Immunotherapy for the Treatment of NSCLC

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Immunotherapy for the treatment of non–small cell lung cancer (NSCLC) is being actively investigated, with promising results being reported. David P. Carbone, MD, PhD, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA, provided an overview of the immune system in lung cancer.

The immune system uses multiple methods to target foreign bodies, including natural killer cells, granulocytes, and macrophages; antibody-dependent cellular immunity; and cellular immunity. Cellular immunity detects neoantigens presented on class I major histocompatibility complex (MHC) and can specifically recognize oncoproteins with somatic mutations. Peptides derived from proteins degraded by proteasomes are then processed by the Golgi complex and transported to the cell surface bound to a MHC I, where the peptides are presented to cytotoxic T cells. This process is modulated by multiple costimulatory and inhibitory interactions mediated by various receptor-ligand pairs [Pardoll DM. *Nat Rev Cancer* 2012].

Mutations in genes that code for MHC I, TAP, and beta-2 microglobulin have been identified and can result in an inability of the cell to present antigens via MHC I. Although there is surveillance for tumor cells by the immune system, up to 10% of tumors are believed to have mutations that affect MHC I presentation, and 90% to 95% of tumors demonstrate a failure to induce an immune response or failure of T cells to kill the afflicted cell.

Roy S. Herbst, MD, PhD, Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven, Connecticut, USA, discussed emerging therapies that target immune checkpoints. Two recently popular targets are programmed death 1 (PD-1) and PD ligand 1 (PD-L1), which play a role in reducing the anti-tumor response.

The anti-PD-1 agent nivolumab was evaluated in a Phase 1 trial in 129 patients with refractory NSCLC. At the 3 mg/kg dose, the result was a median overall survival (OS) of 14.9 months [Brahmer JR et al. ASCO 2013. Abstract 8030], the 1-year OS rate was 42%, and the 2-year OS rate was 24%. Adverse events affecting the skin and the gastrointestinal, pulmonary, endocrine, and hepatic systems occurred, with 8 patients developing drug-related pneumonitis that resulted in 2 deaths. Recently, two Phase 3 trials of nivolumab were completed, although results have not yet been reported.

Another anti-PD-1 antibody is MK-3475, which was evaluated in patients previously treated for NSCLC [Unpublished]. Dr. Herbst pointed out that the outcome of this trial is similar to what was observed in the trial that evaluated nivolumab. The overall response rate was 24%, and the median OS was 51 weeks. A Phase 3 trial is currently recruiting patients who will be randomly assigned to receive two different doses of MK-3475 or docetaxel.

An antibody targeting PD-L1, MPDL3280A, demonstrated a 23% overall response rate in a Phase 1 trial, with some patients responding early in treatment and others later [Gettinger SN et al. WCLC 2013; Spigel DR et al. ASCO 2013. Abstract 8008]. The vaccine was generally well tolerated, with no dose-limiting toxicities. Interestingly, a response was observed in patients who were smokers and in those with EGFR or KRAS mutations [Gettinger SN et al. WCLC 2013]. Frequent adverse events included fatigue (20%), nausea (14%), decreased appetite (12%), and dyspnea (9%) [Gettinger SN et al. WCLC 2013].

Another anti-PD-L1 vaccine is MEDI4736, which was evaluated in a Phase 1 study and demonstrated a response resulting in stable disease or partial response in some patients [Khleif

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SN et al. ESMO 2013. Abstract 802]. The vaccine was well tolerated with no grade 3 or 4 adverse events or deaths reported. Common adverse events included diarrhea (18%), vomiting (18%), and dizziness (18%).

Martin Reck, MD, PhD, Lungen Clinic Grosshansdorf, Germany, discussed combination immunotherapies. Some reasons for combining immunotherapy with systemic treatment are that cell death can generate tumor antigens, alterations in tumor architecture can increase the penetration of immunotherapy, and combination with immunotherapy may help the systemic therapy to overcome resistance. The combination of immunotherapy with systemic therapy began in the treatment of melanoma with the blockade of CTLA-4 by ipilimumab, and it has now moved into experimental lung cancer treatments.

A Phase 2 study evaluated ipilimumab plus paclitaxel and carboplatin in NSCLC and metastatic SCLC [Lynch TJ et al. *J Clin Oncol* 2012]. According to RECIST criteria, progression-free survival (PFS) was improved in the phased schedule, but not in the concurrent schedule. According to histologic type, patients with squamous cell lung cancer appeared to benefit the most from phased combination therapy [Lynch TJ. *J Clin Oncol* 2012]. The sequential schedule of ipilimumab plus chemotherapy is currently being further evaluated in Phase 3 trials.

Combination therapy with nivolumab and chemotherapy is currently being evaluated in a Phase 1 study [NCT01454102]. Patients will be assigned to 1 of 13 treatment arms: (A) cisplatin plus gemcitabine and nivolumab, (B) cisplatin plus pemetrexed and nivolumab, (C) carboplatin plus paclitaxel and nivolumab, (D) maintenance therapy with bevacizumab plus nivolumab, (E) eribulin plus nivolumab in patients with EGFR mutations, (F) nivolumab monotherapy, (G-J) ipilimumab plus nivolumab, (K) maintenance therapy with nivolumab monotherapy after platinum-doublet chemotherapy without progressive disease, (L) maintenance therapy with nivolumab after platinum-doublet chemotherapy with or without bevacizumab without progressive disease, and (M) nivolumab monotherapy in patients with untreated, asymptomatic brain metastases. The first reported efficacy data were reported for arms A through C [Rizvi NA et al. *J Clin Oncol* 2013. Abstract 8072]. The overall tumor response rate was 33%, 47%, 47%, and 50%, for arms A, B, C at 10 mg/kg nivolumab, and C at 5 mg/kg nivolumab, respectively.

Immunotherapy for the treatment of NSCLC has demonstrated promising results across different methodologies, including targeted antibodies and cancer vaccines. Many agents are currently being evaluated in Phase 2 or 3 clinical trials, with their results much anticipated.

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