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OncoHealth FDA Oncology Drug Approvals Report: Q2 2021

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Executive Summary

FDA approval activity in Q2 2021 showed a steady rise in the use of accelerated approval for oncology treatments as the battle against cancer continues. Fifty percent (seven of 14) new oncology indications received accelerated approvals in the quarter – up 14 percent (from 36 percent) from the same quarter in 2020. In the past two years, the FDA has granted 38 accelerated approvals in oncology from July 2019 to June 2021.[1]

Approximately 85% of accelerated approvals in the past 10 years have been granted in oncology.[2] Although there is no debate that cancer has a very high burden of unmet medical need, many are beginning to question the value of these approvals even as they become increasingly commonplace.

FDA activity over the past two years has provided cancer patients with more treatment options than ever before. Despite the agency's appropriate preoccupation with the coronavirus pandemic, the FDA has approved 66 oncology-related drug indications in 2020 alone, far surpassing 2019's pre-pandemic number of 42. Within the first half of 2021, 34 new oncology indications have already been FDA approved, 14 of which occurred in the second quarter of 2021.[1]

In addition to the rise in accelerated approvals, two other trends were evident in regard to oncology FDA approvals in Q2 2021. Immune checkpoint inhibitor expansion in indications and precision medicine approvals both dominated the quarter.

Rise in Accelerated Approvals [1-6]

The FDA accelerated approval pathway expedites authorization of new therapies that show clinical promise in addressing an unmet medical need, based on surrogate endpoints such as overall response rate (ORR) and duration of response (DOR). Drugs with accelerated approval are subject to post-marketing research to confirm safety and efficacy. As the FDA ramps up accelerated approvals, these new indications are being accepted with cautious optimism.

In April, the FDA's Oncology Drugs Advisory Committee (ODAC) reviewed six immune checkpoint inhibitors that received accelerated approval. The members of ODAC voted to continue support of four of the six indications, despite their having failed to meet endpoints in confirmatory clinical trials. Subsequently, the manufacturers for three of the six indications have initiated market withdrawal: (1) nivolumab in previously treated hepatocellular carcinoma, (2) pembrolizumab in third line or later PD-L1 positive metastatic gastric or gastroesophageal junction adenocarcinoma, (3) atezolizumab plus nab-paclitaxel in PD-L1 positive metastatic triple negative breast cancer. Two of these three indications recently withdrawn had been on the market since 2017. This delay in confirmatory trial results, and lack of swift action by the FDA when subsequent studies fail, has led some to question whether the FDA has allowed their evidence standards to become too permissive and inconsistent.

Below are examples of therapies that received accelerated approval in the second quarter of 2021.

Infigratinib (Truseltiq) [7-13]

On May 28, 2021, the FDA granted accelerated approval to infigratinib (Truseltiq) for adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement. FGFR2 gene fusions or rearrangements are the most common oncogenic drivers in intrahepatic cholangiocarcinoma, occurring in 10-15% of patients, although almost no extrahepatic cholangiocarcinomas have FGFR2 alterations.

Efficacy was demonstrated in a phase 2 open-label, single-arm trial, evaluating 108 patients with previously treated, advanced/metastatic cholangiocarcinoma with an FGFR2 fusion or rearrangement. The ORR was 23%, with one complete response and 24 partial responses. Median duration of response (DOR) was five months. Median duration of treatment was 5.5 months. Serious risks include ocular toxicity with Retinal Pigment Epithelial Detachment (RPED) and hyperphosphatemia.

Infigratinib is the second pan-fibroblast growth factor receptor (FGFR) kinase inhibitor on the market, joining pemigatinib (Pemazrye) which was FDA approved April 2020 for the same indication in previously treated patients. Infigratinib and pemigatinib are second-line options for cholangiocarcinoma with FGFR2 fusion or rearrangement following progression on first-line chemotherapy (e.g., gemcitabine plus cisplatin, 5-FU plus oxaliplatin).

Efficacy and toxicity appear very similar between infigratinib and pemigatinib as seen below.

	Infigratinib (CBGJ398X2204 trial)	**Pemigatinib (FIGHT-202 trial)**
Dose	125 mg PO daily for 21 days, then 7 days off therapy, in 28-day cycles	13.5 mg PO daily for 14 days, then 7 days off therapy, in 21-day cycles
ORR	23%	36%
DOR	5 months	9.1 months
Progression-Free Survival	7.3 months	6.9 months
Overall Survival	12.2 month	21.1 months
Toxicity	Hyperphosphatemia (90%), RPED (11%), diarrhea (24%), palmar-plantar erythrodysesthesia (33%)	Hyperphosphatemia (94%), RPED (6%), diarrhea (47%), palmar-plantar erythrodysesthesia (15%)
Median Duration of Therapy	5.5 months	181 days
Dose Interruptions	64%	43%
Dose Reductions	60%	14%

	Infigratinib (CBGJ398X2204 trial)	Pemigatinib (FIGHT-202 trial)
Discontinuation rate	15%	9%
Est. Monthly Cost (AWP)	$25,800	$27,200

Given their similar FDA indications, limited efficacy data based on accelerated approval, common mechanism of action, and consistent toxicity profiles, health plans may explore preferring either infigratinib or pemigatinib through a step therapy initiative. High levels of use are not expected for either agent given the rarity of the tumor subtype.

Pemigatinib has been approved for over a year with the same indication. Accelerated approvals are granted for therapies that meet an "unmet need." The FDA's definition of unmet need is a question that arises in cases where alternative therapeutic options are available. Accelerated approvals are very helpful to expedite new therapeutic options to market for cancer patients in times of need, when no alternative treatments are available. On the other hand, what is the true value in expediting a therapy to market via the accelerated approval pathway when it has similar efficacy and safety data as compared to alternatives?

Dostarlimb-gxly (Jemperli) [14-19]

On April 22, 2021, the FDA granted accelerated approval to the PD-1 inhibitor, dostarlimab-gxly (Jemperli), for adults with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer that has progressed on or following a prior platinum-based regimen. Up to one third of endometrial carcinomas are dMMR.

Efficacy was evaluated in the 71 patients enrolled in the phase I GARNET trial. Participants in the trial had dMMR recurrent or advanced endometrial cancer following platinum-based therapy with no more than 2 lines of therapy for advanced disease. Confirmed ORR was 42.3%. Complete response rate was 12.7% and partial response rate was 29.6%. Median DOR was not reached, with 93.3% of patients having durations ≥6 months.

Dostarlimab is the seventh PD-1/PD-L1 inhibitor to be approved in the US. It is also the third PD-1 inhibitor recommended by NCCN as a single agent in the second-line treatment of dMMR recurrent or advanced endometrial carcinoma, as shown in the table below.

dMMR Endometrial Cancer Data	Dostarlimab (GARNET, n=103)	Pembrolizumab* (KEYNOTE-158, n=49)
ORR	46% (11% CR)	57% (8% CR)

dMMR Endometrial Cancer Data	Dostarlimab (GARNET, n=103)	Pembrolizumab* (KEYNOTE-158, n=49)
Median PFS	NA	25.7 months
18 month DOR	79%	NA
NCCN Support	Useful in certain circumstances as **second-line** treatment for patients with **dMMR** recurrent or advanced disease that has progressed on or following **prior** treatment with a **platinum-containing regimen** (2A)	Useful in certain circumstances as a single agent **second-line** treatment for (1) unresectable or metastatic tumor mutational burden-high **(TMB-H)** (≥10 mut/Mb) tumors, that have progressed following prior treatment and who have no satisfactory alternative treatment options; (2) recurrent, metastatic, or high-risk **microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)** tumors that have progressed following prior treatment (2A)

The most touted benefit of dostarlimab is its high ORR as compared to chemotherapy alternatives and its durability of response, also seen with other PD-1 inhibitors. The number of endometrial carcinoma patients studied under clinical trial with dostarlimab is higher as compared to other PD-1 inhibitors. Pembrolizumab may remain the more commonly used PD-1 inhibitor in dMMR/MSI-H endometrial cancer. Any striking differences between pembrolizumab and dostarlimab are not obvious based on clinical trial results published to date.

Oncology drugs tend to enter the market at a very high price tag. Those with accelerated approval are no exception with no discount for the uncertainty around their effectiveness. Dostarlimab pricing is similar to other single-agent immune checkpoint inhibitors at roughly $13,867 per month. Competition is not driving down oncology drug prices, outside of the introduction of biosimilars. Health plans are asking what more can be done to blunt the ever-rising costs of cancer care. Here, one may consider preferring one immune checkpoint inhibitor regimen over others or explore value-based contracts.

Immune Checkpoint Inhibitor Advances [1, 20-21]

Immune checkpoint inhibitors (e.g., pembrolizumab, nivolumab, dostarlimab) continue to expand in use, solidifying their place as standard of care in over 17 different tumor types and two tumor-agnostic indications—significantly improving the outcomes of cancer patients. One study estimated that the

number of cancer patients with a tumor type and/or biomarker eligible for an immune checkpoint inhibitor increased from 1.5% in 2011 to 43.6% in 2018 alone.

Almost a third (29%) of new oncology indications during the second quarter of 2021 involved an immune checkpoint inhibitor, up from 25% during the same quarter of 2020. A consistent theme has emerged—roughly one in four FDA approvals contains an immune checkpoint inhibitor.
The FDA approved four new immune checkpoint inhibitor-based oncology uses in the second quarter of 2021.

Immune Checkpoint Inhibitor	FDA indication	Combination or Monotherapy	FDA Approval Date
Nivolumab	In combination with fluoropyrimidine- and platinum-containing chemotherapy for advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma	Combination Therapy	April 16, 2021
Dostarlimab-gxly	For adults with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer that has progressed on or following a prior platinum-containing regimen	Monotherapy	April 22, 2021 *Accelerated Approval*
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 (GEJ) adenocarcinoma	Combination Therapy	May 5, 2021 *Accelerated Approval*
Nivolumab	For patients with completely resected esophageal or gastroesophageal junction (GEJ) cancer with residual pathologic disease who have received neoadjuvant chemoradiotherapy	Monotherapy	May 20, 2021

Monotherapy immune checkpoint inhibitor approvals are declining, while combination regimens are on the rise. Half of new immune checkpoint inhibitor approvals were for combination regimens in the second quarter of 2021, a striking increase from only 33% combination therapy approvals in the second quarter of 2020. This trend will only continue. As of September 2020, 2,949 out of the 3,674 active clinical trials including a PD-1/PD-L1 immune checkpoint inhibitor are evaluating the agent in combination with over 200 different drug mechanisms. The growth in combination therapy trials is far

outpacing that of monotherapy.[A] Combination immune checkpoint inhibitor regimens are expected to increase treatment costs and toxicity, potentially driving health plans to evaluate new models for managing costs and measuring quality of care.
Below is an example of a combination immunotherapy regimen approved in the second quarter of 2021.

Nivolumab (Opdivo) Plus Chemotherapy [22-23]

On April 16, 2021, the FDA approved nivolumab (Opdivo) in combination with fluoropyrimidine- and platinum-containing chemotherapy for advanced or metastatic gastric cancer, gastroesophageal junction (GEJ) cancer, and esophageal adenocarcinoma.

Approval was based on the CHECKMATE-649 trial that enrolled 1,581 patients with previously untreated advanced or metastatic gastric cancer, GEJ, or esophageal adenocarcinoma. Patients received either nivolumab in combination with mFOLFOX6 (5-FU, leucovorin, and oxaliplatin) or CapeOx (capecitabine and oxaliplatin) or chemotherapy alone. There was a statistically significant improvement in the primary endpoints of PFS and OS in those with PD-L1 CPS ≥ 5.

CHECKMATE-649	Nivolumab + Chemotherapy (n=789)	Chemotherapy (n=792)
Overall Survival (OS)		
PD-L1+ CPS ≥ 5	14.4 months	11.1 months
	HR 0.71; 95% CI: 0.61, 0.83; p<0.0001	
All randomized patients	13.8 months	11.6 months
	HR 0.80; 95% CI: 0.71, 0.90; p=0.0002	
Progression-Free Survival (PFS)		
	7.7 months	6.0 months
	HR 0.68; p<0.0001	

Nivolumab demonstrated an overall survival benefit, exceeding 1 year in the first-line setting for patients with non-HER2-positive gastric, GEJ, or esophageal adenocarcinoma as demonstrated in the main efficacy outcome in those PD-L1 positive with a CPS ≥ 5, as well as in all randomized patients.

However, the unstratified hazard ratio for OS with nivolumab plus chemotherapy versus chemotherapy for patients with a PD-L1 CPS < 1 was 0.92 and for those with a PD-L1 CPS < 5 was 0.94. These PD-

L1 negative patients or those with a PD-L1 CPS < 5 did not experience an improvement in overall survival with the addition of nivolumab. An unanswered question is whether the PD-L1 CPS ≥ 5 population (60% of all randomly assigned patients) were the main drivers of the 2.2 month absolute overall survival benefit seen in all randomized patients, irrespective of PD-L1 status.

From a managed care perspective, these nuances are of interest as the FDA and NCCN Compendium differ in support for this particular use of nivolumab. The FDA indication for nivolumab plus chemotherapy in metastatic gastric cancer, GEJ, and esophageal adenocarcinoma is irrespective of PD-L1 status, while NCCN supports nivolumab for PD-L1 positive patients in combination with oxaliplatin and fluorouracil or capecitabine as preferred category 1 for PD-L1 CPS ≥ 5, and useful in certain circumstances category 2B for PD-L1 CPS 1-4. Given this, a health plan may consider requiring a certain degree of PD-L1 positivity based on NCCN's recommendation for commercial members; unfortunately, this approach would create coverage that differs by line of business as Medicare coverage would default to the broader FDA indication without respect to PD-L1 status.

Novel Precision Medicine Approvals [1, 24-25]

Oncologists are increasingly turning to germline and somatic tumor testing to better inform treatment decisions. Providers are refining treatment approaches, leveraging molecular tumor boards, and customizing cancer care to an individual tumor's molecular fingerprint. Genetic testing use, especially with broad panel next generation sequencing will only grow throughout 2021.

In the second quarter of 2021, 43% of approved oncology indications were biomarker dependent. Two of the seven new molecular entities (NMEs), or brand new to market oncology drugs approved in the second quarter of 2021 included new molecular targets in advanced/metastatic non-small cell lung cancer (NSCLC). New targeted drugs are also commonly being approved with an FDA designated companion diagnostic.

From the managed care perspective, health plans need to ensure the appropriate biomarker result is present prior to authorization of biomarker-dependent therapy. If therapy is administered without the respective biomarker expression needed to elicit response, cancer patients may be exposed to potentially harmful and ineffective therapies. On the other hand, transparency into the patient's molecular and genetic makeup can help health plans identify potentially more efficacious and cost-effective therapy, should a more appropriate targeted therapy be available for an individual's tumor. Below are two noteworthy precision medicine approvals in the second quarter of 2021.

Sotorasib (Lumakras) [26-30]

On May 28, 2021, the FDA granted accelerated approval to sotorasib (Lumakras), a RAS GTPase family inhibitor, for adults with KRAS G12C-mutated locally advanced/metastatic non-small cell lung

cancer (NSCLC) who received at least one prior systemic therapy. KRAS G12C accounts for roughly 13% of NSCLC mutations.

Sotorasib demonstrated an ORR of 36% with a median duration of response of 10 months in the open-label, single-arm CodeBreaK 100 trial. Here, Sotorasib was evaluated in 124 patients with locally advanced or metastatic NSCLC with KRAS G12C mutations whose disease had progressed on or after at least one prior systemic therapy.

Sotorasib is the first therapy against a promising tumor target once deemed undruggable – KRAS. A number of followers are waiting in the wings. For example, adagrasib is an investigational agent with breakthrough therapy designation that is aiming for the same KRAS G12C–mutated NSCLC indication. From the managed care perspective, line of therapy is key here. Most drugs targeting a driver mutation in advanced NSCLC are given first-line—not this one. Sotorasib is approved second-line or later. Disease progression on prior therapy for advanced NSCLC must be confirmed.

Interestingly, the FDA is requiring a post-marketing trial to investigate whether a lower dose will have a similar clinical effect. The manufacturer intends to proceed with a trial to compare the safety and efficacy of sotorasib 960 mg versus 240 mg orally once daily with results anticipated late 2022.

At a price of roughly $17,900 a month, only about one third of patients treated with sotorasib had a partial or complete response. Fifty percent experienced a serious adverse reaction. 3.4% of all patients experienced a fatal adverse reaction. If the FDA is questioning the appropriate dose, are we subjecting patients to unnecessary toxicity at the approved dose in the setting of an incurable tumor? We'll have to wait a year to find out.

Amivantamab-vmjw (Rybrevant) [31-37]

On May 21, 2021, the FDA granted accelerated approval to amivantamab-vmjw (Rybrevant), an intravenous bispecific EGFR and MET receptor-directed antibody, for adults with locally advanced/metastatic NSCLC with EGFR exon 20 insertion mutations following platinum-based chemotherapy. Tumors with EGFR exon 20 insertion mutations represent less than 3% of all NSCLC and are commonly unresponsive to existing EGFR tyrosine kinase inhibitors, such as erlotinib, that target EGFR exon 19 deletions and exon 21 L858R mutations.

Amivantamab demonstrated an ORR of 40% with a median response duration of 11.1 months based on data from the phase I CHRYSALIS trial in 81 advanced NSCLC patients with EGFR exon 20 insertion mutations and disease progression following platinum-based chemotherapy.

CHRYSALIS Trial	Amivantamab in Prior Platinum-based Chemotherapy Treated (N=81)
Overall Response Rate (95% CI)	40% (29%, 51%)
Complete response (CR)	3.7%
Partial response (PR)	36%
Duration of Response (DOR)	
Median, months (95% CI), months	11.1 (6.9, NE)
Patients with DOR ≥6 months	63%

This signifies the first approval of treatment targeting EGFR exon 20 insertion mutations for advanced NSCLC, and it wasn't the only agent for long. Mobocertinib, on oral EGFR kinase inhibitor, later obtained accelerated approval on September 15, 2021 for the same indication as amivantamab.

Amivantamab costs roughly $57,340 for the first month, and $28,670 per month from the second month forward. Mobocertinib is not far off at roughly $25,000 per month at Wholesaler Acquisition Cost.

While the FDA indication for amivantamab requires use following disease progression on or after platinum-based chemotherapy, the NCCN Compendium expands coverage, supporting amivantamab as "subsequent therapy" without respect to prior platinum chemotherapy. Essentially NCCN supports off-label coverage in chemotherapy naive patients that received prior single-agent immune checkpoint inhibitor for PD-L1+ disease. While most EGFR-targeted therapies are used first-line, prior to chemotherapy or chemo-immunotherapy for metastatic NSCLC, amivantamab is not. Amivantamab is only approved in the second-line or later setting.

Conclusion [37]

Oncology will continue to represent one of the largest components of total healthcare spend. Oncology costs are expected to rise 9-12% annually through 2025, exceeding $260 billion globally. Accelerated approvals are on the rise, leaving many with unanswered clinical questions; immune checkpoint inhibitors continue to expand in use within the oncology market, anticipated to account for 20% of all global oncology spend by 2025; and precision medicine approvals dominated the second quarter of 2021 FDA oncology approvals.

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References:

1. https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications
2. https://www.nejm.org/doi/full/10.1056/NEJMp2104846
3. https://icer.org/wp-content/uploads/2021/04/Strengthening-the-Accelerated-Approval-Pathway-_-ICER-White-Paper-_-April-2021.pdf
4. https://www.pharmacytimes.com/view/value-based-contracting-in-oncology
5. https://www.astrazeneca.com/media-centre/press-releases/2021/voluntary-withdrawal-imfinzi-us-bladder-indication.html
6. https://pubmed.ncbi.nlm.nih.gov/28817753/
7. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-infigratinib-metastatic-cholangiocarcinoma
8. https://www.truseltiq.com/pdfs/prescribing-information.pdf
9. https://www.onclive.com/view/fda-approves-infigratinib-for-cholangiocarcinoma
10. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pemigatinib-cholangiocarcinoma-fgfr2-rearrangement-or-fusion
11. https://www.pemazyre.com/pdf/prescribing-information.pdf
12. https://www.onclive.com/view/pemigatinib-trial-seeks-to-build-on-targeted-advances-in-cholangiocarcinoma
13. https://www.targetedonc.com/view/fgfr-inhibitors-make-inroads-in-cholangiocarcinoma
14. https://www.annalsofoncology.org/article/S0923-7534(20)42348-8/fulltext
15. https://jamanetwork-com.ezproxylocal.library.nova.edu/journals/jamaoncology/fullarticle/2771011
16. https://pubmed.ncbi.nlm.nih.gov/31682550/
17. https://pubmed.ncbi.nlm.nih.gov/31765263/
18. https://clinicaltrials.gov/ct2/show/NCT03981796
19. https://www.fiercepharma.com/manufacturing/glaxosmithkline-s-pd-1-hopeful-dostarlimab-fell-victim-to-covid-related-inspection
20. https://www.nature.com/articles/s41571-019-0260-y
21. https://www.nature.com/articles/d41573-020-00204-y
22. https://pubmed.ncbi.nlm.nih.gov/34102137/
23. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-combination-chemotherapy-metastatic-gastric-cancer-and-esophageal
24. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01099-0/fulltext
25. https://www.ajmc.com/view/how-advances-in-precision-oncology-new-diagnostic-and-treatment-frontier
26. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-sotorasib-kras-g12c-mutated-nsclc
27. https://ascopost.com/issues/june-10-2021/updated-information-on-sotorasib-dose-comparison-study/
28. https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/lumakras/lumakras_pi_hcp_english.ashx
29. https://www.managedhealthcareexecutive.com/view/positive-results-reported-for-lumakras-kras-targeting-lung-cancer-drug-at-asco
30. https://www.nejm.org/doi/full/10.1056/NEJMoa1917239
31. https://www.fda.gov/news-events/press-announcements/fda-approves-first-targeted-therapy-subset-non-small-cell-lung-cancer
32. https://www.takeda.com/newsroom/newsreleases/2021/takeda-announces-u.s.-fda-grants-priority-review-for-new-drug-application-for-mobocertinib-tak-788-as-a-treatment-for-egfr-exon20-insertion-metastatic-non-small-cell-lung-cancer/
33. https://pubmed.ncbi.nlm.nih.gov/34339292/
34. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/RYBREVANT-pi.pdf
35. https://www.takeda.com/newsroom/newsreleases/2021/takeda-presents-updated-results-for-mobocertinib-further-substantiating-the-clinical-benefit-in-patients-with-egfr-exon20-insertion-mnsclc/
36. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-mobocertinib-metastatic-non-small-cell-lung-cancer-egfr-exon-20
37. https://www.takeda.com/4a641a/siteassets/en-us/home/corporate-responsibility/culture-of-compliance/state/co/exkivity-price-form.pdf
38. https://www.iqvia.com/insights/the-iqvia-institute/reports/global-oncology-trends-2021