Immuno-oncology for surgeons

S. L. Lee[1,2,3], A. Al-Shamkhani[2] and A. Mirnezami[1,3]

[1]Southampton Cancer Research UK Centre, and [2]Centre for Cancer Immunology, University of Southampton, and [3]University Surgical Unit, University of Southampton, MP127, Faculty of Medicine, University Hospital Southampton, Southampton, UK

Correspondence to: Professor A. Mirnezami, Southampton Cancer Research UK Centre, University of Southampton, Tremona Road, Southampton SO16 6YD, UK (e-mail: ahm@soton.ac.uk)

Cancer has traditionally been treated with surgery, cytotoxic chemotherapy and/or radiotherapy. The focus of treatment has been the mutated neoplastic cell. Critical advances in genomic and molecular techniques herald the potential for personalized treatments. Incremental breakthroughs in immunology have translated to a step-change in care by providing a mechanistic understanding of the immune system and how it may be mobilized to target cancer cells. As a result, clinical trials of immune-modifying agents have increased at an exponential rate and are revolutionizing cancer care. It is increasingly likely that the surgical oncologist will find themself caring for patients who have had immuno-oncology therapies as part of their neoadjuvant or adjuvant treatment. This review provides an update on immuno-oncology for the surgeon, covering the mechanisms of action of the agents in use. Emerging and surgically relevant toxicities are discussed, and available data on combining and sequencing cancer surgery with immuno-oncology treatments are summarized.

Introduction

The past two decades has seen great strides in understanding of cancer. At the turn of the century, tumorigenesis was understood to be a multistep process involving genomic instability contributing to either gain of oncogene functions or loss of tumour suppressor gene ability, leading to malignant transformation of normal cells[1]. An increasing body of evidence now shows that, besides intrinsic and aberrant genomic and epigenetic instability, cancer cells also recruit an army of normal cells, including various immune and stromal cells, to form a dynamic and complex tumour microenvironment (TME).

Far from being passive bystanders, the cells recruited to the TME are active participants in tumorigenesis and disease progression, contributing diversely to the hallmarks of cancer: sustaining proliferative signalling, evading growth suppressors, avoiding immune destruction, enabling replicative immortality, tumour-promoting inflammation, activating invasion and metastasis, inducing angiogenesis, genome instability and mutation, resisting cell death and deregulating cellular energetics[2].

As a result of these discoveries, cancer treatment is evolving rapidly. Cancer has traditionally been treated with surgery, cytotoxic chemotherapy or radiotherapy, and the focus of treatment has revolved heavily around targeting the mutation-driven neoplastic cell. Advances in genomic and molecular techniques have led to the introduction of personalized cancer treatments, targeting oncogenic pathways such as the human epidermal growth factor receptor 2 pathway in breast cancer and the epidermal growth factor receptor pathway in colorectal cancer[3,4]. However, there remain a significant number of patients who do not respond to traditional therapies or personalized medicine, raising the question of what other cellular, local or systemic characteristics of cancer are unaccounted for that may influence the progression of cancer and limit response to treatment.

There are a number of myeloid and lymphoid immune cells in the TME that constantly and dynamically communicate with the neoplastic cell, the wider TME constituents and the systemic immune system. The consequences of this network can be polarized into protumour and antitumour ecosystems. The aim of immuno-oncology (IO) is to understand this dynamic process and methods to manipulate it. Surgical oncologists will increasingly find themselves facing patients treated with IO-based therapies. Consequently, surgeons must keep up to date with this new method of treatment as it evolves, and remain aware of its advantages and limitations, and how it may influence surgical care.

This article aims to provide a concise guide to IO, with a focus on CD8+ T cells whose cytotoxic ability has been the focus of research in the development of new immunomodulatory drugs. Key concepts in immunoediting and immune escape pathways are introduced, followed by a description of the diverse modalities of immunotherapy, the safety and feasibility of combining immunotherapy with surgery, and what the future is likely to hold.

Immunoediting in cancer

In 1957, Sir Frank MacFarlane Burnet[5] first described the concept of failure of immunological control as a factor that contributes to carcinogenesis. It is now understood that the innate and adaptive immune systems have the ability to destroy tumour cells and control tumour growth. However, they can also be manipulated to become tolerant and even promote cancer evolution.

This dynamic process is termed immunoediting and can be understood in three non-linear phases: elimination, equilibrium and escape[6].

In the first phase, elimination, a competent immune system is able to recognize and destroy transformed cells. Mutagenic tumour cells became visible to the immune system when cancer neoantigens are presented either on cell surfaces or when liberated during cell degradation. Cells from both the innate and adaptive immune systems participate in the elimination. However, central to the immunoediting concept is the priming and recruitment of cytotoxic effector CD8+ T cells to the TME which can eliminate cancer cells. During this phase the balance leans towards antitumour activity; however, the elimination process invariably exerts a selective pressure on tumour cells, which enables some to survive and enter the equilibrium phase.

During the equilibrium phase, surviving transformed cells can coexist with the immune system. Tumour proliferation is suppressed, and the cancer remains dormant, sometimes for years[7]. In this phase, continuous immune pressure ultimately facilitates tumour evolution and the emergence of immune-resistant clones, before eventually presenting clinically as primary cancer, recurrence or metastases. During the equilibrium phase, tumour cells and the TME acquire mechanisms that eventually tip the balance between antitumour and protumour forces, realizing the next phase: escape.

Given that a healthy subject with a competent immune system can still develop cancer, the majority of research in IO has focused on the methods employed by cancer cells to evade death by CD8+ T cells. Immune escape can be accomplished in many ways, involving the tumour cells themselves, the TME or the immune system. The mechanisms can be classified into two broad categories: evading recognition, and deactivation of the cytotoxic T cell response.

The first step of a successful CD8+ T cell response is antigen presentation, which involves neoantigen production by neoplastic cells, either presented by MHC class I molecules or released during cell death, and activation of antigen-presenting cells (APCs), most importantly dendritic cells (*Fig. 1*)[6]. Cancers that have a higher mutational load, such as those with microsatellite instability (MSI), exhibit greater presentation of neoantigens leading to more recruitment of CD8+ T cells to the TME, which is associated with a better response to immunotherapy and survival[8]. Conversely, cancers with a lower mutational load have a poorer outcome. Cancer cells can also manipulate the antigen presentation process by downregulating the MHC class I molecules on tumour cells, or by hindering dendritic cell recruitment[9,10].

When a dendritic cell presents an antigen to a naive T cell, the T cell can be activated only if it receives a second signal from a co-stimulatory molecule in the presence of inflammatory

cytokines such as interleukin 12[11]. Once these conditions have been satisfied, naive CD8+ T cells are primed, and acquire cytotoxicity to become effector CD8+ T cells. In the TME, once effector CD8+ T cells encounter the same antigen, they become activated and undergo clonal proliferation (*Fig. 1*).

In patients with cancer, T cell priming and activation is often impaired. A hallmark of impairment is the increased expression of checkpoint proteins such as programmed cell death protein (PD) 1 and cytotoxic T lymphocyte-associated protein (CTLA) 4 on T cells, which suppress cytotoxic activities through binding to their ligands PD-L1 and CD80/CD86 on APC or tumour cells[12]. The physiological role of checkpoint protein is to serve as an inhibitory impetus to limit the T cell response and prevent autoimmunity. Cancer cells are able to hijack this function to their advantage. Checkpoint proteins are highly expressed in tumour infiltrating T cells, often indicating an exhausted state, and the loss of cytotoxic function and proliferation ability[12]. In the context of IO, the presence of checkpoint proteins and their ligands on cancer cells serve to thwart the cytolytic actions of CD8+ T cells. Different mechanisms of immune escape are summarized in *Fig. 2*.

Modalities of immunotherapy

Understanding the detailed molecular mechanisms underlying immune escape is critical to the development of immunomodulatory agents. In broad terms, three types of immunotherapy are recognized; checkpoint inhibitors, adoptive T cell transfer and cancer vaccines (*Fig. 3*).

At the forefront of immunotherapy are the checkpoint inhibitors, which have revolutionized the treatment of metastatic melanoma. Checkpoint inhibitors block inhibitory checkpoint proteins on CD8+ T cells or their ligands on APC or tumour cells, thus enabling T cell activation and clonal proliferation. The discovery and successful clinical application of such checkpoint inhibitors targeting the CTLA-4/CD80/CD86 and PD-1/PD-L1 axes in cancer therapy culminated in the award of the Nobel Prize in Physiology or Medicine in 2018.

The introduction of ipilimumab, an anti CTLA-4 monoclonal antibody to treat metastatic melanoma, improved the 10-year overall survival rate to 20 per cent[13]. This was further improved with combination therapy using two checkpoint inhibitors, ipilimumab (anti-CTLA) and nivolumab (anti-PD-1) in the phase III CheckMate 067 trial[14], which reported that the 4-year overall survival rate for combined treatment (53 per cent) was superior to that

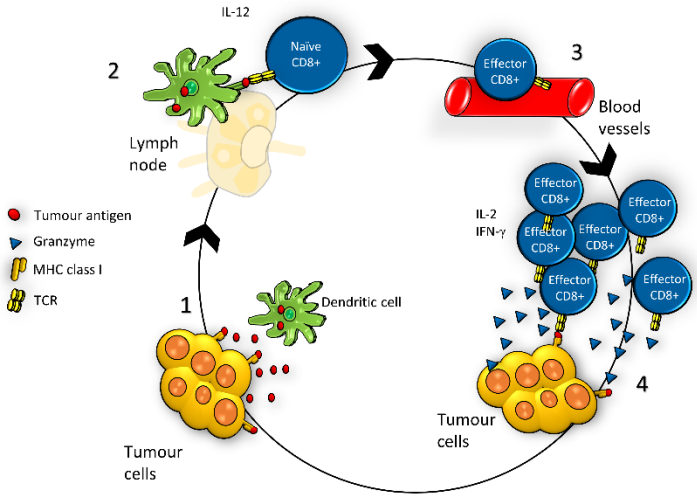

Fig. 1 Priming, activation and recruitment of CD8+ T cells by cancer neoantigens to the tumour microenvironment

1, Dendritic cells transport tumour antigen which are presented by MHC class I or released into the tumour microenvironment (TME). 2, Priming of naive CD8+ T cells in lymph nodes occurs when dendritic cells cross-present tumour antigen to naive T cells via MHC class I. 3, Primed CD8+ T cells (effector T cells) are transported along the blood vessels to reach the tumour site. 4, Primed CD8+ T cells are activated in the TME when tumour antigen is recognized by specific T cell receptors (TCRs). CD8+ T cells develop cytotoxic functions via release of cytokines (interleukin (IL) 2 and interferon (IFN) γ) and granzymes, and undergo clonal proliferation.

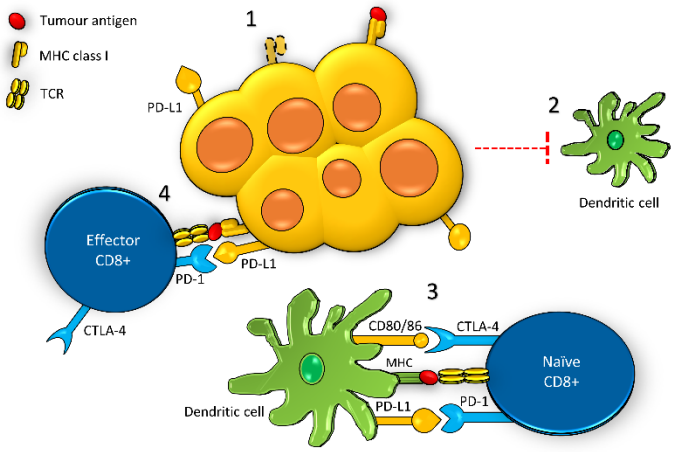

Fig. 2 Mechanisms of immune escape

1, Downregulation of MHC class I leading to lack of antigen presentation, 2, defective dendritic cell recruitment to the tumour microenvironment. 3, The presence of inhibitory proteins, such as cytotoxic T lymphocyte-associated protein (CTLA) 4 or programmed cell death protein (PD) 1, on T cells, which bind to their respective ligands, CD80/86 and PD-L1 on dendritic cells, prevents priming of naive CD8+ T cells. 4, PD-L1 is also present on tumour cells. The binding of PD-1 on effector T cells and PD-L1 on tumour cells prevents CD8+ T cell activation and proliferation.

for nivolumab (46 per cent) or ipilimumab (30 per cent) alone. In patients with metastatic renal cell carcinoma (RCC), median overall survival was 25 months with nivolumab *versus* 19.6 months with everolimus, a mechanistic target of rapamycin (mTOR) inhibitor[15]. In advanced non-small cell lung cancer (NSCLC), nivolumab and pembrolizumab (anti-PD-1) both showed superiority over docetaxel, in terms of overall survival and fewer adverse events[16,17]. One of the most important aspects of immunotherapy is the durable response in some patients. In the Checkmate 067 trial, those who responded to checkpoint inhibitors continued to have long-term survival benefit[14,18]. This is in contrast to targeted therapies such as BRAF or mitogen-activated protein kinase kinase inhibitors which may elicit resistance within 6–8 months after an initial response[19].

The success of checkpoint inhibitors is encouraging, but a number of cancers, such as colorectal, breast and ovarian tumours, remain largely refractory[20,21]. Biomarkers are used to stratify patients who are more susceptible to checkpoint modulation. Mutational burden was identified as a predictor of good response to checkpoint inhibition[22]. It was hypothesized that patients with MSI have a higher mutational load and may respond better to checkpoint inhibitors. A phase II trial[23] based on this hypothesis showed that cancers with greater MSI burden are better responders to pembrolizumab than those without (progression-free survival 78 *versus* 11 per cent). This study also showed that expression of CD8+ T cells and PD-L1 alone was not predictive of response[23]. Encouraged by the association between MSI and response to PD-1 blockade, a phase II trial[24] was conducted in 86 patients with 12 different tumour types harbouring MSI. Objective and complete radiographic responses were observed in 53 and 21 per cent respectively. Similar to other studies, responses were found to be durable, with an estimated overall survival rate of 64 per cent at 2 years.

Adoptive T cell transfer is a further potential immunomodulatory treatment. This involves harvesting T cells from patients and transferring them back following *in vitro* genetic engineering to redirect T cells towards a specific target antigen on a cancer cell. Once back in the patient, these T cells are reactivated when they encounter the antigen, mounting a cytotoxic attack. One type of adoptive T cell transfer that is showing promise is chimeric antigen receptor (CAR) T cell therapy. The CAR is an artificial transmembrane receptor which has an antibody fragment that targets cell surface antigens on cancer cells, and an intracellular domain that activates the CD3 signalling pathway once antigen binding has occurred[25]. As such, a CAR T cell does not require antigen presentation by an MHC class I molecule, enabling it to overcome

escape mechanisms involved in the antigen presentation pathways. CAR T cell therapy is successful in haematological malignancies, where up to 53 per cent complete remission in diffuse large B cell lymphoma has been reported[26]. Its applicability in solid tumours at present is anecdotal[27]. Another strategy for adoptive T cell transfer is to transfer autologous T cells with a genetically modified T cell receptor (TCR) that targets tumour antigens with enhanced affinity. A transgenic TCR has the benefit of recognizing a larger array of potential antigens than a CAR, including intracellular antigens, but requires the peptide to be presented by an MHC class I molecule[28]. Although the value of adoptive T cell therapy in solid tumours is presently limited, this remains a potential therapeutic option for cancers with low immunogenicity or dysfunctional antigen presentation.

In contrast, cancer vaccines have been less successful. Using a similar theory to that for preventative vaccines for infectious diseases, cancer vaccines involve boosting a patient's T cell response against a target antigen that is either associated with, or specific to, cancer cells. The biggest challenge in designing a cancer vaccine lies in choosing a target antigen in a disease that is evolving continuously[29]. Despite these challenges, there have been advances in personalized vaccines which contain RNA that encodes mutated proteins or fragments of mutated proteins from the patient's own tumour[30,31]. Tumour-specific immune responses were observed after vaccination, and patients who responded had sustained progression-free survival for up to 25 months. Interestingly, these two studies[30,31] also showed success in using anti-PD-1 therapy following recurrence after cancer vaccination. Although the number of patients in the two studies was small (6 and 5), similar to CAR T cell therapy, this work has provided proof of principle that personalized immunotherapy is feasible could be effective in patients with cancer.

Toxicity of immunotherapy

Toxicity of immunotherapy occurs as a result of immunomodulatory effects on normal tissues. It differs from the toxicity observed in patients receiving chemotherapy or radiotherapy, and is termed immune-related adverse events (irAEs). Immune-mediated damage can occur at any site in the body but is most common in skin and mucosa, the gastrointestinal tract, the endocrine organs, liver and lungs (*Table 1*)[32]. As checkpoint inhibitors are presently the most commonly used immunotherapy, most toxicity profiles are derived from studies involving anti-CTLA-4 and PD-1/PD-L1 treatment. Skin toxicity can present as rash, pruritus or vitiligo, and tends to occur early in treatment. Gastrointestinal toxicity is common and may be serious; diarrhoea can occur in 27–54 per cent of patients,

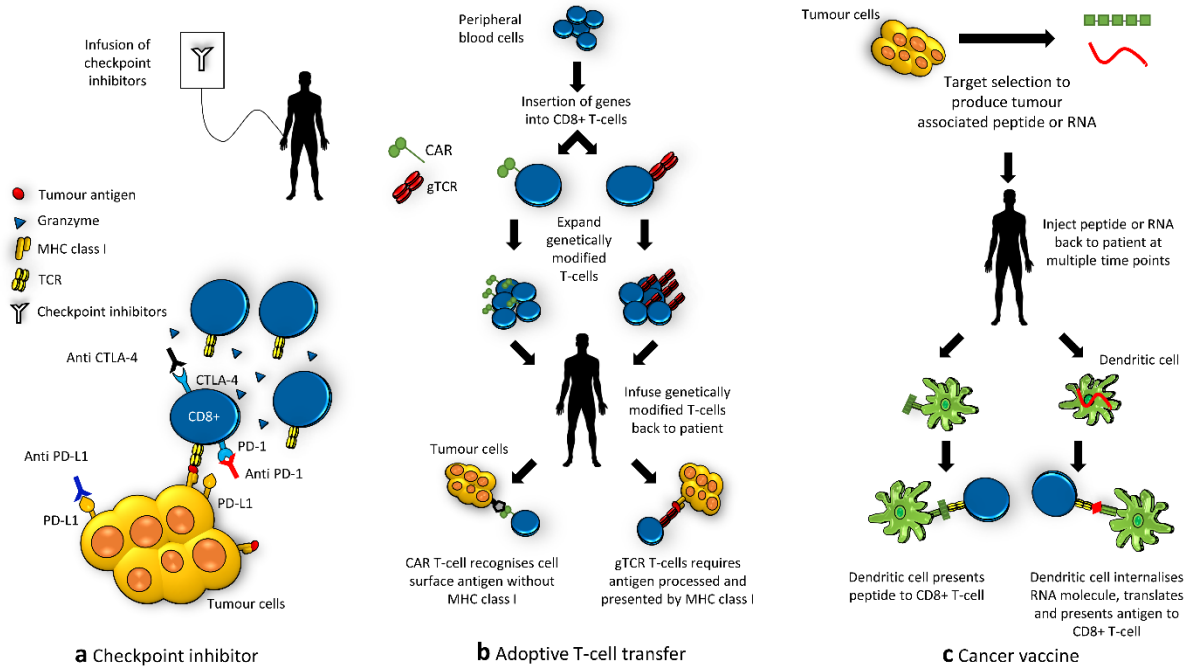

Fig. 3 Modalities of immunotherapy

a Checkpoint inhibitors bind to checkpoint proteins or their ligands. Once the inhibitory signal has been removed, CD8+ T cells are primed, activated and undergo clonal proliferation. **b** CD8+ T cells harvested from the patient's peripheral blood have either chimeric antigen receptor (CAR) or genetically modified T cell receptor (gTCR) inserted. These genetically modified T cells are expanded *in vitro* before intravenous transfer back to the patient. *In vivo*, CAR T cells are able to recognize surface antigen without antigen presentation by MHC class I, whereas gTCR T cells require antigen presentation by MHC class I; **c** Immunogenic tumour-associated peptide or antigen-coding RNA is produced after target selection using tumour cells from the patient. Peptide or RNA is transferred back to the patient at multiple time points to ensure adequate T cell priming. *In vivo*, peptides are presented to T cells by dendritic cells, whereas RNAs are internalized and translated by dendritic cells before the antigen is presented to T cells. TCR, T cell receptor; CTLA-4, cytotoxic T lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; PD-L1, PD-1 ligand.

whereas colitis may be found in 8–22 per cent of those on anti-CTLA-4 treatment[33]. Although most patients improve with steroid treatment or infliximab infusion, 1 per cent of patients with enterocolitis may have bowel perforation[33].

Immune-related endocrine disorders include hyperthyroidism or hypothyroidism, hypophysitis and, rarely, insulin-dependent diabetes secondary to autoimmunity. Hepatitis may occur in around 25–30 per cent of patients receiving combination therapy, but is often asymptomatic and diagnosed only on liver function tests[32]. The majority of side-effects are managed by medical treatment or by withholding immunotherapy. However, life-threatening side-effects such as myocarditis, pneumonitis and bowel perforation mean that patients must be monitored closely throughout treatment.

Safety and feasibility of surgery in patients on immunotherapy

As more patients receive immunotherapy as part of their care, surgeons are increasingly likely to encounter them in the neoadjuvant, adjuvant or emergency setting. Modern surgeons should understand the potential impact of immune modulation on surgical complications and postoperative care.

Immunotherapy affects the immune system in a different way from chemotherapy or targeted therapy, which create an immune suppressive environment that can affect wound healing adversely. There are currently no agreed guidelines on when to terminate immunotherapy before surgery and when to restart it afterwards. However, several small retrospective studies[34–37] have reported outcomes in patients who underwent surgery during or after immunotherapy. In total, these studies reported 55 patients who underwent surgery within 1–147 days of the last dose of checkpoint inhibitor. A wide range of procedures was performed, including lung resection, bowel resection with anastomosis, subcutaneous resection, craniotomy metastasectomy and lymph node dissection[34–37]. No Clavien–Dindo grade III–IV postoperative complications were reported, suggesting that surgery may be safe and feasible in these patients.

With the evident benefit of checkpoint inhibitors in metastatic diseases, there is already a trend towards their use in the neoadjuvant setting. A pilot study[38] investigating neoadjuvant PD-1 blockade in resectable lung cancer had surgical resection planned approximately 2 weeks after the last dose. Of the 22 patients recruited, 21 went on to have surgical resection without delay and with no reported surgical adverse events (the remaining patient was deemed ineligible for study according to the protocol). However, neoadjuvant immunotherapy is not without its drawbacks. A phase II clinical trial[39] investigating neoadjuvant nivolumab *versus* nivolumab and ipilimumab in high-risk resectable stage III and oligometastatic stage IV melanoma was terminated early owing to early disease progression in the nivolumab group (2

of 12 patients) thus preventing surgical resection, and high rates of grade 3 irAEs in the combination group. Of note, no delay or surgical complications secondary to irAEs were reported in this trial. Several other trials of neoadjuvant immunotherapy for resectable solid cancers, including urothelial cancer of the bladder (NCT02845323), RCC (NCT02595918, NCT02575222, NCT03055013, NCT02446860), head and neck squamous cell carcinoma (NCT02296684) and NSCLC (NCT02998528), and a phase III triple-negative breast cancer trial (NCT03036488), are ongoing (*Table S1*, supporting information).

So far, no serious surgical events or organ-specific side-effects attributable to immunotherapy have been reported. The low complication rates in published studies are certainly encouraging; however, it must be noted that surgical complications or outcomes are rarely reported in trial results. The optimal timing of surgery after the last dose of immunotherapy remains to be determined, although most current trials have adopted a 14-day window (NCT02595918, NCT02519322, NCT02296684).

Another consideration is the use of antibiotics and corticosteroids in the peri-operative period for patients on immunotherapy. There is currently no literature available; however, antibiotics may have a negative impact on the efficacy of checkpoint inhibitors. In a retrospective study of patients with 121 patients with RCC and 239 with NSCLC, Derosa and colleagues[40] reported that patients who received oral or intravenous antibiotics 30 days before the start of treatment with checkpoint inhibitors had significantly greater primary disease progression (RCC: 75 *versus* 22 per cent), shorter progression-free survival (RCC: 1.9 *versus* 7.4 months; NSCLC: 1.9 *versus* 3.8 months) and shorter median overall survival (RCC: 17.3 *versus* 30.6 months; NSCLC: 7.9 *versus* 24.6 months). This adverse effect of antibiotics persisted in multivariable analysis. The authors hypothesized that the effect may be have been due to alteration in the diversity and composition of gut microbiota.

Similarly, the use of corticosteroid, an immunosuppressive agent, particularly in patients with brain metastasis or glioblastoma, has been associated with poor outcome after immunotherapy[41]. Keskin and colleagues[42] demonstrated that patients with glioblastoma who received dexamethasone during administration of personalized neoantigen vaccines were unable to generate neoantigen-specific CD4+ and CD8+ responses in both peripheral blood and the TME[42]. Corticosteroids maybe unavoidable in patients with cerebral oedema, but their use for postoperative analgesia and antiemetic effects may need to be reconsidered in patients receiving immunotherapy.

Future perspectives

The combination of ipilimumab and nivolumab targeting different inhibitory checkpoint proteins has proved more successful than single-agent therapy. Future trials will no doubt consider combination immunotherapy. Selecting which combination, the order and timing of therapy, and how surgery may be incorporated into the pathway, will be a key challenge. Individualized combination immunotherapies are likely to have the greatest chance of success. For example, a patient with a tumour with low antigenicity secondary to defective dendritic cell function would benefit from CAR T cell therapy or a cancer vaccine to prime and activate T cells, followed by checkpoint inhibition or cytokine modulation to boost the subsequent T cell responses. There are currently two ongoing phase I trials investigating the combination of personalized cancer vaccine and nivolumab (NCT02897765) or ipilimumab (NCT02950766).

New immunomodulatory drugs targeting inhibitory and stimulatory pathways are also in the pipeline. Antilymphocyte-activation gene 3 (LAG3) and anti-T cell immunoreceptor with Ig and ITIM domain (TIGIT) are both new checkpoint inhibitors currently being evaluated. Another therapeutic pathway of interest involves co-stimulatory molecules of the tumour necrosis factor receptor superfamily such as 4-1BB and glucocorticoid-induced tumour necrosis factor receptor-related protein (GITR), which are present on CD8+ T cells and provide a second activation signal when a T cell binds to an antigen presented by an APC[43]. The combination of a checkpoint inhibitor and activation of co-stimulatory molecules showed synergistic CD8+ T cell-driven anticancer immunity in a transgenic mouse model[44]. This 'removing the brakes and increasing the acceleration' approach is an exciting prospect, particularly for patients who have suboptimal clinical responses to PD-1 blockade.

Although the potential of immunotherapy is undeniable, not every patient responds, highlighting the imperfect understanding of cancer immunology. Currently, there are no reliable biomarkers to indicate resistance to immunotherapy. As mentioned earlier, MSI is used as a predictor of PD-1 blockade in designing clinical trials, but only 53 per cent of patients with MSI showed objective responses[24]. PD-L1 expression has been correlated with response to PD-1/PD-L1 blockade. However, patients with very low or no PD-L1 expression could still benefit from PD-1/PD-L1 blockade, rendering PD-L1 expression a poor biomarker for this purpose[45].

The TCR repertoire, which indicates the presence or absence of T cell clonal expansion in response to tumour neoantigens, is another potential biomarker. The TCR repertoire from peripheral blood changes in response to PD-1/PD-L1 blockade in various tumour types, and can be used to monitor response to immunotherapy[18]. Further stratification based on expression pattern and functional status of tumour infiltrating T cells, such as ratio of effector, memory, exhausted or stem-like T cells, may also help define a better biomarker for response to

immunotherapy. Alternative immune escape pathways have been investigated, including mutation in MHC class I molecules, which present antigens at the cell surface for recognition[46]. Studies[10,47] have already identified certain oncogenic pathways, such as β-catenin or phosphatase and tensin homologue pathways, that are associated with dysfunctional antigen presentation or deactivated T cell function, suggesting that personalized immunotherapy may be the future.

The immune contexture takes into account the density of immune cells, phenotype, and the location of immune cells in relation to the tumour. Besides providing therapeutic options, understanding the immune contexture also provides a useful prognostic tool. An example is the Immunoscore, which uses immunohistochemical techniques to identify expression of CD3+ and CD8+ subsets of lymphocytes in the tumour core (CT) and invasive margin (IM) to classify patients into five groups (I0–I4)[48]. Those with low CD3+ and CD8+ expression in the CT and IM (I0) have the poorest prognosis. The Immunoscore is the first immune-based assay that has been validated internationally in colonic cancer[48]. It has been shown to have a prognostic value that is superior to that of the TNM system and other existing tumour risk parameters[48]. This increased predictive accuracy is likely a reflection of the crucial role of CD8+ T cells. However, it must be noted that this superiority has not been replicated in other cancer types, suggesting that the functional component of the immune contexture is different in different tumours.

Other examples of immune-based prognostic tools include the neutrophil to lymphocyte ratio[49] and Onodera's prognostic nutritional index[50] which uses peripheral lymphocytes as a surrogate measure for systematic adaptive immune responses. In future, an immune-based prognostic system is likely to enter routine clinical practice. Incorporation of the Immunoscore into the TNM staging system has been proposed, culminating in a TNM-Immune (TNM-I) staging system[48].

The introduction of immunotherapy into standard oncological treatment has been a steep learning curve for both oncologists and surgeons. Many variables remain unknown and there is little literature on specific concerns that affect surgical care. As a result, decision-making is challenging and should be collaborative with (immuno-)oncologists. In future, surgical oncologists are increasingly likely to encounter patients with metastatic cancers receiving immunotherapy who have a longer life expectancy than previously. As metastatic cancers are increasingly controlled for longer, surgical oncologists are also likely to find themselves offering surgery to this group of patients, especially for sites of disease subject to IO therapy escape. This may have an impact on conventional surgical strategies, treatment sequencing and clinical outcomes.

Disclosure

The authors declare no conflict of interest.

References

1 Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000; **100**: 57–70.

2 Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; **144**: 646–674.

3 Loibl S, Gianni L. HER2-positive breast cancer. *Lancet* 2017; **389**: 2415–2429.

4 Lièvre A, Bachet JB, Le Corre D, Boige V, Landi B, Emile JF *et al. KRAS* mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res* 2006; **66**: 3992–3995.

5 Burnet M. Cancer; a biological approach. I. The processes of control. *Br Med J* 1957; **1**: 779–786.

6 Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. *Annu Rev Immunol* 2004; **22**: 329–360.

7 Manjili MH. The inherent premise of immunotherapy for cancer dormancy. *Cancer Res* 2014; **74**: 6745–6749.

8 Le DT, Yoshino T, Jäger D, Andre T, Bendell JC, Wang R *et al.* KEYNOTE-164: Phase II study of pembrolizumab (MK-3475) for patients with previously treated, microsatellite instability-high advanced colorectal carcinoma. *J Clin Oncol* 2016; **34(**Suppl): TPS787.

9 Cabrera CM, Jiménez P, Cabrera T, Esparza C, Ruiz-Cabello F, Garrido F. Total loss of MHC class I in colorectal tumors can be explained by two molecular pathways: beta2-microglobulin inactivation in MSI-positive tumors and LMP7/TAP2 downregulation in MSI-negative tumors. *Tissue Antigens* 2003; **61**: 211–219.

10 Spranger S, Bao R, Gajewski TF. Melanoma-intrinsic β-catenin signalling prevents anti-tumour immunity. *Nature* 2015; **523**: 231–235.

11 Mueller DL, Jenkins MK, Schwartz RH. Clonal expansion *versus* functional clonal inactivation: a costimulatory signalling pathway determines the outcome of T cell antigen receptor occupancy. *Annu Rev Immunol* 1989; **7**: 445–480.

12 Jiang Y, Li Y, Zhu B. T-cell exhaustion in the tumor microenvironment. *Cell Death Dis* 2015; **6**: e1792.

13 Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O *et al.* Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. *J Clin Oncol* 2015; **33**: 1889–1894.

14 Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Cowey CL *et al.* Nivolumab plus ipilimumab or nivolumab alone *versus* ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *Lancet Oncol* 2018; **19**: 1480–1492.

15 Motzer RJ, Rini BI, McDermott DF, Redman BG, Kuzel TM, Harrison MR *et al.* Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial. *J Clin Oncol* 2015; **33**: 1430–1437.

16 Horn L, Spigel DR, Vokes EE, Holgado E, Ready N, Steins M *et al.* Nivolumab *versus* docetaxel in previously treated patients with advanced non-small-cell lung cancer: two-year outcomes from two randomized, open-label, phase III trials (CheckMate 017 and CheckMate 057). *J Clin Oncol* 2017; **35**: 3924–3933.

17 Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY *et al.* Pembrolizumab *versus* docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016; **387**: 1540–1550.

18 Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL *et al.* Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 2017; **377**: 1345–1356.

19 McDermott D, Lebbé C, Hodi FS, Maio M, Weber JS, Wolchok JD *et al.* Durable benefit and the potential for long-term survival with immunotherapy in advanced melanoma. *Cancer Treat Rev* 2014; **40**: 1056–1064.

20 Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P *et al.* Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012; **366**: 2455–2465.

21 Adams S, Loi S, Toppmeyer DL, Cescon DW, De Laurentiis M, Nanda R *et al.* Abstract PD6-10: KEYNOTE-086 cohort B: pembrolizumab monotherapy for PD-L1-positive, previously untreated, metastatic triple-negative breast cancer (mTNBC). *Cancer Res* 2018; **78**(Suppl): PD6–PD10.

22 Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A *et al.* Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N Engl J Med* 2014; **371**: 2189–2199.

23 Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD *et al.* PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 2015; **372**: 2509–2520.

24 Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK *et al.* Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017; **357**: 409–413.

25 Elahi R, Khosh E, Tahmasebi S, Esmaeilzadeh A. Immune cell hacking: challenges and clinical approaches to create smarter generations of chimeric antigen receptor T cells. *Front Immunol* 2018; **9**: 1717.

26 Kochenderfer JN, Dudley ME, Kassim SH, Somerville RP, Carpenter RO, Stetler-Stevenson M *et al.* Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. *J Clin Oncol* 2015; **33**: 540–549.

27 Tran E, Robbins PF, Lu YC, Prickett TD, Gartner JJ, Jia L *et al.* T-cell transfer therapy targeting mutant KRAS in cancer. *N Engl J Med* 2016; **375**: 2255–2262.

28 Harris DT, Kranz DM. Adoptive T cell therapies: a comparison of T cell receptors and chimeric antigen receptors. *Trends Pharmacol Sci* 2016; **37**: 220–230.

29 Klebanoff CA, Acquavella N, Yu Z, Restifo NP. Therapeutic cancer vaccines: are we there yet? *Immunol Rev* 2011; **239**: 27–44.

30 Ott PA, Hu Z, Keskin DB, Shukla SA, Sun J, Bozym DJ *et al.* An immunogenic personal neoantigen vaccine for patients with melanoma. *Nature* 2017; **547**: 217–221.

31 Sahin U, Derhovanessian E, Miller M, Kloke BP, Simon P, Löwer M *et al.* Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. *Nature* 2017; **547**: 222–226.

32 Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J *et al.*; ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018; **29**(Suppl 4): iv264–iv266.

33 Gupta A, De Felice KM, Loftus EV Jr, Khanna S. Systematic review: colitis associated with anti-CTLA-4 therapy. *Aliment Pharmacol Ther* 2015; **42**: 406–417.

34 Baker JJ, Stitzenberg KB, Collichio FA, Meyers MO, Ollila DW. Systematic review: surgery for patients with metastatic melanoma during active treatment with ipilimumab. *Am Surg* 2014; **80**: 805–810.

35 Gyorki DE, Yuan J, Mu Z, Zaidi B, Pulitzer M, Busam K *et al.* Immunological insights from patients undergoing surgery on ipilimumab for metastatic melanoma. *Ann Surg Oncol* 2013; **20**: 3106–3111.

36 Elias AW, Kasi PM, Stauffer JA, Thiel DD, Colibaseanu DT, Mody K *et al.* The feasibility and safety of surgery in patients receiving immune checkpoint inhibitors: a retrospective study. *Front Oncol* 2017; **7**: 121.

37 Chaft JE, Hellmann MD, Velez MJ, Travis WD, Rusch VW. Initial experience with lung cancer resection after treatment with T-cell checkpoint inhibitors. *Ann Thorac Surg* 2017; **104**: e217–e218.

38 Forde PM, Chaft JE, Smith KN, Anagnostou V, Cottrell TR, Hellmann MD *et al.* Neoadjuvant PD-1 blockade in resectable lung cancer. *N Engl J Med* 2018; **378**: 1976–1986.

39 Amaria RN, Reddy SM, Tawbi HA, Davies MA, Ross MI, Glitza IC *et al.* Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma. *Nat Med* 2018; **24**: 1649–1654.

40 Derosa L, Hellmann MD, Spaziano M, Halpenny D, Fidelle M, Rizvi H *et al.* Negative association of antibiotics on clinical activity of immune checkpoint inhibitors in patients with advanced renal cell and non-small-cell lung cancer. *Ann Oncol* 2018; **29**: 1437–1444.

41 Parakh S, Park JJ, Mendis S, Rai R, Xu W, Lo S *et al.* Efficacy of anti-PD-1 therapy in patients with melanoma brain metastases. *Br J Cancer* 2017; **116**: 1558–1563.

42 Keskin DB, Anandappa AJ, Sun J, Tirosh I, Mathewson ND, Li S *et al.* Neoantigen vaccine generates intratumoral T cell responses in phase Ib glioblastoma trial. *Nature* 2019; **565**: 234–239.

43 Emerson DA, Redmond WL. Overcoming tumor-induced immune suppression: from relieving inhibition to providing costimulation with T cell agonists. *BioDrugs* 2018; **32**: 221–231.

44 Buchan SL, Fallatah M, Thirdborough SM, Taraban VY, Rogel A, Thomas LJ *et al.* PD-1 blockade and CD27 stimulation activate distinct transcriptional programs that synergize for $CD8^+$ T-cell-driven antitumor immunity. *Clin Cancer Res* 2018; **24**: 2383–2394.

45 Patel SP, Kurzrock R. PD-L1 expression as a predictive biomarker in cancer immunotherapy. *Mol Cancer Ther* 2015; **14**: 847–856.

46 Ozcan M, Janikovits J, von Knebel Doeberitz M, Kloor M. Complex pattern of immune evasion in MSI colorectal cancer. *Oncoimmunology* 2018; **7**: e1445453.

47 Xiao Q, Wu J, Wang WJ, Chen S, Zheng Y, Yu X *et al.* DKK2 imparts tumor immunity evasion through β-catenin-independent suppression of cytotoxic immune-cell activation. *Nat Med* 2018; **24**: 262–270.

48 Pagès F, Mlecnik B, Marliot F, Bindea G, Ou FS, Bifulco C *et al.* International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study. *Lancet* 2018; **391**: 2128–2139.

49 Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A *et al.* Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst* 2014; **106**: dju124.

50 Sun K, Chen S, Xu J, Li G, He Y. The prognostic significance of the prognostic nutritional index in cancer: a systematic review and meta-analysis. *J Cancer Res Clin Oncol* 2014; **140**: 1537–1549.

Table 1 Immune-related toxicities[32]

	% affected	Toxicities
Common toxicities		
Dermatology	13–45	Rash, pruritus
Respiratory	20–40	Cough, dyspnoea, pneumonitis
Endocrine	1–21	Thyroid disorders, hypophysitis, insulin-dependent diabetes
Gastrointestinal	27–54	Diarrhoea, colitis
Liver	5–30	Hepatitis
Rheumatology	2–12	Myalgia
Rare but serious toxicities		
Neurology	1	Polyneuropathy, encephalitis, aseptic meningitis, Guillain–Barré syndrome
Renal	<1	Nephritis
Cardiovascular	<1	Myocarditis, pericarditis, arrhythmias, cardiomyopathy
Eye	<1	Peripheral ulcerative keratitis, uveitis, idiopathic orbital inflammation
Haematological	<1	Aplastic anaemia, autoimmune haemolytic anaemia, immune thrombocytopenic purpura