Editorial Commentary

To be or low TMB (tumor mutational burden)

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Immuno-oncology (IO) is regarded as one of the greatest achievements in modern oncology, but it has been shown to deliver long-term responses of over 5 years in only about 25% of patients. Initially, the programmed death-ligand 1 (PD-L1) tumor status received the most attention as a predictor of response to immune checkpoint blockade (ICB). However, it soon became apparent that a PD-L1-centric approach was overly simplistic, as even PD-L1-negative tumors do occasionally respond to ICB. Since then, substantial efforts have been made to identify individual or combinatory biomarkers that can more accurately (with higher specificity) predict response to ICB therapies.

Tumor mutational burden (TMB), which represents the number of somatic mutations per megabase of the tumor genome, emerged as a promising predictive tool for ICB. However, yet again, the isolated focus on TMB quickly proved to be outdated, particularly following disappointing results from the CheckMate 227 trial, which used dual checkpoint inhibition. More biomarkers were evaluated in the context of IO, with negative predictive effects being noted for *STK11* and *KEAP1*, while positive effects were discussed for *KRAS*, *ARID1A*, and *TP53* mutations. Classical driver mutations, such as EGFR and ALK, typically show poor responses to immunotherapy, leading to the exclusion of these mutations from most ICB trials. Even more, patients harboring a driver mutation (e.g., EGFR) should not be treated by ICB first line anyway, since they may experience limited benefit from immunotherapy and powerful small molecules as a targeted therapy are available.

Despite accumulating data, results have been somewhat inconclusive and at times contradictory, with some patients showing unexpected clinical responses to ICB given their genotype. Previous studies have suggested a more complex landscape of ICB predictors. For instance, Frost *et al.* identified a favorable combination of PD-L1 positivity [tumor proportion score (TPS) >50%], *KRAS* G12C, and *TP53* co-mutations as predictive of better outcomes in pembrolizumab-treated patients with advanced non-small cell lung cancer (NSCLC) (1). In line with this, a recent study identified concomitant *KRAS* and *TP53* mutations as positive predictors for ICB treatment (2). However, neither study included TMB as a parameter. van de Haar and colleagues addressed the need for a more comprehensive model, integrating several biomarkers to retrospectively evaluate responders to IO monotherapy in patients with metastasized *STK11/KEAP1/EGFR*-positive lung cancer, using TMB as a factor (3). The authors used whole-genome sequencing to analyze paired tumor and normal tissue samples, identifying relevant somatic mutations. In an earlier study, the same group applied this approach to over 2,500 patients, identifying genetic variants in 62% of cases that allowed stratification into approved therapies or ongoing clinical trials. In their current study, the next generation sequencing (NGS) assay was used to count tumor-associated mutations and estimate TMB (mutations per megabase), applying the widely accepted cutoff of 10 mutations per megabase in 254 NSCLC patients treated with PD-L1-directed checkpoint monotherapy. Notably,

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the predictive value of mutations in *STK11*, *KEAP1*, and *EGFR* was significantly dependent on TMB. In a low-TMB environment, these mutations conferred resistance to immune monotherapy, but conversely, in high-TMB NSCLC, they predicted positive outcomes in terms of progression-free survival (PFS) and overall survival (OS). Given that somatic mutations in these genes occur with a frequency of about 5–20% in the western world, this subgroup is highly relevant (4,5).

The work by van de Haar *et al*. underscores the importance of testing an increasing number of biomarkers in molecular diagnostics before therapy initiation, demonstrating how combining biomarker results can enhance diagnostic sensitivity. The approach taken in this study—sequencing both healthy and tumor tissues in parallel using whole-genome NGS—requires significant bioinformatic expertise and is associated with high costs and limited reimbursement potential. Additionally, the coverage is often reduced, making it challenging to detect mutations with low allelic frequencies. Thus, routine use of this design currently remains challenging. However, more focused lab-developed or commercial NGS panels have proven effective for detecting TMB, driver mutations, and relevant co-mutations. These panels typically include around 300 genes and ideally use DNA hybrid capture technology, enabling simultaneous detection of mutations, gene rearrangements, amplifications, plus TMB. Although still labor-intensive, these assays reduce the genetic territory analyzed, while maintaining core diagnostic requirements. The data by van de Haar resuscitate the TMB concept and suggest an integrated model of biomarker interpretation with the aim to more specifically predict IO response. The key finding by van de Haar *et al.* that patients with NSCLC who respond to ICB despite the presence of resistance biomarkers in STK11/KEAP1/EGFR almost always harbor a high TMB, suggests an integrated model of biomarker interpretation with the aim to more specifically predict IO response. The authors speculate that ICB treatment may provoke comparatively low antitumor immune responses in cancers with low TMB, while allowing tumors with STK11/KEAP1/EGFR mutations to escape the ICB-driven immune response. However, in the setting of a high TMB, ICB could be powerful enough to outweigh the negative predictive and/or prognostic effects of STK11/KEAP1/EGFR mutations (3). From a clinical point of view, the data might be helpful to decide which patient should not receive ICB monotherapy, and thereby prevent overtherapy. However, in the last years combinations of ICB with chemotherapy, VEGF inhibitors and second ICB (CTLA4) have been approved. Especially, it could be shown that patients harboring *KRAS*, *STK11* and *KEAP1* mutations might benefit from a chemo-double ICB combination according to the POSEIDON trial. Further information, whether TMB might stratify to such a multi-drug combination or is only a negative prognostic factor to all those therapies might be helpful in the future. Additionally, even more factors likely need to be considered in ICB "fine tuning", since response to immunotherapy may be also influenced by germline mutations (6).

The work by van de Haar however bears several limitations. First of all, the numbers are relatively small with even less numbers for *STK11* und *KEAP1* mutations making statistics less reliable. In addition, nearly a quarter of the patients had no information regarding the PD-L1 TPS status which is essential for the treatment with ICB as monotherapy with pembrolizumab is approved by the European Medicines Agency (EMA) for 1st line therapy only with TPS scores ≥50%. Furthermore, the test and training cohorts are hardly comparable due to major differences in demographics. Despite these limitations, the data are at least hypothesis generating and should be confirmed by a prospective trial.

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Footnote

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received consulting fees from Novocure and lecture fees from AstraZeneca, BMS, MSD, and Roche and had an advisory role for Novocure. W.M.B. received payments for presentations from AstraZeneca, Boehringer Ingelheim, Novartis, MSD, BMS, Roche, Lilly, and Pfizer; received support for congress fees from Boehringer Ingelheim, AstraZeneca, Roche, Daiichi Sankyo, and Johnson and Johnson; and he participated in Advisory Boards for AstraZeneca, Boehringer Ingelheim, Novartis, MSD, Lilly Oncology, BMS and Roche and has a patent (EP21183549.1) planned on a model to predict clinical response to checkpoint inhibition. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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