Editorial

A novel indication to treat distinct types of tumors with PD-1 blockade based on mismatch-repair deficiency

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Le *et al.* conducted a prospective study (Clinical-Trials.gov number, NCT01876511) to evaluate effects of programmed death-1 (PD-1) blockade (pembrolizumab) therapy in different kinds of tumors with mismatch repair-deficient (1).

The core issue of immunology is immune response and immune tolerance, T cell inactivation and anti-tumor response as well (2). As a key immune checkpoint mainly expressed on T cells, PD-1 plays dual roles in reactivating T cells to eradicate the cancer cells and maintaining immune inactivation to normal host cells (3). As FDA approved anti PD-1 agents, both pembrolizumab and nivolumab were first used to treat melanoma, non-small cell lung cancer, metastatic head and neck cancer, and Hodgkin's lymphoma. In addition, the former can also be applied to patients with renal cell carcinoma and advanced or metastatic urothelial carcinoma (4,5). Currently, the objective response rate with anti PD-1 antibodies is between 20% and 40%, but most patients obtained long-term benefit health outcome once effective with lower adverse events compared with traditional chemotherapy and may even achieve clinically cured (6,7). Hence, anti PD-1 therapy may have great potential to improve the cure rate and reduce the mortality in cancer patients if we found better indications of drug application. Some biomarkers including PD-L1 expression, RNA expression signatures, mutational burden and lymphocytic infiltrates were considered in order to well predict response of PD-1 blockade in specific cancer subtypes (8-10). However, these markers mentioned previously are narrow and limited according to specific tumor types. Some recently studies have demonstrated that mismatch-repair deficient cancers containing high abundance of mutation-associated neoantigens (MANAs) correlates well with anti PD-1 treatment response (11-13). With the advent of precision medicine era, to treat different forms of cancers with the same avenue comes true.

Dung T. Le *et al.* enrolled 86 mismatch-repair deficient tumor patients whose disease is progression after at least one therapy to evaluate their response after PD-1 blockade treatment via Response Evaluation Criteria In Solid Tumors (RECIST) criteria across 12 different tumor types. The number of patients with complete response is 18 (21%). Partial response and stable disease are 28 (33%) and 20 (23%), respectively. Collectively, objective response rate reaches 53% (n=46) and disease control rate is up to 77% (n=66). In addition, neither the tumor type nor the Lynch syndrome significantly influences the objective responsive rate. Although the follow-up of all participants is not over yet, it's estimated that both progression-free survival (PFS) and overall survival (OS) are higher than expected based on current status and trends. Of note, neither 11 patients with complete response after 2 years milestone nor 7 patients with residual tumor and interruption treatment due to intolerance have disease progression until now,

providing strong evidence for sustained and effective role of pembrolizumab once valid. Among 20 patients who experienced biopsies after 1 to 5 months of treatment, twelve biopsies have no detectable residual tumor cells accompanied with characteristic in immune response. The similar changes were not observed in other 8 patients. Compared with median PFS of 2.9 months in later, the former is achieved to 25.9 months which suggested that the biopsies alteration determine the PFS in patients with immunotherapy. Intriguingly, by exomes sequencing of tumor and matched normal tissue DNA, there is no significant difference between 3 therapy resistance patients (an average of 1,413 non-synonymous mutations) and 15 therapy sensitive patients (an average of 1,644 non-synonymous mutations).

TCR CDR3 sequencing (TCRseq) was performed on tumor tissues from 3 patients with immunotherapy response. Le *et al.* found that some specific T cell clones expanded quickly as pembrolizumab induced and then contracted. Of note, the frameshift mutation is the common characters of MANAs and MMR-deficient cancers. Furthermore, more than 5% of adenocarcinomas of the endometrium, stomach, small intestine, colon and rectum, cervix, prostate, bile duct and liver, as well as neuroendocrine tumors, non-epithelial ovarian cancers and uterine sarcomas, were MMR deficient in 12,019 cancers from 32 kinds of tumors via NGS. Among these, eight percent of stage I to III cancers and 4% of stage IV cancers were MMR-deficient. At present, either polymerase chain reaction or immunohistochemistry is feasible testing to detect mismatch repair-deficiency in distinct tumor types of patients who may benefit from anti-PD-1 therapy.

To sum up, the present study evaluate efficacy of PD-1 blockade in MMR-deficient tumor patients, regardless of its origin. The strengths of the study are as follows. Firstly, the study samples are across most tumor forms rather than focus on solo cancer type. PD-1 blockade therapy has been approved for solid tumor patients with microsatellite instability (MSI-H) or mismatch repair defects (dMMR). In fact, this is the first anti-tumor therapy approved by FDA not according to the source of the tumor, but according to the biomarkers, which is of landmark significance. Secondly, the authors illustrated the potential mechanism of immune response in dMMR patients by WES, TCRseq and NGS methods. Thirdly, the detection avenues of dMMR are more routine and cost-effective which may promote the prevalence of pembrolizumab application. However, there are also some limitations such as the relatively small sample size and short follow-up period. In addition, seventy four percent patients experienced certain adverse events. Fortunately, they are just low grade and easy to manage. Collectively, this study proposed the concept of precision medicine that is treating different diseases with the same way which marks a new stage of cancer awareness.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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