ABSTRACT #: 8574

Identifying Treatment Options for Small Cell Lung Cancer Patients with Multiplexed Clinical Proteomic Testing

Dongyao Yan[1], Eunkyung An[1], Sook-Hee Hong[2], Ho Jung An[2], Sheeno P. Thyparambil[1], Shankar Sellappan[1], Fabiola Cecchi[1], Todd A. Hembrough[1], Tae-Jung Kim[3]

[1]NantOmics, LLC, USA; [2]Division of Medical Oncology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea; [3]Department of Hospital Pathology, College of Medicine, The Catholic University of Korea, South Korea

BACKGROUND

- Patients with small cell lung cancer (SCLC) generally have poor clinical outcomes. Extensive stage SCLC is largely incurable. Even with chemotherapy, median overall survival of advanced SCLC is shorter than 1 year.
- The etoposide / platinum (EP) doublet remains the standard of care for first-line management of SCLC. Despite a response rate of 44% - 78%, responses are often short-lived [1].
- Second-line or later-line therapy for SCLC include topotecan, irinotecan, taxane, temozolomide (TMZ), gemcitabine and others. These agents are usually administered without biomarker information.
- Antibody-drug conjugates (ADCs) targeting tumor-specific proteins DLL3 and TROP2 are being investigated in SCLC [2, 3]. Analyzing protein expression of both antibody target and payload biomarker may precisely identify likely responders to ADCs.
- We propose that proteomic profiling of SCLC can provide actionable information regarding drug sensitivity to chemotherapy and ADCs.

METHODS

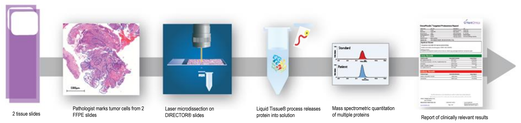


Figure 1. In archived clinical samples of SCLC (n=88), 58 proteins of therapeutic relevance were quantitated with mass spectrometry. In each sample, quantities of tumor protein were compared with pre-defined thresholds based on evidence from clinical studies or quantification limits of proteomic assays.

RESULTS

Expression Distribution of ADC & Payload Targets in SCLC

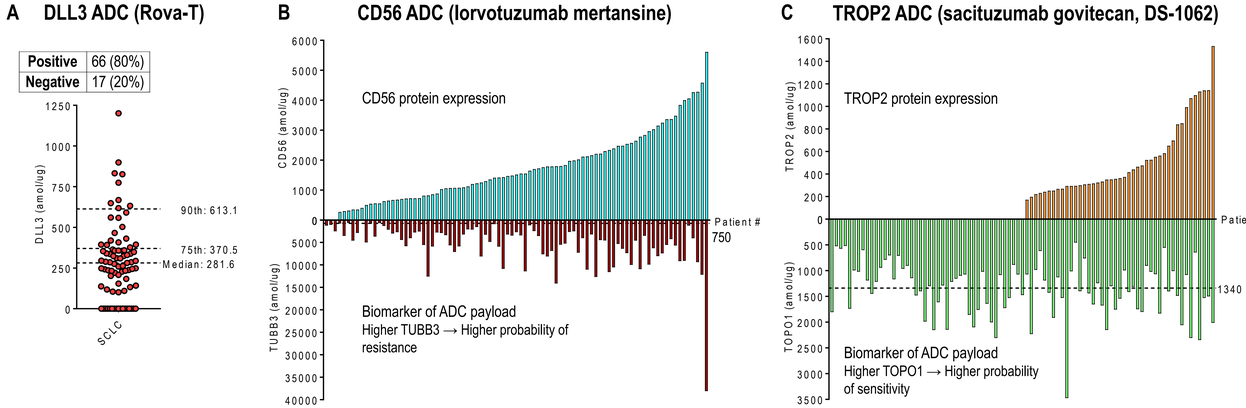


Figure 2. Expression distribution of targets of clinical-stage ADCs. **(A)** DLL3 expression was detected in 80% of SCLC patients (n=83). Expression levels at median, 75th and 90th percentile are indicated by dashed lines. **(B)** CD56 (antibody target) and TUBB3 (payload resistance biomarker) expression in SCLC (n=87). The reference cutoff 750 amol/ug is indicated by dashed line. **(C)** TROP2 (antibody target) and TOPO1 (payload sensitivity biomarker) expression in SCLC (n=87). The reference cutoff 1340 amol/ug is indicated by dashed line.

Expression Distribution of Potential Biomarkers in SCLC

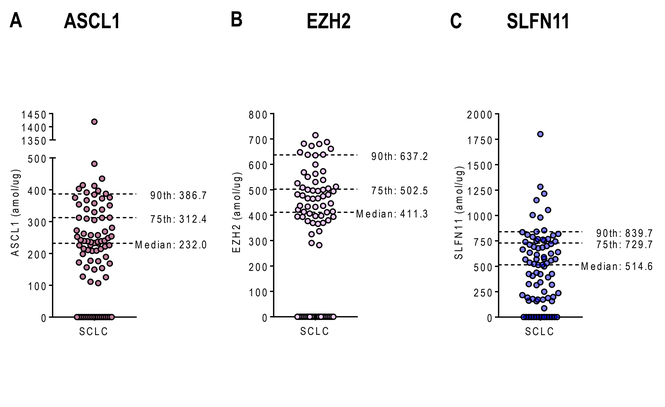


Figure 3. Expression distribution of potential biomarkers. Expression of **(A)** ASCL1 (n=84), a transcription factor regulating neuroendocrine differentiation; **(B)** EZH2 (n=83), a druggable histone methyltransferase involved in epigenetic regulation; **(C)** SLFN11 (n=83), a protein associated with platinum and PARP inhibitor sensitivity.

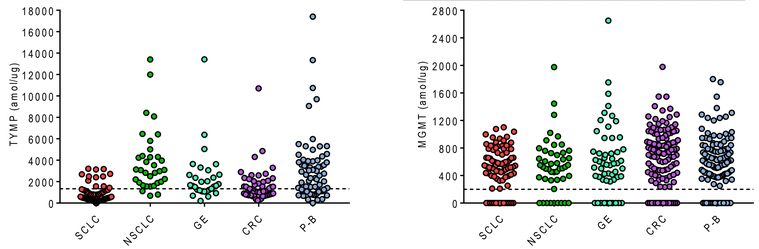
Non-overlapping Chemosensitivity to 5-FU and Temozolomide in SCLC

A TYMP Expression Distribution

Sample Size	83	34	30	55	72
Below Cutoff	71 (84%)	3 (9%)	10 (33%)	32 (58%)	22 (31%)
Above Cutoff	12 (16%)	31 (91%)	20 (67%)	23 (42%)	50 (69%)

B MGMT Expression Distribution

Sample Size	83	47	56	119	123
Below Cutoff	15 (18%)	9 (19%)	12 (21%)	18 (15%)	17 (14%)
Above Cutoff	68 (82%)	38 (81%)	44 (79%)	101 (85%)	106 (86%)



C Non-overlapping Chemosensitivity

TMZ \ 5FU	Insensitive	Sensitive
Insensitive	57 (69%)	11 (13%)
Sensitive	14 (17%)	1 (1%)

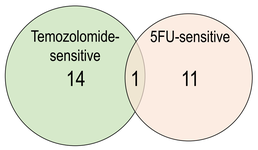


Figure 4. Expression distribution of chemotherapy biomarkers in SCLC and other cancers. **(A)** TYMP (a 5-fluorouracil sensitivity marker) expression. The 1335 amol/ug cutoff is indicated by dashed line. **(B)** MGMT (a TMZ resistance marker) expression. The 200 amol/ug cutoff is indicated by dashed line. **(C)** Proportions of SCLC sensitive / insensitive to 5-FU and TMZ. NSCLC: non-small cell lung cancer (primary and metastatic); GE: primary gastric-esophageal cancer; CRC: primary colorectal cancer; P-B: primary pancreatic-biliary cancer.

CONCLUSIONS

- A fraction of SCLC express high levels of DLL3 and CD56, suggesting potential sensitivity to ADCs targeting these proteins. Quantifying biomarkers associated with cytotoxic payloads may provide valuable information for payload selection;
- Based on pre-defined expression cutoffs, 17% of SCLC are likely responsive to temozolomide, and another non-overlapping 13% are likely sensitive to 5-FU;
- Multiplexed clinical proteomic testing revealed additional treatment options in SCLC patients, which may be useful in first-line or later-line settings.

FUTURE DIRECTION

- Studies are warranted to determine the relationship between treatment response to ADCs and DLL3 / CD56 expression.

REFERENCE

[1] *Transl Lung Cancer Res*. 2018; 7(1):69-79. [2] *Lancet Oncol*. 2017; 18(1):42-51. [3] *Clin Cancer Res*. 2017; 23(19):5711-5719.