2022–2023 Drug Updates: Investigational Therapeutics in the Pipeline

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Presenter's disclosures of conflicts of interest are found at the end of this article.

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Abstract

During JADPRO Live 2023, Sandra Cuellar, PharmD, BCOP, FHOPA, FASHP, discussed investigational therapeutic agents in the drug development pipeline. Dr. Cuellar highlighted new drug classes, novel mechanisms of action, and safety profiles that advanced practitioners should be aware of.

In the past 10 years, the FDA has approved over 330 drugs in the oncology space. The majority of approvals (around 60%) have been label expansions, followed by next-in-class therapies (25%), and new mechanisms of action (16%).

At JADPRO Live 2023, Sandra Cuellar, PharmD, BCOP, FHOPA, FASHP, a clinical associate professor in the Department of Pharmacy Practice at the University of Illinois at Chicago College of Pharmacy, and a clinical oncology pharmacist at UI Health, identified new investigational therapeutics and described the pharmacology of agents currently being evaluated in the hematology/oncology pipeline. Dr. Cuellar also discussed literature supporting the ongoing evaluation of emerging therapeutic agents.

"The alphabet soup of oncology in precision medicine continues to grow, with new targets being identified and novel therapies being developed," said Dr. Cuellar.

CAPIVASERTIB FOR BREAST CANCER

Capivasertib has been studied in hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer. As of November 16 following the conference, it has been approved as a first-in-class drug with fulvestrant for patients with HR-positive/HER2-negative locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN* alterations following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

Around 40% to 60% of patients with metastatic HR-positive breast cancer acquire resistance to endocrine therapy. The most commonly altered pathway is the PI3K/AKT pathway through alternations in *PIK3CA*, *AKT1*, and *PTEN*. AKT signaling has been implicated in the development of this endocrine resistance,

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and therefore has become a target for drug therapy. Capivasertib is a potent selective inhibitor of all three AKT isoforms (AKT 1/2/3). By targeting AKT, the drug interferes with cellular proliferation.

The CAPItello-291 trial was a randomized, double-blind, placebo-controlled, multicenter trial in patients with locally advanced or metastatic HR-positive, HER2-negative breast cancer who progressed on aromatase inhibitor–based treatment. Patients could have received up to two prior lines of endocrine therapy and up to one line of chemotherapy for locally advanced or metastatic disease.

Eligibility criteria that Dr. Cuellar highlighted was that patients needed to have a hemoglobin A1C of less than 8%, and diabetic patients could not be on insulin.

"If we give patients insulin, that would reactivate the PI3K pathway. Because we're trying to shut down this pathway, patients on insulin were not allowed under the eligibility criteria," noted Dr. Cuellar.

In the overall population, the median progression-free survival (PFS) almost doubled; in the combination arm it was 7.2 months vs. 3.6 months with fulvestrant, with an impressive hazard ratio (HR) of 0.6. In patients with AKT-altered tumors, there were similar outcomes of a median PFS of 7.3 months vs. 3.1 months in the placebo arm, with an adjusted HR of 0.5. About 74% of patients were still alive at 18 months vs. 65% in the placebo arm for all comers, with an HR of 0.74. Overall survival (OS) in AKT pathway–altered patients was similar, at 73.2% vs. 62.9%, with an HR of 0.69. Benefits were seen across subsets of populations, including patients who had received prior CDK 4/6 inhibitors or had liver metastases, and the discontinuation rate was low.

Capivasertib is an oral AKT inhibitor with an intermittent dosing schedule in combination with fulvestrant.

Adverse events were primarily rash, diarrhea, and nausea. There was less hyperglycemia seen than with other agents in this pathway, at 16% at any grade.

Since it is approved only for patients with AKT-altered tumors, Dr. Cuellar said, "We have to make sure that we're sending biopsies for panel testing in order to capture these alterations."

TUSAMITAMAB RAVTANSINE FOR NSCLC

Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) is a protein that is abundantly expressed in tumor cells that plays a role in cell migration, cell invasion, as well as cell adhesion. About 25% of nonsquamous non–small cell lung cancers (NSCLCs) are known to highly express CEACAM5.

Tusamitamab ravtansine is an antibody-drug conjugate that binds with CEACAM5 protein and subsequently releases the payload of ravtansine, which is an antimicrotubule. It would be a first-in-class drug if approved.

The CARMEN-LC05 phase II study assessed this antibody-drug conjugate in treatment-naive patients with nonsquamous NSCLC and moderate to high CEACAM5 expression.

"Since CEACAM5 is expressed on the extracellular surface of cells, you would need to obtain tissue for immunohistochemistry (IHC) testing, just as you would for HER2 expression for trastuzumab," noted Dr. Cuellar. "A positive result would be defined as ≥ 2+ intensity in ≥ 50% tumor cell population."

There were three cohorts in the study. All three cohorts included tusamitamab ravtansine and the immune checkpoint inhibitor pembrolizumab. One cohort added platinum-based chemotherapy, and another cohort added platinum-based chemotherapy plus pemetrexed. The objective response rate (ORR) in the entire cohort was 52%, with the disease control rate observed in 88% of patients. A dose-limiting toxicity was increased aspartate aminotransferase (AST). Other grade 3 treatment-related adverse events that occurred in about 68% of patients were nausea, diarrhea, asthenia, and interstitial lung disease. Given the preliminary side effect profile, antiemetics and antidiarrheals may be considered, along with monitoring liver function tests. The dosing is to be determined.

ZENOCUTUZUMAB FOR PANCREATIC CANCER AND NSCLC

Zenocutuzumab is being studied in pancreatic cancer and NSCLC. Genomic rearrangements involving neuregulin 1 (NRG1) have been identified in several solid tumors. These fusions involving NRG1 result in ERbB-mediated pathway

activation, leading to abnormal cell proliferation. Zenocutuzumab is a bispecific monoclonal antibody that binds to HER2 and blocks HER3 signaling in high NRG tumor environments and induces enhanced antibody-dependent cellular cytotoxicity. Unlike bispecific T-cell engagers, it does not cause cytokine release syndrome.

Zenocutuzumab was studied in a phase I/II global, open-access trial that included patients with locally advanced, unresectable, or metastatic solid tumors that were NRG1 fusion protein positive. Patients received zenocutuzumab 750 mg intravenously every 2 weeks until progression or unacceptable toxicity. The majority (57%) had NSCLC and 23% had pancreatic cancer, with a median of two prior lines of therapy. The ORR for NSCLC was 35%, and for pancreatic cancer the ORR was 42%. The 6-month duration of response was 76% in all patients, and 12-month duration of response was about 27%.

In terms of adverse events, 61% of patients experienced treatment-related adverse events, but they were primarily grade 1 and 2. Common adverse events were diarrhea, asthenia, infusion-related reactions, and nausea. Less than 1% of patients discontinued treatment due to toxicity.

As a first-in-class therapy that targets NRG1 fusion protein, it received FDA Breakthrough Therapy designation in NSCLC in July 2023, as well as in pancreatic cancer in June 2023.

"We know with pancreatic cancer that there are very limited biomarker-driven options," commented Dr. Cuellar. "Any time a therapy receives breakthrough designation as zenocutuzumab has, it means there have been impressive data in a setting that doesn't have many therapeutic options."

ZOLBETUXIMAB FOR GASTRIC CANCER

Approximately 38% of patients present with stage 4 gastric cancer, and the median overall survival for patients who have HER2-negative gastric cancer is less than 1 year. Chemotherapy is the current standard of care, and testing for biomarkers such as HER2 expression, dMMR, MSI-high, and PD-1 is recommended.

"If patients with gastric cancer are negative for HER2, PD-1, and MSI-high, then they fall into a poor prognosis. I believe this type of gastric cancer is going to be viewed in a way similar to how we view triple-negative breast cancer," said Dr. Cuellar.

Claudin 18.2 has become a promising novel target in gastric cancer. Claudin 18.2 is a tight junction protein specifically expressed in about 40% of HER2-negative adenocarcinomas of the upper gastrointestinal tract, with little expression anywhere else in the body. About 38% of patients with locally advanced unresectable gastric cancer are claudin 18.2 positive.

Claudin 18.2 is detected in tissue via IHC. Zolbetuximab is a chimeric immunoglobulin monoclonal antibody that binds to claudin 18.2 on the surface of cancer cells and triggers cell death by activating antibody-dependent cellular toxicity and complement-dependent cytotoxicity pathways.

This was investigated in the SPOTLIGHT trial, which was a randomized phase III double-blind study. Patients who were eligible had previously untreated, locally advanced metastatic gastric or gastroesophageal junction cancer. They were claudin 18.2 positive and HER2 negative with good performance status. The study examined zolbetuximab in combination with fluorouracil, leucovorin, and oxaliplatin (FOLFOX) vs. placebo and FOLFOX. Adding zolbetuximab increased PFS, at 10.6 months vs. 8.6 months, with an HR of 0.75 (95% CI = 0.60–0.94; p = .0066). Overall survival also improved, at 18 months vs. 15 months, with an HR of 0.75. The objective response rate was similar among both arms, 48%, and the median duration of response was 9 months in the zolbetuximab arm vs. 8 months in the placebo arm.

There was a statistically higher incidence of nausea and vomiting in the zolbetuximab arm compared with the placebo and chemotherapy arm, at 82% vs. 61% for any-grade nausea and 67% vs. 36% for any-grade vomiting. Therefore, 5-HT3 receptor antagonists and NK-1 receptor antagonists are likely needed. Interestingly, data show that the impact of corticosteroids on the potential efficacy of zolbetuximab is unknown, and it is recommended to avoid them with the first dose. Decreased appetite was also common in the zolbetuximab arm.

"As a pharmacist involved in decisions and building this EPIC plan, I always think about administration, premedications, monitoring parameters, and treatment conditions," said Dr. Cuellar.

Cycles are every 42 days with mFOLFOX administration on days 1, 15, and 29, and zolbetuximab on days 1 and 22.

REVUMENIB FOR AML

Around 10% of adults and 80% of pediatric acute myeloid leukemia (AML) patients harbor the *KMT2A* mutation. Rearrangements of the *KMT2A* gene give rise to *KMT2A*-rearranged AML. It has a poor prognosis, with around less than 25% of adult patients alive after 5 years.

KMT2A genes produce fusion proteins that require interaction with a protein called menin to drive leukemic cancer growth. Disruption of the menin-*KMT2A* interaction has been shown to halt the growth of *KMT2A*-rearranged leukemic cells.

Revumenib is a potent selective inhibitor of that menin-*KMT2A* binding. It disrupts this formation of this protein complex and therefore interrupts the process of AML. When stopped, the cell can undergo differentiation, which leads to one of the adverse events of this menin inhibitor, differentiation syndrome.

The AUGMENT-101 study was a phase I/II study that included adult and pediatric patients with relapsed/refractory *KMT2A*-rearranged, *NPM1*-mutant leukemia subtypes. The patient population was heavily pretreated with a median of four prior lines of therapy, and around 68% had *KMT2A* rearrangement. The complete response was about 30%, and the median duration of response was around 9.1 months. The median overall survival was about 7 months.

"As a reference point, response rates in this population are usually less than 10%. So this complete response rate of 30% is quite impressive," noted Dr. Cuellar.

On top of that, of the patients who had a complete response, they had a minimal residual disease (MRD) negative rate of 78%.

"For those of you who are not familiar with MRD, MRD looks at patients who have complete response but uses different technology to detect residual disease at a much more sensitive level," explained Dr. Cuellar.

Treatment-related adverse events that occurred ≥ 20% of cases included nausea and QTc prolongation, which were mostly asymptomatic. Differentiation syndrome had an incidence of approximately 16% in this study, primarily at grade 2, and was managed with corticosteroids with or without hydroxyurea. Overall, the therapy was tolerable among patients. Revumenib is an oral agent administered every 12 hours for 28 days continuously, although dosing changes in the presence of a CYP3A4 inhibitor or inducer.

Revumenib is a first-in-class agent that received FDA Breakthrough Therapy designation in December 2022.

DENILEUKIN DIFTITOX FOR CTCL

Denileukin diftitox is an anti-CD25 antibody and recombinant fusion protein that combines the IL-2 receptor binding domain and diphtheria toxin fragments. By binding to IL-2 receptors on the cell surface, it causes diphtheria toxin fragments that have entered cells to hinder protein synthesis. The original formulation (Ontak) was approved in 1999 but then voluntarily withdrawn from the market in 2013.

A phase III, open-label, single-arm study studied this new formulation in patients with recurrent or persistent cutaneous T-cell lymphoma that were CD25 positive. The ORR was 36% by Independent Review Committee. The duration of response was 6 months, and the time to response was around 1.5 months.

Capillary leak syndrome was observed at about 20% of patients.

"Capillary leak syndrome can be mitigated with fluid management, looking at patients' serum albumin, monitoring weight, edema, blood pressure, interrupting the drug, and rapid initiation of diuretics," advised Dr. Cuellar.

Other adverse events included chills, nausea, increased ALT, and fatigue. In fall 2023 the FDA requested the manufacturer include stronger product testing, but cited no concerns regarding safety or efficacy. It is given 9 µg/kg/day, days 1-5, every 21 days.

Oncology therapeutics continue to dominate FDA drug approvals, providing patients more options for their specific cancer. ●

Disclosure

Dr. Cuellar received honoraria for serving on speakers bureaus for Mirati and Genentech.