Chapter

Introductory Chapter: Introduction to New Insights and Recent Progress in Immune Checkpoint Inhibitors

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1. Introduction

Immune checkpoint inhibitor (ICI) is an established therapeutic strategy for various cancers. ICI comprises mainly of monoclonal antibodies that block immune regulatory checkpoint molecules, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), Programmed cell death protein-1 (PD-1) and Programmed Death Ligand-1 (PD-L1) [1]. To date, FDA has approved ICIs for various cancer types including anti-CTLA-4 (Ipilimumab, Tremelimumab), anti-PD-1 (Pembrolizumab, Nivolumab, Cemiplimab) and anti-PD-L1 (Atezolizumab, Avelumab, and Durvalumab) [2].

The main mechanism of action of immune checkpoint inhibitors is to target and augment host CD4+ and CD8+ T cell responses. Briefly, CTLA-4 is a T-cell surface receptor that binds costimulatory factors (CD80, CD86) on antigen-presenting cells. This activation transmits inhibitory signal to T cells thus, reducing Interleukin 2 (IL-2) production and T-cell proliferation. Moreover, PD-1 is a cell surface receptor expressed on B cells, T cells and NK cells. Its main function is to promote self-tolerance/prevent autoimmunity via apoptosis of antigen-specific T-cells, suppression of T cell inflammatory activity and downregulation of the immune system. PD-1 has strong binding affinity to its ligands, PD-L1/PD-L2 and this binding delivers a strong inhibitory signal to suppress T cell receptor (TCR) mediated activation of IL-2 production and T cell proliferation for immune regulation [3].

2. Novel immune checkpoint inhibitors/combinatorial therapeutic regimens

Recently, many studies and clinical trials have focused on various aspects of immunotherapy including novel immune checkpoint inhibitors, combination therapeutic regimens, identification of predictive and prognostic biomarkers, management of immune related adverse events etc. The insights from these pre-clinical and clinical studies indicate unexplored pathways that need attention at a global scale to improve the role of these ICIs in cancers. Importantly, the novel immune checkpoint inhibitors, apart from anti-CTLA-4, anti-PD-1 and anti-PD-L1, can serve as a paradigm

shift for patients, giving them a chance for additional treatment options. For e.g. recently, FDA approved anti-LAG-3 (Relatlimab) monoclonal antibody, that targets Lymphocyte-activation gene 3 (LAG-3) immune checkpoint and recommended it for untreated unresectable or metastatic melanoma in patients ≥12 years of age. Relatlimab is approved to be given in combination with anti-PD-1 (Nivolumab) as patients on this combination demonstrate better progression free survival than on Nivolumab alone. However, higher incidence of immune-related side effects have been associated with this combination indicating that new and novel immune checkpoint inhibitors need efficient monitoring for patient management [4]. On the other hand, many novel immune checkpoints are still under still investigation in clinical trials with promising results [5]. Some of these include

- T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) for advanced solid tumors/lymphomas
- B7 homolog 3 protein/B7 homolog 4 protein (B7-H3/B7-H4) for advanced solid tumors/B7-H4 positive solid tumors
- Adenosine A2A receptor (A2AR) for advanced solid tumors
- Cluster of differentiation 73 (CD73) for advanced solid tumors
- Natural Killer Cell receptor NKG2A, for Platinum-resistant, recurrent, or metastatic, head and neck squamous cell carcinoma (HNSCC)
- Poliovirus receptor related immunoglobulin domain (PVRIG)
- Poliovirus receptor-related 2 (PVRL2) for Advanced Solid tumors

In addition to novel immune checkpoints, several studies are also focusing on finding optimal combination therapeutic regimens of ICIs with other biomolecules to augment the immune response for better progression free and overall survival [5]. Some of these include:

- Tyrosine Kinase inhibitor, Focal adhesion kinase (FAK) in combination with Pembrolizumab and chemotherapy gemcitabine for advanced pancreatic adenocarcinoma
- Anti-CD-147-Signal regulatory protein α (SIRPα) fusion drug, ALX148, in combination with pembrolizumab, nivolumab, trastuzumab, rituximab, ramucirumab, 5FU, paclitaxel, or cisplatin for advanced solid tumors or refractory Non-Hodgkin's Lymphoma (NHL)
- Colony stimulating factor 1 (CSF-1 (M-CSF)/CSF-1R) Inhibitor in combination with durvalumab for advanced solid tumors
- B cell activator, Semaphorin 4D (SEMA4D), in combination with avelumab for advanced stage Non-small cell lung cancer (NSCLC)
- Angiopoietin-2 (Ang-2) in combination with pembrolizumab for advanced solid tumors

It is postulated that with the advent of novel and combinatorial immune checkpoint therapies, improved overall survival for solid, hematological, rare, and hard-to-treat cancers will improve the prospect of improved cancer management.

3. Predictive and prognostic biomarkers

In addition to novel therapeutic regimens, another area of immense importance is the identification of predictive and prognostic biomarkers for immune related adverse events/treatment dynamics. This is a vastly growing field, particularly due to the limited response rates (20–40%) observed in patients on ICI treatment. Finding predictive and prognostic biomarkers can not only help stratify patients for optimal treatment regimen but will also reduce the economic cost on patients. Furthermore, it can help to avoid the generation of drug resistance as the use of ICI for a specific cohort (such as responding patients) will control excess use of this precious drug. In lieu of this, soluble biomarkers (secreted in plasma, serum, urine, ascitic fluids etc.) are gaining a lot of attention. This is due to major advantages including ease of sampling, longitudinal monitoring, and less heterogeneity (as compared to tissue biomarkers). Several studies investigating the role of soluble CTLA-4 (sCTLA-4), soluble PD-1 (sPD-1), soluble PD-L1 (sPD-L1) and soluble PD-L2 (sPD-L2), especially in melanoma and NSCLC patients have shown promising results. The studies observed that soluble markers can exert enhancement and inhibitory effects on the immune system including early activation of CD8+lymphocytes, increased lytic activity of macrophages, up regulation of pro- and anti-inflammatory cytokines/chemokines, inhibition of IL-2 production/T cell activation and reverse signaling on dendritic cells (DC) leading to reduction in DC maturation. These soluble markers have also been postulated to bind and block the active site of ICI monoclonal antibodies, thus making the treatment regimen inefficient [6–16]. On the other hand, several predictive biomarkers such as C-Reactive proteins (CRP), Blood cell counts, IL-5, IL-6, IL-8, CXCL9, 10, 11, 13, CCL3, CCR3, sPD-L2 etc. have been associated as predictors of immune related adverse events in ICI treated patients indicating the importance of soluble markers [8, 17, 18]. However, this is still an untapped area with limited studies and larger prospective clinical trials are warranted to fully understand their role in immunotherapy.

Last, but not the least, the gut microbiome is an area of immense interest for their role in ICI treatment dynamics. Emerging evidence/clinical trials suggest that gut microbiota influences clinical response to immunotherapy [19]. For e.g., a study on fecal microbiota transplant (FMT) in metastatic melanoma from responding patients (on anti-PD-1 treatment) to non-responding patient lead to improved response rates [20]. In addition to this, various studies have documented the microbes *Blautia obeum, Collinsella aerofaciens, Enterococcus faecium, Klebsiella pneumonia, Parabacteroides merdae, Roseburia intestinalis, Veillonella parvula, Ruminococcaceae* to be associated with enhanced/inhibitory effects on anti-PD-1 treatment mainly due to their interaction with the cells of the tumor microenvironment [19, 21–23]. Therefore, the value of assessing the gut microbiome in immunotherapy is an area of significant interest and randomized controlled trials, examining modulatory effects of the gut microbiome in ICI treated patients, is recommended for better understanding of treatment dynamics.

In summary, a vast avenue of areas can be explored with regards to immune checkpoint inhibitors to provide novel insights into this emerging field. The

above-mentioned areas are just the tip of the iceberg and exploration of other aspects such as genomics, transcriptomics, proteomics, metabolomics etc. can serve valuable for treatment management and better overall survival for ICI treated patients.

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References

[1] Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, adaptive, and acquired resistance to cancer immunotherapy. Cell. 2017;**168**(4):707-723

[2] Twomey JD, Zhang B. Cancer immunotherapy update: FDA-approved checkpoint inhibitors and companion diagnostics. The AAPS Journal. 2021;**23**(2):39

[3] Iranzo P, Callejo A, Assaf JD, Molina G, Lopez DE, Garcia-Illescas D, et al. Overview of checkpoint inhibitors mechanism of action: Role of immune-related adverse events and their treatment on progression of underlying cancer. Frontiers in Medicine. 2022;**9**:875

[4] Institute NC. Opdualag Becomes First FDA-Approved Immunotherapy to Target LAG-3 2022. 2022. Available from: https://www.cancer.gov/news-events/cancer-currents-blog/2022/fda-opdualag-melanoma-lag-3

[5] Marin-Acevedo JA, Kimbrough EO, Lou Y. Next generation of immune checkpoint inhibitors and beyond. Journal of Hematology & Oncology. 2021;**14**(1):45

[6] Li Y, Xiao Y, Su M, Zhang R, Ding J, Hao X, et al. Role of soluble programmed death-1 (sPD-1) and sPD-ligand 1 in patients with cystic echinococcosis. Experimental and Therapeutic Medicine. 2016;**11**(1):251-256

[7] Zhu X, Lang J. Soluble PD-1 and PD-L1: Predictive and prognostic significance in cancer. Oncotarget. 2017;**8**(57):97671-97682

[8] Costantini A, Julie C, Dumenil C, Helias-Rodzewicz Z, Tisserand J, Dumoulin J, et al. Predictive role of plasmatic biomarkers in advanced non-small cell lung cancer treated by nivolumab. Oncoimmunology. 2018;**7**(8):e1452581

[9] Gu D, Ao X, Yang Y, Chen Z, Xu X. Soluble immune checkpoints in cancer: Production, function and biological significance. Journal for Immunotherapy of Cancer. 2018;**6**(1):132

[10] Okuma Y, Wakui H, Utsumi H, Sagawa Y, Hosomi Y, Kuwano K, et al. Soluble programmed cell death ligand 1 as a novel biomarker for nivolumab therapy for non-small-cell lung cancer. Clinical Lung Cancer. 2018;**19**(5):410-417

[11] Abu Hejleh T, Furqan M, Ballas Z, Clamon G. The clinical significance of soluble PD-1 and PD-L1 in lung cancer. Critical Reviews in Oncology/Hematology. 2019;**143**:148-152

[12] Nixon AB, Schalper KA, Jacobs I, Potluri S, Wang IM, Fleener C. Peripheral immune-based biomarkers in cancer immunotherapy: Can we realize their predictive potential? Journal for Immunotherapy of Cancer. 2019;**7**(1):325

[13] Raza A, Merhi M, Relecom A, Fernandes Q, Inchakalody V, Gul ARZ, et al. Evolving dynamic biomarkers for prediction of immune responses to checkpoint inhibitors in cancer. Advances in Precision Medicine Oncology. 2020

[14] Tiako Meyo M, Jouinot A, Giroux-Leprieur E, Fabre E, Wislez M, Alifano M, et al. Predictive value of soluble PD-1, PD-L1, VEGFA, CD40 ligand and CD44 for nivolumab therapy in advanced non-small cell lung cancer: A Case-Control Study. Cancer. 2020;**12**(2)

[15] Han B, Dong L, Zhou J, Yang Y, Guo J, Xuan Q, et al. The clinical implication of soluble PD-L1 (sPD-L1) in patients with breast cancer and its biological function in regulating the function of T lymphocyte. Cancer Immunology, Immunotherapy. 2021;**70**(10):2893-2909

[16] Ohkuma R, Ieguchi K, Watanabe M, Takayanagi D, Goshima T, Onoue R, et al. Increased plasma soluble PD-1 concentration correlates with disease progression in patients with cancer treated with anti-PD-1 antibodies. Biomedicines. 2021;**9**(12)

[17] Jia XH, Geng LY, Jiang PP, Xu H, Nan KJ, Yao Y, et al. The biomarkers related to immune related adverse events caused by immune checkpoint inhibitors. Journal of Experimental & Clinical Cancer Research. 2020;**39**(1):284

[18] Schalper KA, Carleton M, Zhou M, Chen T, Feng Y, Huang SP, et al. Elevated serum interleukin-8 is associated with enhanced intratumor neutrophils and reduced clinical benefit of immune-checkpoint inhibitors. Nature Medicine. 2020;**26**(5):688-692

[19] Oh B, Boyle F, Pavlakis N, Clarke S, Eade T, Hruby G, et al. The gut microbiome and cancer immunotherapy: Can we use the gut microbiome as a predictive biomarker for clinical response in cancer immunotherapy? Cancers (Basel). 2021;**13**(19)

[20] Baruch EN, Youngster I, Ben-Betzalel G, Ortenberg R, Lahat A, Katz L, et al. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. Science. 2021;**371**(6529):602-609

[21] Erdman SE, Rao VP, Poutahidis T, Rogers AB, Taylor CL, Jackson EA, et al. Nitric oxide and TNF-alpha trigger colonic inflammation and carcinogenesis in Helicobacter hepaticus-infected, Rag2-deficient mice. Proceedings of the National Academy of Sciences of the United States of America. 2009;**106**(4):1027-1032

[22] Erdman SE, Poutahidis T. The microbiome modulates the tumor macroenvironment. Oncoimmunology. 2014;**3**:e28271

[23] Vetizou M, Pitt JM, Daillere R, Lepage P, Waldschmitt N, Flament C, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science. 2015;**350**(6264):1079-1084