Background

Adenocarcinoma with mucinous features represents a subtype of lung adenocarcinoma (LUAD). Among LUAD, invasive mucinous adenocarcinomas are associated with a higher frequency of \textit{KRAS} driver mutations but a lighter smoking history.\(^1\) Information on the efficacy of immune checkpoint inhibitors (ICI) for patients with \textit{LUAD} remains to be defined.

Methods

Clinicopathologic, genomic, and ICI outcomes data were abstracted from patients with LUAD seen at a single academic center. Genomic testing was performed through targeted next-generation sequencing. LUADs with any mucinous component as assessed by a thoracic pathologist (LS) were classified as \textit{LUAD} and compared with the rest of the cohort (\textit{LUADNon-muc}). Multiplexed immunofluorescence (mIF) was performed to assess intratumor CD8, PD1, and FOXP3 expression. Multivariable cox-regression models were used to calculate adjusted hazard ratios (aHR).

Results

Among 2,417 patients with LUAD, 227 (9.4\%) had \textit{LUAD} vs \textit{LUADNon-muc}. Compared with \textit{LUADNon-muc} patients, \textit{LUAD} had a lower tobacco use history (median pack-years: 20 vs 25, \(P=0.01\)), PD-L1 tumor proportion score (median: 0.5\% vs 10\%, \(P<0.0001\)) and tumor mutational burden (median: 6.8 vs 9.1 mut/Mb, \(P<0.0001\)). \textit{KRAS} was the most common driver oncogene in \textit{LUAD} (66.8\% vs 40.2\% in \textit{LUADNon-muc}, \(P<0.001\)) followed by \textit{ALK} fusions (3.7\% vs 1.1\% in \textit{LUADNon-muc}, \(P=0.009\)). Among 1,780 patients with available genomic profiling, mutations in \textit{KRAS}, \textit{STK11}, \textit{SMARC4}, \textit{NKKX2.1} and \textit{GNAS} were enriched in \textit{LUAD} compared with \textit{LUADNon-muc} (\(Q<0.05\)) (figure 1A). Immunophenotyping by mIF (available in 525 [21\%] patients) showed fewer intratumoral CD8\(^+\) cells (P=0.04) and FOXP3\(^+\) cells (P=0.009) in \textit{LUAD} vs \textit{LUADNon-muc} (figure 1B). Among patients with metastatic LUAD who received ICIs, compared with \textit{LUADNon-muc} (N=848), \textit{LUAD} cases had lower objective response rate (ORR) (9\% vs 24\%, \(P=0.002\)), shorter median progression-free survival (mPFS) (2.1 vs 3.5 months, aHR: 0.75, \(P=0.046\)) and median overall survival (mOS) (7.2 vs 13.2 months, aHR: 0.70, \(P=0.02\)) (figure 2A). Similarly, among patients with LUAD who received chemo-immunotherapy, compared with \textit{LUADNon-muc} (N=427), \textit{LUAD} (N=68) achieved lower ORR (21\% vs 41\%, \(P=0.001\)), shorter mPFS (5.0 vs 6.7 months, HR: 0.68, \(P=0.02\)) and mOS (10.2 vs 18.5 months, aHR: 0.55, \(P<0.001\)) (figure 2B).

Conclusions

\textit{LUAD} represents 9\% of LUAD. Compared to \textit{LUADNon-muc}, \textit{LUAD} is characterized by a lighter smoking history, lower PD-L1 expression, tumor mutational burden, and fewer intratumor immune cells; \textit{LUAD} is enriched with \textit{KRAS}, \textit{STK11}, \textit{SMARC4}, \textit{NKKX2.1} and \textit{GNAS} mutations, and demonstrates worse outcomes to ICI-based therapies compared to \textit{LUADNon-muc}.

REFERENCE

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