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ORIGINAL ARTICLE

Immunotherapy beyond progression combined with platinum-based chemotherapy after primary resistance to first-line immunotherapy in patients with advanced NSCLC and PD-L1 ≥50%

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Available online xxx

Background: Primary resistance to immune checkpoint inhibitors (ICIs) remains a major challenge in patients with advanced non-small-cell lung cancer (NSCLC) and programmed death-ligand 1 (PD-L1) expression ≥50%. The benefit of continuing ICIs beyond progression in combination with chemotherapy is unclear.

Patients and methods: This multicenter retrospective study included patients with advanced NSCLC and PD-L1 ≥50% treated with first-line ICI monotherapy at five European centers. Primary resistance was defined as progressive disease as best response or stable disease lasting <6 months. Outcomes of second-line platinum-based chemotherapy alone or combined with ICI were compared. The primary endpoint was progression-free survival 2, defined as time from first-line ICI initiation to second-line progression or death.

Results: Among 293 eligible patients, 119 (38%) showed primary resistance. Compared with those who did not develop primary resistance, patients with primary resistance more often had multisite progression (74% versus 42%) and less often oligoprogression (13% versus 54%) ($P < 0.001$). Second-line platinum-based chemotherapy was administered to 43.7% (52/119) of patients with primary resistance, 34.6% (18/52) of whom received ICI beyond progression. Baseline characteristics were comparable across treatment groups. Patients who received ICI beyond progression, compared with those who received only chemotherapy, had significantly longer median progression-free survival 2 (12.3 versus 7.0 months, $P < 0.001$) and OS (21.8 versus 10.1 months, $P = 0.007$), with similar overall response rate (66.7% versus 39.3%, $P = 0.13$). No relevant safety signals emerged.

Conclusion: In patients with NSCLC and PD-L1 ≥50% showing primary resistance to first-line ICI, continuing immunotherapy beyond progression combined with chemotherapy may improve survival outcomes. These findings should be considered hypothesis-generating and warrant prospective confirmation.

Key words: non-small cell lung cancer, PD-L1 ≥50%, primary resistance, immune checkpoint inhibitors, chemo-immunotherapy, second-line treatment

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have transformed the therapeutic landscape of patients with advanced non-small-cell lung cancer (NSCLC) in recent years. Agents targeting the programmed cell death protein 1 (PD-1) receptor or its ligand, programmed death-ligand 1 (PD-L1) have demonstrated remarkable efficacy in previously untreated, advanced NSCLC, particularly in tumors with PD-L1 tumor proportion score (TPS) ≥50%.[1-4] ICI monotherapy has become a standard of care in the first-line setting for patients with high PD-L1 expressing,

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advanced NSCLC without targetable genomic alterations, with outcomes significantly superior to traditional platinum-based chemotherapy.[5] Despite these advances, up to 30% of patients do not derive any benefit from ICI monotherapy, showing primary resistance to these agents, which is defined as progressive disease (PD) as best response or stable disease (SD) lasting <6 months.[6-8] This early treatment failure is associated with poor prognosis and represents a major clinical challenge.

Although prospective trials have shown the superiority of platinum-based chemotherapy plus ICIs compared with chemotherapy alone, irrespective of PD-L1 expression,[9-11] results from prospective studies comparing ICI monotherapy versus ICI plus chemotherapy are still awaited (NCT04547504).

In Europe, ICI monotherapy is usually preferred for patients with PD-L1 ≥50%, given its favorable toxicity profile and strong and reproducible efficacy data,[1,3,4,12] aside from country-specific regulatory considerations. However, indirect comparisons suggest that adding chemotherapy to pembrolizumab reduces the risk of early (within the first 3-6 months) PD.[13] In clinical practice, histology-driven platinum-doublet chemotherapy is reserved as a sequential approach when resistance to first-line ICI monotherapy occurs,[5] often yielding suboptimal outcomes, though limited observational data are available in this setting.[14]

Evidence from the EMPOWER-Lung 01 phase III trial suggests that there are potential benefits in adding histology-driven platinum-based doublet chemotherapy to cemiplimab when patients with advanced NSCLC with PD-L1 ≥50% experience PD.[3,15] However, the choice to continue the ICI beyond PD was left to the investigator instead of being the result of a randomized assignment, limiting the interpretability of these results.

Here, we aimed to characterize the clinical features of patients with advanced NSCLC and PD-L1 ≥50% who showed primary resistance to ICI monotherapy and to evaluate the efficacy of continuing anti-PD-1 therapy in combination with histology-driven chemotherapy after PD to ICI monotherapy, compared with switching to chemotherapy alone.

PATIENTS AND METHODS

This was a multicenter, retrospective, observational study including patients with advanced NSCLC and PD-L1 TPS ≥50%, treated with first-line ICI monotherapy between 2015 and May 2024 at five European referral centers.

Patients with known *EGFR* mutations (exon 19 deletion, L858R point mutation) or rearrangements in *ALK* or *ROS1* genes were excluded. Remarkably, EGFR, ALK, and ROS1 testing was standard for non-squamous histology. Broader next-generation sequencing (NGS) panels were not mandatory, and their availability varied across centers and time per clinical practice and local reimbursement policies. This variability made it difficult to rule out undetected alterations.

This research was carried out in line with the Declaration of Helsinki (1964) and received approval from the local ethics committees. Data were collected manually from medical records and included age at diagnosis, sex, tumor histology, biomolecular characterization, Eastern Cooperative Oncology Group (ECOG) performance status (PS), specifics of antineoplastic treatments (including type, line, start and discontinuation dates, date of progression), radiological findings at the study entry and throughout its course, the number and location of metastatic sites, treatment-related adverse events (TRAEs), the most recent follow-up, and the date of death.

The primary objective was to assess the efficacy of continuing ICI treatment beyond PD in combination with histology-driven platinum-based chemotherapy compared with standard platinum-based chemotherapy for patients with primary resistance to first-line ICI monotherapy. As per the Society for Immunotherapy of Cancer (SITC) criteria,[8] primary resistance was defined as a best response of PD or SD lasting <6 months. Radiologic assessments were carried out per local schedules without central review. No distinction was made between immune-refractory and immune-resistant disease. Oligoprogression was defined as progression in fewer than four new lesions, considered amenable to local therapy according to investigator assessment. The choice between chemotherapy alone or combined with continued ICI was based on institutional practice and physician choice.

Statistical analysis

The primary endpoint was progression-free survival 2 (PFS2), defined as the time from start of first line to the evidence of a second disease progression or death. If no secondary progression/death event was observed, the patient was censored at the date of the most recent radiographic assessment. PFS2 was selected to capture the effect of the sequential treatment strategy (first-line ICI single-agent followed by second-line treatments), rather than the outcome of a single line. PFS1, defined as the time from start of first line to first progression, was also reported to confirm comparability between groups.

Secondary endpoints were overall survival (OS), defined as the time from the start of first-line treatment until death or last follow-up, and overall response rate (ORR) to the second-line treatment, defined as the percentage of patients achieving a partial or complete response as assessed by physicians according to RECIST 1.1 criteria without central review. Lesion-level data were not pre-planned and not consistently collected, precluding tumor-burden analyses. PFS2 and OS curves were estimated through the Kaplan—Meier method and compared through the log-rank test. The Wilcoxon rank-sum test was used for comparing continuous variables with potentially non-normal distributions. The association between categorical variables was estimated through the Fisher exact test or the chi-square test, as appropriate statistical significance was defined as a two-sided P value < 0.05. Statistical analysis was conducted using R software version 4.2.2.

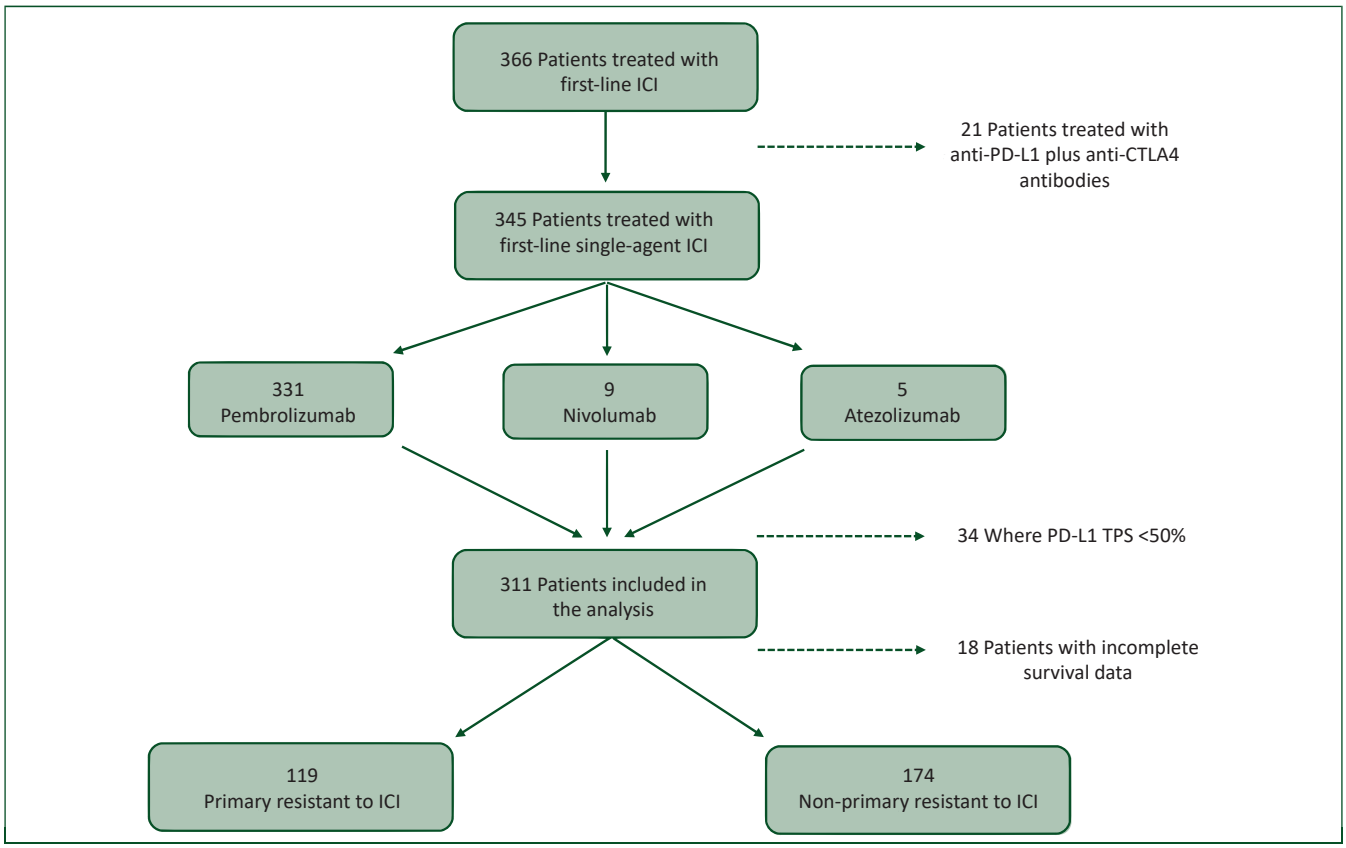

Figure 1. Flowchart of retrospectively included patients.
CTLA4, cytotoxic T-lymphocyte antigen 4; ICI, immune checkpoint inhibitor; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

RESULTS

Baseline demographics

A total of 366 patients with advanced NSCLC and PD-L1 TPS ≥50% received upfront ICI between November 2015 and May 2024. Twenty-one patients received a combination of anti-PD-1 (nivolumab) and anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA4) (ipilimumab) and were therefore excluded from further analyses. Out of the remaining 345 patients, 331 (96%) received pembrolizumab, 9 (3%) received nivolumab, and 5 (1%) received atezolizumab. Among 311 patients with PD-L1 TPS ≥50%, 18 had incomplete survival data and were excluded, resulting in a final cohort of 293 patients (Figure 1).

Most patients were male (n = 185/293, 63%), had adenocarcinoma histology (195/293, 67%), and had a history of tobacco use (n = 269/283, 95%). At baseline, 232/286 (81%) patients had ECOG PS 0-1, and one to three metastatic sites were present in 245/279 patients (88%). Liver and brain metastases were present in 29/293 (10%) and 61/293 (21%) cases, respectively. One patient who had received upfront nivolumab after progression on definitive chemoradiotherapy for stage IIIB disease was included in the final cohort (n = 293). This patient did not present primary resistance and was therefore excluded from the analyses of patients treated in the second-line setting. With a median follow-up of 40.9 months [95% confidence interval (CI) 38.4-46.4 months], median PFS and OS on first-line immunotherapy were 9.2 months (95% CI 6.01-13.7 months) and 22.1 months (95% CI 18.5-30.5 months), respectively. Primary resistance was observed in 119 patients (38%) (Table 1).

Median PFS was 1.9 months (95% CI 1.6-2.4 months) in patients with primary resistance (n = 119, 38%), and 25.9 months (95% CI 20.9-35.7 months) in the non-primary resistant population (n = 174, 62%).

Compared with the non-primary resistant population, patients with primary resistance tended to have multisite progression patterns (n = 75, 74% versus n = 30, 42%, $P < 0.001$), and lower rates of oligoprogression (defined as progression in fewer than four new lesions, considered amenable to local therapy according to investigator assessment) (n = 13, 13% versus n = 38, 54%, $P < 0.001$) (Table 1). A higher proportion of patients in the primary resistant group had ECOG PS ≥2 at baseline compared with the non-primary resistant population (24% versus 15%, $P = 0.07$) (Table 1).

Only half of the patients with primary resistance (n = 61, 51%) received a second-line treatment. In 52 cases (44%) the second-line regimen consisted of a platinum-based doublet with or without the continuation of ICI: 34 patients switched to chemotherapy alone, whereas 18 received ICI and platinum doublet. No statistically significant differences were seen in the distribution of clinical features, including ECOG PS before second-line start, number of metastatic sites, and liver and brain metastasis,

Table 1. Baseline clinical and molecular characteristics of the primary resistant population

	Primary resistant population	Non-primary resistant population	*P* value
	n = 119	*n* = 174	
Age (years)	67 (60, 74)	67 (61, 73)	0.7
Sex			0.8
Male	74 (62)	111 (64)	
Female	45 (38)	63 (36)	
Histology			0.9
Adenocarcinoma	81 (68)	114 (66)	
Squamous carcinoma	17 (14)	28 (16)	
Other	21 (18)	32 (18)	
Smoking history			0.3
Current	107 (90)	160 (92)	
Former	2 (2)	0 (0)	
Never	8 (6)	14 (8)	
Unknown	2 (2)	0	
PD-L1 TPS	80 (70, 90)	80 (60, 90)	0.7
KRAS			0.7
Mutated	54 (45)	72 (41)	
Not mutated	56 (47)	83 (48)	
Unknown	9 (8)	19 (11)	
TP53			0.49
Mutated	35 (29)	53 (31)	
Not mutated	36 (30)	70 (40)	
Unknown	48 (40)	51 (30)	
STK11			0.40
Mutated	4 (3)	11 (6)	
Not mutated	42 (35)	62 (36)	
Unknown	73 (61)	101 (58)	
KEAP1			1.0
Mutated	3 (2)	5 (3)	
Not mutated	40 (34)	61 (35)	
Unknown	76 (64)	108 (62)	
BRAF			0.3
Mutated	4 (3)	11 (6)	
Not mutated	102 (86)	137 (79)	
Unknown	13 (11)	26 (15)	
MET			1.0
Mutated or amplified	3 (2)	5 (3)	
Not mutated	77 (65)	100 (57)	
Unknown	39 (33)	69 (40)	
HER2			1.0
Mutated or amplified	1 (1)	2 (1)	
Not altered	76 (64)	95 (55)	
Unknown	42 (35)	77 (44)	
RET			0.65
Rearranged	3 (2)	2 (1)	
Not rearraged	90 (76)	127 (73)	
Unknown	26 (22)	45 (26)	
ECOG PS			0.07
0-1	87 (73)	145 (83)	
>1	28 (24)	26 (15)	
Unknown	4 (3)	3 (2)	
N metastatic sites			0.5
1-3	103 (87)	142 (82)	
>3	12 (10)	22 (13)	
Unknown	4 (3)	10 (5)	
Liver metastasis			
Present	12 (10)	17 (10)	>0.9
Brain metastasis			
Present	24 (20)	37 (21)	0.8
Progression patterns in patients who progressed	*n* = 119	*n* = 90	
Multisite	75 (63)	30 (33)	<0.001
Mixed response	14 (12)	3 (3)	
Oligoprogression	13 (11)	38 (42)	
Unknown	17 (14)	19 (21)	

Continuous variables are expressed in median (Q1, Q3). Categorical variables are expressed in *n* (%).
Smoking was defined as having smoked at least 100 tobacco cigarettes during one's lifetime.
Smoking status was categorized as follows:
— Never smoker: patients who had smoked fewer than 100 cigarettes in their lifetime.
— Former smoker: patients who had smoked at least 100 cigarettes in their lifetime but were not smoking at the time of diagnosis.
— Current smoker: patients who had smoked at least 100 cigarettes in their lifetime and were actively smoking at the time of diagnosis.
ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

Table 2. Clinical and molecular characteristics of patients treated with ChT or with ICI—ChT as second line

Second-line ChT +/- ICI *n* = 52	ChT *n* = 34	ICI-ChT *n* = 18	*P* value
Age (years)	65 (59, 71)	64 (54, 68)	0.4
Sex			1.0
Male	18 (53)	9 (50)	
Female	16 (47)	9 (50)	
Histology			0.74
Adenocarcinoma	24 (70)	14 (78)	
Squamous carcinoma	5 (15)	2 (11)	
NOS	5 (15)	2 (11)	
Smoking history			0.23
Current or former	33 (97)	14 (78)	
Never	1 (3)	2 (11)	
Unknown	0	2 (11)	
PD-L1 TPS	80 (60, 90)	80 (70, 90)	0.8
KRAS			0.66
Mutated	20 (59)	9 (50)	
Not mutated	13 (38)	9 (50)	
Unknown	1 (3)	0	
TP53			0.27
Mutated	18 (53)	1 (6)	
Not mutated	9 (26)	3 (17)	
Unknown	7 (11)	14 (77)	
STK11			1.0
Mutated	2 (6)	0	
Not mutated	18 (53)	3 (17)	
Unknown	14 (41)	15 (83)	
KEAP1			1.0
Mutated	0	0	
Not mutated	18 (53)	3 (17)	
Unknown	16 (47)	15 (83)	
BRAF			1.0
Mutated	1 (3)	0	
Not mutated	32 (94)	18 (100)	
Unknown	1 (3)	0	
MET			0.41
Mutated or amplified	0	1 (6)	
Not altered	25 (74)	17 (94)	
Unknown	9 (26)	0	
HER2			1.0
Mutated or amplified	1 (3)	0	
Not altered	25 (74)	17 (94)	
Unknown	8 (23)	1 (6)	
RET			1.0
Rearranged	1 (3)	0	
Not rearranged	26 (86)	18 (100)	
Unknown	7 (11)	0	
ECOG PS			1.0
0-1	24 (71)	9 (50)	
>1	8 (23)	3 (17)	
Unknown	2 (6)	6 (33)	
N metastatic sites			0.57
1-3	22 (65)	11 (61)	
>3	8 (23)	7 (39)	
Unknown	4 (12)	0	
Liver metastasis	3 (9)	2 (11)	1.0
Brain metastasis	10 (29)	7 (39)	0.7
PFS to first line (months)	1.7 (95% CI 1.4-3.4)	2.6 (95% CI 1.7-3.9)	0.4

Results of PD-L1 molecular profiling were obtained before the commencement of any treatment. Clinical characteristics, such as the number of metastatic sites, the presence of brain and liver metastases, and ECOG performance status, are referenced with respect to the initiation of second-line treatment. Continuous variables are expressed in median (Q1, Q3). Categorical variables are expressed in *n* (%).

Smoking was defined as having smoked at least 100 tobacco cigarettes during one's lifetime.

Smoking status was categorized as follows:

— Never smoker: patients who had smoked fewer than 100 cigarettes in their lifetime.

— Former smoker: patients who had smoked at least 100 cigarettes in their lifetime but were not smoking at the time of diagnosis.

— Current smoker: patients who had smoked at least 100 cigarettes in their lifetime and were actively smoking at the time of diagnosis.

ChT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; ICI—ChT, immune checkpoint inhibitor—chemotherapy; NOS, not otherwise specified; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TPS, tumor proportion score.

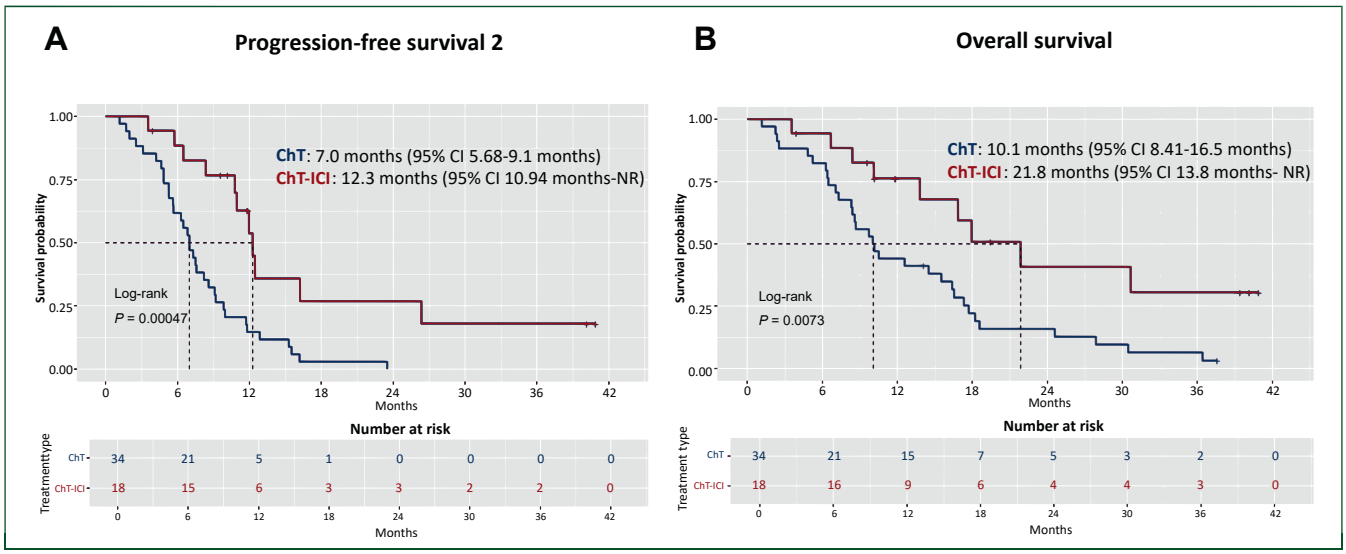

Figure 2. Survival outcome with ChT—ICI or ChT in patients who were primarily resistant to first-line ICI. (A) Progression-free survival 2. (B) Overall survival. ChT, chemotherapy; ChT—ICI, chemotherapy—immune checkpoint inhibitor; CI, confidence interval; NR, not reached.

in these two groups (Table 2). The mutational status of *TP53*, *STK11*, and *KEAP1* was unknown in most cases (Table 2).

Outcomes to second-line treatment

At the time of the analysis, 45 patients (86%) died or progressed on the second-line treatment: 34 of them were treated with chemotherapy only, and 11 with chemotherapy plus ICI. Among these patients, multisite progression was observed in 51% of cases ($n = 23$) (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105897).

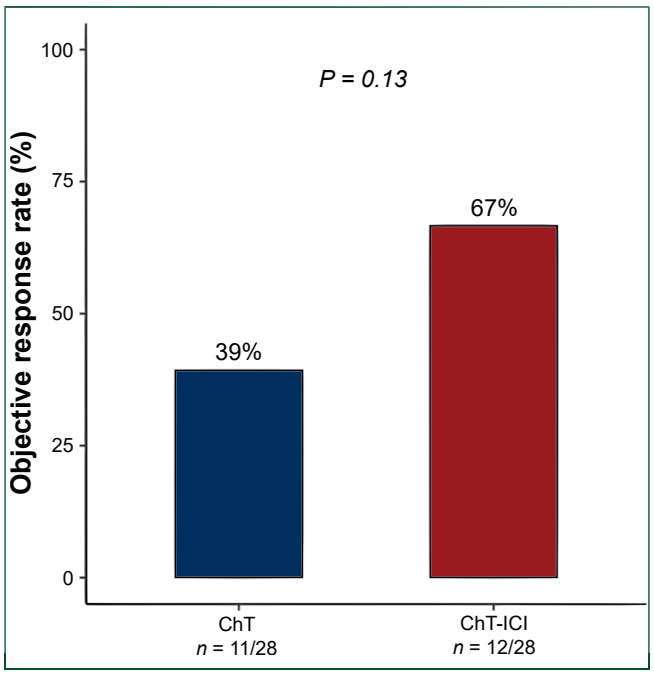

Figure 3. Objective response rate to second-line ChT or ChT—ICI, investigator-assessed by RECIST 1.1.
ChT, chemotherapy; ChT—ICI, chemotherapy—immune checkpoint inhibitor.

Median PFS2 in the overall population was 9.3 months (95% CI 7-11.7 months). Patients treated with chemotherapy plus ICI had longer median PFS2 compared with those who received chemotherapy alone [12.3 months [95% CI 10.94 months to not reached (NR)] versus 7.0 months (95% CI 5.6-9.1 months), hazard ratio (HR) 0.20, 95% CI 0.14-0.60, $P < 0.001$] (Figure 2).

The median OS in the overall population was 14.5 months (95% CI 10.1-17.9 months). Patients treated with chemotherapy plus ICI achieved a significantly longer median OS compared with those treated with chemotherapy alone [21.8 months (95% CI 13.8 months to NR) versus 10.1 months (95% CI 8.4-16.5 months), HR 0.37, 95% CI 0.17-0.78, $P = 0.007$] (Figure 2).

A total of 46/52 (88%) patients were assessable for response. The objective response rate (ORR) was 66.7% in the chemotherapy plus ICI group ($n = 12/18$) versus 39.3% in the chemotherapy group ($n = 11/28$) ($P = 0.13$) (Figure 3). PD as best response occurred in 2 patients (11%) treated with chemotherapy plus ICI versus 12 patients (35%) treated with chemotherapy alone (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105897).

One patient treated with chemotherapy plus ICI experienced pneumonitis as a grade 3 TRAE. No other grade ≥ 3 TRAEs were reported in either group.

DISCUSSION

This multicenter retrospective analysis sheds light on the management of patients with advanced NSCLC and high PD-L1 expression who show primary resistance to first-line ICI. Our findings suggest that there could be a survival benefit in adding histology-driven platinum-based chemotherapy while continuing the ICI beyond progression, compared with switching to chemotherapy alone, without significant additional safety issues, providing a foundation for optimizing treatment in this hard-to-treat population,

although conclusions remain exploratory and hypothesis-generating due to the small sample size.

Primary resistance to ICIs remains a significant clinical challenge in patients with advanced non-oncogene-addicted NSCLC, affecting 38% of our cohort, consistent with other reported series,[7,16] and leaving limited treatment options beyond clinical trials. The slightly higher rate of primary resistance (38%) compared with registrational trials[1-4] likely reflects a less selected real-world population, with higher tumor burden and poorer performance status, as well as center-related variability.

In our population, only half ($n = 61$) of patients experiencing primary resistance to ICI were eligible for second-line treatment and even fewer ($n = 52$) were eligible for a histology-driven platinum-based doublet chemotherapy, which is the recommended second-line treatment of fit patients.[5] Oligoprogressive disease is a particular situation in which patients may be candidates for local therapy with continuation of the same systemic therapy. In our cohort, most patients showing primary resistance to ICI had multisite progression and were therefore not eligible for locoregional treatments. The tendency to progress in multiple metastatic sites suggests an aggressive disease, the biological correlates of which warrant further investigation. In addition, a numerically higher proportion of patients in the primary resistant group had ECOG PS $\geq$2 at baseline (24% versus 15%, $P = 0.07$), a factor known to predict poor outcomes with ICI monotherapy.[7]

Unfortunately, observational data of subsequent chemotherapy alone are unsatisfying. The observational CLARITY study highlighted the poor outcomes associated with chemotherapy alone in patients pretreated with ICIs, particularly those with primary resistance, where subsequent chemotherapy, mostly taxane monotherapy (38.9%) and platinum-based doublets in a minority of cases (29.2%), achieved a median OS of 6.8 months and PFS of 4.1 months.[14] Therefore, improved treatment strategies are necessary.

The results of our retrospective study are in line with the EMPOWER-Lung 01 trial,[15] but our study has almost double the number of patients. This trial remains the only published clinical trial to explore the continuation of anti-PD-1 monotherapy with the addition of chemotherapy after progression, as permitted by the study design regardless of the timing of PD.[15] In a subgroup analysis of 64 patients, the combination of cemiplimab with histology-driven chemotherapy yielded a median PFS of 6.6 months and a post-progression OS of 15.1 months,[15] recently confirmed in a 5-year update presented at ELCC 2025 including 73 patients treated beyond progression.[17] A patient-level analysis within this cohort showed that among 18 individuals who had PD as best response to first-line cemiplimab, 4 achieved objective responses (1 complete response, 3 partial response), 13 achieved SD, and only 1 experienced further progression.[17] Notably, treatment continuation beyond progression was heterogeneous, with some patients receiving additional cycles of cemiplimab monotherapy before chemotherapy initiation.

The improved survival outcomes observed with chemotherapy plus ICI suggest that this combination may salvage early progression and offer a more durable disease control. In our study, we selected PFS2 as the primary endpoint because it reflects the entire sequential strategy, which was the core clinical question. Of note, PFS1 was similar between treatment groups, supporting comparability at the time of second-line initiation, although heterogeneity in imaging schedules per real-world practice remains a limitation.

Sensitivity and resistance to ICIs are driven by complex interactions between tumor-intrinsic factors, the tumor microenvironment, and host immune responses. Specific molecular alterations (e.g. *KRAS* and *STK11/KEAP1* mutations) and laboratory findings (e.g. high lung-immune prognostic index or neutrophil-to-lymphocyte ratio) have been associated with poor outcomes and unfavorable immune profiles.[7,8,16,18-20] Tumors harboring *KRAS* and *STK11/KEAP1* mutations typically exhibit an immunosuppressive phenotype characterized by reduced CD8+ T-cell infiltration and impaired immune surveillance, which may hinder the effectiveness of ICIs.[20,21] Notably, STK11 mutations are currently considered a poor prognostic factor, while no clear predictive value for ICI efficacy has been established.[18,22] In our study, broader NGS panels were not mandatory, and their availability varied across centers and time per clinical practice and local reimbursement policies. This variability made it difficult to rule out undetected alterations.

In a large cohort of 1133 patients with NSCLC treated with ICI monotherapy or chemotherapy plus ICI, Hong et al.[22] confirmed *STK11* mutations as a consistent predictor of early progression in both treatment arms, especially under ICI monotherapy, as elsewhere investigated.[23]

Additionally, an inadequate pre-treatment density of tumor-infiltrating lymphocytes and the presence of immunosuppressive cell populations within the tumor microenvironment have been associated with ICI resistance.[24] Beyond tumor-intrinsic genomic factors, high disease burden has also been linked to ICI resistance through systemic mechanisms such as elevated concentrations of tumor-derived inflammatory cytokines (e.g. interleukin-8, transforming growth factor-α) and increased genomic instability, both of which may contribute to immune escape.[25]

In our real-world cohort, the genomic status of these alterations, as well as CD8+ T-cell infiltration data, were often unavailable, highlighting a persistent gap between translational evidence and clinical practice. In particular, due to the limited availability of genomic data (e.g. STK11, KEAP1), no correlative biomarker analyses were undertaken.

The addition of chemotherapy in combined regimens appears to mitigate the detrimental effects of these genomic features on early progression.[22,23,26-28] From a biological perspective, chemotherapy may synergize with immunotherapy by modulating the tumor microenvironment. Proposed mechanisms include the depletion of regulatory T cells, reduction of myeloid-derived suppressor

cells, induction of immunogenic cell death, and improved antigen presentation.[26] Nonetheless, depending on dosing and timing, chemotherapy may also exert immunosuppressive effects that limit the efficacy of checkpoint blockade.[28] Therefore, identifying optimal combination strategies and patient selection appears critical.

By extrapolating these data to the second-line setting, maintaining immunotherapy beyond progression while introducing platinum-based chemotherapy, as per standard second-line treatment, may represent a promising rescue strategy, as suggested by the higher ORR observed in our cohort and the numerically lower rate of PD as best response.

This study has relevant limitations, including its retrospective design and relatively small sample size, which warrant cautious interpretation and underscore the need for prospective validation. Primary resistance may reflect distinct patterns of tumor aggressiveness, from fast progression or hyper-progression to more indolent disease with early SD lasting $<$6 months[8,29] and it could be that despite similar characteristics, underlying biology could have differed causing the improvement in survival by maintaining ICI with the chemotherapy.

Additionally, the significant proportion of missing data for key variables, including molecular alterations, raises concerns regarding potential selection bias. Although baseline characteristics appeared balanced, unmeasured confounding or clinician-driven selection cannot be excluded due to the retrospective nature. This may have led to the preferential selection of fitter patients for chemotherapy plus ICI, introducing residual selection bias that cannot be excluded. Moreover, radiological assessment windows might not have been homogeneous among different centers. Patterns of progression to second line were reported descriptively, but this variable was not a prespecified endpoint and missingness does not affect the validity of PFS2 as the primary outcome.

Despite its limitations, our study is among the first to characterize the clinicopathological features of primary resistance to ICIs in advanced NSCLC with high PD-L1 expression and to provide real-world evidence from international referral centers supporting the continued use of ICIs combined with chemotherapy.

Conclusion

This study highlights the challenges of primary resistance to single-agent ICIs in advanced NSCLC patients with high PD-L1 expression and suggests a potential survival benefit of continuing ICIs beyond progression in addition to chemotherapy. These findings also support tailored strategies to promptly identify non-responders and adjust therapy. In this context, early radiological reassessment may represent a useful tool to safeguard patients receiving ICI monotherapy by allowing timely treatment adaptation. These findings are exploratory and hypothesis-generating, and further prospective research is needed to refine escalation and de-escalation approaches, balancing efficacy and toxicity to improve outcomes in this poor-prognosis population.

FUNDING

This work was supported by the European Union — NextGenerationEU through the Italian Ministry of University and Research under PNRR — M4C2-I1.3 Project PE_00000019 "HEAL ITALIA" [grant number CUP J33C22002920006 to ADG and ADF]. The views and opinions expressed are those of the authors only and do not necessarily reflect those of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them. The funder had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

DISCLOSURE

ADF honoraria from Society for Immunotherapy of Cancer, advisory role for Hansen-Wade, IQVIA, Novartis, and travel support from Johnson & Johnson and Pfizer. MC Amgen, travel grant; AstraZeneca, travel grant. FGDO research grants by Canceropole Ile-de-France and Fondation Gustave Roussy, outside this work. LH research funding to her institution from Roche Genentech, AstraZeneca, Boehringer Ingelheim, Takeda, Merck, Pfizer, Novartis, and Gilead, Summit and Amgen under negotiation; speaker fees from AstraZeneca, Bayer, Lilly, Merck Sharp & Dohme (MSD), High5Oncology, Takeda, Janssen, GlaxoSmithKline (GSK), Sanofi, Pfizer, MEDTalks, Benecke, VJOncology, and Medimix (some paid to self, others to institution); advisory roles (institutionally compensated) with AbbVie, Amgen, AnHeart, AstraZeneca, Bayer, Bristol Myers Squibb (BMS), Boehringer Ingelheim, Daiichi, Gilead, GSK, Janssen, Lilly, Merck, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, Summit Therapeutics, and Takeda; leadership roles in national and international guideline committees (some compensated); and participation as local principal investigator in clinical trials sponsored by AstraZeneca, GSK, Novartis, Merck, Roche, Takeda, Blueprint, Mirati, AbbVie, Gilead, MSD, Amgen, Boehringer Ingelheim, Pfizer, Daiichi, and BMS (all payments to institution). TG honoraria for lectures from Regeneron and BMS; and travel support from MSD, BMS, Takeda, Lilly, AstraZeneca, and Pierre-Fabre. LM lectures and educational activities: BMS, AstraZeneca, Roche, Takeda, Janssen, Pfizer, MSD, Radonova; consulting, advisory role: Roche, Takeda, Janssen, MSD, Pfizer; research grants: Inivata, AstraZeneca, Gilead; travel, accommodations, expenses: BMS, Roche, Takeda, AstraZeneca, Janssen. FT speaker bureau/honoraria: AstraZeneca, BMS, Novartis, Pierre Fabre, Pfizer, Roche, Takeda. SN advisor, speaker bureau: AstraZeneca, Amgen, BeiGene, Johnson & Johnson, Regeneron, Takeda, Novartis, Roche, Pfizer, MSD, Thermo Fisher, Eli Lilly. FG personal fees or advisory roles from Eli Lilly, Novartis, AstraZeneca, MSD. AA honoraria for the participation to advisory boards and/or for lectures from BMS, Eli Lilly, MSD, AstraZeneca, Roche,

Takeda, Janssen, Sanofi, Novartis, AbbVie, Daiichi. All other authors have declared no conflicts of interest.

DATA SHARING

The data underlying this article cannot be shared due to the privacy of individuals who participated in the study, as stated by the sponsor Ethics Committee (IGR approval no. 2022-132). Additional aggregated data analyses and the underlying analytic R code are available from the authors upon request.

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