Novel Applications of CDK4/6 Inhibitors; Ongoing Clinical Trials

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- **Consultancy:**
  - AstraZeneca, Novartis, Pfizer, Eli Lilly, Roche/Genentech, Puma Biotechnology
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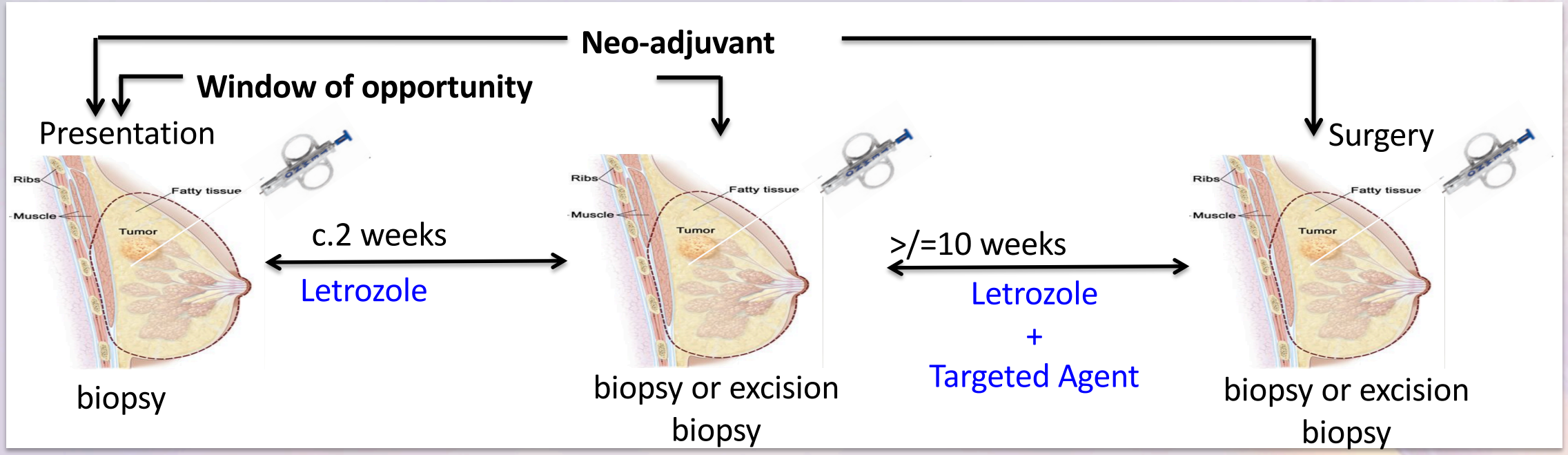
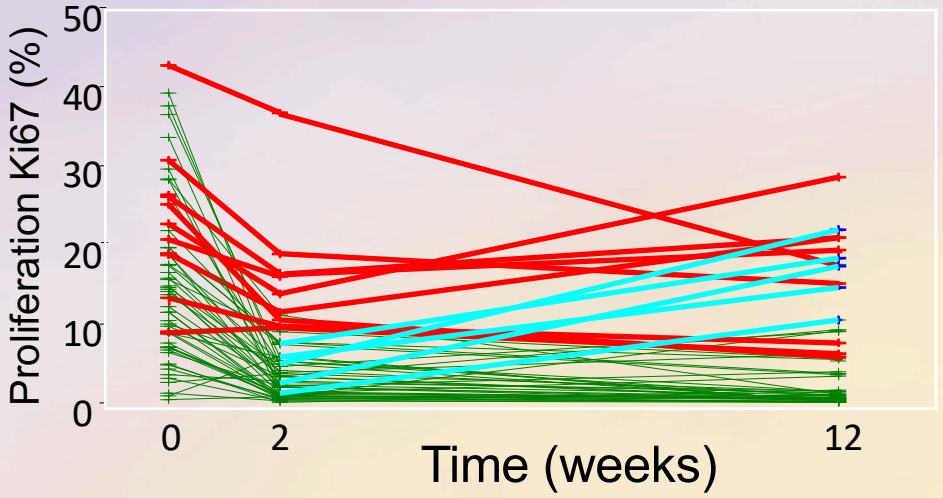
- **Research Funding to Institution:**
  - Pfizer, Puma Biotechnology, AstraZeneca

Improving Endocrine Responsiveness in ER+ Primary BC





- **Measure impact of CDK4/6 inhibition on E-independent Ki-67 (ie. de-novo or acquired endocrine resistance)**
- **Detect biomarkers for resistance / response**

Dowsett et al JNCI 2007 99; 167

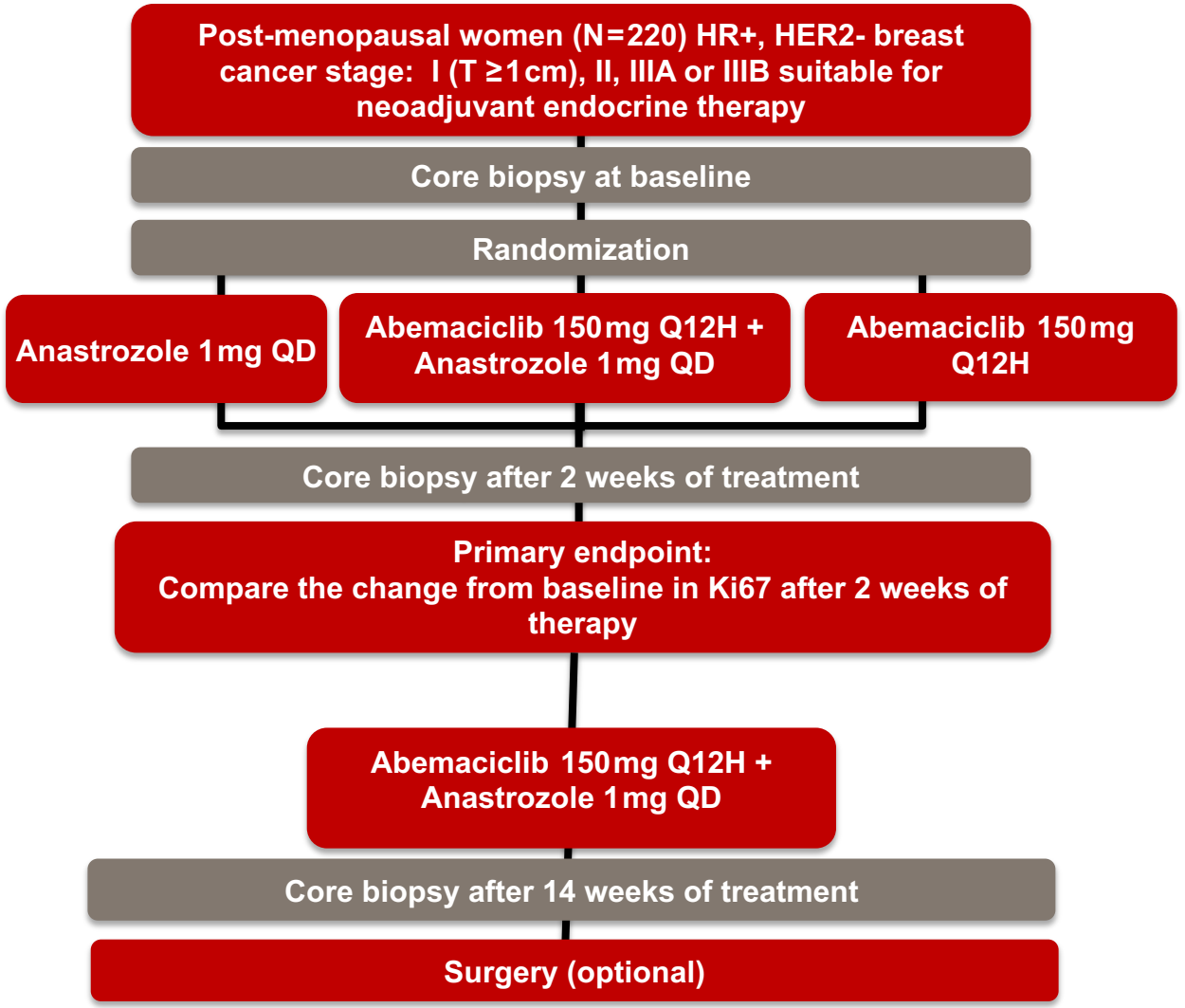
Phase 2 neoMONARCH Study Design

Rationale:

- Change in Ki67 at 2 weeks in neo-adjuvant studies may be predictive of improved disease-free survival in adjuvant studies.[1,2]

Secondary and exploratory objectives:

- Safety, clinical, radiologic and pathological response, cell cycle associated gene expression.



1. Dowsett M et al. *Clin Cancer Res* 2005; 11:951s-958s.
2. Dowsett M et al. *J Natl Cancer Inst.* 2011a;103(22):1656-1664.

Hurvitz S, et al. SABCS 2016 Oral Abstract S4-06

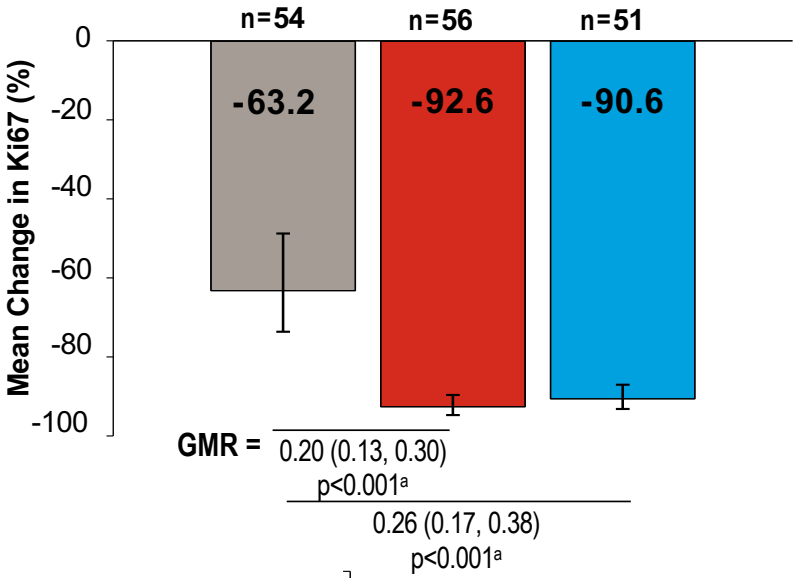
Ki67 Expression and Response at Week 2

Anastrozole 1 mg

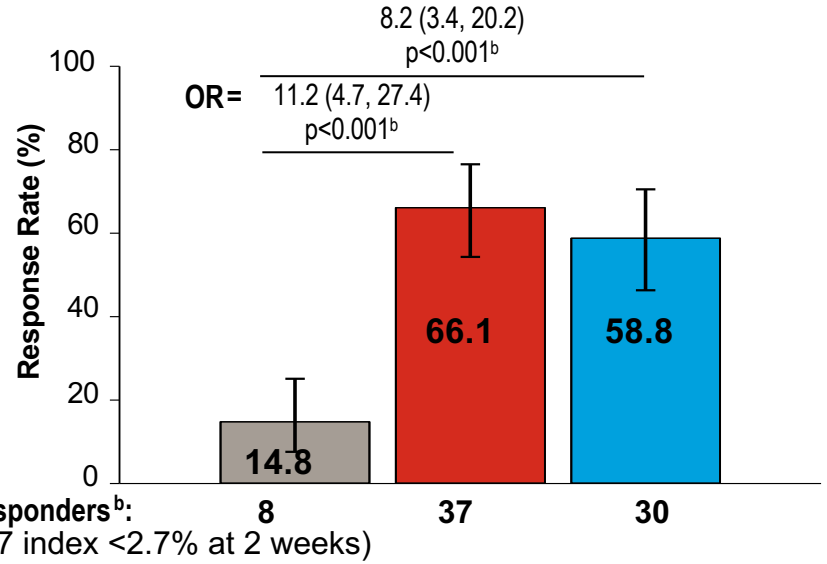
Abemaciclib 150 mg + Anastrozole 1 mg

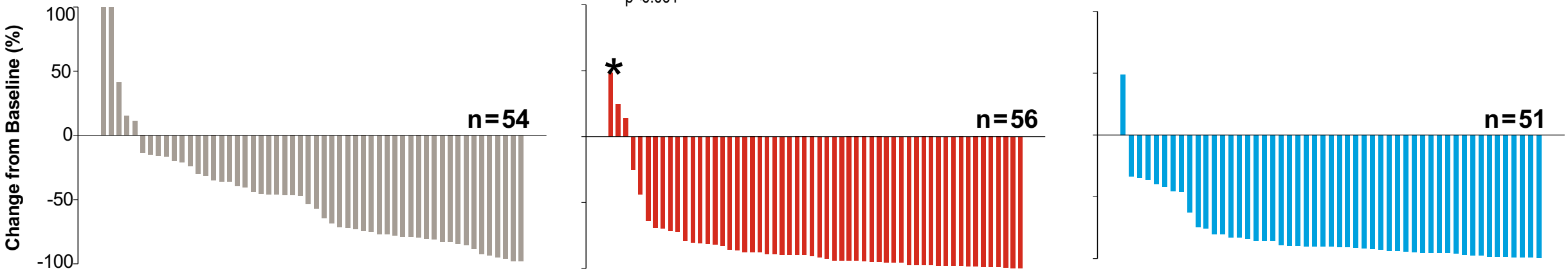
Abemaciclib 150 mg

Geometric Mean Change (Primary Endpoint of Study)



Complete Cell Cycle Arrest





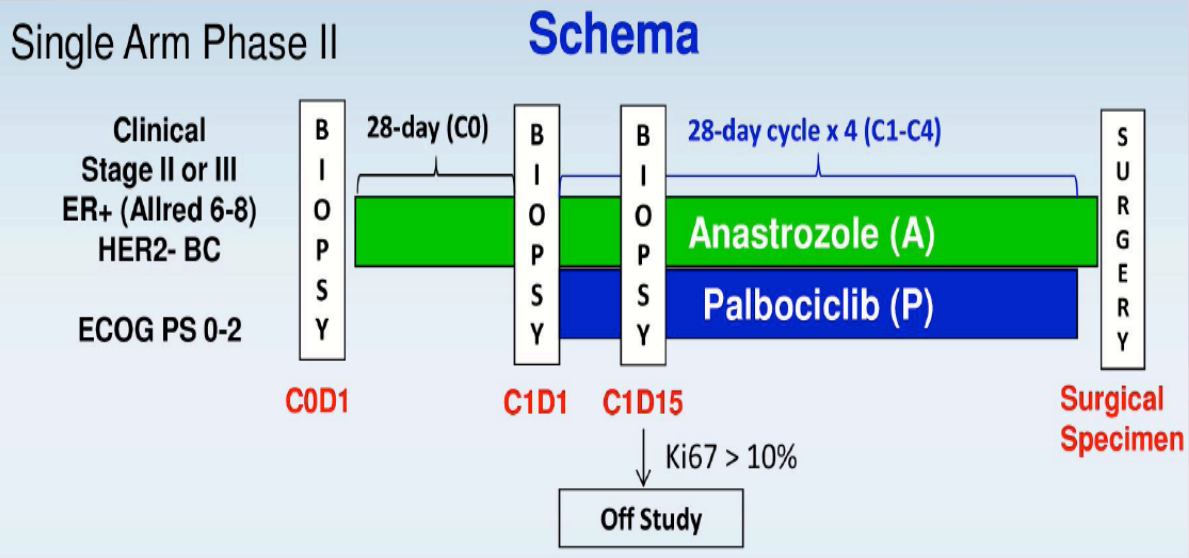
[a]Geometric Mean Ratio (GMR), 2-sided 90% confidence interval (CI), p-value. p-values are based on a one-sided hypothesis test from a linear model with treatment

[b]A responder is identified as a patient with a ln(Ki67) value of less than 1. Odds ratio (OR), 2-sided 90% CI, p value. p value is calculated by Fisher's Exact test of a one-sided hypothesis. * Patient had received dose intensity of 19% for abemaciclib prior to Week 2 biopsy.

Hurvitz S, et al. SABCS 2016 Oral Abstract S4-06

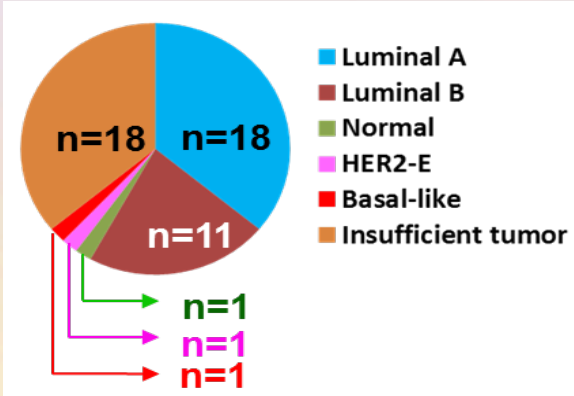
NeoPalAna: Ki67 response by intrinsic subtype:

Neo-adjuvant trial single arm
n = 50 patients HR +ve HER2 -ve

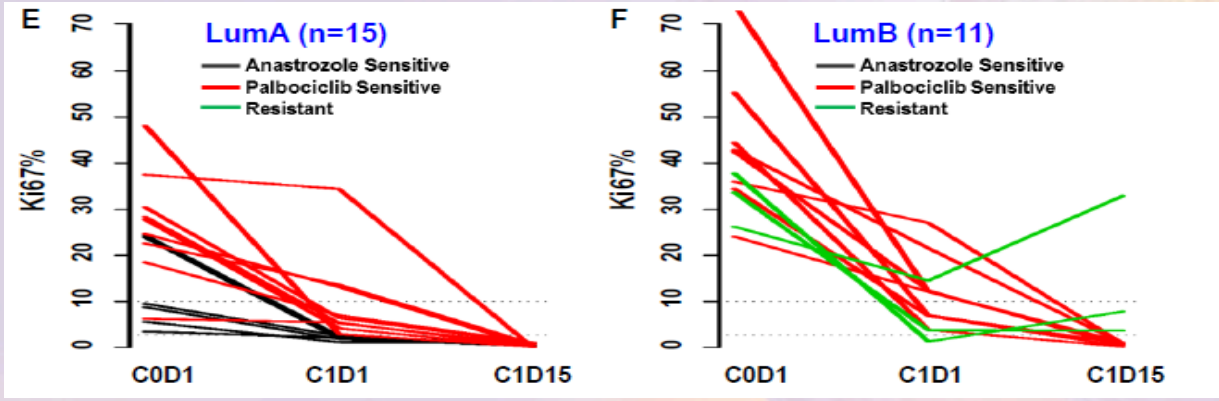


Primary Endpoint: Complete cell cycle arrest (CCCA), defined as Ki67 ≤2.7%, on C1D15 biopsy.

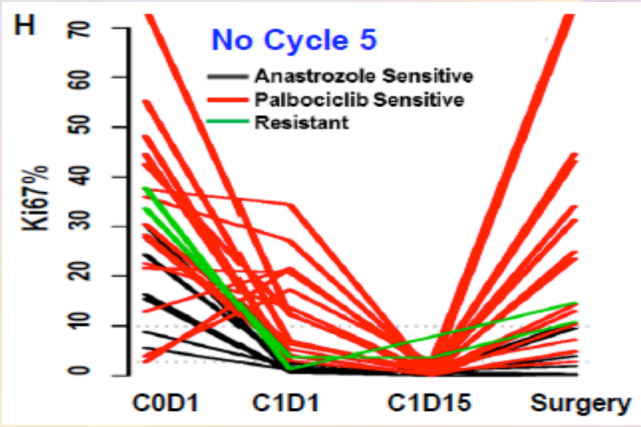
Secondary Endpoints: Clinical, radiographic, and pathologic response, safety profile



CDK4/6 active in luminal A/B
Potentially active in AI resistant?



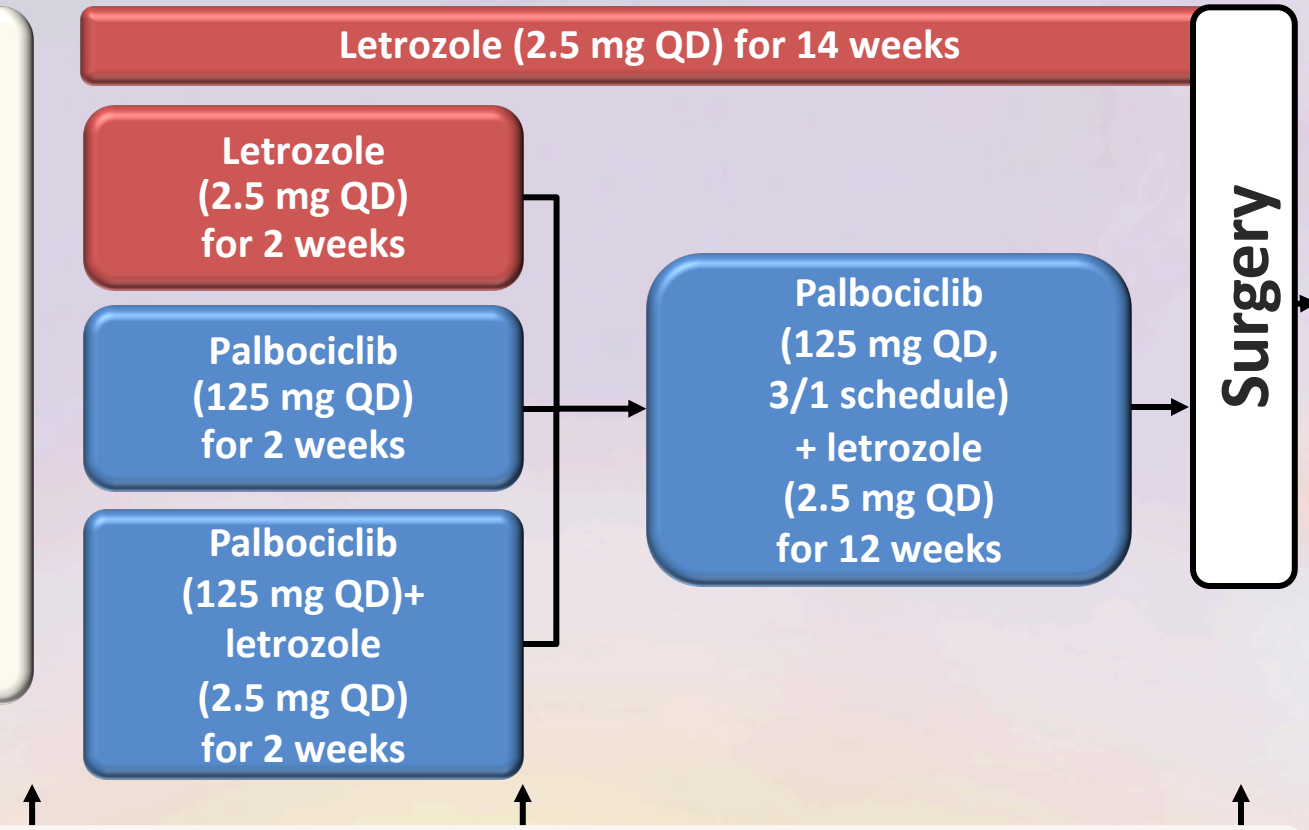
Rebound on stopping CDK4/6



Ma CX, et al. Clin Cancer Res 2017 23(15); 4055-65

Phase II Neo-adjuvant Study (PALLET)
RMH/ICR (UK) & NSABP (USA)

- Localized ER+ HER– invasive early BC (≥2 cm)
- Suitable for neoadjuvant therapy with letrozole
- Post-menopausal
- N=301



Tumour samples: biopsies taken before treatment, and at 2 and 14 weeks

Primary endpoint
- Change in the proliferation marker Ki67 from baseline to week 14
- Clinical response at week 14

Secondary endpoints
- Ki67 at 2 weeks
- ypCR after 14 weeks
- Complete Cell Cycle Arrest (CCCA)
- PEPI score at 14 weeks
- Safety & tolerability

Exploratory endpoints
- Biomarkers that predict benefit
- Molecular effects of therapy

ICR The Institute of Cancer Research

The ROYAL MARSDEN NHS Foundation Trust

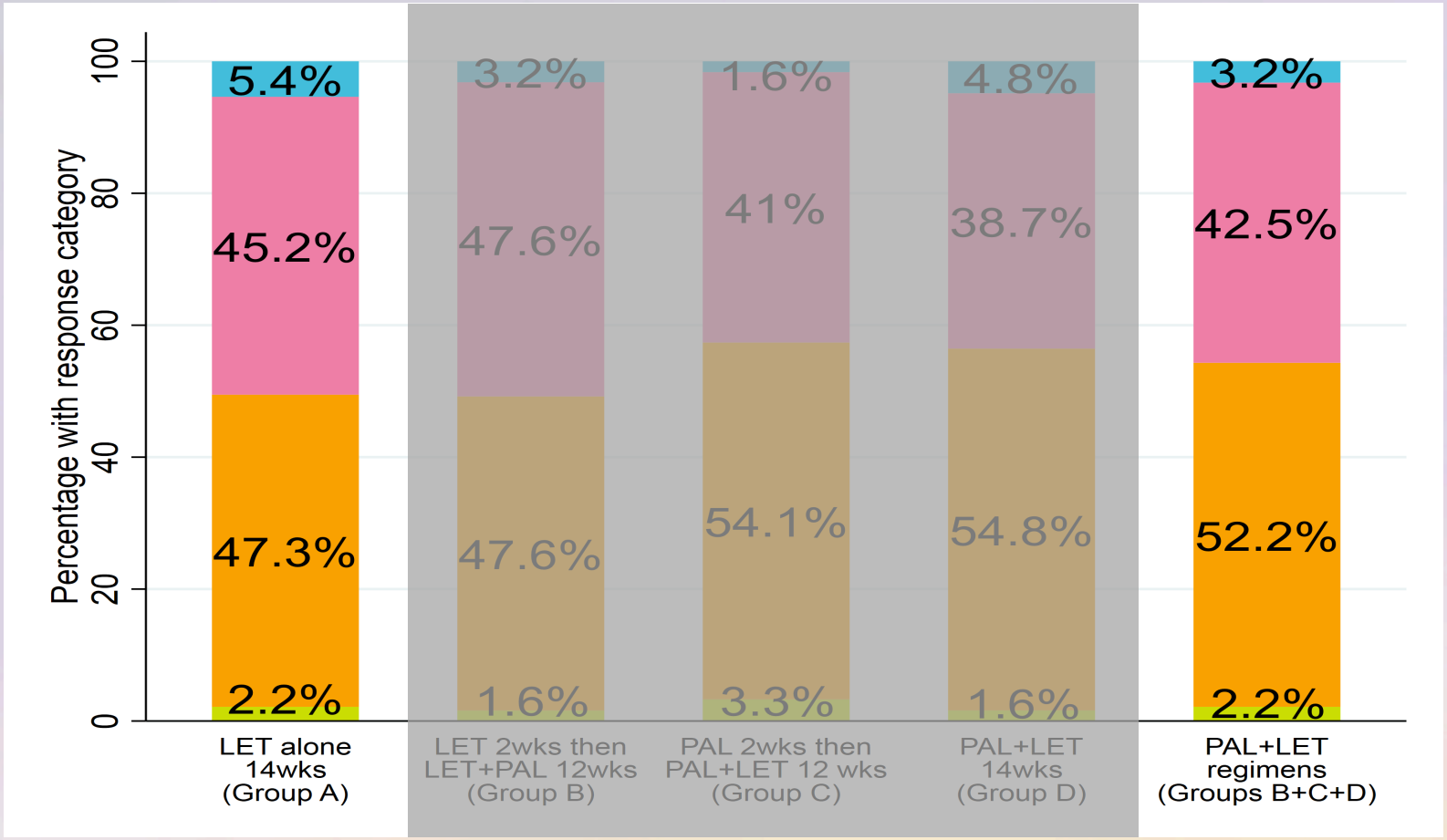
NSABP National Surgical Adjuvant Breast and Bowel Project

CANCER RESEARCH UK

Dowsett M et al. SABCS 2018 GS3-02

Johnston S et al. J Clin Oncol. 2019 Jan 20;37(3):178-189.

PALLET Co-primary endpoints: Clinical response



Clinical response between Group A and Groups B+C+D, p=0.20 Mann-Whitney (ordinal)

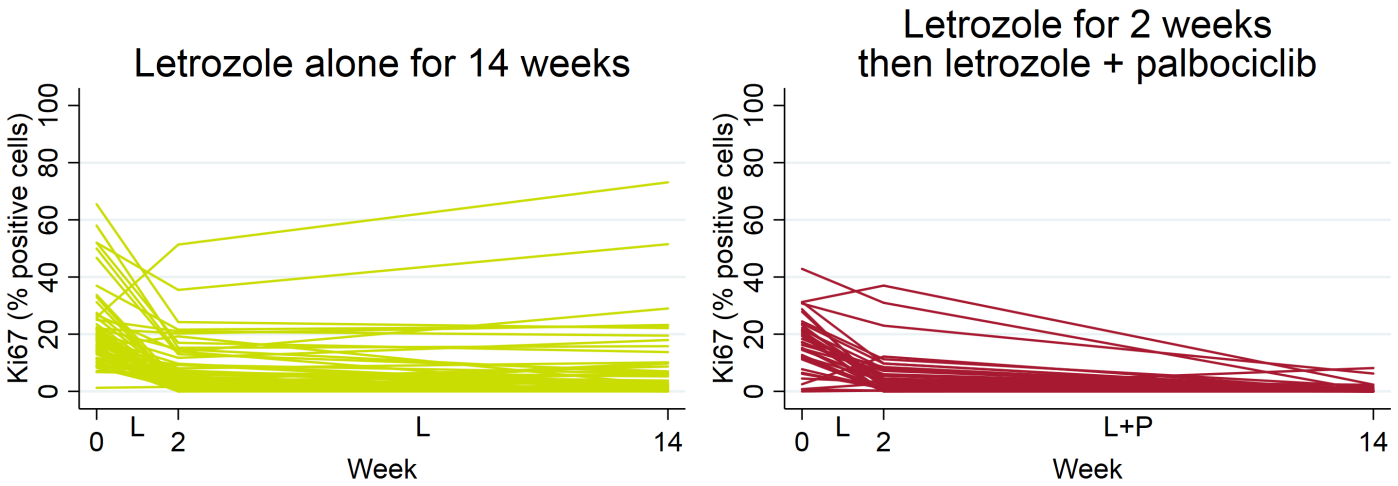
No significant difference in objective response

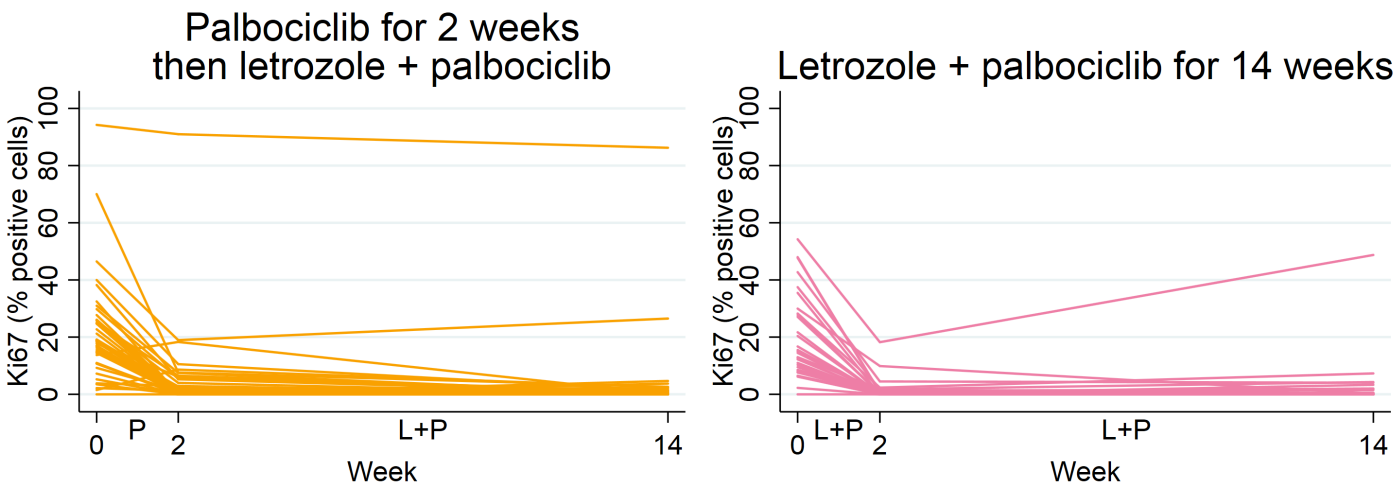
Letrozole alone = 49.5%

Letrozole + Palbo = 54.4%

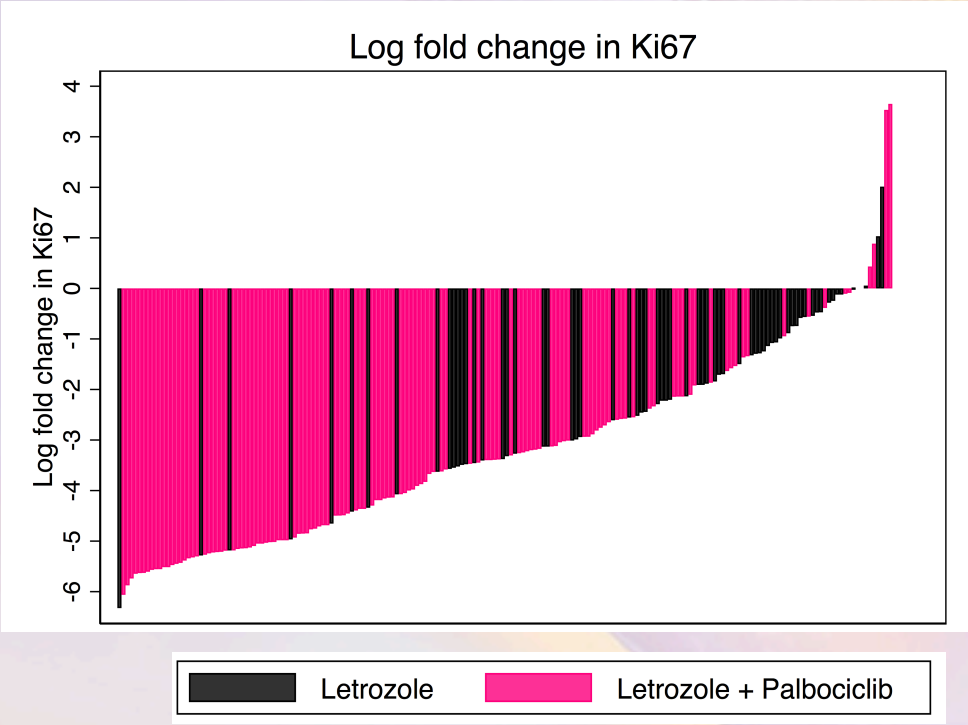
Dowsett et al SABCS 2018, Johnston et al JCO 2019

PALLET Co-primary endpoints: Ki-67





Ki67 at week 14



Enhanced Complete Cell Cycle Arrest

Palbo + Let	90%
Let alone	59% p<0.001

Dowsett et al SABCS 2018, Johnston et al JCO 2019

Ongoing Phase III Trials of CDK4/6 Inhibitors in HR+/HER2- BC

Trial ID	N	Setting	Arms	Primary Endpoint
PENELOPE-B (NCT01864746)	1,250	Postneoadjuvant, Primary BC with high relapse risk	• Palbociclib • Placebo	Invasive DFS
PALLAS (NCT02513394)	5,794	Adjuvant, Early BC	• Palbociclib + ET • ET	Invasive DFS
monarchE (NCT03155997)	4,580	Adjuvant, Early BC	• Abemaciclib + ET • ET	Invasive DFS
NATALEE (NCT03701334)	4,000	Adjuvant, Early BC	• Ribociclib + ET • ET	Invasive DFS

ET = Endocrine therapy, HR = hormone receptor; BC = breast cancer

Clinicaltrials.gov; Accessed December 2019

Phase III POETIC Trial: 2-week Ki-67 on AI therapy detects high risk ER+ EBC

UK POETIC

Postmenopausal women with ER/PgR positive invasive breast cancer

↓

RANDOMISE
2:1 ratio

↓

Group I
PERIOPERATIVE THERAPY
AI treatment for 2 weeks
SURGERY

Group II
NO PERIOPERATIVE THERAPY
SURGERY

↓

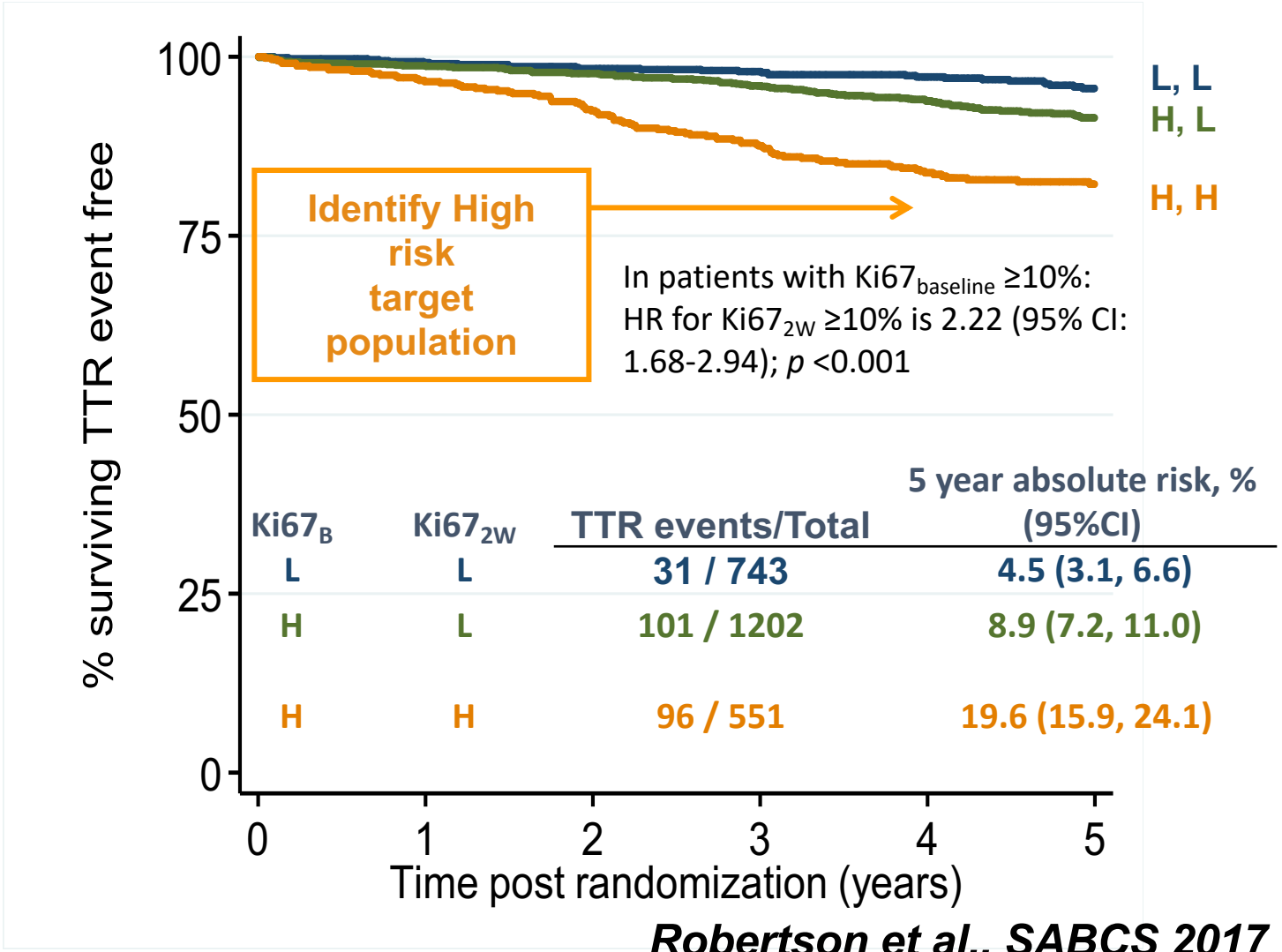
1st follow up visit post-surgery

↓

Complete trial treatment & continue other treatment in accordance with local practice

ClinicalTrials.gov Identifier: NCT02338310

Time to recurrence by Ki67 at baseline and surgery (2 week)



Robertson et al., SABCS 2017

POETIC-A Pre-Operative Endocrine Therapy for Individualised Care with Abemaciclib

Primary Aim: To determine whether a molecular algorithm (AIR-CIS) can identify those postmenopausal women with ER+ HER2- primary breast cancer and poor anti-proliferative response to an aromatase inhibitor (AI) who may derive greatest benefit from additional adjuvant endocrine therapy with abemaciclib.

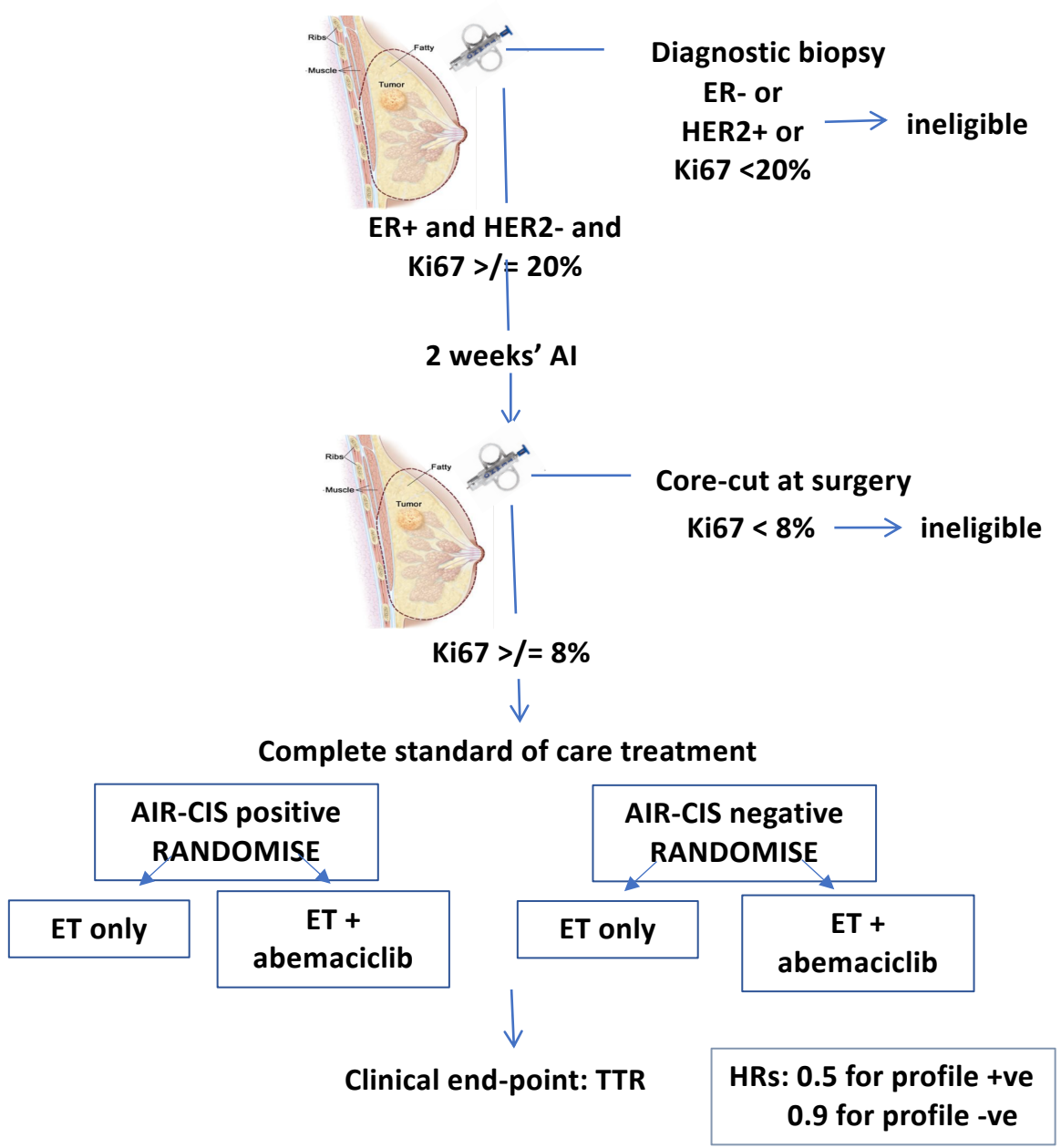
Key Eligibility Criteria:

- ER+, HER2-; Postmenopausal; Palpable tumour of any size or ≥1.5cm by imaging
- Baseline Ki67 ≥ 20% measured at the local site
  OR
- Presence of clinico-pathologic factors that predict (>50% chance) patients with Ki67 ≥ 8% after 2 weeks' AI (grade 3; T > 5cm; PgR -ve or PgR unknown and evidence of vascular invasion)

Treatment period: All patients will receive standard adjuvant endocrine therapy for a minimum of 5 years, and those with abemaciclib for 2 years

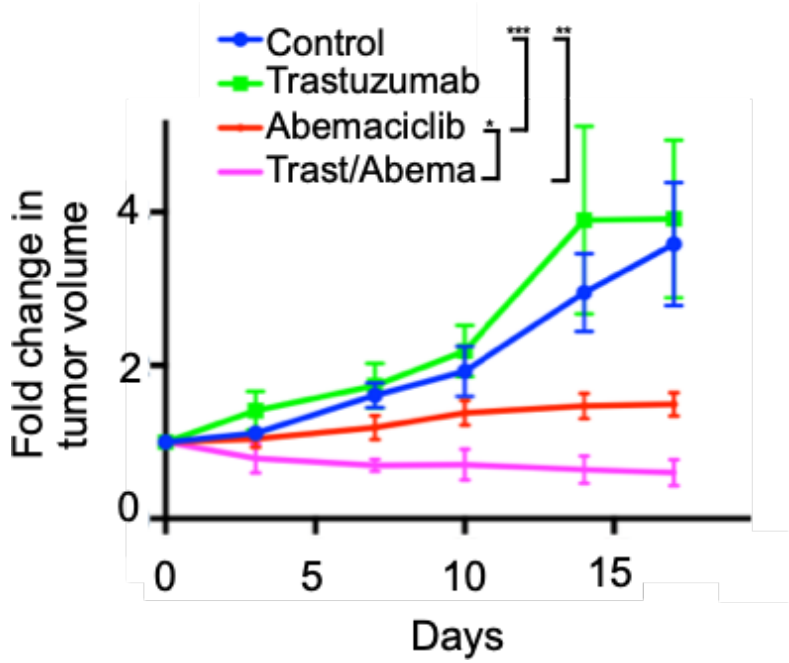
Sample size and recruitment period:

2,500 randomised over 3 years



monarcHER: Rationale for CDK4/6 inhibitors in ER+ HER2+ BC

- Abemaciclib in combination with fulvestrant improved PFS and OS in patients with HR+, HER2- ABC. [1,2]
- Abemaciclib has shown clinical activity in HR+, HER2+ tumors in a Phase 1 study.
  - N=11: ORR 36%, SD 64%, median PFS 7.2 months [3]
- *In vivo,* inhibition of CDK4 & 6 by abemaciclib enhances the activity of HER2-directed agents and has a synergistic effect.[4,5]
- The addition of HER2-directed therapy to ET improved PFS in patients with metastatic HR+, HER2+ breast cancer patients.[6,7,8]



Reprinted from *Cancer Cell*, 29, Goel S et al., Overcoming Therapeutic Resistance in HER2-Positive Breast Cancers with CDK4/6 Inhibitors, 255-269, 2016. *Reproduced with permission from copyright holder.*

1. Sledge et al, *J Clin Oncology* 2017; 2. Sledge et al, *JAMA Oncol* 2019; 3. Patnaik et al, *Cancer Discov* 2016;
4. Goel et al, *Cancer Cell* 2016; 5. Corona et al, *Crit Rev Oncol Hematol* 2017;
6. Kaufman et al, *JCO* 2008; 7. Johnston et al, *JCO* 2009; 8. Burstein HJ et al, *J Clin Oncol* 2014

monarcHER: Phase II Study Design

Eligibility Criteria

- HR+, HER2+ ABC
- ≥2 prior HER2-directed therapies for ABC
- Prior T-DM1 and taxane required
- ECOG PS ≤1
- CDK4 & 6 inhibitor naive
- No untreated or symptomatic CNS metastases

Stratification Factors:

- number of previous systemic regimens (2–3 vs. >3)
- measurable vs nonmeasurable

Randomization
N = 237
1:1:1

Sample Size Calculations:

- 165 PFS events give 80% power at 2-sided alpha of 0.20, Assuming a HR of 0.667

Continue until PD

Arm A
abemaciclib 150 mg PO BID + **trastuzumab** IV q21d + **fulvestrant** IM q28d

Arm B
abemaciclib 150 mg PO BID + **trastuzumab** IV q21d

Arm C
trastuzumab IV q21d + **investigator's choice chemotherapy**[a]

Primary Endpoint

- PFS (A vs. C, then B vs. C)

Secondary Endpoint

- ORR, safety, OS, PRO, PK

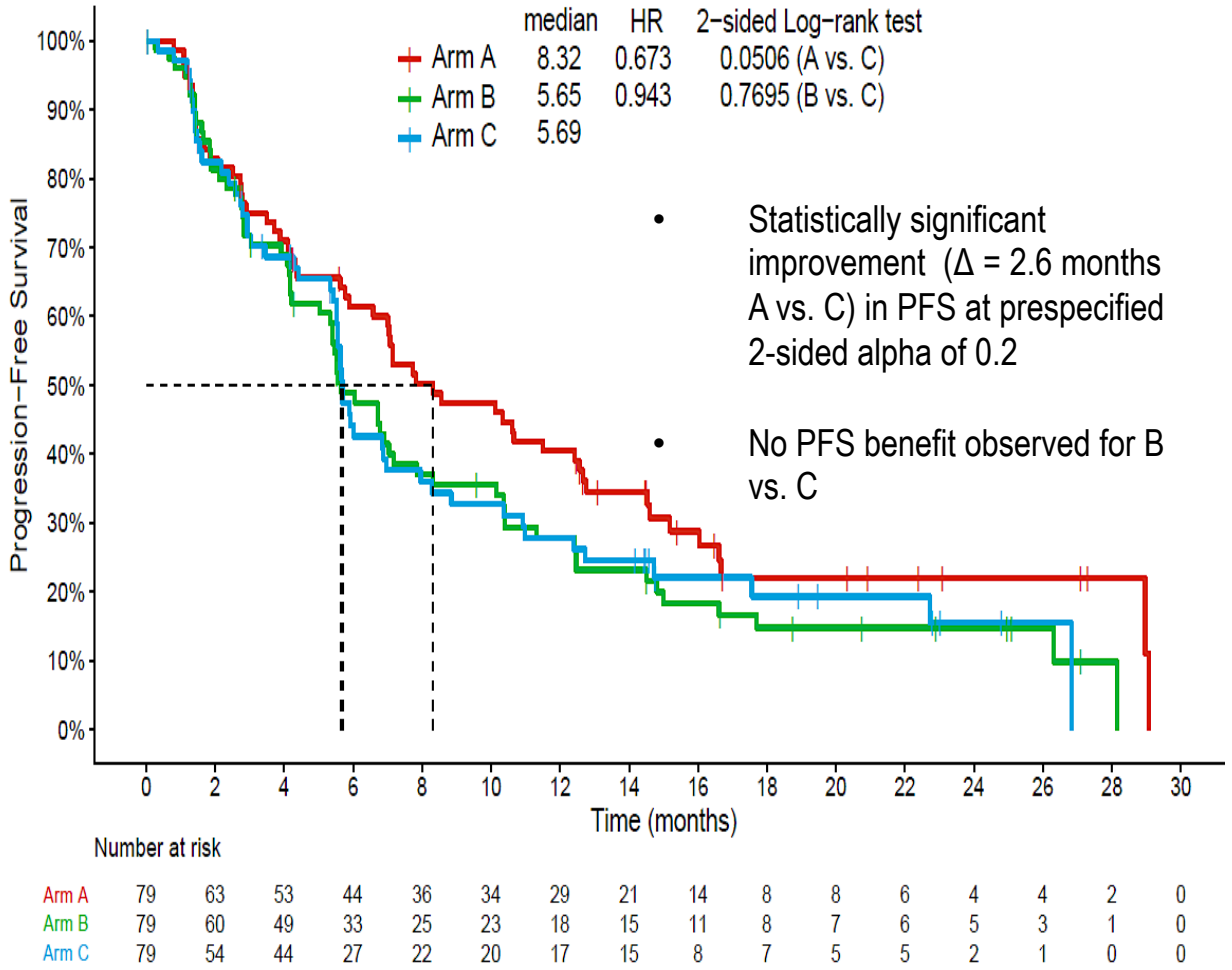
Abbreviations: ABC = advanced breast cancer, HR+ = hormone receptor-positive, HER2(+) = human epidermal growth factor receptor-2 (positive), n = number of patients, PD = progressive disease, BID= twice daily, q21d= every 21 days PFS = Progression Free Survival, ORR = Objective Response Rate, OS = Overall Survival, PRO = Patient Reported Outcomes, PK = pharmacokinetics

[a]Standard-of-care single-agent chemotherapy should include approved drug in breast cancer.

monarcHER: Efficacy

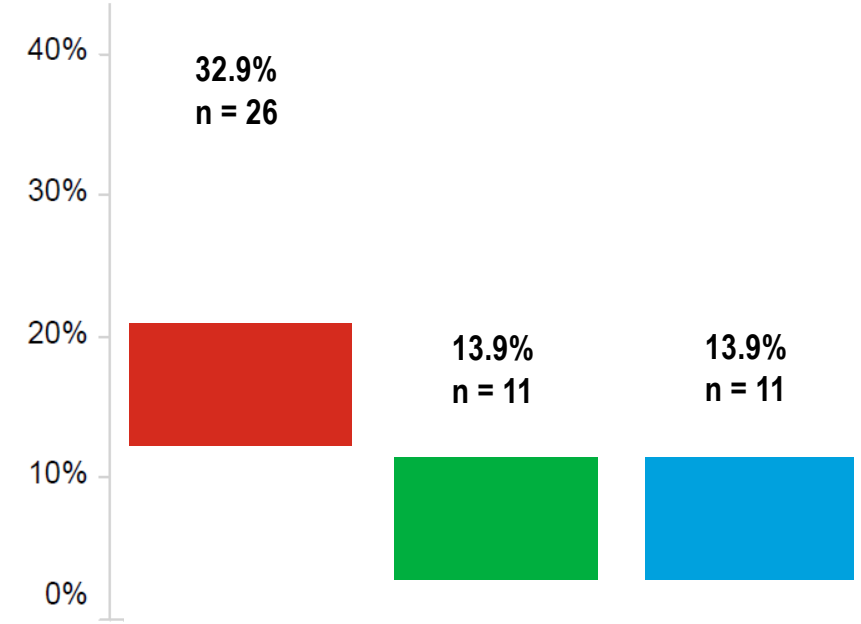
Arm A = abemaciclib + trastuzumab + fulvestrant
Arm B = abemaciclib + trastuzumab
Arm C = trastuzumab + chemotherapy

Investigator Assessed PFS



- Statistically significant improvement (Δ = 2.6 months A vs. C) in PFS at prespecified 2-sided alpha of 0.2
- No PFS benefit observed for B vs. C

Confirmed Best Overall Response



ITT Population
Total N = 237

	Arm A N=79	Arm B N=79	Arm C N=79
95% CI (%)	(22.5-43.3)	(6.3-21.6)	(6.3-21.6)
Stratified 2-sided p-value (vs Arm C)	0.0042	1.0000	-
Duration of Response, months	12.5	9.5	not reached

BARCELONA 2019 ESMO congress

Tolaney et al., ESMO 2019

monarcHER: Safety

Arm A = abemaciclib + trastuzumab + fulvestrant
Arm B = abemaciclib + trastuzumab
Arm C = trastuzumab + chemotherapy

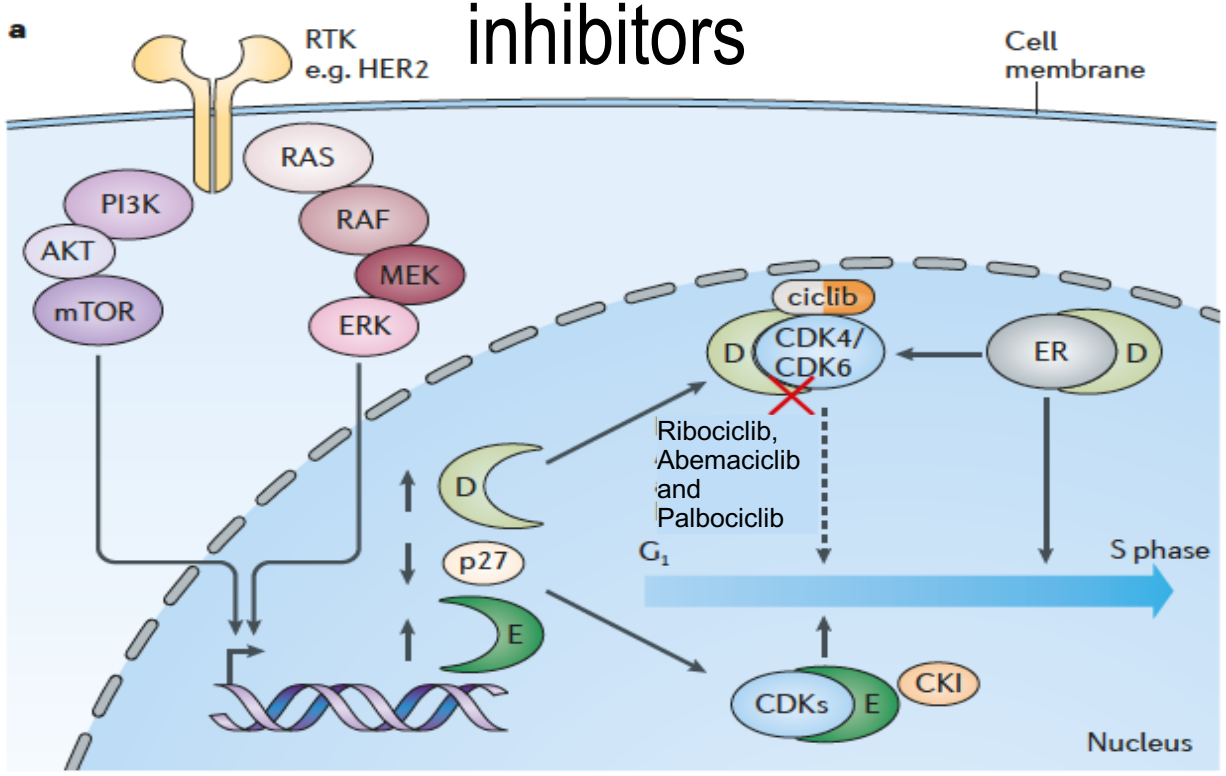
	Arm A N=78	Arm B N=77	Arm C[a] N=72
Patients with >= 1 TEAE, n (%)	53 (67.9)	39 (50.6)	35 (48.6)
Neutropenia[b]	21 (26.9)	17 (22.1)	19 (26.4)
Leukopenia	8 (10.3)	2 (2.6)	7 (9.7)
Thrombocytopenia	8 (10.3)	5 (6.5)	2 (2.8)
Diarrhea	7 (9.0)	5 (6.5)	2 (2.8)
Anemia	7 (9.0)	3 (3.9)	3 (4.2)
Fatigue	3 (3.8)	5 (6.5)	1 (1.4)
Hypokalemia	4 (5.1)	2 (2.6)	2 (2.8)

TEAE =Treatment- Emergent Adverse Event
[a]most common chemotherapy: Vinorelbine (37.5%) , Capecitabine (26.4%) , Eribulin (16.7%), Gemcitabine (11.1%)
[b]Filgrastim use: Arm A, n=3 (3.8%); Arm B, n=2 (2.6%); Arm C, n=9 (12.5%)
PK exposures of abemaciclib and trastuzumab were comparable between Arm A and Arm B. There is no apparent PK interaction between the drugs tested in this study

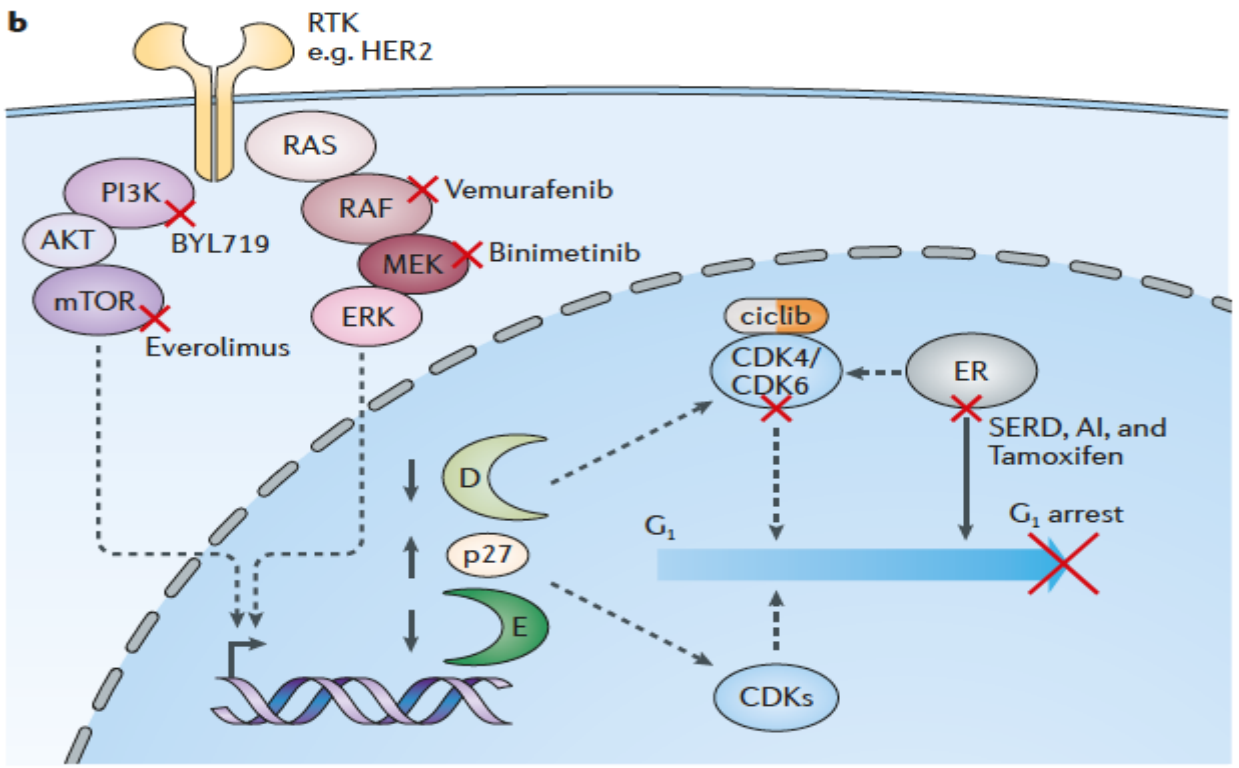
Tolaney et al., ESMO 2019

Combination therapy augments CDK4/6 inhibitors

Bypass of CDK4/6 inhibitors



Combination therapy



O'Leary et al Nat Rev Clin Oncol 2016

Case Presentation: Dr Johnston

2006:

35-year-old woman with history of previous right primary breast cancer
Right WLE / ALND with T2 (2.1 cm) Grade 2 IDC, N1 (1/9), ER 8 PR 6 HER2-negative
Right breast radiotherapy, adjuvant chemotherapy (FEC x 6)
LHRH agonist + Tamoxifen for 2 years, followed by Tamoxifen for 3 years

2011:

Presented with left hip pain whilst still taking tamoxifen:
Bone scan shows isolated metastasis left neck of femur with lytic destruction, confirmed on MRI
Negative staging by PET-CT elsewhere
Required Total Hip Replacement – bone biopsy confirmed IDC, ER 3, PR 0, HER2 3+
Radiotherapy to left hip, Trastuzumab + LHRH agonist (then BSO) + Letrozole + Zoledronic Acid (switched to Denosumab)

Nov 2015:

PD with liver mets; no new sites of bone disease – no further biopsy
Docetaxel x 6 + Trastuzumab with good response after 3 cycles
Continued maintenance Trastuzumab + Denosumab with Exemestane

Case Presentation: Dr Johnston (continued)

Aug 2016:
Progressive disease in liver
T-DM1 (Trastuzumab Emtansine) with stable disease for 7 months

Mar 2017:
Progressive disease in Liver – fresh liver biopsy shows metastatic breast cancer ER8, PR, but HER2 2+ (IHC) and D-DISH negative:
Capecitabine started with good responses on FU scans
Sample sent for mutation analysis (ABC Bio research study) – subsequently showed ESR1 mutation

Jan 2018:
PD in Liver and bone, but LFTs normal and patient well and asymptomatic:
Palbociclib + Fulvestrant started in view of previous liver biopsy result
At 3 months, excellent PR in liver and bone on follow-up PET-CT, with falling CA-15.3

Case Presentation: Dr Johnston (continued)

Aug 2019:

Rising CA-15.3 New sites liver mets on PET-CT following 18-month response to Palbo / Fulvestrant

Plasma DNA analysis revealed:

ESR1 mutation D538G at 52.5% cfDNA

PIK3CA mutation E542K at 39.1% cfDNA

CCND1 amplification (high +++)

Question for Faculty:

Following excellent response to Palbociclib + Fulvestrant, what would the treatment of choice be now in light of ctDNA mutation result?

1. Fulvestrant 500 mg im monthly + Alpelisib
2. Fulvestrant 500 mg im monthly + Abemaciclib 150 mg bid
3. Fulvestrant 500 mg im monthly + Everolimus 10 mg daily
4. Exemestane 25 mg daily + Everolimus 10 mg daily
5. Novel SERD in a clinical trial
6. Chemotherapy with weekly paclitaxel