



Long-term efficacy of immune checkpoint inhibitors in advanced NSCLC: challenges and opportunities – a commentary of the 3-year follow-up of the KEYNOTE-001 trial

Alessandro Russo^{1,2}, Katherine A. Scilla¹, Christian Rolfo¹

¹University of Maryland Medical Center Greenebaum Comprehensive Cancer Center, Baltimore, MD, USA; ²Medical Oncology Unit A.O. Papardo & Department of Human Pathology, University of Messina, Messina, Italy

Correspondence to: Prof. Dr. Christian Rolfo, MD, PhD, MBA, Dr.h.c. Director of Thoracic Medical Oncology and Early Clinical Trials at University of Maryland Medical Center, Greenebaum Comprehensive Cancer Center, 22 S Greene Street Rm. N9E08, Baltimore, MD 21201, USA. Email: christian.rolfo@umm.edu.

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Treatment of advanced non-small cell lung cancer (NSCLC) has evolved considerably over the past two decades, with improved survival outcomes in a significant proportion of patients due to the development of new effective systemic therapies. The refinement of the therapeutic approach with a molecularly-based strategy has led to unprecedented results in selected patient populations harboring actionable oncogene drivers (~20–25% of all NSCLC patients). However, until recently, the survival of non-oncogene-addicted NSCLC patients was only modestly affected by novel anticancer therapies, with median survival ranging from ~10–12 months in squamous NSCLC (1,2) and ~13–15 months in non-squamous NSCLC (3,4) in the pre-immunotherapy era. Over the last few years, the development of immunotherapy has revolutionized lung cancer treatment (5), with four different immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis now approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for multiple clinical indications. Several biomarkers have been studied to help determine which patients will derive the most therapeutic benefit from anti-PD-1/anti-PD-L1 immunotherapy. However, predictive biomarkers for optimal patient selection are lacking, with PD-L1 expression being the main clinically applicable test at this time. A pooled analysis of the randomized phase III trials evaluating ICIs in pre-treated NSCLC showed that patients

with PD-L1 positive tumors (PD-L1 tumor staining of $\geq 1\%$) have significantly higher overall response rate (ORR) compared to PD-L1 negative tumors, suggesting that PD-L1 overexpression is a predictive biomarker (6). However, PD-L1 immunohistochemical expression is an imperfect biomarker. Among those with positive PD-L1 expression, a significant proportion of NSCLC patients do not benefit from ICIs, even when using more stringent cut-off values (ORR ~45% in patients with PD-L1 expression $\geq 50\%$) (7-9). Conversely, NSCLC patients with negative PD-L1 expression may also experience significant benefit from these agents (10-12).

Several questions regarding ICIs remain unanswered, including optimal treatment duration, identification of reliable predictive biomarkers, and long-term safety data among others.

In the *Lancet Respiratory Medicine*, Leighl *et al.* reported the 3-year follow-up of the phase I multicohort study KEYNOTE-001 (13), which evaluated safety and efficacy of pembrolizumab at different doses and schedules in advanced NSCLC in both pre-treated (n=449) and treatment-naïve (n=101) patients, as well as sought to define and validate PD-L1 expression as predictive biomarker. In the original report, after a median follow-up of 10.9 months (range, 5.2–27.5), pembrolizumab was associated with relative favorable safety profile [treatment-related adverse events (AEs) of grade 3 or more reported in 9.5% of the patients], an ORR of 19.4%, a

median progression free survival (PFS) of 3.7 months, and a median overall survival (OS) of 12.0 months in the overall population. A tumor proportion score (TPS) of PD-L1 $\geq 50\%$ was associated with a higher ORR and longer PFS and OS than a TPS $< 50\%$ in both previously untreated patients and previously treated patients (8). In the updated analysis (median follow-up of 34.5 months, IQR 32.2–37.4), Leigh *et al.* further provide evidence of efficacy of this agent in NSCLC in both pretreated and treatment-naïve patients with an ORR of 23% and 41% and median OS of 10.5 months (95% CI, 8.6–13.2) and 22.3 months (95% CI, 17.1–31.5), respectively. The proportion of patients alive at 24 months and 36 months were 49.0% and 26.4% for treatment-naïve patients and 29.9% and 19.0% for previously treated patients (13). Data on pretreated patients are in line with previous reports (14–16), suggesting that approximately 15–20% of patients might derive long-term benefit with ICIs. As expected, PD-L1 TPS $\geq 50\%$ was predictive of higher long-term benefit in both treatment-naïve (66.7% *vs.* 37.3% 24-month rate and 25.2% *vs.* NR 36-month rate for TPS $\geq 50\%$ and 1–49%, respectively) and pretreated patients (38.6% *vs.* 26.2% *vs.* 23.8% 24-month rate and 29.7% *vs.* 13.5% *vs.* 8.5% 36-month rate for TPS $\geq 50\%$, 1–49% and $< 1\%$, respectively) (13).

The results of this updated analysis are noteworthy for several reasons. First, the authors demonstrated no evidence of cumulative immune-related toxicity or late-onset grade 3–5 toxicity with longer exposure to pembrolizumab. This is similar to that reported in other studies with the same compound in NSCLC (7,15) or with other anti-PD-1/PD-L1 agents in NSCLC (16–18), with most grade ≥ 3 treatment-related AEs observed within the first year of treatment (13). In addition, the clinicopathological characteristics of long-term survivors described in this report may help to identify patients deriving more benefit from ICIs.

The majority of patients who completed 2 years or more of pembrolizumab at data cutoff (48 patients) had a partial response (PR) or complete response (CR) as the best overall response (80% and 89% in treatment-naïve and pre-treated patients, respectively) (13). In addition, these results are in line with previous reports (95% of the patients who completed the planned 2 years of treatment in the KEYNOTE-010 and 75% of the 5-year survivors in the CA-209-003 had a PR or CR) (15,17) suggesting that patients experiencing durable response during ICIs derive the greatest benefit.

A possible differential effect of histology on long-term efficacy of ICIs has been suggested in this study, with a

higher proportion of squamous NSCLC among previously treated patients who were 3-year survivors (13). These data are in contrast with the results of the POPLAR study reporting a higher benefit among non-squamous NSCLCs (14) and with those of CA-209-003, CheckMate-017 and CheckMate-057 that did not find any significant correlation between histology and long-term benefit (15–17). Further studies must be conducted in order to clarify this specific issue.

An important emerging clinical question is whether there is optimal treatment duration of immune checkpoint blockade, as well as if ICIs can be resumed on disease progression after discontinuation. Of note, KEYNOTE-001 after an amendment allowed the discontinuation of treatment after 24 months in patients with response or stable disease or after 6 months in patients with CR and allowed for re-initiation of pembrolizumab upon disease progression. However, among 48 patients who completed 2 years of pembrolizumab treatment, 73% chose to continue study treatment and no information regarding subsequent progression or pembrolizumab re-initiation was provided (13). Some clinical data on this important issue are emerging from the KEYNOTE-010. Among 79 patients who completed the planned 35 courses of pembrolizumab, most had an ongoing response after a median follow-up of 43.4 months (35.7–49.8), with only 25 patients (32%) experiencing progressive disease (PD). Of these progressing patients, 14 were re-challenged with the same agent, reporting an ORR of 43% and a disease control rate (DCR) of 79% (15). These data suggest that most of the patients discontinuing treatment after 2 years of pembrolizumab continue to derive benefit without the need of further treatment and that rechallenge with ICIs is feasible after PD after an immunotherapy-free interval. Similar results have been demonstrated in the phase 1 CA 209-003 study with nivolumab (17), albeit the limited number of patients included in this analysis does not allow drawing definitive conclusions. However, the definition of optimal immunotherapy treatment duration is far from clear. In the CheckMate-153 trial, randomization of advanced NSCLC patients after 1 year of nivolumab to continuous treatment versus discontinuation was superior in terms of PFS (HR 0.42) independently of tumor response (CR/PR *vs.* SD), with a favorable trend in OS (HR 0.63). After a median follow-up time post-randomization of 14.9 months, 49% of the patients in the experimental arm progressed and 79% were retreated with nivolumab, with a median duration of treatment of 3.8 months (19). In

addition, a recent retrospective study of 185 patients with advanced melanoma who electively discontinued anti-PD-1 therapy in the absence of disease progression or treatment-limiting toxicity, after a median time on treatment of 12 months (range, 0.7–43) and a median follow-up of 18 months showed that 78% of patients remained progression free. However, the response to treatment in this study was significantly associated with outcome, since subsequent PD was less frequent in patients with CR (14%) compared to patients with PR (32%) and SD (50%). In addition, 6 out of 19 (32%) patients who were retreated with an anti-PD-1 antibody at the time of PD achieved a new anti-tumor response (20). Furthermore, a retrospective study evaluated the outcome of 13 patients with different solid tumors who discontinued ICIs in phase I trials as per protocol without PD. The median time free-treatment after ICI discontinuation was 12.6 months (range, 4–39.7), with 8 patients re-treated upon disease progression. Rechallenge with an ICI was associated with inferior ORR (25% *vs.* 85%), and shorter PFS (12.9 *vs.* 24.4 months) compared to initial treatment course (21).

Data emerging from these studies suggest that selected patients might electively discontinue treatment with ICIs, although the optimal treatment duration and the characteristics of patients benefiting from this strategy are relatively unknown and should be prospectively evaluated in a randomized clinical trial. Until then, treatment with ICIs in NSCLC could be continued according to the approval

label of each drug, taking in consideration the possible increase of drug and cost toxicities.

Another important issue analyzed in the paper of Leigh *et al.* is the impact of radiotherapy on outcome of patients treated with ICIs. An initial report of NSCLC patients treated in the KEYNOTE 001 trial at a single institution (University of California, Los Angeles, CA, USA) suggested that previous treatment with radiotherapy resulted in longer PFS and OS with pembrolizumab compared with patients who did not have previous radiotherapy, with an acceptable safety profile (22). These results suggested a possible positive interaction between the two treatment modalities, resulting in an improved immunotherapy outcome. However, these findings were not confirmed in the overall study population, with no significant differences between patients who had received prior radiotherapy or not in terms of median OS (9.1 *vs.* 13.2 months) and 36-month OS rate (18.4% *vs.* 19.5%) (13).

In summary, emerging long-term follow-up of clinical trials with ICIs in NSCLC can provide useful information in clinical practice (*Table 1*) and the updated results of KEYNOTE-001 add further evidence regarding long-term safety and efficacy of single agent pembrolizumab in advanced NSCLC. However, several questions remain unanswered including optimal treatment duration, ICI rechallenge after elective treatment discontinuation, and identification of reliable predictive biomarkers of long-term response. These unmet medical needs should be addressed in prospective randomized clinical trials.

Table 1 Long-term results with immune checkpoint inhibitors in advanced NSCLC

Trial	Phase	ICI arm(s)	Treatment duration	Population [n]	PD-L1 selection	Median FU	Median OS (95% CI)	2-yr OS	3-yr OS	5-yr OS
KEYNOTE-001 (13)	1	Pembrolizumab	Until PD*	1 st line NSCLC [101] [†]	≥1%	34.5 mos	22.3 (17.1–31.5) mos	49%	26.4%	–
		Pembrolizumab		Pretreated NSCLC [449]	All comers		10.5 (8.6–13.2) mos	29.9%	19%	
KEYNOTE-010 (15)	2/3	Pembrolizumab	24 months or until PD	Pretreated NSCLC [690]	≥1%	42.6 mos	11.8 (10.4–13.1) mos	–	23%/11%	–
KEYNOTE-024 (7)	3	Pembrolizumab	24 months	1 st line, EGFR/ALK WT NSCLC [154]	≥50%	25.2 mos	30 (18.3–NR) mos	70.3%	51.5%	–
CHECKMATE-017 (16)	3	Nivolumab	Until PD	Pretreated squamous NSCLC [131]	All comers	3-yr minimum	9.23 (7.33–12.62) mos	23%	16%	–
CHECKMATE-057 (16)	3	Nivolumab	Until PD	Pretreated non-squamous NSCLC [287]	All comers	3-yr minimum	12.21 (9.66–15.08) mos	29%	18%	–

Table 1 (continued)

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Trial	Phase	ICI arm(s)	Treatment duration	Population [n]	PD-L1 selection	Median FU	Median OS (95% CI)	2-yr OS	3-yr OS	5-yr OS
CA209-003 (17)	1	Nivolumab	96 weeks	Pretreated NSCLC [129]	All comers	58.28 mos minimum	9.9 (7.8–12.4) mos	25%	18%	16%
POPLAR (14,23)	2	Atezolizumab	Until PD	Pretreated NSCLC [144]	All comers	38 mos	12.6 (9.7–16.4) mos	32.2%	18.7%	–
OAK (18)	3	Atezolizumab	Until PD	Pretreated NSCLC [425]	All comers	28 mos	13.8 (11.8–15.7) mos	30.9%	–	–
MYSTIC (24)	3	Durvalumab	Until	1 st line, EGFR/ALK WT NSCLC [374]	All comers	30.2 mos [†]	16.3 (12.2–20.8) [†] mos	38.3% [†]	–	–
		Durvalumab-Tremelimumab	PD**	1 st line, EGFR/ALK WT NSCLC [372]			11.9 (9.0–17.7) [†] mos	35.4% [†]		

NSCLC, non-small cell lung cancer; PD, progressive disease; WT, wild type; mos, months; yr, year; CI, confidence interval; NR, not reached; FU, follow-up. *, after a protocol amendment in April 2016, discontinuation after 24 months of treatment and resume upon disease progression was allowed; **, in the durvalumab-tremelimumab arm, durvalumab was continued until PD after 4 courses of anti-PD1 + CTLA-4 courses; †, after a protocol amendment, the enrollment in this arm was limited to EGFR/ALK WT patients; †, PD-L1 \geq 25% subgroups.

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Footnote

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