

OUTLOOK

Development of immuno-oncology drugs — from CTLA4 to PD1 to the next generations

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Abstract | Since the regulatory approval of ipilimumab in 2011, the field of cancer immunotherapy has been experiencing a renaissance. This success is based on progress in both preclinical and clinical science, including the development of new methods of investigation. Immuno-oncology has become a sub-specialty within oncology owing to its unique science and its potential for substantial and long-term clinical benefit. Immunotherapy agents do not directly attack the tumour but instead mobilize the immune system — this can be achieved through various approaches that utilize adaptive or innate immunity. Therefore, immuno-oncology drug development encompasses a broad range of agents, including antibodies, peptides, proteins, small molecules, adjuvants, cytokines, oncolytic viruses, bi-specific molecules and cellular therapies. This Perspective summarizes the recent history of cancer immunotherapy, including the factors that led to its success, provides an overview of novel drug-development considerations, summarizes three generations of immunotherapies that have been developed since 2011 and, thus, illustrates the breadth of opportunities these new generations of immunotherapies represent.

The concept of mobilizing the human immune system against cancer dates back to at least the mid-nineteenth century, when Rudolf Virchow, a German pathologist, observed immune infiltration in human tumours¹. Later, William Coley, an American surgeon, aimed to induce a therapeutic immune response through injection of bacterial broth (later known as Coley's toxins) into soft-tissue tumours that he could not resect². In response to this treatment, Coley observed inflammatory responses and, in some patients, clearance of the cancer, whereas in others he observed septic complications². At the time, a scientific understanding of immune mechanisms did not exist and progress stalled for nearly a century. From the 1970s onwards, scientific and methodological innovations included the engineering of antibodies³ as tools to engage immune mechanisms and an increasing understanding of pathways

and targets of the immune system, which started to enable the development of new interventions. During the course of the following three decades, several therapeutic approaches, such as cytokine-treatment (with interleukin-2 (IL-2) or interferon- α (IFN α)) or vaccines aimed at stimulating T cell immune responses, were trialled in the clinic — however, these had limited success^{4–6}. These treatments were often investigated in selected and non-representative patient populations and, in case of cytokines, were accompanied by substantial toxicities^{4,5}. Importantly, in the absence of a clear mechanism-based understanding of the dynamics of the immune system, all clinical development was subjected to the established chemotherapy paradigm of oncology drug development. This entailed Phase I safety studies in patients with end-stage disease to establish a maximum tolerated dose (MTD),

characterize safety and detect a signal of activity in form of tumour regression. Subsequent Phase II single-arm studies were conducted to achieve response rates (defined as shrinking of established tumours), and if a new drug candidate showed promise, large, randomized Phase III studies were initiated to identify small improvements in efficacy over existing therapies⁷.

The scientific turning point for cancer immunotherapy came with the understanding that T cell immune responses are controlled through on and off switches, so called 'immune checkpoints' that protect the body from possibly damaging immune responses⁸. The master switch for T cell activation was found to be the CD28–cytotoxic T lymphocyte-associated antigen 4 (CTLA4) interaction, and the CTLA4 gene (*CTLA4*) was cloned in 1987 (REF. 9). Key experiments in mouse models, conducted by Allison and colleagues in the mid-to-late 1990s, elucidated the role of CTLA4 in cancer^{10–12}. In the following years, additional immune checkpoints were identified, such as programmed cell death protein 1–programmed cell death 1 ligand 1 (PD1–PDL1) and several others^{13,14}, with distinctly different mechanisms of action; for example, CTLA4 influences T cell activation and the PD1–PDL1 pathway addresses T cell exhaustion and tolerance. However, CTLA4 and PD1–PDL1 share the underlying principle of being part of a network of positive and negative drivers of the immune response that balance its physiological functions. The modulation of immune checkpoints using monoclonal antibodies can have a universal effect on immune responses that is not dependent on tumour histologies or individual cancer-specific antigens. Much has been written about immune checkpoints, and this topic is extensively reviewed elsewhere^{8,14–16}.

Changing the drug-development paradigm. The translation of preclinical science into clinical success required the re-thinking of the clinical-development paradigm that was established for chemotherapies^{17,18}. Similar to other anticancer therapies, when first entering the clinic, the anti-CTLA4 antibodies ipilimumab (Bristol-Myers Squibb (BMS) and

Table 1 | Progress on two fronts: science and methods

Science progress	Methods progress
Understanding of immune biology	Immunotherapy development paradigm
Novel pathways and targets for intervention	Clinical end points including immune-related response criteria
Influence of targeted therapies on the immune system	Assay use and harmonization for immune biomarkers
Identification of biomarkers	Data reporting guidelines
Collaboration across the field (academia, non-profit organizations, pharmaceutical and biotechnology industries)	Regulatory guidances

more recently the European Academy of Tumour Immunology (EATI) and the American Association of Cancer Research (AACR)²¹. These initiatives resulted in several key insights (TABLE 1), two of which were of particular relevance in enabling ipilimumab to succeed in clinical trials: first, that immunotherapies may produce some mixed or novel types of responses that cannot be captured by conventional chemotherapy criteria such as the Response Evaluation Criteria in Solid Tumours (RECIST) and the criteria set out by the World Health Organization (WHO), and new criteria were needed^{17,22}; and second, that the effects of immunotherapy on time-to-event end points such as survival may take several months to manifest and can lead to delayed separation of Kaplan–Meier survival curves, which needs to be accounted for in the evaluation of randomized clinical trials^{23,24}. These insights were applied to the ipilimumab development programme with transformational effects (FIG. 1; BOX 1). The insights also formed the basis for new criteria to assess clinical response, termed immune-related response criteria (irRC), and associated clinical end points, such as immune-related overall response

Medarex) and tremelimumab (formerly Pfizer, now AstraZeneca) were initially investigated under the chemotherapy drug-development paradigm. Response rates were low and side effects were inflammatory in nature but different to those observed with other cancer drugs, and, in some cases, these side effects were severe^{19,20}. The resulting benefit–risk ratio was not yet convincingly different from the marginal improvements achieved with many conventional oncology drugs. In parallel to the clinical development programmes of ipilimumab and tremelimumab, the Cancer Immunotherapy Consortium (CIC) of the Cancer

Research Institute (CRI) — a community organization founded in 2002 (initially named the Cancer Vaccine Consortium) to facilitate solutions to the development challenges of immunotherapies — systematically instigated initiatives to create an immunotherapy development paradigm²¹. The initiatives of the CIC involved the main stakeholders in the immunotherapy field, namely academic investigators, industry drug developers and regulators, and included collaborations with similar organizations such as the Association for Cancer Immunotherapy (CIMT), the Society for Immunotherapy of Cancer (SITC) and

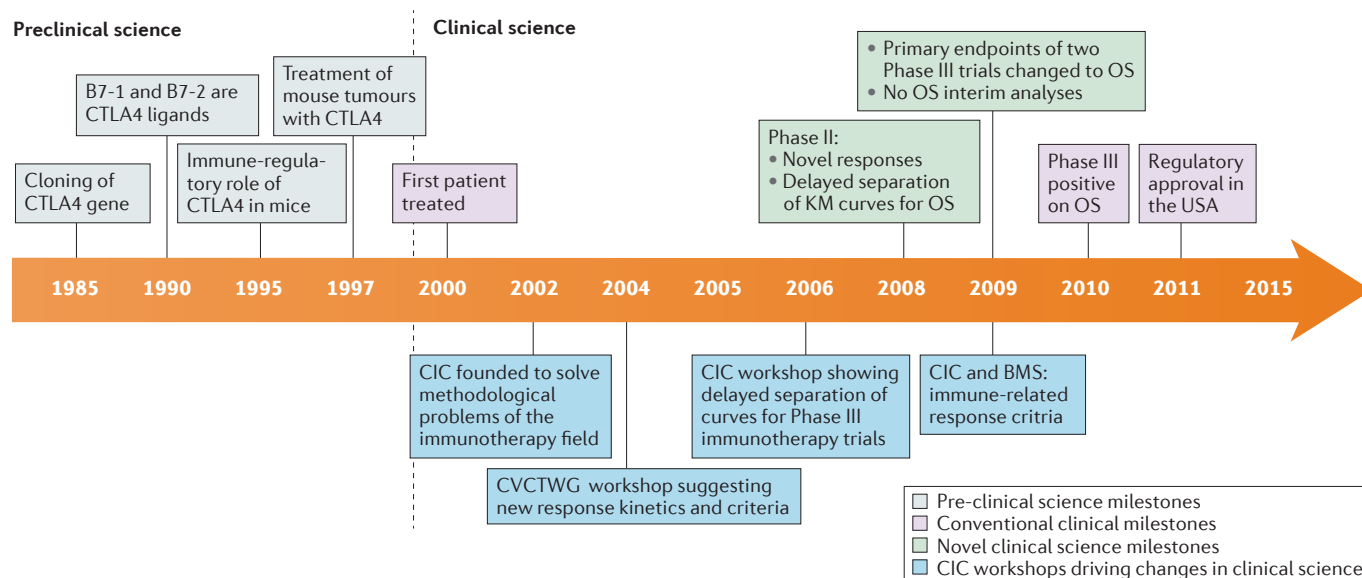


Figure 1 | **Ipilimumab drug-development milestones.** After basic and preclinical scientific advances, ranging from the cloning of the cytotoxic T lymphocyte-associated antigen 4 (CTLA4) gene in 1987 (REF. 9) to the elucidation of its role in tumour immunology by Allison and colleagues^{10,11} in the mid-1990s, the ipilimumab (anti-CTLA4) monoclonal antibody was introduced into clinical trials in melanoma in 2000. Advancement of the clinical science was multi-factorial^{18,21,24}. It included a new clinical development paradigm originating from initiatives of the Cancer Immunotherapy Consortium (CIC) as well as an extensive trial programme by Medarex and Bristol-Myers Squibb (BMS). The lessons learned

with regards to novel response kinetics and delayed separation of survival curves led to the change of primary end points for the ipilimumab pivotal studies from response-based end points (overall response rate or progression-free survival) to overall survival (OS) and ultimately led to a positive Phase III study³⁷. The novel safety profile resulted in the characterization of immune-related adverse events (irAEs) and the creation of irAE treatment algorithms^{25,26,121}. Ipilimumab was approved for metastatic melanoma in 2011. B7-1, T lymphocyte activation antigen CD80; B7-2, T lymphocyte activation antigen CD86; CVCTWG, Cancer Vaccine Clinical Trial Working Group; KM, Kaplan–Meier.

rate (irORR), immune-related disease control rate (irDCR), immune-related progression-free survival (irPFS) and milestone survival^{22,24}. The potential underlying biology for these clinical observations is summarized in BOX 2.

In addition, during the development of ipilimumab, immunotherapy toxicities, termed immune-related adverse events (irAEs)¹⁸, were systematically characterized and their clinical management was defined in treatment algorithms. These algorithms subsequently provided a model for the creation of other safety-management processes for next-generation immunotherapies^{25,26}.

Overall, out of the community initiatives of the CIC and its partners and the ipilimumab drug-development programme, a new clinical-development paradigm emerged for the clinical management of a novel efficacy and safety profile of cancer immunotherapies^{17,18,24} that became a cornerstone of the rapidly evolving field of immuno-oncology (TABLE 2). The early lessons of this paradigm on measuring efficacy and managing safety are widely present in immunotherapy drug development today^{25,27–29}. These insights contributed to the de-risking of the acquisition of Medarex by BMS in 2009, enabling the development of the most advanced immuno-oncology pipeline in the industry at the time. The CIC's initiatives also sparked broad collaboration in the immunotherapy community^{21,30} and provided information that was used in regulatory guidance documents issued by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) — *Guidance for industry: clinical development of therapeutic cancer vaccines* by the FDA in 2011 (REF. 31) and the *Guideline on the evaluation of anticancer medicinal products in man* by the EMA in 2012 (REF. 32). Approximately 4 years after the approval of ipilimumab, at least four major second-generation checkpoint-modulator programmes for PD1 and PDL1 inhibitors are in pivotal trials run by leading pharmaceutical companies (BMS, AstraZeneca, Genentech and Merck (FIG. 1)), and many more are in early clinical development. A CIC workshop held in October 2014 brought these four companies together to assess immunotherapy class effects across their programmes and to demonstrate the utility of the novel clinical end points irORR, irDCR, irPFS and milestone survival, beyond their use as exploratory end points (A. Hoos, unpublished observations).

Three generations of therapies

Since 2011, owing to its potential for a large and sustained clinical benefit^{33,34}, immuno-oncology has become the fastest-growing area not only in oncology but in the entire pharmaceutical industry. Dozens of new biotech ventures in immuno-oncology have emerged. In 2013, *Science* magazine declared cancer immunotherapy the breakthrough of the year³⁵; in 2014 and 2015, immuno-oncology technologies and business deals yielded extreme valuations at the J. P. Morgan investment banking

conference; and health-care analysts have predicted a market size for this sector of US\$35 billion by 2023 (REF. 36).

Despite this success, the field is still young and much potential for growth and substantive translational and clinical improvements exists. The emerging therapies can be categorized into three generations (FIG. 2). Generation 1 encompasses the initiating agents of the immuno-oncology era, ipilimumab and sipuleucel-T (an autologous dendritic cell therapy developed by Dendreon), which were approved based on survival improvements in randomized

Box 1 | Lessons learned from ipilimumab and tremelimumab

At the start of the clinical development programme of ipilimumab — an anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA4) monoclonal antibody — response-based end points (overall response rate (ORR) or progression-free survival (PFS)), as established for chemotherapy, were used as primary end points of all clinical trials¹⁸. Ipilimumab produced relatively low conventional response rates (5–15%)^{19,20} and its potential would have not been recognized on that basis. Based on insights from the Cancer Immunotherapy Consortium (CIC) initiatives and clinical observations with ipilimumab, the criteria for measuring clinical efficacy in the ipilimumab programme were re-defined^{18,24}. By capturing delayed responses, prolonged stable disease and responses in the presence of new lesions, the overall detectable effect rate rose to approximately 30%²⁷. Importantly, these novel patterns of response were associated with favourable survival, thus underscoring their clinical relevance^{22,24}. Owing to the inability of conventional response end points to capture this relevant fraction of patients with clinical effects, the primary end point of the pivotal ipilimumab trials was changed to survival (before unblinding), which would ultimately reflect this novel benefit^{18,24}. Further, owing to the delayed separation of the survival curve at 8 months in a randomized Phase II trial with ipilimumab (first reported at the 2008 American Society of Clinical Oncology (ASCO) conference)^{118–120}, no early interim analyses for survival were conducted in the pivotal studies of ipilimumab in advanced melanoma^{18,37}. The result was a positive Phase III trial in patients with pre-treated metastatic melanoma, demonstrating a hazard ratio (HR) for survival of 0.66 (risk reduction for death 34%) with only a 10% conventional response rate³⁷. Ipilimumab was subsequently approved by the US Food and Drug Administration (FDA) in March 2011 for its improvement in patient survival. In addition to a novel efficacy profile, ipilimumab also became a model for a new immunotherapy safety profile characterized by immune-related adverse events (irAEs)¹⁸. These mostly inflammatory events occurred predominantly in the skin, colon, liver and endocrine organs and distinguished themselves from the well-known clinical autoimmune syndromes such as Crohn disease and ulcerative colitis through their reversibility and manageability with either supportive care or well-established immunosuppressive drugs such as corticosteroids or mycophenolate mofetil^{25,26}. Carefully defined safety management algorithms were created for ipilimumab^{25,26}, including a voluntary Risk Evaluation and Mitigation Strategy (REMS) with the FDA¹²¹. These algorithms became the template for safety management of subsequent checkpoint modulators such as programmed cell death protein 1 (PD1) and PD1 ligand 1 (PDL1) blockers, which share a close safety profile with some differences in frequency or types of irAEs^{27,28,122}.

Parallel to the development of ipilimumab, a similar programme for the anti-CTLA4 monoclonal antibody tremelimumab was carried out in advanced melanoma. Tremelimumab shared similar clinical features with ipilimumab, with a response rate of 10% in the pivotal study and a similar irAE profile¹²³. The dosing schedule was one treatment every 3 months, as compared to that for ipilimumab, which was one treatment every 3 weeks. In metastatic melanoma, the median time to progression was historically ~2 months. Applying the conventional treatment paradigm, in which progression determined treatment cessation, the majority of patients in this trial stopped therapy before the second dose, thus leading to a median tremelimumab dose of 1. Ultimately, tremelimumab failed in Phase III after a Data Monitoring Committee (DMC) recommendation to stop the study owing to an early interim analysis for survival, which did not detect a relevant separation of curves after 7 months median follow up¹²⁴. However, survival follow up continued and 2 years later a moderate separation of curves was reported (HR 0.88)¹²³. Probable reasons for the outcome in this study were the underdosing of patients with a single dose of tremelimumab before progression and the early interim analysis not being able to pick up a delayed separation of survival curves. Tremelimumab, which may have similar clinical effects to ipilimumab, was subsequently licensed by AstraZeneca and has been broadly re-introduced into clinical trials.

Box 2 | **Biologic underpinnings of immunotherapy clinical responses**

The clinical observations that are captured with immune-related response criteria (irRC) as immunotherapy patterns of response may be explained by the dynamic interactions between the immune system and the tumour, which include both anti-tumour immunity and tumour-promoting inflammation. The concept of immunoediting¹²⁵ describes the three states of interaction as elimination, in which the immune response eradicates cancer cells; equilibrium, in which the immune response controls tumour growth; and escape, in which the tumour outgrows the immune response. In the context of immunotherapeutic intervention, these three states may be correlated with the clinical observations of response, stable disease and progression of disease^{119,126}. Owing to the heterogeneity of metastatic cancers — including changes in antigenic profiles (for example, antigen loss), immune-suppressive mechanisms in the tumour microenvironment and the immune status of patients — immune responses to individual lesions and between patients may vary. In some cases, a mixed clinical picture may emerge in which some lesions shrink while others remain stable or grow¹⁷. In other cases, lymphocytic infiltration into tumours may lead to an increase in the volume of a lesion before it can shrink^{127,128}. The latter phenomenon is described as a delayed response under irRC but has also been described as a ‘tumour flare’ or pseudo-progression²². Overall, patient survival may be improved even if there is no detectable tumour shrinkage, so long as the immune system and the tumour are in a state of equilibrium, thus slowing down local tumour growth and reducing the risk of metastases.

Phase III trials in 2010 (sipuleucel-T) and 2011 (ipilimumab)^{37,38}. Sipuleucel-T did not become a commercial success owing to the complexities of scaling production and commercializing this autologous cell therapy; however, it provided important lessons on the regulatory, CMC (chemistry, manufacturing and controls) and commercial aspects of immuno-oncology drug development, which are now proving useful in the development of new cell therapies. Following these first-generation agents, immuno-oncology drug development began to expand rapidly, and new agents against new targets and with new mechanisms of action were emerging, subsumed as generation 2 of immuno-oncology agents. At the centre of these are multiple clinical programmes focused on PD1- and PDL1-blocking antibodies. The first PD1-targeted agents — pembrolizumab (Merck) and nivolumab (BMS) — were approved by the FDA and the EMA in 2014 (pembrolizumab) and 2015 (nivolumab), and the anti-PDL1 agents atezolizumab (MPDL3280A, Genentech/Roche) and durvalumab (MEDI-4736, AstraZeneca/MedImmune) are in pivotal clinical trials (FIG. 2). Pembrolizumab achieved approval in record time, after only 4 years in the clinic³⁹. In addition, blinatumomab (Amgen), a bi-specific T cell engager (BITE) targeting CD19⁺ B cell malignancies, was approved in 2015 (REFS 40–42). Moreover, autologous cell therapies that target CD19 using chimeric antigen receptor (CAR)-transduced T cells (CAR-Ts) are being developed — a field in which Novartis has the most advanced programme. In 2011, CAR-Ts emerged with promising clinical

data in CD19⁺ malignancies⁴³, and in some studies durable response rates as high as 90% were reported⁴⁴. Moreover, talimogene laherparepvec (T-vec), an oncolytic viral therapy, was approved by the FDA in October 2015 for local injection in unresectable melanoma recurrent after initial surgery.

The initial market value projections for immuno-oncology were largely based on the first- and second-generation therapies³⁶. However, there is rapid development of an even larger pool of new technologies that further diversify the immuno-oncology space to fully utilize the potential of the immune system to fight cancer. This next wave of therapies can be summarized as third-generation agents that result from the broad expansion of immuno-oncology across multiple mechanisms and modalities, and this generation of therapies may be the most competitive yet (FIGS 2,3).

Clinical practice-altering data

Clinical data obtained with checkpoint modulators from generations 1 and 2 (such as ipilimumab, pembrolizumab and nivolumab) illustrate the broad potential of immuno-oncology. The first wave of clinical Phase III studies that showed potential to alter the standard of care were conducted with ipilimumab and are, in some instances, still reading out data today¹⁸. Phase III studies for pembrolizumab and nivolumab were carried out more recently, and the speed at which these agents were advanced was influenced by the fact that patients strongly gravitated to studies with these promising new treatments. TABLE 3 summarizes the results of the main Phase III trials with checkpoint inhibitors that

were available as of December 2015. Key observations are as follows: ipilimumab produced survival benefits, with hazard ratios (HRs) between 0.62 and 0.72, reducing the risk of death by 28–38% in two Phase III trials in metastatic melanoma. These data served as a proof of principle for checkpoint modulation, demonstrating that it can substantially improve patient survival and supporting the approval of ipilimumab in pre-treated and untreated metastatic melanoma^{37,45}. Importantly, studies also demonstrated the relevance of the plateau at the ‘tail’ of the survival curve, showing that a proportion of patients (20–25% in metastatic melanoma) experience long-term survival. This prompted the use of milestone survival end points (for example, 1-year or 2-year survival rates), adding meaningful information to the standard measure of median survival and providing a surrogate for the overall survival end point^{24,37}. Another study of ipilimumab in melanoma was conducted by the European Organization for Research and Treatment of Cancer (EORTC) in a high-risk adjuvant melanoma setting⁴⁶. To date, this study has produced recurrence-free survival data with a hazard ratio of 0.75; survival data have not yet matured. The EORTC study offers a different proof of principle: in an adjuvant setting with no macroscopic tumour present, the quantity of available antigen is still sufficient to drive an immune response that can be modulated by ipilimumab and allow for meaningful clinical benefit. It may be possible to extrapolate this finding to other immunotherapies in the adjuvant setting. The fourth ipilimumab study that is currently in the public domain involves patients with castration-resistant prostate cancer (CRPC) who have undergone therapy with taxotere⁴⁷. In this population, patients with visceral metastases have worse outcomes than those without. The study demonstrated a survival difference with a delayed separation of curves for the intention-to-treat population (HR 0.85), but this separation was greater for patients with better prognostic parameters (HR 0.62). Treatment of the intention-to-treat population did not achieve statistical significance ($p = 0.053$) and therefore did not alter the standard of care. Data from another Phase III study in patients with CRPC, who received ipilimumab before treatment with docetaxel (Taxotere, Sanofi), are yet to be publicly disclosed. The recent studies of nivolumab in patients with metastatic melanoma^{48,49} and

advanced squamous non-small cell lung cancer (NSCLC)⁵⁰ showed superiority over chemotherapy standards of care, with higher rates of survival observed in patients treated with nivolumab compared to those previously observed with ipilimumab (HR 0.42 and 0.59, respectively), thus formally eliminating chemotherapy as a standard of care in these settings. Further, the direct comparison of pembrolizumab versus ipilimumab in metastatic melanoma showed a survival advantage of pembrolizumab over ipilimumab (HR 0.63)⁵¹. Overall, these data dramatically changed the treatment landscape for metastatic melanoma, and emerging data suggest a similar development for the treatment of NSCLC. Over time, it can be expected that standards of care utilizing chemotherapy or targeted therapy will be replaced or at least challenged by immunotherapy regimens. New standards of care may utilize monotherapy with immunotherapeutic agents, as shown thus far, or gradually shift to combination therapies. These may include combinations with the current standard agents or new immuno-immuno combinations. The first data from a Phase III study of a combination of ipilimumab plus nivolumab were first presented at the 2015 ASCO conference and indicated a benefit on PFS for the combination over each agent alone (ipilimumab plus nivolumab versus ipilimumab alone, HR 0.42; nivolumab versus ipilimumab, HR 0.57; ipilimumab plus nivolumab versus nivolumab alone, HR 0.74 (no formal comparison))⁵². Survival data were not presented. Within the known and manageable categories of irAEs, the toxicity of the combination therapy with ipilimumab plus nivolumab was substantially increased compared to the toxicity of the agents as monotherapy⁵². Overall, these data indicate the power of immunotherapies to alter existing (and often very unsatisfactory) standards of care. Current immunotherapy drugs and treatment regimens are likely to be followed by more effective future therapies or combinations.

Important to note is the universal nature of the checkpoint-modulatory antibodies discussed above. Their mechanisms of action are entirely centred on the immune system and are independent of cancer histology or specific mutations. Consequently, these antibodies are demonstrating clinical activity across a broad range of different types of cancer. In addition to the trials in melanoma and

Table 2 | The immuno-oncology clinical development paradigm

Paradigm components	Refs	
Breadth of modalities	• A very broad range of modalities with, in some cases, distinct characteristics; only new characteristics not seen with chemotherapy are mentioned here	TABLE 4
Phases of clinical investigation	Two phases: <ul style="list-style-type: none"> • Proof-of-principle trials: first-in-human studies to initiate the safety database, determine dose and schedule, ascertain biological activity (pharmacodynamic effects on disease or immune system) and show signals of clinical activity • Efficacy trials: studies to establish clinical benefit; single-arm studies are possible for high-response-rate agents, but randomized trials are recommended for low-response-rate agents (the category into which the majority of compounds reported to date fall) 	17
Patient populations	• An early focus (often in the first-in-human trial) on well-defined populations, either owing to expression of the target antigen or the advantages of homogenous populations on biological or clinical effect evaluation	17
Efficacy	<ul style="list-style-type: none"> • Variable kinetics of response with at least four immune-related response patterns (conventional or immediate response; delayed response; response with new lesions; and durable, stable disease) • Delayed effects on survival expressed as delayed separation of Kaplan–Meier survival curves not following a proportional hazards model • Survival curves plateau, indicating a proportion of patients with long-term benefit 	17,18, 21,22, 24
Clinical end points	<ul style="list-style-type: none"> • irRC can capture immunotherapy response patterns and are applicable to WHO or RECIST criteria (irWHO or irRECIST); irRC-based end points are irORR, irDCR and irPFS • Overall survival end points in randomized trials may require sensitivity analyses, to address a delayed effect, or modelling of a non-proportional hazard based on available data • Median survival is a less informative data point than in chemotherapy trials and may be replaced by milestone survival assessments at 1, 2 and 3 years • Milestone survival may be a surrogate for overall survival 	18,22, 24,84
Safety	• Inflammatory adverse events termed irAEs, which can be managed with irAE treatment algorithms; the range of irAEs is broad and varies between immunotherapy modalities	25,26
Pharmacodynamics	<ul style="list-style-type: none"> • Biomarkers are focused on pathways and targets of the immune system, and measurements are variable and context-dependent owing to the dynamic nature of the immune system • Novel biomarker assays require validation and harmonization in use to achieve maximum utility 	87,88, 92,98
Pharmacokinetics	<ul style="list-style-type: none"> • Highly variable depending on the modality, for example: protein or peptide vaccines are not metabolized to deliver a clear pharmacokinetic profile; CAR-Ts or TCR-Ts are live cells with dynamic dose and durability parameters <i>in vivo</i>; oncolytic viruses have a first-pass effect after intravenous administration; and antibodies and small molecules follow more standard ADME kinetics • Many modalities may not achieve a conventional MTD owing to a plateau effect 	17,64, 65,71, 72

ADME, absorption, distribution, metabolism and excretion; CAR-Ts, chimeric antigen receptor-transduced T cells; irAE, immune-related adverse event; irDCR, immune-related disease control rate; irORR, immune-related overall response rate; irPFS, immune-related progression-free survival; irRC, immune-related response criteria; MTD, maximum tolerated dose; RECIST, Response Evaluation Criteria in Solid Tumours; TCR-Ts, T cell receptor-transduced T cells; WHO, World Health Organization.

NSCLC as described above, Phase II data also demonstrate activity of checkpoint inhibitors in genito-urinary cancers, such as bladder cancer or renal cell carcinoma, and in colon cancer and Hodgkin lymphoma,

among others^{53–57}. It may be expected that this trend continues, with various versions of next-generation checkpoint modulators showing activity against a range of cancer types.

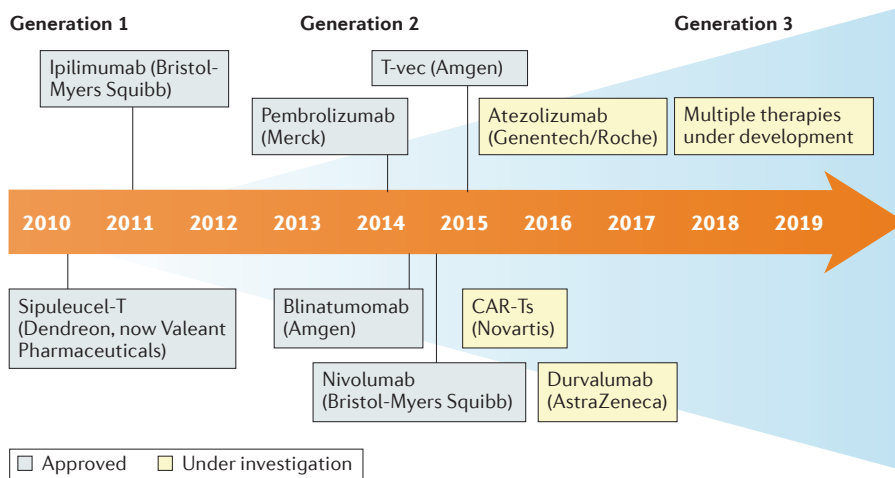


Figure 2 | Three generations of immuno-oncology drugs. The modern era of immuno-oncology commenced with the approval of sipuleucel-T in 2010 and ipilimumab in 2011, providing the first survival improvements by immunotherapies in randomized Phase III trials. These therapies may be summarized as generation 1. Although sipuleucel-T did not become a commercial success, ipilimumab was transformational for the field and contributed to a model for further immuno-oncology drug development. Generation 2 followed on the heels of ipilimumab with a wave of programmed cell death protein 1 (PD1)- and PD1 ligand 1 (PDL1)-blocking antibodies as well as the bi-specific antibody blinatumomab, the oncolytic virus talimogene laherparepvec (T-vec) and emerging cell and gene therapies using CD19⁺ chimeric antigen receptor (CAR)-transduced T cells (CAR-Ts). Pembrolizumab, nivolumab, blinatumomab and T-vec were approved in 2014–2015. Other pivotal programmes with atezolizumab and durvalumab are ongoing and are being followed by many others. Generation 3 is emerging with multiple drug programmes across several modalities (FIG. 3). The breadth and depth of this third generation provides the opportunity for differentiation through diverse modalities, innovative targets and novel combinations and is thus likely to expand the already demonstrated patient benefit (TABLE 3) across various patient populations.

Generation 3: expanding the tool box

Unlike advances in oncology drug development in the past, which have been mostly incremental, the first two generations of immuno-oncology agents have already generated substantial benefit over the previous standards of care. Nevertheless, although some patients may achieve cure or long-term disease control with first- or second-generation treatments, the majority of patients are still in need of a beneficial next-generation treatment. Specifically, many patients are not responding to checkpoint inhibition or they respond and subsequently relapse, thus needing effective follow-on therapies.

FIGURE 3 shows the three main arms of the immune system and how they can be utilized by immunotherapeutic modalities. To date, most of the activity in this field has concentrated on the T cell space. The second branch of the adaptive immune system, B cell immunity, has not yet received much attention for therapeutic purposes. However, it has certainly proven its utility for prophylactic vaccination against infectious diseases, in which it is a central mechanism^{58,59}. Innate immunity

targets and drugs (for example, natural killer (NK) cell-targeting therapies) are gaining great interest, and novel approaches are emerging^{60,61}. Overall, the variety of modalities under investigation include cytokines⁶², chemokines⁶³, cell therapies (including genetically engineered cells)^{64–66}, checkpoint modulatory antibodies¹⁶, cancer vaccines^{67,68}, BITEs that direct T cells to cancer cells (connectors)^{40–42}, dual-specific antibodies that integrate two targeting moieties into one molecule^{69,70}, small molecules⁷¹, oncolytic viruses⁷² and immune adjuvants (for example, toll-like receptor (TLR) agonists)⁷³. This wide range of modalities can be used in various ways to stimulate anticancer activity across the different branches of the immune system. It is likely that these new therapeutics will enable further improvements over the already successful generations 1 and 2. However, the further differentiation of new medicines in this fast-paced space will depend on novel targets in each category, the use of the different modalities as shown in FIG. 3 and the development of rational combinations, as well as the determination of effective biomarkers

that allow physicians to direct patient populations to the right therapies or combinations. Novel targets for this range of therapies can be found for each modality and along the cancer immunity cycle⁷⁴. TABLE 4 summarizes lead characteristics of different immuno-oncology modalities, illustrating the breadth of biological processes that are being harnessed by these agents.

Some aspects of generation 3 immuno-therapeutics are particularly noteworthy. First, cancer vaccines designed to induce T cell responses against tumour cells have been at the centre of cancer immunotherapy for decades but have not yet delivered the desired clinical results^{6,75}. One prominent reason for this may be that these vaccines did not address the role of immunosuppression in cancer, which can now be modulated by checkpoint blockers. This hypothesis will need to be systematically tested through the use of combination therapies. Novel approaches, such as neo-antigen vaccines, which induce an immune response against unique tumour-specific antigens that have arisen through mutation, indicate that more-individualized approaches that are based on new scientific insights into cancer vaccines are entering the immuno-oncology stage^{76–80}. These approaches carry new promise but also have a greater level of complexity than previously developed vaccines and, consequently, they require a higher level of technical innovation and investment regarding CMC and regulatory aspects⁸¹.

Second, oncolytic viruses thus far have been an attractive concept and have been intensively investigated⁷²; however, so far, only one of these has achieved a positive result in a Phase III trial and subsequent regulatory approval^{40–42}. The main challenges to this approach have been the clear characterization of the immune response by which locally injected oncolytic viruses achieve systemic effects and the modification of virus properties to allow systemic administration, thereby achieving broader utility⁸². These aspects are under investigation and, together with combination therapy, will probably define how widely applicable oncolytic virus therapy will be.

Third, cell therapies were initially viewed as attractive options for use as cancer vaccines. For example, it was shown that sipuleucel-T delivered a survival benefit in CRPC³⁸. Following this, more-complex cell and gene therapies emerged in the form of CAR-Ts and T cell

receptor (TCR)-transduced T cells^{64–66}. To build on the success story of CAR-Ts in B cell malignancies, new targets need to deliver similar effects in types of cancer other than CD19⁺ malignancies. Furthermore, toxicity risks such as cross-reactivity with healthy tissues require mitigation or, preferably, preclinical screening or clinical management processes that avoid them altogether⁸³. The cell and gene therapy space is evolving rapidly and receives substantial funding, enabling the development of new technologies. These technologies include gene editing to more precisely insert gene constructs into host cells independent of viral vectors or to knock-out undesired genes; the introduction of safety switches into cells that allow control of the activity of genetically engineered cells *in vivo*; and parallel engineering of several genes (for example, genes encoding for cytokines or checkpoint blockers) to further modulate cell functions. Although there is still some way to go, and CMC as well as commercial challenges for cell and gene therapies are substantial, this area represents a great expansion of our toolbox and holds the promise to have a major role in immuno-oncology in the long term.

Future directions for immuno-oncology

At least five key trends that drive the directions of immuno-oncology have emerged (FIG. 4).

Changes in standards of care. The substantial improvements in survival observed with checkpoint-modulating immunotherapies are starting to change standards of care in oncology. This trend was initiated by first- and second-generation agents and will probably continue with generation 3. As discussed above, new modalities, such as CAR-Ts, are already showing attractive clinical results. However, these new modalities may also carry new toxicity risks, such as the potential for induction of a cytokine storm and cross-reactivity with healthy tissue, that require careful mitigation⁸³. Overall, this trend will probably substantially change the oncology-treatment landscape.

Improvement of end points and research methods. The fast maturation of the immunotherapy space requires reliable tools and mechanisms for conducting and reporting research²¹. Specifically, the extended survival times and novel activity patterns that are observed with

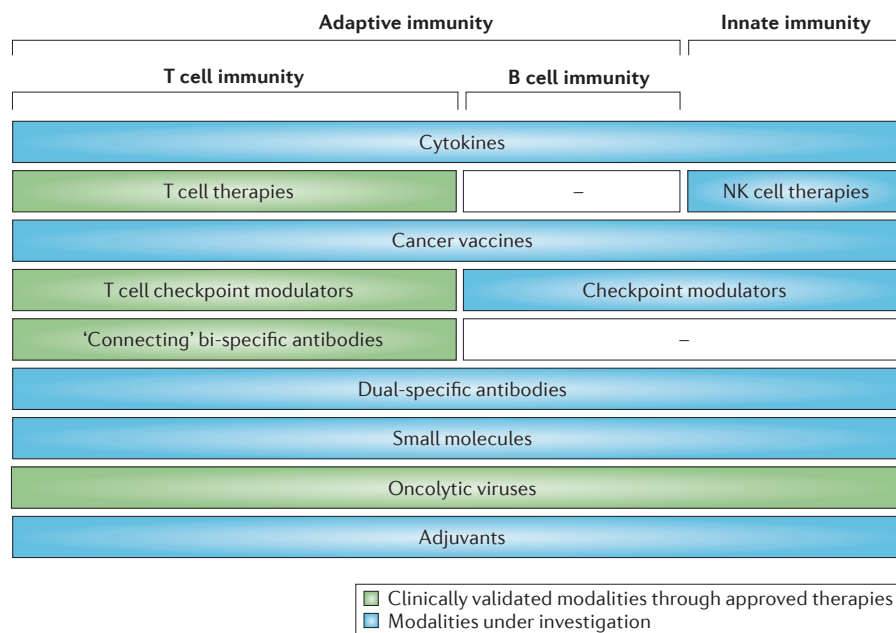


Figure 3 | Generation 3: various immuno-oncology modalities. The adaptive and innate arms of the immune system provide ample opportunity for therapeutic intervention. Most of the focus of the field is still in the area of T cells. However, strategies targeting innate immune mechanisms, as well as B cell therapies (which are currently receiving little attention for therapeutic use), are becoming increasingly attractive. The range of modalities includes cytokines, cell therapies, cancer vaccines, checkpoint modulators, 'connecting' bi-specific antibodies (also referred to as bi-specific T cell engagers (BITEs), dual-specific antibodies, small molecules, oncolytic viruses and immune adjuvants. The first approved modalities using T cell mechanisms are cell therapies (sipuleucel-T), checkpoint modulators (ipilimumab, pembrolizumab and nivolumab), connecting bi-specific antibodies (blinatumomab) and most recently oncolytic viruses (talimogene laherparepvec). NK, natural killer.

new immunotherapies require a formal adjustment of clinical end points to allow timely and complete reporting of efficacy in future randomized trials^{24,84}. Although exploratory end points such as immune-related response and milestone survival have been defined, consensus initiatives by the CIC and others are underway to support the validation of these end points for use in pivotal studies (A. Hoos, unpublished observations). irRC have introduced new concepts for measuring the clinical effects of immunotherapy, including confirmation of progression via subsequent scans to detect delayed responses; measuring new lesions to include them into the total tumour volume; accounting for durable, stable disease as a benefit; and treating patients beyond conventional progression if the clinical situation allows it.

It is noteworthy that, since the introduction of irRC and related immunotherapy end points in 2009, several substantial advances have been made. These include: the transferability of irRC concepts between the WHO

(bi-dimensional tumour measurements) and RECIST (uni-dimensional tumour measurements) guidelines; the application of irRC to diseases beyond melanoma (in which they were first introduced); the inclusion of irRC concepts into regulatory guidance documents from the FDA and the EMA; the expansion of irRC concepts beyond their initial implementation; and the demonstration of an irRC-detected class effect across several immunotherapies^{85,86}.

Several other methodological improvements have been made for cancer immunotherapy development²¹. For example, immune biomarker development has historically been quite variable and burdened by inconsistent assay use as well as inconsistent publication of results. To address these inconsistencies, community-wide initiatives have created validation and harmonization processes for immune biomarker assays to achieve reproducible data generation (for example, ELISPOT, intracellular cytokines and tetramers) as well as consistent reporting of results (for example, Minimal Information About T cell Assays (MIATA)). These

Table 3 | Outcomes of completed Phase III trials with checkpoint-modulating agents as of December 2015

Disease	Comparators	Hazard ratio		n	Impact	Refs
		OS*	PFS†			
Ipilimumab						
Pre-treated advanced melanoma	Ipilimumab versus gp100	0.66	0.64	676	Proof of concept, initial approval and new SOC	37
Untreated advanced melanoma	Ipilimumab plus DTIC versus DTIC alone	0.72	0.76	502	Proof of concept, supportive for approval and new SOC	45
High-risk adjuvant melanoma	Ipilimumab versus placebo	Too early for results	0.75 (RFS)	951	Proof of concept for effectiveness of checkpoint modulators in MRD	46
Post-Taxotere CRPC	Ipilimumab plus radiation therapy versus radiation therapy alone	• 0.85 (ITT) • Lower-risk subgroup: 0.62	0.7 (ITT)	799	Indication for clinical effects in CRPC	47
Nivolumab						
Untreated advanced melanoma	Nivolumab versus DTIC	0.42	0.43	418	New SOC, replacing chemotherapy	48
Pre-treated advanced squamous NSCLC	Nivolumab versus docetaxel	0.59	0.62	272	New SOC, replacing chemotherapy	50
Pre-treated advanced non-squamous NSCLC	Nivolumab versus docetaxel	0.73	Not statistically different	582	New SOC, replacing chemotherapy	113
Pre-treated advanced renal cell carcinoma	Nivolumab versus everolimus	0.73	Not statistically different	821	New SOC	114
Pembrolizumab						
Untreated or pre-treated advanced melanoma	Pembrolizumab versus ipilimumab	0.63	0.58	834	Superiority of PD1 over CTLA4 on OS	51
Pre-treated advanced NSCLC	Pembrolizumab versus docetaxel	0.62	Not statistically different	1034	New SOC, replacing chemotherapy	115
Ipilimumab plus nivolumab						
Advanced melanoma	Ipilimumab plus nivolumab versus nivolumab alone versus ipilimumab alone	Too early for results	<ul style="list-style-type: none"> • Ipilimumab plus nivolumab versus ipilimumab: 0.42 • Nivolumab versus ipilimumab: 0.57 • Ipilimumab plus nivolumab versus nivolumab: 0.74 (no <i>p</i> value) 	945	Superiority of the combination over nivolumab or ipilimumab alone, but increased toxicity with the combination	52

CRPC, castration-resistant prostate cancer; CTLA4, cytotoxic T lymphocyte-associated antigen 4; DTIC, dacarbazine; gp100, a synthetic peptide cancer vaccine; ITT, intention to treat; MRD, minimal residual disease; NSCLC, non-small cell lung cancer; OS, overall survival; PD1, programmed cell death protein 1; PFS, progression-free survival; RFS, relapse-free survival; SOC, standard of care. *Hazard ratio for OS unless otherwise indicated. †Hazard ratio for PFS unless otherwise indicated.

processes are based on extensive initiatives including more than 100 participating laboratories or scientific experts and are described elsewhere^{87–89}.

Immune biomarker development. Similar to the overall drug-development effort, there is substantial progress in immune biomarker development, which was influenced in part by the development of targeted therapies. For targeted therapies, biomarkers for patient selection were urgently needed, and their utility for the development of companion diagnostics that are tied to new drug applications was

established^{90,91}. For immuno-oncology agents, the first emerging clinical immune biomarker is PDL1 expression in the tumour, which enables the identification of patients who are more likely to respond to PD1- or PDL1-blocking agents. The data gathered to date indicate that PD1- and/or PDL1-blocking agents achieve greater response rates and better survival in patients with PDL1+ tumours^{48,52,92–95}; however, the fact that this is a dynamic biomarker for which expression may change has led to some variable results, and its role as a biomarker is still being discussed. For example, for treatment with nivolumab,

there was no correlation of PDL1 expression with outcome in squamous NSCLC, but a correlation was observed in non-squamous NSCLC^{94,95}. In a broader analysis of PDL1-related biomarkers with atezolizumab, a relationship between PDL1 expression, PDL1-suppressed anticancer immunity and responses to PDL1 blockade was suggested⁹⁶. Some PD1-blocking antibodies (such as nivolumab) have obtained labels without a restriction by PDL1 status, whereas others (such as pembrolizumab) have obtained a PDL1 label restriction. However, companion diagnostic assays for the determination

Table 4 | Characteristics of immuno-oncology modalities

Modality	Status	Pre-clinical findings	Pharmacokinetics	Pharmacodynamics	Clinical	
					Efficacy	Safety
Cytokines	IL-2 and IFN α approved but uncommonly used owing to high toxicity and low efficacy	Moderate effects	Clear kinetics	Multiple effects, MoA is complex and hard to attribute to one mechanism	Low	High unspecific toxicity (for example, whole body oedema)
Cellular therapies (CAR-Ts and TCR-Ts)	Multiple CAR-Ts and TCR-Ts in clinical trials; high complexity of manufacture and supply chain; strong target dependency; and few clinically effective targets (for example, CD19 and NY-ESO-1)	Moderate-to-strong effects	<i>In vivo</i> tracing and longevity of infused cells	Clear MoA; target-dependent effects	High response rates depending on the target (up to 90% for CD19, 50–60% for NY-ESO-1) ¹²⁹	Cytokine release syndrome; target-dependent cross-reactivity with healthy tissue
Vaccines	Many types of cancer vaccines in clinical trials (including peptides, proteins, viruses and cells)	Clear effects in mice, but these do not directly translate to humans	No direct pharmacokinetics for peptide- or protein-based vaccines	Measurable immune responses	Minimal as monotherapy; combinations to be explored	Minimal toxicity
Checkpoint-modulatory antibodies	Ipilimumab (targeting CTLA4), pembrolizumab (targeting PD1) and nivolumab (targeting PD1) approved; many compounds (including PDL1 blockers) in clinical investigation	Moderate effects	Clear kinetics	Universal mechanism not bound to histology, specific mutations or cancer antigens; multiple downstream effects after target engagement	Strong effects on survival with long-term survival in a subset of patients	Distinct irAEs; manageable with treatment algorithms
Connecting bi-specific antibodies	Blinatumomab (BITE) approved for CD19 ⁺ B cell malignancies	Strong <i>in vitro</i> cytolytic activity	Clear kinetics	Clear MoA; activating and connecting T cells to target-expressing cancer cells	High response rates	Moderate-to-severe toxicity
Dual-specific antibodies	Multiple antibody formats in discovery	Good effects (depending on the target)	Clear kinetics	Dependent on targets; dual checkpoint inhibition being explored	NA	NA
Small molecules	Several small molecules in clinical trials (for example, targeting IDO) and multiple small molecules in discovery	Strong effects (depending on the target)	Clear kinetics	Clear on-target effects, with several targets located in the tumour microenvironment	Low as monotherapy; combinations under exploration	Potential for off-target toxicities
Oncolytic viruses	T-vec approved for unresectable melanoma recurrent after initial surgery; several others under clinical investigation, most for intra-tumoural injection, with some expanding to systemic administration	Moderate-to-strong effects	Clear kinetics	Systemic immune responses induced by intra-tumoural injection are insufficiently studied	Moderate response rates as monotherapy; systemic effects after local injection	Moderate toxicity for intra-tumoural injection
Adjuvants	None approved, unsuccessfully tested as monotherapies; new investigations now underway for combination therapies	Anti-tumour effects in mice, particularly in combination*	Clear kinetics	Multiple effects, MoA is complex and hard to attribute to one mechanism	Low as monotherapy; combination synergy	High toxicity if administered systemically

CAR-Ts, chimeric antigen receptor-transduced T cells; BITE, bi-specific T cell engager; IDO, indoleamine 2,3-dioxygenase; IFN α , interferon- α ; IL-2, interleukin-2; irAE, immune-related adverse event; MoA, mechanisms of action; NA, not applicable; NY-ESO-1, cancer/testis antigen 1; TCR-Ts, T cell receptor-transduced T cells; T-vec, talimogene laherparepvec. *In combination with with chemotherapy or checkpoint modulators.

of PDL1 status in tumours are based on immunohistochemistry and demonstrate some differences in assay characteristics. As each registered therapy will have its own customized companion diagnostic, this creates complexity for patients in the use

of PD1- and PDL1-blocking agents if they move from one PD1- or PDL1-targeted therapy to another. The oncology community has recognized this challenge quickly and initiated a harmonization effort with participation of the FDA and non-profit

organizations such as the AACR, the ASCO, and CIC-CRI. Importantly, as new assays are being introduced (for example, multi-colour immunohistochemistry), new opportunities emerge to better characterize the underlying biology of PDL1 expression through, for

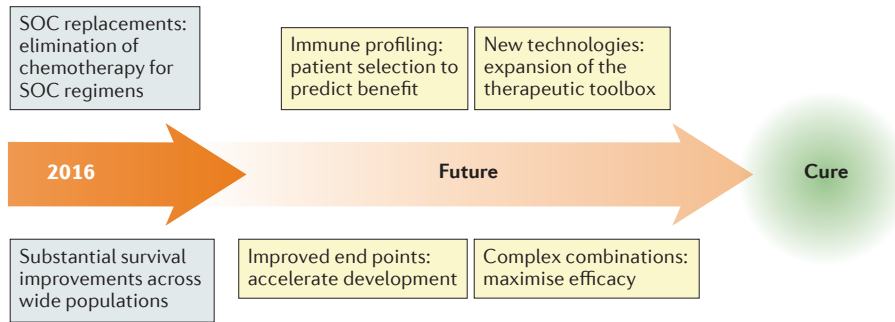


Figure 4 | Key trends defining the future of immuno-oncology. At present, several major trends are apparent that will drive the directions of immuno-oncology. Although replacements of some chemotherapy standards of care (SOCs) have already taken place, the ongoing wave of studies will probably continue this trend. Thus far, such changes to SOC have come with substantial improvements in patient survival (TABLE 3). For the further expansion of immunotherapy impact in new patient populations, additional trends come into play. These include rapid biomarker development for patient selection, the creation of combination therapies to maximize efficacy and the further improvement of end points. With the substantial improvements in survival provided by current immunotherapies like PD-1 blockers, future trials will take much longer to demonstrate additional survival improvements. New endpoints with earlier readouts such as milestone survival at 1, 2 and 3 years are needed to provide realistic study timelines. The last trend is the introduction of several new technologies that expand the toolbox of immunotherapies and underlie the continued progress in the space. Ultimately, the prospect of a cure — functional or real — has never been better for cancer patients.

example, determination of the cell type on which it is expressed and its co-expression with other markers.

Besides PDL1, several other important biomarkers are emerging. For example, the characterization of the immune infiltrate in the tumour has been recognized as a possible prognostic and predictive factor. It can be described in the form of an immunoscore comprised of the frequency of CD3⁺ and CD8⁺ cells in the tumour microenvironment. In resected primary colorectal cancer specimens, the immunoscore has shown stronger prognostic value than the established TNM (tumour, node, metastases) histopathological staging system. The practical utility of this immunoscore will depend on whether it can also be reliably assessed from tumour biopsies^{97,98}. Another central observation is the identification of an immunogenic mode of cell death induced by non-immunotherapies, which is characterized by damage-associated molecular patterns (DAMPs), including high mobility group protein B1 (HMGB1), calreticulin and extracellular ATP released from dying tumour cells. Induction of immunogenic cell death by chemotherapy or targeted therapies may contribute to immune responses that can be modulated by immunotherapies and could guide potential combination strategies with immunotherapeutics⁹⁹. A recent clinical observation relates to the mutation load in colorectal tumours that, in the case of a high rate of mutations, may provide a pool

of targets to enable a higher rate of possibly effective immune responses. Naturally occurring immune responses against these targets may be enhanced by checkpoint-modulating drugs and may lead to clinical activity⁵⁶. A further example of an emerging biomarker is inducible T cell co-stimulator (ICOS), the expression of which is upregulated on activated immune cells, which may help to identify subsets of patients who are likely to benefit from checkpoint modulation^{100,101}. ICOS has recently expanded its utility from a predictive biomarker to a potential therapeutic target that can be stimulated with agonistic antibodies. Another clinical biomarker observation in patients treated with ipilimumab suggests that high levels of soluble CD25, a subunit of the IL-2 receptor, may indicate IL-2 neutralization, thus contributing to resistance to ipilimumab therapy¹⁰². The repertoire of biomarkers for immuno-oncology is continuously increasing, and rapid progress can be anticipated in this area.

Rational combination strategies.

A growing trend in immuno-oncology drug development is the investigation of combination therapies. Immunotherapy modalities are commonly being tested for rational combinations with either chemotherapies or targeted therapies or with other immunotherapies. Meaningful synergistic effects are anticipated with such strategies^{103,104}; for example, the

use of targeted therapies that elicit fast-occurring responses may increase the time to progression and thus afford patients time to build immune responses to immunotherapies. Moreover, the use of combination immunotherapies may convey long-term survival benefits that the targeted therapy may not deliver alone. A desired immunotherapy effect is the plateau at the end of Kaplan–Meier survival curves (which may be further elevated through combinations of immunotherapeutics) representing a greater proportion of patients who achieve long-term survival. It is not yet clear which combinations will be most effective; it seems plausible that combinations of different immunotherapeutic agents may be particularly effective with regard to long-term survival — this was suggested by the elevation of the survival plateau in metastatic melanoma from approximately 20% for ipilimumab alone to approximately 70% for ipilimumab plus nivolumab (Phase I data)¹⁰⁵ — however, Phase III survival data for this combination are still outstanding.

The first chemotherapy–immunotherapy combinations in the clinic were ipilimumab plus dacarbazine in metastatic melanoma⁴⁵ and ipilimumab plus carboplatin or paclitaxel in advanced NSCLC and SCLC¹⁰⁶. These combinations demonstrated some increases in efficacy, albeit with a concurrent (but still manageable) increase in toxicity. Beyond combinations with chemotherapy, combinations with targeted therapies were also tested. In melanoma, combinations of ipilimumab with the BRAF inhibitor vemurafenib¹⁰⁷ or with the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib¹⁰⁸ were the first combinations of targeted therapy with immunotherapy that were clinically tested. The Phase I study for the former combination closed during dose escalation owing to increased hepatotoxicity¹⁰⁷, and the Phase I trial for the latter closed the arm for the triplet combination owing to its incidence of colonic perforations. However, a manageable safety profile was demonstrated for the doublet of dabrafenib and ipilimumab¹⁰⁸. Many other combinations of targeted therapy with immunotherapy are in clinical testing and will read out results in the foreseeable future. As mentioned above, the first immuno–immuno combination to reach the clinic — ipilimumab and nivolumab in metastatic melanoma — delivered

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promising efficacy data with regard to response and survival (Phase I data, presented at the 2013 ASCO conference)¹⁰⁵ and PFS (Phase III data, presented at the 2015 ASCO conference)⁵². However, this combination also substantially increased the rate of high-grade irAEs, which, to date, have remained manageable with the established treatment algorithms⁵². On the heels of these studies follow a variety of combinations with new checkpoint-modulatory antibodies targeting OX40 (also known as tumour necrosis factor receptor superfamily member 4 (TNFSF4)), T cell immunoglobulin mucin receptor 3 (TIM3, also known as HAVcr2), lymphocyte activation gene 3 protein (LAG3), 4-1BB (also known as CD137 or TNFRSF9) or others, which have shown synergy in murine models and are fuelling the rapid trend toward the development of combination therapies^{109–112}.

Expansion of the toolbox of novel immune therapies. As discussed above, the toolbox of novel immune therapies (FIG. 3) is expanding, a trend that underlies the continued rapid progress that is anticipated for this field. This toolbox contains multiple modalities but also novel targets and broad combination opportunities. It is likely that checkpoint modulation will become the backbone of cancer therapy and will be supplemented by combinations with synergistic agents from the toolbox. Clear trends for combinations of checkpoint inhibitors with cancer vaccines, small molecules, oncolytic viruses or other checkpoint inhibitors are evident, and other trends are emerging.

Conclusions

Most of the clinical success in the immunotherapy area is still based on the universal checkpoint modulatory antibodies, but this success promises to expand to other modalities. It remains important to remember that immuno-oncology agents across different modalities, and even within the same modality (for example, different checkpoint modulators), can show distinct clinical efficacy and safety profiles (TABLE 4). Some agents, such as PD1 and PDL1 blockers, can deliver high conventional response rates as a first indicator of efficacy^{28,48,56}, whereas others, such as CTLA4 blockers or cell therapies such as sipuleucel-T, have a more complex efficacy profile with conventional response rates of 10% or less but a broad effect on patient survival^{37,38}. The most unifying

feature of those agents for which clinical activity is established is their effect on survival. Given the diversity of compounds under investigation, the development of immuno-oncology agents either as a monotherapy or in combination with other agents needs careful evaluation using all available tools at our disposal. For a comprehensive characterization of the range of clinical activity patterns that may be induced by different immunotherapies, tools such as irRC may be used. This may enable the detection of activity patterns beyond conventional response, even for agents for which the conventional response rates are commonly high (for example, PD1 blockers). The recent data from nivolumab and pembrolizumab, showing significant improvements in survival but not in PFS^{113–115} (TABLE 3), suggest that even for PD-1 blockers a divide between response-based end points and survival exists in some settings. Similarly, adverse event profiles across different immunotherapy modalities will vary greatly but may share important immune-related features. irAE management principles may therefore be a valuable basis to ensure patient safety in clinical trials. In the case of both irRC and irAE management algorithms, concepts may get expanded and adapted to new immunotherapy modalities and their unique clinical characteristics. For combination therapies, investigations may be designed with an understanding of the underlying mechanism of action, the expected clinical profile and the potential synergistic activity of the agents involved. The resulting effects of these combinations may well exceed the expectations for the individual agents on pharmacodynamics, efficacy and safety when the sum of the combination effect is biologically and clinically different to the simple added effects of both agents. These combination choices should be driven by an understanding of the underlying science¹⁸.

Overall, immuno-oncology agents have the potential to transform cancer care and it is likely that they will become the backbone of cancer therapy in the future. The potential for cure, either on a functional level by turning cancer into a controllable chronic disease (similar to achievements with HIV drugs) or in the true eradication of the disease, may now be a prospect for large numbers of cancer patients^{116,117}. Much more work needs to be done to achieve this; however, the field is moving rapidly, the directions are reasonably clear and the outlook for cancer drug development has never been as good.

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Competing interests statement

The author declares [competing interests](#): see Web version for details.