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Commentary

Expanding Horizons in Cancer Immunotherapy: The Potential of Small Molecule Immune Checkpoint Inhibitors

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The landscape of cancer treatment has witnessed a paradigm shift with the advent of immunotherapy, particularly immune checkpoint inhibitors (ICIs).[1–4] Srivastava *et al*.'s review,[5] "Small molecules as immune checkpoints inhibitors in cancer therapeutics", provides an insightful and comprehensive analysis of the emerging role of small molecules in this transformative field. This commentary aimed to underscore the critical contributions of this review and discuss the broader implications for cancer therapy.

Expanding the arsenal: Small molecule ICIs

Immune checkpoint inhibitors have revolutionized cancer treatment by unleashing the body's immune system to target and destroy cancer cells.[6,7] Traditional ICIs, such as monoclonal antibodies targeting programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4, have been successful in treating various cancers.[8,9] However, they have some limitations, including high production costs, limited tissue penetration, and significant immune-related adverse events.[10,11]

Srivastava *et al*.[5] highlight small molecule ICIs as a promising alternative that addresses many of these limitations. Their review meticulously catalogs various small molecules, including those approved by the U.S. Food and Drug Administration (hereinafter referred to as FDA) and those under clinical trials, highlighting their mechanisms of action, efficacy, and potential advantages over monoclonal antibodies. Small molecules offer several benefits: they are less immunogenic, can be administered orally, and have better tissue penetration, making them an attractive option for cancer therapy.

Table 1 below summarizes the comparative advantages of small molecule ICIs over monoclonal antibodies, highlighting their potential to address many of the limitations of traditional ICI therapies.

Highlighting key advances

The review discusses a range of small molecules, from those disrupting PD-1/PD-L1 interactions to novel compounds targeting other immune checkpoints such as cytotoxic T-lymphocyte-associated protein 4, T cell immunoreceptor with Ig and ITIM domain, and CD47.[12–16] For instance, the authors highlight FDA-approved drugs like Gefitinib and Ruxolitinib, which have shown potential in downregulating PD-L1 expression, thereby enhancing anti-tumor immunity.[17,18] They also discuss emerging molecules such as INCB086550 and CA170, which are currently in clinical trials and show promise in preclinical models.[8,12] An overview of the small molecules explored in this review, including their targets, clinical trial trials, and noted advantages, is presented in Table 2 below.[8,17,19–41]

The meticulous detailing of these small molecules, supported by robust preclinical and clinical data, underscores their potential to overcome resistance mechanisms and reduce immune-related adverse events, which are significant hurdles in the current immunotherapy landscape.

Addressing challenges and future directions

While the review highlights the potential of small molecule ICIs, it also acknowledges the remaining challenges. The development of resistance, the need for biomarkers to predict response, and the management of adverse effects all require ongoing research. Srivastava *et al*.[5] call for more in-depth clinical and biological phenotyping to optimize the therapeutic outcomes of these novel agents.[11,42]

The review's comprehensive nature and forward-looking perspective make it clear that small molecule ICIs are not merely a fleeting trend but a crucial component of the future of cancer immunotherapy. The potential to combine these agents with existing therapies, including monoclonal antibodies and traditional chemotherapies, opens new avenues for synergistic effects and improved patient outcomes.

The review by Srivastava *et al*.[5] represents a significant contribution to the field of cancer immunotherapy, offering a detailed and insightful examination of small molecule ICIs. As the field evolves, the insights presented in this review will undoubtedly serve as a foundation for future research and development. The potential of small molecule ICIs to transform cancer treatment is immense, and this review paves the way for further exploration and clinical advancements.

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Table 1. Comparative advantages of small molecule ICIs over monoclonal antibodies

Feature	Small molecules	Monoclonal antibodies
Administration	Oral availability	Intravenous infusion
Tissue penetration	Better penetration	Limited penetration
Immunogenicity	Less immunogenic	More immunogenic
Production cost	Lower cost	Higher cost
Side effects	Fewer irAEs	More irAEs

ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events.

Table 2. Summary of key small molecules discussed in the review

Small molecule	Target	Clinical trial status	Noted advantages	References
Gefitinib	PD-L1	FDA-approved	Enhances anti-tumor immunity by inhibiting EGF signaling and destabilizing PD-L1	8,17
Ruxolitinib	JAK-STATs	FDA-approved	Downregulates PD-L1 expression in NSCLC and breast cancer cells	19,20
INCB086550	PD-L1	Phase 2	Reduces tumor growth by activating T cells and blocking PD-1/PD-L1 pathways	12,21
CA170	VISTA, PD-L1	Phase 1 and Phase 2	Dual inhibitor that upregulates PD-L1 expression shows efficacy in preclinical models and early clinical trials, orally administered Phase 1 and Phase 2 clinical trials	22,23
Fedratinib	JAK-STATs	FDA-approved	Targets PD-L1 expression, approved for myelofibrosis	24,25
Selumetinib	MEK1/2	FDA-approved	Inhibits PD-L1 in lung adenocarcinoma cells, used for neurofibromatosis type 1 in children	26,27
Belinostat	HDAC	FDA-approved	Increases PD-L1 expression, enhances in vivo anti-PD-1/PD-L1 antibodies	28,29
Azacytidine	DNA hypo-methylating agent	Phase 2	Upregulates PD-L1 expression potentiates anti-PD-L1 antibodies in various cancer models	30,31
Decitabine	DNA hypo-methylating agent	Phase 2	Similar to Azacytidine, used in combination with PARP inhibitors for leukemia	32,33
Romidepsin	HDAC	FDA-approved	Regulates PD-L1 expression, suppresses cellular immune functions in colon cancer	34,35
Panobinostat	HDAC	FDA-approved	Oral DAC inhibitor, used for multiple myeloma	36,37
Vorinostat	HDAC	FDA-approved	Increases PD-L1 expression, enhances the efficacy of anti-PD-1/PD-L1 antibodies	38,39
Metformin	AMPK	Widely used for anti-diabetic drug	Activates T-cells, prevents glycosylation of PD-L1, promotes antitumor immunity	40,41

AMPK, adenosine monophosphate-activated protein kinase; DAC, deacetylase; EGF, epidermal growth factor; FDA, Food and Drug Administration; HDAC, histone deacetylase; JAK-STAT, janus kinase-signal transducer and activator of transcription; MEK1/2, extracellular signal-regulated; NSCLC, non-small cell lung cancer; PARP, poly (ADP-ribose) polymerase; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; VISTA, V-domain immunoglobulin suppressor of T cell activation.

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Conflict of interest

One of the authors, Wenxue Ma has been an editorial board member of *Oncology Advances* since May 2021. The authors have no other conflict of interest to note.

Author contributions

Conceptualization (WM), manuscript writing and editing (TM, WM). All authors have read and agreed to the published version of the manuscript.

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