Analysis of the impact of age and brain metastases in first-line treatment of advanced non-small cell lung cancer (NSCLC) based on real-world data: reveal study

Juan Coves[1], Francisco de A. Aparisi[2], Bartomeu Massuti[3], Ana Cardeña-Gutiérrez[4], Juan Verdún[5], Victoria E. Castellón[6], Javier Garde-Noguera[7], Luis Cabezón-Gutiérrez[8], Ana Cobo Rodríguez[9], Sergio Vázquez[10], Esperanza Arriola[11], Alejandro Navarro[12], Manuel Cobo[13], Soledad Medina[14], Carmen Areses[15], Ana Laura Ortega Granados[16], Néstor Álvarez[17], David Vilanova[17], Carlos Aguado[18]

[1]Hospital Universitario Son Llàtzer, Illes Balears, Spain; [2]Hospital Universitario y Politécnico La Fe, Valencia, Spain; [3]Hospital General Universitario Dr. Balmis ISABIAL Alicante, Alicante, Spain; [4]Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain; [5]Hospital Universitario Miguel Servet, Zaragoza, Spain; [6]Hospital Universitario Torrecárdenas, Almeria, Spain; [7]Hospital Arnau de Vilanova, Valencia, Spain; [8]Hospital Universitario de Torrejón, Madrid, Spain; [9]Consorcio Hospitalario Provincial de Castellón, Castellón, Spain; [10]Hospital Universitario Lucus Augusti, Lugo, Spain; [11]Hospital Universitario Puerta del Mar, Cádiz, Spain; [12]Hospital Clínic Barcelona, Barcelona, Spain; [13]Hospital Regional Universitario de Málaga, Málaga, Spain; [14]Hospital Universitario de León, León, Spain; [15]Complexo Hospitalario Universitario de Ourense, Ourense, Spain; [16]Hospital Universitario de Jaén, Jaén, Spain; [17]Bristol Myers Squibb España, Madrid, Spain; [18]Hospital Clínico San Carlos, Madrid, Spain.

Introduction

- Brain metastases (BM) are a common and significant complication of non-small cell lung cancer (NSCLC), which has the highest incidence of BM among solid tumours. Between 11-26% of patients present with BM at diagnosis, and up to 50% develop BM throughout the course of the disease, which significantly worsens prognosis[1].
- BM contributes to 1 in 3 deaths from NSCLC and is a key reason why lung cancer is the leading cause of death worldwide[1].
- Older adults with advanced NSCLC represent a heterogeneous and vulnerable population in whom comorbidities, functional decline, and frailty significantly affect prognosis and treatment tolerability[2].
- Immunotherapy (IO) has transformed advanced NSCLC treatment, improving survival over platinum chemotherapy (CT)[3,4]. However, its benefit in older patients and those with BM remains uncertain due to their limited representation in pivotal trials.

Objective

- The REVEAL study aimed to collect real-world clinical data on the treatment and management of patients receiving first-line therapy for advanced NSCLC in Spain. In this communication we analyse the impact of age and BM status on clinical outcomes among non-squamous (NSQ) advanced NSCLC patients receiving first-line CT, IO+CT, or double IO+CT in real-world practice.

Methods

- REVEAL was a non-interventional, multicentric, and retrospective chart review study conducted in Oncology Departments of 18 Spanish hospitals. This communication is part of the REVEAL study and preliminary data have previously been presented at the SEOM[5] and GECP[6] Congresses.
- The study included adult patients with advanced NSCLC, without *EGFR* or *ALK* alterations, and with PD-L1 <50% or negative/unknown, who initiated first-line systemic therapy between January 2022 and March 2023.
- Here, we present sub analysis focused on patients with NSQ histology by:
  - » Age: <70 vs ≥70 years
  - » Patients with and without BM at baseline

Results

Patients' characteristics

- A total of 223 patients with NSQ histology were included. By age group, 143 patients (64.1%) were <70 years and 80 patients (35.9%) were ≥70 years. By BM status, 50 patients (22.4%) had BM and 173 patients (77.6%) had no BM.
- **Tables 1** and **2** summarize the main subgroup characteristics according to treatment regimen. Briefly, older patients (≥70 years) showed a higher proportion of males and a slightly better ECOG 0-1 across treatment groups. Brain metastases were more frequent in younger patients, whereas bone metastases predominated in older patients. Interestingly, the proportion of patients with BM was higher in the double IO+CT group (30.0%) compared with IO+CT (19.0%) and CT alone (16.3%).

Table 1. Characteristics of patients according to age group and treatment regimen

	CT alone		IO + CT		Double IO + CT	
	<70y	≥70y	<70y	≥70y	<70y	≥70y
	n=23	n=20	n=62	n=38	n=58	n=22
Age at metastatic disease (years) median (IQR)	60.0 (54.0-64.0)	74.0 (73.0-81.0)	60.5 (56.0-65.0)	74.0 (71.0-77.0)	60.0 (55.0-63.0)	74.0 (70.0-75.0)
Male, n (%)	16 (69.6)	19 (95.0)	37 (59.7)	31 (81.6)	34 (58.6)	17 (77.3)
ECOG (available), n (%)	19 (82.6)	19 (95.0)	56 (90.3)	35 (92.1)	49 (84.5)	22 (100.0)
0-1	12 (63.2)	14 (73.7)	52 (92.9)	32 (91.4)	48 (98.0)	22 (100.0)
PD-L1, n (%)						
Negative	12 (52.2)	13 (65.0)	37 (59.7)	18 (47.4)	42 (72.4)	15 (68.2)
1-49%	10 (43.5)	4 (20.0)	21 (33.9)	17 (44.7)	14 (24.1)	6 (27.3)
Unknown	1 (4.3)	3 (15.0)	4 (6.5)	3 (7.9)	2 (3.4)	1 (4.5)
Metastases, n (%)						
Hepatic	8 (34.8)	6 (30.0)	9 (14.5)	4 (10.5)	10 (17.2)	1 (4.5)
Brain	7 (30.4)	0 (0.0)	12 (19.4)	7 (18.4)	21 (36.2)	3 (13.6)
Bone	5 (21.7)	10 (50.0)	25 (40.3)	20 (52.6)	19 (32.8)	6 (27.3)

CT, Chemotherapy; ECOG, Eastern Cooperative Oncology Group; IO, Immunotherapy; PD-L1, Programmed Death-Ligand 1; y, years

Table 2. Characteristics of patients according to BM status and treatment regimen

Characteristics	CT alone		IO + CT		Double IO + CT	
	BM n=7	Non-BM n=36	BM n=19	Non-BM n=81	BM n=24	Non-BM n=56
Age at metastatic disease (years) median (IQR)	64.0 (61.0-64.0)	71.5 (58.0-74.5)	62.0 (58.0-72.0)	66.0 (60.0-72.0)	59.0 (54.5-63.0)	64.0 (59.5-71.5)
Male, n (%)	5 (71.4)	30 (83.3)	14 (73.7)	54 (66.7)	12 (50.0)	39 (69.6)
ECOG (available), n (%)	5 (71.4)	33 (91.7)	18 (94.7)	73 (90.1)	20 (83.3)	51 (91.1)
0-1 %	2 (40.0)	24 (72.7)	15 (83.3)	69 (94.5)	20 (100.0)	50 (98.0)
PD-L1, n (%)						
Negative	4 (57.1)	21 (58.3)	13 (68.4)	42 (51.9)	15 (62.5)	42 (75.0)
1-49%	3 (42.9)	11 (30.6)	5 (26.3)	33 (40.7)	7 (29.2)	13 (23.2)
Unknown	0 (0.0)	4 (11.1)	1 (5.3)	6 (7.4)	2 (8.3)	1 (1.8)
Metastases, n (%)						
Hepatic	1 (14.3)	13 (36.1)	5 (26.3)	8 (9.9)	4 (16.7)	7 (12.5)
Bone	2 (28.6)	13 (36.1)	7 (36.8)	38 (46.9)	6 (25.0)	19 (33.9)

BM, Brain metastases; CT, Chemotherapy; ECOG, Eastern Cooperative Oncology Group; IO, Immunotherapy; PD-L1, Programmed Death-Ligand 1; y, years

- Prior to systemic therapy, management of BM varied across groups. Corticosteroids were used in 42.9%, 31.6%, and 25.0% of patients with BM in the CT, IO+CT, and double IO+CT groups, respectively. Radiotherapy was the most common intervention, received by 71.4%, 52.6%, and 41.7% of patients. A notable proportion—ranging from 28.6% to 41.7%—did not receive any BM-directed treatment before systemic therapy. Between 28.6% and 41.7% of patients had not received BM treatment prior to systemic therapy.

Impact of age in NSCLC in effectiveness

- When outcomes were analysed by age, no significant differences were found in response or survival across groups.
- Objective response rates (ORR) were numerically higher with IO-based treatments in both age groups. Among patients <70 years, ORR was 58.1% with IO+CT and 50.0% with double IO+CT, compared with 30.4% with CT alone. In patients ≥70 years, ORR remained greater with IO-based regimens (47.4% with IO+CT and 50.0% with double IO+CT) versus 45.0% with CT.
- According to the median of overall survival (OS), numerically higher values were seen in younger patients. Median OS in patients <70 years was 10.5 months (CT), 16.1 months (IO+CT), and 17.6 months (double IO+CT). For patients ≥70 years, median OS was 10.1, 13.1, and 12.3 months, respectively. In both age groups, combinations with IO showed higher OS values compared with CT alone, although this benefit appeared greater in younger patients (**Figure 1**).
- Median progression-free survival (PFS) showed a similar trend, with 5.3, 9.3, and 7.3 months for <70 years and 5.5, 5.4, and 6.2 months for ≥70 years across CT, IO+CT, and double IO+CT, respectively.

Impact of the presence of brain metastasis in NSCLC in effectiveness

- When analysing the presence or absence of BS, no significant differences in response or survival were observed between groups.
- Patients with BM showed lower ORR with CT (14.3% vs 41.7%), while ORR values were similar between BM and non-BM patients with IO+CT (52.6% vs 54.3%) and numerically higher in BM patients receiving double IO+CT (62.5% vs 44.6%).
- Median OS was shorter for BM vs non-BM patients treated with CT (10.0 vs 12.1 months) and IO+CT (10.7 vs 16.3 months), whereas double IO+CT achieved the longest survival in BM patients, with median OS not reached vs 17.2 months in non-BM (**Figure 2**).
- Median PFS was slightly longer for BM vs non-BM patients treated with CT (7.1 vs 4.9 months). A similar pattern was observed in patients treated with IO+CT (10.7 vs 7.9 months). In contrast, among patients receiving double IO+CT, median PFS was comparable between BM and non-BM groups (7.8 vs 7.0 months).

Tolerability according to age group and treatment regimen

- Adverse events (AEs) occurred at similar rates across age groups within each regimen, although the double IO+CT group showed numerically higher AE frequencies (**Table 5**).
- Dose reductions due to AEs were uncommon overall Temporary interruptions and treatment discontinuations varied substantially by regimen and age group and most AEs resolved across all regimens and ages (**Table 5**).

Tolerability according to BM status and treatment regimen

- AEs were generally more frequent in non-BM patients across all treatment groups, with no AEs reported in BM patients treated with CT (**Table 6**).
- Dose reductions, temporary treatment interruptions, and therapy discontinuations showed marked variability across regimens and most AEs resolved regardless of BM status (**Table 6**).

Figure 1. OS according to age group and treatment regimen

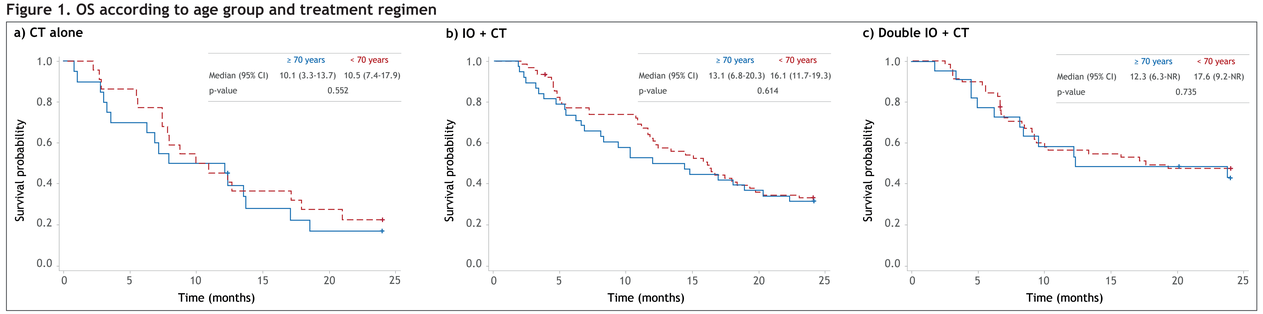

Figure 2. OS according to BM status and treatment regimen

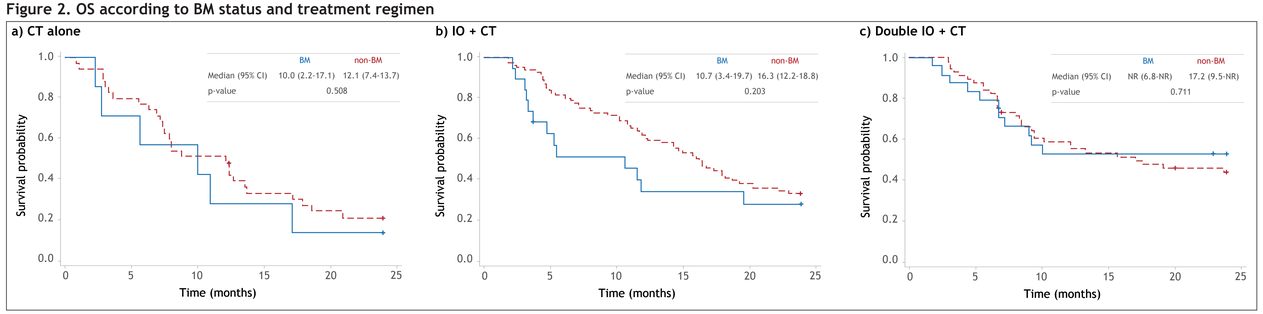

Table 5. AEs and treatment modifications according to age group and treatment regimen

	CT alone		IO + CT		Double IO + CT	
	<70y	≥70y	<70y	≥70y	<70y	≥70y
	(n=23)	(n=20)	(n=62)	(n=38)	(n=58)	(n=22)
Patients with any AE[a], n (%)	6 (26.1)	7 (35.0)	18 (29.0)	10 (26.3)	21 (36.2)	9 (40.9)
Number of AE-related treatment modifications[b]	6	13	29	12	25	13
Dose reduction, n (%)	3 (50.0)	2 (15.4)	4 (13.8)	2 (16.7)	2 (8.0)	0 (0.0)
Temporary interruption, n (%)	2 (33.3)	8 (61.5)	16 (55.2)	1 (8.3)	11 (44.0)	8 (61.5)
Discontinuation of therapy, n (%)	1 (16.7)	3 (23.1)	9 (31.0)	9 (75.0)	12 (48.0)	5 (38.5)
Outcomes, n (%)						
Ongoing	1 (16.7)	1 (7.7)	3 (10.3)	1 (8.3)	5 (20.0)	0 (0.0)
Resolved	2 (33.3)	8 (61.5)	23 (79.3)	7 (58.3)	16 (64.0)	11 (84.6)
Partially improved	2 (33.3)	0 (0.0)	1 (3.4)	0 (0.0)	2 (8.0)	1 (7.7)
Fatal	0 (0.0)	2 (15.4)	1 (3.4)	4 (33.3)	2 (8.0)	0 (0.0)
Unknown	1 (16.7)	2 (15.4)	1 (3.4)	0 (0.0)	0 (0.0)	1 (7.7)

Table 6. AEs and treatment modifications according to BM status and treatment regimen

	CT alone		IO + CT		Double IO + CT	
	BM	Non-BM	BM	Non-BM	BM	Non-BM
	(n=7)	(n=36)	(n=19)	(n=81)	(n=24)	(n=56)
Patients with any AE[a], n (%)	0 (0.0)	13 (36.1)	4 (21.1)	24 (29.6)	8 (33.3)	22 (39.3)
Number of AE-related treatment modifications[b]	0	19	9	32	10	28
Dose reduction, n (%)	-	5 (26.3)	1 (11.1)	5 (15.6)	2 (20.0)	0 (0.0)
Temporary interruption, n (%)		10 (52.6)	5 (55.6)	12 (37.5)	5 (50.0)	14 (50.0)
Discontinuation of therapy, n (%)	-	4 (21.1)	3 (33.3)	15 (46.9)	3 (30.0)	14 (50.0)
Outcomes, n (%)						
Ongoing	-	2 (10.5)	0 (0.0)	4 (12.5)	1 (10.0)	4 (14.3)
Resolved	-	10 (52.6)	8 (88.9)	22 (68.8)	7 (70.0)	20 (71.4)
Partially improved	-	2 (10.5)	0 (0.0)	1 (3.1)	1 (10.0)	2 (7.1)
Fatal	-	2 (10.5)	1 (11.1)	4 (12.5)	1 (10.0)	1 (3.6)
Unknown	-	3 (15.8)	0 (0.0)	1 (3.1)	0 (0.0)	1 (3.6)

[a]Percentages based on the number of patients in each group; [b]Reference values for calculating percentages in the following categories. AE, Adverse event; BM, Brain metastases; CT, Chemotherapy; IO, Immunotherapy

Conclusions

- IO-based regimens were shown to consistently improve OS and PFS compared with CT alone regardless of age. However, the magnitude of benefit was less pronounced in patients ≥70 years.
- In patients with BM, numerically better outcomes were observed with double IO+CT, suggesting the potential value of more intensive IO-based strategies in this group. This observation aligns with evidence from melanoma, among other tumors, where inhibition of PD(L)-1 and CTLA-4- combinations such as nivolumab -ipilimumab have demonstrated significant intracranial activity in patients with BM[7-9]. However, given the non-comparative design, further studies are required to confirm this potential benefit.
- Regarding tolerability, neither older age nor the presence of BM was associated with a significantly higher incidence of AEs.
- Taken together, these findings emphasise the need for more real-world evidence from underrepresented groups, especially older adults and patients with BM.
- Our results suggest that these populations also derive benefit from IO-based combinations without a significant impact on tolerability. Real-world data are therefore essential to support treatment selection and guide clinical decision-making in groups that are typically underrepresented in clinical trials.

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Declaration of interest

JCS declares fees for participation as an invited speaker from Roche, AstraZeneca, BMS, MSD, Pfizer, Lilly, Sanofi, Amgen, Takeda, and Regeneron; participation as an advisory board member for AstraZeneca, BMS, and Sanofi; roles as principal investigator in clinical trials sponsored by Roche, AstraZeneca, BMS (including the study being published), MSD, Pfizer, and Lilly; receipt of travel and congress support from Roche, BMS, MSD, Pfizer, and Lilly; and receipt of educational support from Roche, BMS, MSD, Lilly, and Takeda.

Contact

Correspondence: jcoves@hsll.es