Letter to the Editor

NRF2-pathway mutations predict radioresistance in non-small cell lung cancer

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Approximately 54% of non-small cell lung cancer (NSCLC) patients present with early-stage or locally-advanced disease and are potentially curable, of which 40% receive radiotherapy as a part of their initial course of treatment (1,2). Although biomarkers routinely guide treatment decisions for systemic therapies in NSCLC, there are no clinical biomarkers that predict response to radiotherapy. Two independent studies have recently converged on alterations in the NRF2 pathway as potential biomarkers of radioresistance in NSCLC (3,4).

In *Clinical Cancer Research*, Sitthideatphaiboon *et al.* identify *STK11* (LKB1) mutations as a predictive biomarker of radioresistance in NSCLC (3). The authors retrospectively analyze a cohort of 194 stage I–III patients treated with radiotherapy and find *STK11* mutations to be the strongest predictor of disease-free survival (DFS) and overall survival (OS). They demonstrate that *STK11* and *KEAP1* mutations confer radioresistance in NSCLC xenograft models and identify glutaminase as a potential therapeutic target to overcome NRF2-mediated radioresistance in vitro. This manuscript complements a recent publication in *Cancer Discovery*, which identifies pathogenic *KEAP1/NFE2L2* (NRF2) mutations as a biomarker of radioresistance in NSCLC, which can similarly be reversed by glutaminase inhibition *in vitro* (4). Together, these studies support a unifying theory for NRF2-mediated radioresistance and "glutamine-addiction" in NSCLC (5,6).

The study by Sitthideatphaiboon *et al.* (3) is the first to examine clinical outcomes based on *STK11* status in a radiotherapy cohort. The authors acknowledge limitations, including its retrospective nature, limited sample size, and inability to access *KEAP1* mutations. We, therefore, sought to validate their findings using three large prospective cohorts (*Table 1*). Putative driver (pathogenic) mutations versus variants of unknown significance were defined via OncoKB and Cancer Hotspots annotations in the cBioportal (https://www.cbioportal.org/). Among non-metastatic NSCLC patients in The Cancer Genome Atlas (TCGA) (n=736, 34% prospective) (7), *STK11* pathogenic mutations were associated with poorer OS in patients who received radiotherapy {n=83, HR: 3.03 [95% confidence interval (CI): 1.38–6.68]}, but not in patients who received no radiotherapy (n=547). Including *KEAP1* and *NFE2L2* pathogenic mutations in adenocarcinomas (8) increased the number of patients with potentially radioresistant tumors from 6.9% to 9.8% and was a stronger predictive biomarker. *KEAP1/NFE2L2/STK11* mutations were associated with poorer OS [HR: 3.78 (1.85–7.74)], progression-free survival [3.80 (1.87–7.72)], DFS [4.46 (0.94–21.1)], and disease-specific survival [4.83 (2.20–10.6)] only in patients that received radiotherapy (interaction with treatment P=0.02, 0.09, 0.23, and 0.02, respectively; *Table 1*; *Figure 1*).

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Table 1 Survival by *STK11* and *KEAP1*/NFE2L2*/STK11* mutational status based on treatment subgroup

Treatment subgroup	N	*STK11*				*KEAP1*/NFE2L2*/STK11*			
		HR	95% CI	P value	Interaction	HR	95% CI	P value	Interaction
TCGA Pan-Cancer[1]	736	6.9%				9.8%			
Overall survival					0.09				0.02#
No radiotherapy	547	1.39	0.81, 2.39	0.24		1.44	0.92, 2.24	0.11	
Radiotherapy	83	3.03	1.38, 6.68	0.006#		3.78	1.85, 7.74	<0.001#	
Progression-free survival					0.52				0.09
No radiotherapy		2.30	1.41, 3.75	<0.001#		1.87	1.21, 2.90	0.005#	
Radiotherapy		3.14	1.44, 6.86	0.004#		3.80	1.87, 7.72	<0.001#	
Disease-free survival					0.36				0.23
No radiotherapy		1.89	0.92, 3.90	0.09		1.54	0.82, 2.89	0.18	
Radiotherapy		4.46	0.94, 21.1	0.06		4.46	0.94, 21.1	0.06	
Disease-specific survival					0.20				0.02#
No radiotherapy		1.89	0.95, 3.76	0.07		1.62	0.88, 2.97	0.12	
Radiotherapy		3.54	1.49, 8.37	0.004#		4.83	2.20, 10.6	<0.001#	
TCGA Firehose[2]	767	4.2%				5.3%			
Overall survival					0.21				0.08
R0 resection	592	1.07	0.59, 1.97	0.82		1.04	0.62, 1.76	0.88	
Less than R0	137	2.04	0.80, 5.20	0.13		2.37	1.00, 5.63	0.05#	
Disease-free survival					0.27				0.08
R0 resection		1.47	0.80, 2.71	0.22		1.32	0.76, 2.28	0.32	
Less than R0		2.64	1.11, 6.31	0.03#		3.11	1.37, 7.05	0.007#	
MSK-IMPACT[3]	961	13.7%				16%			
Overall survival					0.79				0.45
Resection	378	1.96	1.02, 3.78	0.05#		1.48	0.77, 2.86	0.24	
Biopsy	407	1.77	1.15, 2.73	0.009#		2.04	1.36, 3.04	<0.001#	
TRACERx[4]	100	7%				13%			
Relapse-free survival					0.36				0.26
Resection, N0	74	1.01	0.13, 7.75	>0.99		1.70	0.47, 6.11	0.41	
Resection, N+	24	2.27	0.62, 8.26	0.21		5.82	1.36, 24.4	0.02#	

*, pathogenic *KEAP1/NFE2L2* mutations in adenocarcinomas; [1], stage I, II, and III represent 52%, 30%, and 18% of patients, respectively; [2], stage I, II, and III represent 44%, 25%, and 15% of patients, respectively; [3], stage not provided; [4], stage I, II, and III represent 62%, 24%, and 14% of patients, respectively; #, statistically significant. TCGA, The Cancer Genome Atlas; N0/+, lymph node negative/positive; HR, hazard ratio; CI, confidence interval.

Additionally, *KEAP1/NFE2L2/STK11* mutations were not prognostic in patients that received R0 resections (n=592), but were associated with poorer OS [HR: 2.37 (1.00–5.63)] and DFS [3.11 (1.37–7.05)] in patients with less than R0 or no resection (n=137), suggesting that *KEAP1/NFE2L2/STK11* status is prognostic in patients who are assumed

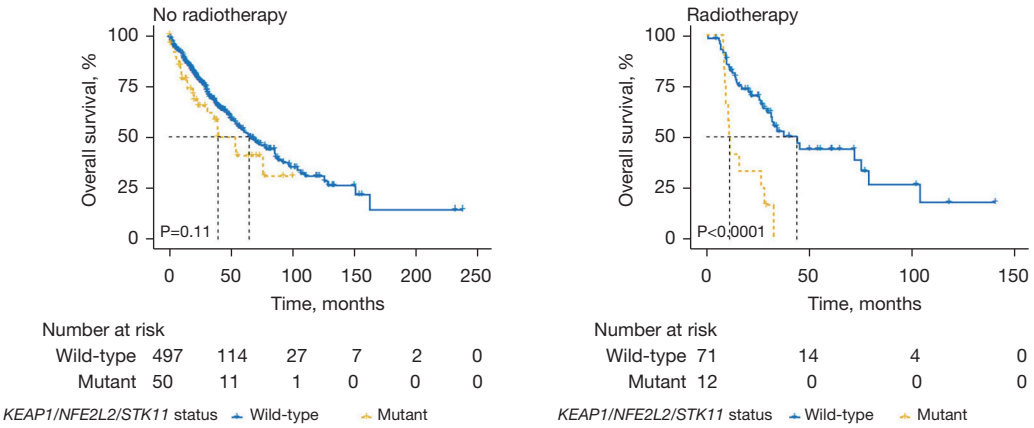

Figure 1 OS of NSCLC patients stratified by radiotherapy status in TCGA database. OS, overall survival; NSCLC, non-small cell lung cancer; TCGA, The Cancer Genome Atlas.

to undergo adjuvant or definitive radiotherapy. These findings were confirmed in multivariable analysis and after stratifying by stage. Consistent with these findings, in MSK-IMPACT (n=961) (9), *KEAP1/NFE2L2/STK11* mutations were associated with poorer OS in tumors that were biopsied [n=407; HR: 2.04 (1.36–3.04)] but not resected (n=378). Similarly, in the TRACERx study (n=100) (10), *KEAP1/NFE2L2/STK11* status was not significantly prognostic in patients who underwent curative resection. However, when stratifying by lymph node status, *KEAP1/NFE2L2/STK11* status was prognostic of recurrence or death [HR: 5.82 (1.36–24.4)] only in patients with positive lymph nodes after surgery (n=24).

Here, we provide further evidence that *KEAP1/NFE2L2/STK11* mutations are common and predictive of outcomes after radiotherapy in the TCGA database. We additionally show in three large prospective cohorts with almost 1,800 patients that *KEAP1/NFE2L2/STK11* mutations are not prognostic in patients who undergo curative surgery. Collectively, these data support further testing of *KEAP1/NFE2L2/STK11* as a biomarker of radioresistance and to identify patients that may be eligible for clinical trials targeting the NRF2 pathway. Limitations of our study include retrospective analysis of datasets with limited clinical information available. Prospective validation of these findings is warranted.

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Footnote

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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.

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