

Optimal Sequence of Endocrine Treatment in Advanced Breast Cancer

Global Breast Cancer Conference 2019

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Disclosures

Research Funding (to MSKCC) from Daiichi Sankyo, Sanofi, Novartis, Genentech, and Eli Lilly.

Ad hoc consulting (to me) with Novartis, Sermonix, Eli Lilly, Context Therapeutics, Sun Pharma and Revolutions Medicine.

Pending patent for several ER PROTACs

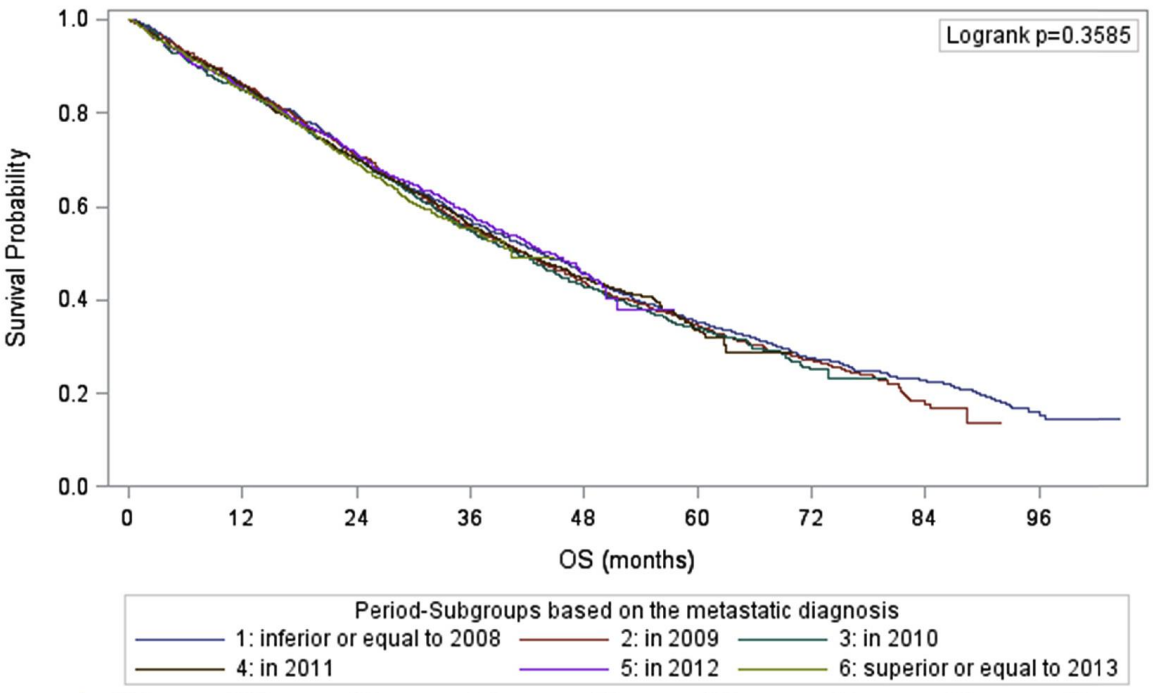
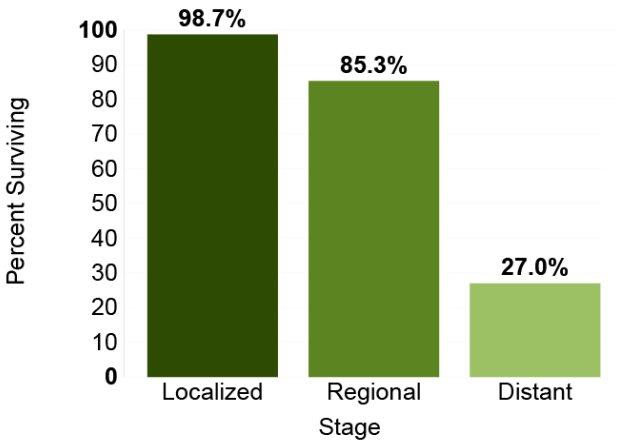


JOEDATOR

“Full disclosure—I really need this hug.”

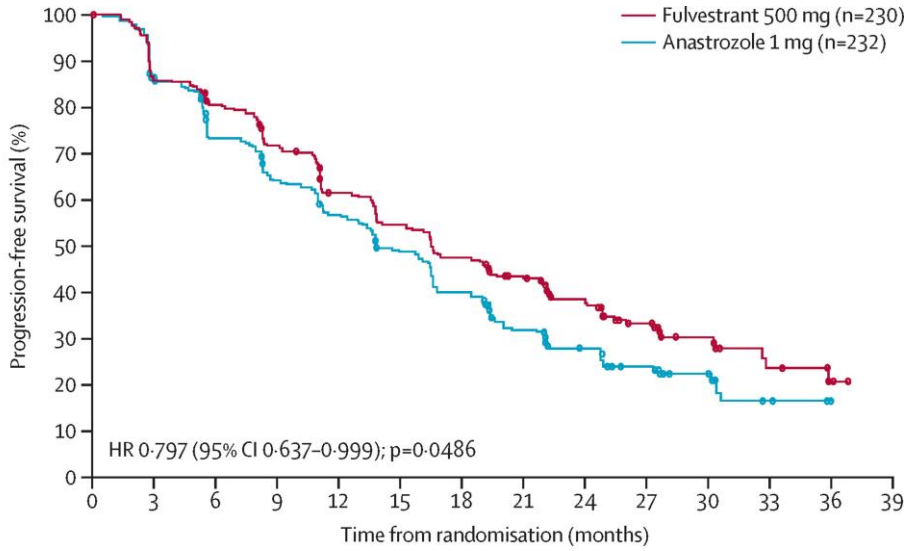
Overall Survival in ER+ MBC Remains Poor in Long-Term

5-Year Relative Survival

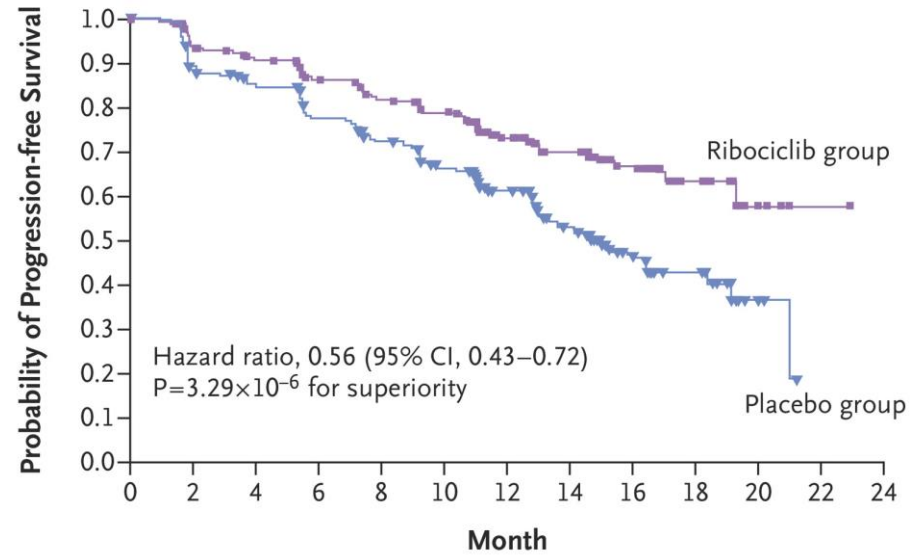


Gobbini et al, Eur J Can 2018

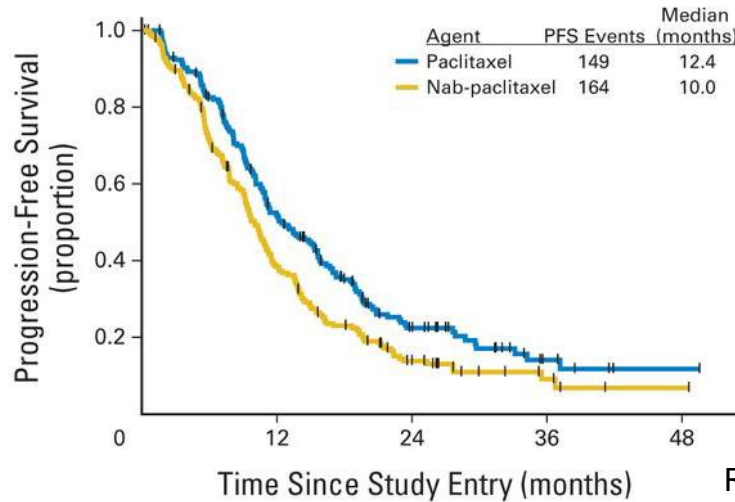
Efficacy of First-line Systemic Therapy for ER+ MBC



Robertson et al. Lancet 2016

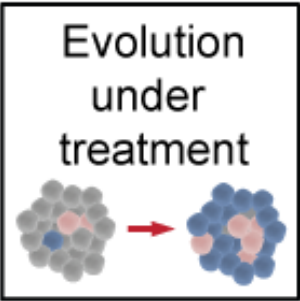
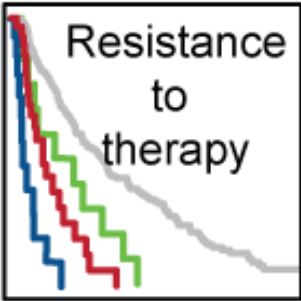
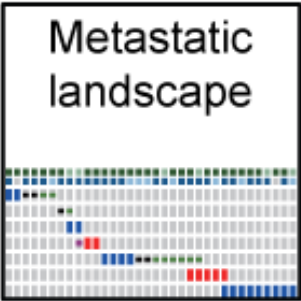
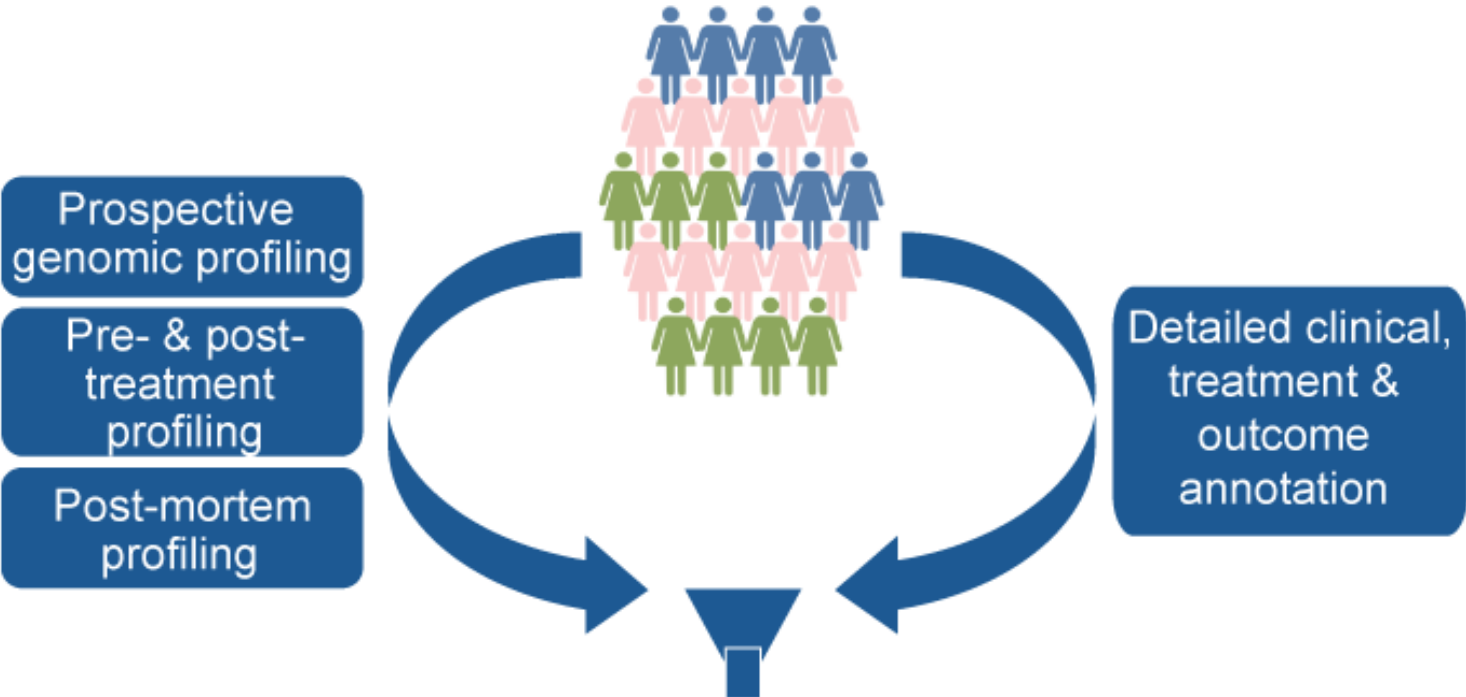


Hortobagyi et al. NEJM 2016

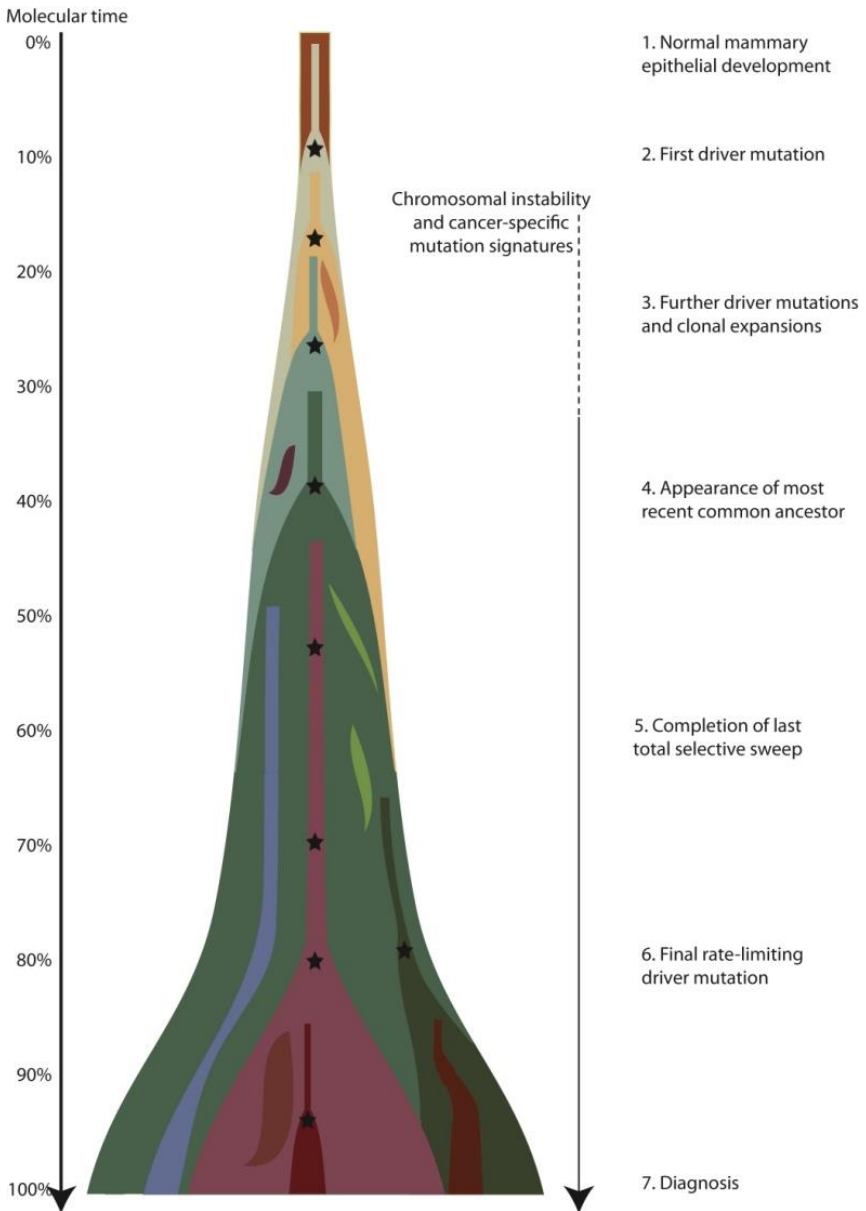


Rugo et al. JCO 2015

Utilizing genomics to solve complex clinical problems

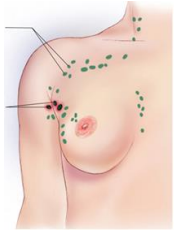


Evolution of Breast Cancer

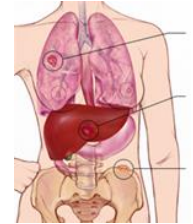


1. Normal mammary epithelial development
2. First driver mutation
3. Further driver mutations and clonal expansions
4. Appearance of most recent common ancestor
5. Completion of last total selective sweep
6. Final rate-limiting driver mutation
7. Diagnosis

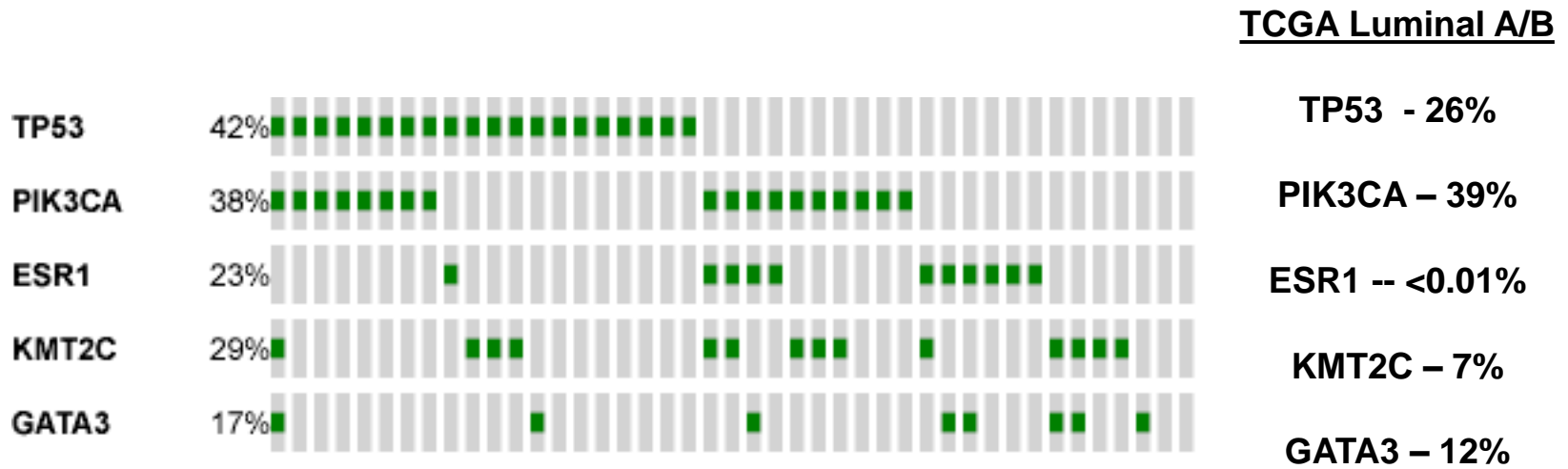
Localized, hormone responsive BrCa



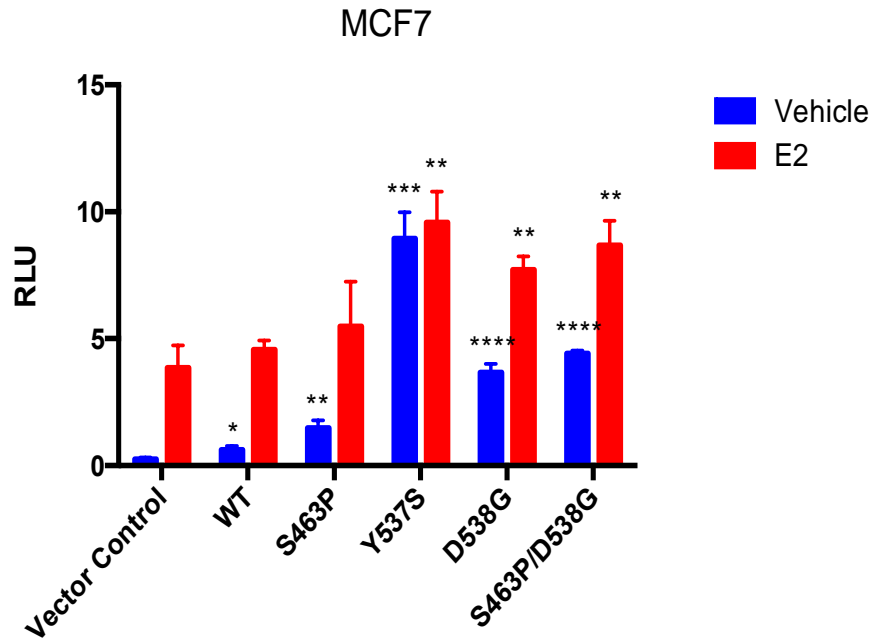
Hormone resistant, lethal BrCa



Genomic analyses of metastatic breast cancer reveals ESR1 mutations

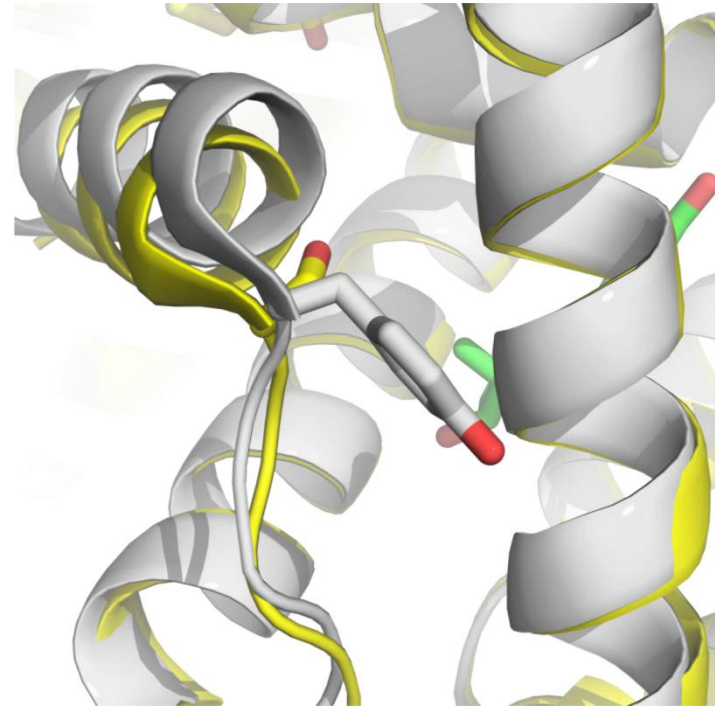


LBD mutants mimic E2 bound WT



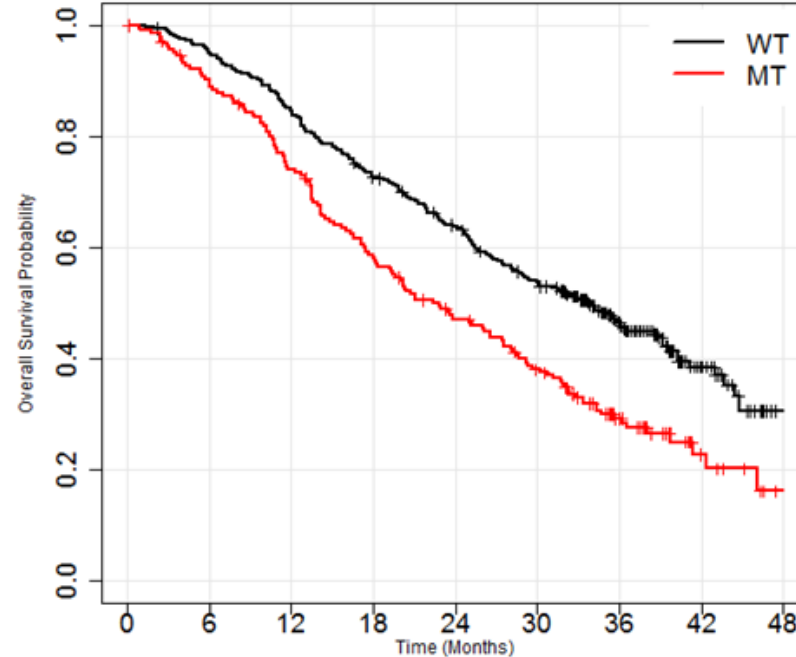
Toy et al, Nature Genetics 2013

Apo Y537S overlay WT plus E2



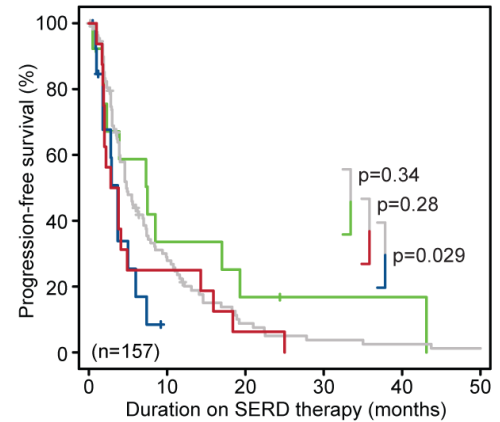
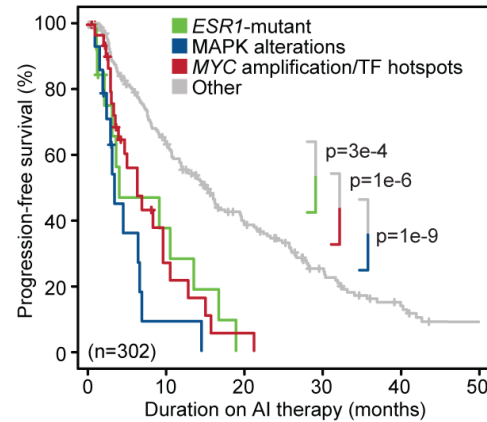
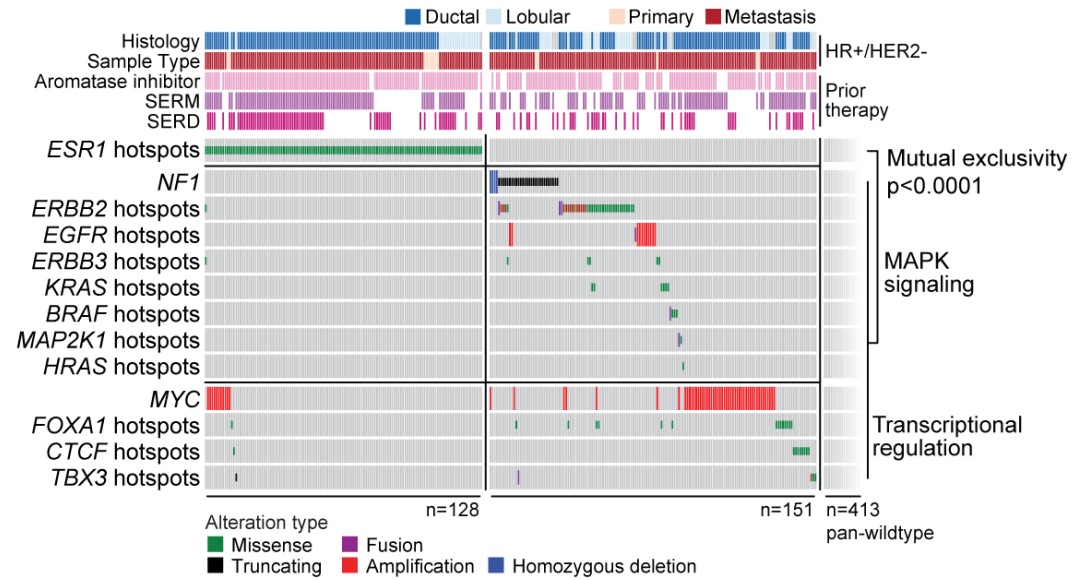
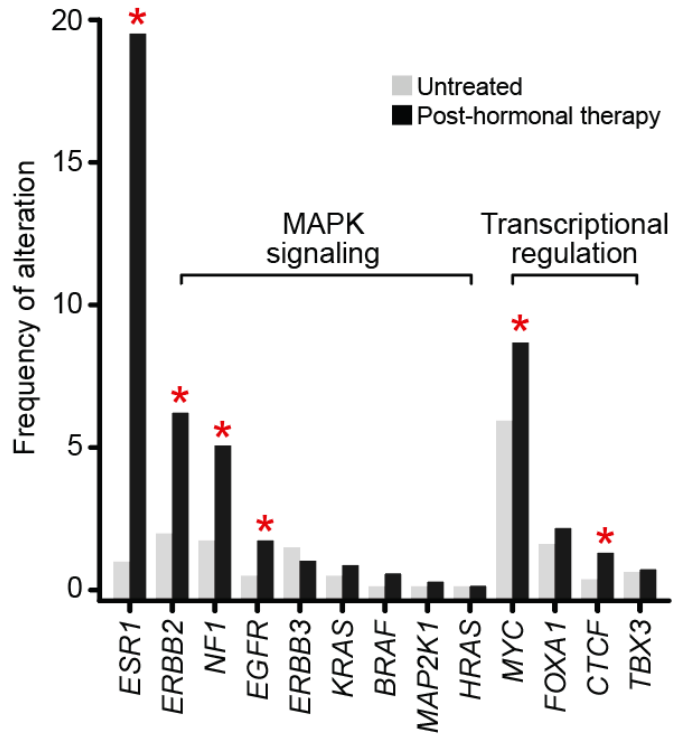
Fanning et al., Elife 2016

ESR1 mutants are prevalent and have shorter OS

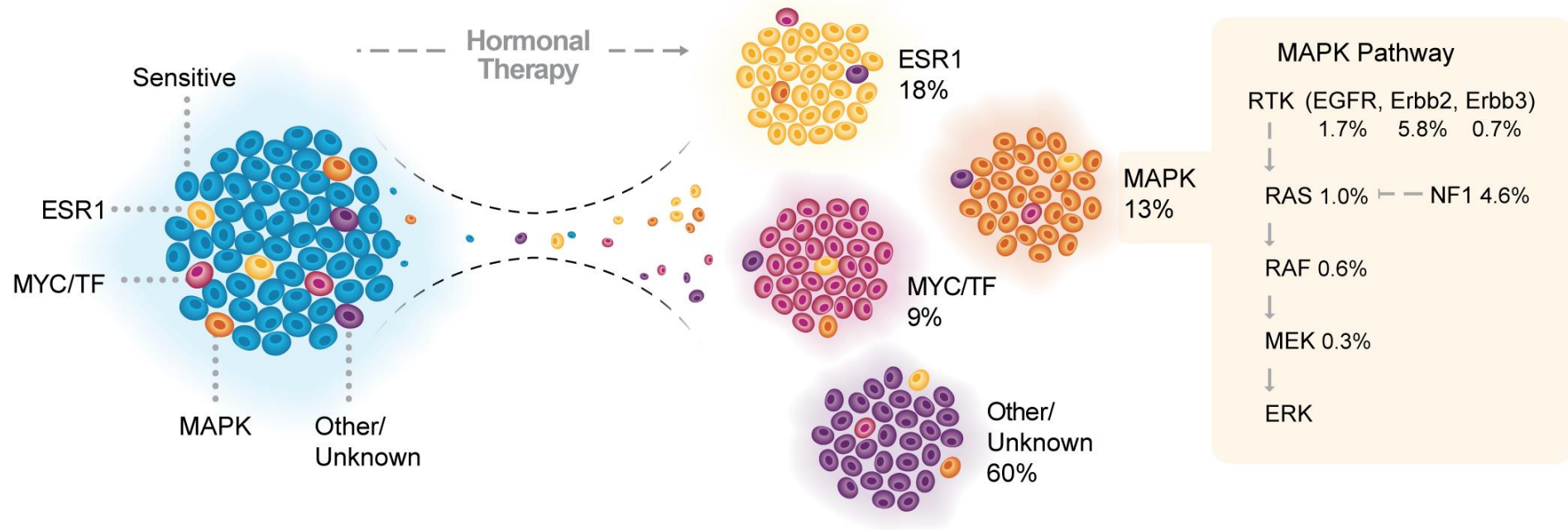


	D538G, Y537S, Y537N, Y537C, and/or E380Q	D538G and/or Y537S mutation	D538G mutation	Y537S mutation	Multiple mutation
Overall, N = 541 (74.7% of ITT)		156 (28.8%)	83 (15.3%)	42 (7.8%)	30 (5.5%)
Overall, N=563 (77.7% of ITT)	207 (36.7%)	189 (33.5%)			72 (12.7%)

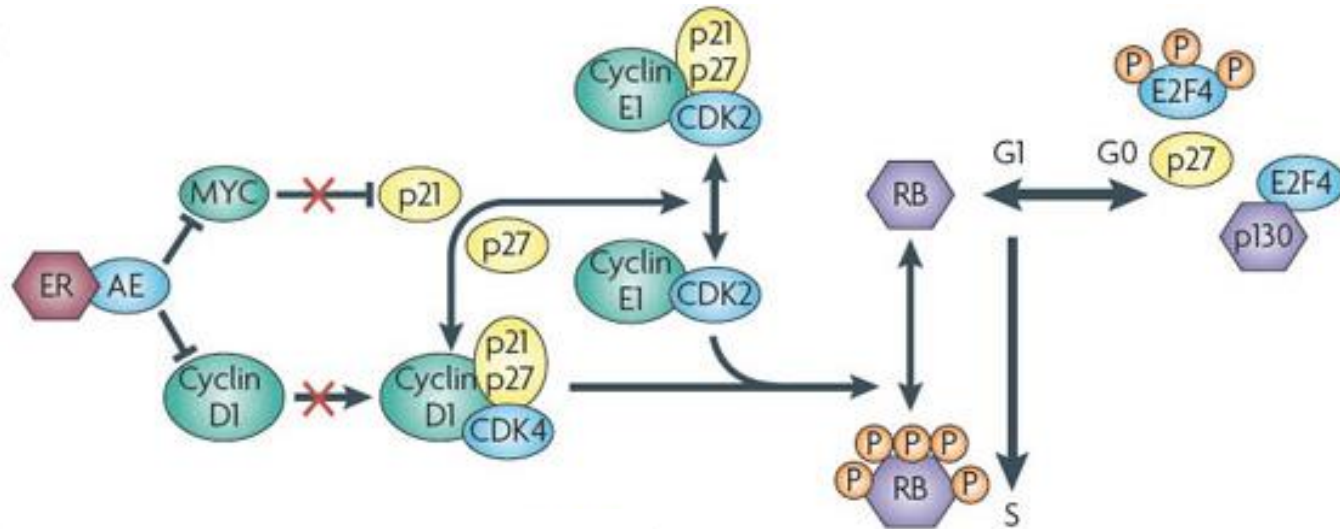
Additional Acquired Genomic Alterations



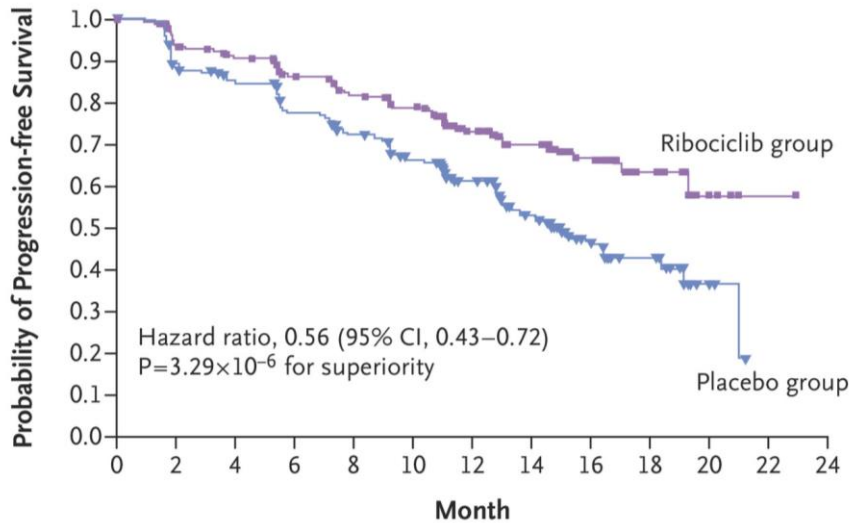
Acquired Genomic Alterations => Endocrine Resistance



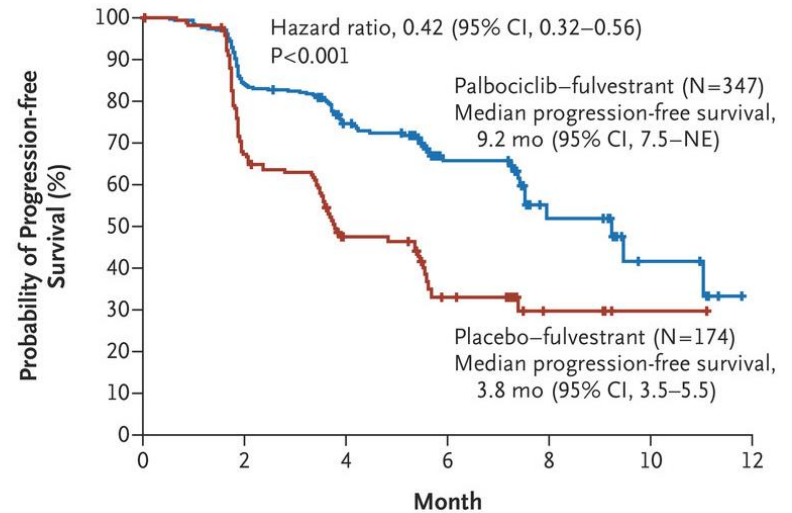
Combination endocrine therapy as a new standard



Nature Reviews Cancer 2015

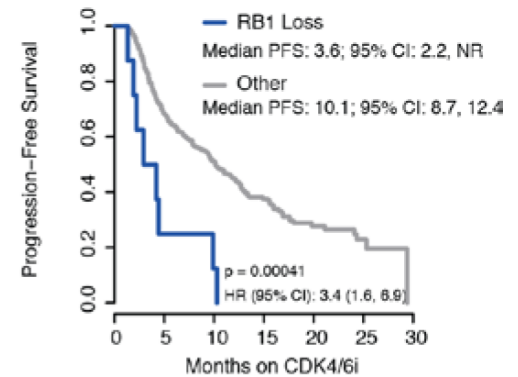
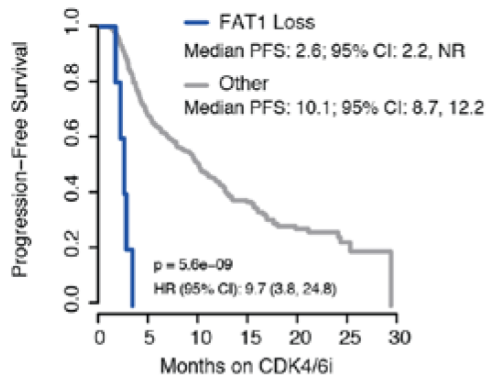
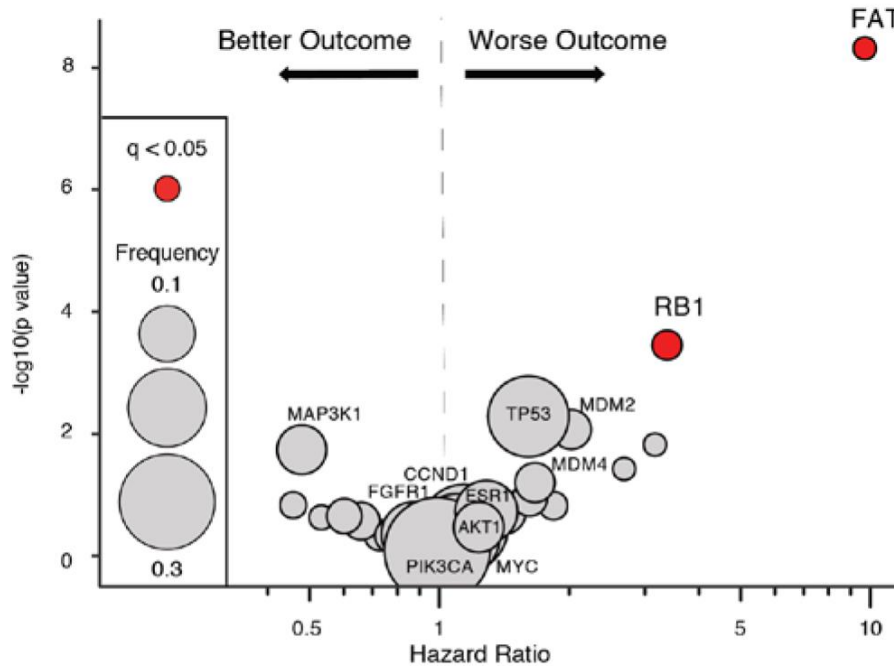


Hortobagyi et al. *NEJM* 2016

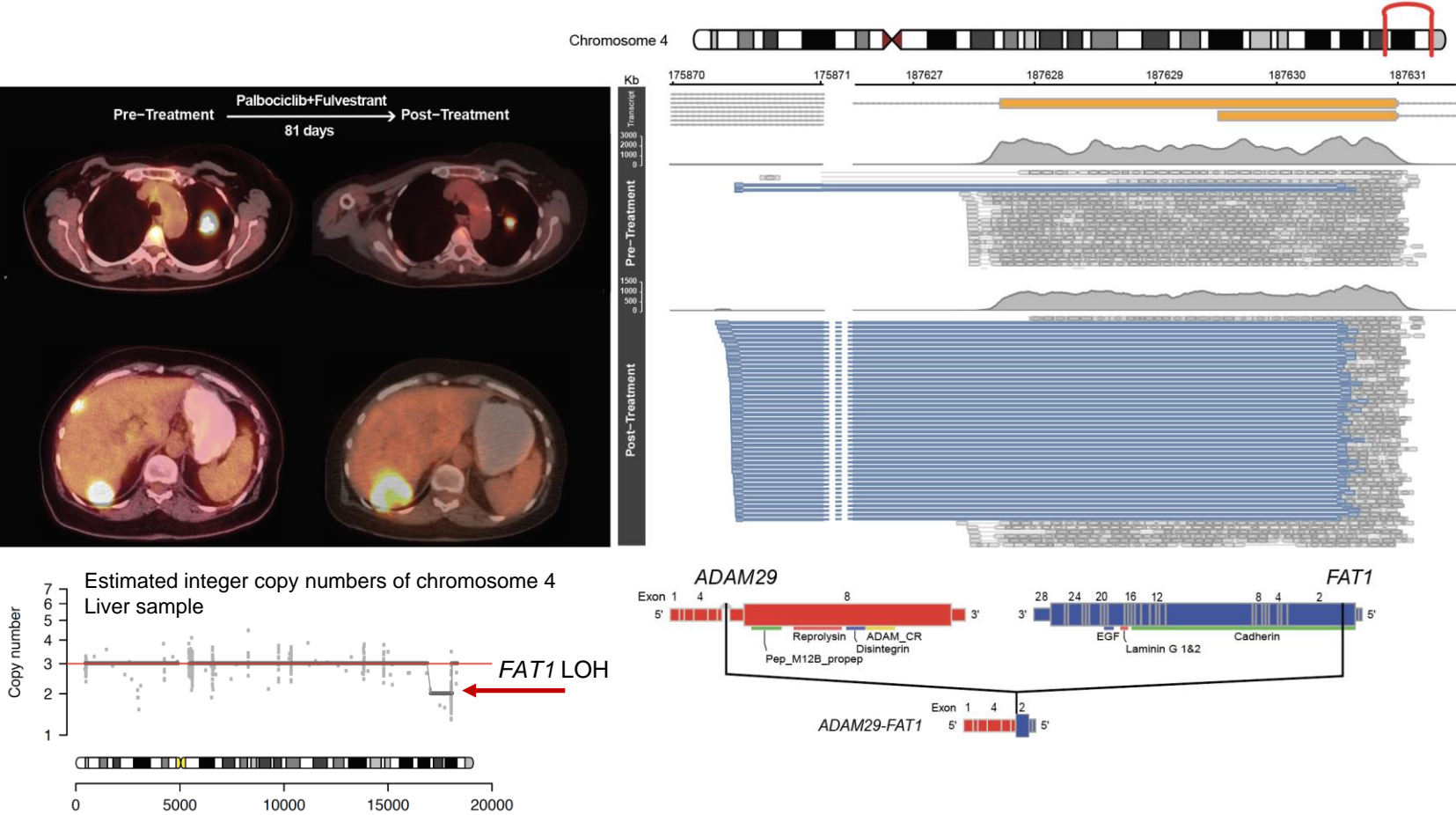


Turner et al. *NEJM* 2015

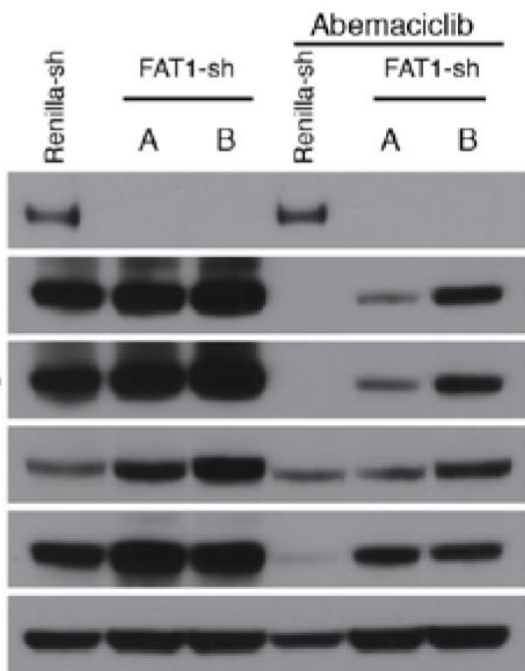
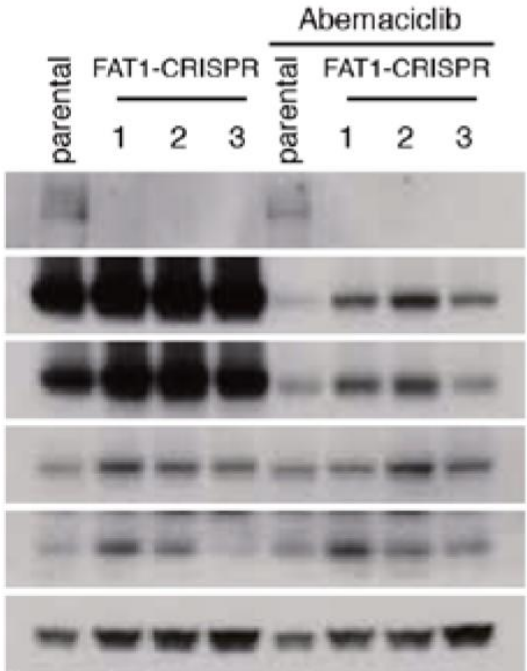
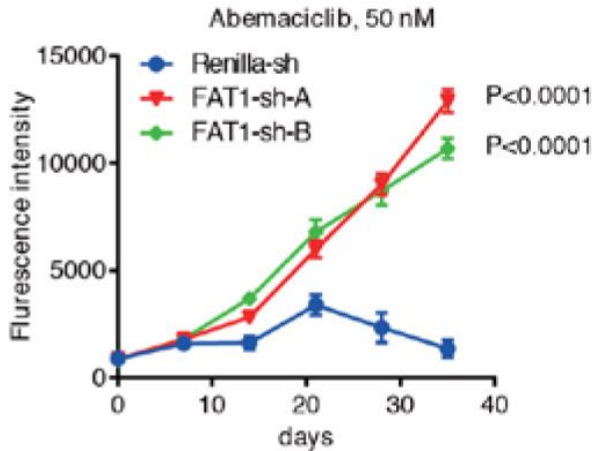
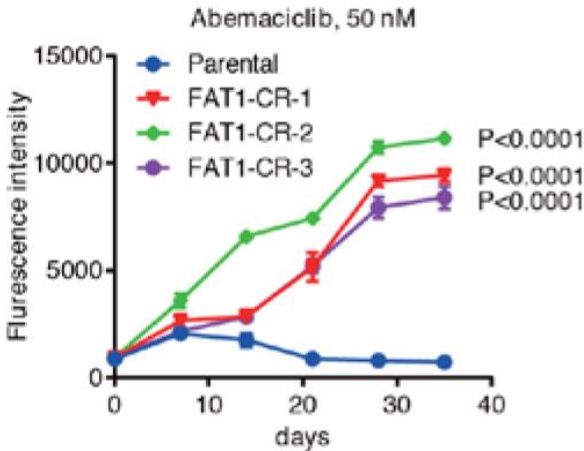
Genomic alterations associated with resistance



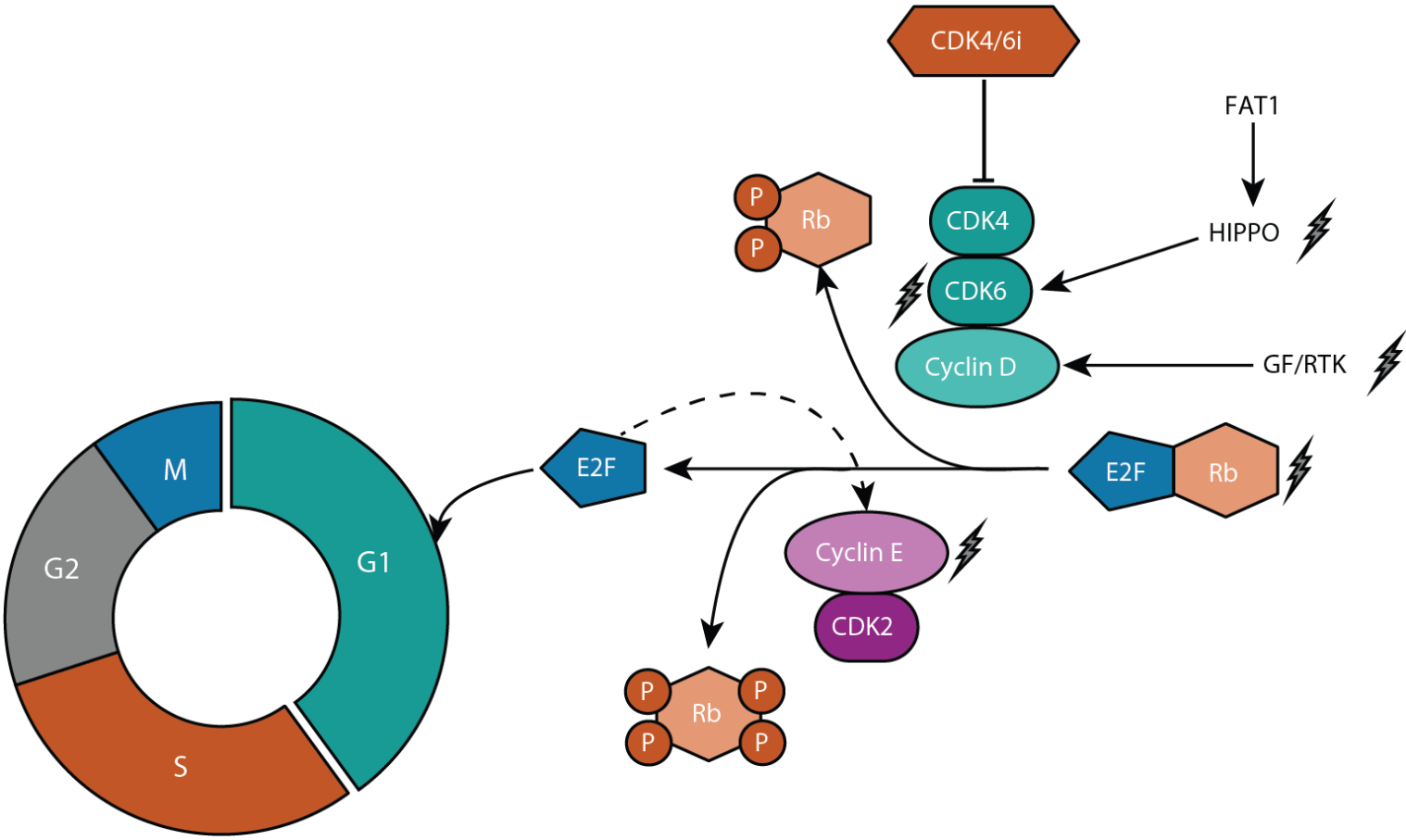
FAT1 loss and clinical resistance



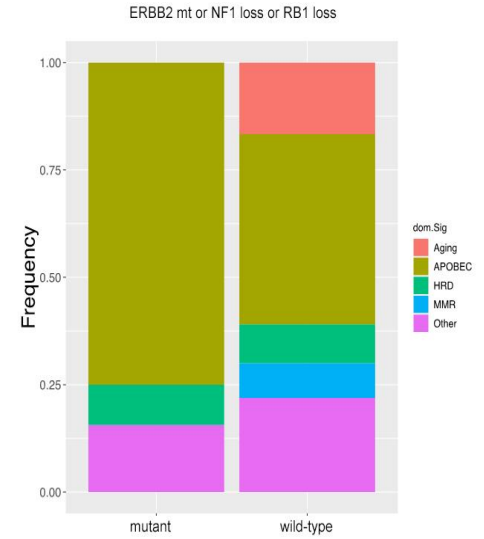
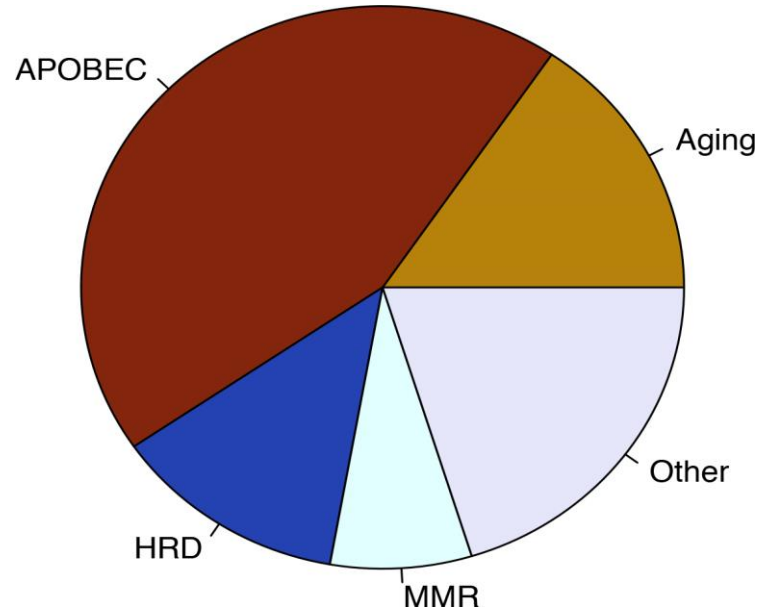
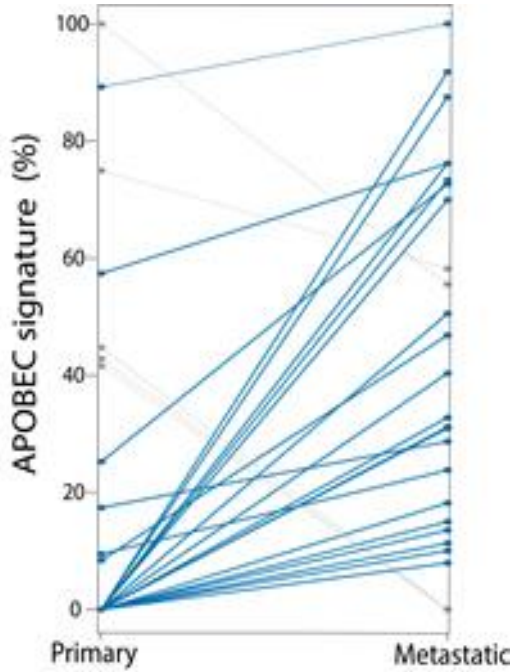
FAT1 suppression promotes CDK4i resistance



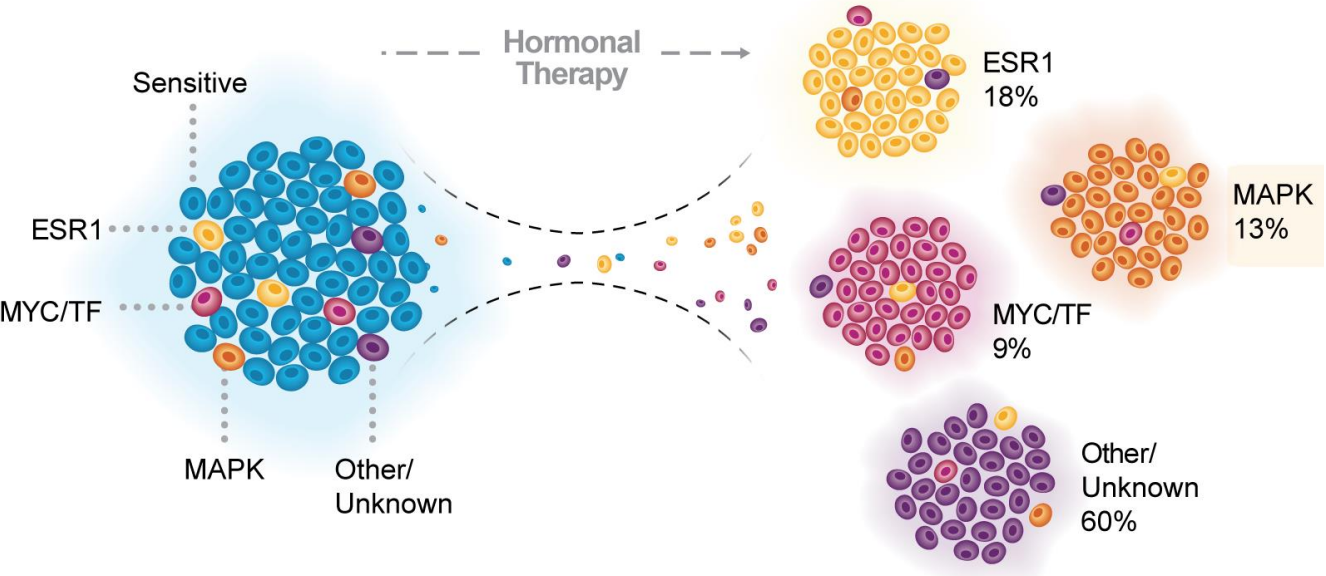
Potential biomarkers for selecting CDK4/6i



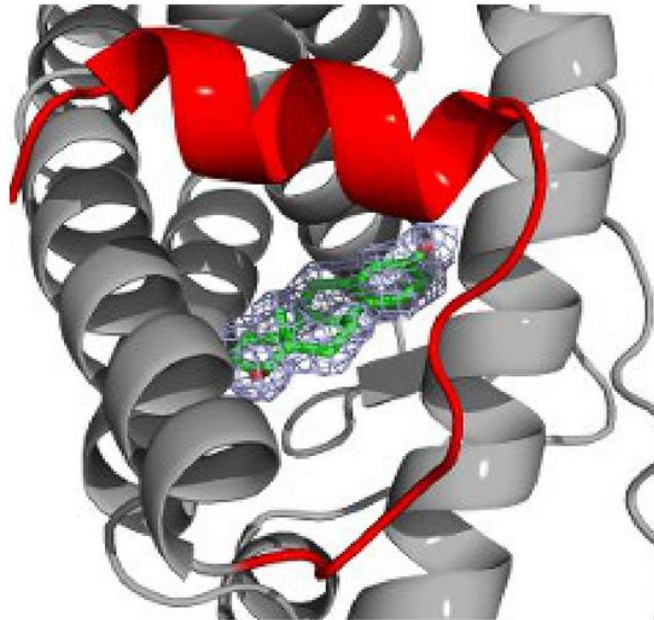
Underlying mutational processes in MBC



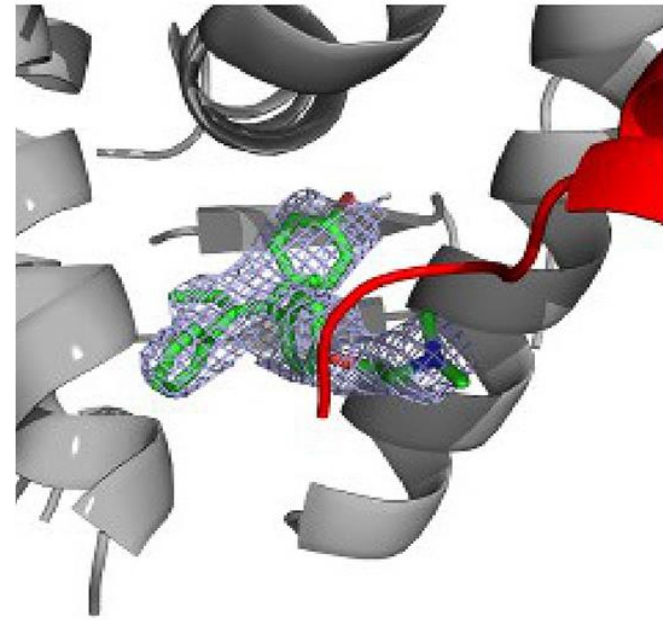
Might Evolutionary Tracks Influence Therapy Choice??



Efficacy of ER antagonists vs ER mutations

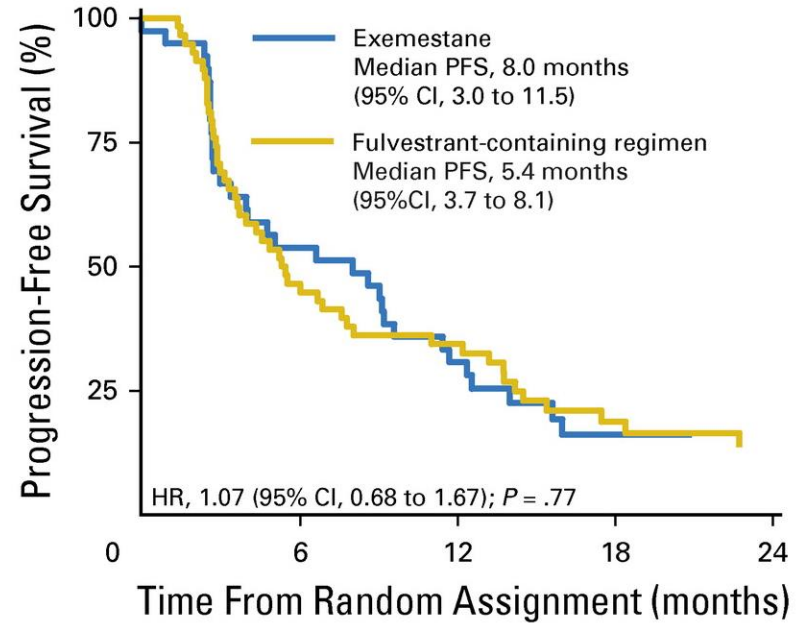
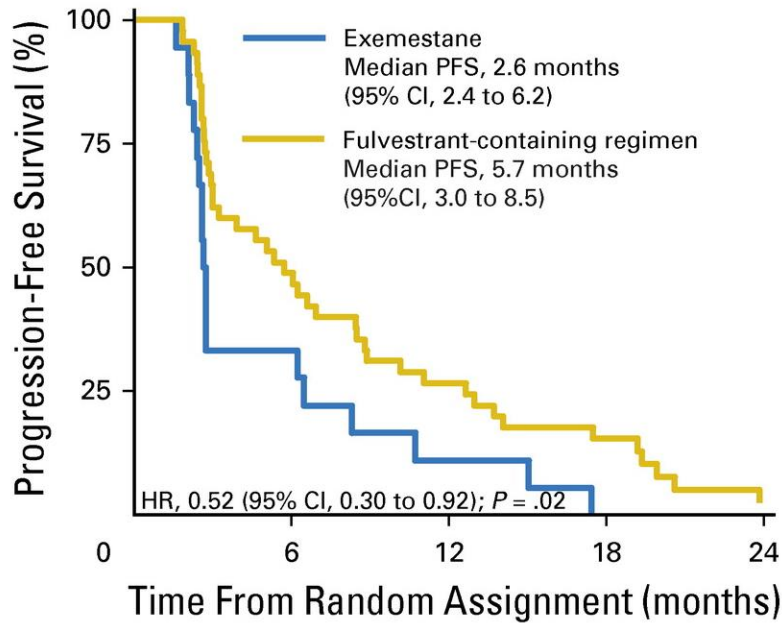


ESR1 D538G + E2

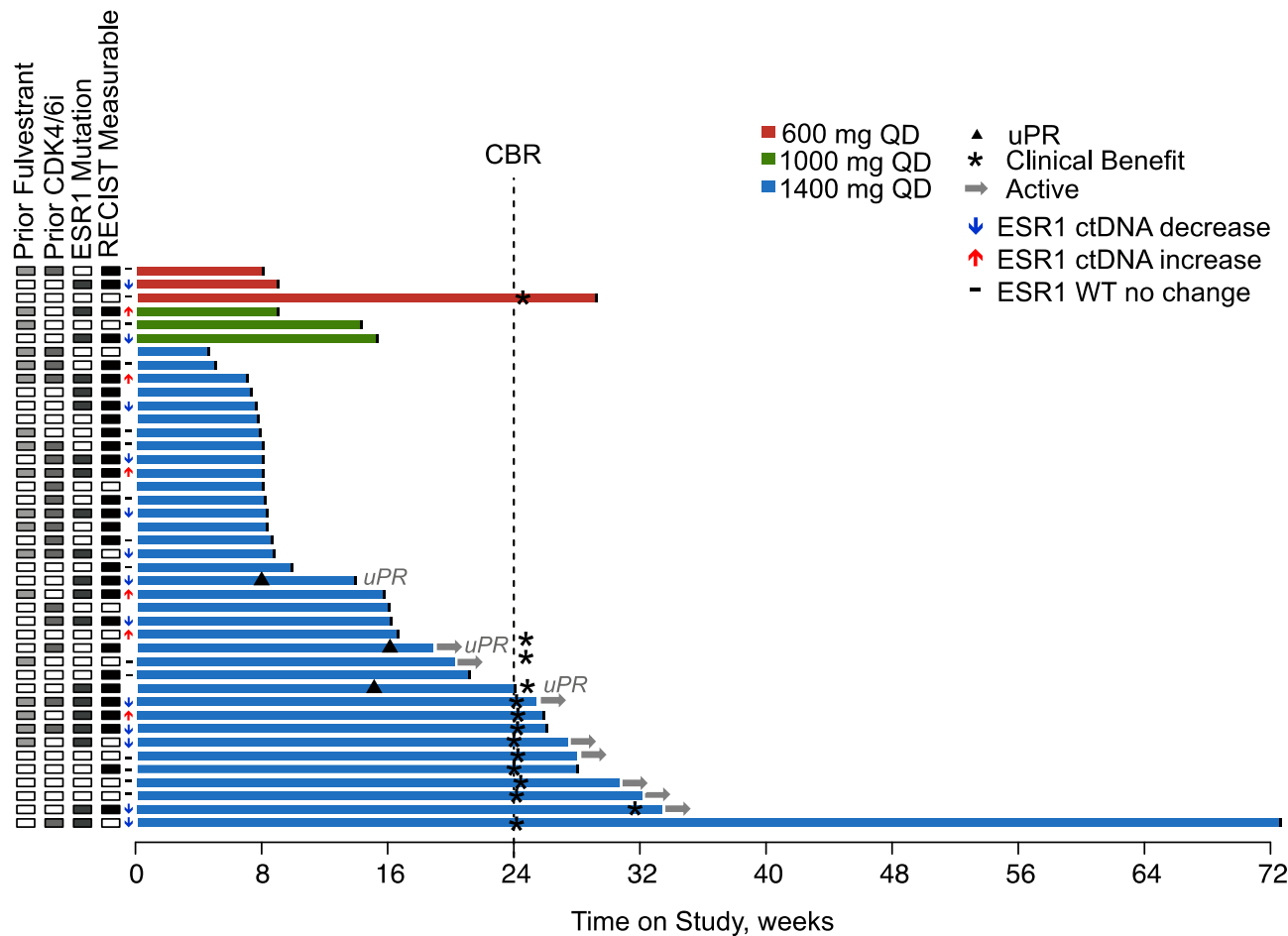


ESR1 D538G + Tam

Clinical efficacy of ER antagonists vs ER mutations



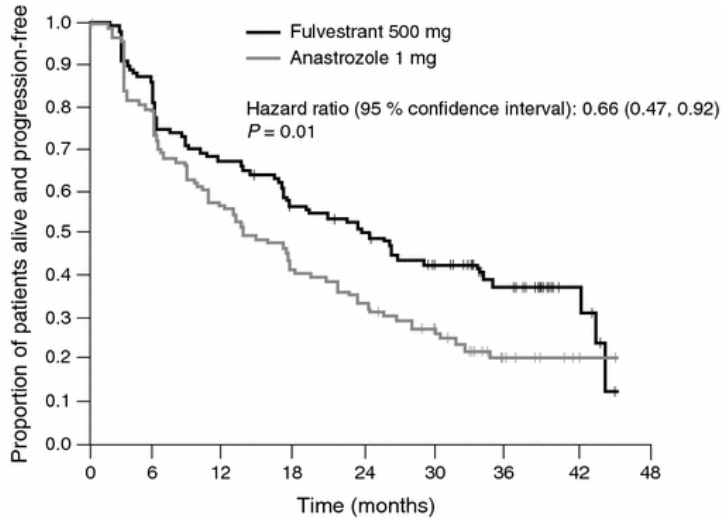
Activity of new oral ER antagonists



Many agents in clinic now:

- RAD1901
- GDC0927
- AZD9496
- LSZ102
- SAR439859
- Bazdoxifene
- H3B6545

Fulvestrant over AI for 1st line?

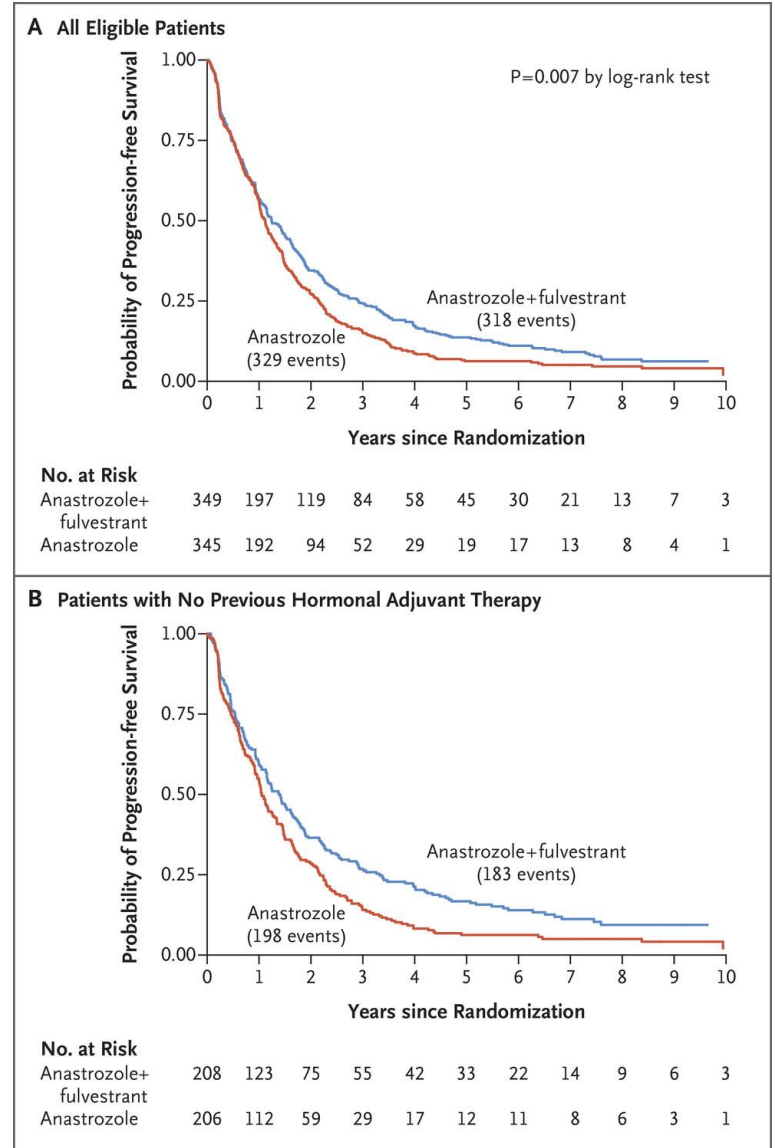


Patients at risk

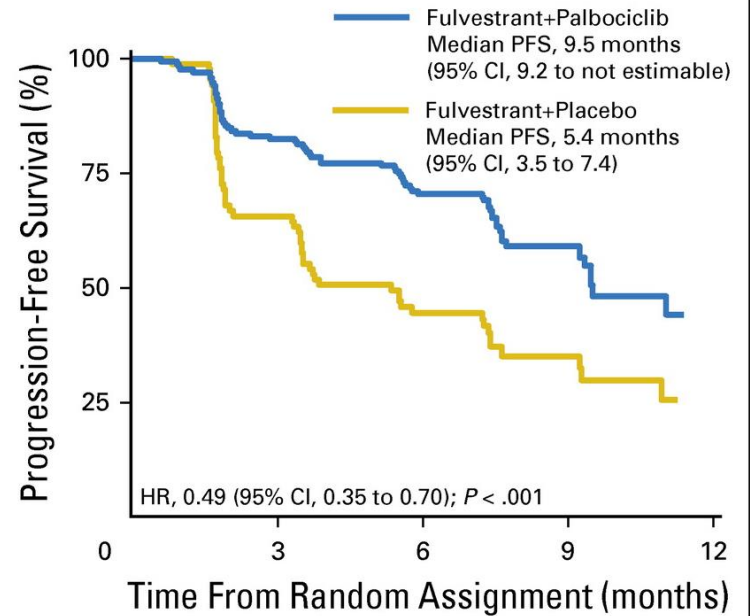
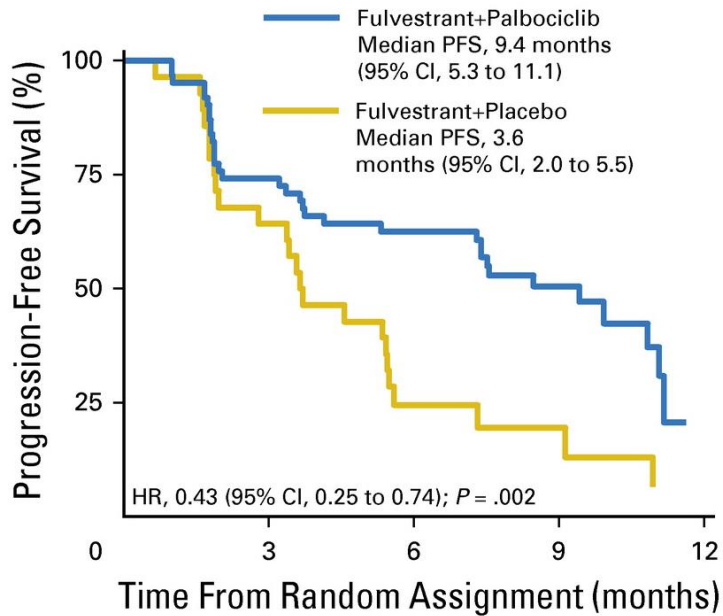
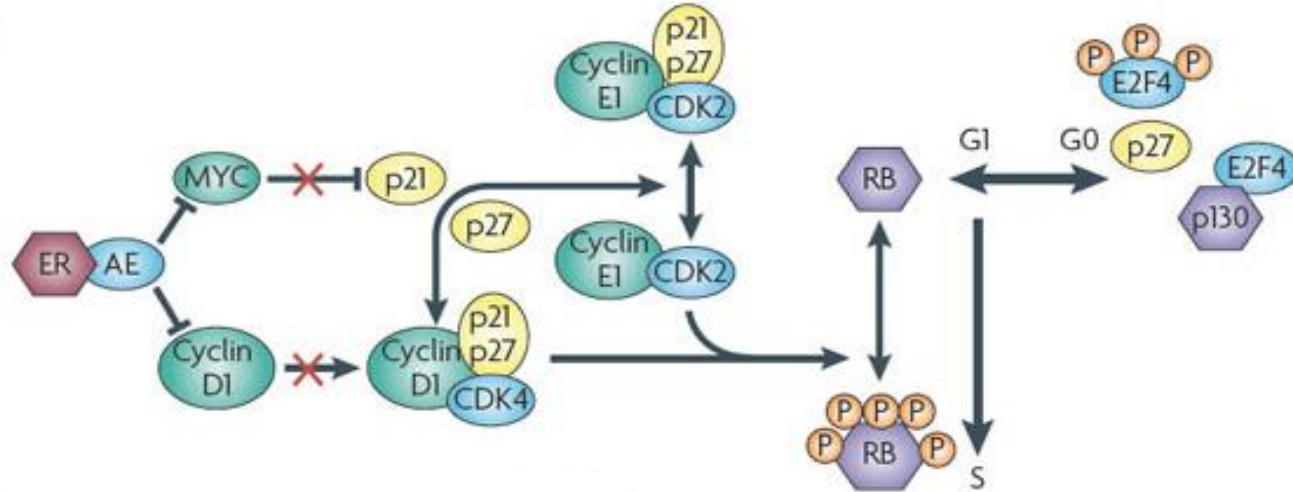
Fulvestrant 500 mg	102	74	65	52	45	34	20	6	0
Anastrozole 1 mg	103	69	55	39	30	21	8	2	0

After the primary data cut-off, progression was determined by investigator opinion

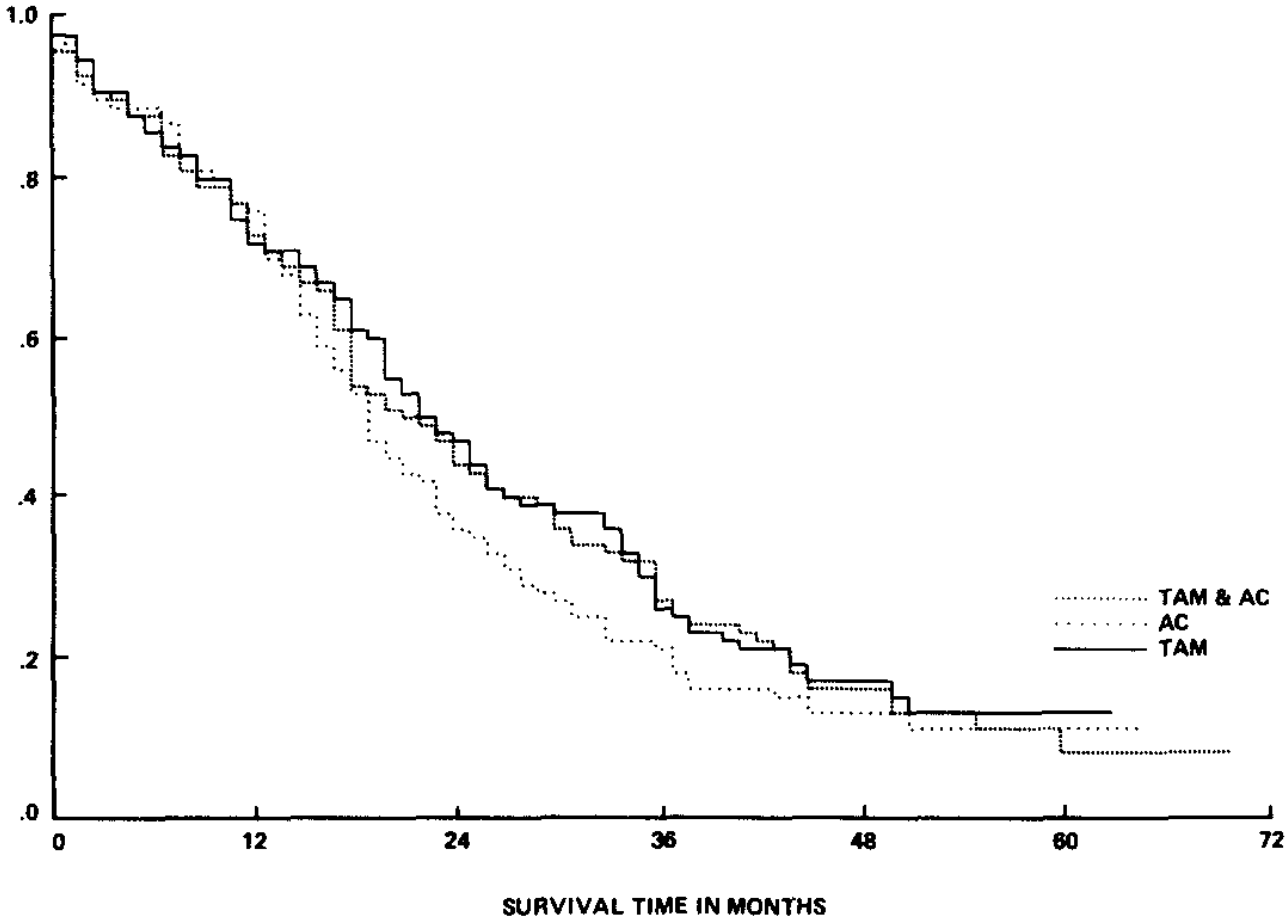
Robertson BCRT 2012



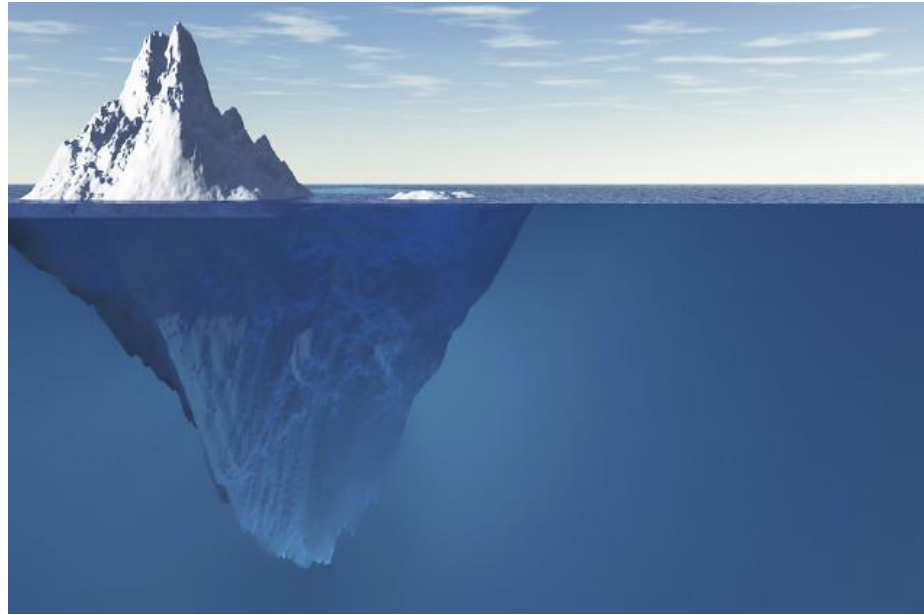
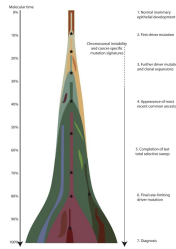
Potentially added rationale for CDK4/6i in 1st line



In the absence of biomarkers...



Conclusions and Future Directions



- 1) Widespread and pervasive genomic evolution in ER+ MBC modulates therapy response**
- 2) Up front fulvestrant plus CDK4/6i carries potential to more effectively target ESR1 mutant clones**
- 3) Clinical standards of upfront endocrine over chemo-therapy rational based on toxicity but unlikely to maximize potential for these diverse and effective therapies.**
- 4) Biomarkers of durable response and prospective/retrospective clinical studies needed to fully inform “precision sequencing of therapy”**

Acknowledgements

Lab members

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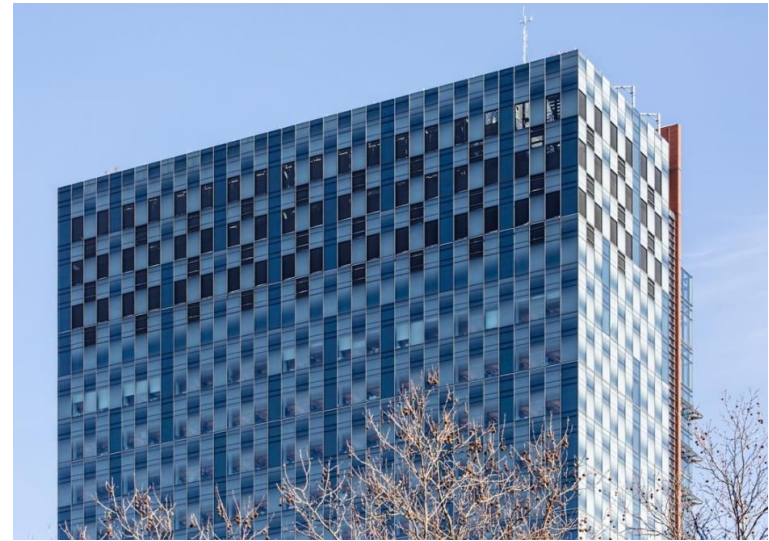
MSK Collaborators

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Mark Robson
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José Baselga (AstraZeneca)
Maura Dickler (Lilly)
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Our Patients!



Damon Runyon
Cancer Research
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