Published in final edited form as:

J Urol. 2018 May ; 199(5): 1353–1354. doi:10.1016/j.juro.2017.11.138.

Reply by Authors:

Re: Prognostic value of PD-1 and PD-L1 expression in patients with high-grade urothelial carcinoma of the upper urinary tract

Laura-Maria Krabbe^{1,2}, Barbara Heitzplatz³, Sina Preuss¹, Ryan C. Hutchinson², Solomon L. Woldu², Nirmish Singla², Martin Boegemann¹, Christopher G. Wood⁴, Jose A. Karam⁴, Alon Z. Weizer⁵, Jay D. Raman⁶, Mesut Remzi⁷, Nathalie Rioux-Leclercq⁸, Andrea Haitel⁹, Leonid M Rapoport¹⁰, Peter V. Glybochko¹⁰, Marco Roscigno¹¹, Christian Bolenz¹², Karim Bensalah¹³, Arthur I. Sagalowsky², Shahrokh F. Shariat⁷, Yair Lotan², Evangelos Xylinas¹⁴, Vitaly Margulis²

¹Department of Urology, University of Muenster Medical Center, Muenster, Germany

²Department of Urology, University of Texas Medical Center, Dallas, TX, USA

³Department of Pathology, University of Muenster Medical Center, Muenster, Germany

⁴Department of Urology, MD Anderson Cancer Center, Houston, TX, USA

⁵Department of Urology, University of Michigan Cancer Center, Ann Arbor, MI, USA

⁶Division of Urology, Penn State Health Milton S. Hershey Medical Center, Hershey, PA, USA

⁷Department of Urology, Medical University of Vienna, Vienna, Austria

⁸Department of Pathology, Centre Hospitalier Universitaire de Rennes, Rennes, France

⁹Department of Pathology, Medical University Vienna, Vienna, Austria

¹⁰Department of Urology and Reproductive Health, Sechenov First Moscow State Medical University, Moscow, Russia

¹¹Department of Urology, Ospedali Riuniti of Bergamo, Bergamo, Italy

¹²Department of Urology, University of Ulm, Ulm, Germany

¹³Department of Urology, Centre Hospitalier Universitaire de Rennes, Rennes, France

¹⁴Department of Urology, Cochin Hospital, APHP, Paris Descartes University, Paris, France

While it is true that some of the current focus regarding prediction of response to immunotherapies centers on the expression of PD-L1 on tumor-infiltrating ICs, our understanding of the issue at hand is far from perfect. The literature is controversial and immunoassays associated with the different immunotherapeutic agents are lacking solid performance.⁵ While the SP142 PD-L1 immunoassay is approved to predict response to atezolizumab, the compound is approved irrespective of PD-L1 status as cases deemed PD-

L1 negative by SP142 also showed significant and long-lasting responses.³ Furthermore, the immunoassays used in the pivotal trials of the 4 other immunotherapeutic agents approved by the Food and Drug Administration for urothelial carcinoma (pembrolizumab, nivolumab, avelumab and durvalumab) all evaluated PD-L1 expression on TCs, either alone or in combination with PD-L1 expression on ICs, acknowledging the complex interaction between ICs and TCs as well as the tumor and immune microenvironment.⁵ The fact that we currently do not have reliable biomarkers despite use of specifically designed assays and scores for the respective agents clearly indicates our current lack of understanding of this complex issue, highlighting the need for further research in this arena.

Thus, we continue to stress the potential importance of PD-L1 expression on TCs in patients with urothelial carcinoma. There is a pressing need to further focus efforts in the field to explore and understand the complexity of the immune system in relation to cancer to improve risk stratification, prediction of response and ultimately oncologic outcomes.

References

1. Bellmunt J, Mullane SA, Werner L et al.: Association of PD-L1 expression on tumor-infiltrating mononuclear cells and overall survival in patients with urothelial carcinoma. *Ann Oncol* 2015; 26: 812. [PubMed: 25600565]
2. Zhang B, Yu W, Feng X et al.: Prognostic significance of PD-L1 expression on tumor cells and tumor-infiltrating mononuclear cells in upper tract urothelial carcinoma. *Med Oncol* 2017; 34: 94. [PubMed: 28409437]
3. Rosenberg JE, Hoffman-Censits J, Powles T et al.: Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet* 2016; 387: 1909. [PubMed: 26952546]
4. Inman BA, Longo TA, Ramalingam S et al.: Atezolizumab: a PD-L1-blocking antibody for bladder cancer. *Clin Cancer Res* 2017; 23: 1886. [PubMed: 27903674]
5. Boegemann M, Aydin AM, Bagrodia A et al.: Prospects and progress of immunotherapy for bladder cancer. *Expert Opin Biol Ther* 2017; 17:1417. [PubMed: 28832261]