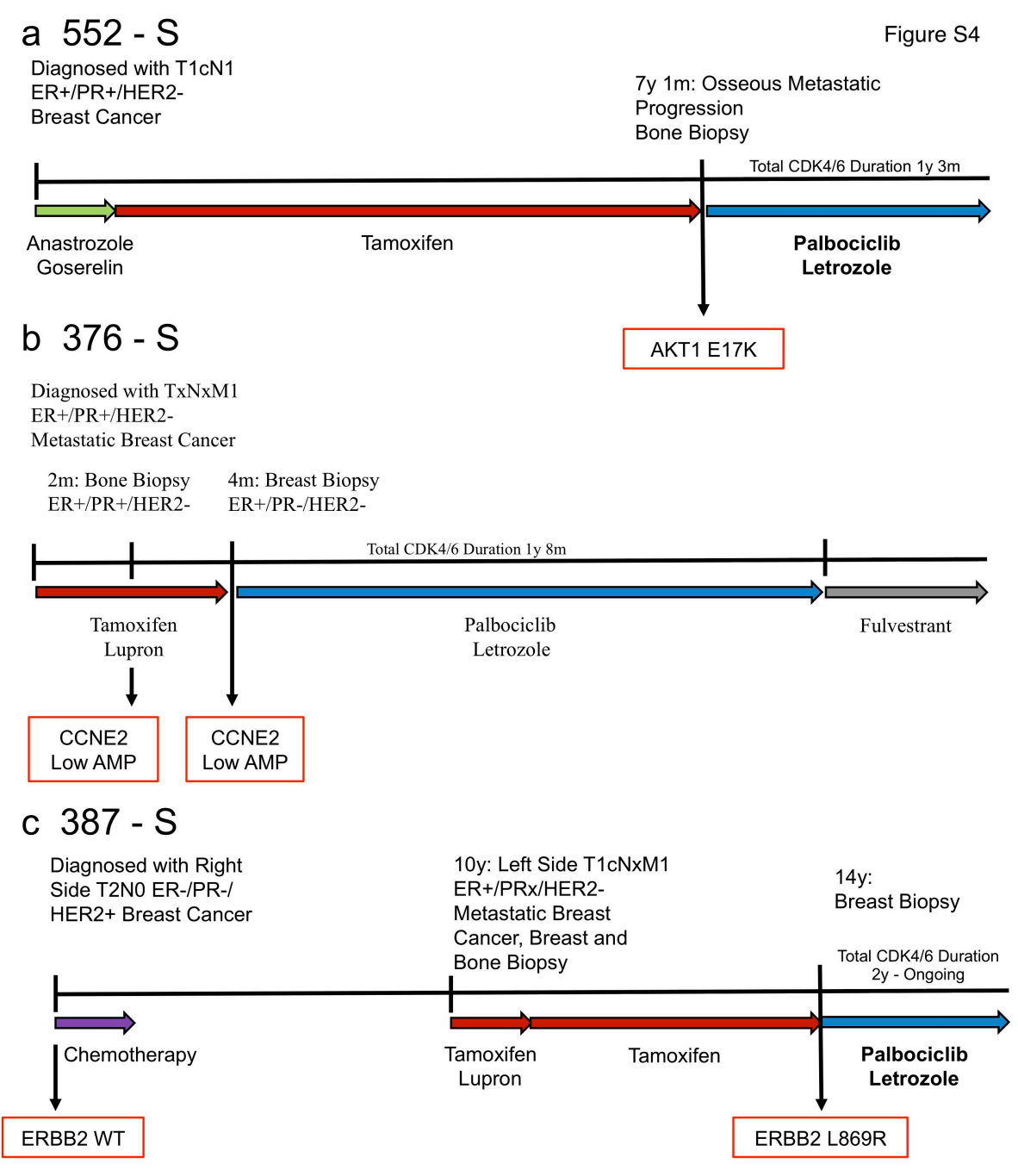
Figure S4


a 552 - S
Diagnosed with T1cN1
ER+/PR+/HER2-
Breast Cancer
7y 1m: Osseous Metastatic
Progression
Bone Biopsy
Total CDK4/6 Duration 1y 3m
Anastrozole
Goserelin
Tamoxifen
Palbociclib
Letrozole
AKT1 E17K
b 376 - S
Diagnosed with TxNxM1
ER+/PR+/HER2-
Metastatic Breast Cancer
2m: Bone Biopsy
ER+/PR+/HER2-
4m: Breast Biopsy
ER+/PR-/HER2-
Total CDK4/6 Duration 1y 8m
Tamoxifen
Lupron
Palbociclib
Letrozole
Fulvestrant
CCNE2
Low AMP
CCNE2
Low AMP
c 387 - S
Diagnosed with Right
Side T2N0 ER-/PR-/
HER2+ Breast Cancer
10y: Left Side T1cNxM1
ER+/PRx/HER2-
Metastatic Breast
Cancer, Breast and
Bone Biopsy
14y:
Breast Biopsy
Total CDK4/6 Duration
2y - Ongoing
Chemotherapy
Tamoxifen
Lupron
Tamoxifen
Palbociclib
Letrozole
ERBB2 WT
ERBB2 L869R

Supplemental Figure 4. Candidate resistance mutations in representative patients – key counterexamples.

Biopsies demonstrating CDK4/6i sensitivity despite the presence of putative resistance drivers were identified and clinical vignettes were generated. (a) A patient with bone-only metastatic progression was placed on first-line CDK4/6i and letrozole. A canonical AKT1 E17K alteration was identified at the time of metastatic progression. This patient has had stable osseous metastatic disease on interval repeat imaging and remained on treatment at the time of data cutoff. (b) A patient with de novo metastatic HR+/HER2- breast cancer was treated with tamoxifen and subsequently received palbociclib and letrozole. Prior to CDK4/6i exposure, which lasted for a duration exceeding one year, a baseline low-level amplification in CCNE2 was identified. (c) A patient was diagnosed with localized HR-/HER2+ breast cancer and treated with chemotherapy. Late metastatic relapse occurred with a new contralateral tumor, now HR+/HER2-. Following progression on tamoxifen, and prior to treatment with CDK4/6i and letrozole, an ERBB2 mutation was identified. Despite the presence of this alteration, the patient has had a durable ongoing response to CDK4/6i-based treatment.