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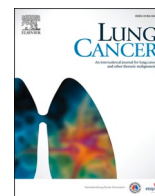
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Impact of immune checkpoint inhibitors on the management of locally advanced or metastatic non-small cell lung cancer in real-life practice in patients initiating treatment between 2015 and 2018 in France and Germany

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ABSTRACT

Objectives: To describe the impact of immune checkpoint inhibitors (ICIs) on treatment patterns and survival outcomes in patients with locally advanced or metastatic non-small cell lung cancer (aNSCLC) in France and Germany.

Materials and Methods: Patients with aNSCLC without known *ALK* or *EGFR* mutations receiving first-line (1L) therapy were included from (i) the retrospective Epidemiological-Strategy and Medical Economics Advanced and Metastatic Lung Cancer cohort (ESME-AMLC, France; 2015–2018) and (ii) the prospective Clinical Research platform Into molecular testing, treatment and outcome of non-Small cell lung carcinoma Patients platform (CRISP, Germany; 2016–2018). Analyses were stratified according to histology. Survival outcomes were

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estimated using Kaplan–Meier methodology and stratified by year of 1L therapy. Data sources were analysed separately.

Results: In ESME-AMLC and CRISP, 8,046 and 2,359 patients were included in the study, respectively. In both countries, approximately 20 % of all patients received pembrolizumab monotherapy as 1L treatment in 2018. In ESME-AMLC, the proportion receiving an ICI over the course of treatment (any line) increased from 42.2 % (2015) to 56.1 % (2018) in patients with squamous histology, and 28.9 % to 51.9 % with non-squamous/other; in CRISP, it increased from 50.6 % (2016) to 65.2 % (2018) with squamous histology, and 40.8 % to 62.7 % with non-squamous/other. Two-year overall survival from 1L initiation was 36.8 % and 25.6 % in the squamous cohorts and 36.5 % and 30.8 % in the non-squamous/other cohorts in ESME-AMLC and CRISP, respectively. No significant change in overall survival was observed over time; however, the follow-up time available was limited in the later years of the analysis.

Conclusion: The results of this joint research from two large clinical databases in France and Germany demonstrate the growing use of ICIs in the management of aNSCLC. Future analyses will allow for the evaluation of the impact of ICIs on long-term survival of patients with aNSCLC.

1. Introduction

As the leading cause of cancer-related death in Europe and worldwide, lung cancer accounts for 18 % of total cancer deaths [1]. During 2020, 48,299 and 64,804 new cases were recorded in France and Germany, respectively. In each country, this represents 10.3 % of all cancers diagnosed, and approximately 20 % of all cancer-related deaths [2].

Lung cancer presents as two main histologic subtypes: small cell lung cancer and non-small cell lung cancer (NSCLC). The majority of cases are NSCLC at approximately 84 %; however, irrespective of histology, diagnosis frequently occurs only after the cancer has become late stage (stage IIIB or IV) [3,4]. Hence, with an overall 5-year survival rate of 26 %, the prognosis is poor [4].

For patients with locally advanced or metastatic NSCLC (stage III or IV) (aNSCLC) and a performance status (PS) of 0–2, the treatment recommended by the European Society for Medical Oncology (ESMO) guidelines, as well as in the national recommendations for both France and Germany, is systemic anti-cancer therapy (defined as any chemotherapy, immunotherapy and targeted biological therapy) [5–8]. Several novel classes of therapy have recently been approved and introduced into clinical practice, including immune checkpoint inhibitors (ICIs) targeting the programmed death receptor 1/programmed death ligand 1 (PD-1/PD-L1) pathway [6,9,10]. In the second-line (2L) setting, ICIs have shown particular promise in clinical trials, demonstrating superiority to chemotherapy in response rates, tolerability and

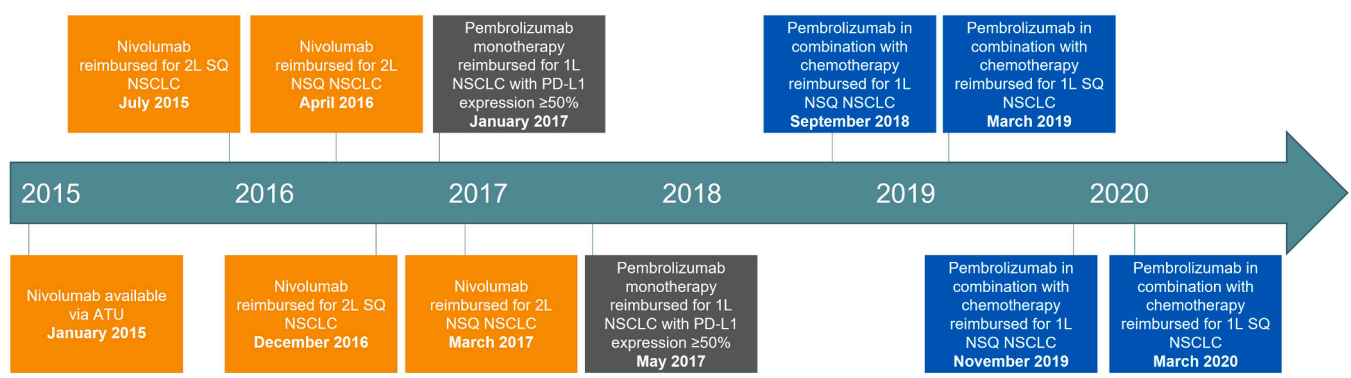
overall survival (OS) [11–15].

Several ICIs (pembrolizumab, atezolizumab, nivolumab) have been approved in Europe for the 2L treatment of NSCLC and the first-line (1L) treatment for aNSCLC [16–18]. Once approved, the process of reimbursement varies across member states. In Germany, new therapies are reimbursed directly after European Medicines Agency (EMA) approval. The first reimbursed ICI for NSCLC was nivolumab, which was launched in the 2L setting in July 2015 for patients with squamous (SQ) cell histology and in April 2016 for patients with non-squamous cell (NSQ) histology in Germany (Fig. 1).

In France, since January 2015, ICIs have been reimbursed for aNSCLC through the early access Autorisation Temporaire d’Utilisation (Temporary Authorization for Use, ATU) programme; the official reimbursement of nivolumab in 2L occurred in December 2016 for SQ and in March 2017 for NSQ.

In the 1L setting, pembrolizumab as monotherapy has been reimbursed for patients with PD-L1 expression $\geq 50\%$ since January 2017 and May 2017 in Germany and France, respectively. Other ICIs (atezolizumab, cemiplimab) have also received approval more recently as monotherapies for 1L treatment of patients with PD-L1 expression $\geq 50\%$. Pembrolizumab in combination with chemotherapy has been approved and reimbursed for patients with NSQ histology since September 2018 and November 2019 in Germany and France, respectively, and for patients with SQ histology since March 2019 and March 2020.

Germany



France

Fig. 1. Reimbursement dates for ICIs in Germany and France

In France, patients with cancer are fully covered for their healthcare expenditures, and hospitals are reimbursed the drug costs on top of the diagnosis-related group tariff. In order to obtain the full reimbursement of drug costs, hospitals need to provide evidence that they follow label indications. 1L, first-line; 2L, second-line; ATU, Autorisation Temporaire d’Utilisation (Temporary Authorization for Use) programme; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; NSQ, non-squamous; PD-L1, programmed death ligand 1; SQ, squamous.

Given the evolving nature of aNSCLC therapies, there is a need to better understand the impact of recently approved ICIs on treatment patterns in aNSCLC. The necessary eligibility criteria within clinical trials make the results challenging to transpose to patients in clinical practice. Therefore, as the standard of care progresses, these real-world data provide valuable evidence in a broader spectrum of patients, complementing data from randomised controlled trials, and contributing to the body of evidence to help inform future treatment decisions.

I-O Optimise is a multinational, observational research initiative providing insights on the emerging lung cancer landscape based on established real-world data sources [19–22]. Focusing on aNSCLC in France and Germany, the aim of this study is to describe the evolution of treatment patterns in real-world practice alongside the broadening of ICI indications between 2015 and 2018, and to evaluate temporal trends in OS and progression-free survival (PFS) during this period. This was performed using the Epidemiological-Strategy and Medical Economics Advanced and Metastatic Lung Cancer (ESME-AMLC) data platform in France and the Clinical Research platform Into molecular testing, treatment and outcome of non-Small cell lung carcinoma Patients (CRISP) data source in Germany.

2. Materials and methods

2.1. Study design

This study is an observational cohort study, based on two existing data sources: ESME-AMLC and CRISP.

2.1.1. ESME-AMLC

The ESME-AMLC research programme is an academic real-world data platform retrospectively collecting and centralising comprehensive data on cancer management from a network of academic and non-academic health facilities (private non-profit comprehensive cancer centres and university or general hospitals). The sites within the network are selected to be representative of the French healthcare system for the treatment of advanced and metastatic lung cancer. At the time of the analysis, 30 sites were contributing to the ESME-AMLC database, although there are now 37 in place.

The dataset (NCT03848052) was authorised by the French data protection authority in 2017 and focuses on adult patients with locally advanced or metastatic lung cancer (stage IIIB/IV) who were diagnosed or initiated treatment from 2015 onwards. Data are compiled from patients' electronic medical records, inpatient hospitalisation records and pharmacy records, and employs rigorous screening procedures. Data from multiple data sources within each centre (e.g. French computerised medical information system, pharmacy records, other databases or search engines) are used to comprehensively identify all patients who meet the selection criteria.

All adult patients diagnosed with aNSCLC in every participating centre were included in the cohort for this study. Data were retrospectively collected from medical records using a well-structured electronic data collection tool approach by trained technicians on-site.

In ESME-AMLC, informed consent was not provided by patients in accordance with the authorisations issued by the French authorities and in compliance with the regulations in force for such a retrospective registry. A website was in place to inform the patients of any studies using their data and patients were able to exercise their rights at any time by contacting the Unicancer Data Protection Officer.

2.1.2. CRISP (AIO-TRK-0315)

CRISP (NCT02622581) is an open, non-interventional, prospective, multicentre clinical research platform that collects data from more than 170 cancer sites (certified lung cancer centres, comprehensive cancer centres, university and non-university hospitals and office-based oncology practices) using electronic case report forms and includes, among other cohorts, adult patients with aNSCLC at the start of 1L

systemic therapy.

Inclusion criteria for patients in CRISP's NSCLC advanced-stage cohort are (i) stage IIIB and IIIC (if the patient is ineligible for curative surgery and/or radiochemotherapy), or stage IV histologically confirmed NSCLC, (ii) signed informed consent no later than 4 weeks after start of 1L treatment and (iii) ability to understand and complete patient-reported-outcome assessment.

The first patient was recruited in December 2015; however, not all sites started recruitment at this time, leading to a limited sample of patients included in 2016. The current dataset represents approximately 3–6 % of the metastatic NSCLC population in Germany.

2.2. Study population

This study included all adult (age ≥ 18 years) patients without known anaplastic lymphoma kinase (ALK) or epidermal growth factor receptor (EGFR) gene mutations (i.e. either tested negative or not tested) receiving a 1L of therapy for aNSCLC (*de novo* or progressed and confirmed by histology or cytology) during the study period. Those with concomitant cancers were excluded (i.e. diagnosis of another cancer at or within 5 years prior to aNSCLC diagnosis or any ongoing systemic anti-cancer therapy regimen at the time of NSCLC diagnosis).

An illustration of study attrition and patient numbers is shown in the appendix (Fig. S1).

Patients were followed up from the start of 1L of therapy (i.e. first systemic anti-cancer therapy regimen received in patients with aNSCLC) to the date of last patient status/last contact of the patient with the centre prior to end of study period, known exit from the data source or death.

2.3. Study period

For ESME-AMLC, the inclusion period was from 1 January 2015 to 31 December 2018 and the follow-up period was until 31 August 2019 (date of last data extraction). For CRISP, the inclusion period was from 1 January 2016 to 31 December 2018, while the follow-up period was until 30 June 2020.

2.4. Statistical analysis

Patient and clinical characteristics were summarised using descriptive statistics, with subsequent analyses stratified into two histological categories: SQ and NSQ/others (including undifferentiated carcinoma). Treatment sequencing was described for the first four lines of therapy using Sankey diagrams.

OS and PFS were estimated using survival methodology, depicted graphically by Kaplan–Meier (KM) curves. OS was defined as the time (in months) from the start date of 1L therapy until the date of death due to any cause. Response evaluation criteria in solid tumours (RECIST) is not feasible in the real-world setting due to missing clinical data, and as such in this study PFS was defined as the time (in months) from the start date of 1L therapy until the date of first disease progression identified in clinical practice or the date of death for any cause, whichever occurred first. Patients who did not die or progress during the study period were censored at time of last contact with the centre.

OS and PFS were stratified by the year of the 1L of therapy start. Log-rank tests (unadjusted analysis) as well as a Cox regression model adjusted for age, sex and Eastern Cooperative Oncology Group (ECOG) PS were used to evaluate the significance of the trend observed over time.

A sensitivity analysis for OS was carried out on the ESME-AMLC data to evaluate the maximum bias that could be introduced by the under-reporting of deaths in the patients' medical records, due to the retrospective data collection. In this analysis, all censored patients who had not been in contact with the centre for more than 12 months at the time of last file update were considered as having died, and the date of death

was defined as 6 months after the date of last contact with the centre. In addition, as some centres in CRISP did not contribute to the initial period of the study (2016), and to confirm that the results observed were not due to the changes in the centres involved over time, an analysis restricting the population to the centres contributing data to the entire study period was carried out.

Each data source was analysed separately, applying consistent variable definitions (where possible) and analytic methods. Due to the differences in the populations captured (i.e. differences in inclusion criteria and centres involved), data collection methods and sources of data with the potential to impact upon the results and their interpretation, reasons for heterogeneity across the two data sources are clearly mentioned and discussed.

3. Results

3.1. Patient characteristics and 1L regimens received

Demographics and baseline characteristics by histology in ESME-AMLC and CRISP are shown in Table 1, and by year of 1L initiation in Table S1. Overall, in ESME-AMLC, 8,046 patients with aNSCLC without known ALK or EGFR mutations starting their 1L of therapy between 2015 and 2018 were identified, including 1,793 patients with SQ histology (22.3 %). In CRISP, 2,359 patients with aNSCLC without known ALK or EGFR mutations starting their 1L between 2016 and 2018 were identified, including 506 patients with SQ histology (21.4 %).

Median age at 1L initiation was similar between the two cohorts; it

was slightly higher in patients with SQ histology compared with NSQ/others in both ESME-AMLC (66.9 vs 62.8 years) and CRISP (69.0 vs 65.0 years). Between 12.2 % and 18.1 % of the patients in both data sources had a reported ECOG of 2 or higher at start of 1L.

At 1L initiation, 88.8 % and 70.9 % of patients with SQ histology and 83.6 % and 68.8 % of patients with NSQ/others, in the ESME-AMLC and CRISP cohorts, respectively, were either current smokers or former heavy smokers.

Among patients with NSQ/other histologies, 81.7 % and 91.7 % had an adenocarcinoma in ESME-AMLC and CRISP, respectively. Most of the patients had at least one metastasis at the time of 1L initiation: 63.1 % and 88.1 % of patients with SQ and 84.9 % and 94.4 % with NSQ/others in ESME-AMLC and CRISP, respectively. The proportion with brain metastases in ESME-AMLC was 13.6 % among patients with SQ histology and 32.2 % among NSQ/others. The proportion with brain metastases in CRISP was 11.5 % in SQ and 25.4 % in NSQ/others.

PD-L1 testing prior to 1L treatment start increased over time in both cohorts. In 2018, 80.5 % and 71.3 % of patients with SQ histology and 83.5 % and 79.3 % of NSQ/others had PD-L1 testing prior to 1L start in ESME-AMLC and CRISP cohorts, respectively. Among tested patients in ESME-AMLC and CRISP cohorts in 2018, the proportion of PD-L1 high expressors (≥ 50 % on tumour cells) was 26.4 % and 27.6 % in SQ and 33.3 % and 29.6 % in NSQ/other patients, respectively; the proportion of PD-L1 expressors between 1 % and 49 % was 41.6 % and 31.6 % in SQ and 27.8 % and 26.9 % in NSQ/other patients, respectively (Table S1).

Table 1
Patient demographics and characteristics at time of first-line initiation by histological subtype in ESME-AMLC and CRISP.

		SQ		NSQ/others	
		ESME-AMLC	CRISP	ESME-AMLC	CRISP
Cohort size	N (%)	1,793 (22.2 %)	506 (21.4 %)	6,253 (77.7 %)	1,853 (78.6 %)
Age, years	Median	66.9	69.0	62.8	65.0
	Range	30.5–91.5	44–91	45.9–79.7	26–89
	≥ 75	341 (19.0 %)	141 (27.9 %)	707 (11.3 %)	324 (17.5 %)
Sex, n (%)	Male	1,457 (81.3 %)	371 (73.3 %)	4,055 (64.8 %)	1,116 (60.2 %)
ECOG PS, n (%)	0–1	818 (45.6 %)	379 (74.9 %)	3,101 (49.6 %)	1,388 (74.9 %)
	2	245 (13.7 %)	63 (12.5 %)	820 (13.1 %)	200 (10.8 %)
	3–4	69 (3.8 %)	6 (1.2 %)	314 (5.0 %)	26 (1.4 %)
	Missing	661 (36.9 %)	58 (11.5 %)	2,018 (32.3 %)	239 (12.9 %)
	Current smoker	608 (33.9 %)	163 (32.2 %)	2,334 (37.3 %)	559 (30.2 %)
Smoking status*, n (%)	Heavy former smoker	984 (54.9 %)	196 (38.7 %)	2,898 (46.3 %)	715 (38.6 %)
	Light former smoker	68 (3.8 %)	44 (8.7 %)	260 (4.2 %)	154 (8.3 %)
	Former smoker, unknown intensity	23 (1.3 %)	30 (5.9 %)	102 (1.6 %)	105 (5.7 %)
	Never smoked	46 (2.6 %)	23 (4.5 %)	429 (6.9 %)	159 (8.6 %)
	Missing	64 (3.6 %)	50 (9.9 %)	230 (3.7 %)	161 (8.7 %)
Stage at initial diagnosis, n (%)	I–II	227 (12.7 %)	26 (5.1 %)	461 (7.4 %)	82 (4.4 %)
	IIIA	286 (16.0 %)	20 (4.0 %)	531 (8.5 %)	35 (1.9 %)
	IIIB–IIIC	413 (23.0 %)	77 (15.2 %)	674 (10.8 %)	133 (7.2 %)
	IV	831 (46.3 %)	365 (72.1 %)	4,483 (71.7 %)	1,512 (81.6 %)
	Missing	36 (2.0 %)	18 (3.6 %)	104 (1.7 %)	91 (4.9 %)
	Epidermoid carcinoma	1,793 (100.0 %)	506 (100.0 %)	0	0
Histology, n (%)	Adenocarcinoma	0	0	5,110 (81.7 %)	1,700 (91.7 %)
	Large cell carcinoma	0	0	251 (4.0 %)	40 (2.2 %)
	Undifferentiated carcinoma	0	0	226 (3.6 %)	NR
	Others	0	0	666 (10.7 %)	113 (6.1 %)
	EGFR mutation testing [†] , n (%)	Wild type	192 (10.7 %)	135 (26.7 %)	4,152 (66.4 %)
ALK rearrangement testing [†] , n (%)	Not tested [‡]	1,601 (89.3 %)	371 (73.3 %)	2,101 (33.6 %)	487 (26.3 %)
	Wild type	212 (11.8 %)	120 (23.7 %)	3,758 (60.1 %)	1,383 (74.6 %)
At least one metastasis at time of 1L initiation, n (%)	Not tested [‡]	1,581 (88.2 %)	386 (76.3 %)	2,495 (39.9 %)	470 (25.4 %)
	1,132 (63.1 %)	446 (88.1 %)	5,309 (84.9 %)	1,749 (94.4 %)	
Metastases locations at time of 1L initiation, n (%)	Bone metastases	391 (21.8 %)	109 (21.5 %)	2,331 (37.3 %)	539 (29.1 %)
	Brain metastases	244 (13.6 %)	58 (11.5 %)	2,012 (32.2 %)	471 (25.4 %)
	Symptomatic brain metastases	86 (4.8 %)	NR	793 (12.7 %)	NR
	Asymptomatic brain metastases	158 (8.8 %)	NR	1,219 (19.5 %)	NR
	Liver metastases	224 (12.5 %)	88 (17.4 %)	900 (14.4 %)	262 (14.1 %)

* Heavy former smoker = defined as patients who quit smoking less than 15 years ago or who quit smoking but had smoked more than 10 pack years; Light former smoker = defined as patients who quit smoking more than 15 years before diagnosis or who quit smoking and had smoked less than 10 pack years. †At any time during the study period. ‡Includes patients tested but with not contributive results (<2%). ECOG, Eastern Cooperative Oncology Group; NR, not reported; NSQ, non-squamous; PS, performance status; SQ, squamous.

3.2. Treatment sequencing and evolution of ICI uptake

Fig. 2 shows the evolution of the proportion of patients receiving an immunotherapy regimen and, among those, the distribution of line of therapy for first ICI received, by year of 1L initiation. Overall, considering all lines of therapy received, an increase in the proportion of patients receiving an ICI regimen (any line) was observed over time in both data sources (Fig. 2A and 2B).

Among patients with SQ histology, in ESME-AMLC, the proportion receiving an ICI regimen increased from 42.2 %/44.3 % in 2015/2016 (period of the ATU early-access programme of 2L ICI) to 47.8 %/56.1 % in 2017/2018 ($p < 0.01$). In parallel, this proportion in CRISP, increased from 50.6 % in 2016 (2L ICI reimbursement in July 2015) to 56.4 %/65.2 % in 2017/2018, respectively ($p < 0.01$; 1L ICI monotherapy reimbursement in January 2017). In 2018, the proportion of patients with SQ histology receiving pembrolizumab monotherapy in first-line was 16.3 % in ESME-AMLC and 24.6 % in CRISP; the proportion of patients receiving pembrolizumab with platinum-based chemotherapy was 6.2 % in CRISP (Fig. 2A).

Among patients with NSQ/others histologies, in ESME-AMLC, the proportion receiving an ICI regimen increased from 28.9 %/32.3 % in 2015/2016, respectively (period of the ATU early-access programme of 2L ICI) to 43.4 %/51.9 % in 2017/2018, respectively ($p < 0.01$; post-2L ICI reimbursement, 1L ICI monotherapy reimbursement mid-2017). In parallel, in CRISP, this proportion increased from 40.8 % in 2016 (2L ICI

reimbursement in April 2016) to 57.4 %/62.7 % in 2017/2018, respectively ($p < 0.01$; 1L ICI monotherapy reimbursement in January 2017, 1L pembrolizumab + chemotherapy reimbursement in September 2018). In 2018, the proportion of patients with NSQ/others histologies receiving pembrolizumab monotherapy in first-line was 18.1 % in ESME-AMLC and 22.5 % in CRISP; the proportion of patients receiving pembrolizumab with platinum-based chemotherapy was 14.1 % in CRISP (Fig. 2B).

The full treatment sequencing for ESME-AMLC and CRISP are shown in Figs. S2 and S3, respectively.

3.3. OS and PFS in patients with NSCLC starting 1L therapy between 2015 and 2018

3.3.1. ESME-AMLC

Among patients with SQ histology, median [95 % confidence interval (CI)] OS from 1L initiation was 15.5 months [14.3–16.7]; 1-year and 2-year OS were 58.2 % and 36.8 %, respectively. No significant changes in 2-year OS from 1L initiation were observed between 2015 and 2017 (35.8 %, 37.7 % and 37.5 %, respectively; insufficient follow-up in 2018) (Fig. 3A; sensitivity analyses by year, considering all censored patients not in contact with the centre for more than 12 months as deceased, can be found in Fig. S4A). One-year PFS from 1L initiation was 18.6 %, 18.4 %, 16.4 % and 26.1 % in 2015, 2016, 2017 and 2018, respectively (Fig. 3A).

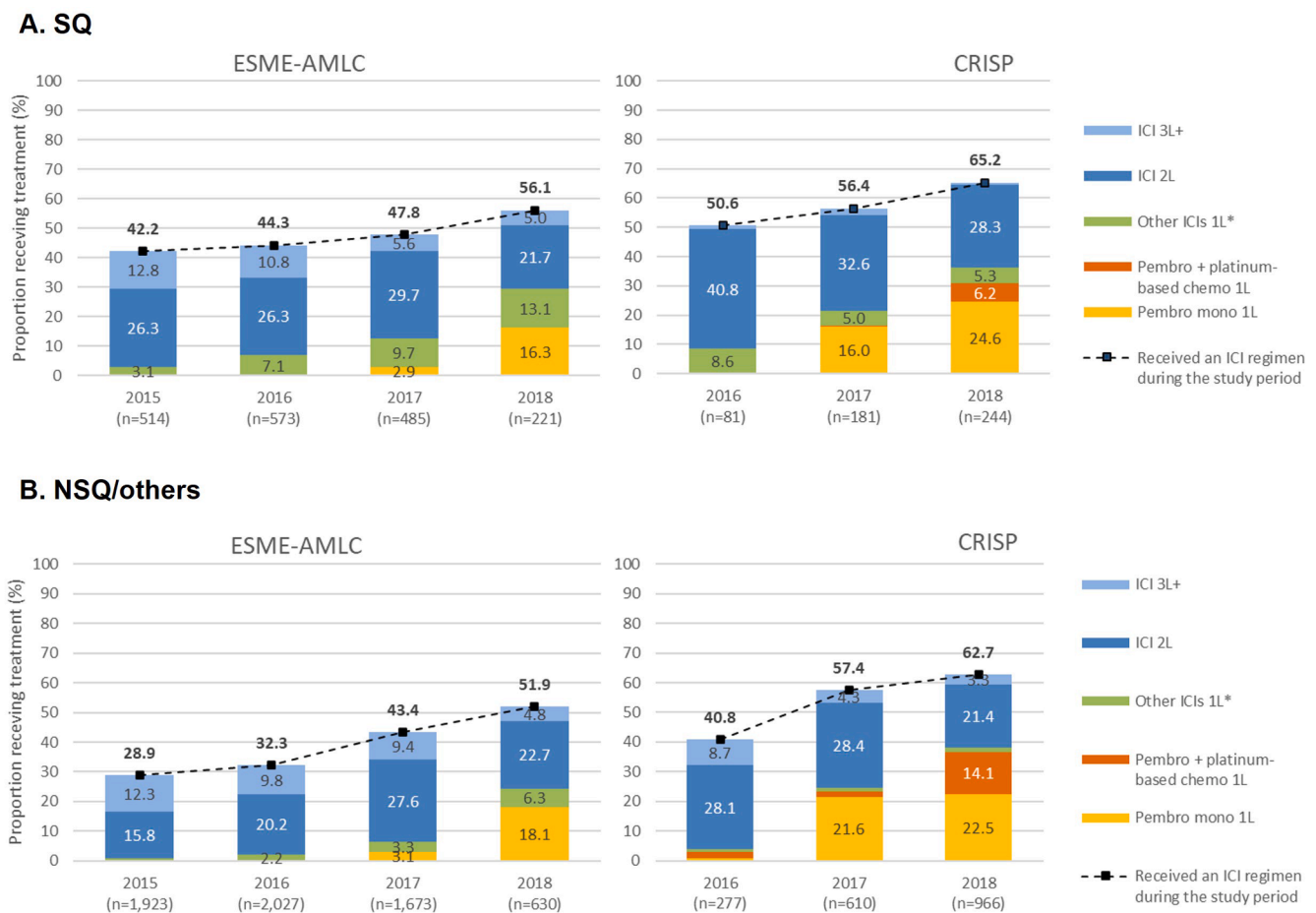


Fig. 2. Proportion of patients treated with ICI and distribution of line of therapy for first ICI therapy received over time, by histological subtype (index date = year of 1L initiation)

*Other ICIs used were atezolizumab, durvalumab and nivolumab. For ICI monotherapy other than pembrolizumab, patients are likely to have been refractory to a previous multimodal treatment administered for non-metastatic disease. As per our study definition, 1L is defined as the first systemic anti-cancer therapy regimen received at locally advanced or metastatic stage. 1L, first-line; 2L, second-line; 3L+, third-line or later; chemo, chemotherapy; ICI, immune checkpoint inhibitor; mono, monotherapy; NSQ, non-squamous; pembro, pembrolizumab; SQ, squamous.

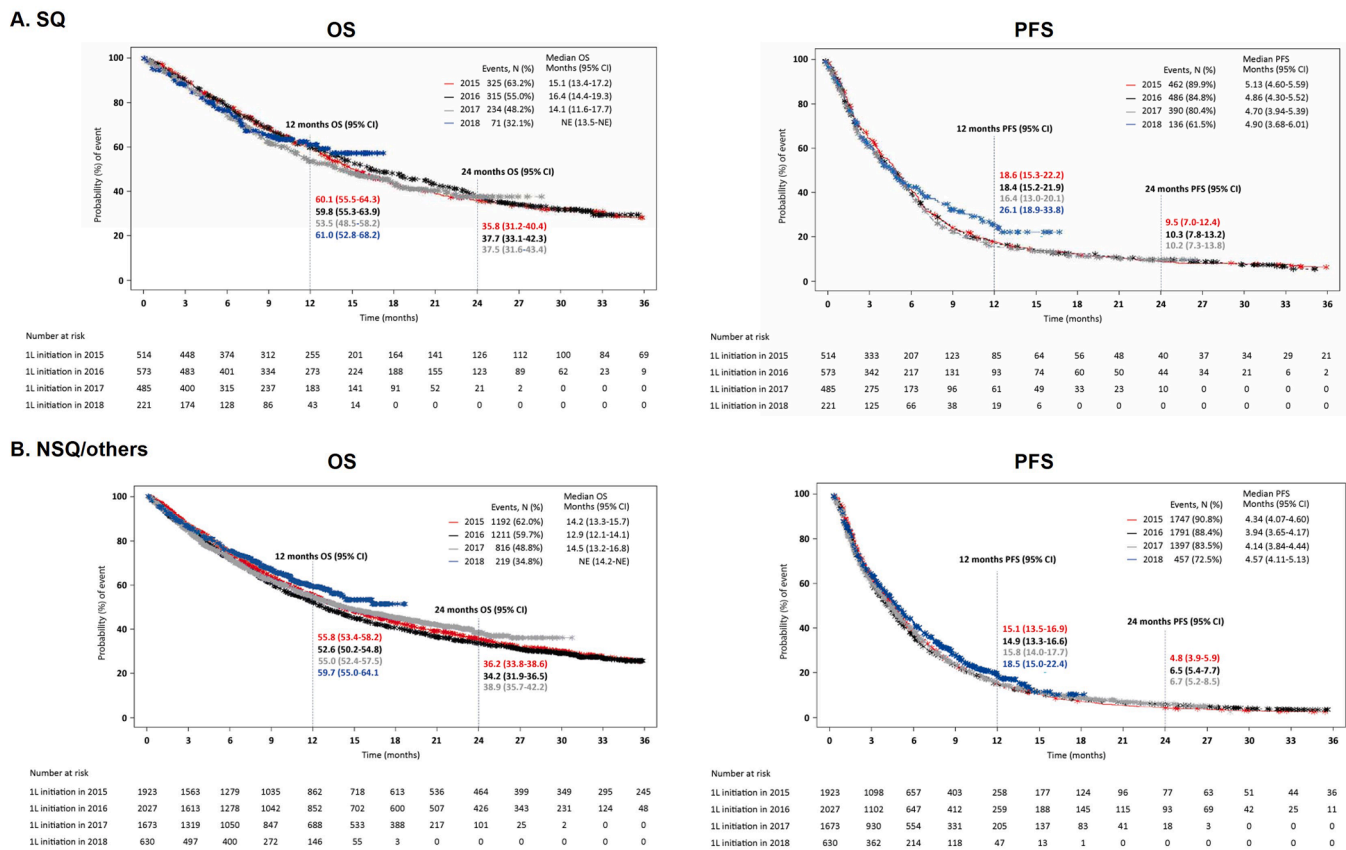


Fig. 3. OS and PFS in patients with NSCLC starting their first line of treatment between 2015 and 2018 in ESME-AMLC, by histological subtype. PFS is defined as the time (in months) from the treatment line start date until the date of first disease progression identified in clinical practice or the date of death for any cause, whichever occur first; OS is defined as defined as the time (in months) from index date until the date of death due to any cause. CI, confidence interval; NSCLC, non-small cell lung cancer; NSQ, non-squamous; OS, overall survival; PFS, progression-free survival; SQ, squamous.

For patients with NSQ/other histologies, median [95 % CI] OS from 1L initiation was 14.1 months [13.4–14.6]; 1-year and 2-year OS were 54.8 % and 36.5 %, respectively. No significant changes in 2-year OS from 1L initiation were observed between 2015 and 2017 (36.2 % in 2015, 34.2 % in 2016 and 38.9 % in 2017) (Fig. 3B); sensitivity analyses by year can be found in Fig. S4B). From 1L initiation, 1-year PFS was 15.1 %, 14.9 %, 15.8 % and 18.5 % in 2015, 2016, 2017 and 2018, respectively (Fig. 3B).

3.3.2. CRISP (AIO-TRK-0315)

For patients with SQ histology in CRISP, median [95 % CI] OS from 1L initiation was 10.9 months [9.8–12.9]; 1-year and 2-year OS were 47.3 % and 25.6 %, respectively. A very high OS was observed in 2016 with a median OS of 15.2 months [8.2–25.9] and a 2-year OS of 42.1 %. Similar OS curves were observed in 2017 and 2018, with a median of 11.0 [8.7–12.7] and 10.5 months [8.3–13.2], respectively, and a 2-year OS of 20.6 % and 23.3 %, respectively (Fig. 4A). Similar values were observed in the sensitivity analysis restricted to centres contributing data to all years (Fig. S5A). One-year PFS from 1L initiation was 29.9 %, 23.1 % and 20.7 % in 2016, 2017 and 2018, respectively (Fig. 4A).

Among patients with NSQ/other histologies in CRISP, median [95 % CI] OS from 1L initiation was 11.9 months [10.9–13.0]; 1-year and 2-year OS were 49.7 % and 30.8 %, respectively. No significant changes in 2-year OS from 1L initiation was observed between 2016 and 2018 (28.0 % in 2016, 29.2 % in 2017 and 32.3 % in 2018; Fig. 4B). Similar values were observed in the sensitivity analysis restricted to centres contributing data to all years (Fig. S5B). One-year PFS from 1L initiation was 21.9 %, 24.5 % and 28.2 % in 2016, 2017 and 2018, respectively (Fig. 4B).

4. Discussion

With the introduction of newer therapies such as ICIs in the 2L+ setting and more recently in 1L as monotherapy or associated with chemotherapy, the treatment landscape for aNSCLC is undergoing a paradigm shift. In this rapidly evolving environment, it is important to understand how treatment patterns change in real-life practice and the health outcomes observed.

Our study provides an overview of the early use of ICI in aNSCLC without known ALK/EGFR mutations in France and Germany between 2015 and 2018 using ESME-AMLC and CRISP cohorts. Given the richness of clinical data collected from both of these well-structured data sources, this study also allows a better understanding of the clinical characteristics of patients with aNSCLC starting a 1L therapy.

Patients starting a 1L therapy in ESME-AMLC were found to be slightly younger than in CRISP. While the reason for this difference between the two countries is not clear, ESME-AMLC covers a smaller number of academic and non-academic sites than CRISP, which may result in a more selected population. These results are consistent with other recent observational studies on large claims databases in France and Germany [23,24]. Most patients (more than 80 % in ESME-AMLC and approximately 70 % in CRISP) were either current smokers at the time of aNSCLC diagnosis, or former heavy smokers. The exclusion of patients with EGFR mutations from the analysis populations may have resulted in a reduced proportion of non-smokers.

ESMO recommends including magnetic resonance imaging of the brain as part of the diagnosis and staging in NSCLC, and in our study the brain was the second most frequent location for metastasis after bone metastases [6]. Brain metastases were present in 13.6 % and 11.5 % of

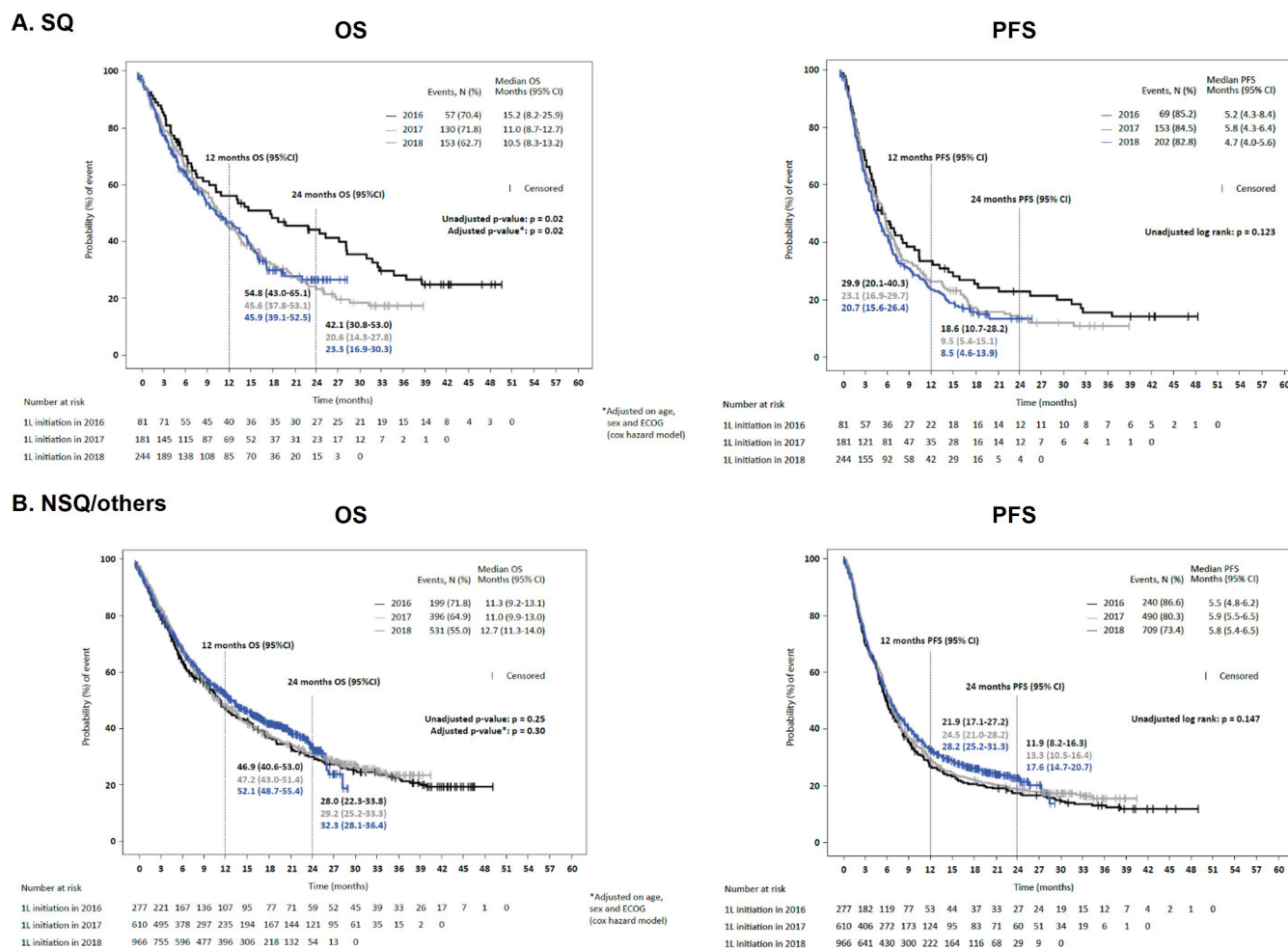


Fig. 4. OS and PFS in patients with NSCLC starting their first line of treatment between 2016 and 2018 in CRISP, by histological subtype. PFS is defined as the time (in months) from the treatment line start date until the date of first disease progression identified in clinical practice or the date of death for any cause, whichever occur first; OS is defined as the time (in months) from index date until the date of death due to any cause. CI, confidence interval; NSCLC, non-small cell lung cancer; NSQ, non-squamous; OS, overall survival; PFS, progression-free survival; SQ, squamous.

patients with SQ histology and 32.2 % and 25.4 % of patients with NSQ/other histologies at the time of 1L therapy start in ESME-AMLC and CRISP, respectively, reflecting previous findings [6,25,26]. In addition, approximately 12–18 % of 1L-treated patients in this study had an ECOG PS score of ≥ 2 . Patients with symptomatic or untreated brain metastases or those with ECOG PS ≥ 2 are typically excluded from clinical trials; however, in clinical practice, as in our study, these characteristics are present in a significant proportion of the patients with aNSCLC. Their inclusion in observational datasets is therefore important to accurately represent the aNSCLC population in the real world.

With reimbursement of pembrolizumab monotherapy in the 1L setting restricted to patients with PD-L1 ≥ 50 %, an increase in PD-L1 testing prior to 1L treatment selection was observed in both countries, from 6 % in 2015 to approximately 70–80 % in 2018. Our study showed the rapid adoption of pembrolizumab monotherapy in the 1L setting for patients with PD-L1 ≥ 50 %, with approximately 20 % of all 1L-treated patients receiving pembrolizumab monotherapy as 1L treatment in 2018 in both countries. Similar results were described in a recently published study in the UK [27].

In Germany, the use of pembrolizumab associated with chemotherapy in the 1L setting was observed in 2018, reflecting the speed of the process in this country in moving from regulatory approval to reimbursement. This treatment group represented 14 % of 1L-treated patients with NSQ/other histologies in 2018, despite the late

reimbursement in the year (September 2018). This confirms the willingness to use immunotherapy as soon as possible in the management of patients with aNSCLC, and, in contrast to France, it also highlights how impactful the duration of the reimbursement process can be in accessing innovative treatments. Future research will help to understand the place of immunotherapy associated with chemotherapy in the 1L setting versus immunotherapy alone in patients with high PD-L1 expression (PD-L1 ≥ 50 %).

Our study does not capture the pre-immunotherapy era, as its use started in 2015 in France and in 2016 for Germany. In Germany (CRISP), in the 2016 cohort, half of the SQ patients and 40 % of NSQ/other patients who started 1L of therapy in 2016 received an ICI over the course of their treatment. In France (ESME-AMLC), in the 2015 and 2016 cohorts, the proportion of patients receiving an ICI over the course of their treatment was approximately 40–45 % in SQ patients and 30 % in NSQ/other patients. This is despite the first ICI indicated in lung cancer (i.e. nivolumab) only being available through an early access programme (ATU) in 2L+, which compensates for the lack of reimbursement in these new therapies in France. An absolute increase of 15 % and 20 % in the proportion of patients treated with ICI was observed over the study period in SQ and NSQ/other patients, respectively. This was similar in the two countries and mostly driven by the increased proportion of patients receiving pembrolizumab monotherapy in 1L.

In term of outcomes, no significant changes in OS were observed over

the study period. A longer follow-up period may be required to appreciate the true impact of ICIs on OS. Interestingly, OS was generally higher in SQ and NSQ/others patients in ESME-AMLC, compared with CRISP, potentially reflecting the difference in age in the two cohorts. The OS may also have been slightly overestimated in ESME-AMLC due to retrospective data collection and potential underreporting of deaths in medical records. In SQ patients in CRISP, a very high OS was observed in 2016, but the reasons for this are unclear. It should be noted, however, that the 2016 cohort included only a small sample of patients ($n = 81$) as a limited number of centres were active at this time. Overall, the OS observed in both data sources showed a 2-year survival from 1L start of approximately 30 %, which is in line with the OS observed in the control arm of the KEYNOTE-189 and KEYNOTE-407 studies, in which approximately 40 % of the patients received an ICI in 2L [28–31]. Furthermore, the 2-year survival estimates are higher than those in studies describing the survival of 1L-treated patients in the pre-ICI era in Europe, in which 2-year OS in non-ALK-EGFR patients was approximately 20 % [20,22]. A study from a German university hospital with more historical data was able to identify significant changes in OS from the pre-ICI (2012–2015) to the post-ICI period (2016–2018) in an NSQ population without targeted mutations (2-year OS increased from 17 % to 37 %) [32].

4.1. Strengths and limitations

An important strength of this study is the concurrent analysis, using the same methodology, of two of the largest real-world clinical datasets on NSCLC from two of the largest countries in Europe. This concurrent analysis is able to provide a broader view of aNSCLC in Europe than single country analyses. The ESME-AMLC research programme is a large-scale academic initiative that centralises data from multiple data sources across multiple French hospitals involved in lung cancer management, with all patients diagnosed with aNSCLC in participating centres being included in the cohort. CRISP is also an academic initiative capturing data prospectively from the start of treatment for patients with NSCLC receiving systemic therapy in Germany.

Both initiatives collect data using a well-structured electronic case report form completed by trained clinical research associates and employ quality control measures to limit inconsistencies in the data collected. Therefore, low variation in data completeness is expected between participating centres within each country. Differences observed between the results of the two data sources need to be interpreted cautiously on the basis of the differences in the design of the two platforms (for example, the use of retrospective or prospective data collection, exhaustive identification of patients with NSCLC through systematic diagnosis search versus clinician-prospective inclusion, and differences in participating centres).

Lung carcinomas and metastases were assessed descriptively by a radiologist and not using RECIST, so the time (in months) from the line of therapy start date until the date of first disease progression identified in clinical practice or the date of death for any cause, whichever occurred first, was used as a proxy measure of PFS. This limitation is due to the real-world nature of these studies. Another limitation of the study is that deaths were not cross-checked with national registries of death, which may have led to an overestimation of OS rates. In ESME-AMLC, a linkage with the national death database is in progress and will allow more precise estimates for future research.

4.2. Conclusion

The results of this concurrent research using two large clinical databases in France and Germany show the importance of ICIs in the management of aNSCLC, with >50 % of 1L-treated patients without known ALK or EGFR mutations receiving an ICI over the course of their treatment.

It is expected that ICIs will be more widely used from 2019 onwards

with the reimbursement of pembrolizumab plus chemotherapy in the 1L setting, allowing for more patients to have access to those therapies. Indeed, the Food and Drug Administration and the EMA approved the combination of nivolumab plus ipilimumab and two cycles of platinum doublet chemotherapy in the 1L setting for patients with metastatic or recurrent NSCLC, with no known EGFR or ALK genomic tumour aberrations, in May 2020 and November 2020, respectively [33,34].

Despite the absence of a historical cohort from the pre-ICI era, the 2-year survival rates observed in both data sources are in line with the improved survival expected with ICI use. Future analyses will allow evaluation of the evolution of practice, the impact of wider ICI use in 1L, and the long-term survival of patients receiving ICI therapies. It will also be possible to compare findings with other European country-specific databases, to expand the application of these real-world data sources.

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CRedit authorship contribution statement

Frank Griesinger: Conceptualization, Investigation, Methodology, Supervision, Visualization, Writing – review & editing. **Maurice Pérol:** Methodology, Resources, Supervision, Writing – review & editing. **Nicolas Girard:** Conceptualization, Supervision, Validation, Writing – original draft, Writing – review & editing. **Isabelle Durand-Zaleski:** Conceptualization, Methodology, Validation, Writing – review & editing. **Stefan Zacharias:** Data curation, Formal analysis, Visualization, Writing – review & editing. **Lise Bosquet:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Martina Jänicke:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Xavier Quantin:** Validation, Writing – review & editing. **Annika Groth:** Funding acquisition, Project administration, Supervision, Writing – review & editing. **Annette Fleitz:** Conceptualization, Methodology, Project administration, Writing – review & editing. **Alan Calleja:** Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Writing – review & editing. **Sonya Patel:** Conceptualization, Methodology, Validation, Writing – review & editing. **Laure Lacoïn:** Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing. **Melinda J. Daumont:** Conceptualization, Methodology, Writing – review & editing. **John R. Penrod:** Conceptualization, Methodology, Writing – review & editing. **Robert Carroll:** Conceptualization, Formal analysis, Methodology, Supervision, Validation, Writing – review & editing. **Daniela Waldenberger:** Conceptualization, Writing – review & editing. **Dorothee Reynaud:** Conceptualization, Methodology, Writing – review & editing. **Michael Thomas:** Conceptualization, Data curation, Project administration, Writing – original draft, Writing – review & editing.

Christos Chouaid: Formal analysis, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Frank Griesinger reports no competing interests.

Maurice Pérol reports fees for advisory Boards, consulting, and as an Invited Speaker from AstraZeneca, Bristol Myers Squibb, Gritstone, Illumina, Merck Sharp & Dohme, Novartis, Roche, Sanofi.

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Alan Calleja is an employee of IQVIA.

Sonya Patel is an employee of IQVIA.

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Melinda J Daumont is an employee of Bristol Myers Squibb and owns stock in the company.

John R. Penrod is an employee of Bristol Myers Squibb and owns stock in the company.

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Daniela Waldenberger is an employee of Bristol Myers Squibb.

Dorothee Reynaud is an employee of Bristol Myers Squibb.

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Appendix A. Supplementary data

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