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Smart therapeutic strategies in immuno-oncology

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For cancer therapies to succeed, induction of an anticancer immune response is required. Immuno-oncology approaches are shaping the treatment landscape for patients with advanced-stage melanoma and other solid tumours. These new approaches may enhance immune system activity to improve outcomes, including the potential to achieve long-term survival benefits in many patients.

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The knowledge that tumour cells can use complex and overlapping mechanisms to avoid immune detection laid the foundations for immuno-oncology to become an anticancer treatment. Current strategies are based on agents that can break immune tolerance. The most recognised class of immuno-oncology agents – checkpoint inhibitors – modulate pathways that either switch off T-cell activity (reducing tumour-induced immune suppression), or stimulate T-cell activity, thus potentiating antitumour responses.[1] These agents are recognised as breakthrough treatments for advanced-stage melanoma; they also show considerable promise in other tumour types, particularly renal cell carcinoma and lung cancer.[1]

Unlike other therapies approved for advanced-stage melanoma that target tumour cells directly, checkpoint inhibitors modulate T-cell activity to enhance antitumour immune responses. The most striking benefit of this approach is durable tumour control and survival.[2] Mature data in thousands of patients have shown that around one in five patients treated with ipilimumab, an antibody that blocks cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), has the potential to survive for at least three years – and up to ten years – from treatment initiation, which more than doubles results with conventional drugs.[2] Similarly, treating patients with antibodies that block the programmed death-1 (PD1) receptor, or its ligand, PD-L1, has proved highly promising.[3,4] Results of extended phase I trials evaluating two anti-PD1 antibodies (nivolumab and MK-3475) showed objective response rates (ORRs) of 30–50% in patients with advanced-stage melanoma, with most responders having durable benefit.[1] Results with nivolumab showed an unprecedented 44% of patients surviving for at least two years.[1] Additional trials could inform the optimal sequencing of anti-PD1 and anti-CTLA-4 therapies: although anti-PD1 therapy is effective following prior treatment with ipilimumab, does the same hold true for the reverse sequence? Anti-CTLA-4 antibodies centrally target the interaction between antigen-presenting cells and T-cells in the lymph-node compartment, whereas anti-PD1 antibodies act mainly peripherally on the interaction between tumour cells and T-cells at the tumour site. Thus, various opportunities for synergy or

optimal sequencing of the drugs are to be explored. Current studies are addressing these questions.

There is little doubt that impressive results have been obtained by inhibiting a single immune checkpoint, but could antitumour immunity be enhanced through dual or triple blockade? Early results seem promising. Among 53 patients with a response to the ipilimumab–nivolumab combination regimen, blocking CTLA-4 and PD1 resulted in an ORR of 40%, and clinical activity was observed in 65% of patients; at the maximum doses associated with an acceptable level of adverse events, most patients had a reduction in tumour volume of at least 80%, according to WHO criteria of response. Responses were deep but also rapid, occurring within 12 weeks.[5] These results, however, might not differ significantly from those results obtained with MK-3475 alone in 135 patients, in whom response rates of 41% were observed using RECIST criteria.[4] However, direct cross-study comparisons of these trials are not scientifically valid owing to differences in patient populations, the number of patients, number and timing of prior therapies and prognostic factors. In contrast to treatment with anti-PD1 alone, the rate of grade 3–4 adverse effects related to the ipilimumab–nivolumab combination regimen was high (53%).[5] Data from phase II and III randomised studies including the ipilimumab–nivolumab regimen are eagerly anticipated to determine if this regimen is superior to anti-PD1 monotherapy and, if so, at what price in terms of toxicity.

Monoclonal antibodies against other immune checkpoint proteins, such as TIM3, LAG3, OX40, and KIRs (killer immunoglobulin-like receptors) are all being investigated in clinical trials and serve as potential components of a combination strategy.[6] It is possible that once the 'brakes' elicited by the immune system have been released with one antibody, the inclusion of an agonistic antibody such as anti-OX40 could augment antitumour immune activity further. In other words, breaking tolerance at the central (anti-CTLA-4) and peripheral (anti-PD1) levels, opens the door for efficacy of agonists, whereas the use of T-cell activators (monoclonal antibodies or cytokines) alone does not lead to appreciable success, as T-cells are neutralised at both the central level as well as the tumour site. Of course, the potential for overlapping and/or additive toxic effects of the individual agents, particularly those resulting from over stimulation of the immune system, would need to be carefully monitored.

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Potential combination strategies are not limited to the different immune checkpoint ligands and receptors. A rationale also exists for combining checkpoint inhibitors with other immunotherapeutic approaches, such as cytokines that increase the number of activated T-cells in the circulation, or conventional cancer therapies, such as targeted kinase inhibitors, chemotherapy or radiotherapy.

Patients with BRAF-mutated advanced-stage melanoma have the option of receiving treatment with ipilimumab or a BRAF inhibitor (such as vemurafenib or dabrafenib). Possibly, in the near future, a combination of a BRAF inhibitor and a MEK inhibitor (dabrafenib plus trametinib), will become the next standard of care, based on the efficacy of this combination to significantly prolong progression-free survival (PFS) compared with dabrafenib alone.[7] Compared with a PFS of approximately two months with dacarbazine, and around six months with a BRAF inhibitor, a PFS of more than nine months was observed with the combination of a BRAF inhibitor and MEK inhibitor.[7] The distinct activity profiles of the two classes of agents, together with recent evidence that BRAF inhibition has immune-enhancing properties, suggest combination therapy might prove beneficial. A phase I study to investigate the combination of ipilimumab and vemurafenib, however, was associated with four to five times higher-than-expected rates of hepatotoxicity, suggesting that concurrent treatment may not be possible.[8] However, the timing of administration of the various agents in this dual approach (immunotherapy and cytotoxic agents of any nature, including tyrosine kinase inhibitors) will be of great interest. In this approach, the administration of agents that induce a quick transient response (such as seen with BRAF and MEK inhibitors) can create the time and space to administer immuno-oncologic agents. Being able to deliver immunotherapy by smart sequencing of different treatments will become an increasingly important strategic goal. Treatment with some chemotherapies can result in tumour cell stress and death that stimulate a tumour-specific immune response, or increase levels of tumour surface molecules that facilitate recognition by the immune system. Immuno-

genic cell-death-inducing agents can thus be successfully combined with an immuno-oncologic agent, resulting in an enhanced anticancer immune response.[9] Another interesting concept is the possibility of inducing immune-mediated abscopal effects, as seen with radiotherapy. Here, significant tumour regression both at the site of irradiation and outside areas support the notion of an enhanced systemic immune response and suggest localised radiotherapy in combination with immuno-oncology is worth pursuing.[10]

Durable tumour control and long-term survival depend on harnessing the power of the immune system. Data with agents that block CTLA-4, PD1 and other checkpoint proteins are not only providing a benchmark against which future therapies will be compared, but are stimulating interest in alternative sequencing or smart combination approaches that could improve outcomes even further. In changing the treatment landscape, immuno-oncology advances currently offer renewed hope to patients with advanced melanoma and to patients with other solid tumours in the near future. ■

"Being able to deliver immunotherapy by smart sequencing ... will become an increasingly important strategic goal"

References for this article can be found at www.cancerworld.org

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