

Neuroendocrine negative SCLC and CDK4/6 inhibition

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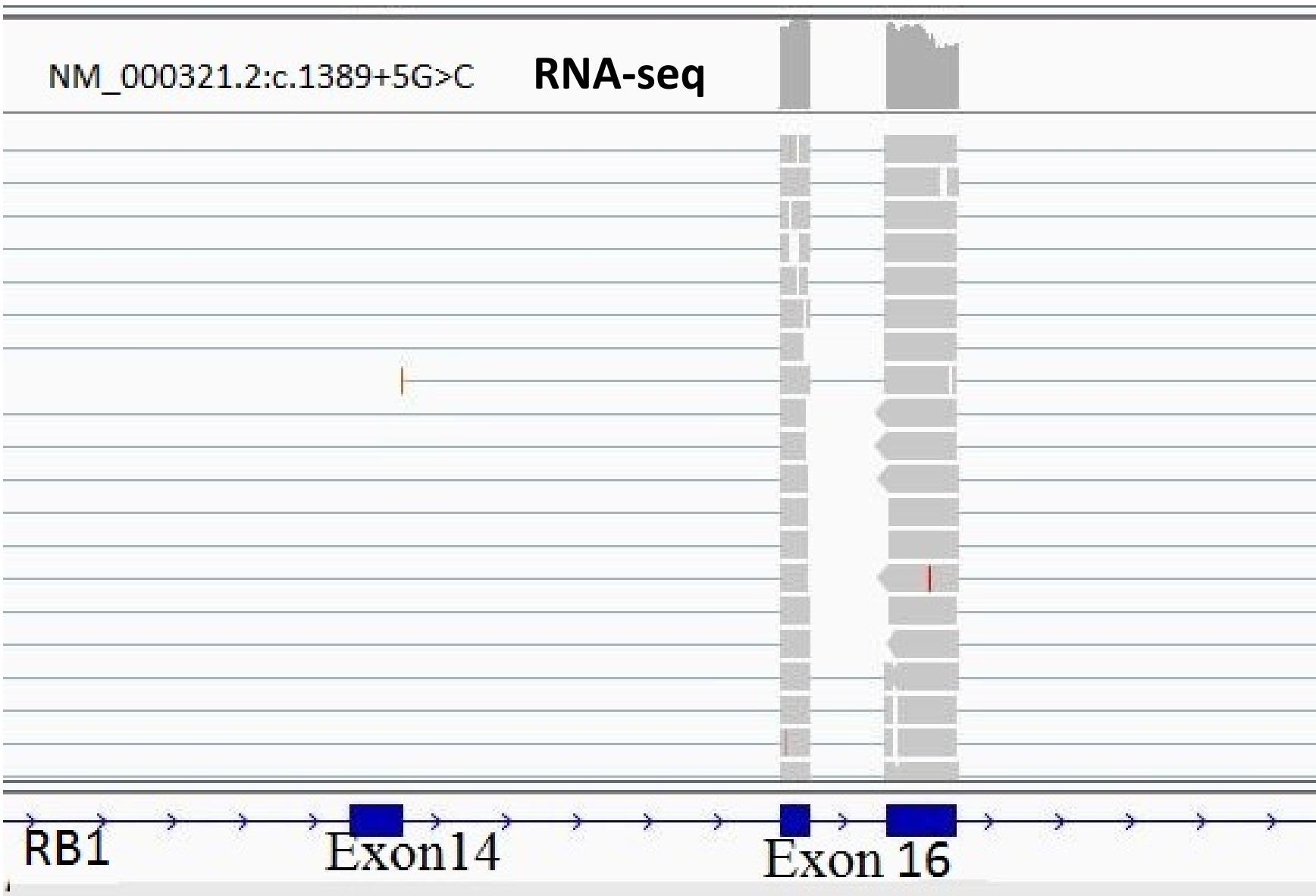
SCLC genomics

- Most SCLC are genetically characterized by homozygous inactivation of RB1 and TP53 tumor suppressor genes.
- The prevailing hypothesis is that RB1 inactivation in SCLC leads to increase in cellular proliferation due to loss of cell cycle control and inactivation of TP53 prevents oncogene induced senescence.
- Regulators of neuroendocrine differentiation such as ASCL1, INSM1, and NEUROD1 are highly expressed in SCLC; however a small fraction of SCLC do not express neuroendocrine lineage markers and transcription factors, such SCLC are often referred as SCLC variant.
- SCLC is sometimes present with another lung cancer subtype(s) such as: large cell neuroendocrine carcinoma, large cell carcinoma, adenocarcinoma and squamous cell carcinoma. These NSCLC subtypes have frequent oncogenic alterations in genes such as: EGFR, KRAS, NRAS, BRAF, NF1, CDKN2A, SMARCA4, PIK3CA, PTEN, KEAP1, SOX2, TP63, etc.

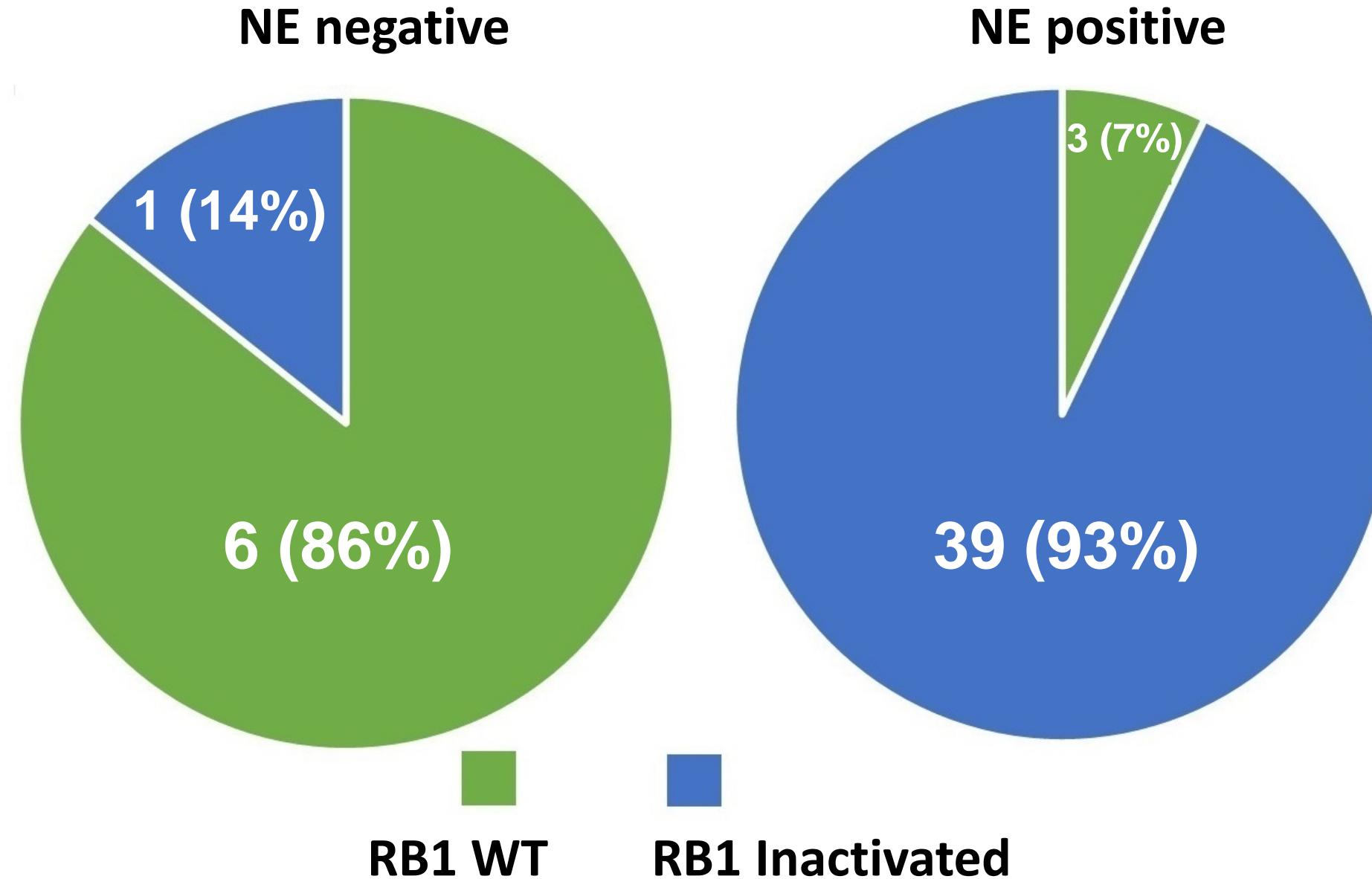
SCLC cell lines

- 49 CCLE SCLC cell lines, 35 from NCI SCLC screen of 420 approved and investigational oncology drugs.
- These SCLC lines have comprehensive, high quality publicly available genomics data:
 - Partial exome sequencing
 - Whole exome sequencing
 - RNA-seq
 - AFFY SNP 6.0 arrays
 - AFFY U133Plus2 mRNA arrays
- RB1 can be inactivated by: deletions, point mutations, truncating mutations, loss of mRNA expression and splice site mutations. RNA-seq data are very useful to confirm correct mRNA splicing.

Example of splice site mutation >3 bases away from exon-intron boundary in COR-L24



Neuroendocrine markers and RB1 status

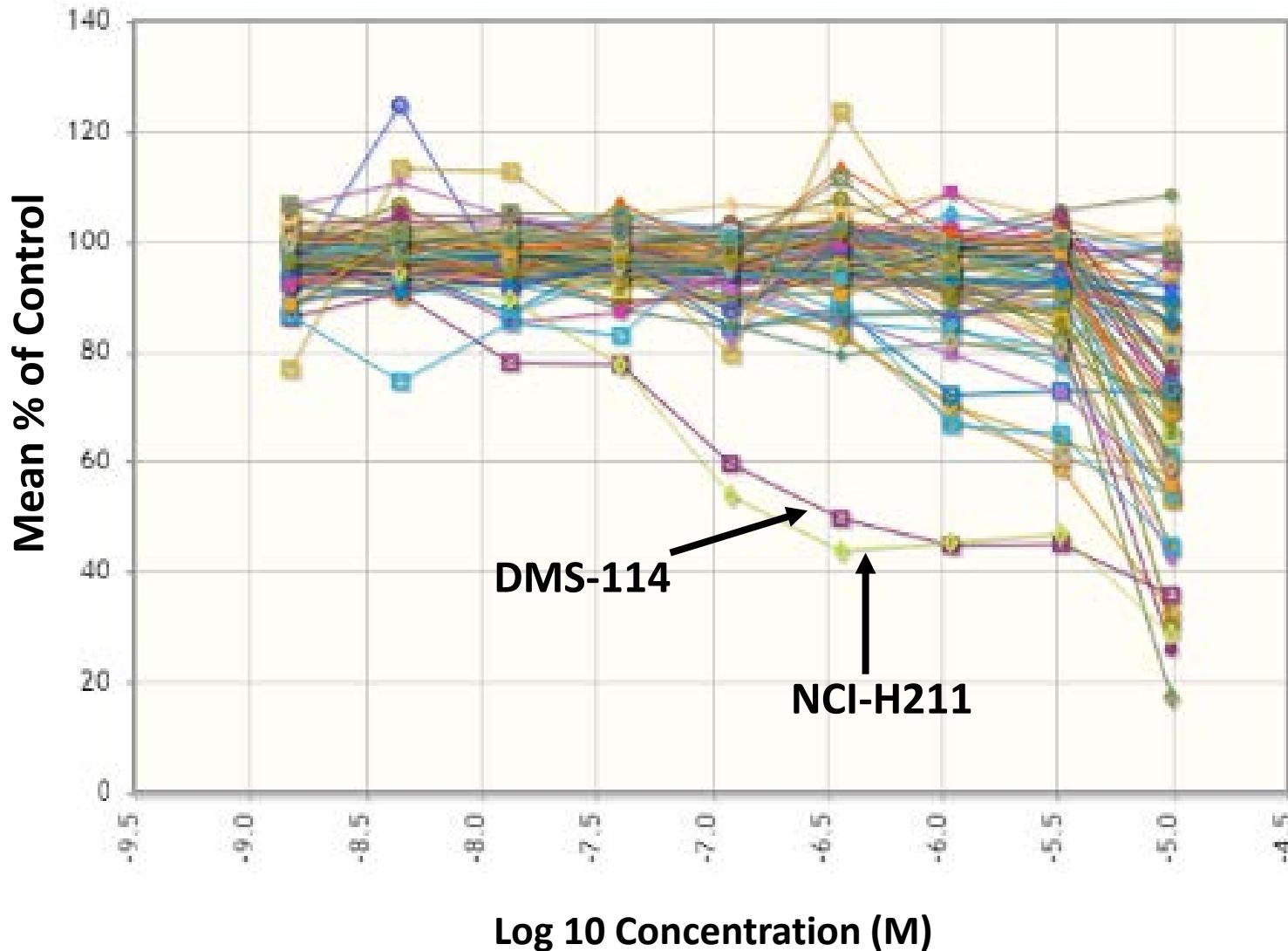


RB1 WT SCLC cell lines Genomics

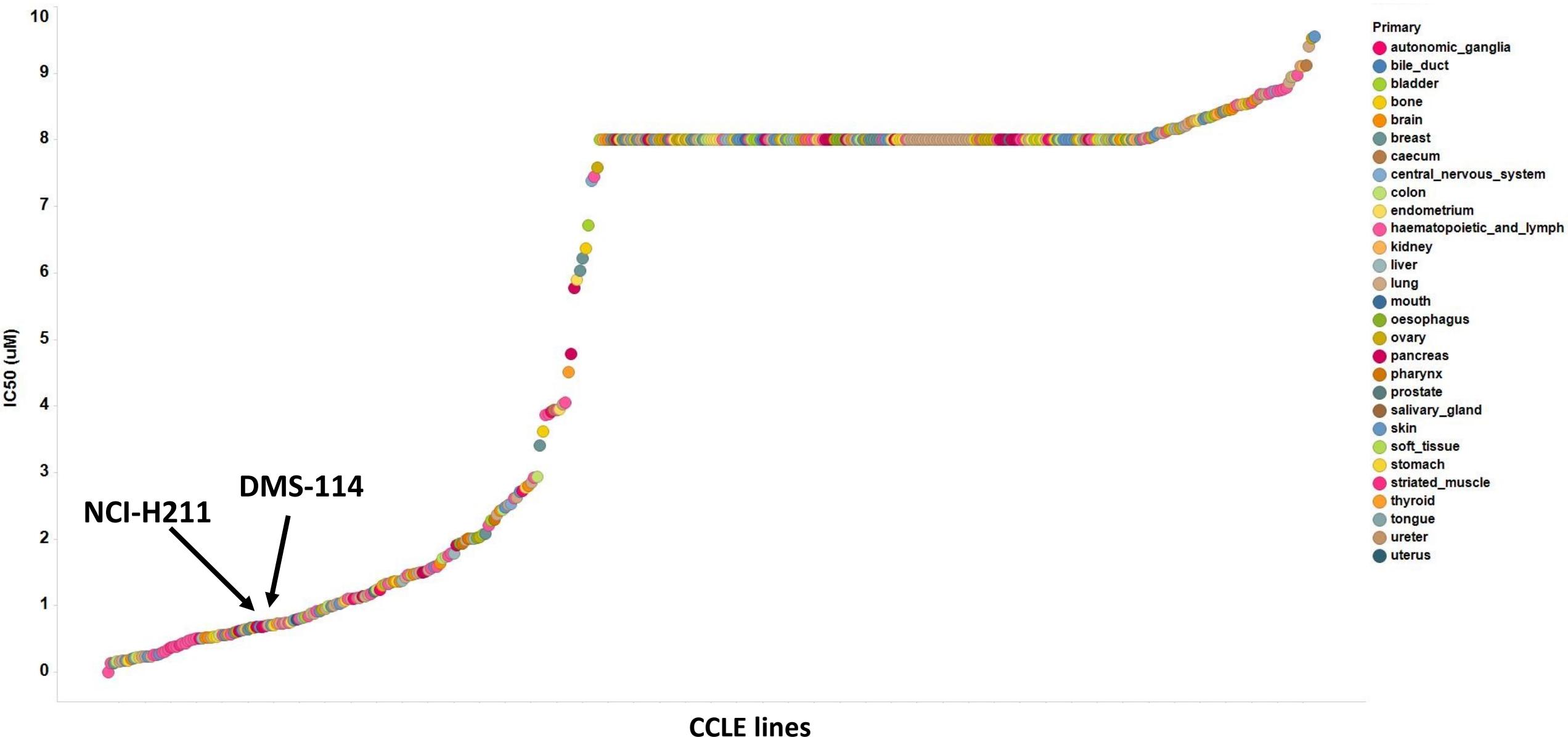
Name	ASCL1	INSM1	NEUROD1	CHGA	NCAM1	DLL3	EGFR	Key alterations	
NCI-H2286	NEG	NEG	NEG	NEG	NEG	LOW	HIGH	TP53 K291* hom, CDKN2A E33* hom TP53 E298* hom, KRAS G12R, PTEN G251C hom,	
NCI-H1339	NEG	NEG	NEG	NEG	NEG	LOW	HIGH	CDKN2A E69* hom , SMARCA4 AA56fs	
NCI-H841	NEG	NEG	NEG	NEG	NEG	LOW	HIGH	TP53 C242S hom, SMARCA4 K934* hom	
SW1271	NEG	NEG	NEG	NEG	NEG	LOW	HIGH	TP53 C277F hom, NRAS Q61R, CDKN2A hom deletion	
DMS-114	NEG	NEG	NEG	NEG	NEG	LOW	LOW	TP53 R213* hom, SMARCA4 E1310* hom, CCND1 9 copies	
SBC-5	NEG	NEG	NEG	NEG	NEG	LOW	LOW	TP53 R248L hom, SMARCA4 AA1243fs hom	
NCI-H1341	NEG	NEG	NEG	POS	POS	LOW	HIGH	PIK3CA E542K, MYC 5 copies	
NCI-H211	NEG	NEG	NEG	NEG	POS	LOW	LOW	TP53 R248Q hom, MYC 5 copies, CCND1 4 copies	
DMS-53	POS	POS	POS	POS	POS	HIGH	LOW	TP53 S241F hom, KRAS 8 copies high mRNA expression	

DMS-114 (IC50 0.36 μM) and NCI-H211 (IC50 0.22 μM) are sensitive to CDK4/6 inhibitor palbociclib
 (<https://sclccelllines.cancer.gov/sclc>)

Palbociclib Concentration/Response in NCI SCLC screen



Palbociclib IC50 (μ M) across 432 CCLE lines



Potential explanations for atypical SCLC genomics

- CCND1 amplifications and, perhaps, CDKN2A inactivation may play similar role to RB1 inactivation resulting in cell cycle control defects.
- KRAS, NRAS, SMARCA4 alteration(s) may originate in pulmonary neuroendocrine progenitor cells, and due to oncogene induced transformation and underlying lineage plasticity lead to partial loss of the neuroendocrine phenotype.
- It is possible that KRAS, NRAS, SMARCA4 alteration(s) originated in a common progenitor cell, resulting in unusual phenotype.
- It is plausible that, some of these cell lines, originated from a tumor with a mixed SCLC/NSCLC phenotype and after passaging the NSCLC clones remained and the SCLC clones were lost.

Summary

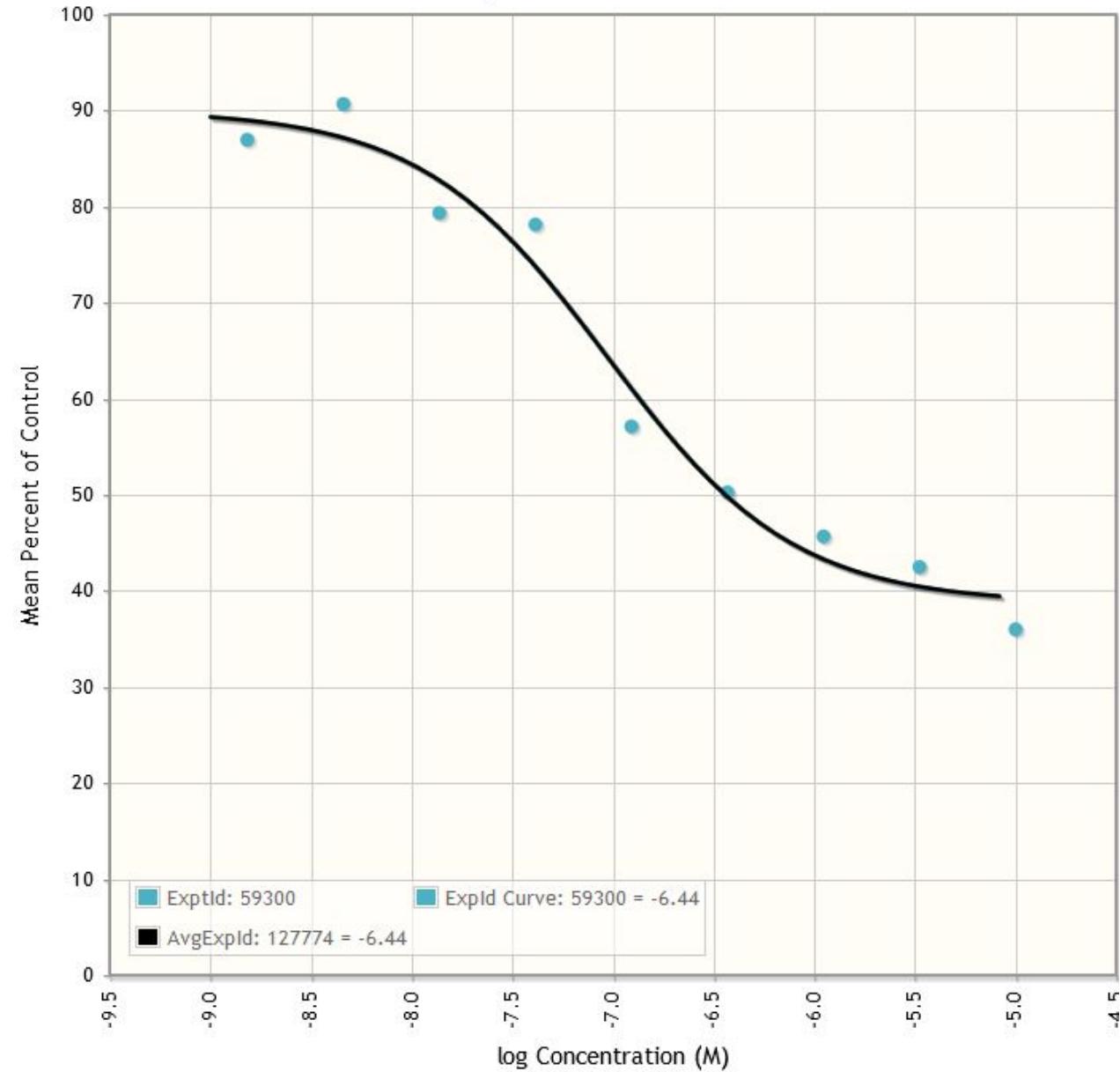
- RB1 WT SCLC tumors are enriched for loss of neuroendocrine lineage markers and may be sensitive to CDK4/6 inhibition.
- RB1 WT SCLC tumors have low DLL3 mRNA expression which is consistent with reports showing neuroendocrine lineage marker negative SCLC tumors to be associated with low DLL3 expression.
- DLL3-targeted antibody-drug conjugate rovalpituzumab tesirine has shown encouraging preliminary efficacy profile in SCLC in the clinic and is undergoing additional testing.
- Patients with RB1 WT SCLC tumors are unlikely to qualify or to respond to DLL3 targeted therapy. However, this may present the opportunity to identify patients with WT RB1 for potential treatment with CDK4/6 inhibitors among patients screened for DLL3 ADC treatment and having no or very low DLL3 expression.

Acknowledgements

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Palbociclib Concentration/Response

DMS-114



NCI-H211

