

Real-World Characterization of Response Kinetics in Patients with Metastatic NSCLC Receiving First-Line Immunotherapy

Background

- Anti-PD-(L)1-based therapy is the preferred 1L treatment for patients with mNSCLC without driver mutations.^{1,2} However, many patients experience disease progression because of inadequate or unsustained response.³
- Understanding tumor response dynamics during IO is crucial to optimally escalate treatment that may enhance anti-PD-(L)1 response and improve survival.

Objective: To characterize the response kinetics for 1L anti-PD-(L)1 treatment in a real-world cohort of patients with mNSCLC and assess the association of depth of response (DepOR) at 3 months with survival.

Methods

Study details
Design: Retrospective study
Population: Patients with mNSCLC undergoing anti-PD-(L)1-based treatment
Sites: 10 US and European institutions
Dataset: Real-world dataset enhanced with radiologist-assessed imaging information ⁴

- Response to IO was assessed per RECIST v1.1 on routine CT scans.
- The agreement between 3-month response and best response was assessed using cross-tabulation.

- DepOR at 3 months after anti-PD-(L)1 initiation =** percent change in the SLD from baseline.⁵ The DepOR at 3-months was selected for each patient as the closest SLD measurement available to 90 days within a search window of 45 to 135 days.
- SLD-R =** any reduction in SLD from baseline measurement.

rwPFS and OS were evaluated in patient subcategories based on 3-month DepOR
≥75 to 100% SLD-R
≥50 to <75% SLD-R
≥30 to <50% SLD-R
≥0 to <30% SLD-R
Stable with SLD increase
Progressive disease

- Various thresholds were iteratively tested for association with survival outcomes in patients with 0 to 100% SLD-R at 3 months, and the SLD-R value that provided the maximum log-rank test statistic was selected as the optimal threshold.

Results

Patient characteristics

- Among 586 patients with mNSCLC undergoing 1L anti-PD-(L)1 treatment with scans available at baseline and at least 1 follow-up, the median (min, max) number of scans per patient in the cohort was 3 (2, 10).
- Median (IQR) time to first scan on therapy was 2.6 (1.9, 3.2) months, based on which the earliest reasonable time to measure DepOR was postulated to be about 3 months.
- A total of 414 patients were identified with evaluable RECIST assessments at both baseline and 3 months after anti-PD-(L)1 initiation (**Table 1**).

Table 1. Patient and tumor characteristics

Characteristics	N=414
Age at IO initiation, years [median (IQR)]	69 (62–76)
Sex, n (%)	
Male	234 (56.5)
Female	180 (43.5)
Race, n (%)	
White	242 (58.5)
Asian	12 (2.9)
Black	6 (1.4)
Indigenous American	2 (<1.0)
Unknown	152 (36.7)
Smoking status, n (%)	
Current/former smoker	148 (35.7)
Non-smoker	13 (3.1)
Unknown	253 (61.1)
Lesion count at IO initiation, median (IQR)	5.0 (3.0–8.0)
IO regimen type, n (%)	
IO monotherapy	179 (43.2)
Dual IO combination	5 (1.2)
IO/chemotherapy combination	230 (55.6)
Histology, n (%)	
Adenocarcinoma	298 (72.0)
Squamous cell carcinoma	78 (18.8)
Other	38 (9.2)
PD-L1 status, n (%)	
High (TPS ≥50%)	203 (49.0)
Low (TPS 1–49%)	88 (21.3)
Negative (TPS <1%)	89 (21.5)
Unknown	34 (8.2)

Depth of response

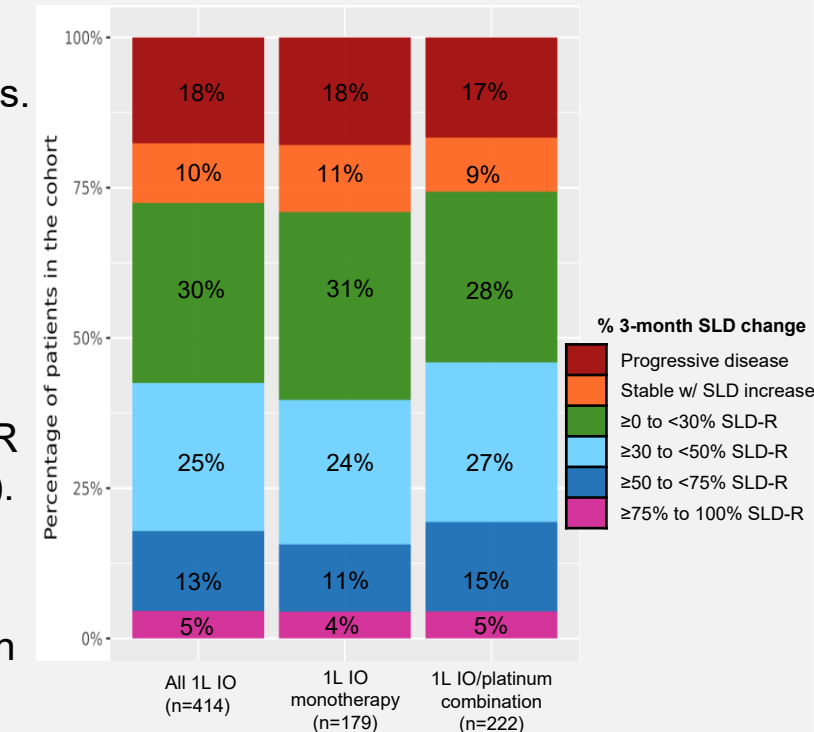
- Most patients achieved best response at 3 months (**Table 2**), where 90% had an additional scan after 3 months or experienced a censoring event soon after (clinical progression/death or loss of follow-up).
- Deepening of response after 3 months was observed in only 8% (32/414) of patients.

Table 2. Patient counts categorized by 3-month tumor response and best response while on 1L anti-PD-(L)1

Best response	3-month response					Total
	CR	PR	SD	PD		
CR	20	3	2	0		25
PR		153	21	2		176
SD			142	4		146
PD				67		67

- At 3 months following anti-PD-(L)1 initiation, 30% of patients had ≥0 to <30% SLD-R and 55% had ≥0 to <50% SLD-R in all patients receiving 1L anti-PD-(L)1 (**Figure 1**).
- ~18% had ≥50% SLD-R around 3 months after initiation of anti-PD-(L)1 treatment.
- 28% of patients demonstrated SLD increase from baseline or progressive disease.
- Patients receiving anti-PD-(L)1 monotherapy and anti-PD-(L)1/platinum combination therapy showed similar distributions of 3-month DepOR.

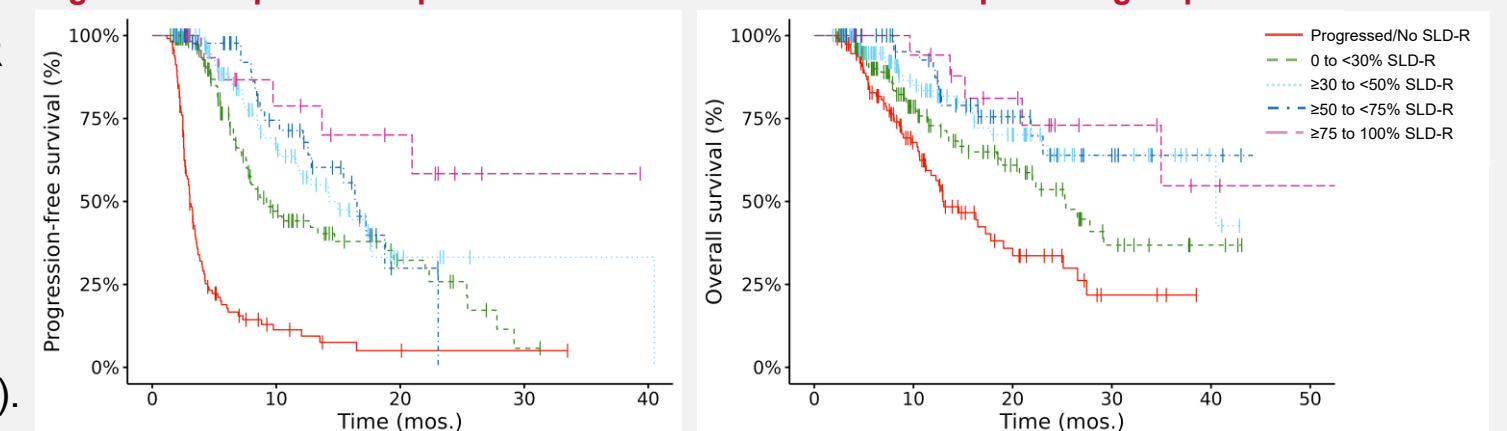
Figure 1. Distribution of initial 3-month tumor burden change



Patient outcomes

- Significantly improved rwPFS and OS was observed in all patients experiencing SLD-R than in those with no tumor shrinkage or progression at 3 months (**Figure 2**).
- Furthermore, patients with ≥50% to 100% SLD-R had significantly improved rwPFS (p=0.023) and a trend toward better OS (p=0.059) compared to those with modest tumor burden reduction (≥0 to <50% SLD-R).

Figure 2. Comparison of patient outcomes across 3-month DepOR subgroups



	Median rwPFS	Unadjusted rwPFS	Adjusted rwPFS*	Median OS	Unadjusted OS	Adjusted OS*
3-month SLD Change From Baseline	N	mPFS (95% CI), months	HR (95% CI)	mOS (95% CI), months	HR (95% CI)	HR (95% CI)
Progressed/No SLD-R	114	3.0 (2.7, 3.5)	Ref.	13.1 (11.3, 20.0)	Ref.	Ref.
0 to <30% SLD-R	124	9.2 (7.7, 18.8)	0.21 (0.15, 0.30)	25.4 (20.7, NR)	0.56 (0.37, 0.84)	0.63 (0.41, 0.97)
≥30 to <50% SLD-R	102	14.3 (11.8, NR)	0.14 (0.09, 0.21)	40.5 (40.5, NR)	0.34 (0.21, 0.55)	0.36 (0.21, 0.59)
≥50 to <75% SLD-R	55	16.5 (12.6, NR)	0.13 (0.08, 0.22)	NR (23.1, NR)	0.27 (0.14, 0.52)	0.29 (0.15, 0.56)
≥75 to 100% SLD-R	19	NR (13.7, NR)	0.07 (0.03, 0.18)	NR (35.0, NR)	0.25 (0.10, 0.63)	0.28 (0.11, 0.71)

*Cox models adjusted for histology, PD-L1 status, and IO regimen type.

Optimal threshold for 3-month SLD-R to identify patients with improved survival outcomes

- Increasing SLD-R was associated with numerically longer median survival times; therefore, we explored the optimal thresholds for 3-month SLD-R associated with survival outcomes.
- The most significant association with rwPFS and OS corresponded to optimal values of 36.5% and 34.8% reduction, respectively, consistent with the RECIST threshold of ≥30% SLD-R for responders.

Conclusions: Patients exhibiting sub-optimal response can be identified early in their treatment trajectory based on 3-month DepOR. If a significant reduction in tumor burden is not achieved at 3 months, the possibility of further tumor shrinkage is low. Tumor response at 3 months may inform patient selection for intensification strategies.

ABBREVIATIONS: 1L, first-line; CI, confidence interval; CR, complete response; DepOR, depth of response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IO, immunotherapy; IQR, interquartile range; mNSCLC, metastatic non-small cell lung cancer; NR, not reached; OS, overall survival; PD-L1, programmed death ligand 1; anti-PD-(L)1, anti-programmed cell death protein-1/ligand 1 inhibitors; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; rwPFS, real-world progression-free survival; rWOS, real-world overall survival; SD, stable disease; SLD, sum of longest diameters; SLD-R, SLD reduction; TPS, tumor proportion score; US, United States

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