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LETTER TO THE EDITOR

The clinical added value of the addition of anti-CTL-4 to anti-PD-1 alone is questionable and clearly increasing toxicity regarding pivotal studies in the treatment of melanoma and renal carcinoma

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Dear Editor,

In recent years, we have witnessed undeniable progress in the treatment of cancer, leading to increased survival of metastatic patients as part of what is considered an incremental progress. The advances that have contributed to it include the development of immunotherapies, like anti-PD-1 and anti-CTL-4 treatments, and the introduction of tyrosine kinase inhibitors (TKi) [1].

Combining drugs of the same class or of different therapeutic classes is a classic strategy in the development of chemotherapy regimens and is recognized in various recommendations. However, we should carefully examine the robustness of evidence, in particular when the combined regimen is associated with a clearly demonstrated increase in toxicity, as is the case for the anti-PD-1/anti-CTL-4 immunotherapy combination [2].

Even though there is a pre-clinical rationale for combining anti-PD-1 and anti-CTL-4 therapeutics [3], the interest of introducing such a combination into clinical practice has to be clearly validated by demonstrating that it provides a survival advantage (increased overall survival or disease-free survival), with no deterioration in quality of life [4]. However, anti-PD-1/anti-CTL-4 combinations, such as nivolumab/ipilimumab promoted by the pharmaceutical company for treatment of metastatic melanoma and renal carcinoma, do not achieve these goals. Still, they have been approved for treatment of metastatic melanoma by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), and of metastatic renal carcinoma with a strong support of key opinion leaders. These approvals were based on two controlled studies, both of which provided only weak or no evidence of treatment benefit associated with this drug combination, while recording more frequent and more pronounced toxicity.

The approval of the nivolumab/ipilimumab combination for treatment of metastatic melanoma by American and European authorities, and its incorporation into the recommendations of the US National Cancer Network (NCCN; category I recommendation) was based on the CA209067 study [5]. It was a double-blind, randomized, phase III trial designed to compare the efficacy and safety of nivolumab monotherapy versus ipilimumab monotherapy as well as that of the nivolumab/ipilimumab combination versus ipilimumab monotherapy, as a first-line treatment in adult patients with unresectable or metastatic melanoma with or without the V600E *BRAF* mutations. However, the objective should not have been to compare nivolumab/ipilimumab versus ipilimumab alone but to show the superiority of nivolumab/ipilimumab over a regimen which was then considered as a therapeutic standard, namely nivolumab monotherapy. The registration study has indeed shown a benefit of the combination over ipilimumab alone, but its superiority to nivolumab is an extrapolation of results that had not been provided for in the protocol. In addition, to evaluate a potential benefit of the nivolumab/ipilimumab combination compared to that of nivolumab, this benefit (measured as overall response rate and disease-free survival) should be weighted by the level of PD-1 expression and is clearly restricted to the patient population expressing PD-1 weakly (less than 5%). Even though, the progression-free survival analyses of patients stratified by the PD-1 and *BRAF* status were provided in the protocol, the alpha risk was not controlled and the number of subjects required to obtain sufficient power was not calculated. As a result, no conclusions can be drawn from subgroup analyses. On the descriptive side, the analyses suggested a benefit (defined as longer progression-free survival and improved response rate) from the nivolumab/

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ipilimumab combo (versus nivolumab) in patients expressing PD-1 at the level of 1% and 5%. However, this effect was indiscriminate of the PD-L1 expression cutoff (1% or 5%) and so no PD-1 expression threshold can be reliably established for the analysis of these data. In general, there is no standardized and validated PD-1 expression threshold value—the cutoffs applied in different studies vary, depending on the molecules evaluated. Therefore, according to the state-of-the-art knowledge, PD-1 expression cannot be used to predict patients' response to treatment in terms of treatment efficiency or tolerance. Moreover, the increased toxicity of the nivolumab/ipilimumab combination has been clearly identified: the proportion of patients with serious adverse effects (grades 3–4) was higher in the nivolumab/ipilimumab group (68.7%) than in the nivolumab (43.5%) and ipilimumab group (55.6%), and the treatment had to be interrupted in 50% of the patients receiving the combination [6].

More recently, FDA has approved the combination of nivolumab and ipilimumab also as first-line treatment for intermediate and poor risk metastatic renal cell carcinoma (mRCC). This was based on the Checkmate 214 study which compared this combined regimen with standard treatment (Sutent) [7]. However, there have been no studies comparing nivolumab versus Sutent for renal cancer treatment, or—even more relevant—comparing directly the nivolumab/ipilimumab combination versus nivolumab alone. Why, only such studies would allow to precisely assess the treatment benefit of the combined regimen compared to monotherapy. In brief, prescribers are encouraged to prescribe the combined treatment without knowing whether monotherapy would not have given a similar result with a lower toxicity. This was pointed out by the EMA's Committee for Medicinal Products for Human Use (CHMP) which recommended during first evaluation, a refusal of the approval extension to include the nivolumab/ipilimumab combo regimen for treatment of renal cell carcinoma [8].

An identical development strategy has been applied for lung cancer treatment: a focus on the comparison of nivolumab/ipilimumab versus chemotherapy and not with nivolumab monotherapy, even though there has been no evidence that adding ipilimumab to nivolumab increases treatment efficiency and that the combined treatment is superior to nivolumab monotherapy [9].

Overall, a kind of postulate is imposed when developing treatment regimens for various cancers, such as melanoma, renal carcinoma and lung cancer, that the anti-PD-1/anti-CTL4 combination works better than the anti-PD-1 monotherapy. However, the evidence to support this assertion is very weak, while increased toxicity of such combinations, in particular autoimmune manifestations or—more recently shown—cardiac toxicity (like myocarditis), has been clearly demonstrated [10]. Given all this scientific data, it seems reasonable to suggest that the development of such combo strategies has been potentially led by the financial interests of pharmaceutical companies. Of note, these drug combinations are most often restricted to pairs of drugs manufactured by certain companies: nivolumab/ipilimumab, durvalumab/tremelimumab. In contrast, the combination of tyrosine kinase inhibitors, like the anti-Mek/anti-B-Raf combo (dabrafenib/trametinib, vemurafenib/cobimetinib and encorafenib/bimetinib) has an overall better outcome as compared to anti-PD-1/anti-CTL4 combinations.

It is seems that the manufacturers have economic interests in promoting combinations of drugs rather than just one of them. In addition, the need of being competitive makes the companies more prone to systematically push for combining drugs rather than testing monotherapeutic regimens. Unfortunately, in case of the anti-PD-1/anti-CTL4 combo, the financial concerns of pharmaceutical companies can interfere with the needs and expectations of our patients. The clinical benefit of this regimen in terms of survival is doubtful and the added value of the combined regimen compared to monotherapy is largely overestimated by the medical and scientific community, in particular given that it is associated with more deleterious effects than monotherapy and so does not improve life quality.

We must rethink the strategy that leads to impose such combined regimens of immunotherapeutics in oncology and integrate a more humanistic dimension, making sure that the development of treatments is centered on the patients and their well-being. The medical community should be more concerned about the relevance of anti-PD-1/anti-CTL4 combo treatments, toxic for our patients and also for the budgets of healthcare systems, regardless of the interests of the pharmaceutical industry that push them to establish the combo treatments as a dogma. For instance, on the French market, adding ipilimumab to nivolumab in melanoma induces an increase in the cost of approximately + 38,000 euros, for 1 year [11]. The clinical benefit of combined immunotherapy and particularly the clinical added value of anti-CTL-4 to anti-PD-1 regimens should imperatively be re-evaluated by new studies designed to precisely quantify the putative added value of ipilimumab in the ipilimumab/nivolumab combination compared to nivolumab monotherapy. Only such studies may provide the reliable answer to the question whether combining these treatments is really beneficial to the patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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