Microsatellite instability status predicts response to anti-PD-1/PD-L1 therapy regardless the histotype: A comment on recent advances

It is well-known that somatic mutations resulting in increased number of neoantigens ("immunogenic antigens") may enhance anti-tumor immune cell reaction. Also, high tumor mutation burden (load) [TML] is associated with improved response, durable clinical benefits and better outcome if a cancer is treated with immune check point inhibitors [anti-programmed cell death protein 1/programmed death-ligand 1 (anti-PD-1/PD-L1) drugs] [1]. A subset of colorectal carcinomas (CRC) and other cancers characterized by mismatch repair deficiency (MMR) and/or microsatellite instability high (MSI-H) profiles may be particularly sensitive to the PD-1/PD-L1 blockade with immune check point inhibitors due to the common PD-L1/PD-L1 expression [2-9]. Several therapeutic antibodies inhibiting either PD-1 (nivolumab, pembrolizumab) or PD-L1 (MPDL3280A, Medi4736, BMS-936559) have been developed and approved for the treatment of various malignancies including malignant melanoma, non-small cell lung carcinoma, renal cell carcinoma, bladder carcinoma, Merkel cell carcinoma, and classical Hodgkin lymphoma [10].

A pivotal phase 2 study by Le et al. [11] highlighted the importance of mismatch-repair status in prediction of the clinical benefit of immune checkpoint blockade with pembrolizumab (anti-PD-1 drug) [11]. The study included 41 patients with progressive cancers of both CRC and non-colorectal origins and known MSI status. For CRC patients, the objective response rate and progression-free survival rate were 40% and 78%, respectively for mismatch repair-deficient tumors and 0% and 11% for mismatch repair-proficient CRCs.

A novel study by Le et al. [12] (ClinicalTrials.gov number, NCT01876511) represents an extended analysis on the efficacy of PD-1 blockade in patients with advanced mismatch repair-deficient cancers. The study included 86 patients with 12 different histologic cancer subtypes and proved mismatch repair-deficiency status assessed by either polymerase chain reaction (PCR) or immunohistochemistry. The data presented in this study indicate objective radiographic responses in 53% of patients while complete responses were achieved in 21% of patients. Based on this and previous data, on May 23, 2017, the U.S. Food and Drug Administration (FDA) granted accelerated approval to anti-PD-L1 drug pembrolizumab (KEYTRUDA®, Merck & Co.) for adult and pediatric patients with unresectable/metastatic MSI-H/MMR deficient solid tumors (regardless the histotype) that have progressed following prior treatment and without satisfactory alternative treatment modalities. The approval also covered MSI-H CRC patients who progressed following treatment with a classic cytotoxic therapy (fluoropyrimidine, oxaliplatin, and irinotecan).

Taken together, these results revolutionize the cancer treatment paradigm as for the first time the cancer treatment was based solely on the molecular characteristics of cancer (in this case microsatellite instability/MSI/ status) regardless the tumor morphology (histotype). This appears to be "the FDA's first tissue/site-agnostic approval".

Certainly, there are still ongoing but unresolved issues regarding these treatments including other merging predictive biomarkers (optimization of PD-L1 and PD-1 evaluation, e.g., tumor versus immune cell expression; cutoffs for positivity; selection of detection antibodies), tumor mutational load and the tumor neoantigen heterogeneity/specificity [13-15]. Further studies should also elucidate the mechanisms of recently described resistance to immune checkpoint inhibitors [16-18].

DECLARATION OF INTERESTS

The author declares no conflict of interests.

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