NEWS IN BRIEF

Immuno-oncology upset in bladder cancer

Roche and Genentech's checkpoint inhibitor atezolizumab did not improve overall survival in a confirmatory phase III trial in patients with advanced bladder cancer. The FDA granted accelerated approval to the anti-programmed cell death protein 1 ligand 1 (PDL1) antibody for this indication in 2016 on the basis of improvement on the surrogate end point of objective tumour response rate, the percentage of patients who experienced complete or partial tumour shrinkage with treatment. The failure of this confirmatory trial now leaves a question mark over the future of this drug in this setting.

Analysts expect the bladder cancer market to generate more than US$2 billion by 2026 in the United States alone. Anti-PD1 and anti-PDL1 antibodies are currently earmarked to capture around $1.7 billion of that market (*Nat. Rev. Drug Discov.* **15**, 599–600; 2016).

The jury is still out on whether this failure represents an opportunity or cause for concern for other checkpoint inhibitors. Bristol-Myers Squibb (BMS)'s anti-PD1 nivolumab, Merck KGaA and Pfizer's anti-PDL1 avelumab and AstraZeneca's anti-PDL1 durvalumab all have accelerated approvals in bladder cancer. (Durvalumab scored this accelerated approval in May, becoming the fifth PD1-modulating antibody to make it to market.) Merck & Co's anti-PD1 pembrolizumab received FDA approval for two bladder cancer indications in May.

Further analyses of results from confirmatory and phase III trials of these drugs will provide clarity on whether atezolizumab's failure was due to specific properties of the antibody, clinical trial design parameters or a more troublesome disconnect between the surrogate and clinical end points in this setting.

Last year BMS's nivolumab unexpectedly failed in a trial that sought to pave the way for the supplemental approval of the antibody in first-line non-small-cell lung cancer (NSCLC). Merck & Co. fared better in this setting with pembrolizumab, possibly because the company used a different approach to select PDL1-positive patients. In May the FDA approved pembrolizumab in combination with chemotherapy for first-line metastatic NSCLC, irrespective of PDL1 expression, adding to its earlier approval as a monotherapy in patients with high PDL1 expression.

Asher Mullard

FDA approves first new ALS drug in over 20 years

The FDA approved Mitsubishi Tanabe Pharma's edaravone for amyotrophic lateral sclerosis (ALS), the first US approval for the deadly neurodegenerative disease since riluzole in 1995.

ALS is a rare disease that attacks and kills the nerve cells that control voluntary muscles, affecting the ability to chew, walk, breath and talk. Most people with ALS die from respiratory failure, usually within 3–5 years from when the symptoms first appear. The FDA approved riluzole, a glutamate antagonist, more than two decades ago after clinical trials showed that it delayed the time to death by 3–4 months.

Japanese regulators granted supplemental approval to edaravone for ALS in 2015; they first approved it there in 2001 for acute ischaemic stroke. Although edaravone's mechanism of action in ALS is unknown, it is a radical scavenger with antioxidant effects that might provide neuroprotection against oxidative stress in motor neurons.

In a pivotal trial in 137 ALS patients, edaravone treatment slowed decline in a 48-point clinical test of daily function that assessed fine motor, gross motor, bulbar and respiratory functions of patients. After 24 weeks of treatment, the scores of edaravone-treated patients fell around 2.5 points less from baseline than those of placebo-treated patients. Common side effects included bruising and gait disturbance. It remains unclear what effect, if any, the drug has on survival times.

A few other ALS candidates are in mid- or late-stage trials, including AB Science's phase III multikinase inhibitor masitinib, which is already under regulatory review for approval in ALS in Europe, and Cytokinetics' phase III trial of the fast skeletal muscle troponin activator tirasemtiv.

Asher Mullard

FDA approves first targeted drug for acute myelogenous leukaemia

The FDA approved Novartis's FLT3 inhibitor midostaurin for acute myeloid leukaemia (AML). The multikinase inhibitor is the first targeted treatment for AML, and the first new FDA approval for AML in decades.

The FLT3 kinase is mutated in around one-third of AML patients, and this mutation is associated with faster disease progression, higher relapse rates and lower survival rates than other forms of AML. In 2002 a pair of studies — one of which assessed the preclinical activity of midostaurin — suggested that FLT3 inhibitors might improve outcomes in AML.

In a phase III trial in 717 patients, newly diagnosed FLT3-positive AML patients who received midostaurin in combination with chemotherapy had a 23% lower risk of death compared with chemotherapy alone. The event-free survival for midostaurin recipients was approximately 8 months, up from 3 months for chemotherapy alone. The most frequent severe or potentially life-threatening adverse effects included febrile neutropenia, mucositis and device-related infection.

Midostaurin has breakthrough designation in this indication, and was approved with a companion diagnostic to check for FLT3 status.

Another set of genetically defined AML patients could also soon be set to benefit from targeted treatment. The FDA is currently reviewing a new drug application for Agios and Celgene's first-in-class mitochondrial isocitrate dehydrogenase (IDH2) inhibitor enasidenib for IDH2-mutated AML. A decision is expected by the end of August.

Pfizer meanwhile is seeking renewed approval for its antibody–drug conjugate (ADC) gemtuzumab ozogamicin, which binds to CD33 to deliver a chemotherapy payload to myeloid cells. The FDA granted the ADC accelerated approved as a monotherapy for AML in 2000, but the company pulled it from the market after confirmatory trials found no clinical benefit and increased risk of fatal induction toxicity. Pfizer has since combined the ADC with standard induction chemotherapy and amended the dosing schedule.

Analysts expect global sales in the AML market to hit US$1 billion by 2020, with chemotherapies commanding the bulk of these sales (*Nat. Rev. Drug Discov.* **15**, 527–528; 2016).

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