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Prognostic benefit of TILs independent of clinicopathological and molecular factors

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TO THE EDITOR:

We would like to thank Almagush et al. [1] for their interest in our recent review in the *British Journal of Cancer*, “Tumour-infiltrating lymphocytes: from prognosis to treatment selection” [2] and we would like to share our thoughts regarding their letter.

We fully agree with the authors that there are many additional important aspects of Tumour-infiltrating lymphocytes (TILs) across different facets of clinical care, for example within the tumour-node-metastasis (TNM)-Immune classification. Regrettably we were not able to elaborate on all of these aspects within the confines of our original manuscript.

As mentioned in our recent review, TILs have a role as prognostic biomarker, next to a predictive value for immune therapy in cancer. However, this effect does not occur in isolation and should be interpreted within the context of other prognosticators, such as p16 status in Human papillomavirus (HPV)-related cancers and molecular subtype in endometrial cancer. Ward et al. [3] and Wakeman et al. [4] both found that the addition of p16 status to TIL scores improved the prediction of prognosis significantly in oropharynx and anal cancer, respectively. Among patients with p16 positive tumours, TIL levels stratified patients into those with good and poor prognosis in terms of Overall Survival (OS), Disease-Specific Survival (DSS), Disease-Free Survival (DFS) and/or Progression-Free Survival (PFS) [3, 4].

In non-HPV related solid tumours, tumours have been frequently sub-classified based on molecular profiling. Perhaps one of the most striking examples is endometrial cancer where the use of molecular classification has substantially impacted our understanding of prognosis and treatment selection [5, 6]. Herein, the prognostic effect of TILs can vary even between different molecular subtypes, and the overall immune profile of the infiltrate. For instance, TIL density has proven a prognostic benefit in patients with a TP53 mutant endometrial carcinoma [7]. However, and perhaps counterintuitively, this prognostic effect of TILs was weaker/absent in the mismatch repair deficient (MMRd) subgroup. By contrast, the presence of organized TIL infiltrate in the context of tertiary lymphoid structures (TLS) had a favourable prognostic impact mainly in the MMRd patients with endometrial cancer, but not within the other molecular subgroups [6]. In addition, a recent study by Lee et al. described the prognostic benefit of TILs was dependent of the expression of p53 in patients with triple negative breast cancer [8]. They found that in the low p53 expression group, the TIL level did not affect the OS and DFS, while in the high and no p53 expression groups, OS and DFS increases with a higher level of TILs. They hypothesize that a subgroup of patients with missense TP53 mutation, can

benefit from immune checkpoint blockade (ICB) because of the presentation of neoantigens and a subsequent TIL response [8].

As the above-described effects are difficult to incorporate into a generalized TNM system, we remain wary of incorporation of TILs directly into this classification, but fully support efforts to work towards the inclusion of TILs as a prognostic and potentially predictive biomarker in addition to the classical TNM and molecular classification. Herein, we support the conclusions of Almagush et al. [1] that further validation of the potential use of TNM-Immune staging is desirable prior to its introduction in clinical practice.

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DATA AVAILABILITY

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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AUTHOR CONTRIBUTIONS

KB and ALE drafted and revised the manuscript. MB and HWN conceived the project, supervised writing, and revised the manuscript. All authors read and approved the final version.

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All authors have approved to publish this manuscript.

ADDITIONAL INFORMATION

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