



Defining the Role of a Novel Immune Checkpoint Modulator: Anti-OX40

Sandrine Aspeslagh^{1*} and Aurelien Marabelle^{1,2}

¹DITEP, Gustave Roussy Cancer Centre, Université Paris-Saclay, F-94805 Villejuif, France

²INSERM U1015, GRCC, F-94805 Villejuif, France

*Corresponding author: Sandrine Aspeslagh, DITEP, Gustave Roussy Cancer Centre, Université Paris-Saclay, F-94805 Villejuif, France, Tel: 33-4-6916-6595; E-mail: Sandrine.aspeslagh@gustaveroussy.fr

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Introduction

The arrival of immune checkpoint blockers such anti-CTLA4 and anti-PD-L1/PD-L1 antibodies has again given hope to many cancer patients with advanced disease. Up to now its success has been demonstrated in more than 15 different cancer types. Tumor responses are durable, and translate into benefits in overall survival for patients. However as only around 20%-30% of patients show responses there is a huge need to find a durable solution for the other 70%-80% of patients. Massive efforts in preclinical research show that targeting activating costimulatory molecules such as OX40 or coinhibitory molecules such as LAG3 among others may also reduce cancer growth [1,3]. The major role of OX40 up regulation on a T cell is to improve the T-cell immune response after antigen recognition. This reaction can be boosted by agonistic anti-OX40 antibodies that are now moving to the clinic. Additionally these antibodies can deplete regulatory T cells and as such enhance native CD8 tumor response in mice. The first phase I study with anti-OX40 antibodies does indeed show a potent immune response but up to now no tumor response comparable to anti-PD-L1 antibodies. However anti-OX40 treatment was very well tolerated [2], and several combination trials have been setup to confirm the very

strong preclinical results from tumor models in immunocompetent mice (eg NCT02205333). These mouse results show synergy especially between strategies that liberate tumor antigens such as radiotherapy, chemotherapy and surgery with anti-OX40. In these situations, anti-OX40 will boost the natural immune response and as such act as a very strong adjuvants to confer immunity against cancer antigens. Additionally a combination with anti-PD-L1 antibodies should be synergistic according to preclinical results [1]. Therefore results from combination trials with OX40 are highly awaited and will help us optimize novel immunotherapeutical possibilities.

References

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