SLFN11 expression in early stage non-small cell lung cancer correlates with benefit from platinum-containing chemotherapy

Vamsidhar Velcheti[1], Sarit Schwartz[2], Christina Yau [2], Fabiola Cecchi[2], Yuan Tian[2], Shankar Sellappan[2], Charles M. Rudin[3], John T. Poirier[3], Todd Hembrough[2]

[1] Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH; [2] NantOmics, LLC, Rockville, MD; [3] Thoracic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY

Background

- Schlafen family member 11 (SLFN11) protein is widely reported to sensitize cancer cells to DNA-damaging agents (1).
- Pre-clinical lung cancer models suggest SLFN11 expression may predict response to cisplatin, PARP inhibitors and topoisomerase inhibitors (1-4).
- Tumor expression of SLFN11 is assessed by immunohistochemistry, RNA expression or DNA methylation; no standard method exists (5).
- We used mass spectrometry to quantify SLFN11 protein in archived patient samples of lung cancer treated with adjuvant platinum plus taxane. We correlated proteomic SLFN11 expression with survival.
- Mass spectrometry-based proteomic analysis objectively quantifies SLFN11 protein and other actionable protein biomarkers in formalin-fixed, paraffin-embedded (FFPE) tissue sections (6).

Hypothesis

- A SLFN11 protein cutoff of 100 amol/ug (predefined based on the assay's limit of quantification) is predictive of benefit in lung cancer patients treated with platinum-containing chemotherapy.

Methods

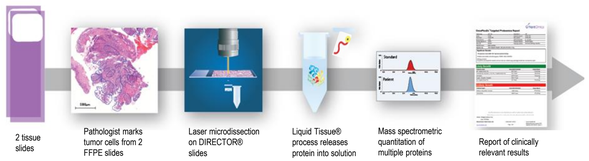


Figure 1. FFPE tissue sections were obtained from 487 patients with lung cancer of multiple subtypes. A pathologist marked the tumor areas, which were microdissected and solubilized. In each tumor sample, multiple protein biomarkers including SLFN11 were quantified with a mass spectrometric assay.

Results

SLFN11 protein expression correlates with longer DFS in patients with platinum-treated NSCLC

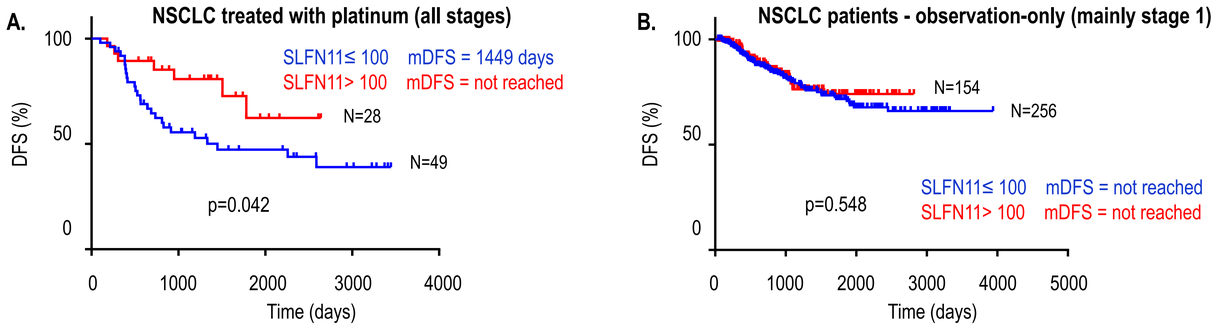
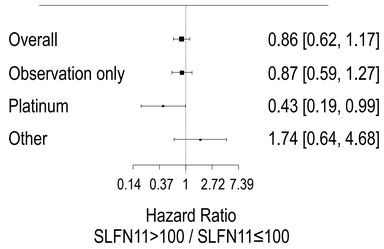


Figure 2. A. Among NSCLC patients treated with platinum-containing chemotherapy (n=77), those with SLFN11 protein levels above the cutoff (n=28) had better disease-free survival (DFS) than patients with SLFN11 levels below the cutoff (HR: 0.43; 95%CI: 0.22-0.88; *p*=0.042). The association between SLFN11 and DFS remains significant after adjusting for clinical stage. **B.** There is no association between SLFN11 protein and DFS in the untreated arm (n=410; SLFN11<100 amol/ug (n=256).

Biomarker-by-treatment interaction



Coefficient for Interaction Term: SLFN11 Low and observation only as Reference

	Exp(Coef) (95% CI)	Wald p
SLFN11 High: Platinum-based	0.52 (0.21-1.29)	0.158

Figure 3. Using the DFS endpoint, the interaction between SLFN11 and platinum is not significant (p=0.158), although the coefficient shows a clear trend. Reference groups are untreated and SLFN11 low (<100 amol/ug).

SLFN11 protein expression is not associated with OS

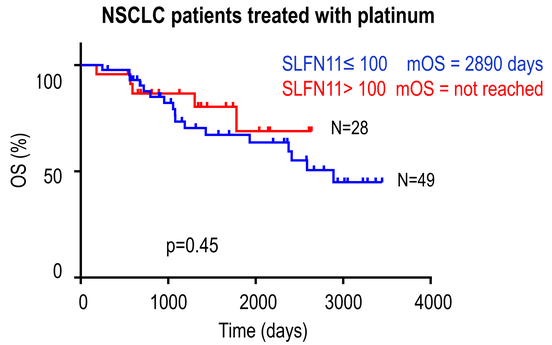


Figure 4. Among NSCLC patients treated with platinum (n=77), there were no statistically significant differences in overall survival (OS) by SLFN11 expression level.

Conclusions

- Quantitative proteomics objectively measures SLFN11 protein in FFPE tumor samples.
- Among platinum-treated NSCLC patients, those with high SLFN11 protein levels had longer DFS than their counterparts with lower SLFN11 levels.
- In patients managed with observation only, there were no differences in DFS between patients with high and low expression of SLFN11.
- Using all patients and the DFS endpoint, the interaction between SLFN11 and platinum was not statistically significant, but the coefficient shows a clear trend.
- Differences in overall survival by SLFN11 expression were not statistically significant in the NSCLC platinum-treated group.
- Mass spectrometry-based proteomics quantifies all these proteins simultaneously in a small tumor sample. SLFN11 is one of 70 different target proteins currently used to support oncologists' decision-making with regard to conventional chemotherapy, targeted therapy and immunotherapy.

Future Plans

Validate the study results in larger cohorts and in other indications including small cell lung cancer.

References

1. Barretina J, Caponigro G, Stransky N, et al:. Nature 483:603-7, 2012
2. Zoppoli G, Regairaz M, Leo E, et al:. Proc Natl Acad Sci U S A 109:15030-5, 2012
3. Lok BH, Gardner EE, Schneeberger VE, et al:. Clin Cancer Res 23:523-535, 2017
4. Gardner EE, Lok BH, Schneeberger VE, et al:. Cancer Cell 31:286-299, 2017
5. Nogales V, Reinhold WC, Varma S, et al: Oncotarget 7:3084-97, 2016
6. Nuciforo P, Thyparambil S, Aura C, et al:. Mol Oncol 10:138-47, 2016

The IASLC 18th World Conference on Lung Cancer, October 15 - 18 2017, Yokohama, Japan