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 asymmetry at the checkpoint](image)

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

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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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