Letter to the Editor

The controversy of immune checkpoint inhibition and risk of mycobacterial infections: the need for further studies and continued discussions on this puzzling issue

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I thank Drs. Wen and Kang for their thoughtful comments (1) on our paper that addressed the controversial issue on whether the use of immune checkpoint inhibitors (ICI) increases the risk of mycobacterial infections (2). They provided three comments which I have responded to below.

First, they noted that relatively few cases of tuberculosis (TB) have been reported despite increasing use of ICI. I agree with this. We had also emphasized in our paper that linking ICI to TB or non-tuberculous mycobacterial (NTM) disease based on case reports or case series is problematic because the cases are fraught with confounders that predispose to TB or NTM (lung) disease (2). These confounders include: (I) immunosuppression from cancer itself; (II) use of other chemotherapeutic agents and/or glucocorticoids that cause collateral immunosuppression; (III) presence of pre-existing co-morbid conditions such as diabetes, smoking, end-stage renal disease, or chronic obstructive pulmonary disease that are not uncommonly present in older individuals with cancer and that also predispose to mycobacterial infections; (IV) structural lung injury from radiation therapy or chemotherapeutic agents; and (V) publication bias; i.e., if no TB or NTM disease occurred with use of ICI, such cases would unlikely to be reported than if mycobacterial infections occurred with their use (2). Furthermore, we had cited two large population studies, despite having some limitations, that showed the incidences of TB in those on ICI are the same as either the general population (3) or in the cancer patient population (4), suggesting that ICI are not risk factors for TB. Another retrospective study of over 6,000 lung cancer patients—of whom 899 were treated with ICI—did not find an association between the use of ICI and active TB (5). Drs. Wen and Kang mentioned a recent paper showing that TB incidence was higher in those on ICI (1.58%) *vs.* those on tyrosine kinase inhibitors (0.68%) (6). We had also discussed this paper (under the subsection titled "*Experimental and clinical evidence implicating that ICIs may predispose to mycobacterial infections*" on page 1609) and had noted that in this cited study, those taking ICI had significantly greater use of glucocorticoids than those on tyrosine kinase inhibitors; thus, this differential glucocorticoid use may have confounded the finding that use of ICI was associated with TB (2). I appreciate that they provided additional papers showing that the incidence of TB is increased among cancer patients overall (7,8)—possibly due to the immunosuppressive effect of the cancer

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itself and/or cancer treatment—supporting two of the confounders mentioned above and in our paper (2). On the whole, I agree with Drs. Wen and Kang that there is a paucity of strong clinical evidence in humans that ICI are associated with mycobacterial infections, which we had also emphasized in our analysis. We had also suggested that a prospective study, preferably in a TB endemic country, with well-matched patient controls (matched for patient demographics, latent TB infection, cancer type, and cancer treatment except for the use of ICI) can provide a more accurate estimate of the risk of TB (or NTM disease) with the use of ICI. Such a study would be challenging to undertake and would likely require a multi-institutional enrollment to recruit adequate number of patients and controls as well as a relatively long period of prospective follow-up.

Second, they emphasized the importance of distinguishing ICI predisposing to TB *vs.* "unmasking" of subclinical TB, the latter due to immune hyperactivation alerting clinicians to investigate for TB. I agree with this comment and had discussed this in our paper under the subsection titled: "*Unmasking of pre-existing subclinical mycobacteria infection without being causative*" (page 1613) (2). We had also contended that these two scenarios are not necessarily mutually exclusive; i.e., both may be occurring in any one patient. They had also commented that PD-1 activation may have opposing effects in conventional T cells (where they cause T cell deactivation/exhaustion/apoptosis) *vs.* T regulatory cells (where they cause activation). We had also noted that whereas immune checkpoints deactivate conventional T cells, they may activate T regulatory cells (Tregs); i.e., ICI would activate conventional T cells and deactivate Tregs (page 1602). We also posited that this ability of ICI to activate conventional T cells and deactivate Tregs would result in excessive immune activation that predisposes to mycobacterial infections through the following mechanisms: (I) excessive influx of ineffective immune cells that dilutes the salubrious immune response and (II) excessive influx of normally protective cell types (e.g., T_H1 cells) resulting in excessive production of interferon-gamma (IFNg), tumor necrosis factor (TNF) and subsequent activation of RIP1 and RIP3 (receptor-interacting serine-threonine kinases 1 and 3) that results in necrotic macrophage death (2,9).

Third, they cited a paper that showed PD-L1 was (highly) expressed in TB granulomas (presumably in myeloid cells) in the lungs of cancer patients taking ICI or not taking them (10). This study is important because it indicates that immune checkpoints may play a role in the formation of TB granulomas but to the best of my knowledge, it remains to be determined whether the level and timing of immune checkpoint expression during TB infection benefits or is deleterious to the host. I agree that a hyperinflammatory response—especially with neutrophils—may jeopardize TB control by not only causing tissue injury but also by interfering sterically with the influx of more host-protective immune cells. Thus, I concur with the comment made by Elkington and colleagues (10) that either "insufficient" or "excessive" immune response may compromise host control of *Mycobacterium tuberculosis*, a paradigm we were trying to convey in *Figs. 2-4* of our paper (2).

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Footnote

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