Real-World Characterization of SEZ6, a Transmembrane Protein Expressed in Various Solid Tumors

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Objective

The aim of this study was to characterize *SEZ6* expression in a large patient population, across multiple tumor types at various disease stages

Conclusions

- ***SEZ6* is highly expressed in small cell lung cancer (SCLC) and tumors of neuroendocrine (NE) origin, particularly prostate and bladder small cell neuroendocrine carcinomas (NECs). In SCLC, expression is stable across disease stages 2–4, and in primary and metastatic tumors**
- **In SCLC, median *SEZ6* expression is greater than that of other targets of antibody–drug conjugates (ADCs) either approved or in development for SCLC; this supports SEZ6 as a promising therapeutic target**
  - **Median *SEZ6* expression is highest in SCLC-N and SCLC-A, which are characterized by high expression of NE transcription factors and are the most common molecular subtypes**
  - **Relatively high median *SEZ6* expression is also observed in SCLC-I, a subtype associated with platinum resistance; this suggests SEZ6 may be a potential therapeutic target in certain patients with platinum-refractory SCLC**
- ***SEZ6* is highly expressed in prostate NEC, with median expression levels greater than those of other therapeutic targets in this setting**
- **There are significant positive correlations between expression of *SEZ6* and that of *DLL3* and *CD56* in SCLC and NECs (including prostate and bladder small cell NECs), indicating the potential for combination approaches**
- **Overall, these results suggest cross-indication applicability of targeting SEZ6, particularly in tumors of NE origin, and highlight its potential as a multitumor ADC target warranting further investigation**
  - **HWK-206 is a next-generation, biparatopic, SEZ6-targeting ADC that has demonstrated potent antitumor activity in preclinical studies. A phase 1 trial is expected in Q3 2026[9]**

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For author disclosures, please refer to the abstract.

Background

- Seizure-related homolog protein 6 (SEZ6) is a cell-surface transmembrane protein involved in neuronal development; it is primarily expressed in central nervous system (CNS) tissues and is a regulator of synaptic connectivity during embryogenesis[1]
- Although it is downregulated in normal adult tissues, aberrant overexpression of the SEZ6 protein and gene has been demonstrated in solid tumors including small cell lung cancer (SCLC)[2] and other high-grade neuroendocrine carcinomas (NECs)[1]
  - In patients with SCLC, SEZ6 expression is correlated with poor survival outcomes[3]
  - Brain metastasis samples from patients with SCLC show similar *SEZ6* mRNA expression as in primary SCLC tumor samples,[4] suggesting that SEZ6-directed therapies have the potential for intracranial activity
- There are four known molecular subtypes of SCLC, defined by high expression of neuroendocrine (NE) transcription factors ASCL1 and NEUROD1 (SCLC-A and SCLC-N, respectively), the non-NE transcription factor POU2F3 (SCLC-P), and an inflamed gene signature (SCLC-I) that has low expression of the three transcription factors and is associated with resistance to platinum chemotherapy[5]
  - Studies suggest that SEZ6 expression is greater in the molecular subtypes of SCLC with NE-high gene signatures (i.e., SCLC-A and SCLC-N)[2–4,6] than in the non-NE subtype (i.e., SCLC-P)[2,3]
  - In an analysis using the ConcertAI/Caris Patient360™ real-world database, the distribution of SCLC molecular subtypes was similar between treatment-naïve (n=127) and post–first-line (n=19) patients, with enrichment of SCLC-A and SCLC-N in both groups[7]
- In SCLC cells, there is significant correlation between mRNA and immunohistochemistry expression of SEZ6 (Spearman's rho [ρ]=0.61; p=0.001), supporting the use of mRNA data as a proxy for protein expression[4]
  - Nonetheless, expression of *SEZ6* in tumor tissues remains poorly understood[3] and available data are limited by small sample sizes (N=52–1318)[2–4,6–8]

Methods

- Data from the de-identified Tempus multimodal real-world database were analyzed for *SEZ6* mRNA expression across multiple tumor types, with a focus on lung, brain/CNS, and NE tumor samples. Gene expression data were derived from a whole-transcriptome RNA-sequencing panel (Tempus' xR) capturing 20,000 genes
  - In SCLC, *SEZ6* expression was compared across SCLC-A, SCLC-N, SCLC-P, and SCLC-I subtypes via hierarchical clustering
  - The gene expression distributions of other therapeutic targets in SCLC and NECs were also analyzed
- Gene expression was quantified as $\log_2$(transcripts per million [TPM]+1). Group differences were analyzed using the Kruskal–Wallis test, and pairwise comparisons were analyzed using the Wilcoxon rank sum test
  - Co-expression of *SEZ6* mRNA with other therapeutic targets in SCLC and NECs was assessed using Spearman correlation

Results

SEZ6 IS HIGHLY EXPRESSED IN SOLID TUMORS

- Across 36,347 tumor samples, of which 17,849 (49.1%) were from metastatic tumors, *SEZ6* mRNA expression was observed in multiple tumor types (**Figure 1**)
  - The highest median *SEZ6* expression ($\log_2$[TPM+1]) occurred in anaplastic oligodendroglioma (7.4; n=117), prostate NEC (6.6; n=176), SCLC (6.5; n=2018), and bladder small cell NEC (6.5; n=139)

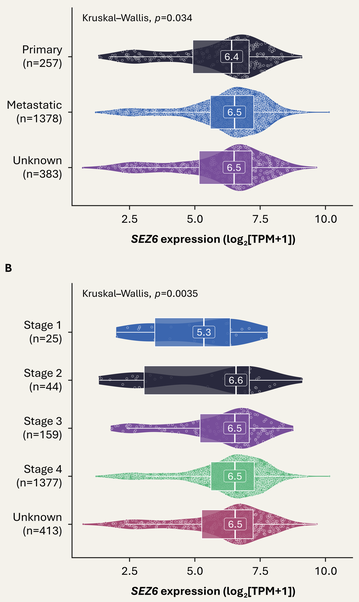
SEZ6 EXPRESSION IS HIGH AND STABLE ACROSS SCLC DISEASE STAGES AND HIGHEST IN NEUROENDOCRINE MOLECULAR SUBTYPES

- *SEZ6* expression was stable irrespective of SCLC metastatic status, with median $\log_2$(TPM+1) values of 6.4 (n=257) and 6.5 (n=1378) in primary and metastatic tumor samples, respectively (**Figure 2A**)
- Median *SEZ6* expression was 5.3 in stage 1 disease (n=25) and was significantly higher across stages 2–4 (6.5–6.6 [n=44–1377]; p=0.00097) (**Figure 2B**)
  - Expression of *SEZ6* significantly increased in stages 3 and 4 compared with stage 1 (p=0.009 and p=0.00064, respectively)

FIGURE 1. *SEZ6* mRNA Expression Across Multiple Tumor Types

NE(C/N/T), neuroendocrine (carcinoma/neoplasm/tumor); **SCLC**, small cell lung cancer; **TPM**, transcripts per million.

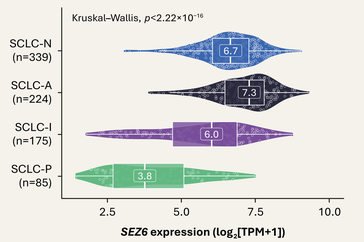
FIGURE 2. *SEZ6* mRNA Expression in SCLC by (A) Metastatic Status and (B) Disease Stage



SCLC, small cell lung cancer; **TPM**, transcripts per million.

- Tumor samples were enriched for the NE-high molecular subtypes SCLC-N (n=339) and SCLC-A (n=224) (**Figure 3**)
  - Median *SEZ6* expression was significantly higher in the SCLC-N (6.7), SCLC-A (7.3), and SCLC-I (6.0 [n=175]) subtypes compared with the SCLC-P (non-NE) subtype (3.8 [n=85]; $p<2.22\times10^{-16}$, $p<2.22\times10^{-16}$, and $p<4.8\times10^{-13}$, respectively)

FIGURE 3. *SEZ6* mRNA Expression by SCLC Molecular Subtype

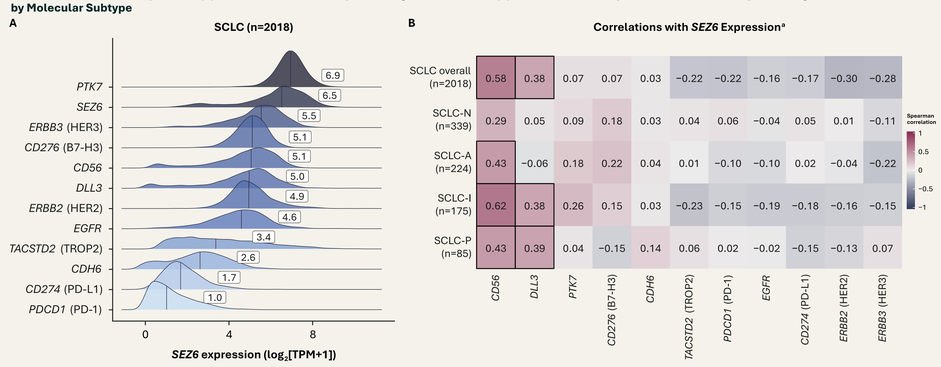


SCLC, small cell lung cancer; **SCLC-A**, ASCL1-high small cell lung cancer; **SCLC-I**, inflamed small cell lung cancer; **SCLC-N**, NEUROD1-high small cell lung cancer; **SCLC-P**, POU2F3-high small cell lung cancer; **TPM**, transcripts per million.

SEZ6 EXPRESSION IS GREATER THAN THAT OF OTHER THERAPEUTIC TARGETS IN SCLC

- In SCLC tumor samples, median expression of *SEZ6* was 3–45-fold higher than that of other biomarkers tested, including *ERRB2* (HER2), *CD276* (B7-H3), and *DLL3* (all 3-fold higher), *EGFR* (4-fold), *CD274* (PD-L1) (28-fold), and *PDCD1* (PD-1) (45-fold) (**Figure 4A**)
- Median *SEZ6* expression in SCLC tumor samples (n=2018) showed significant positive correlations ($p\leq0.05$) with expression of *CD56* and *DLL3*, with moderate effect sizes (ρ=0.58 and ρ=0.38, respectively) (**Figure 4B**)
  - Significant positive correlations ($p\leq0.05$) between expression of *SEZ6* and that of *CD56* and *DLL3* and moderate effect sizes were also observed in SCLC-I (ρ=0.62 and ρ=0.38, respectively) and SCLC-P (ρ=0.43 and ρ=0.39, respectively) molecular subtypes

FIGURE 4. *SEZ6* mRNA Expression (A) Relative to Other Therapeutic Targets in SCLC and (B) Correlated with Expression of Other Therapeutic Targets in SCLC Overall and by Molecular Subtype

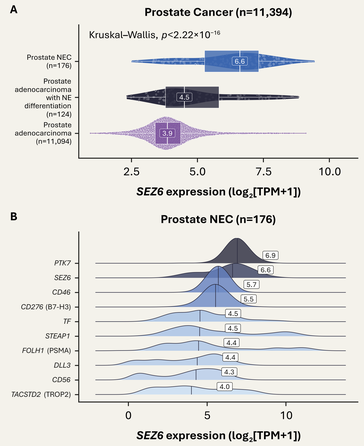


[a]Numbers in boxes on the heatmap denote Spearman's rho (ρ). Black frames indicate $p>0.3$ and statistical significance $p\leq0.05$.
SCLC, small cell lung cancer; **SCLC-A**, ASCL1-high small cell lung cancer; **SCLC-I**, inflamed small cell lung cancer; **SCLC-N**, NEUROD1-high small cell lung cancer; **SCLC-P**, POU2F3-high small cell lung cancer; **TPM**, transcripts per million.

SEZ6 EXPRESSION IS HIGH AND GREATER THAN THAT OF OTHER THERAPEUTIC TARGETS IN PROSTATE NEUROENDOCRINE CARCINOMA

- Across three histologic subtypes of prostate cancer (n=11,394), median *SEZ6* expression was highest in prostate NEC samples (6.6; n=176) (**Figure 5A**)
- In prostate NEC, median expression of *SEZ6* was 2–6-fold higher than that of other biomarkers tested, including *CD276* (B7-H3) (2-fold higher), *DLL3* (5-fold), and *TACSTD2* (TROP2) (6-fold) (**Figure 5B**)

FIGURE 5. *SEZ6* mRNA Expression (A) in Prostate Cancer and (B) Relative to Other Therapeutic Targets in Prostate NEC



NE(C), neuroendocrine (carcinoma); **TPM**, transcripts per million.

SEZ6 EXPRESSION IS POSITIVELY CORRELATED WITH EXPRESSION OF *CD56* AND *DLL3* ACROSS NEUROENDOCRINE CARCINOMAS

- *SEZ6* expression showed significant positive correlations ($p\leq0.05$) with expression of *DLL3* and *CD56* and moderate effect sizes across various NEC samples, including prostate NEC (n=176; ρ=0.55 and ρ=0.56, respectively) and bladder small cell NEC (n=139; ρ=0.44 and ρ=0.60, respectively) (**Figure 6**)
  - In prostate NEC samples, there was a significant negative correlation ($p\leq0.05$) between expression of *SEZ6* and *TACSTD2* (TROP2) (ρ=−0.50)

FIGURE 6. Correlation Between Expression of *SEZ6* and Other Therapeutic Targets Across NEC Samples

[a]Numbers in boxes on the heatmap denote Spearman's rho (ρ). Black frames indicate $p>0.3$ and statistical significance $p\leq0.05$.
NEC, neuroendocrine carcinoma.

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