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EDITORIAL

Next-generation immune checkpoint inhibitors as promising functional molecules in cancer therapeutics

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Cancer is a devastating disease that demands expensive treatment and follow-up patient care. The current intention of cancer therapeutics is to eradicate or slow down the aggressive behavior of cancerous cell infiltration in to systemic circulation and confine its progression. As per the International Agency for Research on Cancer (IARC), by 2040, the worldwide cancer cases are expected to be 27.5 million new cancer cases and 16.3 million deaths globally. The increasing incidence of cancer cases is expected to drive the need for advanced cancer therapies for the effective treatment of patients. The surge in incidence of cancer cases is estimated to accelerate global market expansion of cancer therapeutics in the forthcoming years. A market study published in August 2021 by CISION PR Newswire and Global Industry Analysts Inc. stated that the global market for cancer therapies continuously demonstrated robust growth. By 2024 this segment will touch ~ 204.2 billion US dollar (USD) with 9.7% of compounded annual growth rate (CAGR), whereas Precedence Research quoted that the oncology market size will reach 581.25 billion USD by 2030 with 8.2% of CAGR. North America is going to hold the highest market share followed by Europe region globally.

The global cancer immunotherapy market in 2015 was around 45.471 billion USD which was grown up to 117.114 billion USD in 2022 with a growth rate of ~ 14.5% [1]. According to Grand View Research, cancer immunotherapy market has further potential to grow with 8.7% of CAGR from the year of 2023 to 2030. Several government and non-government institutes funded more than 120 clinical trials and invested around 474 million USD in cancer immunotherapy research. In continuation, the approval of novel cancer immuno-therapeutics is anticipated to propel the market expansion in the future. Very recently, between 2020 and 2022, the FDA has approved numerous anti-PD-1 and PD-L1 antibodies such as Nivolumab, Atezolizumab, Avelumab, and Dostarlimab, for the management of lung, breast, prostate, melanoma, and renal cell carcinomas. Immune-checkpoint modulators/inhibitors are the sub-class of immunotherapy, and their application in cancer management has modernized the oncology segment. It initiates radical changes in the assessment of treatment outcome and adverse effect management with an additional panoramic vision of the cancer patient. The estimated global market size of immune checkpoint inhibitors (ICIs) is predicted to reach up to 56.53 billion USD by 2025, which is the highest growth in all the segment of cancer therapies.

Several inhibitory immunoreceptors have been identified in cancer like PD-1, CTLA-4, LAG3, TIM3, TIGIT, and BTLA. They are known as "immune checkpoints" gatekeepers of immune responses and are normal physiological regulators of the immune system. These check points are critical for self-tolerance, and their role is to provide checks and balances for aberrant immune responses to avoid inappropriate destruction of healthy cells. The immune check points are functional receptors over the surface of immune cells like T-cells. The binding of immune check point receptors with their complementary partner receptor over the other abnormal cells like

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cancer cells, send a "switch off" signal to the T cells. This cellular level interaction prevents the immune cells from eliminating tumor cells. ICIs prevent the "switch off" signal and allow T cells to kill tumor cells. ICIs like anti-CTLA4 and anti-PD-1/PD-L1 antibodies have provided evident advantages in cancer therapeutics with robust clinical outcomes [2].

CTLA4 (also known as CD152), a negative regulator, is expressed over the surface of T-cells which can interact with CD80 and CD86 receptors present over the tumor cells. This cellular interaction attenuates the activity of T-cells. Anti CTLA4 antibodies, such as Tremelimumab (NCT01008358) block CTLA4, prevent T-cell attenuation and stimulate the expression of cytokines like IL2 and interferon gamma (IFNγ) to provide anti-cancerous immunity in renal cancer, melanoma, and non small cell lung cancer (NSCLC). Ipilimumab (NCT01658878) is another anti CTLA4 antibody approved by FDA for melanoma and along with nivolumab for hepatocellular carcinoma (HCC) treatment [1]. The genomic alterations in IFN-γ pathway along with defective genes like JAK2, IRF1, IFNGR1, and IFNGR2 convoyed with amplification of IFN-γ inhibitory genes such as PIAS4 and SOCS1 might play a role in blockade and resistance of anti-CTLA-4 therapy [3].

Anti-PD-1/PDL-1 antibodies are second generation ICIs. PD-1 expresses over the immune cell surface, whereas PDL-1 is present over the tumor cells. The interaction between both receptors represses the hunting ability of immune cells against tumor cells. Nivolumab, a humanized Ig-G4 antibody that interacts with PD-1 protein expressed on activated T-cells, demonstrated effective anti-cancerous activity in phase II clinical trial. Anti PD-1 antibodies (such as pembrolizumab and Cemiplimab) and PDL-1 antibodies (Avelumab and Atezolizumab) effectively block the PD-1 to PDL-1 mediated immune and tumor cells interaction [1, 3] (Fig. 1 A & B). The resistance of PD-1 therapy can cause less infiltration of CD8 T cells within tumors due to the inhibition of the PI3K/AKT pathway. Tumors having reduced anti-PD-1 therapy response may also be attributed to the mutations in JAK1/2 machinery and/or loss of IFN-γ signaling machinery.

The resistance mechanism developed by tumors against anti-CTLA-4 and anti-PD-1/PL-D1 therapies establishes the need for the next-generation ICIs. In that context, lymphocyte activation gene 3 (LAG3), T-cell-Ig-and-ITIM-domain (TIGIT), and TIM3 (T cell immunoglobulin and mucin 3)-based therapies are being sought for better efficacy and outcome. These are co-inhibitory receptors belonging to PD-1 and CTLA-4 category with unique tissue specific functions in the directive of the immune system.

LAG3 is a CD4-like molecule expressed on activated immune cells (T cells, Treg cells, natural killer cells, and dendritic cells), and like PD-1, LAG3 also negatively regulates T-cell activation. Relatlimab (BMS-986016) is an approved LAG3 inhibitor developed by Bristol-Myers Squibb which is under use to treat melanoma in combination with Nivolumab. Anti-LAG3 antibody REGN3767, labelled with zirconium-89 (^{89}Zr-REGN3767) is being utilized for tumor imaging [4]. For Relatlimab (BMS-986016), several Phase 1/2 study (NCT01968109) and Phase 2 studies are under clinical trial to investigate the efficacy of BMS-986016 with and without combination therapy in stomach (NCT02935634), colon (NCT02060188), renal (NCT02996110), and lung (NCT02750514) cancers. There are three more anti-LAG3 antibodies listed, such as IMP321 which is an APC activator followed by LAG525 and MK-4280. Combination therapy with Avelumab (800mg) and IMP321 (6mg) is in phase 1 clinical trial (NCT03252938) in gastric, gallbladder, and colon cancers and pleural mesothelioma indications. Two clinical trials (NCT03598608 and NCT02720068) are undergoing for MK-4280 to establish its safety and efficacy for single and combination therapy in hematological and advanced solid tumors (MK-4280 with/without Pembrolizumab/MK-3475 and with or without Lenvatinib). LAG525, also known as Ieramilimab, is in phase I/II clinical trial (NCT02460224) as monotherapy as well as in combination with anti-PD-1 Spartalizumab (PDR001) for the treatment of patients with advanced metastatic solid tumors [1, 5].

TIGIT is a new class of inhibitor immunoreceptor checkpoint that is being used in immune surveillance against tumors. Basically, TIGIT belongs to the T-cell immunoreceptor (poliovirus receptor/PVR family). CD155 (PVR: higher affinity towards TIGIT) and CD112 (PVRL2) are two ligands for TIGIT. TIGIT has inhibitory action on T and natural killer (NK) cells and also suppresses T cell function by increasing IL-10 secretion of DCs via reverse CD155 signaling [2]. Anti TIGIT and anti PD-1/PD-L1 antibodies possess very impressive outcomes in preclinical models via activation of the T-cells. Presently all the immunotherapies concerned with the TIGIT inhibitors either monotherapy or in combination with anti PD-1/PD-L1 are in phase I clinical trial. MTIG7192a, BMS-986207, and AB154 are anti-TIGIT therapies under clinical trials (phase I) in combination of Atezolizumab (anti PD-L1), Nivolumab (PD-1), and AB122 (PD-1), respectively, whereas OMP-313M32 and MK-7684 monotherapy are in phase I clinical trial [1].

TIM-3 is a transmembrane protein expressed over the surface of immune cells like CD4 + T cells, CD8 + T cells, and myeloid cells. Soluble galactin-9 (GAL-9) is the ligand of TIM-3 which induces T-cell apoptosis. TIM-3 has also been involved in CD8 + T cell debilitation and the overexpression of Th1 and Th17 cytokines [6]. There are several anti-TIM-3 mAbs under trial; MGB453 (from Novartis Pharmaceuticals) is under clinical trial I/IIB for advanced malignancy indications (NCT02608268); TSR-022 (from Tesaro) is in phase-II trial as mono and combinational therapy with anti-PD1

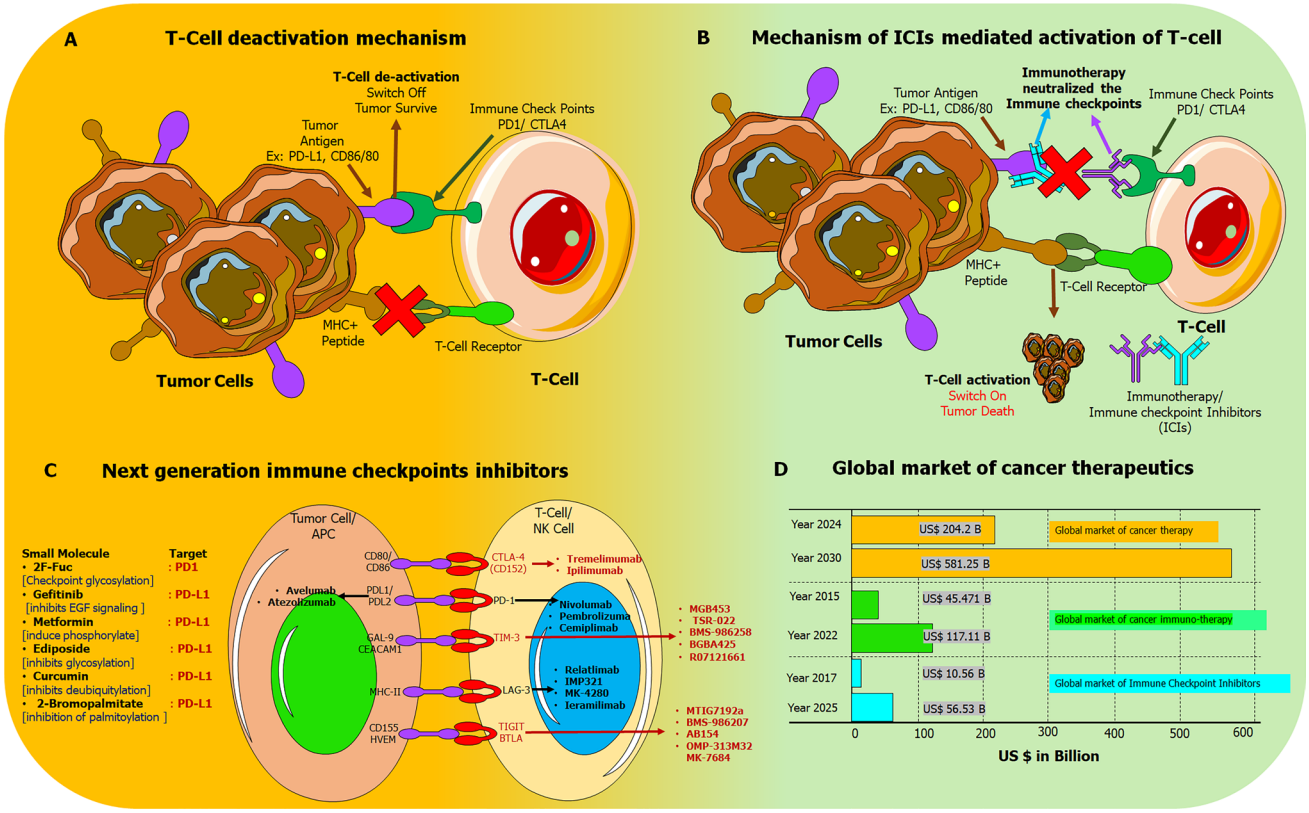

Fig. 1 Mechanism and role of next generation ICIs: **A** the basic procedure of how tumor cell deactivating T-cell; **B** the role of immunotherapy in activation of T-cell; **C** types of next-generation ICIs; **D** global market status of cancer therapeutics

for liver cancer and other solid tumors (NCT02817633 and NCT030680508); BMS-986258 (from Bristol-Myers Squibb) is in phase-I in combination with anti-PD-1 and h-recombinant-hyaluronidase in advanced cancer indications (NCT03446040); BGBA425 (from BeiGene) is under phase-I trial at solid tumor indication (NCT03744468) and R07121661 (Hoffmann-La Roche) also at initial clinical phase I in combination of both anti-TIM-3 and anti-PD-1 at metastatic melanoma and NSCLC (NCT03708328). Apart from that V-domain Ig-containing suppressor of T cell activation (VISTA) and B- and T-lymphocyte attenuator (BTLA) signaling are also very promising and intensively explored pathways for next generation ICIs [3].

There are several FDA-approved MAbs which are still under investigation in clinical trials. These MAbs are effective in combination/monotherapy, but still, the neutralization response rate is very low. In that case, novel strategies are also warranted to support exiting therapies and regulate the surface expression or signal transduction of immune checkpoints. Scientists and companies are working on small molecules that can target checkpoint glycosylation and ubiquitination/degradation pathways.

2-Lluoro-L-fucose (2F-Fuc) reduces the fucosylation (type of checkpoint glycosylation) and surface level of PD-1 on activated T-cells. Gefitinib inhibits EGF signaling to destabilize PD-L1 and activate the anti-tumor activity of immune cells. Metformin is an important anti-diabetic drug, and it could be repurposed to activate T-cells through triggering of AMPK to induce phosphorylate PD-L1 at Serin 195 position, which halts PD-L1 glycosylation. Etoposide, a natural compound used for chemotherapy to treat various cancers, inhibits EMT-induced PD-L1 glycosylation to disrupt surface PD-L1. Disruption of surface PD-L1 in tumor cells by metformin and etoposide improves the effectiveness of anti-CTLA-4 and anti-TIM-3 therapies. The most popular natural compound curcumin also possesses PD-L1 destabilizing ability. Curcumin inhibits deubiquitylation activity of CSN5 (aka Jun activation domain-binding protein 1) and enriches anti-CTLA-4 therapy. Additionally, 2-bromopalmitate directed inhibition of PD-L1 palmitoylation eliminates the suppression of PD-L1 mono-ubiquitination and degradation (Fig. 1C) [2]. Immune checkpoint inhibition with monoclonal antibodies has provided great success in cancer medicine; immunotherapies also suffer from clinically significant toxicities or immune-related adverse events (irAEs). These irAEs are distinct from the toxicities associated with traditional chemotherapy, and they can affect a wide range of organs such as lungs, liver, gastrointestinal,

skin, and endocrine systems due to the nature of the immune system's response. In addition, nephritis and hematological toxicities, myocarditis, and neurotoxicity have also been reported with ICIs [7, 8]. Recognizing and managing these adverse events are of utmost importance to prevent serious morbidity among patients undergoing immunotherapy. Thus, future studies designed in this direction needs to have more rationale design and in-depth clinical and biological phenotyping of ICIs to improve therapeutic outcome of next generation ICIs to effectively participate in global market of cancer therapeutics (Fig. 1D).

In conclusion, in the past decade, ICIs have been established and clinically approved for a broad range of cancer indications. As the field continues to evolve, there is a need for more research into the heterogeneity of irAEs. Each patient's response to immunotherapy and susceptibility to irAEs can vary widely, and a deeper understanding of these variations could lead to personalized treatment strategies. Overall, the use of ICIs looks promising in cancer medicine as their use is widening as alternative therapeutic options in a wide variety of malignancies.

References

1. Dhasmana, A., Dhasmana, S., Kotnala, S., Anukriti, A., Kashyap, V. K., Shaji, P. D., et al. (2022). A topography of immunotherapies against gastrointestinal malignancies. *Panminerva Med, 64*(1), 56–71. https://doi.org/10.23736/s0031-0808.21.04541-9
2. He, X., & Xu, C. (2020). Immune checkpoint signaling and cancer immunotherapy. *Cell Research, 30*(8), 660–669. https://doi.org/10.1038/s41422-020-0343-4
3. Gaikwad, S., Agrawal, M. Y., Kaushik, I., Ramachandran, S., & Srivastava, S. K. (2022). Immune checkpoint proteins: Signaling mechanisms and molecular interactions in cancer immunotherapy. *Seminars in Cancer Biology, 86*, 137–150. https://doi.org/10.1016/j.semcancer.2022.03.014
4. Ge, S., Jia, T., Li, J., Zhang, B., Deng, S., & Sang, S. (2022). Molecular imaging of immune checkpoints in oncology: current and future applications. *Cancer Letters, 548*, 215896. https://doi.org/10.1016/j.canlet.2022.215896
5. Schöffski, P., Tan, D. S. W., Martín, M., Ochoa-de-Olza, M., Sarantopoulos, J., Carvajal, R. D., et al. (2022). Phase I/II study of the LAG-3 inhibitor ieramilimab (LAG525) ± anti-PD-1 spartalizumab (PDR001) in patients with advanced malignancies. *J Immunother Cancer, 10*(2). https://doi.org/10.1136/jitc-2021-003776
6. Haddad, A. F., Young, J. S., Gill, S., & Aghi, M. K. (2022). Resistance to immune checkpoint blockade: Mechanisms, counter-acting approaches, and future directions. *Seminars in Cancer Biology, 86*, 532–541. https://doi.org/10.1016/j.semcancer.2022.02.019
7. Fessas, P., Possamai, L. A., Clark, J., Daniels, E., Gudd, C., Mullish, B. H., et al. (2020). Immunotoxicity from checkpoint inhibitor therapy: Clinical features and underlying mechanisms. *Immunology, 159*(2), 167–177. https://doi.org/10.1111/imm.13141
8. Axelrod, M. L., Meijers, W. C., Screever, E. M., Qin, J., Carroll, M. G., Sun, X., et al. (2022). T cells specific for α-myosin drive immunotherapy-related myocarditis. *Nature, 611*(7937), 818–826. https://doi.org/10.1038/s41586-022-05432-3