

Article type: **Editorial (Position Paper)**

Position of an international panel of lung cancer experts on the decision for expansion of approval for pembrolizumab in advanced non-small cell lung cancer with a PD-L1 expression level of $\geq 1\%$ by the U.S. Food and Drug Administration.

Keywords: KEYNOTE-042, pembrolizumab, non-small cell lung cancer, PD-L1 $\geq 1\%$

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Immune-checkpoint inhibitors (ICIs) have transformed the therapeutic landscape of advanced non-small cell lung cancer (NSCLC) and now represent the new first-line standard of care (SoC), either in combination with platinum-based chemotherapy, achieving a survival benefit independent of histology and programmed death ligand-1 (PD-L1) expression levels [1–4], or as monotherapy in patients whose tumors express PD-L1 in $\geq 50\%$ of the tumor cells [5, 6]. Recently, the phase III KEYNOTE 042 trial reported that pembrolizumab monotherapy (200 mg every 3 weeks for up to 35 cycles) in patients with a PD-L1 tumor proportion score (TPS) of at least 1% significantly improved overall survival (OS) compared to investigators' choice of platinum-based chemotherapy (16.7 months versus 12.1 months, hazard ratio, HR 0.81; 95% CI: 0.71, 0.93; $p=0.0018$) [7]. Based on these results, the U.S Food and Drug Administration (FDA) expanded the originally approved indication of pembrolizumab in the first-line setting to all patients with PD-L1 TPS $\geq 1\%$, without *EGFR* or *ALK* aberrations [7]. The European Medicines Agency (EMA) has not made any definitive recommendation. With this statement, we would like to raise our concerns regarding the possibility of a broad adoption of pembrolizumab monotherapy as standard treatment for all patients with PD-L1 TPS $\geq 1\%$.

In the KEYNOTE 042 trial [7], 1,274 advanced NSCLC patients with tumors with PD-L1 $\geq 1\%$ were enrolled, and randomization was stratified by PD-L1 expression level ($\geq 50\%$ vs. 1–49%). When the study was designed in 2014, the primary endpoint was OS in the subgroup of patients with PD-L1 $\geq 50\%$. In 2015, after enrollment of 662 patients, based on the OS benefit of

second-line pembrolizumab in PD-L1 $\geq 1\%$ tumors in the KEYNOTE 010 trial [8], the protocol was amended and OS in patients with TPS $\geq 1\%$ became a co-primary endpoint. Later, in April 2017, and after enrollment was completed, a new amendment was introduced and the final co-primary endpoints were OS in patients with PD-L1 TPS of $\geq 50\%$, $\geq 20\%$, and $\geq 1\%$ in the intent-to-treat (ITT) population [7]. Pembrolizumab achieved a longer OS compared to chemotherapy in all three PD-L1 populations, without improvement in the secondary endpoints of progression-free survival and objective response rate [7]. Of note, nearly half (46.6%) of the patients enrolled had a TPS of $\geq 50\%$, which represents a potential bias for the over-performing efficacy of pembrolizumab in the ITT population. In the pre-defined OS analysis by PD-L1 expression, a survival benefit from pembrolizumab was not seen in the PD-L1 1-49% subgroup (median OS 13.4 vs. 12.1 months, HR 0.92, 95% CI 0.77-1.11), [7]. This suggests that the observed benefit with pembrolizumab is largely driven by the “high PD-L1 expression” group, in which the HR for OS benefit mirrors that from a similar population in the KEYNOTE 024 trial, (0.69 and 0.63, respectively), [6, 7].

Another important concern in KEYNOTE 042 is that crossover from the chemotherapy arm to pembrolizumab upon progression was not allowed per protocol. The trial enrolled patients from December 9th 2014 to March 6th 2017, during which at least four large randomized clinical trials [8–11] had already reported a survival benefit with second-line ICIs, including the KEYNOTE 010 trial published in December 19th 2015 [8]. Interestingly, crossover was allowed in the KEYNOTE 024 trial, although recruitment started in May 2012 [5]. Despite this evidence, only 20% of patients in the KEYNOTE 042 trial received an approved second-line immunotherapy [7]. Crossover is desirable in settings where a drug has already proven benefit in a subsequent line of therapy and attempts are being made to advance it to an earlier line [12], such as the KEYNOTE 042 trial, which tested a similar question: pembrolizumab upfront or as a sequential strategy for PD-L1 TPS $\geq 1\%$ tumors. Therefore, the treatment received by patients in the control arm of KEYNOTE 042 should be considered suboptimal by current standards.

One of the major concerns about the efficacy of first-line immunotherapy in patients not selected by high PD-L1 expression, is that ICIs may underperform compared to chemotherapy,

as evidenced in the CHECKMATE 026 trial with nivolumab [13]. In KEYNOTE 042, analysis of OS data clearly shows that the effect of pembrolizumab across the ITT population is heterogeneous. In the overall population (PD-L1 \geq 1%) survival curves cross approximately seven months after treatment initiation, with chemotherapy performing better than pembrolizumab during the first six months from randomization. This pattern is also repeated for the subgroup of patients with PD-L1 expression of 1-49% [7], suggesting that a substantial number of patients progress rapidly and die within the first six months of treatment without obtaining any meaningful benefit from immunotherapy. A similar observation has been reported in the phase III MYSTIC trial. In MYSTIC, first-line durvalumab did not improve OS compared to standard chemotherapy in patients with NSCLC and $>$ 25% PD-L1 expression. The OS curves also crossed beyond six months from randomization [14]. These data also highlight the potential risk of hyper-progressive disease with ICIs in a largely unselected patient population. Notably, this risk has not been observed among patients treated with the combination of ICIs and chemotherapy [2, 4].

Two randomized phase III trials in the first-line setting have reported survival benefit with the combination of platinum-based chemotherapy and pembrolizumab compared to chemotherapy alone in patients with non-squamous (KEYNOTE 189) [2, 3] and squamous (KEYNOTE 407) [4] histology, regardless of PD-L1 status, including the subset of tumors with PD-L1 expression of 1-49%. In both trials of chemo-immunotherapy combinations, the OS curves separate early and the corresponding HRs for survival are similar independent of histology (non-squamous: HR 0.62 [0.42-0.92] and squamous: HR 0.57 [0.36-0.90]) [3, 4]. Thus, in patients whose tumors have a PD-L1 TPS of 1-49%, the combination of chemotherapy and immunotherapy should be the standard of care.

Some clinicians may argue that pembrolizumab monotherapy could represent an effective and better-tolerated alternative to the more toxic chemo-immunotherapy combination, mainly in the frail population, such as elderly patients or patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2. However, KEYNOTE 042 only enrolled patients suitable for chemotherapy, with an ECOG PS 0-1 and median age 63 years [7]. A recent pooled

analysis reported survival benefit with pembrolizumab compared with chemotherapy in patients aged ≥ 75 years [15]. Yet, only a randomized clinical trial may define the real benefit in these specific populations.

From a regulatory aspect it is likely that the recent FDA approval was given on the basis of comparable efficacy and better tolerability of pembrolizumab compared to chemotherapy, especially for the PD-L1 1-49% subgroup. Nevertheless, new drug approvals, based only on p-values, without consideration to the dynamic evolution of survival curves, are challenging. In the era of personalized medicine, grouping all patients together based on a solitary -and rather imperfect- biomarker, without attempting to identify confounding determinants of efficacy, may represent a step back in our efforts to implement precision oncology. As an illustrative example, crossing survival curves in the historical IPASS study [16] prompted further investigation to identify potential determinants of efficacy of epidermal growth factor receptor (EGFR) inhibitors, leading to the identification of activating *EGFR* mutations as a robust predictive biomarker.

Finally, financial toxicity is an important issue with novel anticancer therapies. To preserve the sustainability of our health care systems, it is important to apply robust biomarkers for proper patient selection to achieve cost-effective strategies. In this sense, the Magnitude of Clinical Benefit Scale (MCBS), developed by the European Society for Medical Oncology (ESMO), is a useful tool for the evaluation of new anti-cancer treatments. According to this scale (Form 2A, MCBS version 1.1, [17]), pembrolizumab in the ITT population of the KEYNOTE 042 trial receives a score of 2, which translates into a treatment without substantial clinical benefit, unlikely to affect clinical practice. On the contrary, in patients with PD-L1 $\geq 50\%$ from the KEYNOTE 024 trial, pembrolizumab receives a score of 5, illustrating the difference on the magnitude of clinical benefit between the two trials and the value of a robust biomarker.

In conclusion, despite the statistically positive results of the KEYNOTE 042 trial, we are concerned that pembrolizumab monotherapy may not represent the best treatment strategy for patients with tumor PD-L1 of 1-49%, as they may be harmed by rapid progression on treatment. Until trials can further guide us to better identify which patients can benefit from single-agent

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