1108P: Outcomes when stage 4 non-small cell lung cancer (NSCLC-4) patients (pts) harboring oncogenic drivers (OD) are treated initially without tyrosine kinase inhibitors (TKI)

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Background

- Treatment of (advanced) stage IV NSCLC has transformed with the identification of oncogenic driver (OD) mutations and development of targeted treatments
- Despite a survival benefit with TKIs, uptake of genomic testing has been slow and frequently has not employed broad next-generation sequencing (NGS) panels.[1-3] Additionally, long turnaround times often result in initial treatments with chemotherapy, immune checkpoint inhibitors (ICIs), or both,[4] rather than targeted TKIs, despite known poor responses with ICIs[5,6] and inferior outcomes in clinical trials with chemotherapy
- Previous analysis identified a population of patients with OD mutations who were treated initially without TKIs before the mutation was reported.[7] This report details the outcomes of these patients versus a cohort from the same prior analysis who were treated after report of mutation

Methods

Data source: Integra Connect database of electronic health records, practice management, and claims data from 13 large community networks and over 1000 physician caregivers

Patient Population: ≥18yo with newly diagnosed advanced NSCLC with initial diagnosis 1/1/2018-12/31/2020 (data cut-off date: 6/30/2021), positive for mutation in recognized targetable genes

Data Collection

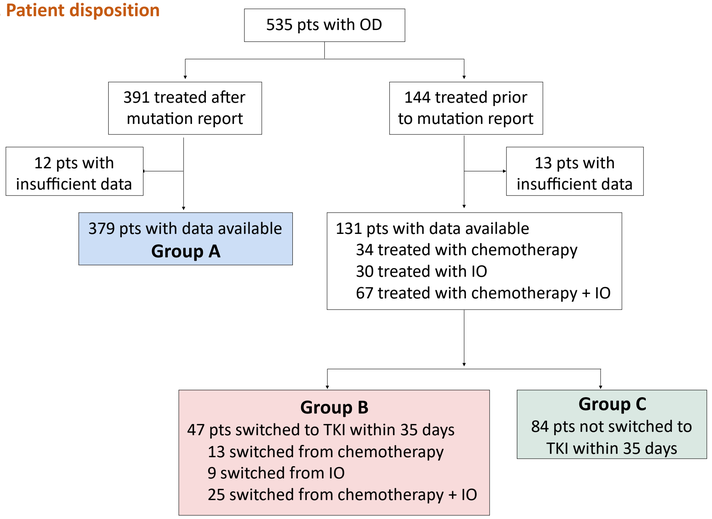
- Demographics: Age, gender, ECOG score, histology, smoking status, and race/ethnicity
- Treatment record: date of order and report of mutation, date of initiation of line of therapy (LOT) 1 and LOT2 (if employed), and date of death via Datavant

Outcomes

- 510 patients were included in outcomes analysis
- Time to next treatment (TTNT): time from day 1 LOT1 to day 1 LOT2 or date of death; in Group B, time from day 1 LOT1 to day 1 LOT after TKI
- Overall survival (OS): time from day 1 LOT 1 until date of death or survival at time of data cut-off

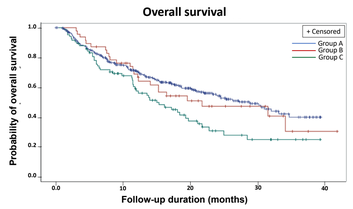
Results

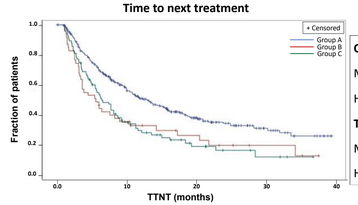
Figure 1. Patient disposition



Outcomes are significantly compromised in pts harboring OD mutation but who are treated initially with C, ICI or both, even in pts quickly switched to TKI.

Figure 2. Kaplan-Meier curves for overall survival and time to next treatment





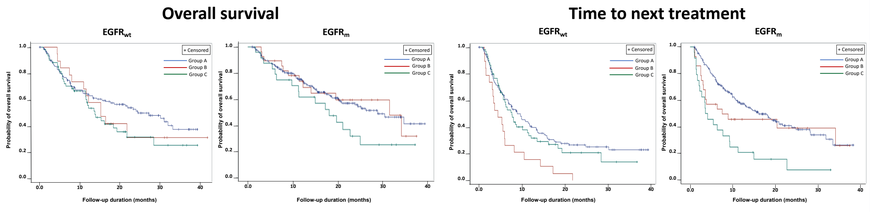
Group A (Reference group): Patients treated after report of mutation

Group B: Patients treated before report of mutation, then **switched** to TKI within 35 days

Group C: Patients treated before report of mutation, then **not switched** to TKI within 35 days

	Group A (N=379)	Group B (N=47)	Group C (N=84)	Group B+C (N=131)
Overall survival				
Median (95% CI, m)	28.8 (23.3, 34.6)	21.7 (12.2, NR)	15.3 (11.5, 19.7)	16.5(12.2, 21.7)
Hazard ratio (P-value)	Reference	1.12 (0.59)	1.62 (0.003)	1.27 (0.27)
Time to next treatment				
Median (95% CI, m)	13 (10.5,15.5)	5.5 (3.4, 8.9)	6.4 (4.9, 8.7)	6.2 (4.9, 8.0)
Hazard ratio (P-value)	Reference	1.73 (0.002)	1.71 (0.0002)	1.72 (<0.001)

Figure 3. Kaplan-Meier curves for overall survival and time to next treatment by EGFR status



	Group A (N=379)		Group B (N=47)		Group C (N=84)		Group B+C (N=131)	
Overall survival	**$EGFR_{wt}$ n=144**	**$EGFR_{m}$ n=235**	**$EGFR_{wt}$ n=19**	**$EGFR_{m}$ n=28**	**$EGFR_{wt}$ n=60**	**$EGFR_{m}$ n=24**	**$EGFR_{wt}$ n=79**	**$EGFR_{m}$ n=52**
Median (m, 95% CI)	27.2 (16.5,33.1)	28.8 (20.8, NR)	15.2 (8, NR)	31.5 (12.2, NR)	13.8 (11.4, 19.2)	18.1 (9.8, 24.9)	13.9 (11.6,19.2)	21.1 (14.0, 34.1)
Hazard ratio (P-value)	Reference		1.12 (0.60)		1.52 (0.01)		1.36 (0.03)	
TTNT	**$EGFR_{wt}$ n=144**	**$EGFR_{m}$ n=235**	**$EGFR_{wt}$ n=19**	**$EGFR_{m}$ n=28**	**$EGFR_{wt}$ n=60**	**$EGFR_{m}$ n=24**	**$EGFR_{wt}$ n=79**	**$EGFR_{m}$ n=52**
Median (m, 95% CI)	8.8 (6.8, 11.7)	16.1 (12.8, 20.8)	4.4 (2.4, 6.0)	7.5 (3.2, 9.3)	7.7 (5.6, 11.3)	3.8 (2.1, 9.3)	6.2 (4.9,8.2)	5.9 (3.4,9.3)
Hazard ratio (P-value)	Reference		1.76 (0.002)		1.49 (0.008)		1.59 (0.0002)	

Table 1. General demographics and clinical characteristics in treated patient subgroups

	All treated pts (N=510)	Treated after test results **Group A (N=379)**	Treated prior to test results		
			All (N=131)	Switched to TKI **Group B (n=47)**	Not switched to TKI **Group C (n=84)**
Age					
Mean (SD)	70.8 (11.2)	71.1 (11.4)	69.9(10.7)	69.7 (10.5)	70.0 (10.8)
Median (range)	72 (31,90)	72 (33,90)	72 (31,90)	72 (50,90)	71.5 (31,90)
Sex, n (%)					
Male	202 (39.6)	140 (36.9)	62 (47.3)	21 (44.7)	41 (48.8)
Female	305 (59.8)	236 (62.3)	69 (52.6)	26 (55.3)	43 (51.2)
Unknown	3 (0.6)	3 (0.8)	0 (0)	0 (0%)	0 (0%)
Race, n (%)					
Black or African American	61 (12)	54 (14.3)	7 (0.05)	4 (8.5)	3 (3.6)
White	323 (63.3)	226 (59.6)	97 (74)	31 (66)	66 (78.6)
Asian	18 (3.5)	17 (4.5)	1 (0.8)	1 (2.1)	0 (0)
Other	108 (21.2)	82 (21.6)	26 (19.8)	11 (23.4)	15 (17.9)
Positive mutations, n (%)					
EGFR	287 (56.3)	235 (62)	52 (39.7)	28 (59.6)	24 (28.6)
BRAF	74 (14.5)	50 (13.2)	24 (18.3)	7 (14.9)	17 (20.2)
ALK	32 (6.3)	27 (7.1)	5 (3.8)	4 (8.5)	1 (1.2)
ROS1	16 (3.1)	11 (2.9)	5 (3.8)	3 (6.4)	2(2.4)
MET	44 (8.6)	23 (6.1)	21 (16)	4 (8.5)	17 (20.2)
RET	10 (2)	4 (1.1)	6 (4.6)	0(0)	6(7.1)
HER2	43 (8.4)	27 (7.1)	16 (12.2)	1 (2.1)	15 (17.9)
NRTK1/2/3	4 (0.8)	2 (0.5)	2 (1.5)	0(0)	2 (2.4)
ECOG, n (%)					
0	122 (23.9)	90 (23.8)	32 (24)	9 (19.2)	23 (27.4)
1	180 (35.3)	135 (35.6)	45 (34.3)	14 (29.8)	31 (36.9)
2	105 (20.6)	77 (20.3)	28 (21.4)	15 (31.9)	13 (15.5)
3	36 (7.1)	23 (6.1)	13 (9.9)	5 (10.6)	8 (9.5)
4	4 (0.8)	3 (0.8)	1 (0.8)	1 (2.1)	0
Unknown	63 (12.4)	51 (13.5)	12 (9.2)	3 (6.4)	9 (10.7)
Histology, n (%)					
Squamous cell carcinoma	33 (6.5)	16 (4.2)	17 (12.9)	4 (8.5)	13 (15.5)
Non-squamous cell carcinoma	451 (88.4)	343 (90.5)	108 (82.4)	42(89.4)	66 (78.6)
Unknown	26 (5.1)	20 (5.2)	6 (4.6)	1 (2.1)	5 (5.9)
Smoking status, n (%)					
Current use – active	55 (14.5)	34 (9)	21 (16)	5 (1.3)	16 (4.2)
Previous use	282 (74.4)	204 (53.8)	78 (59.5)	24 (6.3)	54 (14.2)
Never	164 (43.3)	132 (34.8)	32 (24.4)	18 (4.7)	14 (3.7)
Unclassified	9 (2.4)	9 (2.4)	0 (0)	0 (0)	0 (0)
Type of test, n (%)					
NGS, solid	201 (39.4)	150 (39.6)	51 (38.9)	17 (36.2)	34 (40.5)
NGS, blood	82 (16.1)	47 (12.4)	35 (26.7)	9 (19.1)	26 (30.9)
Other	227 (44.5)	182 (48.0)	45 (34.4)	21 (44.7)	24 (28.6)
Deaths, n (%)	226 (44.3)	152 (40.1)	74 (56.5)	24 (51.1)	50 (59.5)

Discussion

- While subject to the limitations inherent to a retrospective, observational RWD study, these results strongly suggest outcomes are significantly compromised in patients, subsequently proven to harbor an OD mutation, treated prior to this report by chemotherapy, ICI, or both
- The 35-day window for switching therapy in Group B prevented the capture of early deaths in this group and may have contributed to OS not reaching statistical significance for the comparison of Group A versus Group B. Further analysis will provide insight into the extent of the effect on outcomes
- Ultra-fast NGS or liquid biopsy for oncogenic driver NGS testing to minimize turnaround time should be employed to avoid treatment before mutation report.[4] Results in Group C emphasize the need for near-universal non-squamous testing (as well as squamous never-smokers or age < 40), as patients who harbor mutations but are never tested, or tested only later, may have significant outcome impairment
- Finding these outcomes not only confined to *EGFR*-mutated patients emphasizes the need for NGS panels that report all actionable biomarkers (per NCCN guidelines[8])
- These negative outcomes indicate the need to evaluate use of immuno-oncogenics prior to TKI to determine if results are worse than when chemotherapy alone is utilized, and thus validating current NCCN guidelines[8]
- This encourages update of guidelines, as this will never be tested in a prospective, randomized trial

References

1. Gierman. 2019 ASCO Annual meeting, Abstract 1585.
2. HJ West. Medscape. https://www.medscape.com/viewarticle/958537
3. Pennell NA et al. *Am Soc Clin Oncol Educ Book*. 2019;39:531-542.
4. Mileham KF et al. *Cancer Med*. 2022;11(2):530-538.
5. Herbst RS et al. *Lancet*. 2016;387(10027):1540-1550.
6. Borghaei H et al. *N Engl J Med*. 2015;373(17):1627-1639.
7. Smith R et al. AMP 2021. Abstract ST59.
8. NCCN. Clinical Practice Guidelines in Oncology. Non-small cell lung cancer, version 3.2022.

Contact/Declaration of Interest

Disclosures: Dr. Choksi has no conflicts of interest to declare.

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