The Challenge of Rare Subsets of Rare Cancers: A focus on *ESR1* mutations in gynecologic malignancies

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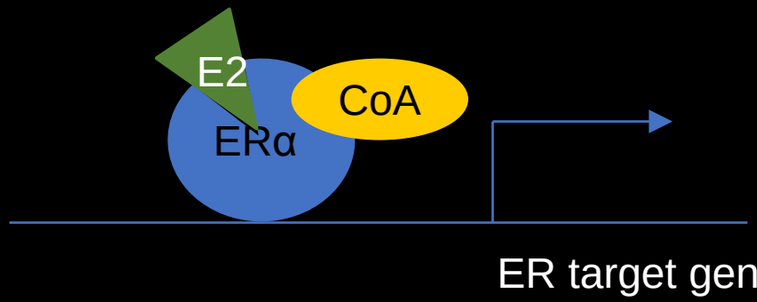
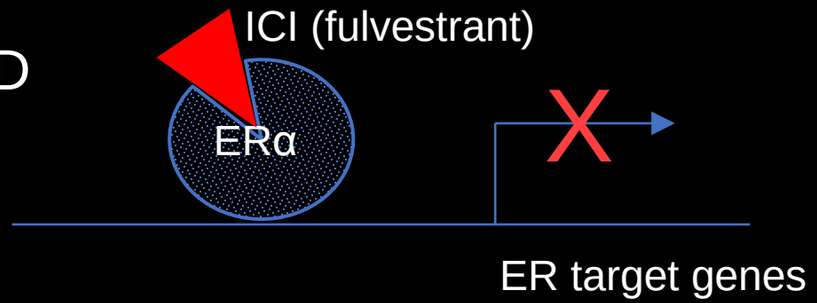
Estrogen Receptor – a ligand-dependent regulator of transcription

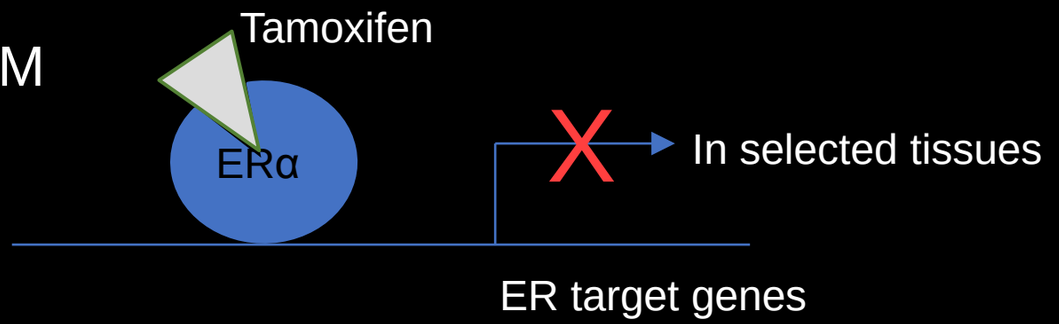


AI

SERD

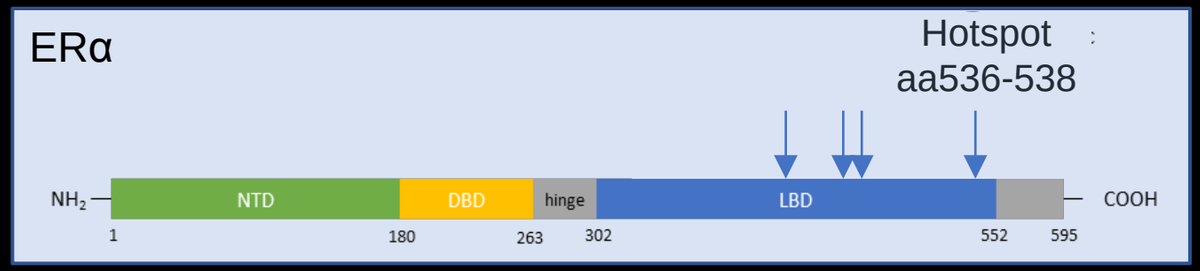


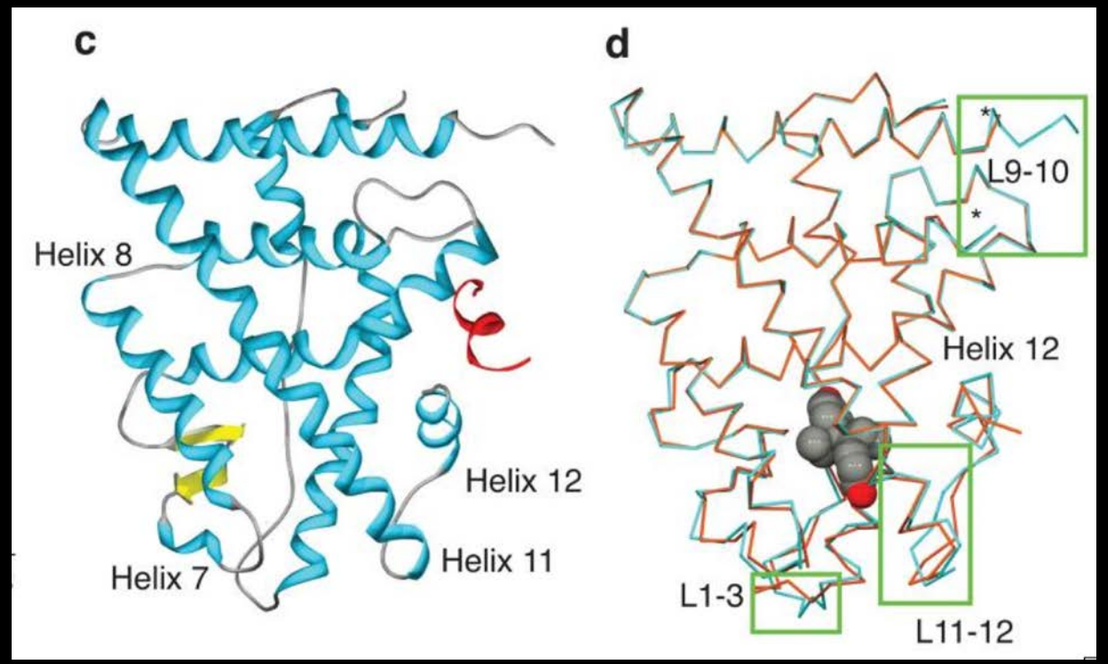
SERM



AI: Aromatase inhibitor
SERD: selective estrogen receptor disruptor
SERM: selective estrogen receptor modulator

Estrogen Receptor (*ESR1*) Activating Mutations are Associated with Resistance to Endocrine Therapy



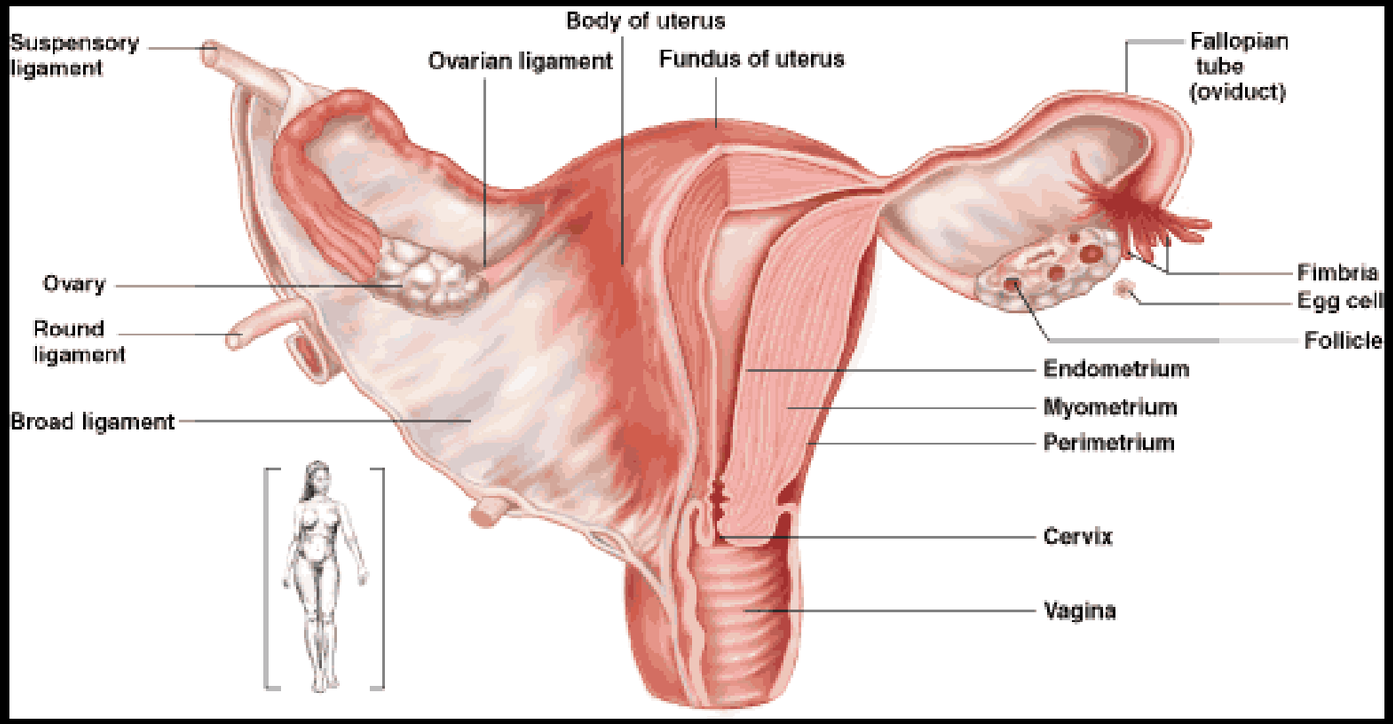


Nettles et al. Nat Chem Biol. 2008

Rare Gynecologic Cancers

OVARY

High-grade serous
Endometrioid
Low-grade serous
Clear cell
Mucinous
Carcinosarcoma
Adenosarcoma
Germ Cell Tumors
Sex Cord -Stromal Tumors (Granulosa Cell Tumors)
Small Cell Carcinoma
Carcinoid
Wolffian Tumors



UTERUS

Endometrioid
High-grade serous
Clear cell
Carcinosarcoma
Leiomyosarcoma
Low-grade endometrial stromal sarcomas
High-grade endometrial stromal sarcomas
Undifferentiated uterine sarcomas

CERVIX

Squamous cell carcinoma
Adenocarcinoma
Adenosquamous carcinoma
Small cell carcinoma

VAGINA/VULVA

Squamous cell carcinoma

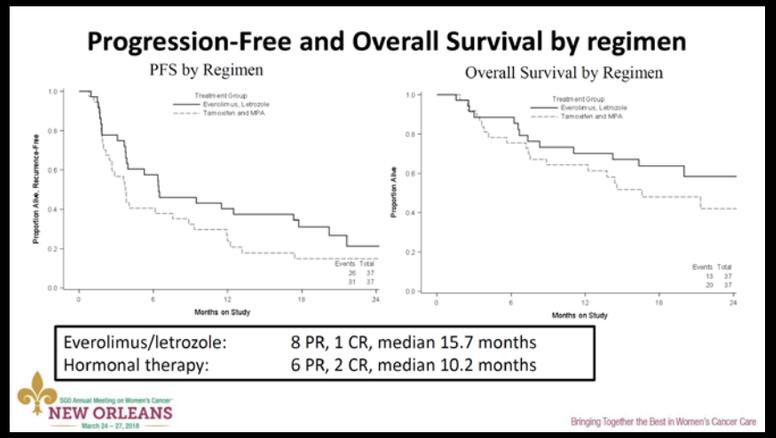
Endocrine Therapy is Associated with Modest Response

Advanced Endometrial Cancer

Table 5
Comparison of objective response rates (ORR) and median progression-free survival (PFS) outcomes with use of targeted and hormonal agents in advanced endometrial cancer.

Study	Agent	ORR (%)	PFS (months)
	Hormonal agents	21.6	2.8
	ER/+PR+	32.5	–
	ER+	26.6	–
	PR+	35.5	–
Leslie [61]	Gefitinib	3.3	1.8
Aghajanian [62]	Bevacizumab	13.2	4.5
Alvarez [63]	Bevaizumab + temsirolimus	24.5	5.6
Bender 2015 [64]	Cediranib	12.5	3.6
Castonguay [65]	Sunitinib	18	3.0
Slomovitz [66]	Everolimus + letrozole	32	3.0
Oza [67]	Erolotinib	12.5	–
Oza [68]	Temsirolimus	13.7	–

Ethier et al 2017 Gyn Onc



Slomovitz 2018 SGO Annual Mtg

Recurrent Low-Grade Serous Ovarian Cancer

9% response rate

Table 4
Summary of complete and partial responses.

Patient-regimen	Primary tumor site[a]	Regimen (no.)	Response	
			Type	Duration, months
1[b]	Peritoneum	Tamoxifen (4)	CR	117.6
2	Peritoneum	Anastrozole (2)	CR	112.2
3	Peritoneum	Letrozole (3)	CR	67.9
4	Peritoneum	Letrozole (4)	CR	52.2
5	Ovary	Letrozole (3)	CR	11.9
6[b]	Peritoneum	Letrozole (2)	CR	42.0
7	Ovary	Letrozole (2)	PR	22.0
8[c]	Peritoneum	Letrozole (4)	PR	1.63

Gershenson et al 2012 Gyn Onc

AI use in adjuvant therapy has been associated with prolonged PFS

Gershenson et al. 2017 JCO
Fader et al. 2017 Gyn Onc

Frequency of *ESR1* alterations in gynecologic malignancies

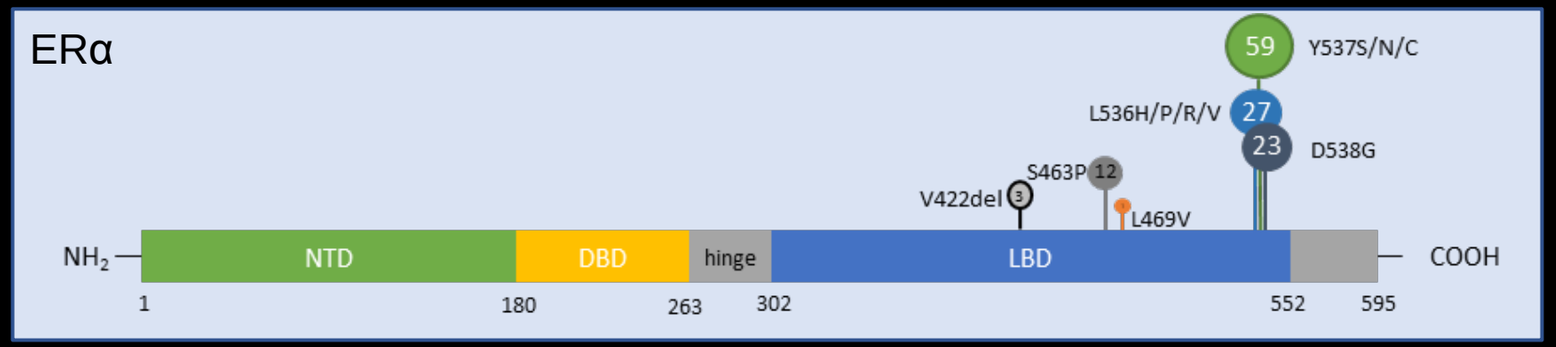
Type of alteration	Frequency N=9645	Ovary/FT N=5594	Uterus N=3101	Cervix N=720	Vulva/Vagina N=216
Total, N (%)	295 (3.1)*	120 (2.1)	160 (5.2)	9 (1.2)	6 (2.8)
Amplification	80 (0.8)	45 (0.8)	34 (1.1)	1 (0.1)	-
Deletion	1 (<0.1)	-	1 (<0.1)	-	-
Fusion	2 (<0.1)	1 (<0.1)	-	-	1 (0.5)
Rearrangements	18 (0.2)	9 (0.2)	9 (0.3)	-	-
Substitution Variants	194 (2.0)	65 (1.2)	116 (3.7)	8 (1.1)	5 (2.3)
Codon 536-538	75 (0.8)	18ᵒ (0.3)	56ᵒ (1.8)	1 (0.1)	-
Other Activating Mut	12 (0.1)	3 (<0.1)	7 (0.2)	-	2 (0.9)

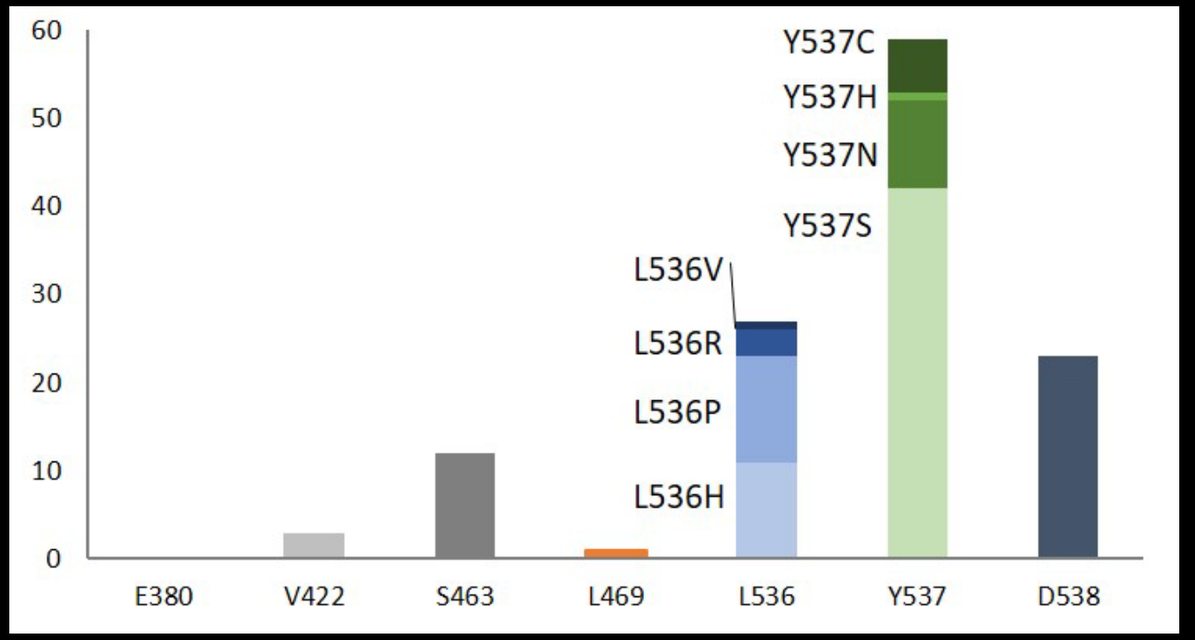
"-": none present, FT: fallopian tube, Mut: mutation *Includes 10 cases with 2 alterations each, ᵒ1 ovarian case & 2 uterine cases w/ 2 codon 536-538 mutations each

ESR1 mutations identified through public databases

	N in dataset	*mutESR1* N (%)	Histology	Ref
LGSOC	26	1 (3.8)	Low-grade serous	1
AACR GENIE				2
Cervix	271	1 (0.4)	Adenocarcinoma	
Ovary	1473	2 (0.1)	2 Endometrioid	
Endometrial	1076	26 (2.4)	26 Endometrioid	
Uterine Sarcoma	199	2 (1.0)	2 ESS	
TCGA				
Uterine Corpus	248	5 (2.0)	5 Endometrioid	3
Ovary		0		4
Cervix		0		5
Uterine Carcinosarcoma	22	1 (4.5)	Carcinosarcoma	6

[1]McIntyre, *Histopathology* 70, 347-358 (2017). [2]A.P.G. Consortium, *Cancer Discov* 7, 818-831 (2017). [3]N. Cancer Genome Atlas Research, *Nature* 497, 67-73 (2013). [4]N. Cancer Genome Atlas Research, *Nature* 474, 609-615 (2011). [5]Merenbakh-Lamin, *Cancer Res* 73, 6856-6864 (2013). [6]Jones, *Nature Comm* 5, 5006 (2014).


ERα
59
Y537S/N/C
L536H/P/R/V
27
23
D538G
S463P
12
V422del
3
L469V
NH2
NTD
DBD
hinge
LBD
COOH
1
180
263
302
552
595


60
50
40
30
20
10
0
Y537C
Y537H
Y537N
Y537S
L536V
L536R
L536P
L536H
E380
V422
S463
L469
L536
Y537
D538

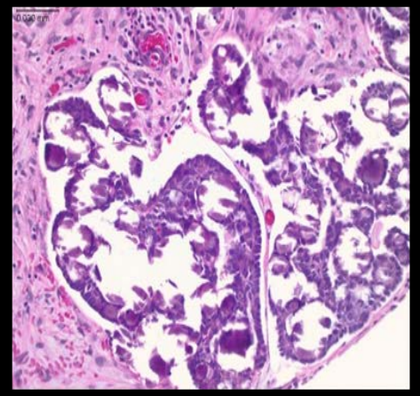
ESR1 mutations are enriched in hormone-responsive histologies

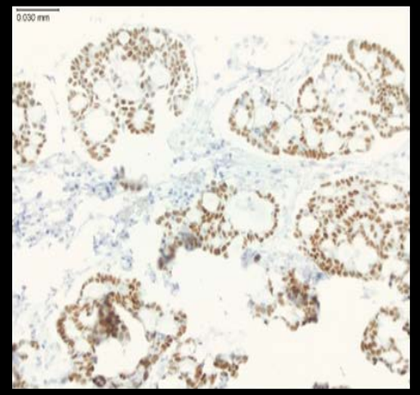
Dataset	Histology	N	*mutESR1* N (%)	p
CGP analysis				
Ovary	serous	3502	12 (0.3)	0.0004
	endometrioid	144	5 (3.5)	
Uterus	serous	446	1 (0.2)	<0.0001
	endometrioid	548	24 (4.4)	
Sarcoma	LMS	421	3 (0.7)	0.09
	ESS	103	3 (3.0)	
AACR GENIE				
Ovary	high-grade serous	687	0	0.006
	endometrioid	57	2	
Uterus	serous	203	0	0.0004
	endometrioid	518	25 (4.8)	
Sarcoma	LMS	113	0	0.018
	ESS	16	2 (12.5)	

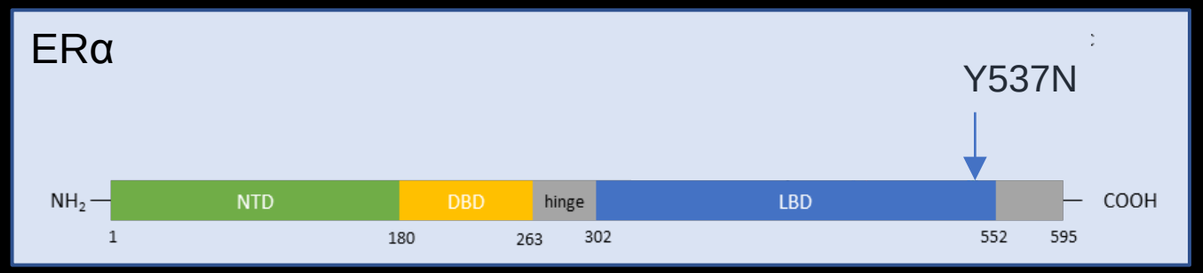
P value calculated using Fisher’s exact test

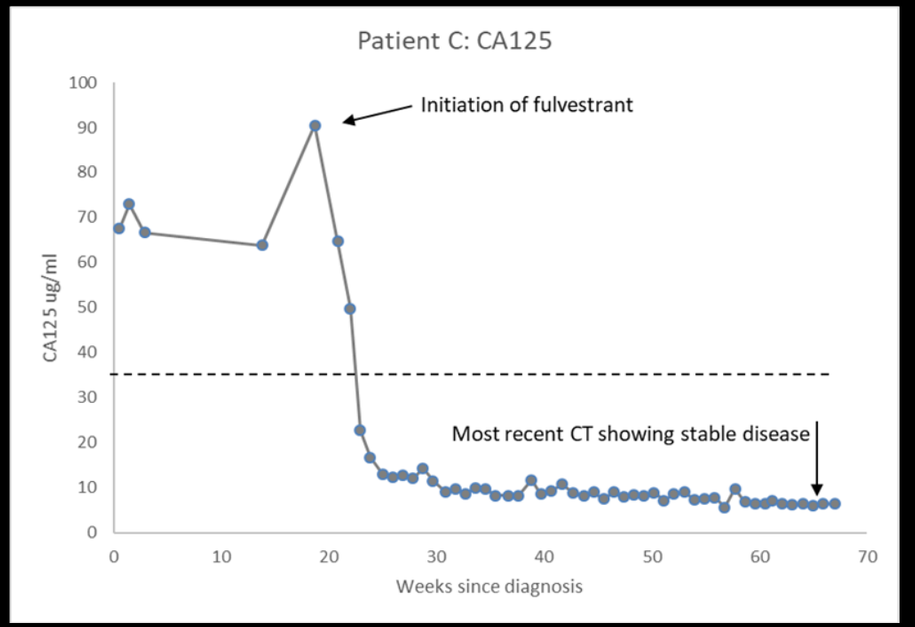
One patient's story:

- 58F diagnosed with low-grade serous papillary carcinoma of gyn origin
  - Neoadjuvant Carboplatin/Paclitaxel
    - 3 cycles
    - CT: No change in calcified peritoneal carcinomatosis, bilateral pulmonary nodules
    - Attempted cytoreductive surgery: tumor engulfing small & large bowel, extensive adhesions

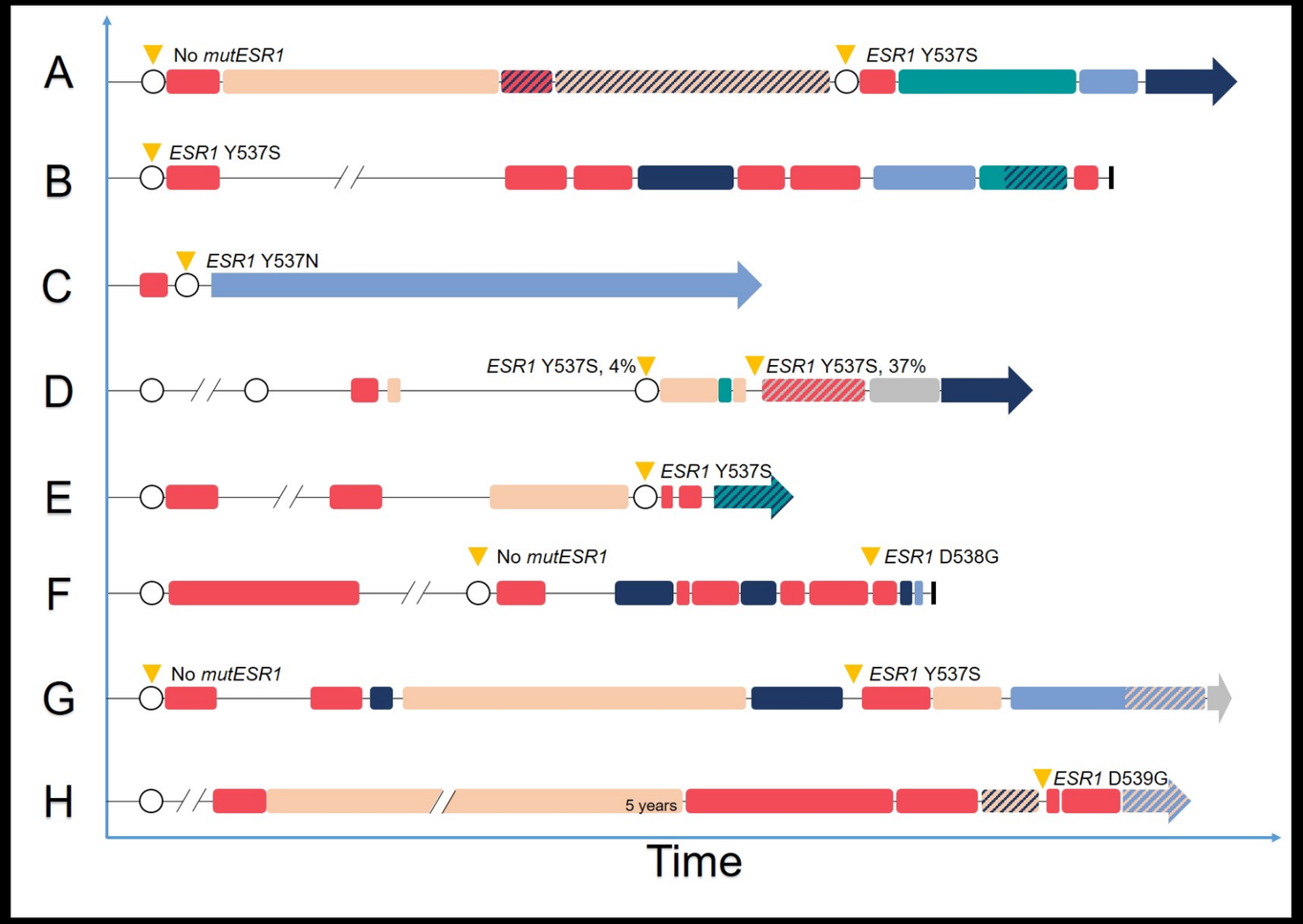






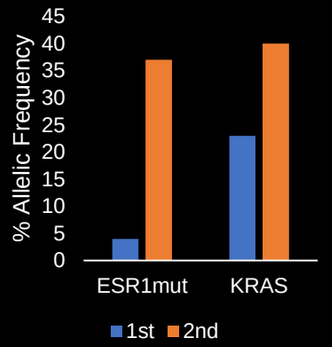


Clinical Relevance of *ESR1* mutations in Gyn Cancers

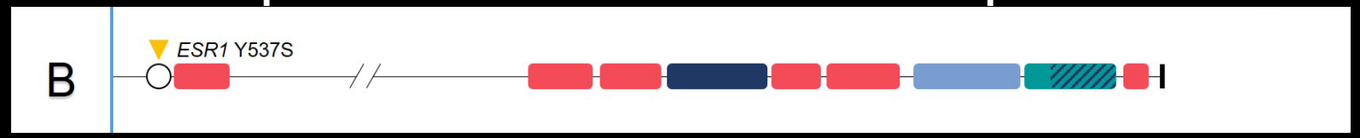


Key Points from Clinical Review

- Prior treatment with aromatase inhibitors in 5 cases
  - Suggests mutation as a mechanism of resistance



- Mutations present in absence of exposure to endocrine therapy



- *mutESR1* tumors may clinically benefit from anti-ER directed therapy

Potential Reasons for Differences in Benefit

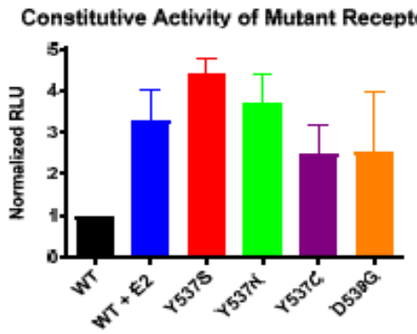
1. the use of hormone therapy in a later phase of the disease course after the cancer has had the opportunity to develop multiple adaptive/resistance mechanisms

2. the influence of co-occurring mutations

3. the specific *mutESR1* present within each tumor

Mutations Confer Partial Resistance

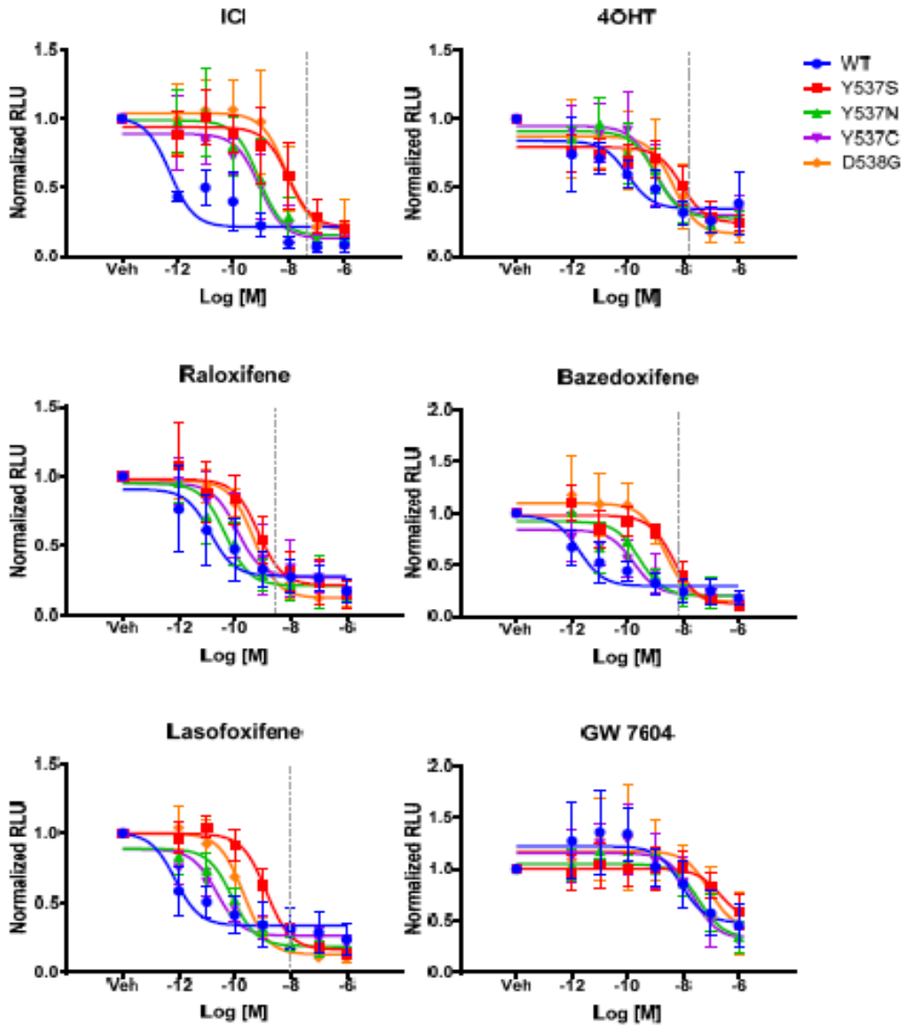
A



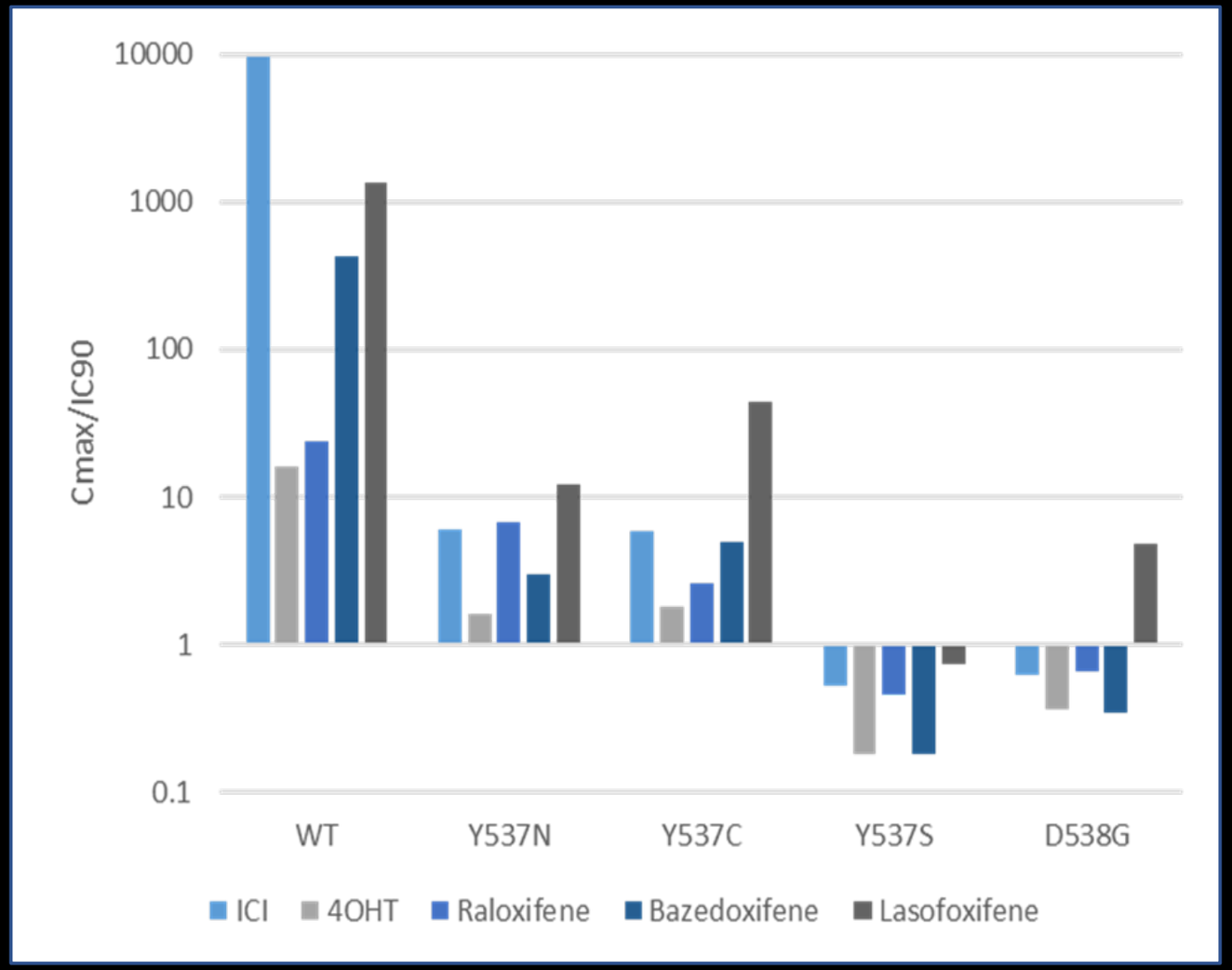
B

	ICI	4OHT	Raloxifene	Bazedoxifene	Lasofoxifene	GW 7604
			IC50 (pM)			
WT	0.53	102.7	13.27	1.867	0.7425	8576
Y537N	830.9	1050	46.98	268.1	82.75	38290
Y537C	887.8	923.1	121.5	166.1	22.69	22270
Y537S	9606	8877	696.8	4548	1351	218900
D538G	8102	4393	487.7	2301	208.5	86870
			IC90 (pM)			
WT	4.76	924	119	16.8	6.68	77200
Y537N	7480	9450	423	2410	745	345000
Y537C	7990	8310	1090	1490	204	200000
Y537S	86500	79900	6270	40900	12200	1970000
D538G	72900	39500	4390	20700	1880	782000

C



Inhibitory Blood Concentrations May Not Be Achievable for some Mutations

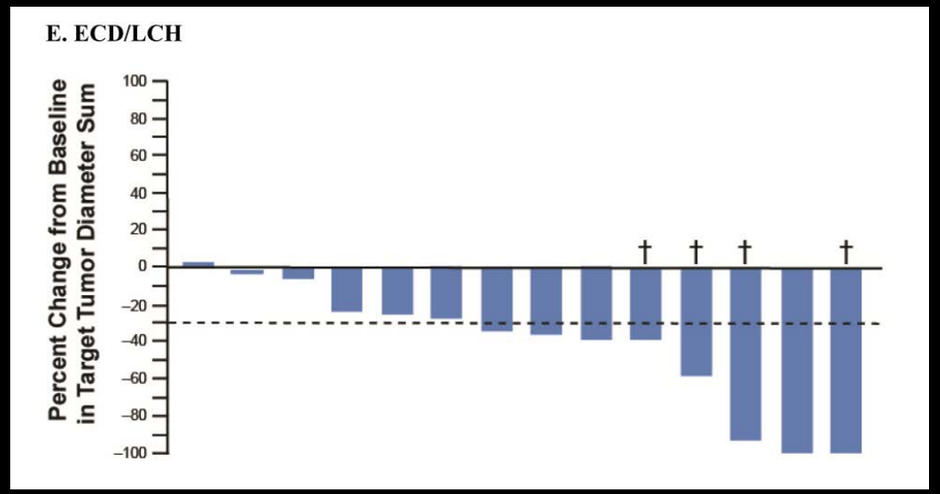


Summary

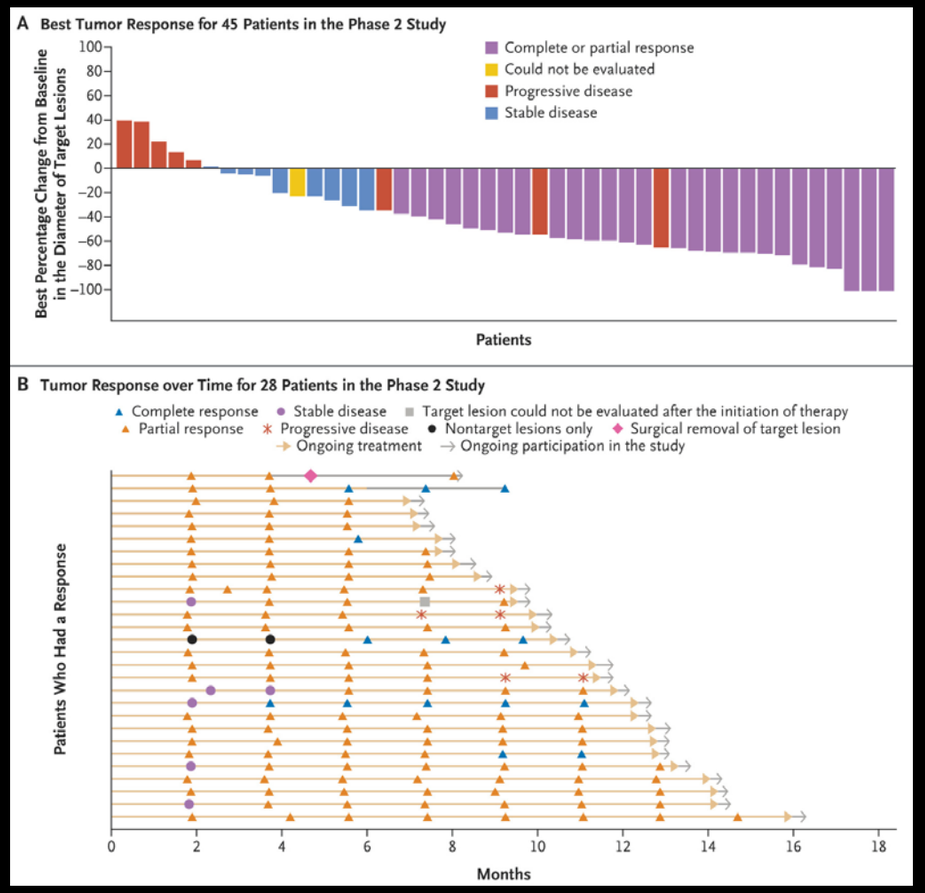
- *ESR1* mutations are rare findings in rare cancers
  - Prevalence may increase with increased use of aromatase inhibitors
  - May be present in the primary tumor
  - Hotspot sequencing may miss some cases of activating mutations
  - Heterogeneity and polyclonality
- Important Treatment implications
  - Resistance to aromatase inhibitors
  - May respond to anti-ER directed therapy (SERMs/SERDs)
  - Relative response may be affected by the mutation(s) present
- Needs
  - Determine the true prevalence and conditions under which they arise
  - Development of drugs that more effectively inhibit mutERα, esp Y537S and D538G

Clinical Trial Implications

- Challenge of recruitment given small numbers
  - Advantage of cooperative group/rare tumor committee



Hyman et al, NEJM 2015



Migden, NEJM 2018

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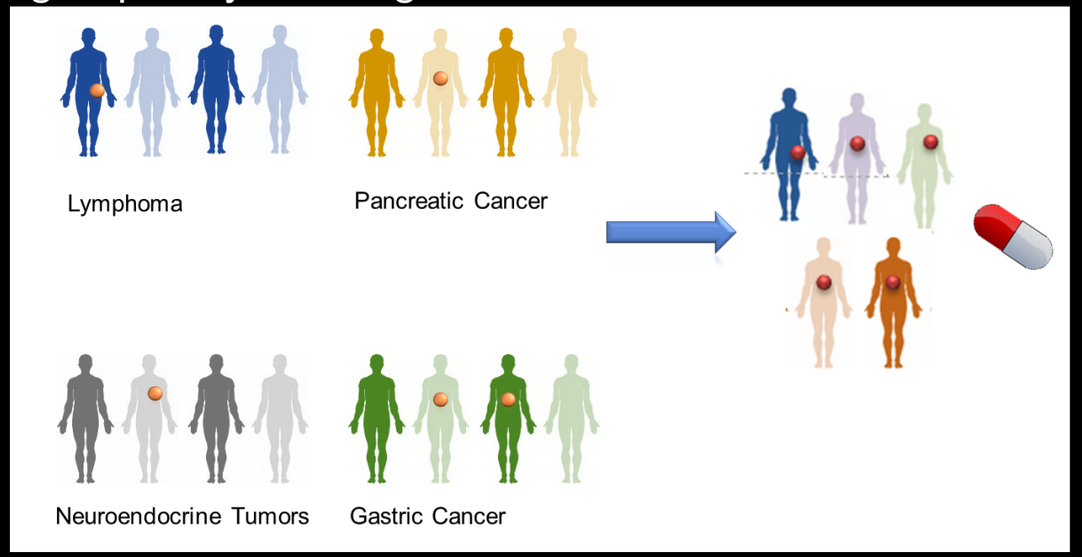
- Modern Trial Designs

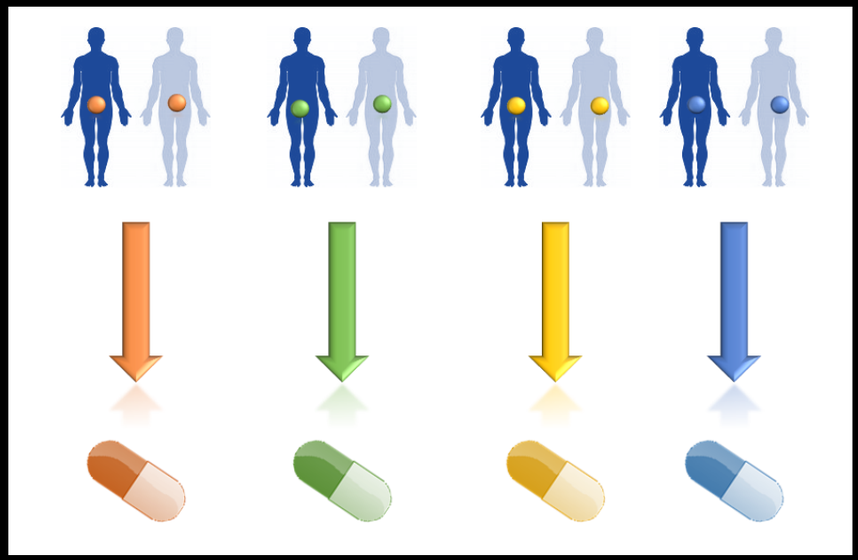
Basket Trials

Multiple tumor/histologic types are grouped by similar genomic alteration



Umbrella Trials

Single tumor type divided by individual genomic alterations



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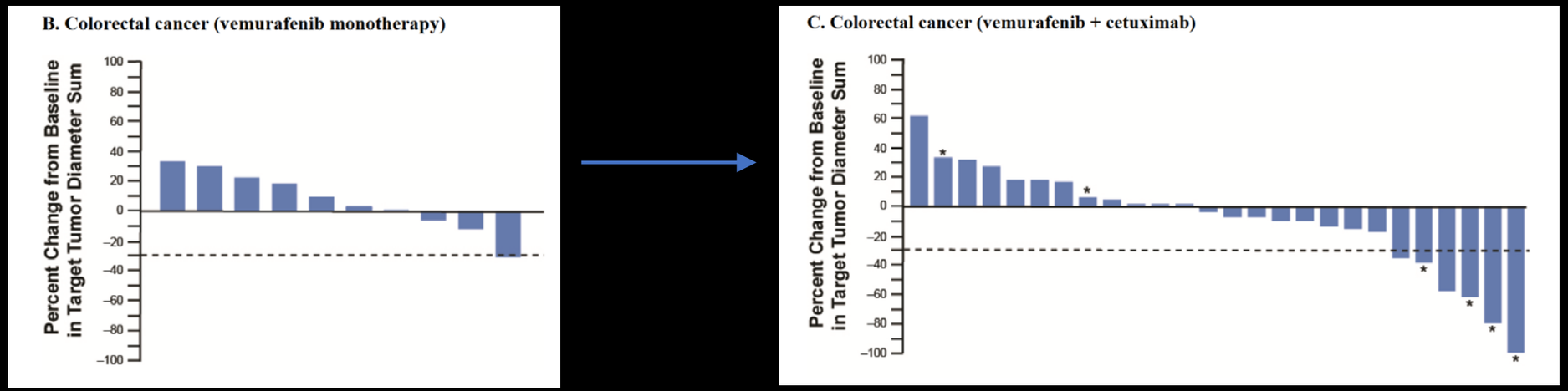
  - Tumor context matters



Hyman, NEJM 2015

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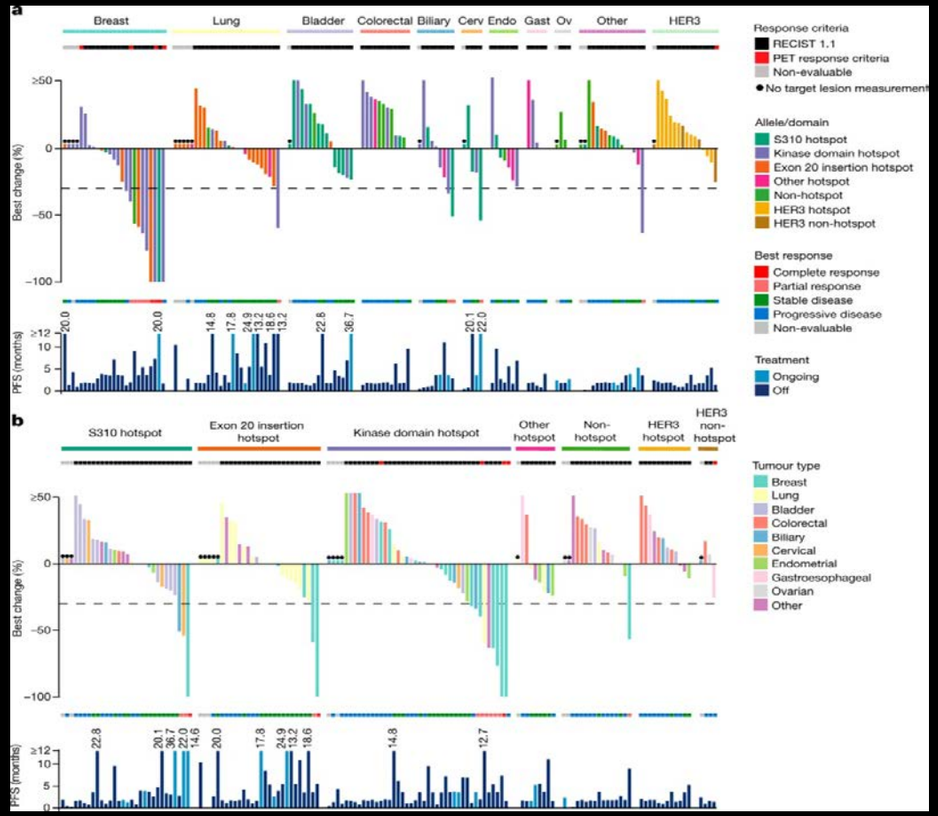

D M Hyman *et al. 2018 Nature*

Clinical Trial Implications

- Challenge of recruitment given small numbers
  - Advantage of cooperative group/rare tumor committee
- Modern Trial Designs
  - Hybrid designs
  - Adaptive designs
- Lessons from prior trials
  - Tumor context matters
  - Not all mutations are the same
- Endpoints need to be selected wisely

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