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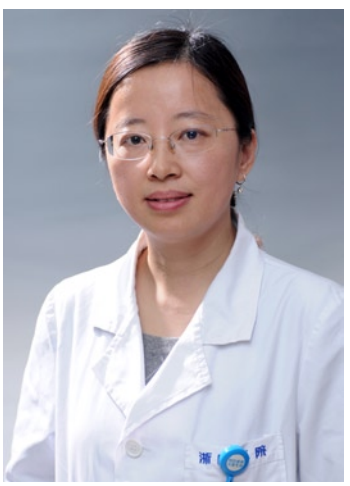
EDITORIAL

Progress of anti-checkpoint therapy in metastatic colorectal cancer*

Lizhen Zhu[1], Xuefeng Fang (Co-first author)[1, 2], Chenhan Zhong[1], Ying Yuan[1, 2] (✉)

[1] Department of Medical Oncology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, China
[2] Key Laboratory of Cancer Prevention and Intervention of Ministry of Education, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, China



Ying Yuan, Professor, Department of Medical Oncology, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang Province, P. R. China. Prof. Yuan has focused on the clinical practice and research on personalized therapy of gastrointestinal cancer, especially of colorectal cancer. Prof. Yuan is also interested in the scientific research. She has acquired several grants and published 99 papers, including 42 SCI papers. Besides, she has achieved a few honors and awards, such as "The Southern California Society of Colorectal Surgeons Award", "Scientific Achievement Award of Zhejiang Province", "National Science and Technology Progress Award", and so on. Her current academic society memberships include: member and director of genetics group, colorectal cancer professional committee of Chinese Society of Clinical Oncology; member of clinical trial committee and molecular targeted drugs committee of Chinese Society of Clinical Oncology; core expert of gastrointestinal cancer rational drug use commission, National Health and Family Planning Commission; expert of colorectal cancer diagnostic and treatment practices group, National Health and Family Planning Commission; permanent member and secretary of colorectal cancer MDT management board, National Health and Family Planning Commission.

In the immune system, antigen-presenting cells, especially dendritic cells, process tumor antigens and present them to anti-tumor CD8+ cytotoxic T cells and CD4+ helper T cells, thereby promoting the proliferation and activity of these cells to kill tumor cells.

When binding to ligands, some receptors on the T cell surface, such as CD28, OX40, GITR, and CD27, can activate T cells and promote their anti-tumor effects. Conversely, some other receptors can suppress T cell activation when binding to their ligands. This results in inhibition of T cell proliferation and cytokine secretion to repress the tumor cell-killing function, and therefore maintain immune homeostasis. These receptors are collectively referred to as immune checkpoints, including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), T-cell immunoglobulin and mucin-domain containing 3 (TIM-3) and lymphocyte-activation gene 3 (LAG-3) [1].

Tumor cells usually express ligands of the checkpoints at high levels to suppress the anti-tumor activity of T cells. Therefore, the discovery of drugs that can target these receptors or their ligands to attenuate their effect on T cells would reverse T cell inhibition and help to restore their anti-tumor activity. In recent years, certain anti-checkpoint receptors or ligands, such as anti-CTLA-4, anti-PD-1 and anti-programmed cell death protein ligand 1 (anti-PD-L1) have shown dramatic responses in some patients with different types of cancers.

In a phase II study conducted by Le DT *et al*, pembrolizumab (an anti-PD-1 drug) showed a great benefit to patients with mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC). The immune-related ob-

✉ Correspondence to: Ying Yuan. Email: yuanying1999@zju.edu.cn
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jective response rate (ORR) and immune-related progression-free survival (PFS) rate were 40% (4/10 patients) and 78% (7/9 patients), respectively, in patients with dMMR mCRC, whereas the ORR was 0% (0/18 patients) and the PFS was 11% (2/18 patients) in patients with mismatch repair-proficient (pMMR) mCRC [2]. The most recent data of this study were presented at the 2016 ASCO meeting, showing that after a median of 9.3 months of follow-up, the ORR was 57% (including 11% showing complete regression and 46% showing partial regression) for patients with dMMR mCRC, whereas the ORR remained at 0 for patients with pMMR mCRC after a median of 6 months follow-up. Interestingly, whole-exome sequencing suggested a mean of 1782 somatic mutations per tumor in dMMR tumors, but only 73 in pMMR tumors. A greater total mutation load would result in more tumor neoantigens, which would increase the activity of tumor-specific T cells to attack. Since anti-PD-1 therapy can promote T cell functions, these results suggest that dMMR mCRC patients would benefit more from anti-PD-1 therapy.

In addition, in a group of treatment-experienced patients with chemo-refractory mCRC, the combination of cobimetinib (an anti-MEK drug) and atezolizumab (an anti-PD-L1 drug) showed promising results, with an ORR of 17% and 6-month overall survival of 72%. Notably, 96% of the patients harbored *KRAS* mutations. The inhibition of MEK leads to upregulation of MHCI in tumor cells, causing intratumoral T cell infiltration, thereby enhancing anti-PD-L1 activity.

Although ipilimumab (an anti-CTLA-4 drug) has substantially improved the outcome of patients with melanoma, patients with mCRC cannot benefit from treatment with either ipilimumab or tremelimumab (another anti-CTLA-4 drug) alone [3–4]. At the 2016 ASCO meeting, Michael Overma demonstrated that the combination of nivolumab and ipilimumab had tolerable safety profiles and showed preliminary positive results, with an ORR of 33.3% for patients with microsatellite instability-high (MSI-H) CRC. Nivolumab monotherapy also demonstrated encouraging results in patients with MSI-H in this same study (ORR 25.5%). Notably, owing to the small sample, the results could not conclusively determine whether the combination of nivolumab and ipilimumab is superior to nivolumab monotherapy, and could also not indicate whether nivolumab is less effective than pembrolizumab.

In particular, in a phase II study of nivolumab in refractory metastatic squamous cell carcinoma of the anal canal (SCCA), among 37 patients who received at least one dose of nivolumab, 2 (5.4%) achieved complete regression and 7 (18.9%) achieved partial regression, and the median PFS was 3.9 months. Nivolumab was well-tolerated in these patients. Since there is currently no consensus treatment approach for SCCA, the results of these studies may offer some promise for these patients. SCCA is mainly driven by immune evasion of human papillomavirus (HPV)-specific CD8 and CD4 T cells; however, it remains unknown whether HPV infection is a predictor of the anti-PD-1 or anti-PD-L1 response, because pembrolizumab and duravalumab (an anti-PD-L1 drug) showed responses in cases of both HPV+ and HPV- squamous cell carcinoma of the head and neck.

In addition to nivolumab, pembrolizumab, atezolizumab, ipilimumab and tremelimumab, there are other drugs targeting PD-1, PD-L1 or CTLA-4 currently undergoing clinical trials. Moreover, clinical trials of drugs targeting other receptors or ligands related to the immune system are also actively recruiting patients, such as drugs targeting LAG-3.

In general, clinical trials of anti-PD-1 or anti-PD-L1 therapy have thus far revealed encouraging responses and safety profiles for patients with mCRC and SCCA, and the combination of anti-PD-1 and anti-CTLA-4 therapy may be tolerable, with promising preliminary responses. In addition, the combination of anti-MEK and anti-PD-L1 may be a potential therapy for *KRAS* mutation-positive mCRC. Moreover, some studies are focusing on the value of anti-checkpoint treatment in combination or in comparison with chemotherapy. Nevertheless, close attention must be paid to the data emerging from more studies.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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