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Acquired resistance to immunotherapy and future challenges

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Abstract

Advances in immunotherapy have resulted in remarkable clinical responses in some patients. However, one of the biggest challenges in cancer therapeutics is the development of resistant disease and disease progression on or after therapy. Given that many patients have now received various types of immunotherapy, we asked three scientists to give their views on the current evidence for whether acquired resistance to immunotherapy exists in patients and the future challenges posed by immunotherapy.

The contributions

Nicholas P.Restifo was educated and trained at the John Hopkins University (Baltimore, Maryland), New York University and Memorial Sloan Kettering Cancer, New York, before joining the National Cancer Institute (NCI), Bethesda, Maryland, USA. His goal is to better understand the basic principles of tumour immunology in order to develop curative treatments for patients with cancer. Thomson Reuters recently named him one of the world's most highly cited researchers.His studies have elucidated the role of T cells in tumour recognition, destruction and escape. He identified a novel human T stem cell memory subset that revealed that each individual T cell clonotype can be capable of true stem cell-like behavior.

Mark J. Smyth is a senior scientist and immunology coordinator at QIMR (Queensland Institute of Medical Research) Berghofer Medical Research Institute (NCI), Bethesda, Maryland, USA (1998–1992), before commencing his independent research career in Australia.Over the past 15 years he was rekindled worldwide interest in cancer immune surveillance, defined immune-mediated dormancy of cancer and the role of the host immune system in therapy responses in mice and humans. More recently, he has provided new means of classifying natural killer (NK) cell subtypes and two new targets for cancer immunotherapy.

Alexandra Snyder is a physician scientist whose research focus is the improvement of our understanding of tumour-intrinsic mechanisms of response and resistance to immunotherapy. Her translational work aims to optimize patient selection and uncover rational targets for combination therapy. Having completed internal medicine training and a medical oncology fellowship on the research track at Memorial Sloan-Kettering Cancer Center (MSKCC). New York, USA, she joined the Gynecologic Medical Oncology and Immunotherapy serevices at MSKCC in January 2015. Her previous work foucused on melanoma and lung cancers, with recent publications describing the contribution of mutation and neoantigen burden to response to therapy in those diseases. She now studies checkpoint blockade in ovarian and bladder cancers.

Competing interests statement

The authors declare competing interests: see Web version for details.

Q Are there examples of acquired resistance to immunotherapy from clinical trials and model systems, and what are the characteristics of acquired resistance?

Nicholas P. Restifo. Before we discuss issues of resistance to immunotherapy, it should be duly noted that immunotherapy is a true paradigm shift in the treatment of patients with metastatic cancer. In terms of lives saved and person-years restored, immunotherapy promises to be more significant than any other form of treatment for patients whose tumours have already metastasized. For patients with metastatic solid tumours, surgery, radiotherapy, chemotherapy and even targeted pathway inhibition with small molecules are generally not curative. Thus, there is a tremendous medical need for curative therapies.

We and many other groups have shown that immunotherapy can induce complete and long-lasting tumour regression[1]. Thus, immune-selective pressure for resistant tumour cells must exist, but cause and effect relationships, especially in humans, cannot be drawn with any certainty. Nevertheless, we can theorize about what seems to be happening in our patients, and it is important to distinguish two major categories of acquired resistance of tumour masses to immunotherapy.

The first type of resistance is a special form of Darwinian natural selection that comes from the selection of genetic or epigenetic heritable traits that pre-exist in the tumour mass before a therapeutic intervention, as we have previously discussed[2]. The main driver for the generation of immunoresistant tumour cell variants via this mechanism seems to be the genomic and epigenomic instability of transformed cells. Darwinian selection of resistant clones from tumour cell populations can result in the survival of tumour cell variants that happen to possess the genetic and epigenetic traits that enable them to evade therapy. Immune-based treatments might induce ‘population bottlenecks’, which result in tumour masses derived from treatment-resistant cells. For example, we have described five patients whose tumours seem to have completely lost β_2 microglobulin (B2M)[3]. B2M is a structural component shared by all major histocompatibility complex (MHC) class I molecules, the structures that present peptides to T cells. The loss of B2M from tumour cells after T cell-based immunotherapy makes cells resistant to tumour-specific $CD8^+$ T cells.

The second type of resistance to immunotherapy is acquired resistance at the level of the individual tumour cell[4]. This occurs because tumour cells alter their gene expression in response to interactions with immune cells or their products. This form of acquired resistance might also be called ‘homeostatic resistance’, because it employs adaptive mechanisms of tissue and immune homeostasis. One clear example of this kind of resistance is when tumour cells induce the expression of programmed cell death protein 1 (PD1) ligand 1 (PDL1; also known as CD274) in response to the secretion of interferon-γ (IFNγ). This is interesting because IFNγ is the same molecule that enables T cells to destroy tumour cells in experimental animal models[5]. Researchers have not yet been able to observe individual tumour cells in humans *in vivo* over time; thus, rigorous evidence that individual tumour cells experience acquired immune resistance is currently not available.

Thus, these two mechanisms of tumour resistance — selection of resistant clones and true acquired homeostatic resistance — can be crisply defined, but are often indistinguishable in patients using currently available technologies.

> "immunotherapy promises to be more significant than any other form of treatment for patients whose tumours have already metastasized"

Mark J. Smyth. Several immunotherapies, in particular immune checkpoint-targeting antibodies and adoptive T cell therapies (ACTs), are beginning to transform the treatment of advanced cancers. The likelihood of response to these immunotherapies differs strongly across tumour types, and even in those cancer types that respond (for example, advanced melanoma and renal cell cancer), non-responsiveness is observed, indicating the presence of intrinsic resistance or acquired immune resistance. In addition, in a subgroup of patients who do initially respond to immunotherapy, the cancer will later recur[6,7], thereby indicating a role of immunotherapy-induced acquired resistance. Intrinsic resistance often occurs in patients with global immunosuppression (for example, patients with HIV and some elderly patients), in tumours that express few molecular cues that can be recognized as foreign to the immune system (for example, non-viral tumours with a low mutational load) or in tumours that display intrinsic resistance to immune-mediated killing mechanisms.

There are many experimental and clinical examples of naturally acquired or immunotherapy-acquired resistance[8]. Multiple inhibitory feedback mechanisms have a role in suppressing T cells in the tumour microenvironment (TME). These comprise the now clinically validated PD1-PDL1 axis and various potentially overlapping immune checkpoint molecules defined by preclinical studies, including lymphocyte activation gene 3 (LAG3), T cell immunoglobulin mucin receptor 3 (TIM3; also known as HAVCR2) and T cell immunoreceptor with Ig and ITIM domains (TIGIT). PD1–PDL1 is the best example of true adaptive immune resistance (defined first by Drew Pardoll[9]) in animals and humans. In this example, tumour-infiltrating T cells produce IFNγ upon binding of cognate antigen, which induces the expression of PDL1 on the tumour cell surface or other infiltrating immune cells, and PDL1 serves to limit further T cell effector function by engaging PD1. Tumour cell PDL1 expression may also be driven by tumour suppressor gene loss, by oncogenes or by *CD274* (which encodes PDL1) gene amplification, as has been reported in Hodgkin lymphoma and some other neoplastic diseases[10]. Notably, IFNγ also drives the expression of the suppressive factors indoleamine 2,3-dioxygenase (IDO)[11] and carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), which heterodimerizes with the inhibitory receptor TIM3 (REF 12).

Natural or therapy-driven antitumour immune responses may select for tumour cell subpopulations with loss of MHC class I expression or other defects in the antigen processing machinery. Melanomas have been shown to acquire ACT resistance through an inflammation-induced reversible loss of melanocytic antigens (tumour necrosis factor (TNF)-induced dedifferentiation)[13]. Recruitment of suppressive T cell and myeloid cell populations to the tumour (and all the associated immunosuppressive factors — for example, transforming growth factor-β (TGFβ)) represents another major form of acquired resistance whereby normal immunoregulatory mechanisms are hijacked by tumour cells. It is already apparent that some patients who initially respond to anti-PD1 therapies relapse months to

years later, even while still on therapy. Possible reasons include: insufficient infiltrating $CD8^+$ T cells, monoclonality of response, loss of neoantigens (discussed further below), lack of sensitivity to IFN signalling, overexpression or loss of PD1 on infiltrating T cells or upregulation of other immune checkpoint receptors. The general mechanisms of therapy-induced acquired resistance are likely to be very similar to those associated with naturally acquired resistance.

Alexandra Snyder. The frequency of acquired resistance to checkpoint blockade immunotherapies has not been systematically documented, although it is well known to clinicians who use such therapies. For example, one of the patients with metastatic melanoma treated at our centre as part of an early study of ipilimumab developed growth of an adrenal tumour despite systemic disease control; after its resection, the patient remained in a complete response. Another patient with melanoma, treated with ipilimumab, who had systemic disease stability, developed a small bowel obstruction from a growing lesion in the bowel wall; similarly, after resection, the patient maintained disease control.

The method commonly used for assessing radiographic response in clinical trials, the response evaluation criteria in solid tumours (RECIST), measures the sum of the longest diameter of target lesions at baseline and at predetermined time points thereafter. Although this system facilitates uniform tumour assessment across institutions, when summarized as a percentage of growth or shrinkage, the RECIST response does not capture the diversity of tumour responses within each patient. As such, it is remarkably difficult to capture the true incidence of mixed responses and acquired resistance by reading published data from clinical trials. The immune-related response criteria (irRC)[14] have been developed to account for the growth patterns unique to immunotherapy-treated patients, specifically to allow for continued treatment on study beyond apparent progression, as some patients experience tumour growth followed by regression. In contrast to RECIST, using irRC, the appearance of new lesions does not automatically indicate progression. In addition, apparent progressive disease must be confirmed 4 weeks after the first immune-related progressive disease (irPD) assessment to qualify as true progression. irRC is often incorporated into immunotherapy trials, although this method does not specifically capture the acquired resistance group. For example, if a patient experiences tumour growth at four out of five sites and tumour shrinkage at one site, the sum of these lesions will still indicate progression, whether measured by RECIST or irRC. Because most studies categorize patients by progression, disease stability or response (partial or complete), published data do not describe in what proportion of patients a mixed response occurred.

Clinically, patients who experience acquired resistance to PD1, PDL1 and cytotoxic T lymphocyte-associated antigen 4 (CTLA4) antagonists can be conceived of in two broad categories: those patients who experience systemic disease control indefinitely with outgrowth of one to three discordant lesions, termed oligometastatic progression; and those patients who experience temporary systemic disease control followed by tumour growth at all or most sites. However, the true frequency and possible agent-specific nature of such phenomena have not yet been studied. Anecdotally, acquired resistance to anti-PD1 therapy (for example, pembrolizumab or nivolumab) seems to occur more often in the second pattern, with fewer cases of isolated discordant lesions such as those that have been

described upon treatment with ipilimumab[15]. However, there are exceptions: a patient with lung adenocarcinoma treated with anti-PD1 therapy at our centre underwent resection of a growing abdominal lymph node and has since maintained disease control.

It is possible that earlier treatment of patients in the metastatic or adjuvant setting could mitigate the development of discordant or escape lesions; however, the exposure of patients (a subset of whom may be cured) to agents that carry a risk of side effects has limited such studies to date. This principle is illustrated by one study in which patients with high-risk stage III melanoma were randomized to treatment with adjuvant ipilimumab at 10 mg per kg or placebo[16]. Recurrence-free survival was 26.1 months in the ipilimumab group compared with 17.1 months in the placebo group (hazard ratio 0.75; 95% confidence interval (CI) 0.64–0.90; $P = 0.0013$). However, 52% of the patients on the ipilimumab arm discontinued treatment because of side effects, and there were five (1%) treatment-related deaths on the ipilimumab arm. Notably, the US Food and Drug Administration (FDA)-approved dose of ipilimumab in metastatic melanoma is 3 mg per kg, so the degree of toxicity might have been less at this dose.

Q Is there evidence of immunoediting as a mechanism of acquired immunotherapy resistance?

N.P.R. As summarized by Lewis Thomas more than four decades ago, there is substantial evidence for immunosurveillance in humans[17]. Elegant work has elucidated a role for immunoediting in mouse models that employ carcinogen-induced sarcomas[7]. Nevertheless, the notion that the immune system is able to ‘edit’ or select against particularly good T cell epitopes is contentious in humans, and the complexities of immunoediting have been discussed by others[18].

The strongest arguments against immunoediting are the powerful, complete and durable responses we observe in the clinic. These responses seem to be the result of T cells recognizing mutated antigens. The presence of very-high-avidity T cells specific for robustly expressed and presented tumour-specific antigens is seemingly at odds with the immunoediting hypothesis.

We now know that high-avidity T cell clones can target mutations that are actually creating peptides that bind with high avidity to a patient’s human leukocyte antigen (HLA) molecules[1]. For example, in an HLA-A*02^{+} patient this would be reflected by a mutational change that results in a leucine or methionine at position 2 or a valine at position 9 in the presented peptide[19]. These amino acids enable the peptide to bind with high avidity to the presenting HLA molecule. There does not seem to be a strong bias against the stochastic creation of epitopes that bind well to HLA that are processed and presented on the surfaces of tumour cells. In addition, it is also straightforward to find and grow high-avidity T cells specific for such mutations and to successfully use them in curative ACT-based immunotherapy[20]. Thus, it seems unlikely that immunoediting completely eliminates highly immunogenic epitopes.

M.J.S. Cancer immunoediting is the process by which the immune system controls tumour outgrowth and shapes tumour immunogenicity, and it comprises three phases: elimination, equilibrium and escape[18]. A central premise of cancer immunoediting is that T cell recognition of tumour antigens drives the immunological destruction (or sculpting) of a developing cancer[21], but clearly other immune cell types can also shape tumour immunogenicity[22]. Initially, tumours arising in immunodeficient mice were shown to be more immunogenic when transplanted into immunocompetent mice[21,23] or sensitive to particular immune rejection mechanisms (for example, TNF-related apoptosis-inducing ligand (TRAIL; also known as TNFSF10)[24]). Using a carcinogen-induced fibrosarcoma model, the prolonged battle of the immune system with occult tumour cells in an equilibrium phase was illustrated[25]. Then, the discovery of neoantigens expressed in nascent tumour cells[26] and a genetically engineered, autochthonous mouse model of sarcomagenesis[27], demonstrated in mice that recognition of tumour-specific antigens by lymphocytes and cancer immunoediting were crucial. Loss of tumour antigen expression or presentation on MHC I was necessary and sufficient for cancer immunoediting as a mechanism of acquired resistance to natural immunity[26–28]. These results highlighted the potential importance of tumour-specific antigen expression in immunotherapy.

> “next-generation sequencing and epitope prediction ... should now allow the natural immunological history of a patient’s tumour to be followed both before and after therapy”

Human data on this topic are currently sparse. The idea that the mutational neoantigen load might predict the long-term clinical benefit of anti-CTLA4 (ipilimumab)[15] and anti-PD1 (pembrolizumab)[29] therapy has been demonstrated and has recently been supported by a larger study[30]. In lung cancer, response to immune checkpoint blockade was also correlated with mutations in genes encoding components in a DNA repair pathway — mismatch repair — that resulted in a higher number of predicted neoantigens[29]. In one patient whose tumour neoantigen was defined, neoantigen-specific T cell responses paralleled tumour regression, implicating a link between the T cell responses and the antitumour effects of anti-PD1 therapy. A similar phenomenon has been observed in colorectal cancer[31]. Of course, natural immunity to human tumours cannot easily be studied functionally in the absence of the genetic tools and controls afforded by animal studies. But advances in next-generation sequencing and epitope prediction now permit the definition of T cell responses against mutant antigens within individual patients[32], and should now allow the natural immunological history of a patient’s tumour to be followed both before and after therapy.

A.S. Preclinical data suggest a multitude of potential mechanisms for tumour evasion of checkpoint blockade immunotherapies; to date, immunoediting has not been confirmed in patients treated with checkpoint blockade, although studies of acquired resistance lesions are under way at our institution and others.

> “Two of the biggest problems facing checkpoint blockade immunotherapy are scientific and societal”

Robert Schreiber and colleagues[26] have provided elegant evidence in mice, illustrating the importance of immunoediting of tumour neoantigens, peptides resulting from somatic

mutations that can be recognized by the immune system. In a 2012 study, they showed that a mouse sarcoma cell line was rejected based on a mutant form of spectrin β2 (also known as SPTBN1), and a T cell-dependent selection process facilitated the immune escape of tumours lacking this mutation. In a subsequent study specific to checkpoint blockade efficacy and neoantigen vaccination in this model[33], the authors did not address the issue of escape lesions, perhaps in part because the neoantigen vaccine plus checkpoint blockade used in the study is so effective in the 30- to 100-day follow-up period studied. Other mechanisms of immune evasion with strong preclinical support include the 'non-inflamed' tumour from which T cells are excluded, either because of tumour-intrinsic β-catenin signalling[34] or because of the effects of stromal cell populations (reviewed in REF 35), as well as upregulation of signalling molecules that dampen T cell activity (such as B and T cell lymphocyte attenuator (BTLA), V-domain Ig suppressor of T cell activation (VISTA; also known as C10orf54), TIM3, LAG3, IDO1 and others.

The mechanisms underlying acquired resistance to checkpoint blockade immunotherapies in patients are under investigation but have not yet been ascertained. Four studies have now illustrated a correlation between elevated mutation burden and response to therapy with anti-CTLA4 or anti-PD1 agents[15,29–31], but these studies evaluate one tumour per patient. These studies also showed that neoantigen burden and mutation burden were correlated, and thus that neoantigen burden is associated with response[29,30]. However, accurate neoantigen prediction in patients remains a challenge[36], and requires optimization using a more sophisticated bioinformatic and statistical approach accompanied by *in vitro* experimentation.

In a study by our group[15], nine lesions in the series represented discordant lesions resected from patients who otherwise experienced disease control; however, these patients represented a group of outliers, and thus this proportion does not reflect the incidence of acquired resistance in an unselected population. Without paired pre- and post-treatment samples, the mechanism for the emergence of such lesions could not be firmly ascertained. In the study by van Allen and colleagues[30], comprising an unselected group of patients with melanoma treated with anti-CTLA4, examples of patients with long-term benefit in the absence of clinical response are shown (Fig. 1B in REF. 30), although the issue of resection of discordant lesions is not specifically addressed.

Q What do you see as currently the biggest problems facing immunotherapy?

N.P.R. To give a short answer to a difficult question, I think there are three problems that deserve to be singled out. It is clear that most successful immunotherapies to date depend on T cells, but the characteristics of highly effective T cells remain largely unknown. Cells with antitumour properties can migrate to tumours and persist long term, but most cancer immunotherapy is not curative, even using optimized conditions. It is very surprising that stem cell-like properties can exist in each T cell clonotype, but the metabolic, transcriptional and epigenetic states of highly effective T cells are not yet fully known. The identification of

T cells with stem cell-like properties in humans may enable the infusion of small doses of highly effective cells that are capable of massive proliferation and indefinite persistence[37].

The second problem concerns elucidation of the realm of structures that can serve as appropriate target antigens on tumour cells. Gene-engineered T cells can recognize virtually any structure on the surface of a tumour. The administration of receptor-engineered T cells can be highly effective in treating patients with B cell leukaemias and lymphomas and has captured the public imagination. This success has driven academic and industrial researchers to develop similar ‘off-the-shelf’ receptors that target shared antigens on epithelial cancers, the leading cause of cancer-related deaths. However, the successful treatment of large numbers of patients with solid cancers using this strategy is unlikely to be straightforward.[38] The reason for this is that there is a paucity of truly tumour-specific antigens shared across tumour types. Effective approaches are likely to require the targeting of private somatic mutations.

This brings me to the third major problem facing researchers in the field of immunotherapy: understanding the nature of the target structures recognized by naturally occurring T cells. Most evidence is consistent with the view that successful antitumour T cells recognize the products of stochastically occurring mutations. Snyder *et al.*[15] have recently claimed “striking similarities among the neoantigens that occurred only in responders [to ipilimumab and tremelimumab]” They go on to assert that they have identified tetrapeptide sequences homologous to known pathogens that are putative T cell receptor (TCR) recognition motifs and enable the prediction of clinical responses[39]. However, some of the authors have recently reported that the ‘validation group’ was also used in the formulation of the tetrapeptide motifs[40]. The lack of an independent validation set would seem to call these purported motifs into question. Some have argued cogently that claims of non-random tetrapeptides in responding patients “violates widely accepted rules governing antigen presentation and T cell recognition” (REF 41). In addition, van Allen *et al.*[30] performed similar analyses and have not observed these tetrapeptide motifs. The specific problem with the analysis by Snyder *et al.*[15] might be one that statisticians call ‘overfitting’ — the use of data sets with too many parameters relative to the number of observations.

As the field moves forward, it seems prudent to offer a more general point about the perils of the statistical analysis of very large data sets. Big data will invariably produce very precise answers, but as the data sets continue to grow the problem of potentially false findings exponentially expands as well. There is no question that high-throughput sequencing has opened vast new horizons. But statisticians since the time of Thomas Bayes have worried about the perils of understanding the world through data. In order to protect ourselves from the traps of big data, we must never forget to take the refuge afforded by cross-validation using independent data sets, especially when the number of parameters available becomes almost inconceivably large.

M.J.S. Immunotherapy faces many problems, including those that have been faced by conventional treatments in the past — for example, therapeutic resistance and affordability to all patients — as well as new challenges such as immune-associated adverse events. Rather than being a problem, the greatest challenge immunotherapy faces is rationalizing,

while broadening, its utility. We recently discussed a simplistic but useful pragmatic framework of stratifying the TME into four types based on the presence or absence of tumour-infiltrating lymphocytes (TILs) and PDL1 expression[42], based on several studies conducted in patients with melanoma[43]. Anti-PD1 and anti-PDL1 monoclonal antibodies will likely represent the foundation of many future cancer treatments in type I tumours (defined as PDL1 positive with TILs driving adaptive immune resistance), and immediately the opportunities to combine these agents with surgery, immunogenic chemotherapy and targeted therapy and radiotherapy are obvious. This will account for a good proportion of patients with immunogenic and highly mutated tumours. While an alternative approach using ACT with chimeric antigen receptor (CAR)-engineered T cells brings together elements of treatment relevant to tumours with a TME that lacks T cells, its specificity will need to be paramount. By giving combination therapies to patients earlier, we would expect that up to 50% or more of some cancer types (such as melanoma and renal cell carcinoma) might be effectively controlled for long periods of time.

A large proportion of tumours with an ‘immune-ignorant’ phenotype (type II; PDL1 negative with no TILs) have a very poor prognosis regardless of any current treatment intervention, and they will require a completely new strategy. This group of patients represents the greatest challenge to immunotherapy and other cancer treatments. It is likely that these tumours will often have strong simple genetic drivers creating no or few neoantigens. Alternatively, any neoantigens that were originally present have since been immunoedited, or the tumour employs a very effective mechanism to keep immune cells out of the tumour. These tumours may contain a substantial number of M2 polarized macrophages that could be switched to an M1 phenotype to control or reduce tumour growth. Immunotherapy will not be a panacea if it cannot impinge on this patient group.

A.S. Two of the biggest problems facing checkpoint blockade immunotherapy are scientific and societal. The success of dual therapy with the anti-CTLA4 agent ipilimumab and the anti-PD1 agent nivolumab in patients with metastatic melanoma[44] suggests that combining such agents holds the promise of benefiting a higher proportion of patients with more durable disease control. However, the number of potential rational combinations is dizzying: for example, multiple pharmaceutical companies have their own anti-PD1 agent that can be combined with drugs targeting other molecules through blockade or agonism. Agents targeting colony-stimulating factor 1 receptor (CSF1R), LAG3, TIM3, IDO, glucocorticoid-induced TNF-like receptor (GITR; also known as TNFSF18) and CD134 (also known as OX40) comprise a subset of those already under study as monotherapy and in combinations. Furthermore, there are preclinical data to suggest that such agents might also be successfully combined with other therapeutic modalities such as radiation[45], chemotherapy[46] or CAR-engineered T cell ACT[47]. In addition, the timing of such combinations is likely to be crucial to their efficacy. For example, steroids are frequently given in conjunction with cytotoxic chemotherapies to prevent hypersensitivity or nausea; however, the effects of steroids on T cells might reduce the efficacy of a concurrently administered checkpoint blockade agent. Furthermore, whereas in preclinical models, engrafted tumours are usually present for one to several weeks, the longer period of development of human tumours may necessitate further optimization of drug dosing schedules. In the setting of such challenges, the publication of

negative data — failed preclinical combinations and dosing schedules — could facilitate the more efficient translation of effective combinations to clinical trials. Finally, although immunotherapy is certainly an important component of cancer therapy, it may not be the universal panacea for all cancers, especially when considered as a single intervention.

The second, societal, issue is intimately tied to the first. Checkpoint blockade immunotherapies are approved by the FDA for advanced squamous cell and non-squamous cell lung cancers, the most common malignancy in the United States, and are already approved or will soon be approved for multiple other malignancies. The high cost of antibody therapies will weigh heavily on health-care systems that are already overstrained, in part by the cost of cancer care (discussed in REF 48). If the durability of benefit seen with ipilimumab and nivolumab combination in melanoma was also seen in other malignancies, the drug cost might be seen as an ‘up-front investment’ in the health of patients who would otherwise be sustained on serial lines of chemotherapies that are themselves costly. Setting a higher bar for response could achieve the goal of only advancing towards the approval process those combinations for which the tremendous cost is offset by sustained efficacy in the majority of patients.

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