Real-World Treatment Patterns and Outcomes After Introduction of Immune Checkpoint Inhibitors in Patients With Advanced/Metastatic Non-Small Cell Lung Cancer in Europe

HSD20

Alexander Slowley[1], Linda Kalilani[2], Jasjit K. Multani[3], Vicky Casey[4], Sheila Mpima[5], Marie Yasuda[5], Chi-Chang Chen[5], Fil Manuguid[4], Jessica Chao[6], Amine Aziez[7], Kelly F. Bell[6], Alexander Stojadinovic[8]

[1]GSK, London, United Kingdom; [2]GSK, Research Triangle Park, NC, USA; [3]IQVIA, Falls Church, VA, USA; [4]IQVIA, London, United Kingdom; [5]IQVIA, Wayne, PA, USA; [6]GSK, Upper Providence, PA, USA; [7]GSK, Basel, Switzerland; [8]GSK, Collegeville, PA, USA

Background

Lung cancer is the leading cause of cancer-related death in Europe.[1]

Non-small cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for 82% of all diagnoses.[2]

Advances in immunotherapies and targeted therapies have dramatically changed clinical practices for the treatment of NSCLC.[3]

Despite this, the 5-year survival upon regional and distant metastasis remains low (33% and 6%, respectively).[2]

Choice of therapeutic approach is increasingly complex for physicians treating patients with advanced and metastatic (a)NSCLC, and real-world evidence describing treatment dynamics and outcomes is limited in Europe.[4]

Aim

This study characterises real-world treatment patterns and clinical outcomes among patients with Stage IIIB/C and Stage IV NSCLC without driver mutations, receiving pembrolizumab-based first-line (1L) maintenance therapy, in France, Germany, Italy, Spain and the United Kingdom (UK).

Methods

Study design

This retrospective patient chart review used an online physician-completed case report form (CRF) to capture data reporting demographics and disease characteristics, treatments received and outcomes from existing patient records.

Physicians were recruited from an IQVIA database and screened for their experience treating patients with NSCLC. CRFs were completed July–August 2021.

Table 1. Inclusion criteria for physicians and patients

Physicians	Patients
Personally treated the patient within 12 months of data extraction	Aged ≥18 years with confirmed Stage IIIB/C or Stage IV NSCLC† with no known driver mutations‡
Maximum of two clinicians from the same treatment centre and one clinician from the same hospital	Achieved SD, PR or CR per clinician's assessment after completion of 4–6 cycles of platinum-based 1L induction chemotherapy with pembrolizumab
Provided information on consecutive patients (i.e., the first 3–4 patients treated within 12 months of data extraction)	Initiated pembrolizumab-based 1L maintenance therapy
Reported data on 1 (for physicians who reported data for 3 treated patients) or 2 (those who reported data for 4 treated patients) deceased patients*	ECOG PS of 0 or 1 at start of 1L maintenance

*In order to obtain a sufficient sample to estimate time to death; †determined by American Joint Committee on Cancer 8th Edition Staging Manual; ‡not positive for *ALK, EGFR, ROS1, BRAF, NTRK, MET*, or *ERBB2*; patients with PD-L1 expression are not excluded. 1L, first line; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small cell lung cancer; PR, partial response; SD, stable disease.

Outcome measures

Study outcome measures were to describe:

- Demographic and clinical patient characteristics.
- Treatment patterns including line of therapy (LOT); 1L induction, 1L maintenance, and second line (2L) choice of regimen; and duration of therapy (DOT).
- Clinical outcomes after 1L induction and 1L maintenance including:
  - Estimated progression-free survival (PFS), defined as time from start of 1L maintenance therapy to the date of first documented progression.
  - Overall survival (OS), defined as time from start of 1L maintenance therapy until date of death from any cause (using the midpoint of the month of death).
  - Duration of response (DOR), defined as time from complete response (CR) or partial response (PR) associated with 1L induction chemotherapy with pembrolizumab to the date of first progression after initiation of 1L maintenance therapy. Patients with no response, stable disease (SD), or progressive disease (PD) at end of 1L induction therapy were excluded.
  - Time to death (deceased patients only), defined as time from start of 1L maintenance therapy until date of death from any cause.

Statistical analysis

All time-to-event analyses (DOT, PFS, OS, DOR, time to death) were evaluated using the Kaplan-Meier (KM) survival method. Log-rank tests were used to test differences among subgroups ($p<0.05$ was considered statistically significant).

Analyses were stratified by country, histology (squamous [SQ] vs non-squamous [NSQ]), response to 1L induction chemotherapy (CR/PR vs SD), and presence vs absence of asymptomatic central nervous system (CNS)/brain metastasis at time of 1L maintenance.

Results

Patient population

At initiation of 1L maintenance therapy, most patients were ≥66 years of age (n=185, 58%), were ex-smokers (n=193, 60%), and most had Stage IV disease (n=303, 94%; **Table 2**).

Chronic obstructive pulmonary disease (n=118, 37%), diabetes mellitus (n=68, 21%), cardiac dysfunction (n=39, 12%) and atrial fibrillation (n=38, 12%) were the most common pre-existing comorbid conditions at initial diagnosis.

Table 2. Patient characteristics at 1L maintenance

Category	France N=61	Germany N=60	Italy N=73	Spain N=67	UK N=61	Total N=322
Male, n (%)	45 (73.8)	44 (73.3)	50 (68.5)	49 (73.1)	41 (67.2)	229 (71.1)
Age group, n (%)						
≤45 years	0 (0.0)	2 (3.3)	2 (2.7)	5 (7.5)	1 (1.6)	10 (3.1)
46-65 years	28 (45.9)	17 (28.3)	33 (45.2)	25 (37.3)	24 (39.3)	127 (39.4)
≥66 years	33 (54.1)	41 (68.3)	38 (52.1)	37 (55.2)	36 (59.0)	185 (57.5)
Smoking status, n (%)*						
Smoker	23 (37.7)	30 (50.0)	22 (30.1)	14 (20.9)	9 (14.8)	98 (30.4)
Ex-smoker	36 (59.0)	28 (46.7)	36 (49.3)	46 (68.7)	47 (77.1)	193 (59.9)
Never smoked	2 (3.3)	2 (3.3)	10 (13.7)	3 (4.5)	5 (8.2)	22 (6.8)
ECOG PS of 1, n (%)	51 (83.6)	48 (80.0)	50 (68.5)	55 (82.1)	43 (70.5)	247 (76.7)
Stage of disease, n (%)						
Stage IIIB/C	3 (4.9)	1 (1.7)	5 (6.9)	5 (7.5)	5 (8.2)	19 (5.9)
Stage IV	58 (95.1)	59 (98.3)	68 (93.2)	62 (92.5)	56 (91.8)	303 (94.1)
Histology, n (%)†						
SQ	22 (36.1)	21 (35.0)	21 (28.8)	9 (13.4)	24 (39.3)	97 (30.1)
NSQ	39 (63.9)	39 (65.0)	49 (67.1)	55 (82.1)	37 (60.7)	219 (68.0)
No asymptomatic CNS/ brain metastasis, n (%)‡	56 (91.8)	58 (96.7)	65 (89.0)	58 (86.6)	51 (83.6)	288 (89.4)

*Smoking status was unknown for 9 patients; †6 patients had mixed histology; ‡CNS/brain metastasis status unknown for 16 patients. 1L, first-line; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSQ, non-squamous; SQ, squamous; UK, United Kingdom.

Treatment patterns across LOTs

Per study design, all patients received 1L induction therapy and started pembrolizumab-based 1L maintenance therapy. Only 11% (n=37) progressed to receive 2L therapy, and <1% (n=2) received third-line (3L) therapy.

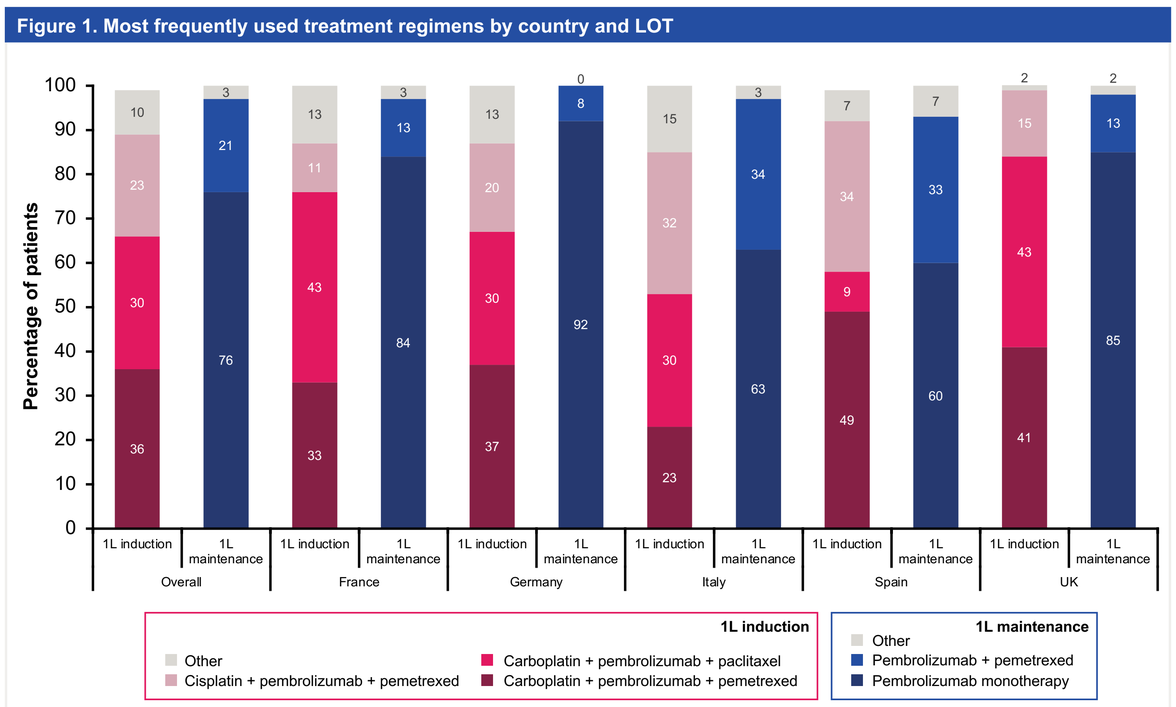
The three platinum-based regimens used most frequently for 1L induction, and two pembrolizumab-based regimens used most frequently for 1L maintenance, accounted for 90% and 97% of the respective LOTs used across countries. However, the rankings of each treatment regimen differed between countries (**Figure 1**).

Pembrolizumab monotherapy was the most common 1L maintenance regimen across histologies (SQ 92.8%, n=90; NSQ 68.0%, n=149), followed by pembrolizumab plus pemetrexed (SQ 4.1% n=4; NSQ 28.8%, n=63).

The overall median DOT for 1L induction therapy was 3.0 months (95% CI: 3.0–3.0), which was similar across all countries.

Germany and the UK had the longest DOT for 1L maintenance therapy, both with a median of 6.0 months (95% CI: 6.0–10.0 for Germany; 3.0–7.0 for the UK). Spain had the shortest DOT for 1L maintenance (median 3.0 months; 95% CI: 1.9–5.0; differences between countries were not statistically significant [p=0.062]).

Figure 1. Most frequently used treatment regimens by country and LOT



Due to rounding of percentages not all categories add up to 100%. 1L, first-line; LOT, line of therapy; UK, United Kingdom.

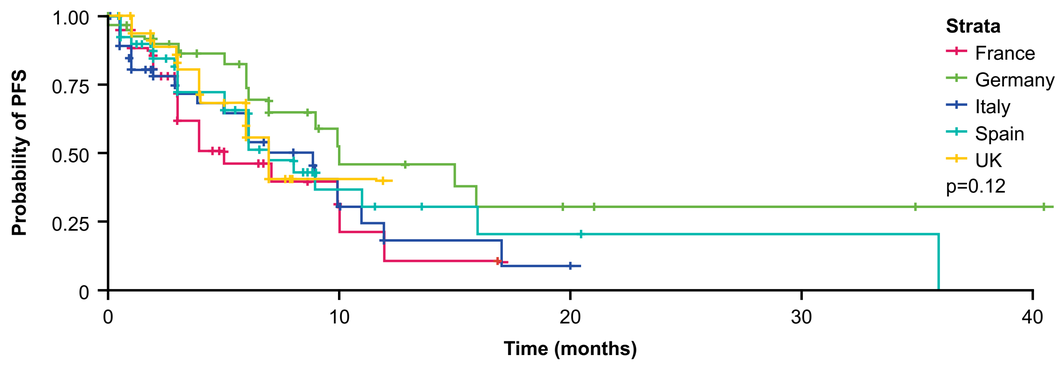
Clinical outcomes of 1L maintenance therapy

Median PFS from the start of 1L maintenance therapy ranged from 10.1 (95% CI: 6–NA) to 5.0 (95% CI: 3–10.1) months across countries; and median OS from the start of 1L maintenance therapy ranged from 9.0 (95% CI: 7–14) to 5.0 (95% CI: 3–9) months across countries; no statistically significant differences were present between countries (**Figure 2, Table 3**).

DOR from the start of 1L maintenance therapy ranged from 12.0 (95% CI: 7–NA) months to 8.0 (95% CI: 7–NA) months across countries; no statistically significant differences were present between countries (**Table 3**).

Patients with NSQ NSCLC (p=0.005), patients who responded (PR or CR) to 1L induction chemotherapy (p<0.0001), and patients without asymptomatic CNS/brain metastasis (p<0.0001) had a significantly longer OS than their comparator cohorts (**Table 3**).

Figure 2. KM curve and estimate of median PFS from the start of 1L maintenance, by country



Country	Median	CI		IQR	
		Lower	Upper	Q1	Q3
Overall	7.0	6.0	10.0	3.0	15.1
France	5.0	3.0	10.1	2.9	10.1
Germany	10.1	6.0	NA	6.0	NA
Italy	7.0	5.0	10.0	2.9	11.0
Spain	7.0	5.0	11.0	3.0	16.0
UK	7.0	6.0	NA	3.9	NA

1L, first-line; CI, confidence interval; IQR, inter-quartile range; KM, Kaplan-Meier; NA, not applicable (not reached); PFS, progression-free survival; Q1, lower quartile; Q3, upper quartile; UK, United Kingdom.

Table 3. Clinical outcomes of 1L maintenance therapy

Stratification	PFS* in months, median (95% CI)	OS† in months, median (95% CI)	Time to death‡ in months, median (95% CI)	DOR§ in months, median (95% CI)
Total	7.0 (6–10), N=322	8.0 (7–8.1), N=322	5.0 (3–6), N=156	10.1 (8.1–12), N=235
By country				
France	5.0 (3–10.1), N=61	5.0 (3–9), N=61	3.0 (2–5), N=30	10.1 (3.9–12), N=49
Germany	10.1 (6–NA), N=60	9.0 (7–14), N=60	7.0 (2–9), N=28	11.0 (6–NA), N=47
Italy	7.0 (5–10), N=73	8.0 (4–11), N=73	2.0 (1–6), N=35	11.0 (6–14), N=48
Spain	7.0 (5–11), N=67	8.0 (5–10), N=67	3.0 (1–8), N=33	12.0 (7–NA), N=48
UK	7.0 (6–NA), N=61	7.0 (6–8), N=61	6.0 (3–8), N=30	8.0 (7–NA), N=43
By histology				
SQ	6.0 (4–9), N=97	6.0 (3–7), N=97	3.0 (2–6), N=55	8.0 (5–11), N=67
NSQ	9.0 (6–10.1), N=219	9.0 (7–10), N=219	6.0 (3–7), N=97	11.1 (10–14), N=163
By response to 1L induction chemotherapy				
PR/CR	10.0 (7–10.1), N=235	9.0 (7–10), N=235	6.0 (3–7), N=91	10.1 (8.1–12), N=235
SD	3.9 (2.9–6), N=87	4.0 (2–7), N=87	2.0 (1–5), N=65	NA
By asymptomatic CNS/brain metastasis status				
Present	3.0 (1–4), N=18	3.0 (1–5), N=18	3.0 (1–5), N=15	1.0 (0.5–1), N=11
Absent	8.1 (6–10), N=288	8.1 (7–10), N=288	5.0 (3–7), N=131	11.0 (9–12), N=213

All clinical outcomes were derived from KM analysis, with censoring for death and end of follow-up (except for time to death). 1L, first-line; CI, confidence interval; CNS, central nervous system; CR, complete response; DOR, duration of response; NA, not applicable (not reached); NSQ, non-squamous; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; SQ, squamous; UK, United Kingdom.

Conclusions

- Treatment patterns following pembrolizumab-based 1L induction therapy and clinical outcomes for Stage IIIB/C and IV NSCLC patients, without driver mutations, differed across five European countries.
- Pembrolizumab monotherapy was the most common 1L maintenance regimen regardless of tumour histology
- These real-world data suggest that, despite advances in treatment, patients with aNSCLC without driver mutations continue to have poor survival rates across Western Europe.
- Outcome differences stratified by histology are concordant with those reported previously in KEYNOTE-189 and KEYNOTE-407, where shorter PFS was observed in SQ patients compared to NSQ.[5,6]
- This study provided valuable insights into various patient subgroups; however, some limitations exist, including low sample size in some groups and potential reporting bias, amongst others. Larger studies are required to confirm the findings of this study.

Disclosures

AA and **KFB** are employees of GSK. **ASlowley**, **LK**, **JC** and **AStojadinovic** are employees of, and hold stocks in, GSK. **JKM**, **VC**, **SM**, **MY**, **CCC** and **FM** are employees of IQVIA.

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Presenting author email: alexander.m.slowley@gsk.com

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