available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. 435–444 of this issue

The Cancer Immunogram: A Pledge for a Comprehensive Biomarker Approach for Personalized Immunotherapy in Urothelial Cancer

Haris Zahoor[a], *Petros Grivas*[b,c,*]

[a] *Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA;* [b] *Division of Oncology, Department of Medicine, University of Washington, Seattle, WA, USA;* [c] *Clinical Research Division, Fred Hutchison Cancer Research Center, Seattle Cancer Care Alliance, Seattle, WA, USA*

Patients with advanced urothelial cancer (aUC) have primarily been treated with platinum-based chemotherapy. Patients who experience disease progression on first-line chemotherapy have limited options, and there was no US Food and Drug Administration (FDA)-approved salvage treatment for platinum-refractory aUC until 2016. Better understanding of tumor and host biology, and of mechanisms of immune surveillance evasion, has led to the development of novel immunotherapies such as immune checkpoint inhibitors (ICIs). These agents have revolutionized the treatment landscape for several solid tumors and five ICIs have received FDA approval for platinum-refractory aUC, two of them for cisplatin-unfit patients in the frontline setting [1–3]. Although ICIs have shown significant activity, only a subset of patients achieve response based on Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1, and some experience severe adverse events [1–3]. Therefore, there is an unmet need for biomarker-enrichment strategies that enable better patient selection.

Several clinical and molecular biomarkers that might predict ICI response are under investigation, including tumor tissue PD-L1 expression, tumor mutational burden, gene expression profiling signatures (molecular subtypes), alterations in DNA damage response genes, and the host microbiome, among others [1–3]. However, prospective validation and clinical utilization of putative biomarkers face challenges such as reproducibility, accuracy, dynamic tumor tissue requirement, tumor heterogeneity, and sampling variability [4]. It is also plausible that a single biomarker might not represent the very complex tumor microenvironment and numerous host-tumor interactions. Therefore, a combination of biomarkers might better meet the above stipulations.

In this issue of *European Urology*, van Dijk et al. [5] propose the concept of a cancer immunogram as a framework for personalized immunotherapy in aUC and future biomarker research. The authors should be commended on this important and elegant manuscript, which can provide overarching principles towards harmonization and alignment for immune-related biomarker evaluation. This theoretical model is based on original work by Blank et al. [6], who proposed this conceptual framework under the fundamental assumption that T-cell activity is the ultimate mechanistic mediator of ICI activity. However, it can be affected by several tumor- and host-specific parameters, including tumor foreignness, immune cell infiltration capacity, checkpoints, soluble inhibitors, inhibitory tumor metabolism, general immune status, and tumor sensitivity to immune effector mechanisms [6].

The authors pursued a well-designed extension of the cancer immunogram concept to aUC, using an extensive literature search and synthesizing existing data for each parameter. It appears to be a very comprehensive and cohesive framework that attempts to incorporate multiple important immune-related aspects, stepping away from the more limited single-biomarker approach. Moreover, it

DOI of original article: https://doi.org/10.1016/j.eururo.2018.09.022.
* Corresponding author. Petros Grivas, Clinical Research Division, Fred Hutchison Cancer Research Center, Seattle Cancer Care Alliance, 825 Eastlake Avenue East, Seattle, WA 98109, USA. Tel. +1 206 6067595; Fax. +1 206 6062042.
E-mail address: pgrivas@uw.edu (P. Grivas).

https://doi.org/10.1016/j.eururo.2018.12.005

provides a visual representation of the seven axes on a radar plot to facilitate potential evaluation of individual patients with discordant characteristics. The data and conclusions presented can inform novel clinical trial designs and contribute towards a collaborative mindset for data sharing and standardization of biomarker assessment across clinical trials. This is very relevant, especially considering the significant variability in the methods, assays, types, time points, and endpoints of correlative studies explored across the spectrum of aUC studies. Furthermore, such a comprehensive paradigm may serve as a guide for the development of prospective biorepositories and registries that support UC-specific biomarker discovery and validation. Similar approaches could be pursued for other tumor types, considering that some biomarkers may be independent of tumor type and more related to the homeostasis, structure, and function of the host immune system.

As discussed by the authors, there are challenges regarding the feasibility of potential application in clinical practice and the incorporation of data points into quantitative predictive models. The relative significance and impact of each axis (and its constituents) might not be easy to define. Therefore, it might be hard to measure precisely the predictive value of a multifaceted model regarding response to specific therapeutic interventions. The authors properly consider the immunogram dynamic over time as we gain further understanding of complex immunologic processes. The high degree of tumor and host heterogeneity, as well as the dynamic evolving nature of tumor biology, could pose further hurdles in successful implementation of a UC-specific immunogram. For example, acquisition of serial tumor tissue over time (before, during, and after immunotherapy) can be difficult for clinical and logistic reasons. The development and inclusion of circulating biomarkers might somewhat circumvent this challenge. Moreover, some factors, such as the gut microbiome, can be relevant across multiple axes of the immunogram, and thus it might be hard to categorize such factors appropriately [7]. Practical issues related to intellectual property and data ownership also frequently temper the enthusiasm for productive collaborations and data sharing across different immunotherapy-based clinical trials, and thus biomarker validation.

Notably, there are a plethora of immunotherapeutic combinations and sequences, disease spaces, and treatment settings, as well as diagnostic tools and follow-up time points, that can also contribute to the complexity and variability of biomarker development. The combination of ICI with other treatment modalities might often be synergistic and is under investigation in aUC [8]. Therefore, biomarkers with discriminatory ability to predict differential responses to monotherapy and/or combination therapies can be helpful. As we pursue various immunotherapeutic approaches, accurate measurement of responses and clinical benefits is also critical. The limitations of conventional response criteria (RECIST) in the context of immunotherapy are well known and formed the basis for the modified immunotherapy-based iRECIST criteria [9]. However, iRECIST implementation in clinical practice faces challenges, while various treatment combinations might also impact selection of the most relevant and appropriate metrics of response.

An additional consideration is the ongoing progress in multiple fields such as proteomics, metabolomics, epigenetics, radiomics, radiogenomics, and functional imaging, to name a few. Such developments might help towards more granular evaluation of the tumor microenvironment and its spatial and temporal heterogeneity via longitudinal invasive and noninvasive approaches [10]. Similarly, the role of functional imaging in detecting CD8 T cells and PD-L1 expression status is also being explored [10]. Furthermore, growth in the fields of big data, bioinformatics, and artificial/augmented intelligence can certainly impact information acquisition and processing. Milestones and breakthroughs for multiple parameters could be included in future deliberations of the cancer immunogram and contribute to its dynamic nature.

In conclusion, single-agent ICIs have brought a paradigm shift in aUC treatment by inducing rapid and durable responses; however, the relatively low response rates and potential toxicity underline the need for optimal patient selection. Therefore, comprehensive, multiparametric, dynamic, and robust biomarker development strategies, such as the cancer immunogram elegantly described by van Dijk and colleagues, can help in achieving the goal of precision immunotherapy. Such multidisciplinary approaches require close and dynamic collaboration among multiple stakeholders, as well as rapid implementation of relevant policies.

Conflicts of interest: Petros Grivas is a consultant for EMD Serono, Janssen, AstraZeneca, Merck & Co., and QED Therapeutics, and has received clinical research support from Pfizer, Bristol-Myers Squibb, Clovis Oncology, Bavarian-Nordic, and Immunomedics, all unrelated to this article. Haris Zahoor has nothing to disclose.

References

[1] Gopalakrishnan D, Koshkin VS, Ornstein MC, Papatsoris A, Grivas P. Immune checkpoint inhibitors in urothelial cancer: recent updates and future outlook. Ther Clin Risk Manage 2018;14:1019–40.

[2] Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015–26.

[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;387:1909–20.

[4] Nishino M, Ramaiya NH, Hatabu H, Hodi FS. Monitoring immune-checkpoint blockade: response evaluation and biomarker development. Nat Rev Clin Oncol 2017;14:655–68.

[5] Van Dijk N, Funt SA, Blank CU, Powles T, Rosenberg JE, Van der Heijden MS. The cancer immunogram as a framework for personalized immunotherapy in urothelial cancer. Eur Urol 2019;75:435–44.

[6] Blank CU, Haanen JB, Ribas A, Schumacher TN. The "cancer immunogram". Science 2016;352:658–60.

[7] Zitvogel L, Ma Y, Raoult D, et al. The microbiome in cancer immunotherapy: diagnostic tools and therapeutic strategies. Science 2018;359:1366–70.

[8] Melero I, Berman DM, Aznar MA, et al. Evolving synergistic combinations of targeted immunotherapies to combat cancer. Nat Rev Cancer 2015;15:457–72.
[9] Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143–52.
[10] Sun R, Limkin EJ, Vakalopoulou M, et al. A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study. Lancet Oncol 2018;19:1180–91.