2023–2024 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 2024, Vincent Harris, PharmD, BCOP, discussed investigational therapeutic agents in the drug development pipeline. Dr. Harris highlighted new drug classes, novel mechanisms of action, and safety profiles that advanced practitioners should be aware of.

The landscape of hematology and oncology is rapidly evolving, with new investigational therapeutics offering promising advancements in treatment. At JADPRO Live 2024, Vincent Harris, PharmD, BCOP, a Clinical Oncology Pharmacist at Atrium Health, shed light on exciting emerging therapies currently in the clinical pipeline, focusing on their mechanisms of action, efficacy, and safety profiles. These novel agents target various hematologic malignancies and solid tumors, addressing unmet clinical needs and potentially reshaping future treatment paradigms.

MEZIGDOMIDE FOR R/R MULTIPLE MYELOMA

Mezigdomide is a novel cereblon E3 ubiquitin ligase modulator being evaluated for relapsed/refractory multiple myeloma. In the CC-92480-MM-001 phase I/II study, patients received mezigdomide at a dose of 1 mg daily for 21 days of a 28-day cycle in combination with dexamethasone. The study demonstrated promising efficacy, with measurable responses in heavily pretreated patients. The primary adverse events included neutropenia, thrombocytopenia, and gastrointestinal disturbances, requiring close monitoring.

Dr. Harris highlighted the side effect profile observed in the clinical trial. The most common side effect reported was neutropenia, with any-grade in 77% of patients, grade 3 in 22%, and grade 4 in 54%, followed by fever, anemia, thrombocytopenia, fatigue, and some cases of deep vein thrombosis.

He further noted, "We saw 54% of patients having grade 4 neutropenia, but with that said, no patients in the study discontinued the drug due to it. However, a lot of patients did have to dose reduce as well as have their therapy interrupted."

"These are the same side effects we see with our immunomodulating agents, which should not be surprising," Dr. Harris further noted.

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PIVEKIMAB SUNIRINE FOR AML

This first-in-class CD123-targeting antibody-drug conjugate is designed for patients with relapsed/refractory CD123+ acute myeloid leukemia (AML). How often is AML CD123 positive?

"Turns out the literature suggests anywhere from 40 to 93% of patients may express CD123," commented Dr. Harris.

Dr. Harris described its mechanism: "The payload for this drug makes it unique. It works by alkylating DNA and causing single strand breaks without cross-linking. This is thought to be more potent against leukemia cells and less toxic to normal bone marrow progenitor cells."

Pivekimab sunirine received FDA breakthrough therapy designation in 2020. The IMGN632 phase I/II study supported its efficacy, particularly in patients with blastic plasmacytoid dendritic cell neoplasm.

In the study, modifications were made once researchers saw the rate of infusion-related reactions. Prior to the change, 31% of patients in schedule A had infusion reactions, but that was decreased to 10% grade 1 or 2 and 7% grade 3 after premedication modifications.

"Initially, patients only received dexamethasone prior to getting the drug. However, they changed to giving dexamethasone 8 mg twice daily the day before pivekimab sunirine in addition to acetaminophen and diphenhydramine."

Additionally, neutropenia (28%) and infection rates (41%) prompted investigators to permit the use of growth factor support.

ZIFTOMENIB FOR R/R AML

Ziftomenib is an investigational menin inhibitor for relapsed/refractory *NPM1*-mutant AML. Approximately 30% of AML patients harbor an *NPM1* mutation. This agent targets the KMT2A-menin pathway and received FDA breakthrough therapy designation in 2024. The KOMET-001 phase I/II study showed encouraging response rates, particularly in *NPM1*-mutant leukemia.

Ziftomenib functions by inhibiting menin, a key component of the KMT2A-menin pathway, which plays a crucial role in leukemogenesis. The drug disrupts the interaction between menin and KMT2A, preventing the activation of oncogenic genes such as HOXA9 and MEIS1. This results in the downregulation of these genes and the induction of normal cell differentiation.

The efficacy and safety of ziftomenib are currently being evaluated in the KOMET-001 phase 1/2 trial. The overall response rate (ORR) was 45%, with 35% of patients achieving complete remission (CR). Among those who achieved CR, 57% were minimal residual disease (MRD) negative. The median duration of complete remission was reported as 6.6 months. A subsequent analysis reported a median overall survival of 5.6 months.

The most common treatment-emergent adverse events included diarrhea, hypokalemia, nausea, and anemia. Treatment-related adverse events were primarily nausea (20%) and differentiation syndrome (20%).

There was a high rate of differentiation syndrome, particularly among patients with *KMT2A* rearrangements. Due to the elevated incidence, enrollment of KMT2A patients in the phase 1b study was discontinued, and the trial protocol was amended to implement closer monitoring and earlier steroid intervention for differentiation syndrome.

Additionally, one patient developed a resistance-associated mutation while on ziftomenib. Although other resistance mutations have been identified, ziftomenib may still have activity against some of them.

XALURITAMIG FOR CASTRATION-RESISTANT PROSTATE CANCER

Xaluritamig is a novel humanized bispecific T-cell engager targeting STEAP1 and CD3, developed for castration-resistant prostate cancer. STEAP1, or Six Transmembrane Epithelial Antigen of the Prostate 1, is expressed in up to 80% of prostate cancers. The drug functions by binding to both the STEAP1 antigen on prostate cancer cells and the CD3 receptor on T cells, facilitating T cell–mediated cytotoxicity against tumor cells (Figure 1).

The AMG 509 study evaluated its maximum tolerated dose, with a recommended schedule of escalating doses from 0.1 mg to 1.5 mg weekly. Clinical efficacy was demonstrated through prostate-specific antigen (PSA) reduction and tumor shrinkage. When evaluated using RECIST criteria, 24% of patients achieved a partial response (PR), while stable disease was observed in 48% of patients overall.

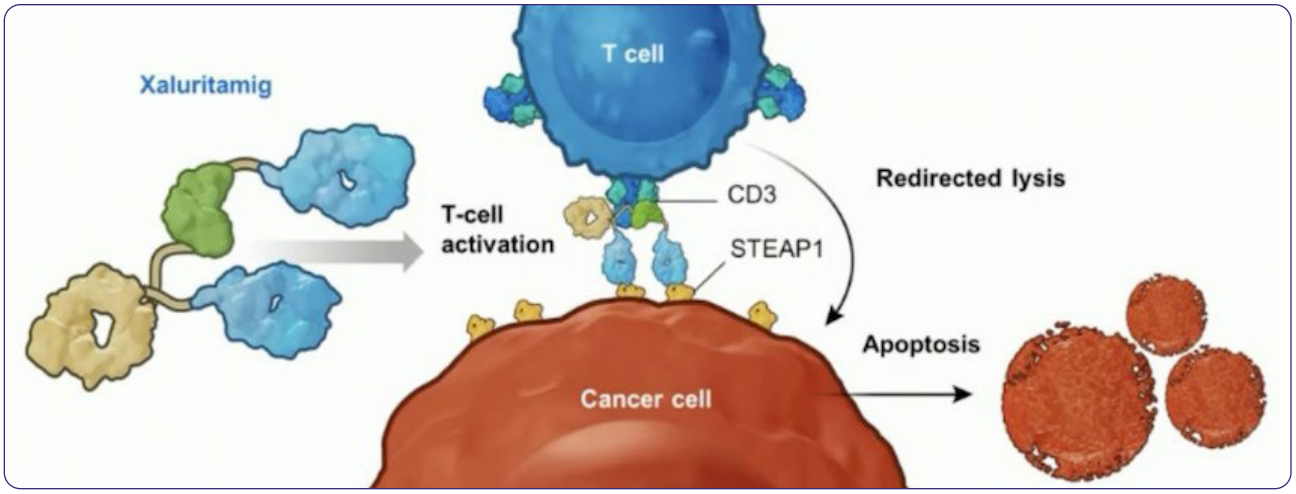

Figure 1. Xaluritamig mechanism of action.

Cytokine release syndrome (CRS) was the primary safety concern, occurring in 72% of patients and requiring prophylactic measures and stepwise dosing.

Dr. Harris described CRS management in the trial: "Prior to those modifications, patients only got dexamethasone 8 mg 1 hour prior to xaluritamig. But when they saw this high rate of grade 3 CRS, they determined that patients needed more premedication. So they got dexamethasone 16 hours prior to the dose and again 1 hour prior to the dose followed by standard hydration therapy."

Other commonly reported side effects included fatigue, fever, rash, decreased appetite, and anemia.

BEMARITUZUMAB FOR METASTATIC GASTRIC AND GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA

Bemarituzumab, a first-in-class humanized monoclonal antibody targeting FGFR2b, is under investigation for locally advanced or metastatic *FGFR2b*-positive, *HER2*-negative gastric and gastroesophageal junction adenocarcinoma. FGFR2B (fibroblast growth factor receptor 2b) is overexpressed in approximately 20% to 30% of gastric cancers, making it a potential therapeutic target.

FGFR2b plays a crucial role in cancer cell survival and proliferation. The drug functions through a dual mechanism.

"Bemarituzumab works in a two-fold way. Not only does it block FGFR2b receptors and stop downstream signaling, but it also enhances antibody-dependent cellular cytotoxicity by activation of CD16a and increased bemarituzumab affinity for natural killer cells.

The phase II FIGHT trial demonstrated improved outcomes when combined with chemotherapy. The median progression-free survival (PFS) was 9.5 months for bemarituzumab vs. 7.4 months for the control group, with a 12-month estimated PFS of 45.5% compared to 22.2% for patients who only received modified FOLFOX6.

Treatment-emergent adverse events included corneal toxicity (such as dry eye and keratitis), stomatitis, and elevated liver enzymes.

"67% of the patients in the bemarituzumab arm had some type of corneal adverse event, with 27% of them being grade three or higher," noted Dr. Harris.

ZONGERTINIB FOR NSCLC

Zongertinib is a HER2 tyrosine kinase inhibitor designed for *HER2* mutation-positive non-small cell lung cancer (NSCLC). The *HER2* mutation is found in approximately 2% to 4% of NSCLC cases. What makes zongertinib unique is its ability to bind not only to *HER2* wild-type but also to mutated *HER2,* including exon 20 mutations.

"Another unique thing about zongertinib is that it's so selective for HER2 that it is thought to minimally react with the EGFR wild-type receptor. In theory, that should result in a lower incidence of EGFR-mediated toxicities," explained Dr. Harris.

It has received both FDA fast track and breakthrough designations. The Beamion LUNG-1 phase Ib study reported an ORR of 72.4% and 72% for the 120 mg and 240 mg doses, respectively.

"The majority of patients had a partial response as far as the disease control rate; they saw 95% for 120 mg and then 100% for 240 mg."

Among patients with asymptomatic brain metastases, response rates were notable: 33% at 120 mg and 40% at 240 mg, with some patients achieving complete responses (15%–20%) and partial responses (19%–20%).

"The majority of patients did have some type of adverse event occur, with the most common being diarrhea, followed by rash and then some increase in liver enzymes," commented Dr. Harris.

These toxicities were predominantly grade 1 or 2, with few grade 3 events reported . As expected with tyrosine kinase inhibitors, gastrointestinal and skin-related side effects were prominent but manageable in patients.

Disclosure

Dr. Harris has nothing to disclose.