

# Five-year overall survival of pembrolizumab in advanced non-small cell lung cancer: another step from care to cure?

## Paolo Bironzo, Francesco Passiglia, Silvia Novello

Department of Oncology, University of Torino, AOU S. Luigi Gonzaga, Orbassano, Italy

Correspondence to: Francesco Passiglia. Department of Oncology, University of Torino, AOU S. Luigi Gonzaga, Regione Gonzole 10, 10043 Orbassano (TO), Italy. Email: francesco.passiglia@unito.it.

Provenance: This is an invited article commissioned by the Section Editor Dr. Song Xu (Department of Lung Cancer Surgery, Tianjin Medical University General Hospital, Tianjin Key Laboratory of Lung Cancer Metastasis and Tumor Microenvironment, Lung Cancer Institute, Tianjin, China).

Comment on: Garon EB, Hellmann MD, Rizvi NA, et al. Five-Year Overall Survival for Patients With Advanced Non-Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. J Clin Oncol 2019. [Epub ahead of print].

Submitted Aug 14, 2019. Accepted for publication Aug 22, 2019. doi: 10.21037/atm.2019.08.91

View this article at: http://dx.doi.org/10.21037/atm.2019.08.91

Immune checkpoint inhibitors (ICIs) directed against programmed cell death protein 1(PD-1) and its ligand (PD-L1) have rapidly changed non-small cell lung cancer (NSCLC) treatment paradigms, leading to unprecedented results, both in metastatic and locally advanced disease. The idea that the immune system could be not just a guardian, but also an active soldier against tumour has been long perceived, since the use of vaccines in the 19th century (1). Currently available monoclonal antibodies are able to remove inhibitory signals from immune system, especially cytotoxic T-cells. While anti cytotoxic T-lymphocyte antigen A (CTLA-4) directed drugs mainly act during T-cell priming, anti PD-1/PD-L1 agents bind their therapeutic targets at the tumour site. The promise of such approach consists of re-educating patients own immune system to react against cancer cells for a long time. The recent publication of the 5-year overall survival (OS) results from the KEYNOTE-001 trial by Garon and colleagues on the Journal of Clinical Oncology suggests that such ambitious goal may be really reached, at least for some patients (2). This study was a multi-cohort phase I trial enrolling patients with advanced solid tumours, including NSCLC. Among them, the treatment-naïve cohort enrolled patients who had not received previous therapy (except for adjuvant chemotherapy at least 1 year before enrolment), without epidermal growth factor receptor (EGFR) activating mutations or anaplastic lymphoma kinase (ALK) rearrangements, and a PD-L1 tumour proportion score

(TPS) of 1% or more detected with 22C3 clone. The other cohorts included advanced NSCLC patients progressing after at least one line of therapy for their metastatic disease. The main exclusion criteria were: central nervous system metastases (unless clinically stable for at least 4 weeks after local treatment) and autoimmune disease requiring systemic corticosteroids and/or immunosuppressive drugs. Initially, Pembrolizumab was administered intravenously at a dose of 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks. In April 2006, a protocol amendment shifted patients to 200 mg every 3 weeks flat dose schedule and allowed patients, who achieved disease control after 24 months of treatment, to discontinue pembrolizumab, resuming treatment in case of disease recurrence/progression. The study primary end-point was objective response rate (ORR) by independent central review using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Investigator-assessed ORR using immune related response criteria (irRECIST), OS and duration of response (DOR) were secondary end-points. The study enrolled 550 patients, 449 of them previously treated and approximately 80% with non-squamous histology. In the treatment naïve cohort, 60 patients (59%) were male, 57 (56%) with ECOG PS of 1, and most (90, 89%) current or former smokers. When looking at pre-treated patients, 229 (51%) were male, 299 (67%) had ECOG PS of 1, 324 (72%) current or former smokers, and 82 patients (18%) had EGFR mutations or ALK rearrangements. At a median follow-up of 60.6 months

(range, 51.8–77.9), the median treatment duration was 3.3 months (range, 1 day to 75.9 months), with 100 patients still alive. The median OS was 22.3 months (95% CI, 17.1-32.3) for previously untreated and 10.5 months (95% CI, 8.6–13.2) for pre-treated patients, with an estimated 5 years OS of 23.2% and 15.5%, respectively. The ORR by irRECIST was 41.6% (95% CI, 31.9-51.8) and 22.9% (95% CI, 19.1-27.1) for treatment-naïve and previously treated patients, respectively, while a lower percentage was evident using RECIST 1.1 (24.8% and 18.0%, respectively). Notably, the median time to response was 2.1 months in all groups and the median DOR was 16.8 months in untreated patients (range, 2.1-55.7) and 38.9 months among the others (range, 1.0–71.8). When stratifying patients using PD-L1 expression levels, a TPS of 50% or greater was associated with increased OS so that the median OS was 35.4 months (n=27; 95% CI, 20.3-63.5) in treatment naïve patients, with a 5-year rate of 29.6% as compared to 19.5 months (n=52; 95% CI, 10.7-26.3) and 15.7% in those with TPS between 1% and 49%. Using the same cut-off for the other cohorts, the median OS was 15.4 months (n=138; 95% CI, 10.6-18.8) for high PD-L1 patients as compared to 8.5 (n=168; 95% CI, 6.0-12.6) and 8.6 months (n=90; 95% CI, 5.5-10.6) for those with TPS of 1% to 49% and less than 1%, respectively. In these subgroups the 5-year OS rate were 25.0%, 12.6%, and 3.5%, respectively.

These long-term results are in line with those reported for another anti-PD-1 agent, nivolumab, in the phase I CA209-003 trial (3). In this study, among the 129 pretreated metastatic NSCLC patients, the ORR (by RECIST 1.0) was 17.1%, with a DCR of 41.9% and a median DOR of 19.1 months (8.7 to not estimable). With a minimum follow-up of 58.3 months, the median OS was 9.9 months (95% CI, 7.8–12.4), while the 5-year survival rate was 15.6% (95% CI, 9.6–22.9). The consistency of survival outcomes among these two different studies suggests, once again, that phase I clinical trials provide reliable efficacy results, which should be carefully considered in the further steps of clinical investigation.

However, how can we put these data in the current treatment scenario? Starting from the publication of the KEYNOTE-024 trial, demonstrating a clear survival benefit of pembrolizumab as compared to platinum doublets in treatment naïve advanced NSCLC patients with PD-L1 TPS of 50% or more (4), and then moving to KEYNOTE-189 and KEYNOTE-407 studies, showing that upfront immune-chemotherapy combination was superior to chemotherapy alone (5,6), regardless of tumour

histotype and PD-L1 expression levels, ICIs are being moved in the front-line setting worldwide. Moreover, the recent approvals by the U.S. Food and Drug Administration (FDA) of pembrolizumab monotherapy in treatment naïve advanced NSCLC patients with a PD-L1 TPS of 1% or more based on KEYNOTE-042 results (7), and of atezolizumab (anti-PD-L1 mAb) in combination with carboplatin, paclitaxel and bevacizumab irrespective of PD-L1 levels in non-squamous histology (8), further complicated the already crowded landscape. At the first sight, updated results from KEYNOTE-001 seems of minor interest and look just as another piece of the mosaic. It appears obvious that the effects of single agent ICIs could not be straightforward transposed in naïve patients receiving combination treatments (accounting for the majority of patients, nowadays) as the effects of cytotoxic drugs on both tumour cells and immune system must be taken into account. However, some hints from this publication could enlarge our current knowledge. First, this update clearly demonstrates that using ICIs during advanced NSCLC patient treatment journey lead to unprecedented survivals, at least in non-oncogene-addicted population. The evidence that 15% of previously treated patients, and about 30% of naive with PD-L1 TPS of 50% or greater, could survive at 5 years from first ICI dose administration is something judged impossible few years ago. At the same time, also safety doesn't seem an issue, even as time goes on. With this long follow-up, only 13% of grade 3 to 5 treatmentrelated adverse events (trAEs) have been reported, requiring treatment discontinuation only in 31 patients (6%), six of them with ongoing response. Focusing on immune-related AEs (irAEs), the incidence was low (17%, with only 4% of grade 3 to 5), with no difference at 3 or 5 years of follow-up. Interestingly, as already reported by Topalian and colleagues for nivolumab (3), the occurrence of irAEs is a strong predictive factor of disease response and survival benefit even with pembrolizumab. These information are of great value in supporting daily clinical practice, as oncologists can safely decide to stop treatment when irAEs occur, even in those patients who are gaining benefit from ICIs. This marks a real paradigm shift as compared to the classic approach with chemotherapy. Third, this study confirms that PD-L1 expression, even if still far from being a sturdy predictor of efficacy, remains a reliable stratification factor. Unfortunately, no other clinical, laboratory, or molecular biomarkers have been reported by the Authors. Recent literature suggests that simple clinical variables such as ECOG PS, the presence of liver or bone metastases (3), or Lung Immune

Prognostic Index score (9) as well as (*STK11/LKB1* genes mutations or other rare oncogenic alterations) (10,11) could further dissect this apparently homogenous group. Moreover, such data could be of priceless value especially in patients achieving the longest benefit from ICIs.

In conclusion, the updated results of KEYNOTE-001 confirm long-term efficacy of single agent ICI in pre-treated patients with metastatic disease, and show for the first time unprecedent 5-year survival associated to the upfront use of pembrolizumab in high PD-L1 expressors, laying another stone on the road from care to cure for advanced NSCLC patients.

#### **Acknowledgments**

None.

#### **Footnote**

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

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.

### References

- Hall SS. A common in the blood: life, death, and the immune system. 1st edition. New York: Henry Holt & Co., 1997.
- Garon EB, Hellmann MD, Rizvi NA, et al. Five-Year Overall Survival for Patients With Advanced Non-Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. J Clin Oncol 2019. [Epub ahead of print].
- 3. Topalian SL, Hodi FS, Brahmer JR, et al. Five-Year

Cite this article as: Bironzo P, Passiglia F, Novello S. Five-year overall survival of pembrolizumab in advanced non-small cell lung cancer: another step from care to cure? Ann Transl Med 2019;7(Suppl 6):S212. doi: 10.21037/atm.2019.08.91

- Survival and Correlates Among Patients With Advanced Melanoma, Renal Cell Carcinoma, or Non-Small Cell Lung Cancer Treated With Nivolumab. JAMA Oncol 2019. [Epub ahead of print].
- Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.
- Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:2078-92.
- Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med 2018;379:2040-51.
- Mok TS, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 2019;393:1819-30.
- Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med 2018;378:2288-301.
- Mezquita L, Auclin E, Ferrara R, et al. Association of the Lung Immune Prognostic Index With Immune Checkpoint Inhibitor Outcomes in Patients With Advanced Non-Small Cell Lung Cancer. JAMA Oncol 2018;4:351-7.
- Skoulidis F, Goldberg ME, Greenawalt DM, et al. STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Lung Adenocarcinoma. Cancer Discov 2018;8:822-35.
- Mazières J, Drilon A, Lusque A, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. Ann Oncol 2019. [Epub ahead of print].