Supplementary Fig. S1 Consort Diagram

Registered (n=50)

Withdrew before C1D15 (n=2)

Unable to obtain C1D15 Ki67 (n=3)
- 2 unable to visualize tumor for C1D15 biopsy
- 1 had insufficient tissue on biopsy

Evaluable for Primary Endpoint (CCCA C1D15) **(n=45)**

PIK3CA Mut (n=16)
PIK3CA WT (n=28)
PIK3CA unknown (n=1)

Off study due to C1D15 Ki67 >10% (n=4)

C1D15 Ki67 $\leq$10% (n=41)

Off study due to Goserelin E2 failure (n=1)

Off Therapy Early (n=2)
- 1 withdrew treatment in C1
- 1 physician decision, off in C1

Completed at least 3 cycles of combination therapy (n=38)

Off study drug post C3 (n=1)

No surgery (n=1)

n=36

Completed Study Therapy and Surgery (n=39) $\leftarrow$ n=3

(10 patients received cycle 5 therapy prior to surgery, including 8 discontinued palbociclib the day prior to surgery)
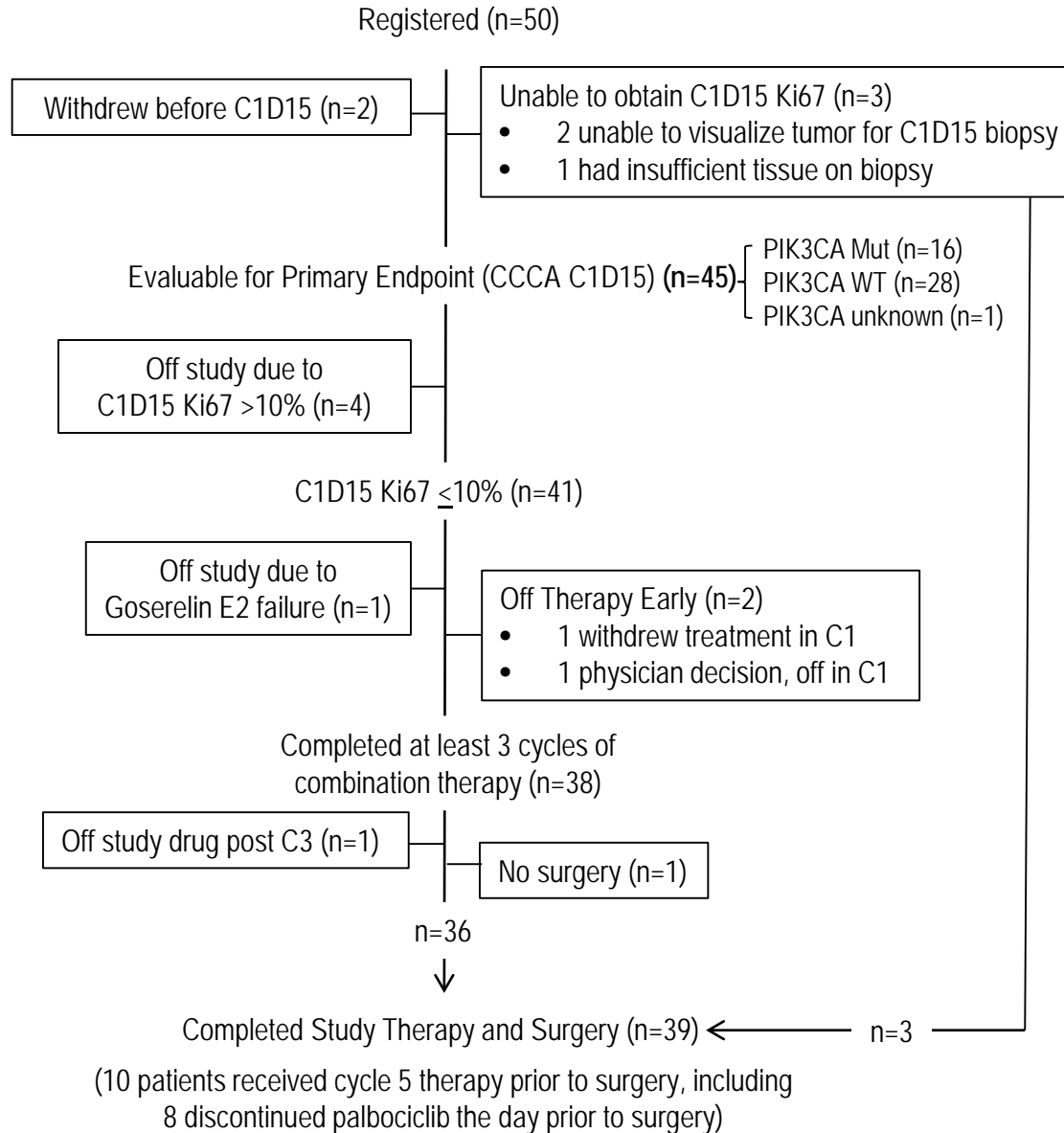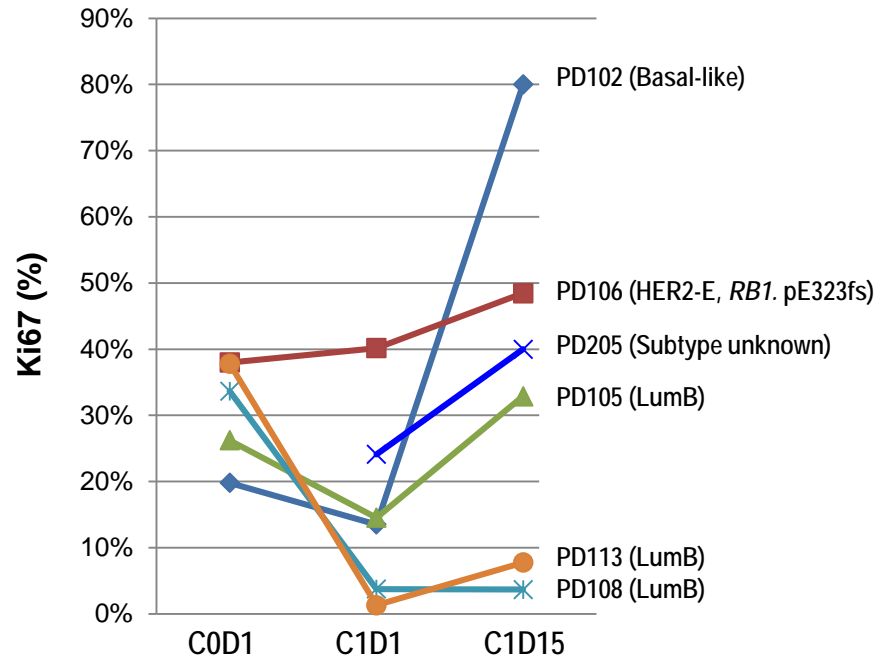
Supplementary Fig. S2 Clinicopathologic and molecular features of the 6 palbociclib resistant tumors

PD102: 49 year-old premenopausal woman with grade 3, ER+/PgR+ invasive ductal carcinoma (IDC) that was basal-like and carried mutations in *TP53* (S127F), in addition to *NCOR1* and *PIK3R1*.

PD106: 59 year-old postmenopausal woman with grade 3, ER+/PgR+ IDC that was HER2-E and carried mutations in *TP53* (K132N/M), *RB1* (E323fs), *PTEN* (T319fs), *MLL2*, and *MALAT1*
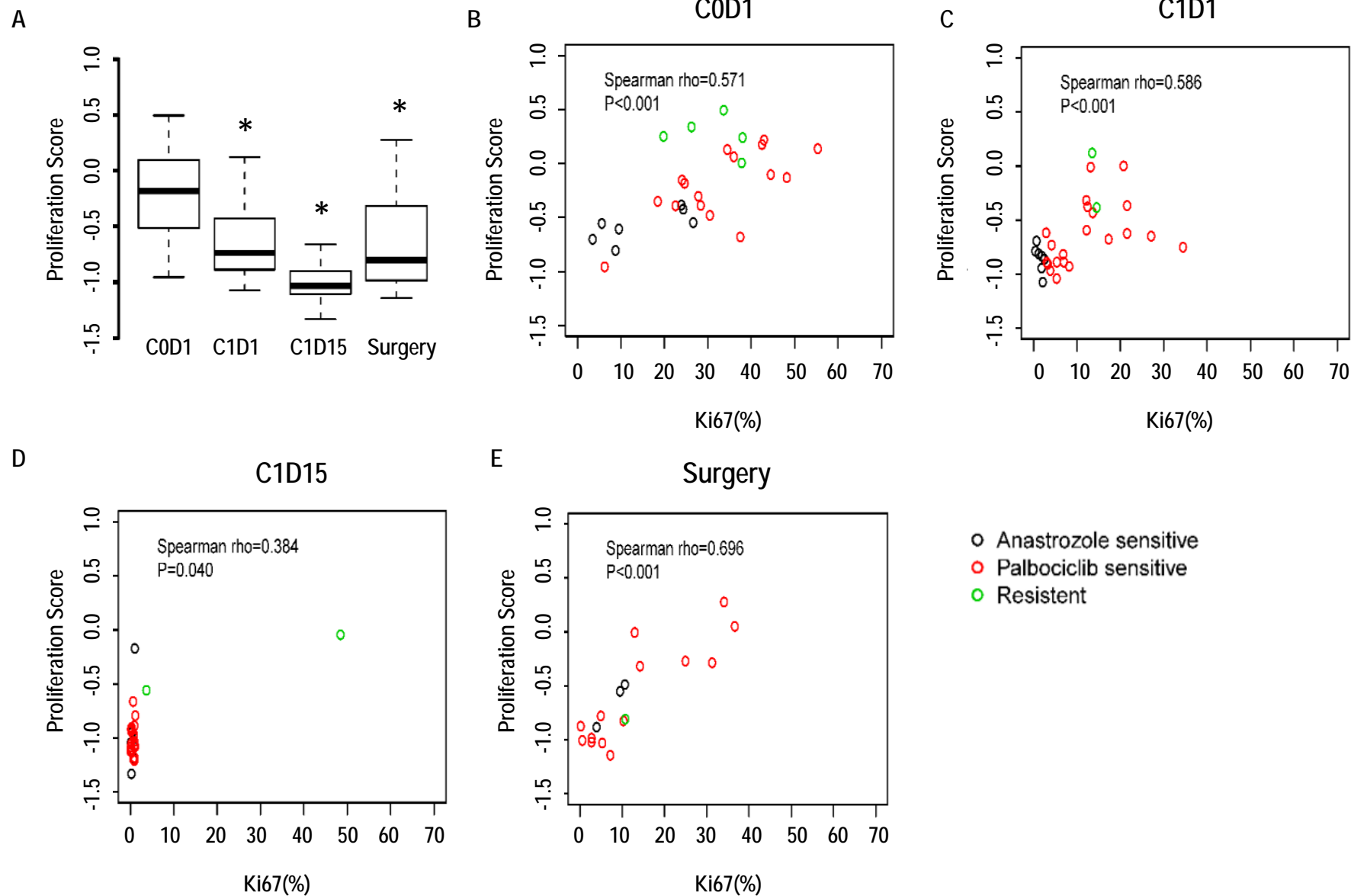
PD205: 40 year-old premenopausal woman with grade 2 ER+/PgR+ IDC of unknown subtype or mutations.

PD105: 64 year-old postmenopausal woman with grade 1 ER+/PgR- IDC that was LumB and without detectable tier 1 mutations in the 83 genes sequenced.

PD113: 57 year-old postmenopausal woman with grade 2 ER+/PgR+ ILC that was LumB and with mutations in multiple genes including *ATR, MAP3K1, GATA3, MLL, BRCA2, FOXA1, AKT1,* and *CDH1*.
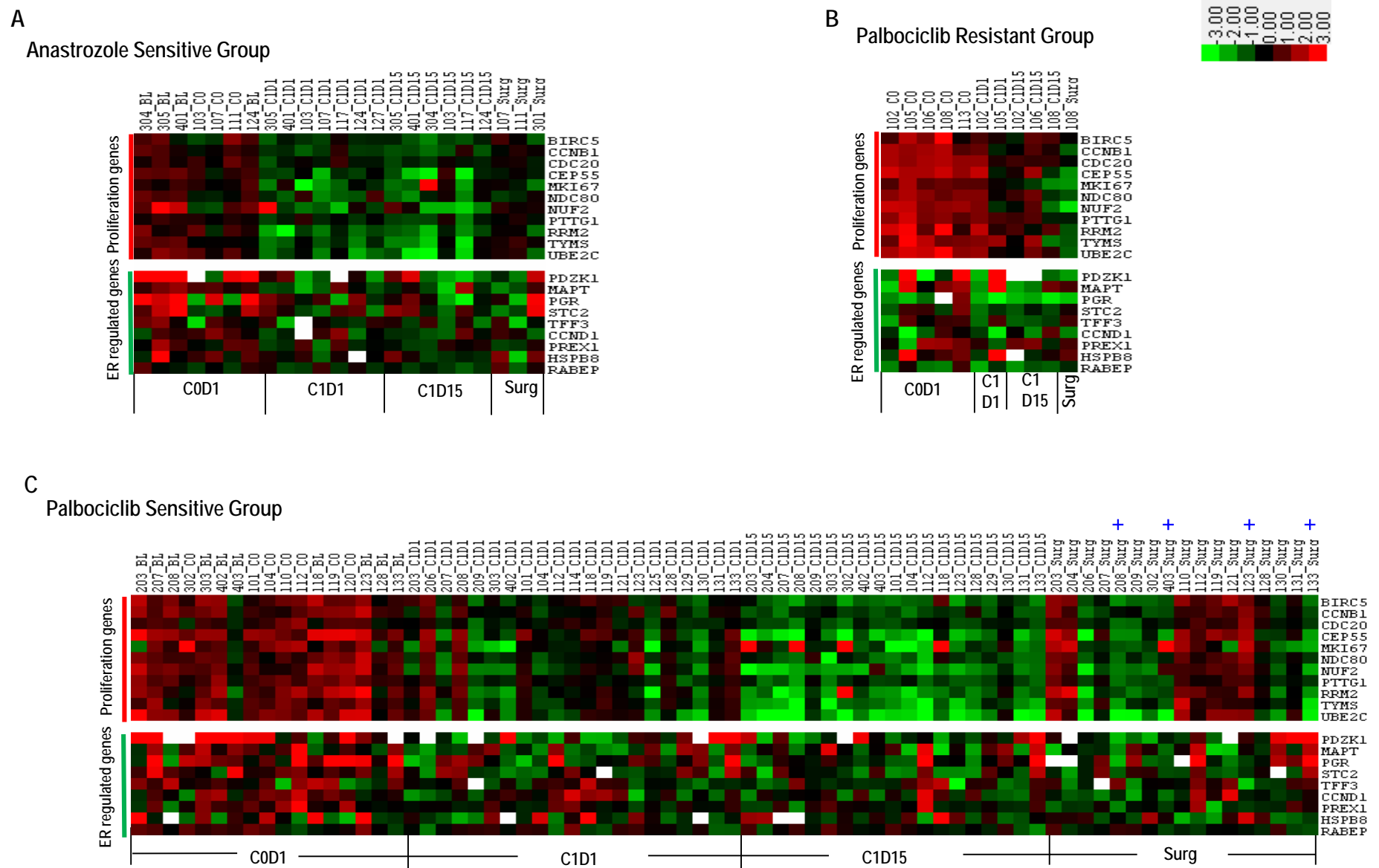
PD108: 58 year-old postmenopausal woman with grade 2 ER+/PgR- IDC that was LumB and carried *TP53* T18fs.

Supplementary Fig. S3 PAM50 11-gene proliferation score by time points (A) and its correlation to Ki67 at different time points, baseline (C0D1) (B), C1D1 (C), C1D15 (D), and at surgery (E).

Ki67 response of each individual tumor is annotated by the color of circle in panels B-D. * indicates p <0.005 when the proliferation scores were compared to that of the previous time point.

Supplementary Fig. S4 Heatmap of the 11 PAM50 proliferation genes and 9 ER regulated genes of individual tumor at each time point for the anastrozole sensitive group (A), palbociclib resistant group (B), and palbociclib sensitive group (C)