2024–2025 Drug Updates in Solid Tumors

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

https://doi.org/10.6004/jadpro.2026.17.2.6

Abstract

At JADPRO Live 2025, Kevin Y. Chen, PharmD, MS, BCOP, CPP, reviewed therapeutic advances in solid tumors with an emphasis on newly approved targeted therapies and antibody–drug conjugates (ADCs). The session underscored the expanding role of biomarker-driven treatment selection and comprehensive molecular profiling. Dr. Chen also emphasized the role of oncology advanced practitioners in monitoring patients and managing toxicities of these agents in order to optimize outcomes.

The session "New Drug Updates in Solid Tumors" presented on October 24, 2025, at JADPRO Live 2025 in National Harbor, Maryland, provided an overview of recently approved therapies in diseases such as breast, lung, and ovarian cancer, with a focus on novel mechanisms of action and practical management considerations for oncology advanced practitioners (APs).

Led by **Kevin Y. Chen, PharmD, MS, BCOP, CPP,** a clinical pharmacist practitioner at the University of North Carolina Medical Center, the session highlighted how understanding the mechanisms of action of targeted therapies and antibody-drug conjugates is crucial to evaluating potential toxicities of treatments.

"We're not trying to treat our patients at the expense of their quality of life. We're trying to treat them while preserving their quality of life as best as possible," said Dr. Chen. "And we all play an integral role in that."

NRG1 FUSION–POSITIVE TUMORS

Neuregulin 1 (*NRG1*) gene fusions occur in less than 1% of cancers overall. In non–small cell lung cancer (NSCLC), these fusions are found in approximately 0.14% to 0.4% of cases, while in pancreatic cancer they occur in 0.13% to 0.5% of patients (Laskin et al., 2020; Drilon et al., 2021). These fusions signal through the binding of the NRG1 protein to HER2/HER3 heterodimers, driving tumor growth and progression.

Dr. Chen emphasized the importance of comprehensive testing: "Optimal detection is through paired DNA and RNA sequencing. We want to make sure we're not missing these

J Adv Pract Oncol 2026;17(suppl 1):3–8

gene fusions, which can happen if you only use the DNA assay."

Zenocutuzumab (Bizengri) is a bispecific antibody designed to target the HER2/HER3 signaling pathway. It is approved for the treatment of advanced or metastatic NSCLC and pancreatic adenocarcinoma harboring *NRG1* gene fusions in patients whose disease has progressed on or after prior systemic therapy.

Zenocutuzumab is administered at a dose of 750 mg intravenously every 2 weeks until disease progression or unacceptable toxicity. The initial infusion is given over 4 hours, with patients monitored for 1 hour afterward for infusion-related reactions.

Adverse Event Management

The safety profile of zenocutuzumab was generally manageable (Merus N. V., 2025).

"This is a well-tolerated treatment," said Dr. Chen. "The most common side effect was diarrhea, which happened in only 29% of patients. There was also a bit of nausea and fatigue."

Premedication requirements differ between the first and subsequent cycles.

"Although relatively well tolerated, there is a risk of infusion-related reactions. Recommendations for premedications include acetaminophen, diphenhydramine, and dexamethasone for the first cycle, and acetaminophen plus diphenhydramine for subsequent cycles."

Key monitoring parameters include baseline assessment of left ventricular ejection fraction.

"Because this is a HER2-directed monoclonal antibody, we worry about left ventricular ejection fraction reductions," explained Dr. Chen. "Ensure you get an echocardiogram at baseline and periodically throughout the duration of treatment."

OVARIAN CANCER

Low-grade serous ovarian cancer (LGSOC) is a rare but clinically distinct subtype of epithelial ovarian cancer, often affecting younger patients and characterized by indolent growth yet poor responsiveness to conventional cytotoxic chemotherapy in recurrent or metastatic settings.

Avutometinib (Avmapki) is a dual RAF–MEK inhibitor designed to suppress paradoxical MAPK pathway reactivation that can occur with MEK inhibition alone. However, compensatory signaling through focal adhesion kinase (FAK) has been found to be an additional resistance mechanism. Defactinib (Fakzynja), a selective FAK inhibitor, was therefore combined with avutometinib (Figure 1).

Dr. Chen summarized, "When MEK is blocked by itself, there is a paradoxical activation of RAS signaling...so you have to block both pathways to increase effectiveness."

The FDA approval of avutometinib plus defactinib for *KRAS*-mutated recurrent LGSOC was based on results from the phase II ENGOT-ov60/GOG-3052/RAMP 201 trial (Banerjee et al., 2025). The regimen of avutometinib 3.2 mg twice weekly plus defactinib 200 mg twice daily (administered for 3 weeks of a 4-week cycle) demonstrated superior efficacy compared with avutometinib monotherapy, particularly in *KRAS*-mutated disease.

Adverse Event Management

Dr. Chen cautioned APs, saying, "Most people needed a dose interruption and almost half needed a dose reduction."

Common adverse events included creatine phosphokinase (CPK) elevation, nausea, fatigue, rash, diarrhea, edema, ocular events, and transaminase elevations.

Monitoring recommendations include frequent liver function tests, creatine phosphokinase (CPK) levels, and baseline and periodic ophthalmologic examinations. Given the moderate-to-high emetogenic potential and dermatologic toxicity risk, prophylactic antiemetics, sun protection, and early intervention for musculoskeletal or ocular symptoms are recommended. To help with the complex administration schedule, Dr. Chen recommended creating a calendar and making sure patients have the tools to take the drug appropriately.

BREAST AND LUNG CANCERS

Datopotamab Deruxtecan

Switching gears from dual-targeted therapies, Dr. Chen discussed antibody-drug conjugates.

Datopotamab deruxtecan (Dato-DXd; Datroway) is a TROP2-directed antibody-drug conjugate approved for patients with unresectable or metastatic HR-positive, HER2-negative breast cancer after prior endocrine therapy and chemotherapy,

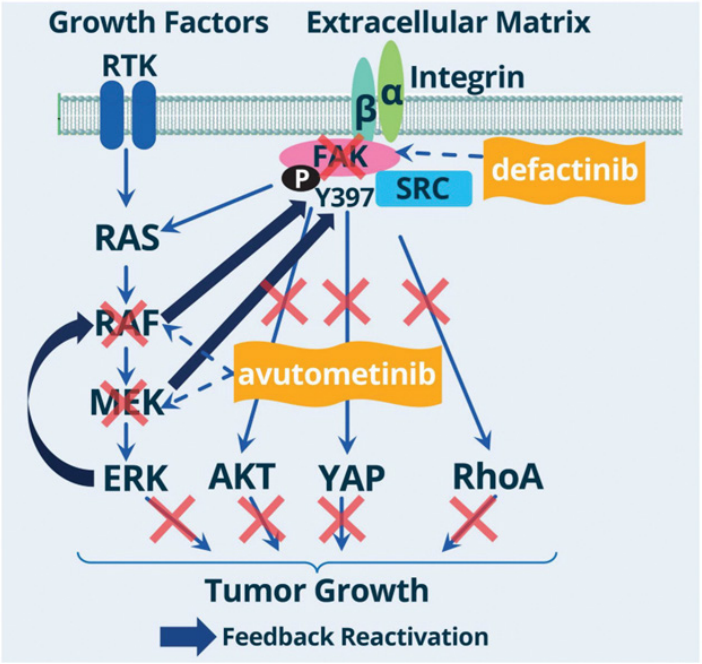

Figure 1. Mechanism of action of avutometinib and defactinib. Adapted from Grisham et al. (2023).

and for patients with *EGFR*-mutant NSCLC following EGFR-directed targeted therapy and platinum-based chemotherapy.

Dato-DXd combines a monoclonal antibody targeting TROP2 with a membrane-permeable topoisomerase I inhibitor payload. This design enables selective tumor targeting while allowing for a "bystander effect," in which the released payload diffuses into neighboring tumor cells.

Clinical efficacy was demonstrated in the phase III TROPION-Breast01 trial, where Dato-DXd improved objective response rate (36.4% vs 22.9%) and median progression-free survival (6.9 vs 4.9 months) compared with investigator's choice of chemotherapy in HR+/HER2- metastatic breast cancer (Bardia et al., 2025). In *EGFR*-mutant NSCLC, pooled analyses from TROPION-Lung01/05 showed an objective response rate of 43% and median progression-free survival of 5.8 months in a heavily pretreated population (Ahn et al., 2025).

Datopotamab deruxtecan is administered intravenously at 6 mg/kg every 3 weeks, with a dose cap of 540 mg for patients weighing 90 kg or over.

Adverse Event Management

"Although these ADCs are targeted chemotherapy, they don't completely spare patients from chemotherapy-like side effects," commented Dr. Chen.

Stomatitis is the most common adverse event, occurring in approximately 60% to 70% of patients. Ice chips during infusion can help with this.

Nausea, fatigue, alopecia, myelosuppression, pneumonitis, and interstitial lung disease were also observed. Supportive care includes prophylactic dexamethasone mouth rinses, baseline and annual ophthalmologic monitoring, and use of preservative-free artificial tears four times daily. Use of institution-specific antiemetic regimens for highly emetogenic chemotherapy is recommended.

Telisotuzumab Vedotin

Telisotuzumab vedotin (Emrelis) adds a biomarker-driven option for patients with metastatic non-squamous NSCLC who have limited durable responses after standard systemic therapies.

It is indicated for patients with metastatic, non-squamous, *EGFR* wild-type NSCLC with high c-MET expression and who have received prior systemic therapy.

The early-stage trial design included broader NSCLC subgroups, but the approval ultimately narrowed to the population most likely to benefit based on response.

"I want to highlight that you should not be using this in patients who are squamous cell or *EGFR* mutant," emphasized Dr. Chen.

Telisotuzumab vedotin is an ADC. Dr. Chen described, "We have a c-MET targeting antibody linked to MMAE, which is a microtubule disrupting agent as the payload."

Approval was based on the phase II LUMINOSITY study (Camidge et al., 2024). Stage 1 included those who were *EGFR* mutant as well as squamous cell, while Stage 2 was only in those with non-squamous and *EGFR* wild type.

Efficacy data were stratified by c-MET protein expression level. The high-expression group was defined as "greater than 50%, 3+ IHC staining," while the intermediate group was "25% to 50%, 3+ IHC staining."

In high expressors, there was an overall response rate of 35% compared with low expressors at 23%, and slightly increased durability of response of 9 months vs. 7.2 months. However, median PFS and OS were similar between these groups.

A major point was that the therapy did not perform well in subgroups that were initially evaluated in Stage 1. There was a response rate of about only 11% in patients with *EGFR* mutations or squamous histology, thus the specific approval.

Adverse Event Management

Peripheral neuropathy was seen with telisotuzumab vedotin, but the remainder of the toxicity profile was manageable, including fatigue, nausea, and myelosuppression.

The dose cap is 190 mg for patients weighing more than 100 kg. Unlike some antibody therapies with standard premedication regimens, telisotuzumab vedotin does not require routine premedication up front. Instead, supportive premedication is added only when needed.

Intravenous ADCs can have drug interactions.

"Normally we think of drug interactions particularly with the oral therapies...but specifically MMAE is hepatically metabolized," noted Dr. Chen. "For those patients who are on concurrent CYP inhibitors, it may actually increase MMAE concentrations and therefore increase the risk of drug toxicities."

Zongertinib

Zongertinib (Hernexeos) is an oral, selective HER2 tyrosine kinase inhibitor approved for metastatic *HER2*–TKD–mutant NSCLC. *HER2* mutations occur in about 2% to 3% of NSCLC patients, and these are often exon 20 insertion mutations.

"Keep in mind, this is unlike breast cancer and different from HER2 amplification or protein overexpression," clarified Dr. Chen.

Zongertinib was approved based on the Beamion LUNG-01 trial (Heymach et al., 2025). The efficacy results presented were striking for the pretreated targeted therapy population. Dr. Chen highlighted the "very high response rate, 75%, which is exciting for a targeted therapy." The median PFS was 12.4 months in the pretreated population.

Efficacy was not uniform across mutation subtypes: In patients with non-TKD mutations, the therapy did not work as well.

In addition, for the cohort receiving the therapy after prior HER2 ADC therapy, particularly trastuzumab deruxtecan (T-DXd), responses decreased, although activity persisted: "response rates are diminished but still there," with about a 50% response rate and PFS of about 6.8 months.

Dosing is weight stratified.

"They actually approved the 180 mg dose specifically for those patients who are greater than 90 kg," Dr. Chen said, while "for those who are less than 90 kg, it's the 120 mg dose."

Adverse Event Management

The toxicity appeared manageable overall. Diarrhea was a common adverse event, likely owing to the EGFR/HER2 family inhibition. Rash, some transaminitis, a little bit of bilirubin and fatigue, were also observed. Liver function tests should be performed at baseline, every 2 weeks for first 3 months, then monthly. Left ventricular ejection fraction should be taken at baseline then periodically.

Taletrectinib

Taletrectinib (Ibtrozi) is a next-generation ROS1 inhibitor with strong activity in both TKI-naive and TKI-pretreated patients with advanced/metastatic NSCLC, including patients with CNS

disease and G2032R resistance mutations. It is approved in both first- and second-line settings.

ROS1 fusions are rare gene rearrangements that occur in only 1% to 2% of all NSCLCs. Gene fusions are best detected with paired DNA and RNA testing.

"You may see that you can do a ROS1 IHC test. This is a good screening test, but it's not a definitive test," explained Dr. Chen. "ROS1 is actually expressed on healthy, noncancerous lung tissue. And so it may stain positive, but that may not necessarily mean that they have an oncogenic ROS1 gene fusion."

Taletrectinib enters an already crowded ROS1 space, with three other FDA approved targeted therapies: crizotinib, entrectinib, and repotrectinib. However, it has improved activity against G2032R, a known resistance mutation to earlier generation inhibitors. In addition, less TRK activity translates to favorable CNS tolerability, avoiding adverse events such as dizziness, ataxia, dysgeusia, and asthenia.

Taletrectinib was approved based on TRUST-1 and TRUST-2 (Pérol et al., 2025). The trials included ROS1 fusion–positive patients who were either treatment-naive or previously treated.

"The data that I'm presenting and the approval are currently for the 600-mg dose...we still await data for the dose finding 600-mg vs. 400-mg arm," noted Dr. Chen.

The highest efficacy was seen in patients who had not received prior ROS1 TKIs.

"Particularly in the TKI-naive patients, you see a remarkable response rate of 89%," Dr. Chen outlined. "The median duration of response was 44 months and the median PFS was 45 months; that's nearly 4 years."

Given the high CNS burden in ROS1 disease, Dr. Chen called out intracranial activity: "This drug has an overall response rate of 77% with previous treatment."

Adverse Event Management

The most common side effect was transaminitis, so patients are generally asymptomatic. However, the incidence rate was high: "When I see a side effect of 85% to 87%, that's striking."

Liver function should be monitored frequently due to the high incidence of transaminitis, and therapy should be held or reduced when elevations occur. There was also GI symptom burden, with diarrhea, nausea, and vomiting. There were low rates of dizziness, likely reflecting reduced TRK inhibition relative to other inhibitors.

DIFFUSE MIDLINE GLIOMA

Dordaviprone (Modeyso) is a first-in-class therapy with dual mitochondrial and dopamine receptor–mediated mechanisms, approved for both adult and pediatric patients with progressive H3 K27M-mutant diffuse midline glioma.

Diffuse midline glioma (DMG) with H3 K27M mutation carries a poor prognosis, with median overall survival of less than a year. Radiation remains a cornerstone of treatment, as other systemic option have not demonstrated improvement.

"This is the first drug that I'm aware of that works this way," remarked Dr. Chen.

The dual mechanism involves mitochondrial stress and dopamine receptor/RAS pathway signaling blockade, which combined leads to increased apoptosis.

Because the mutation is rare, evidence came from pooled trials (Arrillaga-Romany et al., 2024). There was an overall response rate of 20% with the therapy, and a median overall survival of 13.7 months.

Even with modest radiographic responses, the therapy led to reduction in steroid doses in half of patients and increased patients' performance status in about 1/5 of patients.

Dordaviprone is administered as a once weekly dose, which differs from other drugs in the space.

Adverse Event Management

Fatigue, headache, and nausea should be monitored carefully and treated with standard supportive approaches. Neurologic changes should prompt reassessment to determine whether symptoms are due to disease progression or drug effect, and imaging should be obtained when differentiation is unclear. Steroid doses should be tapered when possible because approximately half of patients in the pooled analysis were able to reduce steroid use. ●

Disclosure

Dr. Chen has received research support from Eli Lilly & Company and served on advisory boards for Amgen, Bristol Myers Squibb, Daiichi Sankyo, Johnson & Johnson, Merck, and Pfizer.

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