2021 ASCO® ANNUAL MEETING

REAL-WORLD MULTIOMIC CHARACTERIZATION OF SMALL CELL LUNG CANCER SUBTYPES TO REVEAL DIFFERENTIAL EXPRESSION OF CLINICALLY RELEVANT BIOMARKERS

Sonam Puri, Abdul R Naqash, Andrew Elliott, Kathleen C. Kerrigan, Shiven B. Patel, Andreas Seeber, Florian Kocher, Dipesh Uprety, Hirva Mamdani, Amit Kulkarni, Gilberto Lopes, Balazs Halmos, Hossein Borghaei, Wallace L. Akerley, Stephen V. Liu, Wolfgang M. Korn, Trudy G. Oliver, Taofeek K. Owonikoko

CARIS POA™ PRECISION ONCOLOGY ALLIANCE

HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

HEALTH UNIVERSITY OF UTAH

Abstract # 8508

Background and Methods

- Small cell lung cancer (SCLC) can be classified into four subtypes (SCLC-A, SCLC-N, SCLC-Y , and SCLC-P) based on the dominant expression of four lineage-defining transcription factors (*ASCL1*, *NEUROD1*, *YAP1*, or *POU2F3 respectively*) [1].
  - Emerging data suggests YAP1 expression is associated with an inflamed T cell gene expression profile [2].
  - SCLC has significant intra-tumor heterogeneity mediated by MYC-driven activation of NOTCH signaling [3].
- We conducted comprehensive molecular profiling of 437 small cell lung neuroendocrine tumors (including 7.3% high-grade neuroendocrine lung carcinomas) using next-generation DNA sequencing (592-gene panel), RNA sequencing (whole transcriptome), and immunohistochemistry at Caris Life Sciences (Phoenix, AZ).
- Tumors were categorized into 5 subtypes (SCLC-A/N/Y/P and -mixed) based on the relative expression of the four transcription factors.
- Differences in gene expression and key signature scores [4-7] in SCLC subtypes were analyzed. Significance was tested by Chi-square, Fisher's exact test, or Mann-Whitney U test.

1. Rudin CM et al. Nat Rev Cancer. 2019 May;19(5):289-297.
2. Owonikoko TK et al. J Thorac Oncol. 2021 Mar;16(3):464-476.
3. Ireland AS at al. Cancer Cell. 2020 Jul 13;38(1):60-78.e12
4. Ott PA et al. J Clin Oncol. 2019;37:318– 327.
5. Cursons J et al. Cancer Immunol Res. 2019 Jul;7(7):1162-1174.
6. Flood BA et al, Immunol Rev. 2019 Jul;290(1):24-38
7. Becht et al, Genome Biology. 2016 Oct; 17(1):218

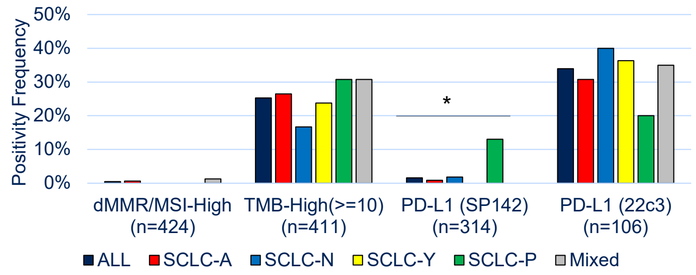
RESULTS: BASELINE CHARACTERISTICS

Table 1: Patient demographics

Characteristic	All SCLC Subtypes	SCLC-A	SCLC-N	SCLC-Y	SCLC-P	Mixed	P-value (test)
Total, N cases (%)	437 (100%)	156 (35.7%)	77 (17.6%)	92 (21.1%)	28 (6.4%)	84 (19.2%)	-------
Median Age, years (SD) - Age Range, years	66 (9.44) 31-90+	63 (9.26) 43-85	70 (8.03) 45-86	65.5 (11.01) 31-85	67.5 (7.44) 57-80	64.5 (9.28) 36-90+	P=0.0164* (Wilcoxon)
Female/Male, N cases - (% Female/% Male)	221/216 (50.6%/49.4%)	77/79 (50.6%/49.4%)	37/40 (48.1%/51.9%)	46/46 (50.0%/50.0%)	12/16 (42.9%/57.1%)	47/37 (56.0%/44.0%)	P=0.7638 (Chi-square)
Metastatic/Primary, N cases - (% Metastatic/% Primary)	294/143 (67.3%/32.7%)	113/43 (72.4%/27.6%)	54/23 (70.1%/29.9%)	42/50 (45.7%/54.3%)	21/7 (75.0%/25.0%)	64/20 (76.2%/33.8%)	P=3.99e-5** (Chi-square)

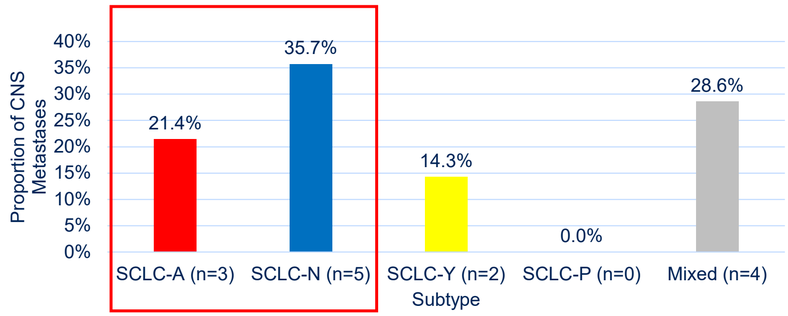
Notes: *Pairwise comparisons found significantly different age distribution between ASCL1 and NEUROD1 subtypes only.
**Pairwise comparisons found the proportion of metastatic specimens to be significantly lower in YAP1 compared to each other subtype (no other comparisons were statistically significant).

Figure 1: Clinically relevant biomarkers of response to immunotherapy



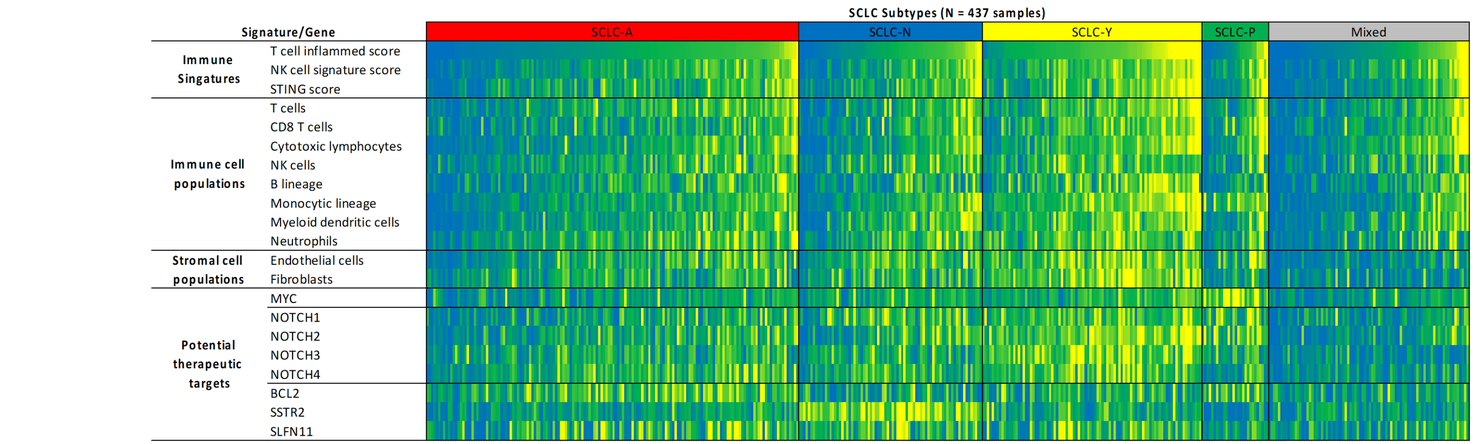
dMMR/MSI-High: Deficient-mismatch repair / high-microsatellite instability
TMB: Tumor mutational burden

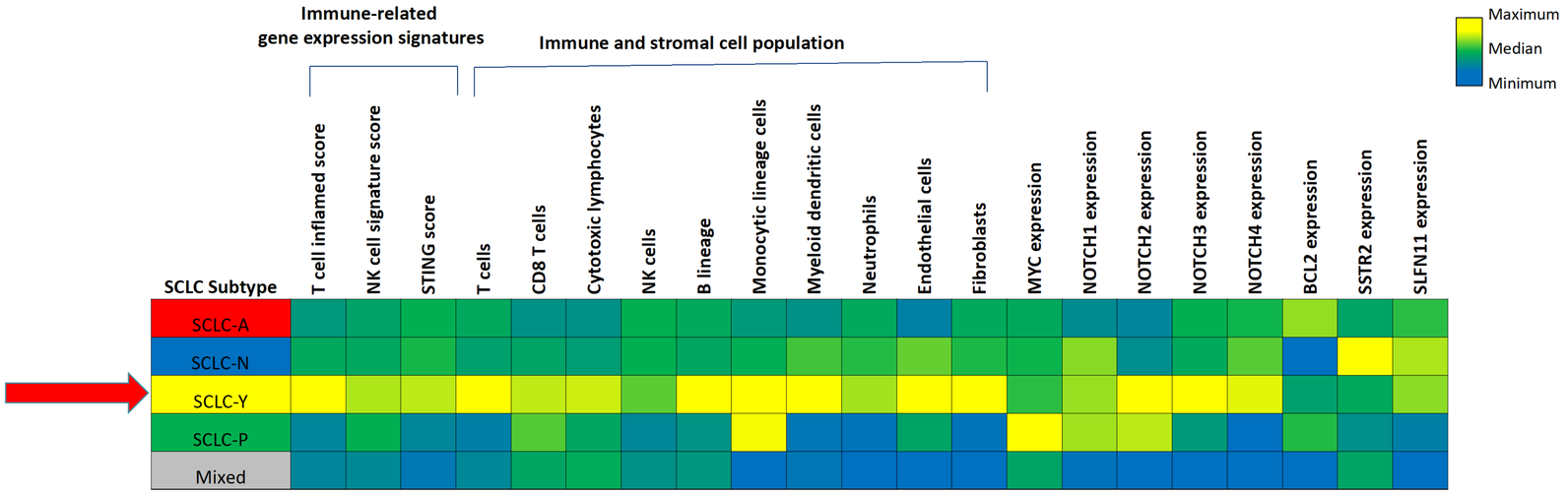
Figure 2: Characteristics of small cell lung cancer from CNS metastasis



N=14, CNS: Central Nervous System

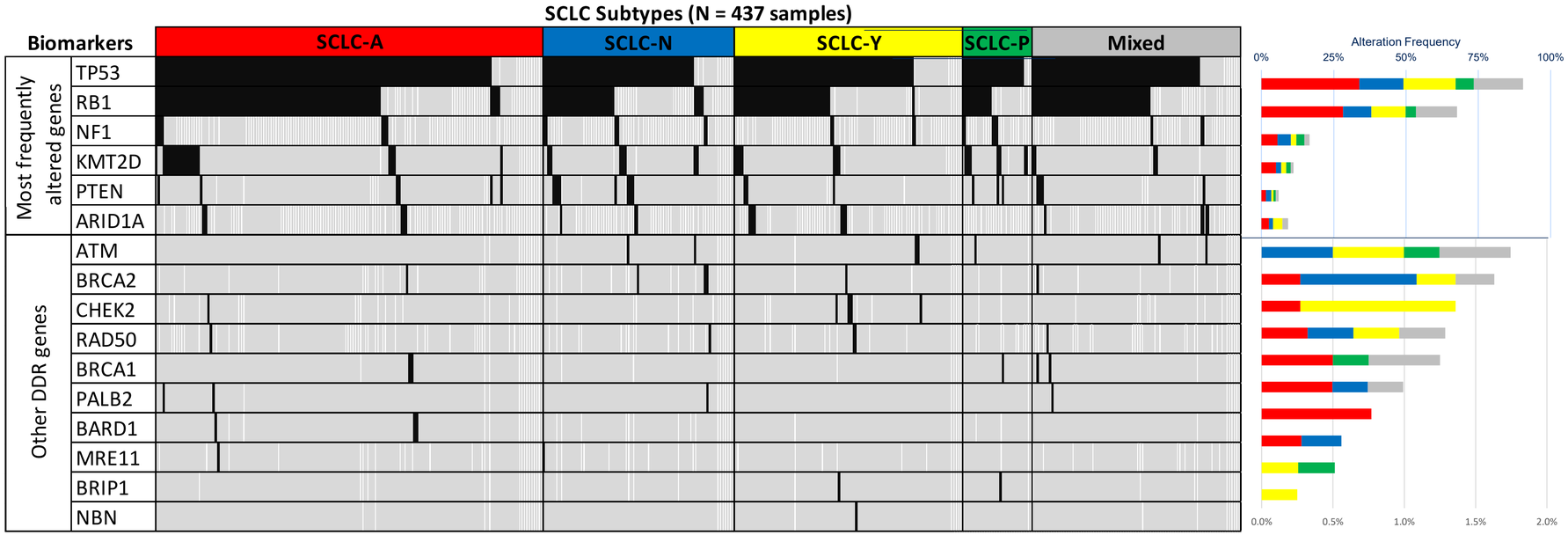
RESULTS: KEY CORRELATIONS OF THERAPEUTIC SIGNIFICANCE





Top: Spectrum of gene expression and signature scores in the SCLC subtypes (n=437)
Bottom: Median expression of key genes in SCLC subtypes

RESULTS: GENOMIC ALTERATIONS IN SMALL CELL LUNG CANCER



EGFR mutation	Total	SCLC-N	SCLC-A	SCLC-Y	SCLC-P	Mixed
E746_A750del	4	3	0	0	0	1
E746_S752delinsV	1	0	1	0	0	0
L747_P753delinsS	1	0	0	1	0	0
V843I	1	1	0	0	0	0
L858R	1	1	0	0	0	0
E709K	1	1	0	0	0	0
G719A	1	1	0	0	0	0
E709A	1	1	0	0	0	0
G719C	1	1	0	0	0	0
L747_A755delinsAN	1	0	0	0	0	1

Note: 3 SCLC-NEUROD1 samples harbored 2 concurrent EGFR mutations.

Left: ***RB1* mutation frequency was highest in ASCL1 (79.2%) and lowest in YAP1 (49.4%) subgroup**
Right: *EGFR*-sensitizing mutations (L858R and Exon 19 deletions) were recurrent (5.2%, n = 4) in the SCLC-N tumor subtype
DDR: DNA damage Repair

CONCLUSIONS

- Our analysis represents the largest real-world dataset of human SCLC tumors profiled by NextGen DNA and whole transcriptomic sequencing.

- **The differential expression of immune genes and predictive biomarkers across transcriptionally defined SCLC subtypes may inform therapeutic vulnerabilities for rational and personalized treatment approaches in SCLC.**
  - SCLC-Y Subtype is associated with the highest median expression of key immunogenic gene and tumor micro-environment cell population signatures; may predict response to immunotherapy.
  - Highest median expression of *SLFN11* and *SSTR2* genes was observed in SCLC-N subtype, while *MYC* gene expression was highest in SCLC-P.

- Further prospective studies are warranted to validate the utility of SCLC subtyping to predict patient response or distinct therapeutic vulnerabilities.