2020–2021 Drug Updates in Solid Tumors

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Abstract

During JADPRO Live Virtual 2021, Christine Cambareri, PharmD, BCPS, BCOP, CSP, briefed advanced practitioners on drugs and biologics that were approved for the treatment of solid tumors from late 2020 to late 2021, including their adverse event profiles. The trend of more oral dosage forms and the significant number of checkpoint inhibitors approved points towards changing treatment paradigms in the field.

Between October 2020 and September 2021, there were 32 drug approvals in solid tumor oncology, including 23 regular approvals and 9 accelerated approvals. During JADPRO Live Virtual 2021, Christine Cambareri, PharmD, BCPS, BCOP, CSP, of the University of Pennsylvania Abramson Cancer Center, reviewed the approved label indications of many new drugs and biologics in oncology. Dr. Cambareri also discussed the adverse events associated with some of these newly approved agents.

"It is amazing, although not surprising, that half of the approvals in solid tumor oncology involve checkpoint therapy," said Dr. Cambareri. "This speaks to the changing treatment paradigm over the past five or six years. Immunotherapy has moved from the advanced and metastatic setting to having multiple first-line approvals in many solid tumors."

RELUGOLIX: ADVANCED PROSTATE CANCER

Results of the phase III HERO trial showed that relugolix (Orgovyx) achieved rapid, sustained suppression of testosterone levels that was superior to that with leuprolide in men with advanced prostate cancer, with a 54% lower risk of major adverse cardiovascular events (Shore et al., 2020).

The first oral option within this class of therapy, relugolix also demonstrated better outcomes in patients with cardiac history. According to Dr. Cambareri, therapy with relugolix should be considered for patients with cardiac comorbidities due to these outcomes data over other androgen deprivation therapies.

"The ideal patient for relugolix is one who only needs androgen deprivation therapy for prostate cancer and is not on concomitant P-gp inhibitors/CYP3A4 inducers," said Dr. Cambareri.

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MARGETUXIMAB-CMKB: HER2-POSITIVE BREAST CANCER

In the phase III SOPHIA trial, margetuximab (Margenza) plus chemotherapy demonstrated acceptable safety and a statistically significant improvement in progression-free survival compared with trastuzumab plus chemotherapy in HER2-positive advanced breast cancer after progression on two or more prior anti-HER2 therapies (Rugo et al., 2021). Patients with active brain metastases were not included in the study. Overall survival data published in September 2021 did not demonstrate statistically significant advantage for margetuximab over trastuzumab. However, patients in the CD16A 158F allele subgroup did have greater overall survival with margetuximab than with trastuzumab (MacroGenics, 2021).

"There are multiple options available after second-line therapy, with no data to guide optimal orders of treatment," said Dr. Cambareri, who noted that patients who are unable, or unwilling, to tolerate toxic effects of other novel therapies may be suited for margetuximab.

"The use of margetuximab may also be justified in carriers of the CD16A 158F allele, given its favorable side-effect profile and its more pronounced progression-free survival and overall survival benefits in this particular subset," she added.

PEMBROLIZUMAB: TRIPLE-NEGATIVE BREAST CANCER

There were two recent approvals for pembrolizumab (Keytruda) in triple-negative breast cancer: (1) in combination with chemotherapy for locally recurrent unresectable or metastatic disease and (2) for high-risk, early-stage disease in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

Results of the KEYNOTE-355 trial demonstrated a significant and clinically meaningful improvement in progression-free survival with the addition of pembrolizumab in patients with metastatic triple-negative breast cancer with PD-L1–positive status indicated by a combined positive score (CPS) of 10 or more (Cortes et al., 2020).

Results of the KEYNOTE-522 trial demonstrated the benefits of pembrolizumab in patients with untreated nonmetastatic disease (Schmid et al., 2020). In early triple-negative breast cancer, there was a significantly higher percentage of patients with a pathologic complete response in the pembrolizumab plus neoadjuvant chemotherapy arms than those who received neoadjuvant chemotherapy alone. Unlike in metastatic disease, however, a benefit was seen regardless of PD-L1 status.

According to the National Comprehensive Cancer Network (NCCN) guidelines, neoadjuvant pembrolizumab plus chemotherapy now carries a Category I recommendation for preferred first-line therapy along with atezolizumab (Tecentriq) plus nab-paclitaxel for triple-negative breast cancer.

"As we all know, triple-negative breast cancer behaves much more aggressively than other types of breast cancer and with earlier relapses and poor survival outcomes," said Dr. Cambareri. "These are huge approvals for this space, and more exciting information is coming for this rare and more aggressive form of breast cancer."

SACITUZUMAB GOVITECAN: TRIPLE-NEGATIVE BREAST CANCER

Another approval for triple-negative breast cancer, sacituzumab govitecan (Trodelvy), a Trop-2-directed antibody-drug conjugate, was approved for patients with metastatic disease who have received at least two prior therapies for metastatic disease.

Results of the ASCENT trial showed significantly longer progression-free survival with sacituzumab vs. single-agent chemotherapy, and median overall survival nearly doubled from 6.7 months to 12.1 months with the antibody-drug conjugate (Bardia et al., 2021).

PEMBROLIZUMAB PLUS LENVATINIB: ENDOMETRIAL CARCINOMA

The first immunotherapy plus targeted therapy combination in endometrial cancer, pembrolizumab with lenvatinib (Lenvima) was approved for patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following chemotherapy, and are not candidates for curative surgery or radiation.

Dr. Cambareri reported an improvement in median overall survival from 12 months to 17.4

months with the combination of immunotherapy and targeted therapy (Makker et al., 2020).

DOSTARLIMAB-GXLY: ENDOMETRIAL CANCER

Another immunotherapy for endometrial cancer, dostarlimab-gxly (Jemperli) was associated with clinically meaningful and durable antitumor activity with an acceptable safety profile for patients with deficient mismatch mutation repair endometrial cancers after prior chemotherapy. Results of an ongoing, phase I multicenter study showed an overall response rate of 41.6% with a very long median duration of response at 34.7 months (Oaknin et al., 2020).

NIVOLUMAB PLUS IPILIMUMAB: MESOTHELIOMA

Nivolumab (Opdivo) plus ipilimumab (Yervoy) was approved as first-line treatment for patients with unresectable malignant pleural mesothelioma, a rare and highly aggressive disease with a median survival of less than 1 year for previously untreated patients and a 5-year overall survival rate of 10%.

The CheckMate 743 trial randomized patients to either combination immunotherapy for up to 2 years or 6 cycles of chemotherapy (Baas et al., 2021). Results showed improvements in median overall survival, progression-free survival, overall response rate, and duration of response.

OSIMERTINIB: NSCLC

Osimertinib (Tagrisso), a third-generation EGFR tyrosine kinase inhibitor, was approved for adjuvant therapy after tumor resection in patients with non–small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (*EGFR*) exon 19 deletions or exon 21 L858R mutations.

Results of the ADAURA trial showed that median disease-free survival has not been reached in patients who had a complete tumor resection with or without prior adjuvant therapy who received osimertinib (Wu et al., 2018).

"Osimertinib is the first targeted therapy approved for resectable *EGFR*-mutated NSCLC and the first and only targeted therapy approved to help prevent disease recurrence," said Dr. Cambareri. "This is a huge breakthrough."

LORLATINIB: NSCLC

Lorlatinib (Lorbrena) was approved for patients with metastatic NSCLC whose tumors are anaplastic lymphoma kinase (*ALK*)-positive. In the CROWN trial, median progression-free survival was not reached in the lorlatinib arm vs. 9.3 months with crizotinib (Shaw et al., 2020).

"Most impressively, the intracranial overall response rate was 82% with lorlatinib, while it was only 23% with crizotinib," said Dr. Cambareri. "The penetration of the blood-brain barrier really makes this agent unique."

AMIVANTAMAB-VMJW: NSCLC

Amivantamab (Rybrevant), a third-generation EGFR tyrosine kinase inhibitor, yielded robust and durable responses with tolerable safety in patients with NSCLC with *EGFR* exon 20 insertion mutations after progression on platinum-based chemotherapy (Park et al., 2021). According to Dr. Cambareri, however, this early phase study is still ongoing (estimated completion in 2024), and the current data only represent a subset of exon 20 insertion population.

SOTORASIB: NSCLC

In patients with locally advanced or metastatic NSCLC, the KRAS inhibitor sotorasib (Lumakras) demonstrated an overall response rate of 37.1%, a median duration of response of 11.1 months, median progression-free survival of 6.8 months, and a median overall survival of 12.5 months (Skoulidis et al., 2021). The CodeBreaK100 Trial was the first trial to demonstrate *KRAS* G12C as targetable in NSCLC, said Dr. Cambareri, which represents approximately 13% of lung adenocarcinomas.

The ideal patient to receive sotorasib has *KRAS* G12C mutation and has progressed on one systemic therapy without brain metastases.

TEPOTINIB: NSCLC

Tepotinib (Tepmetko), a MET tyrosine kinase inhibitor, is approved for patients with advanced NSCLC with a confirmed *MET* exon 14 skipping mutation. In the phase II VISION trial, the use of tepotinib was associated with a partial response in approximately half the patients (Paik et al., 2020). This is the only approved once-daily oral MET inhibitor.

PRALSETINIB: THYROID CANCER

Pralsetinib (Gavreto) was approved for advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) requiring systemic therapy or RET (REarranged during Transfection) fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory.

Results of the ARROW trial showed an overall response rate of 89% in patients with no prior targeted therapies who were refractory to radioactive iodine (Subbiah et al., 2021).

NIVOLUMAB PLUS CABOZANTINIB: RENAL CELL CARCINOMA

The combination of nivolumab and cabozantinib (Cabometyx) was approved as first-line treatment for patients with advanced renal cell carcinoma based on results of the CheckMate 9ER trial, which showed a doubling of progression-free survival vs. sunitinib (16.6 months vs. 8.3 months; Choueiri et al., 2021). Results also favored the combination of immunotherapy and VEGF inhibitor with respect to overall response rate and overall survival.

PEMBROLIZUMAB PLUS LENVATINIB: RENAL CELL CARCINOMA

The combination of lenvatinib and pembrolizumab was also approved for first-line treatment of patients with advanced renal cell carcinoma based on results of the phase III CLEAR trial, which showed significantly longer progression-free survival (23.0 months vs. 9.2 months) and overall survival vs. sunitinib (Motzer et al., 2021).

Dr. Cambareri noted that the survival data for the combination of lenvatinib and pembrolizumab was higher than the data from the CheckMate 9ER trial of nivolumab and cabozantinib, but the CLEAR trial enrolled a more favorable risk group of patients. Cabozantinib plus nivolumab may also have a lower toxicity burden.

According to Dr. Cambareri, the choice between treatment regimens becomes nuanced and more patient specific. Patients who can handle toxicity and want to "go big" for complete response may opt for pembrolizumab plus lenvatinib, while nivolumab plus cabozantinib is a more tolerated effective regimen with demonstrated health-related quality-of-life benefits over sunitinib. Dual checkpoint inhibition with nivolumab plus ipilimumab, on the other hand, is for "patients with uncontrolled hypertension and a need for cytoreductive nephrectomy," she said.

TIVOZANIB: RENAL CELL CARCINOMA

For patients with relapsed or refractory advanced renal cell carcinoma who have received two or three prior systemic treatments, including at least one VEGF tyrosine kinase inhibitor, tivozanib (Fotivda) demonstrated improved progression-free survival and was better tolerated versus sorafenib. Results of the TIVO-3 trial showed a median progression-free survival of 5.6 months on tivozanib vs. 3.9 months on sorafenib (Rini et al., 2020). Because the study did not control for subsequent therapies, however, the impact on overall survival is difficult to assess. According to Dr. Cambareri, the ideal patient for tivozanib has seen more than two systemic therapies, including other VEGF tyrosine kinase inhibitors or checkpoint inhibitors.

NIVOLUMAB: UROTHELIAL CARCINOMA

Immunotherapy continues to see expanded indications in the treatment landscape of urothelial or bladder cancer. Nivolumab was approved for adjuvant treatment for patients with urothelial carcinoma who are high risk for recurrence after radical resection. Results of the CheckMate 274 trial showed that the addition of immunotherapy with nivolumab allowed for a near doubling of median disease-free survival compared with placebo (Bajorin et al., 2021). Moreover, in patients with high PD-L1 status (greater than 1%), median disease-free survival has not been met. Benefit was seen regardless of PD-L1 status, said Dr. Cambareri.

ENFORTUMAB VEDOTIN: UROTHELIAL CARCINOMA

The first antibody-drug conjugate in urothelial cancer, enfortumab (Padcev) was granted full approval for adult patients with locally advanced or metastatic urothelial cancer have received checkpoint inhibition and platinum-containing chemotherapy or are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy. The pivotal EV-201 trial showed an overall response rate of 44% and a

median duration of response of 7.6 months (Powle et al., 2021).

SACITUZUMAB: UROTHELIAL CARCINOMA

Accelerated approval for another antibody-drug conjugate in urothelial cancer, sacituzumab, was granted for patients with locally advanced or metastatic disease who previously received a platinum-containing chemotherapy and either PD-1 or PD-L1 inhibitor. Results of the pivotal TROPHY trial showed an overall response rate of 27.7% and a median duration of response of 7.2 months with sacituzumab (Tagawa et al., 2021).

PEMBROLIZUMAB: GASTROINTESTINAL CANCER

Accelerated approval was granted to pembrolizumab in combination with trastuzumab, fluoropyrimidine-, and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction adenocarcinoma. In the pivotal KEYNOTE-811 trial, the addition of pembrolizumab had a substantial and statistically significant increase in overall response rate vs. trastuzumab and chemotherapy alone (Chung et al., 2021).

Pembrolizumab was also approved in combination with platinum chemotherapy based on data from the KEYNOTE-590 trial, which demonstrated improved overall survival in patients with previously untreated locally advanced or metastatic squamous esophageal cancer with a CPS of 10 or more (Sun et al., 2021).

FAM-TRASTUZUMAB DERUXTECAN: GASTROINTESTINAL CANCER

Fam-trastuzumab deruxtecan-nxki (Enhertu), an anti-HER2 antibody-drug conjugate, was approved for patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal adenocarcinoma who have received a prior trastuzumab-based regimen. The pivotal DESTINY-Gastric01 trial showed a 51% response rate with fam-trastuzumab deruxtecan compared with only 14% with standard chemotherapy and a median duration of response of 11.3 vs. 3.9 months (Shitara et al., 2020).

NIVOLUMAB: GASTROINTESTINAL CANCER

Nivolumab was approved in combination with fluoropyrimidine- and platinum-containing chemotherapy for advanced or metastatic HER2 negative gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma. The addition of nivolumab demonstrated superior progression-free and overall survival compard with chemotherapy alone and can be offered as first-line therapy for patients with this disease. Nivolumab is the first immunotherapy approved in gastric cancer, said Dr. Cambareri.

Nivolumab also demonstrated positive data in the CheckMate 577 trial for patients who have residual pathologic disease after neoadjuvant chemotherapy (Kelly et al., 2021).

INFIGRATINIB: CHOLANGIOCARCINOMA

The FGFR inhibitor infigratinib (Truseltiq) was associated with promising anticancer activity and a manageable side effect profile in patients with advanced, refractory cholangiocarcinoma with an *FGFR2* gene fusion or rearrangement.

IVOSIDENIB: CHOLANGIOCARCINOMA

Ivosidenib (Tibsovo) was approved for patients with previously treated, locally advanced or metastatic cholangiocarcinoma with an *IDH1* mutation. As Dr. Cambareri reported, ivosidenib is the first and only targeted therapy approved for patients with previously treated *IDH1*-mutated cholangiocarcinoma. Results of the pivotal ClarIDHy trial showed a progression-free survival of 2.7 months with ivosidenib vs. 1.4 months with placebo (Abou-Alfa et al., 2020).

Disclosure

The presenter had no conflicts of interest to disclose.

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