

## Checkmate with Checkpoint Inhibitors: Hope and Hype

Cancer immunotherapy has taken the center stage among different therapeutic options for the treatment of cancer. While conventional treatment modalities such as surgery, radiotherapy, and chemotherapy have offered substantial benefit for the eradication of primary tumors, the incidence of disease relapse remains a commonly encountered problem. The recent advances in immunotherapy such as utilization of cancer vaccines, chimeric antigen receptor T cell therapy, and immune checkpoint blockade (ICB) therapy have fueled renewed interest in the field. Currently, five ICB antibodies are Food and Drug Administration approved for the treatment of a broad spectrum of tumor types.<sup>[1]</sup> These therapeutic antibodies have offered long-term durable responses in a subset of patients with treatment-refractory metastatic cancer. In the current era, our knowledge and understanding of the mechanisms and pathways that regulate the immune system's response to cancer has been tremendously enhanced by high-quality researches. However, there are many areas which are yet to be fully explored.<sup>[2]</sup> These include lack of prediction of response and efficacy, inadequate biomarkers, immune resistance, suboptimal study designs, and financial toxicity.<sup>[3-7]</sup> Researchers are working to solve many such obstacles by more targeted treatments, precision biomarker developments, combination therapies, and immunoprevention to decrease cancer incidence, relapses, and management costs.<sup>[8-11]</sup>

The immune checkpoint pathway includes a series of cellular interactions that prevent excessive effector T cell activity under normal conditions to maintain T cell homeostasis. Immune response is regulated by an exquisite system of checks and balances that enable protective immunity and tolerance. The effector functions of innate and adaptive immune cells are controlled by the expression of immune checkpoints on these cells. T cell activation is based on the two-signal concept as proposed by Lafferty and Cunningham.<sup>[12,13]</sup> The first signal for T cell activation is provided by the T cell receptor (TCR) expressed on T cells with the peptide/major histocompatibility complex expressed on the antigen-presenting cell (APC) which confers specificity to the response. The second co-stimulatory signal is provided by the interaction between CD28 expressed on T cells with its ligand CD80 (B7-1) and CD86 (B7-2) expressed on APC. Engagement of signal 1 and signal 2 is needed for T-cell activation. Cytotoxic T lymphocyte antigen-4 (CTLA-4) was identified as a CD28 homolog that possesses potent inhibitory functions. Engagement of CTLA-4 with CD80/CD86 was capable of limiting the threshold of T cell activation and duration of the immune response and was responsible for regulating autoimmunity and inflammation.<sup>[12,13]</sup>

Ligation of the programmed cell death protein (PD-1, also known as CD279) with PD-1 ligand 1 (PD-L1, also known as B7-H1 or CD274) activates a critical immune checkpoint leading to T-cell dysfunction, exhaustion, and tolerance. Monoclonal anti-PD-1 and anti-PD-L1 antibodies that block PD-1/PD-L1 interaction can reverse the immune checkpoint and release the brakes on the T cell responses. The binding of PD-1 to PD-L1 alters the immune activity by modulating it to inhibit autoimmune diseases or chronic inflammation.<sup>[14]</sup>

Cancer cells have hijacked the inhibitory checkpoints to evade recognition by immune cells. PD-L1 is also constitutively expressed in certain tumors and plays an important role in preventing T cell-mediated killing, thus evading immune attack. These inhibitory checkpoints are also key mediators of T-cell exhaustion in patients. Besides CTLA-4 and PD-1, there exist a number of inhibitory and stimulatory regulators that can modulate TCR-mediated signals,<sup>[15-17]</sup> for example, T cell immunoglobulin and mucin domain-containing protein 3 (Tim-3) and lymphocyte activation gene-3 (LAG-3). These molecules are, therefore, attractive targets for removing the inhibition and enabling cytotoxic T cells to attack cancer cells. PDL1+-expressing tumor cells and APC engage PD-1+ T cells and bring about apoptosis, anergy, and exhaustion in T-cells. PD-L1 thus acts as a molecular shield to protect tumor cells from an immune attack.<sup>[15-17]</sup>

Clinically, PD pathway blockade has demonstrated clinical responses across a spectrum of solid tumor types and hematological malignancies. The objective response rates are varied as reported in different clinical trials. The key question is whether there are good biomarkers that can predict therapeutic responsiveness to these antibodies. Ongoing efforts to identify predictive biomarkers have examined the expression level of PD-L1 on tumors to predict clinical response. While in some malignancies PD-L1 expression was an indicator of poor prognosis for patient survival, in others, it showed no correlation with the clinical response. Considering the limitations of clinical sampling methods, it appears that PD-L1 expression on tumor cells and immune cells may not be a definitive predictive biomarker. More recently, tumor mutation burden has been proposed as a biomarker of response to immune checkpoint inhibitors (ICIs). There is evidence to support a link between PD pathway blockade and tumor mutation-derived antigen-specific T-cell responses. A common feature among various cancers, with higher probability of response to ICIs, is the higher prevalence of somatic mutations in their genomes, for example, melanoma and non-small cell lung cancer, both these genomically unstable tumor types are malignancies which show maximum response to anti-PD-1

therapy.<sup>[18,19]</sup> Similarly, cancers with microsatellite instability or mismatch repair (MMR) deficiency are known to respond to ICIs. MMR deficiency induces frameshift mutations in tumors, increasing the likelihood of neoantigen expression in these tumors.<sup>[20]</sup>

However, this model does not hold true in all cases. For instance, renal cell carcinoma which is a cancer with low tumor mutational burden responds to ICIs.<sup>[21]</sup> Similarly, human papillomavirus (HPV)-positive head-and-neck squamous cell carcinoma (HNSCC) has mutation load comparable to HPV-negative HNSCC, but patients with HPV-positive HNSCC have better outcomes.<sup>[22]</sup> High level of mutations may not necessarily result in the expression of immunogenic neoantigens which are capable of generating T-cell responses that will eliminate tumors.

The importance of immune infiltrate as a prognostic marker is gaining a lot of attention. The location, type, density, and spatial organization of the immune cell infiltrate in the tumor are becoming increasingly relevant to predict and guide immunotherapeutic responsiveness.<sup>[23]</sup> Lymphocyte infiltration in the tumor results from an immune response, which is thought to improve disease control and might serve as a prognostic biomarker. Hot (inflamed tumors) tumors are having better prognosis than cold tumors as they are more immunogenic.<sup>[24]</sup> Immune cells such as myeloid-derived suppressor cells, regulatory T-cells, and M2 macrophages impede immune responses and result in resistance to immunotherapy. Preexisting tumor infiltrating immune cells and TH1-type chemokines have been shown to correlate with clinical response to PD-1 pathway.<sup>[25,26]</sup> Current research focuses on identifying epigenetic biomarkers that can establish which patients will not benefit from anti-PD-1 or anti-PD-L1 monotherapy. Methylation status of FOXP1 could be associated with validated predictive biomarkers such as PD-L1 expression and mutational load to select patients who will respond to checkpoint blockade therapy.<sup>[27]</sup>

Accumulating evidence in preclinical models and patients suggests that gut microbiome affects the therapeutic efficacy of cancer immunotherapy, particularly, of the ICIs.<sup>[28,29]</sup> Stratification of patients based on the gut microbiome and investigating their immune responses and clinical outcomes during the course of immunotherapy will be an interesting aspect to pursue.

As compared to chemotherapy and molecular targeted therapy, a relatively higher rate of primary resistance to ICIs is observed in patients, which leads to disease progression or relapse. The mechanisms of resistance are not well understood, but several tumors related as well as host related factors play a role. These include PD1 expression, lack of tumor antigen expression/presentation, cellular signaling pathways, tumor microenvironment, and epigenetic modification. New combination treatment strategies are being explored to improve the efficacy of

ICIs in a broader patient population without exacerbating the toxic effects.

Another complexity is the heterogeneity of response observed in patients receiving checkpoint blockade therapy, which includes pseudoprogression where tumor burden or number of tumor lesions increases initially before decreasing and hyperprogression where accelerated tumor growth is observed after immunotherapy.<sup>[30,31]</sup> Unlike pseudoprogression, patients with hyperprogression exhibit worst survival outcomes. This phenomenon is associated with age, higher metastatic load, and prior irradiation. Murine Double Minute Homolog 2 and 4 (MDM2/MDM4) amplification and epidermal growth factor receptor aberrations have been shown as potential biomarkers for hyperprogression after single-agent checkpoint inhibitor therapy.

### Cost of Cancer Immunotherapy

The economic sustainability of health-care systems is global.<sup>[9]</sup> The introduction of ICBs has revolutionized the cancer therapy, and we have a chance to talk about “indefinite survival” in clinics with preserved quality of life. However, the financial toxicity is a real concern.<sup>[9]</sup>

The IMS Health data revealed that, in 2014, U.S. cancer drugs’ expenditure touched \$42.4 billion.<sup>[8]</sup> This is alarming, and implication in low- and middle-income countries is even more. There is dire need for collaborative efforts among the medical community.<sup>[9]</sup> We need to predict *a priori* which patients are likely to have best benefit with these “magic drugs” with least toxicity; this biomarker-based selection of appropriate patients can substantially reduce costs.<sup>[9]</sup> Other cost saving measures could be analysis for cost-effectiveness, and quality-adjusted life years; policies for drug reimbursement etc.<sup>[9]</sup> A fraction of patients receiving ICB treatment have prolonged survival benefits, so this potential outcome may justify treatment costs.<sup>[6-10]</sup>

### Indian Scenario: Immuno-Oncology Society of India

Because immunotherapy is in nascent stage in India and majority of the patients cannot afford ICBs at this point, an interest group conceptualized the Immuno-Oncology Society of India (I-OSI) for the promotion and advancement of scientific knowledge and research in immuno-oncology (IO) which helps in the translation of laboratory discoveries to patient care. The I-OSI will help increasing the awareness among all the stakeholders, including public, regarding IO in country. It will increase interdisciplinary interactions among all stakeholders dealing with IO at national and international levels and strive to develop guidelines that will assist government and nongovernmental agencies in all matters pertaining to IO. The I-OSI’s head quarter is at Tata Memorial Centre,

and all the details regarding the society are available at the website.<sup>[32]</sup>

## Conclusion

The understanding of IO has increased exponentially; however, many impediments are yet to be overcome. The present hurdles will likely be taken care by smart strategies including precision immunotherapies, targeted approach with IO, and efficient combinations with chemo or targeted therapies. There is a need to focus on the prevention aspects of cancer through immune-based strategies.

### Jyoti Bajpai, Shubhada V Chiplunkar<sup>1</sup>

Department of Medical Oncology, Tata Memorial Centre, Tata Memorial Hospital, Mumbai, <sup>1</sup>Advanced Centre for Treatment Research and Education in Cancer, Tata Memorial Centre, Homi Bhabha National Institute, Navi Mumbai, Maharashtra, India

#### Address for correspondence:

Dr. Shubhada V Chiplunkar,

Advanced Centre for Treatment Research and Education in Cancer, Tata Memorial Centre, Homi Bhabha National Institute, Kharghar, Navi Mumbai - 410 210, Maharashtra, India.  
E-mail: shubhachiplunkar@gmail.com

## References

- Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov* 2018;8:1069-86.
- Alatrash G, Jakher H, Stafford PD, Mittendorf EA. Cancer immunotherapies, their safety and toxicity. *Expert Opin Drug Saf* 2013;12:631-45.
- Chiriva-Internati M, Bot A. A new era in cancer immunotherapy: Discovering novel targets and reprogramming the immune system. *Int Rev Immunol* 2015;34:101-3.
- Yang Y. Cancer immunotherapy: Harnessing the immune system to battle cancer. *J Clin Invest* 2015;125:3335-7.
- Pardoll D. Cancer and the immune system: Basic concepts and targets for intervention. *Semin Oncol* 2015;42:523-38.
- Zugazagoitia J, Guedes C, Ponce S, Ferrer I, Molina-Pinelo S, Paz-Ares L, *et al.* Current challenges in cancer treatment. *Clin Ther* 2016;38:1551-66.
- Wayteck L, Breckpot K, Demeester J, De Smedt SC, Raemdonck K. A personalized view on cancer immunotherapy. *Cancer Lett* 2014;352:113-25.
- Adams KT. Cancer immunotherapies – And their cost – Take center stage at ASCO's 2015 annual meeting. *Manag Care* 2015;24:30-2.
- Tartari F, Santoni M, Burattini L, Mazzanti P, Onofri A, Berardi R, *et al.* Economic sustainability of anti-PD-1 agents nivolumab and pembrolizumab in cancer patients: Recent insights and future challenges. *Cancer Treat Rev* 2016;48:20-4.
- Grady D. Harnessing the Immune System to Fight Cancer. *The New York Times*; 30 July, 2016. Available from: <http://www.nytimes.com/2016/07/31/health/harnessing-the-immune-system-to-fightcancer.html>. [Last accessed on 2016 Aug 17].
- National Cancer Institute. Checking in on Cancer Checkpoint Inhibitors. *National Cancer Institute*; 18 December, 2015. Available from: <http://www.cancer.gov/newsevents/cancer-currents-blog/2015/gulley-checkpoint>. [Last accessed on 2016 Oct 26].
- Lafferty KJ, Cunningham AJ. A new analysis of allogeneic interactions. *Aust J Exp Biol Med Sci* 1975;53:27-42.
- Fuchs EJ, Matzinger P. Is cancer dangerous to the immune system? *Semin Immunol* 1996;8:271-80.
- Chen L, Han X. Anti-PD-1/PD-L1 therapy of human cancer: Past, present, and future. *J Clin Invest* 2015;125:3384-91.
- Matsuzaki J, Gnjatic S, Mhawech-Fauceglia P, Beck A, Miller A, Tsuji T, *et al.* Tumor-infiltrating NY-ESO-1-specific CD8+ T cells are negatively regulated by LAG-3 and PD-1 in human ovarian cancer. *Proc Natl Acad Sci U S A* 2010;107:7875-80.
- Johnston RJ, Comps-Agrar L, Hackney J, Yu X, Huseni M, Yang Y, *et al.* The immunoreceptor TIGIT regulates antitumor and antiviral CD8(+) T cell effector function. *Cancer Cell* 2014;26:923-37.
- Chauvin JM, Pagliano O, Fourcade J, Sun Z, Wang H, Sander C, *et al.* TIGIT and PD-1 impair tumor antigen-specific CD8+ T cells in melanoma patients. *J Clin Invest* 2015;125:2046-58.
- Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, *et al.* Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 2015;348:124-8.
- Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, *et al.* Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N Engl J Med* 2014;371:2189-99.
- Maby P, Tougeron D, Hamieh M, Mlecnik B, Kora H, Bindea G, *et al.* Correlation between density of CD8+ T-cell infiltrate in microsatellite unstable colorectal cancers and frameshift mutations: A Rationale for personalized immunotherapy. *Cancer Res* 2015;75:3446-55.
- Voss MH, Hellmann MD, Chen Y, Gold TM, Lambert CR, VanAllen E, *et al.* Mutation burden and tumor neoantigens in RCC patients (pts) treated with nivolumab. *J Clin Oncol* 2016;34 Suppl 2:514.
- Gameiro SF, Ghasemi F, Barrett JW, Koropatnick J, Nichols AC, Mymryk JS, *et al.* Treatment-naïve HPV+ head and neck cancers display a T-cell-inflamed phenotype distinct from their HPV – Counterparts that has implications for immunotherapy. *Oncoimmunology* 2018;7:e1498439.
- Binnewies M, Roberts EW, Kersten K, Chan V, Fearon DF, Merad M, *et al.* Understanding the tumor immune microenvironment (TIME) for effective therapy. *Nat Med* 2018;24:541-50.
- Maleki Vareki S. High and low mutational burden tumors versus immunologically hot and cold tumors and response to immune checkpoint inhibitors. *J Immunother Cancer* 2018;6:157.
- Powles T, Eder JP, Fine GD, Braithel FS, Loria Y, Cruz C, *et al.* MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. *Nature* 2014;515:558-62.
- Tematek PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJ, Robert L, *et al.* PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature* 2014;515:568-71.
- Duruiseaux M, Martínez-Cardús A, Calleja-Cervantes ME, Moran S, Castro de Moura M, Davalos V, *et al.* Epigenetic prediction of response to anti-PD-1 treatment in non-small-cell lung cancer: A multicentre, retrospective analysis. *Lancet Respir Med* 2018;6:771-81.
- Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, *et al.* Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients.

Science 2018;359:97-103.

29. Matson V, Fessler J, Bao R, Chongsuwat T, Zha Y, Alegre ML, *et al.* The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science* 2018;359:104-8.
30. Fuentes-Antrás J, Provencio M, Díaz-Rubio E. Hyperprogression as a distinct outcome after immunotherapy. *Cancer Treat Rev* 2018;70:16-21.
31. Wang Q, Gao J, Wu X. Pseudoprogression and hyperprogression after checkpoint blockade. *Int Immunopharmacol* 2018;58:125-35.
32. I-OSI | Home Available from: <http://www.immunooncologyindia.com/>. [Last accessed on 2019 Apr].

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

#### Access this article online

##### Quick Response Code:



##### Website:

[www.ijmpo.org](http://www.ijmpo.org)

##### DOI:

10.4103/ijmpo.ijmpo\_103\_19

**How to cite this article:** Bajpai J, Chiplunkar SV. Checkmate with checkpoint inhibitors: Hope and hype. *Indian J Med Paediatr Oncol* 2019;40:159-62.