

## The Promising Link Among Tumor Mutational Burden, Immune-Related Adverse Events, and Immune Checkpoint Inhibitors Efficacy in SCLC



### To the Editor:

I read with interest the research article recently published by Ricciuti et al.,<sup>1</sup> about the significant association between immune-related adverse event (irAE) occurrence and improved clinical outcomes of patients with SCLC receiving immune checkpoint inhibitors.

With the 16.9% of patients experiencing grade 3 to grade 4 irAEs, they confirmed the favorable safety profile, and that the spectrum of irAEs was aligned with that reported in the literature. Considering that 73.7% of the patients received immunotherapy in the second-line setting, the objective response rate of 27.4%, the median progression-free survival of 3.8 months and the overall survival of 13.8 months reported in patients who experienced irAEs, seem impressively good. They correctly dealt with the immortal time bias related to treatment exposure by treating the irAE occurrence as a time-varying covariate; besides that, they also reported impressive adjusted hazard ratios for risk of disease progression and death (0.44 and 0.46, respectively).

In the light of the questioned beneficial results of immunotherapy in the first-line setting for extensive-stage SCLC (significant but limited),<sup>2</sup> the results of Ricciuti et al.<sup>1</sup> should be carefully taken into account, because the irAE occurrence could be used as a true predictive marker for patients selection. From this perspective, the reported significant association between irAE occurrence and a higher tumor mutational burden

(TMB) raises some interesting reflections. A high TMB has already been related to improved outcomes during immunotherapy in patients with SCLC<sup>3</sup>; however, the association with irAEs could make us consider the relationship between TMB and immunotherapy efficacy in a different way. Rightly, Ricciuti et al.<sup>1</sup> cited the work of Bomze et al.,<sup>4</sup> which indicated that tumors with a high TMB (e.g., melanoma) are associated with a higher irAE odd ratio during treatment with programmed cell death protein 1 checkpoint inhibitors. Intriguingly, in another study, the same group performed a patient-matched T-cell receptor (TCR) sequencing from both tumors and skin samples of patients with NSCLC treated with programmed cell death protein 1 inhibitors who had developed autoimmune skin toxicities.<sup>5</sup> The authors found that the TCR sequences of tumors and skin lesions were identical, suggesting that the same T-cell clonotypes react against shared antigens in the two sites. With an *in silico* bioinformatic analysis and after a peripheral blood mononuclear cell stimulation, they also isolated interferon gamma-positive T-cells from responders with autoimmune skin toxicity, finding the same identical TCR sequences.<sup>5</sup>

To summarize, we are allowed to assume that the higher the TMB, the higher the tumor antigenicity; and the higher the tumor antigenicity, the higher the probability of cross-reactivity between the tumor and healthy tissue antigens (and of TCR overlapping), which underlie the irAE occurrence. The question is, would it be beneficial to look at the TMB more as a qualitative, rather than an exclusively quantitative parameter? From this perspective, in the first-line setting (in which limited but significant improvement with immunotherapy has been reached), would it be useful to look for an immunologic evaluation of the TMB, searching for the more likely irAE-inducing mutations among the pathogenetic and antigenic ones?

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## Reply to Cortellini A



### To the Editor:

We appreciate Dr. Cortellini's interest in our recent article entitled "Association between immune-related adverse events and clinical outcomes to PD-1/PD-L1 blockade in small cell lung cancer," in which we found a statistically significant correlation between the development of immune-related adverse events (irAEs) and improved clinical outcomes to programmed death-ligand 1 (PD-L1) inhibition among patients with extensive-stage SCLC.<sup>1</sup>

As noted by Dr. Cortellini, we also found that tumors from patients with irAEs had a significantly higher median tumor mutational burden (TMB) compared with those from patients without irAEs (14.2 versus 8.4 mutations per megabase,  $p < 0.001$ ). Dr. Cortellini suggested that patients with high-TMB cancers, such as SCLC, NSCLC, and melanoma, might have a greater likelihood of developing irAEs with immunotherapy, possibly because of a higher chance of developing molecular mimicry between cancer-related antigens and normal tissues. In support of this, a recent study of 47,304 irAEs in 16,397 patients treated with anti-PD-L1 monotherapy across 19 different cancer types found a statistically significant association between the odds of developing an irAE and a higher median number of coding somatic mutations per megabase of DNA.<sup>2</sup>

Although these associations are certainly of interest, additional preclinical and clinical validation is needed to dissect the mechanisms underlying the development of irAEs. The relationship between TMB and irAE onset can be challenging, given the known correlation between

high TMB and improved survival with PD-L1 blockade. Patients with high-TMB tumors that are more likely to respond to immunotherapy, and, therefore, have longer treatment exposure; thus, they are more likely to develop irAEs over time. Therefore, studies evaluating the relationship between TMB and irAEs should be interpreted with caution, and adequate statistical approaches should be undertaken when exploring the clinical and genomic correlates of treatment-related toxicities.

Whether specific somatic mutations are more immunogenic than others is under active investigation. Although the neoantigen burden is proportional to the nonsynonymous single nucleotide variant (nsSNV) burden, recent studies have revealed that less than 1% of nsSNVs in expressed genes result into detectable CD4-positive or CD8-positive T-cell reactivity in tumor-infiltrating lymphocytes.<sup>3-5</sup> In contrast, frameshift mutations may generate three times as many predicted neoantigens as nsSNVs, and a high load of insertions and deletions has been reported to correlate with improved outcomes to programmed cell death protein 1 inhibition across different cancer types.<sup>6</sup> However, whether this increased immunogenicity might also lead to the development of irAEs remains to be determined.

Currently, despite the clinical need to understand as to why some patients develop high-grade immunologic toxicities, very little is known on this topic. The hypothesis that antigens shared between tumors and normal cells in high-TMB cancers is of great scientific interest warranting further study.

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