CENTRE HENRI-BECQUEREL

CENTRE DE LUTTE CONTRE LE CANCER DE HAUTE-NORMANDIE

Hormono-résistance : nouvelles données biologiques et possibles applications circulantes

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November 8th 2017

Disclosure

- Research funding
  - Novartis
- Honoraria
  - Novartis
  - Astra Zeneca

Plan

- Hormone therapy in breast cancer
- Endocrine therapies resistance and associated biomarkers
  - PI3K pathway
  - *ESR1* alterations
  - *HER2* alterations
  - Cdk4/cdk6 targeting
  - Others pathways
- Take home messages

Early and Metastatic (M+) breast cancer incidence

- Overall breast cancer incidence in France
  - 50 000 cases/year
- Metastatic cases
  - 10% at diagnosis
  - +/- 20% following initially localized stage
- → 15 000 M+ cases/year
- → 10 000 M+ HR+/Her2- cases/year

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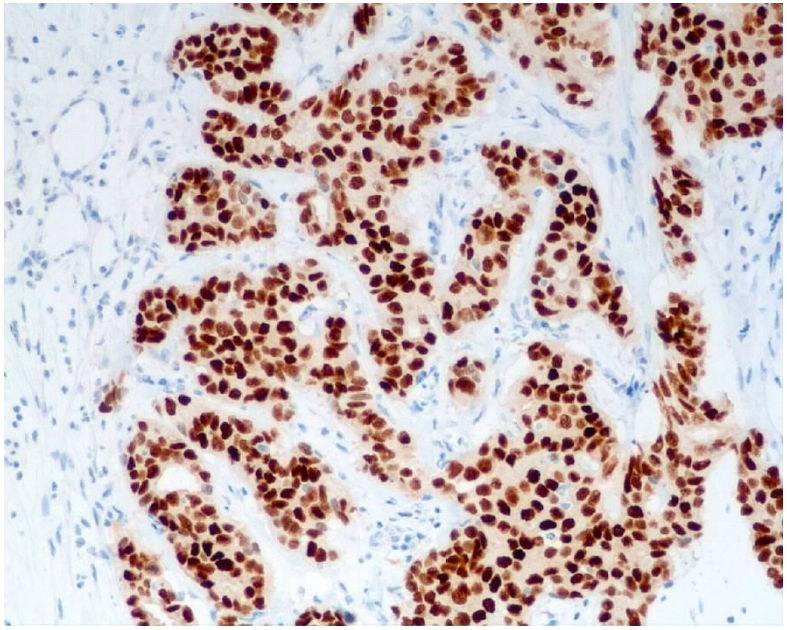
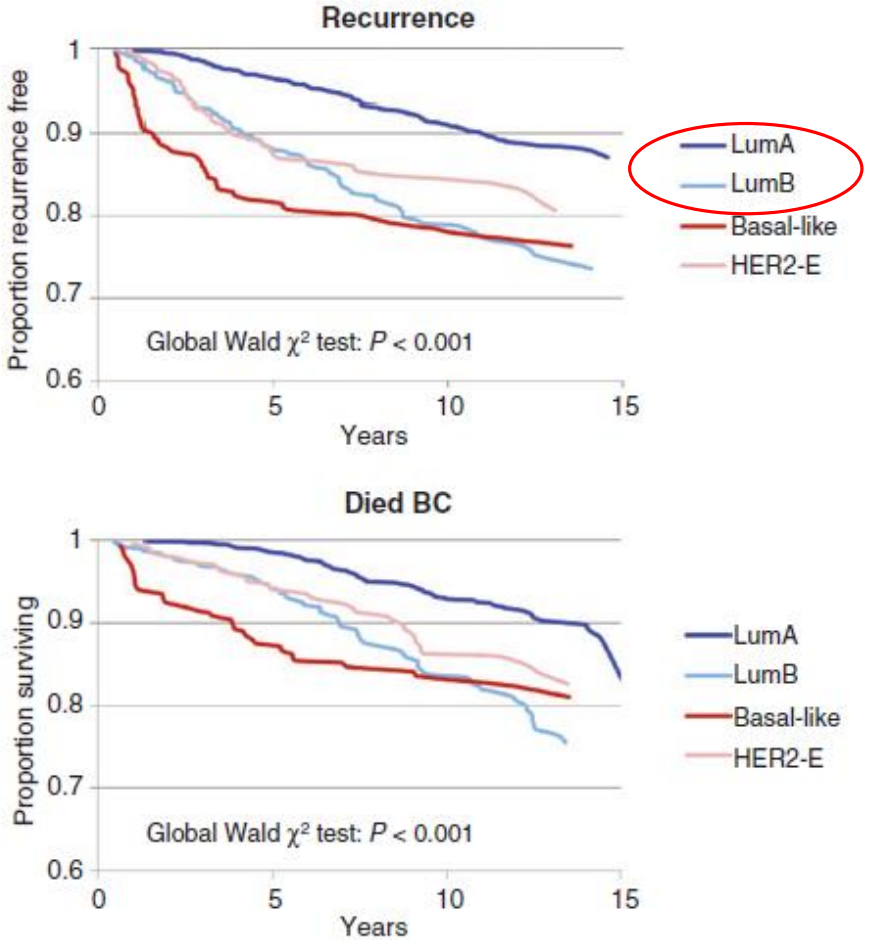
Hormone receptor positive = luminal breast cancer

HR+=70% of breast cancers



CoPath 2014



Caan Can Ep Bio Prev 2014

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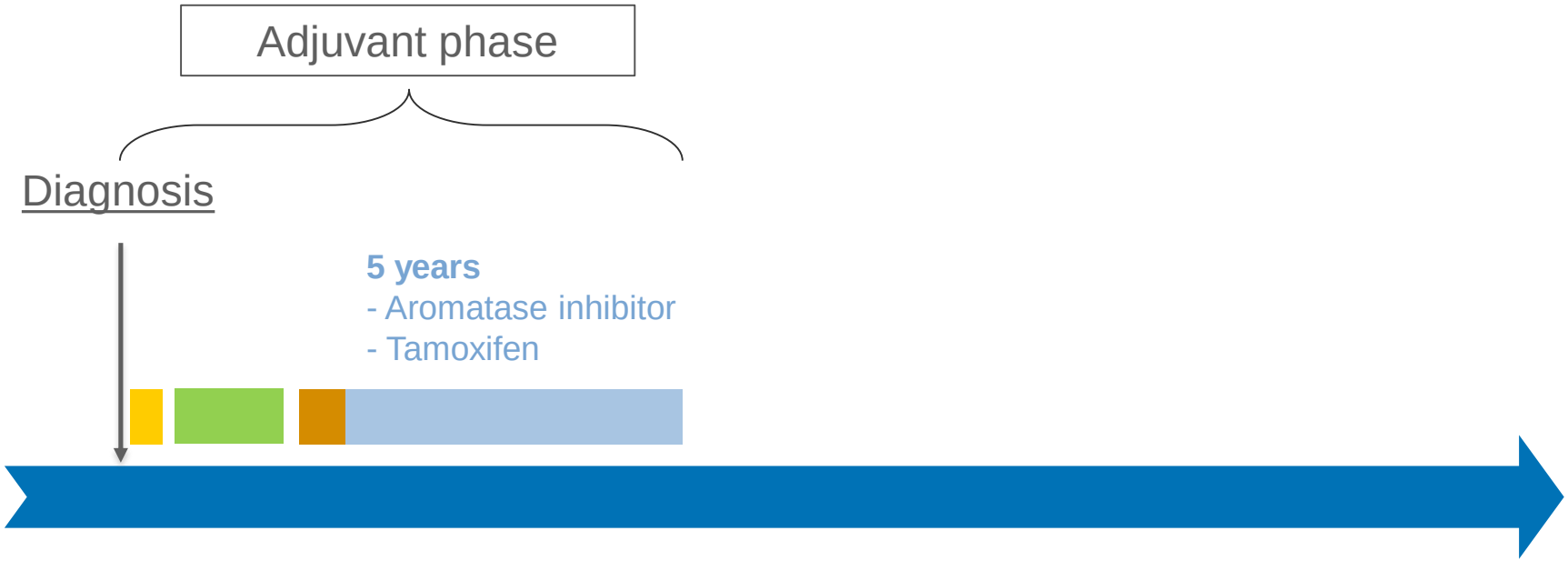
Treating breast cancer with endocrine therapies



Surgery

Chemotherapy

Radiation therapy

Endocrine therapy

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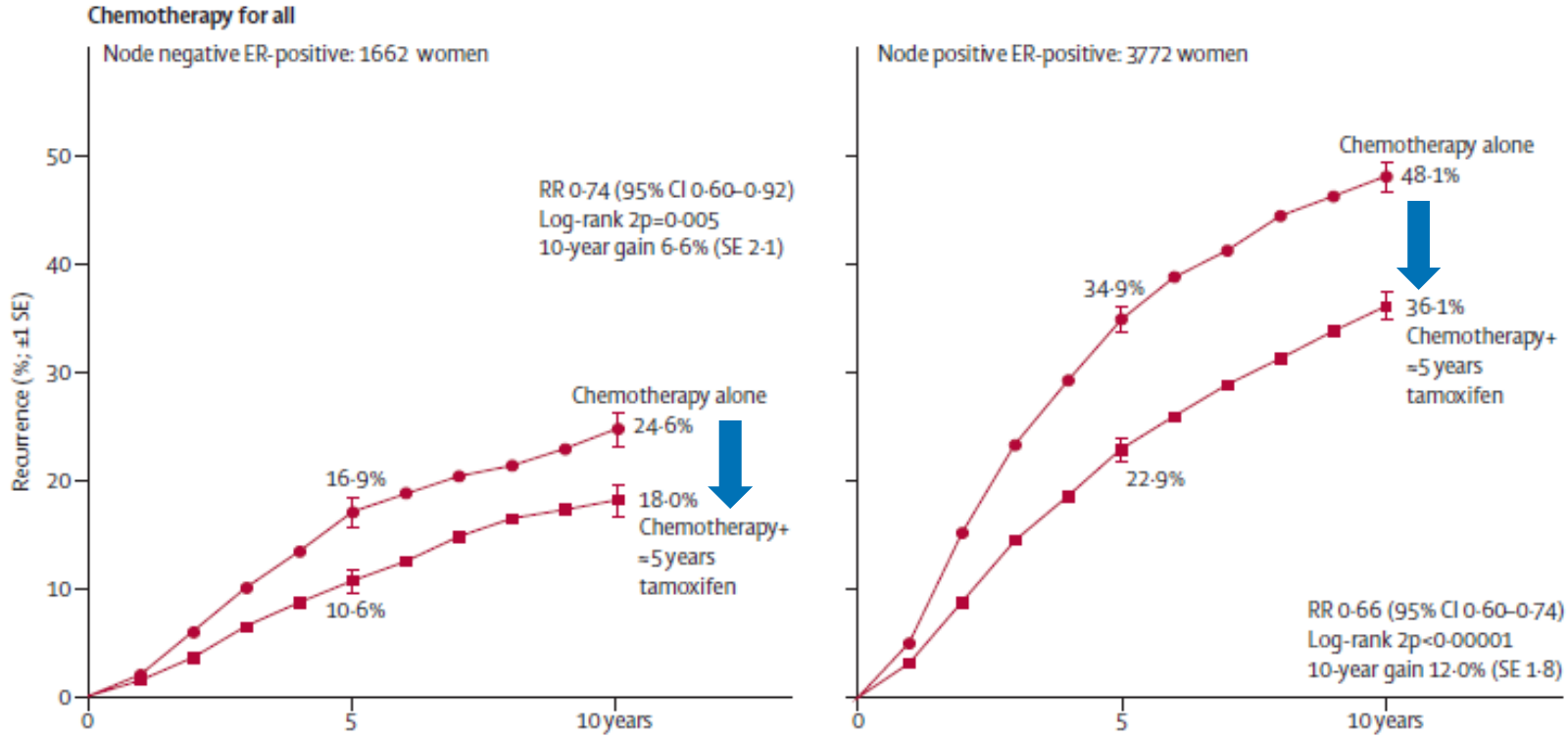
Adjuvant endocrine therapy

25 % additional benefit of endocrine therapy



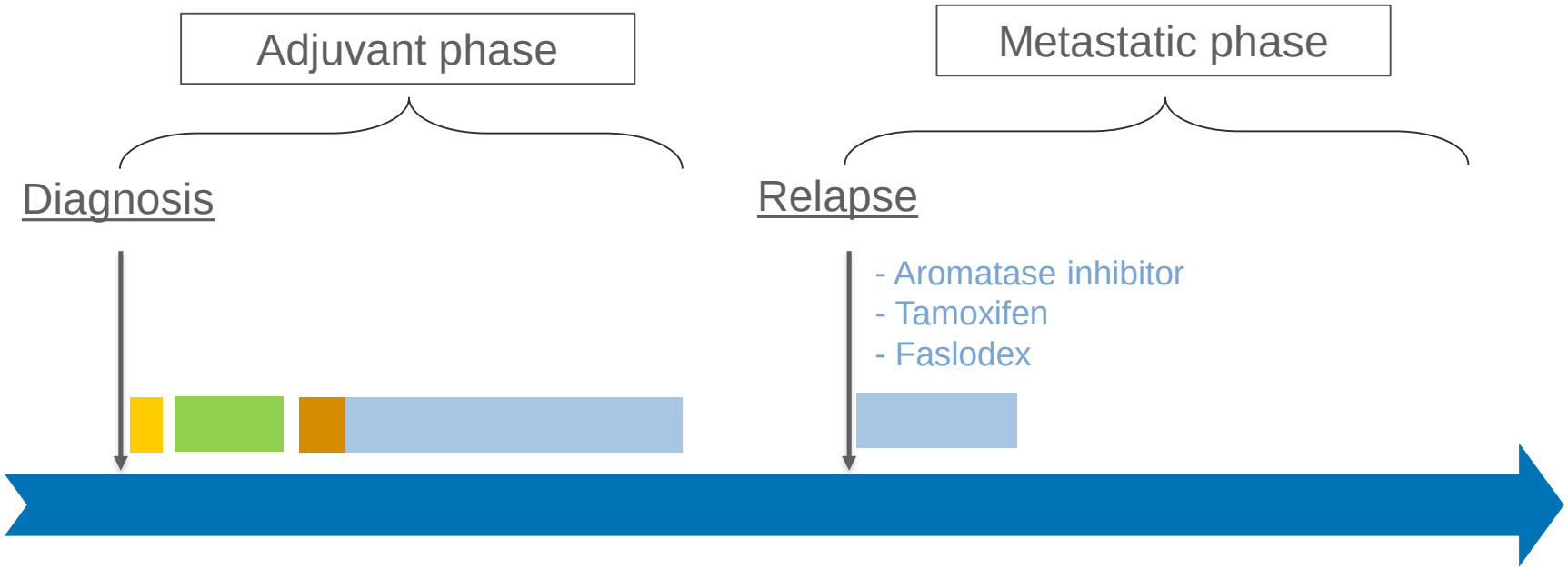
Recurrence rates (% per woman-year) and log-rank analyses

	Years 0–4	Years 5–9	Year 10+	Years 0–4	Years 5–9	Year 10+
Tamoxifen	2·28 (86/3775)	1·81 (54/2991)	1·44 (24/1667)	5·29 (429/8108)	3·89 (180/4624)	3·60 (64/1777)
Control	3·61 (133/3681)	1·91 (54/2829)	1·12 (18/1610)	8·49 (632/7440)	4·75 (177/3728)	3·38 (43/1273)
Rate ratio	0·61 (SE 0·11)	0·92 (SE 0·19)	1·21 (SE 0·35)	0·60 (SE 0·05)	0·80 (SE 0·10)	1·03 (SE 0·21)
(O–E)/V	–25·8/51·9	–2·2/26·1	1·9/10·0	–125·6/242·9	–18·5/83·2	0·8/24·2

Figure 3: Relevance of nodal status and of background chemotherapy to the effects of tamoxifen on the 10-year probability of recurrence, for ER-positive disease

EBCTCG 2011

Treating breast cancer with endocrine therapies



Surgery

Chemotherapy

Radiation therapy

Endocrine therapy

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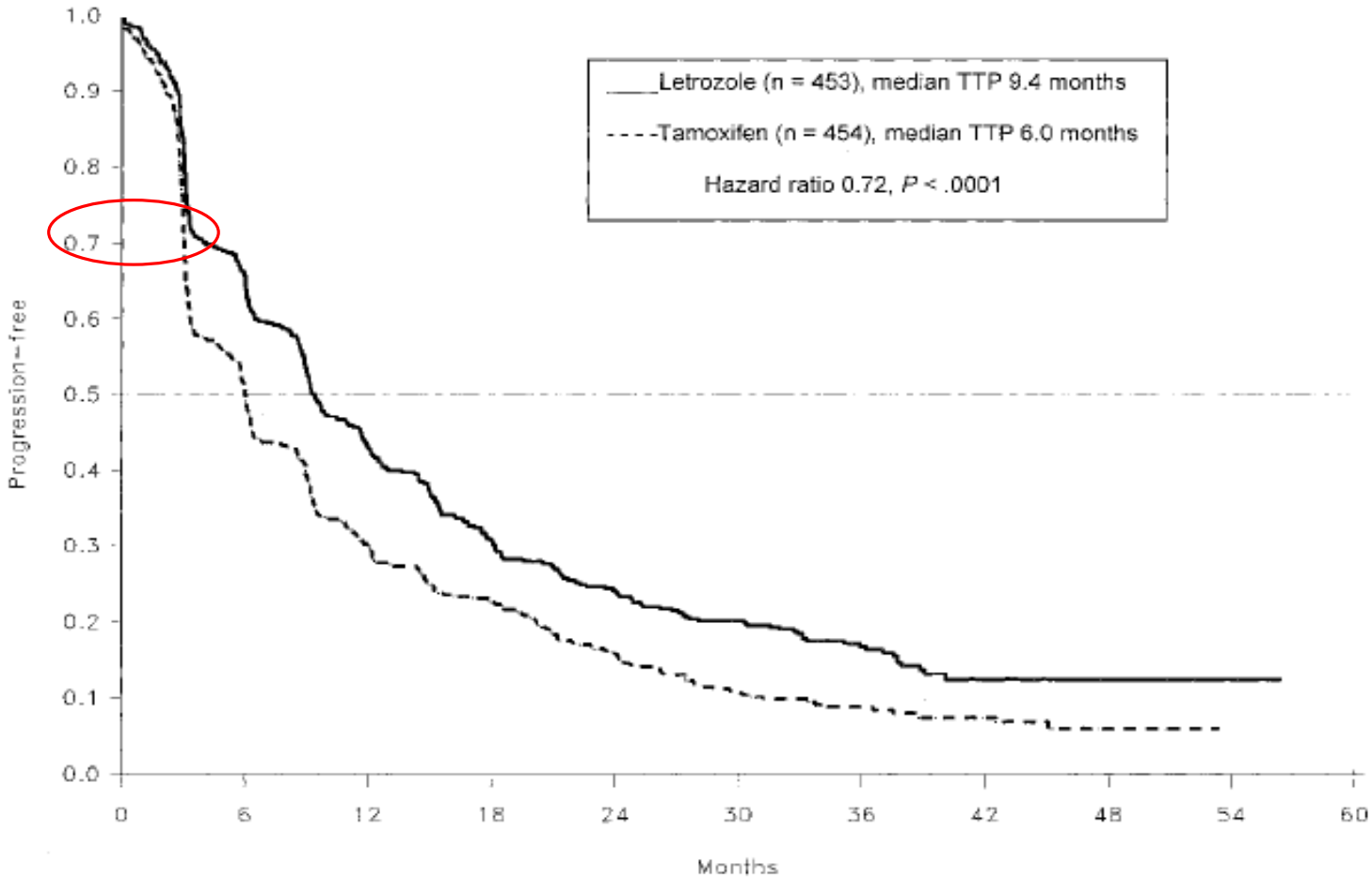
1st line M+ (yet…): aromatase-inhibitor



Mouridsen JCO 2001

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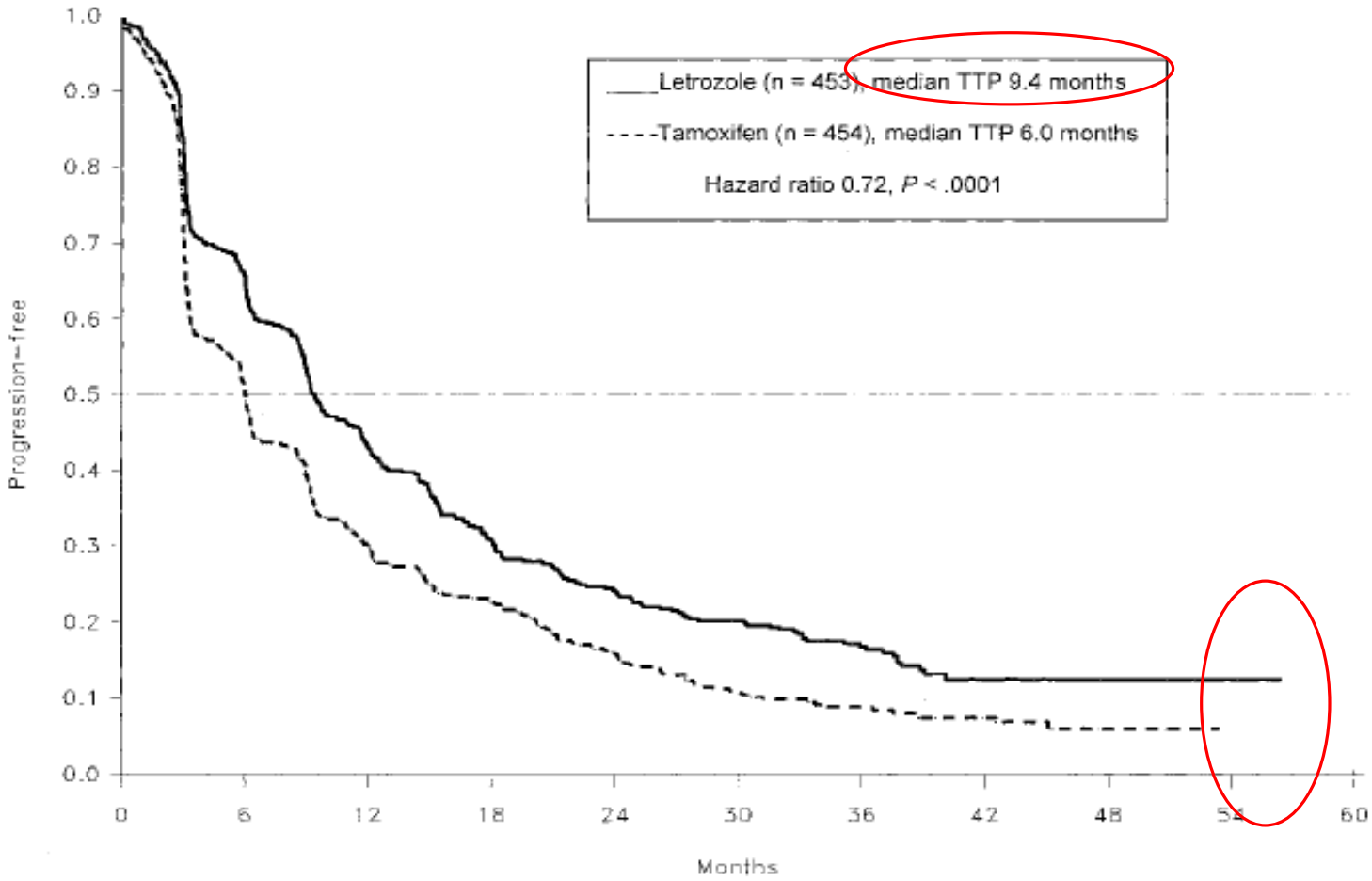
Metastatic endocrine therapy



Mouridsen JCO 2001

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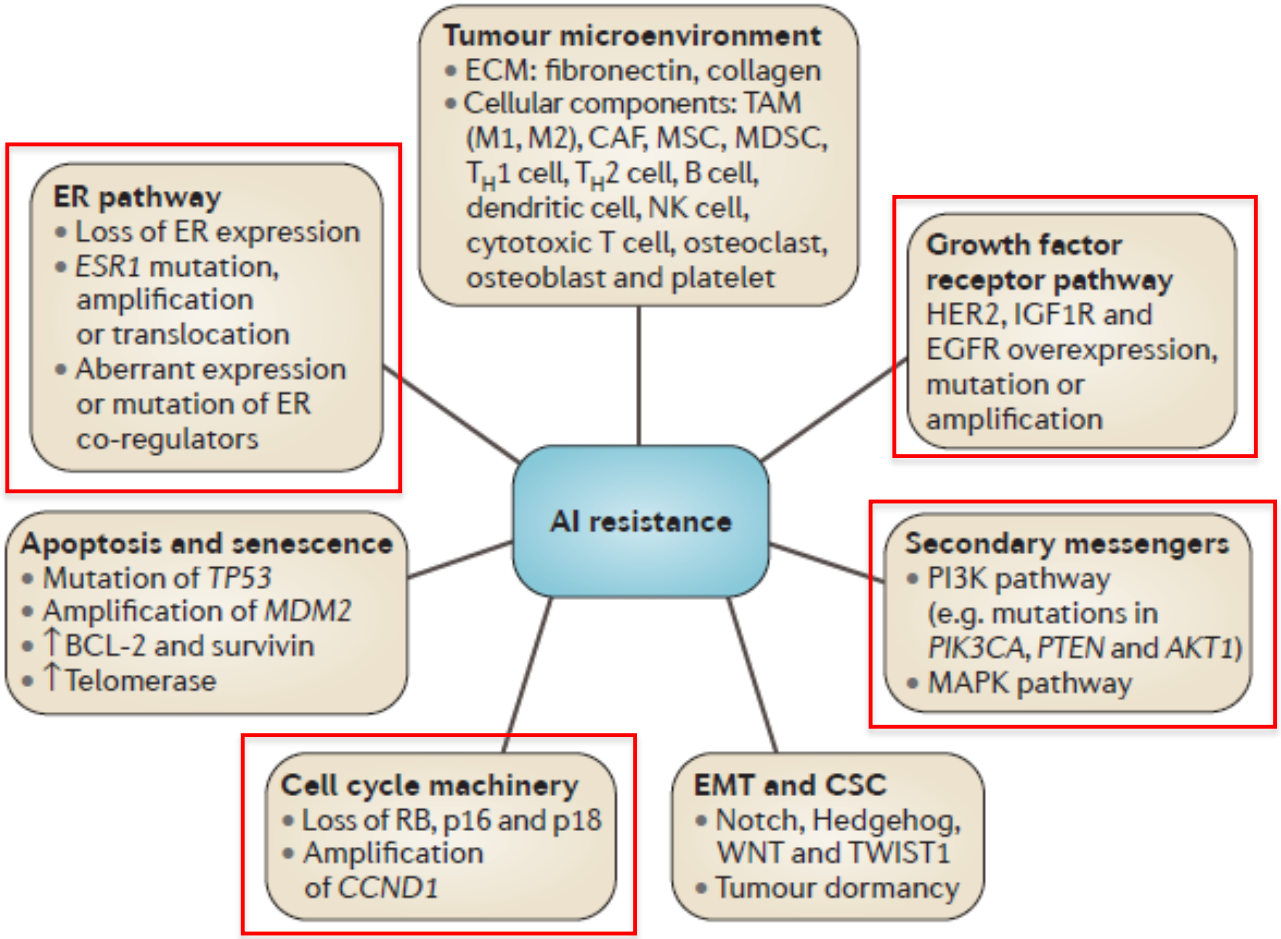
Endocrine therapies: mechanisms of resistance



Ma, Nat Rev 2015

Centre Henri-Becquerel

PI3K pathway

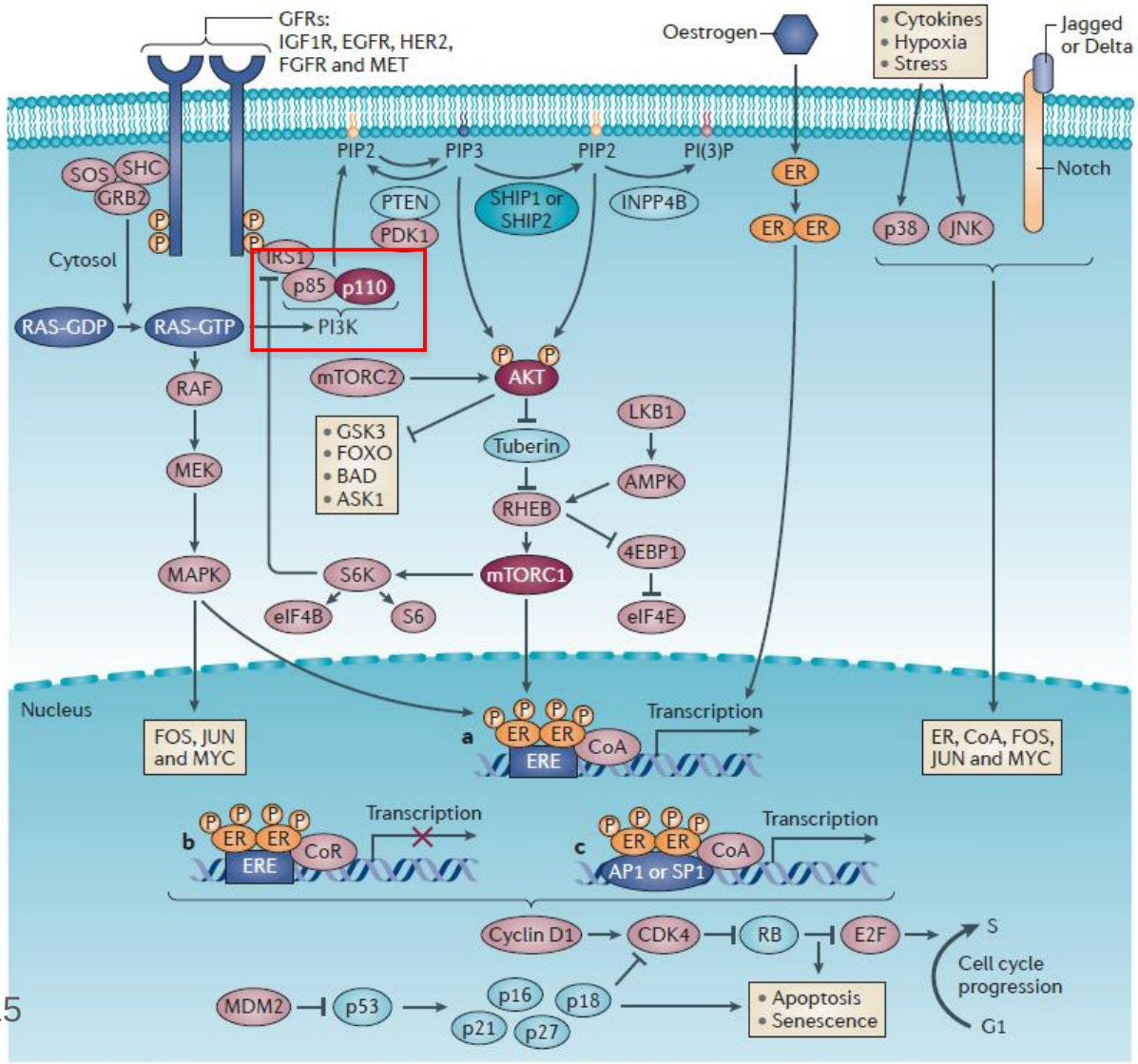


Figure 6 | **Growth factor receptor signalling, PI3K, MAPK, ER and the p53–RB pathway in ER⁺ breast cancer.**

Ma, Nat Rev 2015

PI3K pathway

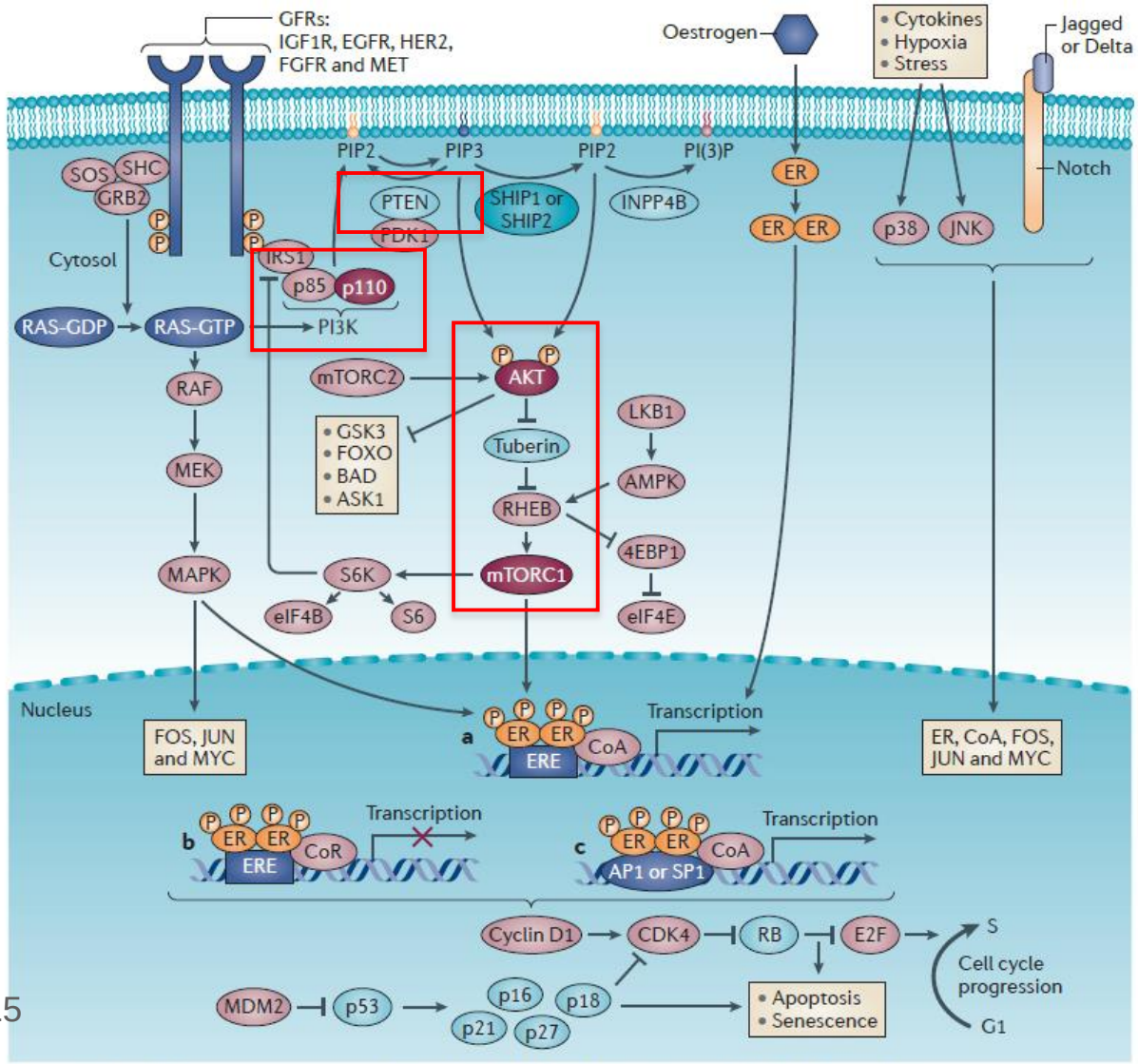
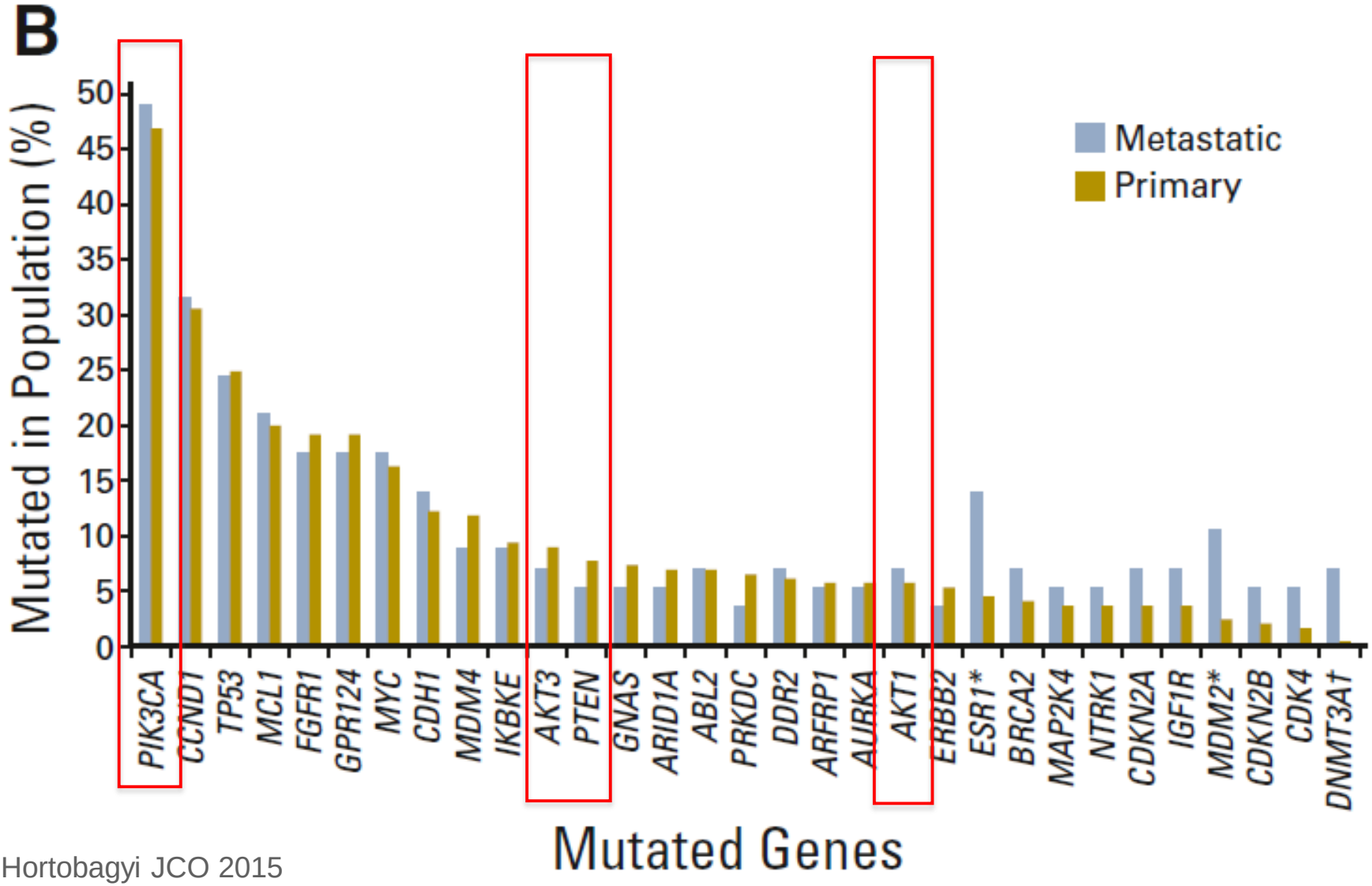


Figure 6 | **Growth factor receptor signalling, PI3K, MAPK, ER and the p53–RB pathway in ER⁺ breast cancer.**

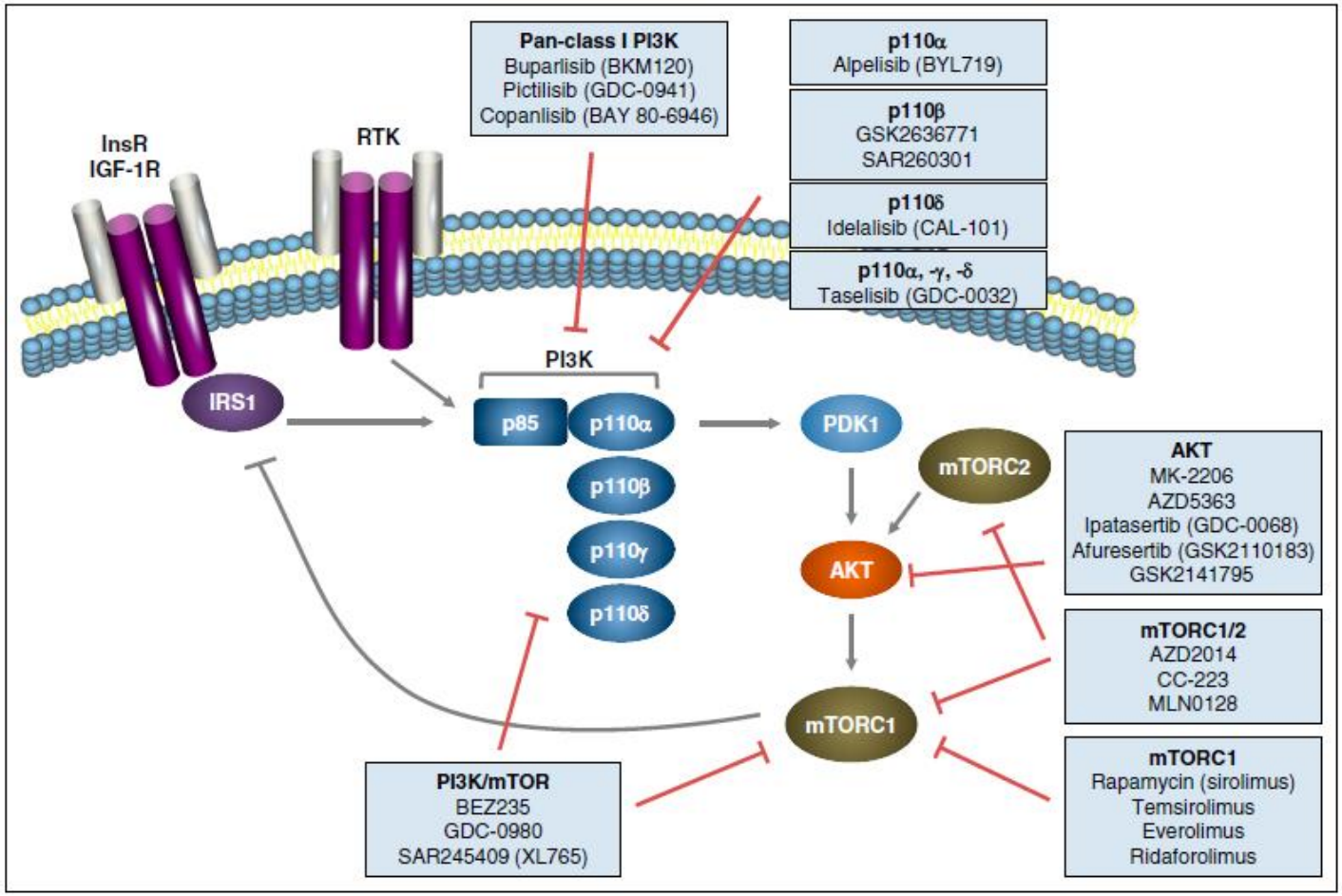
Ma, Nat Rev 2015

PI3K pathway mutations during cancer evolution



Hortobagyi JCO 2015

PI3K Inhibitors



Mucci Lo Ruso JCO 2016

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Targeting mTOR: everolimus

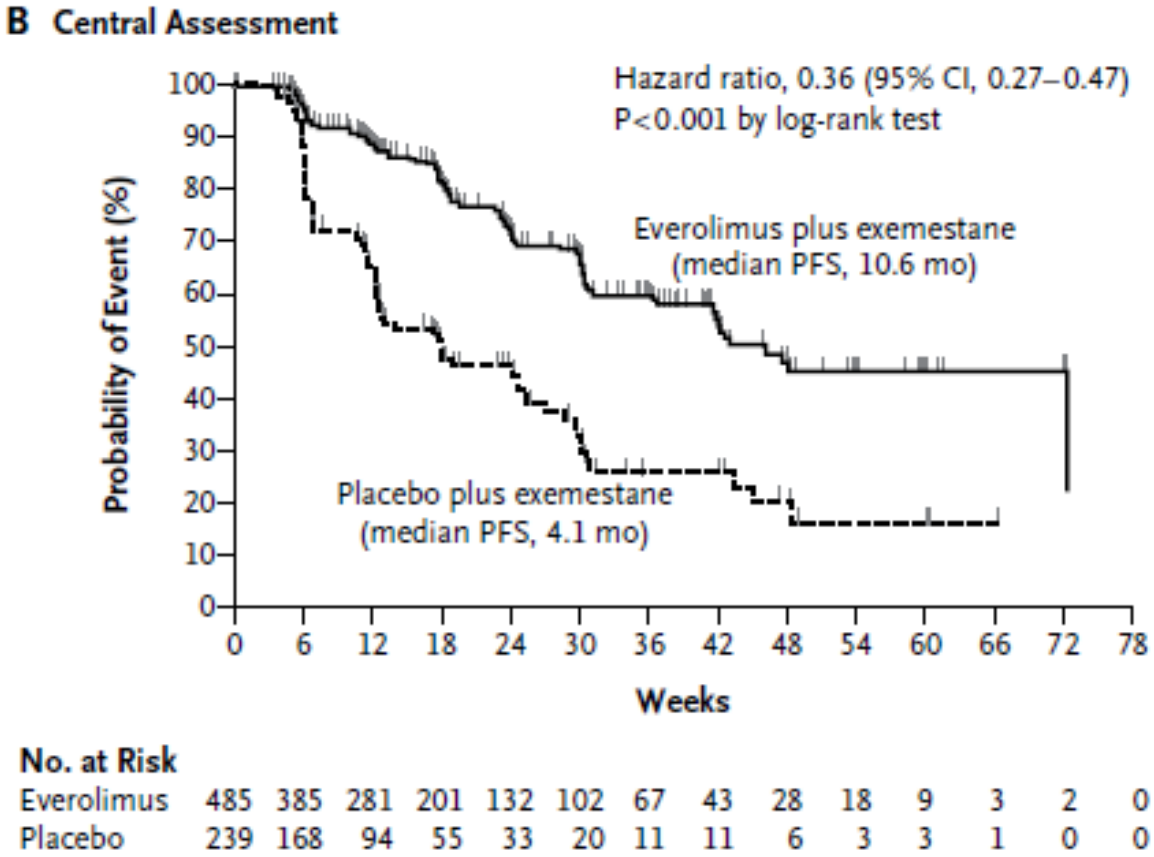

Figure 1. Kaplan–Meier Plot of Progression-free Survival.

Baselga NEJM 2012

Bolero 2 Trial
- **724 HR + BC**
- **Resistance to endocrine therapies**

PI3K mutation→better sensitivity ?

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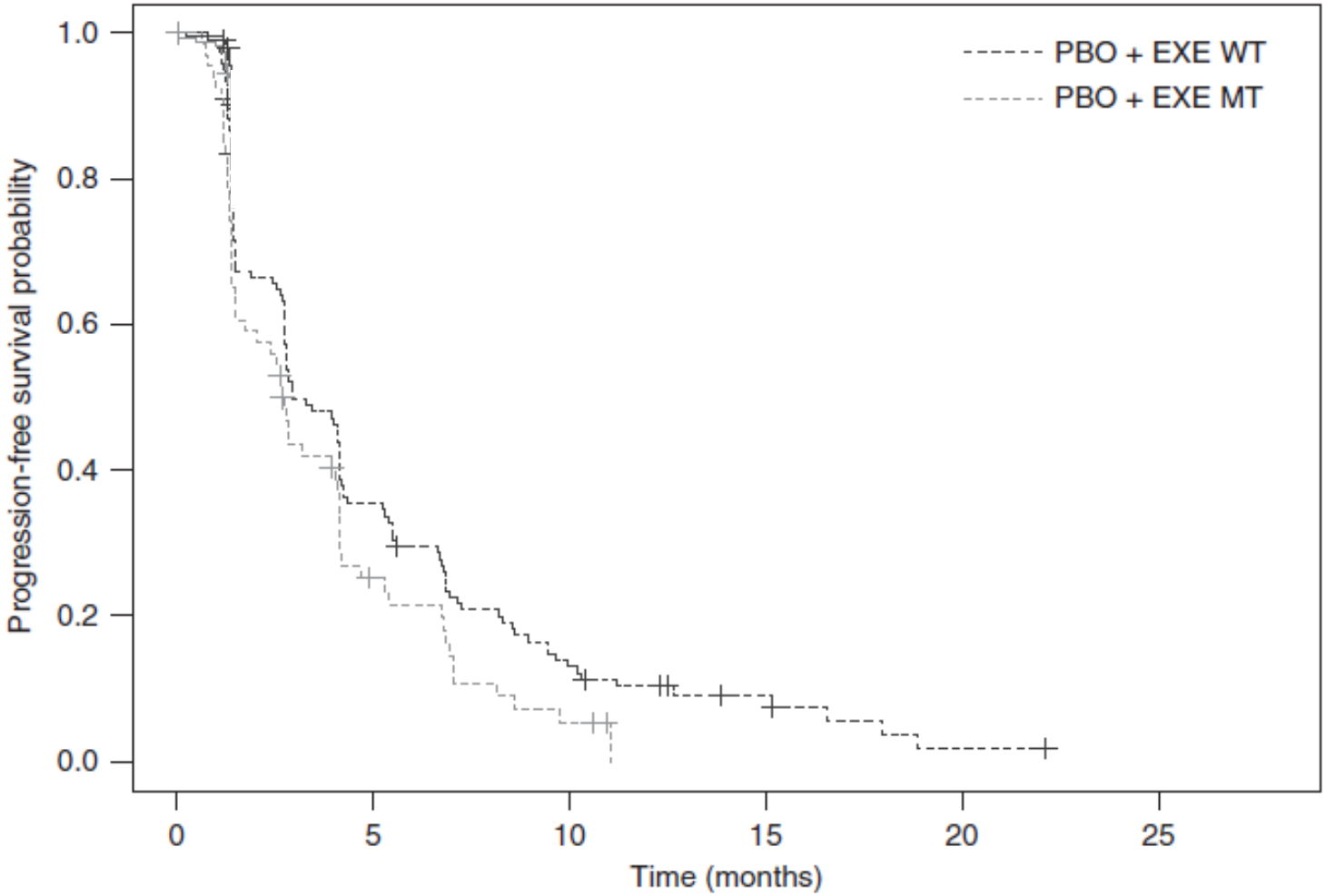
Predictive value of circulating *PIK3CA* mutations



Moynahan BJC 2017

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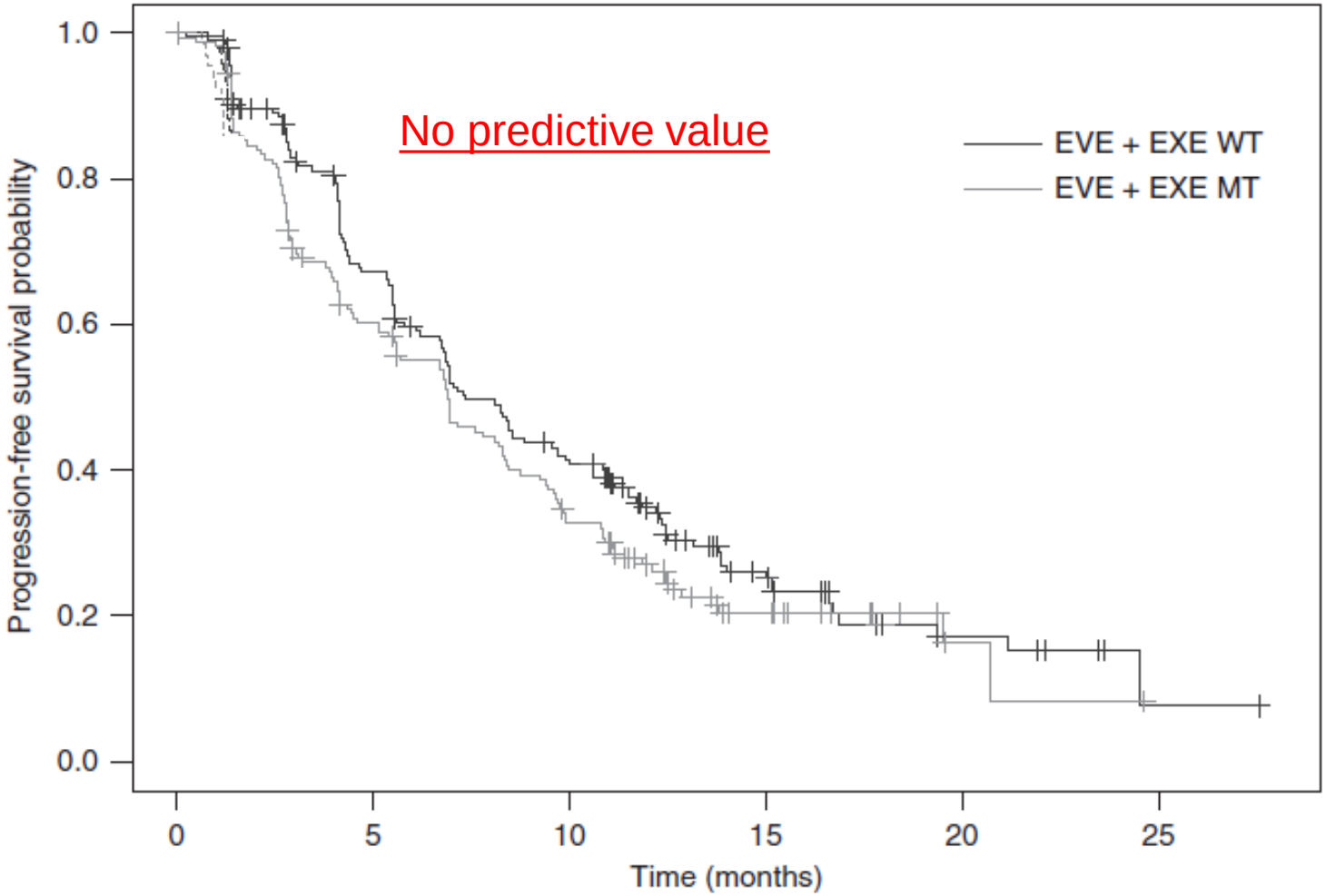
Predictive value of circulating *PIK3CA* mutations

Same outcome whatever the *PIK3CA* status and the treatment arm



Moynahan BJC 2017

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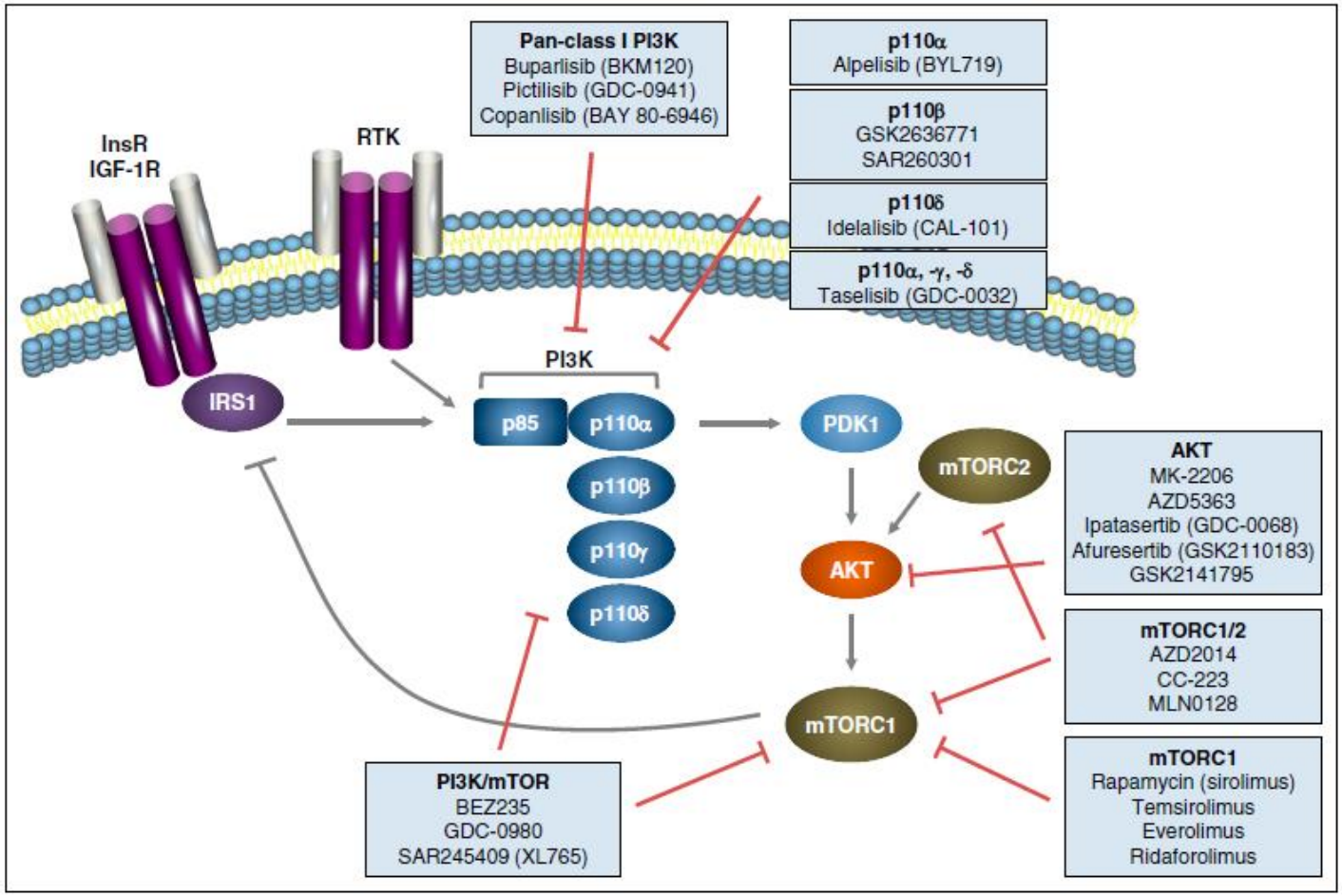

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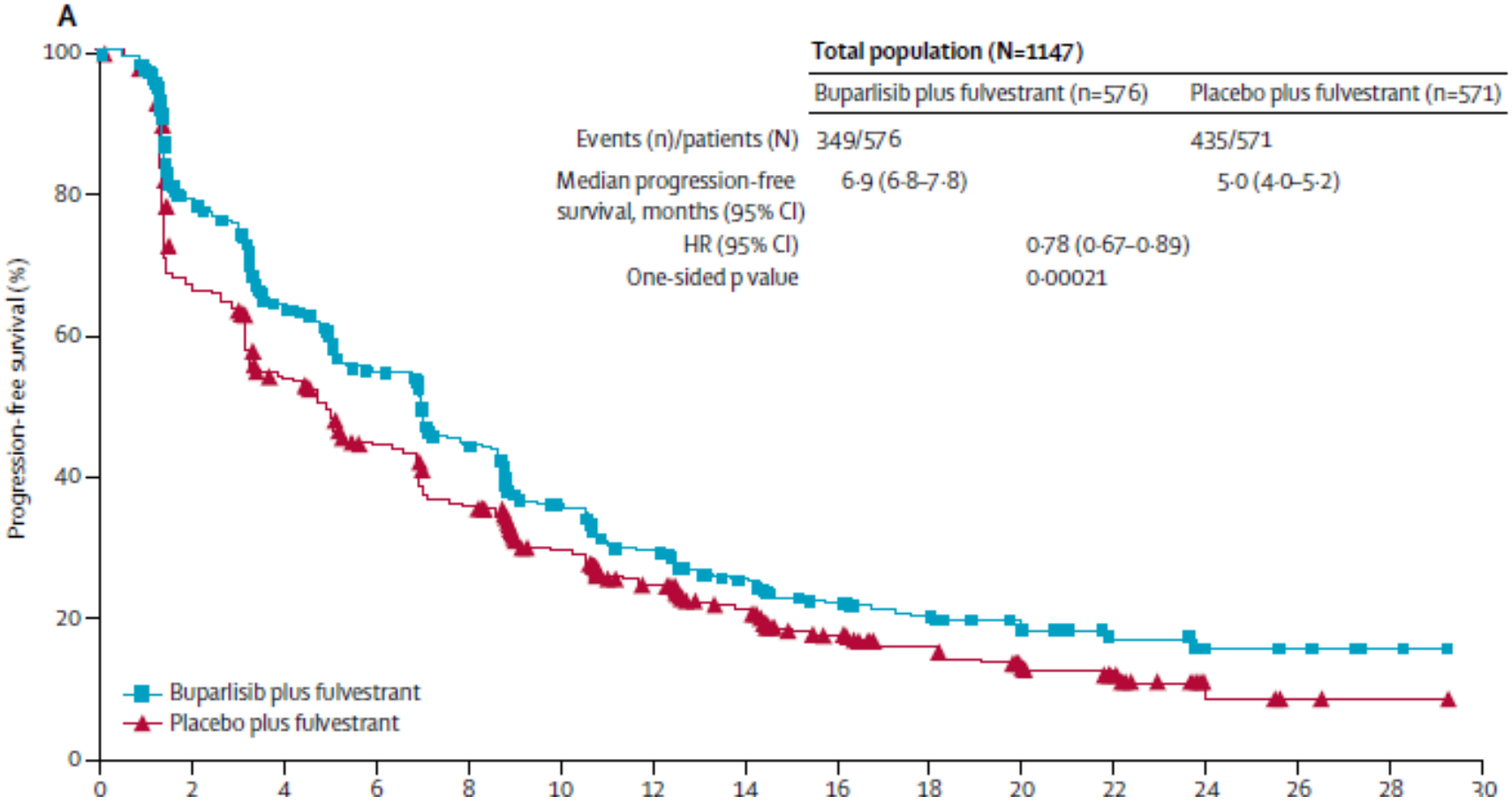
Overall buparlisib is effective but too toxic



Total population (N=1147)		
	Buparlisib plus fulvestrant (n=576)	Placebo plus fulvestrant (n=571)
Events (n)/patients (N)	349/576	435/571
Median progression-free survival, months (95% CI)	6·9 (6·8–7·8)	5·0 (4·0–5·2)
HR (95% CI)	0·78 (0·67–0·89)	
One-sided p value	0·00021	

Baselga, Lancet Oncol 2017

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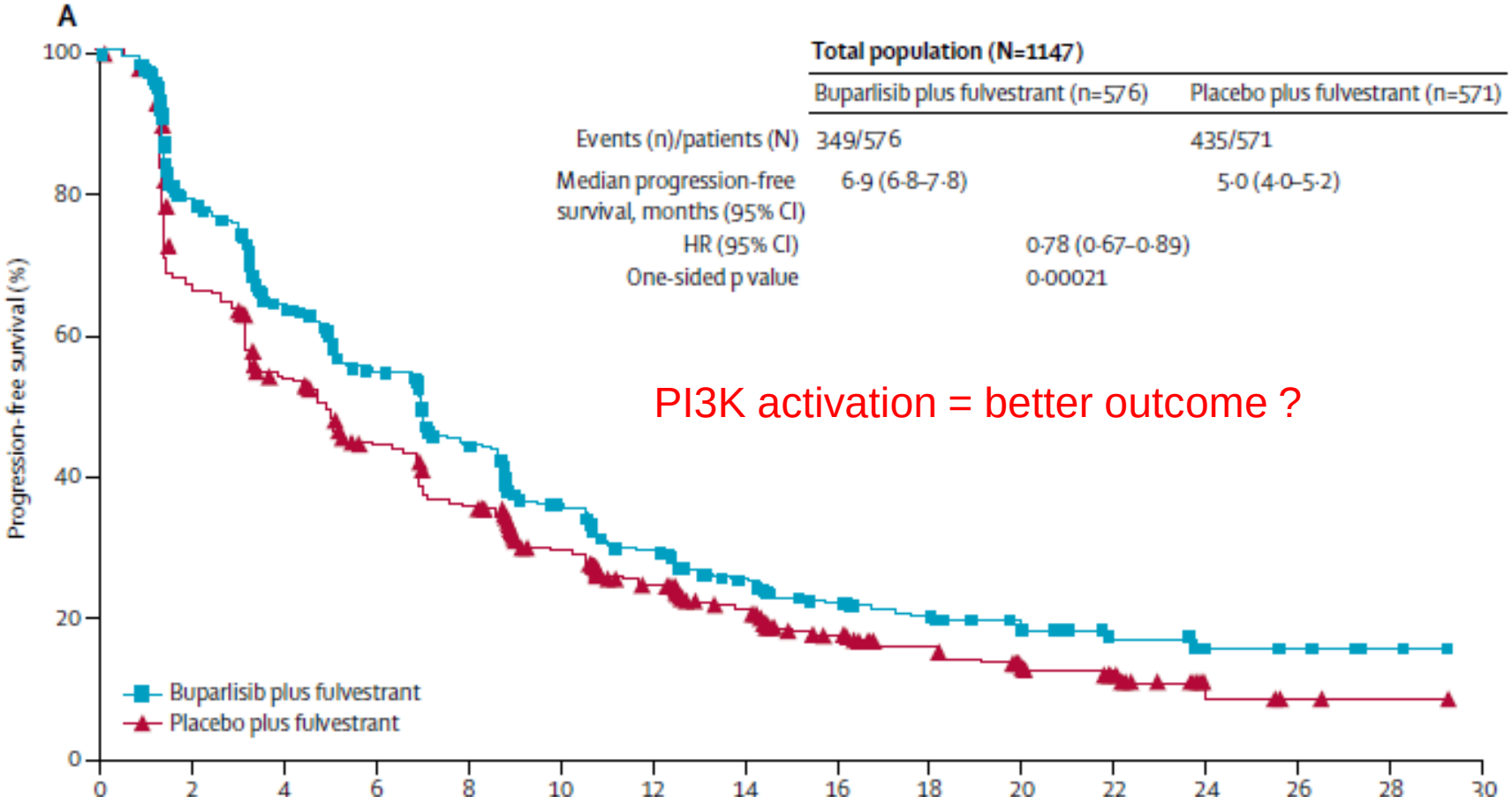

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PI3K activation = better outcome ?

Baselga, Lancet Oncol 2017

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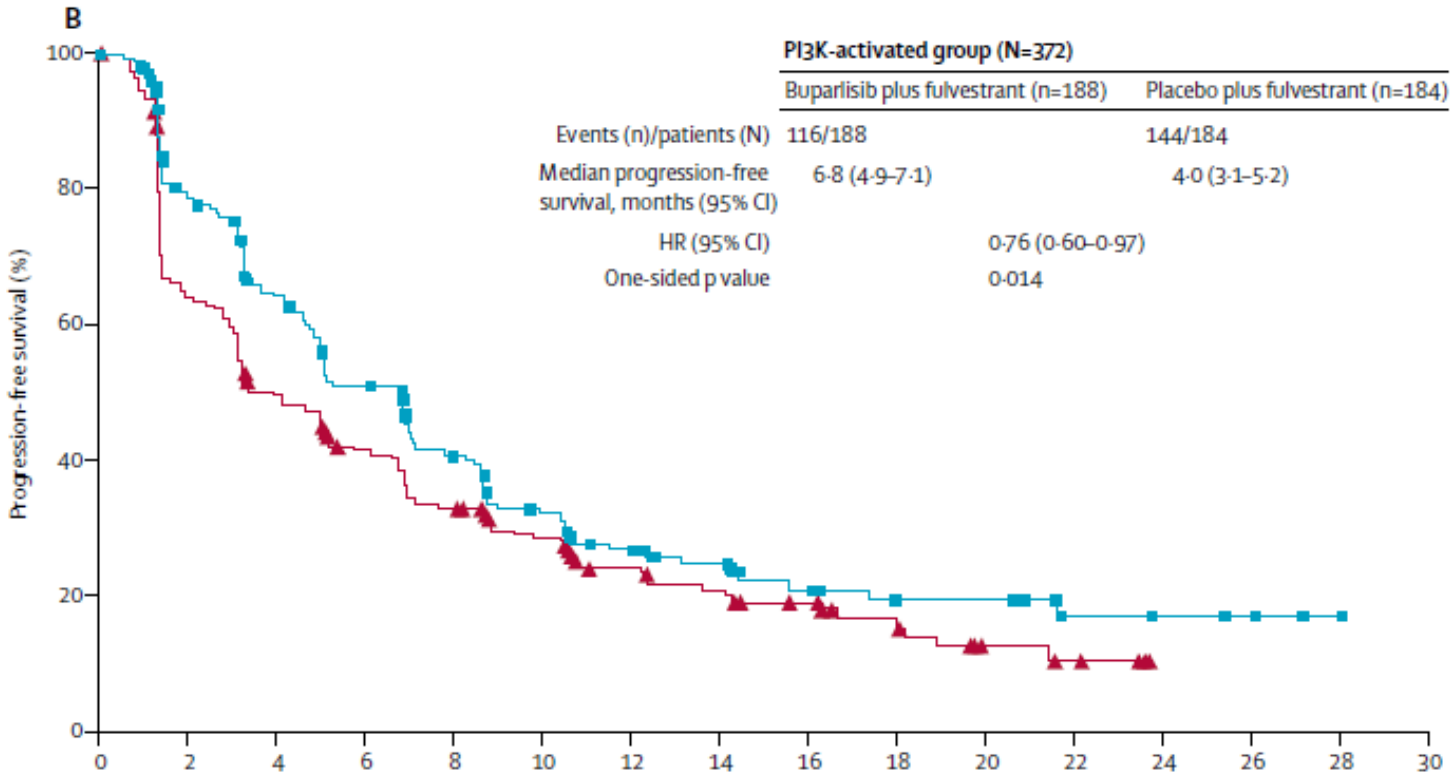
PI3K « activated » on tumor tissue…

PI3K activation: any *PIK3CA* mutation or no *PTEN* expression



	PI3K-activated group (N=372)	
	Buparlisib plus fulvestrant (n=188)	Placebo plus fulvestrant (n=184)
Events (n)/patients (N)	116/188	144/184
Median progression-free survival, months (95% CI)	6·8 (4·9–7·1)	4·0 (3·1–5·2)
HR (95% CI)	0·76 (0·60–0·97)	
One-sided p value	0·014	

Baselga, Lancet Oncol 2017

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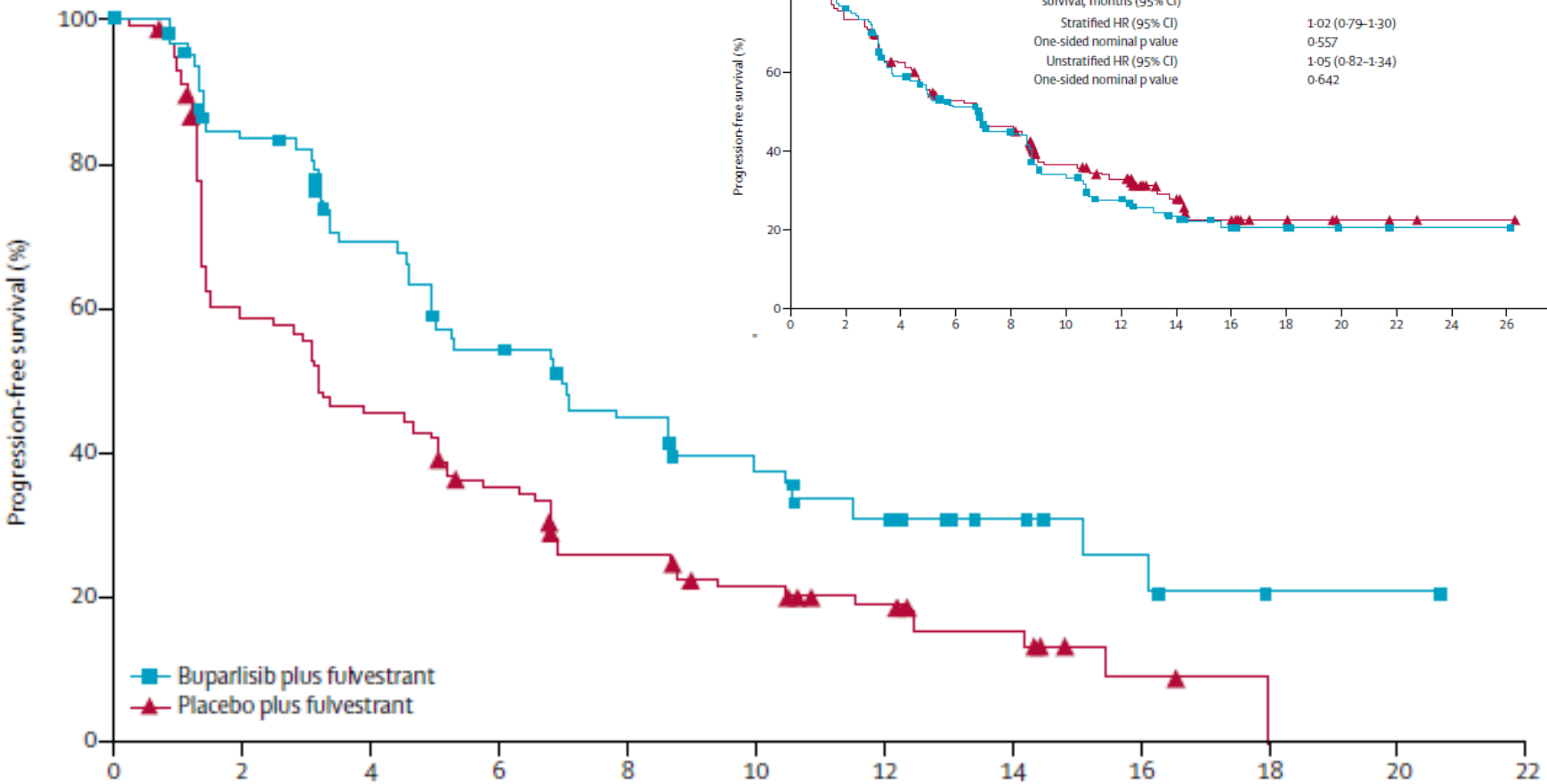
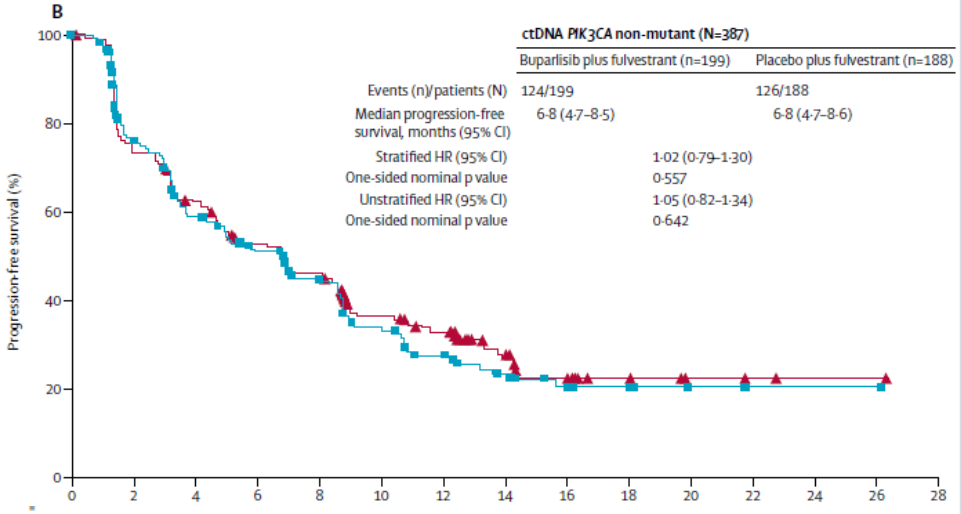
Circulating *PIK3CA* mutation correlates with outcome





ctDNA *PIK3CA* non-mutant (N=387)	Buparlisib plus fulvestrant (n=199)	Placebo plus fulvestrant (n=188)
Events (n)/patients (N)	124/199	126/188
Median progression-free survival, months (95% CI)	6·8 (4·7–8·5)	6·8 (4·7–8·6)
Stratified HR (95% CI)	1·02 (0·79–1·30)	
One-sided nominal p value	0·557	
Unstratified HR (95% CI)	1·05 (0·82–1·34)	
One-sided nominal p value	0·642	

Baselga, Lancet Oncol 2017

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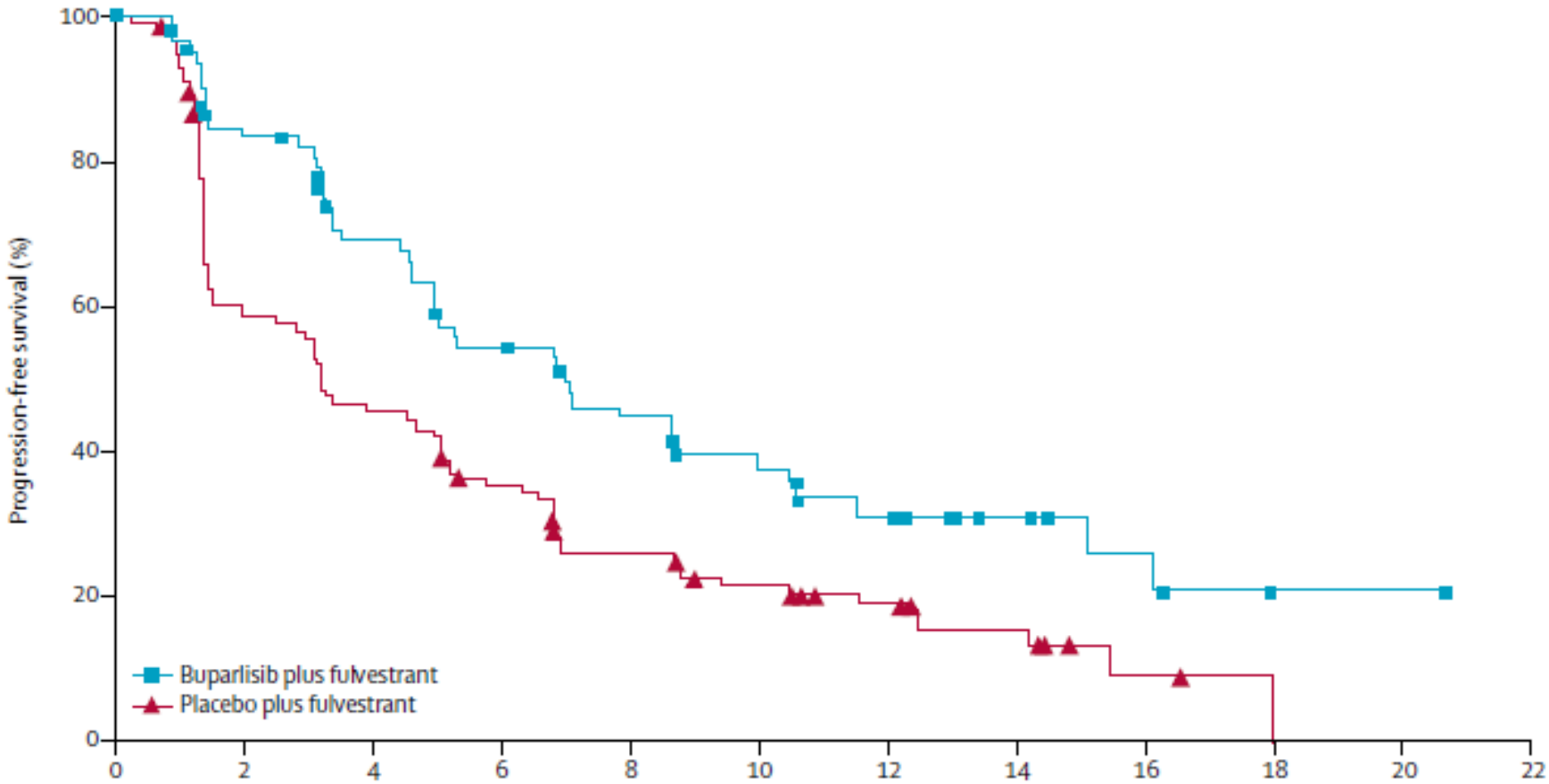
Circulating *PIK3CA* mutation correlates with outcome

Circulating *PIK3CA* works as a liquid biopsy



Baselga, Lancet Oncol 2017

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Assessing circulating *PIK3CA* mutations

- Recurrent mutations (3 mutations = 80% of all mutations)
- Frequent (50%)
- Not correlated with prognosis
- Correlated with buparlisib (targeting PIK3) response but not with everolimus (targeting mTORC)
- Ongoing trials based on ctDNA detection and *PIK3CA* and selective PI3K inhibitors

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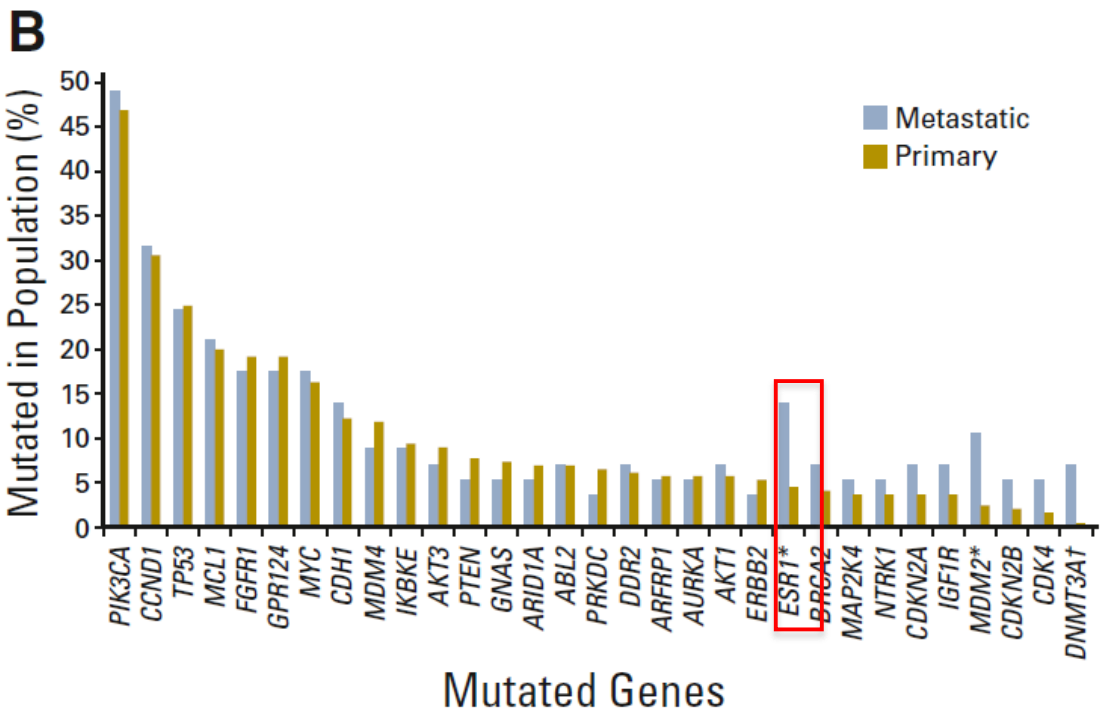
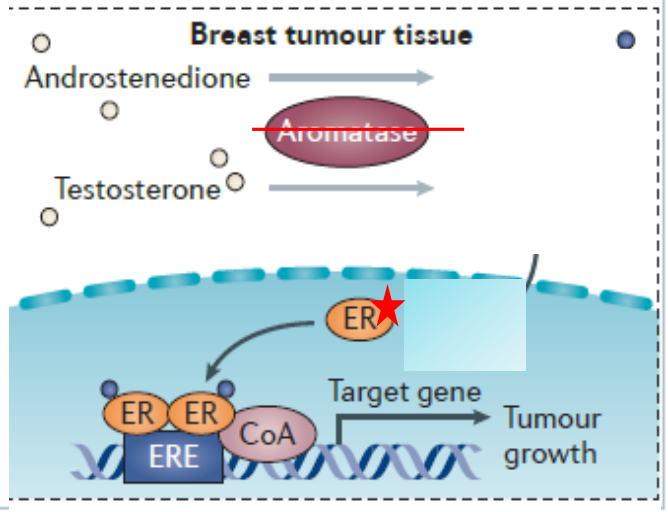
ESR1 mutations: a late event



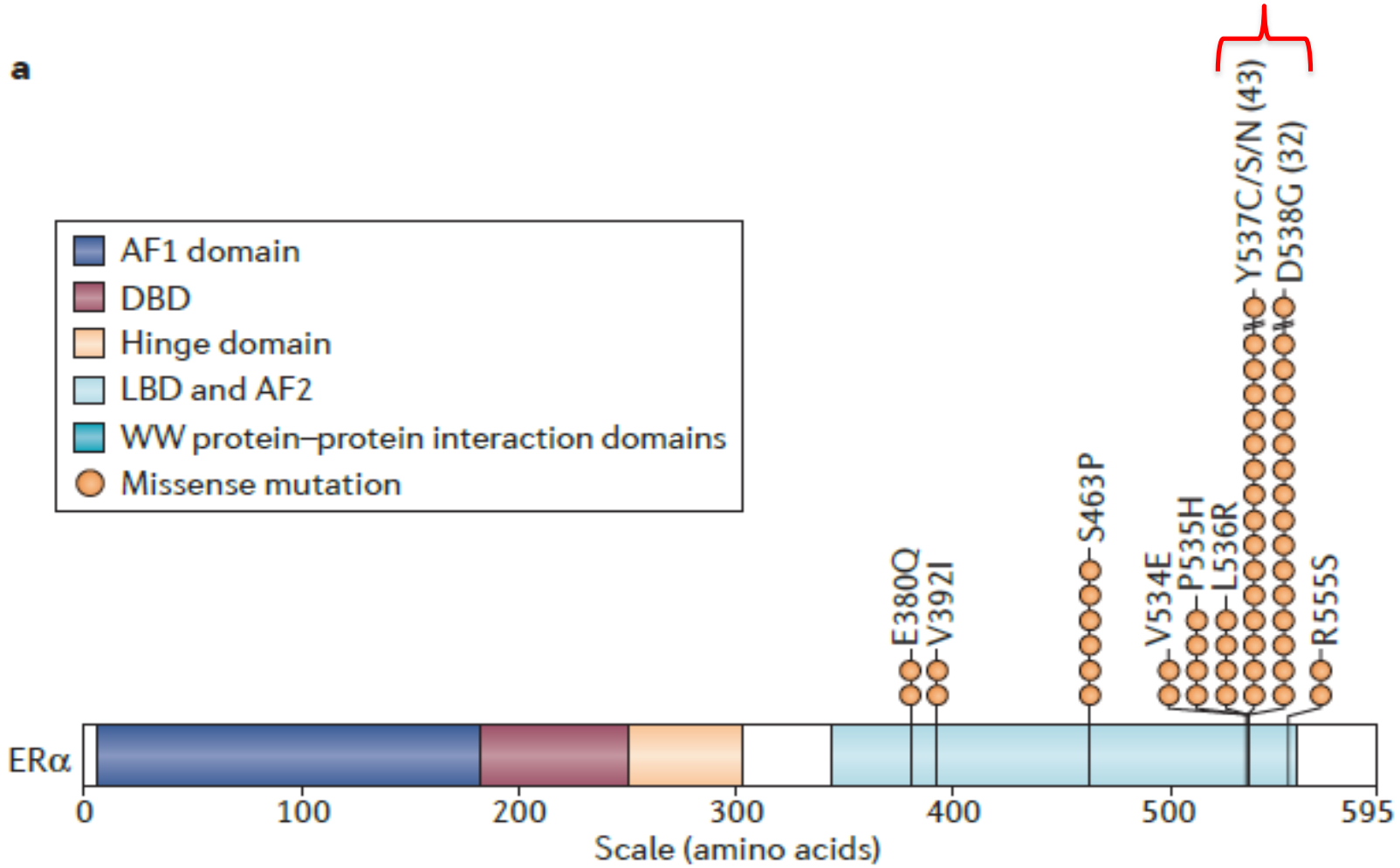


Acquired, activating mutation under AI

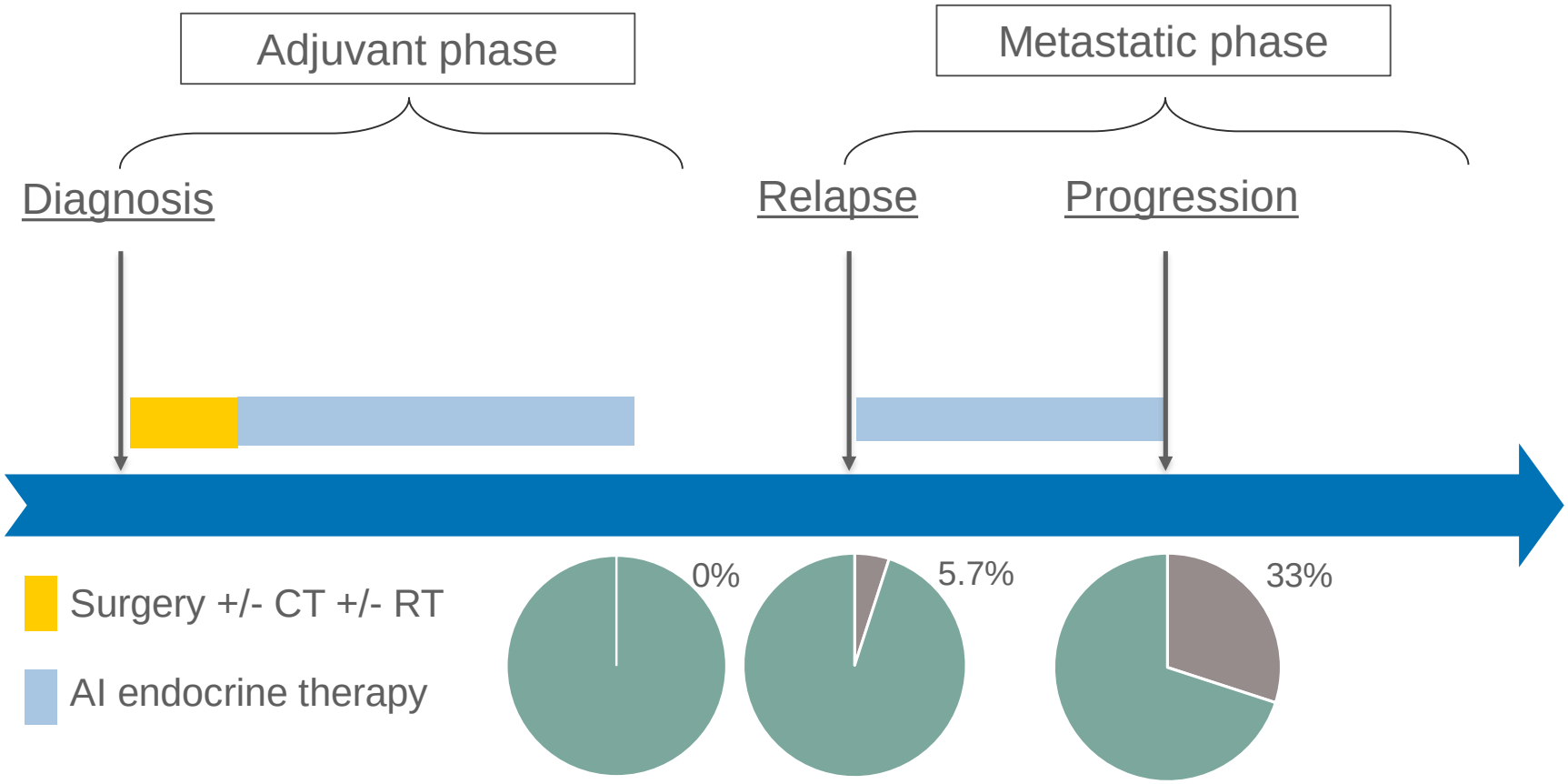
Hortobagyi JCO 2015

ESR1 mutations: recurrent mutations

74 % of the mutations



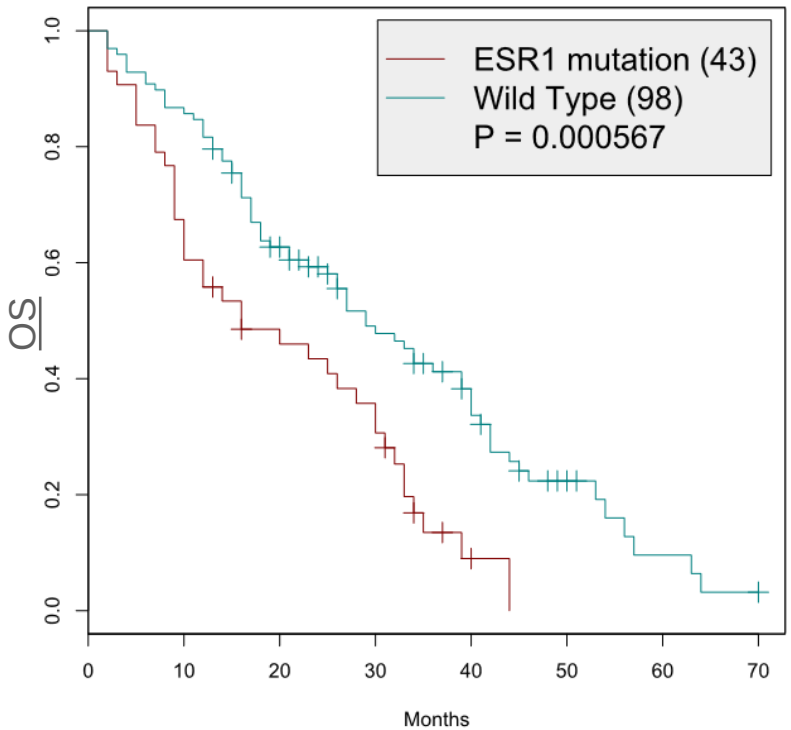
Treating breast cancer with endocrine therapies



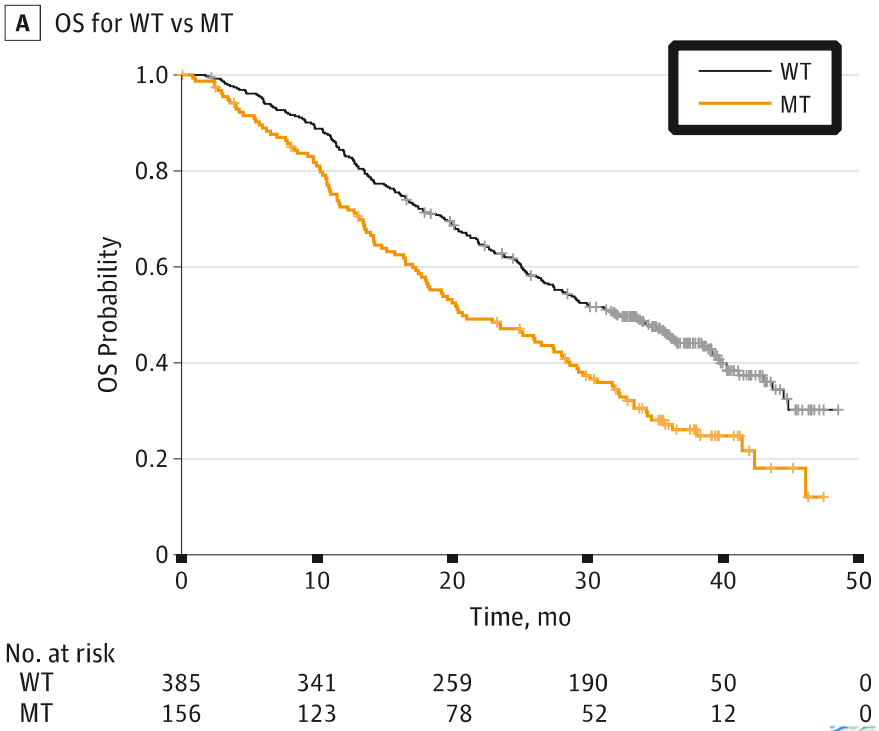
Allouchery, ESMO 2017

ESR1 circulating mutation: prognostic value

Multivariate analysis
HR = 1.9 [1.3-3], p=0.002



Multivariate analysis
HR = 1.6 [1.3-2], p<0.001



Clatot Oncotarget 2016; Chandarlapaty Jama Oncol 2016

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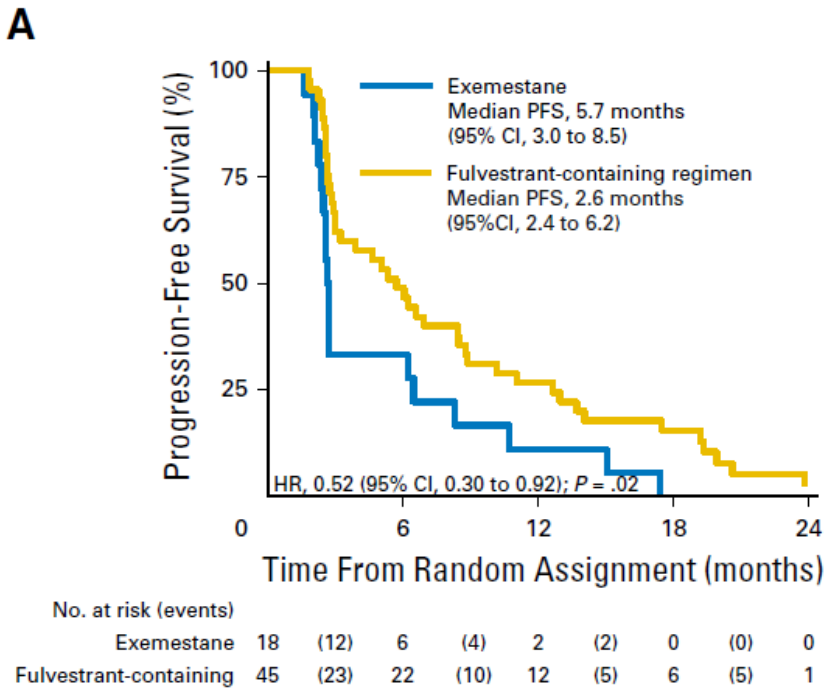
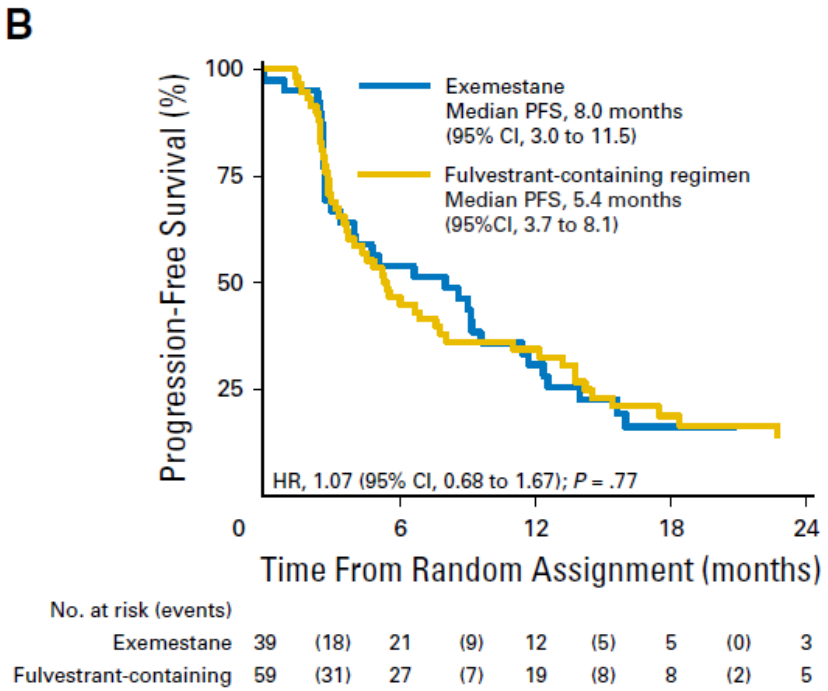
ESR1 mutations: poor outcome under aromatase inhibitors

ESR1 mutation



ESR1 wild type



Fribbens JCO 2016

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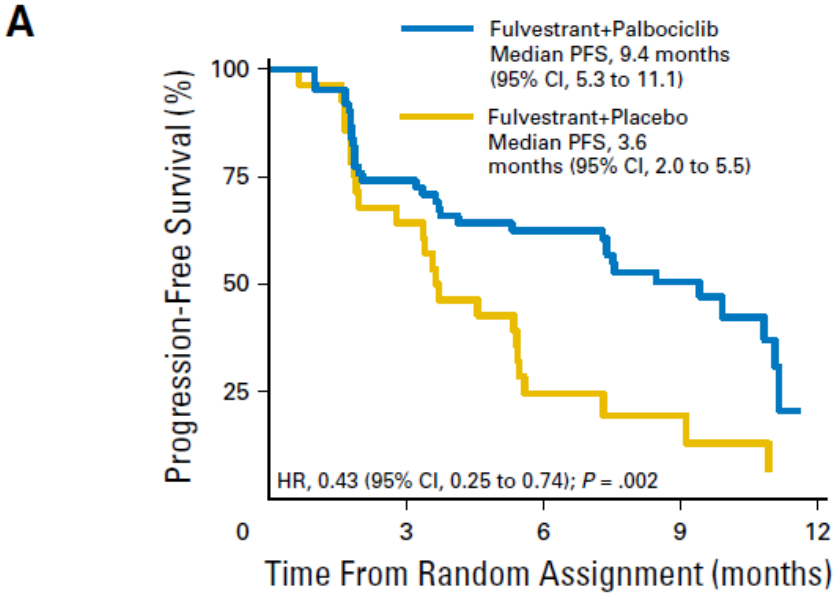
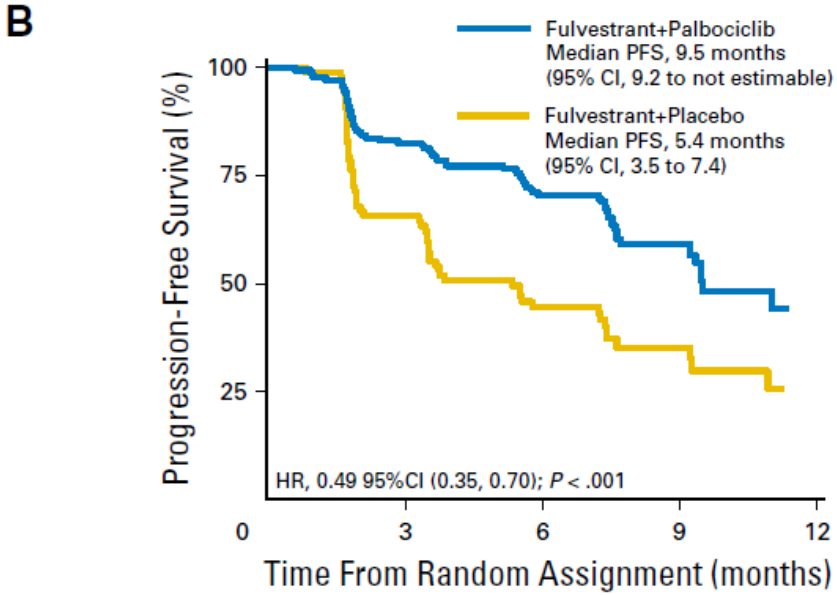
ESR1 mutations: same outcome under fulvestrant + palbociclib

ESR1 mutation



No. at risk (events)									
Fulvestrant+Placebo	28	(10)	18	(11)	6	(1)	3	(2)	1
Fulvestrant+Palbociclib	63	(16)	45	(7)	36	(6)	22	(5)	0

ESR1 wild type



No. at risk (events)									
Fulvestrant+Placebo	92	(30)	57	(18)	35	(6)	16	(3)	0
Fulvestrant+Palbociclib	177	(30)	142	(20)	108	(13)	50	(7)	6

Fribbens JCO 2016

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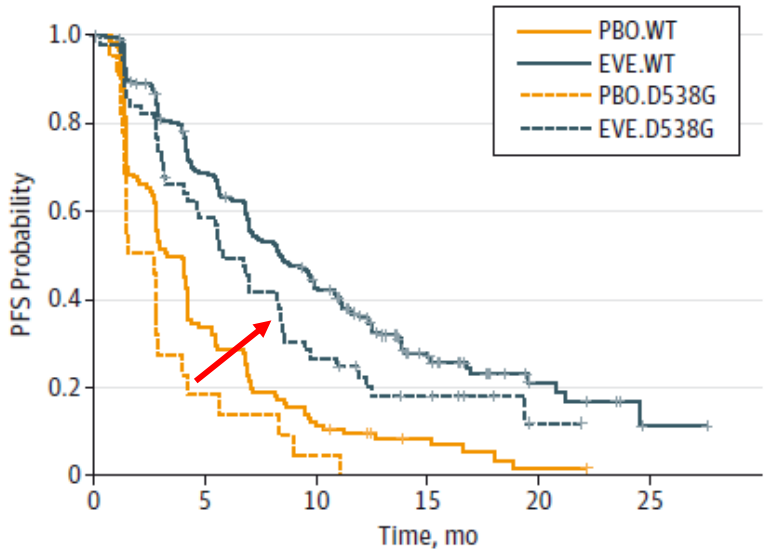
Different mutation = different outcome ?



Patient with *ESR1* D538G mutation benefit from EVE addition

Chandarlapaty Jama Oncol 2016

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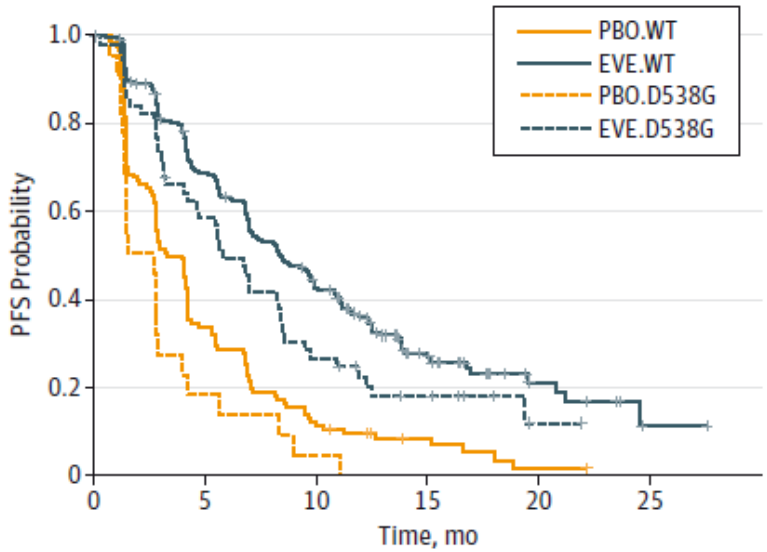
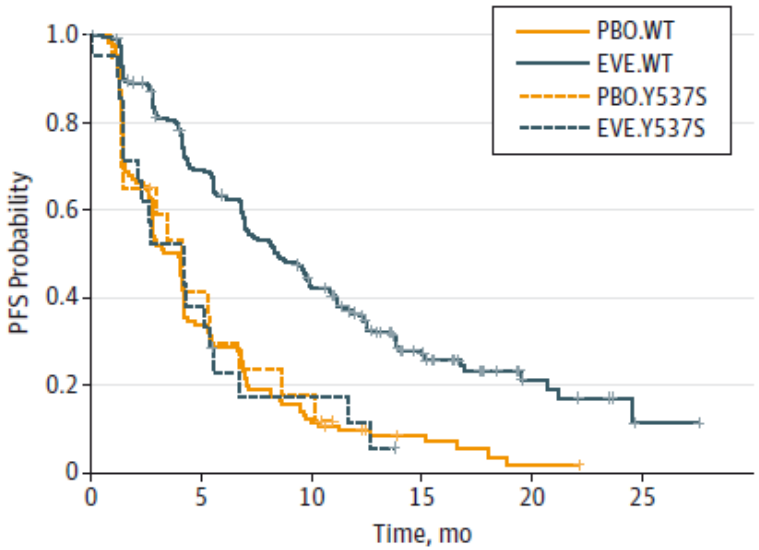
Different mutation = different outcome ?





Patient with *ESR1* D538G mutation benefit from EVE addition

Patient with ESR1 Y537S mutation do not benefit from EVE

Chandarlapaty Jama Oncol 2016

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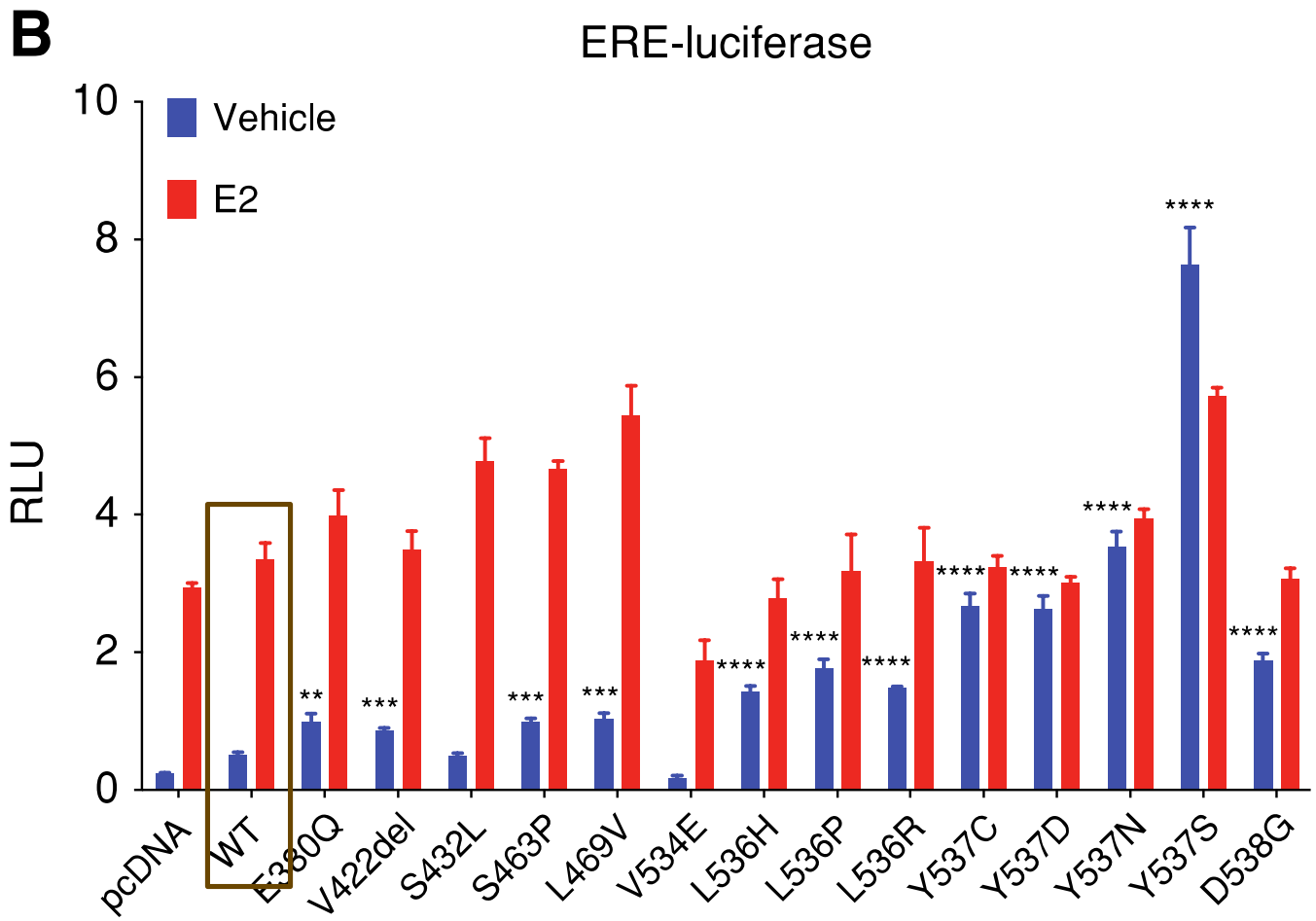
Estrogen activation of *ESR1* mutants



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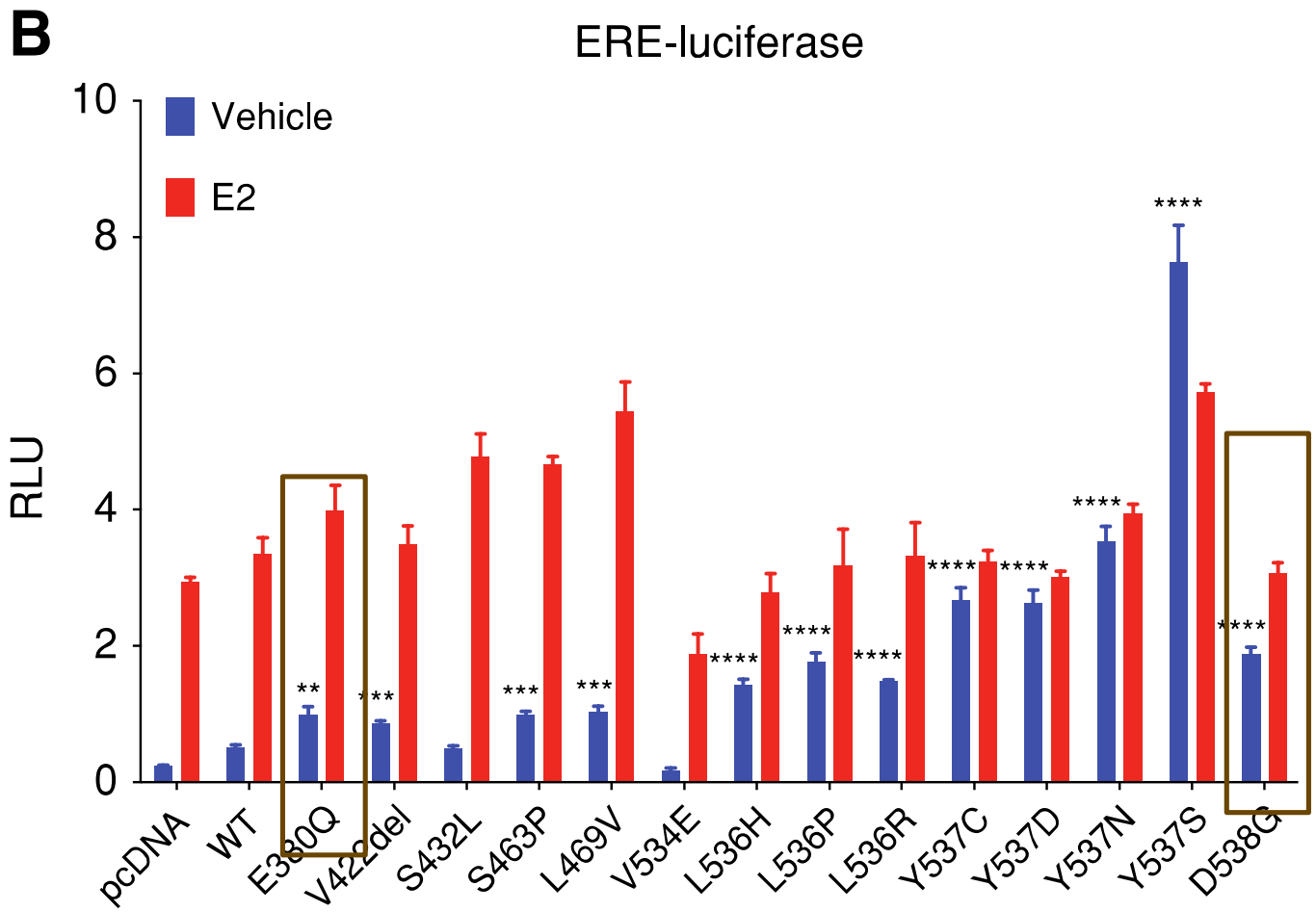
Toy Cancer Discov 2017

Estrogen activation of *ESR1* mutants



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Toy Cancer Discov 2017

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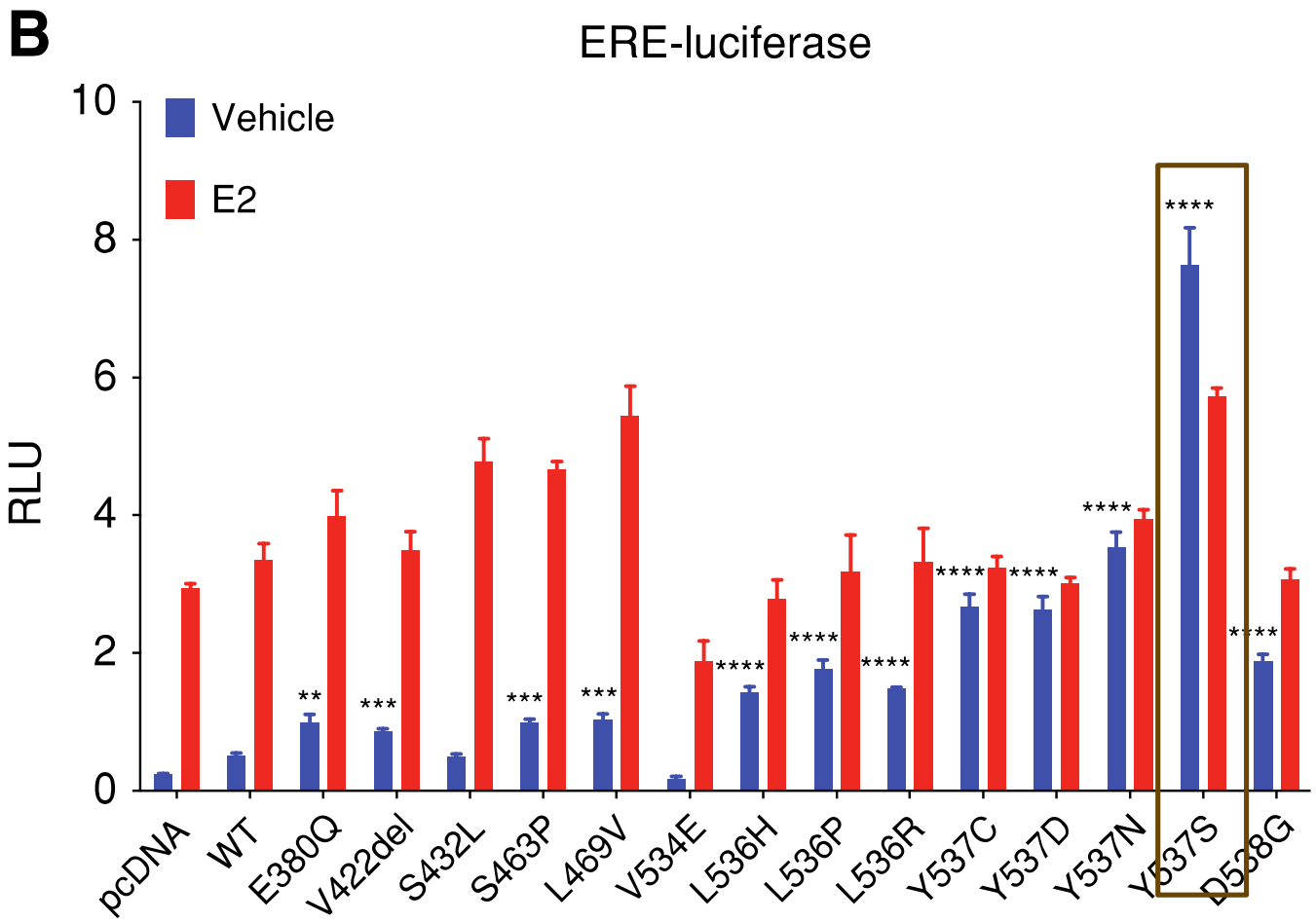

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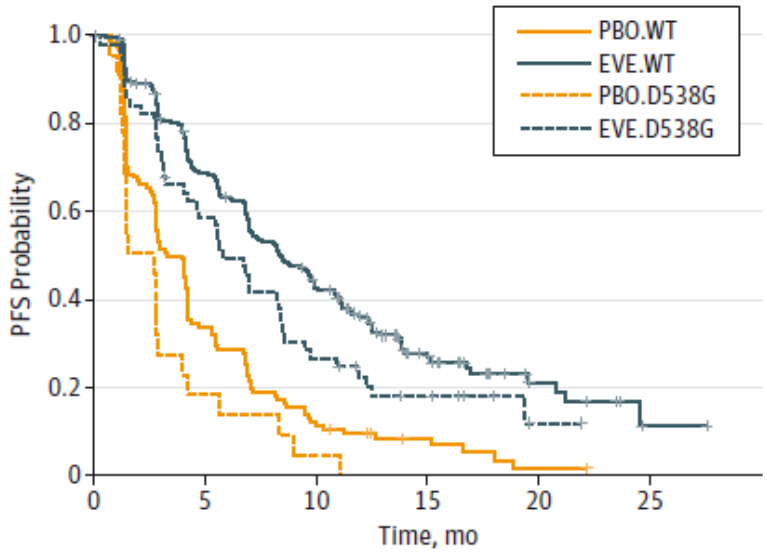
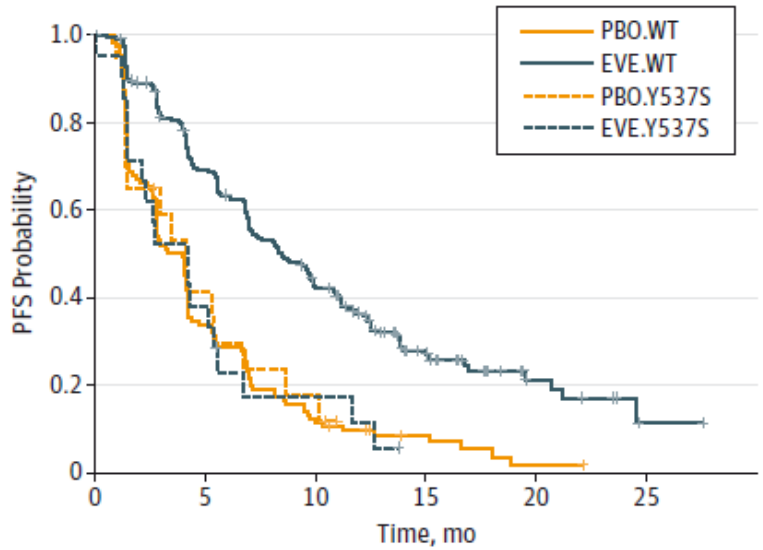
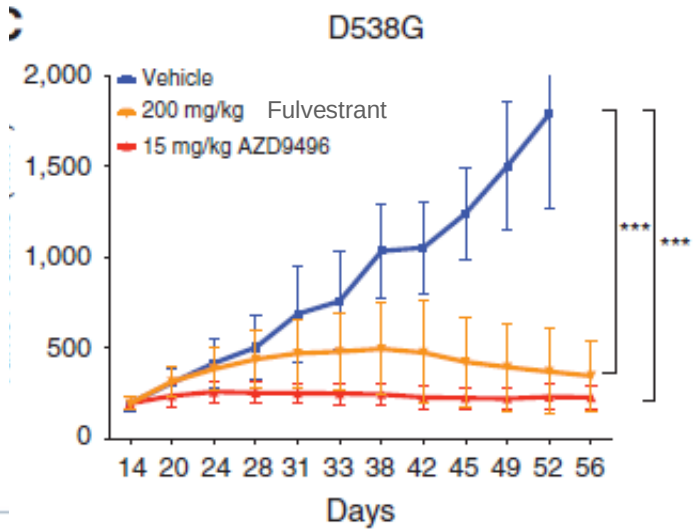
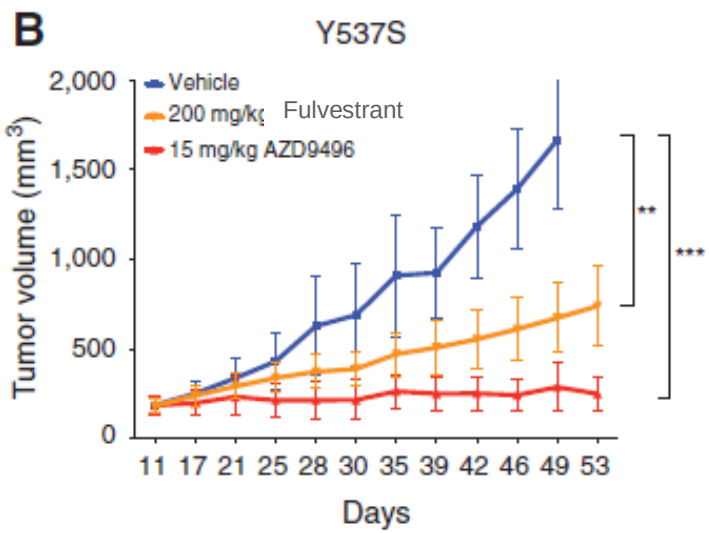
Different mutation = different outcome ?



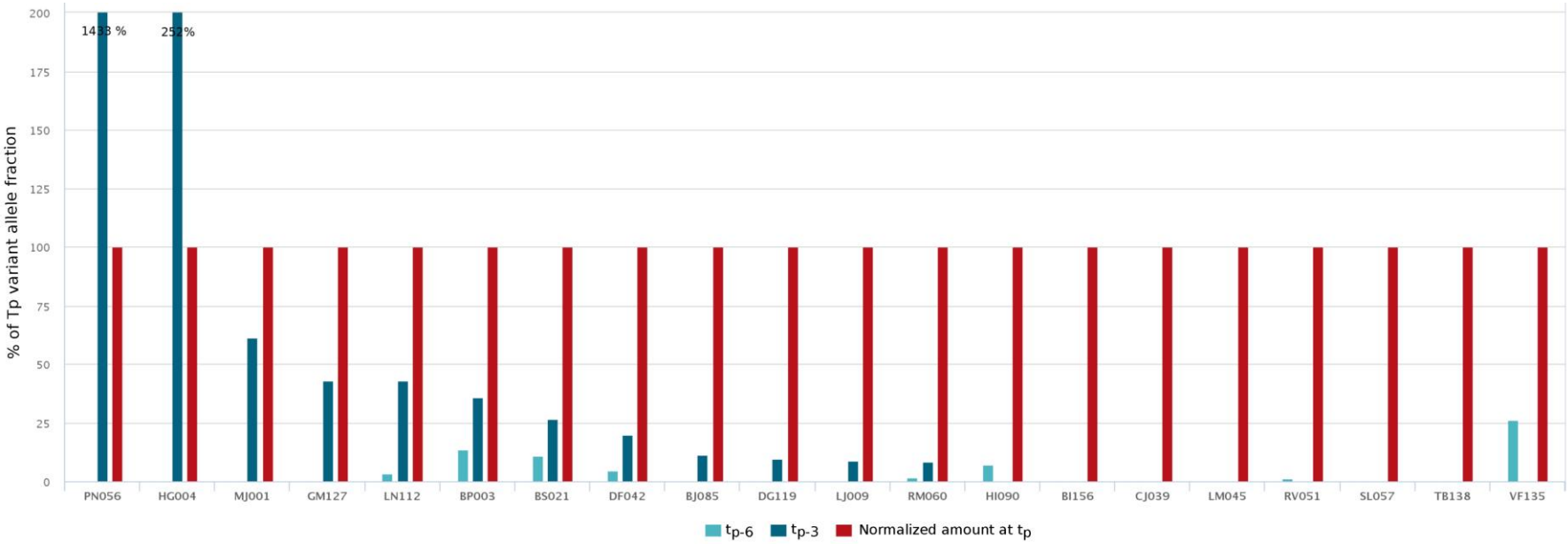






Chandarlapaty Jama Oncol 2016; Toy Cancer Discov 2017

ESR1 mutations: 6 months lead time detection in ctDNA



75% of the cases: detection 3-6 months before clinical progression

Clatot Oncotarget 2016

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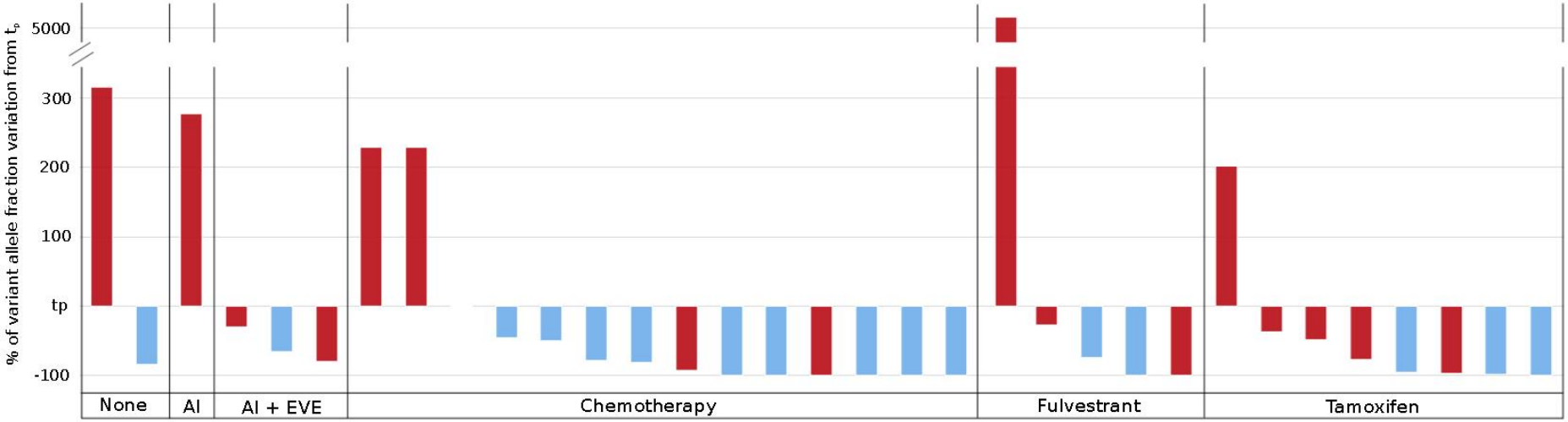
ESR1 mutations post progression



- Increased amount (n=6) : 100% progressing disease
- Decreased amount (n=26) : 60% stability/PR but 40% PD

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Clatot, Oncotarget 2016

Assessing circulating *ESR1* mutations

- Recurrent mutations
- Frequent (30%) in the metastatic setting after AI exposure
- Correlated with prognosis
- Correlated with poor response on AI
- Ongoing trials based on ctDNA detection and early treatment change (PADA-1)
- Differential outcome when considering peculiar mutations
- Next generation endocrine therapies on development

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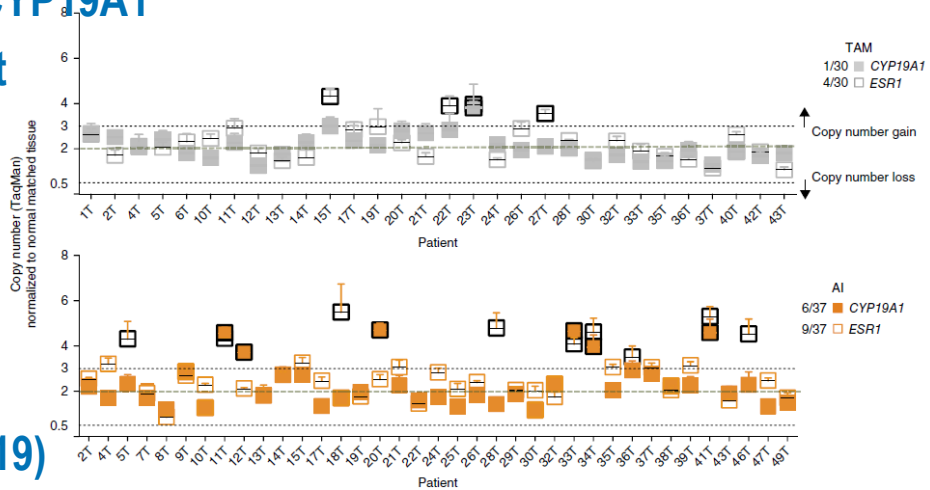
Copy number alterations (CNA) of *ESR1* or *CYP19A1*

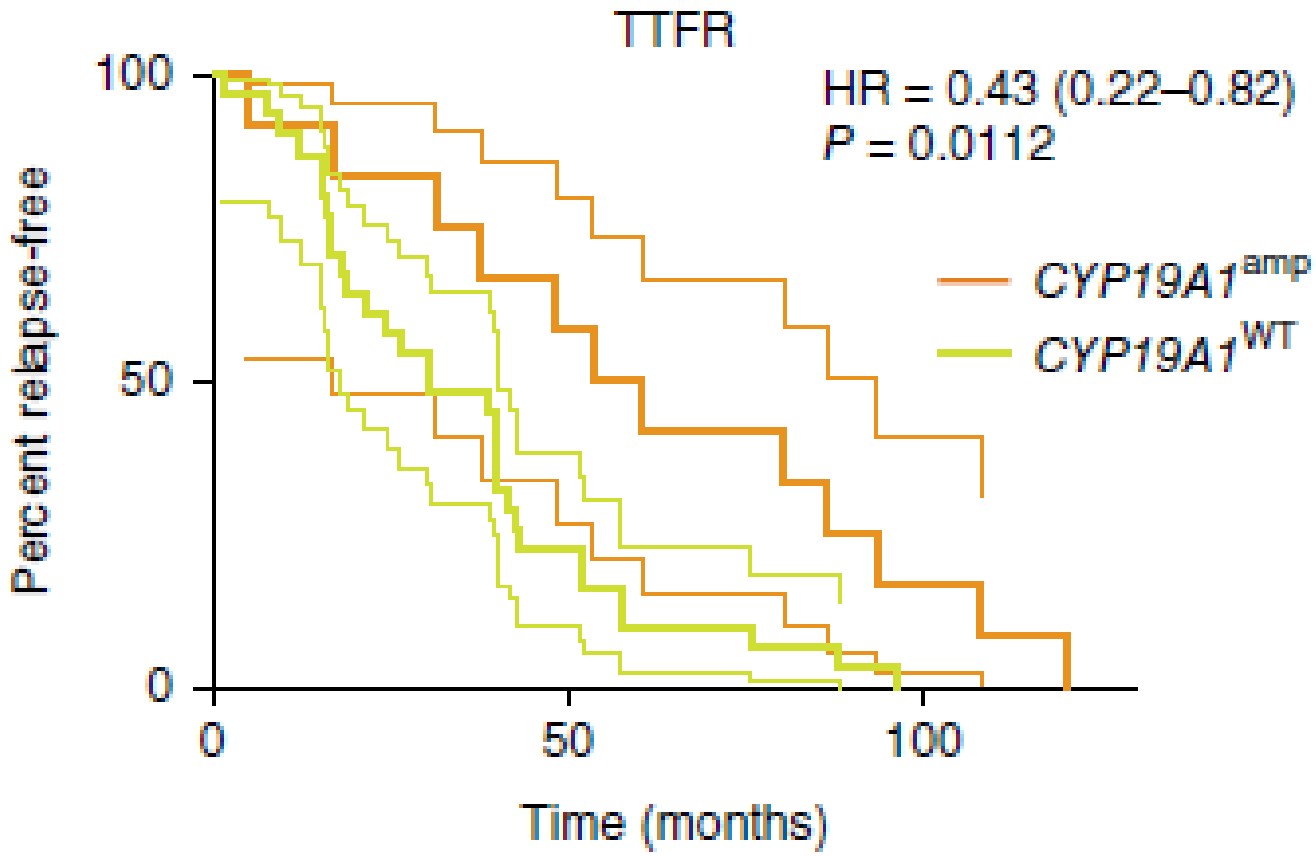
- **Comparison tumor/normal tissues**
  - **No CNA in primary both for ESR1 or CYP19A1**
  - **CYP19A1 amplification after treatment**
    - *6/37 (16%) after AI exposure*
    - *1/30 (3%) after tam exposure*
  - **ESR1 amplification after treatment**
    - *9/37 (24%) after AI exposure*
    - *4/30 (13%) after tam exposure*
  - **Confirmed on validations cohorts (n=19)**
    - *CYP19A1 : 32% amp under AI vs 5% under Tam*
    - *ESR1 : 21% under AI vs 0% under tam*



- **AI exposure is related to higher acquired CNA of both CYP19A1 and ESR1 than Tam exposure**

Magnani Nature genetics 2017

Impact on PFS of *CYP19A1* amp under AI



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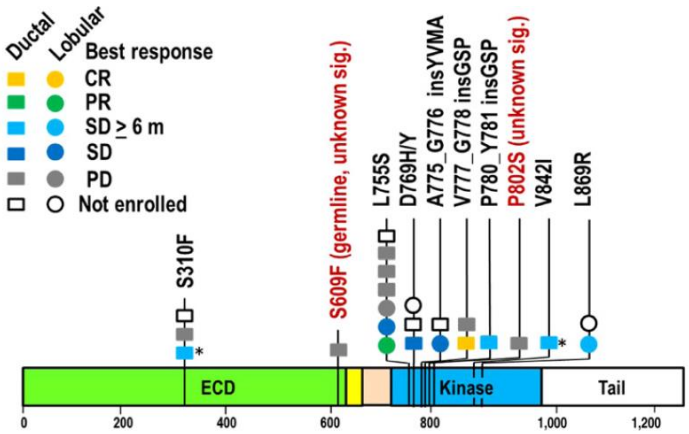
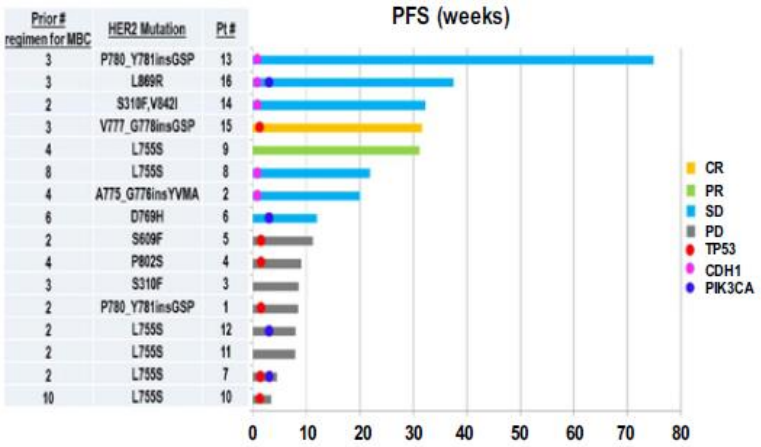
Magnani Nature genetics 2017

HER2 mutations

- Activating mutations
- Rare
  - 3% in 12 905 BC cases
  - Detectable in ctDNA in 84% of the cases
  - L755S, V777L and D769H/Y = 53% of the mutations
- Neratinib effect
  - Heavily preteated patients
  - 16 weeks PFS (n=16)





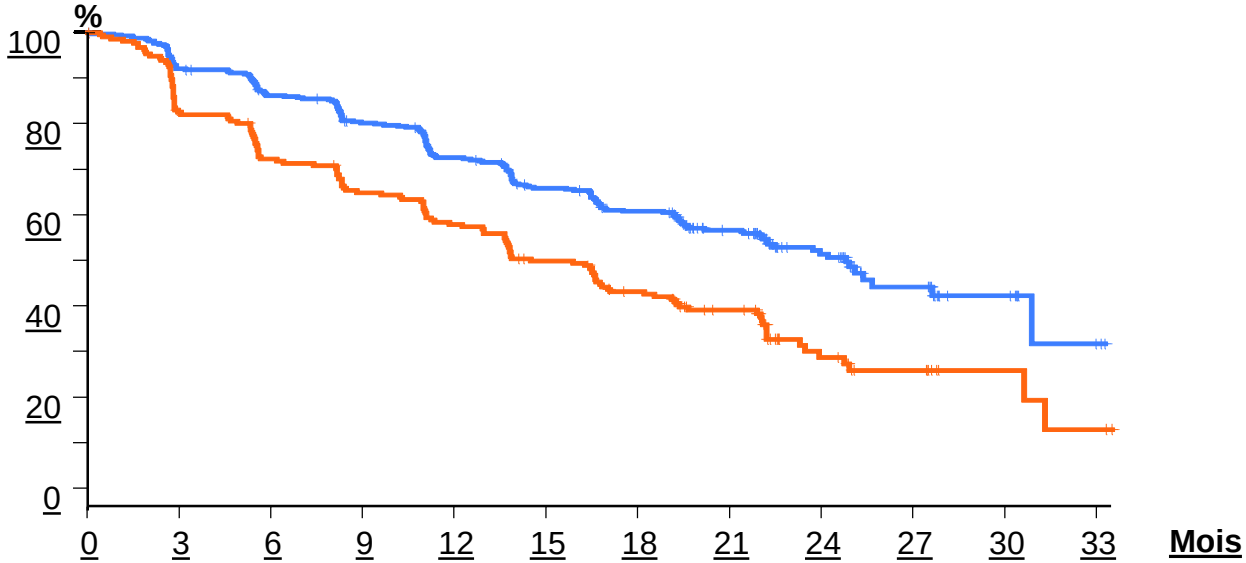
Ma CCR 2017, Petrelli BCRT 2017

Next standard of care: cdk4/6

Finn NEJM 2016

Hortobagyi NEJM 2016

Di leo ESMO 2016



Patientes à risque

	0	3	6	9	12	15	18	21	24	27	30	33
PAL + LET	444	395	360	328	295	263	238	154	69	29	10	2
PCB + LET	222	171	148	131	116	98	81	54	22	12	4	2

- PALOMA 2: Létrozole +/- palbociclib, Phase 3, n=666
- MONALEESA 2: Letrozole +/- ribociclib, Phase 3, n=668
- MONARCH 3: Letrozole or anastrozole +/- abemaciclib, Phase 3, n=493

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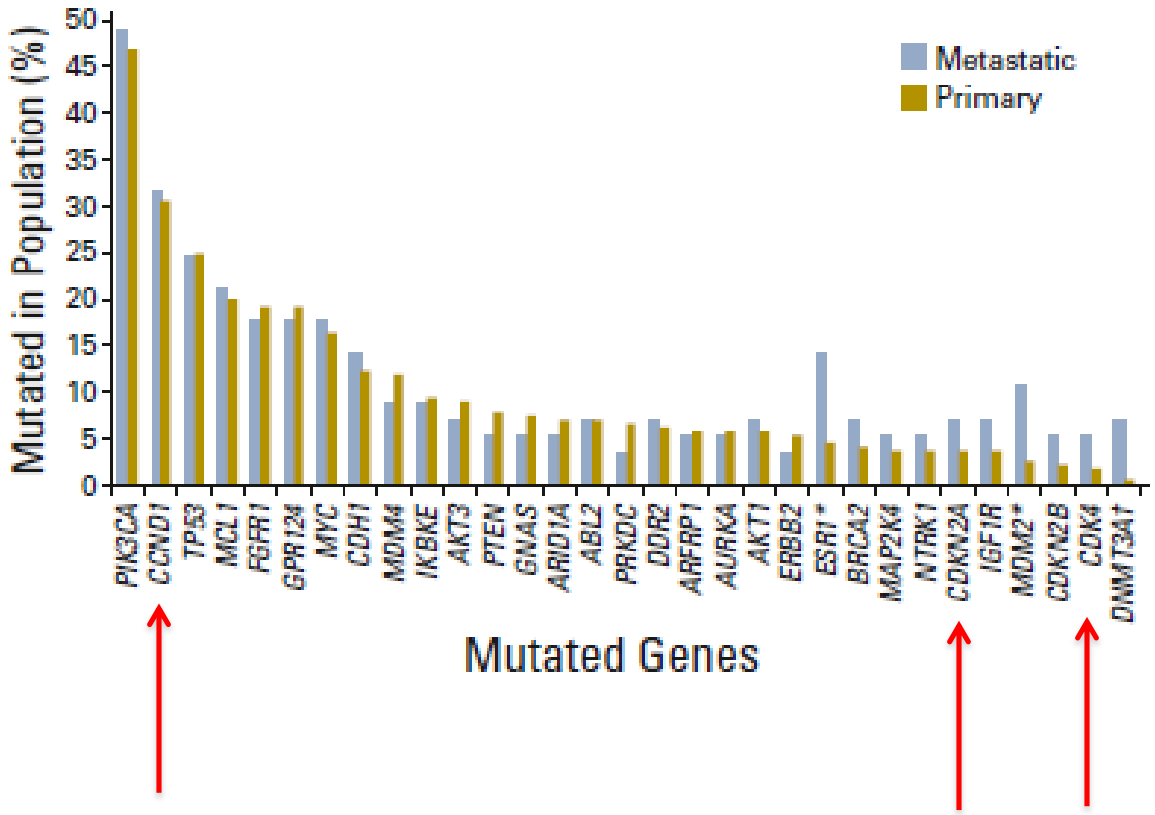
Mutations in cell cycle pathway



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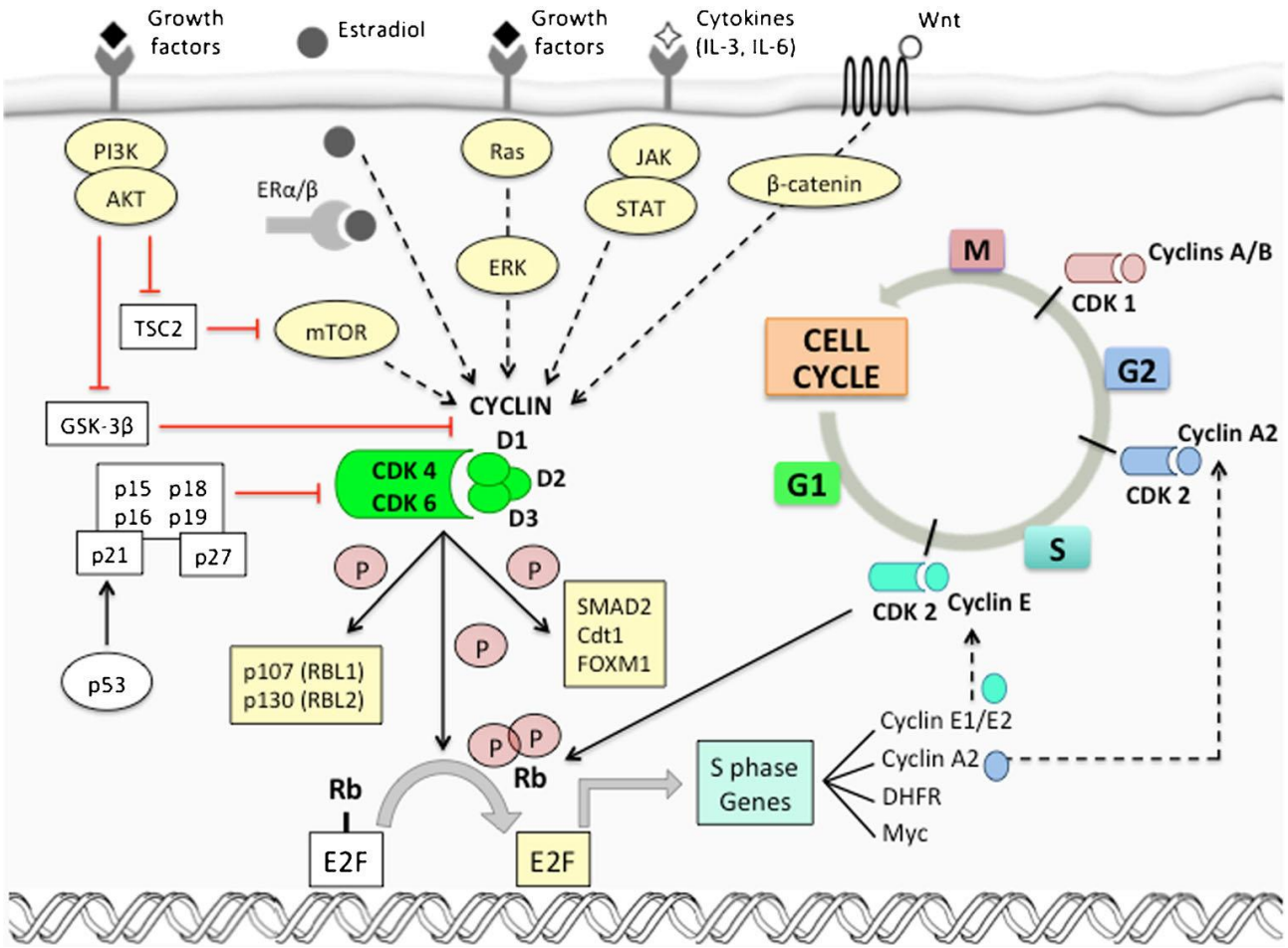
Cell cycle regulation



Garrido Castro Cur Breast Rep 2017

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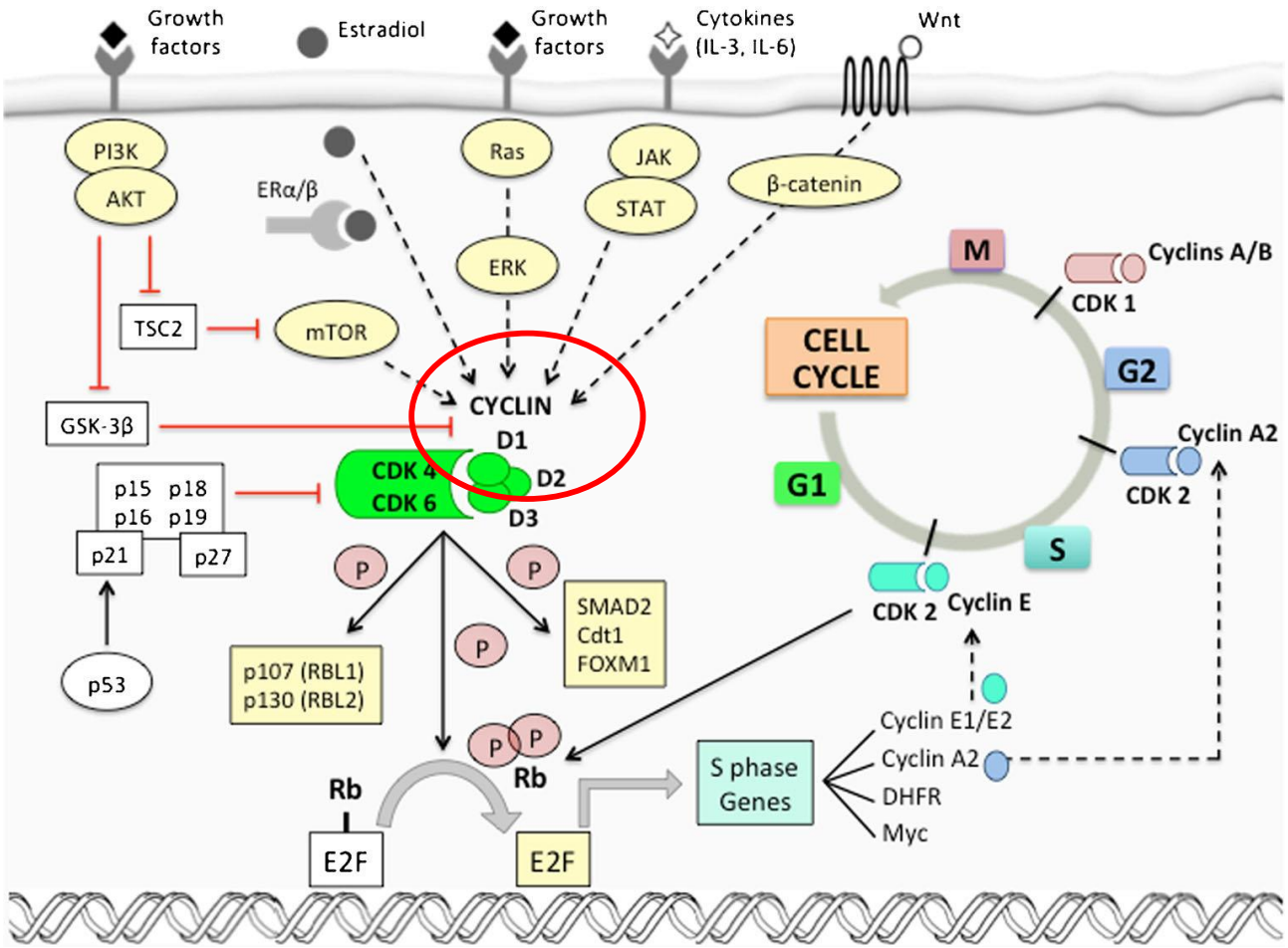
Theoretical biomarkers of cdk4/6 inhibition response



Cyclin D1 amplification→higher impact of cdk4/6 inhibition

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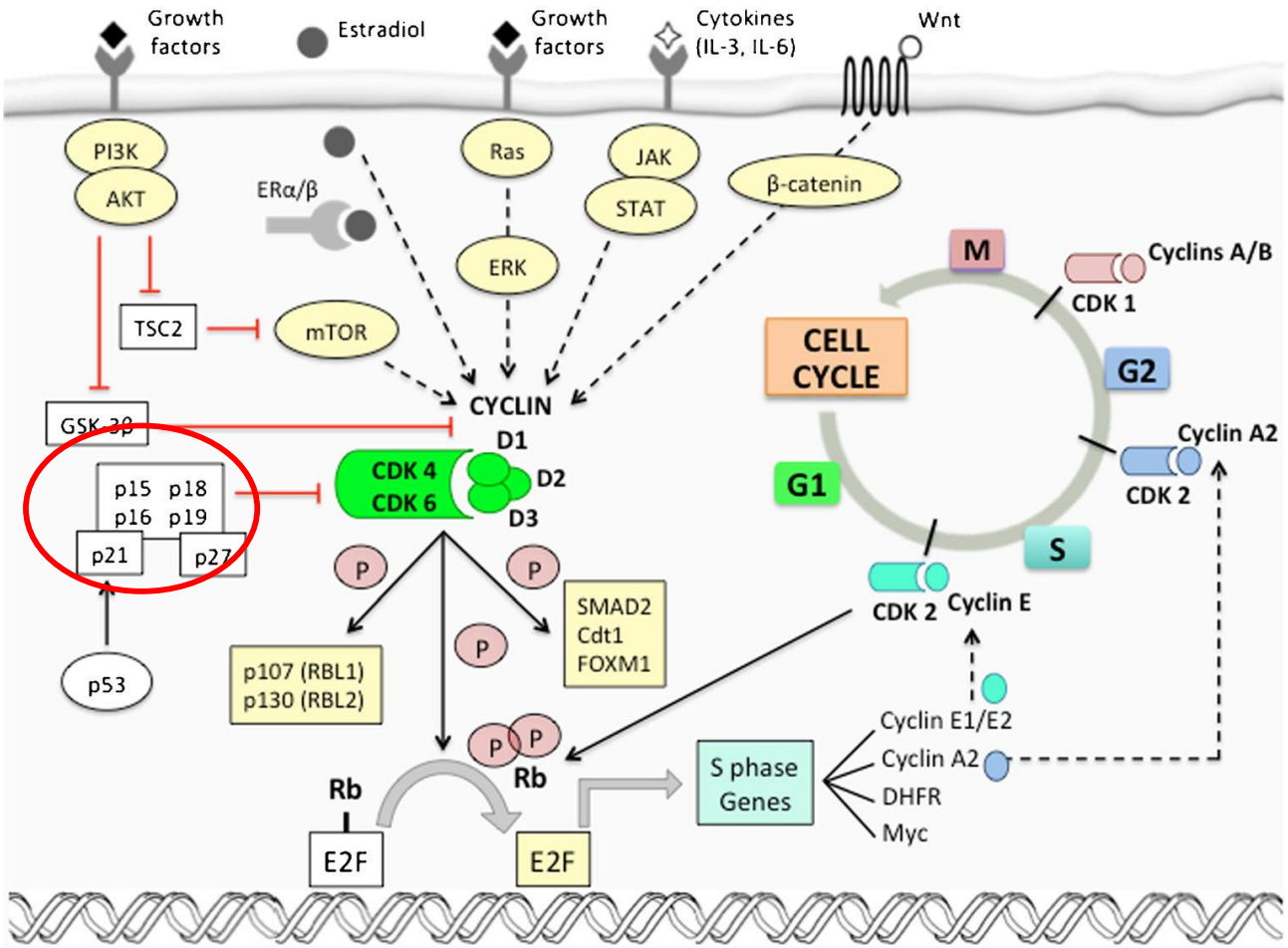
Theoretical biomarkers of cdk4/6 inhibition response



Cyclin D1 amplification→higher impact of cdk4/6 inhibition

High p16 expression → no impact of cdk4/6 inhibition

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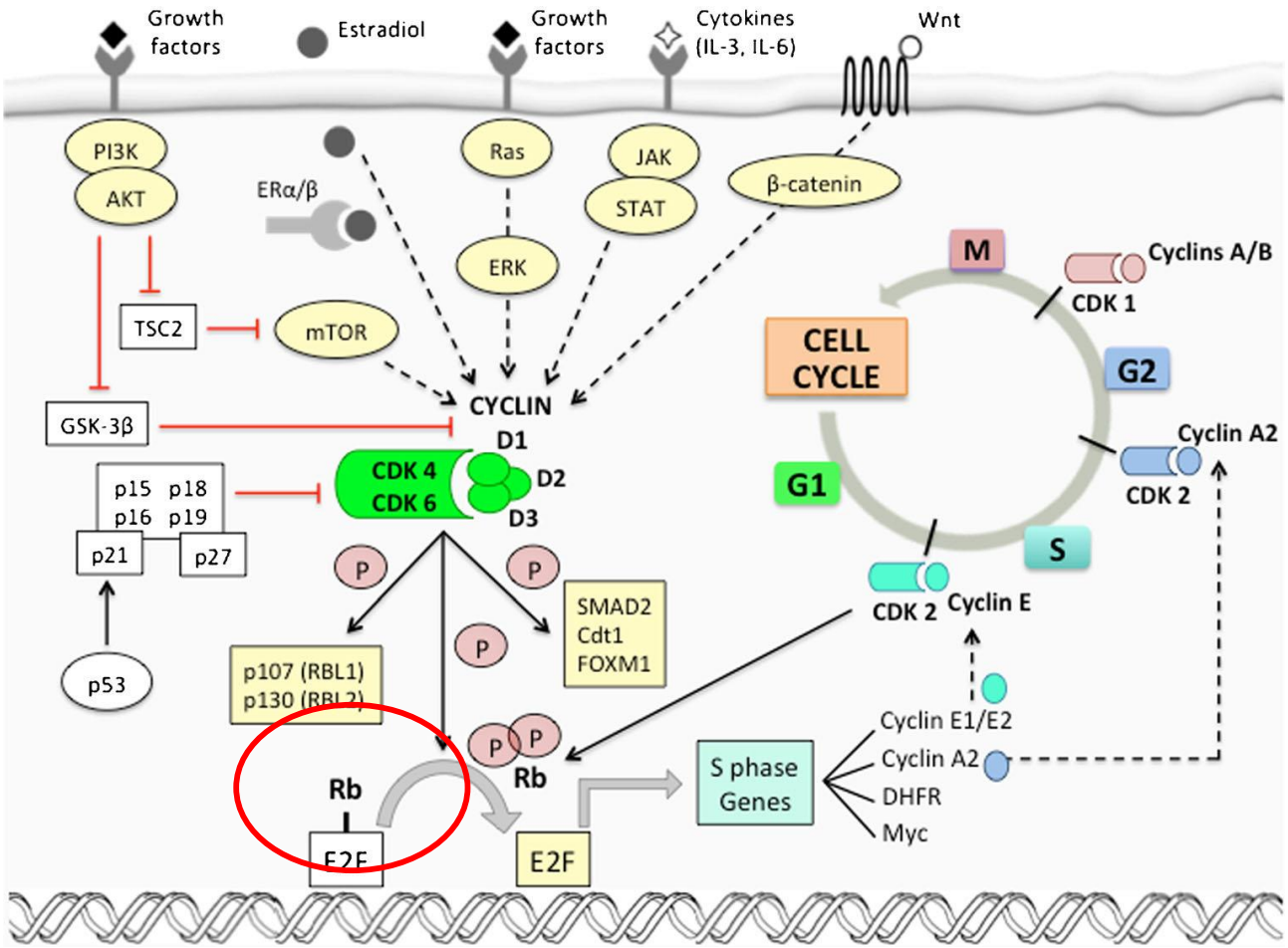
Theoretical biomarkers of cdk4/6 inhibition response



Cyclin D1 amplification→higher impact of cdk4/6 inhibition

High p16 expression → no impact of cdk4/6 inhibition

Rb loss → no impact of cdk4/6 inhibition

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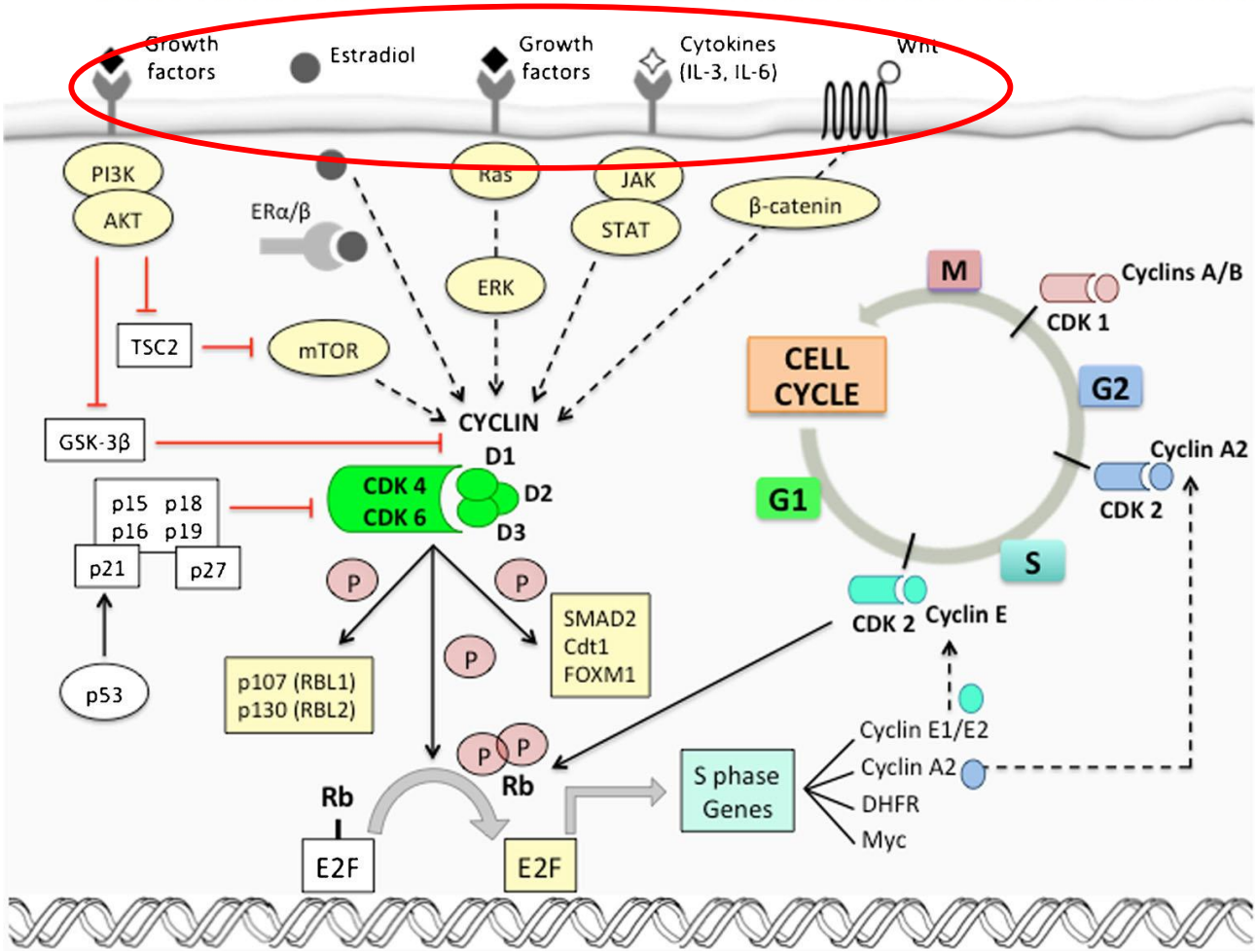
Theoretical biomarkers of cdk4/6 inhibition response



Cyclin D1 amplification→higher impact of cdk4/6 inhibition

High p16 expression → no impact of cdk4/6 inhibition

Rb loss → no impact of cdk4/6 inhibition

No proliferation→no impact of cdk4/6 inhibition

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Real life (phase 2: n=37 and 165, phase 3: n=666)

- Cyclin D1 amplification
  - No impact
- p16 expression
  - No impact
- Rb loss
  - No impact
- Proliferation
  - No impact

DeMichele CCR 2015; Finn Ann Oncol 2016

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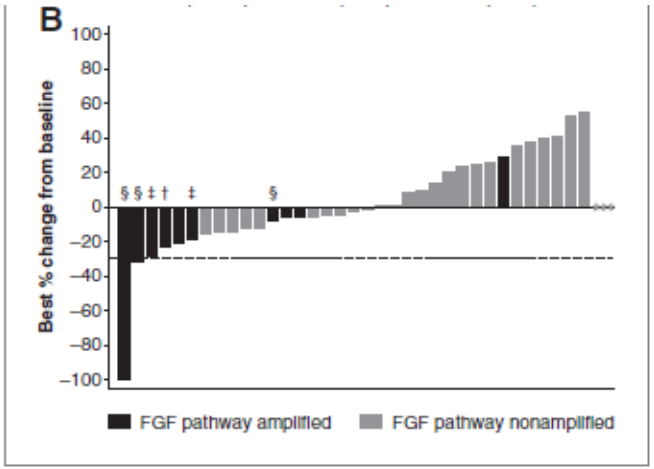
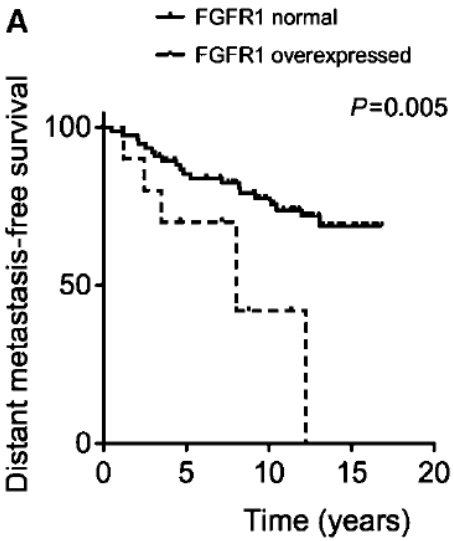
FGFR amplification

- Frequent among luminal B tumors
- Correlated with PFS
- Possible efficacy of dovitinib FGFR1,2,3 inhibitor) ?
  - Expression assessed by qPCR

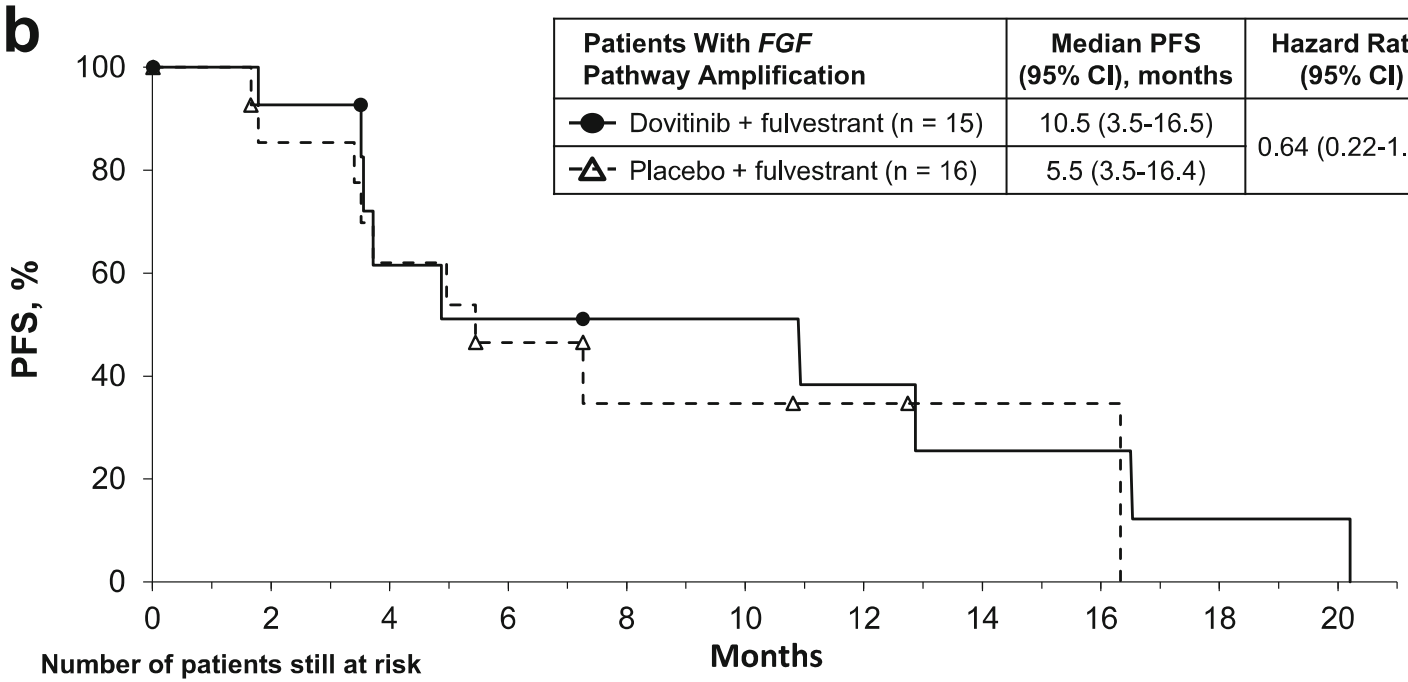




Phase II ended 2 years ago : Fulvestrant +/- Dovitinib, n=97, resistant to endocrine therapy.

Andre CCR 2013

Musolino et al. BCR 2017



Patients With *FGF* Pathway Amplification	Median PFS (95% CI), months	Hazard Ratio (95% CI)
Dovitinib + fulvestrant (n = 15)	10.5 (3.5-16.5)	0.64 (0.22-1.86)
Placebo + fulvestrant (n = 16)	5.5 (3.5-16.4)	

Number of patients still at risk

Dovitinib + fulvestrant	15	13	9	9	6	5	5	5	4	4	4	3	3	2	2	2	2	1	1	1	1
Placebo+ fulvestrant	16	14	11	11	8	7	5	5	3	3	3	2	2	1	1	1	1	0	0	0	0

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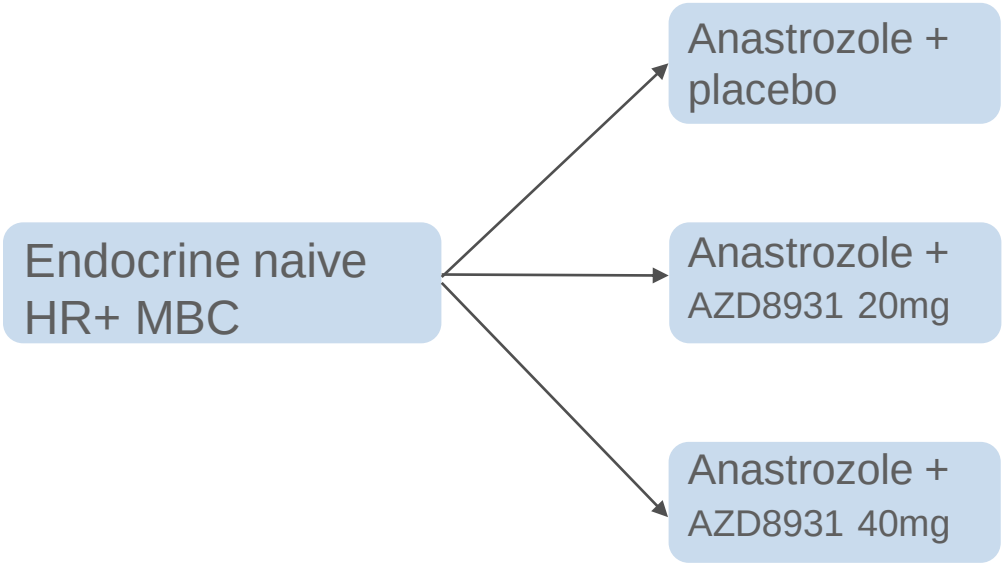
Pan-HER blockade : MINT study

- Phase II randomized study (n=359)
- AZD8931: EGFR+HER2+HER3 inhibitor
- Obj I : PFS



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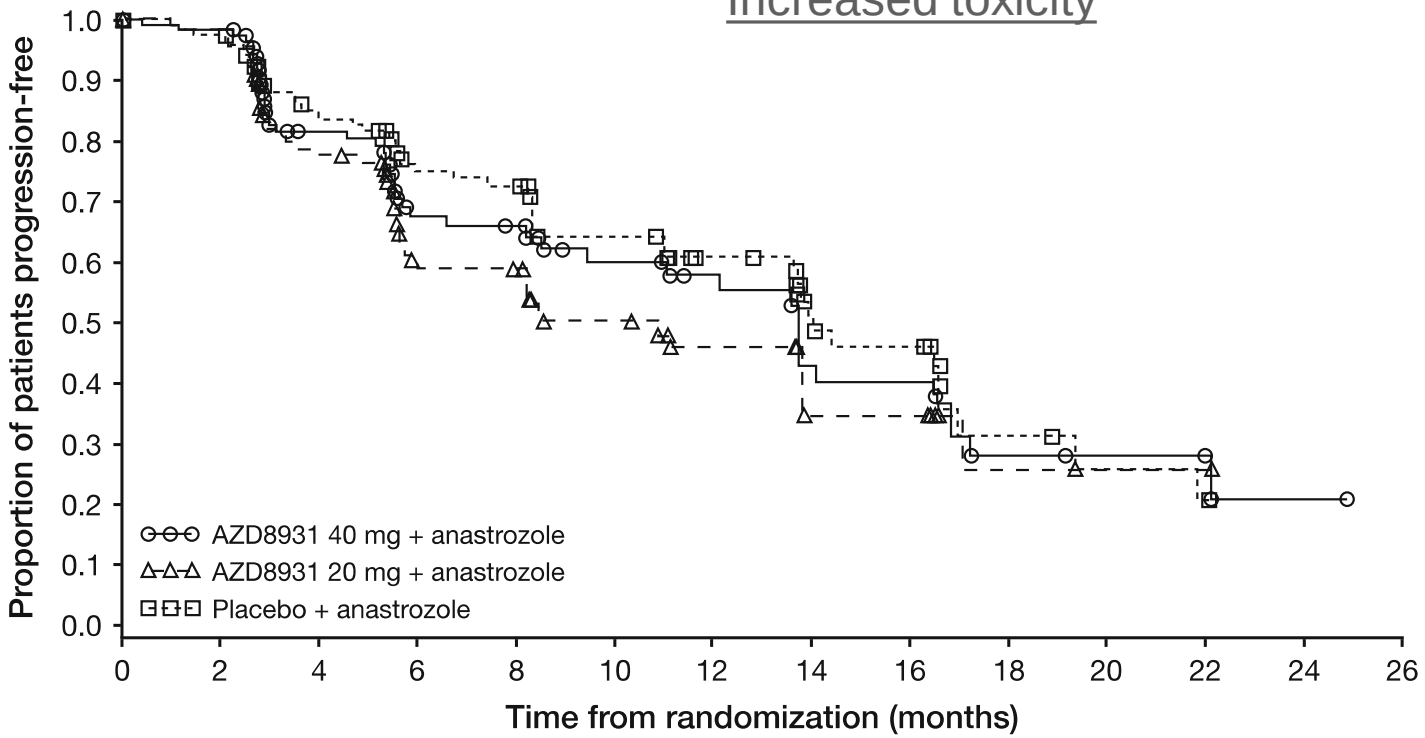
MINT study

No benefit of AZD8931
Increased toxicity



Number of patients at risk:

AZD8931 40 mg	120	113	72	42	40	28	24	17	16	7	5	4	2	0
AZD8931 20 mg	118	110	69	39	37	26	19	10	10	3	1	1	0	0
Placebo	121	114	76	53	51	37	29	20	17	7	5	4	0	0

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 Johnston BCRT 2016

Take home messages

- BC cancer and endocrine therapies resistance
  - Major problem of metastatic BC cancer
- CtDNA potential to date: in the metastatic setting
  - Screening patients before PIK3 inhibition
  - Patient monitoring for early AI failure
  - Screening patients with *ESR1* mutants for new endocrine therapies
- Cdk4/6 inhibitor
  - « First line » intuitive biomarkers failed
  - Signatures ongoing (Rbsig)

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Treating breast cancer with endocrine therapies