2021–2022 Drug Updates in Solid Tumors

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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, Kirollos Hanna, PharmD, BCPS, BCOP, briefed advanced practitioners on key FDA approvals from late 2021 to late 2022. He described mechanisms of action that are unique across some malignancies, as well as mechanisms of action that clinicians can utilize through an expanded indication or across other solid malignancies. Finally, he discussed safety profiles and what advanced practitioners can and should do in monitoring across solid tumors.

From late 2021 to late 2022, there were around 20 drug approvals for solid tumors, including four approvals in breast cancer, three in melanoma, three in lung cancer, and two in cervical cancer. During JADPRO Live 2022, Kirollos Hanna, PharmD, BCPS, BCOP, of M Health Fairview and Mayo Clinic College of Medicine, discussed the approved label indications, described mechanisms of action, and provided insights into developing plans to monitor and manage side effects associated with the administration of newly approved drugs and biologics in oncology.

BREAST CANCER

Abemaciclib

The international, randomized, open-label, phase III monarchE trial evaluated the addition of abemaciclib (Verzenio) plus endocrine therapy as adjuvant treatment for patients with early-stage, high-risk, hormone receptor–positive, HER2-negative breast cancer (Martin et al., 2021). The study enrolled patients who had prior adjuvant chemotherapy and no distant metastases, and who were within 16 months of surgery. Patients were randomized to either abemaciclib plus endocrine therapy or endocrine therapy alone.

Findings from the study showed that the addition of CDK4/6 inhibition improved disease-free survival and recurrence-free survival, with a 2-year invasive disease-free survival of 92% and a distant recurrence-free survival of 94%.

As Dr. Hanna explained, abemaciclib is a CDK4/6 inhibitor, which works by preventing the proliferation of breast cancer cells by inhibiting cellular signaling. The indication for abemaciclib is in combination with endocrine therapy, such

as tamoxifen or aromatase inhibitors, for adjuvant treatment in adult patients with this type of breast cancer who have a Ki-67 score of 20% or greater. Abemaciclib is dosed at 150 mg twice a day, with adjustments for creatinine clearance less than 30 and severe impairment of liver function.

The drug may interact with CYP3A and CYP3A4 enzymes, said Dr. Hanna, who noted that it is important to avoid coadministration with strong inhibitors and inducers or to reduce the dosage if this is not possible. Common side effects of CDK4/6 inhibitors include diarrhea, neutropenia, nausea, and vomiting.

Olaparib

The international, randomized, double-blinded, phase III OlympiA trial evaluated the role of poly(ADP-ribose) polymerase (PARP) inhibition in the treatment of patients with *BRCA*-mutated breast cancer (Tutt et al., 2021). The study enrolled men and women with hormone receptor–negative, high-risk primary breast cancer who completed standard local treatments and had at least six cycles of chemotherapy containing anthracyclines or taxanes. The study aimed to determine if olaparib (Lynparza), a PARP inhibitor, could improve outcomes in this patient population.

As Dr. Hanna explained, PARP inhibitors like olaparib work by inhibiting the PARP protein, which plays a role in repairing DNA in cells with homologous recombination deficiencies, such as those with *BRCA* mutations. In *BRCA*-mutated cells, PARP inhibition prevents the mechanism of repair, leading to the death of cancer cells.

The OlympiA trial used olaparib at a dose of 300 mg twice a day for 1 year, or placebo, and evaluated invasive disease-free survival as the primary endpoint, with overall survival and safety as secondary endpoints.

"Results of the study showed that olaparib treatment resulted in a significant improvement in 3-year invasive disease-free survival and a 42% reduction in the risk of disease recurrence (hazard ratio, 0.58)," said Dr. Hanna. "There was a significant benefit seen in both the triple-negative breast cancer subgroup and the hormone receptor–positive, HER2-negative subgroup. However, overall survival benefit was not achieved in the study."

Common side effects of PARP inhibitors include nausea, vomiting, anemia, and fatigue. Other potential side effects include hematologic adverse events and gastrointestinal side effects. Importantly, said Dr. Hanna, PARP inhibitors may cause extreme fatigue, especially in frail patients, who may have lost a lot of weight and have low albumin levels. Additionally, PARP inhibitors may have drug interactions with CYP3A and CYP3A4 inhibitors.

In March 2022, olaparib was approved as an adjuvant treatment for adult patients with *BRCA* mutations or suspected *BRCA* mutations, HER2-negative, high-risk early breast cancer, who have been treated with neoadjuvant or adjuvant chemotherapy.

Trastuzumab Deruxtecan

Trastuzumab deruxtecan (Enhertu) and trastuzumab emtansine (Kadcyla) are both antibody-drug conjugates that target HER2-positive breast cancer, but have different payloads and therefore different mechanisms of action. Trastuzumab deruxtecan is composed of a humanized anti-HER2 antibody linked to a topoisomerase I inhibitor, while trastuzumab emtansine is composed of a humanized anti-HER2 antibody linked to a microtubule-inhibiting agent.

The DESTINY-Breast03 trial evaluated the efficacy of trastuzumab deruxtecan vs. trastuzumab emtansine (T-DM1) in patients with unresectable or metastatic HER2-positive breast cancer who had progressive disease during or after previous therapy with a trastuzumab-based and a taxane-based regimen in advanced or metastatic settings (Cortés et al., 2022). The trial randomized patients to receive either trastuzumab deruxtecan or trastuzumab emtansine every 3 weeks, and the primary endpoint was progression-free survival by blinded review.

Results of the study showed that median progression-free survival for trastuzumab deruxtecan was not reached, while it was 6.8 months for trastuzumab emtansine.

"The 12-month progression-free survival rate was 76% for trastuzumab deruxtecan vs. 34% for trastuzumab emtansine, which is a significant benefit," said Dr. Hanna. "Additionally, the trial found that trastuzumab deruxtecan had higher

objective response rates and a longer duration of response compared with trastuzumab emtansine."

The most common side effects with trastuzumab deruxtecan were nausea, vomiting, alopecia, fatigue, and constipation.

"It should be noted that trastuzumab deruxtecan can also cause interstitial lung disease (ILD) or pneumonitis, which can be serious or fatal, so it is important to closely monitor patients for signs and symptoms of ILD or pneumonitis and interrupt or discontinue treatment if ILD or pneumonitis is suspected or confirmed," Dr. Hanna noted.

Trastuzumab deruxtecan was also evaluated in the DESTINY-Breast04 trial in patients with HER2-low unresectable or metastatic breast cancer who had one to two prior lines of chemotherapy in the metastatic setting or had a recurrence less than 6 months after adjuvant chemotherapy (Modi et al., 2022). Patients with stable brain metastases were also included in the study. Patients were randomized to either trastuzumab deruxtecan or investigator's choice of chemotherapy, and the primary endpoint was progression-free survival in hormone receptor-positive patients.

Findings from DESTINY-Breast04 showed a median progression-free survival of 9.9 months for trastuzumab deruxtecan compared with 5 months for investigator's choice of chemotherapy, resulting in a significant benefit for trastuzumab deruxtecan. The study found that overall survival was also improved with trastuzumab deruxtecan compared with investigator's choice of chemotherapy.

"This trial is significant as it shows the efficacy of trastuzumab deruxtecan in HER2-low breast cancer patients and in patients with brain metastases, which is a population that has been traditionally excluded from breast cancer trials," said Dr. Hanna. "It provides a new treatment option for patients with HER2-low breast cancer who have progressed after previous chemotherapy and endocrine therapies."

MELANOMA

Relatlimab

The National Comprehensive Cancer Network (NCCN) has updated its guidelines to include relatlimab, a new LAG-3 inhibitor, plus nivolumab (the combination is called Opdualag), for the treatment of unresectable or metastatic melanoma in adult and pediatric patients 12 years of age or older.

The global phase II/III RELATIVITY-047 trial was conducted to evaluate the efficacy of this new treatment compared with nivolumab alone (Tawbi et al., 2022). The trial included patients with previously untreated unresectable or metastatic melanoma and a performance status of zero or one. Patients were randomized to receive relatlimab plus nivolumab or nivolumab alone. The primary endpoint of the trial was progression-free survival, with secondary endpoints of overall survival and response rates.

Results of the trial showed that the combination therapy of relatlimab plus nivolumab significantly improved progression-free survival compared with nivolumab alone. Specifically, there was a 22% reduction in the risk of progression in patients receiving the combination therapy. The combination therapy also improved overall survival, with a 20% reduction in the risk of death compared to nivolumab alone. The median overall survival benefit was not reached with the combination therapy, compared with 34 months with nivolumab alone. Additionally, the response rate was significantly higher in patients receiving the combination therapy, with a 43% response rate compared with 32% with nivolumab alone.

The medication comes in a single vial, and the dosing schedule is 480 mg of nivolumab and 160 mg of relatlimab every 4 weeks until progression or toxicity. No dose adjustments have been established for patients with renal or hepatic impairment, and there are no known drug interactions.

"The combination therapy of relatlimab plus nivolumab is a promising new treatment option for patients with unresectable or metastatic melanoma," said Dr. Hanna.

Mobocertinib

Updated NCCN Guidelines also include mobocertinib (Exkivity), an irreversible EGFR inhibitor, for the treatment of adult patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) with *EGFR* exon 20 insertion mutation who have progressed on platinum-based chemotherapy.

The phase I/II open-label, nonrandomized EXCLAIM study included a dose escalation cohort that looked at patients with NSCLC who could have the *EGFR* exon 20 insertion mutation (Zhou et al., 2021). The primary inclusion criteria for the study were adult patients with locally advanced NSCLC who were ineligible for definitive treatment or had metastatic NSCLC and had measurable disease per RECIST v1.1 criteria. The study aimed to determine if patients with this specific mutation would benefit from mobocertinib.

"This mutation is extremely rare, so this was a very small cohort of patients. Cohort 5, which is the cohort that led to the approval, enrolled 20 patients," said Dr. Hanna. "Investigator-assessed response was approximately 20%, confirmed response rates were 40%, and confirmed disease control rate was approximately 18% of patients. In 18% of patients, the median duration of response was 13 months."

Mobocertinib is an irreversible EGFR inhibitor that also inhibits *HER2* and *HER4*, which are part of the *EGFR* family. The dosing schedule is 160 mg once daily until progression or toxicity.

"As long as patients have an estimated glomerular filtration rate of greater than 30, no dose adjustments for hepatic or renal dysfunction are needed, but below 30, there is no established dose," said Dr. Hanna. "For severe hepatic impairment (bilirubin above three times the upper limit of normal and any aspartate aminotransferase), there is also no established dosing schedule."

The most common side effects are diarrhea, rash, nausea, vomiting, dry skin, and decreased appetite. Concomitant use with strong or moderate CYP3A inhibitors should be avoided.

CERVICAL CANCER

Tisotumab Vedotin

Tisotumab vedotin (Tivdak), an antibody-drug conjugate, is indicated for the treatment of recurrent or metastatic cervical cancer in patients who have progressed on chemotherapy. According to Dr. Hanna, this patient population has therapeutic options and has already received multiple lines of therapy.

The multicenter, single-arm, phase II innovaTV 204 trial was conducted to evaluate the efficacy of tisotumab vedotin in patients who had progressed during or after doublet chemotherapy and had received either two or fewer prior regimens with a standard performance status of zero or one (Coleman et al., 2021).

Tisotumab is administered at a dose of 2.0 mg/kg as a 30-minute infusion, every 3 weeks, until progressive disease or toxicity. The primary endpoint of the trial was confirmed objective response rate, and the secondary endpoints were duration of response, time to recurrence, progression-free survival, and others.

Results of the study showed a median duration of response of approximately 8 months, with a confirmed response rate of approximately 24%.

Common side effects include thrombocytopenias and neutropenias, neuropathy, gastrointestinal side effects such as constipation and diarrhea, and ocular toxicities. According to Dr. Hanna, tisotumab is the only drug that requires patients to have ice packs placed on their eyes during the infusion to minimize the risk of ocular toxicities. Patients also need to use eye drops before, during, and after treatment, and should be evaluated by an ophthalmologist. Ocular toxicities are unique to tisotumab and require close monitoring and management by health-care providers.

"Dose adjustments are not needed for creatinine clearance above 15, but it should be avoided in patients with moderate or severe hepatic impairment, as monomethyl auristatin E can cause toxicities in the presence of hepatic impairment," said Dr. Hanna.

PROSTATE CANCER

The international, randomized, double-blind, placebo-controlled trial ARASENS trial, which was conducted across more than 280 sites in 23 countries and enrolled over 1,300 patients, was a significant study in the field of prostate cancer, as it aimed to investigate the potential benefits of adding darolutamide (Nubeqa) to the standard treatment regimen for patients with newly diagnosed metastatic castration-sensitive prostate cancer (Smith et al., 2022).

Patients were randomized to receive either androgen deprivation therapy plus docetaxel plus darolutamide, androgen deprivation plus

docetaxel, or placebo. The primary endpoint of the trial was overall survival, with secondary endpoints including time to castration resistance, time to pain progression, and other safety and efficacy measures.

The results of the trial were promising, said Dr. Hanna, with the Kaplan-Meier curve showing a clear benefit for patients receiving darolutamide in combination with androgen deprivation and docetaxel. The median overall survival was not reached in the darolutamide arm, compared with 49 months in the androgen deprivation plus docetaxel arm. Additionally, the adverse events profile was similar between the two treatment arms, said Dr. Hanna, who noted that the addition of darolutamide did not significantly increase the risk of adverse events.

As a result of these findings, darolutamide gained FDA approval as a treatment option for adult patients with castration-sensitive prostate cancer in combination with docetaxel.

The standard dosing for darolutamide is 600 mg twice daily, with food, until progressive disease or unacceptable toxicity. It is also important to note that docetaxel should be administered within the first 6 weeks of initiating darolutamide treatment, said Dr. Hanna.

"Patients with severe renal impairment, as long as they are not on hemodialysis and have a glomerular filtration rate between 15 and 29, can receive a 50% dose reduction to 300 mg twice daily," said Dr. Hanna. "In case of moderate hepatic impairment, a 50% dose reduction to 300 mg twice daily is also recommended. However, for patients with severe hepatic impairment, no established dosing schedule is available."

The most common adverse events associated with darolutamide are gastrointestinal side effects, weight changes, and hypertension. Overall, darolutamide is well-tolerated, and its incorporation in the treatment of metastatic castration-sensitive prostate cancer has demonstrated significant improvement in overall survival for patients, Dr. Hanna concluded. ●

Disclosure

Dr. Hanna has served as an advisor and on speakers bureaus for BeiGene, BMS, and Seagen Inc., and as a consultant for BeiGene and Seagen Inc.

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