2023–2024 Drug Updates in Solid Tumors

PRESENTED BY MEGAN B. MAY, PharmD, BCOP, FAPO, FHOPA

From Baptist Health Lexington, Lexington, Kentucky

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

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Abstract

At JADPRO Live 2024, Megan B. May, PharmD, BCOP, FAPO, FHOPA, provided an overview of recent advances in therapies for solid tumors, highlighting 42 new FDA-approved indications between October 2023 and October 2024. Dr. May discussed pivotal trial results, mechanisms of action, indications, and management strategies for drugs in lung, breast, melanoma, rare tumors, and more. The presentation also emphasized the importance of biomarker-driven therapies and next-generation sequencing.

Between October 2023 and October 2024, there were 42 new indications in solid tumors, including 14 novel therapies and 15 expanded indications. At JADPRO Live 2024, Megan B. May, PharmD, BCOP, FAPO, FHOPA, Clinical Oncology Pharmacy Specialist at Baptist Health Lexington in Lexington, Kentucky, updated oncology advanced practitioners on new indications along with their mechanisms of action and how to manage and monitor side effects of these agents.

NSCLC

Some of the biggest advancements of the year were in the treatment of non–small cell lung cancer (NSCLC). Three trials focused on the patient population with resectable stage 2 to 3A or 3B NSCLC receiving neoadjuvant immunotherapy with chemotherapy, surgery, and then adjuvant immunotherapy—a "sandwich" approach. The KEYNOTE-671 study evaluated pembrolizumab (Keytruda) in combination with chemotherapy and demonstrated improved event-free and overall survival. The AEGEAN trial assessed durvalumab (Imfinzi) with chemotherapy, showing event-free survival benefits. The CheckMate-77T study investigated nivolumab (Opdivo) with chemotherapy and resulted in an approval for perioperative use. "These three trials will likely change how we manage this patient population," said Dr. May.

Dr. May also emphasized the importance of a multidisciplinary approach. "Treatment is regardless of PD-L1 status in these patients, so although these patients usually show up to the surgeons first, we also need to see them in medical oncology to recommend treatment if needed."

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Another development was the approval of alectinib (Alecensa) in the adjuvant setting for patients with completely resected stage IB, II, or IIIA *ALK*-positive NSCLC. The FLAURA2 study found that osimertinib (Tagrisso) combined with chemotherapy in the first-line setting increased progression-free survival (PFS) in patients with locally advanced or metastatic *EGFR*-mutated NSCLC, while the PAPILLON study established amivantamab (Rybrevant) plus chemotherapy as a first-line option for *EGFR* exon 20 insertion mutations. The MARIPOSA-2 study examined the use of amivantamab with chemotherapy in the second-line setting for NSCLC patients with *EGFR* mutations who had already received osimertinib. Results showed an increase in median PFS.

A new agent, lazertinib (Lazcluze), was approved in combination with amivantamab for first-line treatment of *EGFR*-mutated NSCLC. A third-generation tyrosine kinase inhibitor (TKI), lazertinib is highly selective, can penetrate the central nervous system (CNS), and exhibits fewer wild-type EGFR effects than osimertinib. The MARIPOSA study showed lazertinib plus amivantamab significantly increased PFS compared to osimertinib alone.

Repotrectinib (Augtyro) was approved for locally advanced or metastatic *ROS1*-positive NSCLC. The TRIDENT-1 study showed clinical activity in patients with *ROS1* fusion–positive NSCLC, regardless of whether they had previously received a *ROS1* TKI.

Adverse Event Management

Perioperative immunotherapy in NSCLC increases the risk of immune-related toxicities. Combination therapy can lead to higher toxicity rates. In the combination of lazertinib and amivantamab, rash was more frequent with lazertinib, while diarrhea was more common with osimertinib. A key safety concern was venous thromboembolism (VTE), occurring in 21% of patients before the protocol was updated to require VTE prophylaxis for the first 4 months using direct oral anticoagulants or low molecular weight heparin. Dr. May commented, "In my institution, we use rivaroxaban because it's a once-a-day dosing."

Another concern was infusion-related reactions associated with IV amivantamab. The SKIP-Pirr trial demonstrated that using higher doses of prophylactic dexamethasone significantly reduced infusion reactions.

Repotrectinib was noted for its unique withdrawal pain when discontinued, described as severe muscle and joint aches. Therefore, it is recommended to do a slow taper in order to minimize this withdrawal pain, particularly before surgery. Also, because repotrectinib causes dizziness, its dosage should be titrated gradually.

SMALL CELL LUNG CANCER

Tarlatamab (Imdelltra) is the first bispecific T-cell engager approved in a solid tumor. It targets DLL3 and is approved in the second-line setting for extensive-stage small cell lung cancer. The DeLLphi-301 trial showed a 40% overall response rate, which Dr. May highlighted as particularly encouraging, stating, "These patients all had two or more previous lines of therapy, and we still had two complete responses."

Adverse Event Management

Tarlatamab carries a high risk of cytokine release syndrome (CRS) and neurotoxicity. After the first two doses of tarlatamab, it is recommended to monitor patients for 22 to 24 hours in an appropriate health-care facility. After those first two doses, patients are recommended to stay within 1 hour of the health-care facility for an additional 24 hours with a caregiver.

NASOPHARYNGEAL CARCINOMA

Toripalimab (Loqtorzi) received dual approvals on the same day for nasopharyngeal carcinoma (NPC). It was approved as a first-line treatment in combination with chemotherapy for metastatic or recurrent locally advanced NPC and as monotherapy in the second-line setting. Toripalimab is a PD-1 immune checkpoint inhibitor. The JUPITER-02 trial found that the addition of toripalimab to chemotherapy as first-line treatment for recurrent/metastatic NPC provided statistically significant and clinically meaningful PFS and overall survival (OS) benefits compared with chemotherapy alone. In the POLARIS-02 trial, toripalimab demonstrated a durable clinical response in patients with chemo-refractory metastatic NPC in the second-line setting.

Adverse Event Management

There was no significant increase in severe toxicities when adding toripalimab to chemotherapy in JUPITER-02. Infusion-related reactions are possible but can be managed with gradual infusion.

BREAST CANCER

The NATALEE Study demonstrated that ribociclib (Kisqali) combined with endocrine therapy provided benefit in hormone receptor (HR)-positive, HER2-negative early-stage breast cancer. The CAPItello-291 study led to the approval of capivasertib (Truqap) with fulvestrant for HR-positive, HER2-negative tumors with *PIK3CA*, *AKT1*, or *PTEN* alterations. The INAVO120 study introduced a triplet regimen with inavolisib for patients with a *PIK3CA* mutation, plus palbociclib and fulvestrant for first-line metastatic breast cancer.

Adverse Event Management

Ribociclib has been associated with QT prolongation. There are also now updated FDA guidelines.

"The QT prolongation in NATALEE for all grades was 4.3%. So the recommendation for how often you have to get an EKG was changed. Now, you only have to get it at baseline and then at day 14," noted Dr. May.

Capivasertib and inavolisib, both targeting the PI3K/AKT pathway, pose risks of diarrhea and hyperglycemia. Oral hydration, loperamide, and metformin prophylaxis are recommended. Additionally, stomatitis prevention with dexamethasone mouthwash was used in inavolisib trials.

PROSTATE CANCER

Enzalutamide received an expanded indication for non-metastatic, castration-sensitive prostate cancer with biochemical recurrence. The EMBARK trial revealed that patients could pause and restart treatment based on prostate-specific antigen levels.

Adverse Event Management

Enzalutamide can cause fatigue, cognitive impairment, and cardiovascular toxicities. Advanced practitioners should educate patients on the potential risks of hypertension and thromboembolic events.

GASTROINTESTINAL CANCERS

In colorectal cancer, the FRESCO-2 study led to the approval of fruquintinib (Fruzaqla) for refractory metastatic colorectal cancer, showing improved survival. The CRYSTAL-1 Study combined adagrasib with cetuximab and secured approval for *KRAS* G12C-mutant colorectal cancer after two previous lines of therapy, including platinum-based chemotherapy. In gastric and esophageal cancer, zolbetuximab (Vyloy) was approved in the first-line setting in combination with chemotherapy for tumors that are claudin 18.2 positive. The NAPOLI-3 study supported the first-line approval of liposomal irinotecan (Onivyde) in combination with chemotherapy for metastatic pancreatic adenocarcinoma.

Adverse Event Management

Fruquintinib has vascular endothelial growth factor (VEGF)-related toxicities, including hypertension and proteinuria.

"When I meet with patients, I provide a blood pressure log, and I make sure they have access to a blood pressure cuff," said Dr. May.

Due to the risk of hypersensitivity reactions with zolbetuximab, "You give the first dose slower and then you can speed it up after that. You also need to monitor your patients for 2 hours after this infusion," advised Dr. May.

Uniquely, zolbetuximab has a high emetogenic potential, requiring antiemetic prophylaxis.

DESMOID TUMORS

Nirogacestat (Ogsiveo), a gamma-secretase inhibitor, was approved for progressing desmoid tumors requiring systemic treatment by blocking activation of the Notch receptor.

Adverse Event Management

Nirogacestat has significant ovarian toxicity, with 75% of women experiencing menstrual cycle changes, hot flashes, night sweats, or vaginal dryness due to its impact on follicular activation, maturation, and growth. However, "This resolved in about 74% of patients that experienced ovarian toxicity," Dr. May noted.

Additionally, nirogacestat is a CYP3A4 substrate, requiring caution with strong CYP3A4 inducers and acid-reducing agents.

Table 1. FDA-Approved Pan-Tumor Treatments

Pembrolizumab	Tumor mutational burden-high cancer, unresectable or metastatic. Microsatellite instability-high (MSI-H) or mismatch repair–deficient (dMMR) cancer, unresectable or metastatic
Dostarlimab	Solid tumors, recurrent or advanced, dMMR
Larotrectinib	Solid tumors with neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion
Entrectinib	Solid tumors, locally advanced or metastatic, *NTRK* gene fusion positive
Repotrectinib	Solid tumors, *NTRK* gene fusion positive
Fam-trastuzumab deruxtecan	Solid tumors, unresectable or metastatic, *HER2* positive
Selpercatinib	Solid tumors, *RET* fusion positive
Dabrafenib + trametinib	Solid tumors, unresectable or metastatic, with *BRAF* V600E mutation

NEUROBLASTOMA

For high-risk neuroblastoma, eflornithine (Iwilfin) has been approved to reduce the risk of relapse in adult and pediatric patients with high-risk neuroblastoma who have demonstrated at least a partial response to prior agents.

Adverse Event Management

Eflornithine may lead to weight loss due to appetite suppression. It is dosed on body surface area.

"It is recommended to recalculate this dose at least every 3 months to make sure the patient is appropriately dosed," said Dr. May.

GYNECOLOGIC CANCER

For stage 3 and 4 cervical cancer, the KEYNOTE-A18 study demonstrated that pembrolizumab plus chemoradiotherapy significantly improved PFS in patients with newly diagnosed, high-risk, locally advanced cervical cancer. The FDA approval is specifically in stage III-IVA cervical cancer.

In endometrial cancer, the DUO-E study led to FDA approval of durvalumab in combination with chemotherapy followed by maintenance durvalumab due to a PFS benefit in patients with deficient mismatch repair (dMMR) advanced or recurrent endometrial cancer. Additionally, the KEYNOTE-868 and RUBY studies led to expanded approvals for pembrolizumab and dostarlimab (Jemperli) in advanced or recurrent endometrial carcinoma, as both agents showed PFS benefits regardless of MMR status.

Adverse Event Management

The addition of immunotherapy was initially suspected to increase the risk of colitis, given the combination with radiation therapy. However, the studies showed that patients did not have an increased risk of colitis with these regimens. Immune-related adverse events (irAEs), such as thyroid dysfunction, pneumonitis, and hepatotoxicity, should still be monitored.

MELANOMA

Lifileucel (Amtagvi), the first tumor-infiltrating lymphocyte (TIL) therapy, was approved for unresectable or metastatic melanoma in patients previously treated with immune checkpoint or BRAF inhibitor therapy. The C-144-01 trial showed a 31.5% overall response rate, with eight complete responses.

Adverse Event Management

Lifileucel requires lymphodepleting chemotherapy before TIL infusion, which increases the risk of toxicities and necessitates hospitalization.

"These patients are hospitalized throughout this time, and they stay there until they have hematologic recovery, which is usually about 14 days," Dr. May said.

There is a warning for hypersensitivity reaction. Tumor-infiltrating lymphocyte therapy did not appear to cause serious immune-related side effects.

BLADDER CANCER

Nogapendekin alfa (Anktiva), a first-in-class IL-15 receptor agonist, was approved with Bacillus Calmette-Guérin (BCG) for patients with BCG-unresponsive non-muscle invasive bladder cancer with carcinoma in situ, with or without papillary tumors.

Adverse Event Management

Nogapendekin alfa requires intravesical administration with bladder retention for 2 hours, a process that may lead to bladder irritation.

PAN-TUMOR APPROVALS

Dr. May wrapped up the presentation with a list of pan-tumor approvals (Table 1).

"As we find mutational targets expressed in multiple different cancers, we're seeing more approvals for treatments across different tumors," Dr. May concluded. "Performing next-generation sequencing will become even more important going forward."

Disclosure

Dr. May has served on advisory boards for AstraZeneca, Daiichi Sankyo, Genentech, GlaxoSmithKline, and Lilly, on speakers bureaus for Amgen and AstraZeneca, and as a consultant for Lilly.