Combining TNF blockade with immune checkpoint inhibitors in patients with cancer

Anne Montfort, Mathieu Virazels, Céline Colacios, Nicolas Meyer and Bruno Ségui

TNF is involved in various autoimmune diseases and in immune-related adverse events (irAEs) that occur in patients with cancer being treated with immune checkpoint inhibitors (ICIs)[1,2]. In their Review (Chen, A. Y., Wolchok, J. D., & Bass, A. R. TNF in the era of immune checkpoint inhibitors: friend or foe? *Nat. Rev. Rheumatol.* **17**, 213–223 (2021))[3], Chen and colleagues nicely reviewed the literature, from basic studies[4,5] to clinical observations[6,7], discussing whether TNF can be considered as a putative target in the treatment of irAEs in patients with cancer undergoing ICI therapy. Important questions were raised regarding TNF inhibitor safety and efficacy in this setting, but unfortunately, the authors missed out discussions of the TICIMEL phase Ib clinical trial (NTC03293784), the results of which we think help address some of these questions.

Initiated in 2018, the TICIMEL trial investigated the effects of treatment with the ICIs ipilimumab (an anti-CTLA4 antibody) and nivolumab (an anti-PD1 antibody) in combination with a TNF inhibitor (infliximab or certolizumab) in patients with advanced melanoma[8]. The results from 14 patients enrolled in the first phase of this trial were published in December 2020 (REF.[9]). Although the low number of patients warrants caution as regard to the interpretation of data, the results are informative.

One question raised by Chen and colleagues relates to whether TNF inhibitors are safe in the management of patients with cancer and ICI-induced irAEs. Results from the TICIMEL trial indicate that concomitant administration of ipilimumab, nivolumab and an anti-TNF drug (infliximab or certolizumab) is indeed safe in the short-term and potentially in the long-term.

Chen and colleagues also compiled evidence from pre-clinical studies showing that TNF promotes cancer progression and inhibits anti-tumour immune responses. They conclude that although TNF blockade and/or deficiency in mouse models of cancer can, via the promotion of $CD8^+$ T cell-mediated anti-tumour immune responses and a decrease in immune regulatory responses, impede tumour growth, these observations have to be confirmed in humans. Especially, they noted that this hypothesis has to be evaluated in the context of combined ICI and anti-TNF treatment.

In line with these observations, results from the TICIMEL trial show a high objective response rate in the certolizumab cohort, with all evaluable patients responding to treatment, including four complete responses out of seven objective responses. By comparison, only half of the patients in the infliximab cohort responded to treatment (including one complete response out of three objective responses). These treatments were associated with increased numbers of T helper 1 cells and increased plasma concentrations of IFNγ. Whether and how these responses differ to the ones occurring in patients with advanced melanoma being treated with the combination of ipilimumab and nivolumab remains to be evaluated.

Emerging evidence reported by Chen and colleagues and our recent clinical trial suggest that TNF inhibitors are safe and beneficial in the treatment of patients with cancer and irAEs. We are further assessing these parameters in the second phase of the TICIMEL trial[8,9].

There is a reply to this letter by Chen. A. Y., Wolchock, J. D. & Bass, A. R. *Nat. Rev. Rheumatol.* https://doi.org/10.1038/s41584-021-00654-7 (2021).

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Competing interests
B.S. has worked as investigator, consultant and speaker for BMS. N.M. has worked as investigator and/or consultant and/or speaker for BMS, MSD, Roche, Novartis, Pierre Fabre, Amgen, Incyte, Abbvie. B.S. and C.C. have a patent US10144772B2 issued, a patent WO2015173259A1 pending, a patent EP3142685B1 issued, a patent ES2748380T3 issued. B.S., C.C. and N.M. have a patent EP3407911A1 pending, a patent JP2019503384A pending, a patent US20190038763A1 pending, and a patent WO2017129790A1 pending. The other authors declare no competing interests.

Reply to: Combining TNF blockade with immune checkpoint inhibitors in patients with cancer

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We would like to thank Montfort and colleagues for their correspondence (Montfort, A. et al. Combining TNF blockade with immune checkpoint inhibitors in patients with cancer. *Nat. Rev. Rheumatol.* https://doi.org/10.1038/s41584-021-00653-8 (2021))[1] on our Review (Chen, A. Y., Wolchok, J. D. & Bass, A. R. TNF in the era of immune checkpoint inhibitors: friend or foe? *Nat. Rev. Rheumatol.* **17**, 213–223 (2021))[2].

We appreciate their highlighting early results of TICIMEL, an open-label phase Ib two-arm study of 14 patients that combined one of two TNF inhibitors, certolizumab or

infliximab, with two immune checkpoint inhibitors (ICIs), ipilimumab and nivolumab, for the treatment of melanoma[3]. This study was published after our manuscript was submitted to reviewers.

The finding in TICIMEL that all seven evaluable patients treated with certolizumab plus ICI therapy achieved an objective response[3] is tantalizing, but the numbers are too small to compare to historical cohorts of patients not treated with a TNF inhibitor. In addition, given that certolizumab and infliximab are both biologic drugs that target TNF (the two drugs differ in that certolizimab is a PEGylated, Fc-free monovalent antibody), how to evaluate the two arms individually is challenging.

An unexpected finding was the high rate of grade 3 or 4 immune-related adverse events (irAEs) in patients in the TICIMEL trial, despite concomitant TNF inhibitor treatment (75% in the certolizumab arm and 50% in the infliximab arm)[3]. The rate of high-grade irAEs was similar to that in CheckMate 067, a large melanoma trial that also used combination ICI therapy in which 59% of patients experienced high grade irAEs[4]. This finding suggests that in TICIMEL, TNF inhibition might not have lessened the rate of adverse events. As with the efficacy analysis, however, the small number of enrolled patients in TICIMEL precludes firm conclusions about toxicity. We look forward to future results, after additional patients have been enrolled in TICIMEL, and congratulate the authors on performing this important study.

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Competing interests

J.D.W. is a consultant for Adaptive Biotech, Amgen, Apricity, Arsenal, Ascentage Pharma, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, F Star, Imvaq, Kyowa Hakko Kirin, Merck, Neon Therapeutics, Psioxus, Recepta, Sellas, Serametrix, Surface Oncology, Syndax and Syntalogic, Takara Bio, Trieza and Truvax; receives research support from AstraZeneca, Bristol Myers Squibb and Sephora; and has equity in Adaptive Biotechnologies, Apricity, Arsenal, BeiGene, Imvaq, Linnaeus, Tizona Pharmaceuticals. The other authors declare no competing interests.