Editorial

Efficacy and immune activation of ipilimumab in early-stage lung cancer patients

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Immune checkpoint inhibitors, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody and programmed death-1 (PD-1) antibody, improve the prognosis in several types of cancer patients, and they modulate the effector T-cell activation, proliferation and function (1). Ipilimumab is a monoclonal antibody targeting CTLA-4 (2). Generally, B7 receptors, represented by B7.1 (CD80) and B7.2 (CD86), are expressed on antigen-presenting cells (APCs), and T-cells are activated by the binding of B7.1/B7.2 and CD28, which is the principal co-stimulating receptor of T-cells (2). CTLA-4 preferentially binds B7.1/B7.2 (CD80/CD86) over CD28 because of a stronger affinity of CTLA-4 for B7.1/B7.2 (CD80/CD86) than CD28 on APCs, and the connection between B7 receptors and CTLA-4 downregulates the proliferation and activation of T-cells (2), resulting in the enhancement of the immune response against the tumor.

The recent article by Yi *et al.* (3) reported that neoadjuvant chemotherapy due to ipilimumab in addition to carboplatin/paclitaxel showed additive efficacy compared with carboplatin/paclitaxel chemotherapy in early-stage non-small cell lung cancer (NSCLC). Several reports of the efficacy of ipilimumab in lung cancer have been published, and the concurrent combination therapy of carboplatin/paclitaxel and ipilimumab did not improve the progression-free survival (PFS) compared with carboplatin/paclitaxel chemotherapy only. However, phased ipilimumab did improve the immune-related PFS versus chemotherapy only (HR =0.64; P=0.03) in a phase II study of lung cancer (4,5). In the study by Yi *et al.* (3), a phased ipilimumab and carboplatin/paclitaxel regimen was selected based on previous studies (2,4). Recently, however, the carboplatin/paclitaxel plus ipilimumab regimen used in a phase III study failed to prolong the overall survival (OS) compared with chemotherapy alone in patients with advanced squamous cell carcinoma (13.4 *vs.* 12.4 months; P=0.25) (6); therefore, ipilimumab in addition to carboplatin/paclitaxel might not be a promising regimen. Of note: combination therapy of nivolumab and ipilimumab in the first-line treatment of NSCLC patients showed a higher objective response rate (43%) than nivolumab only (23%) and showed tolerable safety in CheckMate 012 (1), especially in patients with high levels of tumor PD-L1 [tumor proportion score (TPS)].

The characteristics of ongoing clinical trials are shown in *Table 1*. Many of these ongoing clinical trials evaluate the efficacy and safety of the combination with nivolumab/pembrolizumab and ipilimumab (*Table 1*). In addition, the efficacy of monotherapy with ipilimumab has not been shown in lung cancer patients. Therefore, we want to determine the influences of the combination therapy of nivolumab/pembrolizumab and ipilimumab for the immune response as below.

Curran *et al.* reported that anti-CTLA-4 inhibitor leads to an increase in $CD4^+/CD8^+$ effector T cells in mice (7), and Kitano *et al.* also reported that it induces and enhances the cytotoxic function of $CD4^+$ T cells, in addition to $CD8^+$ T cells, specialty to cancer antigens in melanoma patients (8). Thus, CTLA-4 blockade induces an expansion of CD4 T

Table 1 Clinical trials of ipilimumab for patients with lung cancer

Type of lung cancer	Study code	Study design	Allocation	Estimated enrollment	Combination therapy for ipilimumab
NSCLC	BMS # CA209-632	Phase 1	–	45	Radiation therapy
	–	Phase 1	–	59*	Enoblituzumab (MGA271)
	CheckMate 012	Phase 1	Randomized	472	Nivolumab
	–	Phase 1/2	Non-randomized	98	Nivolumab, nintedanib
	KEYNOTE 021	Phase 1/2	Randomized	267	Pembrolizumab
	TOP 1201 IPI	Phase 2	–	30	Cisplatin/carboplatin, paclitaxel
	NA_00092076	Phase 2	Non-randomized	30	Nivolumab
	–	Phase 2	–	35	Nivolumab
	–	Phase 2	–	50	Nivolumab
	–	Phase 2	Randomized	66	Nivolumab
	CheckMate 592	Phase 2	–	100	Nivolumab
	–	Phase 2	Non-randomized	100	Nivolumab
	–	Phase 2	Randomized	108	Nivolumab
	–	Phase 2	Randomized	169*	Nivolumab, cabozantinib-s-malate
	–	Phase 2	Randomized	184	Nivolumab
	–	Phase 2	Randomized	201	REGN2810 (anti-PD-1 antibody)
	FRACTION-Lung	Phase 2	Randomized	504	Nivolumab
	CheckMate 568	Phase 2	Non-randomized	507	Nivolumab, chemotherapy
	–	Phase 2	Randomized	907*	BMS986205, nivolumab
	Lung MAP	Phase 2/3	Randomized	10,000	Nivolumab
	LONESTAR	Phase 3	Randomized	270*	Nivolumab, local consolidation treatment (surgery and/or radiation)
	Lung MAP sub study	Phase 3	Randomized	350	Nivolumab
	CheckMate 9LA	Phase 3	Randomized	420	Nivolumab, cisplatin/carboplatin, paclitaxel/pemetrexed
	CheckMate 722	Phase 3	Randomized	465	Nivolumab
	KEYNOTE 598	Phase 3	Randomized	548	Pembrolizumab
	CheckMate 816	Phase 3	Randomized	642	Nivolumab
	–	Phase 3	Randomized	690	REGN2810 (anti-PD-1 antibody), platinum-based chemotherapy
	–	Phase 3	Randomized	867	Carboplatin, paclitaxel
	CheckMate 227	Phase 3	Randomized	2,220	Nivolumab
	–	Phase 4	–	1,200	Nivolumab

Table 1 (*continued*)

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Type of lung cancer	Study code	Study design	Allocation	Estimated enrollment	Combination therapy for ipilimumab
SCLC	COSINR	Phase 1	Randomized	80	Nivolumab, either sequential or concurrent SBRT
	–	Phase 1	Non-randomized	90	Nivolumab
	–	Phase 1/2	–	52	Nivolumab, radiation
	–	Phase 2	–	41	Nivolumab, dendritic cell p53 vaccine
	STIMULI	Phase 2	Randomized	260	Nivolumab
	CheckMate 451	Phase 3	Randomized	940	Nivolumab
NSCLC and SCLC	KEYNOTE 011	Phase 1	Non-randomized	84*	Pembrolizumab
	–	Phase 1	–	84*	Nivolumab
	BIOLUMA	Phase 2	Non-randomized	106	Nivolumab
	–	Phase 2	Randomized	120*	Sequential or concurrent SBRT

*, including the number of cases of other carcinomas except lung cancer. NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SBRT, stereotactic body radiotherapy.

cells in addition to engaging specific subsets of exhausted-like CD8 T cells (9). Yi *et al.* (3) demonstrated the increased activation of peripheral blood $CD4^+$ and $CD8^+$ T cells after ipilimumab therapy in lung cancer patients. Their results suggest that ipilimumab affects not only CD8 but also CD4 T cells, especially CD4 T cells expressing the activation markers inducible T-cell co-stimulator (ICOS), human leukocyte antigen-antigen D related (HLA-DR), CTLA-4, and PD-1, among peripheral blood mononuclear cells (PBMCs) at several time points after ipilimumab administration. In addition, blood regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSCs) as well as the PD-1 expression on CD8 T cells were not influenced by ipilimumab treatment, suggesting that ipilimumab treatment itself may not be sufficient but is nevertheless necessary for a therapeutic immune effect in patients with NSCLC. These results also suggest that the stratification of lymphocyte activation was not associated with the overall response to ipilimumab, although it is reported that an increase in $ICOS^+$ T cells was associated with a good prognosis (10).

The reason why the activation of these factors was not associated with a positive OS may be due to the small sample size and other immunotherapeutic effects (3). Therefore, large multicenter trials with a large number of patients are necessary to clarify this association. In addition, no correlation was noted between the degree of PD-L1 expression on the tumor cells and the therapeutic effects of nivolumab in patients with squamous cell carcinoma (11); however, the PD-L1 expression on immune cells locally infiltrating around the tumor was correlated more strongly with the therapeutic effects of nivolumab than the expression on the tumor cells themselves (12).

Yi *et al.* (3) suggested that the correlation between the activation of $CD4^+$/$CD8^+$ T cells in tumor-infiltrating lymphocytes (TILs) and the prolongation of the OS may be the next question that should be explored. Recent understanding of the correlation of TIM-3 and PD-1 antibody in lung cancer immunity, immunological changes and clinical impacts induced by an administration of ipilimumab are what we now want to know, in addition to the changes of PBMCs after surgical resection of cancer.

CTLA-4 is also expressed on the surface of Tregs (2), which are a key factor in ipilimumab treatment. $CD4^+CD25^+$ Tregs suppress the antitumor immune response in animal models (13), and the tumor shrinkage effect depends on the removal of Tregs within the tumor by antibody-dependent cellular cytotoxicity (ADCC) (14). Yi *et al.* (3) clarified that ipilimumab had little or no effect on the frequencies of circulating Tregs, and data on the significance of the frequencies of circulating Tregs are insufficient at present. Further investigations of the response of Tregs in tumor tissues

are necessary to elucidate the antitumor effects of ipilimumab.

Yi *et al.* (3) showed that the activation of $CD8^+$ T cells can be $CD28^+$-dependent, but the CD28 expression did not change in response to chemotherapy or ipilimumab treatment; however, these findings cannot explain the clinical efficacy of all immunotherapeutic agents. In addition, Kitano *et al.* reported that low levels of MDSCs (<14.9%) were associated with a significantly prolonged OS (15), and two patients with high MDSCs (≥15%) showed a poor response in the study of Yi *et al.* (3). The authors (3) partially explain the mechanism underlying the activation and maintenance of peripheral blood/tumor-infiltrating T lymphocytes in early-stage NSCLC patients, but further understanding of the sequential mechanism underlying the clinically-effective immunological responses induced by a combination of immunotherapeutic agents in these patients is needed. In addition, no useful biomarkers have yet been established for estimating the clinical efficacy of ipilimumab treatment in lung cancer patients. As such, further investigations of good biomarkers, including CD28 and MDSCs, are needed, as ipilimumab treatment requires a takes long time to achieve antitumor effects.

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Footnote

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

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