Anticancer Immunotherapy – A New Weapon Against Cancer

JONATHAN STEPHENS, MPHIL
SENIOR ANALYST, ONCOLOGY
A robust new approach

Since its inception in the mid-20th century, chemotherapy has been the mainstay of cancer treatment and has become increasingly specific and effective. But with the increasing incidence of cancer worldwide, new treatment options are constantly being sought.

Immunotherapy represents a relatively new approach to cancer therapy, and acts by harnessing the abilities of the human immune system to fight cancer. Due to the unique features of the immune system – specificity, memory capacity and potency when directed against specific targets, immunotherapies have the potential to yield effective, safe and long-lasting results against many cancers. This report discusses the growing trend of immunotherapy in drug development, and highlights some of the major areas of interest.

A rising trend

Immunotherapy for cancer is itself a relatively new concept, with development of such therapies originating in the mid-1990s and the last few years seeing a rapid surge in new immunotherapies. Pharmaprojects data shows the first anticancer immunotherapy drug (defined as a drug exerting anticancer activity by utilising an immune-related mechanism) appearing in 1995, with numbers rising to 171 therapies in active development as of May 2015 (Figure 1).

Figure 1. Numbers of anticancer immunotherapy drugs over the period 1995-2015

The surge of research interest in such therapies has so far yielded 3 drugs that have been successfully launched for cancer indications. The first of these is Bristol-Myers Squibb’s ipilimumab. This fully-human monoclonal antibody (MAb) is directed against T-lymphocyte-associated antigen 4 (CTLA4), a receptor that down-regulates the immune system by providing inhibitory signalling to T-cells. In a pivotal randomized, double-blind, placebo-comparator Phase III trial (CA184-029) in 1211 patients with high risk stage III melanoma, ipilimumab 10mg/kg significantly improved recurrence-free survival vs placebo, with an observed 25% reduction in the risk of recurrence or death. At 3yr, an estimated 46.5% of patients treated with ipilimumab were disease-free compared to an estimated 34.8% of patients on placebo. The median RFS was 26.1mth for ipilimumab vs 17.1mth for placebo. Following its first launch in April 2011 for unresectable or metastatic melanoma, ipilimumab is now launched as Yervoy in several major markets including Canada, the EU, Switzerland and the US for the treatment of advanced melanoma, including unresectable or metastatic disease. With Phase III trials currently ongoing in several other cancers, the drug seems set for label expansion in the future.

Nivolumab has been developed by Ono and Bristol Myers-Squibb and is currently launched in Japan, South Korea and the US for the treatment of metastatic or unresectable melanoma. It is a fully-human MAb against PD-1, a cell surface receptor involved in down-regulation of T-cell signalling. In the Phase III CheckMate-066 trial in 418 patients with previously untreated BRAF wild-type unresectable Stage III and IV melanoma, nivolumab met the primary endpoint of overall survival (OS). One year survival was 73% for nivolumab vs 42% for dacarbazine, with an observed 58% decrease in the risk of death for patients treated with nivolumab. The drug has also been approved in the US for non-small cell lung cancer (NSCLC). EU filings for both melanoma and NSCLC have been validated for review by the EMA, with the filing for melanoma being granted accelerated assessment.

Merck & Co’s anti-PD-1 MAb pembrolizumab makes up the last of the three marketed anticancer immunotherapies, having been launched in the US in 2015 as Keytruda, for the treatment of melanoma in patients previously treated with ipilimumab. A pivotal Phase III trial of pembrolizumab (KEYNOTE-006) in 834 patients with advanced melanoma was stopped early after primary endpoints of progression-free survival (PFS) and OS were met, with pembrolizumab achieving median PFS of 5.5 months compared to 2.8 months for ipilimumab. In March 2015 Keytruda became the first medicine to be made available under the UK’s Early Access to Medicines Scheme (EAMS), allowing melanoma patients to benefit from treatment. An EU MAA filing has also been accepted for review.
A look at Pharmaprojects data (Figure 2) shows that while development of anticancer immunotherapies is ongoing in earnest; the vast majority of these drugs have yet to hit the clinic. At present, 116 of these drugs are still in preclinical development, with a further 49 drugs in early clinical trials. Six drugs are currently in Phase III, including the anti-PD-L1 MAb durvalumab, under development by AstraZeneca for head and neck cancer and NSCLC. Another promising Phase III drug is tremelimumab, a MAb targeting CTLA-4. A Phase II/III trial (D4880C00003) in 564 patients with mesothelioma is currently ongoing, with completion expected in 2016. Other Phase III candidates include KAEL-GemVax’s GV-1001, Biothera’s Imprime PGG, Roche’s atezolizumab and Merck KGaA’s avelumab.

**Hot targets**

The diverse nature of the immune system naturally presents a vast array of potential targets for new anticancer immunotherapies. A look at the top targets for immunotherapies shows that the most popular approach currently is blockade of PD-1 signalling, with 23 PD-1 targeted drugs currently in development (Figure 3). This cell surface receptor plays an important role in immune regulation through promotion of apoptosis in antigen-specific T-cells and simultaneous reduction of apoptosis in regulatory T cells (Tregs). The overall effect of PD-1 blockade is to down-regulate the immune system and reduce autoimmunity. Blockade of PD-1 signalling (either directly via PD-1 itself or via its ligand PD-L1) can lead to immune activation against cancer cells, making it a key target for immunotherapies.

As discussed earlier, two anti-PD-1 drugs are already claiming market share in the immunotherapy space. Apart from these marketed drugs, several other PD-1 antagonists are currently in Phase II trials. These include Curetech’s pidilizumab, which has already completed Phase II trials in non-Hodgkin’s lymphoma, colorectal cancer and melanoma, and Amplimmune’s Phase II candidate AMP-514, which currently being investigated in a Phase II trial for B-cell lymphoma as well as early-stage trials in other cancers.
A closely linked and similarly popular mechanism for immunotherapies is targeting of PD-L1, essentially achieving blockade of PD-1 signalling indirectly by targeting the ligand of PD-1 rather than PD-1 itself. This approach has proved popular, with 16 such drugs in development (Figure 3), and has already seen several drugs reach Phase III trials. As mentioned above, AstraZeneca’s durvalumab is currently in several Phase III trials for head and neck cancer, with filings for this indication in the EU, Japan and the US expected during 2016. Filings for NSCLC are also expected. Roche’s RG-7446 also targets PD-L1 and is currently in several Phase III trials in several cancer indications, including renal cancer, NSCLC and bladder cancer. Having already received breakthrough designation in the US for bladder cancer and NSCLC, filings for all three indications are in the pipeline and could be expected as early as 2016. Another addition to the anti-PD-L1 landscape is Merck KGaA’s avelumab, which is in joint development with Pfizer. It is currently in a Phase III trial in patients with platinum-resistant NSCLC, with further pivotal Phase III trials expected in 2015.

Another set of drugs showing promise within the immunotherapy space are chimaeric antigen receptor (CAR) therapies. These drugs consist of T-cells genetically engineered to express specialised surface receptors called chimeric antigen receptors (CARs). These CARs allow the T-cells to recognise a specific protein (antigen) on tumour cells, and to mount a specific immune response against it. A key target of CAR therapies at present is CD19, a cell surface receptor found on B-cells that has become the focus of several early to mid-stage clinical drugs. Kite Pharma and Juno Therapeutics have already progressed two CAR therapies each into Phase II trials, with a further promising Phase II candidate being Novartis’ CAR-T therapy, tisagenlecleucel-t.
Biggest players

The potential of immunotherapies as targeted therapies has understandably attracted attention, with pharma and biotech companies of all sizes seeking to add immuno-oncology drugs to their pipelines. Looking at the top companies in the immunotherapy space, Pharmaprojects data (Figure 4) shows that in terms of drugs in development Cellectis leads the way with 15 drugs, although it has yet to reach the clinic with any of these candidates. Closely following is Juno Therapeutics with 14 drugs, having already advanced several of its CAR-T therapies into clinical trials. Kite Pharma currently has several of its CAR-T and T-cell receptor (TCR) therapies in clinical trials, and has a total of 11 immunotherapies in development.

There then follows a group of companies with a more modest pipeline of immunotherapy drugs in development. Big Pharma is represented among these, with Novartis having 10 immunotherapies in active development, followed by Bristol-Myers Squibb with 7 drugs. BMS of course has two such drugs already marketed, while Novartis’ tisagenlecleucel-t is its only entry into clinical trials at present. Also with 7 drugs in development are Servier and Sorrento Therapeutics, both with largely preclinical immunotherapy pipelines aside from Servier’s enoblituzumab, which is in clinical trials.

![Figure 4. Top companies developing immunotherapies, by phase of development](source)
The changing focus of immunotherapy

The promise of anticancer immunotherapy is not an altogether new phenomenon. Last year’s annual meeting of the American Society of Clinical Oncology (ASCO 2014) highlighted PD-1 and PD-L1 blockade in the shape of BMS’ nivolumab and Roche’s atezolizumab as novel and effective approaches for the treatment of solid tumours such as melanoma and bladder cancer, and pembrolizumab was demonstrating activity in NSCLC and head and neck cancer. This year’s ASCO meeting gave a clear indication that immunotherapies now appear to be making headway into some of the more notorious, ‘tough to treat’ cancers. Merck & Co reported data from the Phase I KEYNOTE-012 study showing clinically meaningful responses in patients with PDL-1 positive head and neck cancer. In addition, near-final data from Celldex’s Phase II ReACT study showed that rindopepimut, a peptide vaccine targeting the EGFR variant, EGFRvIII induced potent immune responses and induced tumour regression in patients with glioblastoma multiforme, significantly prolonging survival when administered in combination with bevacizumab.

What this appears to suggest is not only that immunotherapies may have some flexibility in treating a wider range of cancers including the more resilient solid tumour types, but that they may also be able to be used effectively in combination with existing therapies. The more recent use of immunotherapies in combination trials is a potentially important development, and could represent a shift away from their initial use as standalone therapies. ASCO 2015 reported data from an NCI-sponsored Phase I trial showing that combination with ipilimumab enhanced the efficacy of Bavarian Nordic’s Prostvac anticancer vaccine in the treatment of castrate-resistant prostate cancer through a possible synergy of mechanism of action. Staying with combination therapy, another highlight from ASCO 2015 was data from the CheckMate 069 study, showing that combination therapy with ipilimumab and nivolumab significantly improved ORR and PFS compared to ipilimumab monotherapy, while maintaining a manageable safety profile. Taken together, these examples suggest another potential future for immunotherapies could be their increased use alongside more conventional targeted drugs, as well as in combination with other immunotherapies.

PD-1 and PDL-1 blockade by various drugs has emerged as the star of anticancer immunotherapy thus far, and this is unlikely to change anytime soon. Their initial success in the treatment of melanoma has now been followed by promise in other solid tumours such as NSCLC, and this widening array of potential uses can only bode well for continued commercial success. Moreover, while the human immune system naturally throws up many potential targets for immunotherapies such as TIM3, LAG3, OX40, and CD40 among others, oncologists have also noted that successful targeting of cancers by these mechanisms may well hinge on a successful PD-1/PD-L1 blockade in the first instance, potentially making these drugs the lynchpin of immunotherapy for some time to come.

Hot on the heels of the anti-PD-1/PD-L1 agents will likely be the CAR-T therapies, which may have even bigger long-term potential. With the combined efforts of Novartis, Juno Therapeutics and Kite Therapeutics producing no fewer than fifteen such drugs in early to mid-stage development, these drugs are already showing high response rates in haematological cancers such as acute lymphocytic leukaemia (ALL) and B-cell lymphoma (BCL). With this considered, these targeted T-cell therapies offer another interesting avenue of immunotherapy. However, instances of potentially serious side effects such as cytokine release syndrome remain an obstacle to the use of such therapies.

In summary, the surge in development of immunotherapy has already seen the biggest advance in cancer therapy since modern chemotherapy agents became commonplace. Time will show if the ‘age of targeted therapy’ will give way to the ‘age of immunotherapy’ when it comes to cancer treatments, but with immunotherapies occupying an ever larger portion of pharmaceutical research, the future of immuno-oncology looks increasingly bright.
Citeline provides the world’s most comprehensive and reliable real-time R&D intelligence to the pharmaceutical industry, covering global clinical trial, investigator and drug intelligence. Our data is meticulously curated from over 30,000 unique sources by the industry’s largest team – over 250 full-time expert analysts and editors.

Citeline’s therapeutic area analysts and product managers regularly produce reports on key aspects of the industry, new therapy developments and relevant trends. Enjoy free access to these insights by downloading our latest reports and whitepapers at www.citeline.com/resource-center/whitepapers.