



NCI Exceptional Responders Initiative: Phenotype to Genotype



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**Special thanks to
all the patients
who donated tissue
and data!!**

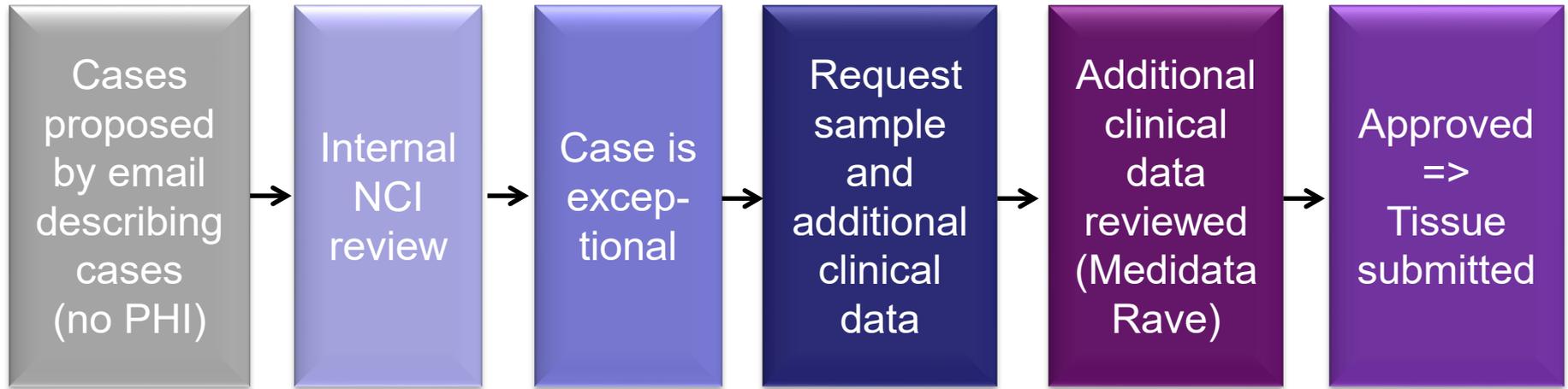
Exceptional Responders Initiative: Rationale

- Up to 10% of patients respond exceptionally well to drugs that do not go on to receive FDA approval for that indication.
- Certain agents deemed 'inactive' are actually active in a subset of patients.
- Specific genomic lesions or patterns of expression might explain these Exceptional Responses.
- Identification of these molecular changes could lead to development of predictive assays.
- Improved biologic understanding of Exceptional Responses may point to new diagnostic/therapeutic avenues.

Exceptional Responders Initiative: Definition

- Complete response to a regimen in which complete response is expected in $< 10\%$ of similarly treated patients
- PR > 6 months in a regimen in which PRs > 6 months are expected in $< 10\%$ of patients with similar disease treated with same or similar regimen
- Standard treatment with response lasting 3X longer than median response duration in clinical trials of that agent.

Screening for Potential Exceptional Responders



Cases Accepted for In Depth ER Analysis

- ER cases accepted for further review: 478
- ER Cases with preliminary approval: 224
- Not approved after review: 184
- Lost to follow-up: 70
- Approved cases 119

Cases Accepted for In Depth ER Analysis

Demographics: n=119 (12/13/2018)

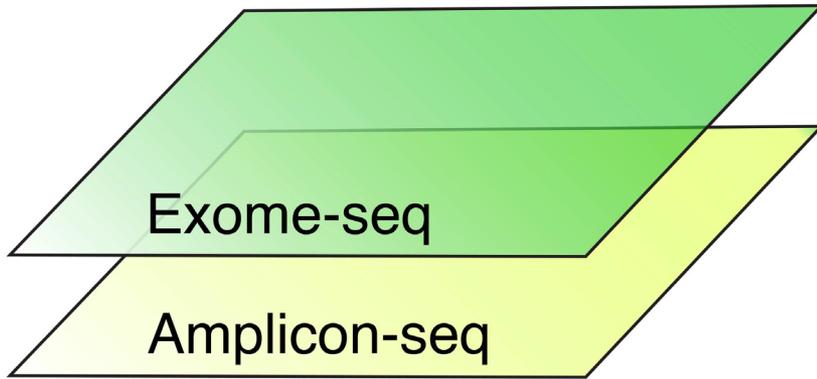
- Male: 57
- Female: 62
- On a clinical trial: 35 (29.4%)
- Age at diagnosis: 57 (22-89), mean (range)

- Tumor histology:

Colorectal	22	Renal	5
Esophagogastric	18	Urothelial	4
Lung	11	Hepatobiliary	4
Central Nervous System	10	Pancreas	3
Breast	10	GIST	2
Ovary	9	Soft Tissue Sarcoma	2
Other GYN	5	Sq Head/Neck	1
Melanoma	6	Papillary Primary, Sqam. anal, Merkel cell, small cell colon CA, prostate CA	1 ea.

Mutli-platform Genomic Profiling of Exceptional Responders

Previous studies of
Exceptional Responders





Exceptional Responder Level of Evidence



- **Level 1 (25% of cases)**
Molecular evidence relevant to therapy and plausible hypothesis from literature.
- **Level 2**
Molecular evidence possibly relevant to therapy but weak/no literature support
- **Level 3**
Genomic analysis uninformative

Exceptional Responder “Baskets”



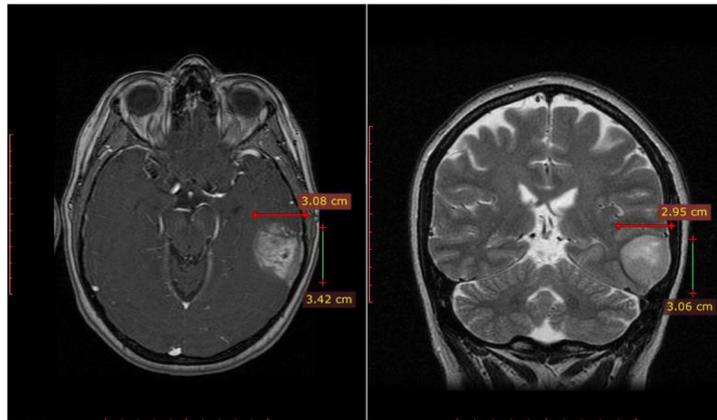
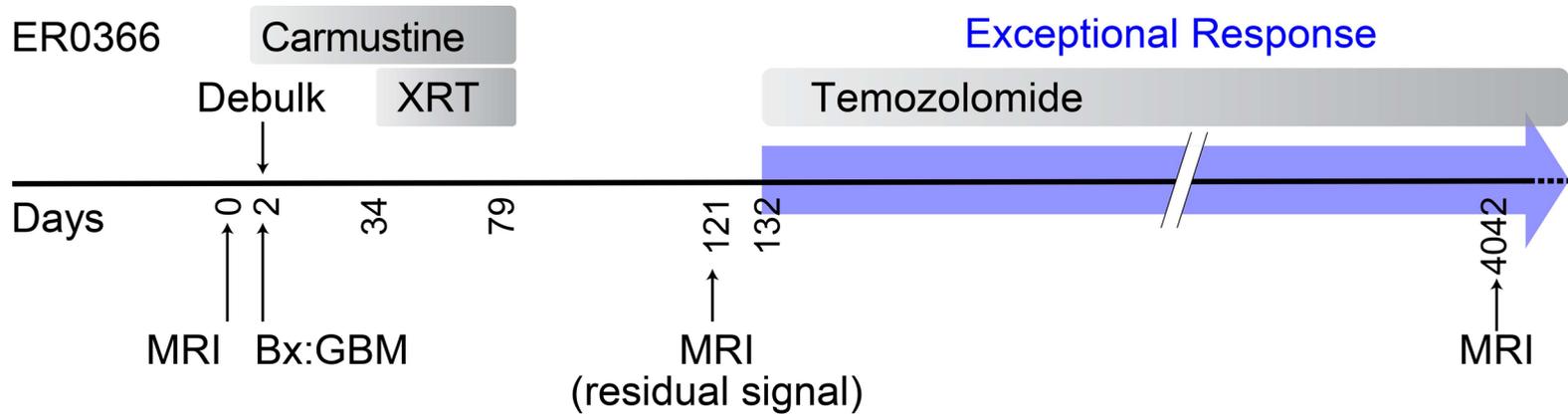
- DNA damage
- Signaling
- Immune
- Prognostic genetics



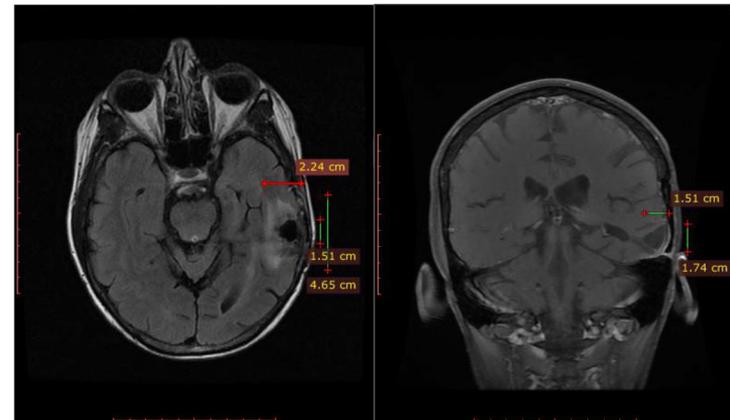
Exceptional Responses to DNA Damaging Agents

ER0366 GBM: Clinical

- 58 year old female
- Diagnosis: Glioblastoma multiforme (WHO Grade 4) at age 48
- ER induced treatment: Gliadel wafer + XRT + Temozolomide
- ER outcome: CR for greater than 84 months



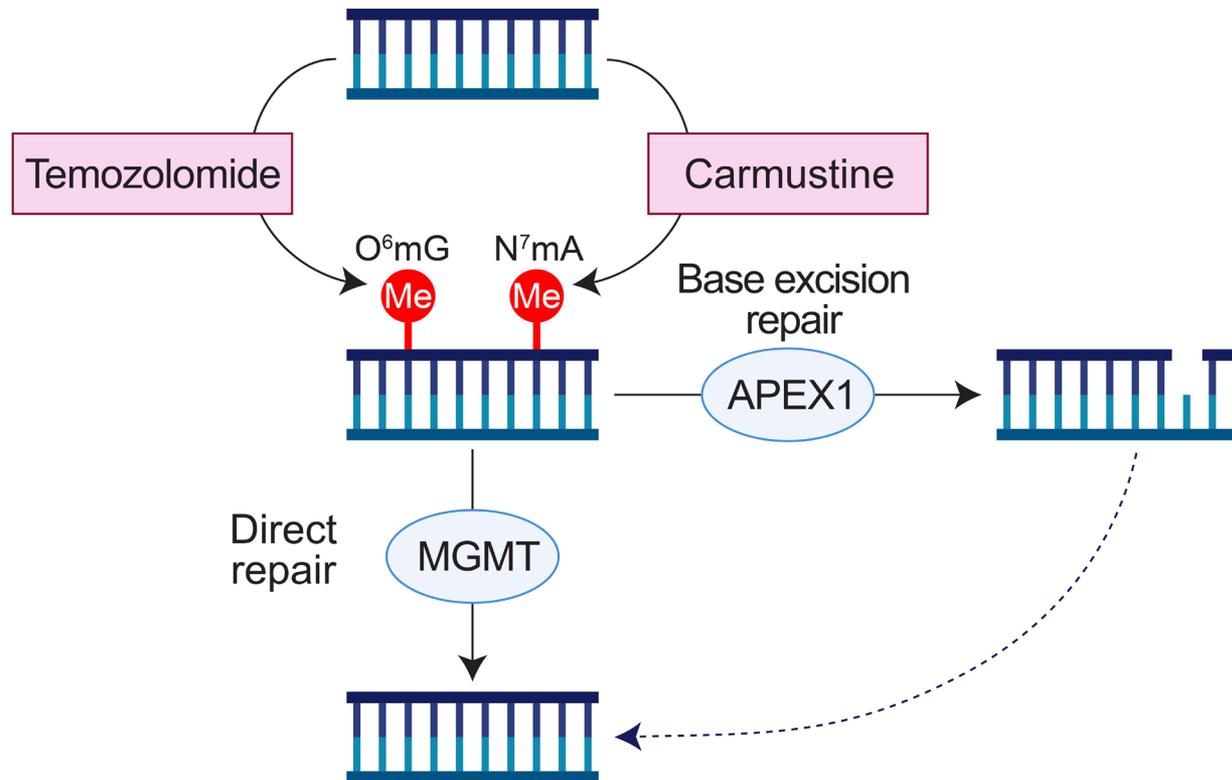
Pre-treatment



11yr Post-treatment

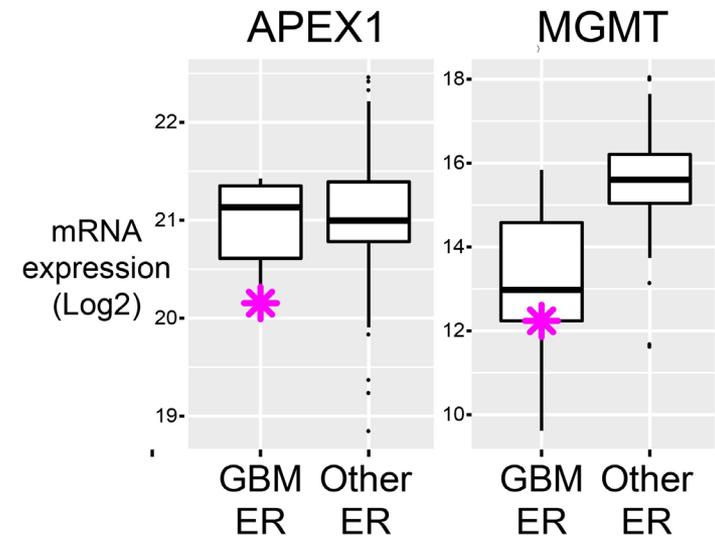
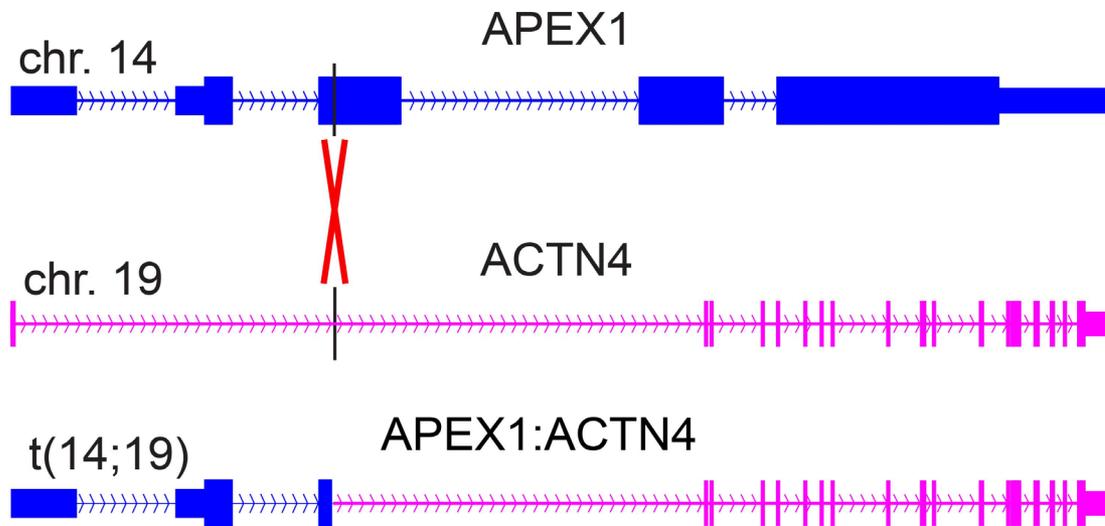
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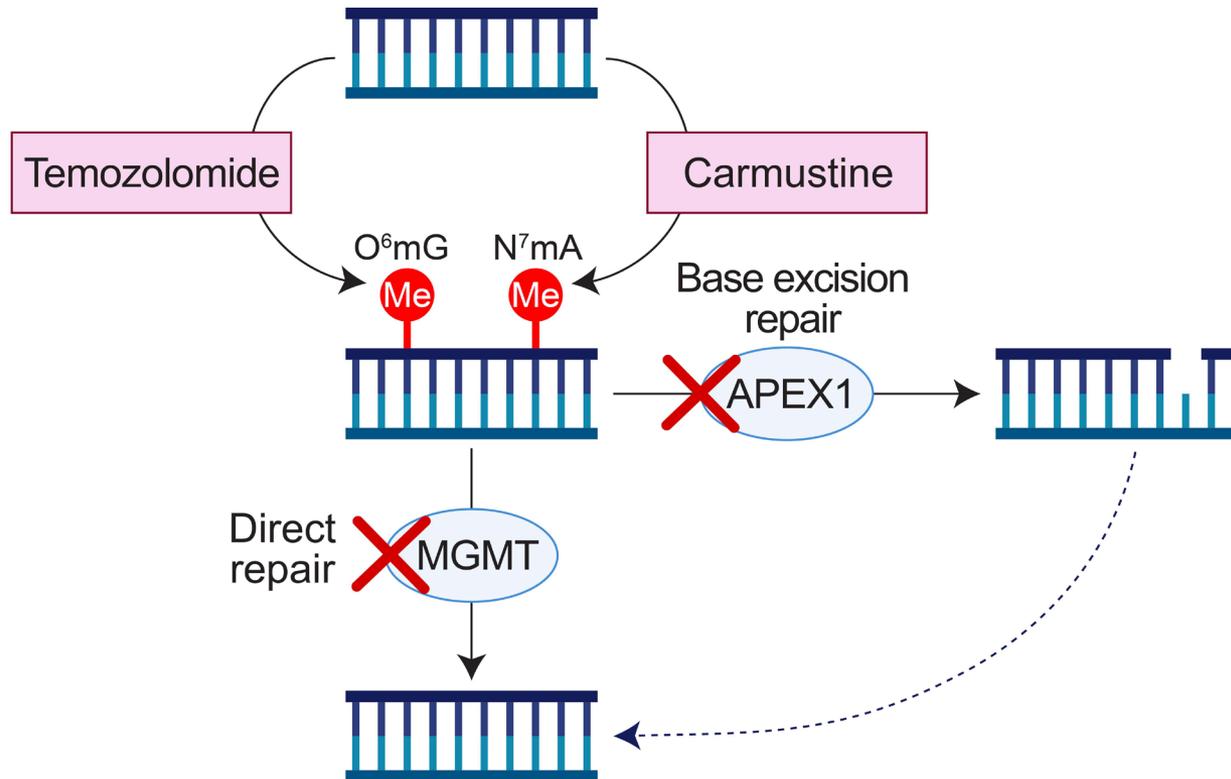
ER0366 GBM: Molecular

- Somatic translocation of APEX1 (apurinic/apyrimidinic endodeoxyribonuclease) to ACTN4
- Low expression of APEX1 by RNA-seq => translocation likely inactivating
- Low expression of MGMT by RNA-seq MGMT promoter hypermethylation



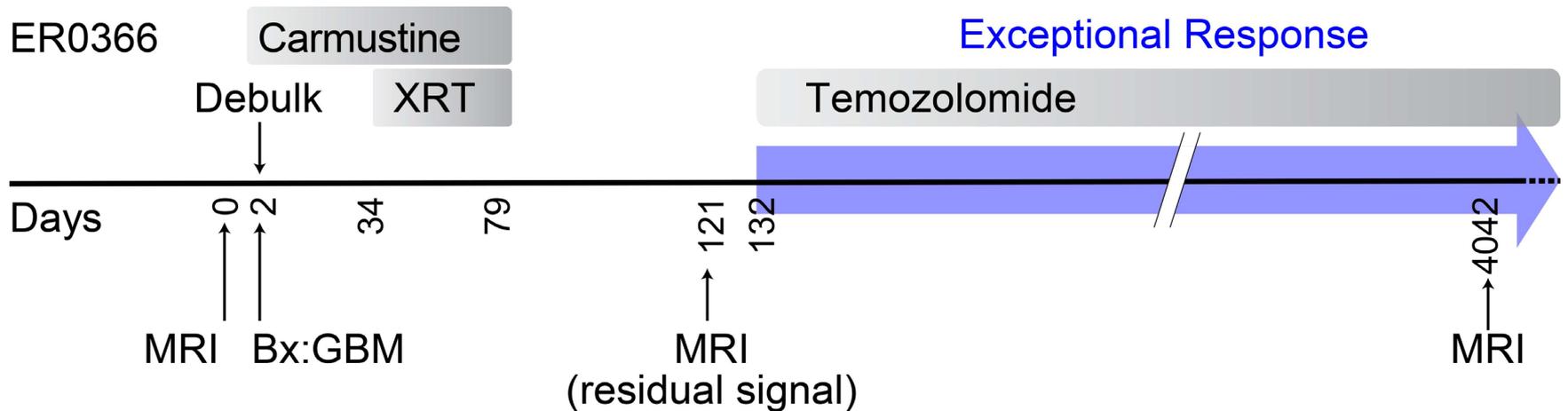
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=> translocation likely inactivating
- Low expression of MGMT by RNA-seq
MGMT promoter hypermethylation



ER0366 GBM: Mechanism

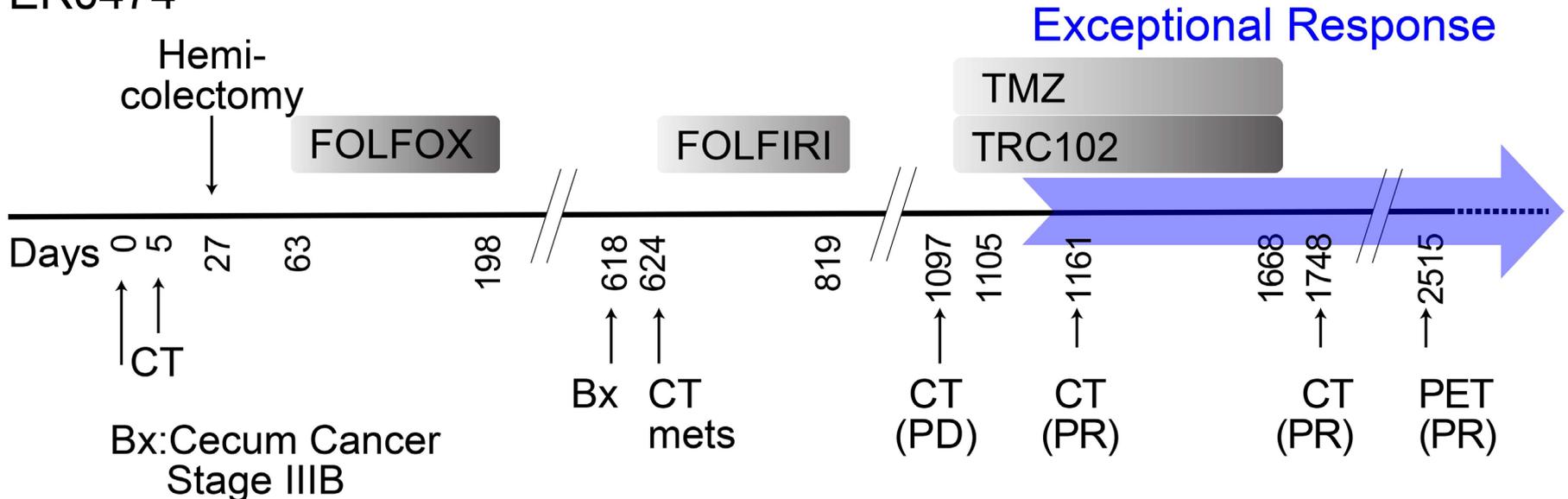
- Synthetic lethality of Temozolomide and Carmustine in a tumor with defective base excision repair and direct repair pathways



ER0474 Colorectal Carcinoma: Clinical

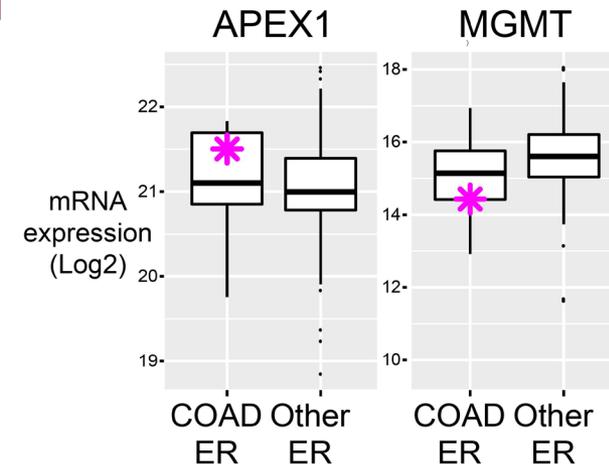
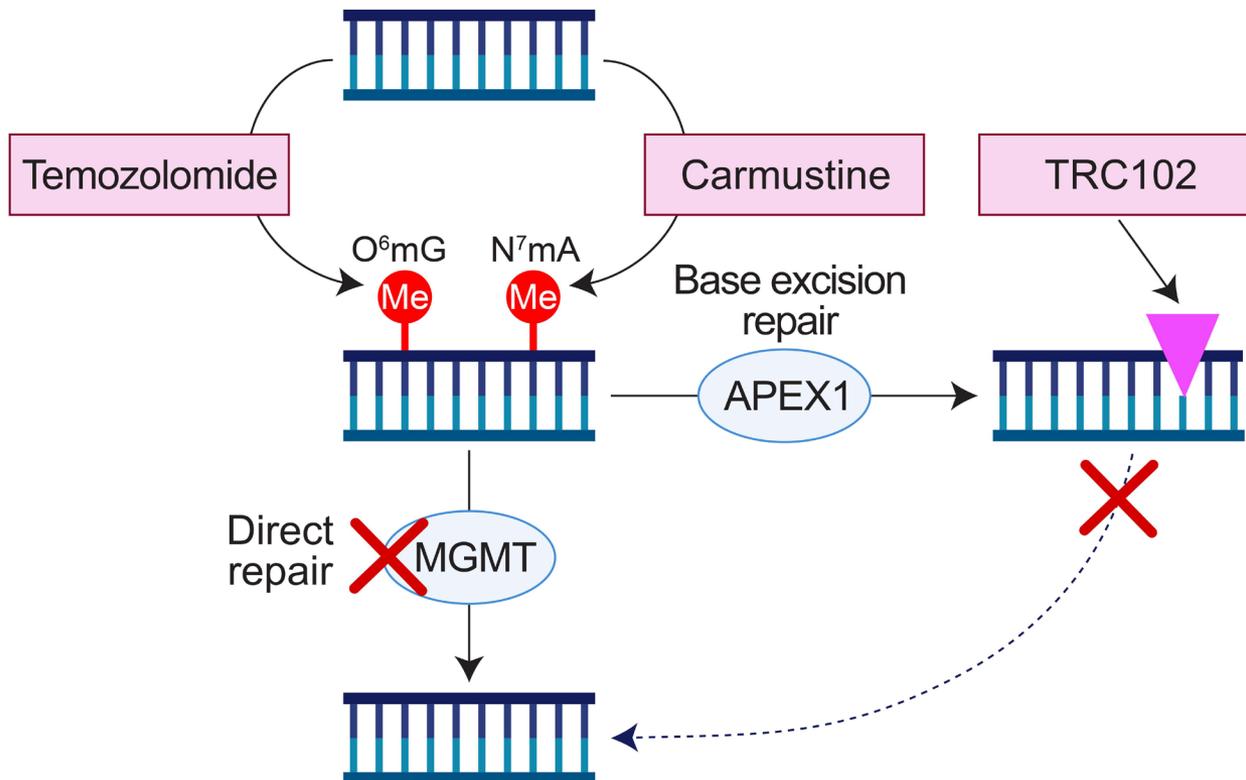
- 66 year old male
- Diagnosis: Colorectal carcinoma of the cecum, Stage IIIB
- Relapse following FOLFOX and FOLFIRI
- ER induced treatment: Temozolomide plus TRC102
- ER outcome: Ongoing PR for greater than 47 months

ER0474



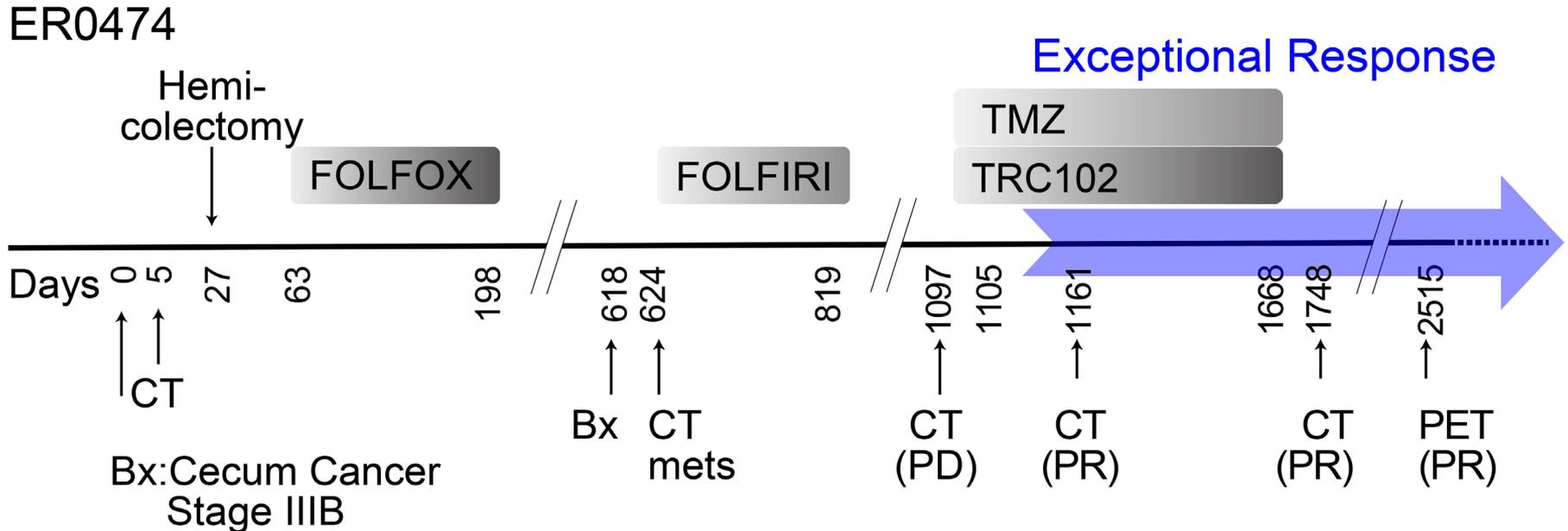
ER0474 Colorectal Carcinoma: Molecular

- MGMT promoter methylation and low expression
- High expression of Topoisomerase 2A/B
 - => TRC102-modified DNA is a substrate for Topo2, but lesion can't be resolved => DNA damage



ER0474 Colorectal Carcinoma: Mechanism

- Synthetic lethality of Temozolomide and TRC102 in a tumor with MGMT silencing.

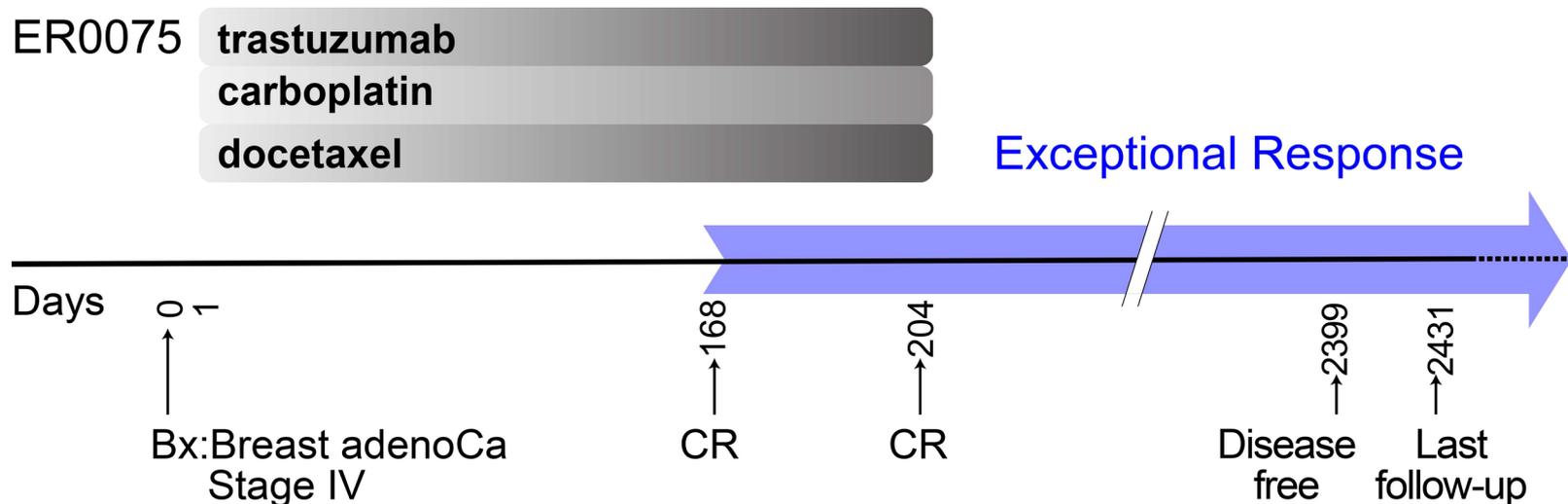




Exceptional Responses to Signaling Inhibitors

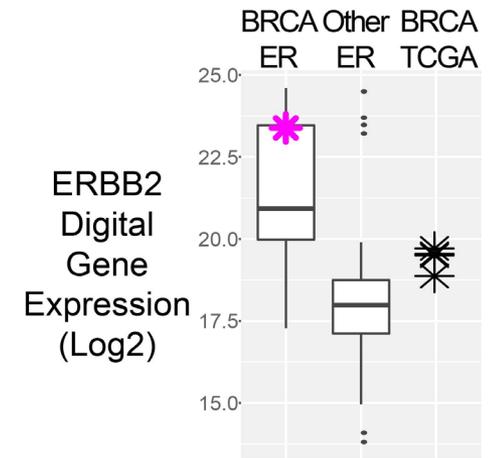
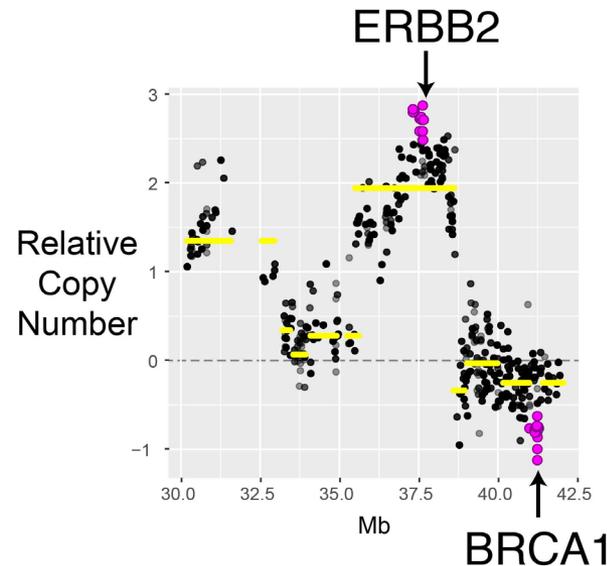
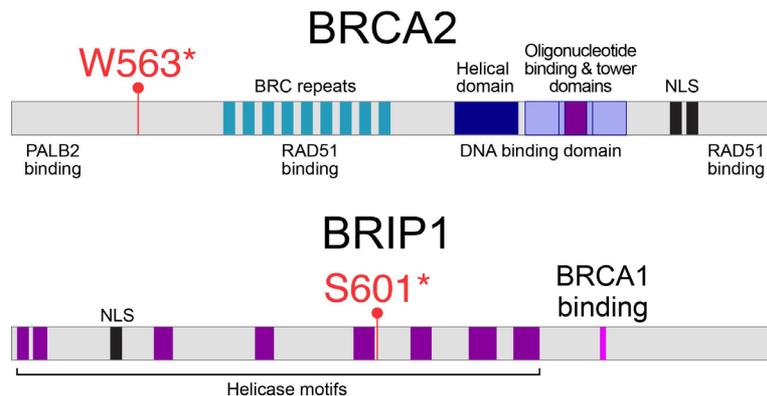
ER0075 Breast Cancer: Clinical

- 63 year old female
- Diagnosis: Metastatic carcinoma of the breast
bilateral breast tumors + multiple metastases to liver and bone
ER+, PR+, HER2+,
- ER induced treatment: carboplatin + docetaxel + trastuzumab
- ER outcome: CR for 84 months
- Published CR rate is 17%, duration is 9.4 months



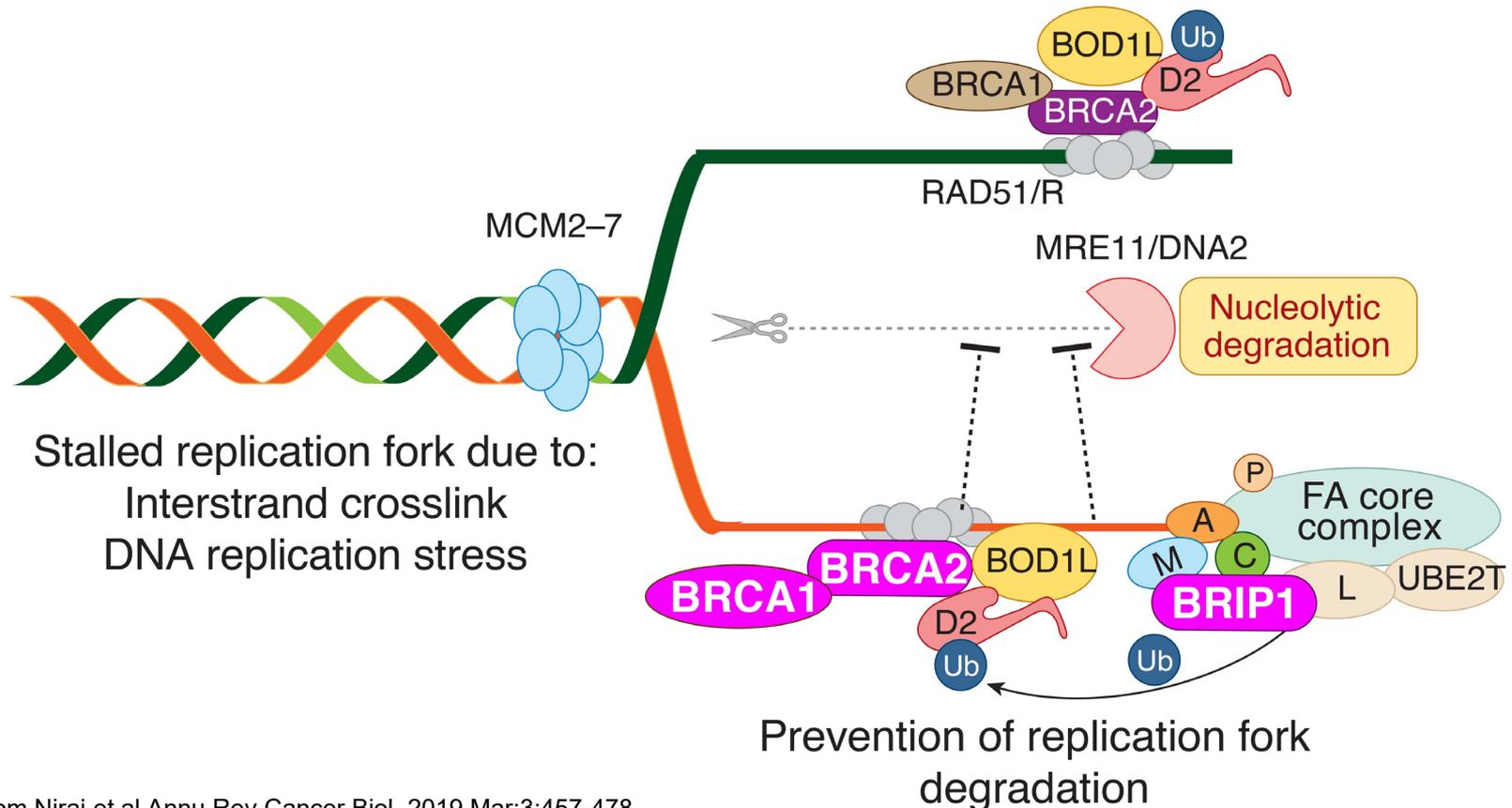
ER0075 Breast Cancer: Molecular

- Somatic BRCA2 deleterious mutation
- Somatic BRIP1 deleterious mutation
- BRCA1 homozygous deletion
- Her2 amplification (22x copy number) and overexpression



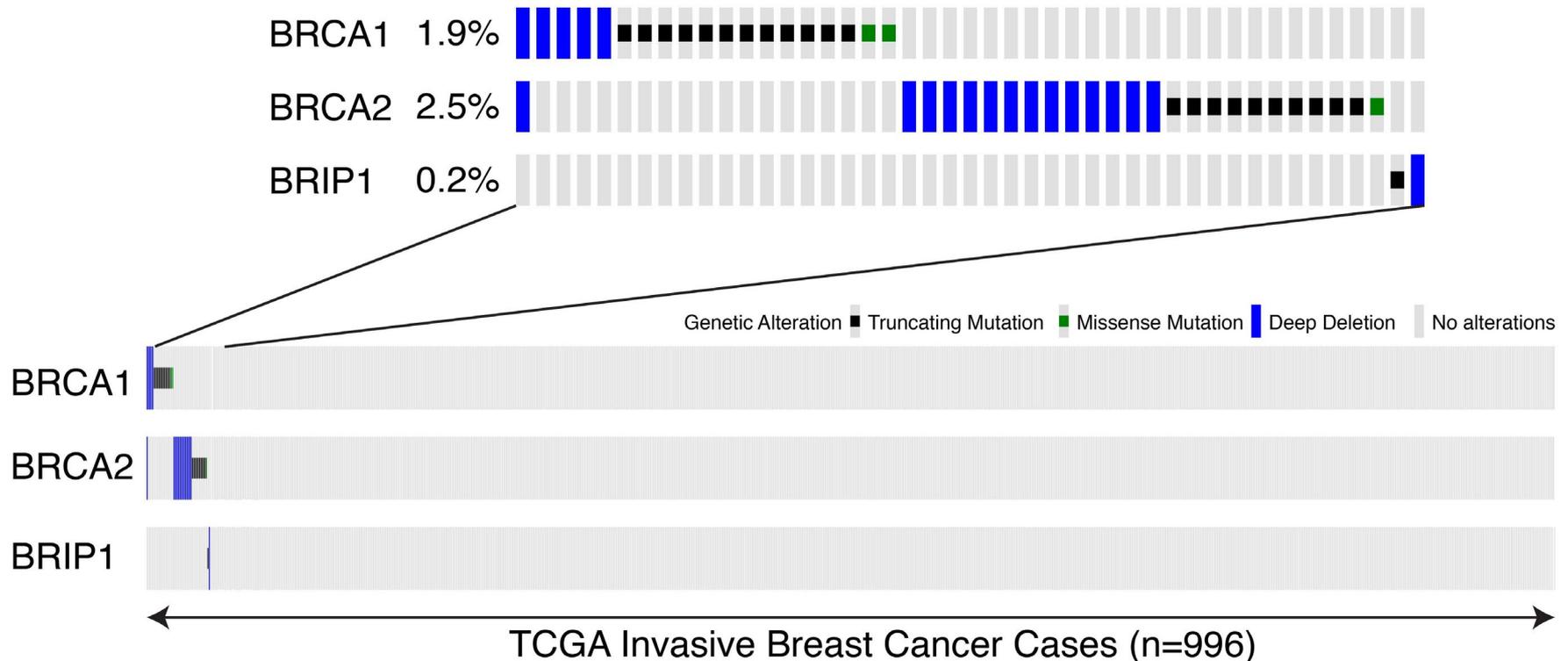
ER0075 Breast Cancer: Molecular

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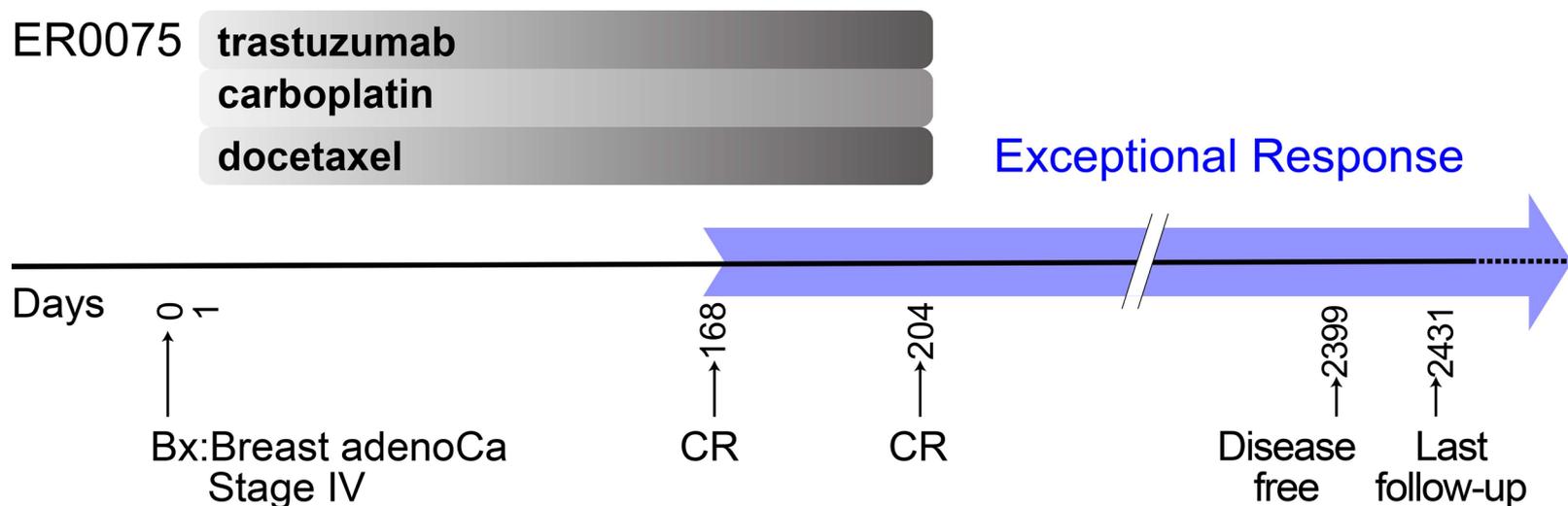
ER0075 Breast Cancer: Molecular

- Somatic BRCA2 deleterious mutation
- Somatic BRIP1 deleterious mutation
- BRCA1 homozygous deletion
- Her2 amplification (22x copy number) and overexpression



ER0075 Breast Cancer: Mechanisms

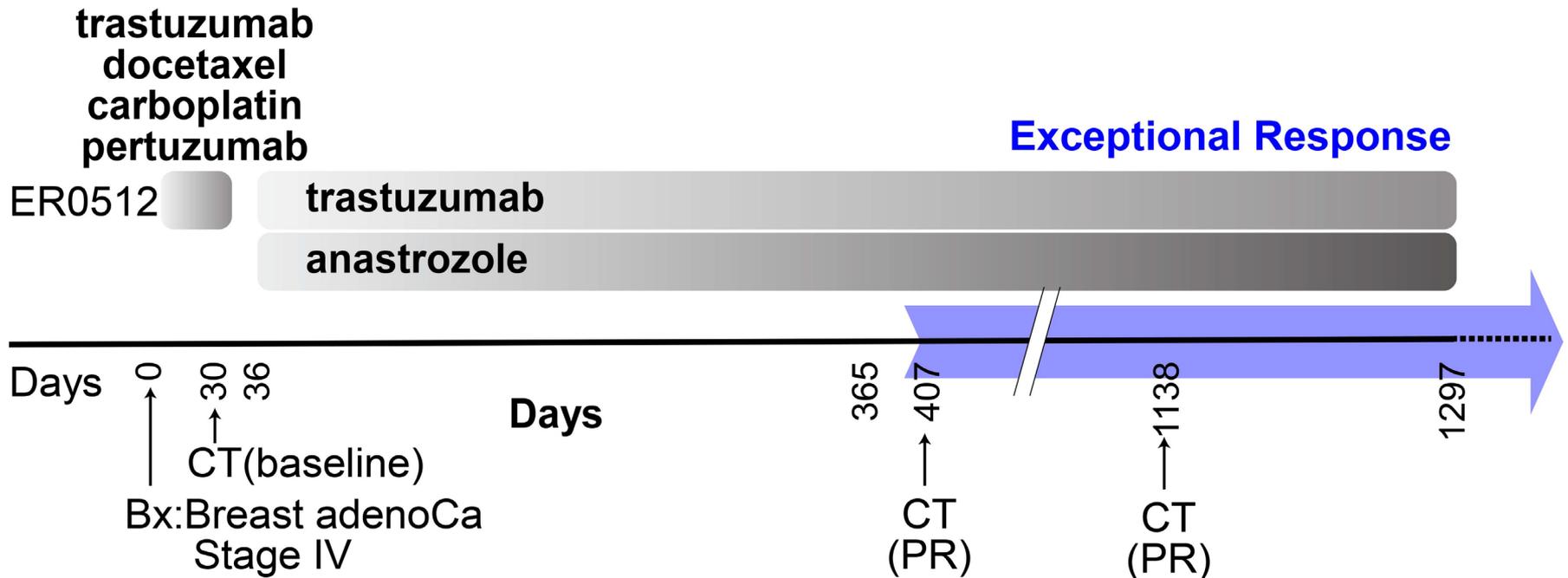
- Her2 amp
=> sensitivity to trastuzumab
- DNA repair defect (BRCA1, BRCA2, BRIP1 inactivation)
=> sensitivity to carboplatin
- High tumor proliferation rate
=> sensitivity to carboplatin + docetaxel
- Immune activation (CD8⁺ TIL)





ER0512 Breast Adenocarcinoma: Clinical

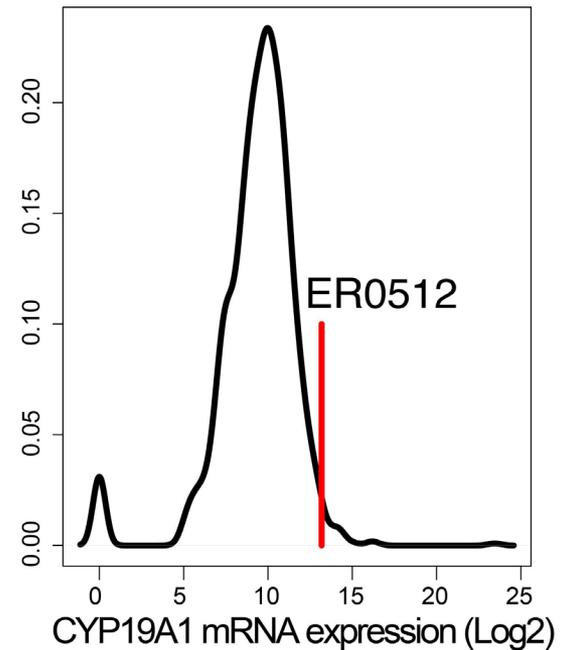
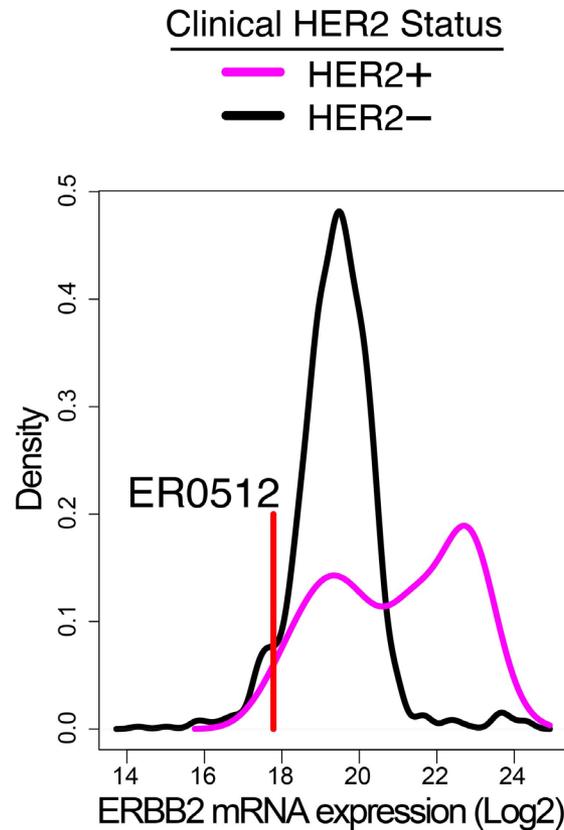
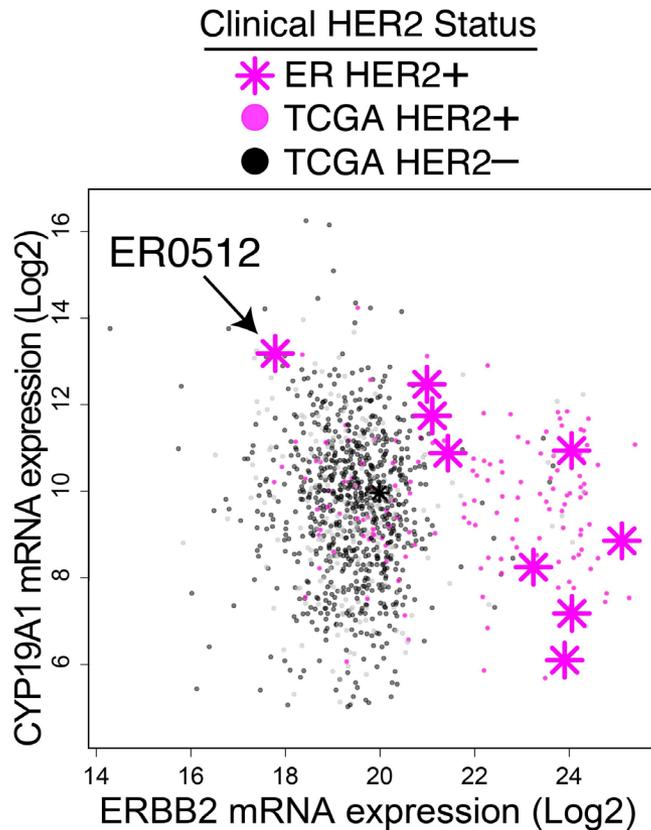
- 63 year old female
- Diagnosis: Breast adenocarcinoma Stage IV
- HER2+ by clinical assay
- ER induced treatment: Anastrozole
- ER outcome: PR for greater than 35 months





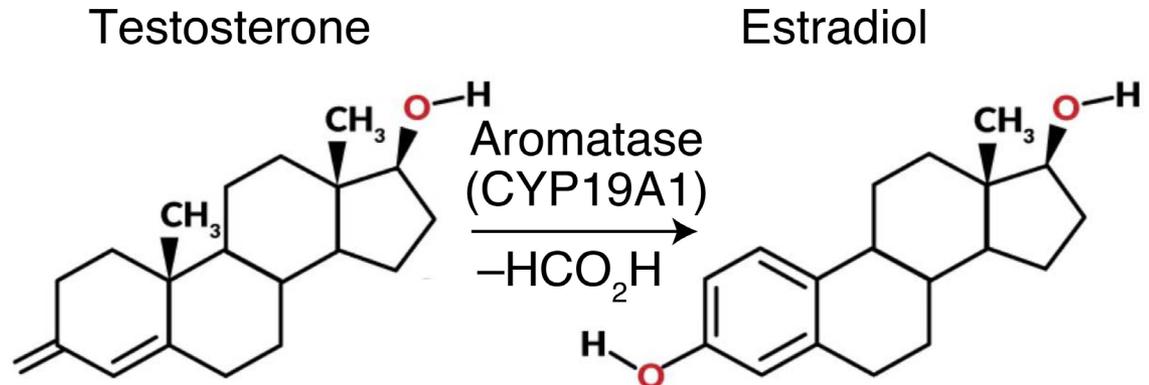
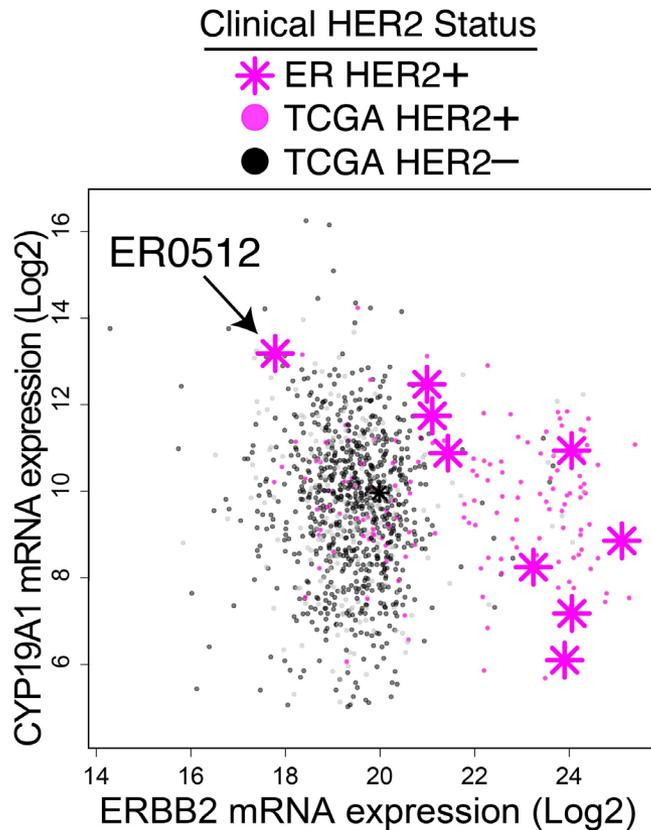
ER0512 Breast Adenocarcinoma: Molecular

- High level HER2 amplification but HER2 expression silenced => Trastuzumab is a red herring!
- Extremely high CYP19A1 (aromatase) expression



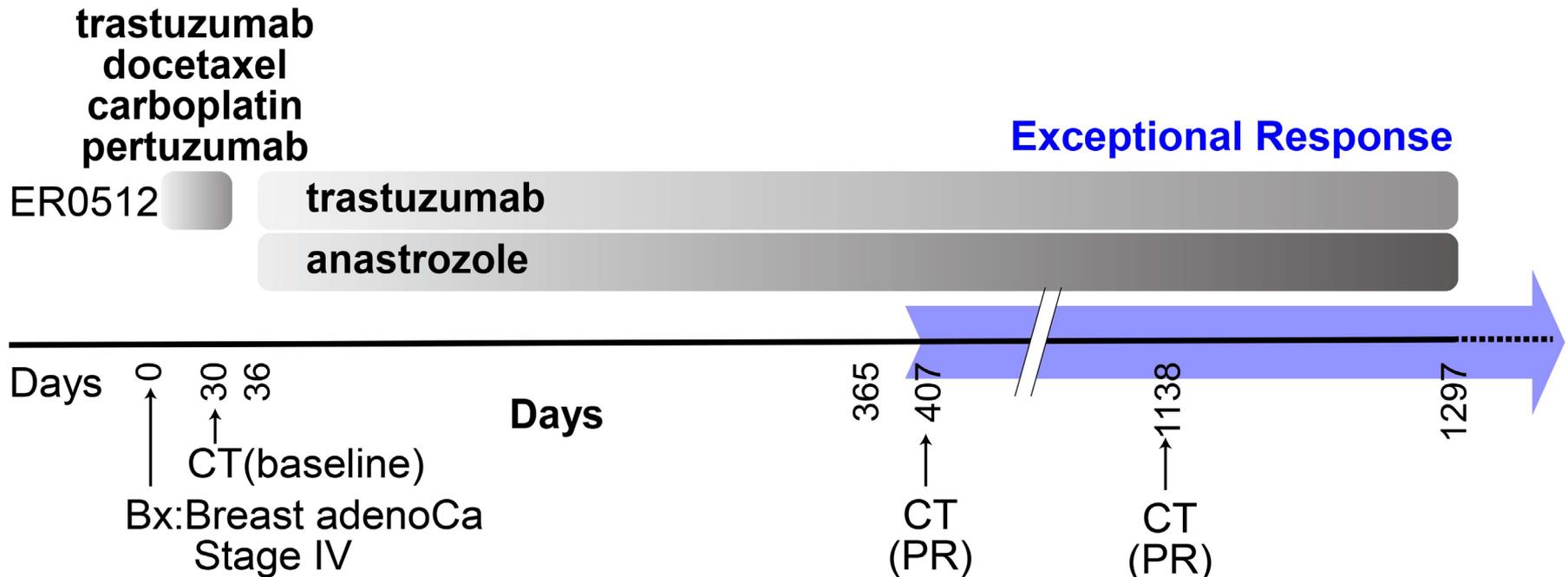
ER0512 Breast Adenocarcinoma: Molecular

- High level HER2 amplification but HER2 expression silenced => Trastuzumab is a red herring!
- Extremely high CYP19A1 (aromatase) expression



ER0512 Breast Adenocarcinoma: Mechanisms

- Response to anastrozole due to hyperaddiction of a tumor to estrogen derived from high expression of aromatase.





Exceptional Responses Attributable to Immune Engagement



Enrichment of Activated NK Cells and B Cells in Exceptional Responder Tumors

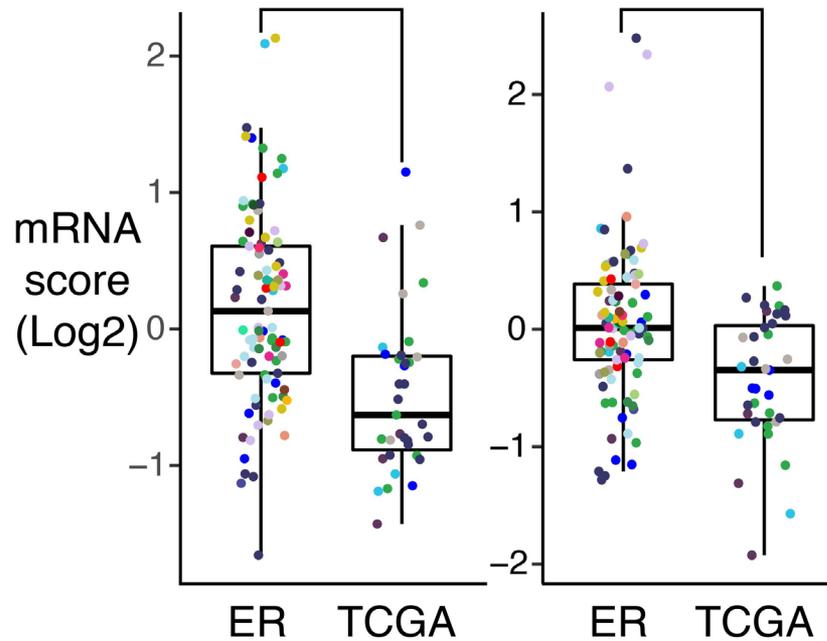
NK CD56-dim
(Activated NK)

cell score

$p=0.0002$
($p=0.0036^{**}$)

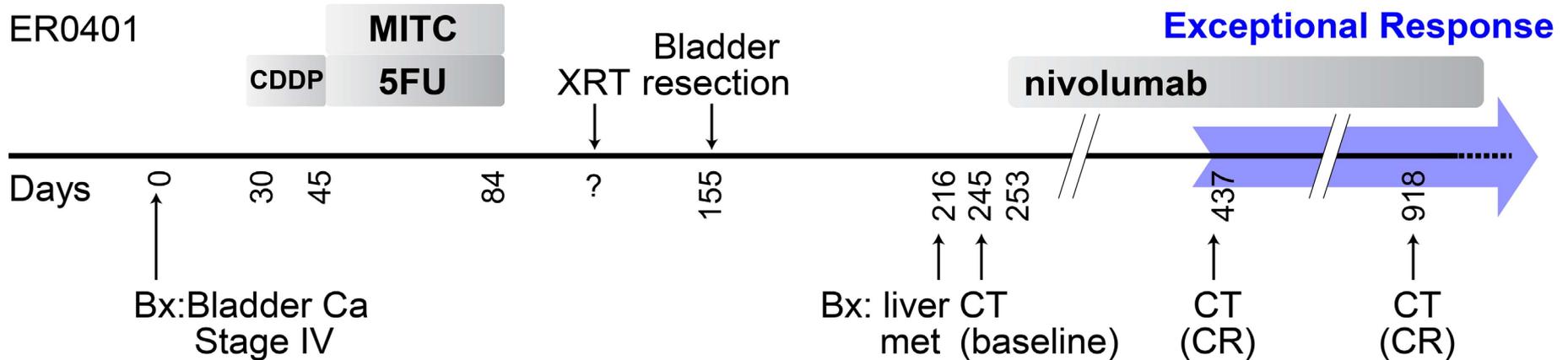
B cell score

$p=0.004$
($p=0.079$)



ER0401 Bladder carcinoma: Clinical

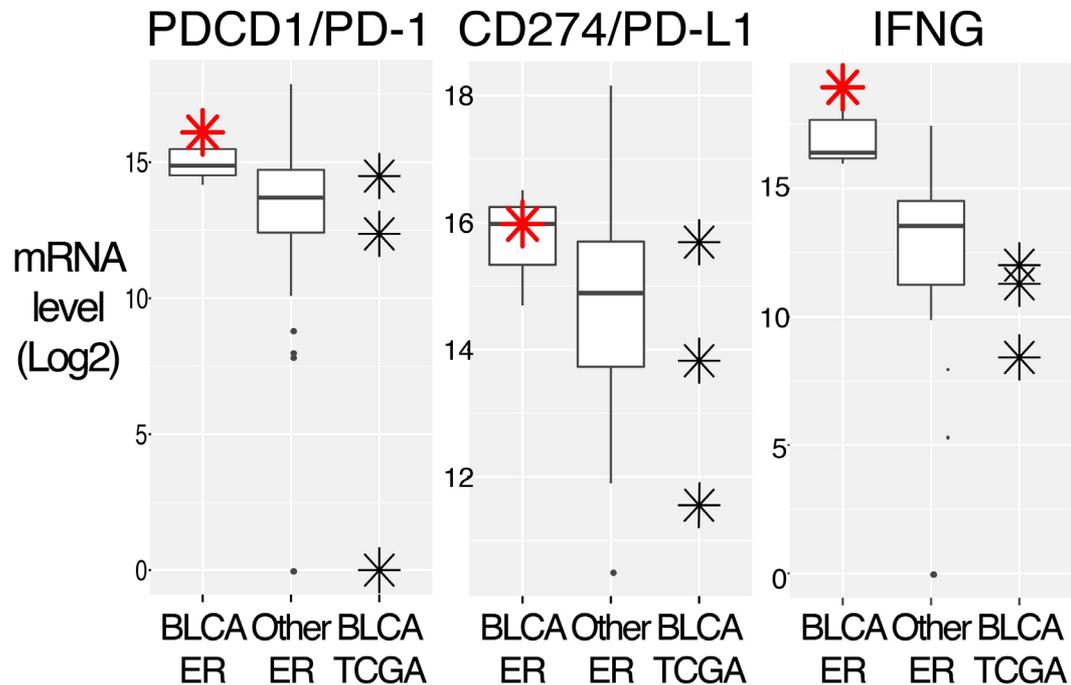
- 75 year old male
- Diagnosis: Bladder carcinoma Stage IV
- Metastatic disease following neoadjuvant bladder resection
- ER induced treatment: Nivolumab
- ER outcome: Ongoing CR for greater than 16 months





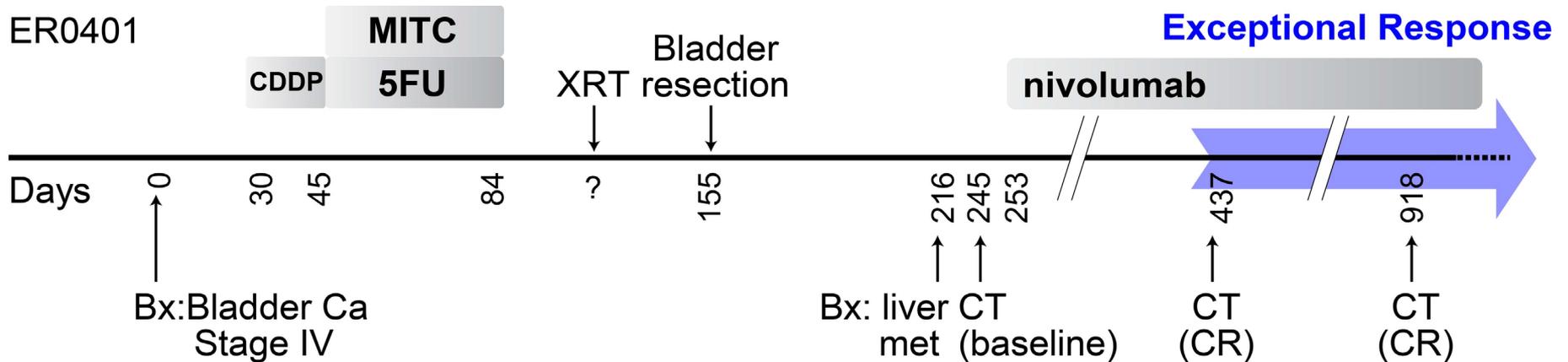
ER0401 Bladder carcinoma: Molecular

- Highest expression of PD-1 among ER cases
- Expression of PD-L1
- Highest expression of IFNG
- High level amplification of IFNG locus



ER0401 Bladder carcinoma: Mechanisms

- Exceptional response to immune checkpoint inhibitor in a tumor with hyperproduction of IFNG and PD-1⁺ T cells

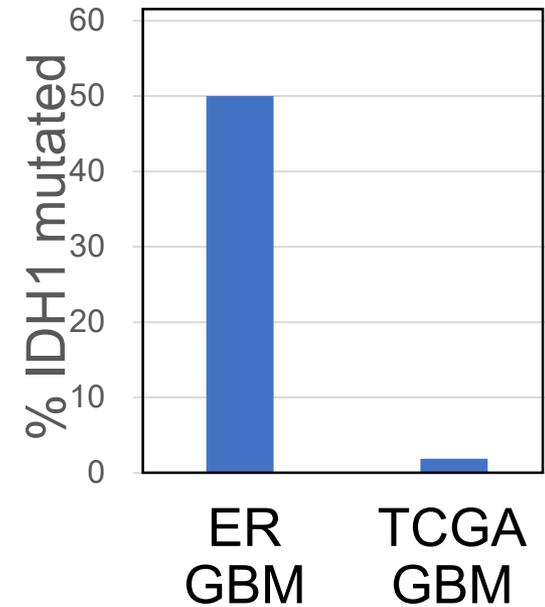




Exceptional Responses Attributable to Prognostic Genetics

Frequent Mutations in IDH1, ATRX, and TP53 in Exceptional Responder High Grade Gliomas

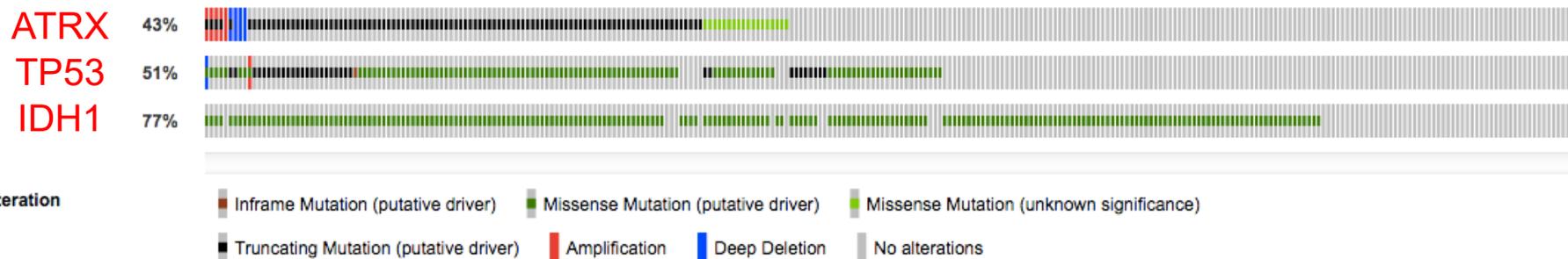
Disease	ERRPC ID	Age Gender	Treatment	Micro Sat	IDH1 R132	Tel maint ^a	TP53
GBM	366	48 F	TMZ, RT	S	-	TERTp	-
GBM (Astrocy G4)	431	51	TMZ	S	-	TERTp	-
GBM	484	76	TMZ	S	-	TERTp	mut
GBM (Astrocy G4)	187	26	Cediranib Cilengitide	S	H	-	mut
GBM	394	29	TMZ, RT	S	H	ATRX M1839K	mut
GBM	486	35	TMZ, Irinotecan	S	C	ATRX fs	mut
Astrocytoma (G3)	151	45	Irinotecan Bevacusumab	S	H	ATRX fs	mut
Astrocytoma (anaplastic G3/4)	305	28	Carbozantinib	S	H	ATRX I2050N	mut
Astrocytoma (G3/4)	256	25	TMZ, Irinotecan Bevacizumab	I	-	-	mut



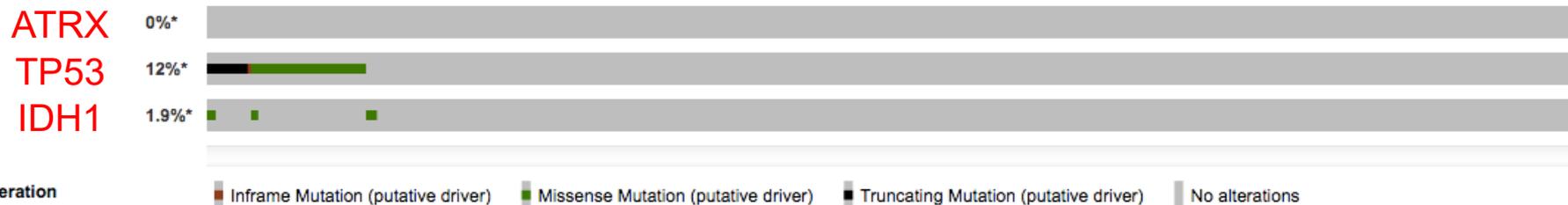


Co-occurrence of ATRX, TP53, IDH1 Mutations in Low Grade Gliomas

Low Grade Glioma n=286



Glioblastoma Multiforme n=791

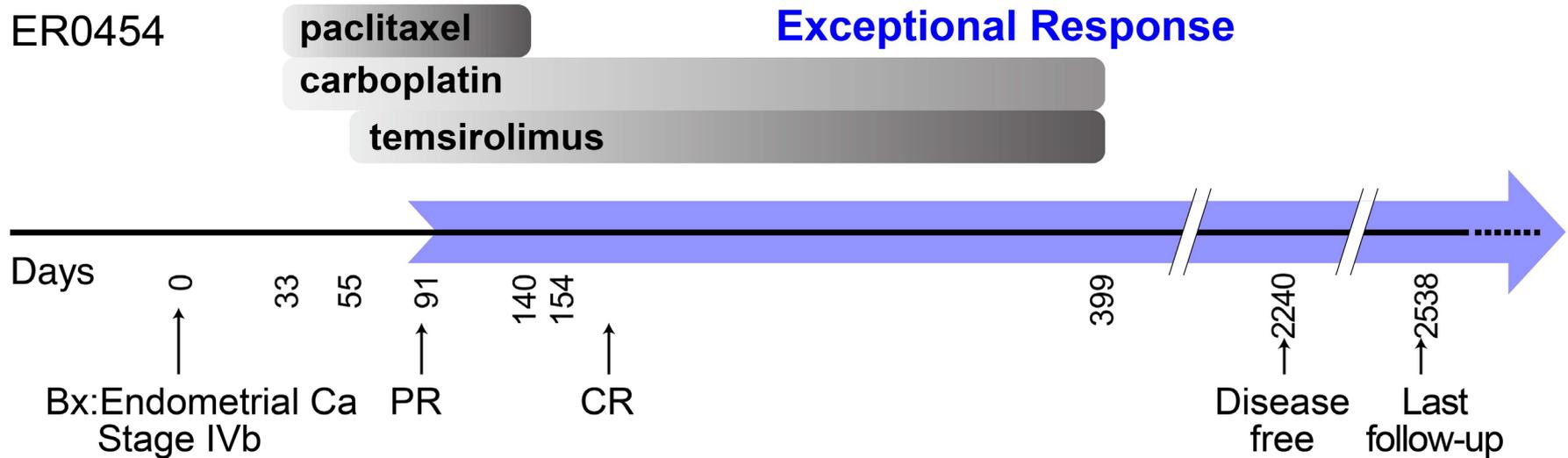




Exceptional Response Attributable to a Double Whammy

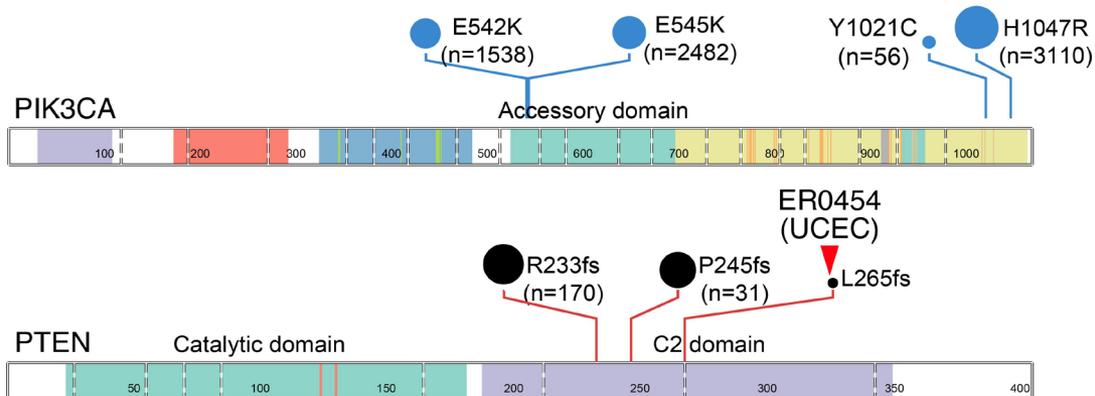
ER0454 Endometrial Carcinoma: Clinical

- 55 year old female
- Endometrial adenocarcinoma - Stage IVB
- ER induced treatment: carboplatin + paclitaxel + temsirolimus
- ER outcome: Ongoing CR >70 months



ER0454 Endometrial Carcinoma: Molecular

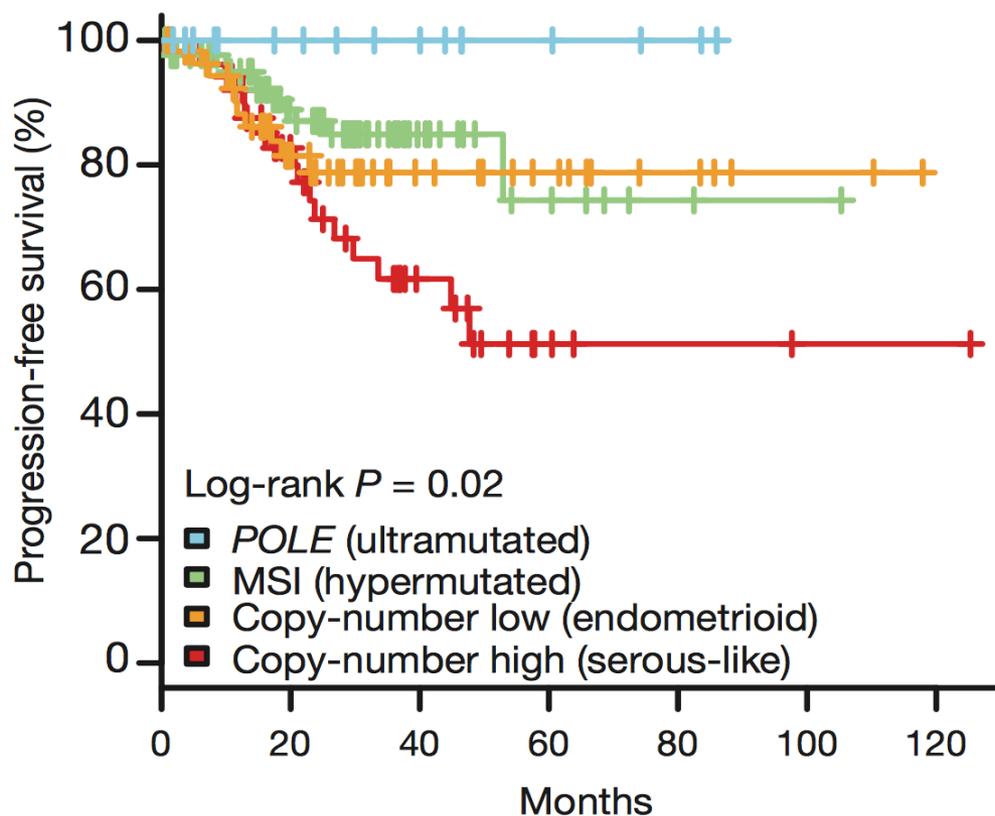
- Activating PIK3CA and inactivating PTEN mutations
- MLH1 methylation and low expression; microsatellite instability
- High immune mRNA signature score; infiltration of CD8 T cells





ER0454 Endometrial Carcinoma: Mechanisms

- Sensitivity to temsirolimus due to PI3 kinase pathway activation
- Immune recognition due to MSI-H + high mutational burden
- Favorable prognosis of MSI-H in endometrial Ca





Exceptional Responders Program: Conclusions

- Multi-platform genomics is needed to understand ERs.
- Even so, ~75% of ERs remain a mystery.
- Some “ERs” occur in tumors that appear aggressive pathologically but have the genetics of an indolent cancer.
- The immune system appears to play an important role in ERs treated with standard therapies (not just immunotherapies).
- Multiple lesions in the same pathway generate synthetic lethality
- Need to develop a much better pathway-based understanding of therapeutic response and resistance!

