Immuno-oncology agents for cancer therapy

SOPHIE CARTER & DAVID E THURSTON

Abstract: Until recently, cancer therapy comprised of four main types of treatment: surgery, radiotherapy, chemotherapy and targeted therapy. Over the past decade, immuno-oncology (IO) has emerged as a novel and important approach to cancer treatment through the stimulation of the body’s own immune system to kill cancer cells. This newly recognised role of treating cancer is rapidly developing, with many accelerated approvals by the US Food and Drug Administration and European Medicines Agency in 2019.

Several therapeutic classes have emerged within IO, and are the focus of this review article. In particular, the immune checkpoint inhibitor antibodies have had remarkable success across multiple malignancies, and are the most well-established therapeutic class of IO agents in data. Biomarker testing for the programmed death ligand 1 (PD-L1) checkpoint target has been developed and is now obligatory before treatment with pembrolizumab (Keytruda, Merck) when used for non-small-cell lung carcinoma, gastric cancer, head and neck squamous cell carcinoma and cervical cancer, as well as before treatment with atezolizumab (Tecentriq, Roche) when used for urothelial carcinoma. However, ambiguity remains as to the relevance of PD-L1 expression — the tumour was small and well-defined.

Immuno-oncology agents kill highly proliferating cells. Crucially, introduction of the first immuno-oncology agents have shown a significantly lower incidence of leukaemia later in their lives.

Introduction

Cancer incidence rates have steadily increased over the past 20 years, while mortality rates have shown a considerable decline. Although significant variation in survival rates is still observed across cancer types (i.e. there are more 2010 distinct diseases recognised), for most types, survival is improving owing to earlier diagnosis and improved treatments.

Treatment has undergone a slow evolution from its start in the 1800s, with the sequential development of four main recognised modes of treatment. The first was surgery, which was made possible after the discovery of general anaesthetics in the late 1800s. The second development was radiation therapy, established at the end of the 19th century, which utilises X-rays and or-C-rays to damage the DNA within tumour cells, thus blocking essential biochemical processes and leading to cell death.

The third development was chemotherapy, discovered in the 1940s, during World War II, when it was observed that individuals exposed to mustard gas suffered myelosuppression. Clinicians speculated that patients with proliferative diseases (e.g. leukaemia) might benefit from treatment with agents of this type that kill highly proliferating cells. Crucially, introduction of the first chemotherapy agents (analogs of nitrogen mustard gas) meant that cancers which were more complex or had metastasised, and could not be successfully treated by surgery or radiotherapy, could now be addressed.

Furthermore, chemotherapeutic agents have since been developed that work at different stages of the cell cycle and can be used in combination to prevent the development of resistance.

The fourth development was targeted cancer therapy (also known as precision therapies). This was established with the discovery of imatinib (Glivec; Novartis) in the late 1990s — a small-molecule kinase inhibitor targeted to the mutant BCR-ABL protein present in the tumour cells of patients with chronic myeloid leukaemia (CML), but not in their healthy cells.

This concept of using modern structural biology and drug discovery methods to produce small molecules, proteins, antibodies and even cellular therapies designed to target unique biomarkers associated with tumour cells, but not healthy cells, is now considered to be the ‘gold standard’ approach for discovering new cancer treatments. Currently, four major treatment modes — surgery, radiotherapy, chemotherapy and targeted agents — are frequently used in combination to ensure that all cancer cells are eradicated from the body. During the past decade, the first immuno-oncology (IO) treatments (e.g. checkpoint inhibitors) have emerged, which work by harnessing the body’s own immune system to kill tumour cells.

Keywords: Biomarkers; cancer; immune checkpoint inhibitors; immuno-oncology, oncology.

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Figure 1

Some of the main ligands and receptors present on the surface of tumour and immune cells that are targets for approved and emerging immuno-oncology therapies.

Immune-checkpoint inhibitors target the interaction between the PD-L1/PD-1 pathway or other pathways which govern immune response.

Immune cell

Tumour cell

GITR

CD27

TigIT

LAG3

CD13

CD11b

PD-L1

4-1BB

CD70

CD40

OX40

CTLA-4

CD8

CD22

CD86

CD28

History of immuno-oncology

It has long been known, but is now increasingly appreciated, that tumour cells can be recognised and disabled by the immune system. Some tumours show evidence of spontaneous regression early in their development, suggesting that the immune system may be capable of recognising and eliminating early-stage tumour cells.

Observation of spontaneous remissions in patients led to the foundations of the area of IO. A spontaneous remission is defined as a reduction in severity of, or disappearance of, the signs and symptoms of a disease, without any apparent cause and in the absence of treatment. This is most often noted in patients who have recurrently had acute infections, especially when these result in fever which appears to stimulate the immune system. It is now recognised that, in some cases, the immune system is capable of completely eliminating a tumour. Spontaneous remissions have been observed in most cancer types, but most frequently in advanced melanoma, renal cell carcinoma (RCC) and urothelial carcinomas, although the phenomenon has also been reported in breast cancer, neuroblastomas, some sarcomas and embryonal cancers.

William Coley was the first to investigate the potential for IO, and successfully treated malignancies based on immune stimulation in the 1890s. After discovering that cancer patients who contracted post-surgical infections seemed to improve faster than those who did not, he investigated the use of bacteria to stimulate and enhance the body’s natural immune response to fight cancer. Through these studies, he later developed Coley’s toxin, which was based on attenuated bacteria and is thought to be the first known IO therapy.

A later development involved the Bacillus Calmette-Guérin (BCG) vaccine, originally produced in the early 1900s for use against tuberculosis (TB) and first used therapeutically for TB in the 1920s. However, its role in cancer therapy dates back to 1929 when a reduced incidence of cancer among patients with TB was observed at autopsy. Experiments revealed that BCG produced a profound stimulation of the immunological phagocyte system (also known as the reticuloendothelial system), which was recognised as an important defense against cancer. Furthermore, it was observed that neonates who had been immunised with BCG had a significantly lower incidence of leukaemia later in their lives.

This background and basic understanding of IO sparked an interest in the use of BCG for other types of malignancies, in particular cancer of the cervix. SOBRE 1940s, during World War II, when it was observed that individuals exposed to mustard gas suffered myelosuppression. Clinicians speculated that patients with proliferative diseases (e.g. leukaemia) might benefit from treatment with agents of this type that kill highly proliferating cells. Crucially, introduction of the first immuno-oncology (IO) treatments (e.g. checkpoint inhibitors) have emerged, which work by harnessing the body’s own immune system to kill tumour cells. They are presently showing great promise in the clinic, and are the main focus of this review.

Immune-checkpoint proteins are found on the surface of T-cells and act as regulators of the immune system. These are crucial for self-tolerance, and prevent the immune system from attacking the body’s own cells indiscriminately, thus allowing a distinction to be made between ‘self’ and ‘non-self’. Immune checkpoints also play a vital role in preventing uncontrolled immune responses, by modulating the duration and amplitude of a physiological immune response, thus preventing collateral damage, which is why the term ‘off switch’ is sometimes used to describe their role. It is known that tumours adopt certain immune checkpoint pathways as a mechanism to evade an immune response towards them.

For example, some tumour cell types express these proteins on their surface to disguise themselves as ‘self’, allowing them to go unnoticed by the immune system and promoting tumour progression.

PD-1 (programmed death ligand 1) is an example of an inhibitory checkpoint receptor protein found on the surface of T-cells that normally acts as an ‘off-switch’ after interaction with the PD-1 ligand (PD-L1), a protein expressed on the surface of normal cells. However, PD-L1 is expressed by many types of tumour cells and upregulated in some; thus activating the ‘off-switch’ and protecting the malignant cells from an immune attack.

Immune-checkpoint inhibitors (ICPis), such as the anti-PD-1/PD-L1 agents, prevent the interaction between PD-L1 on tumour cells and PD-1 on T-cells, allowing the immune system to launch an anti-tumour response.

Many observers believe that, over the next decade, IO agents could become the fifth acknowledged cancer treatment modality. Some of the main ligands and receptors present on the surface of tumour and immune cells that are targets for approved and emerging IO therapies are summarised in Figure 1.
Classification of immuno-oncology agents

The categorisation of IO agents as challenging and there is significant crossover and ambiguity with emerging agents. The classification devised and utilised throughout this review is represented in Tables 1–4. For example, ICIs (see Table 1) are sometimes classified separately to monoclonal antibodies (mAbs, see Table 2), yet the ICIs are, themselves, monoclonal antibodies. The main groups are now divided into two broad approaches to classification based on treatment type or cancer type22. Few observers employ the three very broad categories that have emerged over the years: non-specific cytokines, cancer vaccines and mAbs25. Another approach is to classify IO agents from a mechanistic perspective as active or passive. However, this is perhaps too simplistic, as it ignores the many possible complex drug-host-tumour interactions26,27. In this review, passive nakeled mAbs, such as the ICIs (see Table 1) and those targeted at other external and internal cellular targets (see Table 2) are grouped adjacently, while conjugated mAbs (i.e. antibody-drug conjugates and immunoconjugates) are placed in Table 3 and active vaccines in Table 1 are classified separately.

Emergent biomarkers

There are too many emergent biomarkers in the IO area toenumerate in detail in this review; however, some examples are outlined below.

Tumour mutational burden (TMB) is a measure of the number of somatic mutations present in the cancer genome and is shown to be associated with a favourable outcome for ICPS. For example, many tumours that respond to anti-PD-1 agents (e.g. melanoma) have a TMB score of greater than 10 mutations per Mb DNA load29. Some studies have attempted to correlate mutational load in NSCLC and melanoma with a response to ICPS, but the results have been unable to prove that a high mutational load also enhances the response to therapy; therefore, its clinical utility is presently unclear29.

Although clinically validated biomarkers for predictiveneutrality are lacking, there are several emerging transplant markers that may improve the identification of patients who are more likely to benefit. Despite this, it remains a challenge to determine the best therapy for the individual patient, particularly in the case of non-small cell lung cancer (NSCLC) which is the most common cancer in both men and women29. This is due to the heterogeneity of NSCLC, and the fact that patients with NSCLC are generally older and have a poor prognosis due to the common presence of comorbidities29. To address this, clinical trials have been conducted to compare available data and collate sufficient evidence to support clinical use30. Pharmacogenomic and precision medicine approaches to immuno-oncology

Drug discovery and development in the IO area is moving rapidly toward a pharmacogenomic approach, where biomarkers are identified and validated. This can be achieved through the development of drugs using a precise approach to select patients who are most likely to benefit.
As above for nivolumab

CTLA-4 plays an important role in the regulation of T-cell activity. Inhibition of CTLA-4 blocks T-cell inhibitory signals induced by the CTLA-4 pathway, therefore releasing the brake on inhibition. This results in proliferation and activation of T-effector cells which can mobilise and mount an immune response against tumour cells. Selective depletion of T-regulatory cells at the tumour site leads to an increase in intra-tumoural T-effector/T-regulatory ratio, thus driving tumour cell death.

Tremelimumab
Fully humanised (lgG2)
CTLA-4
As above for ipilimumab

Nivolumab (Opdivo, Brisol-Myers Squibb)
Human (lgG4)
PD-1
Binds to PD-1 receptor preventing interaction with PD-L1/2 antigens on APCs/other cells in the tumour microenvironment. PD-1 is a negative regulator of T-cell activity, thus when inhibited by anti-PD-1 agents potentiates T-cell proliferation and cytokine secretion.

Atezolizumab (Tecentriq, Roche/Genentech Ltd)
Human (lgG1)
PD-L1
 binds directly to PD-L1 and produces dual blockade of PD-1 and CD80, thus releasing PD-L1/PD-1-mediated inhibition of T-cell activity. The PD-L2/PD-1 interaction remains.}

TABLE 1
Approved immune checkpoint inhibitors as of April 2020

<table>
<thead>
<tr>
<th>Immuno-oncology agent</th>
<th>Type</th>
<th>Target</th>
<th>Mechanism of action</th>
<th>Indications (with approval dates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iplimumab (Yervoy, Brisol-Myers Squibb)</td>
<td>Human (lgG1)</td>
<td>CTLA-4</td>
<td>CTLA-4 plays an important role in the regulation of T-cell activity. Inhibition of CTLA-4 blocks T-cell inhibitory signals induced by the CTLA-4 pathway, therefore releasing the brake on inhibition. This results in proliferation and activation of T-effector cells which can mobilise and mount an immune response against tumour cells. Selective depletion of T-regulatory cells at the tumour site leads to an increase in intra-tumoural T-effector/T-regulatory ratio, thus driving tumour cell death.</td>
<td>• Late stage melanoma (second-line, March 2019; US Food and Drug administration [FDA] and European Medicines Agency [EMA]) • Unresectable or metastatic melanoma (age 12 years and over, July 2017) • Adjuvant treatment of melanoma (October 2016) • Intermediate and poor risk advanced renal cell carcinoma (in combination with nivolumab, 2018 [FDA]) • Colorectal Cancer (resembled or refractory microsatellite instability high/mismatch repair deficient in combination with nivolumab, 2018 [FDA])</td>
</tr>
<tr>
<td>Tremelimumab</td>
<td>Fully humanised (lgG2)</td>
<td>CTLA-4</td>
<td>As above for ipilimumab</td>
<td>• Melanoma mesothelioma (2015 [FDA] — orphan drug)</td>
</tr>
<tr>
<td>Nivolumab (Opdivo, Brisol-Myers Squibb)</td>
<td>Human (lgG4)</td>
<td>PD-1</td>
<td>Binds to PD-1 receptor preventing interaction with PD-L1/2 antigens on APCs/other cells in the tumour microenvironment. PD-1 is a negative regulator of T-cell activity, thus when inhibited by anti-PD-1 agents potentiates T-cell proliferation and cytokine secretion.</td>
<td>• Adjuvant in melanoma, with lymph node involvement or metastatic disease after re-section (June 2018 [EMA], 2014 [FDA]) • Non-small cell lung cancer (NSCLC) / metastatic disease (2015 [FDA]) • Metastatic renal cell carcinoma (RCC; 2015 [FDA]) • Classical Hodgkin lymphoma (2016 [FDA]) • Metastatic/recurrent squamous cell carcinoma of the head and neck (SSCHN, 2017 [FDA]) • Metastatic gastric gastrointestinal stromal tumour (GIST, 2017 [EMA]) • Hepatocellular carcinoma (2017 [FDA]) • RCC (2018 [FDA]) • RCC (2017 [FDA] — first line in combination with ipilimumab) • Metastatic oatseous squamous cell carcinoma (2019 [FDA])</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda, Merck &amp; Co Inc.)</td>
<td>Human (lgG4)</td>
<td>PD-1</td>
<td>As above for nivolumab</td>
<td>• Advanced melanoma / adjuvant treatment of melanoma (in adults with lymph node involvement who have undergone complete resection. Approved by the EMA in October 2018 for adjuvant melanoma therapy, 2019 [FDA], 2018 [EMA]) • Metastatic NSCLC (2015 [FDA], 2018 first line in October 2018 in combination with pemetrexed or nab-pemetrexed, expanded monotherapy 2019) • Recurrent SSCHN (2016 [FDA]) • Classical Hodgkin lymphoma (2017 [FDA]) • Metastatic uveal melanoma (2017 [FDA]) • Metastatic gastric gastrointestinal stromal tumour (2017 [FDA]) • Metastatic gastric gastrointestinal stromal tumour (2017 [FDA]) • Recurrent or metastatic cervical cancer (second-line, PD-L1+; 2018 [FDA]) • Primary mediastinal large B-cell lymphoma (PMBL; relapsed after 2 or more prior lines of therapy, 2018 [FDA]) • Hepatocellular carcinoma (2018 [FDA]) • Merkel cell carcinoma (2018 [FDA]) • Merkel cell carcinoma (2018 [FDA]) • Stage III NSCLC (first-line, PD-L1+, not amenable to surgery or chemo-radiotherapy, 2019 [FDA]) • Advanced RCC (2017 [FDA]) • Merkel cell carcinoma (2016 [EMA]) • Endometrial carcinoma (2018 [FDA]) — in combination with bevacizumab • BCGR-lesionless, high-risk, non-muscle invasive bladder cancer (2020 [FDA]) • Merkel cell carcinoma (MOC) 2017 [FDA and EMA]) • Urothelial carcinoma (if disease progression during or following platinum-based chemotherapy, 2017 [FDA] and EMA) • Advanced RCC (in combination with chemotherapy, May 2019 [FDA])</td>
</tr>
<tr>
<td>Avelumab (Bavencio, Merck &amp; Co Inc.)</td>
<td>Human (lgG1)</td>
<td>PD-L1</td>
<td>Binds to the PD-L1 antigen preventing interaction with PD-L1/CD80 receptors, thus removing the suppressive effects of PD-L1 on CD8+ T cells and allowing a cytotoxic T-cell response to prevail. An induction of NK cell-mediated direct tumour cell lysis via the ADCC mechanism can also occur.</td>
<td>• Melanoma cell carcinoma (MOC) 2017 [FDA and EMA]) • Urothelial carcinoma (if disease progression during or following platinum-based chemotherapy, 2017 [FDA] and EMA) • Advanced RCC (in combination with chemotherapy, May 2019 [FDA])</td>
</tr>
<tr>
<td>Durvalumab (Imfinzi, AstraZeneca)</td>
<td>Human (lgG1)</td>
<td>PD-L1</td>
<td>As above for avelumab</td>
<td>• Locally advanced (Stage III) NSCLC (non-progressive while on chemotherapy, 2017 [EMA], 2018 [FDA]) • Metastatic uveal melanoma (progression during or following platinum-based chemotherapy, 2017 [FDA])</td>
</tr>
<tr>
<td>Atezolizumab (Tecentriq, Roche/Genentech Ltd)</td>
<td>Human (lgG1)</td>
<td>PD-L1</td>
<td>Atezolizumab binds directly to PD-L1 and produces dual blockade of PD-1 and CD80, thus releasing PD-L1/PD-1-mediated inhibition of T-cell activity. The PD-L2/PD-1 interaction remains.</td>
<td>• Urothelial carcinoma or Metastatic NSCLC (if disease progression during or following platinum-based chemotherapy, 2016 [FDA]) • NSCLC (first line approval in December 2018 in combination with bevacizumab (Avastin), carboplatin and paclitaxel, 2018 [FDA]) • NSCLC in combination with chemotherapy for initial treatment (2018 [FDA]) • Extensive stage small cell lung cancer (first-line, in combination with chemotherapy, 2019 [FDA]) • Unresectable, triple-negative breast cancer (first-line, PD-L1+, 2019 [FDA])</td>
</tr>
</tbody>
</table>

### APPROVED IMMUNO-ONCOLOGY AGENTS DIRECTED AGAINST EXTERNAL AND INTERNAL TARGETS AS OF APRIL 2020

<table>
<thead>
<tr>
<th>Immuno-oncology agent</th>
<th>Type</th>
<th>Target</th>
<th>Mechanism of action</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>AlectCmdzumab (Lemtrada; Campath, Genzyme)</td>
<td>Humanised (IgG1)</td>
<td>CD52</td>
<td>Selectively binds to CD52 which is expressed at high levels on T- and B-lymphocytes. Following treatment with AlectCmdzumab, rapid and long-lasting depletion of CD52-bearing B and T cells occurs. The mechanism is not fully understood.</td>
<td><img src="https://via.placeholder.com/50x50" alt="image" /></td>
</tr>
<tr>
<td>Rituximab (Rituxan; Malthera, Genentech)</td>
<td>Chimeric (IgG1)</td>
<td>CD20</td>
<td>Binds specifically to the Type I CD20 antigen on pre-B and mature B lymphocytes which is expressed on &gt;90% of the B lymphocytes of B-cell non-Hodgkin lymphoma patients. Binding results in lysis and death of the B-lymphocytes.</td>
<td><img src="https://via.placeholder.com/50x50" alt="image" /></td>
</tr>
<tr>
<td>Tositumomab (Bexxar, GlaxoSmithKline)</td>
<td>Murine (IgG2a)</td>
<td>CD20</td>
<td>Binds specifically to the Type I CD20 antigen on pre-B and mature B lymphocytes which is expressed on &gt;90% of the B lymphocytes of B-cell non-Hodgkin lymphoma patients. Binding results in lysis and death of the B-lymphocytes.</td>
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</tr>
<tr>
<td>Obinutuzumab (Gazyva/Gazyvara, Roche)</td>
<td>Humanised (IgG1)</td>
<td>CD20</td>
<td>Binds specifically to the Type I CD20 antigen on pre-B and mature B lymphocytes which is expressed on &gt;90% of the B lymphocytes of B-cell non-Hodgkin lymphoma patients. Binding results in lysis and death of the B-lymphocytes.</td>
<td><img src="https://via.placeholder.com/50x50" alt="image" /></td>
</tr>
<tr>
<td>Ofatumumab (Arzerra, Novartis)</td>
<td>Human (IgG3)</td>
<td>CD20</td>
<td>Binds specifically to the Type I CD20 antigen on pre-B and mature B lymphocytes which is expressed on &gt;90% of the B lymphocytes of B-cell non-Hodgkin lymphoma patients. Binding results in lysis and death of the B-lymphocytes.</td>
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</tr>
<tr>
<td>Itolizumab (Ixuisumab; Zevalin, Biogen Idec)</td>
<td>Murine (IgG1) — Yttrium (90Y) conjugated</td>
<td>CD20</td>
<td>Binds specifically to the Type I CD20 antigen on pre-B and mature B lymphocytes which is expressed on &gt;90% of the B lymphocytes of B-cell non-Hodgkin lymphoma patients. Binding results in lysis and death of the B-lymphocytes. The Fab domain binds to CD20 allowing the associated 90Y isotope to kill B-cells through radiation.</td>
<td><img src="https://via.placeholder.com/50x50" alt="image" /></td>
</tr>
<tr>
<td>Dinuzumab (Unibuxin, United Therapeutic Europe)</td>
<td>Chimeric (IgG1)</td>
<td>CD2</td>
<td>Binds to CD2 thus inducing ADCC/ Complement-Dependent Cytotoxicity (CDC) mechanisms and causing apoptosis and inhibition of proliferation.</td>
<td><img src="https://via.placeholder.com/50x50" alt="image" /></td>
</tr>
<tr>
<td>Blinatumomab (Blincyto, Amgen)</td>
<td>Murine (IgG3)</td>
<td>CD19/ CD3</td>
<td>As a bispecific antibody, it binds to both CD19 on B-cells and CD3 on T-cells thus bringing them into close proximity. This up-regulates cellular adhesion molecules, the production of cytokines and the proliferation of T-Cells.</td>
<td><img src="https://via.placeholder.com/50x50" alt="image" /></td>
</tr>
<tr>
<td>Daratumumab (Darzalex, Janssen-Cilag)</td>
<td>Human (IgG3)</td>
<td>CD38</td>
<td>Binds to CD38, inducing broad spectrum apoptosis by Fc-mediated cross-linking, CDC, ADCC and immune-mediated tumour cell lysis.</td>
<td><img src="https://via.placeholder.com/50x50" alt="image" /></td>
</tr>
<tr>
<td>Isatuximab-irfo (Sarclisa, Baxo5)</td>
<td>Chimeric (IgG1)</td>
<td>CD38</td>
<td>Binds to CD38, inducing broad spectrum apoptosis by Fc-mediated cross-linking, CDC, ADCC and immune-mediated tumour cell lysis.</td>
<td><img src="https://via.placeholder.com/50x50" alt="image" /></td>
</tr>
<tr>
<td>Elotuzumab (Empliciti, Bristol-Myers Squibb)</td>
<td>Humanised (IgG1)</td>
<td>SLAMF7</td>
<td>Direct activation of NK cells via the SLAMF7 pathway. Mediation of cell death via ADCC.</td>
<td><img src="https://via.placeholder.com/50x50" alt="image" /></td>
</tr>
</tbody>
</table>

**Table 2**

Approved immuno-oncology agents directed against external and internal targets as of April 2020

*Continued from page S6*
Binds to the HER-2 proto-oncogene found on 20-30% of breast cancer cells, thus leading \(\alpha\) to cell death through the ADCC and CDC mechanisms.

Panitumumab (Vectibix, Amgen) Human (IgG2) EGFR α Competitively binds to EGFR, inhibiting the binding of EGF and TGF-α and preventing activation of EGFR. The binding of anti-EGFR drugs to EGFR on the cell surface induces receptor internalisation and degradation. EGFR is over-expressed by many human cancers, namely colorectal cancer. Activation of EGFR results in cell proliferation, differentiation, migration, adhesion and inhibition of apoptosis. Binding of IgGs to EGFR plays a role in angiogenesis and metastasis of tumour cells.

Neovastatamab (Portrazza, Eli Lilly) Human (IgG3) EGFR α Competitively binds to EGFR, inhibiting the binding of EGF and TGF-α and preventing activation of EGFR. The binding of anti-EGFR drugs to EGFR on the cell surface induces receptor internalisation and degradation. EGFR is over-expressed by many human cancers, namely colorectal cancer. Activation of EGFR results in cell proliferation, differentiation, migration, adhesion and inhibition of apoptosis. Binding of IgGs to EGFR plays a role in angiogenesis and metastasis of tumour cells.

Catumaxomab (Removab, Vivenzia, Presenix Biosicht) Humanised Ep-CAM α Binds to CD3 on T-cells, EpCAM on tumour cells and Fc-α on macrophages and NK cells, causing accumulation of immune cells around EpCAM-positive tumour cells. Catumaxomab stimulates bound NK cells to release cytotoxic mediators. These can phagocytose and process tumour cells so that their antigens are presented on MHC II leading to the activation of T-Helper/Killer cells. When antibodies reach higher concentrations, they can stimulate CDC.

Trastuzumab (Herceptin, Roche) Humanised (IgG1) HER2 α Binds to the HER-2 proto-oncogene found on 20-30% of breast cancer cells, thus leading to cell death through the ADCC and CDC mechanisms.

Pertuzumab (Perjeta, Genentech) Humanised (IgG2) HER2 α Binds to the HER-2 proto-oncogene found on 20-30% of breast cancer cells, thus leading to cell death through the ADCC and CDC mechanisms.

Olaratumab (Lartrivo, Eli Lilly) Human (IgG3) PDGF-Res α Binds to PDGF-Res and blocks ligand-induced tumour cell proliferation.

Bevacizumab (Avastin, Genentech) Humanised (IgG1) VEGF α Binds to VEGF-A, an isoform of VEGF, preventing its interaction with VEGF receptors (VEGFRs) such as Flt-1 and KDR on the surface of endothelial cells, thus inhibiting angiogenesis and reducing tumour growth.

Ramucirumab (Cynariza, Eli Lilly) Human (IgG3) VEGF R2 α Binds to VEGF Receptor 2 (VEGFR2) on the surface of endothelial cells, thus preventing the binding of ligands such as VEGF-A, -D and -D2, and reducing proliferation, permeability and migration.

Imiromizod (Aldara; Zyclara, Valeant Pharma International) Small molecule TRIT α Binds to the TRIT receptor found on macrophage and dendritic cells, stimulating an innate and acquired immune response leading to infiltration of inflammatory cytokines (IL-6, IL-8 and TNF-α) and stimulation of apoptosis in tumour cells.

Tocilizumab — also known as atilumab (Astellas, Chugai, Hoffmann-La Roche/Genentech) Humanized (IgG1) IL-6 α Inhibits the binding of IL-6 to the interleukin-6 receptor (IL-6R), thus reducing pro-inflammatory cytokine-based responses by competing for both the soluble and membrane-bound forms of IL-6R.

**Mechanism of action**

- **Advanced CRC (patients who's cells express EGFR and contain wild-type versions of RAS): 2004 [FDA] and [EMA]**
- **Late-stage BOC-HN (2011 [FDA]; 2006 [EMA])**
- **Metastatic CRC (Conditional MA 2007, full MA 2015 [EMA], 2008 [FDA])**
- **Wild-type RAS metastatic CRC (2007 [FDA])**
- **Advanced NSCLC (EGFR positive 2016 [FDA], 2016 [EMA])**
- **Malignant ascites (2000 [EMA]) (Removab was withdrawn from the United States in 2013 and the EU in June 2017 at the request of the MA holder)**
- **HER-2+ metastatic breast cancer (2006 [FDA])**
- **HER-2+ metastatic gastric cancer (in combination with other anticancer agents 2010 [EMA]; 2011 and 2017 [FDA]) (The FDA approved Ovyx) (trastuzumab-dikist, Mylan), a biosimilar for the treatment of HER2 over-expressing breast or metastatic gastric cancer, in 2017)**
- **Advanced soft tissue sarcoma (orphan medicine 2015 [EMA], 2016 [FDA])**
- **Metastatic CRC (2004 [FDA], 2006 [EMA])**
- **NSCLC (combined with chemotherapy/biologic: 2006 [FDA], 2006 [EMA])**
- **Advanced/HER-2+ breast cancer (with/without; 2015 [FDA], 2016 [EMA])**
- **Glioblastoma (progressed following prior therapy; 2009 [FDA])**
- **Renal cell carcinoma (2009 [FDA], 2007 [EMA])**
- **Metastatic cervical cancer (2014 [FDA])**
- **Advanced ovarian cancer (2018 [FDA], 2019 [EMA])**
- **Gastric cancer (2014 [FDA], 2014 [EMA])**
- **Aggressive NSCLC (2014 [FDA], 2015 [EMA])**
- **Second-line in combination with folic acid; IL-2 and interferon in metastatic CRC**
- **Hepatocellular carcinoma (2019 [FDA])**
- **Basal cell carcinoma (small and slow growing; 1998 [EMA]) — Aldara**
**TABLE 3**

<table>
<thead>
<tr>
<th>Antibody-drug conjugates</th>
<th>Approval</th>
<th>Indication</th>
<th>Target</th>
<th>Payload</th>
<th>Linker type</th>
<th>Linker composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxetumumab pasudotox-tidk (Lumoxyt, AstraZeneca)</td>
<td>September 2019 (FDA)</td>
<td>Hairy cell Leukaemia</td>
<td>CD79B</td>
<td>Pseudomonas exotoxin A (bacterial toxin)</td>
<td>Cleavable</td>
<td>Disulfide-bonded using engineered cysteine residues</td>
</tr>
<tr>
<td></td>
<td>October 2012 (EMA)</td>
<td>First line of stage III or IV classical Hodgkin lymphoma in combination with chemotherapy (Nov 1 of March 2018)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab emtansine (Kadcyla, Roche)</td>
<td>2013 (FDA &amp; EMA)</td>
<td>HER2-positive metastatic breast cancer</td>
<td>HER2</td>
<td>DM1 (tubulin inhibitor)</td>
<td>Cleavable</td>
<td>Valve-citrulline</td>
</tr>
<tr>
<td></td>
<td>2017 (FDA &amp; EMA)</td>
<td>Relapsed/refractory B-cell precursor Acute-Lymphoblastic Leukaemia (ALL)</td>
<td>CD22</td>
<td>Calicheamicin (DNA cleaving agent)</td>
<td>pH and Redox Sensitive</td>
<td>AcBud Disulfide</td>
</tr>
<tr>
<td></td>
<td>September 2017 (FDA)</td>
<td>Acute myeloid leukaemia</td>
<td>CD33</td>
<td>Calicheamicin (DNA cleaving agent)</td>
<td>pH and Redox Sensitive</td>
<td>AcBud Disulfide</td>
</tr>
<tr>
<td></td>
<td>April 2018 (EMA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targinaxipep-erzr (Ebixor, Bleterni)</td>
<td>December 2019 (FDA)</td>
<td>Blastic plasmacytoid dendritic cell neoplasm (SPONC)</td>
<td>CD123</td>
<td>Diphtheria toxin</td>
<td>Fusin</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>June 2019 (FDA)</td>
<td>Relapsed/refractory diffuse large B-cell lymphoma</td>
<td>CD70E</td>
<td>Auristatin</td>
<td>Cleavable</td>
<td>Valve-citrulline</td>
</tr>
<tr>
<td></td>
<td>December 2019 (FDA)</td>
<td>Locally advanced or metastatic urothelial cancer</td>
<td>Nectin-4</td>
<td>Monomethyl auristatin E (tubulin inhibitor)</td>
<td>Cleavable</td>
<td>Valve-citrulline</td>
</tr>
<tr>
<td></td>
<td>December 2019 (FDA)</td>
<td>Unresectable or metastatic HER2-positive breast cancer after previous HER2 treatments</td>
<td>DXd (topoisomerase I inhibitor)</td>
<td>Cleavable</td>
<td>Glycine-glycine-phenylalanine-glycine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>December (FDA)</td>
<td>Metastatic triple-negative breast cancer (mTNBC)</td>
<td>Triple-2</td>
<td>(topoisomerase I inhibitor)</td>
<td>Cleavable</td>
<td>Peg-lisynase-PAB (CL2A)</td>
</tr>
</tbody>
</table>

Sources: Journal of Experimental & Clinical Cancer Research (Europe), Ocl-Oncol Cancer Res (Europe), Oncol Cancer Res. (Europe), European Medicine Agency (EMA), US Food and Drug Administration (FDA)
CD19

BCG live (TheraCys; TICE; FAP

Aldesleukin binds to IL-2 on immune cell receptors creating

Indication

Engineered T-cells bind to CD19-expressing tumour cells

Mechanism of action

Immuno-oncology agent

Continued from page S12

T-Cell therapy

Small molecule tyrosine kinase inhibitor that targets CSF-1R, KIT and FLT3, thereby inhibiting the proliferation of cell lines dependent on CSF-1R.

Aldesleukin (Proleukin, Novartis AG)

Other immune regulators

Metastatic Melanoma (1999 [FDA])

Interferon Alfa 2a/2b (Roferon A/Intron A, Sumitomo Dainippon Pharma/Cadila Health care / Merck & Co Ltd)

Interferon

Complex and not fully understood mode of action; up-regulation of MHC Class I proteins which leads to enhanced activation of CD8+ T cells.

Aldesleukin binds to IL-2 on immune cell receptors creating an activated receptor complex that results in the growth and differentiation of T-cells.

Lymphokine

IL-2R

Metastatic Renal Cell Carcinoma (1992 [FDA])

Penicillamine (Turalio)

Small molecule

CSF-IR pathway

Tenosynovial giant cell tumour (2019 [FDA])

Vaccines

BCG live (TheraCys; TICE; ImmuCyst, Shire Plc)

Attenuated

FAP

Urothelial Carcinoma (1990 [FDA])

Epuleucel-T (Provenge, Dendreon)

Cell transplant therapy

PSA

Prostate cancer (metastatic/hormone resistant; 2010 [FDA] 2013 [EMA] [Withdrawn in the EU in May 2015 at the request of the Marketing Authorisation holder for commercial reasons])

Oncolytic virus therapy

H101 (Onconine, Shanghai Sunway Biotech Co Ltd)

Serotype 5 human adenovirus

Viral-induced marker of cellular stress (e.g. MCM-A/B)

Head and neck cancer (2006 [FDA] and SFDA)

Talmogose laherparvovir (T-Vax; Imlygic, Amgen Inc.)

Herpes Simplex Virus 1

Surface necrosis

Modified HBVI (deletion of ICP43.6 and ICP47) with the ability to preferentially replicate in and lyse cancer cells, causing the release of tumour-derived antigens.

Melanoma (injectable, but non-resectable lesions in the skin and lymph nodes; 2015 [FDA] 2016 [EMA])

Melanoma (intralesional, but non-resectable lesions in the skin and lymph nodes; 2014 [FDA] 2016 [EMA])

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Melanoma (intralesional, but non-resectable lesions in the skin and lymph nodes; 2014 [FDA] 2016 [EMA])
be a relatively established area of IO, there are ongoing efforts to discover novel agents of this class to treat new indications.

Importantly, five-year follow-up data from the phase 3 KEYNOTE-006 trial reported in 2019 have confirmed that pembrolizumab is superior to ipilimumab for the treatment of melanoma in patients who have had no more than one prior systemic therapy. The median OS was 5.27 years for pembrolizumab versus 4.29 years for ipilimumab.[14,15] There are currently only two anti-CTLA-4 agents (ipilimumab and tremelimumab) approved for use in both melanoma and nonsmall-cell lung cancer (NSCLC). Although this narrow spectrum of indications compared with the anti-PD-1/PD-L1 agents suggests this might be an area for further development, there have been multiple reports of high grade toxicities.[16] Despite this, CTLA-4 blockade is associated with durable and consistent survival benefits in some patients.[17] Therefore, researchers are keen to find ways to manage or overcome these toxicities so that new indications and combination therapies can be explored.

Current research

As of September 2017, 58% of all clinical trials evaluating IO therapies were combination trials, 82% of which involved either another IO agent, a targeted therapy and/or a cytotoxic agent. While around 60% of combination trials involved PD-1 antagonists and 20% of CTLA-4 inhibitors,[18] however, as of September 2019, there were 1,669 more active clinical trials evaluating PD-1/PD-L1 mAbs alone or in combination with other agents, with 76% of these active trials investigating combination therapies.[19]

For example, NSCLC, melanoma and non-Hodgkin’s lymphoma have been at the forefront of IO research since its infancy, although, in recent years, interest in other malignancies such as renal, pancreatic and advanced (metastatic) cancer have significantly increased.[20] However, since 2014 the average number of planned enrolments has declined from an average of 429 to 129 patients per trial, reflecting the shift in focus from major tumour types (e.g. melanoma and breast cancer) to rarer cancers with a significantly smaller eligible population.[21]

Current clinical research efforts are focused largely on combining recently approved IO agents with either another IO agent or an existing treatment (i.e. chemotherapy or radiotherapy).[22] Data from 2018 shows that there are more than 1,700 clinical trials worldwide assessing combinations of anti-PD-1/PD-L1 agents with other immune checkpoint inhibitors, with 76% of these trials investigating combination therapies, while around 16% of combination trials involved PD-L1 antagonists and 20% CTLA-4 inhibitors.[23] Another IO agent, a targeted therapy and/or a cytotoxic agent, are being evaluated in several phase I/II clinical trials, either as a monotherapy or in combination with other IO agents.[24]

Recent evidence suggests that activation of the STING pathway, a major innate immune pathway, is involved in the generation of spontaneous antitumour T-cell responses. STING activation within antigen-presenting cells in the tumour microenvironment leads to production of IFNβ and spontaneous generation of antitumour CD8+ T-cell responses. In addition, it has been observed that a deficiency in this pathway increases susceptibility to tumour progression. Therefore, the deliberate activation of the STING pathway has been identified as a major research area for the future[25].

Indoleamine-pyrrole 2,3-dioxygenase (IDO) is a heme-containing enzyme encoded by the IDO1 gene. With other related enzymes it catalyzes the first and rate-limiting step in the kynurenine pathway (i.e. the oxygen-dependent oxidation of L-tryptophan to N-formylkynurenine). It has been implicated in immune modulation by limiting T-cell function

Another T-cell co-stimulatory receptor, TIGIT (T-cell immunoreceptor with Ig and ITIM domains), that plays a role in suppressing the antitumour immune response within the tumour microenvironment. Therefore, blockade of binding to the ligand PVR may suppress its immunosuppressive signalling and allow the co-receptor CD-226 to resume its T-cell activating functions.[26] The NCT02794571 and NCT02913161 trials are investigating TIGIT-blocking antibodies, both as monotherapies and as part of a combination with the PD-1/PD-L1 blocking antibodies atezolizumab and nivolumab, respectively.[27] The trial NCT03189428 that was evaluating the safety and tolerability of OMP-31M32 as a single agent or in combination with nivolumab was terminated in 2019.[28]

OX40, a member of the TNF receptor family, is primarily expressed on CD8 T-cells, NK cells and neutrophils. Its ligand, OX40L, is expressed by B-cells and macrophages, and binding of OX40 to its ligand modulates T-cell activation and effector function. Studies in pre-clinical models have demonstrated that anti-OX40 antibodies can increase tumour immunity and improve tumour-free survival.[29] Currently, multiple OX40-targeted therapies are being evaluated in several phase I/II clinical trials, either as a monotherapy or in combination with other IO agents.[30]

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The most common immune-related adverse events associated with the use of immune checkpoint inhibitors

Abx: Antibiotics; CRP: C-reactive protein; G: grade; irAE: immune-related adverse event

Mitigating endocrine toxicity
- Thyroxine initiated according to blood results/symptoms (hypothyroidism)
- Mitigating respiratory toxicity
- Review at 48h — no improvement start infliximab, commence IV steroids and empiric antibiotics
- Respiratory toxicity
- Common in 20-30% of patients, monitored closely
- Magnetic resonance imaging (MRI)
- Management — >G2 withhold treatment, initiate HRT, consider high dose steroids for neurological complaints.

Mitigating GI toxicity
- Monitor patient for symptoms (e.g. diarrhoea, bloated, anorexia), repeat testing when indicated
- Review at 48h — no improvement start infliximab, continue IV steroids

Endocrine toxicity
- More common in combinations
- Rarely higher than G2, often long-term
- Mitigating endocrine toxicity
- Monitor TSH and FSH T4 prior to any infusion, at least once a month
- Beta-blockers for symptomatic patients (especially if overactive)
- Where carbamazepine or steroids are required, withhold treatment until recovery from symptoms
- Rare endocrine toxicity
- Hypothyroidism — inflammation of the anterior lobe of pituitary gland
- Diagnosis — brain MRI
- Management — IOT3 withhold treatment, initiate HRT, consider high dose steroids for neurological complaints

Hepatotoxicity
- Occurs in 5-10% of patients during monotherapy, 20-30% in combination
- Mitigating hepatotoxicity
- Measure serum transaminases and bilirubin before every treatment and review medications

Mitigating respiratory toxicity
- Radiographic changes/mild/moderate new symptoms — withhold treatment, monitor symptoms every 2-3 days
- Start antibiotics if suspected infection — no improvement arrest IV add in steroids
- Discontinue treatment, admit patient and carry out toxicology/blood tests
- Commence IV steroids and empiric antibiotics
- Review at 48h — no improvement start infliximab, continue IV steroids

Dermatological toxicity
- Common in IOT3 (often first to develop)
- Mitigating skin toxicity
- Avoid skin irritants. Use regular topicals (e.g. emollients)
- Withhold treatment, start potent topical steroids
- Initiate oral IV steroids
- Review at 48h — no improvement start infliximab, continue IV steroids

Gastrointestinal toxicity
- Most frequent and severe (G3 or higher) of irAEs associated with anti-CTLA-4 treatment
- Mitigating GI toxicity — Monitor patient for symptoms (e.g. diarrhoea, bloated, anorexia), repeat testing when indicated
- Continue treatment and manage as described (oral fluids, slippery rice and avoid high fibre/latex diet). If patient is unwilling manage as per severe and withhold treatment. Consider steroids if no bloody stools.

Hepatotoxicity — nivolumab and ipilimumab is currently approved for advanced mela

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The results of a prospective study published in early 2020 have shown that the monitoring of thyroid dysfunction (i.e. destructive thyroiditis and hypothyroidism) in patients undergoing PD-1 inhibitor therapy is essential. Of 137 patients who were treated with either nivolumab or pembrolizumab, 165 patients testing negative at baseline. The results also support the 6–7 week presentation timeline for thyroid dysfunction as indicated by previous studies, as no new cases occurred after 24 weeks post-treatment.

In another study, clinical benefit associated with irAEs was observed in NSCLC patients receiving anti-PD-1 therapy who were treated with nivolumab or pembrolizumab. The study involved baseline measurements of anti-thyroid antibodies and follow-up thyroid function tests. The results showed a 25–50% of patients treated with ICPIs fell into this population of responders. This relatively poor ORR has led to significant interest in combining ICPIs with additional treatment modalities, including other IO agents, with the aim of improving response rates and duration of response. This is evident from the recent growth in combination clinical trials. For example, in the three-year period from 2014 to 2017, there was a 70% increase in the number of combination trials, and a 42% decline in enrolment for monotherapy trials. Combination therapy is attractive because it offers a means to target several mechanisms of tumour cell killing simultaneously in order to improve tumour growth and the development of resistance.

To date, the combination of ipilimumab with nivolumab to simultaneously target CTLA-4 and PD-1, respectively, is the only approved combination therapy as a first-line treatment for metastatic melanoma in adults. In 2018, the FDA also approved this combination for patients with melanoma, or those who had tested negative. PFS was also significantly improved by median 10 months vs. 3 months as well as an improvement in OS. In addition, durable clinical responses without the side effects observed in the latter was not deemed significant on multivariate analysis.

Another study, published in early 2020, has shown that patients who experience irAEs during anti-PD-1/I therapy have a higher chance of achieving an objective response compared with those who do not. This suggests that providing patients with the potential to predict the likely efficacy of treatment, potentially allowing more informed decisions about whether treatment should be continued in certain patients. The study involved 306 patients who were treated with either nivolumab or pembrolizumab over a two-year period; the most common irAEs were thyroid dysfunction and nephritis. For the cohort was 41.5% (n=14), but these patients represented 82.5% (n=40) of those who did not (i.e. 10 months vs. 1 month) as well as an improvement in OS in order to predict the likely efficacy of treatment. There would be significant cost implications associated with IO-based therapies. As of mid-2018, there were 439 CAR-T combination clinical trials. The rationale for combining IO agents and chemotherapy is that the efficacies may be additive, but toxicity profiles should be driven primarily by patients testing positive for rheumatoid factor, antinuclear or antithyroid antibodies. There would be significant cost implications associated with IO-based therapies. As of mid-2018, there were 439 CAR-T combination clinical trials.
Eleven systematic reviews of the global ICL landscape have been conducted. 22,23 Over a one-year period, between September 2017 and August 2018, it was established that the global number of ICLs increased by 63%, with cell therapies showing the most significant increase of 117%. In the number of active agents, followed by other immunomodulatory (e.g., aleksinavir and interferons). 79–79 and T-cell-targeted immunomodulatory approaches. 80–86

Importantly, the number of ICL targets also increased by 50% from September 2017 to August 2018, suggesting that there could be significant broadening of the ICL landscape in the future. Both new and existing IO agents are having clinical development, a large percentage are concentrated on only a few targets (e.g., PD-1, PD-L1, and CTLA-4). 27,28 In addition to the five antigens already approved for IO development in the UK, the Cancer Research Institute has identified 164 agents in clinical development targeting either PD-1 or PD-L1, with 50 of these at the clinical stage. This suggests that there is significant potential for IO development targeting as yet other targets. It is evident that a longer-term more-sustainable research and development strategy for novel IO therapies is required.

Conclusion
IO is a fundamentally different approach to cancer therapy and is redefining the way that both solid and haematological tumours are treated. However, this new treatment paradigm is still in its infancy, and there is a long way to go in optimising the use of these novel therapies, minimising their toxicities and learning how to integrate them into the current standard of care. Furthermore, given their high cost, there are challenges ahead in incorporating these agents into the standard of care for several diseases through treatments that could improve the standard of care in many different cancer types.

References