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

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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 ≥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 ≥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-naive (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
The efficacy of ICIs has been suggested in this study, with the greatest benefit. The CA-209-003 had a PR or CR (15,17) suggesting that these results are in line with previous reports (95% of the 3-year survivors described in this report may help to identify long-term survivors). In addition, the clinicopathological characteristics of long-term survivors 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*          | 1st line NSCLC [101] | ≥1%            | 34.5 mos  | 22.3 (17.1–31.5) mos | 49%    | 26.4%  | 49%    |
|                 |       |            |                    |                | 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 [449] | ≥1%            | 42.6 mos  | 11.8 (10.4–13.1) mos | –      | 23%/11%| –      |
| KEYNOTE-024 (7) | 3     | Pembrolizumab | 24 months or until PD | 1st line, EGFR/ALK WT NSCLC [154] | ≥50%           | 25.2 mos  | 30 (18.3–NR) mos | –      | –      | –      |
| 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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Footnote

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