Optimizing the Use of CDK4/6 Inhibitors in the Management of ER-Positive Metastatic Breast Cancer (MBC)

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CP1229323-1

Disclosures

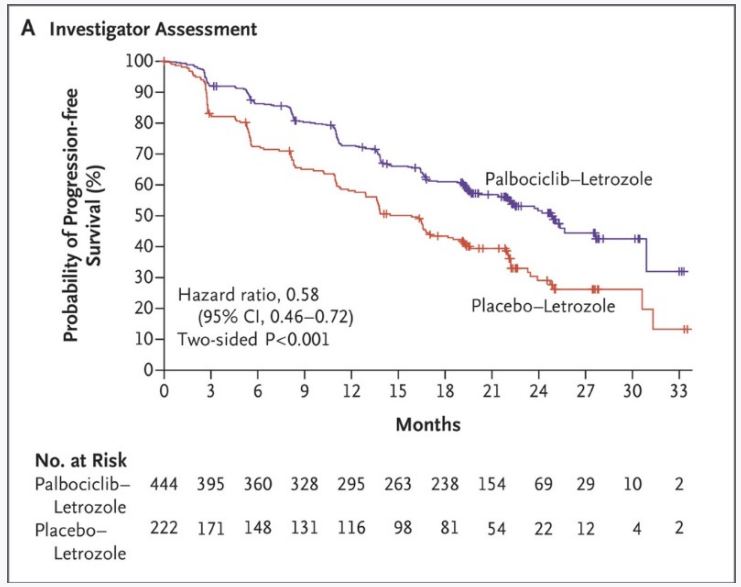
Advisory Committee	bioTheranostics Inc, Biovica, Context Therapeutics, Lilly, Novartis, Pfizer Inc, Sermonix Pharmaceuticals

Case Presentation: Dr Goetz (continued)

Patient receives radiation therapy followed by oophorectomy and letrozole. Near the completion of the 5-year course of letrozole and at the age of 46 (2017), the patient developed abdominal pain and imaging demonstrated multiple hypodense liver lesions. A bone scan, in addition to the liver lesions, revealed an area of uptake in the right ilium as well as the left femoral head.

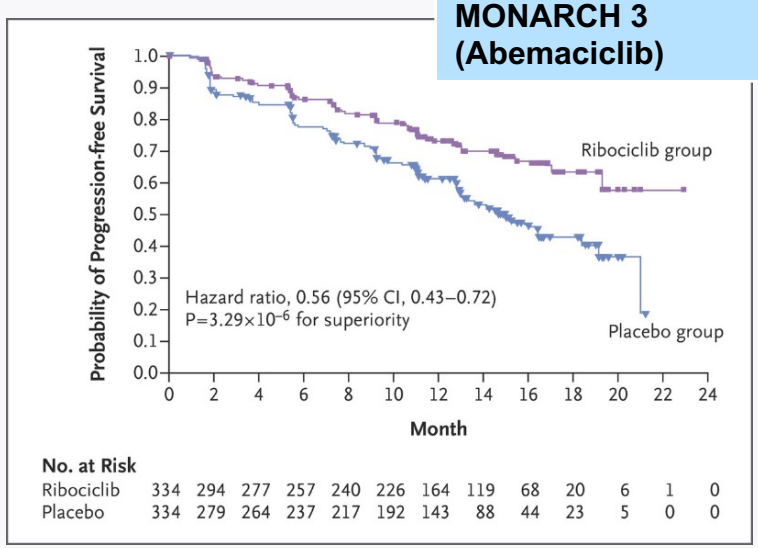
A biopsy of liver lesion revealed moderately differentiated adenocarcinoma, estrogen receptor-positive, PR-negative, HER2- negative.

First-line Metastatic ER+/HER2- Breast Cancer PALOMA-2, MONALEESA-2, and MONARCH 3

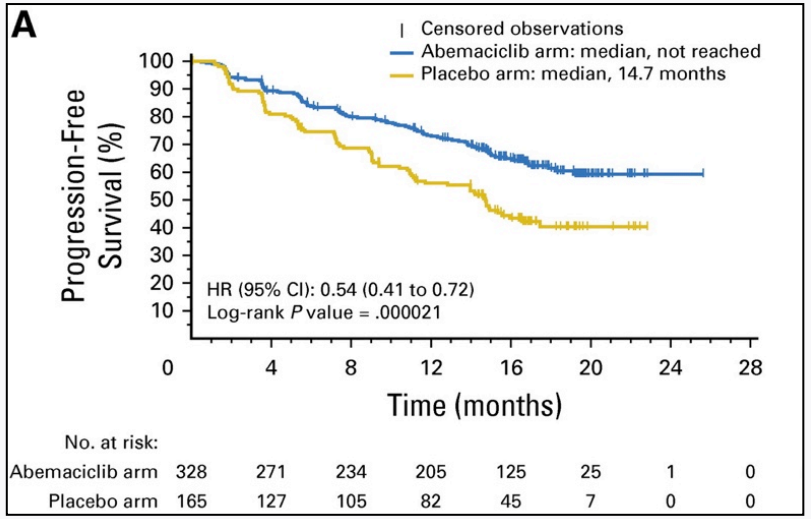


ORR: 55.3%

	HR	AI-Placebo	AI- CDK4/6i
PALOMA-2 (Palbociclib)	0.58	14.5 m	24.8 m
MONALEESA-2 (Ribociclib)	0.56	14.7 m	Not Reached
MONARCH 3 (Abemaciclib)	0.54	14.7 m	Not Reached



ORR: 52.7%



ORR: 59.2%

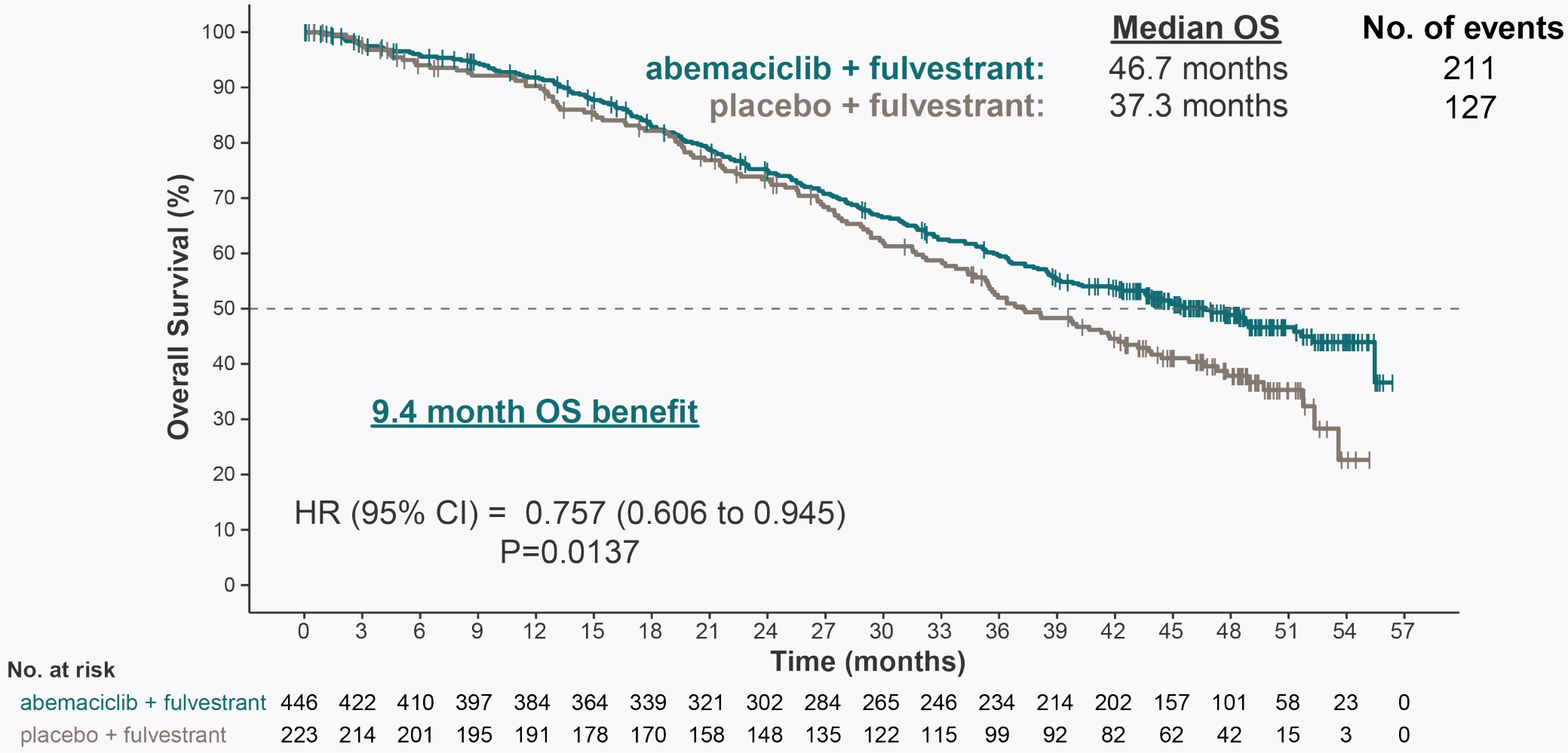
1) Finn et al. NEJM 2016
2) Hortobagyi et al. NEJM 2016
3) Goetz et al. JCO 2017

Survival Data from the 1st and 2nd line Settings

- First line premenopausal setting (MONALEESA-7)
  - Ribociclib + ET prolonged OS compared with ET alone (HR 0.71; 95% CI, 0.54 to 0.95; P=0.00973)
- Combined 1st/2nd line postmenopausal setting (MONALEESA-3)
  - Ribociclib + fulvestrant (F) prolonged OS vs F alone (HR 0.724; 95% CI, 0.57 to 0.92; P=0.004).
  - HR similar in 1st and 2nd line setting
- 2nd line pre and postmenopausal setting
  - MONARCH 2: 9.4 month OS benefit comparing Abemaciclib + F vs F alone
  - PALOMA-3: OS benefit in Endocrine sensitive cohort

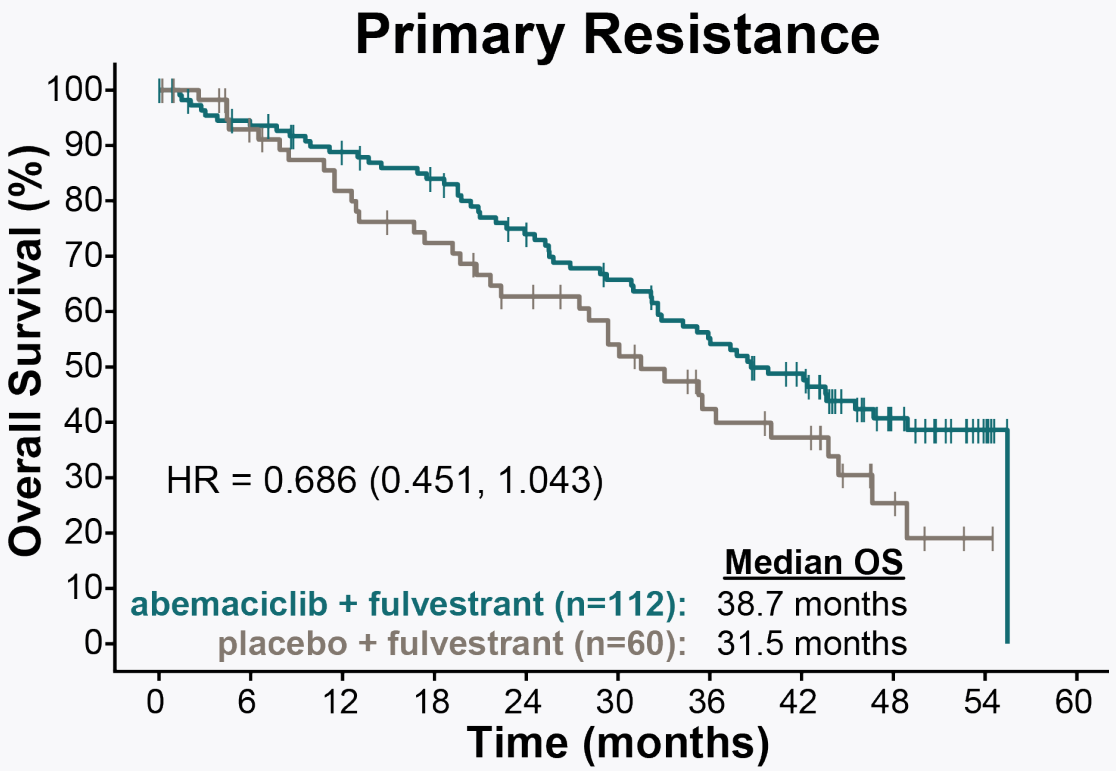
Im et al. NEJM 2019
Slamon et al. ESMO 2019
Sledge et al. JAMA Oncology 2019

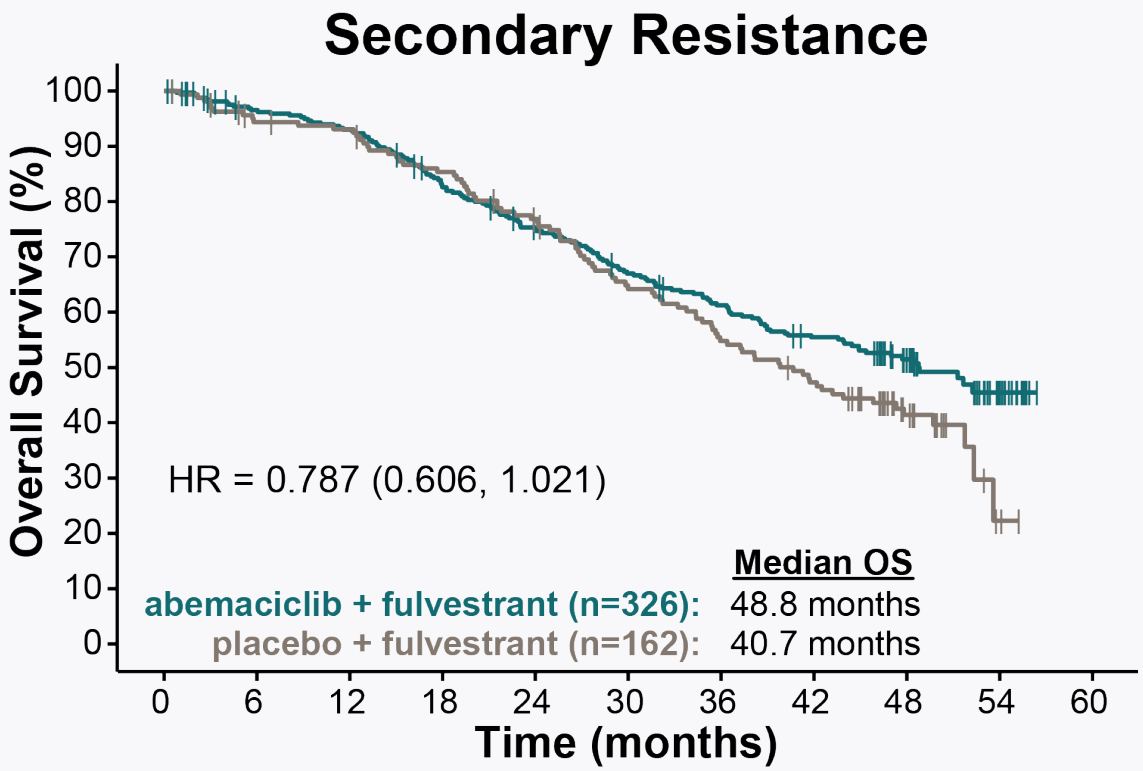
MONARCH 2: Overall Survival



Sledge et al. JAMA Oncology 2019

MONARCH 2: Overall Survival by Resistance to Endocrine Therapy

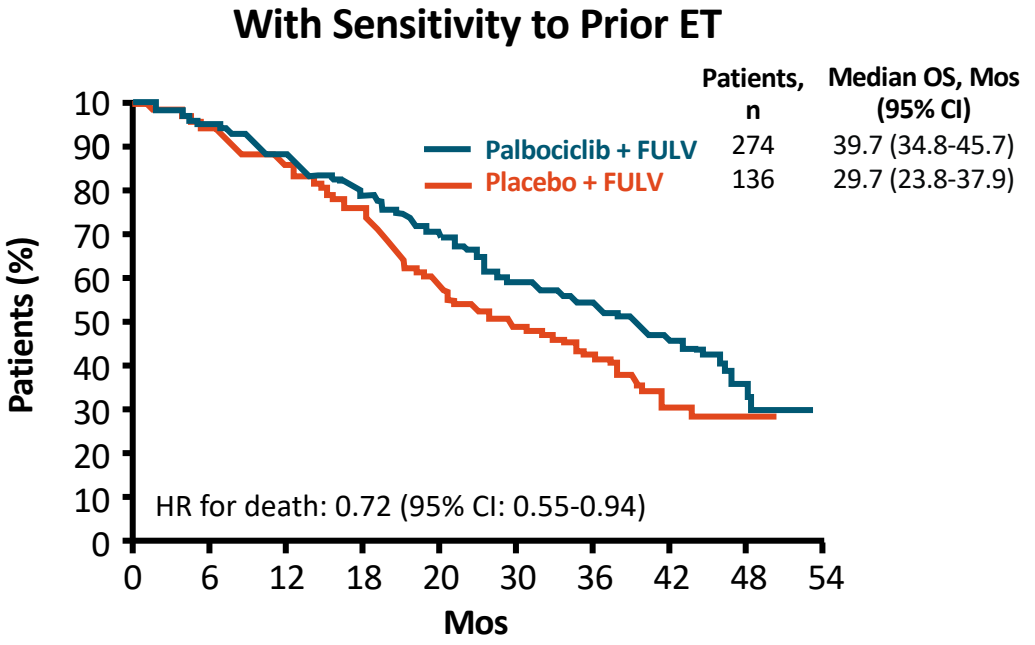


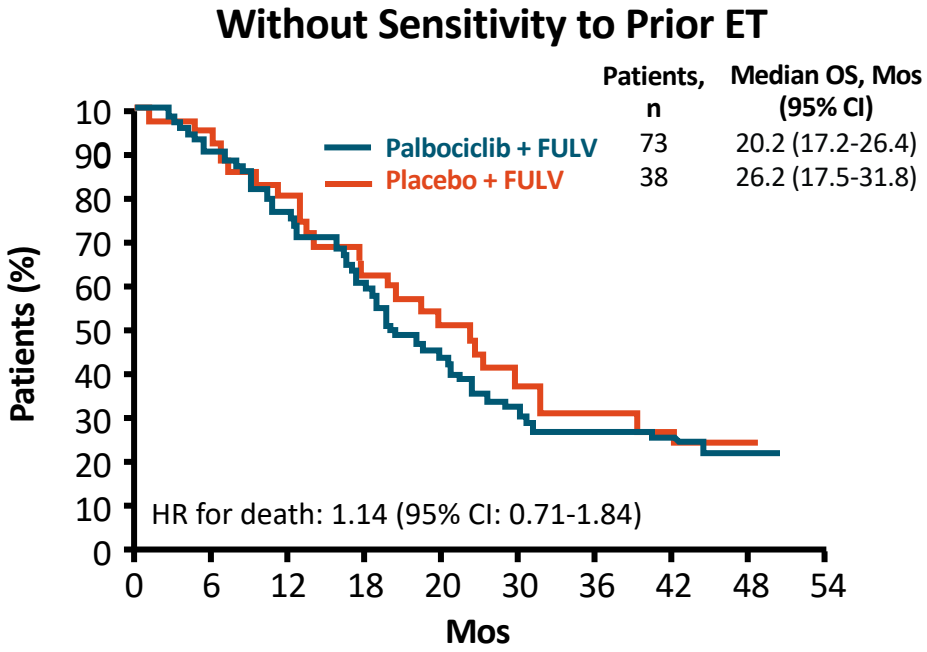


Interaction P-value: 0.588

Sledge et al. JAMA Oncology 2019

Phase III PALOMA-3: OS With Palbociclib + Fulvestrant by Sensitivity to Endocrine Therapy





- OS in ITT population: 34.9 mos with palbociclib vs 28.0 mos with placebo (HR: 0.81; *P* = .09)
- Long responders (> 18 mos) to palbociclib + fulvestrant more likely to have 1 site of MBC, less pretreatment, WT *ESR1* and *PIK3CA*, PgR+ disease

Turner. NEJM. 2018;379:1926.

Summary of Phase 3 Trials

- Survival advantage for Ribociclib + ET in premenopausal and combined 1st/2nd line postmenopausal settings
- Abemaciclib prolonged OS in 2nd line setting
  - Marked benefit in patients with endocrine resistance
- Palbociclib (PALOMA-3): OS Benefit in endocrine sensitive cohort
- Direct comparisons of CDK4/6i are lacking
  - Important differences in toxicity profiles
  - Are there differences in antitumor activity?

Cross-Trial Comparison of Toxicity: PALOMA-2, MONALEESA-2, and MONARCH 3

Adverse Event ≥5%	Palbociclib plus Letrozole			Ribociclib + Letrozole			Abemaciclib plus AI		
	Any (%)	G 3 (%)	G 4 (%)	Any (%)	G 3 (%)	G 4 (%)	Any (%)	G 3 (%)	G 4 (%)
Neutropenia	79.5	56.1	10.4	74.3	49.7	9.6	41.3	19.6	1.6
Diarrhea	26.1	1.4	0	35.0	1.2	0	81.3	9.5	0
Nausea	35.1	0.2	0	51.5	2.4	0	38.5	11.0	0.9
Vomiting	15.5	0.5	0	29.3	3.6	0	28.4	1.2	0
Increased ALT			<0.01	15.6	7.5	1.8	15.6	5.8	0.3

VTE: abemaciclib (4.9%)
Prolonged QTcF: Ribociclib (2.7%)

Other Distinguishing Differences

- Different toxicity profiles
  - Neutropenia: palbociclib and ribociclib >> abemaciclib
  - GI toxicity: abemaciclib >> ribociclib > palbociclib
  - Uncommon side effects:
    - abemaciclib (VTE, 4.9%)
    - ribociclib (prolonged QTcF interval, 2.7%)
- CNS penetration:
  - Abemaciclib>>palbociclib
  - Ribociclib exhibits BBB penetration

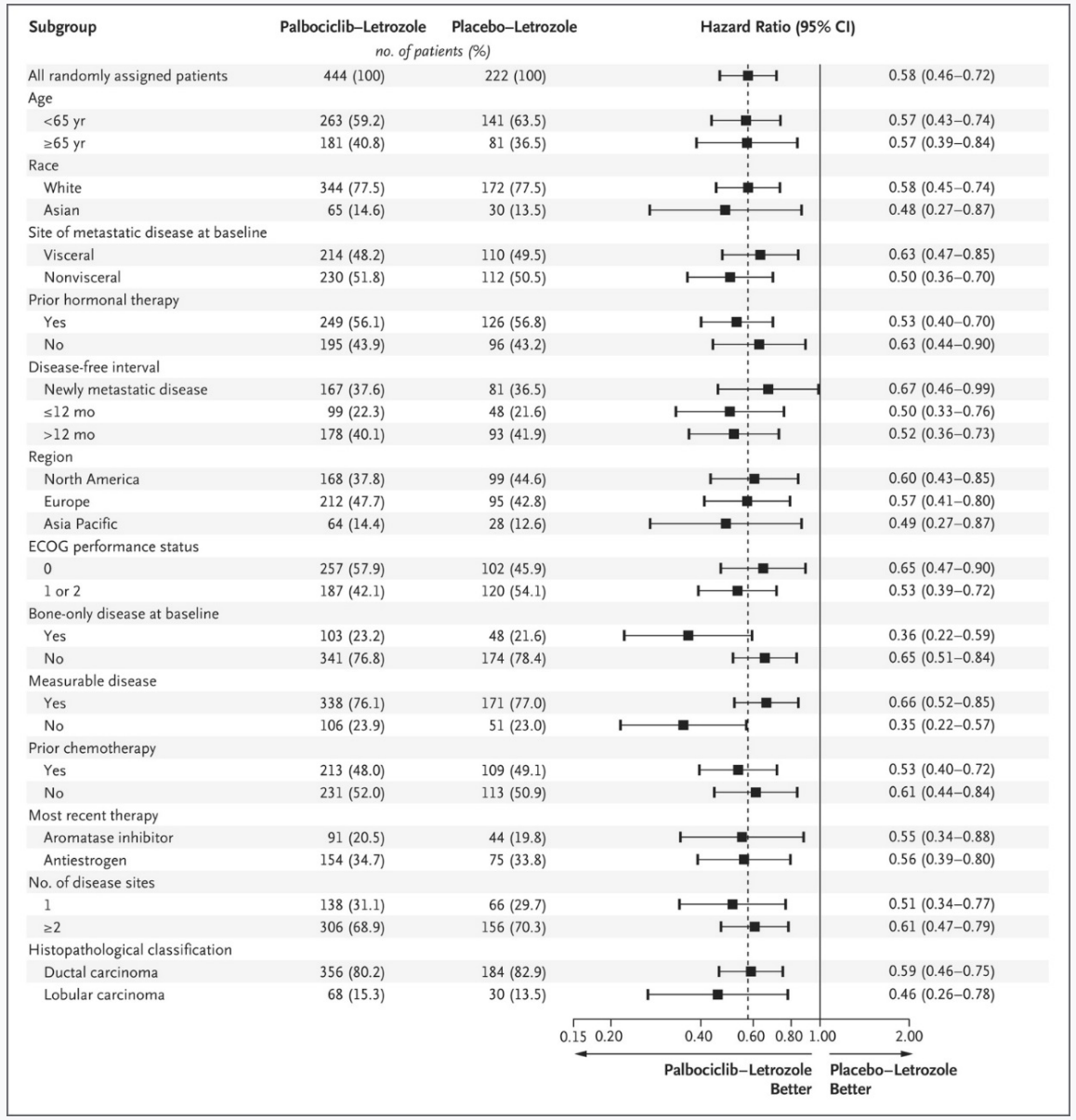
Patel YT, et al. Neuro Oncol 2016;18Suppl 6. Abstract nr PDTB-12
Raub et al. Drug Metabolism and Disposition 2016

FDA Warning About Rare Severe Lung Inflammation with CDK4/6 Inhibitors

- The FDA is warning that palbociclib, ribociclib, and abemaciclib used to treat some patients with advanced breast cancers may cause rare but severe inflammation of the lungs.
- The FDA has approved new warnings about this risk to the prescribing information and Patient Package Insert for the entire class of the CDK4/6 inhibitors.
- The overall benefit of CDK4/6 inhibitors is still greater than the risks when used as prescribed.
- **Patients** should notify health care professionals right away about any new or worsening symptoms involving the lungs, as they may indicate a rare but life-threatening condition that can lead to death. Symptoms to watch for include:
  - Difficulty or discomfort with breathing
  - Shortness of breath while at rest or with low activity
- **Health care professionals** should monitor patients regularly for pulmonary symptoms indicative of interstitial lung disease (ILD) and/or pneumonitis. Signs and symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams in patients in whom infectious, neoplastic, and other causes have been excluded.
  - Interrupt CDK4/6 inhibitor treatment in patients who have new or worsening respiratory symptoms, and permanently discontinue treatment in patients with severe ILD and/or pneumonitis

https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-severe-lung-inflammation-ibrance-kisqali-and-verzenio-breast-cancer

Subgroup Analysis of PFS: PALOMA-2



Subgroup	Palbociclib–Letrozole	Placebo–Letrozole	Hazard Ratio (95% CI)
	no. of patients (%)		
All randomly assigned patients	444 (100)	222 (100)	0.58 (0.46–0.72)
Age			
<65 yr	263 (59.2)	141 (63.5)	0.57 (0.43–0.74)
≥65 yr	181 (40.8)	81 (36.5)	0.57 (0.39–0.84)
Race			
White	344 (77.5)	172 (77.5)	0.58 (0.45–0.74)
Asian	65 (14.6)	30 (13.5)	0.48 (0.27–0.87)
Site of metastatic disease at baseline			
Visceral	214 (48.2)	110 (49.5)	0.63 (0.47–0.85)
Nonvisceral	230 (51.8)	112 (50.5)	0.50 (0.36–0.70)
Prior hormonal therapy			
Yes	249 (56.1)	126 (56.8)	0.53 (0.40–0.70)
No	195 (43.9)	96 (43.2)	0.63 (0.44–0.90)
Disease-free interval			
Newly metastatic disease	167 (37.6)	81 (36.5)	0.67 (0.46–0.99)
≤12 mo	99 (22.3)	48 (21.6)	0.50 (0.33–0.76)
>12 mo	178 (40.1)	93 (41.9)	0.52 (0.36–0.73)
Region			
North America	168 (37.8)	99 (44.6)	0.60 (0.43–0.85)
Europe	212 (47.7)	95 (42.8)	0.57 (0.41–0.80)
Asia Pacific	64 (14.4)	28 (12.6)	0.49 (0.27–0.87)
ECOG performance status			
0	257 (57.9)	102 (45.9)	0.65 (0.47–0.90)
1 or 2	187 (42.1)	120 (54.1)	0.53 (0.39–0.72)
Bone-only disease at baseline			
Yes	103 (23.2)	48 (21.6)	0.36 (0.22–0.59)
No	341 (76.8)	174 (78.4)	0.65 (0.51–0.84)
Measurable disease			
Yes	338 (76.1)	171 (77.0)	0.66 (0.52–0.85)
No	106 (23.9)	51 (23.0)	0.35 (0.22–0.57)
Prior chemotherapy			
Yes	213 (48.0)	109 (49.1)	0.53 (0.40–0.72)
No	231 (52.0)	113 (50.9)	0.61 (0.44–0.84)
Most recent therapy			
Aromatase inhibitor	91 (20.5)	44 (19.8)	0.55 (0.34–0.88)
Antiestrogen	154 (34.7)	75 (33.8)	0.56 (0.39–0.80)
No. of disease sites			
1	138 (31.1)	66 (29.7)	0.51 (0.34–0.77)
≥2	306 (68.9)	156 (70.3)	0.61 (0.47–0.79)
Histopathological classification			
Ductal carcinoma	356 (80.2)	184 (82.9)	0.59 (0.46–0.75)
Lobular carcinoma	68 (15.3)	30 (13.5)	0.46 (0.26–0.78)

Benefit of palbociclib consistently observed across all subgroups

Finn et al. NEJM 2016

Abemaciclib: Outcomes in Prognostic Subgroups from MONARCH 2 and 3

MONARCH 2			
	placebo arm (%)	abemaciclib arm (%)	delta (%)
PgR - Negative	9.68	43.94	34.26
Liver Metastases - Yes	15.25	48.65	33.39
High Grade	20.83	51.32	30.48
Bone-only Disease - No	21.79	49.50	27.70
Low/intermediate Grade	19.51	47.06	27.55
ECOG PS - 0	20.59	47.47	26.89
ECOG PS - 1	22.58	49.17	26.59
PgR - Positive	25.40	50.00	24.60
Liver Metastases - No	24.76	47.83	23.06

MONARCH 3			
	placebo arm (%)	abemaciclib arm (%)	delta (%)
Liver Metastases - Yes	20.69	54.17	33.48
PgR - Negative	27.59	59.02	31.43
High Grade	39.29	69.09	29.80
ECOG PS - 1	42.86	65.18	22.32
Low/intermediate Grade	43.84	64.29	20.45
Bone-only Disease - No	42.98	60.32	17.34
PgR - Positive	48.51	59.31	10.80
ECOG PS - 0	44.44	54.84	10.40
Liver Metastases - No	50.50	60.27	9.77

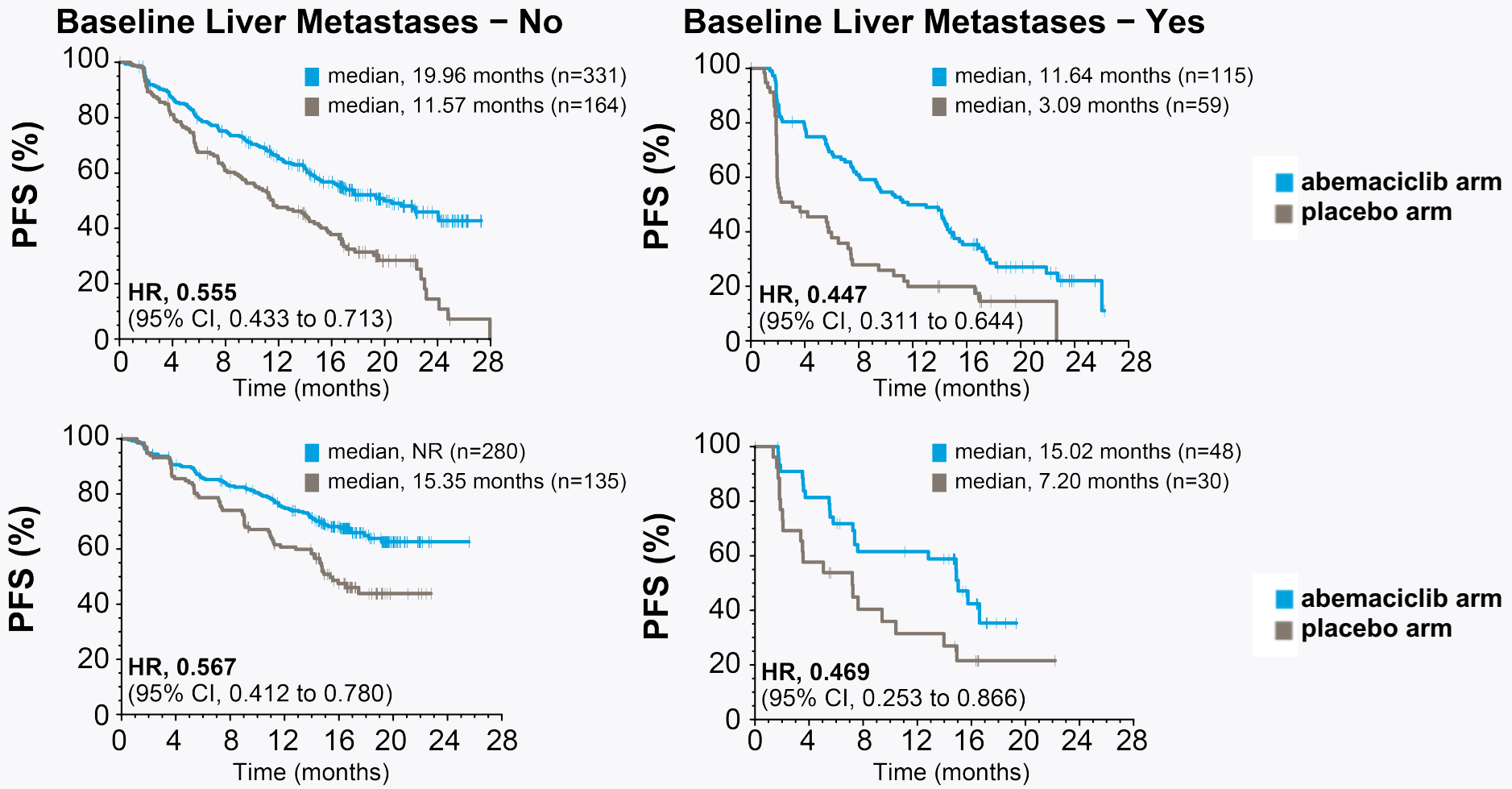
Note: *Response rates are not reported for bone-only disease since the majority of lesions were not measurable*

Goetz et al. SABCS 2017
Di Leo A, et al. NPJ Breast Cancer 2018

Liver Metastases

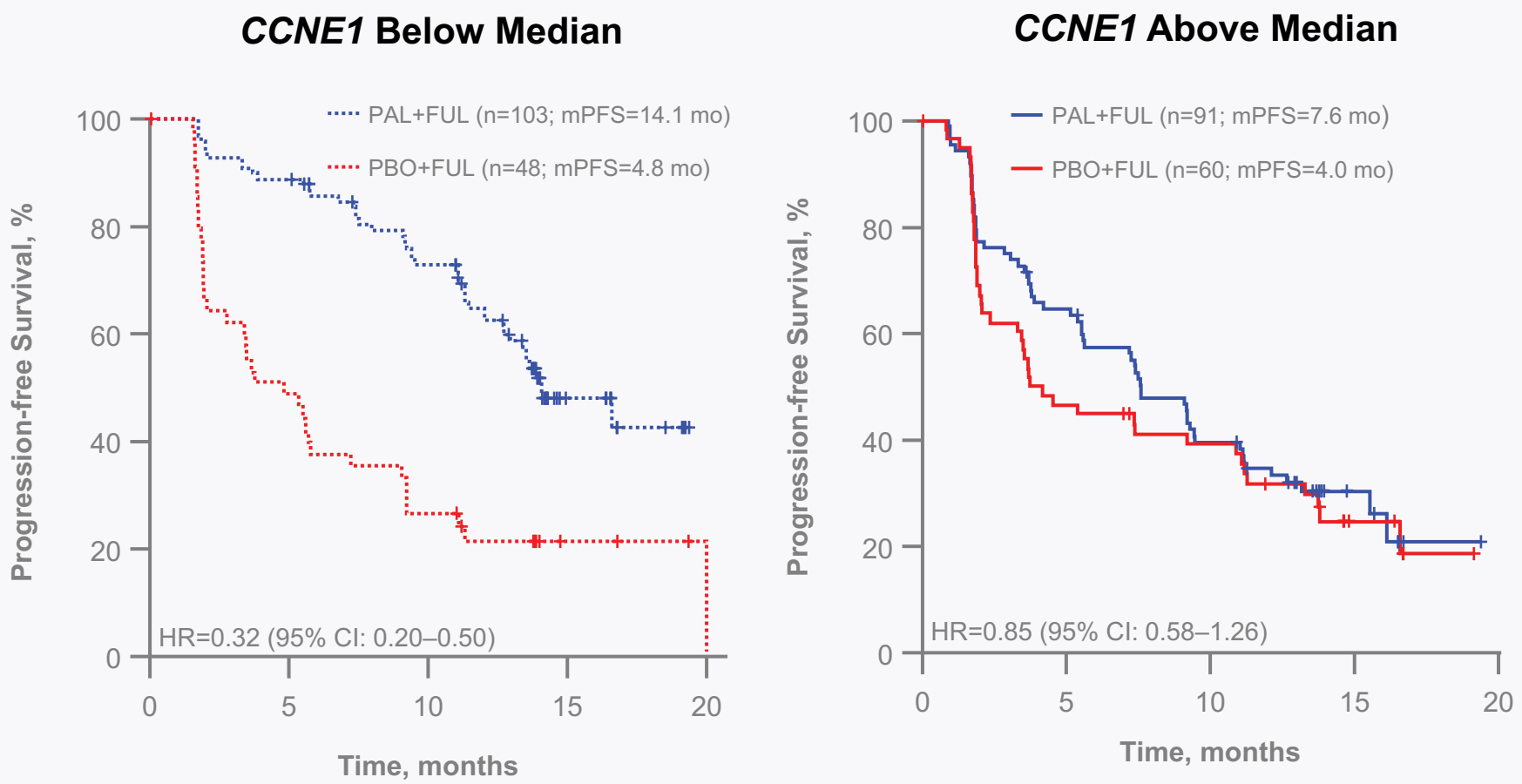
MONARCH 2
fulvestrant +/- abemaciclib

MONARCH 3
NSAI +/- abemaciclib



Goetz et al. SABCS 2017
Di Leo A, et al. NPJ Breast Cancer 2018

CCNE1 Expression and Palbociclib Benefit



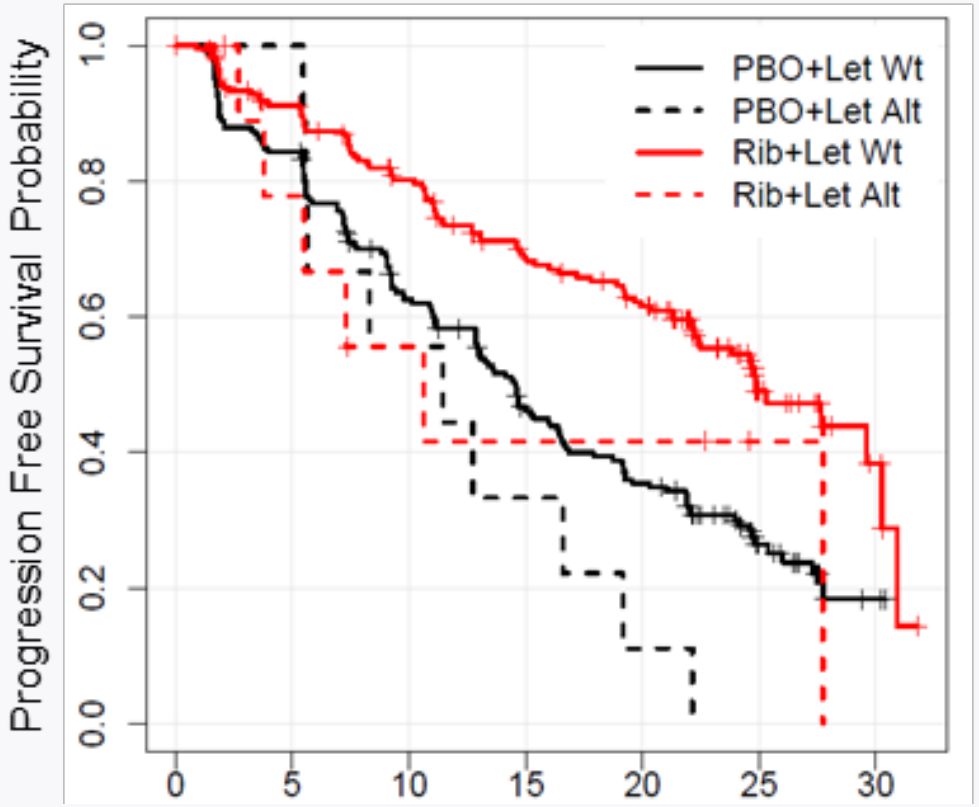
Interaction *P*=0.00238

CCNE1 expression retained association with benefit from palbociclib after adjusting for prognostic baseline characteristics

Turner et al. J Clin Oncol 2019

FGFR1 amplification ctDNA and early progression on ribociclib

MONALEESA-2



Legend	Group	N	Median PFS	HR (95% CI)	*p*
———	Rib + Let FGFR1/ZNF703 WT	202	24.84	2.14 (0.93 – 4.94)	$7.50e\text{-}^{0.2}$
·····	Rib + Let FGFR1/ZNF703 ALT	10	10.61		
———	PBO + Let FGFR1/ZNF703 WT	205	14.59	1.61 (0.82 – 3.17)	$1.70e\text{-}^{0.1}$
·····	PBO + Let FGFR1/ZNF703 ALT	10	11.43		

Formisano et al. Nat Commun 2019

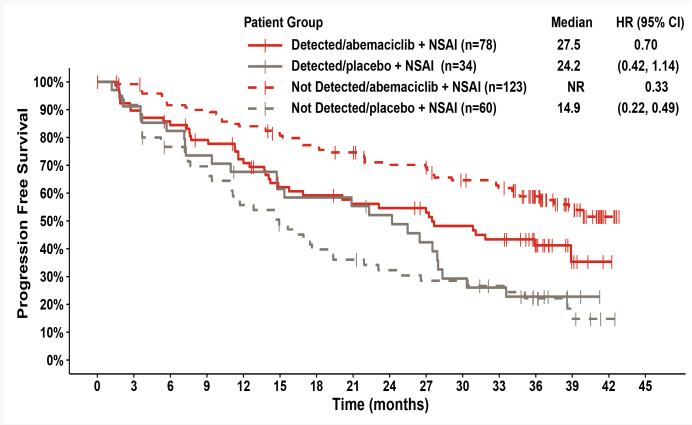
Efficacy of abemaciclib based on genomic alterations detected in baseline circulating tumor DNA from the MONARCH 3 study of abemaciclib plus nonsteroidal aromatase inhibitor

Matthew P. Goetz,[1] J. Thaddeus Beck,[2] Mario Campone,[3] Sara A. Hurvitz,[4] Seock-Ah Im,[5] Stephen Johnston,[6] Antonio Llombart-Cussac,[7] Miguel Martin,[8] Joohyuk Sohn,[9] Masakazu Toi,[10] Lacey M. Litchfield,[11] Hillary T. Graham,[11] Hong Wang,[11] Sameera R. Wijayawardana,[11] Valerie M. Jansen,[11] Angelo Di Leo[12]

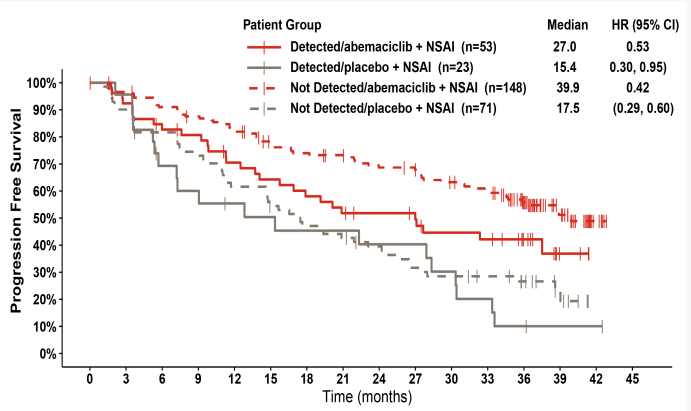
Goetz et al. SABCS 2019 Spotlight Poster Discussion

PFS in Patients with Target Genomic Alterations and Signaling Pathways

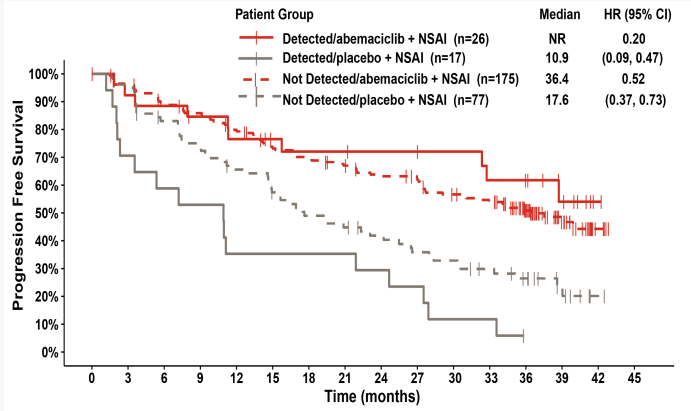
PIK3CA



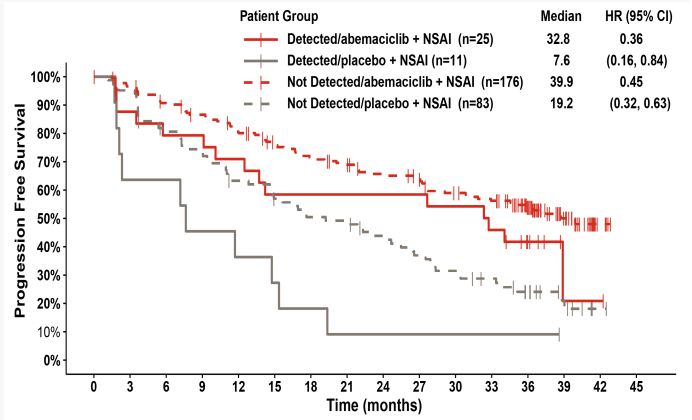
TP53



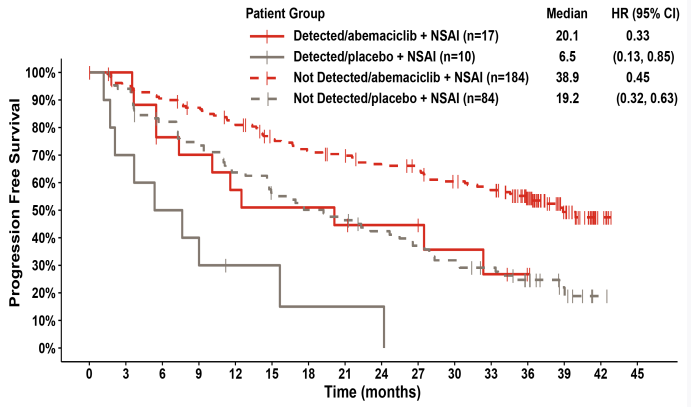
EGFR



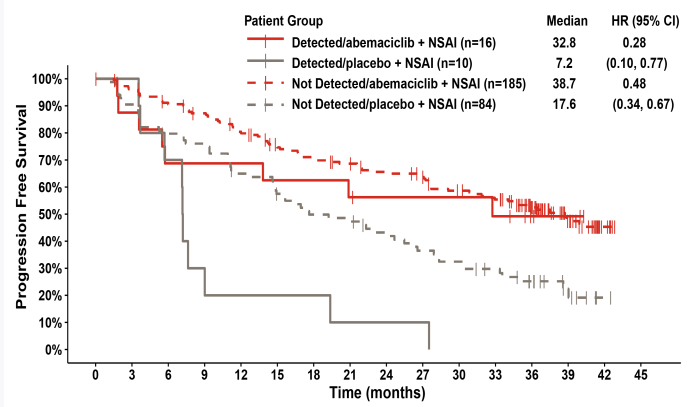
FGFR1



MYC



CCND1



CI, confidence interval; HR, hazard ratio; n, number of patients at risk; NR, not reached; NSAI, nonsteroidal aromatase inhibitor; PFS, progression-free survival

Goetz et al. SABCS 2019 Spotlight Poster Discussion

Summary

- Emerging survival data suggest that CDK4/6i are a critical component of proper endocrine treatment in MBC
- Differences in CDK4/6i toxicity profiles may be used to individualize treatment
- Conclusions regarding differences in antitumor activity not possible without “head to head” trials
- There may be considerations for certain CDK4/6i in poor prognosis risk groups:
  - Abemaciclib in poor prognostic subgroups (e.g. liver metastases) or patients with predicted primary endocrine resistance (ctDNA alterations in FGFR, EGFR, MYC)
  - Abemaciclib and ribociclib improved OS in difficult to treat settings
    - ribociclib in premenopausal setting
    - abemaciclib in 2nd line setting

Case Presentation: Dr Sparano

49 year old black male presented with left breast mass and cough in September 2018.

- Workup showed lung and bone mets, confirmed left breast mass. Biopsy of both lung and breast showed ER+, PR+, HER2- ductal carcinoma. Genetics negative.
- Began tamoxifen, had PE 2 weeks later. Abemaciclib and denosumab added.
- Symptoms and left breast mass resolved. CA 22-29 declined from 786 to 99, scans improved, lytic lesions now blastic.