

Real-world outcomes for first-line nivolumab + ipilimumab + chemotherapy in PD-L1<1% metastatic non-small cell lung cancer

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Objective

To describe patient characteristics, treatment patterns, and clinical and safety outcomes among United States (US) patients with PD-L1 negative (PD-L1 <1%) metastatic non-small lung cancer (mNSCLC) treated with first-line (1L) nivolumab + ipilimumab + chemotherapy (NIC) in predominantly community settings

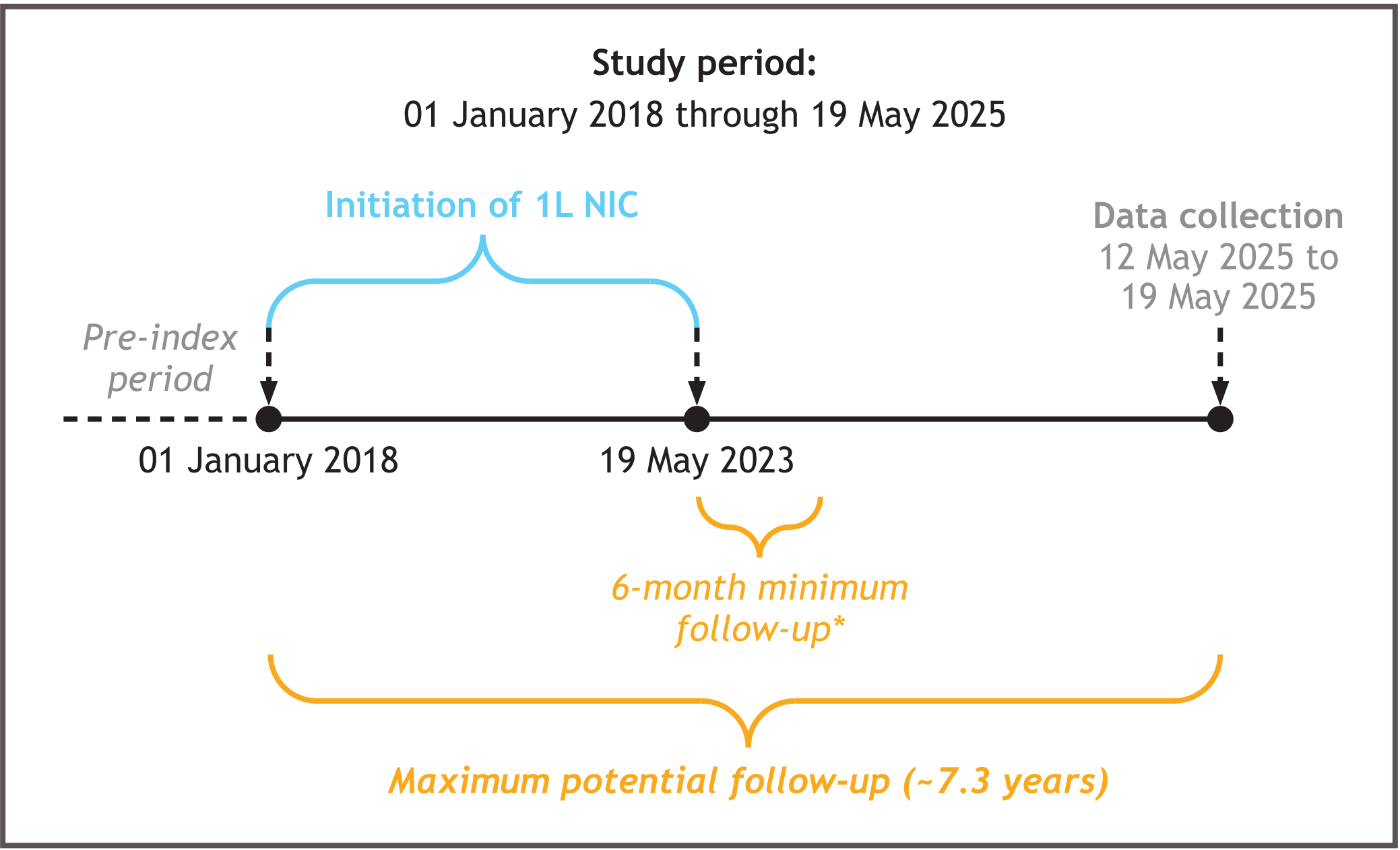
Background

- First line treatment selection for mNSCLC is guided by tumor genomics and PD-L1 expression, with immunotherapy-based approaches demonstrating greater benefit in patients with higher PD-L1 expression and fewer therapeutic options available for patients with PD-L1<1%^{1,2}
- In the CheckMate-9LA trial, 1L NIC demonstrated clinical benefit over chemotherapy alone in patients with mNSCLC^{3,4}
 - For patients with PD-L1<1% mNSCLC in CheckMate-9LA, results supported long-term clinical benefits for 1L NIC compared to chemotherapy alone (6-year overall survival [OS]: 20% vs 7%)^{3,4}
 - Based on CheckMate-9LA, 1L NIC received approval from the US Food and Drug Administration (FDA) on May 26, 2020 for patients with mNSCLC and no *EGFR* or *ALK* tumor mutations
- However, real-world evidence on 1L NIC use for patients with PD-L1<1% mNSCLC remains limited

Methods

- This retrospective, chart-review study used the Cardinal Health Oncology Provider Extended Network (OPEN)
- Participating physicians (N=18) abstracted patient-level data from medical charts into an electronic case report form for up to 10 patients in chronological order starting with the first eligible patient
- Patient Inclusion Criteria**
 - At least 18 years old at confirmed diagnosis with mNSCLC (stage IV), squamous or non-squamous histology
 - Initiated 1L NIC regimen between 01 January 2018 and 19 May 2023
 - Tumor PD-L1 negative expression (i.e., PD-L1 <1%); PD-L1 status was based on local test results
 - No *EGFR*, *ALK*, or *ROS1* genetic mutation (i.e., wild type)
 - Minimum of 6 months of follow-up after initiation of 1L NIC (patients who died prior to 6 months post-initiation of index were still eligible)
 - Baseline scan completed within 6 weeks prior to initiation of 1L NIC
- Patient Exclusion Criteria**
 - Any prior systemic therapy for mNSCLC
- Patients were followed from 1L NIC initiation until date of last contact as of data collection (19 May 2025) or death, whichever occurred first (**Figure 1**)
- Patient characteristics, treatment patterns, and safety outcomes were analyzed using descriptive statistics, including frequency counts and proportions for dichotomous and categorical variables as well as measures of centrality and spread for continuous variables
- Time-to-event outcomes (progression-free survival [PFS], overall survival [OS], time to discontinuation) were estimated using the Kaplan-Meier (KM) method
- All analyses were performed using SAS v9.4 (SAS Institute, Cary, NC, USA)

Figure 1. Study schema for this retrospective chart review study



Results

Patient characteristics

- Overall, data were abstracted for 103 patients treated with 1L NIC for PD-L1 <1%, mNSCLC (**Table 1**)
- Median age at 1L NIC initiation was 64.8 years (Q1-Q3: 60.0-69.8) and the majority of patients were male (64.1%)
- The patient population was racially and ethnically diverse, including White (54.4%), Black or African American (33.0%), Hispanic (8.7%), and Asian (6.8%) patients; an estimated 14.4% of the US adult population self-identifies as Black⁵
- Most patients had good ECOG performance status (0-1: 83.5%) and were treated in community settings (89.3%)
- Seven patients had a known *HER2*, *NTRK*, or *RET* mutation at 1L NIC initiation
- As of last follow-up, median follow-up from 1L NIC initiation was 19.1 months (Q1-Q3: 12.3-24.6) overall and 25.8 months (min-max: 24.1-74.3) among patients who were alive

Table 1. Patient characteristics

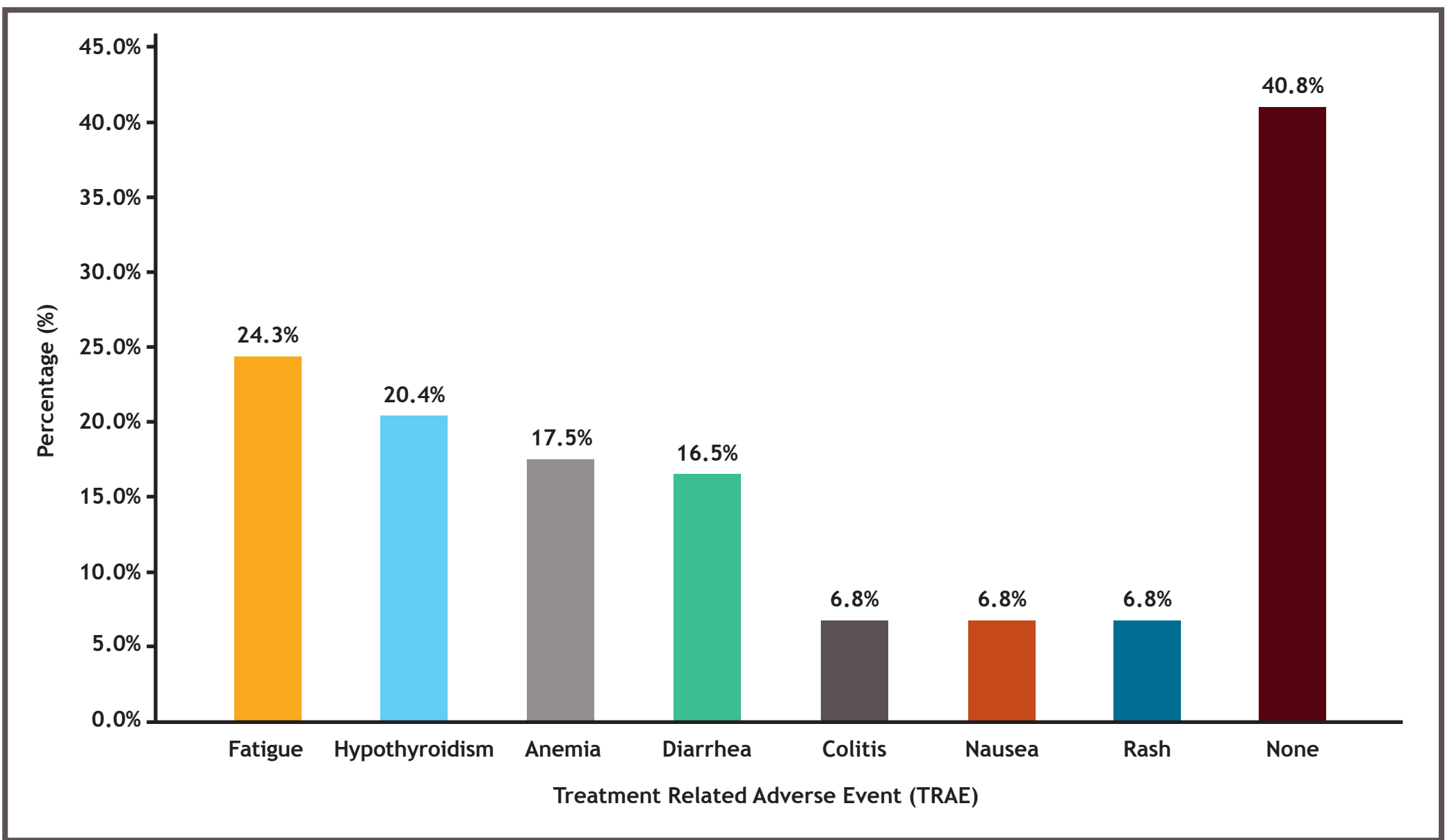
	All Patients N=103
Follow-up since 1L NIC initiation in months, median (Q1-Q3)	19.1 (12.3-24.6)
Age at 1L NIC initiation in years, median (Q1-Q3)	64.8 (60.1-69.8)
Male sex, n (%)	66 (64.1)
Race/ethnicity, n (%)*	
White	56 (54.4)
Black or African American	34 (33.0)
Hispanic or Latino	9 (8.7)
Asian	7 (6.8)
ECOG performance status at 1L NIC initiation, n (%)	
0-1	86 (83.5)
2	17 (16.5)
NCI Comorbidity Index, median (Q1-Q3)	0.3 (0.0-0.8)
Smoking status at 1L NIC initiation, n (%)	
Former smoker	73 (70.9)
Current smoker	25 (24.3)
Never smoked	5 (4.9)
Known genetic mutations present, n (%)*	
<i>KRAS</i>	16 (15.5)
<i>KEAP1</i>	6 (5.8)
<i>STK11</i>	6 (5.8)
<i>HER2</i>	4 (3.9)
<i>BRAF</i>	3 (2.9)
<i>RET</i>	2 (1.9)
<i>NTRK</i>	1 (1.0)
<i>TP53</i>	1 (1.0)
NSCLC histology, n (%)	
Squamous	25 (24.3)
Non-squamous	78 (75.7)
Practice setting for treatment, n (%)	
Community	92 (89.3)
Academic medical center/teaching hospital	11 (10.7)

*Categories of response not mutually exclusive, total may sum to more than column total

Treatment-related adverse events (TRAEs)

- TRAEs (based on treating physician's assessment) during 1L NIC were reported in 59.2% of patients, including fatigue (24.3%), hypothyroidism (20.4%), anemia (17.5%), and diarrhea (16.5%; **Figure 2**)
- Ten patients (9.7%) experienced grade 3/4 events at first occurrence
- No grade 5 TRAEs were reported
- Patients who experienced TRAEs also experienced dose reductions or interruptions in 11% of cases and discontinuations in 8.7% of cases

Figure 2. Frequency of TRAEs (any grade) observed during treatment with 1L NIC for mNSCLC, for events with frequency ≥5%



Treatment patterns

- 15 patients (14.6%) experienced dose modifications or interruptions during 1L NIC (**Table 2**)
- At last follow-up, 99 patients (96.1%) had discontinued 1L NIC. Most patients (n=88) discontinued nivolumab and ipilimumab concurrently, primarily due to disease progression (70/88 [79.5%])
- For the 11 patients who discontinued nivolumab and ipilimumab separately, ipilimumab was discontinued before nivolumab in all cases and for varied reasons (5/11 for toxicity, 4/11 for patient preference)
- Median time to discontinuation for 1L NIC was 11.0 months (95% confidence interval [CI]: 9.7-13.2) and time to next treatment was 13.3 months (95% CI: 10.8-15.4)
- Second-line therapy was reported for 57 patients (57.6%) who discontinued 1L NIC; patients did not proceed to second-line therapy after 1L NIC discontinuation primarily due to patient choice (20/42), remission (10/42), and death (9/42)

Table 2. Treatment patterns among patients receiving 1L NIC for PD-L1<1% mNSCLC

	All Patients N=103
Patient experienced at least one treatment modification (reduction, increase, interruption) in 1L NIC, n, %	
Yes	15 (14.6)
No	88 (85.4)
Discontinuation status for nivolumab and ipilimumab in 1L NIC at last follow-up, n (%)	
Discontinued both nivolumab and ipilimumab	99 (96.1)
Discontinued nivolumab alone (i.e., still on ipilimumab)	0 (0.0)
Discontinued ipilimumab alone (i.e., still on nivolumab)	1 (1.0)
Still on both nivolumab and ipilimumab	3 (2.9)
Patient discontinued nivolumab and ipilimumab on the same date, among patients who discontinued both, n (%)	
Yes	88 (88.9)
No	11 (11.1)
Reason(s) for discontinuation of 1L NIC, among patients who discontinued nivolumab and ipilimumab at the same time, n (%)*	
Disease progression	70 (79.5)
Scheduled duration of treatment complete	9 (10.2)
Patient preference	5 (5.7)
Adverse event/toxicity	3 (3.4)
Lack of efficacy/effectiveness	3 (3.4)
Death	2 (2.3)
Time to discontinuation of 1L NIC therapy in months (KM)*	
N of censored (%)	4 (3.9)
N of events (%)	99 (96.1)
KM Median [95% CI]	10.6 [9.5-12.5]
Time to next treatment from 1L NIC initiation in months (KM)*	
N of censored (%)	15 (14.6)
N of events (%)	88 (85.4)
KM Median [95% CI]	13.3 [10.8-15.4]
Patient received second-line (2L) therapy, among patients who discontinued 1L NIC, n (%)	
Yes	57 (57.6)
No	42 (42.4)
Primary reason patient did not initiate 2L therapy, among patients who discontinued 1L NIC but did not receive 2L therapy, n (%)	
Patient choice	20 (47.6)
Remission	10 (23.8)
Death	9 (21.4)
Poor performance status	3 (7.1)
Treatment-free interval between 1L NIC discontinuation and 2L initiation, among patients who received 2L therapy (months)	
n (%)	57 (57.6)
Median, Q1-Q3	0.5 (0.4-0.8)

*Categories of response not mutually exclusive, total may sum to more than column total

*Time from 1L NIC initiation to the last date of discontinuation of the three treatments (nivolumab, ipilimumab, chemotherapy) or death (events) or last day of follow-up if patient was still on therapy (censored)

*Time from 1L NIC initiation to initiation of subsequent systemic treatment or death (events), or date of last follow-up (censored)

Clinical outcomes

- At last follow-up, 73 (70.9%) patients were deceased; 7 patients (6.8%) were on active surveillance
- Median PFS from initiation of 1L NIC was 11.6 months (95% CI: 10.3-14.7; **Figure 3**), with a 2-year PFS rate of 19.4% (95% CI: 12.4%-27.5%)
- Median OS from initiation of 1L NIC was 19.1 months (95% CI: 15.7-21.8; **Figure 4**), with a 2-year OS rate of 34.0% (95% CI: 25.0%-43.1%)
- OS results were similar among patients with *KEAP1*, *KRAS*, or *STK11* mutations
- In a sensitivity analysis excluding patients with *HER2*, *RET*, or *NTRK* alterations (n=7), OS and time to next treatment results were consistent, suggesting limited impact on the overall clinical outcomes

Figure 3. PFS among patients treated with 1L NIC for PD-L1<1% mNSCLC

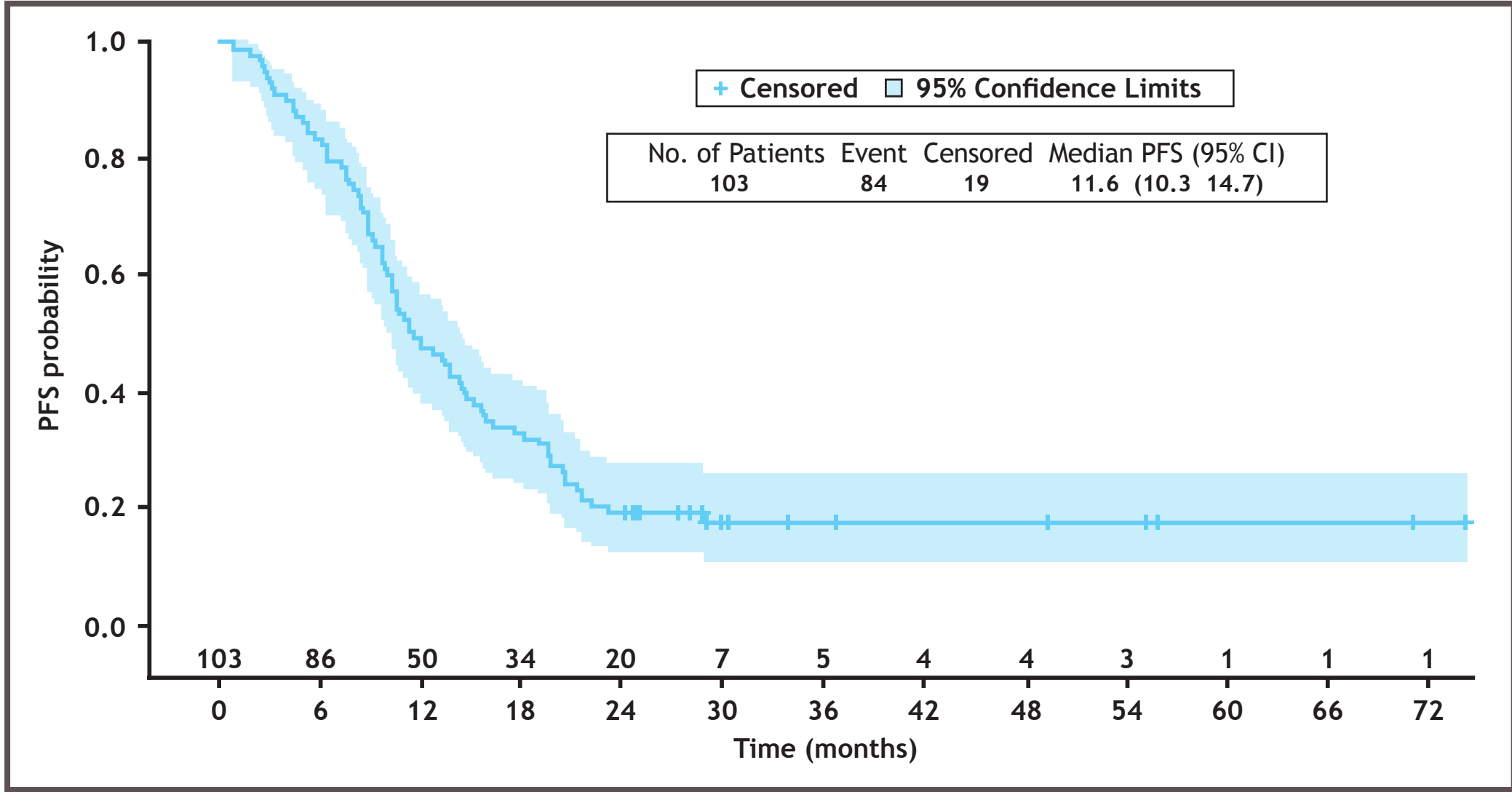
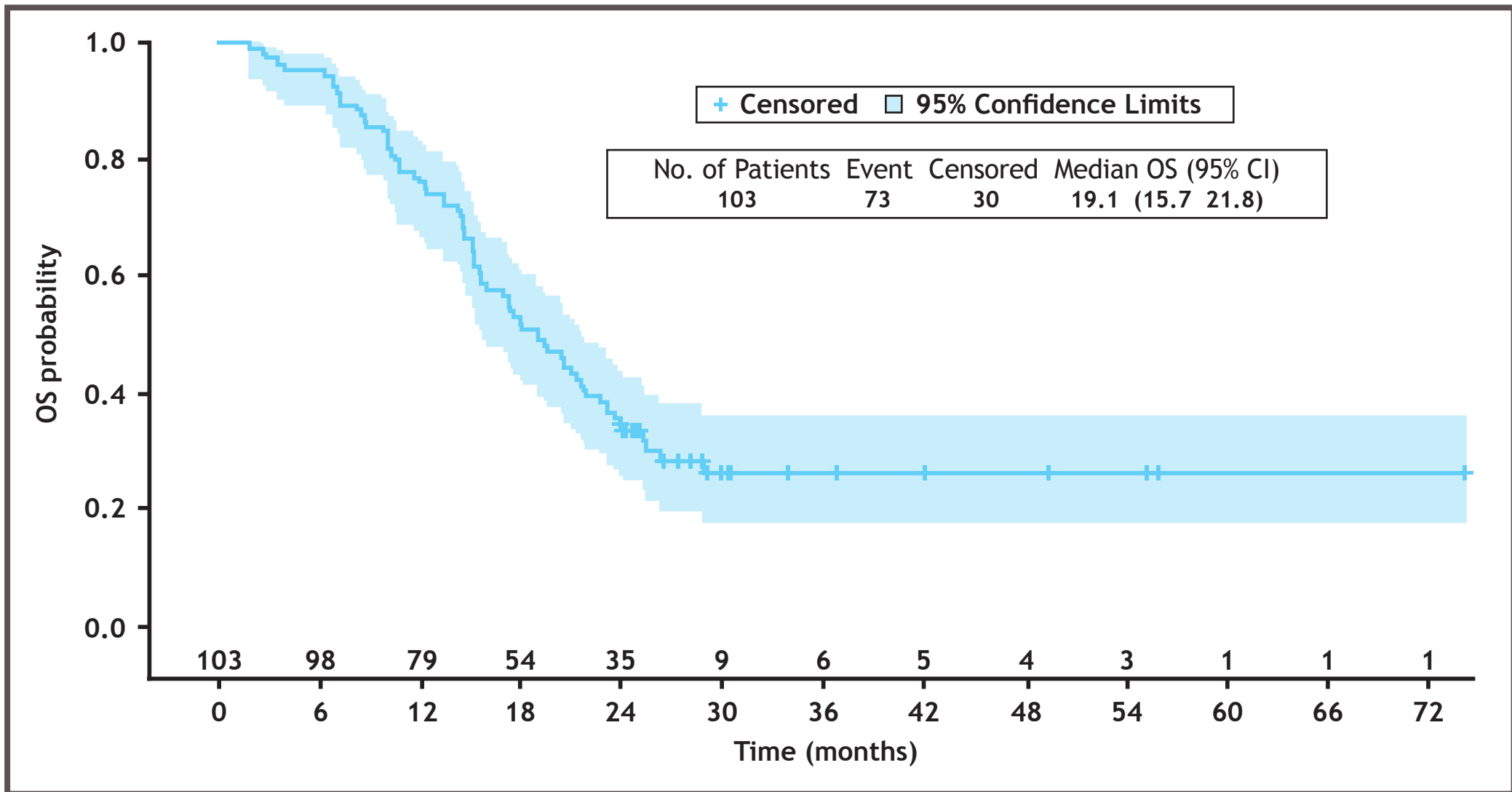


Figure 4. OS among patients treated with 1L NIC for PD-L1<1% mNSCLC



Limitations

- These results represent only patients abstracted by oncologists who participated in the study, which may not be representative of the broader patient population with mNSCLC who are treated with 1L NIC
- A minimum six months of follow-up after 1L NIC initiation was required unless patients died within this time, which could introduce bias if patients lost to follow-up differed systematically from those who remained under care
- Several patients carried genetic mutations (*HER2*, *RET*, *NTRK*) with known targeted therapies, which may have affected long-term outcome estimates (e.g., shorter time to next treatment; longer OS)

Conclusions

- In this US-based real-world study of patients with PD-L1 <1% mNSCLC treated with 1L NIC, findings were consistent with the CheckMate-9LA clinical trial results and support the efficacy of 1L NIC in a diverse patient population
- While 2-year clinical outcomes were relatively mature, additional follow-up is needed to estimate long-term outcomes

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