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Commentary

Quantity of Immune Cells Predict Response to Immunotherapy in Cancer

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What are the prerequisites of a good biomarker for confident prediction to immunotherapy? If a clinical trial that includes a biomarker for treatment allocation is considered positive, the assay used to identify that biomarker is considered as a Companion Diagnostic Assay (CDx) by the US-FDA, but only if the drug company submits the drug and assay for regulatory co-approval. It is generally perceived that a CDx is the only or at least the best assay that oncologists are permitted to rely upon for safe and effective prescribing of the drug, regardless of the availability of better alternatives. Moreover, FDA-approval of assays is not based on the highest level of analytical and clinical evidence of the assay. Consider for example the approval of the FoundationOne CDx assay as a Companion Diagnostic Assay for Larotrectinib. The FDA-approval of this assay was based on a retrospective analysis of patient samples of several clinical trials [1]. Furthermore, CDx do not necessarily perform better compared to laboratory-developed tests [2]. Some of them have reproducibility issues [3].

This approach has reached its limits [4]. This is conceptualized by the issues seen with PDL1-assays in the immunotherapy field. The multitude of PDL1-assays available in different tumor types, all developed and validated in different settings, with not always equivalence between the different assays, not even in the same tumortype, show how non-harmonized assay development can lead to confusion for pathologists, clinicians, the regulatory instances, as well as patients.

It is in this context that the results of Feng Li and colleagues published in *EClinicalMedicine* are informative [5]. These authors have performed a meta-analysis, investigating in 33 different tumor types, in more than 2500 patients whether CD8+ tumor-infiltrating lymphocytes (CD8+ TILs) are associated with outcome when given immunotherapy. They convincingly show that irrespective of the immunotherapy drug, the quantity of CD8+ TILs predict benefit for all outcome endpoints. Considering the dominance of PDL1-assays in the immunotherapy arena, the authors need to be applauded for their initiative. The significance of their findings is two-fold: 1. Quantity of the immune cells matters for prediction to immunotherapy, and it probably doesn't matter whether these are determined morphologically, through immunohistochemistry or even through DNA-sequencing, and 2. Other biomarkers, beyond the well-known CDx can help identify patients for immunotherapy.

Tumor infiltrating lymphocytes (TILs), as defined by the International Immuno-Oncology Biomarker Working Group (www.tilsinbreastcancer.org), are mostly CD8+ TILs [6]. Two phase 3 Triple Negative Breast Cancer clinical trials, KN119 and Impassion130, both demonstrate that the quantity of TILs predicts outcome to immunotherapy [7]. Moreover, in Impassion130, benefit to immunotherapy using TILs is nearly similar to that of the CDx, using an assay that is known to be less sensitive than other well-known PDL1-assays [8]. PDL1-results, thus treatments for patients in breast cancer, will differ depending on the assay used, and this is well known also for urothelial cancer [9].

The findings of Feng Li and colleagues need to be confirmed, preferably in prospective trials. Thorough validation of CD8-immunohistochemistry assays needs to be performed, and programs of evaluation of performance between pathologists need to be installed. Yet, considering the different performances of the anti PD-L1 assays, even when used in the same tumortype, why not use a biomarker that relates to the quantity of the immune cells and that is independent of the assay used? This would obviate many of the issues the scientific community is today facing with PDL1-assays. TILs, thus CD8+ TILs correspond to this definition. Some PDL1-assays either rely on immune cells (in breast) or on immune cells combined with tumor cells (in head and neck and urothelial cancer). Consider a patients' cancer that has many immune cells but is PDL1-negative. This situation may provide dilemma's in daily practice. What will the clinician or pathologists do? Either consider the PDL1-stain as negative, irrespective of the presence of many TILs, either reconsider the staining or even redo the PDL1-stain with another assay?

Finally, will the drug industry will ever consider the quantity of immune cells as a reliable biomarker for selection of patients for immunotherapy in their trials? This can only be achieved if the drug industry considers other biomarkers beyond PDL1 as selection criterion for patients in their immunotherapeutic trials. Changing the current narrative that a clinical trial serves to validate an assay, not a biomarker, into a narrative where the clinical trial serves to validate a biomarker, and not an assay, will certainly help. If this is achieved,

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then TILs, using morphology, evaluated according to established guidelines, or with immunohistochemistry for CD8, or even by DNA-sequencing [10], may one day be used in daily practice in a rational and biological plausible manner.

Declaration of Competing Interest

The authors declare no conflicts of interest related to this manuscript.

Author Contribution

Both authors contributed equally to the content of this manuscript.

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