

Immunotherapy efficacy and gender: discovery in precision medicine

Bryan C. Ulrich¹, Nicolas Guibert²

¹Emory School of Medicine, Atlanta, GA, USA; ²Thoracic Oncology Department, Larrey Hospital, University Hospital of Toulouse, Toulouse, France

Correspondence to: Nicolas Guibert. Thoracic Oncology Department, Larrey Hospital, University Hospital of Toulouse, Toulouse, France.

Email: guibert.n@chu-toulouse.fr.

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Immunotherapy is transforming the care of cancer. In the past five years, checkpoint blockade agents targeting the PD-1/PD-L1 checkpoint (e.g., nivolumab, pembrolizumab) have garnered FDA approvals in diverse indications including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, and more (1-5). While these agents produce durable responses for some patients, the science of identifying responders remains inexact; further work is needed to identify biomarkers which better predict patient response than current clinical practice. At present, PD-L1 expression on tumor cells is assessed via immunohistochemistry of tumor tissue (6). High PD-L1 expression (i.e., >50% PD-L1) generally predicts better response to checkpoint inhibitors, with less than 1% indicating a lack of response, and therefore being the cutoff in some FDA-approvals (7-9). However, some patients with low/no PD-L1 levels respond to these agents, and some patients with high PD-L1 expression do not respond. Therefore, biomarker discovery has been an area of active investigation, and several new (e.g., tumor mutational burden) biomarkers of response are promising (10,11).

It is within this context that Conforti and colleagues published a systematic review and meta-analysis investigating the relationship between patient gender and response to checkpoint inhibitors (12). The data shows increased efficacy in male patients versus female patients, and the authors suggest this is possibly due to

sex differences in the immune system, tumor biology, and risk factors. Given the potentially substantial clinical implications that this data has, a thorough understanding and critical review of this paper is important. Herein, we call into question the authors' explanations for this data and propose likely reasons for this relationship while encouraging further research with more recent clinical trials. The analysis of this paper and its implications also has important lessons for discovery in the age of precision medicine, which is biomarker-dominated. Thus, any such analysis of two cohorts must first adjust for differences in these biomarkers.

Results

In their systematic review using clinical trial data published up to late November 2017, Conforti *et al.* assess the relationship between gender and efficacy of checkpoint inhibitors versus standard of care (primarily chemotherapy). Their dataset uses 20 randomized, controlled trials covering several malignancies and clinical indications, with melanoma and non-small cell lung cancer trials being the major contributors to the dataset. They then calculated pooled hazard ratios in each gender versus their control, standard of care group. The data from this analysis suggests that men had significantly reduced risk of death (HR =0.72, 95% CI, 0.65–0.79) versus standard of care groups than women

(HR =0.86, 95% CI, 0.79–0.93). Notably, both hazard ratios are significantly below 1, indicating greater efficacy for immunotherapy in these trials than current standard of care. This relationship also held up when excluding studies that tested immunotherapeutic agents/combinations versus other immunotherapeutic agents. Additionally, they found greater variability in trial results for men than for women.

Evaluating the evidence

Although the methodology and high-quality dataset used by the authors should be lauded, this study fails to immediately inform our understanding of immunotherapeutic agents and their clinical use because of the absence of several data points. Most importantly, the authors did not investigate the relationship between PD-L1 expression or tumor mutational burden (TMB) and gender. Differences in these parameters are a potential explanation for this data, and this analysis will be absolutely necessary.

In assessing PD-L1 expression/TMB and gender, there are two possibilities: either PD-L1 expression/TMB is significantly higher/lower in men thereby contributing to the results seen here, or there are no significant differences in PD-L1 expression/TMB among men and women. Given the higher efficacy of checkpoint blockade seen in men in this study, it is likely that if PD-L1 expression/TMB is different, men would have higher levels. This relationship has to be explored, because a difference in these is the most likely explanation for the difference in immunotherapy efficacy (13). Furthermore, such a relationship would obviously change the clinical relevance of this study. This is because PD-L1 expression is the very indication on which immunotherapeutic agents are prescribed. Thus, even if men did have higher PD-L1 levels than women, this knowledge would not change the individual clinical decision. However, this relationship would pose an interesting research question regarding why men have higher PD-L1 levels. Other biomarkers of response also deserve the same analysis, with tumor mutational burden having shown to be significantly higher in men (14–16).

Upon this re-analysis and adjusting for PD-L1 expression/TMB, the second, less probable, possibility is that no differences in PD-L1/TMB are found. This suggests another phenomenon occurring that accounts for significantly different responses between men and women with the same levels of our current biomarkers of response. Such a result would be fascinating and would have

immediate clinical consequences, namely the development of sex-specific cutoffs for PD-L1 expression level to predict response to checkpoint blockade. These would also raise challenges, such as the identification of different levels of involvements of other immune checkpoints. In the introduction, Conforti and colleagues propose possible reasons for such a finding. Well-characterized differences in immune system function/activity, particularly stronger immune response in women than men, may explain the significant difference in efficacy of checkpoint blockade agents. The authors propose a form of selection: because women have stronger immune systems, tumors that become clinically relevant need to be less immunogenic and enriched with stronger mechanisms of immune escape than in men. However, if so, “stronger mechanisms of immune escape” should include increased PD-L1 levels. If women have stronger immune responses, one would expect that releasing the inhibition of these responses should lead to better efficacy of checkpoint inhibitors than in men. This reasoning shows that biological intuition can be used to explain either outcome, or no difference, in this context, and thus rigorous discovery must determine the actual reasons for any such difference if found.

Overall, the possibility of differences in PD-L1 expression, or other biomarker of response, between men and women must be investigated, before drawing strong conclusions regarding selection based on gender.

Conclusions

In their systematic review and meta-analysis on immunotherapy efficacy and gender, Conforti *et al.* demonstrate that immunotherapy efficacy relative to current standard of care for various cancer types is lower in women than in men. If this study was very useful, this will need adjustments for genetic and protein biomarkers to better decipher the differences observed. Before taking into account gender in the clinical decision, subsequent investigations into this question must adjust for the PD-L1% of men and women, tumor mutational burden, as well as specific alterations that are known to be associated (transversion mutations in particular in *KRAS* or *TP53*) or not (*EGFR* mutations, *STK11* mutations) with response to these agents.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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