

2018–2019 Drug Updates in Solid Tumors

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

<https://doi.org/10.6004/jadpro.2020.11.3.8>

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Abstract

Sally Barbour, PharmD, BCOP, CPP, FHOPA, updated attendees on the FDA-approved therapies for initial or expanded indications for solid tumors across the past year, as well as their supporting clinical trial data and best practices for safe and effective dosing and administration, drug monitoring, and adverse event management.

Targeted agents and immunotherapy continue to redefine the oncology treatment landscape but have also introduced a slew of side effects that pose unique challenges for providers. At JADPRO Live 2019, Sally Barbour, PharmD, BCOP, CPP, FHOPA, reviewed the pharmacology of oncology agents approved between September 27, 2018, and September 26, 2019. Dr. Barbour also discussed literature supporting the approval of the agents and clinical pearls to guide the management of adverse events (Table 1).

CEMIPLIMAB

Cemiplimab, a new programmed cell death protein 1 (PD-1) antibody, was approved in September 2018 for the treatment of metastatic cutaneous squamous cell carcinoma or locally advanced cutaneous squamous cell carcinoma in patients who are not candidates for curative surgery or radiation. As Dr. Barbour, Director of

Oncology Pharmacy Programs and clinical pharmacist at Duke University Hospital, reported, data that led to the approval of cemiplimab were based on two studies: a phase I study looking at cemiplimab in patients with a variety of solid tumors and a phase II study looking at cemiplimab in patients specifically with cutaneous squamous cell carcinoma. In the phase II study, objective response was between 47% and 50% (Migden et al., 2018).

“We tend to forget how amazing the effectiveness of these drugs can be,” said Dr. Barbour. “Patients who respond to treatment tend to have a fairly durable response.”

As with all checkpoint inhibitors, immune-related adverse events need to be monitored appropriately, said Dr. Barbour, who noted that the majority of patients experienced some kind of side effect.

“Patients need to be educated about potential side effects and know when to call,” she continued. “How-

Table 1. New Drug Approvals in Solid Tumors: September 2018 to September 2019

Generic name	Brand name	Approval date
<i>Novel mechanism</i>		
Larotrectinib	Vitrakvi	November 2018
Erdafitinib	Balversa	April 2019
Pexidartinib	Turalio	August 2019
Entrectinib	Rozlytrek	August 2019
<i>Biosimilar approval</i>		
Trastuzumab-pkrb	Herzuma	December 2018
<i>Established mechanism</i>		
Cemiplimab-rwlc	Libtayo	September 2018
Dacomitinib	Vizimpro	September 2018
Talazoparib	Talzenna	October 2018
Lorlatinib	Lorbrena	November 2018
Trastuzumab and hyaluronidase-oysk	Herceptin Hylecta	February 2019
Alpelisib	Piqray	May 2019
Darolutamide	Nubequ	July 2019

Note. Information from U.S. Food & Drug Administration (2019).

ever, the number of patients who had to stop treatment due to toxicity was pretty low.”

Cemiplimab is the only PD-1 inhibitor approved for metastatic or locally advanced cutaneous squamous cell carcinoma.

DACOMITINIB

As Dr. Barbour reported, EGFR is detectable in approximately 80% to 85% of patients with non–small cell lung cancer (NSCLC). The two main mutations that activate EGFR confer drug sensitivity—exon 19 deletions (45%) and exon 21 L858R mutations—are present in up to 20% of patients with NSCLC.

Dacomitinib is a second-generation EGFR inhibitor and was approved in September 2019 based on phase III data that showed a benefit in progression-free survival vs. gefitinib (14.7 months vs. 9.2 months) in first-line NSCLC (Mok et al., 2018). Side effects observed on dacomitinib were typical of this class of agents and included rash and diarrhea.

Although dacomitinib was approved in the first-line treatment of metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substi-

tion mutations, Dr. Barbour noted that osimertinib should be standard of care.

LORLATINIB

Lorlatinib is a third-generation tyrosine kinase inhibitor with activity against *ALK* and *ROS1* as well as various other mutations. It was approved in November 2018 for the treatment of *ALK*-positive metastatic NSCLC following disease progression on crizotinib and at least one other *ALK* inhibitor, or alectinib or ceritinib as first therapy. As Dr. Barbour reported, *ALK* activation is found in approximately 3% to 5% of patients with NSCLC. Approval for lorlatinib came from a phase II study that enrolled patients into six different expansion cohorts on the basis of *ALK* and *ROS1* status and previous therapy (Solomon et al., 2018). Data from the study showed an overall response rate of 47% as well as several complete responses.

“The exciting thing about lorlatinib is that even patients who had every possible *ALK* inhibitor still responded to this drug,” said Dr. Barbour. “We also saw a very good rate of intracranial response.”

According to Dr. Barbour, however, there are side effects to be aware of, namely hypercholesterolemia and hypertriglyceridemia. The median time to the onset of grade 3 or 4 hypercholesterolemia and hypertriglyceridemia was 15 days for both. Approximately 7% of patients required temporary discontinuation, and 80% of patients required initiation of lipid-lowering medications, said Dr. Barbour. In addition, overall central nervous system (CNS) effects occurred in more than half of patients, and 9% of patients required temporary discontinuation for a CNS effect.

TALAZOPARIB

Talazoparib, a PARP inhibitor, was approved in October 2018 for the treatment of deleterious or suspected germline *BRCA*-mutated *HER2*-negative locally advanced or metastatic breast cancer. As Dr. Barbour reported, approval was based on a phase III study that randomized patients with advanced breast cancer with this germline mutation to receive either talazoparib or standard single-agent chemotherapy. Data showed a 3-month improvement in progression-free survival on talazoparib vs. standard chemotherapy (Litton et al., 2018).

The most common adverse events seen on talazoparib were anemia, fatigue, and nausea. Surprisingly, said Dr. Barbour, 55% of patients in the study arm had a grade 3 or 4 hematologic adverse event, which is “unusual for an oral agent,” and 9% of patients had to discontinue treatment due to toxicity.

ALPELISIB

Alpelisib, a PI3K inhibitor, was approved in May 2019 in combination with fulvestrant for the treatment of postmenopausal women and men with hormone receptor–positive, HER2-negative, *PIK3CA*-mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen. As Dr. Barbour explained, PI3K plays a role again in downstream signaling resulting in tumor growth and progression of cancer cells.

Approval came from the phase III, randomized SOLAR-1 study that looked at the efficacy and safety of alpelisib in combination with fulvestrant or placebo in combination with fulvestrant (André et al., 2019). In *PIK3CA*-mutated patients, investigators observed a significant benefit in progression-free survival with alpelisib compared with the control arm (11 months vs. 5.7 months). However, as Dr. Barbour reported, 25% of patients had to discontinue treatment due to adverse events. The most common side effects of alpelisib are hyperglycemia, rash, and diarrhea.

Regarding rash, which was observed in more than half of patients, Dr. Barbour noted that a subgroup receiving prophylaxis with antihistamines reported rash less frequently (27% vs. 54%). It is now standard to initiate an antihistamine prior to patients’ starting on this medication, said Dr. Barbour. Regarding hyperglycemia, Dr. Barbour said that 87% of patients are managed with antidiabetic medication. “It’s critical that these patients are followed closely,” she emphasized.

DAROLUTAMIDE

Darolutamide, a competitive antigen-receptor inhibitor, was approved in July 2019 for the treatment of nonmetastatic castration-resistant prostate cancer based on a phase III, multicenter, double-blinded, placebo-controlled study in men who are at high risk for the development of metastases (Fizazi et al., 2019).

As Dr. Barbour reported, metastasis-free survival was significantly better in the darolutamide arm compared to placebo (40.4 months vs. 18.4 months), and progression-free survival was improved as well. Adverse events of darolutamide included fatigue, pain, rash, and some lab abnormalities, but these were manageable, said Dr. Barbour.

“In talking to our pharmacists, one of the benefits they’ve seen with darolutamide is less fatigue and CNS side effects compared to some of the other agents that they have used for the same patient population,” she added.

ENTRECTINIB

As Dr. Barbour explained, gene fusions involving *NTRK* (neurotrophic receptor tyrosine kinase) genes result in the expression of chimeric TRK proteins with uncontrolled kinase activity, which can lead to a variety of different tumor types.

Entrectinib, which was approved in August 2019, inhibits multiple receptors, including tropomyosin receptor tyrosine kinases (TRK), ROS1, ALK, JAK2, and TNK2.

Entrectinib is approved for adult and pediatric patients 12 years of age and older with solid tumors that have an *NTRK* gene fusion without a known acquired resistance mutation, are metastatic or in whom surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory standard therapy. It is also indicated in adults with metastatic NSCLC whose tumors are *ROS1* positive.

As Dr. Barbour reported, approval was based on an interim analysis of three, small, single-arm clinical trials encompassing 12 different tumor types. The overall response rate was 78%, and response duration was 12 months or longer for 55% of patients.

LAROTRECTINIB

Another drug in this class of TRK inhibitors, larotrectinib, was approved in November 2019 for adult and pediatric patients with solid tumors who have an *NTRK* gene fusion without a known acquired resistance mutation, are either metastatic or in whom surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment.

As Dr. Barbour reported, approval was based on an evaluation of the first 55 patients who had solid tumors with this mutation (Drilon et al., 2018). Similarly to entrectinib, a variety of different tumor types were represented in this study despite being a rare mutation.

Overall response rate was 75% (22% complete responses and 53% partial responses). Response duration was 6 months or longer for 73%, nine months or longer for 63%, and 12 months or longer for 39% of patients, said Dr. Barbour.

ERDAFITINIB

Finally, erdafitinib is a fibroblast growth factor receptor (FGFR) kinase inhibitor that is approved for second-line treatment of locally advanced or metastatic urothelial carcinoma that has susceptible *FGFR2* or *FGFR3* genetic alterations and progressed during or following at least one line of prior platinum-containing chemotherapy.

Approval was based on phase II data that showed an overall response rate of 42% but only a 3% complete response rate (Siefker-Radtke et al., 2018). Among patients who had received prior immune checkpoint inhibitors, however, overall response rate was 70%, said Dr. Barbour. The most common adverse events on erdafitinib included hyperphosphatemia (69%), stomatitis (47%), and diarrhea (42%). ●

Disclosure

Dr. Barbour has consulted for Astellas, Eisai, Genentech, Heron Therapeutics, and Seattle Genetics.

References

- André, F., Ciruelos, E., Rubovszky, G., Campone, M., Loibl, S., Rugo, H. S.,...Juric, D. (2019). Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *New England Journal of Medicine*, 380(20), 1929–1940. <http://doi.org/10.1056/NEJMoa1813904>
- Drilon, A., Laetsch, T. W., Kummar, S., DuBois, S. G., Lassen, U. N., Demetri, G. D.,...Hyman, D. M. (2018). Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *New England Journal of Medicine*, 378(8), 731–739. <http://doi.org/10.1056/NEJMoa1714448>
- Fizazi, K., Shore, N., Tammela, T. L., Ulsy, A., Vjaters, E., Polyakov, S.,...Smith, M. R. (2019). Darolutamide in non-metastatic, castration-resistant prostate cancer. *New England Journal of Medicine*, 380(13), 1235–1246. <http://doi.org/10.1056/NEJMoa1815671>
- Litton, J. K., Rugo, H. S., Ettl, J., Hurvitz, S. A., Goncalves, A., Lee, K. H.,...Blum, J. L. (2018). Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *New England Journal of Medicine*, 379(8), 753–763. <http://doi.org/10.1056/NEJMoa1802905>
- Migden, M. R., Rischin, D., Schmults, C. D., Guminski, A., Hauschild, A., Lewis, K. D.,...Fury, M. G. (2018). PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *New England Journal of Medicine*, 379(4), 341–351. <http://doi.org/10.1056/NEJMoa1805131>
- Mok, T. S., Cheng, Y., Zhou, X., Lee, K. H., Nakagawa, K., Niho, S.,...Wu, Y.-L. (2018). Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non-small-cell lung cancer and EGFR-activating mutations. *Journal of Clinical Oncology*, 36(22), 2244–2250. <http://doi.org/10.1200/JCO.2018.78.7994>
- Siefker-Radtke, A. O., Necchi, A., Park, S. H., Garcia-Donas, J., Huddart, R. A., Burgess, E. F.,...Loriot, Y. (2018). First results from the primary analysis population of the phase 2 study of erdafitinib (ERDA; JNJ-42756493) in patients (pts) with metastatic or unresectable urothelial carcinoma (mUC) and FGFR alterations (FGFRalt). *Journal of Clinical Oncology*, 36(15), 4503–4503. http://doi.org/10.1200/JCO.2018.36.15_suppl.4503
- Solomon, B. J., Besse, B., Bauer, T. M., Felip, E., Soo, R. A., Camidge, D. R.,...Shaw, A. T. (2018). Lorlatinib in patients with ALK-positive non-small-cell lung cancer: Results from a global phase 2 study. *Lancet Oncology*, 19(12), 1654–1667. [http://doi.org/10.1016/S1470-2045\(18\)30649-1](http://doi.org/10.1016/S1470-2045(18)30649-1)
- U.S. Food & Drug Administration. (2019). Hematology/Oncology (Cancer) Approvals & Safety Notifications. <https://www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications>