Approvals in 2016: the march of the checkpoint inhibitors

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In 2016, FDA Oncology approved five new molecular entities and 17 efficacy supplements, including six accelerated approvals, 17 priority reviews, and 11 approvals of breakthrough-designated therapies. The FDA also approved five companion diagnostics, including a liquid biopsy test. One new anti-PD-L1 antibody was approved, along with six supplementary approvals of anti-PD-1/PD-L1 antibodies.

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2016 saw the approval of new molecular entities for patients with urothelial carcinoma and for those with certain types of ovarian cancer or haematological cancer (Supplementary information S1 (table)). The FDA granted accelerated approval of the first anti-programmed cell death 1 ligand 1 (PD-L1) antibody, atezolizumab, for patients with locally advanced or metastatic urothelial carcinoma whose disease progressed during or following platinum-containing chemotherapy[1]. This approval decision was based on the overall response rate (ORR) and duration of response (DoR) observed in a single-arm trial[1,2]. A complementary diagnostic test, the Ventana PD-L1 (SP142) Assay, was also approved based on the finding that the ORR and DoR seem to be higher in patients with PD-L1 expression on ≥5% of tumour-infiltrating immune cells. To confirm and verify the clinical benefits of atezolizumab, the drug sponsor will submit the results of a randomized controlled trial (RCT) comparing the efficacy of atezolizumab with that of chemotherapy in patients with advanced-stage or metastatic urothelial carcinoma after progression on platinum-based chemotherapy.

The FDA also approved six efficacy supplements for previously approved anti-programmed cell death protein 1 (PD-1)/PD-L1 immune-checkpoint inhibitors, thus expanding their indications. After the accelerated approval of atezolizumab in urothelial carcinoma, this agent was granted regular approval for patients with metastatic non-small-cell lung cancer (NSCLC) after platinum-based therapy, based on data from an RCT demonstrating superior patient survival compared with treatment with docetaxel. For the anti-PD-1 antibody pembrolizumab, the FDA granted accelerated approval for the treatment of patients with refractory head-and-neck squamous-cell carcinoma (HNSCC) after platinum-containing chemotherapy, based on the ORR and DoR results from a single-arm study. An ongoing RCT investigating the efficacy of pembrolizumab versus that of chemotherapy will serve as the confirmatory study. Regular approval was also granted for use of pembrolizumab in patients with previously untreated metastatic NSCLC and high levels of PD-L1 expression (>50%) on tumour cells. This decision was based on the results of an RCT that demonstrated superior progression-free survival (PFS) and overall survival for patients treated with pembrolizumab compared with platinum-doublet chemotherapy[3]. Pembrolizumab was also granted regular approval for use in patients with metastatic NSCLC whose tumours have any level of PD-L1 expression, based on superior PFS and overall survival durations reported in an RCT that compared pembrolizumab with docetaxel in the second-line setting. Nevertheless, the Dako pharmDx PD-L1 assay was also approved as a companion diagnostic for these indications for use of pembrolizumab. The FDA also granted accelerated approval for use of the anti-PD-1 antibody nivolumab in patients with refractory classical Hodgkin lymphoma, based on the promising ORR and DoR obtained in a single-arm trial, and regular approval for use in patients with refractory HNSCC, based on a finding of superior overall survival duration in an RCT compared with the investigator’s choice of chemotherapy[4].

Notable approvals of targeted therapies included accelerated approval of venetoclax, an inhibitor of the apoptosis regulator Bcl-2, for patients with chronic lymphocytic leukaemia (CLL) with the 17p deletion who have received at least one prior line of therapy. This approval decision was based on ORR and DoR data from a single-arm trial[5]. A companion diagnostic CLL fluorescence *in situ* hybridization (FISH) probe kit was also approved, to detect the 17p deletion. As a condition of accelerated approval, the sponsor will submit the results of an RCT comparing the efficacy of venetoclax and rituximab with that of bendamustine and rituximab in patients with relapsed or refractory CLL, including patients harbouring the 17p deletion.

Also of note, crizotinib received approval for the treatment of patients with *ROS1*-rearranged metastatic NSCLC[6]. This regular approval was based upon an ORR

of 66% and median DoR of 18.3 months in a single-arm trial involving 50 patients. The FDA determined that the ORR and DoR were of sufficient magnitude and that the risk:benefit ratio was favourable, and comparative safety data were already available from two RCTs providing comparisons of crizotinib with chemotherapy in patients with *ALK*-positive metastatic NSCLC. As a post-marketing commitment, the sponsor will submit data to support approval of a companion diagnostic assay to select patients with *ROS1* fusions.

In late 2016, the FDA granted accelerated approval to the poly [ADP-ribose] polymerase (PARP) inhibitor rucaparib for the treatment of patients with *BRCA*-mutation-positive advanced-stage ovarian cancer who have been treated with two or more chemotherapies. Concurrent with this approval, the FDA also approved the FoundationFocus CDxBRCA assay for the detection of deleterious *BRCA1* and *BRCA2* mutations — the first next-generation sequencing (NGS) companion diagnostic assay to be approved in oncology. As a condition of this accelerated approval, the sponsor will submit the results of an RCT investigating the efficacy of rucaparib as a switch maintenance therapy after platinum-containing therapy in patients with relapsed, high-grade serous or endometrioid ovarian cancer in order to confirm clinical benefit.

The year 2016 was also notable for the approval of the cobas *EGFR* Mutation Test v2 as a plasma-based companion diagnostic assay to detect *EGFR* exon 19 deletions and the L858R substitution mutation in order to select patients with advanced-stage NSCLC for treatment with erlotinib, and to detect the exon 20 T790M resistance mutation in the same gene in order to select patients for treatment with osimertinib when a tissue biopsy is not feasible. Thus, 2016 marked the first approval of a 'liquid biopsy' test in oncology to assist in patient selection for treatment.

In the coming years, we are likely to see the continued expansion of the therapeutic landscape of immune-checkpoint inhibitors, targeted therapies, and novel companion and complementary diagnostics, including the further development of multiplex genomic testing platforms (including novel tissue-based or blood-based NGS assays)[7]. Short-term and longer-term FDA oncology priorities include the use of 'real-world evidence' (RWE) to enable evidence generation outside of clinical trials[8]. RWE can be generated from multiple sources, including electronic health records, patient registries, mobile health applications, and social media. Such evidence could be useful for the expansion of labelled indications to patients with rare cancers, potentially enabling a better understanding of patient populations not typically studied in pivotal trials, and of the various dosing and safety issues that arise in clinical practice. Other FDA oncology priorities include facilitating a culture of data sharing[9] to ensure that clinical trial data that currently exist in silos can be more broadly used by the biomedical community to rapidly translate basic and clinical observations to improve patient care. Also, the FDA will continue to support the expansion of patient eligibility criteria in oncology clinical trials, thus improving generalizability and access to trials while ensuring patient safety. The creation of the Oncology Center of Excellence will focus agency resources on cancer as a disease and its effects on patients, and will better integrate the considerable regulatory expertise across the various product review centres at the FDA[10].

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Competing interests statement
The authors declare no competing interests.

FURTHER INFORMATION
Hematology/Oncology (Cancer) Approvals & Safety Notifications: http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm

SUPPLEMENTARY INFORMATION
See online article: S1 (table)

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