Multidimensional analysis of *B7 homolog 3* (*B7-H3*) RNA expression in small cell lung cancer (SCLC) molecular subtypes

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PURPOSE

- B7-H3 (CD276), a transmembrane protein showing low expression in normal tissues but overexpression in SCLC and other solid tumors, is a promising target for ADCs[1,2]
- We performed a multidimensional analysis of *B7-H3/CD276* RNA expression in SCLC molecular subtypes, comparing expression with that of another key molecular target in SCLC, DLL3[3]
- We also analyzed the relationship of *B7-H3* RNA expression with the expression of other immune-related genes and gene signatures

CONCLUSIONS

- *B7-H3* showed high and consistent expression across subgroups of patients with SCLC defined by the tumor molecular subtype or prior immunotherapy use
- The relative expression of *B7-H3* was higher and less variable among molecular subtypes than for *DLL3*, which is another potential molecular target in this tumor type[3]
- *B7-H3* expression had limited association with *PD-L1* expression, supporting a role as a distinct therapeutic target

INTRODUCTION

- SCLC is an aggressive cancer with a poor prognosis and a high unmet need for new treatment options[4]
- Based on transcriptional profiling, four molecular subtypes of SCLC have been identified[5]:
  - SCLC-A (high *ASCL1* expression)
  - SCLC-N (high *NEUROD1* expression)
  - SCLC-P (high *POU2F3* expression)
  - SCLC-I (low *ASCL1*, *NEUROD1*, and *POU2F3* expression, with an inflamed gene signature)
- These molecular subtypes differ in their biology, genetics, prognosis and/or potential sensitivity to different drug classes[4–6]
- To our knowledge, the expression of *B7-H3*, a promising target for ADCs,[1,2] has not yet been characterized according to SCLC molecular subtype

METHODS

- Clinical and molecular data for a cohort of patients with SCLC were derived from a real-world database (Caris Life Sciences, Irving, TX, USA)
- Tumor RNA expression data were used to assign the SCLC molecular subtype derived from non-negative matrix factorization
- PD-L1 protein expression was assessed by IHC (antibody 22c3), with PD-L1–positivity defined as TPS >1%
- Demographic, clinical, and molecular data were summarized by SCLC subtype or *B7-H3* expression quartile
- Spearman's correlation coefficient (*r*) was used to evaluate correlations between expression of *B7-H3* and other immune-related genes and gene signatures

RESULTS

B7-H3 expression in SCLC molecular subtypes

- The cohort included 1721 patients, among whom 904 (52.5%) were female, and the median age was 67 years (range, 18–90+)
- SCLC molecular subtype was assigned as SCLC-A in 848 (49.3%), SCLC-N in 202 (11.7%), SCLC-P in 142 (8.3%), and SCLC-I in 291 patients (16.9%), while the subtype was equivocal in the remaining 238 patients (13.8%)
- Patient characteristics were similar among the molecular subtypes (**Table 1**)
- Across the molecular subtypes, *B7-H3* expression was high and remarkably consistent ($q>0.05$; **Figure 1A**)
- Lower and more variable expression was observed for *DLL3* ($q<0.0001$; **Figure 1B**)

Relationship between *B7-H3* expression and other immune-related parameters

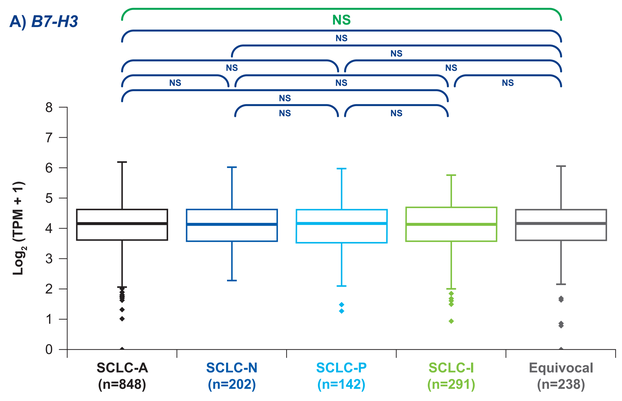
- Median *B7-H3* expression across all samples was 16.75 TPM (range, 0–68.21) (**Figure 2**)
- The proportion of PD-L1-positive patients by IHC was similar across *B7-H3* expression quartiles (**Figure 3**)
- Among patients with available treatment information (n=232), *B7-H3* expression was similar between patients with prior immunotherapy (n=24; median: 14.43 TPM; 95% CI: 11.64–21.17) and patients without (n=208; median: 14.20 TPM; 95% CI: 13.00–15.91) (**Figure 4**)
- *B7-H3* expression was not correlated with T cells, but showed strong correlation with some immune checkpoint genes, including *HAVCR2/TIM3* ($r=0.63$), *CD86* ($r=0.61$), and *PDCD1LG2/PD-L2* ($r=0.61$), as well as M2 macrophages ($r=0.58$) (**Figure 5**)

Table 1: Patient characteristics according to SCLC molecular subtype

	SCLC-A (n=848)	SCLC-N (n=202)	SCLC-P (n=142)	SCLC-I (n=291)	Equivocal[a] (n=238)
Age, median (range), years	67 (18–90+)	68 (32–90+)	69 (33–88)	68 (36–89)	66.5 (44–90+)
Sex, n (%)					
Female	467 (55.1)	93 (46.0)	61 (43.0)	164 (56.4)	119 (50.0)
Male	381 (44.9)	109 (54.0)	81 (57.0)	127 (43.6)	119 (50.0)
Smoking status[b], n (%)					
Smoker	225 (98.7)	69 (97.2)	33 (100)	50 (100)	57 (100)
Non-smoker	3 (1.3)	2 (2.8)	0	0	0
Biopsy site, n (%)					
Primary	259 (30.5)	72 (35.6)	56 (39.4)	144 (49.5)	83 (34.9)
Metastasis	583 (68.8)	128 (63.4)	86 (60.6)	144 (49.5)	154 (64.7)
Unclear	6 (0.7)	2 (1.0)	0	3 (1.0)	1 (0.4)
TMB, median (range), mutations/Mb	7 (0–59)	6 (1–38)	7 (1–29)	8 (0–34)	8 (0–26)

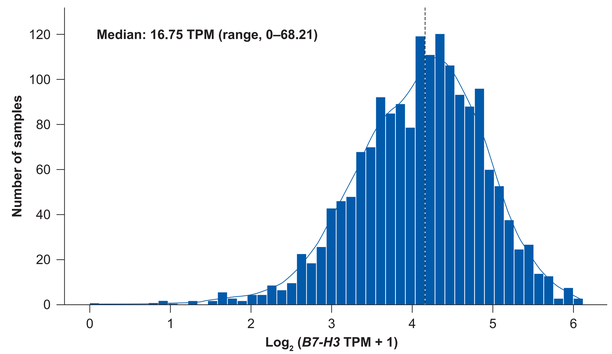
[a]If ≥50% of the predictive models used agreed on the molecular subtype, the subtype was assigned based on this consensus classification. Samples with less than 50% agreement are called "equivocal".[7]
[b]Smoking status was available for 439 patients overall.

Figure 1: Expression of *B7-H3* and *DLL3* according to SCLC molecular subtype



***q<0.001; ****q<0.0001.
q-values were calculated using the Mann–Whitney *U* test with Benjamini–Hochberg adjustment for multiple testing.
q-values in green refer to the overall comparison between groups, while those in blue refer to pairwise comparisons.

Figure 2: Distribution of *B7-H3* expression across all samples



The dashed black line indicates the median value and the solid blue line indicates the density curve.

Figure 3: PD-L1–positivity (TPS >1%) according to *B7-H3* expression quartile

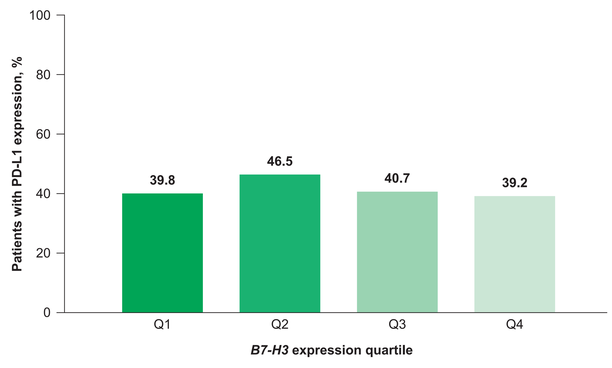
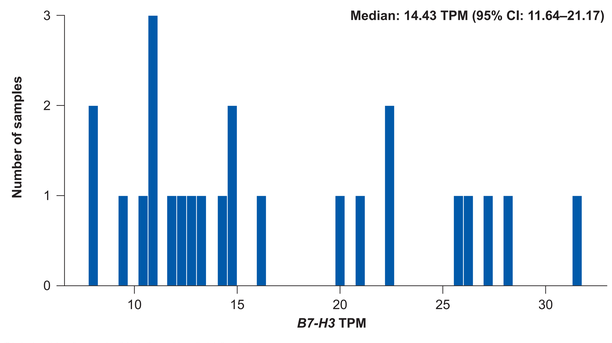


Figure 4: Distribution of *B7-H3* expression according to prior immunotherapy use (n=232[a])

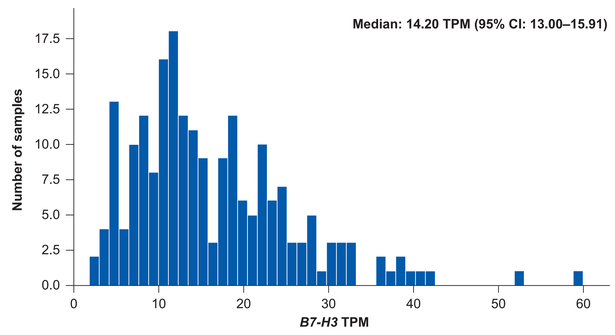
A) Prior immunotherapy (n=24)



[a]Prior treatment information was not available for the remaining patients in the cohort.

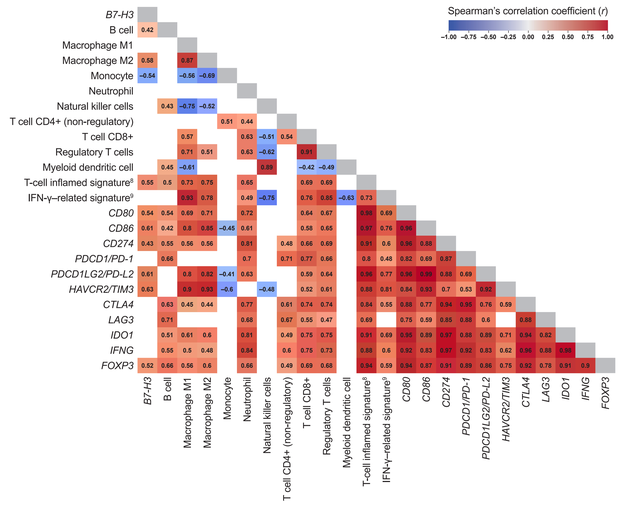
Figure 4 (cont.): Distribution of *B7-H3* expression according to prior immunotherapy use (n=232[a])

B) No prior immunotherapy (n=208)



[a]Prior treatment information was not available for the remaining patients in the cohort.

Figure 5: Heat map showing Spearman's correlation matrix for pairwise comparisons of gene expression variables



Spearman's correlation coefficient (*r*) value and associated color coding are shown only for correlations that were significant ($p<0.05$).

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ABBREVIATIONS

ADC, antibody–drug conjugate; B7-H3, B7 homolog 3; CD, cluster of differentiation; CI, confidence interval; DLL3, delta-like ligand 3; IFN-γ, interferon-γ; IHC, immunohistochemistry; NS, not significant; PD-L1, programmed death-ligand 1; Q, quartile; SCLC, small cell lung cancer; TMB, tumor mutational burden; TPM, transcripts per million; TPS, tumor proportion score.

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