the phase 2 TRANSCEND FL trial (NCT04245839).[15] In the study, liso-cel demonstrated high complete response rates and durable remissions among patients with high-risk R/R follicular lymphoma when given in the second line.

According to results in a poster presented at the 2023 American Society of Hematology Annual Meeting and Exposition, 89.8% of patients with follicular lymphoma who were treated with the CD19-targeted CAR T-cell therapy were likely to experience a sustained response at 12 months.[16] The PFS rate among these patients was 91.3% at 12 months. At median follow-ups of 16.8 months and 17.8 months, the median DOR and PFS were not reached.

Looking at safety, the most common grade 3 or higher TEAEs were cytopenias. Neutropenia was the most common, seen in 52% (n = 12) of patients. Twelve patients (52%) had CRS; however, none were grade 3 or higher. The median times to onset and resolution of CRS were 6 days (range, 2-9) and 3 days (range, 2-7), respectively.[16]

Seventeen percent of patients (n = 4) experienced neurological events, 1 of which was deemed grade 3. The median times to onset and resolution of neurological events were 8.5 days (range, 6-11) and 2.5 days (range, 1-4), respectively. Tocilizumab (Actemra) or steroids were given to 13% of patients for CRS or neurological events.[16]

In the TRANSCEND FL trial, patients were pretreated with intravenous (IV) fludarabine at 30 mg/m2/day and IV cyclophosphamide at 300 mg/m^2/day for 3 days. Liso-cel was then given to patients at a target dose of 100 × 10^6 CAR-positive viable T cells.[17]

Enrollment was open to patients with R/R FL who had received at least 1 prior line of anti-CD20 and alkylating agent therapy, as well as 1 previous line of systemic therapy. An ECOG performance status of 0 or 1, adequate organ function, and adequate vascular access for the leukapheresis procedure were all criteria for enrollment.

Patients with central nervous system involvement, history of another primary malignancy, history of active human immunodeficiency virus, or history of uncontrolled infection were excluded from the study.

The primary end point of TRANSCEND FL was ORR, and secondary end points included complete response rate, DOR, PFS, OS, AEs, and pharmacokinetics.

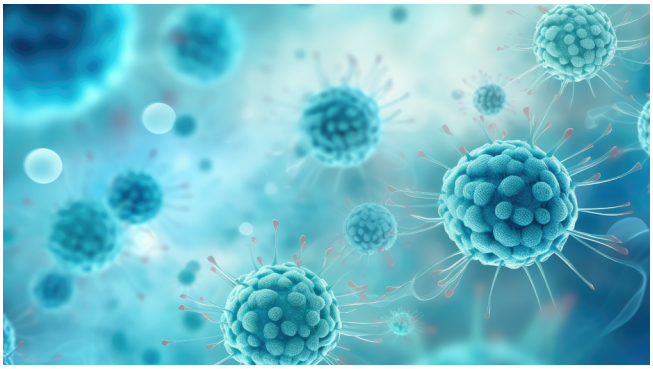
NEW DRUG APPLICATION

Avutometinib (VS-6766) with defactinib (VS-6063)

A rolling submission of a new drug application (NDA) to the FDA has been initiated, seeking accelerated approval of **avutometinib (VS-6766)**, an RAF/MEK clamp given in combination with **defactinib (VS-6063)**, a selective FAK inhibitor, for the treatment of adult patients with recurrent KRAS-mutated low-grade serous ovarian cancer (LGSOC) previously treated with at least 1 prior systemic therapy.[18] The rolling review process allows Verastem Oncology to submit completed sections of the NDA for FDA review before the entire application is finalized.

The company will submit a primary efficacy analysis from the ENGOT-ov60/GOG-3052/RAMP 201 trial (NCT04625270) with 12 months of follow-up data. In the phase 2 registration-directed RAMP 201 trial, avutometinib and defactinib are being studied in patients with recurrent LGSOC. Enrollment in RAMP 201 is complete, and 115 patients are being treated at the recommended phase 2 dose of avutometinib, which is 3.2 mg twice a week along with 200 mg of defactinib twice a day for 3 out of every 4 weeks. Follow-up continues.

As of February 2024, interim data from the study continued to demonstrate high response rates, regardless of the number of prior lines of therapy patients had received. A total of 45% (n = 13; 95% CI, 26%-46%) of patients (n = 29) had a confirmed response. Patients with KRAS mutations (n = 15) had an ORR of 60%, and patients with KRAS wild-type disease (n = 14) had an ORR of 29%.[19] Further, tumor regression was seen in 86% of patients treated with the combination. Confirmed responses were observed in 3 out of 4 patients who had previously received MEK inhibitors. Among the 13 patients with stable disease, 10 achieved tumor shrinkage, with 6 having at least a 15% reduction in tumor size. The median time from the last line of treatment was 1.84 months.



INVESTIGATIONAL NEW DRUG

ACTM-838

The FDA has approved an investigational new drug (IND) application that initiates a phase 1 trial (NCT06336148) of **ACTM-838** for the treatment of solid tumors.[20] ACTM-838 delivers immunomodulatory payloads, engineered IL-15 plex, and STING, to tumor-resident phagocytic antigen-presenting cells within the tumor microenvironment (TME).

The first-in-human trial of ACTM-838 will assess its safety, tolerability, payload delivery, and preliminary efficacy when given at escalating doses and used as a single agent. The open-label, monotherapy, dose-escalation study will enroll patients with advanced solid tumors that are resistant to standard-of-care treatments. In part 1a, investigators will examine the safety, tolerability, and activity of ACTM-838 to estimate the maximum tolerated dose and/or the optimum biological dose when given alone. This will be utilized to determine the recommended dose for part 1b, which will further evaluate the agent in patients with advanced specific tumor types.[21]

Patients are eligible for enrollment if they have an advanced solid tumor that does not respond to standard curative therapy, there is no therapy with a demonstrated survival benefit for the tumor, or they are ineligible to receive or refuse to receive such therapy. Other requirements include having at least 1 measurable lesion per RECIST v1.1 that is amenable for biopsy and radiographically apparent on CT or MRI; an ECOG performance status of 0 or 1; adequate hematologic, hepatic, and cardiac function; and CD4 count of greater than 500/mL at screening. Primary end points include incidence and severity of adverse events; dose-limiting toxicities; objective response rate; clinical benefit rate; duration of response, progression-free survival; change in tumor markers; and amount of ACTM-838 in the blood, urine, and feces, as measured by digital droplet–polymerase chain reaction.[21]

PRIORITY REVIEW

Pembrolizumab (Keytruda)

The supplemental biologics license application for **pembrolizumab (Keytruda)** given in combination with chemotherapy for the frontline treatment of patients with unresectable or metastatic malignant pleural mesothelioma

has been granted priority review by the FDA[22] with a Prescription Drug User Fee Act target action date of September 25, 2024.

In the pivotal phase 2/3 IND.227/KEYNOTE-483 trial (NCT02784171), the combination elicited a statistically significant improvement in OS vs chemotherapy alone (HR, 0.79; 95% CI, 0.64-0.98; 2-sided P = .0324), as well as PFS; HR, 0.80; 95% CI, 0.65-0.99; 2-sided P = .0372) in this patient population. Data from the final analysis of the trial demonstrated an OS of 17.3 months with the addition of pembrolizumab to chemotherapy (95% CI, 14.4-21.3) compared with 16.1 months (95% CI, 13.1-18.2) among patients treated with chemotherapy alone. At this time, the median PFS was 7.13 months (95% CI, 6.93-8.12) vs 7.16 months (95% CI, 6.83-7.69) among patients given the combination vs chemotherapy alone.[23] These data support the FDA's decision.

The trial showed that at 12 and 24 months the estimated PFS rate was 26% and 9% with the combination vs 17% and 4% with chemotherapy alone. OS rates at 24 and 36 months were 39% and 25% with the combination vs 33% and 17% with chemotherapy alone. A higher objective response rate was seen in patients treated with the addition of pembrolizumab compared with those given chemotherapy alone, at 62% vs 38%, respectively (P < .0001). A total of 32% of patients had stable disease in the experimental arm compared with 47% of patients in the control arm. Another 4% and 5% of patients, respectively, had disease progression. The median duration of response with the addition of pembrolizumab was 5.8 months (95% CI, 5.5-7.0) vs 5.5 months (95% CI, 4.2-6.0) with chemotherapy alone (P =.185).[23]

Zanidatamab (ZW25)

The FDA has granted priority review of the biologics license application for **zanidatamab (ZW25)** for the treatment of patients with previously treated, HER2-positive, unresectable, locally advanced or metastatic biliary tract cancer.[24] A Prescription Drug User Fee Act target action date of November 29, 2024, has been set.

Data from the phase 2b HERIZON-BTC-01 trial (NCT04466891) support this regulatory decision. Cohort 1 of the study, which included patients with HER2-positive BTC (n = 80), showed a confirmed objective response rate of 41.3% (95% CI, 30.4%-52.8%) by independent review committee assessment. This included a complete response rate of 1.3% and a partial response rate of 40%. Further, 27.5% of patients had stable disease, 30% achieved progressive disease, and 1.3% were not evaluable for response.[25]

Zanidatamab is an investigational HER2-targeted bispecific antibody. The agent simultaneously binds 2 nonoverlapping epitopes of the HER2 receptor, which results in multiple mechanisms of action, including dual HER2 signal blockade, removal of HER2 protein from the cell surface, and immune-mediated cytotoxicity leading to encouraging antitumor activity in patients.

Inavolisib (GDC-0077)

The new drug application of **inavolisib (GDC-0077)**, an investigational oral treatment, in combination with palbociclib and fulvestrant for the treatment of patients with hormone receptor–positive, HER2-negative breast cancer with a PIK3CA mutation has been granted priority review by the FDA. A Prescription Drug User Fee Act target action date of November 27, 2024, has been set.[26]

The priority review is supported by findings from the phase 3 INAVO120 study (NCT04191499). In the study, inavolisib plus palbociclib (Ibrance) and fulvestrant (Faslodex) reduced the risk of disease progression or death by 57% vs palbociclib and fulvestrant alone, delivering a PFS of 15.0 months vs 7.3 months, respectively (HR, 0.43; 95% CI, 0.32-0.59; P = .0001). Although OS data were not mature at the time of analysis, a positive trend was observed (stratified HR, 0.64; 95% CI, 0.43-0.97; P = .0338), and follow-up for OS will continue. The study has an anticipated completion date of September 30, 2030.[26]

The randomized, double-blind, placebo-controlled INAVO120 study enrolled 325 patients with PIK3CA-

mutant, hormone receptor–positive, HER2-negative, locally advanced or metastatic breast cancer who experienced disease progression during or within 12 months of completing adjuvant endocrine therapy.[27] The study's primary end point is PFS, and secondary end points include objective response rate, best ORR, duration of response, clinical benefit rate, time to deterioration (TTD) in pain, TTD in physical function, TTD in role function, TTD in global health status, and incidence of adverse events.

Isatuximab (Sarclisa) plus bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone (VRd)

Isatuximab (Sarclisa) plus **bortezomib (Velcade)**, **lenalidomide (Revlimid)**, and **dexamethasone (VRd)** has been granted priority review by the FDA for the treatment of patients with transplant-ineligible newly diagnosed multiple myeloma (NDMM). A Prescription Drug User Fee Act target action date of September 27, 2024, has been set. The European Union also is reviewing a regulatory submission.[28] If approved, isatuximab would be the first anti-CD38 therapy in combination with VRd for this intent-to-treat population, and it would be the third indication for isatuximab.

The supplemental biologics license application is supported by the phase 3 IMROZ trial (NCT03319667). In December 2023, it was announced that the trial met its primary end point of PFS.[29] IMROZ enrolled 475 patients with transplant-ineligible, NDMM and randomized them to receive VRd with or without isatuximab.[30] PFS was the study's primary end point, and secondary end points included CR rate, minimal residual disease (MRD) negativity rate for patients with a CR, very good partial response or better rate, OS, ORR, time to progression, duration of response, time to first response, time to best response, PFS on next line of therapy, PFS in MRD-negative patients, incidence of adverse events, and pharmacokinetics.[30]

Patients were required to have an ECOG performance status of 0 or 1, have adequate organ values, not have received prior treatments for myeloma, and not have any other ongoing health conditions incompatible with the study objectives.[30]

BIOLOGICS LICENSE APPLICATION

Zolbetuximab (Vyloy)

The FDA has acknowledged the resubmitted biologics license application for **zolbetuximab (Vyloy)** for the first-line treatment of patients with locally advanced unresectable

or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors are claudin (CLDN)18.2 positive.[31]

The submission is supported by data from the phase 3 SPOTLIGHT (NCT03504397) and GLOW (NCT03653507) studies. A new target action date of November 9, 2024, has been set. Adding zolbetuximab to a chemotherapy regimen significantly improved OS and PFS in patients with advanced, HER2-negative, CLDN18.2-positive gastric/GEJ cancer in these 2 studies.[32,33]

In the SPOTLIGHT study, zolbetuximab plus oxaliplatin, leucovorin, and fluorouracil (mFOLFOX6) was compared with placebo plus mFOLFOX6. The SPOTLIGHT study enrolled 565 patients with advanced, HER2-negative, CLDN18.2-positive gastric/GEJ cancers who were given either zolbetuximab with mFOLFOX6 or placebo with mFOLFOX6.[33] In the experimental vs active comparator arms, the median PFS was 10.61 (95% CI, 8.90-12.48) vs 8.67 months (95% CI, 8.21-10.28). At 12 and 24 months, PFS rates were 49% and 24% in the zolbetuximab arm and 35% and 15% in the placebo arm, respectively.

In the GLOW study, investigators evaluated zolbetuximab plus capecitabine and oxaliplatin (CAPOX) vs placebo plus CAPOX. A total of 507 patients were enrolled in the GLOW trial and treated with zolbetuximab plus mFOLFOX6 (n = 254) or placebo plus mFOLFOX6 (n = 253). At a median follow-up of 12.62 months in the experimental arm and 12.09 months in the comparator arm, the median PFS rates were 8.21 months (95% CI, 7.46-8.84 months) vs 6.80 months (95% CI, 6.14-8.08 months), respectively (HR, 0.687; 95% CI, 0.544-0.866; P = .0007). At 12 months, the PFS rates were 35% in

the experimental arm vs 19% with placebo/CAPOX, and at 24 months, these rates were 14% vs 7%, respectively.[32]

FAST TRACK DESIGNATION

AGuIX

The FDA has granted a fast track designation to **AGuIX** for treating patients with malignant gliomas and glioblastoma.[34] AGuIX is a nanodrug composed mostly of gadolinium. It offers strong contrast imaging capabilities, which allows for precise tumor delineation using MRI. It also has the potential to indirectly improve the efficacy of radiotherapy.

AGuIX has demonstrated a manageable safety profile, as seen in data from the first-in-human, phase 1b trial NANO-RAD trial (NCT02820454). AGuIX is currently undergoing evaluation in 4 clinical trials. Three of these studies, NANORAD2 (phase 2; NCT03818386), NANO-GBM (phase 1/2; NCT04881032), and NANOBRAINMETS (phase 2; NCT04899908), are expected to provide data updates by the end of 2024.

NANORAD2 is evaluating AGuIX in combination with whole-brain radiotherapy for the treatment of 100 patients with brain metastases. The study has finished recruitment; investigators expect interim efficacy results by the second half of 2024. NANOBRAINMETS is assessing AGuIX when given with stereotactic radiotherapy. Approximately 134 patients with brain metastases are being evaluated, and findings from the interim efficacy analysis are anticipated in November 2024. NANO-GBM is assessing treatment with AGuIX in approximately 62 patients with glioblastoma. An interim efficacy analysis is expected by the end of 2024.

CHANGES IN LABELED INDICATIONS

Blinatumomab (Blincyto)

Patients who have down syndrome and are 10 years and older may have greater risk of seizures with the use of **blinatumomab (Blincyto)**.[35]

For patients who are 1 month or less the safety and efficacy of blinatumomab has not been established for any indication. However, for pediatric patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia, safety and efficacy has been established through the E1910 study (NCT02003222).

(Extensive changes; please refer to the drug label for further information.)

Zanubrutinib (Brukinsa)

Patients treated with BTKs including **zanubrutinib (Brukinsa)**, in some cases have experienced hepatotoxicity. This includes severe life-threatening and potentially fatal cases of drug-induced liver injury (DILI). Patients prescribed this treatment should be informed of this information. Healthcare providers are directed to monitor liver function through blood tests before and during treatment with zanubrutinib. Patients should inform their clinician if they experience any liver issues such as discomfort or pain in the stomach, yellow skin and eyes, or dark-colored urine.[36]

Acalabrutinib maleate (Calquence)

Patients receiving **acalabrutinib maleate (Calquence)** have reported experiencing serious cardiac arrhythmias, and there were 0.9% of patients who experienced grade 3 or higher ventricular arrhythmia. The following AEs have been added including cardiac arrhythmias and hepatotoxicity (including DILI).[37]

Patients must be informed of the possible AEs associated with the use of this agent prior to starting treatment. Patients should inform their clinician if they experience abdominal discomfort, dark urine, or jaundice if liver related and palpitations, dizziness, fainting, chest discomfort, and shortness of breath if cardiac related. Liver or cardiac problems associated with the use of acalabrutinib maleate can be severe or life-threatening. Liver function should be monitored throughout treatment.

Gemcitabine hydrochloride (Gemzar)

A newly added subsection highlights severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis, which can be life-threatening or fatal, have been reported with **gemcitabine hydrochloride (Gemzar)**.[38]

It is crucial to monitor patients for signs of SCARs and to permanently discontinue gemcitabine if these reactions develop. Inform patients about the risks of these AEs, and that they should contact their healthcare provider immediately if they experience any signs of severe skin rash, skin peeling, blistering, or mouth sores.

For the most recent prescribing information, visit www.pfizer.com.

Dexamethasone (Hemady)

Kaposi's sarcoma has been reported in patients undergoing corticosteroid therapy, typically for chronic conditions associated with **dexamethasone (Hemady)** treatment. The condition may improve upon discontinuation of the steroids. Infections associated with corticosteroid use can range from mild to severe and potentially fatal, with higher doses of corticosteroids increasing the risk of infectious complications.[39]

(Extensive changes; please refer to the drug label for further information.)

Durvalumab (Imfinzi)

In 14% (34/235) of patients receiving **durvalumab (Imfinzi)** with carboplatin and paclitaxel, immune-mediated hypothyroidism occurred, requiring endocrine therapy in all cases, though it resolved in 8 patients. Durvalumab is prescribed for adults with endometrial cancer that is advanced or recurrent and mismatch repair deficient, used with chemotherapy (carboplatin and paclitaxel) followed by durvalumab alone.[40]

Common AEs in patients with endometrial cancer include nerve inflammation (causing numbness, weakness, tingling, or burning pain), muscle or bone pain, nausea, hair loss, fatigue, abdominal pain, constipation, rash, low magnesium levels, increased liver function tests, diarrhea, vomiting, cough, low potassium levels, shortness of breath, headache, high alkaline phosphatase levels, and decreased appetite.

(Extensive changes; please refer to the drug label for further information.)

Pirtobrutinib (Jaypirca)

A newly added subsection highlights that hepatotoxicity, including severe, life-threatening, and potentially fatal cases of DILI, has occurred in patients treated with BTK inhibitors like **pirtobrutinib (Jaypirca)**.[41]

The label recommends evaluating bilirubin and transaminases at baseline and during treatment. If abnormal liver tests develop, more frequent monitoring is advised, and pirtobrutinib should be withheld if DILI is suspected and discontinued if confirmed. Patients should be informed about the risk of severe liver issues and advised to contact their healthcare provider immediately if they experience abdominal discomfort, dark urine, or jaundice.

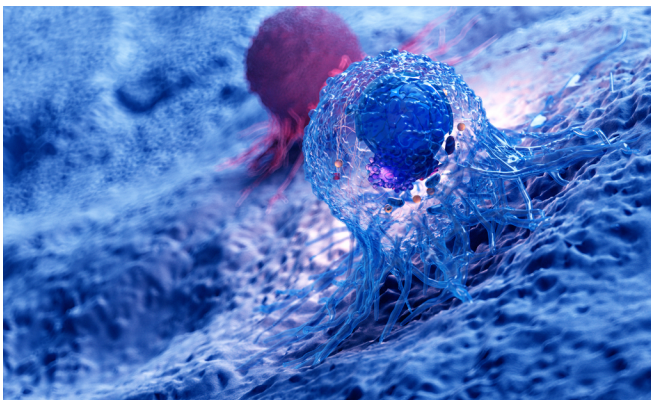
Selpercatinib (Retevmo)

Clinically relevant AEs occurred in less than 15% of patients treated with **selpercatinib (Retevmo)** and include hypothyroidism (13%), pneumonia (11%), and hypersensitivity (6%). Interstitial lung disease/pneumonitis, chylothorax, chylous ascites, and tumor lysis syndrome also occurred in less than 2% of patients each.[42]

(Extensive changes; please refer to the drug label for further information.)

Teclistamab-cqyv (Tecvayli)

Clinically relevant AEs occurred in fewer than 10% of patients treated with **teclistamab-cqyv (Tecvayli)**. AEs reported include febrile neutropenia, sepsis, ICANS,



seizures, Guillain-Barré syndrome, hepatic failure, and new or reactivated viral infections such as adenovirus, hepatitis B, cytomegalovirus, varicella zoster, herpes simplex, and progressive multifocal leukoencephalopathy.[43]

REFERENCES

1. U.S. Food and Drug Administration approves Bristol Myers Squibb's Breyanzi as a new CAR T cell therapy for relapsed or refractory mantle cell lymphoma. News release. FDA. May 30, 2024. Accessed May 30, 2024. https://news.bms.com/news/corporate-financial/2024/U.S.-Food-and-Drug-Administration-Approves-Bristol-Myers-Squibbs-Breyanzi-as-a-New-CAR-T-Cell-Therapy-for-Relapsed-or-Refractory-Mantle-Cell-Lymphoma/default.aspx

2. Wang M, Siddiqi T, Gordon LI, et al. Lisocabtagene maraleucel in relapsed/refractory mantle cell lymphoma: primary analysis of the mantle cell lymphoma cohort from TRANSCEND NHL 001, a phase I multicenter seamless design study. J Clin Oncol. 2024;42(10):1146-1157. doi:10.1200/JCO.23.02214

3. Palomba ML, Siddiqi T, Gordon LI, et al. Lisocabtagene maraleucel (liso-cel) in patients (Pt) with R/R MCL: subgroup analyses in pts with high-risk disease features from the MCL cohort of the TRANSCEND NHL 001. Presented at: 2024 Transplantation and Cellular Therapies Meeting; February 21-24, 2024; San Antonio, TX. Abstract 17 .

4. Wang M, Siddiqi T, Gordon LI, et al. Lisocabtagene maraleucel in relapsed/refractory mantle cell lymphoma (MCL): primary analysis of the MCL cohort from TRANSCEND NHL 001, a phase I multicenter seamless design study. J Clin Oncol. December 10, 2023. doi: 10.1200/jco.23.02214

5. Study evaluating the safety and pharmacokinetics of JCAR017 in B-cell non-Hodgkin lymphoma (TRANSCEND-NHL-001). ClinicalTrials.gov. Updated March 3, 2023. Accessed March 13, 2024. https://tinyurl.com/2r43ykrj

6. Breyanzi. Prescribing information. Bristol Myers Squibb; 2024. Accessed March 13, 2024. https://tinyurl.com/bdfkb7tn

7. FDA grants accelerated approval to selpercatinib for pediatric patients two years and older with RET-altered metastatic thyroid cancer or solid tumors. News release. FDA. May 29, 2024. Accessed May 29, 2024. https://tinyurl.com/3ykektts

8. A study of oral LOXO-292 (selpercatinib) in pediatric participants with advanced solid or primary central nervous system (CNS) tumors (LIBRETTO-121). ClinicalTrials.gov. Updated March 7, 2024. Accessed May 29, 2024. https://clinicaltrials.gov/study/NCT03899792

9. Laekna announces FDA approval for the phase III clinical trial protocol of LAE002 (Afuresertib) plus LAE001 for the treatment of prostate cancer. News release. Laekna Inc. May 23, 2024. Accessed May 23, 2024. https://tinyurl.com/3bhwtbum

10. 2023 ESMO Laekna (2105.HK) announces phase I/II data of LAE001 plus afuresertib in mCRPC. News release. Laekna Inc. October 24, 2023. Accessed May 23, 2024. https://tinyurl.com/y35kwrdf

11. FDA grants accelerated approval to tarlatamab-dlle for extensive stage small cell lung cancer. News release. FDA. May 16, 2024. Accessed May 16, 2024. https://tinyurl.com/bddwjpk2

12. Paz-Ares L, Ahn M, Felip E, et al. Tarlatamab for patients (pts) with previously treated small cell lung cancer (SCLC): primary analysis of the phase II DeLLphi-301 study. Presented at: European Society for Medical Oncology Congress 2023; October 20-24, 2023; Madrid, Spain. Abstract LBA92.

13. FDA grants priority review to Amgen's tarlatamab application for advanced small cell lung cancer. News release. Amgen. December 13, 2023. Accessed April 19, 2024. https://tinyurl.com/4zrvyfrk

14. Ahn MJ, Cho BC, Felip E, et al; DeLLphi-301 Investigators. Tarlatamab for patients with previously treated small-cell lung cancer. N Engl J Med. 2023;389(22):2063-2075. doi:10.1056/NEJMoa2307980

15. FDA grants accelerated approval to lisocabtagene maraleucel for follicular lymphoma. FDA. May 15, 2024. Accessed May 15, 2024. https://tinyurl.com/mvp4mrt3

16. Morschhauser F, Dahiya S, Palomba ML, et al. TRANSCEND FL: phase 2 study primary analysis of lisocabtagene maraleucel as second-line therapy in patients with high-risk relapsed or refractory follicular lymphoma. Presented at: 2023 American

Society of Hematology Annual Meeting and Exposition, December 9-12, 2023; San Diego, CA. Abstract 602.

17. A study to evaluate the efficacy and safety of JCAR017 in adult subjects with relapsed or refractory indolent B-cell non-Hodgkin lymphoma (NHL) (TRANSCEND FL). ClinicalTrials.gov. Updated November 30, 2023. Accessed March 29, 2024. https://clinicaltrials.gov/study/NCT04245839

18. Verastem Oncology announces the initiation of a rolling submission of NDA to FDA seeking accelerated approval of avutometinib and defactinib combination for the treatment of adult patients with recurrent KRAS mutant low-grade serous ovarian cancer. News release. Verastem Oncology. May 24, 2024. Accessed May 29, 2024. https://tinyurl.com/2fufcdj2

19. Banerjee SN, Van Nieuwenhuysen E, Santin AD, et al. Avutometinib + defactinib in recurrent low-grade serous ovarian cancer (LGSOC): a subgroup analysis of ENGOT-ov60/GOG-3052/RAMP 201 part A. Presented at: 2024 Society of Gynecologic Oncology Annual Meeting on Women's Cancer; March 16-18, 2024; San Diego, CA.

20. Actym Therapeutics announces IND clearance for phase 1 clinical trial investigating lead program ACTM-838 in patients with solid tumors. News release. PR Newswire. May 30, 2024. Accessed May 30, 2024. https://tinyurl.com/nhkke53u

21. A phase 1a/1b study of ACTM-838 in patients with advanced solid tumors. ClinicalTrials.gov. Updated March 28, 2024. Accessed May 30, 2024. https://clinicaltrials.gov/study/NCT06336148

22. FDA grants priority review to Merck's application for KEYTRUDA (pembrolizumab) plus chemotherapy as first-line treatment of patients with unresectable advanced or metastatic malignant pleural mesothelioma. News release. Merck. May 29, 2024. Accessed May 29, 2024. https://tinyurl.com/wsh3hnkr

23. Chu QS, Piccirillo MC, Greillier L, et al. IND227 phase III (P3) study of cisplatin/pemetrexed (CP) with or without pembrolizumab (pembro) in patients (pts) with malignant pleural mesothelioma (PM): a CCTG, NCIN, and IFCT trial. J Clin Oncol. 2023;41(suppl 17):LBA8505. doi:10.1200/JCO.2023.41.17_suppl.LBA8505

24. Zanidatamab granted priority review for HER2-positive metastatic biliary tract cancer. News release. Jazz Pharmaceuticals plc. May 29, 2024. Accessed May 29, 2024. https://tinyurl.com/mr4c2d6n

25. Harding JJ, Fan J, Oh DY, et al; HERIZON-BTC-01 Study Group. Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study. Lancet Oncol. 2023;24(7):772-782. doi:10.1016/S1470-2045(23)00242-5

26. FDA grants priority review to Roche's inavolisib for advanced hormone receptor-positive, HER2-negative breast cancer with a PIK3CA mutation. News release. Roche. May 29, 2024. Accessed May 29, 2024. https://tinyurl.com/yhrfrccw

27. A study evaluating the efficacy and safety of inavolisib + palbociclib + fulvestrant vs placebo + palbociclib + fulvestrant in patients with PIK3CA-mutant, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (INAVO120). ClinicalTrials.gov. Updated May 23, 2024. Accessed May 29, 2024. https://clinicaltrials.gov/study/NCT04191499

28. Sarclisa accepted for FDA priority review for the treatment of transplant-ineligible newly diagnosed multiple myeloma. News release. Sanofi. May 27, 2024. Accessed May 28, 2024. https://tinyurl.com/53hhdwwj

29. Sarclisa (isatuximab) phase 3 trial met primary endpoint of progression free survival in patients with newly diagnosed multiple myeloma not eligible for transplant. News release. Sanofi. December 7, 2023. Accessed May 28, 2024. https://tinyurl.com/4dx545d4

30. Clinical benefit of SAR650984, bortezomib, lenalidomide, and dexamethasone combination in NDMM patients not eligible for transplant. ClinicalTrials.gov. Updated April 8, 2024. Accessed May 28, 2024. https://clinicaltrials.gov/study/NCT03319667

31. U.S. FDA acknowledges Astellas' resubmission of biologics license application for zolbetuximab and sets new action date. News release. Astellas Pharma Inc. May 30, 2024. Accessed May 31, 2024. https://www.astellas.com/en/news/29186

32. Shah MA, Shitara K, Ajani JA, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. Nat Med. 2023;29(8):2133-2141. doi:10.1038/s41591-023-02465-7

33. Shitara K, Lordick F, Bang YJ, 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. Published April 12, 2023. doi:10.1016/S0140-6736(23)00620-7

34. NH TherAguix receives FDA fast track designation. News release. NH TherAguix. May 30, 2024. Accessed May 30, 2024. https://www.globenewswire.com/news-release/2024/05/30/2890749/0/en/NH-TherAguix-receives-FDA-Fast-Track-designation.htm

35. Blinatumomab. Prescribing information. Amgen Inc; 2024. Accessed June 17, 2024.https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=383

36. Zanubrutinib. Prescribing information. BeiGene, Ltd; 2024. Accessed June 17, 2024. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=2529

37. Acalabrutinib maleate. Prescribing information. AstraZeneca; 2024. Accessed June 17,2024.https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=2122

38. Gemcitabine hydrochloride. Prescribing information. Eli Lilly and Company; 2024. Accessed June 17, 2024. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=2122

39. Dexamethasone. Prescribing information. Edenbridge Pharmaceuticals LLC; 2024. Accessed June 19, 2024. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=2967

40. Durvalumab. Prescribing information. AstraZeneca Pharmaceuticals LP; 2024. Accessed June 19, 2024. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=1457

41. Pirtobrutinib. Prescribing information. Eli Lilly and Company; 2024. Accessed June 19, 2024. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=2970

42. Selpercatinib. Prescribing information. Eli Lilly and Company; 2024. Accessed June 19, 2024.https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=2398

43. Teclistamab-cqyv. Prescribing information. Janssen Biotech, Inc; 2024. Accessed June 19, 2024. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=2827