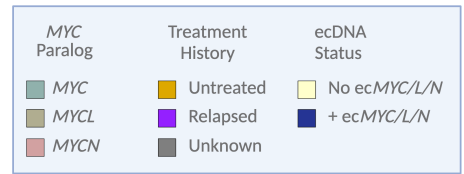
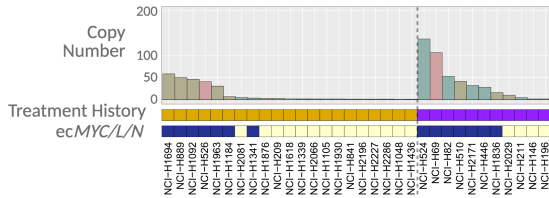


Supplementary Figure S13

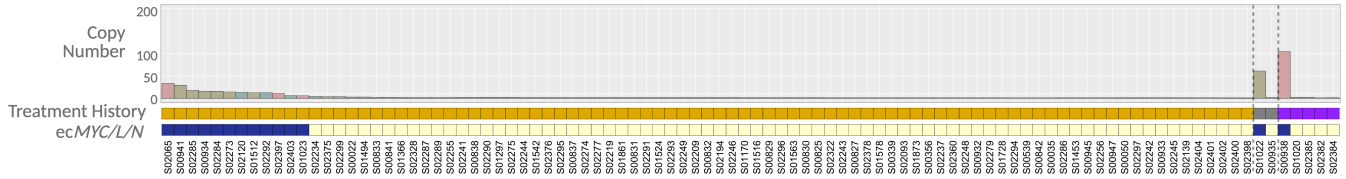
A. Established Cell Lines

WGS: Ghandi et al., *Nature* 2019
 CNA and AA: Pongor et al., *Can. Disc.* 2023
 Clin. Hx: Phelps et al., *JCB* 1996

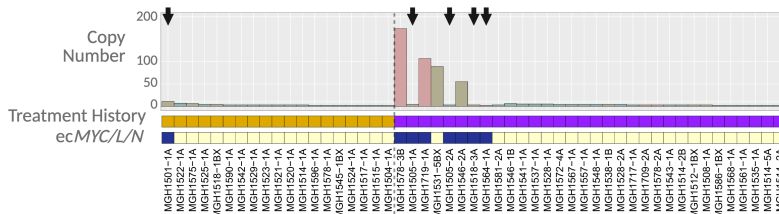


B. Patient Tumor Samples

WGS and Clin. Hx: George et al., *Nature* 2015
 CNA and AA: Pongor et al., *Can. Disc.* 2023

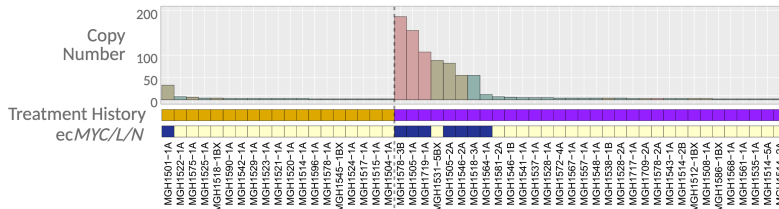


C. PDX Models -- Segmented CNA



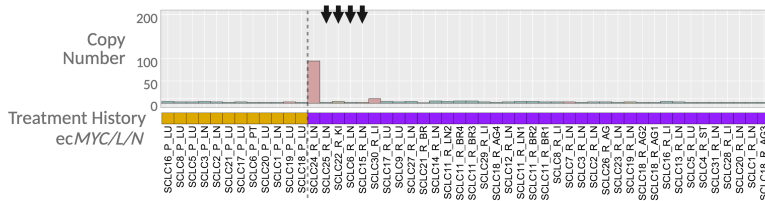
↓ ecDNA amplifications missed by segmented CNA

D. PDX Models -- Unsegmented CNA



E. Patient Tumor Samples -- Segmented CNA

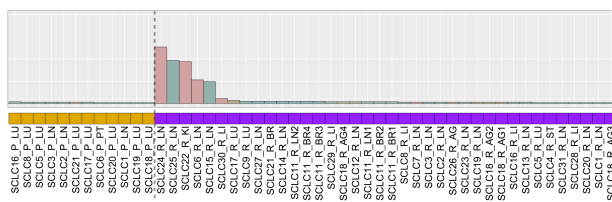
WES: Wagner et al., *Nat. Comm.* 2018



↓ high-level focal amplifications not detected by segmented CNA

F. Patient Tumor Samples -- Unsegmented CNA

WES: Wagner et al., *Nat. Comm.* 2018



Supplementary Figure S13. MYC paralog copy number and ecDNA status in SCLC cell lines, PDX models and biopsy samples derived before treatment or after relapse. (A-D) Maximum copy number (CN) of *MYC*, *MYCL*, or *MYCN* from WGS of SCLC cell lines, PDX models and patient tumor samples, with annotated treatment histories (untreated vs. relapsed) and ec*MYC/L/N* status derived from AmpliconArchitect (AA) reconstruction. **(A)** SCLC cell lines established at the NCI-Navy Medical Oncology Branch from 1977-1992, with treatment histories as reported in Phelps et al., 1996 (83). For this subset, WGS performed as part of the Cancer Cell Line Encyclopedia project (60). *MYC* paralog CN and AA reconstruction were reported in Pongor et al., 2023 (44). **(B)** Patient tumor samples with WGS and treatment histories as reported in George et al., 2015 (61), and *MYC* paralog CN and AA reconstruction as reported in Pongor et al., 2023 (44). **(C)** PDX models with *MYC* paralog CN estimated by segmented exon analysis misses 5/8 ec*MYC/N/L* identified by AA reconstruction. **(D)** PDX models with *MYC* paralog CN estimated by unsegmented (raw) exon analysis finds all 8 ec*MYC/N/L* amplifications, without false positives. **(E-F)** Maximum CN of *MYC*, *MYCL*, or *MYCN* in SCLC patient tumor samples, with whole exome sequencing and annotated treatment histories (untreated vs. relapsed) as reported in Wagner et al., 2018 (62). Post-relapse samples were obtained from 30 patients, with multiple biopsies from 2 patients (SCLC11 and SCLC18). For 12/30 patients, samples obtained prior to treatment were also reported. **(E)** Segmented CN analysis identified only 2 patients with relapsed samples harboring high-level *MYC* paralog amplifications (CN > 10 in SCLC24 and SCLC30). **(F)** Unsegmented CN analysis identified 4 additional patients with relapsed samples harboring *MYC* paralog amplifications with CN > 45 (SCLC25, SCLC22, SCLC6, and SCLC 15). No *MYC* paralog amplifications were detected among the untreated samples, including patient SCLC 6 for which the paired relapsed sample had *MYCN* CN = 53. (created with BioRender.com)