Current Trends & Future Directions in Bedside to Bench Translational Research in ER+ Breast Cancer

Carlos L. Arteaga, MD
Professor of Medicine
Director, UTSW Harold C. Simmons Comprehensive Cancer Center
Lisa K. Simmons Distinguished Chair in Comprehensive Oncology
Associate Dean of Oncology Programs
Disclosures

• **Grant support**
  – Pfizer, Lilly, Radius, PUMA Biotechnology, Bayer, Takeda

• **Advisory role**
  – Abbvie, Novartis, Lilly, Sanofi, Radius, TAIHO Oncology, PUMA Biotechnology, Merck, H3Biomedicine, Symphogen, OrigiMed

• **Stock options**
  – Provista, Y-TRAP

• **Scientific Advisory Board**
  – Susan G. Komen for the Cure Breast Cancer Foundation
Approaches to Discover Mechanisms of Endocrine Resistance in ER+ Breast Cancer

- **Short presurgical** (aka, ‘window’) and neoadjuvant therapeutic trials
- Biopsy and molecular profiling of recurrent (drug-resistant) metastases
- Interrogation of exceptional responders to targeted therapies
# Endocrine Resistance: Mechanisms and Targeted Therapies

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- **Short presurgical** (aka, ‘window’) and neoadjuvant therapeutic trials
- Biopsy and molecular profiling of recurrent (drug-resistant) metastases
- Interrogation of exceptional responders to targeted therapies
Profiling ER+ breast cancer to discover mechanisms of resistance

Glitiande et al. Science Trans Med 2017

Baseline biopsy

37%

2 wks post-letrazole

0%
Profiling ER+ breast cancer to discover mechanisms of resistance

Sensitive (n = 78, 56%)  
\( \text{In} \leq 1.0 \) (≤27%)

Intermediate (n = 32, 23%)  
\( \text{In} > 1.1 \) and <1.9

Resistant (n = 30, 21%)  
\( \text{In} \geq 2.0 \) (≥74%)

Amplification  
CCND1 and FGFR1

ESR1 fusions

Glitnane et al Science Trans Med 2017
Most frequent recurrent somatic alterations associated with resistance to estrogen deprivation (letrozole)

<table>
<thead>
<tr>
<th></th>
<th>% MUT</th>
<th>% AMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8p12 WHSC1L1</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>8p12 FGFR1</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>11q13 CCND1</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>11q13 FGF3,4,19</td>
<td></td>
<td>*</td>
</tr>
</tbody>
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Fisher’s Exact
* p≤0.05
** p≤0.01
ER+/FGFR1-amplified PDXs do not shrink with fulvestrant alone but are potently inhibited by fulvestrant and FGFR TKI lucitanib

CDK4/6 inhibitors are first-line therapy in advanced ER+ breast cancer

PALOMA2

MONALEESA2

MONARCH3

Finn et al NEJM 2016

Hortobagyi et al NEJM 2016

De Leo et al JCO 2017
Dual blockade of the ER pathway with ER and CDK4/6 inhibitors
CCNE1 mRNA overexpression in presurgical studies correlates with resistance to CDK4/6 inhibitors

POP Trial
2 weeks Palbociclib

NeoPalAna
Anastrozole → Palbociclib


Ma C et al CCR 2017
Implications

• Neoadjuvant and short term presurgical trials can be used as a platform to discover mechanisms of antiestrogen resistance

• And also to identify patients that can be considered for treatment with adjuvant targeted therapies (i.e., CDK4/6 inhibitors)
Approaches to Discover Mechanisms of Endocrine Resistance in ER+ Breast Cancer

- Short presurgical (aka, ‘window’) and neoadjuvant therapeutic trials
- **Biopsy and molecular profiling of recurrent (drug-resistant) metastases** – including plasma ctDNA
- Interrogation of exceptional responders to targeted therapies
ER+ breast cancer evolution under endocrine therapy (Razavi et al. Cancer Cell 2018)

- WES in 30 treatment-naïve primary tumors, post-progression (hormonal therapy) specimen, and matched normal control
- Acquired mutations not found in primary tumors, including with higher depth sequencing using MSK-IMPACT (sensitivity to 1.3% of cancer cells)
- Additional targeted sequencing on matched pre- and post progression tumors from 44 additional patients
- Acquired mutations often subclonal

ERBB2 (82%) and EGFR (60%) of alterations present prior to therapy
NF1, KRAS, MAP2K1, and BRAF mutations usually acquired
~50% of MYC, FOXA1, and CTCF alterations present before therapy

n=74 (pre- and post-progression matched biopsies)
Loss of the FAT1 Tumor Suppressor Promotes Resistance to CDK4/6 Inhibitors via the Hippo Pathway

Li Z, .... Chandarlapaty S. Cancer Cell 2018
Loss of FAT1 tumor suppressor promotes resistance to CDK4/6 inhibitors via Hippo pathway-dependent CDK6 overexpression

Li Z, .... Chandarlapaty S. Cancer Cell 2018
FGFR pathway alterations in ctDNA are associated with progression on CDK4/6 inhibitors

Guardant 360 (plasma tumor DNA):
14/34 (41%) FGFR pathway alterations:
- 9/34 FGFR1 amplification
- 2/34 FGFR2 amplification
- 1/34 FGFR1 mutation (N546K)
- 2/34 FGFR2 mutation (N549K, V395D)
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Approaches to Discover Mechanisms of Endocrine Resistance in ER+ Breast Cancer

• Short presurgical (aka, ‘window’) and neoadjuvant therapeutic trials

• Biopsy and molecular profiling of recurrent (drug-resistant) metastases

• Interrogation of exceptional responders to targeted therapies
Extraordinary response of patient with breast cancer to HER2 (ERBB2) tyrosine kinase inhibitor neratinib

ERBB2 mutant (L755_E757delinsS) ER+/HER2– breast carcinoma

Baseline 8 weeks 16 weeks

Confirmed PR: 70% reduction by RECIST following neratinib monotherapy
HER2 (ERBB2) mutations occur in 2-4% of breast cancers.
HER2-T798I gatekeeper mutation mediates acquired resistance to neratinib

HER2 L869R lobular breast cancer

untreated 100 nM neratinib 1 µM neratinib

WT L869R vector

Progression on neratinib

Neratinib clinical trial

Baseline Post-Treatment (20 days)

Hanker et al. Cancer Discovery 2017
Efficacy in HER2-mutant tumors by cancer type

Response criteria:
- RECIST 1.1
- PET response criteria
- Not evaluated

*No target lesion measurement

Allele/domain:
- S310 hotspot
- Kinase domain hotspot
- Exon20 insertion hotspot
- Other hotspot
- Non-hotspot

Treatment:
- Ongoing
- Off

Hyman et al. Nature 2017
HER2 mutations confer resistance to estrogen deprivation and to fulvestrant

**Growth in Estrogen Deprivation**

<table>
<thead>
<tr>
<th></th>
<th>WT</th>
<th>G309A</th>
<th>L755S</th>
<th>V777L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell Count x10^4/mL</td>
<td>10</td>
<td>5</td>
<td>15</td>
<td>20</td>
</tr>
</tbody>
</table>

**Long Term Estrogen Deprivation**

**Growth in 1 μM Fulvestrant**

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<th>L755S</th>
<th>V777L</th>
</tr>
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<tbody>
<tr>
<td>% Viability compared to DMSO control</td>
<td>ns</td>
<td>10</td>
<td>20</td>
<td>30</td>
</tr>
</tbody>
</table>

**ERE Reporter Assay**

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>Estradiol</th>
<th>Fulvestrant</th>
<th>Fulv + E2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fold Change of Relative to DMSO controls</td>
<td>1.0</td>
<td>1.5</td>
<td>2.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>
Estrogen rescues ER+/HER2 mutant cells: Combined blockade of HER2 and ER is required

Figure 1
SUMMIT study design (Amendment 4)

**Key inclusion criteria**
- Documented HER2 mutation (locally assessed)
- ECOG status of 0 to 2

**HER2-mutant tumors**

**Key exclusion criteria**
- Prior treatment with any pan-HER TKI (eg, lapatinib, afatinib, dacomitinib, neratinib)
- Symptomatic or unstable brain metastases

**Breast HR+**
- Neratinib + fulvestrant

**Breast HR−**
- Neratinib monotherapy

**Bladder**
- Neratinib + Paclitaxel

**Biliary tract**
- Neratinib monotherapy

**Cervical**

**Ovarian**

**Salivary gland**

**Solid tumors (NOS)**

**Primary endpoint**
- Objective response rate at first (8wks) post-baseline tumor assessment (ORR₈)

**Secondary endpoints**
- ORR (confirmed)
- Duration of response (DoR)
- Clinical benefit rate (CBR)
- Progression-free survival (PFS)
- Safety
- Biomarkers

**Simon 2-stage design**
- If ≥1 response in first evaluable 7 patients, expand cohort to Stage 2 (N=18)
- If ≥4 responses in Stage 2, expand or breakout

**Tumor assessments**
- RECIST v1.1 (primary criteria)
- PET response criteria (RECIST non-evaluable)

**Statistical methods**
- ORR₈, ORR, CBR: associated 95% CI
- Median PFS: KM estimate with 95% CI

Neratinib: oral 240 mg daily
Fulvestrant: intramuscular 500 mg on day 1, 15 and 29; once every 28 days thereafter (labeled dose)
Paclitaxel: intravenous 80 mg/m² on day 1, 8 and 15; every 28 days
Loperamide prophylaxis: oral 12 mg days 1–14, 8 mg days 15–18; as needed thereafter
Figure 3

Waterfall plot – best % change in tumor size

Not shown: 5 patients in whom no % change in tumor size could be calculated (n=1 died before first post-baseline assessment; n=1 ended treatment due to AEs before first post-baseline assessment; n=3 non-target lesions only)
HER2 kinase domain mutations exhibit enhanced dimerization with HER3 (ERBB3)

**HER3**

1% Input

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<td>HER2</td>
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<tr>
<td>HER2</td>
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<tr>
<td>GAPDH</td>
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**IP: HER3**

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**p-HER3 Y1197**

N = 200 nM Neratinib  F = 1 μM Fulvestrant

**HER2**

- p110α
- p85
- PI3K
- AKT
- TK

**HER3**

- HER3
- p-HER3 Y1197
- HER3
- GAPDH

**siRNA HER3**

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<th></th>
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<th>II</th>
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<td>HER3</td>
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<td></td>
<td></td>
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<td>p-p70</td>
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**Cell Count x 10^4/mL**

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<th></th>
<th>Control</th>
<th>SiRNA I</th>
<th>SiRNA II</th>
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<tbody>
<tr>
<td>F</td>
<td>-</td>
<td>-</td>
<td>-</td>
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**V777L**

**Her2 kinase domain mutations exhibit enhanced dimerization with HER3 (ERBB3)**

Croessmann *et al.* *Clin. Cancer Res.* 2018
HER2 kinase domain mutations rely on PI3K/AKT/mTOR signaling
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**PIK3CA** (p110α) mutations are gain-of-function oncogenes

MCF10A cells

Vector | Wild-type | E545K | H1047R

DMSO

BKM120

Chakrabarty *et al*. Oncogene 2010
Gain of interaction of p110α helical domain mutants with IRS-1 is required for its oncogenicity

Combination of PI3Kα inhibitor alpelisib and letrozole is active against breast cancers with mutant PIK3CA

Duration on therapy: Letrozole + BYL719 (alpelisib)

**PIK3CA mutation**

- H1047R
- E542K
- E545K
- H1047R, E542Q
- E545K, I273V
- H1047R
- Q546K
- H1047R
- E545K, I273V
- C420R
- H1047R, E542Q
- E545K
- E545K
- E542K
- D939G, E78K, E726K
- Q546P
- E545K
- H1047R

**Patients**

- Duration on therapy: Letrozole + BYL719 (alpelisib)

- Best response (RECIST)
  - PD
  - SD
  - PR
  - Toxicity

SOLAR-1: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial (NCT02437318)\(^1\)

**Men or postmenopausal women with HR+, HER2− ABC**
- Recurrence/progression on/after prior AI
- Identified PIK3CA status (in archival or fresh tumor tissue\(^a\))
- Measurable disease or ≥ 1 predominantly lytic bone lesion
- ECOG performance status ≤ 1 (N = 572)

**PIK3CA-mutant cohort (n = 341)**

**PIK3CA-non-mutant cohort (n = 231)**

- The primary endpoint included all randomized patients in the PIK3CA-mutant cohort; PFS was analyzed in the PIK3CA-non-mutant cohort as a proof of concept
- Safety was analyzed for all patients who received ≥ 1 dose of study treatment, in both cohorts

**Primary endpoint**
- PFS in PIK3CA-mutant cohort (locally assessed)

**Secondary endpoints include**
- OS (PIK3CA-mutant cohort)
- PFS (PIK3CA-non-mutant cohort)
- PFS (PIK3CA mutation in ctDNA)
- PFS (PIK3CA-non-mutant in ctDNA)
- ORR/CBR (both cohorts)
- Safety

---

\(^a\) More than 90% of patients had mutational status identified from archival tissue.

\(^b\) Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28-day cycles.


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Primary Endpoint: Locally Assessed PFS in the *PIK3CA*-mutant Cohort$^{1,a}$

<table>
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<tr>
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<th>ALP + FUL (n = 169)</th>
<th>PBO + FUL (n = 172)</th>
</tr>
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<tbody>
<tr>
<td>Number of PFS events, n (%)</td>
<td>103 (60.9)</td>
<td>129 (75.0)</td>
</tr>
<tr>
<td>Progression</td>
<td>99 (58.6)</td>
<td>120 (69.8)</td>
</tr>
<tr>
<td>Death</td>
<td>4 (2.4)</td>
<td>9 (5.2)</td>
</tr>
<tr>
<td>Censored</td>
<td>66 (39.1)</td>
<td>43 (25.0)</td>
</tr>
<tr>
<td>Median PFS (95% CI)</td>
<td>11.0 (7.5-14.5)</td>
<td>5.7 (3.7-7.4)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.65 (0.50-0.85)</td>
<td></td>
</tr>
<tr>
<td>One-sided $P$ value</td>
<td>0.00065</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

At final PFS analysis, superiority was declared if one-sided, stratified log-rank test $P$ value was ≤ 0.0199 (Haybittle–Peto boundary).

$^a$ Mutation status determined from tissue biopsy.


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Best Percentage Change in Sum of Target Lesion Diameters Based on Local Investigator Assessment in PIK3CA-mutant Cohort\textsuperscript{a,b}

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<td>Decrease in best percentage change from baseline</td>
<td>75.86%</td>
<td>43.51%</td>
</tr>
<tr>
<td>Increase/zero change in best percentage change from baseline</td>
<td>18.10%</td>
<td>35.88%</td>
</tr>
<tr>
<td>Percent change in target lesion contradicted by overall lesion response = PD</td>
<td>6.03%</td>
<td>20.61%</td>
</tr>
</tbody>
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PD, progressive disease; UNK, unknown.

Patients for whom the best % change in target lesions was not available and patients for whom the best % change in target lesions was contradicted by overall lesion response = UNK were excluded from the analysis, percentages above use n as denominator. Only patients with measurable disease at baseline are presented.

\textsuperscript{a} Mutation status determined from tissue biopsy. \textsuperscript{b} Change from baseline in sum of target lesion diameters.

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Locally Assessed PFS by Tissue or Plasma ctDNA-determined Mutation Status

**PIK3CA** mutant patients determined by ctDNA

### Table: Locally Assessed PFS by Tissue or Plasma ctDNA-determined Mutation Status

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<tr>
<td></td>
<td>Event n/N</td>
<td>Median PFS</td>
<td>Event n/N</td>
<td>Median PFS</td>
</tr>
<tr>
<td>Patients with <strong>PIK3CA</strong> mutation: tissue</td>
<td>103/169 (60.9)</td>
<td>11.0</td>
<td>129/172 (75.0)</td>
<td>5.7</td>
</tr>
<tr>
<td>Patients with <strong>PIK3CA</strong> mutation: plasma</td>
<td>57/92 (62.0)</td>
<td>10.9</td>
<td>75/94 (79.8)</td>
<td>3.7</td>
</tr>
<tr>
<td>Patients without <strong>PIK3CA</strong> mutation: tissue</td>
<td>49/115 (42.6)</td>
<td>7.4</td>
<td>57/116 (49.1)</td>
<td>5.6</td>
</tr>
<tr>
<td>Patients without <strong>PIK3CA</strong> mutation: plasma</td>
<td>92/181 (50.8)</td>
<td>8.8</td>
<td>103/182 (56.6)</td>
<td>7.3</td>
</tr>
</tbody>
</table>

**Note:**
- ctDNA, circulating tumor DNA; HR, hazard ratio; PFS, progression-free survival; QD, once daily.
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Adverse events in the total population

<table>
<thead>
<tr>
<th>AEs ≥20% in either arm, %</th>
<th>Alpelisib + fulvestrant N=284</th>
<th>Placebo + fulvestrant N=287</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>282 (99.3)</td>
<td>183 (64.4)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>181 (63.7)</td>
<td>93 (32.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>164 (57.7)</td>
<td>19 (6.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>127 (44.7)</td>
<td>7 (2.5)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>101 (35.6)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Rash*</td>
<td>101 (35.6)</td>
<td>28 (9.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>77 (27.1)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>76 (26.8)</td>
<td>11 (3.9)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>70 (24.6)</td>
<td>7 (2.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>69 (24.3)</td>
<td>10 (3.5)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>58 (20.4)</td>
<td>5 (1.8)</td>
</tr>
</tbody>
</table>

- Eighteen patients (6.3%) discontinued alpelisib due to hyperglycemia and 9 patients (3.2%) due to rash; no patients discontinued placebo due to either hyperglycemia or rash
- Maculopapular rash was observed in 14.1% of patients (all-grade) and 8.8% (grade 3) in the alpelisib arm, vs 1.7% and 0.3%, respectively, in the placebo arm
- The safety profile of the alpelisib group and the placebo group was similar in PIK3CA-mutant and PIK3CA-non-mutant cohorts

*Single preferred term of “rash” does not include preferred term of “maculopapular rash”.

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Inhibition of PI3Kα blocks glucose uptake and increases insulin levels (Juric et al. JCO 2018)
Reduction in FDG uptake by PET correlates with clinical benefit from pan-PI3K inhibitor buparlisib

Mayer et al. JCO 2014
Insulin is highly elevated in the serum following treatment with PI3K inhibitors and remains high for hours.
Peak in serum glucose and serum insulin can be reduced by both a sodium-glucose transporter (SGLT) inhibitor and by a ketogenic diet. Metformin is not as effective.

SGLTi → ↓ glucose reabsorption in the kidney
Ketogenic diet → depletes glycogen, ↓ gluconeogenesis

Hopkins B, ..... Cantley L. Nature 2018
90 min post-dosing a PIK3CA mutant/PTEN-null endometrial tumor with BKM120, P-InsR increases and this increase is prevented when mice are on a ketogenic diet.

Implication: This insulin rebound partially maintains PI3K activity in Ins/IGF1R+ tumors and prevents complete inhibition of FDG uptake, thus limiting the effect of therapeutic inhibitors.
A ketogenic diet markedly improves response to PI3K inhibitors in orthotopic allografts of murine KRAS-mutant/TP53 deleted pancreatic cancer
Reasons why therapeutic inhibition of PI3K in cancer has not had a better outcome

- Mutant PIK3CA is a weak oncogene
- Lack of optimal patient selection
- ‘Dialing up’ inhibition of PI3K causes severe rash and hyperglycemia, thus inhibition of PI3K is suboptimal and transient
- Use of pan-PI3K (± mTOR) inhibitors with poor tolerance
- Therapeutic inhibition of PI3K is followed by compensatory upregulation of several RTKs (ERBB receptors, Ins/IGF-IR, FGFRs), ERα, BCL2
- Lack of emphasis on combination trials
- Insulin production is increased upon inhibition of PI3K
- Lack of mutant specific inhibitors

Hanker et al. Cancer Discovery 2019
Approaches to Discover Mechanisms of Endocrine Resistance in ER+ Breast Cancer

- Short presurgical (aka, ‘window’) and neoadjuvant therapeutic trials
- Biopsy and molecular profiling of recurrent (drug-resistant) metastases
- Interrogation of exceptional responders to targeted therapies → trials with targeted therapies, all informed by metastatic tumor profiling
- Big increase in combinations of targeted therapies with standard of care anti-ER therapy all informed by serially assessed tumor evolution
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Convergent PTEN-null phenotype developed by parallel evolution under selective pressure with BYL719