Keynote 407: the combination of pembrolizumab and chemotherapy cracks the shell of squamous cell lung cancer

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On September 2018, Paz-Ares *et al*. published at the *New England Journal of Medicine* "Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer". They reported the results of the Keynote-407 (1) study, a multicentric, double-blind, placebo controlled, randomized trial which investigated the role of the addition of pembrolizumab to platinum doublet chemotherapy (carboplatin and paclitaxel or nanoparticle albumin-bound paclitaxel) compared to placebo in first-line setting for patients with advanced squamous non-small-cell lung cancer (SqNSCLC). After induction treatment of 4 cycles, a pembrolizumab/placebo maintenance was indicated up to 35 cycles. Crossover to pembrolizumab monotherapy in case of treatment failure in the placebo-group was allowed. A total of 559 patients were randomized and stratified, among other factors, by PD-L1 tumor proportion score (TPS) negativity (<1%) or positivity (≥1%) determined by immunohistochemistry (IHC, Dako 22C3 antibody). The trial met its primary endpoints, progression-free survival (PFS) and overall survival (OS), as well as its secondary endpoints. In summary, response rate (RR) was superior in the pembrolizumab-combination group (57.9%) compared to placebo group (38.4%) and PD-L1 TPS score did not correlated with the magnitude of radiological

response; median PFS was significantly superior in the pembrolizumab-combination compared to placebo in all prespecified groups (6.4 *vs.* 4.8 months), but patients with higher PD-L1 derived more benefit; finally, median OS was significantly superior in the pembrolizumab group (15.9 *vs.* 11.3 months) regardless of PD-L1% TPS score status. Globally, hazard ratio (HR) for disease progression or death was 0.56 in favor to pembrolizumab. Safety profile was similar between both groups, but dose reductions in chemotherapy agents and discontinuation of any or all treatment components was numerically higher in the pembrolizumab arm. Immune-related adverse event (AE) were present in 28.8% in the pembrolizumab arm, as expected, more prevalent than in placebo arm (3.2%).

Since SqNSCLC displays a different proteogenomic and less targetable oncogenic landscape (2) compared to lung adenocarcinoma (LUAD) and lacks effective approaches of systemic treatment, the discovery of new therapeutic options in this setting has become an urgent need for patients and physicians. Recent results have demonstrated efficacy in advanced NSCLC regardless histology using immune checkpoint inhibitors (ICIs): as a first-line monotherapy in tumors with >50% expression of PD-L1 and as a second-line therapy regardless PD-L1

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status, paving the way for further explorations of cancer immunotherapy in SqNSCLC.

ICI-chemotherapy combination for SqNSCLC is a game-changer that has broaden and revitalized the clinical spectrum of possibilities for thoracic oncologists. The robust positive results of Keynote-407 have led to both FDA (3) and EMA (4) approvals of pembrolizumab combined with carboplatin and paclitaxel/nab-paclitaxel for frontline therapy in advanced SqNSCLC, with the support of scientific societies in USA (5,6) and Europe (7).

Of note, cost-effectiveness of chemotherapy-ICI is under intense debate for health systems in developed countries (i.e., USA, China) (8). For developing or low-income countries, the cost of the treatment is simply unaffordable for a majority of patients.

ICI-chemotherapy combination rationale relays on the potential effects of chemotherapy (particularly paclitaxel) in upregulating the innate immune response (9,10) (permeability for granzyme B, secretion of cytokines by macrophages, and activation of dendritic cells (DCs), natural killers and T-cells) and remodeling of tumor microenvironment (TME) by modulation of Tregs or myeloid-derived suppressor cells (MDSC) (11). All these changes are claimed to synergize with ICI, with the result of clinical survival benefit for a yet to be characterized group of patients.

Clinical factors such as tumor burden, cancer-related symptoms, comorbidities that contraindicate ICI and tumor characteristics such as PD-L1 score can determine the clinical decision of frontline monotherapy treatment (first-line chemotherapy or immunotherapy). Based on the accumulated evidence, no biomarker has been able to replace the use of PD-L1. Although an arbitrary cut-off of 50% for high expression has been set for prescribing monotherapy with pembrolizumab in first-line, new data based on retrospective reports yield interesting information on how pembrolizumab clinical outcomes are optimized in those patients who have a PD-L1 TPS of ≥75% to 90% (12). Based on this information PD-L1 expression should be treated as a continuous variable in which increasingly higher expression levels identify a population with better chances of clinical benefit. On the other hand, there is still a significant proportion of patients with high expression of PD-L1 that do not respond to ICI, reflecting that a single biomarker cannot predict immunotherapy outcomes. New evidence has shown that glycosylation of PD-L1 may shield the PD-L1 antibody binding, hence skewing the PD-L1 score and undermining clinical decisions (13). For this situation, de-glycosylation of PD-L1 of NSCLC biopsies before ICI may trace back more reliable PD-L1 signal retrieval and theoretically redirect treatment decisions. Other prognostic biomarkers such as combined index score of blood markers such as lactate dehydrogenase (LDH) levels and absolute neutrophil and lymphocyte counts have shown positive significant correlation with clinical outcomes with ICI in advanced NSCLC (14). Tumor mutational burden (TMB), another predictive biomarker to response to ICI have shown contradictory results (15-17) and given its immature definition and non-routine use in clinical practice (18) still needs validation in prospective studies.

Although ICI-chemotherapy in first-line setting has shown to improve the survival outcomes with clinical benefit and acceptable toxicity profile, the majority of patients (around 70–80%) eventually progress and die. For most cases who experience disease progression a question is raised: may the use of this combo condition the loss of a suitable second-line therapy? Until now second-line therapy consisted in docetaxel or more recently anti-PD-1/PD-L1. Keynote 407 proposed combo schedule used in first-line exhausts both options upfront.

Future perspectives for clinical trial designs should incorporate new combination options for advanced squamous NSCLC that could lead to more effective clinical outcomes. Intriguing published data suggest a potential synergism of gemcitabine with anti-PD-1 antibodies (19) supporting the interest of combining platinum-gemcitabine-anti-PD-1/PD-L1 in first-line in other thoracic malignancies such as pleural mesothelioma.

Necitumumab, an epidermal growth factor inhibitor that combined with platinum-based chemotherapy doublet showed modest but positive survival results in first-line squamous NSCLC (20) could be an interesting option for future ICI-chemotherapy combination clinical trials in squamous NSCLC, especially if it associates extensive predictive biomarker research. At present, a clinical trial investigating the role of avelumab (an anti PD-L1 inhibitor) in combination with cetuximab and chemotherapy (cisplatin and gemcitabine) for patients with advanced SqNSCLC is underway (NCT03717155).

New ways to combine chemotherapy and ICI are being explored in the ongoing INSIGNA trial (NCT03793179): patients with non-squamous advanced NSCLC are randomized to receive pembrolizumab alone as a first-line treatment, followed by platinum doublet with or without pembrolizumab after disease progression. Interestingly, CheckMate-9LA study (NCT03215706) explores

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the potential of inducing fast tumor responses with 2 cycles of nivolumab-ipilimumab plus platinum-based chemotherapy followed by a maintained course of anti-PD-1 monotherapy. Recent press release of the results of CheckMate-9LA trial reported pre-specified interim analysis superiority of OS for the experimental arm and these data will be presented at the upcoming oncology meetings.

Besides anti-PD-1/PD-L1 inhibition, other strategies including vaccines against tumor associated antigens (TAA) or co-inhibitory signaling blockade are under clinical investigation (NCT02654587) for patients with NSCLC and progressive disease to prior ICI. Other ICIs different from PD-1/PD-L1 are on early phase of clinical investigation. Lymphocyte-activating gene-3 (LAG-3) is a transmembrane protein with affinity to bind major histocompatibility complex II (MHC-II) molecules. LAG-3 assumes an immune suppressive role by binding to MHC-II and maintaining negative regulation of T-cell activity and consequently immune evasion by tumor cells. High expression of LAG-3 was correlated with poor response to anti-PD-1 blockade (21). Clinical trials with LAG-3 inhibitors in solid and hematologic malignancies (22) and combination of dual blockade of PD-1 axis and LAG-3 monoclonal antibodies (NCT03156114) for patients with failure to previous ICI treatment are ongoing.

OX40, a co-stimulatory receptor related to T cell priming and proliferation highly expressed by activated T cells, B cells, DCs, neutrophils and natural killer cells (NKs). OX40 and OX40 ligand (OX40L) are negatively correlated with PD-1/PD-L1 expression. OX40/OX40L agonist with or without PD-1/PD-L1 inhibitors or tyrosine kinase inhibitors combination is still on early clinical trials development in solid tumors (23). T-cell immunoglobulin and mucin domain-3 (TIM3) a transmembrane protein co-stimulatory signal present in T-cells which binds with galectin-9 present in tumor cells resulting in immune suppressive effects in TME: T-helper apoptosis, suppressed DC response, downregulation of NKs, and reduced levels of TNF-α and IFN-γ (24). According to preclinical data, TIM3 inhibition may restore exhausted CD8 cell functions (25); and dual blockade of PD-1/PD-L1 axis and TIM3 may lead to better response outcomes compared to exclusive TIM3 inhibition. Phase I clinical trials investigating the combination anti-TIM3 antibodies and anti-PD-1/PD-L1 strategies for solid tumors are underway (NCT02817633, NCT03099109, NCT03066648).

In conclusion, Keynote 407 confirms that ICI-chemotherapy combinations represent an innovative and long-awaited alternative for the frontline treatment of advanced SqNSCLC, but we strongly believe that its use in clinical practice should be customized for each individual case based on clinical characteristics, tumor features and available predictive biomarkers. Intense research on better predictive tools and newer combinations hold the promise of potentially curative treatments for advanced SqNSCLC patients.

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Footnote

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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