When and how to use the CDK4/6 inhibitor in metastatic breast cancer

Masakazu Toi, M.D., Ph.D.

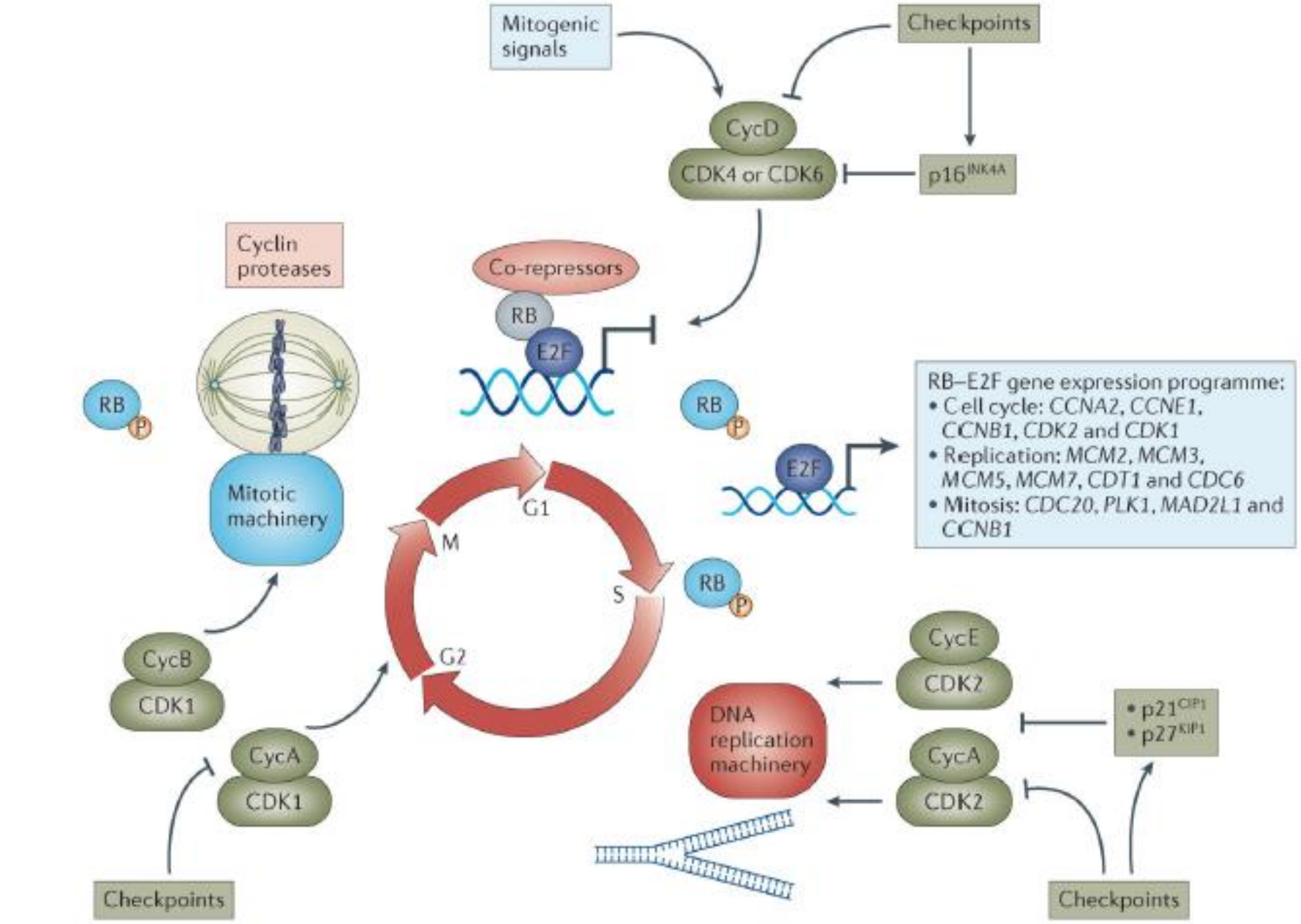
Kyoto University Graduate School of Medicine

SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

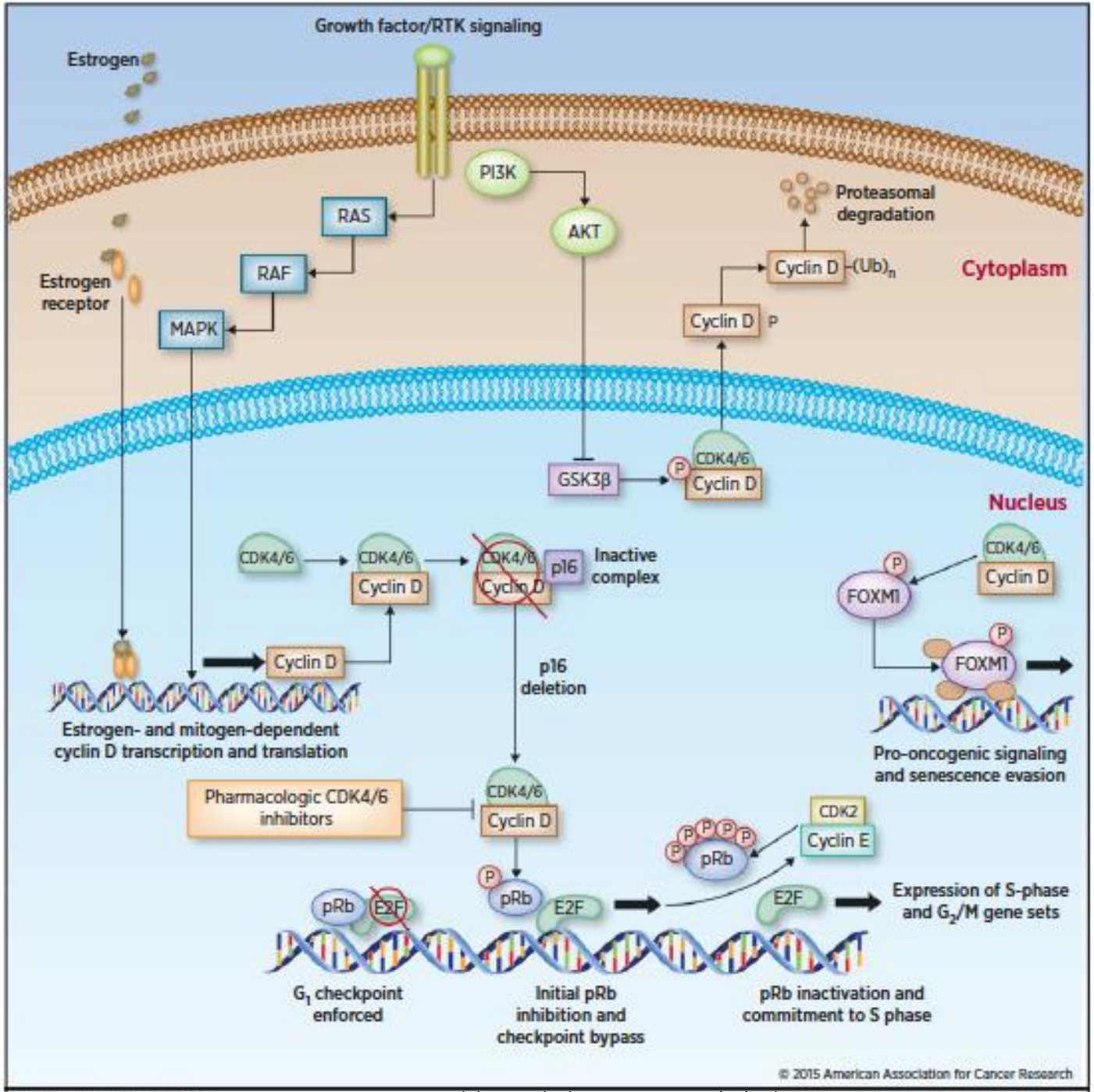
Disclosure slide

Research grant from:

Novartis, Taiho Pharmaceutical Co. Ltd, Chugai Pharmaceutical Co. Ltd



Uzma Asghar et al. The history and future of targeting cyclin-dependent kinases in cancer therapy Nat Rev Drug Discov. 2015 February ; 14(2): 130–146.



VanArsdale T et al Clin Cancer Res; 21(13) July 1, 2015,

TCGA molecular portraits

	Luminal A	Lum B	Basaloid	HER2-E
P53 pathway	TP53 mt 12% MDM2 gain 14%	32% 31%	84% 14%	75% 30%
PIK3CA/PTEN	PIK3CA 49% PTEN loss 13%	32% 24%	7% 35%	42% 19%
RB pathway	Cyclin D1 amp 29% CDK4 gain14% Low CDKN2C, High RB1	58% 25%	RB1 mut/loss 20% Cyclin E1 amp 9% High CDKN2A, Low RB1	Cyclin D1 amp 38% CDK4 gain 24%
Copy N	Most diploid	Most aneuploid	High Instability, Most aneuploid	High instability, Most aneuploid

The Cancer Genome Atlas, Nature 490:61, 2012

Cell lines from most sensitive (low IC50) to least sensitive (high IC50)

Cyclin D1, p16 & RB1 are predictive biomarkers in BC Lines

Cell line	IC50g	GSK461364	Subtype	ER-status	HER2 Status	p16-INK	Cell line	13q loss	RB1	RB1-RNA	RB1-prot	9p loss	p16	p16-RNA	p16-prot	Cyclin D1	Cyclin D1-RNA	Cyclin D1-prot	CDK4	CDK4-RNA	CDK4-prot
MB-175	4	0.4	Luminal-A	Pos	Normal		MDA-MB-1	No	Wild-type	+	+	No	Wild-type	+	±	Gain	++	+	Balanced	+	+
ZR75-30	5	0.5	Luminal-A	Pos	Amplified		ZR75-30			+	+	No	Wild-type	+	+	Balanced	+	++	Balanced	+	+
CAMA-1	8	0.4	Luminal	Pos	Normal		CAMA-1	No	Wild-type	+	+	No	Wild-type	+	+	Gainamp	++	++	Balanced	+	+
MB134	13	1.3	Luminal-A	Pos	Normal		MDA-MB-1	No	Wild-type	+	+	No	Wild-type	+	?	Gainamp	++	++	Balanced	+	+
HCC202	21	2.3	Luminal-B	Pos	Amplified																
UACC-893	24	1.6	Luminal-B	Pos	Amplified		UACC893	Yes	Wild-type	±	+	No	Methylated	±	+	Balanced	+	+	Balanced	+	+
EFM19	27	12.3	Luminal-A	Pos	Normal	D															
SUM190	28	1.3	Luminal	Pos	Amplified																
EFM192A	42	21.2	Luminal	Pos	Amplified																
MB-361	44	4.1	Luminal-A	Pos	Amplified	M	MDA-MB-3	Yes	Wild-type	+	+	Yes	Mutant	+	±	Balanced	+	+	Balanced	+	+
HCC1500	45	22.6	Luminal-A	Pos	Normal																
HCC1419	51	3.7	Luminal-A	Pos	Amplified																
HCC38	64	14.8	Basal	Neg	Normal	D															
MB-415	64	6.6	Luminal	Pos	Normal		MDA-MB-4	No		++	+	No	Mutant*	++	±	Gainamp	++	++	Balanced	+	+
MCF-10A	92	0.1	n/a	Neg	Immortalized																
UACC-812	96	4.6	Luminal-A	Pos	Amplified		UACC812	Yes	Wild-type	+	+	No	Methylated	±	+	Balanced	+	+	Balanced	+	+
HCC2218	100	17	Luminal-B	Pos	Amplified																
ZR75-1	110	54.1	Luminal-A	Pos	Normal		ZR75-1	Yes	Wild-type	+	+	No	Methylated	±	+	Gainamp	++	++	Balanced	+	+
MDAMB453	115	1.4	Luminal-B	Neg	Amplified		MDA-MB-4	No	Wild-type	+	+	Yes	Wild-type	+	±	Balanced	+	+	Balanced	+	+
184A1	118	2	n/a	Neg	Immortalized																
T47D	127	15	Luminal-A	Pos	Normal	WT	T47D	Yes	Wild-type	+	+	Yes	Methylated	?	?	Balanced	+	+	Balanced	+	+
MCF7	148	25.7	Luminal-A	Pos	Normal	D	MCF-7	Yes	Wild-type	+	+	Yes	Deleted	?	?	Balanced	+	+	Balanced	+	+
BT-20	177	3.1	Basal	Neg	Normal	D	BT20	Yes	Mutant?	+	+	Yes	Deleted	?	?	Balanced	+	±	Balanced	+	+
MDAMB435	201	7.5	post-EMT	Neg	Normal	M	MDA-MB-4	Yes	Wild-type	+	+	Yes	Mutant	++	+	Balanced	±	±	Balanced	+	+
BT474	240	64.5	Luminal-A	Pos	Amplified		BT474	Yes	Wild-type	+	+	Yes	Wild-type	+	+	Gain	+	+	Balanced	+	+
SKBR3	300	83	Luminal-B	Neg	Amplified		SK-BR-3	Yes	Wild-type	+	+	No	Wild-type	+	+	Balanced	+	+	Balanced	+	+
KPL-1	327	64.3	Luminal	Pos	Normal																
HCC1143	359	99.7	Basal	Neg	Normal																
MDAMB231	470	16	post-EMT	Neg	Normal		MDA-MB-2	Yes	Wild-type	+	++	Yes	Deleted	?	?	Balanced	+	+	Balanced	+	+
HCC1395	472	39.8	post-EMT	Neg	Normal	D															
SUM-225	503	55.7	Luminal	Neg	Amplified																
HS578T	524	12.3	post-EMT	Neg	Normal	D	Hs578T	Yes	Wild-type	±	+	Yes	Deleted	?	?	Balanced	+	+	Balanced	+	+
184B5	538	41.1	n/a	Neg	Immortalized																
UACC732	744	14.9	Luminal	Pos	Amplified																
CAL-51	905	0	post-EMT	Neg	Normal																
BT549	1000	n/a	post-EMT	Neg	Normal	WT	BT549	Yes	Deleted	?	?	No	Wild-type	++	++	Balanced	±	±	Balanced	+	+
HCC1187	1000	n/a	Basal	Neg	Normal																
HCC1937	1000	n/a	post-EMT	Neg	Normal		HCC1937	Yes	Deleted	+	?		Wild-type	++	++	Balanced	+	+	Balanced	+	+
HCC1954	1000	n/a	Basal	Neg	Amplified																
HCC70	1000	n/a	Basal	Neg	Normal																
HCC1569	1000	n/a	post-EMT	Neg	Amplified																
HCC1806	1000	n/a	Basal	Neg	Normal	D															
COLO824	1000	n/a	Basal	Neg	Normal																
DU4475	1000	n/a	Basal	Neg	Normal		DU4475	Yes	Deleted	?	?	No	Wild-type	+	?	Balanced	±	±	Balanced	+	+
MB157	1000	n/a	post-EMT	Neg	Normal		MDA-MB-1	Yes	Wild-type	±	+	Yes	Wild-type	++	++	Balanced	+	+	Balanced	+	+
MB-436	1000	n/a	post-EMT	Neg	Normal		MDA-MB-4	Yes	Mutant	±	?	Yes	Wild-type	++	++	Balanced	±	±		+	+

IC_{50} < 20 nM
100% High cyclin D1
100% normal RB1

IC_{50} < 100 nM

IC_{50} < 100 nM

IC_{50} < 100 nM

IC_{50} < 100 nM

IC_{50} 100 nM -200nM

IC_{50} 100 nM -200nM

IC_{50} 200 nM -500nM

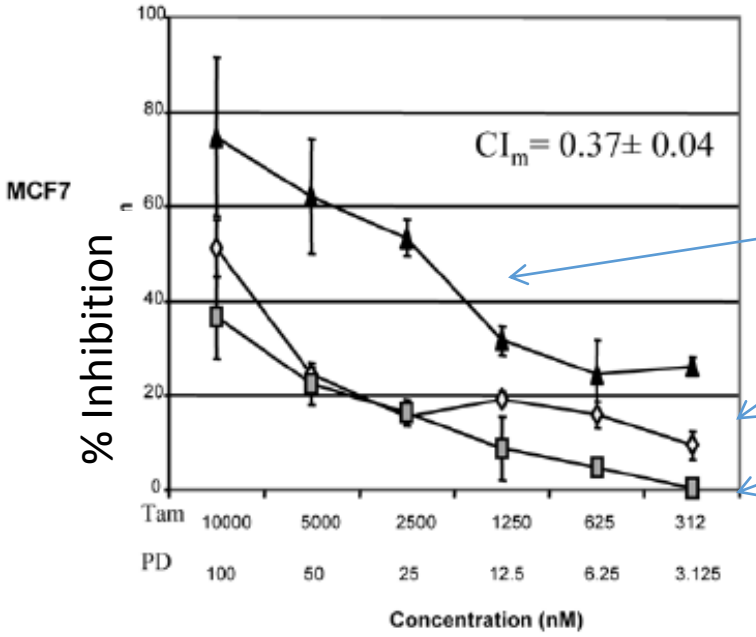
IC_{50} 200 nM -500nM

IC_{50} 500 nM 1000nM

IC_{50} > 1000 nM
100% normal p16
0% normal RB1

Richard S Finn et al. Breast Cancer Research 2009, 11:R77 (doi:10.1186/bcr2419)

MCF7 Cell line (WT)



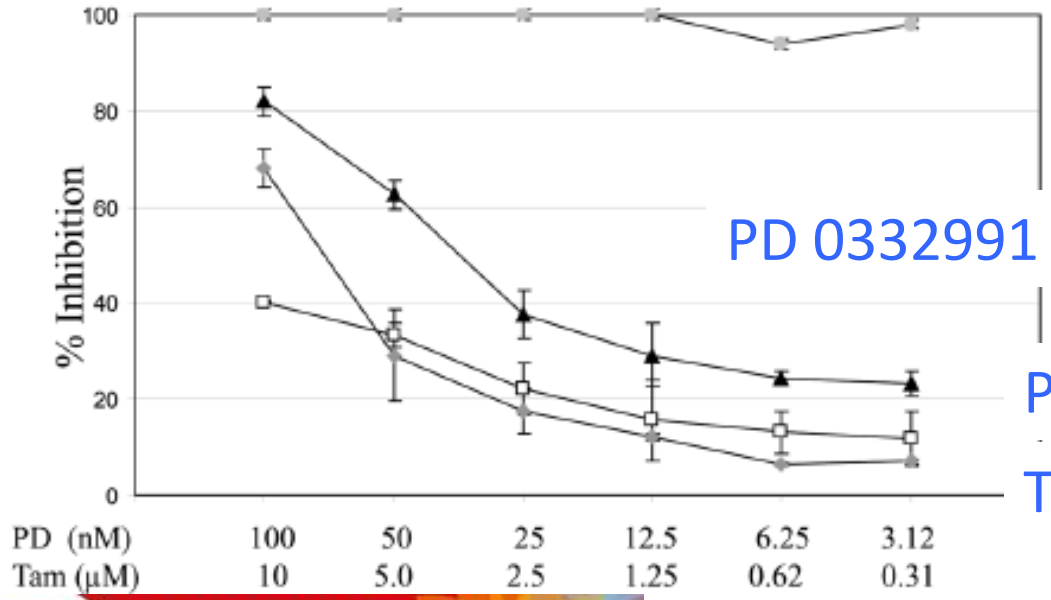
PD 0332991 + Tamoxifen

Tamoxifen

PD 0332991

MCF7 parental with tamoxifen alone

MCF7 (Tamoxifen-insensitive)



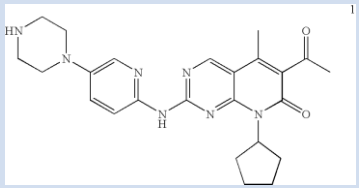
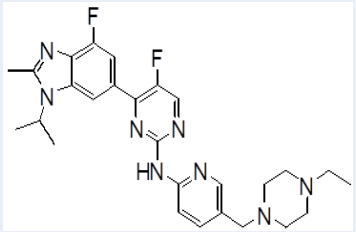
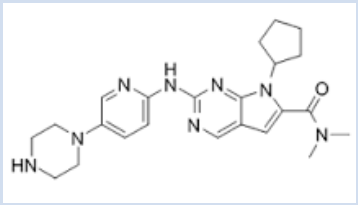
PD 0332991 + Tamoxifen

PD 0332991

Tamoxifen

Richard S Finn et al. Breast Cancer Research 2009, 11:

CDK4/6 inhibitors

Agent	Structure	CDK	Activity
Palbociclib		CDK4/ cyclin D1 CDK4/ cyclin D3 CDK6/ cyclin D2	IC50 11nM 9nM 15nM
Abemaciclib		CDK4/ cyclin D1 CDK6/ cyclin D3 CDK9	Ki (ATP) (nM) 0.6 ± 0.3 8.2 ± 1.1 57nM
Ribociclib		CDK4 CDK6	IC50 10nM 39nM

Fry DW et al. Mol Cancer Ther 2004;3(11), 1427-37.
Gelbert LM et al. *Invest New Drugs* 2014;32:825-37
Rader et al. Clin Cancer Res; 2013; 19(22): 6173-82

Toxicity Profile

Hematological toxicity

GI toxicity

Others

Comparison between 3 drugs (All Grades)
(+letrozole for palbociclib or ribociclib, monotherapy for abemaciclib)

Adverse Event	Palbociclib (n=83) n (%)	Abemaciclib (n=47) n (%)	Ribociclib (n=13) n (%)
Neutropenia	62 (74)	36 (77)	11 (85)
Leucopenia	36 (43)	41 (87)	5 (39)
Lymphopenia	NA	37 (78)	3 (23)
Fatigue	34 (40)	21 (45)	3 (23)
Anemia	29 (35)	38 (81)	3 (23)
Nausea	21 (25)	28 (60)	5 (39)
Diarrhea	17 (21)	32 (69)	1 (8)
Thrombocytopenia	14 (16)	31 (66)	NA
Vomiting	12 (14)	21 (45)	0 (0)

Finn *et al.*, *Lancet Oncol*, **16**, 25-35 (2015) (PALOMA-1)
Phase 1a study abemaciclib monotherapy in breast cancer (JPBA)
Munster *et al.*, Ph 1b study of LEE011 and BYL719 in combination with letrozole in ER+, HER2- breast cancer. ASCO, Sep 2014

Comparison between 3 drugs (Grade 3-4)
(+letrozole for palbociclib or ribociclib, monotherapy for abemaciclib)

Adverse Event	Palbociclib (n=83) n (%)	Abemaciclib (n=47) n (%)	Ribociclib (n=13) n (%)
Neutropenia	45 (54)	9 (19)	6 (46)
Leucopenia	16 (19)	9(19)	2 (4)
Lymphopenia	NA	12 (25)	3 (23)
Fatigue	4 (4)	1 (2)	NA
Anemia	5 (6)	3 (6)	0 (0)
Nausea	2 (2)	2 (4)	NA
Diarrhea	3 (4)	4 (9)	NA
Thrombocytopenia	2 (2)	3 (6)	NA

Finn *et al*., *Lancet Oncol*, **16**, 25-35 (2015) (PALOMA-1)
Phase 1a study abemaciclib monotherapy in breast cancer (JPBA)
Munster *et al*., Ph 1b study of LEE011 and BYL719 in combination with letrozole in ER+, HER2- breast cancer. ASCO, Sep 2014

Summary (1)

Cyclin D1 expression and CDK4 gain are enhanced in Luminal and HER2 disease.

The activity of CDK4/6 inhibitor is potent.

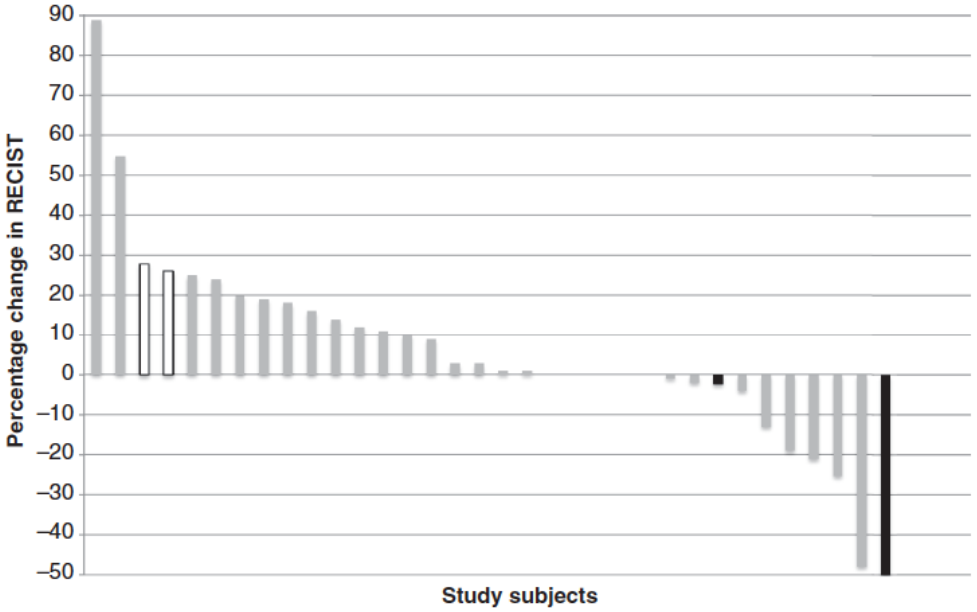
Combination with hormonal therapy is active even for tumors having resistance to hormone therapy.

The major adverse effects are neutropenia and diarrhea, and toxicity profile seem to differ slightly among 3 agents.

Efficacy Profile

- Palbociclib
- Abemaciclib
- Ribociclib

Palbociclib monotherapy



Response	No (%) ER+ 33pts
CR	0
PR	2 (6%)
SD (≥24wks)	5 (16%)
SD (<24wks)	13 (39%)
PD	13 (39%)

DeMichele A et al. Clin Cancer Res; 21(5) March 1, 2015

Palbociclib trials

Study		Endpoint	No
Palbociclib in combination with letrozole versus letrozole alone as first-line treatment of ER+, HER2-, advancedBC(PALOMA-1/TRIO-18)	rII	PFS	165
Combination with letrozole versus letrozole for first-line treatment of postmenopausal women with ER+/HER2-advanced BC (PALOMA-2)	III	PFS	650
Combined with fulvestrant in HR+, HER2- MBC after endocrine failure (PALOMA-3)	III	PFS	417
Letrozole and CDK 4/6 inhibitor as neoadjuvant therapy for ER+, HER2- BC in postmenopausal women	II	Response rates	45
PD 0332991 and anastrozole as neoadjuvant therapy for stage II or III ER+, HER2- BC	II	Cell cycle arrest	29
Adjuvant palbociclib in addition to standard endocrine treatment in HR+, HER2- patients with residual disease after neoadjuvant chemotherapy and surgery (PENELOPE)	III	Invasive DFS	800
Combination with exemestane versus chemotherapy (capecitabine) in HR+/HER2- MBC with resistance to nonsteroidal AIs (PEARL)	III	PFS	348

Neelima Vidula, Hope S. Rugo Clinical Breast Cancer 2015, Modified

ABC-3 (Lisbon 5-7/Nov)

Q1: The addition of the CDK4/6 inhibitor palbociclib to an aromatase inhibitor, as 1st line therapy, for post-menopausal patients, provided important PFS benefit in a randomized phase 2 study.
Results from the phase 3 trial (PFS and OS) are awaited before it can be considered as a recommended treatment option

YES 51.1%
NO 39.5%
A 9.3%

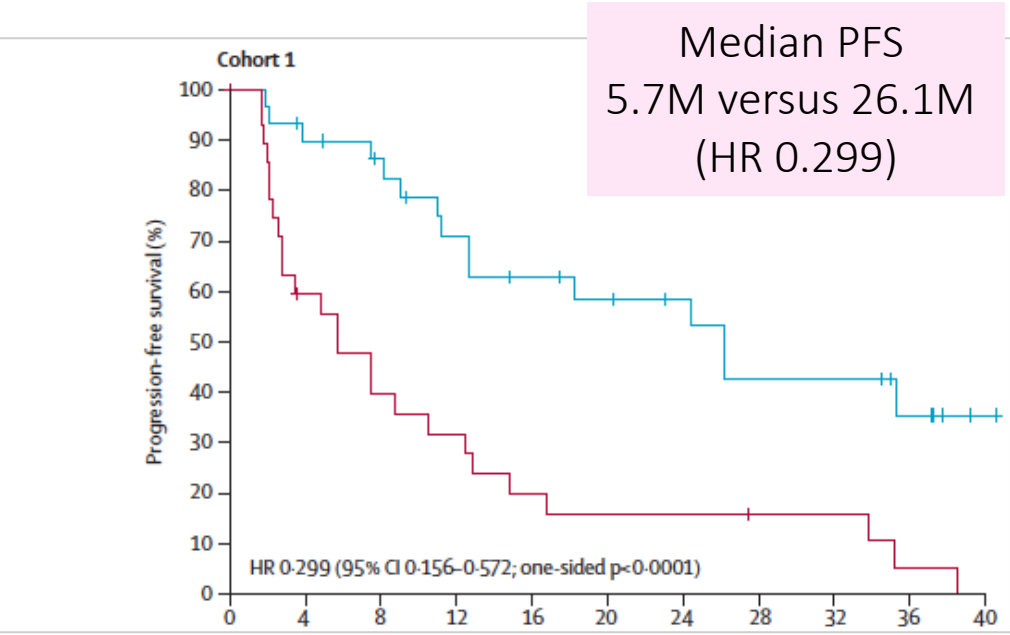
ABC-3 (Lisbon 5-7/Nov)

Q2: The addition of CDK/4/6 inhibitor palbiciclib to fulvestrant, beyond 1st line therapy, for pre/peri/post-menopausal patients, provided significant improvement in PFS (about 5 months) as well as improvement of QoL, and is a treatment option. OS results are awaited. For pre/peri-menopausal pts, LHRH-agonist must also be used.

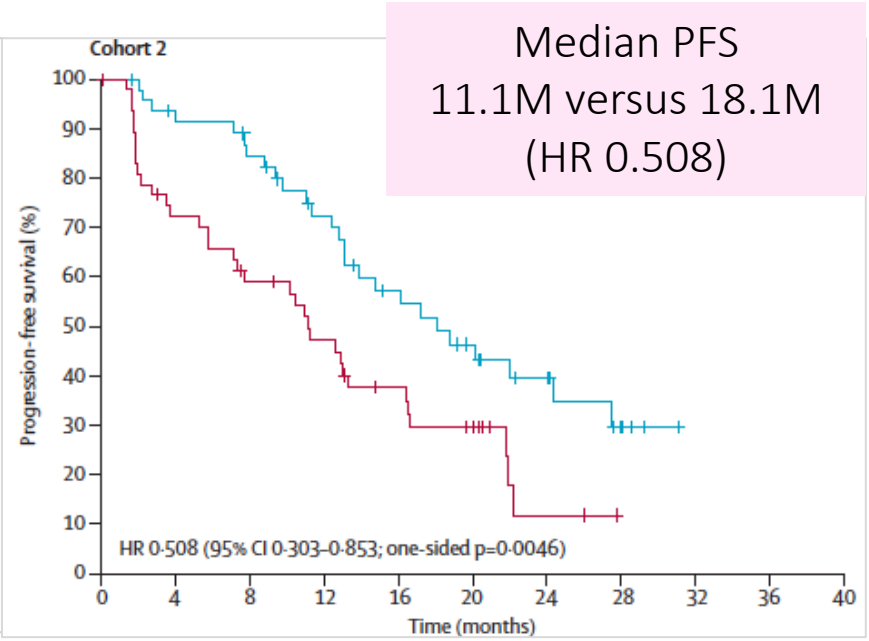
At present, no predictive biomarker other than hormone receptor status exists to identify patients who will benefit.

YES	85.7%
NO	4.7%
A	9.5%

Palbociclib + letrozole versus letrozole alone as 1st-line Tx in ER+/ HER2- MBC (PALOMA-1/TRIO-18: rP-II)



Median PFS
5.7M versus 26.1M
(HR 0.299)



Median PFS
11.1M versus 18.1M
(HR 0.508)

Cohort 1

ER+/HER2- alone (n=66)

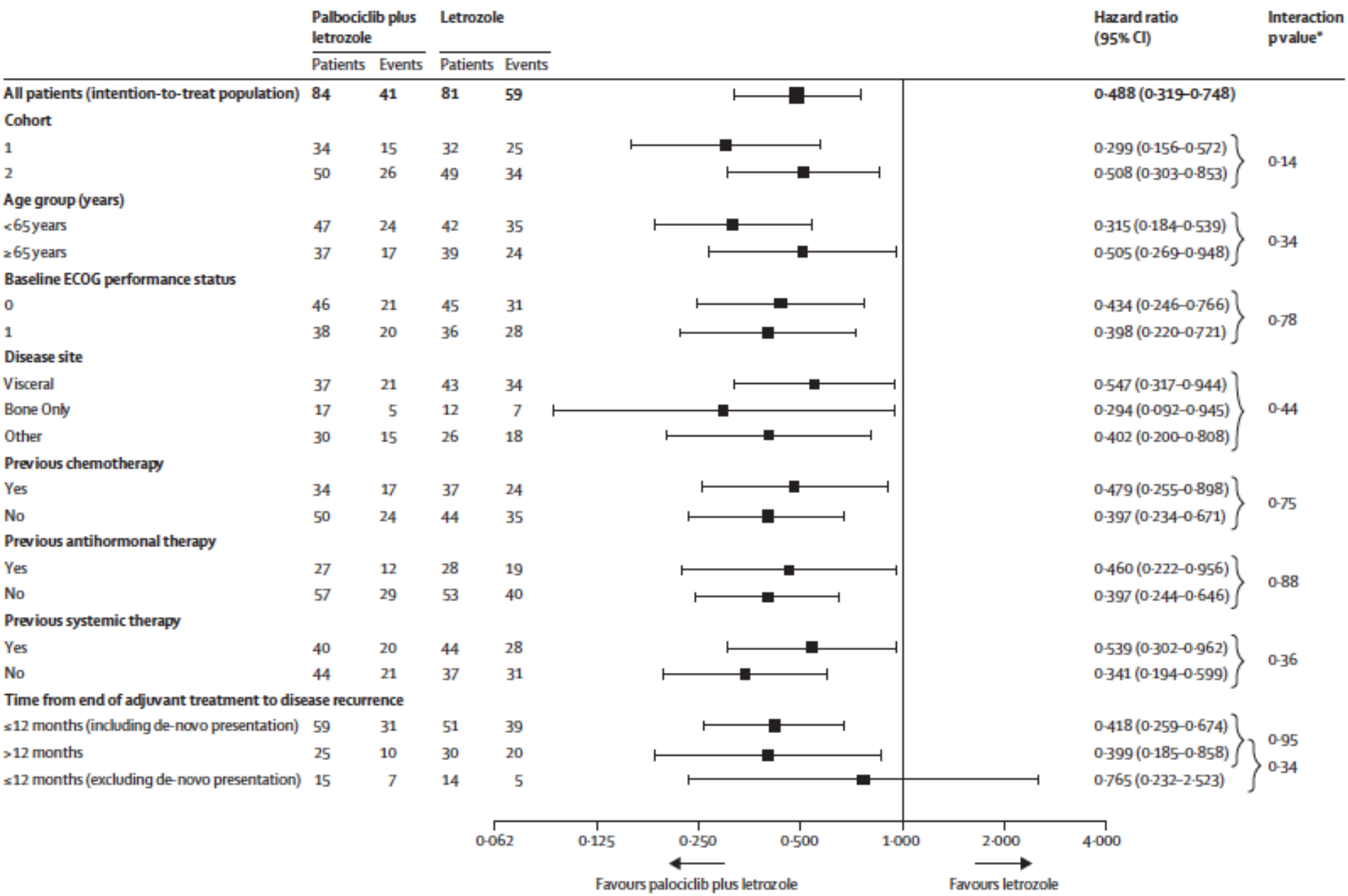
Cohort 2

ER+/HER2- (n=99) with cyclin D1 amplification, loss of p16 or both

Oral palbociclib 125 mg, given once daily for 3 weeks followed by 1 week off in 28-day cycles.

The mean relative dose intensity for palbociclib in the combination group was 94%

Finn RS et al. Lancet Oncol 2015; 16: 25–35



Finn RS et al. Lancet Oncol 2015; 16: 25–35

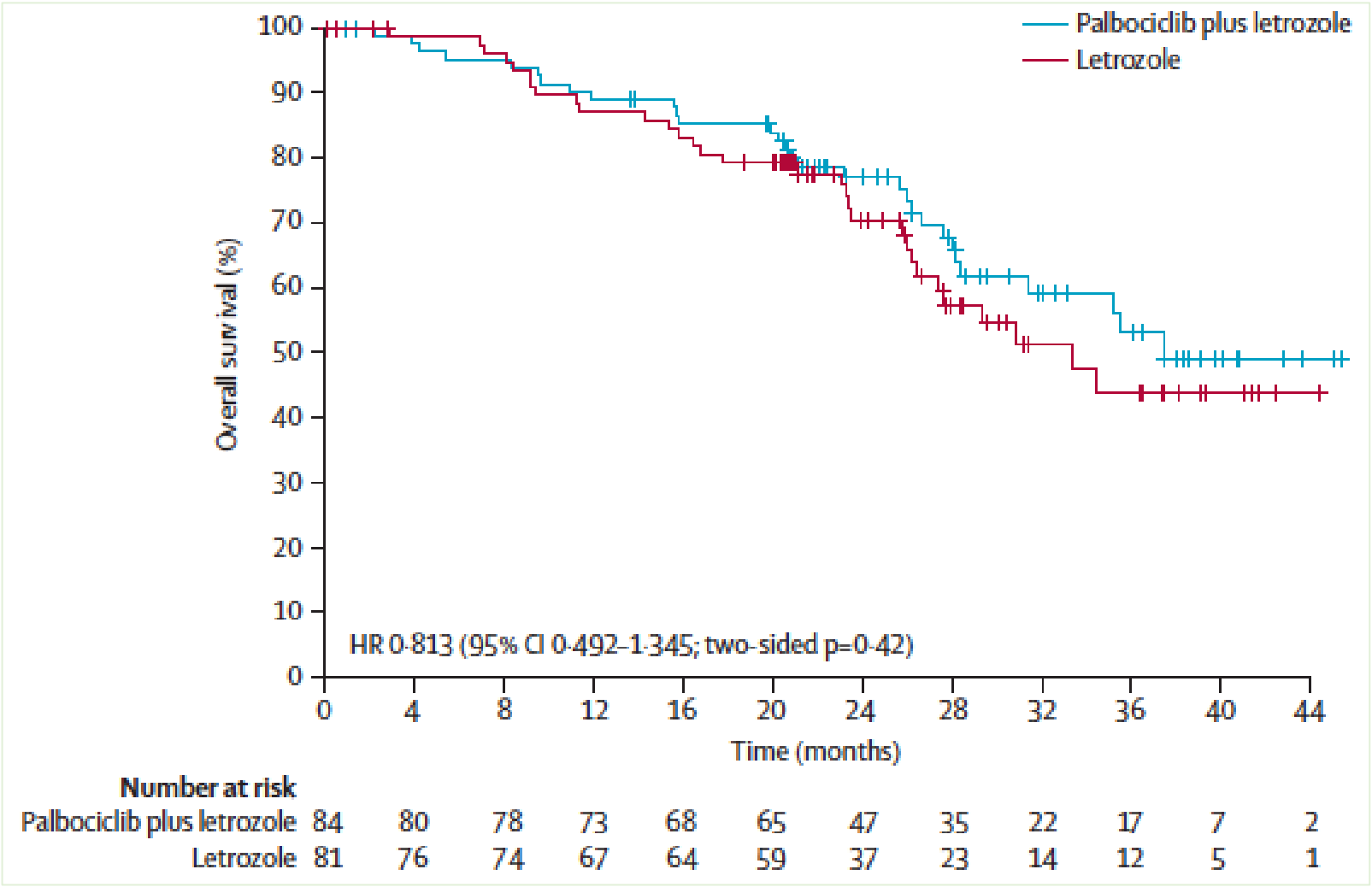
Palbociclib + letrozole versus letrozole alone as 1st-line Tx in ER+/ HER2- MBC (PALOMA-1/TRIO-18: rP-II)

-Measurable Diseases-

Response	Palbociclib	Placebo
CR	1 (2%)	0
PR	35 (54%)	26 (39%)
SD	20 (31%)	22 (33%)
PD	2 (3%)	15 (23%)
Indeterminate	7 (11%)	3 (5 %)

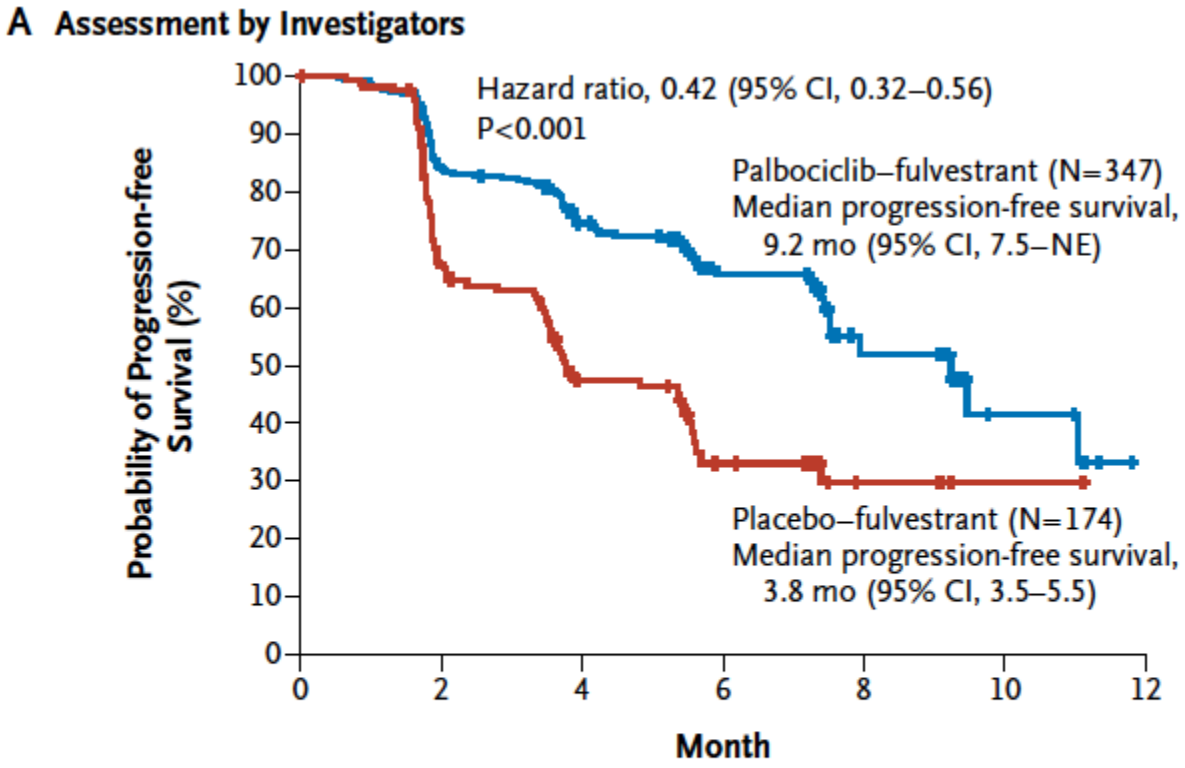
Finn RS et al. Lancet Oncol 2015; 16: 25–35

Palbociclib + letrozole versus letrozole alone as 1st-line Tx in ER+/ HER2- MBC (PALOMA-1/TRIO-18: rP-II)



Finn RS et al. Lancet Oncol 2015; 16: 25–35

Phase 3: Advanced HR+, HER2– BC that had relapsed or progressed during prior endocrine therapy N=521



No. at Risk						
Palbociclib–fulvestrant	347	279	132	59	16	6
Placebo–fulvestrant	174	109	42	16	6	1

N Engl J Med 2015;373:209-19.

ER+ and HER2+

Study of Palbociclib and Trastuzumab With or Without Letrozole in HER2-positive Metastatic Breast Cancer (PATRICIA)

- 2015.7-
- Phase II, open-label
- Post-menopausal patients with HER2-positive
- Locally advanced or metastatic breast cancer who have received chemotherapy and treatment with trastuzumab for their metastatic disease
- PFS, Safety

Abemaciclib trials

Study		Endpoints	No.
A study of LY2835219 in participants with previously treated BC that has spread (MONARCH-1)71	II	Objective response rate	128
Neoadjuvant study in postmenopausal women with HR+, HER2- (neoMONARCH)	II	Ki67 changes baseline to 2 wks	220
Abemaciclib in participants with BC that has spread to the brain	II	CR or PR rate intracranial	120
Combined with fulvestrant in women with HR+, HER2- BC with disease progression during previous hormone therapy (MONARCH-2)	III	PFS	550
Nonsteroidal aromatase inhibitors with abemaciclib as first-line therapy in post-menopausal women with BC (MONARCH 3)	III	PFS	450

Neelima Vidula, Hope S. Rugo Clinical Breast Cancer 2015, Modified

Ribociclib trials

Ribociclib		Endpoint	No
Study of LEE011, BYL719, and letrozole in advanced ER+ BC	Ib/II	Ib: toxicity II: PFS	300
Combination with everolimus and exemestane in the ER+/ HER2- ABC	Ib/II	Ib: toxicity II: PFS	185
A pharmacodynamics presurgical study in PBC (MONALEESA-1)	II	Cell cycle response	120
Combination with fulvestrant and BYL719 or BKM120 in advanced BC	Iib/III	Ib: toxicity II: PFS	216
LEE011 in postmenopausal women with advanced BC Letrozole +/- (MONALEESA-2)	III	PFS	650
LEE011 in combination with fluvestrant in premenopausal ER+, HER2 BC (MONALEESA-3)	III	PFS	660

Neelima Vidula, Hope S. Rugo Clinical Breast Cancer 2015, Modified

Summary (2)

In the first-line therapy for metastatic disease, the addition of palbociclib doubles PFS rates in combination with letrozole.

In the endocrine refractory setting of metastatic disease, combination with fulvestrant improved PFS remarkably as compared with fulvestrant alone (HR=0.42).

Other trials containing abemaciclib or ribociclib are ongoing in the similar settings.

Sensitivity and Resistance

- In the subgroup analysis of clinical trials for luminal disease, no particular factor or marker has been identified.

- Various preclinical investigation are on-going.

Pro-proliferation and anti-proliferation factors

Pro

- CCND transcription
- CycD stabilization
- CynD nuclear transport

- CDK4 and/or CDK6 activation
- RB phosphorylation
- Degradation of CIP and/or KIP

Anti

- CCND regression
- CycD degradation
- CDK4 phosphorylation
- Induction of INK4

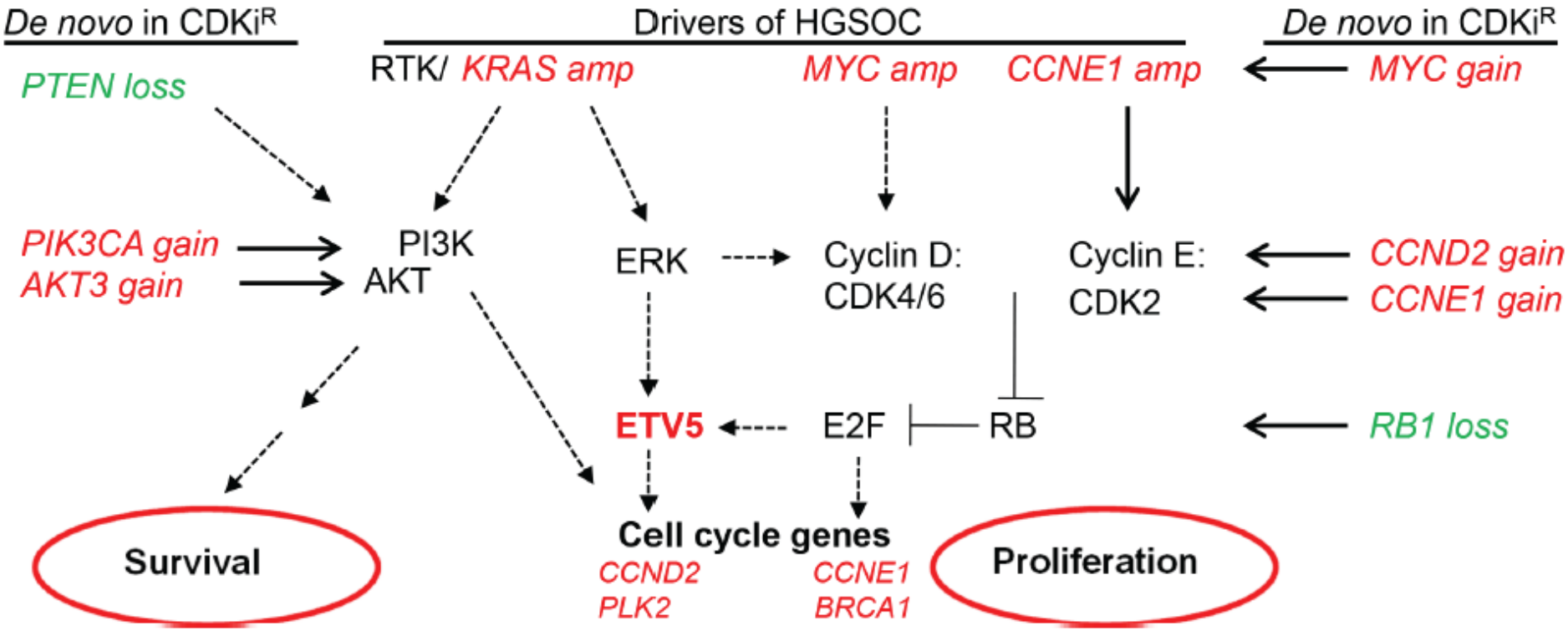
- Induction of CIP and/or KIP
- CDK2 phosphorylation

Deregulation in cancer

RB loss, CCND1 amplification, HPV infection, INK4 loss,
E2F3 amplification, CCNE1/2 amplification, p27Kip1 loss

Uzma Asghar et al. The history and future of targeting cyclin-dependent kinases in cancer therapy Nat Rev Drug Discov. 2015 February ; 14(2): 130–146. (modified)

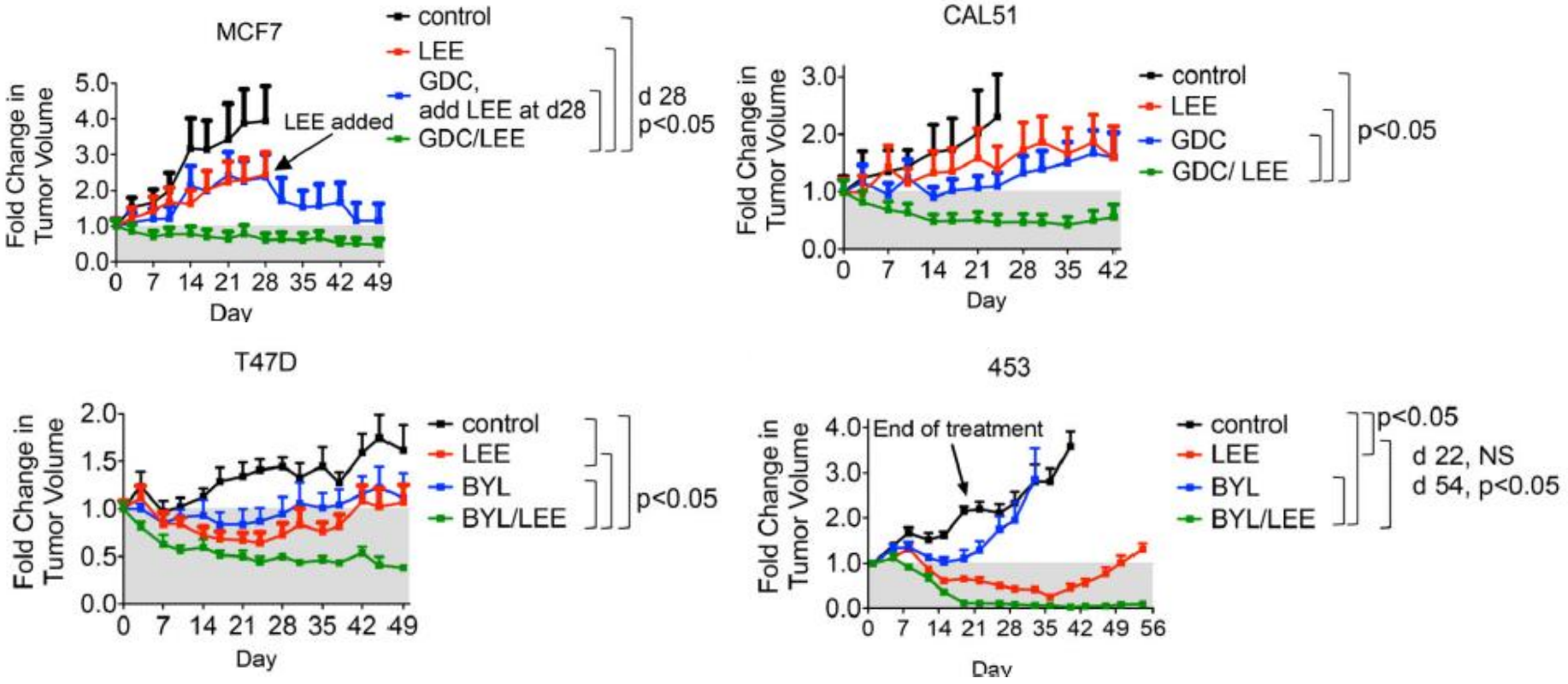
Mechanisms of resistance to CDK4/6 inhibition



Taylor-Harding B et al. Oncotarget 6;696-714

CDK4i + Pi3Ki

- Ribociclib + p110α -isoform specific inhibitor BYL719, GDC0941
- PIK3CA mt

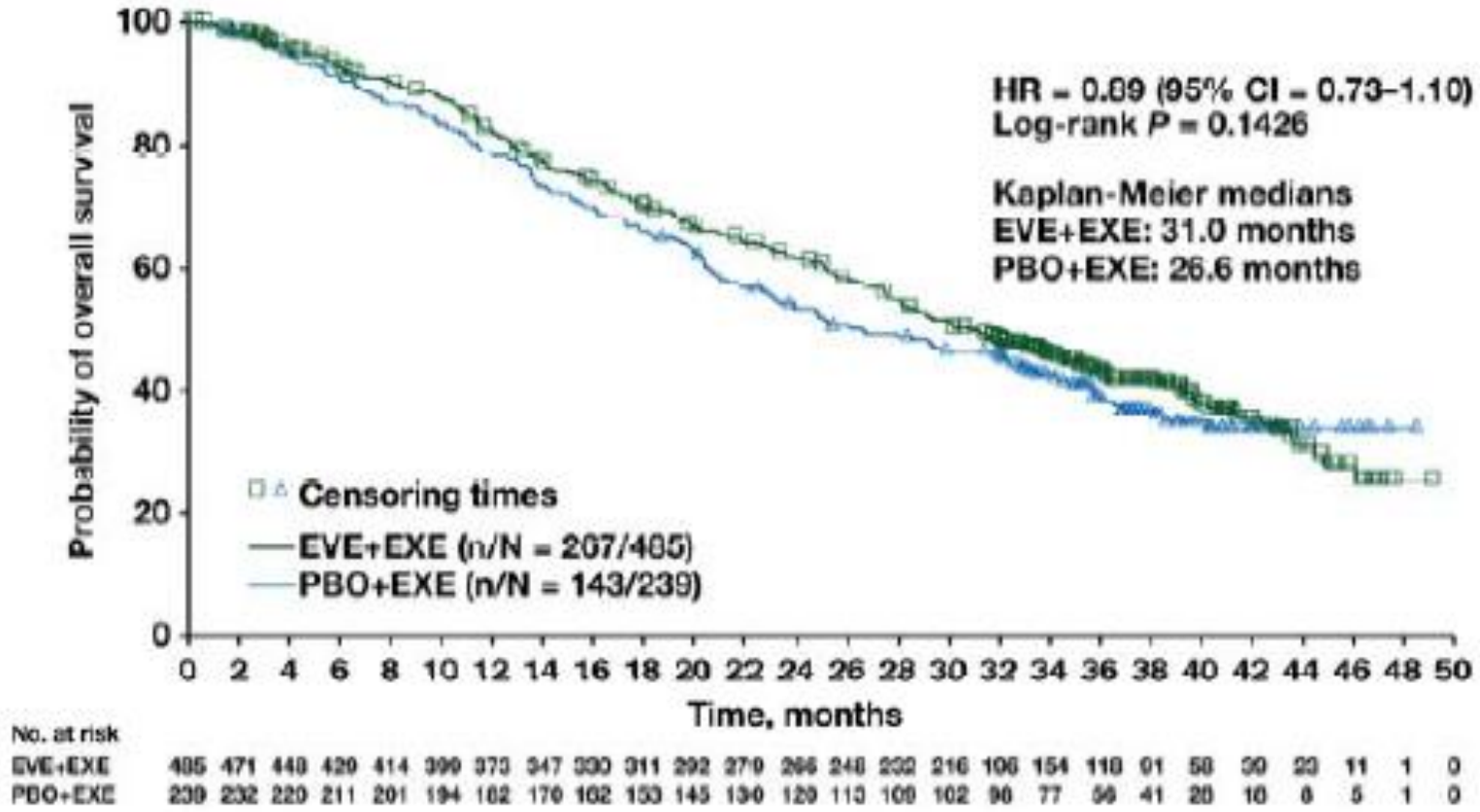


Sadhna R. Vora et al. CDK 4/6 inhibitors sensitize PIK3CA Mutant Breast Cancer to PI3K inhibitors. Cancer Cell. 2014 July 14; 26(1): 136–149.

Comparison with other treatments

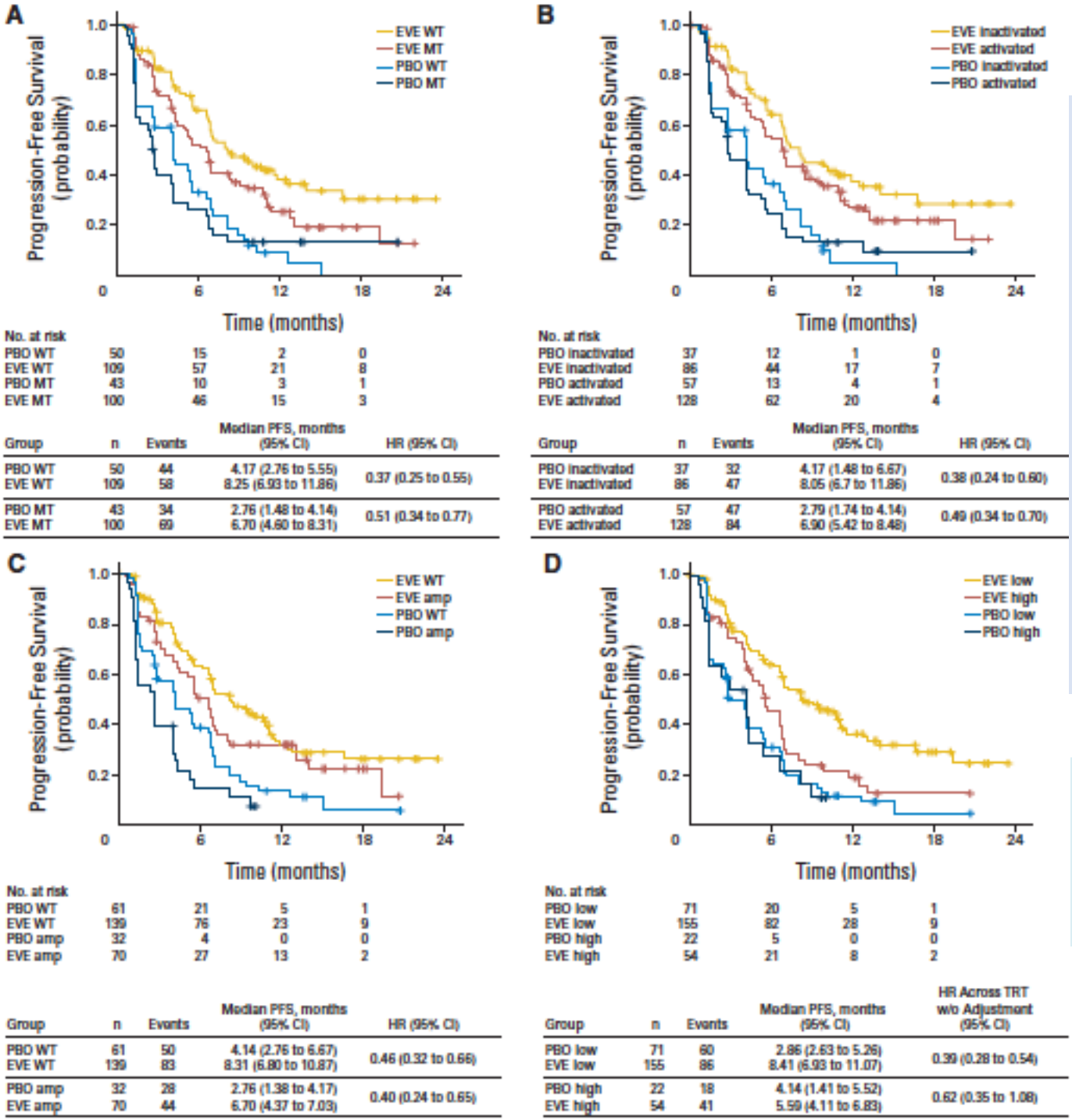
- Everolimus, mTOR inhibitor, + hormone therapy
- Oral FU
- Bevacizumab containing therapies

Everolimus (Bolero 2) MBC



Baselga J et al. N Engl J Med 2012;366:520-9.

Piccart M et al. Ann Oncol. 2014 Dec;25(12):2357-62



Biomarker

NGS

- gene mutation (MT) versus wild-type (WT)
- amplification (amp)
- chromosomal instability (CIN) score low or high

Pathway activity

(A) PIK3CA mutation status

(B) PI3K pathway status

(C) Cell-cycle genes

(D) Chromosomal instability score in which the 75th percentile was used as the cutoff

EVE, everolimus;

HR, hazard ratio;

PBO, placebo;

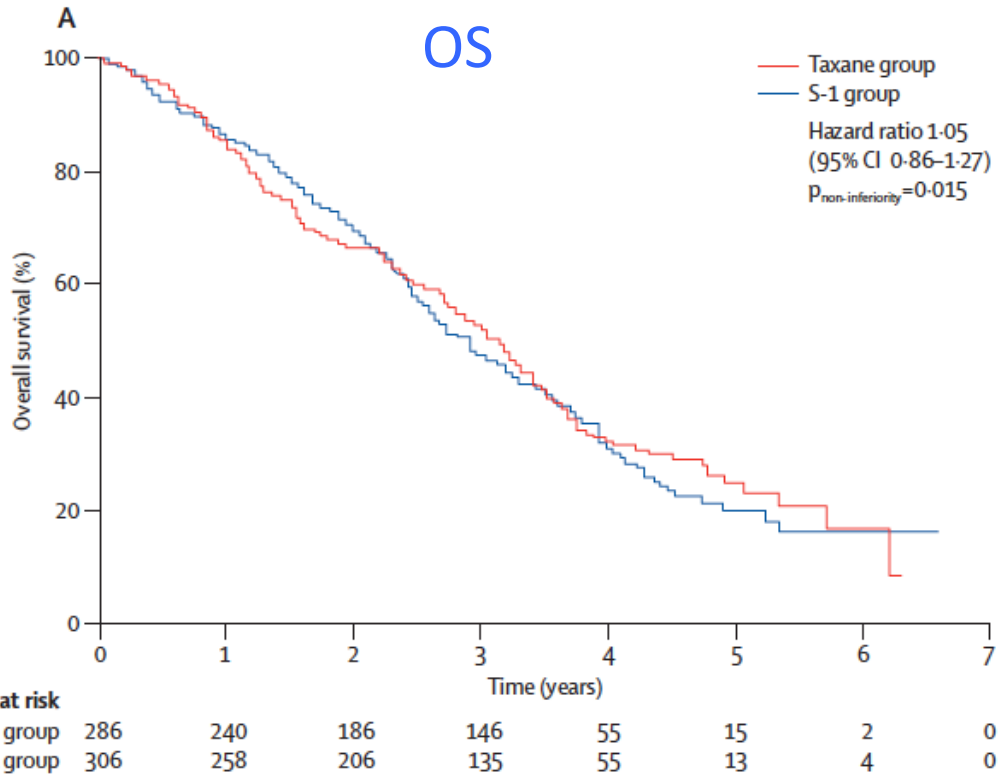
TRT, treatment; w/o, without.

Hortobagyi GN et al.
J Clin Oncol. 2015 Oct 26.

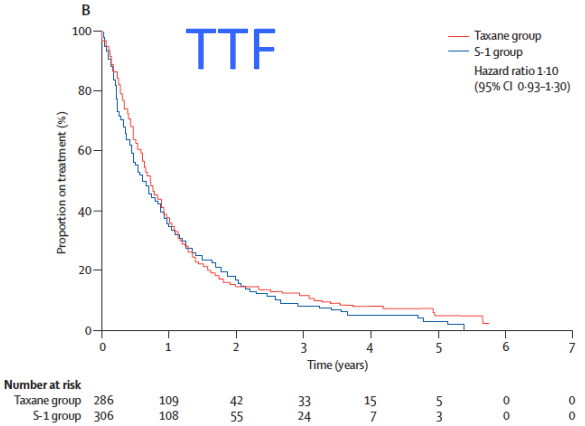
Taxanes versus S-1 as the first-line chemotherapy for metastatic breast cancer (SELECT BC): an open-label, non-inferiority, randomised phase 3 trial

Tsutomu Takashima, Hirofumi Mukai, Fumikata Hara, Nobuaki Matsubara, Tsuyoshi Saito, Toshimi Takano, Youngjin Park, Tatsuya Toyama, Yasuo Hozumi, Junji Tsurutani, Shigeru Imoto, Takanori Watanabe, Yoshiaki Sagara, Reiki Nishimura, Kojiro Shimozuma, Yasuo Ohashi, for the SELECT BC study group

OS



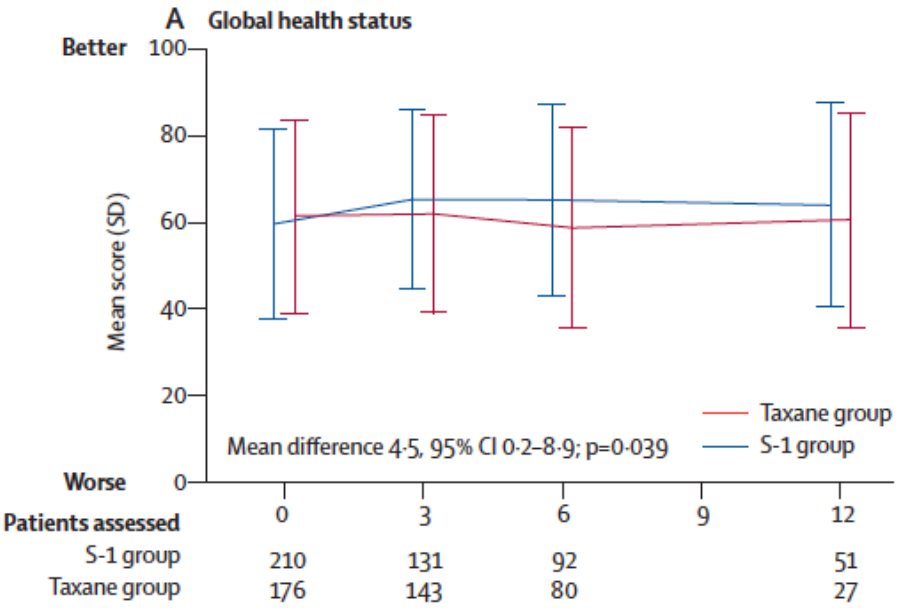
TTF

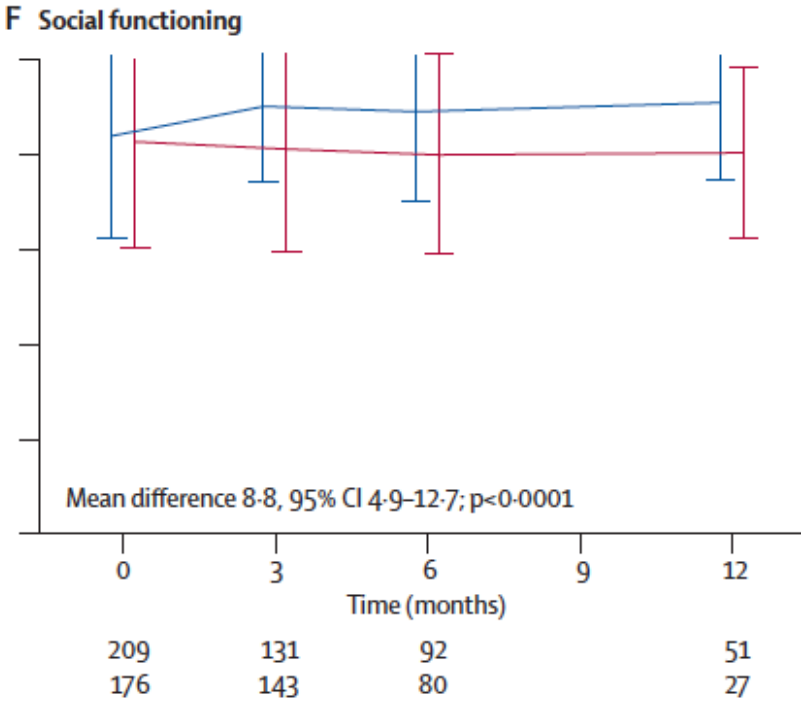


Lancet Oncol 2015

Published Online
November 23, 2015

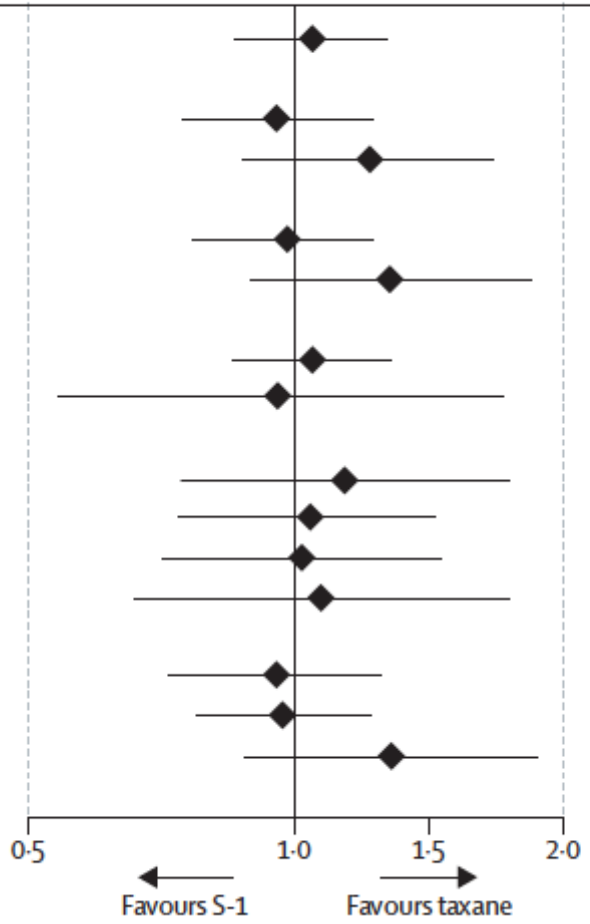
QoL: Oral FU (S1) versus Taxane in MBC





Oral FU (S1) versus Taxane in MBC SELECT BC Trial

	Number (events/patients)		HR (95% CI)
	S-1	Taxane	
All	**206/306**	**191/286**	**1·05 (0·86–1·27)**
Liver metastasis			
No	124/203	125/190	0·96 (0·75–1·23)
Yes	82/103	66/96	1·22 (0·88–1·68)
Adjuvant treatment with taxane			
No	147/226	136/206	0·98 (0·77–1·23)
Yes	59/80	55/80	1·28 (0·89–1·85)
Adjuvant treatment of fluorouracil			
No	185/271	166/247	1·05 (0·85–1·30)
Yes	21/35	25/39	0·96 (0·54–1·71)
Metastasis after surgery			
<2 years	43/60	40/57	1·14 (0·74–1·75)
2–5 years	71/103	66/98	1·04 (0·74–1·45)
≥5 years	58/94	54/86	1·02 (0·71–1·48)
No surgery	34/47	31/45	1·08 (0·66–1·75)
Hormone status			
ER positive and PgR positive	96/152	104/154	0·96 (0·72–1·26)
ER positive or PgR positive	142/223	138/212	0·97 (0·77–1·22)
ER negative and PgR negative	59/76	50/71	1·29 (0·88–1·89)



PFS and OS results

Agent	Trial (Phase)	Median PFS	Median PFS (Control)	Median OS	Median OS (Control)
Palbociclib (1st-line)	Letrozole +/- (rII)	20.2 M	10.2 M	37.5 M	33.3 M
Palbociclib (2nd-line)	Fluvestrant +/- (III, Placebo)	9.2	3.8	N.A.	N.A.
Everolimus (Multi-line)	Exemestane +/- (III, Placebo)	6.9	2.8	31.0	26.6
Bevacizumab (1st-line)	Letrozole or Fluvestrant +/- (III, Open)	19.3	14.4	52.1	51.8
S1/ Taxan, 1st Non-HER2	S1 vs Taxane (III, non-inferiority)	9.6	11.0	35.0	37.2
Bevacizumb (Chemo, 1st)	Paclitaxel +/- (III)	11.3	5.8	26.7	25.2

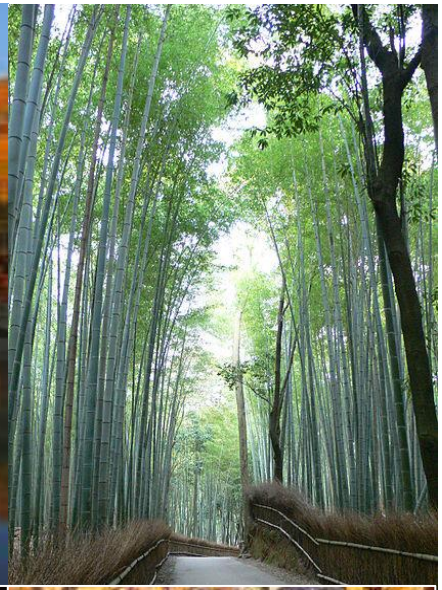
Summary (3)

CDK4/6 inhibitor provides favorable disease control in the 2nd-line therapy, and maybe in the 1st-line as well.

Therefore, it will be a therapeutic option for HER2-luminal metastatic diseases.

However, biomarkers are required for tailoring and optimizing the treatment.

Cost effectiveness needs to be investigated further.

THANK YOU !

SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE