2021–2022 Drug Updates: Investigational Therapeutics in the Pipeline

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Presenter's disclosure of conflict of interest is found at the end of this article.

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Abstract

During JADPRO Live 2022, Donald C. Moore, PharmD, BCPS, BCOP, DPLA, FCCP, discussed investigational therapeutic agents in the drug development pipeline. Dr. Moore highlighted agents that represent either a new drug class, a novel mechanism of action, a rethinking of how to approach treating a disease, or those that have recently received FDA Breakthrough Designation status that advanced practitioners should be aware of.

The pipeline for investigational therapeutics in hematology/oncology is constantly evolving, with many promising new treatments being developed to address the unmet needs of patients. While these treatments are still in the investigational stage, they offer hope for patients who currently have limited treatment options.

During JADPRO Live 2022, Donald Moore, PharmD, BCPS, BCOP, DPLA, FCCP, of Levine Cancer Institute, Atrium Health, identified new investigational therapeutics and described the pharmacology of agents currently being evaluated in the hematology/oncology pipeline. Dr. Moore also discussed literature supporting the ongoing evaluation of emerging therapeutic agents (Table 1).

HEMATOLOGY

Pirtobrutinib

As Dr. Moore explained, bruton tyrosine kinase (BTK) inhibition has been under investigation in hematology for many years. Currently, there are covalent BTK inhibitors such as ibrutinib (Imbruvica) and acalabrutinib (Calquence) that bind to the cysteine-481 site on BTK, but non-covalent BTK inhibitors are also under evaluation. These inhibitors do not bind to the same site as covalent inhibitors, which may be an option for patients who have developed acquired mutations due to *BTK* C481 mutations, one of the most common types of acquired mutations that leads to BTK inhibitor resistance in chronic lymphocytic leukemia (CLL).

One noncovalent BTK inhibitor currently under development is pirtobrutinib. This oral medication is highly selective, reversible, and has equal low nanomolar potency against both wild type and *C481*-mutated BTK.

"Pirtobrutinib achieves greater than 300-fold sensitivity for BTK compared with a host of other

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Table 1. Updates on Selected Investigational Agents

Agent	Update
Bempegaldesleukin	Did not meet primary endpoint in melanoma phase III trial; investigations ongoing in renal cell carcinoma
Tiragolumab	Phase III trial in NSCLC did not meet PFS endpoint; OS endpoint immature → trial ongoing
Adavosertib	Phase II and III trials recently terminated
Teclistamab	Biologic license application submitted to FDA for R/R multiple myeloma
Talquetamab	Granted breakthrough designation by FDA for R/R multiple myeloma
Glofitimab	Phase II data in R/R diffuse large B-cell lymphoma presented at ASCO 2022
Magrolimab	Trials in AML/MDS were put on hold 2/2022 and then partial hold lifted 4/2022

Note. AML = acute myelogenous leukemia; MDS = myelodysplastic syndrome; NSCLC = non–small cell lung cancer; OS = overall survival; PFS = progression-free survival; R/R = relapsed/refractory.

kinases," Dr. Moore reported. "This means it is more selective for its pharmacologic target, reducing the potential for off-target toxicities by not inhibiting many of the non-BTK kinases. Pirtobrutinib is also designed to achieve greater than 90% of maximal BTK inhibition at trough, thereby achieving effective target inhibition throughout the dosing interval."

Pirtobrutinib was recently evaluated in the first-in-human multicenter open-label phase I/II BRUIN trial (Mato et al., 2021). This trial included patients with B-cell malignancies who had received at least two prior lines of therapy. The protocol was amended, however, to include patients with CLL/small lymphocytic lymphoma who had only one prior line of therapy, which included a covalent BTK inhibitor.

The BRUIN trial included a wide range of dosing cohorts, ranging from 25 mg once a day all the way up to 300 mg once a day. The trial included over 300 patients with a median age of 68. Approximately half of patients had CLL while the other half included follicular lymphoma, marginal zone lymphoma, and diffuse large B-cell lymphoma (DLBCL). According to Dr. Moore, this was a heavily treated patient population, with a median of three prior lines of therapy.

"Overall, pirtobrutinib is a promising investigational therapeutic in the pipeline for hematology, specifically for patients with B-cell malignancies who have developed resistance to covalent BTK inhibitors," said Dr. Moore. "Further studies will be needed to evaluate the efficacy and safety of pirtobrutinib in larger patient populations."

Mosunetuzumab

Bispecifics, a type of immunotherapy that binds to two different targets on cancer cells (often one target on cancer cells and the other on CD3 on T cells), are an area of continuing therapeutic advancement in B-cell lymphoma with agents such as epcoritamab, glofitamab, and mosunetuzumab. Bispecifics are designed to bring T cells to the cancer cells and help the immune system to attack and kill the cancer cells, said Dr. Moore, who noted that this approach has the potential to overcome resistance to other therapies in B-cell lymphomas.

Mosunetuzumab is a full-length, humanized IgG1 bispecific antibody targeting CD20 on B cells and CD3 on T cells. The CD20 protein is found on the surface of B cells and is a target for the treatment of B-cell lymphomas, while the CD3 protein is found on the surface of T cells and is a target for the treatment of T-cell lymphomas.

Mosunetuzumab has recently been approved by the European Medicines Agency for the treatment of relapsed or refractory follicular lymphoma, which is a type of B-cell lymphoma, making it one of the first bispecifics to receive regulatory approval.

The safety and efficacy of mosunetuzumab was recently evaluated in a phase I/Ib, multicenter, open-label, dose-escalation, and expansion study (Budde et al., 2021). This study included patients with relapsed or refractory B-cell lymphomas who had received prior treatment with rituximab. Findings from the study showed that mosunetuzumab was well-tolerated with an acceptable safety profile.

"The overall response rate was high, with a significant number of patients achieving a complete response," said Dr. Moore, who noted that nearly half of patients with indolent non-Hodgkin lymphoma achieved a complete response. "These results suggest that mosunetuzumab is an effective and safe option for patients with relapsed or refractory B-cell lymphomas who have received prior treatment with rituximab."

Zilovertamab Vedotin

Zilovertamab vedotin is an investigational agent that targets a novel oncofetal protein called receptor tyrosine kinase-like orphan receptor 1 (ROR1). ROR1 is present on many cancers but is not found in normal tissues, said Dr. Moore, who noted that ROR1-expressing tumors have a high potential for self-renewal and are associated with poor outcomes.

Zilovertamab vedotin is an antibody-drug conjugate targeting extracellular ROR1, which has a cleavable linker and a monomethyl auristatin E antimicrotubule cytotoxic payload, which allows for the targeted delivery of the cytotoxic agent directly to the cancer cells, reducing the potential for off-target toxicities.

A phase I study was recently conducted to investigate the pharmacokinetics, efficacy, and safety of zilovertamab vedotin in B-cell lymphomas (Wang et al., 2022). The study included 32 patients with lymphoid cancer who had progressed after prior treatment or were not transplant candidates. Zilovertamab vedotin was administered intravenously over 30 minutes.

Findings from the study showed an overall response rate of 60% in DLBCL and mantle cell lymphoma, with 40% achieving a complete response.

"The patient population was small and further studies are needed to confirm these findings, but the results of this study are promising," said Dr. Moore. "Zilovertamab vedotin shows potential in the treatment of B-cell lymphomas, but the potential applications of zilovertamab vedotin and other ROR1-targeting agents are not limited to B-cell lymphomas."

"ROR1 is expressed in a wide range of cancer types, and further research is being conducted to investigate the potential of zilovertamab vedotin and other ROR1-targeting agents in the treatment of other cancer types as well," he added.

SOLID TUMORS

Elacestrant

Elacestrant, a novel nonsteroidal oral selective estrogen receptor degrader, is under development for the treatment of endocrine-resistant breast cancer. Elacestrant works by degrading the estrogen receptor alpha in a dose-dependent manner, inhibiting estradiol-dependent estrogen receptor directed gene transcription and tumor growth, including in patients who harbor *ESR1* mutations associated with endocrine resistance.

Elacestrant was evaluated in the EMERALD trial, an international, randomized open-label, phase III trial of postmenopausal women or men over the age of 18 who had estrogen receptor–positive/HER2-negative breast cancer that was either recurrent or in the metastatic setting (Bidard et al., 2022). Elacestrant was shown to have a promising response rate compared with standard of care, which was investigator's choice of either fulvestrant or an aromatase inhibitor. As Dr. Moore reported, 12-month progression-free survival was 22.3 months for patients randomized to elacestrant vs. just 9.4 months on the standard-of-care arm.

Interim analysis for overall survival also favored elacestrant compared with standard of care for both the overall study population (hazard ratio [HR], 0.75; $p = .08$) and patients with *ESR1* mutations (HR, 0.59; $p = .03$)

Elacestrant has also demonstrated a favorable safety profile. In the EMERALD trial, the most common adverse events observed with elacestrant were fatigue and nausea, said Dr. Moore, which were generally mild to moderate in severity, and no new safety signals were identified with elacestrant compared with the standard-of-care arm.

Mirvetuximab Soravtansine

Mirvetuximab soravtansine is a first-in-class antibody-drug conjugate that targets folate receptor alpha and contains maytansinoid DM4, a tubulin-targeting cytotoxic payload, similar to the cytotoxic payload in trastuzumab emtansine (T-DM1) used in breast cancer.

In the FORWARD I trial, the primary endpoint of progression-free survival was not met; however, secondary endpoints such as overall response rate, CA-125 biochemical responses, and

patient-reported outcomes showed improvement in the folate receptor alpha–high subgroup.

"This suggests that targeting specific subgroups of patients may be a viable approach for future drug development," said Dr. Moore.

The SORAYA trial, which was presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting, evaluated mirvetuximab soravtansine in patients with platinum-resistant, high-grade, serous ovarian cancer who were highly expressive of folate receptor alpha (Matulonis et al., 2022). The trial, which included 106 patients, demonstrated an overall response rate of 32.4%. The most common treatment-related adverse events were ocular toxicity, such as blurred vision and keratopathy, as well as gastrointestinal toxicity.

The FDA granted mirvetuximab soravtansine priority review for the treatment of patients with folate receptor alpha–high, platinum-resistant ovarian cancer who have received one to three prior systemic therapies.

"Mirvetuximab soravtansine is a promising new agent for the treatment of gynecologic malignancies," said Dr. Moore. "It's currently being studied in several ongoing clinical trials, including in combination with carboplatin in first-line neoadjuvant chemotherapy in the advanced stage for ovarian cancer and as a single agent in folate receptor alpha–high endometrial cancer."

Telisotuzumab Vedotin

Finally, telisotuzumab vedotin is an antibody-drug conjugate targeting c-Met overexpressing non–small cell lung cancer (NSCLC). The LUMINOSITY trial, recently presented at the 2022 ASCO Annual Meeting, evaluated the efficacy of telisotuzumab vedotin in patients with locally advanced or metastatic NSCLC with varying levels of c-Met expression, and who had two or fewer prior lines of therapy and one or no prior lines of cytotoxic chemotherapy (Camidge et al., 2022).

According to Dr. Moore, the most promising patient cohort was the c-Met–overexpressing, nonsquamous, *EGFR* wild-type, c-Met-high group, with an overall response rate of 52%. However, the intermediate group, which had an overall response rate of 25%, is also being included in further drug development. The most common adverse events with telisotuzumab vedotin were peripheral neuropathy, nausea, and hypoalbuminemia.

Telisotuzumab vedotin received breakthrough designation status by the FDA in early 2022 and is being evaluated further for the use in patients with advanced/metastatic *EGFR* wild-type, nonsquamous NSCLC who have high c-Met expression and have progressed on or after platinum-based chemotherapy. ●

Disclosure

Dr. Moore has served on advisory boards for AstraZeneca, Janssen, Oncopeptides, and Pfizer.

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