

## Immune checkpoint inhibitors: A strategy to tackle cancer?

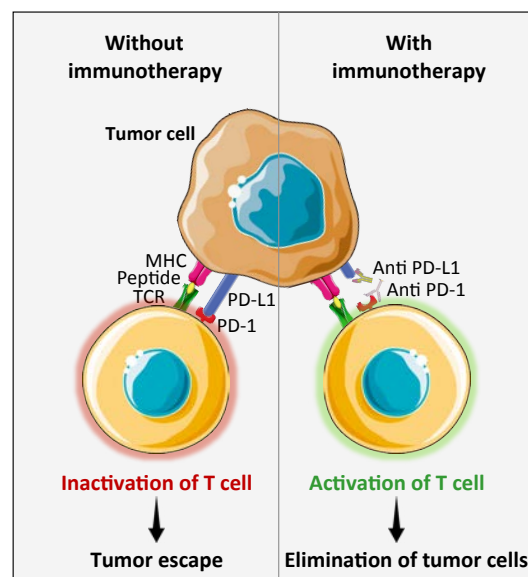
Commentary by Alessia Armezzani, PhD

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Our immune system is constantly on the lookout for pathogens and, once it encounters one, it mounts a strategic attack to fight it: it is the so-called immune response. To minimize the potential collateral damage to healthy cells and tissues though, this response needs to be tuned down.<sup>(1, 2)</sup> And that is precisely the role of inhibitory immune checkpoints, a plethora of molecules naturally expressed both on T cells and antigen-presenting cells that maintains self-tolerance and limits tissue damage by recognizing ligands expressed on self-tissues.<sup>(3)</sup> In the past 30 years, a broad range of immune checkpoint molecules have been identified, including cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) whose discoveries have earned James P. Allison and Tasuku Honjo the Nobel Prize in medicine in 2018. Both proteins act as negative regulators of T cell activation, thereby preventing unwanted immune responses.<sup>(4, 5, 6, 7, 8)</sup>

Immune checkpoints are also expressed on many tumor cells, allowing them to cleverly evade host immune response and divide uncontrollably.<sup>(9)</sup> Interestingly, several *in vivo* studies have demonstrated that antibodies directed against key immune checkpoints such as PD-1 and CTLA-4 inhibit their function, thereby allowing the elimination of certain tumor cells.<sup>(2, 10, 11, 12)</sup>

These findings have provided a rationale for targeting immune checkpoints to enhance antitumor immunity, and revolutionized cancer therapy. Indeed, several immune checkpoint molecules, including PD-1 and CTLA-4, have been approved by the Food and Drug Administration (FDA) for treating certain types of cancers, while others are under clinical trials.<sup>(12)</sup> These new immunotherapies, known as checkpoint inhibitors, represent a highly effective treatment for solid cancers, such as metastatic melanomas, non-small-cell lung carcinomas and liver cancer, and offer patients a durable remission from diseases whose outcomes were previously invariably terminal.<sup>(12, 13, 14)</sup>



Accumulating evidence suggests that only a number of patients benefit from checkpoint inhibitors, and that a fraction of those develop a wide range of severe autoimmune responses.<sup>(3, 13, 15, 16)</sup> These observations have given rise to the need to develop predictive biomarkers to differentiate between responders and non-responders, avoid any adverse effect, and facilitate the decision-making process to select the best immune checkpoint inhibitor-based therapy for each patient.<sup>(12, 17)</sup> Ongoing clinical studies have already identified some of them (e.g., immune cell counts, neoantigens, gene mutations)<sup>(12)</sup> and others are underway, which could represent an important first step toward personalized medicine in cancer treatment.

*Alessia Armezzani is scientific communication manager at genOway.*

References:

1. Ceeraz S, Nowak EC, Noelle RJ (2013) B7 family checkpoint regulators in immune regulation and disease. *Trends Immunol* 34: 556.
2. Peggs KS, Quezada SA, Allison JP (2009) Cancer immunotherapy: co-stimulatory agonists and co-inhibitory antagonists. *Clin Exp Immunol* 157: 9.
3. Paluch C, Santos AM, Anzilotti C, Cornall RJ, Davis SJ (2018) Immune checkpoints as therapeutic targets in autoimmunity. *Front Immunol* 9: 2306.
4. Linsley PS, Ledbetter JA (1993) The role of the CD28 receptor during T cell responses to antigen. *Annu Rev Immunol* 11: 191.
5. Qureshi OS, Zheng Y, Nakamura K, Attridge K, Manzotti C, Schmidt EM, Baker J, Jeffery LE, Kaur S, Briggs Z, Hou TZ, Futter CE, Anderson G, Walker LS, Sansom DM (2011) Trans-endocytosis of CD80 and CD86: A molecular basis for the cell-extrinsic function of CTLA-4. *Science* 332: 600.
6. Sharpe AH, Pauken KE (2018) The diverse functions of the PD1 inhibitory pathway. *Nat Rev Immunol* 18: 153.
7. Khailaie S, Rowshanravan B, Robert PA, Waters E, Halliday N, Badillo Herrera JD, Walker LSK, Sansom DM, Meyer-Hermann M (2018) Characterization of CTLA4 trafficking and implications for its function. *Biophys J* 115: 1330.
8. Wei SC, Duffy CR, Allison JP (2018) Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov* 8: 1069.
9. Pardoll DM (2012) The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 12: 252.
10. Curran MA, Montalvo W, Yagita H, Allison JP (2010) PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. *Proc Natl Acad Sci USA* 107: 4275.
11. Selby M, Englehardt J, Lu L-S, Quigley M, Wang C, Chen B, Korman AJ (2013) Antitumor activity of concurrent blockade of immune checkpoint molecules CTLA-4 and PD-1 in preclinical models. *J Clin Oncol* 31 (suppl; abstr 3061).
12. Darwin P, Toor SM, Sasidharan Nair V, Elkord E (2018) Immune checkpoint inhibitors: recent progress and potential biomarkers. *Exp Mol Med* 50: 165.
13. Auslander N, Zhang G, Lee JS, Frederick DT, Miao B, Moll T, Tian T, Wei Z, Madan S, Sullivan RJ, Boland G, Flaherty K, Herlyn M, Ruppin E (2018) Robust prediction of response to immune checkpoint blockade therapy in metastatic melanoma. *Nat Med* 24: 1545.
14. Xu F, Jin T, Zhu Y, Dai C (2018) Immune checkpoint therapy in liver cancer. *J Exp Clin Cancer Res* 37: 110.
15. Harada K, Abdelhakeem AAF, Ajani J (2019) A balancing act: Dual immune-checkpoint inhibition for oesophagogastric cancer. *Nat Rev Clin Oncol* 16: 9.
16. Teufel A, Zhan T, Härtel N, Bornschein J, Ebert MP, Schulte N (2019) Management of immune related adverse events induced by immune checkpoint inhibition. *Cancer Lett.* 2019 Apr 30.
17. Janjigian YY, Bendell J, Calvo E, Kim JW, Ascierto PA, Sharma P, Ott PA, Peltola K, Jaeger D, Evans J, de Braud F, Chau I, Harbison CT, Dorange C, Tschaika M, Le DT (2018) CheckMate-032 study: efficacy and safety of nivolumab and nivolumab plus ipilimumab in patients with metastatic esophagogastric cancer. *J Clin Oncol* 36: 2836.