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Second-Line Real-World Treatment Patterns and Outcomes in Patients with Advanced/Metastatic Non-Small Cell Lung Cancer Treated with First Line Immuno-Oncology Monotherapy

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INTRODUCTION

- First-line immune checkpoint inhibitor monotherapy (1L IO mono-tx) for advanced NSCLC is an option based on recent clinical trials[1,2]
- As there are few data regarding treatment sequencing following 1L IO mono-tx for NSCLC, there is interest in seeking evidence to identify optimal treatment sequences in this setting
- This analysis explored the use of second-line (2L) systemic treatment and OS in patients with NSCLC following 1L IO mono-tx in a real-world setting

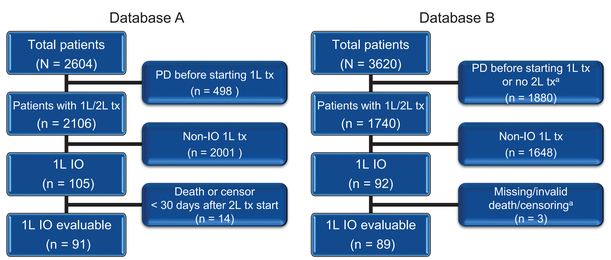
OBJECTIVES

- Evaluate OS for 2L+ therapy after 1L IO mono-tx in the real world
- Explore the feasibility of pooling 2 different RWD databases and sharing the lessons learned

METHODS

- Database A (EHR-derived database)
  - A retrospective analysis of 2604 randomly selected patients with stage IIIB/IV NSCLC treated in US practices (156 community and 3 academic sites) between January 2013 and December 2018
  - Treatment regimens were defined using only therapies initiated in the first 30 days of treatment (1L treatment, treatment received prior to disease progression [PD]; 2L treatment, first treatment after first PD)
- Database B
  - An additional analysis was implemented using a different RWD source to explore whether trends in treatment effect were consistent across databases. Of the 7015 patients with any stage/histology, 3620 patients with advanced NSCLC from > 40 contributing academic and community oncologist provider sites and hospital systems were identified between January 2013 and December 2018
- Considerations for pooling data led to an in-depth evaluation of RWE generation using multiple RWD sources
- 2L treatment patterns and OS were assessed in patients treated with 1L IO mono-tx. OS and 95% CIs were estimated using Kaplan-Meier (K-M) methods

Figure 1. Database A and B Population Flowcharts



[a] Differences in data curation required that slightly different criteria be applied for Database B.

RESULTS

- Patients treated with 1L IO mono-tx (initiated after 1 January 2016) at each site were identified in Database A (N = 105) and Database B (N = 92)
- Patients in Database B do not have dates other than year and quarter of initial diagnosis. All time-related variables are presented as interval change from initial diagnosis, so imputation was required to determine treatment start based on metastatic NSCLC (mNSCLC) diagnosis date
- Demographics and baseline characteristics are reported by database in Table 1; differences in these characteristics existed between the 2 databases

Table 1. Demographics and Baseline Characteristics

Characteristic	Database A (N = 105)	Database B (N = 92)
Age, years		
Median (range)	72 (47 - 84)	67 (35 - 87)
≥ 70, n (%)	64 (61.0)	34 (37.0)
Men, n (%)	65 (61.9)	46 (50.0)
Race, n (%)		
White	73 (69.5)	68 (73.9)
Nonwhite	21 (20.0)	19 (20.7)
Unknown	11 (10.5)	5 (5.4)
ECOG PS, n (%)		
0 - 1	54 (51.4)	46 (50.0)
≥ 2	17 (16.2)	6 (6.5)
Unknown	34 (32.4)	40 (43.5)
Smoking history, n (%)		
No history of smoking	10 (9.5)	14 (15.2)
History of smoking	95 (90.5)	78 (84.8)
Unknown	0	0
Histology, n (%)		
Squamous cell carcinoma	50 (47.6)	22 (23.9)
Nonsquamous/NSCLC NOS	55 (52.4)	70 (76.1)
Time to first PD, n (%)		
< 6 Months	79 (75.2)	55 (59.8)
≥ 6 Months	26 (24.8)	16 (17.4)
Unknown	0	21 (22.8)

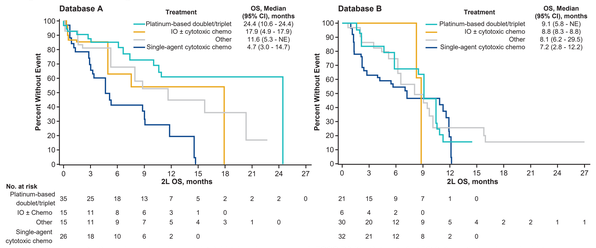
- 91 (Database A) and 89 (Database B) patients were eligible for the initial exploratory analysis; results are presented in Table 2
  - Database A: Patients received platinum-based doublet/triplet (n = 35 [38.5%]), single-agent chemo (n = 26 [28.6%]), IO ± chemo (n = 15 [16.5%]), or other (n = 15 [16.5%]) treatment as 2L therapy
  - Database B: Patients received platinum-based doublet/triplet (n = 21 [23.6%]), single-agent chemo (n = 32 [36.0%]), IO ± chemo (n = 6 [6.7%]), or other (n = 30 [33.7%]) treatment as 2L therapy
- A multivariate-adjusted K-M analysis of 2L OS revealed a similar trend for longer median survival time with platinum-based doublet/triplet vs single-agent chemo (Table 2; Figure 2)

Table 2. Adjusted 2L OS in Patients Treated With 1L IO Mono-Tx

Treatment Group	Database A		Database B	
	Events/Total, n/N	OS, Median (95% CI), months	Events/Total, n/N	OS, Median (95% CI), months
Platinum-based doublet/triplet	13/35	24.4 (10.6 - 24.4)	12/21	9.1 (5.8 - NE)
IO ± cytotoxic chemo	7/15	17.9 (4.9 - 17.9)	2/6	8.8 (8.3 - 8.8)
Other[a]	11/15	11.6 (5.3 - NE)	16/30	8.1 (6.2 - 29.5)
Single-agent cytotoxic chemo	19/26	4.7 (3.0 - 14.7)	22/32	7.2 (2.8 - 12.2)

[a] Includes targeted mono tx/doublets, chemo/monoclonal antibody doublets, chemo doublets, clinical study drugs, and 1 unknown.

Figure 2. Adjusted[a] K-M Plot of 2L OS by 2L Treatment for Patients Treated With 1L IO Mono-Tx of Original Result Using Database A Data and New Result Using Database B Data



[a] Model adjusted for age (≥ 70 years), sex (male), race (white), histology (nonsquamous), ECOG PS (0 - 1), time to first PD (≥ 6 months), and smoking history (positive/unknown).

Explanation for Differences in Medians for 2L Platinum Doublet

- Differences in follow-up time, high percentage of right censoring (22/35) in the Database A data, and/or source data curation likely account for the numeric differences
  - Point estimate of median using product-limit method is the first event time where survival is ≤ 0.5 (Table 3)
  - Median of 24.4 months for Database A occurs at the last event time because the product-limit survival estimate at previous event time is > 0.5

Table 3. Product-Limit Survival Estimates in 2L Platinum-Doublet Groups for Database A (A) and Database B (B)

A

OS2L	Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.0000	1.0000	0	0	0	35
0.0329	0.9714	0.0286	0.0282	1	34
0.3285	0.9429	0.0571	0.0392	2	33
0.4600	0.9143	0.0857	0.0473	3	32
0.5589+	.	.	.	3	31
0.6242+	.	.	.	3	30
0.6571+	.	.	.	3	29
1.5113	0.8828	0.1172	0.0552	4	28
1.8384+	.	.	.	4	27
2.7269	0.8501	0.1499	0.0621	5	26
2.7269+	.	.	.	5	25
3.0554	0.8161	0.1839	0.0683	6	24
3.1869+	.	.	.	6	23
3.4497+	.	.	.	6	22
3.4829+	.	.	.	6	21
4.3039+	.	.	.	6	20
4.7901+	.	.	.	6	19
5.0924+	.	.	.	6	18
6.0780	0.7707	0.2293	0.0781	7	17
6.1797+	.	.	.	7	16
6.4155+	.	.	.	7	15
6.6386	0.7193	0.2807	0.0862	8	14
7.3593	0.6680	0.3320	0.0957	9	13
10.0205	0.6166	0.3834	0.1012	10	12
10.6119	0.5652	0.4348	0.1050	11	11
10.9076	0.5138	0.4862	0.1073	12	10
11.1047+	.	.	.	12	9
11.1378+	.	.	.	12	8
11.8304+	.	.	.	12	7
13.3060+	.	.	.	12	6
13.5031+	.	.	.	12	5
15.1786+	.	.	.	12	4
16.8542+	.	.	.	12	3
17.1828+	.	.	.	12	2
24.0493+	.	.	.	12	1
24.4107	0	1.0000	.	13	0

+ Censored observation.

B

OS2L	Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.0000	1.0000	0	0	0	21
1.4127+	.	.	.	0	20
1.6099	0.9500	0.0500	0.0487	1	19
1.8727+	.	.	.	1	18
1.9384	0.8972	0.1028	0.0689	2	17
2.1355	.	.	.	3	16
2.1355	0.7917	0.2083	0.0928	4	15
3.4825+	.	.	.	4	14
4.5996+	.	.	.	4	13
4.6653	0.7308	0.2692	0.1037	5	12
4.9281+	.	.	.	5	11
5.5852+	.	.	.	5	10
5.8152	0.6577	0.3423	0.1163	6	9
8.5092	0.5846	0.4154	0.1242	7	8
8.8049+	.	.	.	7	7
9.1006	0.5011	0.4989	0.1316	8	6
10.4805	0.4176	0.5824	0.1336	9	5
10.5462	0.3341	0.6659	0.1304	10	4
10.8747	0.2505	0.7495	0.1216	11	3
11.2361	0.1670	0.8330	0.1059	12	2
14.2001+	.	.	.	12	1
14.5616+	0.1670	.	.	12	0

+ Censored observation.

Lessons Learned and Challenges

- Small sample sizes, which can influence medians substantially, and differences in population characteristics are potential reasons for the disparate results observed between the 2 databases
- Data-curation differences
  - Advanced-disease/NSCLC population confirmed per data provider vs having to select population based on independent staging and histology information
    - Potential for misclassification of patients with advanced NSCLC

Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EHR, electronic health records; m, metastatic; NE, not estimable; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; OS, overall survival; RWD, real-world data; RWE, real-world evidence; tx, therapy.

Lessons Learned and Challenges (continued)

- Having exact date for mNSCLC diagnosis vs imputing date based on year or quarter of initial diagnosis and subsequent interval to mNSCLC diagnosis
  - Imputation of initial date and subsequent mNSCLC date gives less-precise understanding of mNSCLC diagnosis and exact time of first IO treatment
- Derived treatment regimen using both medication orders and administrations vs "physician-stated" treatment regimen
  - Derived treatment regimen: there is no information about why treatment was stopped or switched, so PD was used to define line of therapy (LOT)
  - Physician-stated regimen: reason for stopping/switching treatment was available, but only if present in abstracted data (not completely reliable)
  - It has been previously demonstrated that different LOT definitions can impact the definition of 2L treated patient population[3]
- Pooled analysis of this data would require understanding of both data curation differences and the appropriate methodology for standardizing data elements without significantly changing their meaning
- This is an ongoing challenge with RWE generation based on multiple data sources

CONCLUSIONS

- Although the longest survival was in the platinum-based cohort, the unknown treatment strategy for 1L IO mono-tx and small sample size limit the generalizability of the data
- Although numeric differences were observed between the 2 approaches, the results show a similar trend of longer median survival time with 2L platinum-based doublet/triplet regimens vs single-agent chemotherapy
- These analyses demonstrate how effect estimates can vary across different real-world patient populations and the importance of examining a research question in multiple RWD databases to ensure consistency in results for hypothesis confirmation
  - Consistency is one of Hill's Criteria for Causation[4] and is highly relevant here
  - Product-limit survival estimates demonstrate how small sample sizes can influence results
- These results should be interpreted with caution because further research with larger sample sizes or different RWD on the efficacy of 2L platinum therapy after 1L IO mono-tx is needed

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DISCLOSURES

DT: reports receipt of support for educational events from Celgene; **SMF, TJO, EDF:** report employment and stock ownership with Celgene.

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