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Invited Comment

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Immunotherapy is becoming widely used in non-small cell lung cancer (NSCLC) treatment due to the impressive results in first and second line.[1] However, we need to accept that not all patients have the possibility to be treated with this approach and, even if we are going in the correct direction to control for this lethal disease, there is still a lot to do in order to improve these results. Combining the new immunotherapeutic agents with the current therapies, like chemotherapy or tyrosine kinases inhibitors (TKI), can bring us good and bad consequences. For example the combination of pembrolizumab and platinum doublet chemotherapy in first line treatment impacted on the progression free survival (PFS) and overall response rates (ORR) allowing its approval by FDA.[2] Unfortunately, after the encouraging clinical activity of the combination of osimertinib, a third generation EGFR TKI, with durvalumab (anti-PD-L1 monoclonal antibody)[3] ,the increase in the toxicity profile was an important concern for its further development. As such, we can say that the major challenge in oncology now is to find a combination with new drugs and new mechanisms of action that improves the results of the current standard of care and simultaneously provides lesser toxicities to our patients. In this context, Wrangle et al.[4] presented the first clinical results on the combination of a PD-1/PD-L1 blocker with an interleukin (IL-) 15 receptor agonist - more specifically nivolumab and the IL-15 superagonist ALT-803 - in NSCLC patients. Even if they are preliminary, these clinical results of such a combination are eagerly awaited, since both IL-15 and PD-1/PD-L1 blockers are ranked in the top 3 of immunotherapy drugs that could cure cancer.[5,6] The reason is that IL-15 triggers the activation of both innate and adaptive immunity for an optimal cancer attack. Amongst other effects, this is reflected by IL-15-induced proliferation and activation of both natural killer cells and CD8+ T-cells as effective killer cells. Furthermore, IL-15 is a better choice for cancer immunotherapy than its family member IL-2, because its function is clearly distinct from IL-2 with regard to activation-induced cell death and maintenance of immunosuppressive CD4+CD25+ regulatory T cells. In the study of Wrangle et al, ALT-803 is being used as an IL-15 superagonist. It is a molecule that contains mutant IL-15,[7] coupled to an IL-15 receptor α/IgG1 Fc fusion protein. This soluble heterodimeric complex results in improved pharmacokinetics and antitumour immune responses compared to uncoupled IL-15.[8] Historically, cytokine-based therapies raised toxicity concerns. However, Wrangle et al. succeeded in identifying a safe and tolerable weekly dose of 20 mcg ALT-803/kg that does not add to toxicity of nivolumab and compares favourably to nivolumab plus ipilimumab. Importantly, ALT-803

was injected subcutaneously, giving similar pharmacokinetics as continuous infusion in an easier way.

In general, best results of immunotherapeutic drug combinations are expected from compounds that intervene at different phases of the cancer-immunity cycle as defined by Chen and Mellman.[9] Theoretically, maximal effect of ALT-803 would be expected in the priming and activation phase of lymphocytes in the lymph nodes. Activated lymphocytes will then travel to the tumour site, where they need to infiltrate, recognize the cancer cells and exert their killing effects. Although the PD-1 blocking antibody nivolumab might also enhance priming and activation of lymphocytes, it is believed to exert its major antitumour effect at the killing stage in the tumour. In short, ALT-803 activates the antitumour effector cells, whereas nivolumab also blocks an immune escape mechanism of cancer cells. The combination of these two different approaches might work synergistically to eliminate cancer cells. Although it is too early to draw conclusions on efficacy, the results of Wrangle et al. point towards added value of ALT-803 in different treatment settings, strikingly also in patients with relapsed disease following anti-PD-1 therapy only.

Combinations will be leading the very near future of immunotherapy. This is an interesting journey and we can say that we are in the beginning of the trip, but efforts like Wrangle and colleagues lay the foundation for further clinical investigation of an IL-15 agonist combined with PD-1/PD-L1 blocking antibodies, as an immunotherapy-based treatment strategy with the potential to improve the outcome of patients with lung cancer and also other cancer types. There are still a lot of questions regarding biomarkers, identification of deeper and faster responders and role of these combinations in refractory/resistant patients to immunotherapy: this is another chapter, but certainly we are on the right path to reach our destination.

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