Memorial Sloan Kettering
Cancer Center

ESR1 mutations and resistance to endocrine therapy

Sarat Chandarlapaty

5/8/2015

Disclosure Information
IMPAKT 2015
Sarat Chandarlapaty

I have the following financial relationships to disclose:

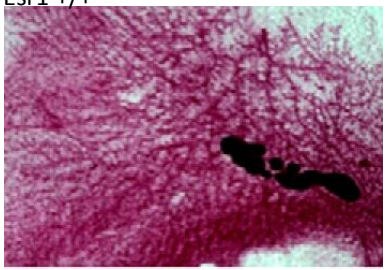
Grant/Research support from: *Novartis*

- and -

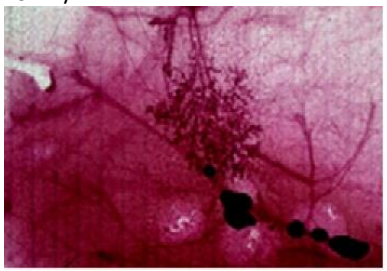
I will not discuss off label use in my presentation but will discuss drugs in clinical trial testing stage.

Central role for estrogen receptor in normal and cancerous breast

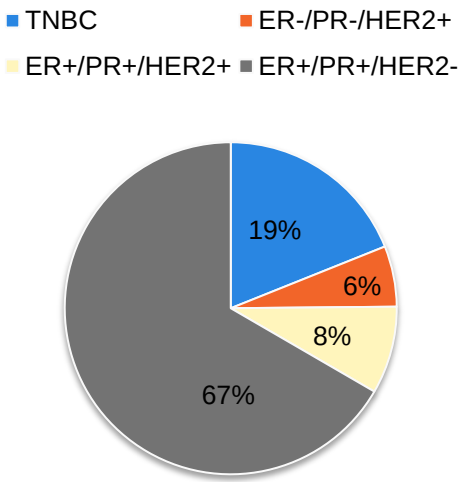
Esr1 +/+

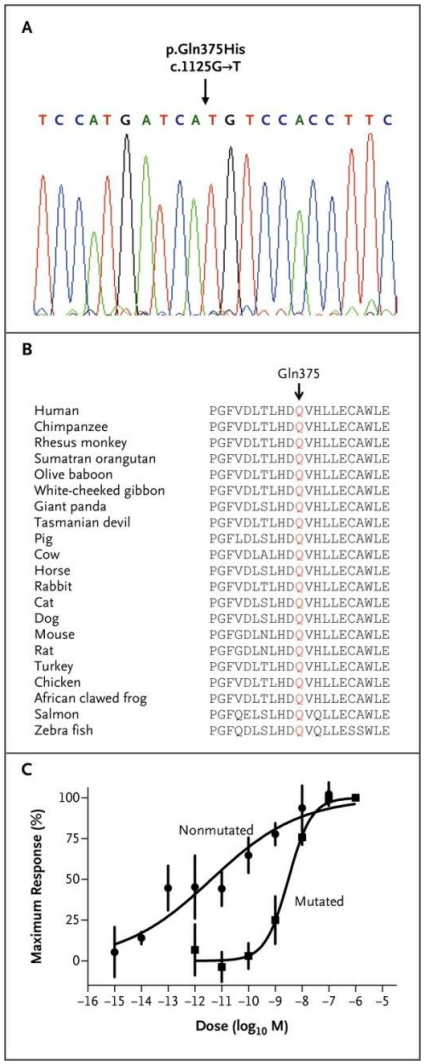


Esr1 -/-



Rumi et al. Endocrinology 2014

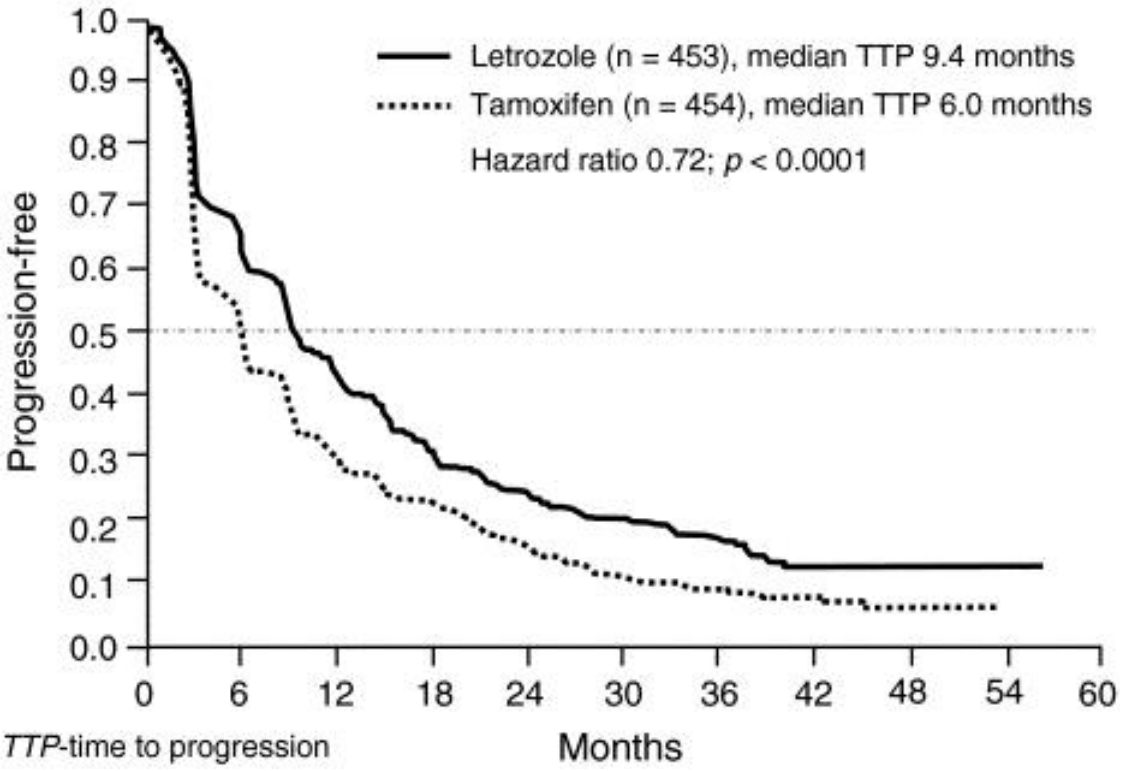




Quaynor et al. N Engl J Med 2013

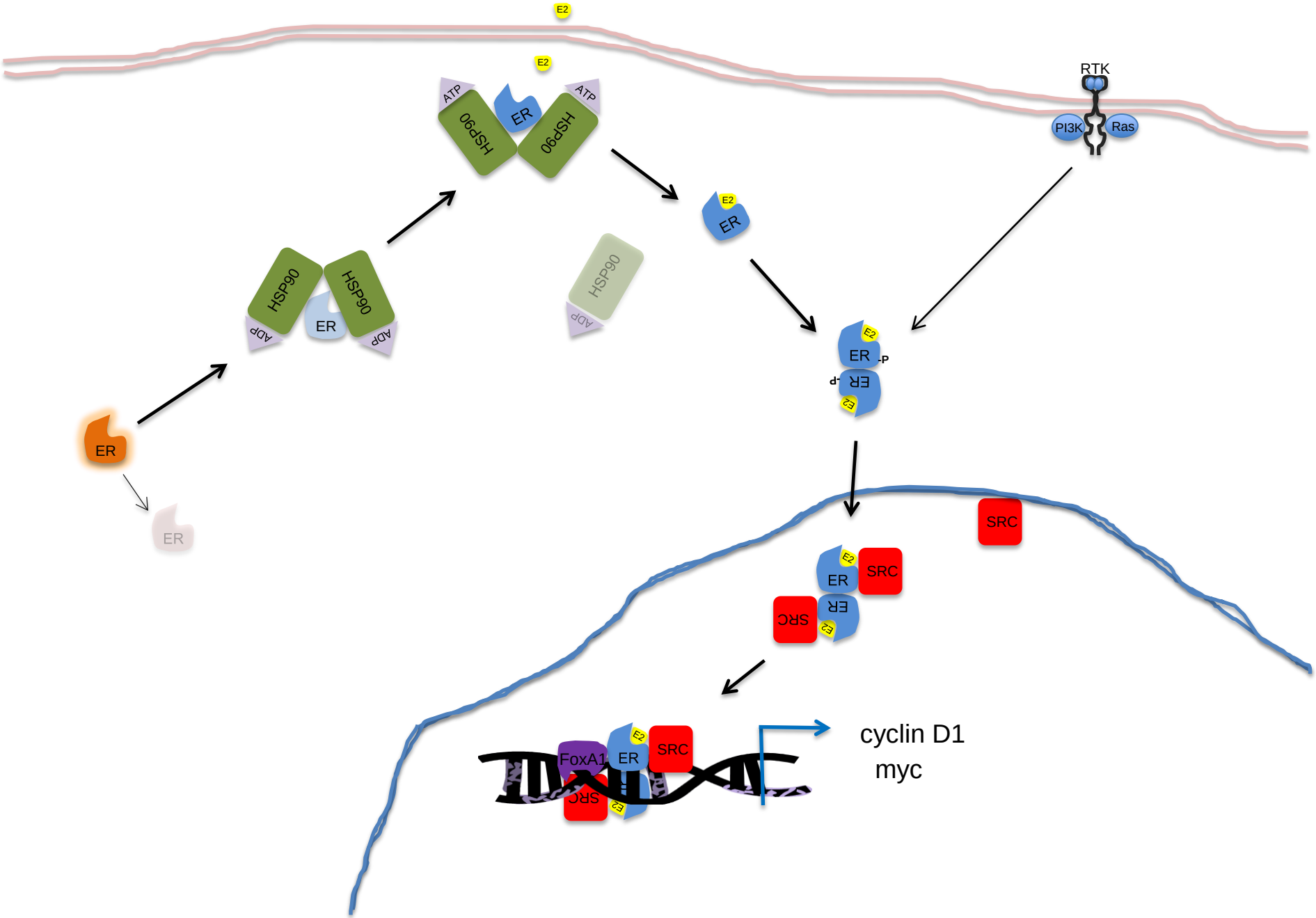
Memorial Sloan Kettering Cancer Center

Benefit of hormone therapy for ER+ metastatic breast cancer



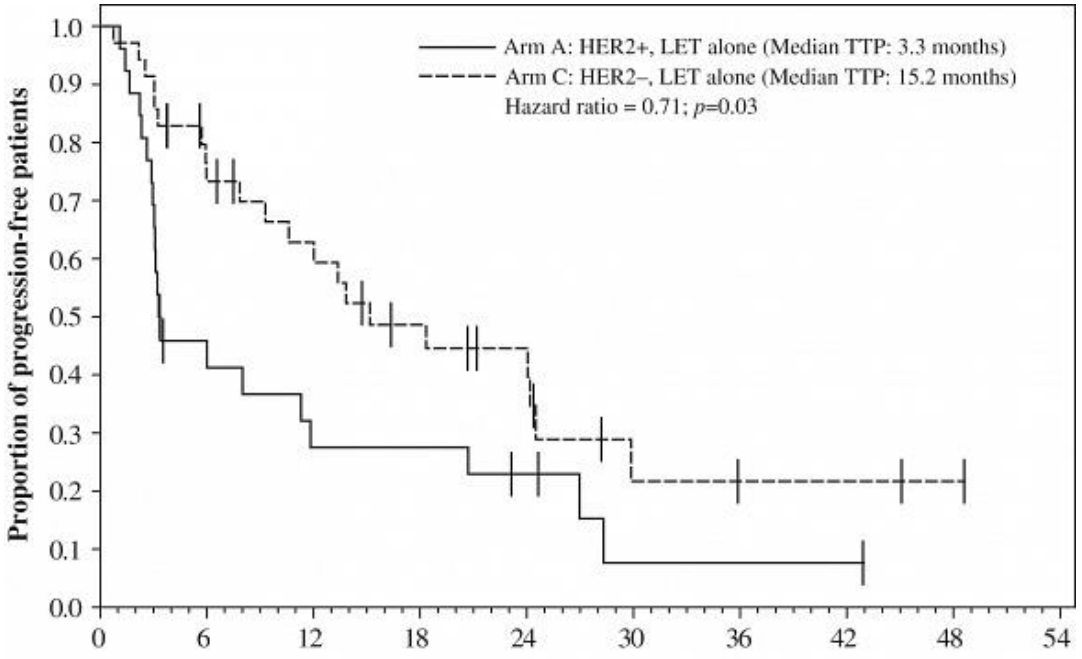
Mouridsen H et al. JCO 2003

Model for estrogen receptor activation



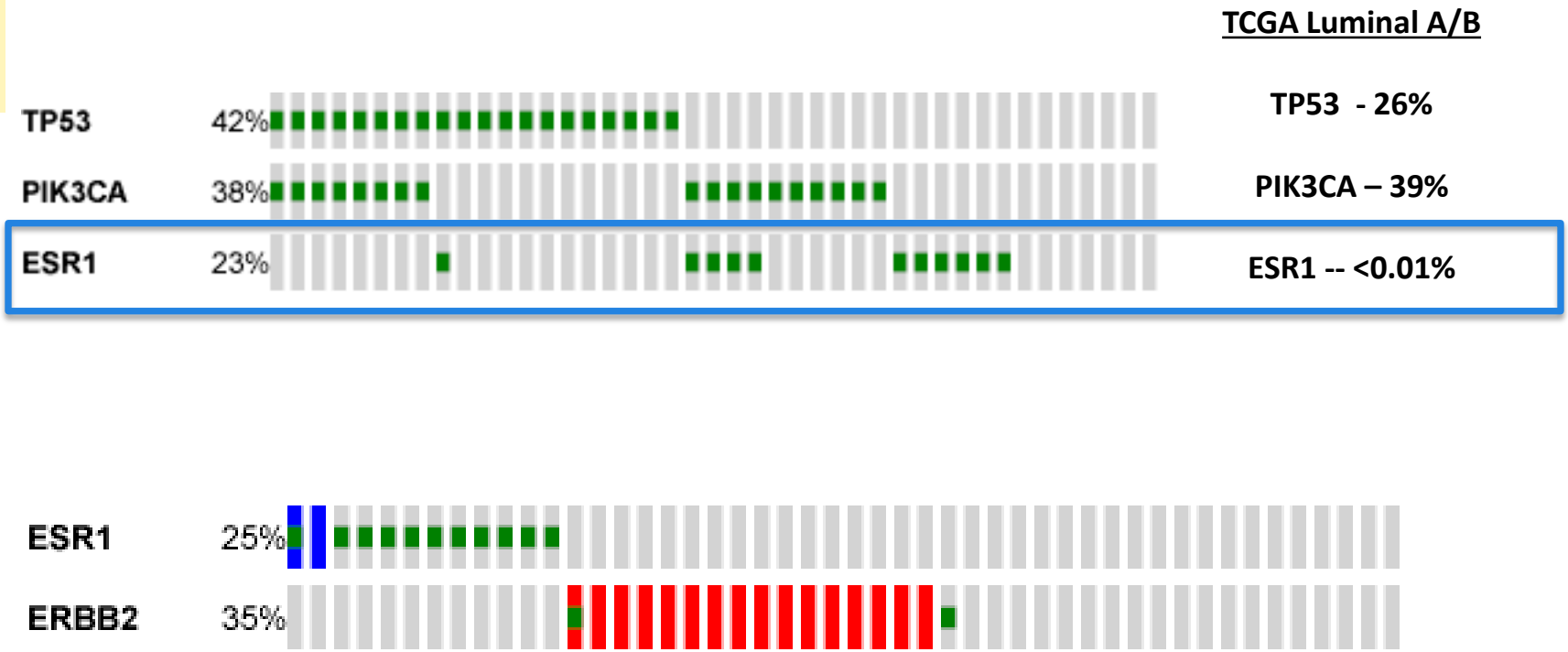
Genomic alterations in EGF signaling promote endocrine resistance

TCGA



Huober et al. 2012

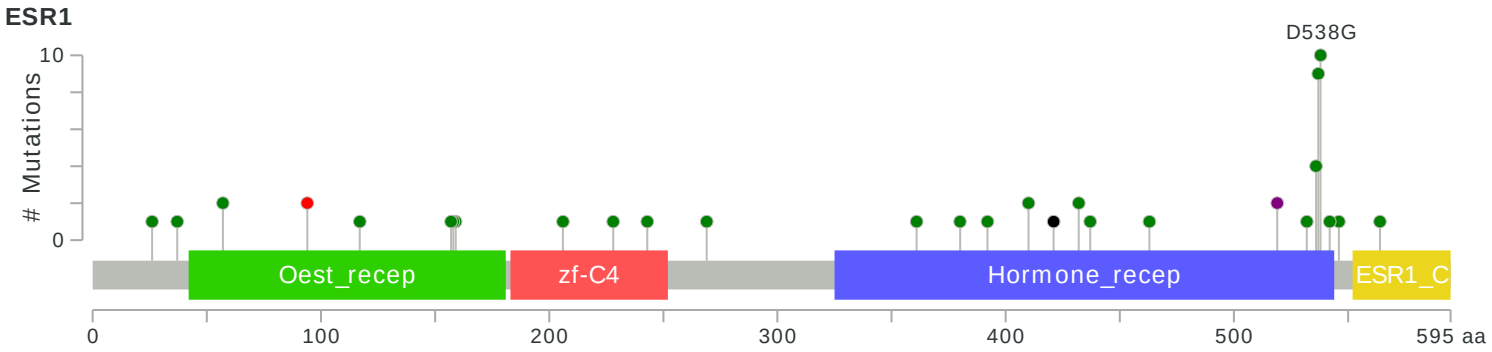
ESR1 mutations in metastatic breast cancer



Antecedent therapy for ESR1 mutant cases

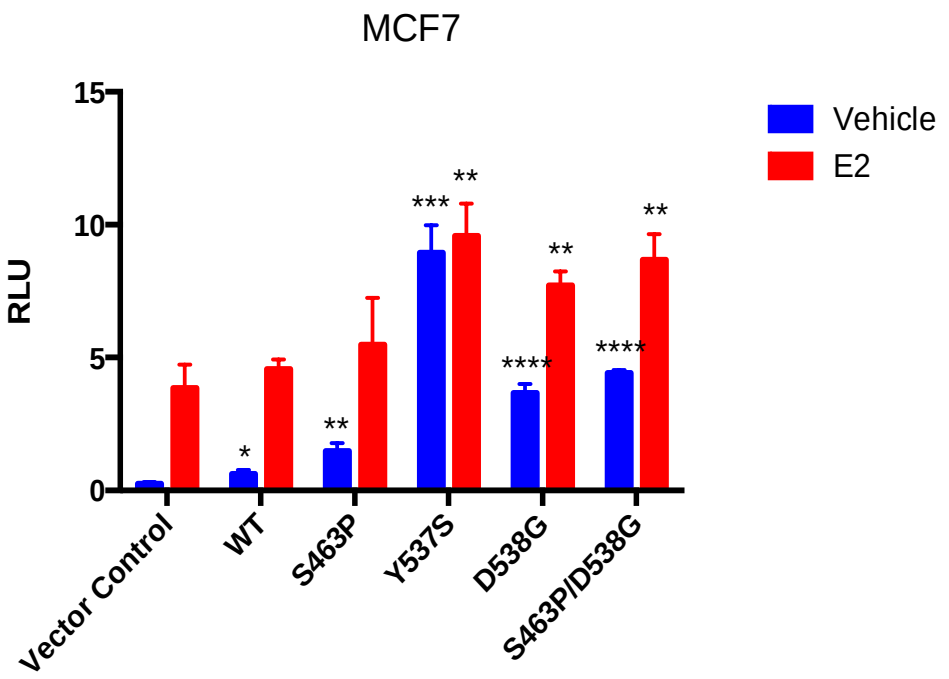
ESR1 mutation(s)	Primary tumor	Mutation Frequency	Duration of hormonal therapies (years)	Types of hormonal therapies given
Y537S	WT	0.528	2.5	AI, SERM
D538G	WT	0.285	6.5	AI, SERM
S463P/D538G	N/A	0.122/0.280	7.5	AI, SERM
Y537S/D538G	N/A	0.082/0.103	3.3	AI, SERD, SERM
L536R	N/A	0.114	10	AI, SERM
V534E	N/A	0.056	5.5	AI, SERD
Y537N	N/A	0.839	5.5	AI, SERM
Y537S	N/A	0.253	1.5	AI,SERD
Y537S	N/A	0.265	2.0	AI,SERM,SERD

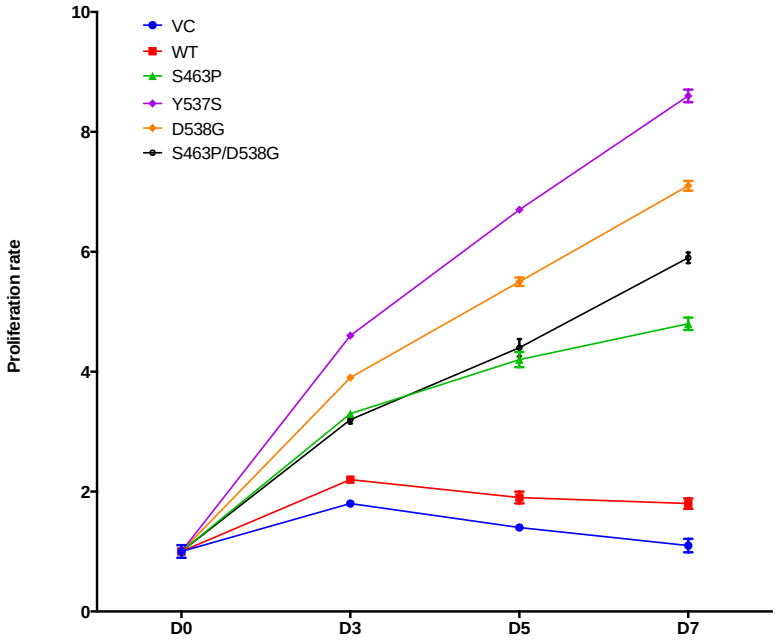
Mutations in ESR1 cluster to hotspot in LBD



Somatic mutations occur throughout gene in ~15-20% ER+ MBC
Rare amplifications and deletions
Hotspot mutations clustering to amino acids L536, Y537, and D538 within LBD – these patient all with prior aromatase inhibitor

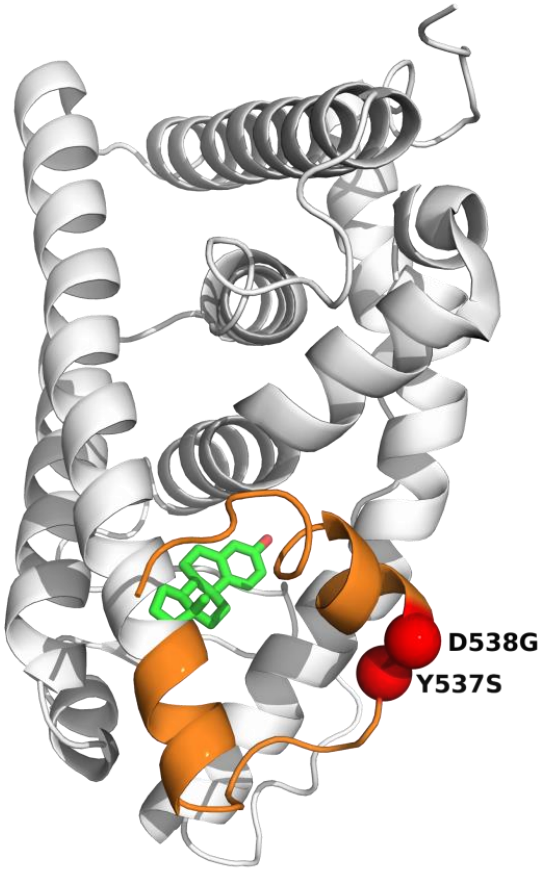
ESR1 mutations promote E2-independent transcription and proliferation





Common LBD mutations locate to region key to ER activation

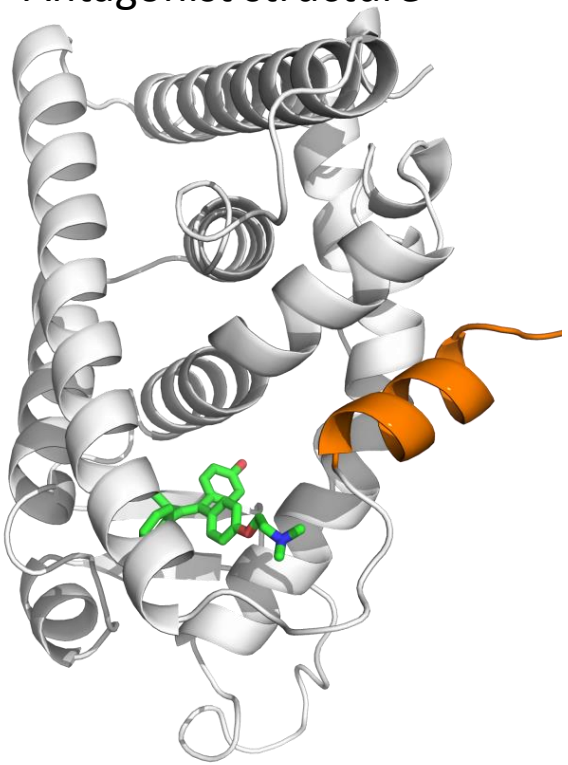
Agonist structure

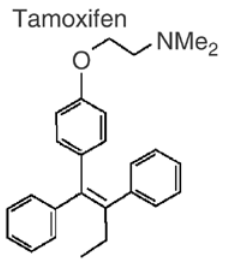


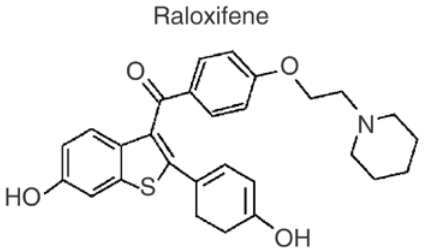
Sean Fanning and Geoffrey Greene

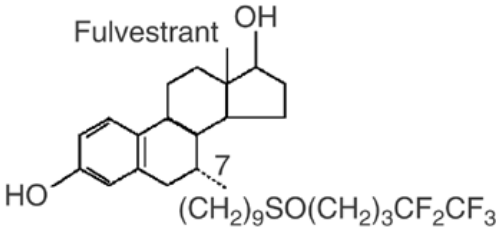
Therapy – Receptor antagonists

Antagonist structure

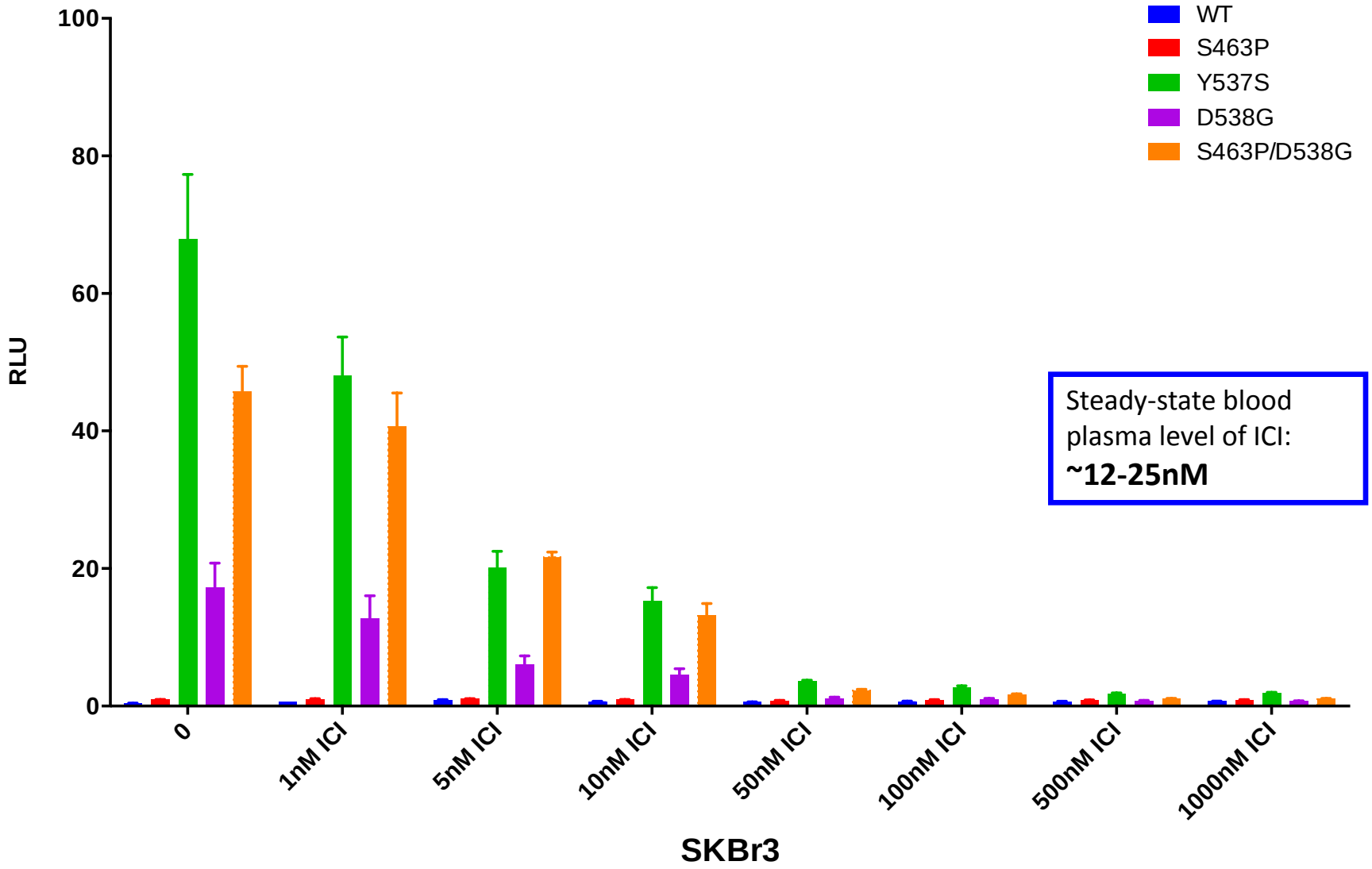




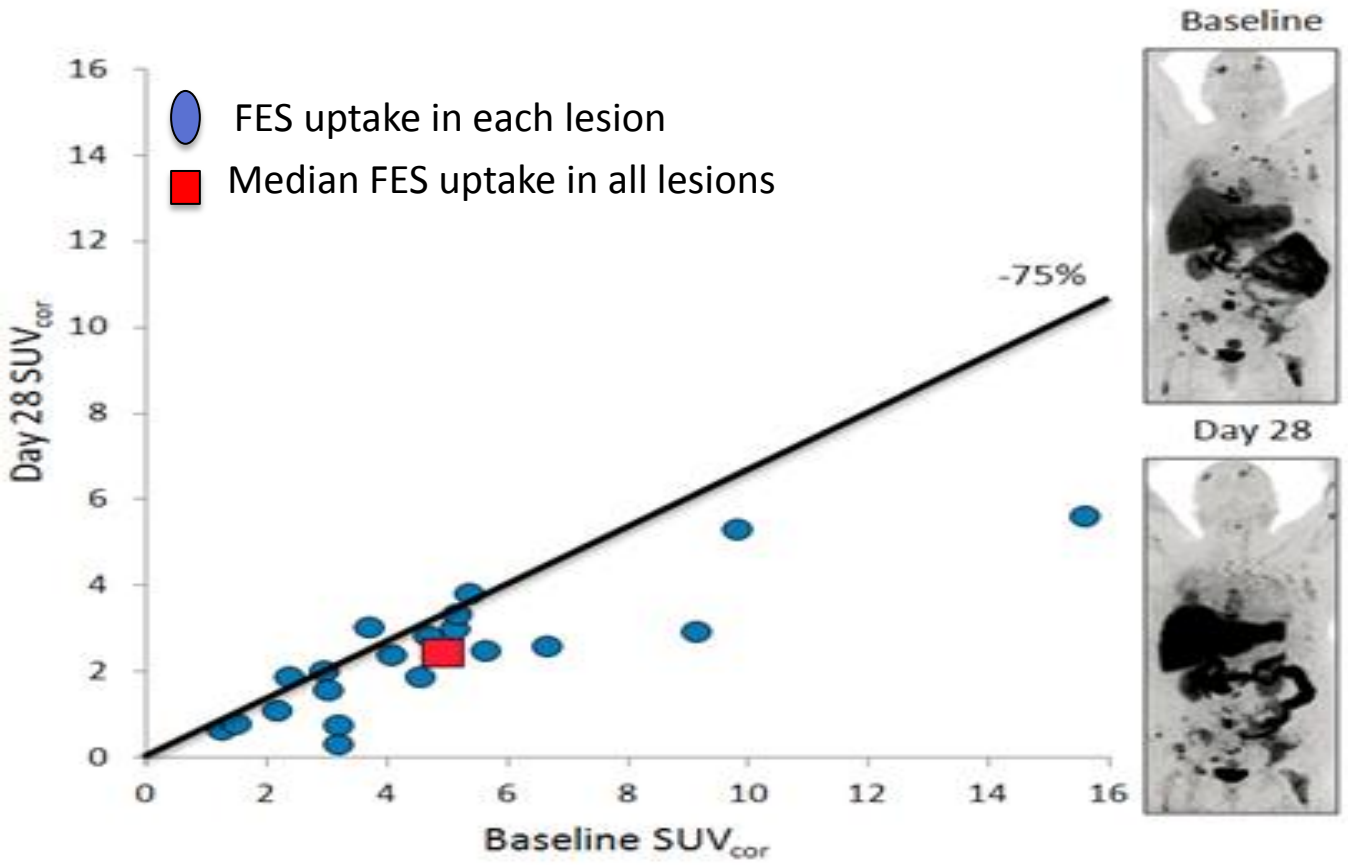




SERD sensitivity - Fulvestrant



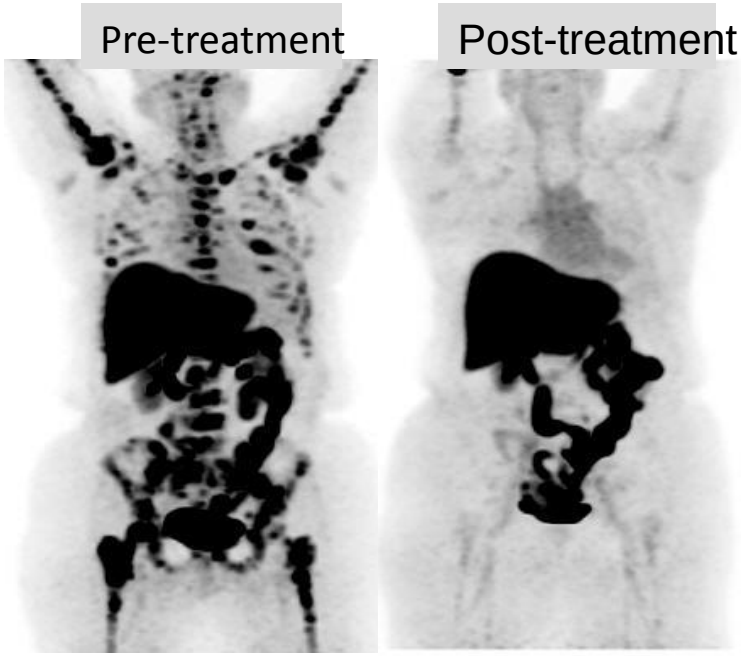
Residual estradiol binding (FES) on fulvestrant therapy

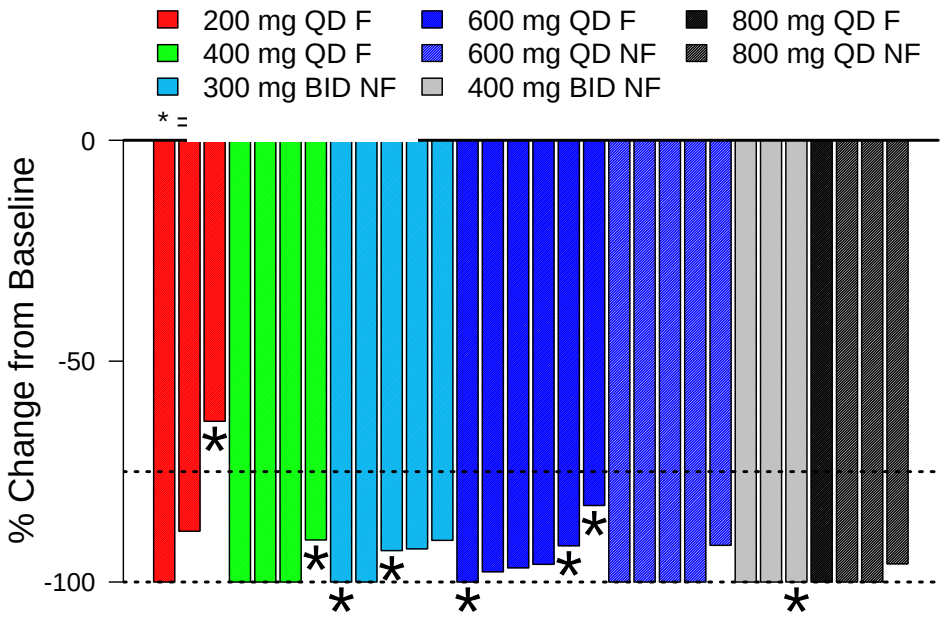


- Residual ER detected in 6/16 (38%) pts
- Associated with progressive disease by CT imaging

Van Kruchten, De Vries et al., ASCO, 2014

GDC-0810 [^{18}F]-fluoroestradiol (FES)-PET Data Shows Robust Target Engagement Across All Doses



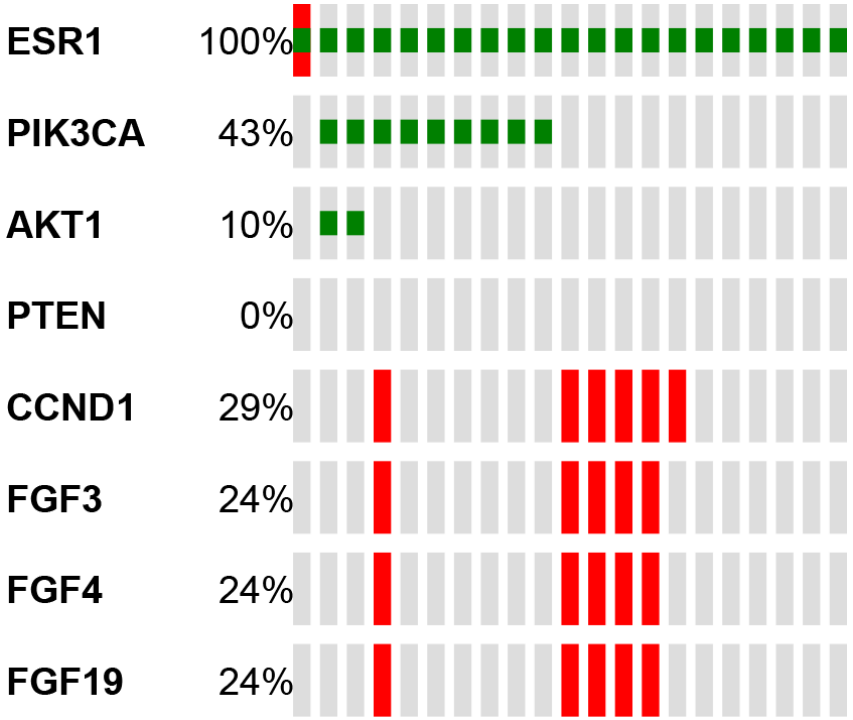


- Scan performed ~20 hrs post dose (600 mg)
- Supports QD dosing

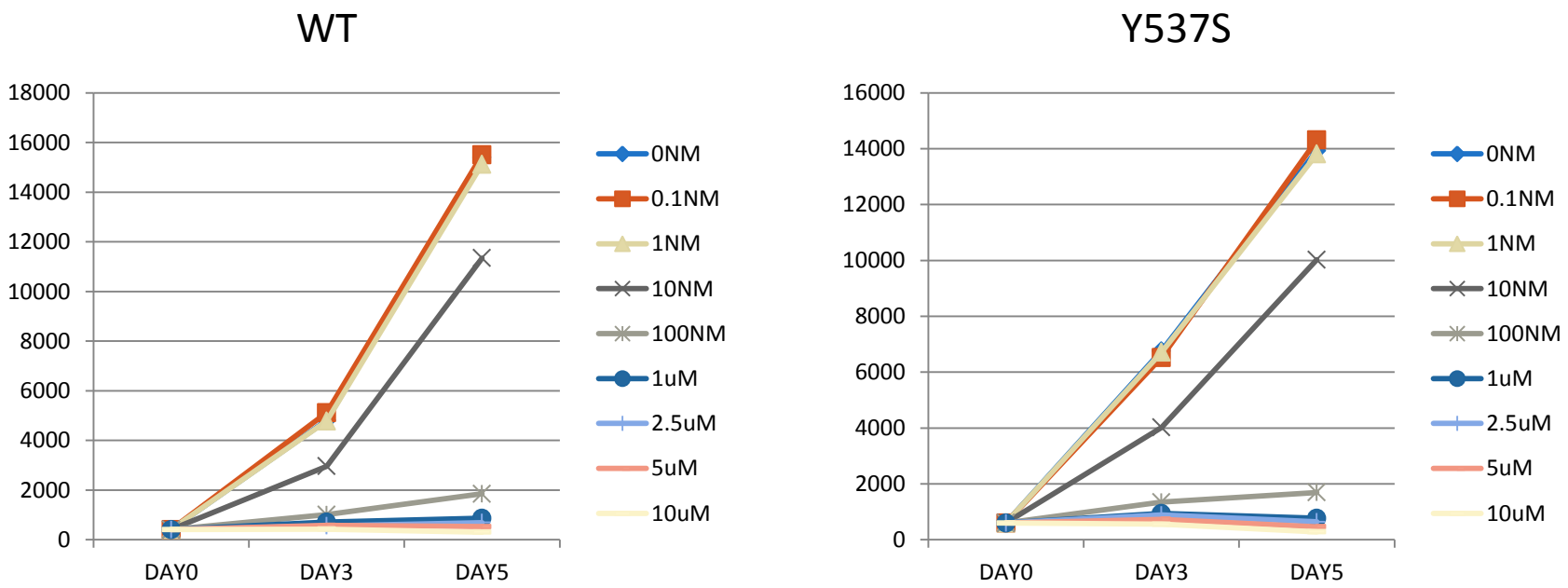
* ESR1 mutant

Dickler et al., AACR 2015

Drugging ER mutant cancers: co-mutation patterns

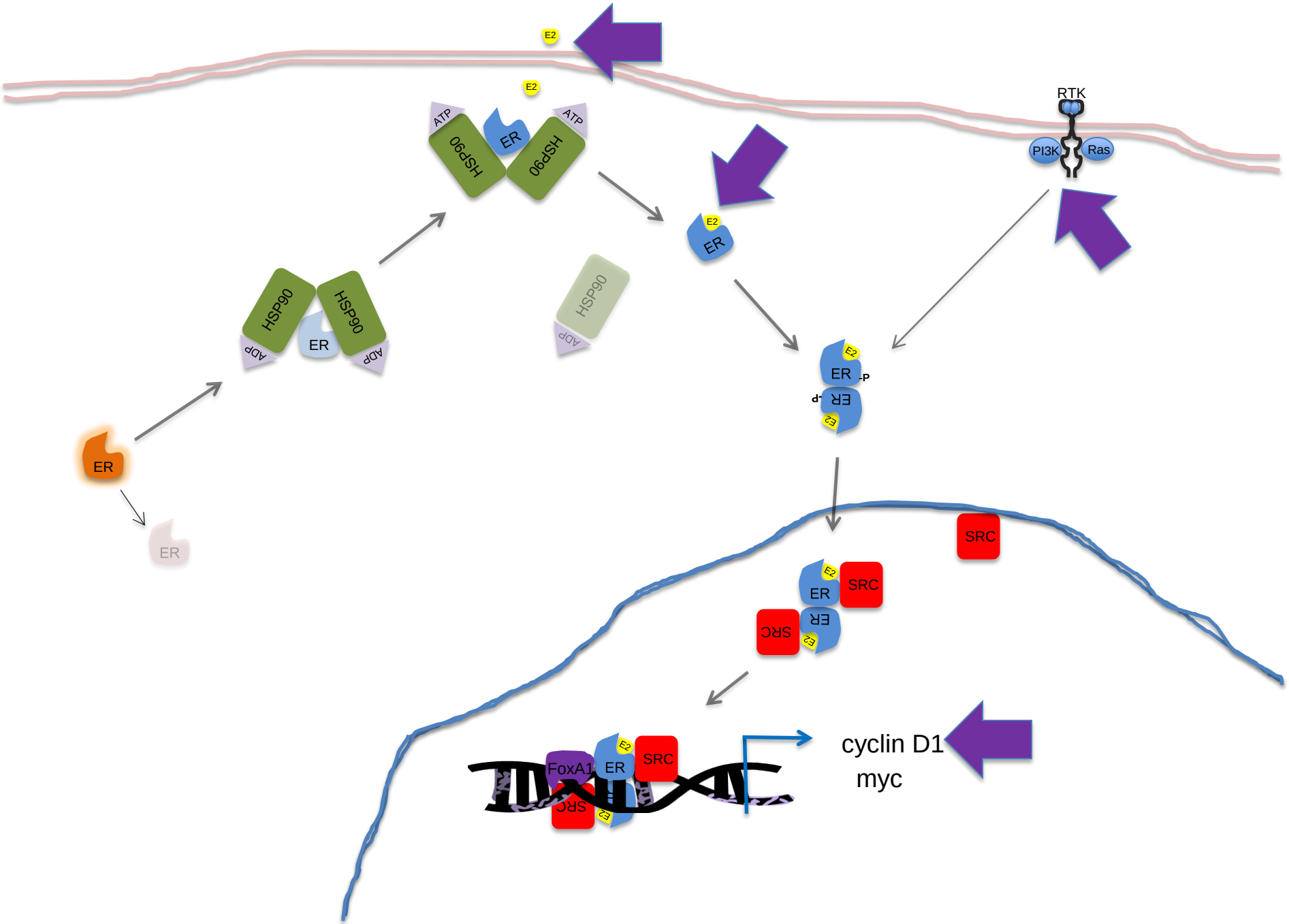


Other drivers still relevant: e.g. PIK3CA mutation



GDC0032

Major points for therapeutic intervention



Acknowledgements

Weiyi Toy
John (Zhiqiang) Li
Kinisha Gala
Sharmeen Uddin
Chengcheng Yang

Collaborators
Geoffrey Greene (University of Chicago)
John Katzenellenbogen (University of Illinois)
Neal Rosen
José Baselga
Maurizio Scaltriti
Michael Berger
Maura Dickler
Yang Shen (Texas A&M)
Hazel Weir (Astra Zeneca)

Funders
Department of Defense
Damon Runyon Foundation
Susan G. Komen
NCI
MSKCC (Metastasis Research Center)

Patients