



# Long-term survivors with immunotherapy in advanced NSCLC: is 'cure' within reach?

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Lung cancer represents the main cause of cancer-related death globally. In recent years, the introduction of immune checkpoint inhibitors (ICIs) have changed prognosis in a relevant proportion of non-small cell lung cancer (NSCLC) patients, especially in immunogenic tumors, such as the smoke-related ones.

Pembrolizumab is the only ICI approved as monotherapy in the first-line setting of non-oncogene addicted NSCLC harboring programmed death ligand-1 (PD-L1) expression on at least 50% of tumor cells. The recently published 5-year outcomes of phase Ib KEYNOTE (KN)-001 trial is the longest efficacy and safety update for patients affected by NSCLC treated with immunotherapy (1). This study demonstrated the safety and efficacy with a prolonged overall survival (OS) benefit in NSCLC patients treated with pembrolizumab monotherapy (2). In KN-001 trial, 550 patients with advanced NSCLC were treated with pembrolizumab monotherapy, with a schedule of 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks, and after a protocol amendment (April 2016) 200 mg flat dose every 3 weeks. Patients were either treatment-naïve (n=101) or pre-treated patients (n=449). The primary study endpoint was objective response rate (ORR). Secondary endpoints were OS and duration of response (DoR). After 60.6 months of median follow-up, ORR was 41.6% [n=42; 95% confidence interval (CI): 31.9–51.8] in treatment-naïve and 22.9% (n=103; 95% CI: 19.1–27.1) in previously-

treated patients. In terms of secondary endpoints, median OS was 22.3 (95% CI: 17.1–32.3) and 10.5 months (95% CI: 8.6–13.2) with a 5-year OS rate of 23.2% and 15.5% for treatment-naïve and previously-treated patients, respectively. The greatest benefit was observed in patients treated frontline and with high PD-L1 expression [tumor proportion score (TPS)  $\geq$ 50%]. For PD-L1  $\geq$ 50% patients a 5-year OS rate of 29.6% and a median OS of 35.4 months (95% CI: 20.3–63.5) were reported. There was a positive correlation between PD-L1 expression and longer OS, higher ORR. A median DoR of 16.8 and 38.9 months were described for treatment-naïve and pre-treated patients, respectively. In the subgroup of patients who received 2 or more years of pembrolizumab (n=60), the estimated 5-year OS was 78.6% in the first-line setting (n=14) and 75.8% in the second and further-line group (n=46). Median DoR was 52.0 (range, 10.2–55.7) months for treatment-naïve patients and not reached (range, 12.5–71.8) for previously-treated patients. Pembrolizumab monotherapy was overall well-tolerated with grade 3 to 5 adverse events (AEs) occurring in 13% of patients (n=69). The most common side effect was hypothyroidism (9%) and the most serious was pneumonitis (5%, of which 2% grade 3–5).

According to the results of KN-001, the PD-L1 cut-off for selecting NSCLC patients eligible for ICI monotherapy in first-line was established at  $\geq$ 50%. In this setting, the phase III study KN-024 validated the use of pembrolizumab

monotherapy as first-line therapy in NSCLC highly expressing PD-L1 (3). In this trial, pembrolizumab demonstrated to improve the primary endpoint PFS, as well as OS and ORR, with a favorable toxicity profile compared with platinum-based chemotherapy. After a median follow-up of 44.4 months, median OS was 26.3 months with pembrolizumab and 14.2 months with chemotherapy [hazard ratio (HR): 0.65; 95% CI: 0.50–0.86;  $P=0.001$ ]. Of interest, in the KN-024 trial, OS benefit was observed although 64.9% of patients crossed over from chemotherapy to an anti-PD-(L)1 agent after disease progression (4). Similarly, the phase III KN-042 trial showed that pembrolizumab significantly prolonged OS over platinum-based chemotherapy as first-line therapy for non-oncogene addicted NSCLC expressing PD-L1  $\geq 1\%$ , although a greater magnitude of benefit was reported in the subpopulation with PD-L1  $\geq 50\%$  reporting a significant OS advantage (20.0 *vs.* 12.2 months, HR: 0.69; 95% CI: 0.56–0.85;  $P=0.0003$ ) (5).

Based on a strong biological rationale, recent evidence from clinical trials in first-line have demonstrated that the combination of immunotherapy and chemotherapy (with or without antiangiogenic) or other immunotherapeutic agents provides a clinically meaningful benefit compared with standard-of-care in NSCLC patients, mainly irrespective of PD-L1 expression (6-15). Results of main clinical trials exploring immunotherapy in first-line treatment of NSCLC are listed in *Table 1*.

In the rapidly evolving landscape of lung cancer treatment, important questions have arisen mainly focusing on patient's selection for immunotherapy. As demonstrated by the KN-001 results, which are consistent with long-term follow-up of trials applying immunotherapy in pre-treated NSCLC (16), a proportion of patients (around 15%) is likely to achieve a long-term clinical benefit from immunotherapy alone. In this light, the crucial question is whether it is possible and how to identify these patients who may be spared from chemotherapy-immunotherapy combination (and its potential toxicity), without detrimentally impacting on their survival outcomes.

In terms of candidate predictors, to date no singularly-considered clinical factors allow the selection of those patients eligible to single agent immunotherapy instead of combination. In fact, in KN and IMpower trials the benefit deriving from immunotherapy (alone or in combination) was observed across all patients' subgroups. Histology did not significantly impact on immunotherapy efficacy, nor alone (3-5) or in combination with chemotherapy (6,7)

or another immunotherapeutic agent (14). Among the populations of interest, the presence of liver metastases is associated with a poor prognosis and a decreased likelihood of response to pembrolizumab in patients affected by NSCLC (17). Immunotherapy alone, as well as in combination with chemotherapy has provided superior outcomes compared with chemotherapy, irrespective of liver metastases, although the worse overall prognosis (18,19). In IMpower150 trial, including liver metastases as a prespecified stratification factor, the quadruple treatment with atezolizumab, carboplatin-paclitaxel and bevacizumab resulted in a 3.9-month difference in OS among patients with liver metastases, representing a 48% reduction in risk of disease progression or death (20). Although there is no clear evidence in randomized trials that patients with liver metastases should be treated differently than patients without, stratification based on presence of liver metastases is a reasonable perspective. Clinically meaningful populations, such as patients with ECOG Performance Status 2 or brain metastases, have been systematically excluded from clinical trials with immunotherapy therefore real-world data together with dedicated studies are fundamental in the investigation about effectiveness and safety of immunotherapy in a wider range of patients. Regarding elderly patients, pooled data from three randomized trials (KN-010, KN-024 and KN-042) showed improved OS in patients ages  $\geq 75$  years affected by advanced PD-L1-positive NSCLC treated with pembrolizumab versus those treated with chemotherapy (HR: 0.76; 95% CI: 0.56–1.02) together with a more favorable safety profile and with a greater benefit in patients with PD-L1  $\geq 50\%$  (HR: 0.41; 95% CI: 0.23–0.73) (21). In KN-189 study, the median age enrolled was around 65, making uncertain the tolerability and efficacy of combination in this patients' subgroup. With the available data, to date no indication coming from immunotherapy studies, either a single agent or a combination, has validated age as a choice criteria. Although in elderly patients immunotherapy alone may represent a reasonable option, candidate immunosenescence biomarkers have recently emerged and in future may be considered in selecting elderly patients for the most appropriate therapy. Another crucial aspect that clinicians should consider during treatment selection is toxicity. Although, randomized clinical trials as well as a systematic review and network meta-analysis including KN-189 and KN-407 studies found no significant increment in incidence of AEs grade  $\geq 3$  between pembrolizumab plus chemotherapy and chemotherapy alone (22), this

**Table 1** Results of main clinical trials exploring immunotherapy in first-line treatment of NSCLC

Study: characteristics	Treatment arms	N pts	OS		PFS		ORR (%)	AEs G3-5 (%)	IrAEs G3-5 (%)
			OS (months)	HR (95% CI); P value	PFS (months)	HR (95% CI); P value			
KN-001 (1): phase 1; NSCLC; PD-L1 ≥1%	Pembrolizumab	101	22.3	–	NA	–	41.6	13.0	4.0
KN-024 (3,4): phase 3; NSCLC; PD-L1 ≥50%	Pembrolizumab vs. platinum-based chemotherapy	154	26.3	0.65	10.3	0.50	44.8	31.0	13.0
		151	14.2	(0.50–0.86); P=0.001	6.0	(0.37–0.68); P<0.001	27.8	53.0	1.0
KN-042 (5): phase 1; NSCLC; PD-L1 ≥1%	Pembrolizumab vs. platinum-based chemotherapy	637	16.7	0.81	5.4	1.07	27.3	17.8	8.0
		637	12.1	(0.71–0.93); P=0.0018	6.5	(0.94–1.21)	26.5	41.0	1.5
KN-189 (6): phase 3; non-squamous NSCLC; any PD-L1 expression	Pembrolizumab + platinum-pemetrexed vs. placebo + platinum-pemetrexed	410	22.0	0.56	9.0	0.48	48.0	71.9	10.9
		206	10.7	(0.45–0.70); P<0.00001	4.9	(0.40–0.58); P<0.00001	19.4	66.8	4.5
KN-407 (7): phase 3; squamous NSCLC; any PD-L1 expression	Pembrolizumab + carboplatin-taxane vs. placebo + carboplatin-taxane	278	15.9	0.64	6.4	0.56	57.9	69.8	10.8
		281	11.3	(0.49–0.85); P=0.0008	4.8	(0.45–0.70); P<0.0001	38.4	68.2	3.2
IMpower150 (8): phase 3; non-squamous NSCLC; any PD-L1 expression	Atezolizumab + carboplatin-paclitaxel and bevacizumab (Arm B) vs. carboplatin-paclitaxel and bevacizumab (Arm C)	400	19.2	0.78	8.3	0.62	63.5	67.5	NA
		400	14.7	(0.64–0.96); P=0.02	6.8	(0.52–0.74); P<0.001	48.0	63.7	NA
IMpower130 (9): phase 3; non-squamous NSCLC; any PD-L1 expression	Atezolizumab + carboplatin-nab-paclitaxel vs. carboplatin-nab-paclitaxel	451	18.6	0.79	7.0	0.64	49.2	85.8	NA
		228	13.9	(0.64–0.98); P=0.033	5.5	(0.54–0.77); P<0.0001	31.9	76.3	NA
IMpower131 (10,11): phase 3; squamous NSCLC; any PD-L1 expression	Atezolizumab + carboplatin-nab-paclitaxel (Arm B) vs. carboplatin-nab-paclitaxel (Arm C)	343	14.2	0.88	6.3	0.71	49.0	82.0	13.0
		340	13.5	(0.73–1.05); P=0.1581	5.6	(0.60–0.85); P=0.0001	41.0	70.0	2.0
IMpower132 (12,13): phase 3; non-squamous NSCLC; any PD-L1 expression	Atezolizumab + platinum-pemetrexed vs. placebo + platinum-pemetrexed	292	18.1	0.81	7.6	0.60	47.0	69.0	NA
		286	13.6	(0.64–1.03); P=0.0797	5.2	(0.49–0.72); P<0.0001	32.0	59.0	NA
CheckMate 227 (14,15): phase 3; NSCLC; any PD-L1 expression	Nivolumab + ipilimumab vs. histology-based chemotherapy; TMB ≥10 mut/Mb	139	23.0	0.77	7.2	0.58	45.3	32.8	NA
		160	16.7	(0.56–1.06)	5.5	(0.41–0.81); P<0.001	26.9		
		396	17.1	0.79	5.1	0.82	35.9	36.0	NA
	Nivolumab + ipilimumab vs. histology-based chemotherapy; PD-L1 ≥1%	397	14.9	(0.65–0.96); P=0.007	5.6	(0.69–0.97)	30.0		

AEs of any cause are included in the table. KN-001: only data from treatment-naïve patients were reported (apart from toxicity); IMpower150: Arm B vs. Arm C data and results in the WT population are reported. IrAEs are only individually reported; IMpower130: IrAEs are only individually reported; IMpower131: Arm B vs. Arm C data are reported; IMpower132: IrAEs are only individually reported; CheckMate 227: the analysis of the dual primary endpoints are reported: PFS with nivolumab + ipilimumab vs. chemotherapy in patients with tumor mutational burden ≥10 mut/Mb (OS from Press Release) and OS for nivolumab + ipilimumab vs. chemotherapy in pts with tumor PD-L1 ≥1%). Treatment-related AEs are reported for all patients treated with nivolumab + ipilimumab or chemotherapy. IrAEs are only individually reported. OS, overall survival; PFS, progression free survival; ORR, overall response rate; AEs, adverse events; IrAEs, immune-related adverse events; N pts, number of patients; HR, hazard ratio; CI, confidence interval; KN, KEYNOTE; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand-1; NA, not available; WT, wild type.

percentage is relevantly higher when compared to mono-immunotherapy (Table 1). Moreover, patients included in trials of chemotherapy-immunotherapy combination were very selected with high screening failure rates, therefore the impact of toxicity in real life setting may be even higher than in clinical trials.

In terms of predictive bio-molecular factors, the association between tumoral PD-L1 expression and outcome is quite consistent among clinical trials with immunotherapy both alone and in combination. In strong positive PD-L1-expressing NSCLC, adding chemotherapy to pembrolizumab significantly decreased tumor size and delayed disease progression compared to pembrolizumab monotherapy ( $P < 0.001$ ) with a trend toward a quantitative interaction in OS ( $P = 0.16$ ) (23). When results of randomized clinical trials evaluating the combination of immunotherapy with chemotherapy (or chemotherapy-antiangiogenic agent) in first-line treatment of advanced NSCLC patients are analyzed with a meta-analytic approach, the combinatorial strategy provides a significant differential effect in terms of both OS and PFS, regardless of PD-L1 expression on tumor and/or immune cells (24). Considering the lack of an exclusive correlation with response/outcome, PD-L1 expression alone is not sufficient to explain the rates of long-term benefit described in patients affected by different cancer types, therefore other biomarkers are currently under investigation. Among them, tumoral mutational burden (TMB) has long been considered a candidate predictive biomarker for immunotherapy. Recent findings showed no significant association between TMB and efficacy of pembrolizumab-platinum-based chemotherapy, as well as nivolumab-ipilimumab, versus platinum-based chemotherapy alone, regardless of histology (15,25). Based on this data, the scientific community agreed that TMB is not ready for being included into the therapeutic decision-making process.

Although the detection of a 'classic' oncogene-addiction (mainly *EGFR* mutations and *ALK* translocations) has been recognized as a negative predictor for immunotherapy alone activity and efficacy, several genomic alterations are currently under investigation to define their potential prognostic and/or predictive impact. Among them, *STK11*, *KEAP1* and *ARID1A* mutations are in the spotlight.

In conclusion, 5 years results of KN-001 study have confirmed that immunotherapy alone has long term efficacy in a subgroup of NSCLC patients (similarly to previous

findings in pre-treated NSCLC), but for the first time this prolonged benefit was extended to treatment-naïve patients, mainly strong PD-L1-expressors. In the rapidly changing landscape of lung cancer cure, where the combination of immunotherapy-chemotherapy recently revolutionized treatment possibilities, this finding strengthens the need to identify and validate innovative biomarkers in order to avoid overtreatment in those patients who may benefit from monotherapy alone. In light of the complexity of immune system-cancer interface, identifying a unique predictive biomarker is likely to be unrealistic and too simplifying. Thanks to the integration of different technologies, expertises and data, the recognition of crucial factors for immunotherapy response/resistance might lead to the real breakthrough point, allowing the accurate definition of the best therapeutical approach for each NSCLC patient.

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*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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## References

- 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;37:2518-27.
- Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015;372:2018-28.
- 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.
- Reck M, Rodríguez-Abreu D, Robinson AG, et al. OA14. 01 KEYNOTE-024 3-year survival update: pembrolizumab vs platinum-based chemotherapy for advanced non-small-cell lung cancer. *J Thorac Oncol* 2019;14:S243.
- Mok TSK, 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.
- Gadgeel SM, Garassino MC, Esteban E, et al. KEYNOTE-189: Updated OS and progression after the next line of therapy (PFS2) with pembrolizumab (pembro) plus chemo with pemetrexed and platinum vs placebo plus chemo for metastatic nonsquamous NSCLC. *J Clin Oncol* 2019;37:abstr 9013.
- 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.
- 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.
- West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2019;20:924-37.
- Jotte RM, Cappuzzo F, Vynnychenko I, et al. IMpower131: Primary PFS and safety analysis of a randomized phase III study of atezolizumab+ carboplatin+ paclitaxel or nab-paclitaxel vs carboplatin+ nab-paclitaxel as 1L therapy in advanced squamous NSCLC. *J Clin Oncol* 2018;36:LBA9000.
- Jotte R, Cappuzzo F, Vynnychenko I, et al. OA14. 02 IMpower131: final OS results of carboplatin+ nab-paclitaxel ± atezolizumab in advanced squamous NSCLC. *J Thorac Oncol* 2019;14:S243-4.
- Papadimitrakopoulou V, Cobo M, Bordoni R, et al. IMpower132: PFS and safety results with 1L atezolizumab+ carboplatin/cisplatin+ pemetrexed in stage IV non-squamous NSCLC. *J Thorac Oncol* 2018;13:S332-3.
- Barlesi F, Nishio M, Cobo M, et al. LBA54 IMpower132: Efficacy of atezolizumab (atezo)+ carboplatin (carbo)/cisplatin (cis)+ pemetrexed (pem) as 1L treatment in key subgroups with stage IV non-squamous non-small cell lung cancer (NSCLC). *Ann Oncol* 2018;29:mdy424.066.
- Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med* 2018;378:2093-104.
- Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med* 2019;381:2020-31.
- Gettinger S, Borghaei H, Brahmer J, et al. OA14. 04 five-year outcomes from the randomized, phase 3 trials CheckMate 017/057: nivolumab vs docetaxel in previously treated NSCLC. *J Thorac Oncol* 2019;14:S244-5.
- Tumeh PC, Hellmann MD, Hamid O, et al. Liver metastasis and treatment outcome with anti-PD-1 monoclonal antibody in patients with melanoma and NSCLC. *Cancer Immunol Res* 2017;5:417-24.
- Garassino MC, Gadgeel S, Esteban E, et al. Abstract CT043: Outcomes among patients (pts) with metastatic nonsquamous NSCLC with liver metastases or brain metastases treated with pembrolizumab (pembro) plus pemetrexed-platinum: results from the KEYNOTE-189 study. *Cancer Research* 2019;79:CT043.



19. Vokes EE, Ready N, Felip E, et al. Nivolumab versus docetaxel in previously treated advanced non-small-cell lung cancer (CheckMate 017 and CheckMate 057): 3-year update and outcomes in patients with liver metastases. *Ann Oncol* 2018;29:959-65.
20. Reck M, Mok TSK, Nishio M, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. *Lancet Respir Med* 2019;7:387-401.
21. Nosaki K, Hosomi Y, Saka H, et al. 103O\_PR Safety and efficacy of pembrolizumab (Pembro) monotherapy in elderly patients (Pts) with PD-L1-positive advanced NSCLC: Pooled analysis from KEYNOTE-010, -024, and -042. *Ann Oncol* 2019;30:mdz063.001.
22. Dafni U, Tsourti Z, Vervita K, et al. Immune checkpoint inhibitors, alone or in combination with chemotherapy, as first-line treatment for advanced non-small cell lung cancer. A systematic review and network meta-analysis. *Lung Cancer* 2019;134:127-40.
23. Pilotto S, Carbognin L, Rossi A, et al. Avoiding chemotherapy for advanced nononcogene addicted NSCLC overexpressing PD-L1: rule or option? *Semin Oncol* 2018;45:176-80.
24. Rossi A, Noia VD, Gkoutakos A, et al. PD-L1 for selecting non-small-cell lung cancer patients for first-line immuno-chemotherapy combination: a systematic review and meta-analysis. *Immunotherapy* 2019;11:921-30.
25. Paz-Ares L, Langer CJ, Novello S, et al. LBA80 Pembrolizumab (pembro) plus platinum-based chemotherapy (chemo) for metastatic NSCLC: Tissue TMB (tTMB) and outcomes in KEYNOTE-021, 189, and 407. *Ann Oncol* 2019;30:mdz394.078.

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