Approvals in 2021: dangling Accelerated Approvals, drug dosing, new approvals and beyond

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In 2021, policy areas of focus for FDA Oncology included the Accelerated Approval programme, expanding eligibility criteria, dose optimization and patient-reported outcomes. The FDA continued to be active with approvals of both new drugs and supplementary applications, including three new chimeric antigen receptor T cell products, two antibody–drug conjugates and several new targeted agents.

> “This reappraisal of dangling Accelerated Approvals started with … anti-PD-(L)1 … antibodies, resulting in the voluntary withdrawal of four indications”

In 2021, the FDA initiated a reappraisal of drugs approved under the Accelerated Approval pathway for which the required post-marketing trials did not confirm benefit. For some of these indications the treatment paradigm had changed, necessitating a reconsideration of the place of these agents in the current treatment landscape. This reappraisal of dangling Accelerated Approvals started with anti-PD-1 or anti-PD-L1 (hereafter, anti-PD-(L)1) antibodies, resulting in the voluntary withdrawal of four indications: atezolizumab and durvalumab for urothelial carcinoma after platinum-based chemotherapy, and pembrolizumab and nivolumab as third-line therapies for small-cell lung cancer. Six additional indications were discussed during Advisory Committee meetings held on 27–29 April 2021[1]. Following the meetings, one additional indication was voluntarily withdrawn (nivolumab in hepatocellular carcinoma previously treated with sorafenib), with the planned withdrawal of another (pembrolizumab as third-line therapy for PD-L1$^+$ gastric cancer[2]). The Advisory Committees voted to recommend retaining the remaining four indications pending the assessment of subsequent data, which included atezolizumab or pembrolizumab for urothelial carcinoma not eligible for cisplatin-containing chemotherapy, atezolizumab for PD-L1$^+$ triple-negative breast cancer, and pembrolizumab for hepatocellular carcinoma previously treated with sorafenib.

Since these meetings, the manufacturer of romidepsin has voluntarily withdrawn the relapsed or refractory (R/R) peripheral T cell lymphoma indication that had received Accelerated Approval. In addition, the manufacturer of panobinostat (which had received Accelerated Approval for R/R multiple myeloma) announced that they requested that the FDA withdraw the approval of the New Drug Application for panobinostat[3].

Of the ten dangling Accelerated Approvals for anti-PD-(L)1 antibodies discussed, nine had been approved on the basis of results from single-arm trials using objective response rate (ORR) and duration of response as end points. Seven of the indications had ORRs of 10–20%. Considering this information, the FDA held an additional Advisory Committee meeting on 24 June 2021 to discuss the licensing application of retifanlimab for advanced-stage anal cancer. This agent has a reported ORR of 13.8%, and thus the committee voted 13 to 4 to recommend delaying approval pending completion of the sponsor’s ongoing randomized trial[4]. During this meeting, the FDA stressed the need for early initiation of randomized trials as well as the fact that randomized studies also can support Accelerated Approvals — for example, through interim analysis of ORRs[4]. Such an approach had supported the approval of pembrolizumab in combination with trastuzumab and chemotherapy for HER2$^+$ gastric cancer on 5 May 2021.

During 2021, the FDA continued its efforts to encourage expansion of trial eligibility criteria and promote the enrolment of diverse trial populations to ensure that clinical trial results are applicable to the whole of the US population[5]. To facilitate enrolment in clinical trials, the FDA finalized a document providing guidance for the evaluation of patients with CNS metastases, and issued a draft guidance document addressing trial eligibility criteria based on prior therapies, to enable recruitment of patients who have not received all approved therapies[6]. The FDA also launched ‘Project Optimus’, intended to direct sponsors towards conducting adequate dose optimization during drug development[7]. For the May 2021 approval of sotorasib for metastatic non-small-cell lung cancers (NSCLCs) harbouring *KRAS*^{G12C} mutations, the FDA required a post-marketing study to evaluate lower doses[7]. Other guidance documents published by the FDA in 2021 included one facilitating the development of alternative dosing regimens for anti-PD-(L)1 immune-checkpoint inhibitors (ICIs)

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established on the basis of pharmacokinetic criteria, as well as another with recommendations regarding the collection of core patient-reported outcomes in clinical trials to further facilitate anticancer drug development and better support labelling claims[6].

Despite the continued COVID-19 pandemic in 2021, the FDA was active in approving new molecular entities (Supplementary Table 1). These include three chimeric antigen receptor T cell products: the CD19-targeted product lisocabtagene maraleucel for certain R/R B cell lymphomas, the BCMA-targeted product idecabtagene vicleucel for R/R multiple myeloma and the CD19-targeted product brexucabtagene autoleucel for R/R B cell precursor acute lymphoblastic leukaemia. In 2021, the FDA also approved two new antibody–drug conjugates (ADCs): the anti-tissue factor ADC tisotumab vedotin-tftv for recurrent or metastatic cervical cancer with disease progression on or after chemotherapy, and the anti-CD19 ADC loncastuximab tesirine-lpyl for R/R large B cell lymphomas after ≥2 lines of systemic therapy.

The FDA approved two new monoclonal antibodies in 2021. The first one, dostarlimab-gxly, is the seventh monoclonal anti-PD-(L)1 antibody approved by the FDA. This ICI was first approved for mismatch repair-deficient endometrial cancers progressing after platinum-based chemotherapy, and then for mismatch repair-deficient solid tumours in patients with disease progression on or following treatment and who have no satisfactory alternative treatment options. The second antibody, amivantamab-vmjw, was approved for locally advanced or metastatic NSCLC harbouring *EGFR* exon 20 insertion mutations progressing on or after platinum-based chemotherapy. This approval is the first for a monoclonal EGFR–MET bispecific antibody.

In 2021, the FDA continued to be active in the review of targeted anticancer therapies. Most of the new molecular entities approved as targeted therapies were for rare diseases, or rare or uncommon mutations that can occur in more common tumours. The FDA approved three small-molecule agents for subgroups of patients with advanced-stage NSCLC: mobocertinib for tumours with *EGFR* exon 20 insertion mutations, sotorasib for tumours with $KRAS^{G12C}$ mutations and tepotinib for tumours harbouring *MET* exon 14-skipping alterations. The FDA also approved infigratinib for advanced-stage cholangiocarcinomas harbouring *FGFR2* fusions or rearrangements. Other patient populations with rare cancers served by new-drug FDA approvals in 2021 include those with malignant perivascular epithelioid cell tumours and those with von Hippel–Lindau disease-associated cancers, for which sirolimus protein-bound particles for injectable suspension and the HIF2α inhibitor belzutifan, respectively, were approved. Finally, the FDA approved the multitarget tyrosine-kinase inhibitor tivozanib for R/R advanced-stage renal cell carcinoma following ≥2 prior systemic therapies.

New molecular entities approved in 2021 for haematological malignancies include the BCR–ABL inhibitor asciminib for Philadelphia chromosome$^+$ chronic myeloid leukaemia following ≥ 2 tyrosine-kinase inhibitors or harbouring the T315I mutation in *BCR–ABL1*, and the PI3Kδ/CK1ε inhibitor umbralisib for R/R marginal zone lymphoma after at least one prior anti-CD20-based regimen and R/R follicular lymphoma following ≥3 prior lines of systemic therapy. The FDA also approved asparaginase erwinia chrysanthemi (recombinant)-rywn for patients with acute lymphoblastic leukaemias or lymphoblastic lymphomas with hypersensitivity to *Escherichia coli*-derived asparaginase, and the ROCK inhibitor belumosudil for chronic graft-versus-host disease following ≥2 prior lines of systemic therapy.

Labelling expansions for PD-(L)1 ICIs, either as monotherapy or in combination with other drugs, continued in 2021 and included pembrolizumab, nivolumab, cemiplimab-rwlc and atezolizumab for various indications (Supplementary Table 1). Although >85 indications have been approved for drugs of this class, some reflect duplicative development efforts that might be diverting resources from clinical trials of innovative drugs[8]. Rather than duplicating clinical trials, FDA has publicly encouraged increased collaborations between companies to develop new drugs that, alone or in combination with ICIs (or other drugs as appropriate), will improve outcomes in patients with cancer[8].

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Competing interests
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