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EDITORIAL

Clinical Studies

Immune checkpoint inhibitor combinations—current and emerging strategies

In an attempt to overcome resistance to immune checkpoint inhibitors (ICI), an ever-increasing number of trials are exploring combination treatment approaches. Outcomes of a novel ICI doublet presented by Desai and colleagues are discussed along with emerging novel strategies and a view to future ongoing rational trial design maximising patient benefit.

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Immune checkpoint inhibitors (ICI) have changed the oncology treatment landscape since their initial approval in melanoma. While there is much enthusiasm in patients exhibiting deep and durable responses, the majority still do not respond to single-agent ICI, exhibiting either primary or secondary treatment resistance. Combination regimens involving ICI have been studied to overcome this problem, with successes in ICI-chemotherapy and ICI-anti-angiogenic doublets in Phase III trials across multiple tumour groups [1]. ICI-ICI combinations have also been extensively trialled with the initial success of nivolumab and ipilimumab in melanoma and renal cell carcinoma (RCC); however, results have been disappointing beyond such anti-PD-1/PD-L1 and anti-CTLA-4 combinations. The Phase III study of pembrolizumab and indoleamine-2,3 dioxygenase-1 inhibitor, epacadostat, yielded negative results in advanced melanoma as did SKYSCRAPER-02 in untreated extensive-stage small cell lung carcinoma, with the addition of tiragolumab (anti-TIGIT) to the standard of care carboplatin, etoposide and atezolizumab failing to improve progression-free or overall survival [1, 2]. Nonetheless, the recent approval of relatlimab, targeting lymphocyte-activation gene 3 (LAG-3) in combination with nivolumab in advanced melanoma and encouraging interim results of zimberelimab (anti-PD-1) combined with domvanalimab (anti-TIGIT) in the randomised Phase II ARC-7 in PD-L1 high non-small cell lung carcinoma have bucked this trend, shining renewed hope on ICI-ICI combination therapy as a viable approach in overcoming treatment resistance [2, 3].

Desai et al. present their Phase I/II study of anti-PD-L1 BGB-A333 alone (Phase Ia) and in combination with anti-PD-1 tislelizumab (Phase Ib/II). The safety and tolerability of this novel combination appear in line with other anti-PD-1/PD-L1 combination studies but the presence of two patient deaths associated with treatment-emergent adverse events in the Phase Ib/II group ($n = 24$) should be noted. The Phase II portion enrolled patients with advanced pre-treated but immunotherapy-naive urothelial carcinoma (UC) and reported an overall response rate (ORR) of 41.7%. With the caveat of cross-trial comparisons, this appears favourable when compared to reported ORR for single-agent tislelizumab (24%) or pembrolizumab (21%) in advanced UC but is limited by a small sample size and single-arm design [4].

In the current UC treatment landscape, a vital question remains in where this combination could be positioned, with many patients exposed to avelumab as switch maintenance after platinum chemotherapy and the potential first-line combination of enfortumab vedotin and pembrolizumab on the horizon pending results of the ongoing Phase III EV-302 trial. An unmet need remains patients (UC and non-UC) progressing on single-agent anti-PD-L1/anti-PD-1 therapy. However, such patients were excluded from this study and there is limited evidence to suggest the superiority of combination anti-PD-L1 and anti-PD-1 agents over single-agent therapy with a prior study of MEDI0680 (anti-PD-1) combined with durvalumab failing to outperform nivolumab alone in advanced immunotherapy naive RCC [5].

From a scientific standpoint, the rationale of dual blockade of anti-PD-1 with anti-PD-L1 has been conflicting. Both PD-L1 and PD-L2 are ligands of PD-1, and PD-L2 expression has been shown to be upregulated after administration of anti-PD-L1 therapy, suggesting a role for adding anti-PD-1 therapy to enhance PD-1 signalling blockade. However, the use of anti-PD-1 therapy alone should block signalling by both ligands, questioning the need for this specific combination given the potential toxicities harboured. Other reports differ in their conclusions, with preclinical evidence of interaction between PD-L1 and PD-1 that are co-expressed on antigen-presenting cells. Inhibition of this by anti-PD-1 alone allows PD-L1 interaction with PD-1 expressed on T cells in *trans*, resulting in immunosuppressive signalling. Furthermore, PD-L1 has been shown to interact with B7-1 (CD80), with blockade of this through anti-PD-L1 use potentially allowing increased B7-1-CTLA-4 inhibitory signalling [6]. Given the multitude of immunotherapeutic agents available today, consideration of combination with other pathways in the immune regulatory cycle may be more appealing.

Novel combination strategies to overcome ICI resistance are in rapid development (Fig. 1) with numerous ongoing clinical trials. Bi-specific antibodies (bsAbs) allow the targeting of specific mechanisms of resistance in a single molecule, with dual checkpoint inhibition of PD-L1 and LAG-3 being an example showing promising preclinical results. Other bsAbs combine ICI with non-ICI immunotherapy, such as PD-L1 antibody and a transforming growth factor-β (TGF-β) trap, a key player in the development of an immunosuppressive tumour microenvironment (TME) [1]. Combinations with non-ICI immunotherapy in other forms are also encouraging, including immunostimulatory

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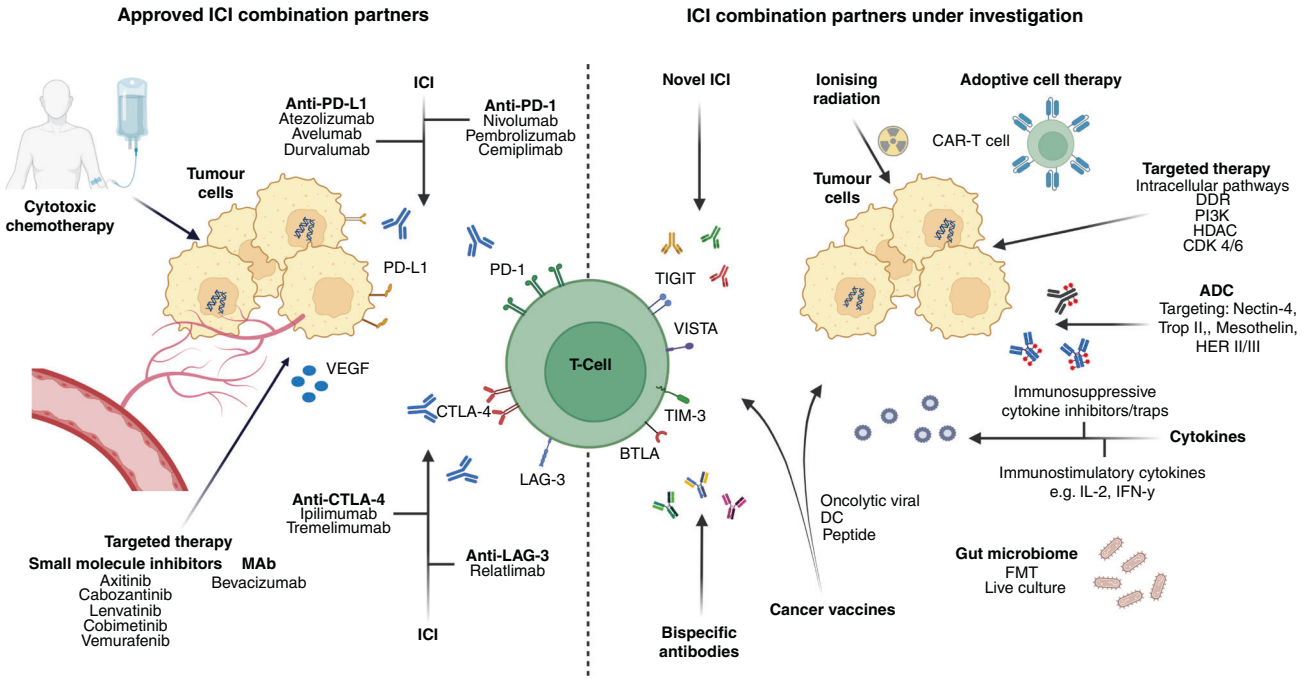

Fig. 1 Currently approved (left) and emerging (right) strategies in immune checkpoint inhibitor (ICI) combination therapy. ADC antibody–drug conjugate, BTLA B- and T-lymphocyte attenuator, CAR-T chimeric antigen receptor T cell, CDK4/6 cyclin-dependent kinase 4 and 6, CTLA-4 cytotoxic T-lymphocyte-associated antigen 4, DC dendritic cell, DDR DNA damage repair, FMT faecal microbiota transplant, HDAC histone deacetylase, IFN-γ interferon-γ, IL-2 interleukin-2, LAG-3 lymphocyte-activation gene 3, MAb monoclonal antibody, PD-1 programmed death 1, PD-L1 programmed death ligand 1, PI3K phosphatidylinositol 3-kinase, TIGIT T-cell immunoreceptor tyrosine-based inhibition motif domain, TIM-3 T-cell immunoglobulin mucin domain-3 protein, VEGF vascular endothelial growth factor, VISTA V-domain immunoglobulin-containing suppressor of T-cell activation.

cytokines (e.g., recombinant interleukin-2, interferon-α), cancer vaccines and adoptive cell therapy. Vaccine therapy combined with ICI potentiates anti-tumour effect in preclinical models and a promising ORR of 33% was reported in a Phase II study combining human papilloma virus-16 (HPV16) specific peptide vaccine with nivolumab in advanced HPV16-positive malignancies [7]. Chimeric antigen receptor (CAR) T-cell therapy has shown significant benefit in specific relapsed/refractory haematological malignancies but limited success in solid organ tumours. Combining CAR-T with ICI may overcome some of the issues encountered, with such a combination in a murine glioblastoma model leading to increased tumour-infiltrating lymphocytes and other early-phase clinical trials showing promise [7].

In addition, approaches beyond solely immunotherapy-based regimens are actively investigated, including ICI administered with ionising radiation and ICI combined with targeted therapies directed at cellular processes, including the DNA damage repair, phosphatidylinositol 3-kinase and histone deacetylase pathways. Treatment harnessing the microbiome with faecal microbiota transplantation or live culture preparations in tandem with ICI is undergoing investigation in multiple trials, with early-phase studies suggesting improved responses with such combinations over ICI alone [1, 8].

There remains great promise in immunotherapy combination therapy, and crucial to their success will be pursuing combinations bedded in rational preclinical studies, which can be aided by improved syngeneic murine models allowing assessment in immunocompetent hosts that more aptly replicate the TME [1]. This will allow us to take forward combinations with positive early results and provide capacity to study ICI resistance mechanisms. Biomarker development allowing appropriate patient selection is crucial, a factor lacking to date with the most widely used biomarker for ICI treatment, PD-L1, having many drawbacks that have been well described previously [9]. Ultimately, a clear and logical approach to combination study design is required to derive the greatest benefit of these practice-changing therapies for patients.

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