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SUSAN F. SMITH CENTER FOR WOMEN'S CANCERS

DANA-FARBER CANCER INSTITUTE

HARVARD MEDICAL SCHOOL

CDK 4/6 Inhibition in Hormone-Receptor Positive Breast Cancer

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Disclosures

Advisory Committee	AstraZeneca Pharmaceuticals LP, Merck, NanoString Technologies, Nektar, Puma Biotechnology Inc
Consulting Agreements	AstraZeneca Pharmaceuticals LP, Merck, NanoString Technologies, Nektar, Puma Biotechnology Inc
Contracted Research	AstraZeneca Pharmaceuticals LP, Exelixis Inc, Genentech BioOncology, Lilly, Merck, Nektar, Novartis, Pfizer Inc

Case presentation: Dr Brooks

65-year-old woman

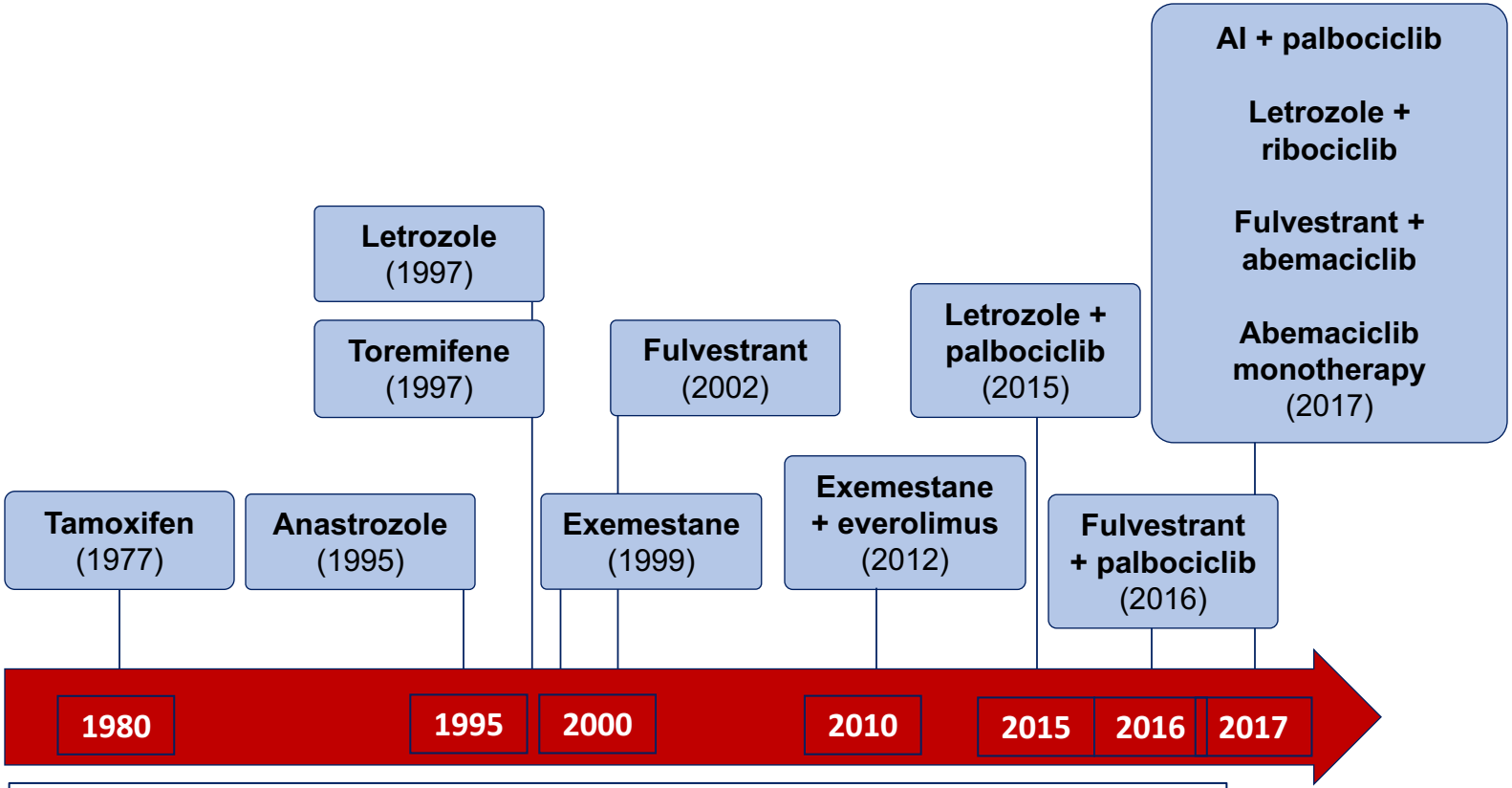
- 2004: ER/PR-positive, HER2-negative lobular carcinoma with 1 positive sentinel lymph node → MRM → adjuvant AC-T → anastrozole for 5 years
- 2016: Bone metastases → fulvestrant + palbociclib → in continuous CR x 1.5 years
- Plasma genomic assay showed multiple mutations, including PIK3CA; 3.2% mutation load

Case presentation: Dr Peswani

59-year-old nurse

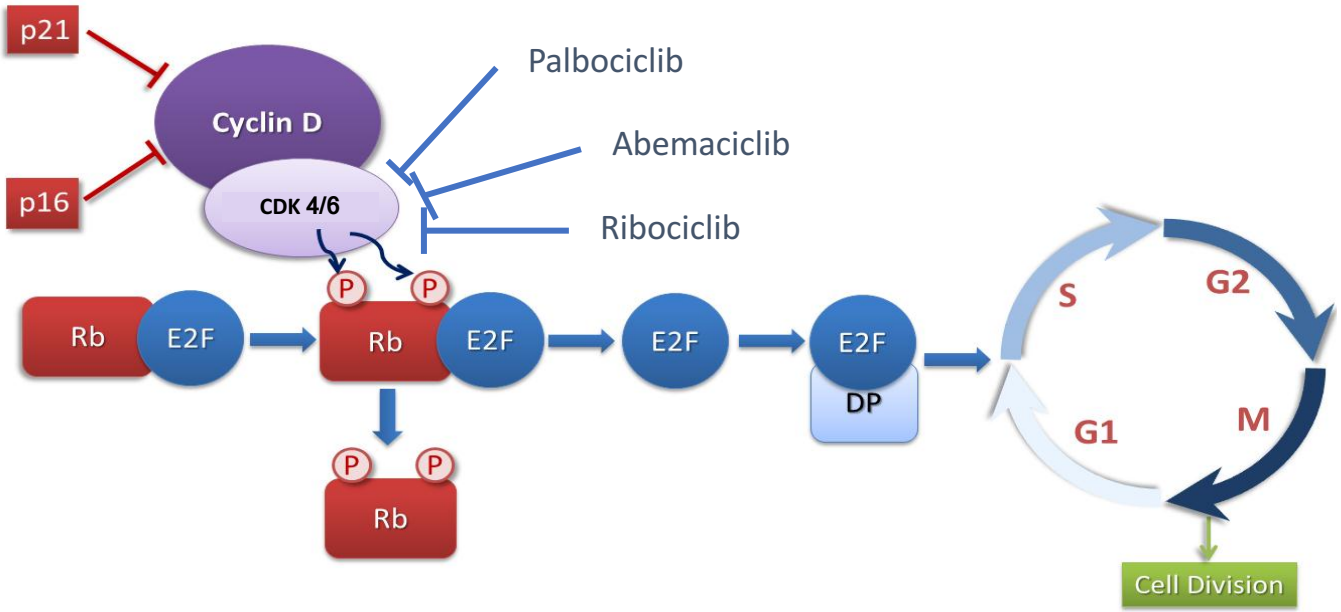
- 2014: ER/PR-positive, HER2-negative, node-negative breast cancer
  - 21-gene Recurrence Score: 36 (high)
  - Lumpectomy → XRT
  - Refused adjuvant chemotherapy; noncompliant with anastrozole
- 2015: Metastatic BC chest wall → palbociclib + letrozole
  - Noncompliant with CBC testing on palbociclib → neutropenic sepsis → letrozole continued
- 2017: New liver mets → palbociclib + fulvestrant

Examples of Hormonal Therapies for ER+ Breast Cancer (and Year of FDA Approval)



AI, aromatase inhibitor; ER+, estrogen receptor positive.
US Food and Drug Administration. http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm.

CDK 4/6 Regulates G1→S Cell Cycle Progression



CDK 4/6, cyclin-dependent kinase 4/6; M, mitosis; Rb, retinoblastoma.
Adapted from Finn et al, *Breast Cancer Res*. 2016; DOI: 10.1186/s13058-015-0661-5.

Differences Among the 3 CDK 4/6 Inhibitors

	Palbociclib		Abemaciclib		Ribociclib	
IC_{50}	CDK 4: 9-11 mM CDK 6: 15 mM		CDK 4: 2 mM CDK 6: 5 mM		CDK 4: 11 mM CDK 6: 39 mM	
Dosing	125 mg daily (3 weeks on, 1 week off)		**150 mg twice daily (continuously) with endocrine therapy OR 200 mg po bid**		600 mg daily (3 weeks on, 1 week off)	
ORR in monotherapy*	6%		**9.5%/20%**		3%	
CNS penetration	No		Yes		No	
Common adverse events (%)*	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Neutropenia	95	**54**	88	27	46	**29**
Thrombocytopenia	76	19	42	2	37	10
Fatigue	68	0	65	13	29	3
Diarrhea	16	0	90	**20**	22	3
Nausea	23	0	65	5	46	2
Vomiting	5	0	35	2	25	0
QTc prolongation	NR	NR	NR	NR	8	0

CDK, cyclin-dependent kinase; HR, hormone receptor; IC_{50}, half-maximal inhibitory concentration; NR, not reported; ORR, objective response rate; QTc, corrected QT interval.
*The single-agent activity and common adverse events shown in this table are those reported n [23, 29, 14] for palbociclib, abemaciclib, and ribociclib, respectively.
Adapted from: Barroso-Sousa et al, *Breast Care* 2016;11:167-173.

Impact of CDK 4/6 inhibition on PFS

1st Line Trials

2nd Line Trials

	PALOMA-1	PALOMA-2	MONALEESA-2	MONARCH 3	PALOMA-3	MONARCH 2
Design	Ph 2 1st Line	Ph 3 1st Line	Ph 3 1st Line	Ph 3 1st Line	Ph 3 2nd Line	Ph 3 2nd Line
Endocrine partner	Letrozole	Letrozole	Letrozole	Letrozole or Anastrozole	Fulvestrant	Fulvestrant
CDK 4/6 inhibitor	Palbociclib	Palbociclib	Ribociclib	Abemaciclib	Palbociclib	Abemaciclib
Patients on study, n	165	666	668	493	521	669
HR	0.49	0.58	0.56	0.54	0.46	0.55
PFS (months)	20.2 vs 10.2	24.8 vs 14.5	25.3 vs 16	NR vs 14.7	9.5 vs 4.6	16.4 vs 9.3
ORR	56% vs 39%	55.3% vs 44.4%	52.7% vs 37.1%	59% vs 44%	25% vs 11%	48.1% vs 21.3%

Finn RS et al, Lancet Oncology 2015
Finn RS et al, NEJM 2016
Hortobagyi GN et al, NEJM 2016
Goetz MP et al, J Clin Oncol 2017
Cristofanelli M et al, The Lancet 2016
Sledge GW et al, J Clin Oncol 2017

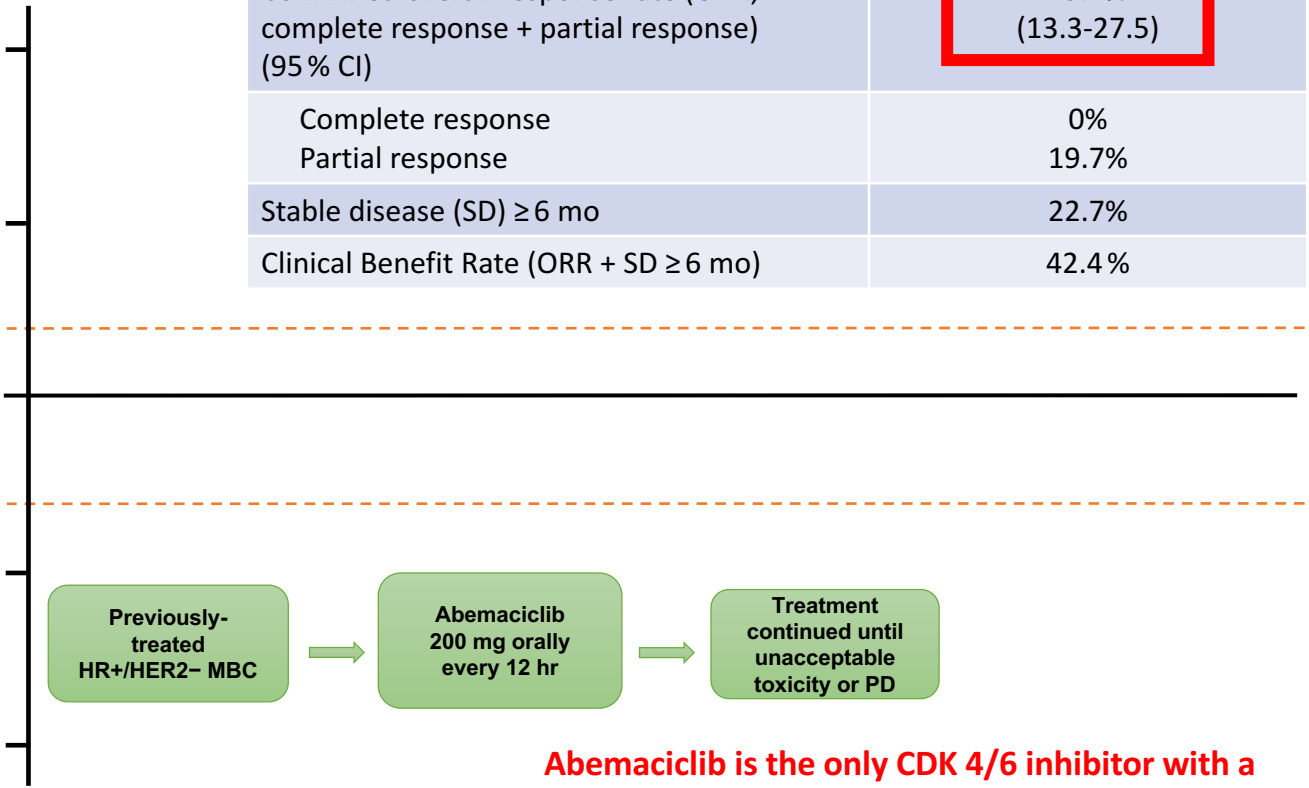
Very Different Patient Populations

Any # prior endocrine tx
1 prior chemo allowed

Only 1 prior endocrine tx
No prior chemo allowed

Abemaciclib Monotherapy: MONARCH 1

Investigator Assessed Response[a]	Abemaciclib 200 mg (N = 132)
Confirmed overall response rate (ORR; complete response + partial response) (95 % CI)	19.7% (13.3-27.5)
Complete response	0%
Partial response	19.7%
Stable disease (SD) ≥ 6 mo	22.7%
Clinical Benefit Rate (ORR + SD ≥ 6 mo)	42.4 %



Abemaciclib is the only CDK 4/6 inhibitor with a monotherapy indication

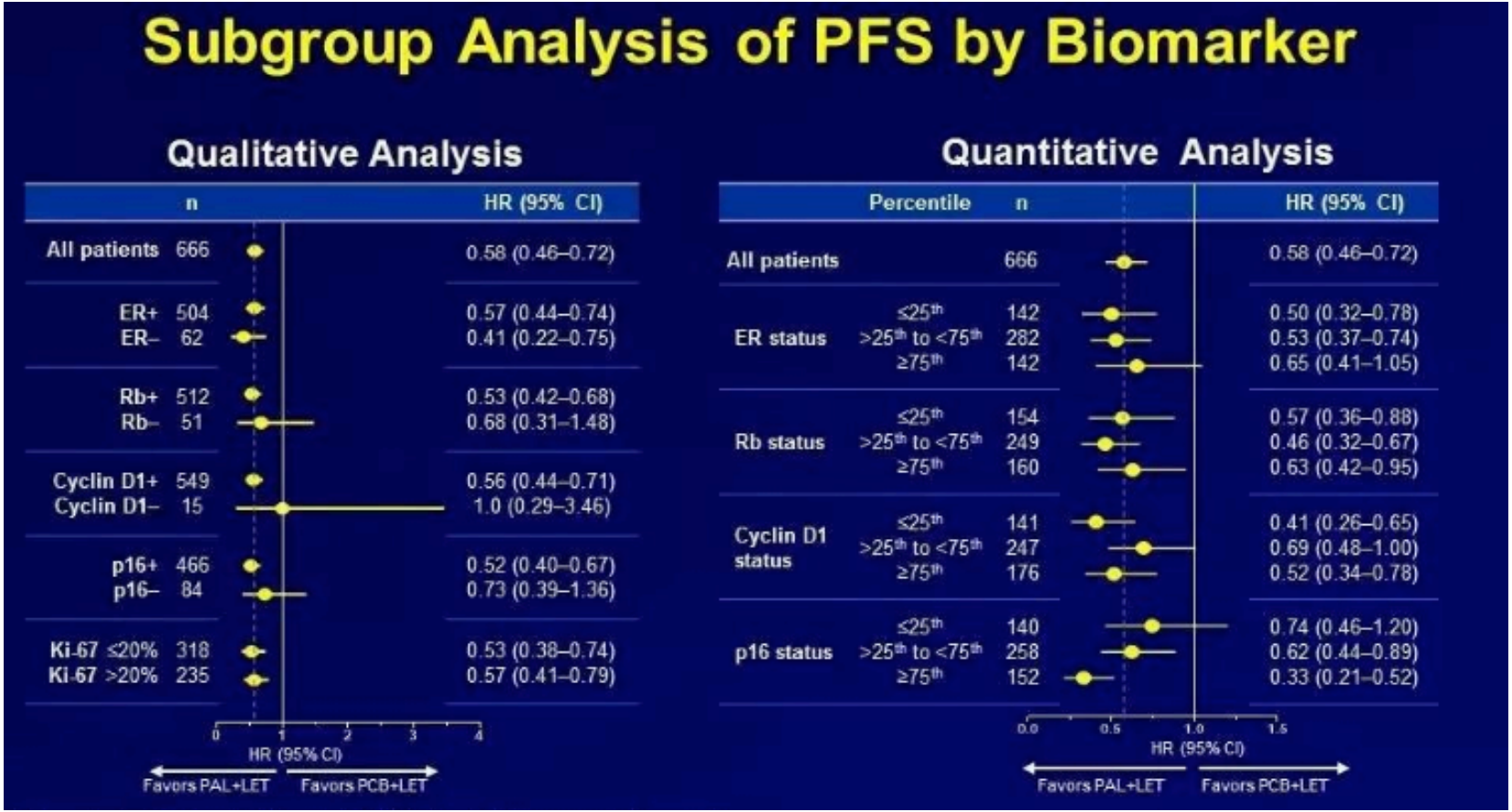
[a]Assessments based on independent review were comparable.
Dickler et al. *J Clin Oncol*. 2016;34: abstract 510.

Remaining Questions

- What is the biomarker for response to CDK4/6 inhibition?
- Is there a role for continuation of CDK4/6 inhibition beyond progression?
  - What is the mechanism of resistance?
- Is there a survival benefit?
- Is there a role in the adjuvant setting?
- Will these agents have a role in other breast cancer subtypes?
- What other novel combination therapies may be beneficial?

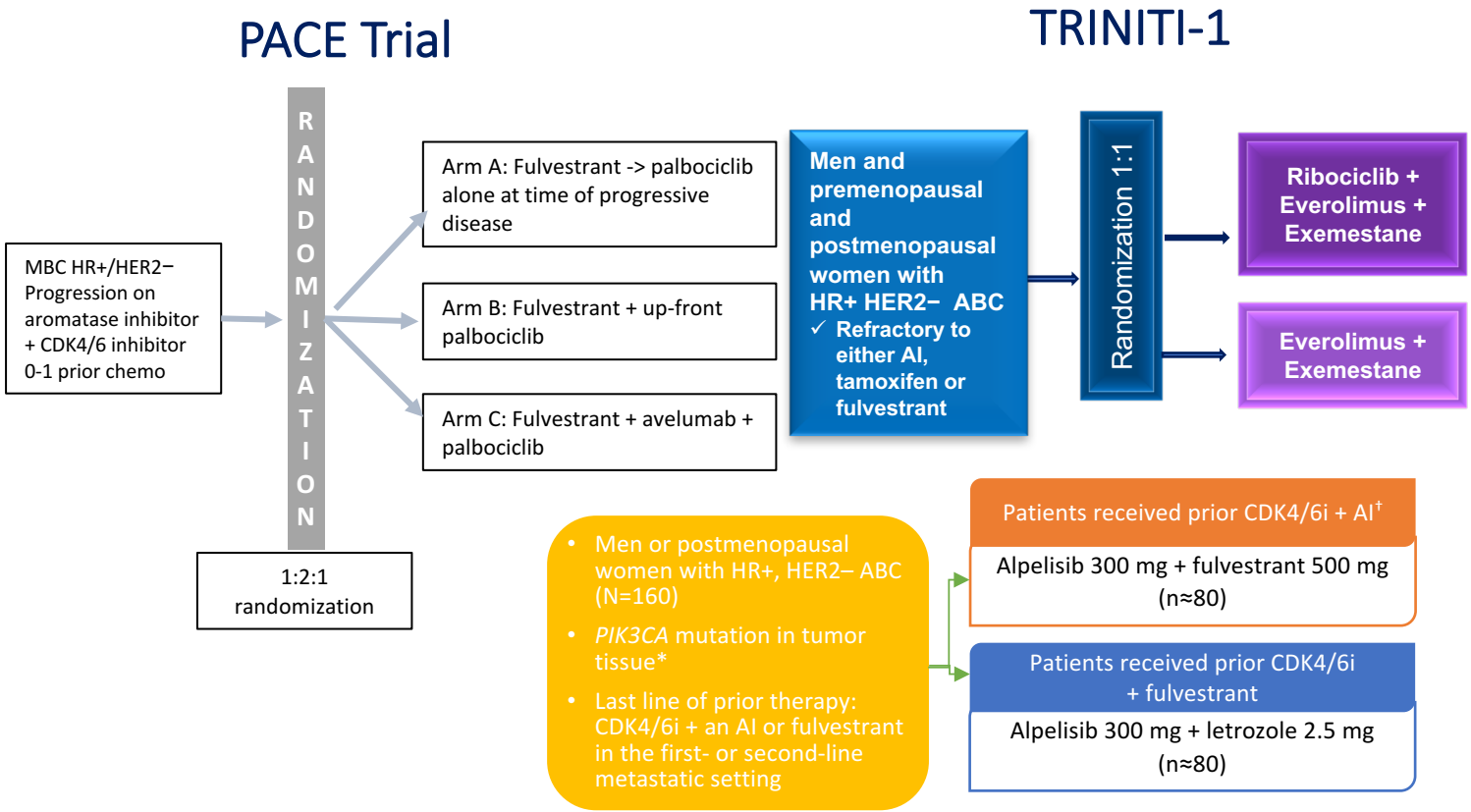
Is there a biomarker for response?

PALOMA-2

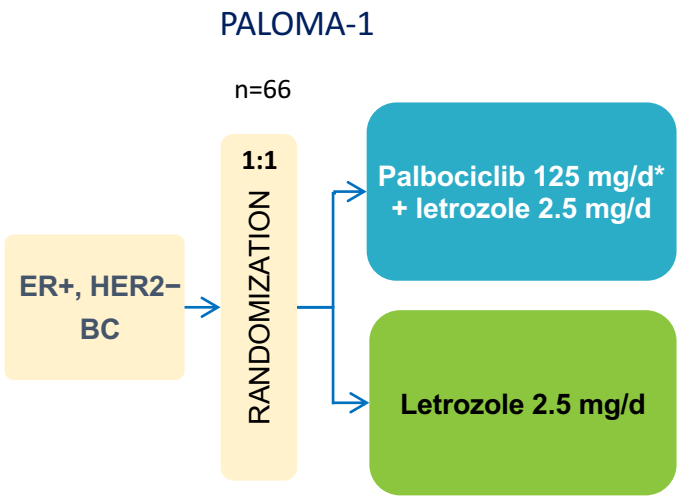


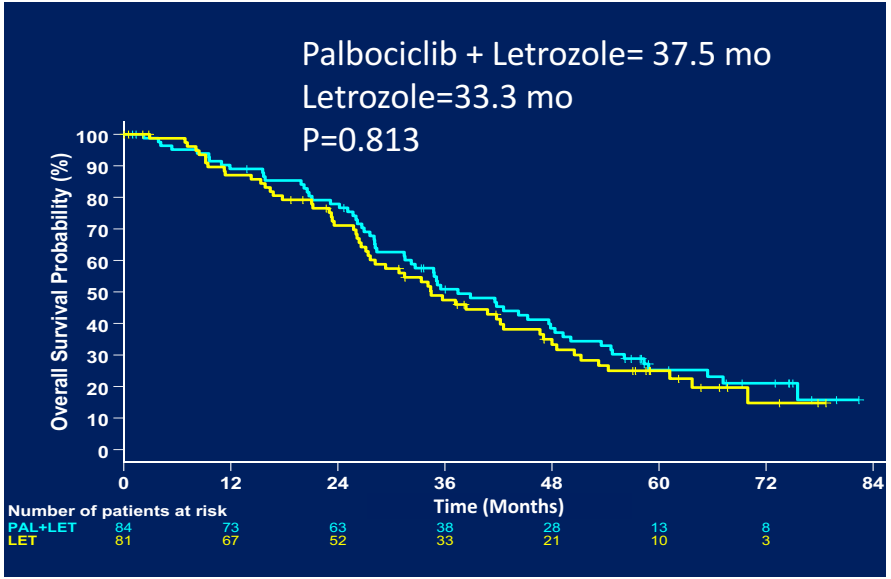
Finn RS et al, ESMO 2016

Is there a role for continuing CDK4/6 inhibition beyond progression?



Are CDK4/6 inhibitors associated with a survival benefit?





No OS benefit seen in this small phase 2 trial, but need to await longer term follow-up data from the pivotal phase 3 studies

Finn RS et al, ASCO 2017

Is there a role for CDK4/6 inhibition in the adjuvant setting?

monarchE
EARLY BREAST CANCER

Patients with HR+, HER2- node positive early stage invasive breast cancer at high risk for recurrence

At least one of the following **high risk clinical pathology (ITT)** criteria:
- ≥ 4 lymph nodes
- high grade tumor (Grade 3)
- primary tumor size > 5 cm;

OR
- Low clinical pathology and **Ki67 > 20%** – separate cohort, not included in ITT

Standard endocrine therapy + 150mg BID abemaciclib

~3580 patients randomized
1:1 randomization

Standard endocrine therapy alone

EarLEE-1

PALLAS

RANDOMIZATION

Arm A
Palbociclib (2 yrs)
+
Endocrine treatment
(5+ yrs)

Arm B
endocrine treatment
(5+ yrs)

- Men and women with AJCC Prognostic Stage Group III HR+, HER2– EBC
- Plans to receive 5+ years standard adjuvant ET†
- No prior neoadjuvant ET
- Completed local therapy

Randomization (1:1)

N≈2000

Ribociclib (600 mg/d)
3-weeks-on/1-week-off
+
Standard adjuvant ET‡

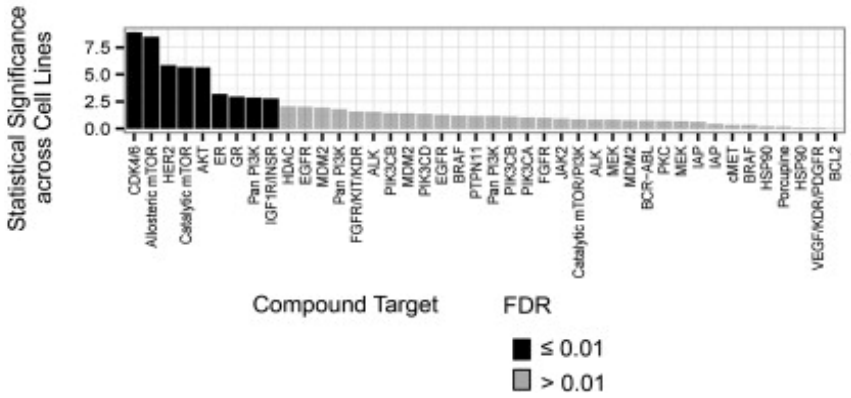
Placebo
+
Standard adjuvant ET‡

Intermediate Risk Adjuvant Study Pending with Ribociclib

Patient population
- N = 4600
- Inclusion Criteria:
  - HR+ and HER2-
  - Stage II or III (IIA limited to 1000 Patients)

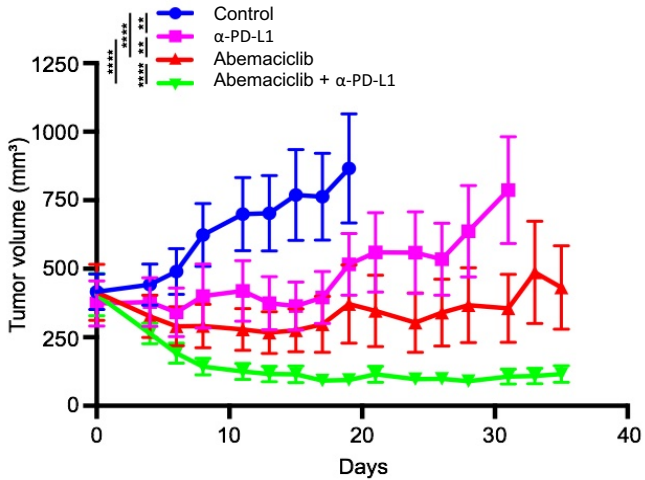
What other novel combinations may be beneficial?

- Combinatorial drug screen on PIK3CA mutant cancers with decreased sensitivity to PI3K inhibitors revealed CDK4/6 + PI3K inhibition was synergistic



Vora et al, *Cancer Cell 2014*

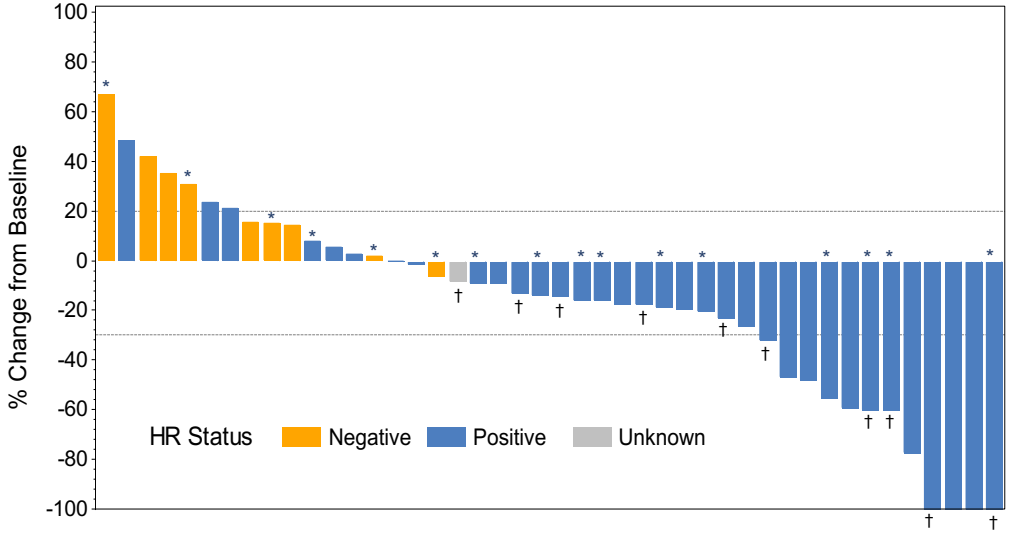
- CDK4/6 inhibition triggers anti-tumor immunity, increases antigen presentation and appears to be synergistic with immune checkpoint inhibition



Goel S et al, *Nature* 2017

Is there a role for CDK4/6 inhibition in other breast cancer subtypes?

JPBA Cohort D (Monotherapy)



4/16 HER2+: PR

[a]3 non-evaluable patients are not shown. All patients in Part D were required to have measurable disease.

* Indicates HER2+

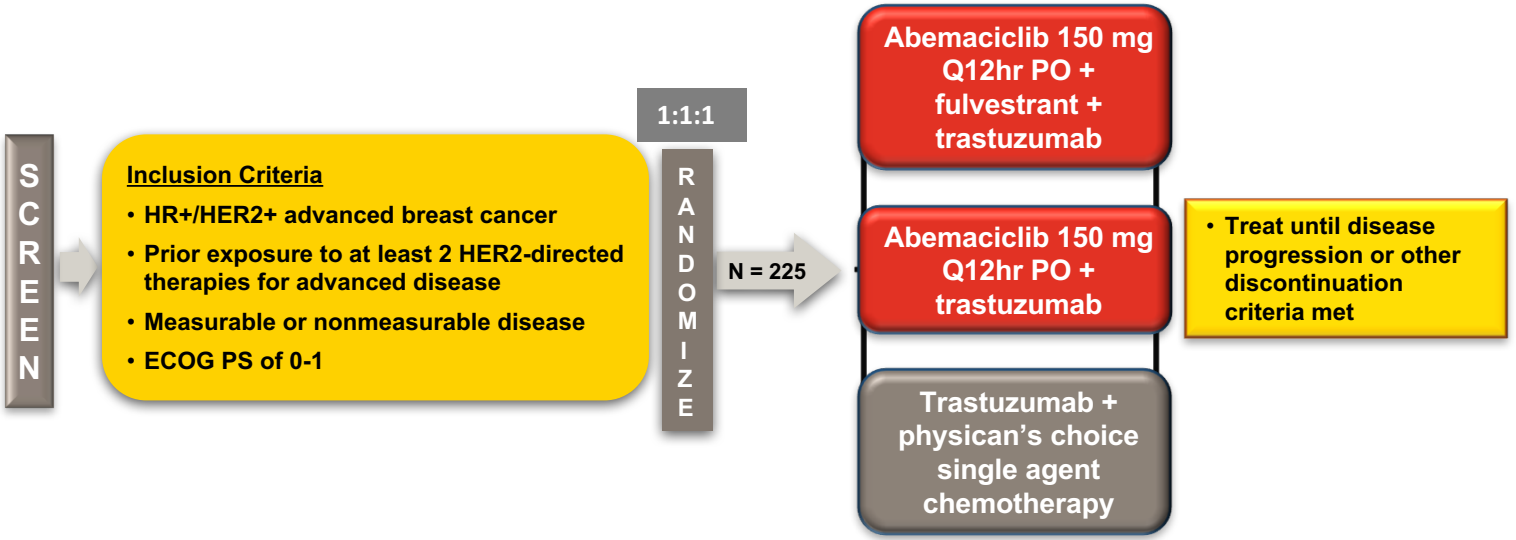
† Patient progressing on endocrine therapy before study entry and continued on that specific therapy

	All (N=47)	All HR+ (N=36)	HR+ Mono (N=27)	HR+ Hormonal (n=9)
ORR (PR)	12 (26%)	12 (33%)	7 (26%)	5 (55%)
CBR (PR+SD>=6 mo)	23 (49%)	22 (61%)	13 (48%)	9 (100%)

Tolaney SM et al. SABCS 2014. Abstract 763

Phase 2 Study: monarcHER (JPBZ)

A Phase 2, Randomized, Multicenter, 3-Arm, Open-Label Study to Compare the Efficacy of Abemaciclib Plus Trastuzumab With or Without Fulvestrant to Standard-of-Care Chemotherapy of Physician's Choice Plus Trastuzumab in Women With HR+, HER2+ Locally Advanced or Metastatic Breast Cancer



Study Design	Phase 2, Randomized, Multicenter, 3-Arm, Open-Label Study to Compare the Efficacy of Abemaciclib plus Trastuzumab with or without Fulvestrant to Standard-of-Care Chemotherapy of Physician's Choice plus Trastuzumab in Women with HR+, HER2+ Locally Advanced or Metastatic Breast Cancer
Primary End Point	Progression-Free Survival (PFS)
Secondary End Points	Overall Survival (OS), Objective Response Rate (ORR), Duration of Response (DOR), Disease Control Rate (DCR), Clinical Benefit Rate (CBR), Pharmacokinetics, and Changes in QoL measures

PI: S. Tolaney/F. Andre

Conclusions

- Combining CDK4/6 inhibition with hormonal therapy is now standard option for first or second line metastatic therapy given significant increase in PFS (though no OS benefit yet seen)
  - Unclear if one agent is better than the other
  - Unclear which patients may do just as well with endocrine therapy alone
- Unclear if there will be a benefit of continuing CDK4/6 inhibition beyond progression
- There are ongoing studies to see if there may be a role of CDK4/6 inhibition in the adjuvant setting
- Work is ongoing looking at these agents for the treatment of brain metastases and for metastatic HER2+ disease and TNBC