IMPAKT BREAST CANCER CONFERENCE

IMProving cAre and Knowledge through Translational research

New drugs and trials on the horizon:

Targeting the CDK 4/6 pathway

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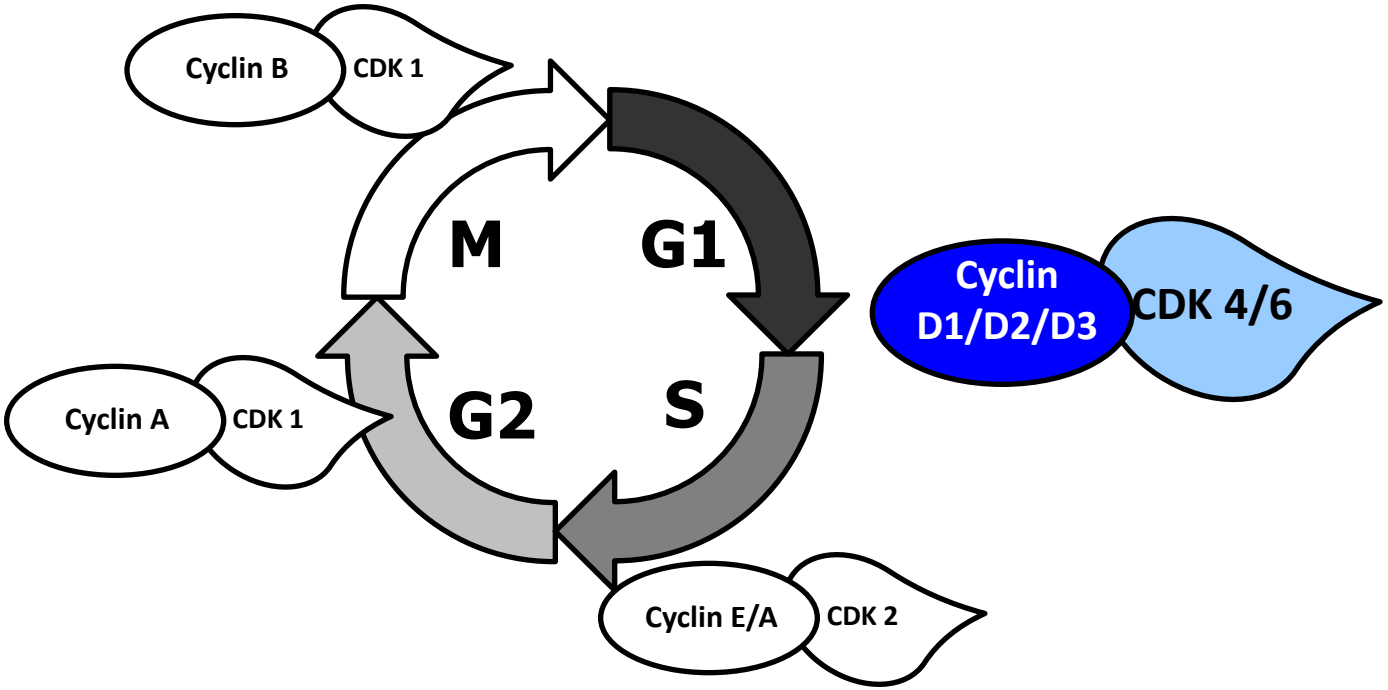
Disclosures

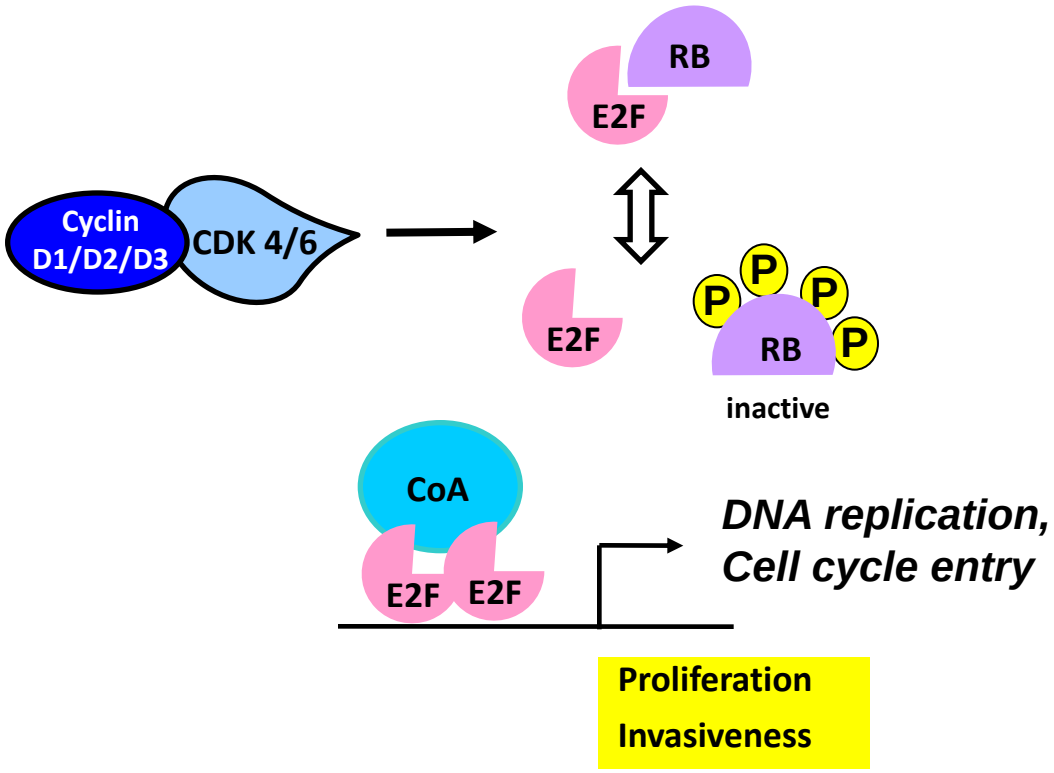
- Research support from Pfizer

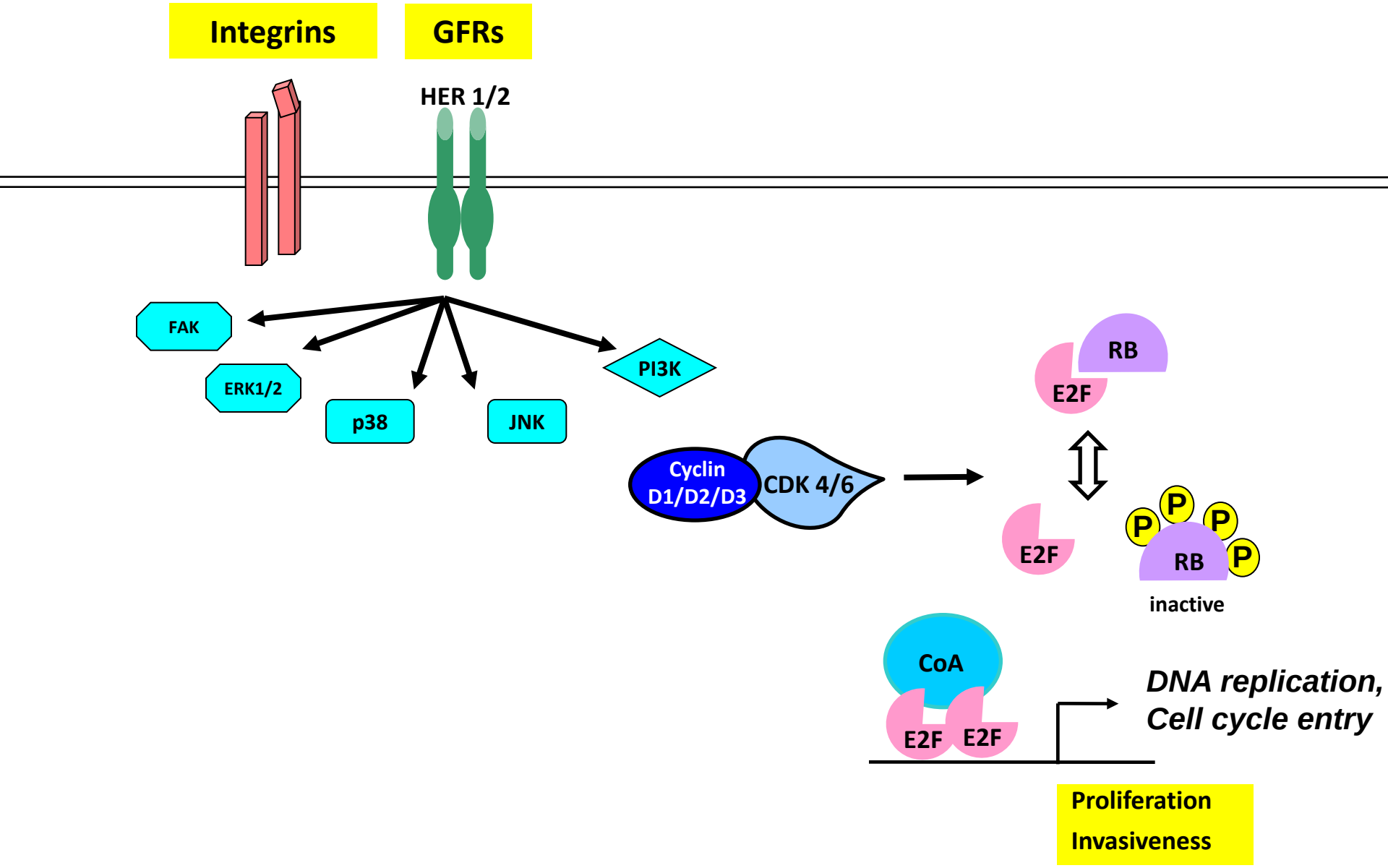
Outline

- Introducing the CDK4/6 pathway
- Pre-clinical background of CDK4/6 in BC subtypes:
  - ✓Luminals
  - ✓HER2
  - ✓TN
- Available clinical data with CDK4/6 inhibitors

CDK 4/6 as a key regulator of cell cycle




RB
E2F
Cyclin
D1/D2/D3
CDK 4/6
E2F
P
P
P
RB
P
inactive
CoA
E2F
E2F
DNA replication,
Cell cycle entry
Proliferation
Invasiveness


Integrins
GFRs
HER 1/2
FAK
ERK1/2
p38
JNK
PI3K
Cyclin D1/D2/D3
CDK 4/6
RB
E2F
E2F
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E2F
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DNA replication,
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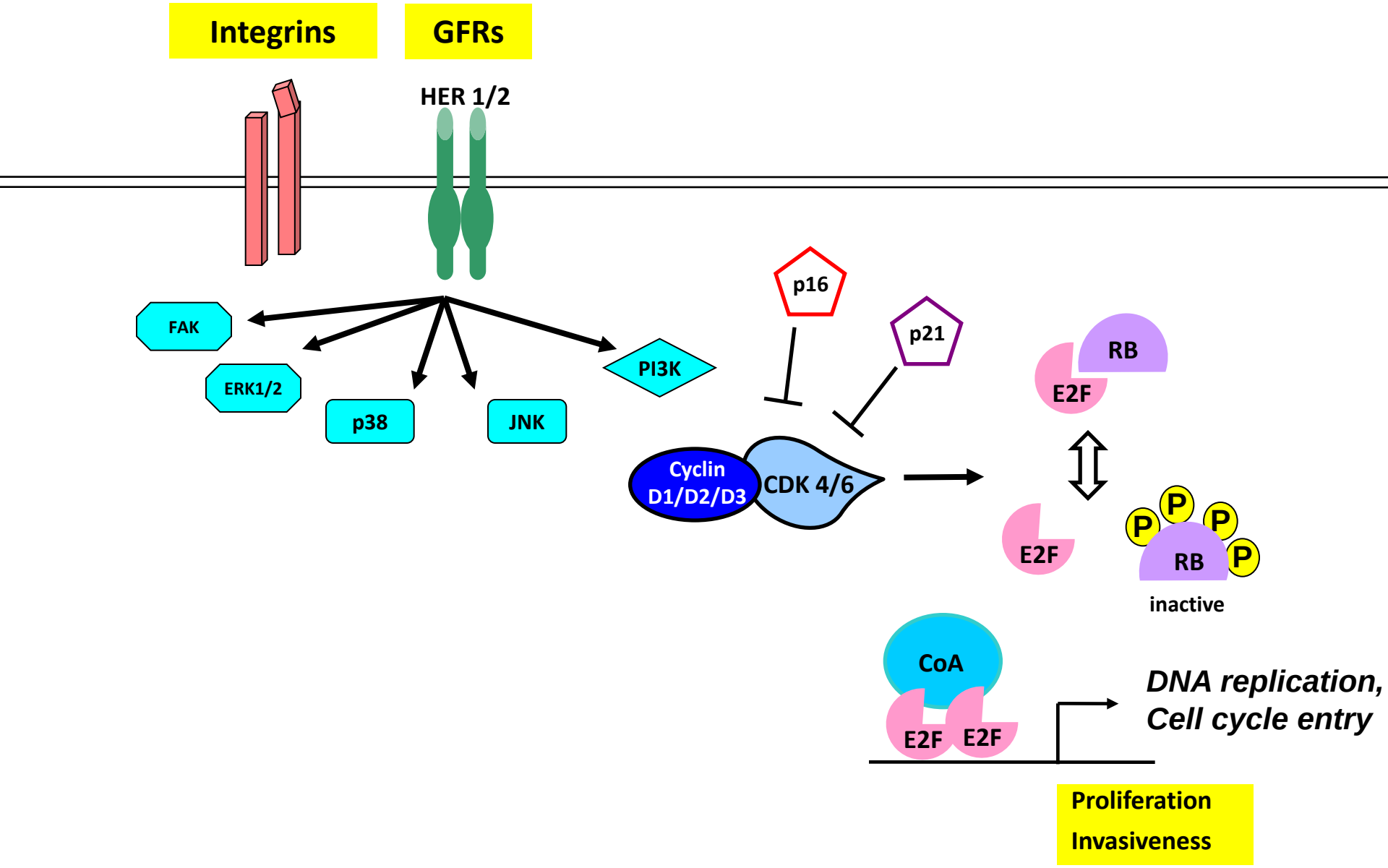
Integrins
GFRs
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ERK1/2
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PI3K
p16
p21
Cyclin D1/D2/D3
CDK 4/6
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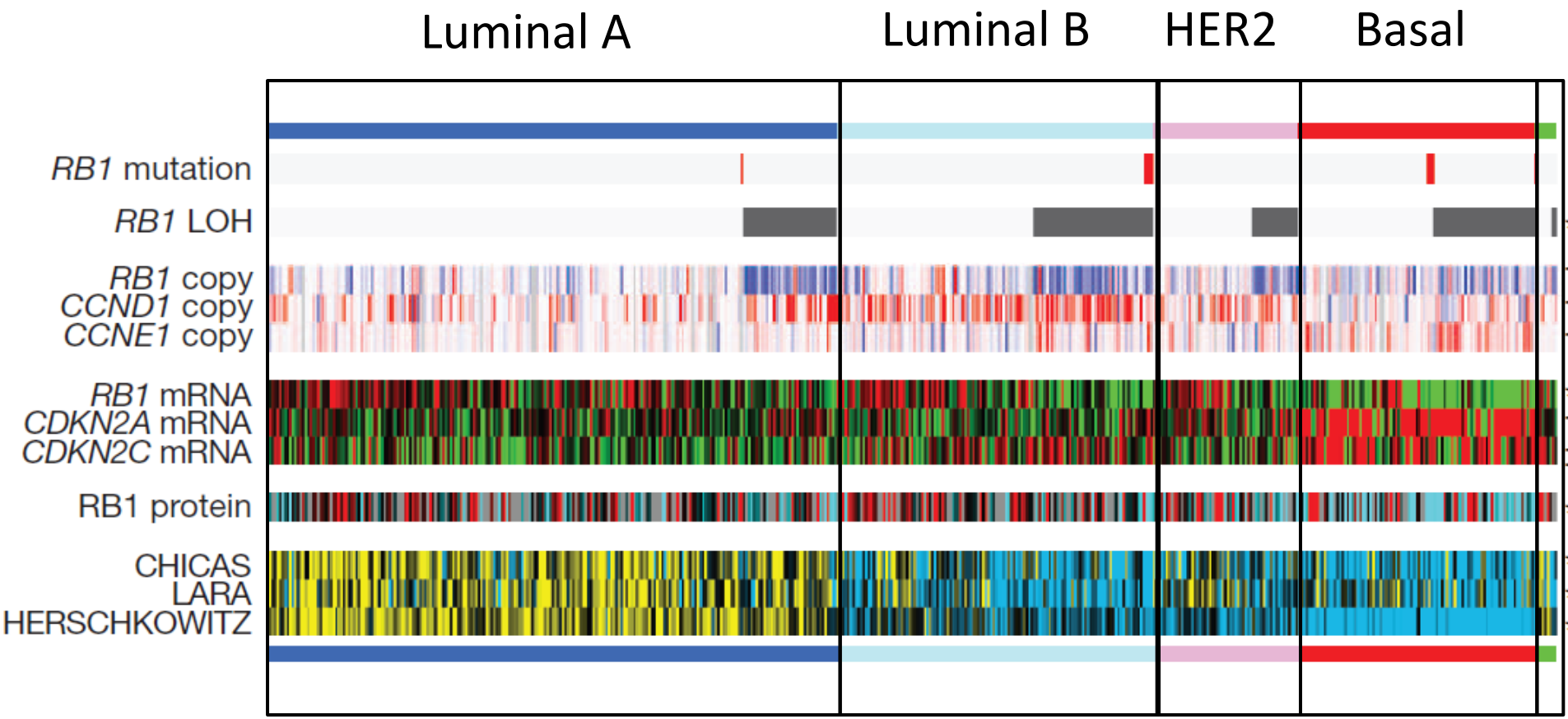
Deregulation of CDK 4/6 pathway in BC subtypes

Luminal A	Luminal B	HER2 enriched	Basal-like
Cyclin D1 amp (29%)	Cyclin D1 amp (58%)	Cyclin D1 amp (38%)	Cyclin E1 amp (9%)
CDK4 gain (14%)	CDK4 gain (25%)	CDK4 gain (24%)	
11q13.3 amp (24%)	11q13.3 amp (51%)		
			RB1 mut/loss (20%)
Low expression of p18/high expression of RB1	High FOXM1		High expression of p16/ low expression of RB1

The Cancer Genome Atlas Network, Nature 2012



The Cancer Genome Atlas Network, Nature 2012

Outline

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  - ✓TN
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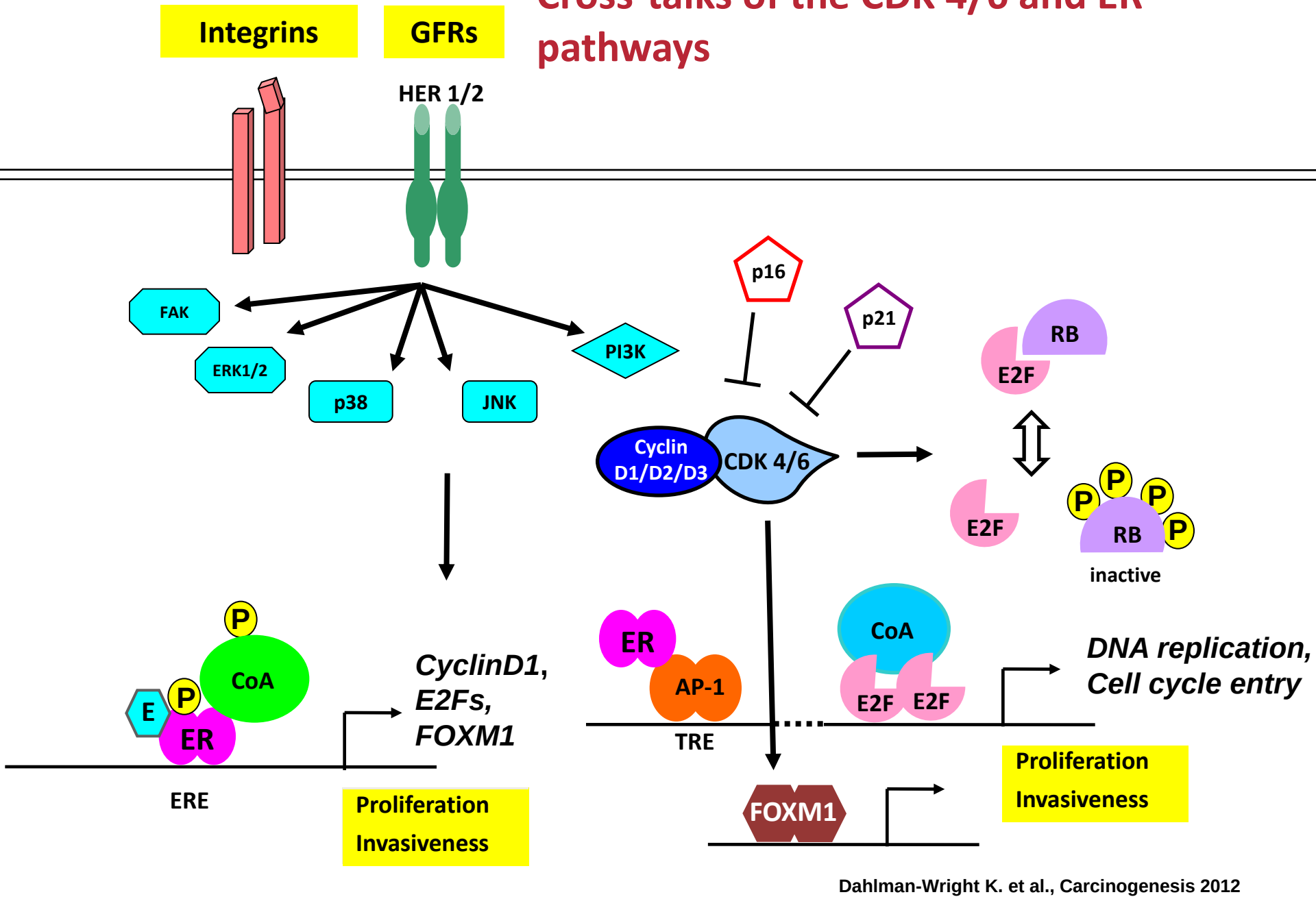
Cross-talks of the CDK 4/6 and ER pathways

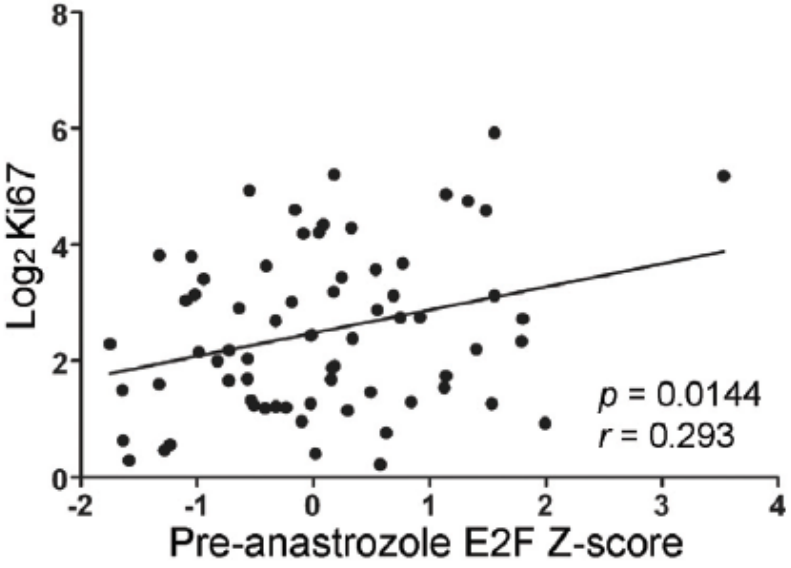


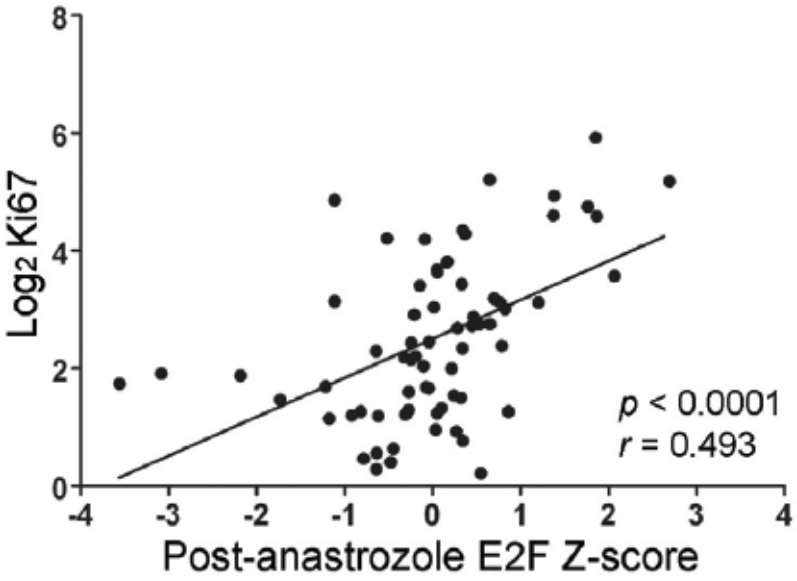
Dahlman-Wright K. et al., Carcinogenesis 2012

- **Estrogen modulation of E2F1 is critical for hormone regulation of the proliferative program of breast cancer cells (Stender J.D. et al, Mol. Endo. 2007)**

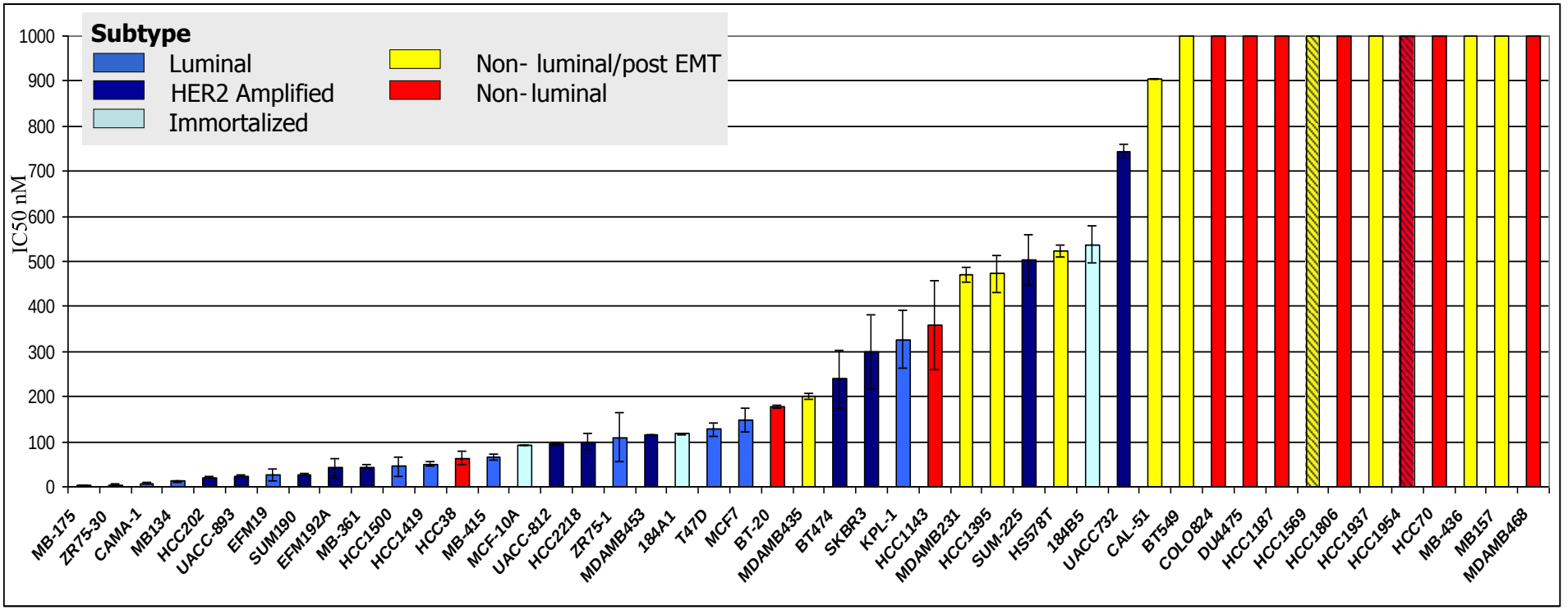
- **In long term estrogen deprived cells, ER retains genomic activity and drives a CDK4/E2F dependent transcriptional program despite estrogen deprivation therapy (Miller T.W. et al, Cancer Discovery 2011)**

A gene expression signature of E2F activation correlates with poor tumor response to AIs in patients.





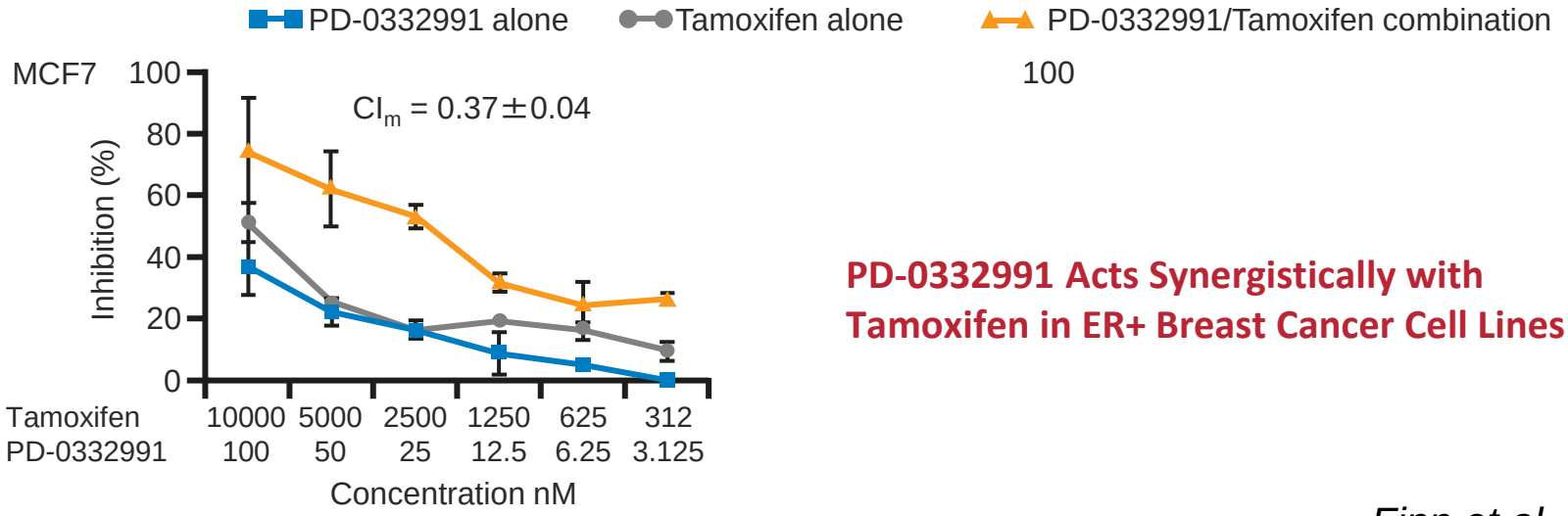
Miller T.W. et al, Cancer Discovery 2011



The CDK 4-6 inhibitor PD 0332991 has shown activity preferentially on ER+, luminal breast cancer cell lines with or without HER2 amplification.

Finn et al, BCR 2011

CDK 4/6 inhibitor + Endocrine therapy



PD-0332991 Acts Synergistically with Tamoxifen in ER+ Breast Cancer Cell Lines

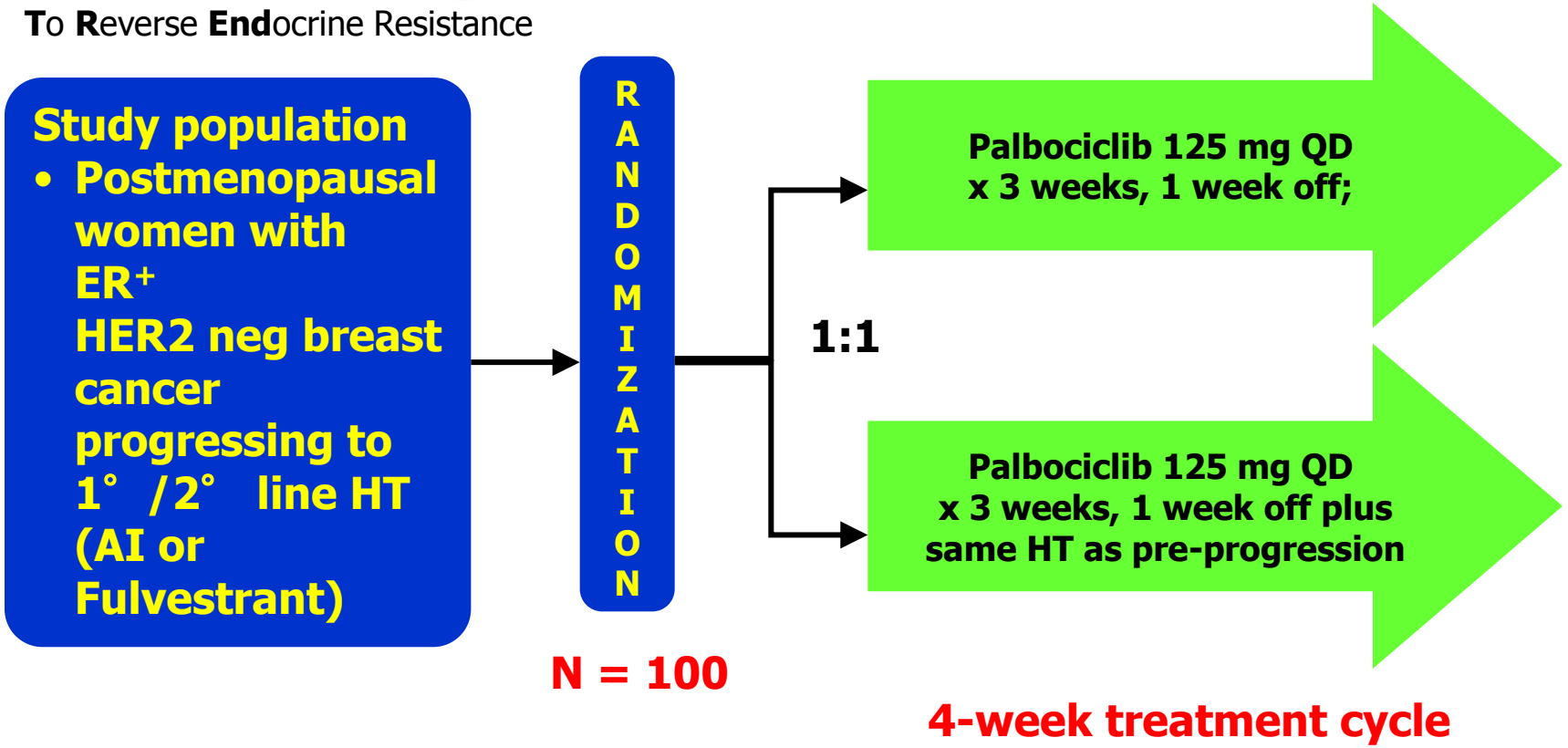
Finn et al, BCR 2011

PD-0332991 improves efficacy of Fulvestrant and Letrozole in Luminal BC models

Koehler M. et al, IMPAKT meeting Poster walk 2014

TREnd Study design

To **R**everse **End**ocrine Resistance



Stratification Factors

1. Disease site (visceral vs bone only vs other)
2. number or prior lines of endocrine treatment (1 vs. 2)
3. duration of prior line of endocrine treatment (>6 vs. ≤6 months);
4. treating center

Summary: CDK4/6 inhibition in Her2+ breast cancer

Mechanisms of bypass of Her2-targeted agents are complex

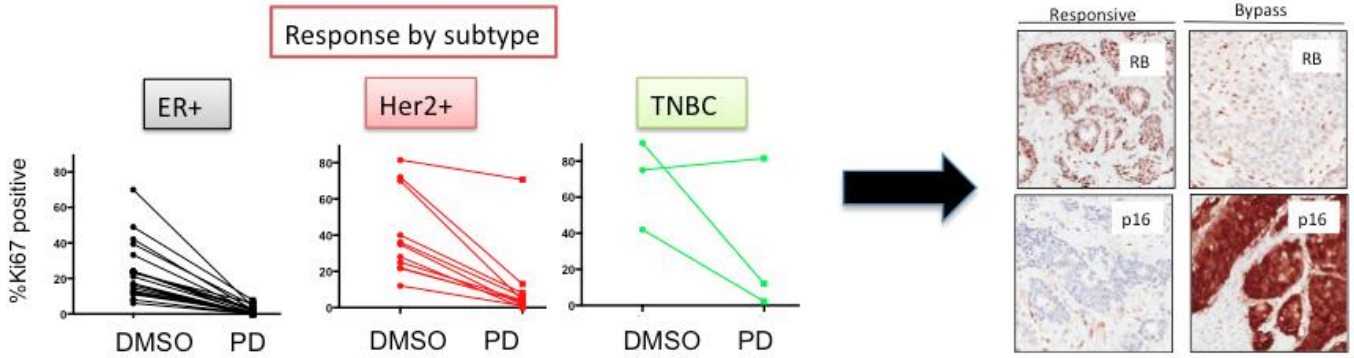
*Aberrant cellular proliferation in the presence of agents

*Common deregulated signaling that feeds into CDK4/6

CDK4/6 inhibition has activity against Her2-positive models

*Cell Culture models, xenografts, GEMMS, tumor explants

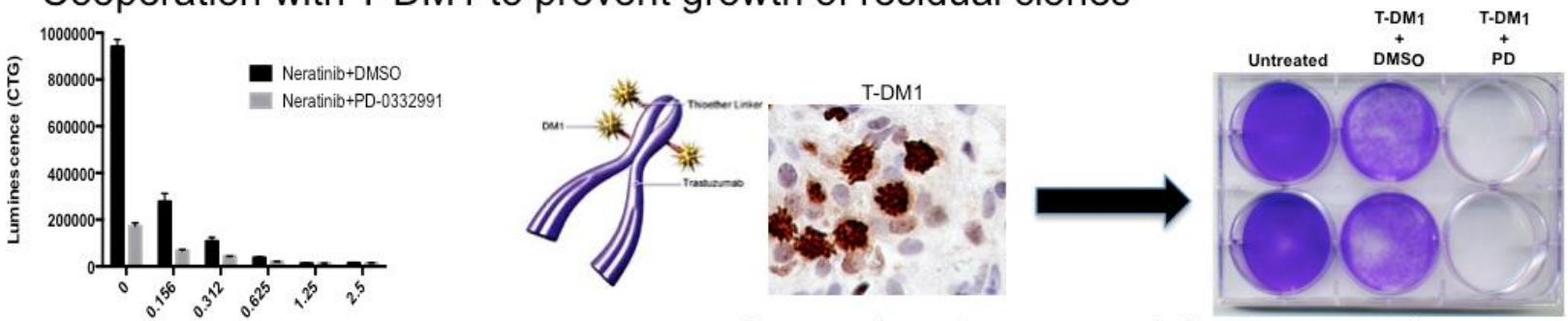
*Markers of resistance (p16 and RB) can be identified in clinical specimens



CDK4/6 inhibitors cooperate with Her2-targeted agents

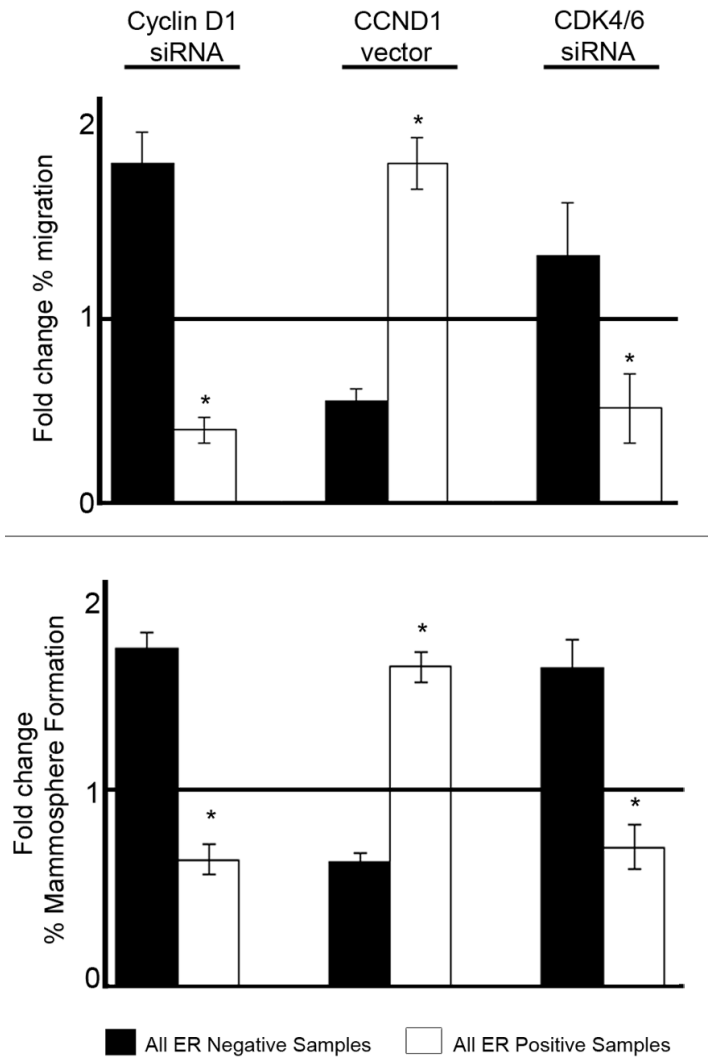
*Cooperation with multiple small molecule inhibitors (e.g. neratinib) in Her2-positive models

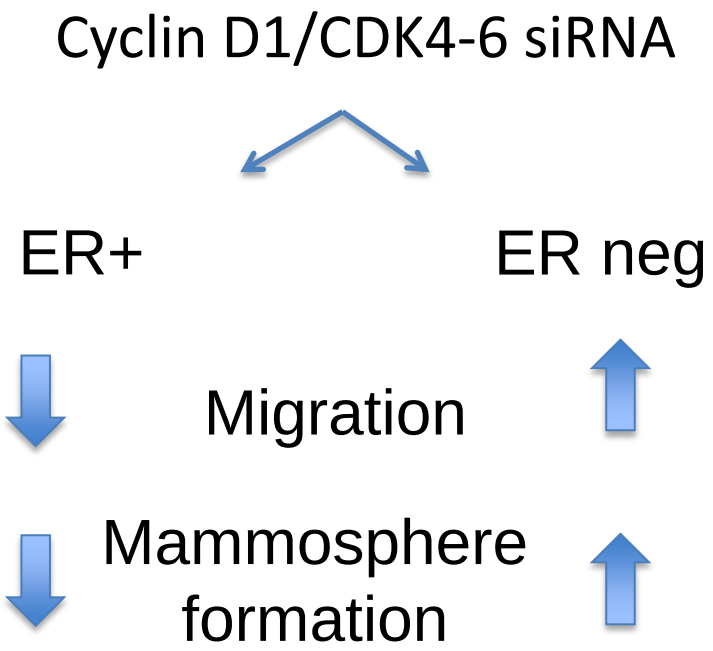
*Cooperation with T-DM1 to prevent growth of residual clones



Courtesy of E. Knudsen (summary of data presented at IMPAKT 2014)

Cyclin D1 or CDK 4/6 siRNA has opposite effects in ER+ vs ER neg BC cell lines





Lamb R., *Cell Cycle* 2013

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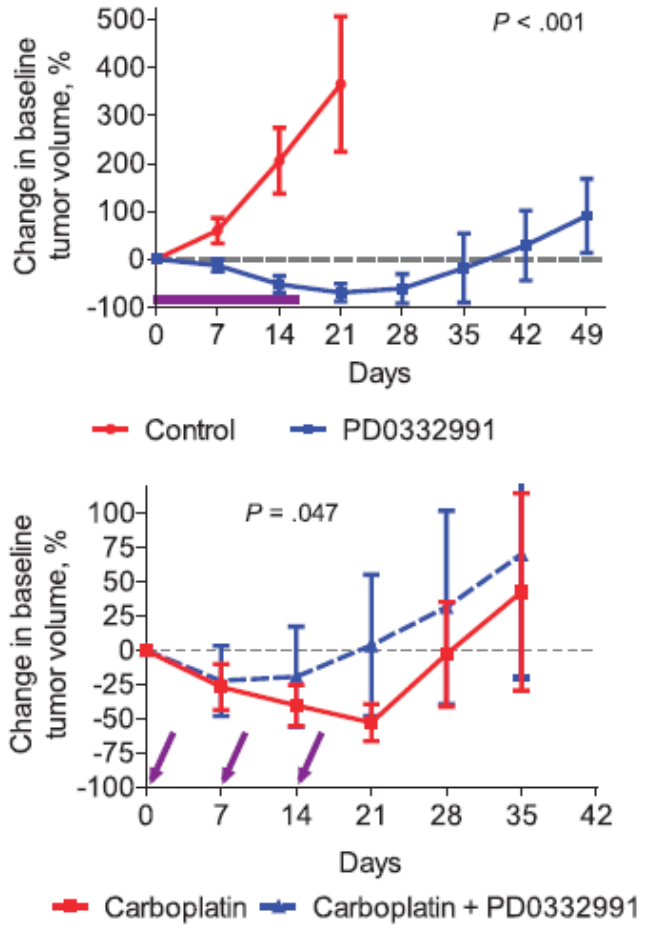
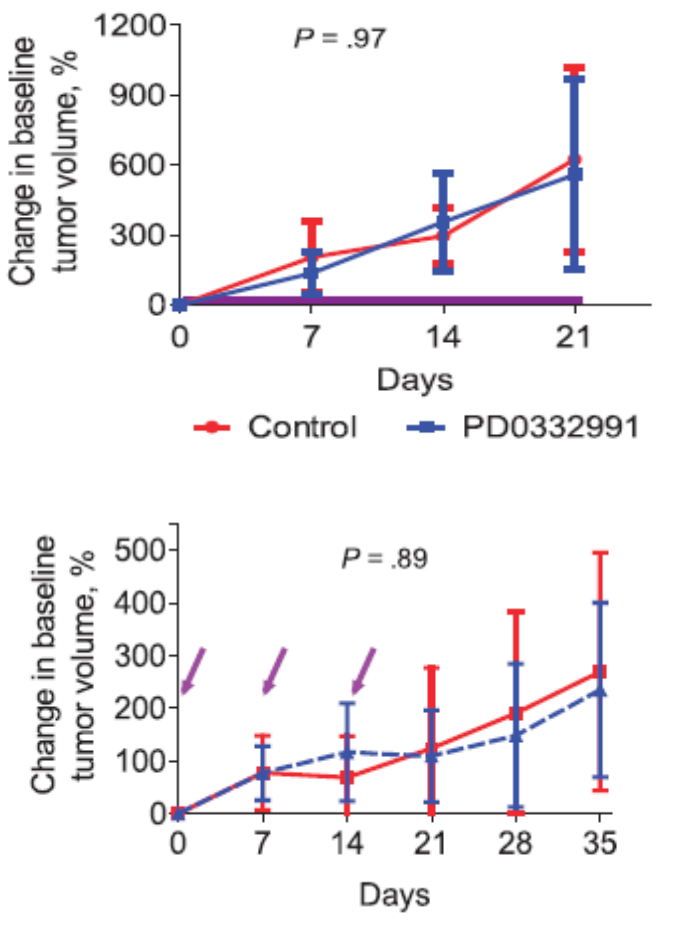
Interaction of CDK 4/6 inhibition with chemotherapy

MMTV-neu (Rb competent)

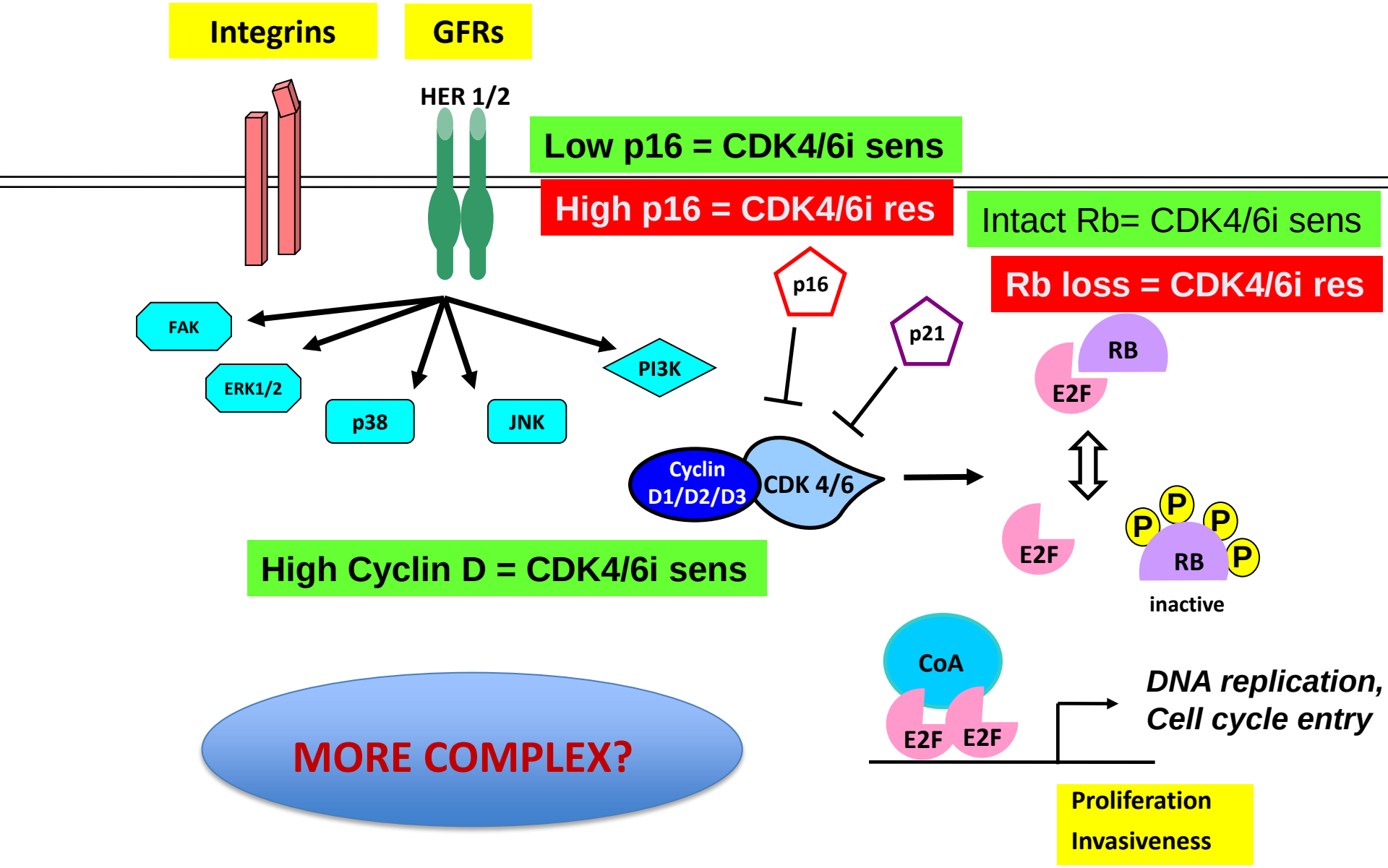


C3-TAg (Rb incompetent)



Roberts P.J. et al, *JNCI* 2012

Molecular determinants of response to CDK4/6 inhibitors



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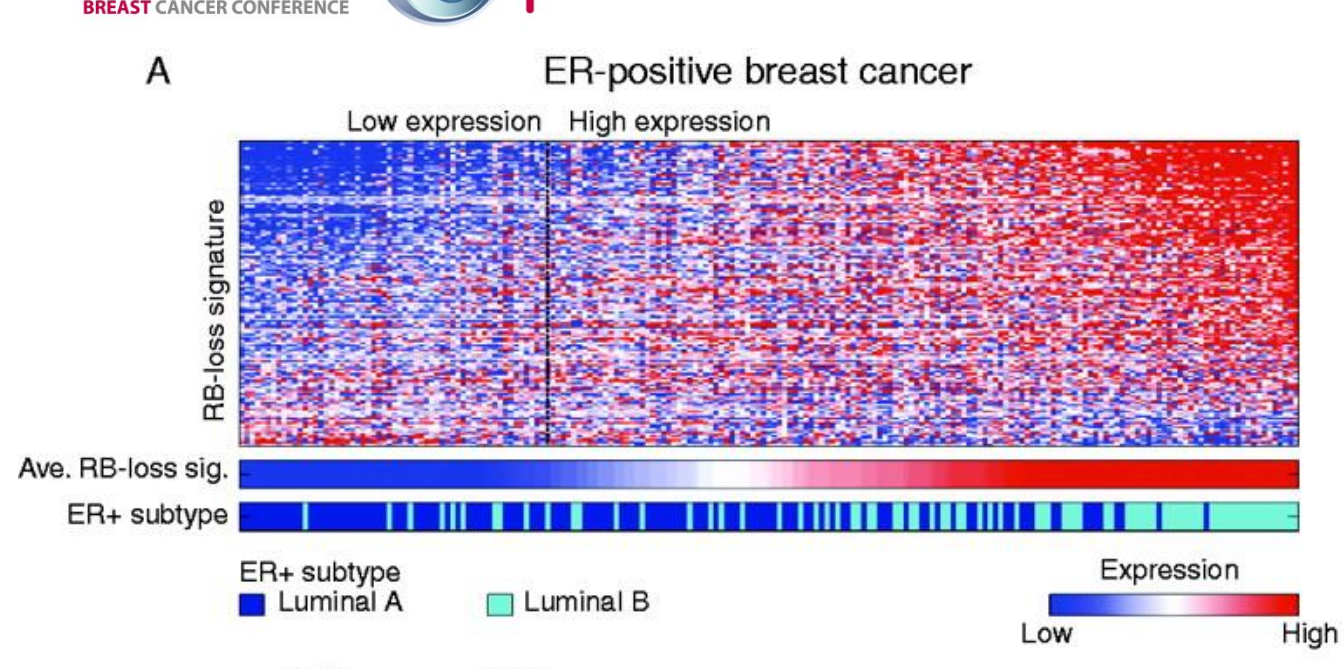
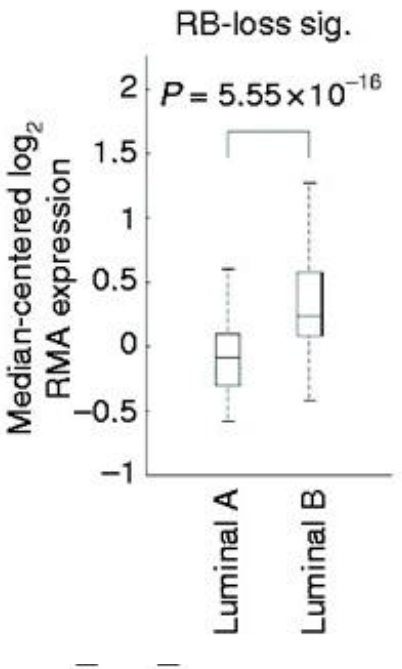
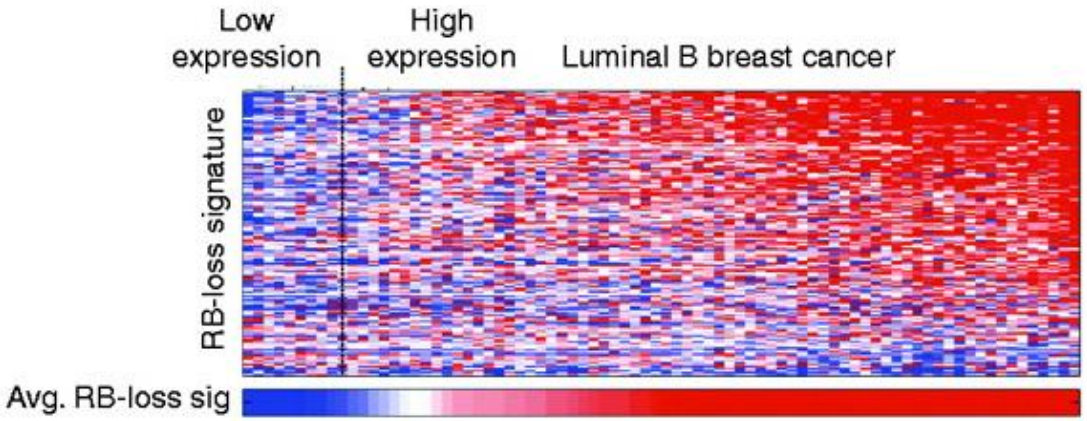
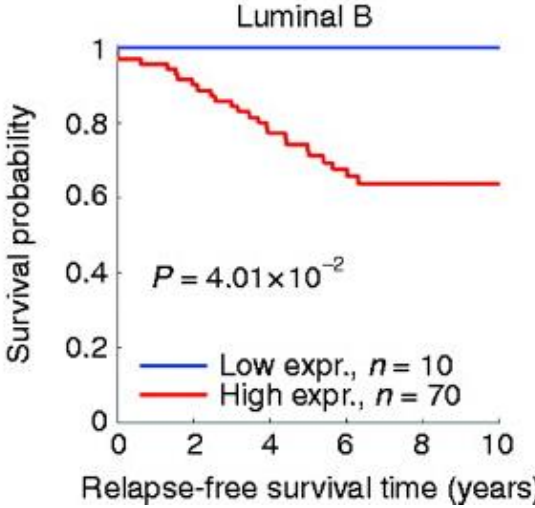
Rb loss signature in Luminal BC









Thangavel C et al. Endocr Relat Cancer 2011

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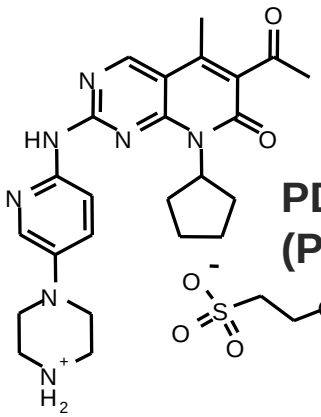
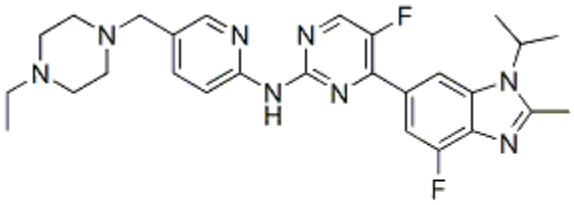
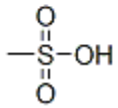
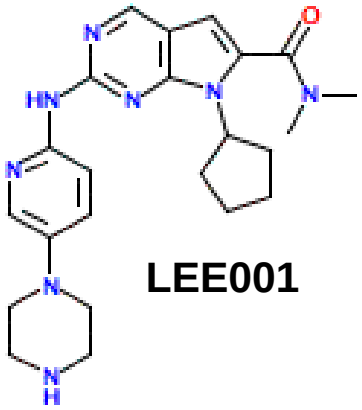


PD-0332991 (Palbociclib)





LY2835219 (Bemaciclib)



LEE001

CDK (Cyclin partner)	IC_{50} (μM)
CDK4/Cyclin D1	0.011
CDK4/Cyclin D3	0.009
CDK6/Cyclin D2	0.015
CDK2/Cyclin A	>5
CDK1/Cyclin B	>5
CDK5/p25	>5

CDK	IC_{50} (μM)
CDK4	0.002
CDK6	0.009
CDK1	1.6

CDK (Cyclin partner)	IC_{50} (μM)
CDK4/cyclin D1	0.010
CDK6/cyclin D3	0.039
CDK1/cyclin B	113
CDK2/cyclin A	76
CDK5/p25	45
CDK9/cyclin T1	1.5

Fry DW, et al. *Mol Cancer Ther* 2004;

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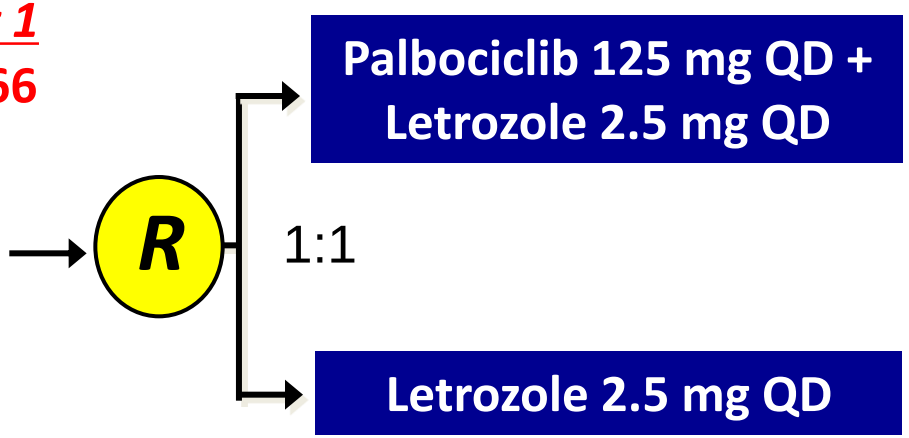
Paloma 1/TRIO 18 phase II study

- Post-menopausal
- No prior treatment for advanced disease
- ER+, HER2– BC status

Part 1

N=66



- Same as part 1 but with CCND1 amplification and/or loss of p16

Part 2

N=99

Key Eligibility Criteria

- Measurable disease (RECIST 1.0) or bone-only disease
- ECOG PS of 0 or 1
- Adequate blood counts and organ function
- No prior/current brain metastases

Stratification Factors

- Disease Site (Visceral vs Bone only vs Other)
- Disease-Free Interval (>12 vs ≤12 mo from end of adjuvant to recurrence or de novo advanced disease)

Finn R., et al. AACR meeting 2014, oral presentation.

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Phase II Study 1006 Palbociclib

- **Breast cancer cohort comprised patients with histologically confirmed, RB-positive, stage IV, pretreated breast cancer (median nr of prior HT for MBC=2; median nr of prior CT for MBC=3) (NCT01037790)**
- **Palbociclib administered as single agent 125 mg/day g1-21 of a 28 day cycle**

Group	n	Complete response n (%)	Partial response n (%)	Stable disease <6 mo n (%)	Stable disease ≥6 mo n (%)	Progressive disease n (%)	Clinical benefit* n (%)
HR+	30	0	2 (7)	14 (47)	3 (10)	11 (36)	5 (16)
HR-/HER2-	6	0	0	0	1 (17)	5 (83)	1 (17)
Total	**36**	**0**	**2 (6)**	**14 (39)**	**4 (11)**	**16 (44)**	**6 (17)**

*Partial response or stable disease ≥6 months

- **Modest single-agent activity in this heavily pretreated population**
- **Well tolerated. Only grade 3/4 toxicity observed was neutropenia and thrombocytopenia, mostly uncomplicated**

DeMichele A, et al. ASCO 2013. Abstract 519.

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Phase I Study Bemaciclib

- **Open lable phase I study: breast cancer expansion cohort**
- **Bemaciclib was administered at 150 mg or 200 mg orally b.i.d. days 1-28 of a 28-day cycle**
- **Patients (n=47) with heavily pretreated MBC (median nr of prior systemic tx= 7)**

Possibly Related Treatment-emergent Adverse Events in ≥15% of Patients

Adverse Event (N = 47)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)
Diarrhea	20 (42.6)	8 (17.0)	3 (6.4)	0 (0.0)	31 (66.0)
Nausea	17 (36.2)	8 (17.0)	2 (4.3)	0 (0.0)	27 (57.4)
Fatigue	11 (23.4)	8 (17.0)	1 (2.1)	0 (0.0)	20 (42.6)
Neutrophil count decreased	3 (6.4)	6 (12.8)	9 (19.1)	1 (2.1)	19 (40.4)
Vomiting	14 (29.8)	4 (8.5)	1 (2.1)	0 (0.0)	19 (40.4)
Platelet count decreased	9 (19.1)	1 (2.1)	5 (10.6)	0 (0.0)	15 (31.9)
White blood cell decreased	1 (2.1)	7 (14.9)	5 (10.6)	0 (0.0)	13 (27.7)

Patnaik A. AACR 2014

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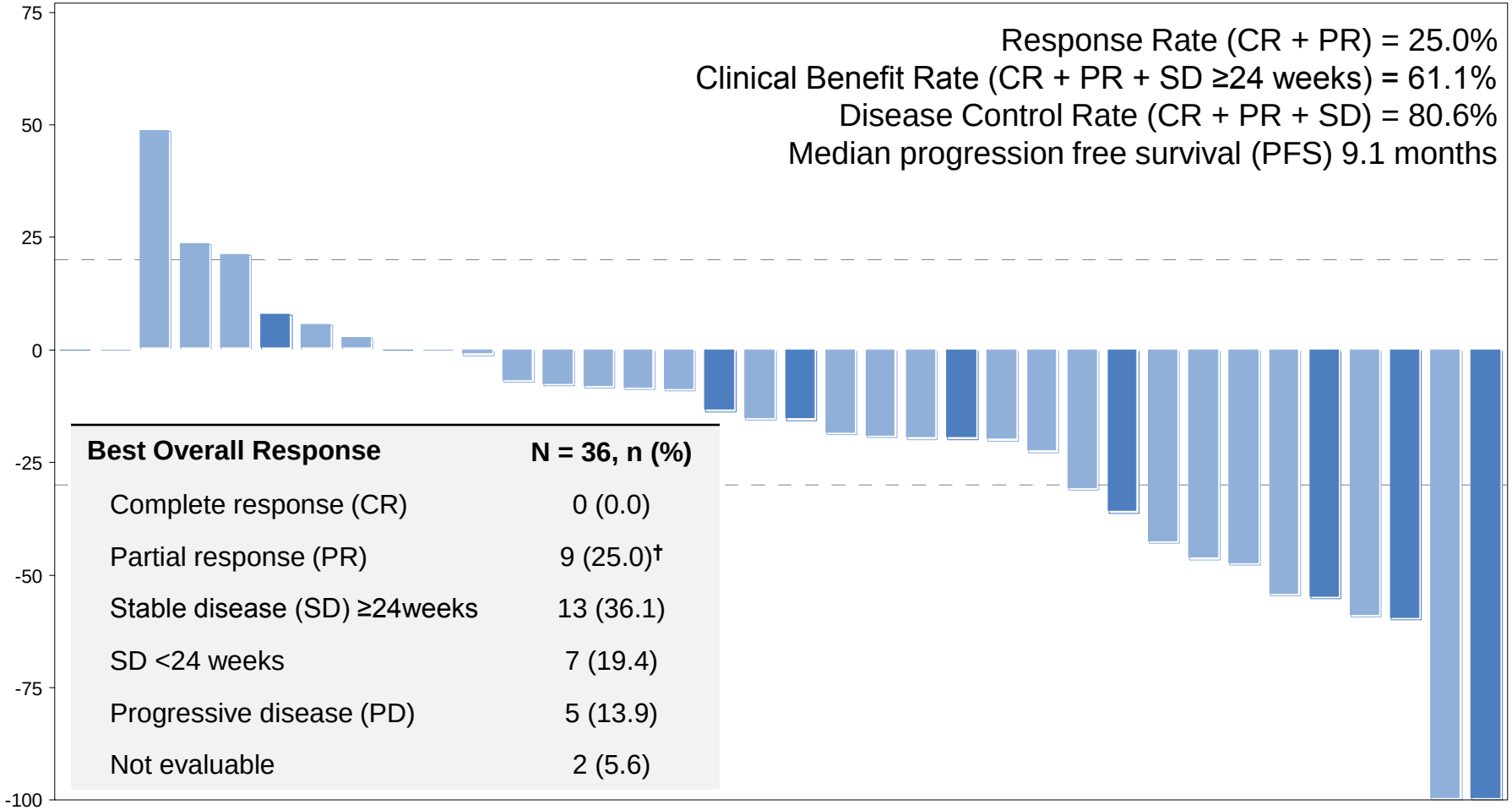
Change in Tumor Size at Best Response HR + Patients



Best Overall Response	N = 36, n (%)
Complete response (CR)	0 (0.0)
Partial response (PR)	9 (25.0)†
Stable disease (SD) ≥24weeks	13 (36.1)
SD <24 weeks	7 (19.4)
Progressive disease (PD)	5 (13.9)
Not evaluable	2 (5.6)

Patnaik A. AACR 2014

CLEE011X2101: Phase I Study LEE001

- **Open lable phase I study (dose escalation n=30), multiple cancers expansion cohort (n=40)**
- **Doses tested: 50–1200 mg; MTD: 900 mg; RP2D: 600 mg/day – 3 weeks on/1 week off**
- **All pts tumors RB+**

Treatment emergent AE

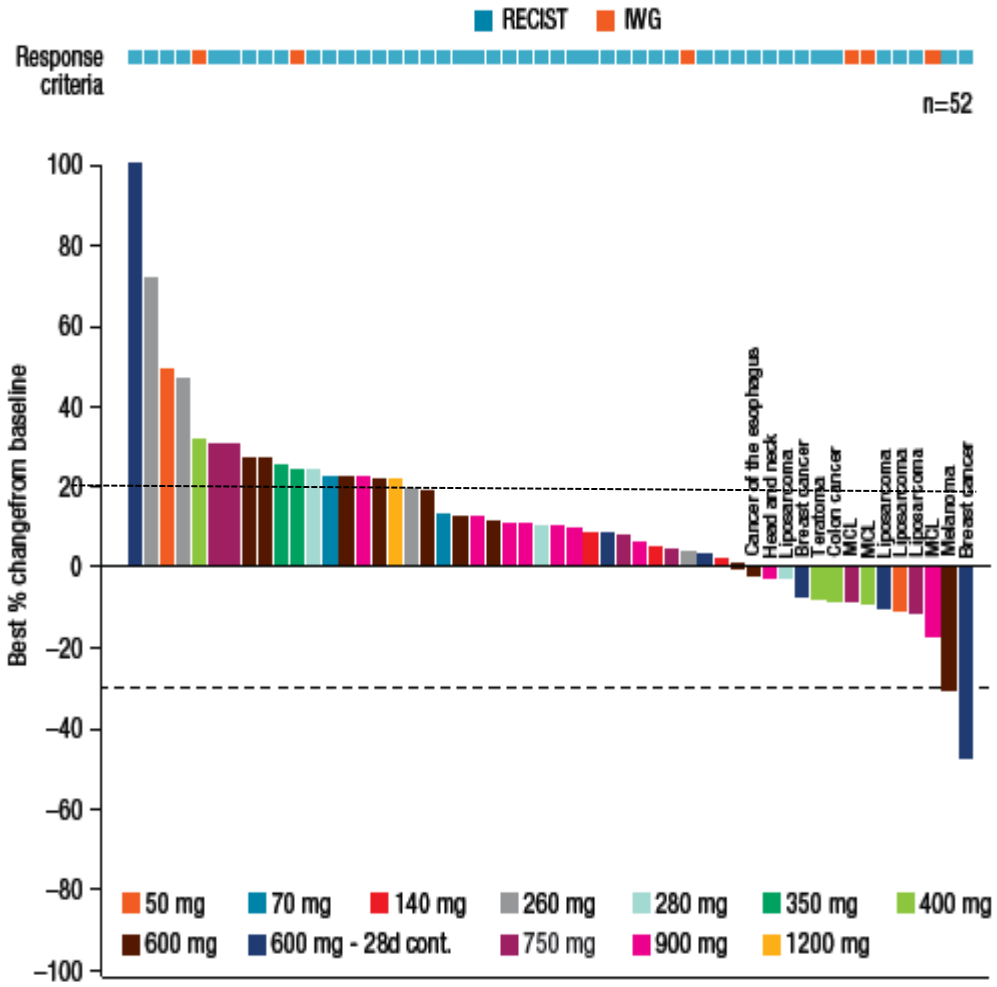
Preferred terms	All Grades N=78 n (%)	Gr 3/4 N=78 n (%)
Hematologic		
Neutropenia*	31 (40)	15(19)
Lymphopenia	17 (22)	11(14)
Leukopenia	28 (36)	9 (12)
Thrombocytopenia	19 (24)	2 (3)
Non hematologic		
Nausea	27 (35)	2 (3)
Prolonged QTcF**	10 (13)	2 (3)
Hyponatremia	2 (3)	2 (3)

*Onset of neutropenia occurs by Day 15, reaching a nadir in the 3rd or 4th wk with recovery during the wk of drug holiday. Some patients require additional time for recovery (7–14 days).

** QTcF changes become evident in the first cycle by Day 8.

Infante JR et al. AACR-NCI-EORTC Meeting 2013

CLEE011X2101: Preliminary Efficacy Data (dose escalation)



- 70 evaluable patients
- 1 confirmed PR at 600 mg in a ER+ breast cancer patient
- 1 unconfirmed PR response at 600 mg in a *BRAF/NRAS* wild-type melanoma patient
- 18/70 patients with SD for 4 cycles and more
- 10/70 patients with SD for 6 cycles and more

Infante JR et al. AACR-NCI-EORTC Meeting 2013

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Ongoing Trials

CDK4/6 inhibitor	Trial identifier	Trial status	Phase	Other drugs	Tumor type	Menopausal status	Biomarkers
Palbociclib	NCT01684215	Active, not recruiting	Phase 1/2	Letrozole (phase 2)	ER+ HER2- ABC (phase 2)	Post	No
	NCT01976169	Not yet recruiting	Phase 1b	T-DM1	HER2+ ABC	Pre and post	Rb, p16
	NCT01723774	Recruiting	Phase 2	anastrozole	ER+ HER2- EBC or LABD	Pre and post	No
	NCT01864746	Recruiting	Phase 3	endocrine	ER+ HER2- with residual after neoadjuvant	Pre and post	Rb,Cyclin D1
	NCT01740427	Recruiting	Phase 3	letrozole	ER+ HER2- ABC	Post	No
	NCT02028507	Recruiting	Phase 3	exemestane	ER+ HER2- HT pretreated MBC	Post	No
	NCT00721409	Active, not recruiting	Phase 1/2	letrozole	ER+ HER2- ABC	Post	CCND1 p16
	NCT02040857	Recruiting	Phase 2	endocrine	ER+ HER2- stage II/III (no T2N0)	Post	No
	NCT01942135	Recruiting	Phase 3	Fulvestrant	ER+ HER2- HT pretreated MBC	Pre and post	No
LEE011	NCT02088684	Not yet recruiting	Phase 1b/2	Fulvestrant, BYL719 BKM120	ER+ HER2- ABC	Post	No
	NCT01872260	Recruiting	Phase 1b/2	letrozole, BYL719	ER+ HER2- ABC	Post	No
	NCT01857193	Recruiting	Phase 1b/2	Everolimus Exemestane	ER+ HER2- LABC or MBC	Post	No
	NCT01958021	Recruiting	Phase 3	letrozole	ER+ HER2- ABC	Post	No
	NCT01919229	Recruiting	Phase 2	letrozole	ER+ HER2- EBC, presurgery	Post	No
LY2835219	NCT02057133	Recruiting	Phase 1b	AI, Tam, everolimus	ER+ HER2- MBC, including HT pretreated	Pre and post	No
	NCT02102490	Not yet recruiting	Phase 2	no	ER+ HER2- MBC CT pre-treated	Pre and post	No
	NCT02107703	Not yet recruiting	Phase 3	Fulvestrant	ER+ HER2- LABC or MBC, including HT pretreated	Post	No

Acknowledgements

Fondazione Sandro Pitigliani
per la lotta contro i tumori - ONLUS

ITT Istituto Toscano Tumori

SST Azienda USL 4 Prato
Servizio Sanitario della Toscana

Thank you

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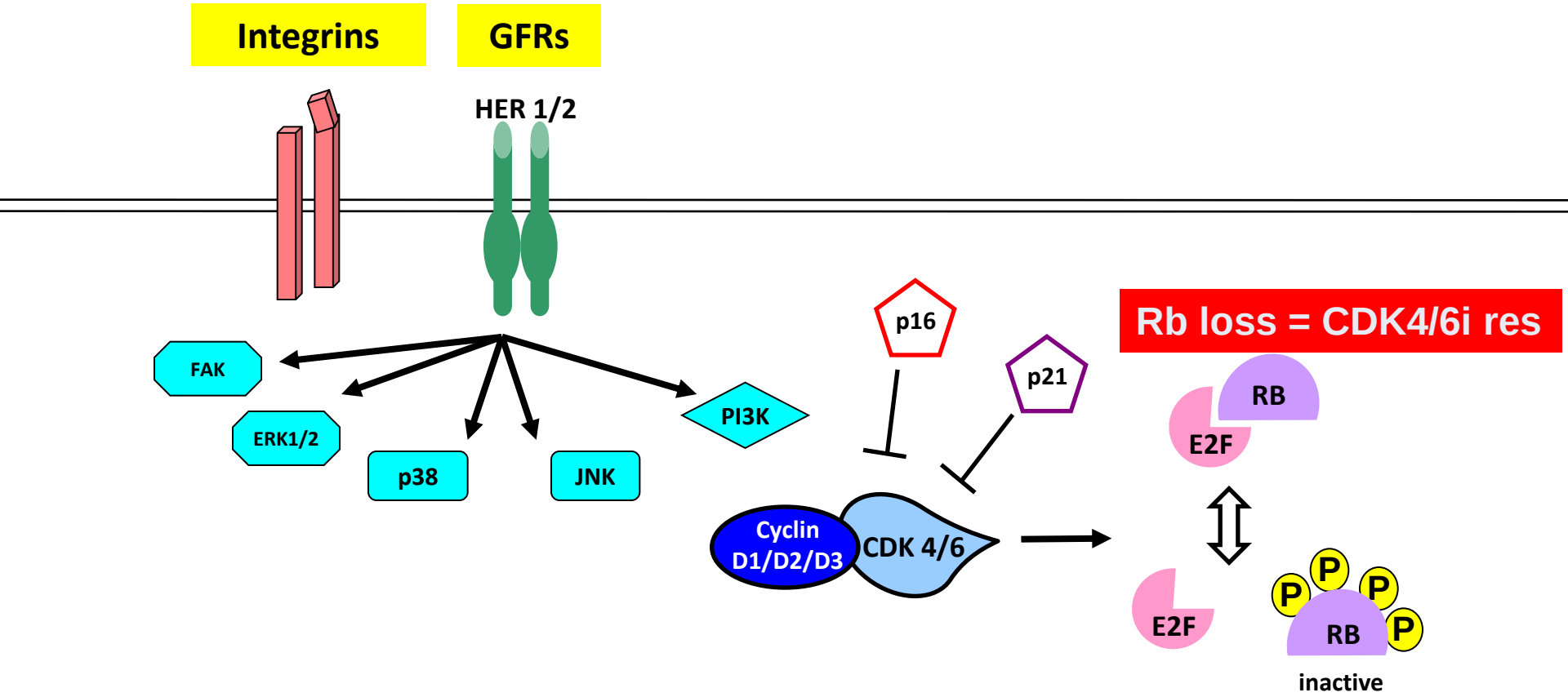
Backup

Molecular determinants of response to CDK4/6 inhibitors



Rb loss GENETIC = CDK4/6i res

Rb functional inactivation = CDK4/6i sens?