Long-term survival and health-related quality of life in patients treated with nivolumab for advanced non-small cell lung cancer: a wide prospective French real-world study (EVIDENS)

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Background

- Nivolumab is an anti-PD-1 antibody that improved overall survival (OS) and had a more favourable safety profile than docetaxel in phase III trials in patients with advanced squamous (CheckMate 017[1]) and non-squamous (CheckMate 057[2]) non-small cell lung cancer (NSCLC) that had progressed during/after prior chemotherapy.
- The EVIDENS (lung cancer patients trEated with niVolumab: a longItuDinal, prospEctive, observatioNal, multicentric Study; NCT03382496) study was initiated in order to assess the usage, effectiveness and safety of nivolumab in patients with lung cancer in the real-world setting in France.
- Preliminary results from EVIDENS in patients with NSCLC have been reported previously,[3,4] and showed outcomes consistent with those from randomised clinical trials.
- Here, we report long-term survival, safety and health-related quality of life (HRQoL) results.

Methods

- EVIDENS is a prospective, observational, cohort study that enrolled patients with lung cancer who began treatment with nivolumab between October 2016 and November 2017 at 146 centres in France.
- The primary objectives of the study are: (a) to describe the sociodemographic and clinical characteristics of patients at initial diagnosis and after initiation of nivolumab treatment; and (b) to estimate 3-year OS after initiation of nivolumab.
- Descriptive statistics for patients with NSCLC were calculated. Unless otherwise specified, data not reported by the investigators were excluded from the analysis and thus from percentage calculations.
- OS and investigator-assessed progression-free survival (PFS) were estimated using the Kaplan-Meier method with 95% confidence intervals (CIs).
- OS was also estimated for subgroups defined by best overall response at 6 months, and by treatment status at 6, 12 and 24 months.
- Longitudinal HRQoL was assessed using the EuroQol-5D 3-level (EQ-5D-3L) questionnaire and visual analogue scale (VAS), which provides a self-rated health status ranging from 0 ('worst imaginable') to 100 ('best imaginable').

Results

- A total of 1421 patients with NSCLC were enrolled in the EVIDENS study and followed up for a median of 34.1 months (range 29.1–42.0).
- Baseline patient and tumour characteristics and clinical data are shown in **Tables 1 and 2.** Most patients (91.4%) had stage IV disease at enrolment, and all except four had received prior chemotherapy. Nivolumab was a second-line or ≥ third-line regimen in 73.6% and 26.1% of patients, respectively.
- **Table 3** shows baseline EQ-5D-3L data for all patients with NSCLC and for the subgroup of patients with EQ-5D-3L data at 24 months.

Survival outcomes

- Median OS and PFS were 11.2 months and 3.0 months, respectively **(Figure 1)**.
- OS was 29.4% (95% CI: 26.9–32.0) at 24 months and 18.5% (95% CI: 15.6–21.6) at 36 months. At the same time points, PFS rates were 13.1% (95% CI: 11.3–15.1) and 7.6% (95% CI: 5.6–9.9). These findings are consistent with previously reported results from a pooled analysis of data from two pivotal clinical trials, CheckMate 017 and 057 (3 year OS and PFS: 17.1% and 10.2%, respectively).[5]
- In contrast with a previous multivariate analysis,[4] patients experiencing at least one grade III or IV treatment-related adverse event (TRAE) had significantly longer survival in the updated multivariate analysis: median OS 14.6 months (95% CI: 11 .0-22.4) vs 10.8 months (95% CI: 9.6-12.2); *P* = 0.013).
- The patients who had an ECOG PS ≥2 had a significantly shorter OS than ECOG PS ≤1 subgroups: median OS 4.8 (95% CI: 4-6.2) vs 13 (95% CI: 12-14.6), *P* < 0.001, respectively. Conversely, brain metastasis showed no significant relationship with OS: median OS for patients with at least one brain metastasis was 9.8 (95% CI: 7.6-12.4) vs 11.8 (95% CI: 10.2-12.8) for patients with no brain metastasis, *P* = 0.236.
- Over 50% of patients who had an ongoing complete or partial response at 6 months, or whose best response at 6 months was complete or partial response, were still alive at 24 months (median OS not reached; **Figure 2**). In contrast, median OS was 15.6 months (95% CI: 13.8-17.0) among those with stable disease or disease progression at 6 months (or whose best response at 6 months was stable or progressive disease).
- Median OS was not reached at 36 months in subgroups of patients who were alive and on treatment at 6, 12 or 24 months **(Figure 3)**. Patients who were alive but had stopped treatment by these time points had median OS times of 13.4, 22.6 and 33.2 months, respectively (*P* < 0.001).

Table 1. Baseline demographics and clinical characteristics for all patients with NSCLC and for the subgroup of patients with EQ-5D-3L data at 24 months

Characteristic	All patients (n = 1421)	Patients with EQ-5D-3L data at 24 months (n = 111)
Sex, n (%) Male	986 (69.4)	69 (62.2)
Median age, years (min-max)	66 (35-91)	63 (39-91)
Smoking status,* n (%) Non-smoker Former or current smoker	145 (10.2) 1273 (89.6)	8 (7.2) 103 (92.8)
ECOG PS at inclusion visit,** n (%) 0 or 1 2 3 or 4	1173 (83.0) 192 (13.6) 49 (3.5)	101 (91.0) 9 (8.1) 1 (0.9)

*3 missing values; **7 missing values; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Table 2. Disease characteristics and prior treatments for all patients with NSCLC and for the subgroup of patients with EQ-5D-3L data at 24 months

	All patients (n = 1421)	Patients with EQ-5D-3L data at 24 months (n = 111)
Tumour characteristics at inclusion, n (%)		
Tumour histology, n (%) Squamous Non-squamous	438 (30.8) 983 (69.2)	28 (25.2) 83 (74.8)
TNM classification I/II IIIA IIIB IV	4 (0.3) 24 (1.7) 94 (6.6) 1299 (91.4)	1 (0.9) 1 (0.9) 5 (4.5) 104 (93.7)
Metastatic sites Liver Brain Bone	239 (16.8) 282 (19.8) 446 (31.4)	15 (13.5) 22 (19.8) 33 (29.7)
Previous lung cancer treatment, n (%)		
Curative definitive surgery **Chemotherapy** **Radiotherapy** Thoracic curative Cerebral Other (palliative or analgesic) **Targeted therapy*** **Other immunotherapy**	247 (17.4) 1417 (99.7) 658 (46.3) 314 (22.1) 214 (15.1) 224 (15.8) 245 (17.2) 8 (0.6)	32 (28.6) 110 (99.1) 48 (43.2) 25 (22.5) 14 (12.6) 15 (13.5) 19 (17.1) 0 (0.0)

*The proportion of patients with oncogenic addiction is 4.76% EGFR and ALK mutations among the 903 patients tested

Table 3. Baseline EQ-5D-3L data for all patients with NSCLC and for the subgroup of patients with EQ-5D-3L data at 24 months

	All patients (n = 1421)	Patients with EQ-5D-3L data at 24 months (n = 111)
Mobility, n (%) I have no problems in walking I have problems in walking I have to stay in bed *Not available*	698 (58.4) 471 (39.4) 27 (2.3) 225	81 (75.7) 25 (23.4) 1 (0.9) *4*
Self-care, n (%) I have no problems taking care of myself I have problems washing or dressing myself alone I am unable to wash or dress myself alone *Not available*	981 (82.1) 187 (15.6) 27 (2.3) 226	99 (92.5) 6 (5.6) 2 (1.9) *4*
Usual activities, n (%) I have no problem doing my usual activities I have problems doing my usual activities I am unable to do my usual activities *Not available*	563 (47.1) 500 (41.8) 132 (11.0) 226	68 (63.6) 30 (28.0) 9 (8.4) *4*
Pain-discomfort, n (%) I have no pain or discomfort I have moderate pain or discomfort I have extreme pain or discomfort *Not available*	333 (27.9) 748 (62.6) 114 (9.5) 226	42 (39.3) 58 (54.2) 7 (6.5) *4*
Anxiety-depression, n (%) I am not anxious or depressed I am moderately anxious or depressed I am extremely anxious or depressed *Not available*	557 (46.6) 531 (44.4) 108 (9.0) 225	59 (55.1) 40 (37.4) 8 (7.5) *4*
VAS score, median (interquartile range) *Not available*	60.0 (50.0-80.0) 274	70.0 (57.5-85.5) *11*

Health-related quality of life

- At 24 months, the EQ-5D-3L questionnaire and VAS were completed by 111 (7.8%) and 109 (7.7%) patients, respectively.
- The mean VAS score was 71.7 (95% CI: 68.2-75.2) at baseline and 74.5 (95% CI: 71.1-77.8) at 24 months, corresponding to a non-significant mean improvement from baseline of +2.8 (95% CI: -0.7-6.2). Mean change in VAS score over time is shown in **Figure 4**.
- At 24 months, the proportions of patients reporting no change/improvement from baseline in the five dimensions of EQ-5D-3L were: mobility, 72.0%/7.5%; self-care, 84.1%/4.7%; usual activities, 66.4%/14.0%; anxiety-depression, 70.1%/15.9%; and pain-discomfort, 64.5%/19.6% **(Figure 5)**.

Figure 1. Three-year OS (A) and PFS (B)

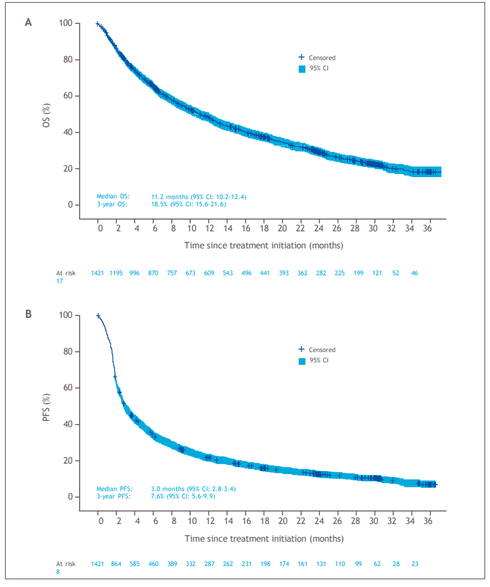


Figure 2. OS according to best overall response after 6 months

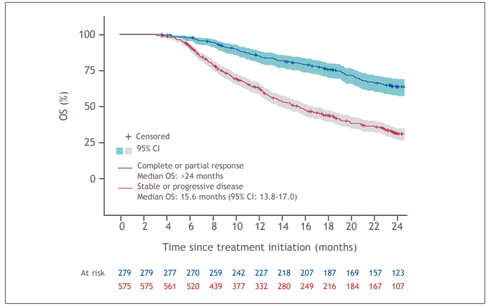
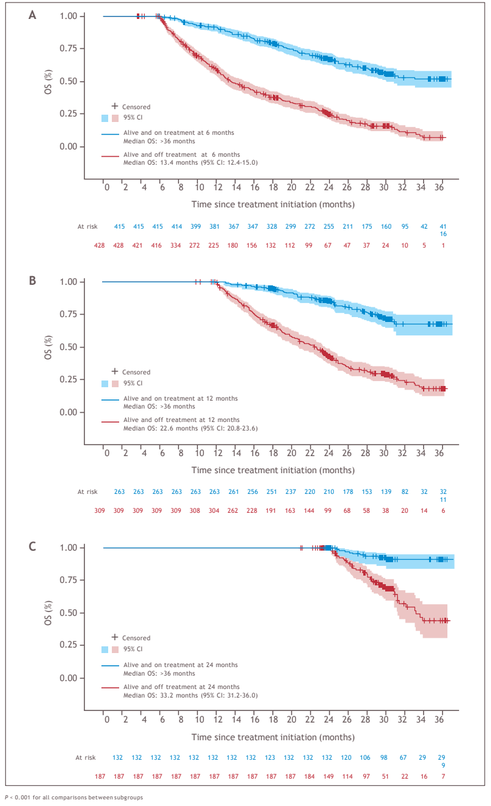


Figure 3. OS by treatment status (on or off treatment) at: (A) 6 months; (B) 12 months; and (C) 24 months.

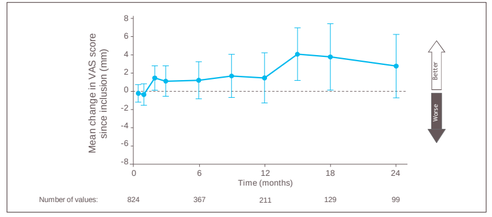


P < 0.001 for all comparisons between subgroups

Safety

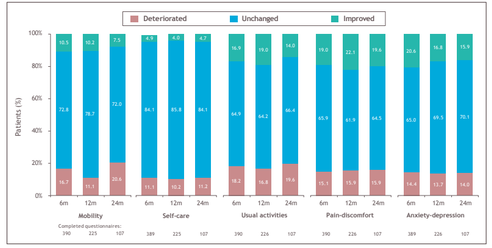
- Five hundred and four patients (35.5%) experienced TRAEs and 143 (10.1%) experienced a serious TRAE.
- TRAEs by severity grade were: grade I, 271 patients (19.1%); grade II, 250 (17.6%); grade III, 112 (7.9%); grade IV, 13 (0.9%).
- There were 8 reported deaths due to treatment-related adverse events (1 intestinal inclusion, 1 encephalitis, 1 infectious pneumonitis, 1 interstitial lung, 1 hemoptysis, 1 vasculitis NOS, 1 following vomiting and profuse diarrhea with dehydration and 1 of unknown cause), the relationship between the death and TRAEs was confirmed by experts from scientific committee.

Figure 4. Mean change from baseline in VAS score since inclusion (mm).



Bars indicate 95% CIs

Figure 5. Change in response to individual dimensions of the EQ-5D-3L questionnaire at 6, 12 and 24 months



Conclusions

- In this long-term observational study of nivolumab treatment in a large cohort of real-world patients with NSCLC in France, the median OS estimate of 11.2 months and OS at 3 years of 18.5% is demonstrated to be consistent with the findings of randomised controlled trials.[5]
- The results suggest that treatment duration may be related to overall survival and this warrants further investigation including assessment of the reasons for treatment discontinuation.
- Most patients receiving nivolumab did not experience any deterioration in HRQoL over 24 months.
- These data confirm the efficacy and clinical utility of nivolumab as a treatment option for previously treated NSCLC.
- No new safety signals were reported.

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Disclosures

This study was sponsored by Bristol Myers Squibb (BMS). The authors declare the following conflicts of interest: [1]AstraZeneca (AZ), Bristol Myers Squibb (BMS), Boehringer Ingelheim, Eli Lilly, F. Hoffmann-La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre, Pfizer, Takeda; [2]BMS, Roche, Novartis, MSD, AZ, Boehringer Ingelheim, Amgen, Eli Lilly; [3]BMS, Roche, Pfizer, MSD, Boehringer Ingelheim, AZ, Chugai Pharmaceuticals, Eli Lilly, Novartis, GSK, Sandoz, Chiesi; [4]BMS; [5]BMS, Roche, AZ, Boehringer Ingelheim, MSD, Amgen, Pfizer; [6]BMS; [7]BMS; [8]BMS, MSD, Eli Lilly, Abbvie, AZ, Boehringer Ingelheim, Takeda, Roche, Pfizer; [9]BMS, AZ, Boehringer Ingelheim, Eli Lilly, Novartis, Pfizer, Roche, MSD; [10]BMS; [11-14]BMS employees; [15]BMS, Roche, Eli Lilly, Pfizer, MSD, Boehringer Ingelheim, Novartis, Pierre Fabre, Takeda, Clovis, AZ.

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