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Reply to Francesco Piva, Matteo Santoni, Marina Scarpelli, Alberto Briganti, Antonio Lopez-Beltran, Liang Cheng, Rossana Berardi, Francesco Montorsi, and Rodolfo Montironi's Letter to the editor re: Daniel M. Geynisman. Anti-programmed Cell Death Protein 1 (PD-1) Antibody Nivolumab Leads to a Dramatic and Rapid Response in Papillary Renal Cell Carcinoma with Sarcomatoid and Rhabdoid Features. *Eur Urol* 2015;68:912-4

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We thank Piva and colleagues for the interesting comments on our research letter [EURUROL-D-16-00023]. Piva et al. focus on a detected variant of unknown significance (VUS) in the polybromo-1 (PBRM1) gene and propose a hypothesis linking PBRM1 to PD-L1 expression. Specifically, the authors speculate that expression of PD-L1 by renal cell carcinoma (RCC) tumor cells is downregulated through p53-induced expression of miR-34a, with PBRM1 variants disrupting expression of p53 and thus inhibiting downregulation of PD-L1. We find this hypothetical model intriguing, but would like to highlight several important points, including possible alternative, perhaps more parsimonious, explanations for the dramatic response to nivolumab described in the research letter [1].

First, we are hesitant to assign functional relevance to VUS without substantial clinical or experimental evidence. Not only is it not clear if the PBRM1 variant (P1388L) detected in the patient's tumor is functionally relevant – SIFT [2] predicts it to be non-damaging (SIFT score = 1; < 0.05 is predicted to be damaging) – there was also no data regarding p53, no screening of PD-L1 expression, and no assessment of miR-34a. Furthermore, our analysis of data for 413 renal cell carcinoma specimens provided by The Cancer Genome Atlas (TCGA) network does not seem to support the hypothesis proposed by Piva et al. Out of the 413 cases, 175 had either homozygous deletions, mutations (missense and truncating), or transcriptional downregulation of PBRM1; of these 175 cases, 3 had transcriptionally downregulated p53 and one had deleted p53. Five of the 175 cases had transcriptionally

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Conflicts of interest

The authors have nothing to disclose.

upregulated p53. PD-L1 overexpression was not detected in any of the p53 downregulated cases (although post-translational regulation cannot be ruled out). Furthermore, a large phase III clinical study of nivolumab in RCC published by Motzer et al. corroborated previous evidence that high levels of PD-L1 are associated with poor survival [3–5], which, unless the Piva model is exclusively applicable to tumors with sarcomatoid features, presents further challenges to the hypothesis.

To substantiate the proposed model, it would be necessary to experimentally validate all aspects of the PBRM1-p53-miR34a-PD-L1 axis in RCC, including improved response to nivolumab. Most importantly, clinical evidence would have to be provided to show that consideration of PBRM1 status meaningfully supplements PD-L1 and PD1 expression data. Although it is not clear at present how the model proposed by Piva et al. would change clinical assessment of patients and substantiate the diagnostic value of PD-L1 and PD1 expression, their commentary does suggest that tumors with sarcomatoid features should perhaps be studied independently for this purpose.

In summary, we believe the remarkable response to nivolumab described in the research letter may have been due to several factors: (1) significant burden of non-synonymous mutation and neoantigens [6], (2) increased sensitivity specifically related to sarcomatoid features, as also suggested by Piva et al. and others [7], and/or (3) an immuno-allergic process, as indicated by robust eosinophilia (from 1 – 2% to ~30%) post-nivolumab treatment. We concur with Piva et al. that finding reliable response predictive biomarkers for immunotherapy is a critical ongoing endeavor.

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