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Targeting prognostic proinflammatory biomarkers to improve outcome on IO drugs

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The number of patients treated with immune checkpoint inhibitors, especially anti-PD-1 and anti-PD-L1 drugs, has been increasing over the past years as a result of Food and Drug Administration (FDA) and European Medicine Agency (EMA) approvals of these medications for a growing number of cancer types. Unfortunately, the objective response rate (ORR) has in general not improved, with about one out of five treated cancer patients responding to these therapies. Selective or predictive biomarkers of response to anti-PD-(L)1 are currently mostly lacking with the exception of PD-L1 expression being 50% or higher in non-small cell lung cancer (NSCLC) tissue, and the presence of mismatch repair deficiency in tumour cells, for which pembrolizumab was given a tumour agnostic label by FDA. In the near future, tumour mutational burden may discriminate patients with NSCLC who benefit from single-agent or dual-immune checkpoint blockade (dual-ICB), however, complementary diagnostic tests in development use different platforms and cut-offs and require careful comparison and validation which is currently ongoing.

The majority of biomarkers depend on tumour tissue, which restricts their use, as acquisition requires invasive methods and tumour cell content and immune infiltrate may differ considerably between and within tumour types, or even be insufficient, making their routine use challenging.

In addition, many of the mentioned biomarkers have next to being predictive also prognostic value. PD-L1 expression in metastatic renal cell cancer for instance is correlated with poor outcome, but patients with PD-L1 positive tumours do have a higher ORR and survival to ICB.[1 2] This makes estimation of the true predictive value of a biomarker even more complex. The main difference between a prognostic and predictive biomarker is that the first predicts outcome independent of treatment, whereas the latter predicts outcome in the presence of a specific treatment (for instance immunotherapy) but not another therapy (for instance chemotherapy).

From a clinical and practical perspective, biomarkers coming from liquid biopsies have many advantages over tissue biopsies. Apart from the more challenging biomarkers such as TMB measured in cell free or plasma DNA, routinely measured markers, such as serum lactate dehydrogenase, C-reactive protein (CRP), interleukin-6 (IL-6), erythrocyte sedimentation rate, absolute lymphocyte count, neutrophil-to-lymphocyte ratio have been explored as predictive biomarkers for response to immunotherapy. Importantly, many of these blood-based markers have been demonstrated to be prognostic next to have predictive value.[3–6]

In this issue of *ESMO Open*, Iivanainen *et al* describe the measurement of baseline CRP levels in patients that are being treated with anti-PD-(L)1 therapy and show that patients with elevated CRP have a poor progression-free survival (PFS) and overall survival (OS) in comparison with patients with normal CRP. The cut-off for elevated CRP was 10 mg/mL, a value that appears to be accepted as elevated CRP. The study contained a test cohort and a validation cohort, showing that using this cut-off of CRP, elevated CRP had clinically relevant statistically significant prognostic value for PFS and OS in the validation cohort. The authors question whether patients with elevated CRP should be offered treatment with anti-PD-(L)1 therapy. The results are coming from a real-world population of patients with metastatic melanoma, NSCLC and renal cell cancer. Unfortunately, no data are provided of a control group treated with non-immuno-oncology (IO) drugs which makes it impossible to distinguish whether CRP has any predictive value as well. These data are in line with a retrospective analysis

from Wilgenhof *et al*, showing the correlation of CRP with prognosis in ipilimumab treated melanoma patients.[7]

Recently, at the annual meeting of the American Society for Clinical Oncology, similar data on the use of CRP and IL-6 levels measured pretreatment, coming from three randomised melanoma studies, Checkmate-064, Checkmate-066 and Checkmate-067[8] were presented. Checkmate-066 was the only study that randomised checkpoint inhibition with nivolumab to chemotherapy (dacarbazine). IL-6, a cytokine with pleiotropic effects on immune cells, stimulates the liver to produce CRP, so CRP levels reflect IL-6 levels in the blood. These data clearly show that both CRP and IL-6 are prognostic markers and do not or only have limited predictive value, as for dacarbazine treatment, elevated IL-6 and CRP were associated with poor survival.

How these biomarkers are correlated with poor survival is still subject of ongoing research. Preclinical data indicate that IL-6 and other proinflammatory cytokines, including IL-1β and tumour necrosis factor (TNF)-α impact in several ways on the tumour microenvironment, favouring a myeloid inflammatory response with myeloid derived suppressor cells (MSDC) and neutrophils, directly affect T cell and dendritic cell function, promote tumour growth and affect metastatic potential.[9–11] Therefore, the question needs to be addressed whether these poor prognostic markers can be targeted directly in order to change the outcome of patients. Recently, investigations in several preclinical models showed that combination of IL-6 and PD-(L)1 blockade reduced development and progression of cancer.[12] In a very recent study, anti-TNF-α, when given at the start of anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) plus anti-PD-1 treatment, not only lowered the chance of ICB-induced colitis, but also showed synergism in antitumour immunity in preclinical tumour models.[13] Based on these encouraging findings, there is growing interest in combining blockade of these proinflammatory cytokines with ICB to overcome resistance to ICB alone. Importantly, clinical trials have already started or are being initiated combining either anti-IL-6 or anti-IL-6 receptor with anti-PD-(L)1 or anti-IL-1β or IL-1RA together with ICB in order to improve outcome in patients with cancer. It would be highly interesting if these combinations would especially be effective in patients with elevated levels of IL-6 or CRP or other signs of myeloid inflammation.

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