Understanding the Real-World (RW) Impact of Time Between Treatment Regimens on Clinical Outcomes in Patients with Metastatic NSCLC Previously Treated with Immunotherapy (IO) in the US Community Oncology Setting

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Background

- Non-small cell lung cancer (NSCLC) accounts for approximately 80-85% of lung cancers with varying 5-year survival rate estimates ranging from 64% for localized disease to 8% for metastatic NSCLC (mNSCLC).[1-2]
- For first-line treatment (1L) of mNSCLC, options consist of several different combinations of immunotherapy (IO) and/or chemotherapy such as pembrolizumab plus platinum-based chemotherapy, nivolumab plus ipilimumab, nivolumab plus ipilimumab plus limited platinum-based chemotherapy, though patients with intolerance and disease progression require subsequent treatment.[3]
- With this evolution, there is a newfound need to understand the optimal sequencing and timing of regimens.
- This study investigated real-world treatment patterns and clinical outcomes among patients with mNSCLC who were previously treated with 1L IO regimens.

Methods

Study design and population

- This was a real-world retrospective observational study utilizing electronic health record (EHR) data from The US Oncology Network to evaluate patients with mNSCLC receiving 1L IO regimens in US community oncology practices.
- Patients with the following criteria were included in this analysis:
  - Age ≥ 18 years at diagnosis of NSCLC,
  - ≥ 2 visits to a US Oncology Network clinic,
  - Initiated 1L IO regimens, defined as the first IO therapy for mNSCLC during study identification period (January 1, 2015, to December 31, 2020), and
  - Initiated a second/subsequent regimen after 1L IO during the study identification period.
- Patients were excluded from the study if they received treatment for other documented primary cancer diagnoses up to 3 years prior to the start of the observation period through the end of the observation period (01-Jan-2012 to 31-Mar-2022), or EGFR-, ALK-, or ROS1-targeted therapy.
- Patients were indexed on the date of initiation of the subsequent regimen after 1L IO and followed for up to 15 months through the end of the study observation period, date of last visit, or date of death, whichever occurred first.

Data source

- Study data were sourced from structured fields of The US Oncology Network's EHR system, iKnowMed (iKM), which includes over 1.2 million patients treated annually within community-based outpatient practices receiving treatment across the network.[4]
- The Social Security Administration's Death Master File was used to supplement the data available in iKM on vital status and death dates.

Statistical analysis

- Descriptive analyses were performed on demographic and clinical characteristics and treatment patterns.
- Kaplan-Meier (K-M) methods were used to describe real-world overall survival (rwOS), time to treatment discontinuation (rwTTD) and time to next treatment (rwTTNT) from initiation of the post-IO regimen.
- Subgroup analyses were presented by post-1L IO treatment-free interval (TFI), defined as the duration between last 1L IO administration date and the subsequent regimen start date. Patients were categorized by post-1L IO TFI ≤30 days, 31-60 days, 61-90 days, and >90 days.
- Analyses were conducted using SAS v.9.4.

Results

Sample size and patient characteristics

- Overall, 1,116 patients were identified (median follow-up 7.2 months).
- Most patients were age ≥65 years (62%), White (73%), and had a history of tobacco use (82%) **(Table 1)**.
- There were no statistically significant differences in age, sex, race, tobacco use, ECOG or histology by post-1L IO TFI category **(Table 1)**.

Table 1. Demographic and Clinical Characteristics of Patients with mNSCLC Initiating Subsequent Treatment after 1L IO, Overall and by Post-IO TFI

Variable	Overall	Post-1L IO TFI (days)			
		≤30	31-60	61-90	>90
N	**1,116**	**499**	**345**	**79**	**193**
Age at index, median (IQR)	68 (61, 75)	68 (61, 74)	69 (61, 76)	67 (60, 75)	68 (61, 77)
Age group, n (%)					
<65 years	411 (37)	193 (39)	119 (34)	31 (39)	68 (35)
65+ years	692 (62)	301 (60)	222 (64)	47 (59)	122 (63)
Not documented	13 (1)	5 (1)	<5	<5	<5
Sex, n (%)					
Female	525 (47)	232 (46)	163 (47)	34 (43)	96 (50)
Male	578 (52)	262 (53)	178 (52)	44 (56)	94 (49)
Not documented	13 (1)	5 (1)	<5	<5	<5
Race, n (%)					
Black or African American	98 (9)	47 (9)	27 (8)	8 (10)	16 (8)
Caucasian/White	811 (73)	358 (72)	255 (74)	55 (70)	143 (74)
Other	36 (3)	19 (4)	7 (2)	5 (6)	5 (3)
Not documented	171 (15)	75 (15)	56 (16)	11 (14)	29 (15)
Tobacco use, n (%)					
Current	197 (18)	78 (16)	64 (19)	14 (18)	41 (21)
Former	718 (64)	331 (66)	212 (61)	52 (66)	123 (64)
Never	110 (10)	52 (10)	35 (10)	6 (8)	17 (9)
Not documented	91 (8)	38 (8)	34 (10)	7 (9)	12 (6)
Time (weeks) from mNSCLC diagnosis to index, median (IQR)	33 (19, 55)	26 (15, 44)	30 (19, 43)	37 (25, 64)	58 (43, 98)
ECOG group at index (within 30 days), n (%)					
0	130 (12)	70 (14)	39 (11)	7 (9)	14 (7)
1	505 (45)	224 (45)	160 (46)	36 (46)	85 (44)
2	191 (17)	72 (14)	69 (20)	17 (22)	33 (17)
3+	14 (1)	6 (1)	6 (2)	0	2 (1)
Not documented	276 (25)	127 (25)	71 (21)	19 (24)	59 (31)
Histology at initial NSCLC diagnosis, n (%)					
Non-squamous	817 (73)	364 (73)	258 (75)	53 (67)	142 (74)
Squamous	266 (24)	117 (23)	82 (24)	25 (32)	42 (22)
Not documented	33 (3)	18 (4)	5 (1)	<5	9 (5)

Note: some percentages may not add up to 100 due to rounding.

Treatment patterns

- The most common 1L IO regimens consisted of pembrolizumab in combination with platinum chemotherapy and pemetrexed (36%, overall; 35-37% by post-1L IO TFI), and pembrolizumab monotherapy (35%, overall; 30-36% by post-1L IO TFI) **(Table 2)**.

Table 2. 1L Treatment Patterns of Patients with mNSCLC Initiating Subsequent Treatment after 1L IO, Overall and by Post-IO TFI

Variable	Overall	Post-1L IO TFI (days)			
		≤30	31-60	61-90	>90
N	**1,116**	**499**	**345**	**79**	**193**
1L IO regimens, n (%)					
Pembrolizumab+Platinum+Pemetrexed	401 (36)	173 (35)	129 (37)	29 (37)	70 (36)
Pembrolizumab monotherapy	387 (35)	178 (36)	118 (34)	24 (30)	67 (35)
Pembrolizumab+Platinum+Paclitaxel[a]	140 (13)	59 (12)	45 (13)	15 (19)	21 (11)
Nivolumab±Ipilimumab	96 (9)	49 (10)	18 (5)	6 (8)	23 (12)
Other IO[b]	109 (8)	40 (8)	35 (10)	5 (6)	12 (6)
Treatment duration (weeks), median (IQR)	21 (10, 35)	21 (9, 34)	19 (10, 34)	22 (10, 43)	21 (11, 41)

Note: some percentages may not add up to 100 due to rounding.
[a]Includes paclitaxel and nab-paclitaxel; [b]Other categories include regimens with <5 patients in at least one subgroup: atezolizumab+bevacizumab+platinum+paclitaxel (n=15), atezolizumab monotherapy (n=13), atezolizumab+platinum+paclitaxel[a] (n=11), pembrolizumab+pemetrexed (n=11), and durvalumab (n=9). All other regimens/combinations not listed were n≤5.

- Subsequent treatment was initiated within 30 days following 1L IO discontinuation in 499 (45%) patients, whereas 193 (17%) patients had a post-1L IO TFI >90 days **(Table 3)**.
- Subsequent treatments after 1L IO varied by post-1L IO TFI **(Table 3)**.
  - Most patients with post-1L IO TFI ≤90 days initiated non-IO regimens such as docetaxel with or without ramucirumab (26-34%), platinum-based chemotherapy with pemetrexed or paclitaxel (18-25%), or gemcitabine (8-9%).
  - Conversely, 62% of patients with post-1L IO TFI >90 days resumed or switched to a different IO regimen.

Table 3. Index Regimens of Patients with mNSCLC Initiating Subsequent Treatment after 1L IO, Overall and by Post-IO TFI

Variable	Overall	Post-1L IO TFI (days)			
		≤30	31-60	61-90	>90
N	**1,116**	**499**	**345**	**79**	**193**
Non-IO regimens, n (%)	**782 (70)**	**363 (73)**	**279 (81)**	**66 (84)**	**74 (38)**
Docetaxel±Ramucirumab	307 (28)	132 (26)	126 (37)	27 (34)	22 (11)
Platinum+Pemetrexed	119 (11)	52 (10)	47 (14)	12 (15)	8 (4)
Platinum+Paclitaxel[a]	89 (8)	45 (9)	26 (8)	8 (10)	10 (5)
Gemcitabine	87 (8)	45 (9)	29 (8)	7 (9)	6 (3)
Other non-IO[b]	180 (16)	89 (18)	51 (15)	12 (15)	28 (15)
IO regimens, n (%)	**334 (30)**	**136 (27)**	**66 (19)**	**13 (16)**	**119 (62)**

Note: some percentages may not add up to 100 due to rounding.
[a]Includes paclitaxel and nab-paclitaxel; [b]Other categories include regimens with <5 patients in at least one subgroup: gemcitabine+platinum (n=31), pemetrexed (n=26), targeted therapy alone or in combination with chemotherapy (n=25), bevacizumab+platinum+pemetrexed or paclitaxel (n=21), vinorelbine (n=11), and nab-paclitaxel (n=7). All other regimens/combinations not listed were n≤5

Clinical outcomes

- Unadjusted K-M analysis and median (95% CI) rwOS, TTNT, and TTD are presented by post-1L IO TFI category in **Figures 1-3** and **Table 4**.

Figure 1. K-M Analysis of rwOS in Patients with mNSCLC Initiating Subsequent Treatment after 1L IO by Post-IO TFI

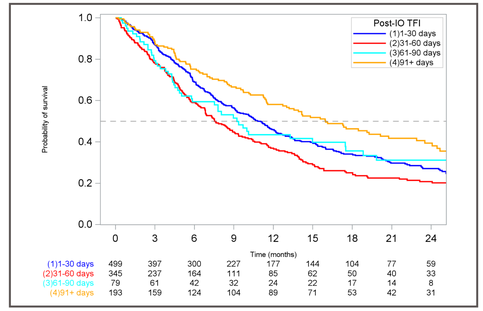


Figure 2. K-M Analysis of rwTTNT in Patients with mNSCLC Initiating Subsequent Treatment after 1L IO by Post-IO TFI

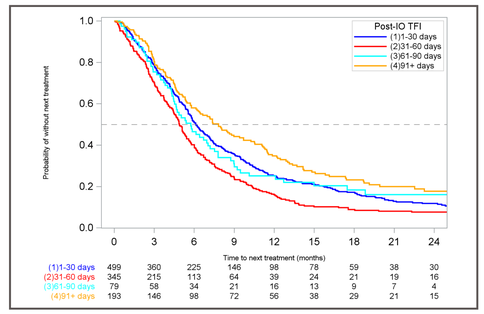
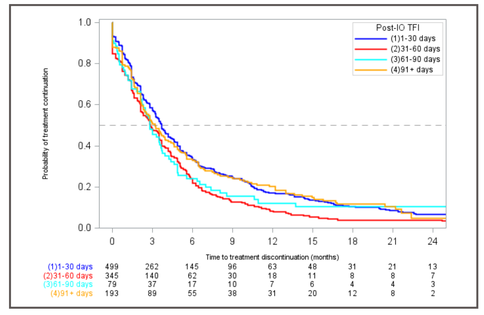


Figure 3. K-M Analysis of rwTTD in Patients with mNSCLC Initiating Subsequent Treatment after 1L IO by Post-IO TFI



Clinical outcomes (cont.)

- Patients with post-IO TFI 31-60 days had a higher risk of death or next treatment relative to patients with post-IO TFI ≤30 days **(Figures 1-2)**.
- Median (95% CI) rwOS was 16.0 (12.7, 20.8) months in patients with post-1L IO TFI >90 days and 7.5 (6.8, 9.1) months in patients with post-1L IO TFI 31-60 days **(Table 4)**.

Table 4. Unadjusted Median (95% CI) rwOS, rwTTD, and rwTTNT in Patients with mNSCLC Initiating Subsequent Treatment after 1L IO by Post-IO TFI

Variable	Post-1L IO TFI (days)				Logrank P-value
	≤30	31-60	61-90	>90	
N	**499**	**345**	**79**	**193**	-
rwOS (months), median (95% CI)	10.8 (9.2, 12.2)	7.5 (6.8, 9.1)	9.2 (5.8, 17.5)	16.0 (12.7, 20.8)	<0.0001
rwTTNT (months), median (95% CI)	6.1 (5.7, 6.7)	4.9 (4.5, 5.4)	5.7 (4.5, 7.2)	7.8 (6.1, 9.7)	<0.0001
rwTTD (months), median (95% CI)	3.7 (3.3, 4.2)	2.9 (2.3, 3.5)	2.8 (2.2, 3.6)	3.2 (2.4, 4.0)	0.0025

Limitations

- Because this was a retrospective analysis of structured EHR data, certain variables such as reason for treatment discontinuation (i.e. progression) could not be assessed.
- Data were collected as part of routine clinical practice and not solely for research purposes. As such, data may be subject to missingness and misclassification.
- Practices that participate in The US Oncology Network may have patient populations and/or prescribing practices that differ from other community oncology clinics outside of the network.

Conclusions

- This RW study highlights the variation in treatments and outcomes by TFI among patients with mNSCLC previously treated with IO.
- TFI ≤30 days may represent avoided delays in treatment, whereas TFI >90 days may include patients with long-term response to IO.
- Further research is needed to optimize treatment strategies in this setting.

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Declaration of interests

- AO reports employment with McKesson/Ontada.

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