Editorial

Immunotherapy: remember the host

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Sung *et al.* present data that is a powerful immunotherapy reminder of not forgetting the host (1). Tumor-host interactions are an important aspect of treating cancer. These interactions are particularly impactful in immuno-oncology (IO) as immune checkpoint inhibitors have no direct treatment effects against the tumor but are just targeting the host's immune system for better cancer cell recognition and effective T-cell cytotoxicity. Predictive immune biomarkers assessing both the tumor and the host are needed to best reflect IO treatment benefit.

Tissue programmed death ligand-1 (PD-L1) protein expression is the recognized tumor-based predictive immune biomarker in metastatic non-small cell lung cancer (NSCLC). However, in clinical trials with tissue PD-L1 expression and immune checkpoint inhibitors alone (monoIO) or combined chemotherapy concurrently with IO (chemoIO), 5-year overall survivals are reported to be only 8–12% better than cytotoxic chemotherapy alone (2). And a lack of tissue PD-L1 expression does not preclude a therapeutic benefit with chemoIO regimens (3). The leaves a limited clinical impact of tissue PD-L1 as a tumor-based predictive immune biomarker. The gut microbiome is a powerful host-based predictive biomarker of IO treatment benefit (4). However, the gut microbiome cannot easily be assessed in the clinic. IO treatment needs better predictive immune biomarkers, and these biomarkers need to be able to be easily assessed in the clinic.

This study assessed two of the most frequently tested host immune biomarkers. A high neutrophil-lymphocyte ratio (NLR) reflects a cellular immune evasive tumor microenvironment and has been associated with poor IO treatment benefit (5-7). C-reactive protein (CRP) levels reflect interleukin-6 (IL-6) production which plays a dual role in the host immune defense and cancer progression. Elevated baseline levels of CRP/IL-6 are associated with a variety of immune tumor evasive effects resulting in poor IO treatment outcomes (8-10). Lactate dehydrogenase (LDH) can reflect malignant cell proliferation and overall tumor burden but also is elevated due to a variety of tissue and cellular effects limiting clinical utility. NLR and CRP are predictive of IO benefit and are easily tested in the clinic with little cost.

The best global summation parameter of cancer effect on the host is performance status (PS). The simple clinical Eastern Cooperative Oncology Group (ECOG) PS scale has been a powerful host assessment of patient symptoms and functional status with poor PS associated with detrimental effects on cancer treatment outcomes. (ECOG PS 0 is asymptomatic; PS 1 is minimally symptomatic carrying on normal daily activities; PS 2 is symptomatic and unable to work but can perform self-care and be up and out of bed more than half the day; PS 3 is limited self-care and in bed more than the day; PS 4 is symptomatic requiring hospitalization.) The seminal clinical IO trials excluded patients with an ECOG PS of 2 or worse only including patients with an ECOG PS of 0 or 1. Real-

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world data of patients with metastatic NSCLC and an ECOG PS of 2 or worse treated with IO regimens confirms significantly poorer survival compared to patients less symptomatic with ECOG PS of 0 or 1 irrespective of tissue PD-L1 expression (11). Host parameters clearly impact IO treatment outcomes. Although easily assessed with no direct cost, ECOG PS can be clinically subjective especially in differentiating ECOG PS of 1 from 2 impacting consistent reproducibility.

There are more sophisticated (and more costly) blood-based proteomic assays to assess the host. VeriStrat® and PROphet® are commercial proprietary blood-based proteomic assays that reflect host inflammatory proteins (12,13). They have both been evaluated as predictive host immune biomarkers in first-line IO treatment in metastatic NSCLC patients. Inflammatory signatures are associated with poorer IO treatment benefit. 'VeriStrat® poor' patients with an inflammatory proteomic classification have always been associated poorer outcomes whether targeted epidermal growth factor receptor therapies or chemotherapy than patients 'VeriStrat® good' with a non-inflammatory proteomic classification. VeriStrat® has been re-named 'host immune classifier (HIC)' with IO-treated patients demonstrating an inflammatory HIC-C (cold) classification doing much poorer than patients with a non-inflammatory HIC-H (hot) classification. Inflammatory 'PROphet® negative' patients also demonstrated much poorer outcomes than non-inflammatory 'PROphet® positive' patients. However, both assays were only evaluated in ECOG PS 0 or 1 patients leaving IO treatment outcomes based upon proteomic assays in ECOG PS 2 or worse patients unknown.

The true clinical impact of a tumor or host immune biomarker rests with whether it can be modified to improve IO treatment benefit or help with individual IO treatment decision making. Host PS is unchangeable unless there is a response to treatment. However, even that global host biomarker can have important clinical management value. It provides a framework to openly and honestly discuss with a patient the lower likelihood of IO treatment benefit needing to be balanced by potential treatment immune toxicity, certain financial toxicity, and the time toxicity spent in the health care system. These can be important and impactful quality of life issues for patients.

VeriStrat® and PROphet® can have potential IO treatment decision making impact in the setting of tissue PD-L1 tumor proportion score of ≥50%. Patients with metastatic NSCLC and tissue PD-L1 negative or 1–49% expression have a significant and meaningful survival benefit with chemoIO compared to monoIO treatment. However, within the group of PD-L1 ≥50% patients, a chemo-free regimen of monoIO can be just as effective. This is where VeriStrat® or PROphet® can be clinically helpful by identifying the individuals with PD-L1 ≥50% who will receive a greater survival benefit with the addition of chemotherapy to IO. In the multi-institutional INSIGHT registry study, patients with tissue PD-L1 ≥50% and VeriStrat® poor/HIC-C significantly benefited from chemoIO compared to monoIO, whereas patients VeriStrat® good/HIC-H had a similar benefit whether chemoIO or monoIO (12). In the international multi-institutional PROPHETIC study, PROphet® negative patients with tissue PD-L1 ≥50% demonstrated a significantly better overall survival with chemoIO compared to monoIO (13). However, there was no difference between chemoIO and monoIO outcomes in PROphet® positive patients. In the group of patients with tissue PD-L1 expression of <50%, chemoIO was better than monoIO whether PROphet® was negative or positive.

CRP has a potential unique role as a host immune biomarker. Elevated CRP levels are associated with poorer IO treatment outcomes and IO treatment immune toxicity. It can also be mitigated with an anti-IL-6 receptor monoclonal antibody. Tocilizumab has been shown to effectively treat steroid refractory IO treatment toxicities as well as prevent the development of these toxicities with no discernible adverse effect on IO treatment outcomes (14-16). What is not known yet is whether tocilizumab with IO treatment in the setting of an elevated baseline or on treatment CRP has any additional anti-tumor immune effect. This is being actively studied and needs to be actively followed by oncologists.

Some host parameters can be physiologically and/or pharmacologically modified. Exercise can enhance anti-tumor immunity. Natural killer and $CD8^+$ cytotoxic T-cells expand, and immune suppressive myeloid-derived suppressor cells are reduced with exercise (17-19). Murine models have also shown that aerobic exercise and IL-15 activation will sensitize pancreatic tumor to IO treatment (20). Another host modification that has been shown to be effective in improving IO treatment outcomes is the discontinuation or avoidance of detrimental oral drugs. Use of concomitant antibiotics, corticosteroids, proton pump inhibitors, opioids, and acetaminophen are all associated with poorer IO treatment outcomes (21,22).

Tumor-host interactions remain an important aspect of

IO treatment benefit in cancer. This study reminds us that the host matters in IO treatment outcomes. Just as treating both the tumor and the host to enhance IO treatment benefit is vital in continuing to improve and extend survival in metastatic NSCLC, we must also recognize tumor only immune biomarkers do not fully predict IO treatment benefit. As we strive to improve IO treatment outcomes, we need to integrate host parameters into better composite tumor-host predictive immune biomarker assays that can be easily assessed and utilized in the clinic.

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