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Cancer Horizons

New emerging targets in cancer immunotherapy beyond CTLA-4, PD-1 and PD-L1: Introducing an "ESMO Open – Cancer Horizons" Series

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The ability of tumour cells to escape the surveillance and elimination by the immune system represents one of the hallmarks of cancer.[1 2] This concept of immune control against cancer development, recognised more than 60 years ago by Paul Ehrlich, has recently led to the development of novel different treatment approaches (ie, cancer immunotherapy) aiming to reinvigorate the capability of the immune system to recognise and eliminate tumour cells.[3] For this purpose, while the use of tumour antigenic material as a cancer vaccine has not proven to be particularly successful so far,[4] the advent of therapies able to inactivate inhibitory immune receptors (ie, immune checkpoints) leading to a subsequent increased anti-tumour response has radically changed the natural history of many malignancies including of several aggressive and orphan diseases.

The immunotherapy tsunami has started with the advent of ipilimumab, a monoclonal antibody blocking the immune checkpoint cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) for the treatment of patients with advanced melanoma.[5] The subsequent introduction of other antibodies blocking the immune checkpoints programmed cell death protein-1 (PD-1) and its ligand (PD-L1), including pembrolizumab, nivolumab, durvalumab and atezolizumab, has further generated a major impact on the prognosis of patients with many solid tumours and haematological malignancies.[6] More recently, combination strategies with direct (ie, reducing tumour burden) or indirect (ie, increasing tumour immunogenicity) anti-tumour effects have shown to be possible approaches to improve at a greater extent the efficacy of cancer immunotherapy.[3] Specifically, concurrent administration of chemotherapy with the available checkpoint inhibitors[7–11] as well as combined CTLA-4 and PD-1 blockade[12–14] have already proved to be highly effective in phase III clinical trials.

Nevertheless, despite the significant success of these approaches, not all treated patients derive benefit from the use of the currently available immunotherapy-based treatments, and in those with initial tumour response, disease progression can occur.[15] Indeed, primary tumour refractoriness as well as acquired tumour resistance to the available immune checkpoint inhibitors is one of the major challenges to overcome in the field of cancer immunotherapy.[16] In addition, these treatments can lead to the development of several adverse events that can involve all organs and, in some cases, may be very serious and even lethal.[17] Recently, many new inhibitory or stimulatory molecules have been identified as potential targets to overcome these issues for further improving the ability of the immune system to eradicate cancer cells.[18 19] With a series of mini-reviews on this topic, '*ESMO Open—Cancer Horizons*' aims at providing an update of the most interesting and upcoming targets in cancer immunotherapy highlighting their biological mechanism, the existing targeted agents under investigation and their current stage of clinical development.

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