2019–2020 Drug Updates in Solid Tumors

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

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Abstract

During JADPRO Live Virtual 2020, Kirollos S. Hanna, PharmD, BCPS, BCOP, updated the audience on the pharmacology, new indications, and the clinical trial data of novel medications as well as expanded indications in solid tumors. Dr. Hanna also discussed signs and symptoms of potential serious and life-threatening adverse events, and how new therapeutic entities will impact the advanced practice setting.

Despite the COVID-19 pandemic, numerous oncology drugs have been approved by the U.S. Food & Drug Administration (FDA) over the past 12 months for initial or expanded indications for the management of patients with solid tumors (Table 1).

During JADPRO Live Virtual 2020, Kirollos S. Hanna, PharmD, BCPS, BCOP, of M Health Fairview and Mayo Clinic College of Medicine, discussed the pharmacology, indications, and clinical trial data of newly approved oncology drugs in solid tumors. Dr. Hanna also identified the signs and symptoms of serious or life-threatening adverse effects associated with these new agents.

ENFORTUMAB VEDOTIN-EJFV FOR BLADDER CANCER

As Dr. Hanna explained, standard of care for advanced bladder cancer in the first-line setting is platinum-based chemotherapy. Patients who progress then typically receive an immune checkpoint inhibitor in the second line. Following progression on both of these regimens, patients can receive enfortumab vedotin (Padcev), which is a Nectin-4-directed antibody-drug conjugate.

Enfortumab was approved based on data from the single-arm, multicenter, pivotal phase II EV-201 trial, which demonstrated "unprecedented outcomes," said Dr. Hanna (Rosenberg et al., 2019).

While immunotherapy is associated with response rates of 20% to 25% in this heavily pretreated population, patients treated with enfortumab had a response rate of 44%, including 12% complete response (CR) and 32% partial response (PR). Duration of response was 7.6 months, and subgroup analyses showed "consistent responses across the board," said Dr. Hanna.

With respect to safety profile, the most common adverse events (any

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Table 1. New Drug Approvals From 2019 to 2020

- Enfortumab vedotin-ejfv for metastatic urothelial cancer
- Fam-trastuzumab deruxtecan-nxki for breast cancer
- Avapritinib for gastrointestinal stromal tumor
- Tazemetostat for epithelioid sarcoma
- Selumetinib for neurofibromatosis type 1
- Tucatinib for breast cancer
- Pemigatinib for metastatic cholangiocarcinoma
- Sacituzumab govitecan-hziy for breast cancer
- Capmatinib for non–small cell lung cancer
- Selpercatinib for *RET* fusion
- Ripretinib for gastrointestinal stromal tumor

grade) were fatigue, rash, and peripheral neuropathy due to the monomethyl auristatin E (MMAE) conjugation. Hyperglycemia was also frequently observed. Overall, however, grade 3 and 4 toxicities were "fairly low," said Dr. Hanna.

Importantly, although enfortumab is dosed at 1.25 mg/kg, the dose should be capped at 125 mg in patients over 100 kg.

FAM-TRASTUZUMAB DERUXTECAN-NXKI FOR HER2+ BREAST CANCER

Approval of fam-trastuzumab (Enhertu) was based on the phase II DESTINY-Breast01 trial in adult patients with HER2-positive unresectable or metastatic breast cancer who had received prior trastuzumab emtansine (T-DM1; Modi et al., 2020).

"Patients with metastatic breast cancer who progress on front-line therapies generally have aggressive disease and tend not to do well, so there's a real unmet need in this population," said Dr. Hanna.

Results of the DESTINY II trial showed an overall response rate (ORR) of 61%, with the majority of patients achieving either stable disease (36%) or PR (55%). Disease control rate was 97%, and 6-month clinical benefit rate was 76%. Median duration of response was 14.8 months, and median time to response was 1.6 months.

Despite the high rate of response in this pretreated patient population, any-grade treatment-related toxicities occurred in nearly all patients, and grade 3 or higher toxicities occurred in almost half of all patients (48%). In addition, almost one quarter of patients required dose reductions, and more than one third of patients required dose interruptions.

Interstitial lung disease (ILD) is an adverse event of special interest. Although the majority of these events were low grade, there were four fatal cases of ILD, with onset occurring between 63 and 148 days after the start of treatment.

"This is not something that we need to monitor up front, but these toxicities could manifest later in the patient's treatment course," said Dr. Hanna.

Cardiac failure also occurred in two patients, but these were grade 1 and 2. Nevertheless, said Dr. Hanna, cardiac exams at baseline should be considered before initiating treatment.

TUCATINIB FOR HER2+ BREAST CANCER

Tucatinib (Tukysa) was approved in combination with capecitabine as well as trastuzumab for patients with HER2-positive metastatic breast cancer based on data from the phase II HER2CLIMB study. Patients enrolled in the study had received prior trastuzumab, pertuzumab, and T-DM1 therapy and were randomized to either capecitabine plus trastuzumab or tucatinib plus trastuzumab and capecitabine.

The primary endpoint of the HER2CLIMB study was progression-free survival, and secondary endpoints included overall survival, progression-free survival among patients with brain metastases, confirmed objective response rate, and safety.

"Overall survival in the intent-to-treat population was unprecedented and quite impressive," said Dr. Hanna, who reported 1-year overall survival of 70% in patients receiving tucatinib vs. only 47% in the control arm. "This is not something typically seen in this patient population."

Also impressive were the outcomes in patients with brain metastases. Progression-free survival at 1 year improved from 0% in the control arm of trastuzumab and capecitabine to 35% with the addition of tucatinib. Overall survival at 1 year in patients with brain metastases also improved from 41% to 72%.

"Patients with brain metastases do not often do well," said Dr. Hanna. "Having a tyrosine kinase inhibitor that is able to cross the blood-brain barrier, however, really demonstrates that benefit that we see in this population."

With respect to the safety profile, toxicities were slightly increased in the tucatinib arm, but the majority were grade 1 and 2. There were few grade 3 and 4 toxicities and few discontinuations due to tucatinib.

Although capecitabine must be administered with food, dosing with tucatinib is very flexible. However, it must be dispensed in the original container. Because tucatinib comes in a 30-day supply container, providers must keep that in mind when managing patients, said Dr. Hanna.

SACITUZUMAB GOVITECAN-HZIY FOR BREAST CANCER

Sacituzumab govitecan (Trodelvy), another recently approved antibody-drug conjugate, targets TROP-2, a cell surface receptor found to be overexpressed in patients with breast cancer.

Approval of sacituzumab govitecan came from the phase I/II, multicenter, single-arm IMMU-132 trial, which demonstrated a response rate of 33% and duration of response of almost 8 months in patients with metastatic triple-negative breast cancer who had received at least two prior lines of therapy in the metastatic setting (Bardia et al., 2019).

At least 25% of patients receiving sacituzumab govitecan had the following adverse events: nausea, neutropenia, diarrhea, fatigue, anemia, vomiting, alopecia, constipation, rash, decreased appetite, or abdominal pain.

"Unlike enfortumab, which is conjugated to MMAE, sacituzumab govitecan is conjugated to SN-38, which is implicated in gastrointestinal toxicities," said Dr. Hanna.

The first infusion of sacituzumab govitecan is administered over 3 hours to assess for infusion reactions. Based on tolerability, said Dr. Hanna, subsequent infusions are administered over 1 to 2 hours.

ADDITIONAL APPROVALS

Dr. Hanna discussed several additional approvals and key information.

Avapritinib (Ayvakit; 1/9/20)

- Unresectable or metastatic gastrointestinal stromal tumor (GIST) with *PDGFRA* exon 18 mutation, including D842V mutations
- 300 mg orally once daily on an empty stomach
- NAVIGATOR trial: ORR 84%, 7% CR, 77% PR
- Safety (≥ 20%): edema, nausea, fatigue/asthenia, cognitive impairment, vomiting, decreased appetite, diarrhea, hair color changes, increased lacrimation, abdominal pain, constipation, rash and dizziness

Tazemetostat (Tazverik; 1/23/20 and 6/18/20)

- Metastatic or locally advanced epithelioid sarcoma not eligible for complete resection
- EZH2 inhibitor, R/R FL positive for an *EZH2* mutation and after two prior systemic therapies, R/R FL with no satisfactory alternative treatment options
- 800 mg taken orally twice daily taken with or without food
- Study E7438-G000-101: ORR 69%, 12% CR, 57% PR
- Safety (≥ 20%): fatigue, upper respiratory tract infection, musculoskeletal pain, nausea, and abdominal pain

Selumetinib (Koselugo; 4/10/20)

- 2 years of age and older; with neurofibromatosis type 1 who have symptomatic, inoperable plexiform neurofibromas
- 25 mg/m^2 orally twice a day on an empty stomach
- SPRINT trial: ORR 44%, all patients had PR
- Safety (≥ 40%): vomiting, rash, abdominal pain, diarrhea, nausea, dry skin, fatigue, musculoskeletal pain, fever, acne, stomatitis, headache, paronychia, and pruritus

Pemigatinib (Pemazyre; 4/17/20)

- Unresectable locally advanced or metastatic cholangiocarcinoma with an *FGFR2* fusion or other rearrangement
- 13.5 mg orally once daily for 14 consecutive days followed by 7 days off therapy in 21-day cycles.
- FIGHT-202 trial: ORR 36%, 3 CR
- Safety (≥ 20%): hyperphosphatemia, alopecia, diarrhea, nail toxicity, fatigue, dysgeusia, nausea, constipation, stomatitis, dry eye, dry mouth, decreased appetite, vomiting, arthralgia, abdominal pain, hypophosphatemia, back pain, and dry skin

Capmatinib (Tabrecta; 5/6/20)

- Non–small cell lung cancer (NSCLC) with a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping
- 400 mg orally twice daily taken with or without food

- GEOMETRY mono-1 trial: ORR 68%; 69 previously treated patients, ORR 41%
- Safety (≥ 20%): peripheral edema, nausea, fatigue, vomiting, dyspnea, and decreased appetite

Selpercatinib (Retevmo; 5/8/20)

- RET fusion-positive NSCLC; metastatic RET-mutant medullary thyroid cancer that requires systemic therapy; metastatic RET fusion-positive thyroid cancer that requires systemic therapy and is radioactive iodine-refractory
- 120 mg for patients less than 50 kg, and 160 mg for those 50 kg or greater twice daily taken with or without food
- Trial: LIBRETTO-001
- Safety (≥ 25%): increased aspartate aminotransferase, increased alanine aminotransferase, increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation

Ripretinib (Qinlock; 5/15/20)

- GIST after 3 or more kinase inhibitors, including imatinib
- 150 mg orally once daily taken with or without food
- INVICTUS trial: median PFS was 6.3 months vs. 1.0 month for placebo; median OS 15.1 months vs. 6.6 months (HR of 0.36)
- Safety (≥ 20%): alopecia, fatigue, nausea, abdominal pain, constipation, myalgia, diarrhea, decreased appetite, palmar-plantar erythrodysesthesia, and vomiting

IMMUNOTHERAPY: EXPANDED INDICATIONS

Finally, said Dr. Hanna, immunotherapy also saw a number of approvals this year, including the combination of ipilimumab (Yervoy) and nivolumab (Opdivo) in renal cell carcinoma and atezolizumab (Tecentriq)-based combinations in various solid malignancies.

In addition, pembrolizumab (Keytruda) was approved for the following expanded indications: non-muscle invasive bladder cancer, solid tumors with high tumor mutation burden, metastatic cutaneous squamous cell carcinoma, and microsatellite instability-high or mismatch repair deficient colorectal cancer. ●

Disclosure

Dr. Hanna has served as a consultant for AbbVie and Seattle Genetics, on the speakers bureaus for AbbVie, Astellas, BMS, and Seattle Genetics BeiGene, on advisory boards for AstraZeneca, Heron Therapeutics, Incyte, Rigel, Sandoz, and Taiho Oncology, and holds stock in or is a shareholder of CVS Health.

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