1530: Evaluation of outcomes in patients (pts) with stage 4 non-small cell lung cancer (NSCLC 4) harboring actionable oncogenic drivers (AOD) when treated prior to report of mutation without tyrosine kinase inhibitors (TKI): An Integra Connect Database (ICD) retrospective observational study

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Background

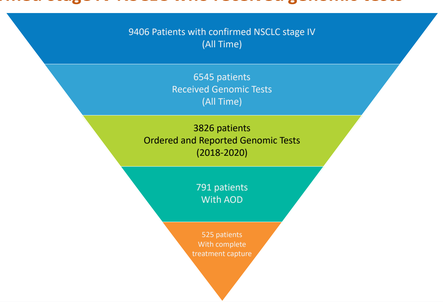
- Treatment of (advanced) stage IV NSCLC has transformed with the identification of oncogenic driver mutations and development of targeted treatments
- Despite an overall survival (OS) benefit with TKIs, uptake of genomic testing has been slow and frequently has not employed broad next-generation sequencing (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 harboring potential AODs who were treated initially without TKIs before the mutation was reported.[7] This report details the outcomes of these patients compared to a cohort from the same prior analysis treated after report of AOD

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, if employed, LOT2
  - Note: Due to expert determination for HIPAA compliance, we are unable to report actual date of death; instead we recorded apparent death, defined as date of last evidence of office visit, treatment, lab value, or communication. If this occurred >60 days from data cut-off, date of visit +30 days was recorded. If evidence of visit occurred within 60 days of cut-off, the patient was considered alive on 6/30/2021
- **Outcomes**
  - Time to next treatment (TTNT): time from day 1 LOT1 to day 1 LOT2 or apparent death; in Group B, time from day 1 LOT1 to day 1 LOT after TKI
  - Apparent survival (AS): time from day 1 LOT 1 until apparent death, or if visit recorded within the last 60 days before data cutoff, patients were considered alive on June 30, 2021

Results

Figure 1. Pts with confirmed stage IV NSCLC who received genomic tests



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

Figure 2. Treatment Utilization and Test Result Timing

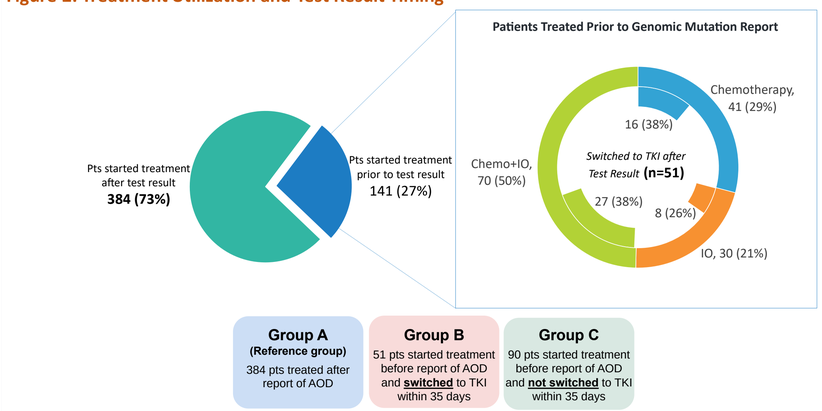
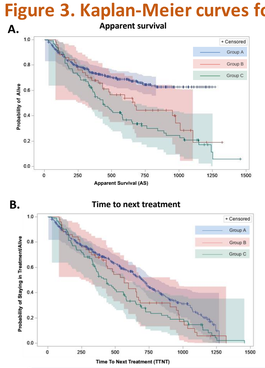


Figure 3. Kaplan-Meier curves for apparent survival and time to next treatment



	Group A (N=384)	Group B (N=51)	Group C (N=90)
Apparent survival			
Median (range)	Not reached	672 (433-1010)	435 (350-560)
Hazard ratio	Reference	1.719	2.360
P-value	-	0.0090	<.0001
Time to next treatment			
Median (range)	706 (631-762)	565 (433-658)	435 (350-560)
Hazard ratio	Reference	1.347	1.523
P-value	-	0.08	0.0017

AS and TTNT results apply to pts with and without *EGFR* mutation

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

	All treated pts (N=525)	Treated after test results Group A (N=384)	Treated prior to test results: Switched to TKI Group B (n=51)	Treated prior to test results: Not switched to TKI Group C (n=90)
Age				
Mean (SD)	70.76 (11.24)	71.31 (11.01)	69.86 (10.59)	70.20 (10.66)
Median (range)	72 (31-90)	71 (33-90)	71 (50-90)	72 (31-90)
Sex, n (%)				
Male	208 (40%)	142 (37%)	28 (55%)	47 (52%)
Female	314 (60%)	239 (62%)	23 (45%)	43 (48%)
Unknown	3 (1%)	3 (1%)	0 (0%)	0 (0%)
Race, n (%)				
Black or African American	62 (12%)	54 (14%)	4 (8%)	4 (4%)
White	333 (63%)	228 (59%)	35 (69%)	70 (78%)
Asian	20 (4%)	19 (5%)	1 (2%)	0 (0%)
Other	110 (21%)	83 (22%)	11 (22%)	16 (18%)
Positive mutations, n (%)				
EGFR	293 (56%)	238 (62%)	29 (57%)	26 (29%)
BRAF	77 (15%)	50 (13%)	8 (16%)	19 (21%)
ALK	33 (6%)	27 (7%)	5 (10%)	1 (1%)
MET	46 (9%)	24 (6%)	5 (10%)	17 (19%)
RET	10 (2%)	4 (1%)	0 (0%)	6 (7%)
ROS-1	16 (3%)	11 (3%)	3 (6%)	2 (2%)
ERBB2	44 (8%)	28 (7%)	1 (2%)	15 (17%)
NTRK 1/2/3	6 (1%)	2 (1%)	0 (0%)	4 (4%)
ECOG, n (%)				
0	125 (24%)	90 (23%)	9 (18%)	26 (29%)
1	181 (34%)	135 (35%)	15 (29%)	31 (34%)
2	109 (21%)	77 (20%)	18 (35%)	14 (16%)
3	37 (7%)	23 (6%)	5 (10%)	9 (10%)
4	4 (1%)	3 (1%)	1 (2%)	0 (0%)
Unknown	69 (13%)	56 (15%)	3 (6%)	10 (11%)
Histology, n (%)				
Adenocarcinoma	458 (87%)	342 (89%)	46 (90%)	70 (78%)
Squamous cell carcinoma	31 (6%)	17 (4%)	4 (8%)	10 (11%)
NSCLC, NOS	24 (5%)	19 (5%)	1 (2%)	4 (4%)
Unknown	12 (2%)	6 (2%)	0 (0%)	6 (7%)
Smoking status, n (%)				
Current use – active	59 (11%)	36 (9%)	6 (12%)	17 (19%)
Previous use	290 (55%)	205 (53%)	26 (51%)	59 (66%)
Never	167 (32%)	134 (35%)	19 (37%)	14 (16%)
Unclassified	9 (2%)	9 (2%)	0 (0%)	0 (0%)
Type of test, n (%)				
NGS, solid	227 (43%)	172 (44%)	22 (43%)	33 (37%)
NGS, blood	166 (32%)	113 (29%)	14 (27%)	39 (43%)
Other	132 (25%)	99 (26%)	15 (29%)	18 (20%)

Discussion

- While subject to the limitations inherent to a retrospective, observational real-world evidence study, these results strongly suggest outcomes are significantly compromised in patients, subsequently proven to harbor an AOD mutation, treated prior to this report by chemotherapy, ICI, or both. Inferior outcomes are even seen in patients quickly switched to an appropriate TKI
- This encourages update of guidelines as this will never be tested in a prospective, randomized trial
- 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])
- Finally, these results need confirmation with actual date of death and report of overall survival, which is in progress. Also, the inferiority even in Group B indicates 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]

References

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