Original Article

Outcomes of patients with stage III non-small cell lung cancer (NSCLC) that harbor a *STK11* mutation

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Background: *STK11* mutation (*STK11*^{m}) in patients (pts) with stage IV non-small cell lung cancer (NSCLC) is associated with inferior survival and poor response to immune checkpoint inhibitors (ICI). The significance of *STK11*^{m} in stage III NSCLC pts treated with concurrent chemoradiation (CCRT) with or without consolidation ICI is unknown.

Methods: Stage III NSCLC patients who received CCRT and had known *STK11* mutational status were included in this retrospective study. The data on the *STK11*^{m} pts were collected from 4 cancer institutions. A cohort of pts with wild type *STK11* (*STK11*^{w}) from the University of Iowa served as a comparison group. Patient demographics and clinical characteristics were collected. Cox regression models were used to explore the effect of *STK11* mutation on survival.

Results: 75 pts with stage III NSCLC who had known *STK11* mutational status were identified. 16/75 (21%) had *STK11*^{m}. 5/16 with *STK11*^{m} did not receive CCRT so they were excluded from the analysis. The clinical and demographic characteristics for the 11 *STK11*^{m} and 59 *STK11*^{w} pts were not statistically different (*STK11*^{m} *vs.* *STK11*^{w}): mean age: 57 *vs.* 64 yrs, non-squamous histology: 8/11 (73%) *vs.* 37/59 (63%), *KRAS* mutation: 3/11 (27%) *vs.* 11/59 (19%), *TP53* mutation: 6/11 (55%) *vs.* 15/59 (25%), PD-L1 ≥50%: 1/8 (13%) *vs.* 10/32 (31%), and consolidation ICI 6/11 (55%) *vs.* 17/59 (29%). Regarding the 6 *STK11*^{m} pts who received ICI (4 pembrolizumab, 2 durvalumab), the median number of ICI infusions was 8 (range, 3–17) *vs.* 6 (range, 1–25) in the 17 pts with *STK11*^{w} who received ICI (durvalumab). After adjusting for performance status and cancer stage, multivariable analysis showed that progression free survival (PFS) for the *STK11*^{m} pts was significantly worse than *STK11*^{w} pts (HR =2.25; 95% CI, 1.03–4.88, P=0.04), whereas overall survival (OS) showed no significant difference for *STK11*^{m} *vs.* *STK11*^{w} patients (HR 1.47, 95% CI, 0.49–4.38, P=0.49).

Conclusions: In stage III NSCLC patients who received CCRT, *STK11*^{m} was associated with worse PFS compared to *STK11*^{w}. Larger studies are needed to further explore the prognostic implications of *STK11*^{m} in stage III NSCLC and whether ICI impacts survival for this subgroup.

Keywords: Non-small cell lung cancer (NSCLC); immunotherapy; *STK11*; *KRAS*; *TP53*

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Introduction

Unresectable stage III non-small cell lung cancer (NSCLC) in patients with good performance status is treated with concurrent platinum based chemotherapy with definitive dose radiation (CCRT) followed by the PD-L1 inhibitor, durvalumab (1). The addition of durvalumab to CCRT improved survival from 55.6% to 66.3% at 24 months (1). Although this improvement in survival is practice changing, a large number of stage III NSCLC patients still have a poor prognosis. In 2020, it is estimated there will be 229,000 new cases of lung cancer (2) of which stage III cancer is expected in approximately 30% of all NSCLC cases.

Serine/threonine kinase 11 (*STK11*), also known as liver kinase B1 (*LKB1*), is a gene found on chromosome 19p13. Germline mutation of *STK11* is associated with Peutz-Jeghers Syndrome (PJS) (3). Patients with PJS can develop intestinal hamartomatous polyps and are more likely to develop malignancies such as gastrointestinal, testis, ovary, and breast cancers (3). In lung cancer, somatic mutations of *STK11* are seen in up to 42% of NSCLC; however, most studies have shown a mutation frequency of approximately 20% (4). *STK11* functions as a tumor suppressor gene and is involved in the activation of AMP-activated protein kinase (AMPK), which modulates cell glucose and lipid metabolism (5). More importantly, *in-vivo* studies indicate that *STK11* is involved in the differentiation and metastases of lung cancer (6). *STK11* inactivation leads to increase in pro-inflammatory cytokines such as CXCL7 and causes a shift in the microenvironment with neutrophil accumulation and decrease in T cell lymphocytes (7,8).

The effect of *STK11*^{m} on outcomes of stage III NSCLC treated with curative intent is unknown. It is unclear whether *STK11*^{m} affects prognosis of stage III NSCLC or predicts response to ICI consolidation after CCRT. In advanced stage NSCLC, *STK11*^{m} has been associated with poor response to chemotherapy and ICI, and inferior survival outcomes (9-15). In this study, we sought to explore *STK11*^{m} as a prognostic genetic alteration in stage III NSCLC patients managed with definitive chemoradiation +/− consolidative ICI. We present the following article in accordance with the REMARK reporting checklist (available at https://dx.doi.org/10.21037/tlcr-21-177).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The informed consent from the patients were waived. The study was approved by institutional Review Boards (IRBs) of University of Iowa Hospitals and Clinics, Indiana University Health, Northwestern Memorial Hospital, and the University of Illinois at Chicago. The 4 institutions provided a total of 16 patients with stage III NSCLC known to have *STK11*^{m} diagnosed between 2013 and 2019. Of these, 11 received CCRT and were included in the study. A comparison group of 59 patients with *STK11*^{w} stage III NSCLC who received CCRT diagnosed between 2013 and 2019 were identified at University of Iowa and served as a comparison group. Stage III NSCLC, receiving any CCRT, and having a known *STK11* mutational status were requirements for inclusion in the analysis in this study.

The patients' charts were reviewed for clinical and demographic characteristics. These included age, sex, smoking history, stage, ECOG performance status, histology, *STK11*, *KRAS* and *TP53* status, PD-L1 expression, and treatment details including radiation, chemotherapy and immunotherapy. *STK11*^{m} was identified by next generation sequencing of the tumor tissue using the platform of choice available in the institutions participating in this study. Specific *STK11* locus alteration information was not collected. Information about other NSLCC driver mutations such as *EGFR* and *ALK* were not collected.

Statistical analysis

Chi-squared or Fisher's exact tests were used to compare categorical variables, and Wilcoxon rank sum tests were used to compare continuous variables between *STK11* wild type and mutant. Survival probabilities were estimated and plotted using the Kaplan-Meier method. Cox regression models were used to assess the effects of clinical, pathologic, and treatment variables on progression-free survival (PFS) and overall survival (OS). The time for PFS was calculated from the date of diagnosis until progression or death due to any cause. The time for OS was calculated from the date of diagnosis until death due to any cause. Estimated effects

Table 1 Demographics and clinical data for *STK11*^{m} and *STK11*^{w} stage III NSCLC

Variable	Level	Total, N=70, n (%)	STK11, n (%)		
			STK11^{w}, N=59	STK11^{m}, N=11	P value
Sex	F	35 (50.0)	31 (52.5)	4 (36.4)	0.32
	M	35 (50.0)	28 (47.5)	7 (63.6)	
Age	≤65 years	41 (58.6)	32 (54.2)	9 (81.8)	0.11
	>65 years	29 (41.4)	27 (45.8)	2 (18.2)	
Smoking history	Current	65 (92.9)	54 (91.5)	11 (100)	1.00
	Never smoker	5 (7.1)	5 (8.5)	0 (0)	
ECOG	0–1	60 (85.7)	49 (83.1)	11 (100)	0.34
	2–3	10 (14.3)	10 (16.9)	0 (0)	
Histology	Non-squamous	45 (64.3)	37 (62.7)	8 (72.7)	0.73
	Squamous	25 (35.7)	22 (37.3)	3 (27.3)	
Stage	IIIA	38 (54.3)	32 (54.2)	6 (54.5)	0.98
	IIIB/C	32 (45.7)	27 (45.8)	5 (45.5)	
KRAS	No	56 (80.0)	48 (81.4)	8 (72.7)	0.68
	Yes	14 (20.0)	11 (18.6)	3 (27.3)	
TP53	No	49 (70.0)	44 (74.6)	5 (45.5)	0.07
	Yes	21 (30.0)	15 (25.4)	6 (54.5)	
PD-L1	<1%	21 (52.5)	16 (50.0)	5 (62.5)	0.66
	1–50%	8 (20.0)	6 (18.8)	2 (25.0)	
	>50%	11 (27.5)	10 (31.3)	1 (12.5)	
	Missing	30	27	3	
ICI consolidation	No	47 (67.1)	42 (71.2)	5 (45.5)	0.16
	Yes	23 (32.9)	17 (28.8)	6 (54.5)	
Cycles of ICI	N	70	59	11	0.10
	Median	0	0	3	
	Range	(0-25)	(0-25)	(0-17)	

NSCLC, non-small cell lung cancer.

of predictors are reported as hazard ratios (HR) along with 95% confidence intervals. All statistical testing was two-sided and assessed for significance at the 5% level using SAS v9.4 (SAS Institute, Cary, NC).

Results

Patient demographics and clinical characteristics

After excluding the 5 patients with *STK11*^{m} who did not receive CCRT, a total of 70 pts with stage IIIA-C NSCLC were included in the analysis; 11 patients with *STK11*^{m} and 59 patients with *STK11*^{w} (*Table 1*). When *STK11*^{m} patients were compared to *STK11*^{w}, there was no significant difference in the gender distribution among the two groups. Numerically, the proportion of age ≤65 years in the *STK11*^{m} group compared to *STK11*^{w} was higher but this was not statistically significant (82% *vs.* 54%, P=0.11). When all patients including the 5 with *STK11*^{m} who did not receive CCRT were accounted for in the analysis,

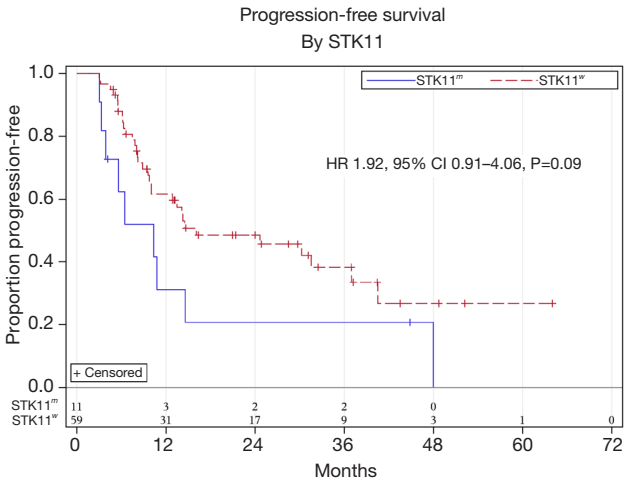

Figure 1 Progression free survival for *STK11*^{m} and *STK11*^{w} stage III NSCLC. NSCLC, non-small cell lung cancer.

the *STK11*^{m} patients were significantly younger (≤65 years) (P=0.05) (Data not shown). Majority of the patients included were current/former smokers regardless of the *STK11* mutational status. Regarding performance status, most of the patients included in the study had an ECOG performance status of 0-1. Histology was divided into non-squamous and squamous NSCLC. Non-squamous histology was predominant in both the *STK11*^{w} *and STK11*^{m} groups comprising 62.7% and 72.7%, respectively, without noticing statistically significant difference (P=0.73). There was no significant difference in the frequency of stage IIIA versus stage IIIB/C among the groups. The frequency of *KRAS* or *TP53* mutations were not significantly different between the *STK11* groups. PD-L1 expression was <1% in 63% of the *STK11*^{m} patients, but there was no significant difference in the PD-L1 expression categories among the *STK11*^{m} and *STK11*^{w} groups.

Treatments

All patients included in the analysis received CCRT (*Table 1*). ICI consolidation was delivered to 17/59 *STK11*^{w} and 6/11 *STK11*^{m} patients. Of note, 20/59 *STK11*^{w} and 4/11 *STK11*^{m} patients were diagnosed with NSCLC after the publication of the PACIFIC trial (16) which was the first phase III randomized trial to show improvement in PFS when using consolidation durvalumab after CCRT in stage III NSCLC. The ICI consolidation given to the 6 *STK11*^{m} patients included pembrolizumab, which was delivered on a clinical trial, for 4 patients and durvalumab for 2 patients. All ICI delivered for the *STK11*^{w} group was durvalumab.

Survival outcomes

Median follow up time was 15.7 months. Univariate analysis showed a trend towards worse PFS for *STK11*^{m} compared to *STK11*^{w} patients; however, this was not statistically significant (HR 1.92, 95% CI, 0.91–4.06, P=0.09) (*Figure 1*). There was no statistically significant difference in PFS based on sex, age, ECOG performance status, histology, stage, *KRAS*, *TP53*, PD-L1 level, or ICI consolidation (*Table 2*). On multivariable analysis adjusting for ECOG performance status and stage (*Table 3*), there was a significantly worse PFS for *STK11*^{m} compared to *STK11*^{w} patients (HR 2.25, 95% CI, 1.03–4.88, P=0.04). OS by univariate analysis was not statistically different for the *STK11*^{m} *vs. STK11*^{w} (HR 1.47, 95% CI, 0.49–4.38, P=0.49) (*Figure 2*).

Discussion

To our knowledge, this is the first study to explore *STK11*^{m} as a prognostic mutation in stage III NSCLC patients who received CCRT. Our results showed that PFS, after adjusting for performance status and cancer stage, was worse for stage III NSCLC patients who had *STK11*^{m} compared to *STK11*^{w} (HR 2.25, 95% CI, 1.03–4.88). Although data in the literature showed association of *STK11*^{m} with poor outcomes in advanced stage NSCLC (9,11,15), its impact on stage III NSCLC has not been established. In a study examining the prognostic impact of *STK11*^{m} in stage I-IV NSCLC (10), 21 patients had stage III disease. The median OS for all patients included was worse for the *STK11*^{m} compared to *STK11*^{w} patients (24 *vs.* 69 months, P=0.005), but there were no survival outcomes reported specifically for the stage III NSCLC patients (10). Another retrospective analysis which included 23 patients with a mix of stage IIIB and IV NSCLC also did not identify the stage III cases as a subgroup for analysis (17). Our study included only stage III NSCLC patients who received CCRT with or without ICI consolidation.

The effect of *STK11*^{m} on benefit from ICI consolidation post CCRT in stage III NSCLC could not be concluded in our study due to the small sample size. In advanced stage NSCLC, *STK11*^{m} was associated with low PD-L1 expression and resistance to PD-1/PD-L1 ICIs (11). However, the association of *STK11*^{m} and poor response to ICI is still debatable as other reports showed good response

Table 2 Progression free survival (PFS) by univariate analysis

Variable	Level	N	Progression-free survival			
			Hazard ratio	95% CI		P value
Sex	M	35	1.07	0.58	1.98	0.83
	F	35	Ref	–	–	
Age	≤65 years	41	1.61	0.83	3.13	0.16
	>65 years	29	Ref	–	–	
ECOG	2–3	10	1.96	0.89	4.31	0.10
	0–1	60	Ref	–	–	
Histology	Non-squamous	45	1.31	0.67	2.58	0.43
	Squamous	25	Ref	–	–	
Stage	IIIB/C	32	1.53	0.82	2.85	0.18
	IIIA	38	Ref	–	–	
STK11	Yes	11	1.92	0.91	4.06	0.09
	No	59	Ref	–	–	
KRAS	Yes	14	1.10	0.50	2.42	0.81
	No	56	Ref	–	–	
TP53	Yes	21	1.02	0.52	1.99	0.96
	No	49	Ref	–	–	
PD-L1	<1%	21	1.54	0.54	4.39	0.40
	1-50	8	2.27	0.69	7.52	
	>50%	11	Ref	–	–	
ICI consolidation	Yes	23	1.18	0.60	2.31	0.63
	No	47	Ref	–	–	

Table 3 Progression free survival (PFS) by multivariate analysis

Covariate	Level	N	Progression-free survival			
			Hazard ratio	95% CI		P value
ECOG	2–3	10	2.49	1.10	5.65	0.03
	0–1	60	Ref	–	–	
Stage	IIIB/C	32	1.65	0.88	3.08	0.12
	IIIA	38	Ref	–	–	
STK11	Yes	11	2.25	1.03	4.88	0.04
	No	59	Ref	–	–	

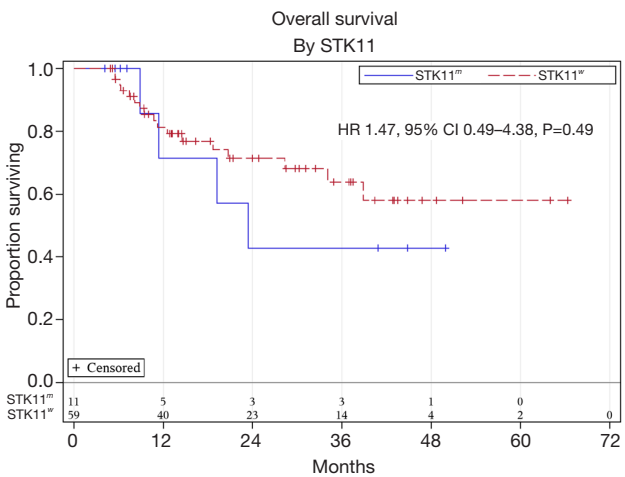

Figure 2 Overall survival for *STK11*^{m} and *STK11*^{w} stage III NSCLC. NSCLC, non-small cell lung cancer.

of advanced stage *STK11*^{m} NSCLC to ICI (18-20). In another driver mutation, the *EGFR* rather than *STK11* mutation, it was questioned on retrospective studies whether there is significant benefit from durvalumab after CCRT (21,22). In a cohort of 60 patients with *STK11*^{m} cancers that included NSCLC and others, *STK11*^{m} correlated with poor prognosis without specifically observing inferior outcomes associated with immunotherapy (23). Potential mechanisms for the *STK11*^{m} resistance to ICI include impaired activity of effector T cells, epigenetic changes of tumor cells, modification of the cytokine and/or chemokine milieu, and diminished tumor antigenicity (11). In our study, 5/11 (63%) *STK11*^{m} patients had PD-L1 <1% and 6/11 (55%) received ICI consolidation. The ICI consolidation used included durvalumab or pembrolizumab (pembrolizumab received on a clinical trial). No conclusions can be made about resistance of *STK11*^{m} to ICI consolidation or whether a specific PD-1/PD-L1 inhibitor would function differently in the setting of *STK11*^{m} in stage III NSCLC. This will need to be further studied in future trials.

The presence of other mutations that could impact the outcomes of *STK11*^{m} NSCLC were also examined. Co-mutations of *STK11* with either *KRAS* or *TP53* in NSLCC have been described in advanced stage NSCLC (12-14,24). Although *KRAS* mutation was associated with better response to ICI (14), the co-mutation of *STK11* and *KRAS* was associated with inferior survival (12-14,24). A retrospective review of patients treated with first-line therapy for metastatic NSCLC found that *STK11* and *KRAS* co-mutations were associated with worse survival compared to *STK11* and *TP53* co-mutation (13). In our study, only 2 patients had *STK11*^{m} without co-mutation in *KRAS* or *TP53*.

Other clinical and demographic features of stage III NSCLC patients with *STK11*^{m} were explored. The *STK11*^{m} patients were more likely to be ≤65 years old (82%); however, there was no significant difference in age between the *STK11*^{m} and *STK11*^{w} patients. This is consistent with another retrospective study that examined *STK11*^{m} in patients with stage I–IV non-squamous NSCLC where patients with *STK11*^{m} were found to be significantly younger than *STK11*^{w} patients (mean age of 58.6 *vs.* 61.9 years, respectively) (10). This retrospective study (10) also noted smoking to be associated with *STK11*^{w} which was not seen in our study.

The authors acknowledge limitations that apply to this study. First, the retrospective nature, the small sample size, and the imbalance in the number of *STK11*^{w} versus *STK11*^{m} patients are recognized. Second, the majority of patients in this study were identified from stage IV NSCLC databases who were initially diagnosed and treated for stage III disease. This might inherently reflect a selection bias of stage III NSCLC with more aggressive biology and tendency for metastases. Third, it is unknown if *STK11*^{m} was present at diagnosis of stage III NSCLC or was acquired subsequently upon progression to stage IV.

Conclusions

In stage III NSCLC patients who received CCRT, *STK11*^{m} was associated with worse PFS compared to *STK11*^{w}. Larger studies are needed to explore whether *STK11*^{m} plays a role in predicting less benefit from ICI consolidation in stage III NSCLC.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://dx.doi.org/10.21037/tlcr-21-177

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tlcr-21-177). MF serves as an unpaid editorial board member of *Translational Lung Cancer Research* from Sep 2019 to Sep 2021. TK reports personal fees from AstraZeneca for consulting and advisory board, and personal fees AstraZeneca, OncLive, and Targeted Oncology for speaking. NHH's institution received grant support from BMS, Genentech, Merck on studies that in which he is the PI, and is the medical writer for UptoDate and served on a DSMB for a study sponsored by Beyond Spring. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The informed consent from the patients were waived. The study was approved by institutional Review Boards (IRBs) of University of Iowa Hospitals and Clinics, Indiana University Health, Northwestern Memorial Hospital, and The University of Illinois at Chicago.

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