Actionable Mutation Profiles and Survival Outcomes in Invasive Mucinous Adenocarcinoma of the Lung

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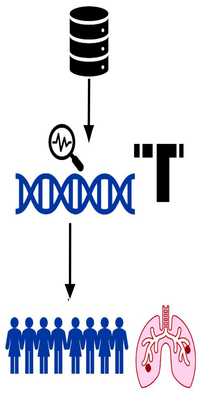
INTRODUCTION

- Invasive mucinous adenocarcinoma (IMA) is a rare histologic variant of lung adenocarcinoma, characterized by unique clinicopathologic features and limited therapeutic options.
- Comprehensive genomic comparisons between IMA and non-IMA, particularly regarding actionable mutations and their prognostic implications, remain scarce.
- This study aimed to characterize actionable and other clinically significant mutations in IMA versus non-IMA and to assess their association with survival outcomes.

METHODS



De-identified records of 3,428 patients diagnosed with primary lung adenocarcinoma

Sequencing with the Tempus xT and xR assays

Patients were stratified by histology into IMA (n = 78) and non-IMA (n = 3,350).

- Clinical and demographic characteristics were compared using Wilcoxon rank sum and Pearson's Chi-squared tests.
- Actionable mutations were identified per NCCN guidelines, and protective mutations were defined as *EGFR* (exon 19, L858R, G719X) or *ERBB2* alterations, and *ALK*, *ROS1*, or *RET* fusions.
- Prevalence of actionable and clinically relevant genes was compared between groups using Pearson's Chi-squared and Fisher's exact tests.
- Risk-set adjusted real-world overall survival (rwOS) was calculated from first line (1L) treatment start to death from any cause.

DISCUSSION AND CONCLUSION

- IMA exhibits a distinct mutational profile compared with non-IMA, showing differences in both frequency and prognostic impact.
- While actionable mutations were linked to improved survival in non-IMA, their prognostic value was less evident in IMA.
- STK11 mutations suggested a potentially worse overall survival in non-IMA.
- Further analyses of clinically significant mutations in a larger IMA cohort will clarify the biological differences underlying these distinct tumor behaviors.

RESULTS

Table 1. Baseline Demographic and Clinical Characteristics of IMA and Non-IMA Cohorts

Characteristic	Overall, N = 3,428[1]	Non-IMA, N = 3,350[1]	IMA, N = 78[1]	p-value[2]
Age at Diagnosis				0.13
Median (Q1, Q3)	66 (60, 73)	66 (60, 73)	70 (62, 75)	
Mean (SD)	66 (10)	66 (10)	67 (10)	
Min, Max	0, 88	0, 88	41, 84	
Unknown	45	44	1	
Sex				0.021
Female	1,760 (51%)	1,730 (52%)	30 (38%)	
Male	1,668 (49%)	1,620 (48%)	48 (62%)	
Race				0.055
White	2,196 (77%)	2,139 (77%)	57 (88%)	
Black or African American	322 (11%)	320 (12%)	2 (3.1%)	
Other Race	178 (6.3%)	173 (6.2%)	5 (7.7%)	
Asian	151 (5.3%)	150 (5.4%)	1 (1.5%)	
Unknown	581	568	13	
Ethnicity				0.10
Not Hispanic or Latino	2,055 (93%)	2,008 (93%)	47 (87%)	
Hispanic or Latino	156 (7.1%)	149 (6.9%)	7 (13%)	
Unknown	1,217	1,193	24	
Smoking Status				0.2
Ex-smoker	1,827 (56%)	1,780 (56%)	47 (62%)	
Current smoker	740 (23%)	729 (23%)	11 (14%)	
Never smoker	688 (21%)	670 (21%)	18 (24%)	
Unknown	173	171	2	
Stage				0.003
Stage 4	2,922 (88%)	2,869 (88%)	53 (76%)	
Stage 3	316 (9.5%)	302 (9.3%)	14 (20%)	
Stage 1	47 (1.4%)	47 (1.4%)	0 (0%)	
Stage 2	36 (1.1%)	33 (1.0%)	3 (4.3%)	
Unknown	107	99	8	
Metastatic Status at Biopsy				<0.001
Metastatic	2,928 (88%)	2,875 (88%)	53 (73%)	
Pre-metastatic	412 (12%)	392 (12%)	20 (27%)	
Unknown	88	83	5	

[1] n (%); [2] Wilcoxon rank sum test; Pearson's Chi-squared test

IMA patients were older at diagnosis (median 70 vs. 66 years), more frequently White (88% vs. 77%), and less often female (38% vs. 52%) compared with non-IMA.

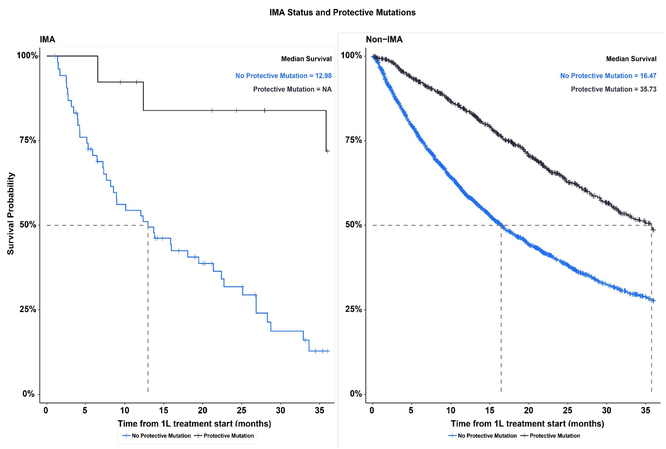
Table 2. Prevalence of Selected Genomic Alterations in IMA and Non-IMA

Mutation Type	Overall, N = 3,428[1]	Non-IMA, N = 3,350[1]	IMA, N = 78[1]	p-value[2]
Actionable				
KRAS P/LP	944 (28%)	902 (27%)	42 (54%)	<0.001
EGFR Exon 19 Deletion	322 (9.4%)	321 (9.6%)	1 (1.3%)	0.013
EGFR L858R	233 (6.8%)	231 (6.9%)	2 (2.6%)	0.13
BRAF P/LP	222 (6.5%)	217 (6.5%)	5 (6.4%)	>0.9
ALK Fusion	149 (4.3%)	144 (4.3%)	5 (6.4%)	0.4
MET Exon 14 Skipping	62 (1.8%)	62 (1.9%)	0 (0%)	0.4
ERBB2 P/LP	59 (1.7%)	55 (1.6%)	4 (5.1%)	0.044
EGFR Exon 20 Insertion	48 (1.4%)	48 (1.4%)	0 (0%)	0.6
EGFR G719X	31 (0.9%)	31 (0.9%)	0 (0%)	>0.9
RET Fusion	46 (1.3%)	45 (1.3%)	1 (1.3%)	>0.9
ROS1 Fusion	37 (1.1%)	36 (1.1%)	1 (1.3%)	0.6
EGFR L861Q	24 (0.7%)	24 (0.7%)	0 (0%)	>0.9
EGFR S768I	21 (0.6%)	21 (0.6%)	0 (0%)	>0.9
NTRK3 Fusion	6 (0.2%)	6 (0.2%)	0 (0%)	>0.9
NTRK1 Fusion	3 (<0.1%)	3 (<0.1%)	0 (0%)	>0.9
NTRK2 Fusion	1 (<0.1%)	0 (0%)	1 (1.3%)	0.023
Clinically Relevant				
STK11	479 (14%)	458 (14%)	21 (27%)	<0.001
KEAP1	293 (8.5%)	284 (8.5%)	9 (12%)	0.3

[1] n (%); [2] Pearson's Chi-squared test; Fisher's exact test

IMA demonstrated higher KRAS (54% vs. 27%, p < 0.001), ERBB2 (5.1% vs. 1.6%, p = 0.044), and STK11 (27% vs. 14%, p < 0.001) mutation frequencies, and lower EGFR exon 19 deletions (1.3% vs. 9.6%, p = 0.013) compared with non-IMA.

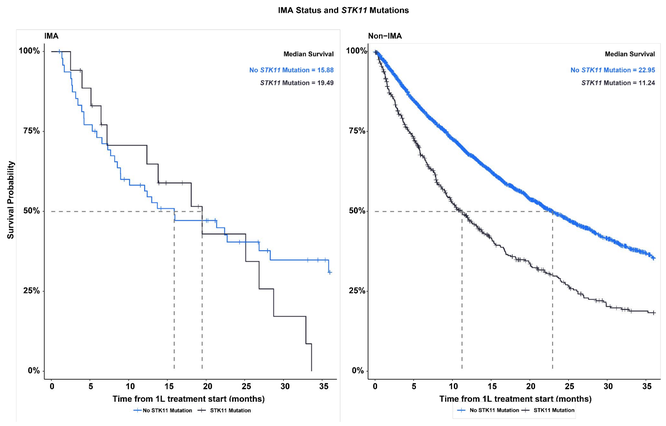
Figure 1. rwOS by Actionable or Protective Mutation Status



Strata	# of Obs.	# of Events	Median rwOS	Lower 95% CL	Upper 95% CL
Non-IMA, No Protective Mutation	2490	1334	16.47	15.35	17.85
Non-IMA, Protective Mutation	860	286	35.73	31.49	NA
IMA, No Protective Mutation	64	44	12.98	8.19	22.39
IMA, Protective Mutation	14	3	NA	35.83	NA

In non-IMA, actionable mutations were associated with longer median rwOS (35.73 vs. 16.47 months). IMA showed a similar trend (not reached vs. 12.98 months), though limited by small sample size (n=14).

Figure 2. rwOS by IMA Status and *STK11* Mutation



Strata	# of Obs.	# of Events	Median rwOS	Lower 95% CL	Upper 95% CL
Non-IMA, No *STK11* Mutation	2892	1336	22.95	21.56	24.75
Non-IMA, *STK11* Mutation	458	284	11.24	9.37	13.31
IMA, No *STK11* Mutation	57	33	15.88	8.94	35.83
IMA, *STK11* Mutation	21	14	19.49	12.36	NA

Non-IMA patients with STK11 mutations had shorter median rwOS (11.24 vs. 22.95 months). No significant trend was observed in IMA, which may be due to smaller sample size.

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