Real-world treatment and response patterns in patients with metastatic non-small cell lung cancer in Spain: REVEAL study

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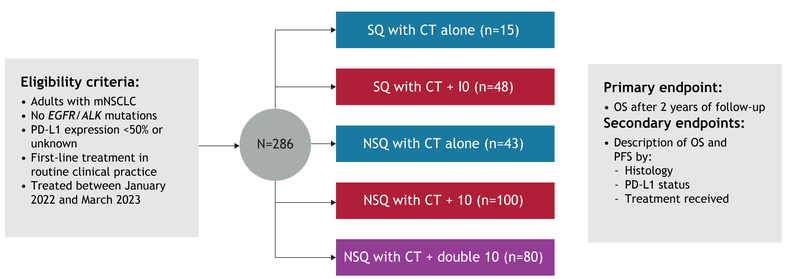
Introduction

- Immunotherapy (IO) has transformed the first-line treatment for metastatic non-small cell lung cancer (mNSCLC) without driver mutations, demonstrating superior survival outcomes compared with platinum-based chemotherapy (CT)[1,2].
- Most approved IO-based combinations are indicated for patients with tumor PD-L1 expression <50%, but real-world patients often present with broader clinical heterogeneity than those typically included in clinical trials[3-6].
- However, real-world evidence (RWE) on the effectiveness and safety of the different IO-containing regimens remains limited, particularly in routine practice settings where patient profiles are more diverse.
- The objective of the REVEAL study was to describe real-world treatment patterns and clinical outcomes in patients with mNSCLC receiving first-line therapy in Spain, including hard-to-treat patient populations such as those with squamous (SQ) histology, PD-L1-negative tumors, or brain metastases.

Methods

- A summary of the study design is shown in **Figure 1**.
  - REVEAL was a non-interventional, multicentric, and retrospective chart review study conducted in Oncology Departments of 18 Spanish hospitals.
  - This study included adult patients with mNSCLC without *EGFR*/*ALK* mutations, and with PD-L1 expression <50% or unknown, who initiated first-line treatment in routine clinical practice between January 2022 and March 2023. Patients representing different histological subtypes and approved therapeutic approaches were included.
  - The primary endpoint was overall survival (OS). Secondary endpoints included clinical outcomes (OS, progression-free survival [PFS], and objective response rate [ORR]) stratified by histology, PD-L1 status, and treatment received.

Figure 1. Study design



Results

Patients' characteristics

- The median age at diagnosis was 65.0 years (interquartile range [IQR]: 59.0-72.0), with 15.4% of patients being ≥75 years old. Most patients (87.2%) had an ECOG performance status of 0-1, while 12.8% had an ECOG ≥2 (ECOG 2: 11.6%; ECOG 3: 1.2%).
- Regarding PD-L1 expression, 61.3% of patients were negative, and 31.7% had PD-L1 expression of 1-49%; PD-L1 status was unknown for 7.0% of the population.
- Sociodemographic and clinical characteristics of the study population have been reported previously[7].

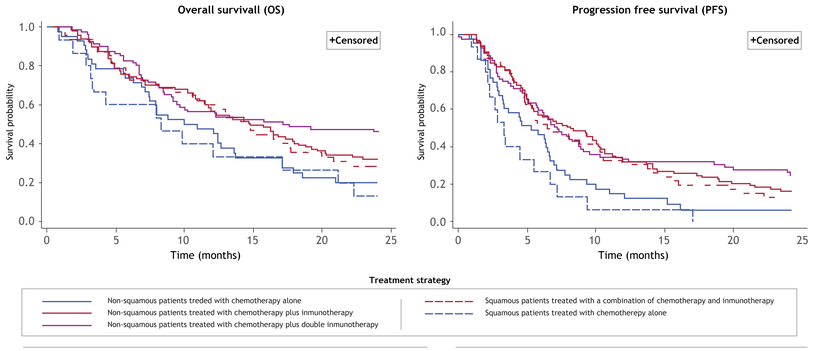
Follow-up and overall outcomes (OS and PFS)

- At database lock (June 2025), 69.2% of patients were no longer under follow-up; death accounted for 95.5% of these cases, with disease progression being the leading cause (82.5%).
- The median follow-up time was 9.8 months (IQR: 4.3-17.9) for patients treated with CT (n=57) and 14.8 months (IQR: 6.7-24.0) for those receiving any CT+IO regimen (n=228).
- Median OS and PFS for the overall population were 13.6 months (95% CI: 11.7-16.5) and 6.5 months (95% CI: 5.6-7.6), respectively.

Survival outcomes by histology and treatment regimen

- Across both SQ and non-squamous (NSQ) histologies, patients treated with CT alone showed the poorest OS and PFS compared with those receiving any IO-containing regimen (**Figure 2A and 2B**). Part of these survival findings have been reported previously[8].
- Two-year OS rates followed the same pattern, with substantially lower survival among patients receiving CT alone compared with those treated with IO-containing regimens, particularly patients with NSQ tumors receiving double IO (**Figure 2A**).

Figure 2. Overall survival (A) and progression-free survival (B) by histology and treatment in patients with mNSCLC



Histology/Treatment strategy	N	Median OS, months (95% CI)	HR (95% CI)	*p*-value HR*	2-year OS (95% CI)
SQ / CT alone	15	8.3 (2.83; 17.10)	Reference group for SQ	-	0.1 (0.02; 0.35)
SQ / CT + IO	48	14.8 (10.61; 17.78)	0.6 (0.33; 1.20)	0.132	0.3 (0.17; 0.42)
NSQ / CT alone	42	10.5 (7.40; 13.61)	Reference group for NSQ	-	0.2 (0.10; 0.34)
NSQ / CT + IO	100	15.0 (11.61; 18.00)	0.7 (0.47; 1.08)	0.098	0.3 (0.23; 0.42)
NSQ / CT + double IO	80	17.6 (9.48; NA)	0.5 (0.34; 0.85)	0.007	0.5 (0.35; 0.57)

CI, confidence interval; CT, chemotherapy; HR, hazard ratio; IO, immunotherapy; N, total number of patients; NA, not available; NSQ, non-squamous; OS, overall survival; SQ, squamous. *Log-rank test.

Histology/Treatment strategy	N	Median PFS, months (95% CI)	HR (95% CI)	*p*-value HR*
SQ / CT alone	15	3.3 (1.97; 5.52)	Reference group for SQ	-
SQ / CT + IO	48	6.6 (4.78; 10.47)	0.40 (0.22; 0.77)	0.004
NSQ / CT alone	43	5.3 (3.20; 6.60)	Reference group for NSQ	-
NSQ / CT + IO	99	8.1 (5.45; 10.10)	0.60 (0.41; 0.90)	0.010
NSQ / CT + double IO	78	7.2 (5.68; 8.86)	0.53 (0.35; 0.81)	0.003

CI, confidence interval; CT, chemotherapy; HR, hazard ratio; IO, immunotherapy; N, total number of patients; NA, not available; NSQ, non-squamous; PFS, progression-free survival; SQ, squamous. *Log-rank test.

Survival outcomes by PD-L1 expression

- OS and PFS analyses stratified by PD-L1 expression categories (negative, 1-49%, unknown) are summarized in **Table 1**.
- Patients with unknown PD-L1 expression showed markedly poorer OS and PFS compared with PD-L1-negative or PD-L1 1-49% groups, as reflected in the significantly higher hazard ratios for both endpoints.
- In patients with negative or unknown PD-L1 expression, previously presented data showed markedly improved OS in NSQ tumors treated with CT + double IO, while in SQ tumors CT + IO achieved better outcomes than CT alone[8].

Table 1. Median overall survival and progression-free survival by PD-L1 expression

PD-L1 expression	Overall survival				Progression-free survival			
	N	Median (95% CI)	HR (95% CI)	*p*-value*	N	Median (95% CI)	HR (95% CI)	*p*-value*
Negative	176	14.1 (10.84; 17.63)	Ref. group	-	174	6.6 (5.61;8.07)	Ref. group	-
1%-49%	89	16.7 (12.43; NA)	0.80 (0.57; 1.10)	0.180	90	7.1 (5.25;8.79)	0.98 (0.73; 1.29)	0.869
Unknown	20	4.1 (2.83; 7.90)	3.00 (1.76; 4.82)	0.000	20	2.8 (1.87;5.71)	2.03 (1.22; 3.20)	0.004

CI, confidence interval; HR, hazard ratio; N, total number of patients. *Log-rank test.

Response outcomes by histology and treatment regimen

- Response outcomes for the first-line treatment are summarized in Table 2, stratified by histological subtype and treatment regimen.
- Across treatment groups, IO-based combinations yielded higher ORR and DCR and longer DOR than CT alone, with response outcomes generally more favorable in NSQ than in SQ tumors.
- When comparing outcomes by histological group, NSQ tumors showed higher ORR and longer DOR than SQ tumors, independently of the treatment received.

Table 2. Response outcomes by histology and treatment regimen

	SQ histology, treated with:		NSQ histology, treated with:			Total (N=286)
	CT alone (N=15)	CT + IO (N=48)	CT alone (N=43)	CT + IO (N=100)	CT + double IO (N=80)	
Duration of first-line treatment (months), median (IQR)	2.1 (1.4-2.8)	6.0 (2.9-12.6)	3.6 (1.8-6.3)	6.7 (3.4-13.2)	5.9 (2.8-11.8)	5.1 (2.4-10.4)
Best response achieved, n (%)						
Complete response	0 (0.0)	4 (8.3)	1 (2.3)	9 (9.0)	4 (5.0)	18 (6.3)
Partial response	6 (40.0)	26 (54.2)	15 (34.9)	45 (45.0)	36 (45.0)	128 (44.8)
Stable disease	1 (6.7)	9 (18.8)	11 (25.6)	24 (24.0)	20 (25.0)	65 (22.7)
Disease progression	5 (33.3)	5 (10.4)	10 (23.3)	18 (18.0)	18 (22.5)	56 (19.6)
Not evaluable	3 (20.0)	4 (8.3)	6 (14.0)	4 (4.0)	2 (2.5)	19 (6.6)
ORR, n (%)	6 (40.0)	30 (62.5)	16 (37.2)	54 (54.0)	40 (50.0)	146 (51.0)
DCR, n (%)	7 (46.7)	39 (81.3)	27 (62.8)	78 (78.0)	60 (75.0)	211 (73.8)
DOR, median months (95% CI)	3.4 (0.9; NR)	7.0 (3.9; 12.2)	4.7 (3.8; 13.6)	10.5 (6.8; 15.7)	9.5 (4.1; NR)	7.7 (6.1; 11.0)
	SQ histology		NSQ histology			*p*-value
ORR, n (%)	36 (57.1)		110 (49.3)			0.273*
DOR, median months (95% CI)	6.3 (3.0; 12.1)		8.5 (5.8; 14.1)			0.040**

CI, confidence interval; CT, chemotherapy; DCR, disease control rate; DOR, duration of response; IO, immunotherapy; IQR, interquartile range; n, number of patients with event; N, total number of patients; NSQ, non-squamous; ORR, objective response rate; SQ, squamous. *Chi-squared test, **Log-rank test.

Safety

- In this RWE study, adverse events (AEs) leading to dose adjustments, temporary interruption, or definitive treatment discontinuation were recorded.
- As shown in Table 3, a total of 90 treatment-related AEs were reported in 68 (23.8%) patients, resulting in definitive treatment discontinuation in 38 (13.3%) patients.
- Definitive AE-related discontinuations were more frequent in IO-containing regimens (in particular, CT + double IO), while no permanent discontinuations were observed in the SQ CT-alone group.
- The most commonly reported AE categories were blood and lymphatic system disorders, gastrointestinal disorders, and renal/urinary disorders.

Table 3. Treatment-related adverse events by histology and treatment regimen

Adverse events	SQ histology, treated with:		NSQ histology, treated with:			Total (N=286)
	CT alone (N=15)	CT + IO (N=48)	CT alone (N=43)	CT + IO (N=100)	CT + double IO (N=80)	
Patients with ≥1 treatment-related AE, n (%)	0 (0.0)	6 (12.5)	11 (25.6)	24 (24.0)	27 (33.8)	68 (23.8)
Definitive treatment discontinuation due to AE, n (%)	0 (0.0)	4 (8.3)	4 (9.3)	15 (15.0)	15 (18.8)	38 (13.3)
Blood and lymphatic system disorders	0 (0.0)	2 (4.2)	6 (14.0)	12 (12.0)	4 (5.0)	24 (8.4)
Gastrointestinal disorders	0 (0.0)	1 (2.1)	1 (2.3)	5 (5.0)	8 (10.0)	15 (5.2)
Renal and urinary disorders	0 (0.0)	0 (0.0)	1 (2.3)	6 (6.0)	2 (2.5)	9 (3.1)
Respiratory, thoracic, and mediastinal disorders	0 (0.0)	2 (4.2)	0 (0.0)	1 (1.0)	4 (5.0)	7 (2.4)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	4 (5.0)	5 (1.7)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (6.3)	5 (1.7)

AE, adverse event; CT, chemotherapy; IO, immunotherapy; n, number of patients with event; N, total number of patients; NSQ, non-squamous; SQ, squamous.

Conclusions

- This study provides a comprehensive description of patients with mNSCLC treated in routine clinical practice in Spain, including diverse histological subtypes, PD-L1 expression levels (<50% or unknown), and first-line treatment strategies, reflecting a more heterogeneous population than those typically enrolled in clinical trials.
- IO-containing regimens were consistently associated with improved clinical outcomes across histologies, including longer OS, PFS, ORR, DCR, and DOR compared with CT alone.
- Two-year OS analyses supported these findings, with the most durable survival observed in patients with NSQ tumors treated with CT + double IO.
- Among PD-L1-negative tumors, CT + double IO showed the most favorable OS outcomes, reinforcing its potential value in this challenging subgroup.
- The safety profile of the different treatment strategies was consistent with that reported in clinical trials, with no unexpected safety signals emerging in this real-world cohort.
- As real-world datasets continue to expand, studies such as REVEAL may support a more tailored, histology- and biomarker-guided treatment selection in patients with mNSCLC.

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Conflict of interest

Dr. Carlos Aguado reports financial and non-financial relationships with MSD, AstraZeneca, Janssen, Pierre Fabre, BMS, Regeneron, and Roche, including roles as invited speaker, principal investigator, and advisory board member.
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