Letters to the Editor

A possible asymmetry at the checkpoint

Immune checkpoint inhibitors targeting programmed cell death 1 (PD-1) and PD ligand 1 (PD-L1) have opened a new era of progress in cancer care for a wide range of tumor types [1]. Although the targeted molecular mechanism induced by the anti-PD-1 and anti-PD-L1 agents is the same, i.e. the reactivation of cytotoxic T cell activity, one can wonder whether the clinical activity conferred by these two categories of agents is superimposable or not. A recently published systematic review and meta-analysis indicated that anti-PD-1 treatment may confer superior survival outcomes as compared to anti-PD-L1 [2].

It is interesting to examine the potential factors able to explain this finding (Fig. 1). In a first analysis, one can advocate that with application of anti-PD-L1 the tumor may escape antitumor immune response through the PD-1/PD-L2 axis. There are other differences between anti-PD-1 and anti-PD-L1 therapeutic monoclonal antibodies (McAb) which may shed light for explaining the anti-PD-1/anti-PD-L1 differences in therapeutic impact. First, the tumoral access for McAb represents a true limitation for anti-PD-L1 targeting mainly the tumoral cells [3] but not for anti-PD1 for which the drug-lymphocyte interaction may occur in the tumor environment and at circulating level [4]. Secondly, the IgG subclasses of anti-PD-1 and anti-PD-L1 McAb differ, with anti-PD-1 belonging to IgG4 and anti-PD-L1 to IgG1 [5]. This subclass difference is of importance since only IgG1, but not IgG4, are able to develop ADCC (antibody-directed-cellular-cytotoxicity). ADCC significantly complements the cytotoxic activity conferred to McAb through a specific interaction between the Fc part of the antibody and the Fc receptor carried by immune cells [5] particularly macrophages and NK cells. In fact, anti-PD-L1 are divided between those IgG1 McAb

Therapeutic monoclonal antibodies: opposite strengths for a possible asymetry at the chekpoint

Strength	Targeting PD-1	Targeting PD-L1
Target	accessibility (T cells) outside the tumoral bed ■	limited access to tumoral cells
PD-1/ PD-L2 axis	Inactivated by anti-PD-1 ■	Not impacted by anti-PD-L1
ADCC	Anti-PD-1 are IgG4 not players for ADCC	Anti-PD-L1 are IgG1 with possible ADCC impact depending upon the modification or not of the FC arm and the tumor/immunity cell repartition for PD-L1 expression ■
Cumulated effects	Favor anti-PD-1 ■	Favor anti-PD-L1

Fig. 1. Therapeutic monoclonal antibodies: opposite strengths for a possible asymmetry at the checkpoint.

which, like atezolizumab, have a modified Fc structure preventing ADCC (thus avoiding a potential destruction of immune cells carrying the PD-L1 target) and those which, like avelumab, maintain the full integrity of the Fc part, hence aiming to reinforce the cytotoxic activity against the tumoral cell itself [6]. Conversely, avelumab may also partly diminish the immune activity through a more or less marked destruction of immune cells due to ADCC. Indeed, elevated and variable expression of PD-L1 has been reported among tumor infiltrating B cells [7].

It would be therefore interesting to distinguish among retrospective studies [2] what could be the respective impacts of avelumab and atezolizumab on treatment outcome and whether avelumab itself may play a significant part in the anti-PD-L1/anti-PD-1 differential therapeutic effect. The notion of a potential therapeutic advantage in favour of anti-PD-1 agents is of importance and remains to be prospectively confirmed by appropriately designed clinical trials.

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Gerard Milano

Scientific Promotion Unit, Centre Antoine Lacassagne, 33 avenue Valombrose 06189 Nice France

E-mail address: gerard.milano@nice.unicancer.fr.

References

[1] A. Ribas, J.D. Wolchok, Cancer immunotherapy using checkpoint blockade, Science 359 (6382) (2018) 1350–1355, https://doi.org/10.1126/science.aar4060.

[2] J. Duan, L. Cui, X. Zhao, et al., Use of immunotherapy with programmed cell death 1 vs programmed cell death ligand 1 inhibitors in patients with cancer: a systematic review and meta-analysis, JAMA Oncol. (2019)https://doi.org/10.1001/jamaoncol.2019.5367.

[3] E. Cruz, V. Kayser, Monoclonal antibody therapy of solid tumors: clinical limitations and novel strategies to enhance treatment efficacy, Biologics 13 (2019) 33–51, https://doi.org/10.2147/BTT.S166310.

[4] A.C. Huang, M.A. Postow, R.J. Orlowski, et al., T-cell invigoration to tumour burden ratio associated with anti-PD-1 response, Nature 545 (7652) (2017) 60–65, https://doi.org/10.1038/nature22079.

[5] S.L. Picardo, J. Doi, A.R. Hansen, Structure and optimization of checkpoint inhibitors, Cancers (Basel) 12 (1) (2019)https://doi.org/10.3390/cancers12010038 pii: E38.

[6] R.L. Ferris, H.J. Lenz, A.M. Trotta, et al., Rationale for combination of therapeutic antibodies targeting tumor cells and immune checkpoint receptors: harnessing innate and adaptive immunity through IgG1 isotype immune effector stimulation, Cancer Treat. Rev. 63 (2018) 48–60, https://doi.org/10.1016/j.ctrv.2017.11.008.

[7] H. Wu, L. Xia, D. Jia, et al., PD-L1$^+$ regulatory B cells act as a T cell suppressor in a PD-L1-dependent manner in melanoma patients with bone metastasis, Mol. Immunol. 119 (2020) 83–91, https://doi.org/10.1016/j.molimm.2020.01.008.