Beneficial outcome of combination therapy with 4-1BB mAb targeting antibody

M. Ramelet1, J.-F. Mirodatos1, D. France1, L. Norgard1, X. Tizot2, L. Arnould1, H. Hillairet de Bosseron1

1Oxonol siege, Dijon (France), 2Centre Georges François Leclerc, Dijon (France)

Immunotherapy based on mAbs targeting cancer cells is now developed as a valid approach to treat cancer. Suppressor mechanisms in immune responses normally play a critical role in maintaining immune homeostasis. However, these suppressive mechanisms are also considered as one of the main reasons for the failure of cancer immunotherapies because they induce peripheral tolerance of tumor-specific immune responses and allow tumor growth.

CD4+ CD25+ Foxp3+ regulatory T-cells have been revealed as the most important population of immune suppressors, and their depletion has been reported to enhance antitumor immune responses. CTLA-4 (Q252) was recognized as a critical target for regulatory-T-cell function [1] and thus blockade of CTLA-4 mediated signals has been suggested as a possible strategy to treat cancers. The first anti-CTLA-4 human monoclonal antibody (ipilimumab), was approved in 2011 by the FDA for use in metastatic melanoma. Success for ipilimumab was reported in a large phase III clinical trial involving patients with metastatic melanoma, who had undergone previous failed treatment [2].

Moreover, programmed death-1 (PD-1) mediated signals was also reported as a critical inhibitory mechanism regulating antitumor immune responses [3]. Nivolumab, a fully human mAb that blocks the programmed death-1 (PD-1) protein showed responses lasting over 1 year in previously treated metastatic melanoma patients. Combination therapy concurrently targeting PD-1, PD-1-L and CTLA-4 immune checkpoints leads to remarkable antitumor effects [4].

While these promising results have led to a great expectancy in treatments for cancer, these approaches are also show adverse toxicities associated with continuous treatment. To study these adverse side toxicities, we chose to characterize the murine orthotopic 4T1 mammary carcinoma model, known for his hypersensitivity reactions to monoclonal antibody (mAb) administration in this model. These effects were also studied with 4-1BB mAb combined to these immune checkpoint.

In-vivo experiments

Mice (BALB/c, Charles River, FR) were orthotopically injected with 4T1 syngeneic breast tumor cell lines on DO. They were randomized on 018 mean tumor volume of about 170 mm3 and then treated with anti-PD-1 clone RMP1-14, anti-PD-L1 mAb clone 10F.9G2 at 10 mg/kg (Q2Dx4), anti-CTLA-4 clone 9H10, or with anti-4-1BB mAb clone 3H3 at 10 mg/kg (Q3Dx3).

Survival increase by co-treatment with anti-4-1BB highlights anti-tumor activities of immune checkpoint antibodies

Anti-PD-1 mAb
Anti-PD-L1 mAb
Anti-CTLA-4 mAb
Anti-4-1BB mAb

Unmatched
Lymphocyte infiltration score: 0

Anti-PD-1 mAb + anti-PD-L1 mAb
Anti-CTLA-4 mAb + anti-4-1BB mAb

Lymphocyte infiltration score: 1+

Conclusions and perspectives

Combinations of anti-4-1BB mAb with immune checkpoint inhibitors prevent adverse side effects of ICIs alone in the murine 4T1 mammary carcinoma model. This increased survival then allowed to observe antitumor activity of checkpoint inhibitor antibodies when combined to anti-4-1BB antibody.

References