

— 2nd Annual —

Atlanta Breast Cancer CONFERENCE

Future Directions in Multi-disciplinary Breast Cancer Care – The Radiation Oncologist's Perspective

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Disclosures

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No intention to discuss off-label and/or investigational use of pharmaceutical or devices

N.B: Unpublished, confidential data will be shared...

NGS and how it may affect local therapy / radiation therapy in breast cancer patients

Possible read outs enabled by
NGS

↓

LOF
mutations in
key alleles

↓

Signature analysis/
inferences for HRD

↓

Phylogeny
inferences

↓

ctDNA read
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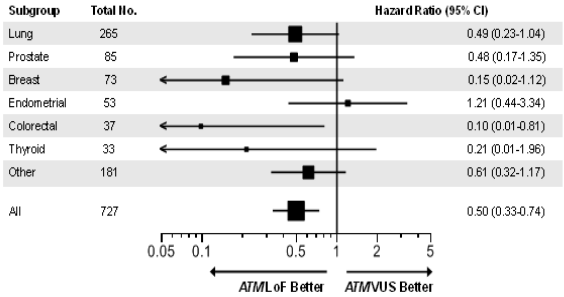
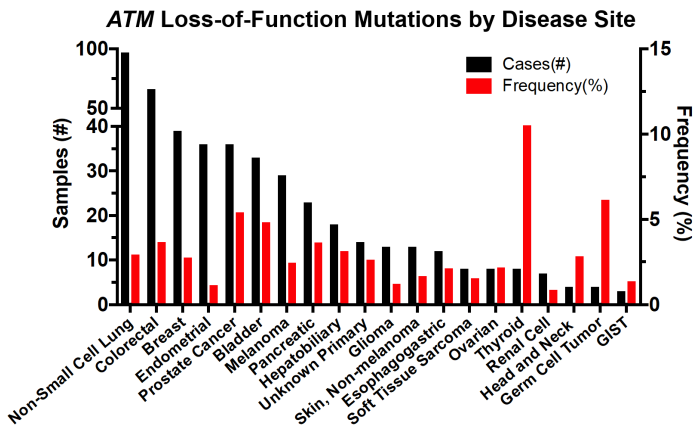
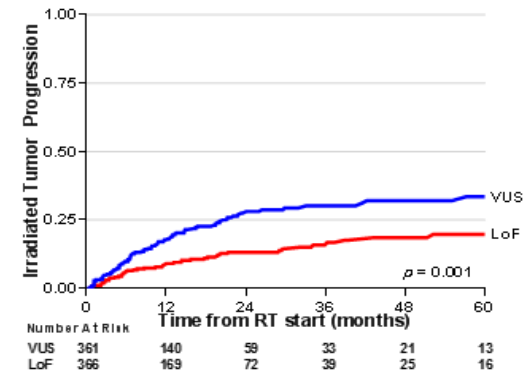
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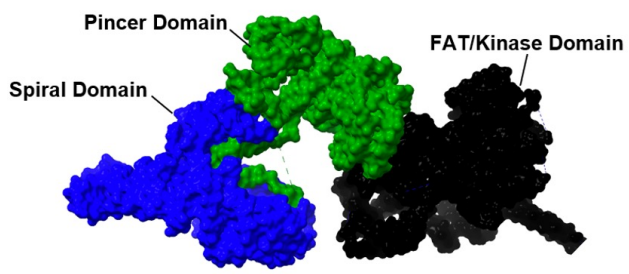
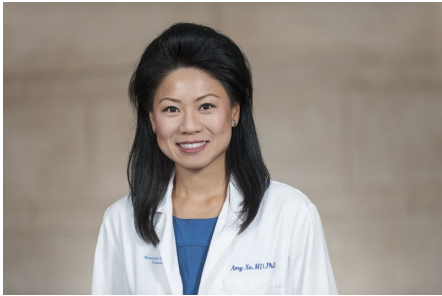
Patients with ATM LoF Exhibit Increased Sensitivity to RT

ATM LoF Associated with Clinical Benefit from RT



Pitter, Casey, Pathogenic ATM Mutations in Cancer and a Genetic Basis for Radiotherapeutic Efficacy, *JNCI*, 2021

Basket Trial Design PI: A Xu



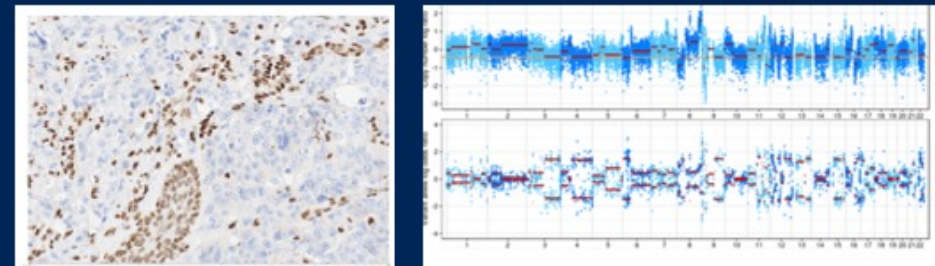
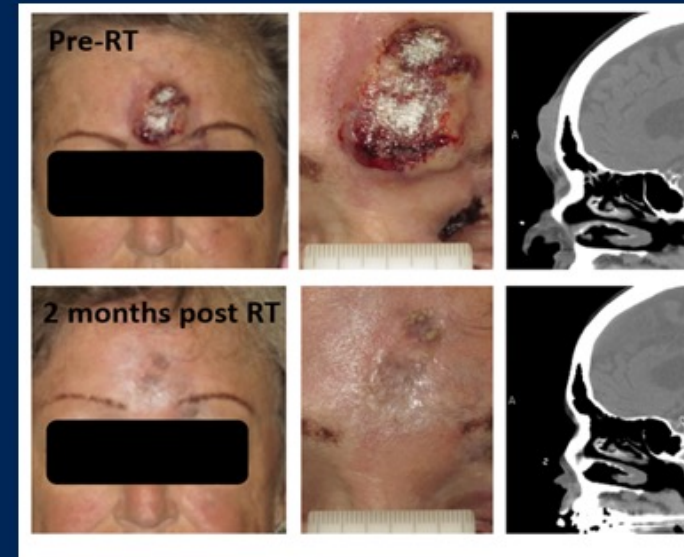
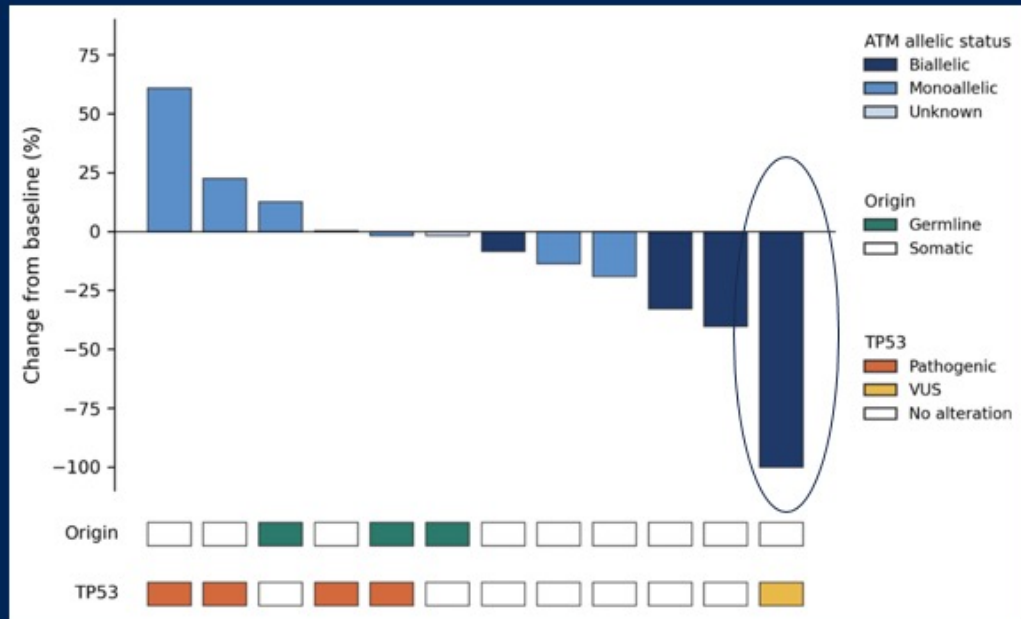
Hypothesis:
Tumors with pathogenic mutations in ATM can be controlled with lower doses of RT

Intervention:
Major Dose De-Escalation (40-80% reduction in dose)

21-310 (PI: Amy Xu) Exceptional Responder

Cutaneous Angiosarcoma

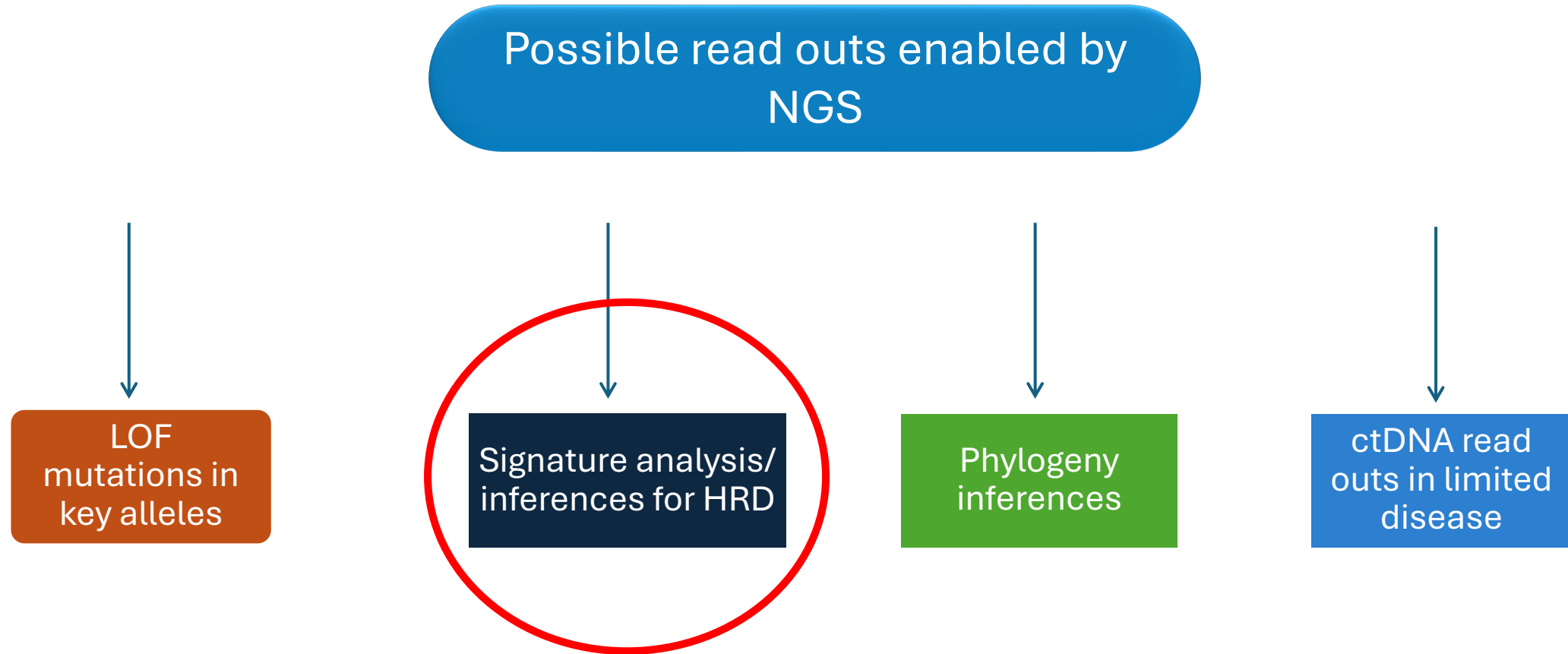
Tumor Response



ATM Biallelic Somatic R1466 Nonsense
TP53 P98S VUS

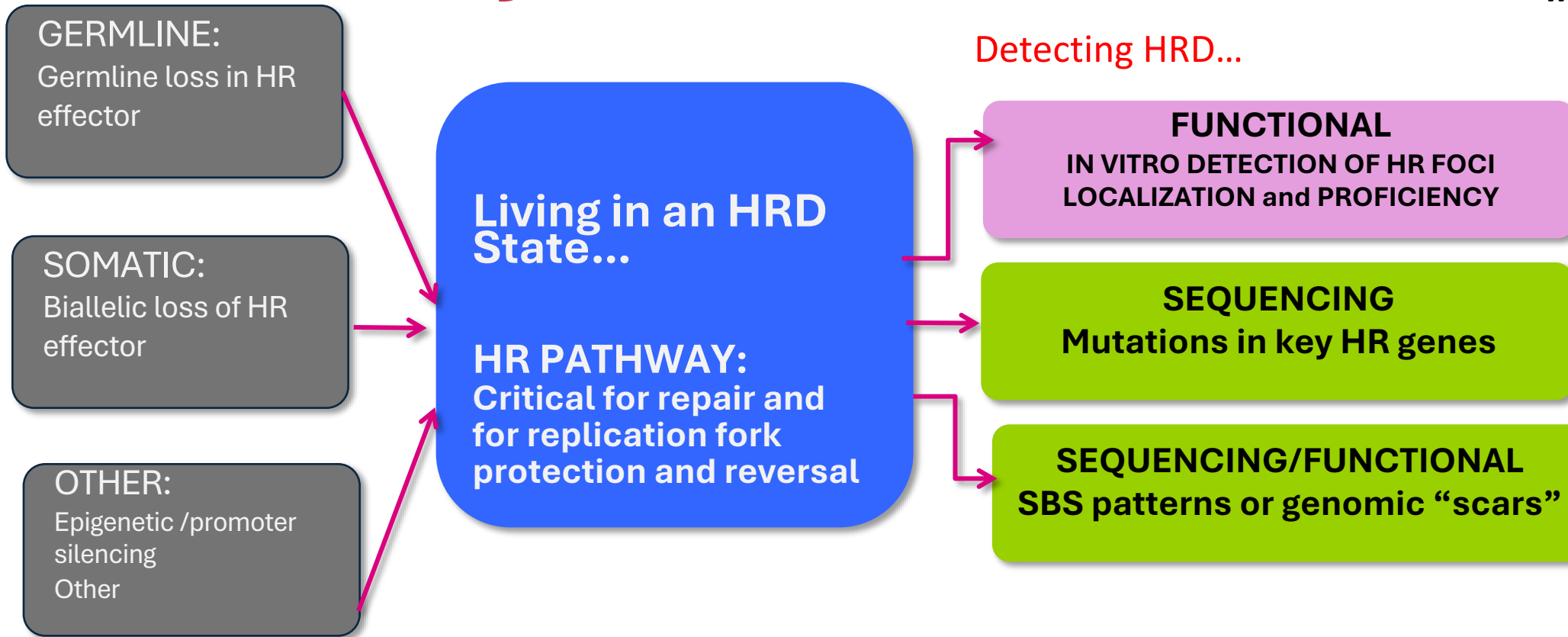
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NGS and how it may affect local therapy / radiation therapy in breast cancer patients

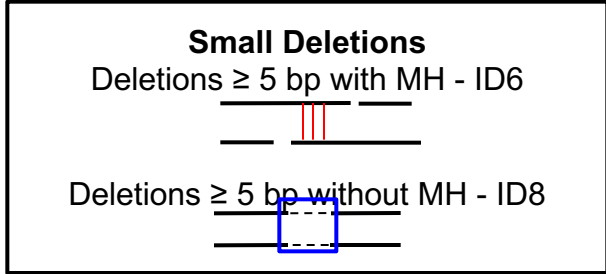
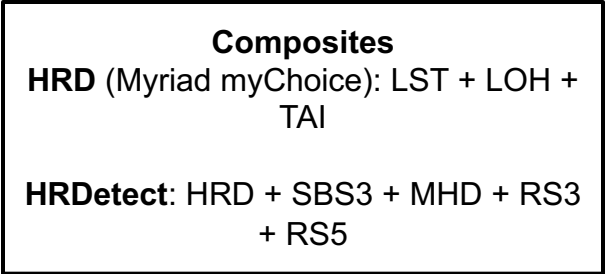
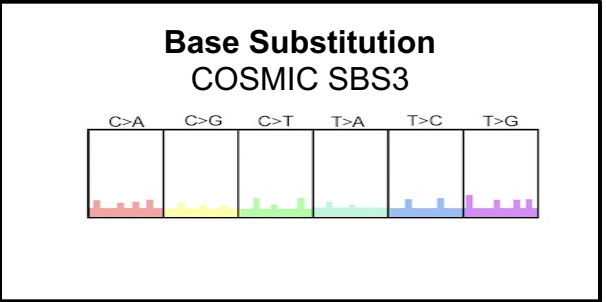
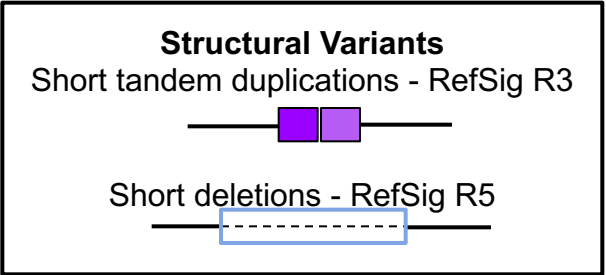
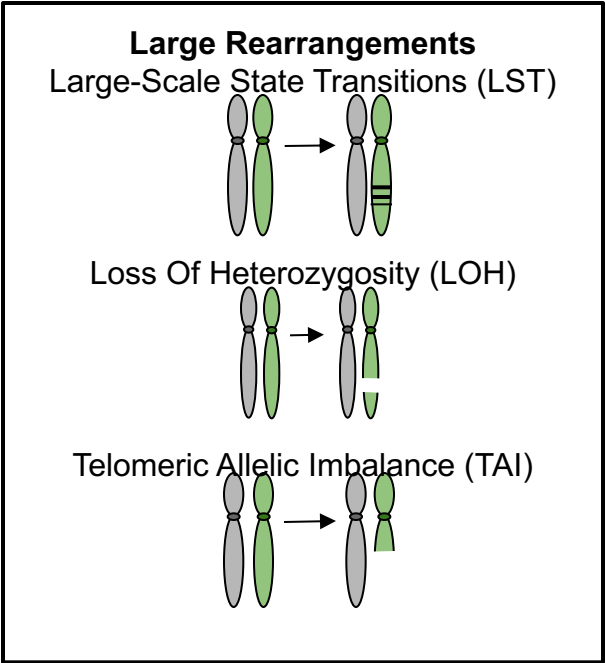


Understanding Homologous Repair Deficiency

in one slide...

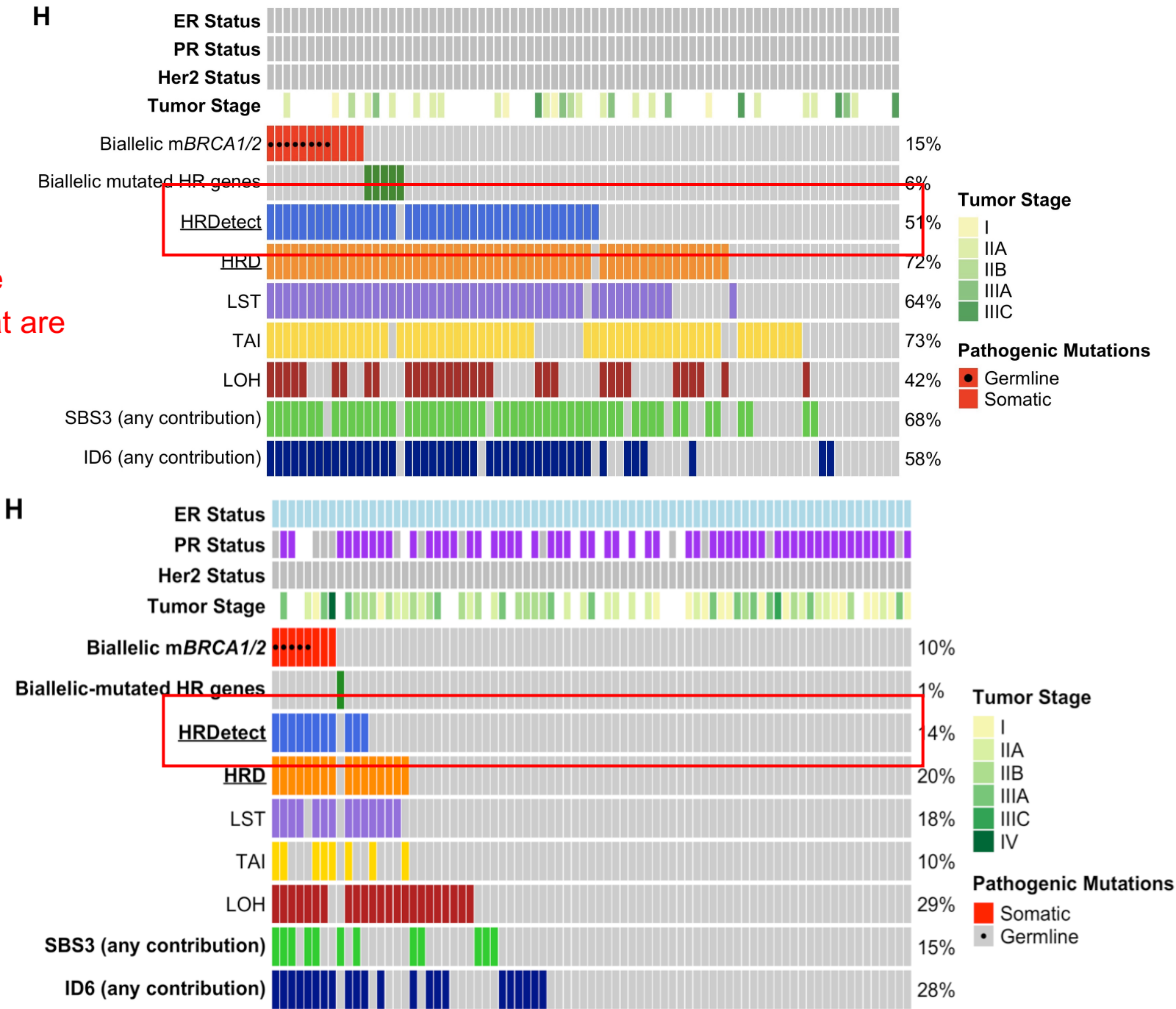
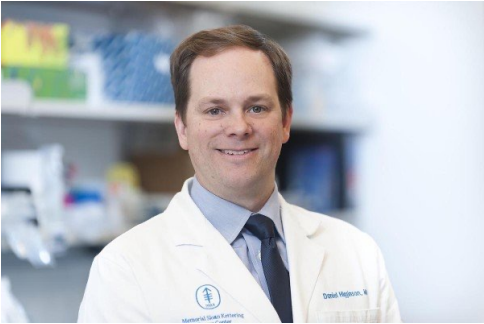


HRD causes genomic scars that can be measured and classified

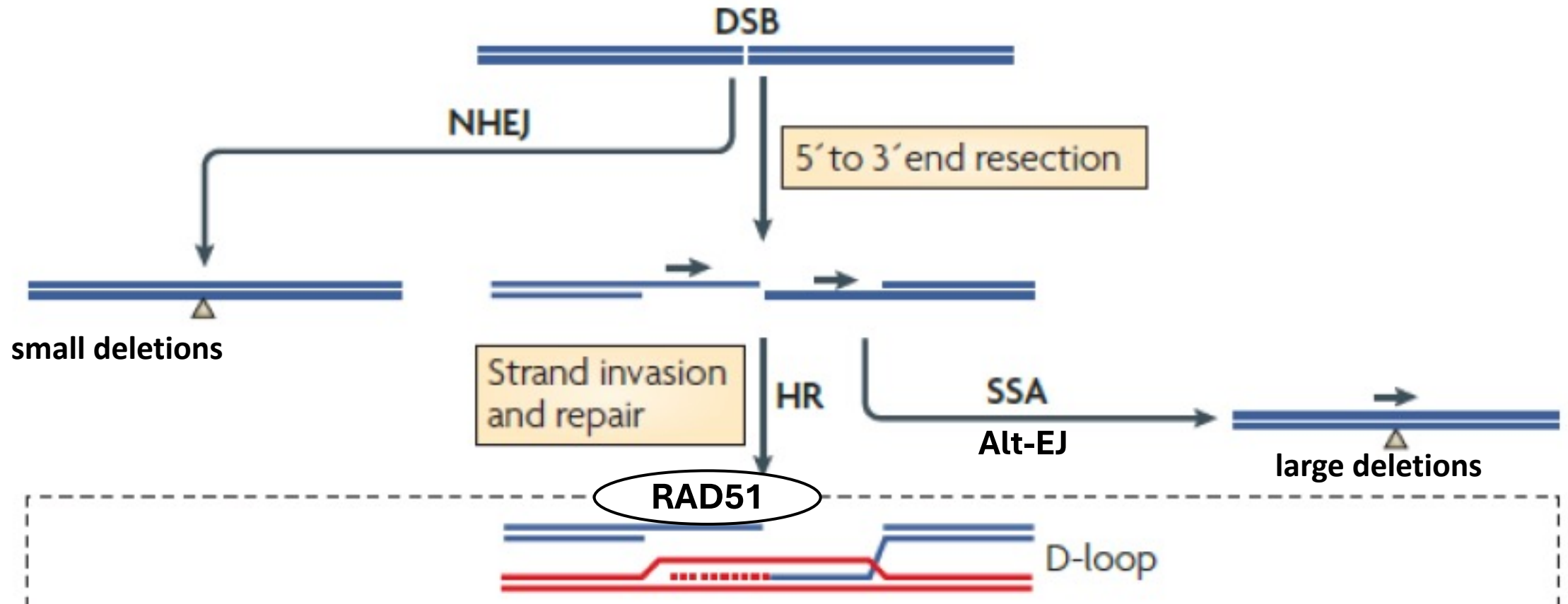


HRD in TNBC and ER+ breast cancer in PCAWG

N.B HRD in ER+ breast cancer at 15% is more absolute number of cases than HRD cases that are TNBC



Homologous Recombination and Backup DSB Repair



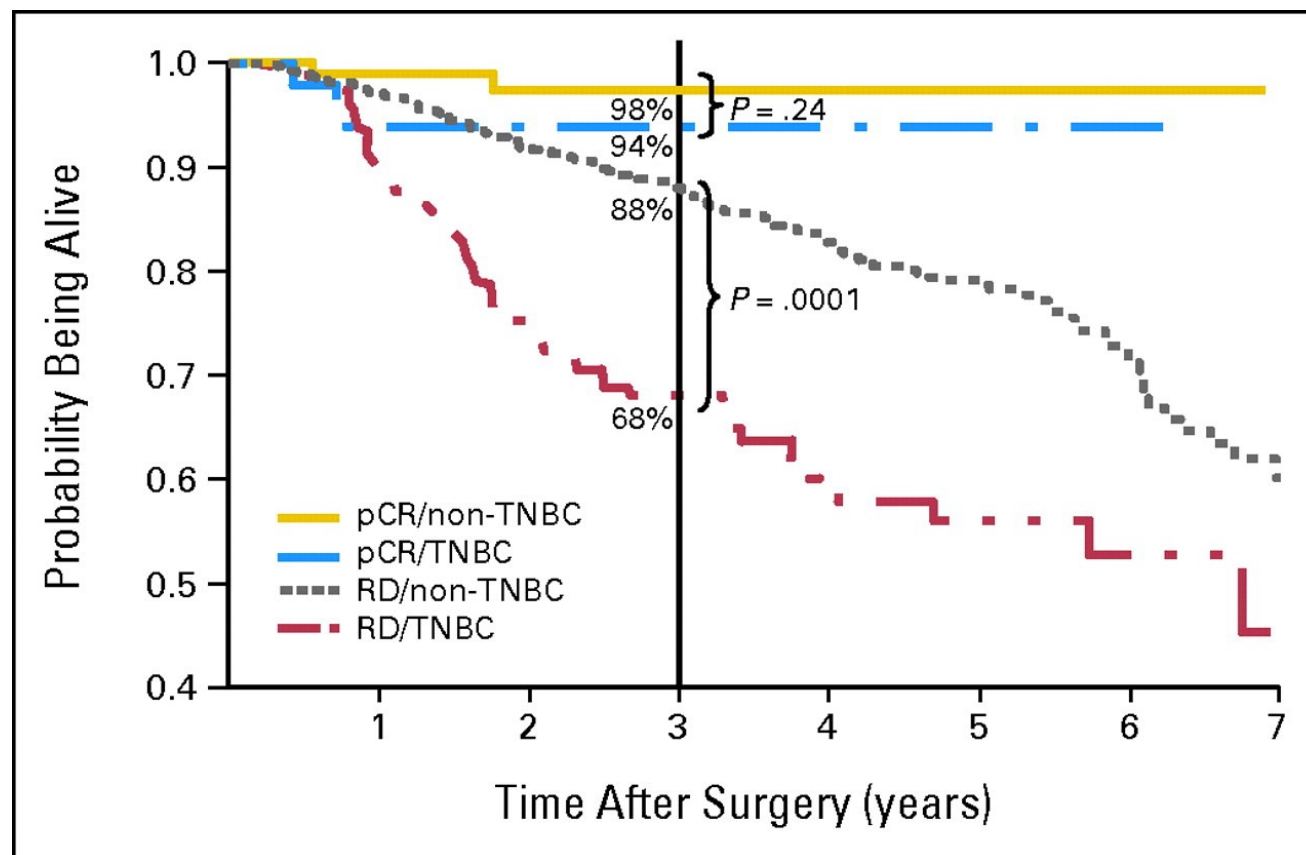
A pathway of double-strand break repair, with a critical role in preventing structural alterations

Given these data...

- Can we combine RT with HRD-directed treatment in high-risk patients?

Response to Neoadjuvant Therapy and Long-Term Survival in Patients With Triple-Negative Breast Cancer

Cornelia Liedtke, Chafika Mazouni, Kenneth R. Hess, Fabrice André, Attila Tordai, Jaime A. Mejia, W. Fraser Symmans, Ana M. Gonzalez-Angulo, Bryan Hennessy, Marjorie Green, Massimo Cristofanilli, Gabriel N. Hortobagyi, and Lajos Pusztai



The Effect of Molecular Subtype and Residual Disease on Locoregional Recurrence in Breast Cancer Patients Treated with Neoadjuvant Chemotherapy and Postmastectomy Radiation

T. Jonathan Yang, MD¹, Monica Morrow, MD², Shanu Modi, MD³, Zhigang Zhang, PhD⁴, Kate Krause, BS¹, Chun Siu, BS¹, Beryl McCormick, MD¹, Simon N. Powell, MD, PhD¹, and Alice Y. Ho, MD¹

Ann Surg Oncol (2015) 22:S495–S501

TABLE 3 Five-year actuarial locoregional recurrence (LRR) rates according to number of positive nodes and response to neoadjuvant chemotherapy

Patients	TN [LRR at 5 years/total patients (actuarial LRR)]	HER2+ [LRR at 5 years/total patients (actuarial LRR)]	HR+ [LRR at 5 years/total patients (actuarial LRR)]	<i>p</i> value
pCR				
Yes	0/13 (0 %)	0/11 (0 %)	0/8 (0 %)	NA
No	10/44 (26 %)	3/42 (7 %)	4/115 (4 %)	<0.001
Number of positive nodes				
0	0/29 (0 %)	0/21 (0 %)	1/19 (5 %)	0.33
1–3	6/16 (46 %)	2/16 (13 %)	0/38 (0 %)	<0.001
4+	4/12 (35 %)	1/16 (7 %)	3/64 (5 %)	<0.001

TN triple negative, HER2+ human epidermal growth factor receptor-2 positive, HR+ hormonal receptor positive, pCR pathologic complete response

KN522 - TNBC with high residual cancer burden (RCB) after chemo/immunotherapy have high rates of local and distant recurrence

Table 1. Summary of first EFS events by RCB category										
Event	RCB-0		RCB-1		RCB-2		RCB-3		Overall ^a	
	Pembro + chemo N = 497	Placebo + chemo N = 219	Pembro + chemo N = 69	Placebo + chemo N = 45	Pembro + chemo N = 145	Placebo + chemo N = 79	Pembro + chemo N = 40	Placebo + chemo N = 26	Pembro + chemo N = 784	Placebo + chemo N = 390
Any EFS event	5.2%	7.3%	17.4%	20.0%	25.5%	44.3%	72.5%	69.2%	15.7%	23.8%
Secondary primary malignancy	0.2%	0	1.4%	2.2%	1.4%	3.8%	2.5%	0	0.8%	1.0%
PD precluded definitive surgery	0	0	1.4%	2.2%	1.4%	5.1%	10.0%	7.7%	1.4%	3.8%
Local recurrence	0.6%	1.4%	4.3%	6.7%	6.9%	8.9%	25.0%	7.7%	3.6%	4.4%
Distant recurrence	3.2%	5.5%	8.7%	8.9%	15.2%	22.8%	35.0%	53.8%	7.7%	13.1%
Brain only	1.8%	3.2%	4.3%	2.2%	2.1%	3.8%	2.5%	3.8%	2.0%	3.3%
Other only ^b	1.2%	2.3%	4.3%	6.7%	13.1%	19.0%	32.5%	46.2%	5.5%	9.5%
Brain and other ^b	0.2%	0	0	0	0	0	0	3.8%	0.1%	0.3%
Death	1.2%	0.5%	1.4%	0	0.7%	3.8%	0	0	1.9%	1.5%

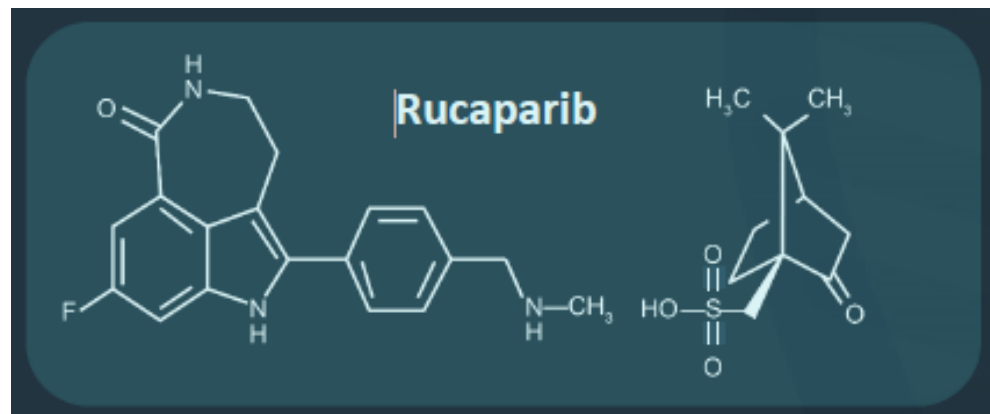
EFS, event free survival; PD, progressive disease; RCB, residual cancer burden.

^aIncludes patients with missing RCB data; among all patients (n = 1174), 54 patients (4.6%) had missing RCB categorical data: 33 (4.2%) in the pembrolizumab group and 21 (5.4%) in the placebo group.

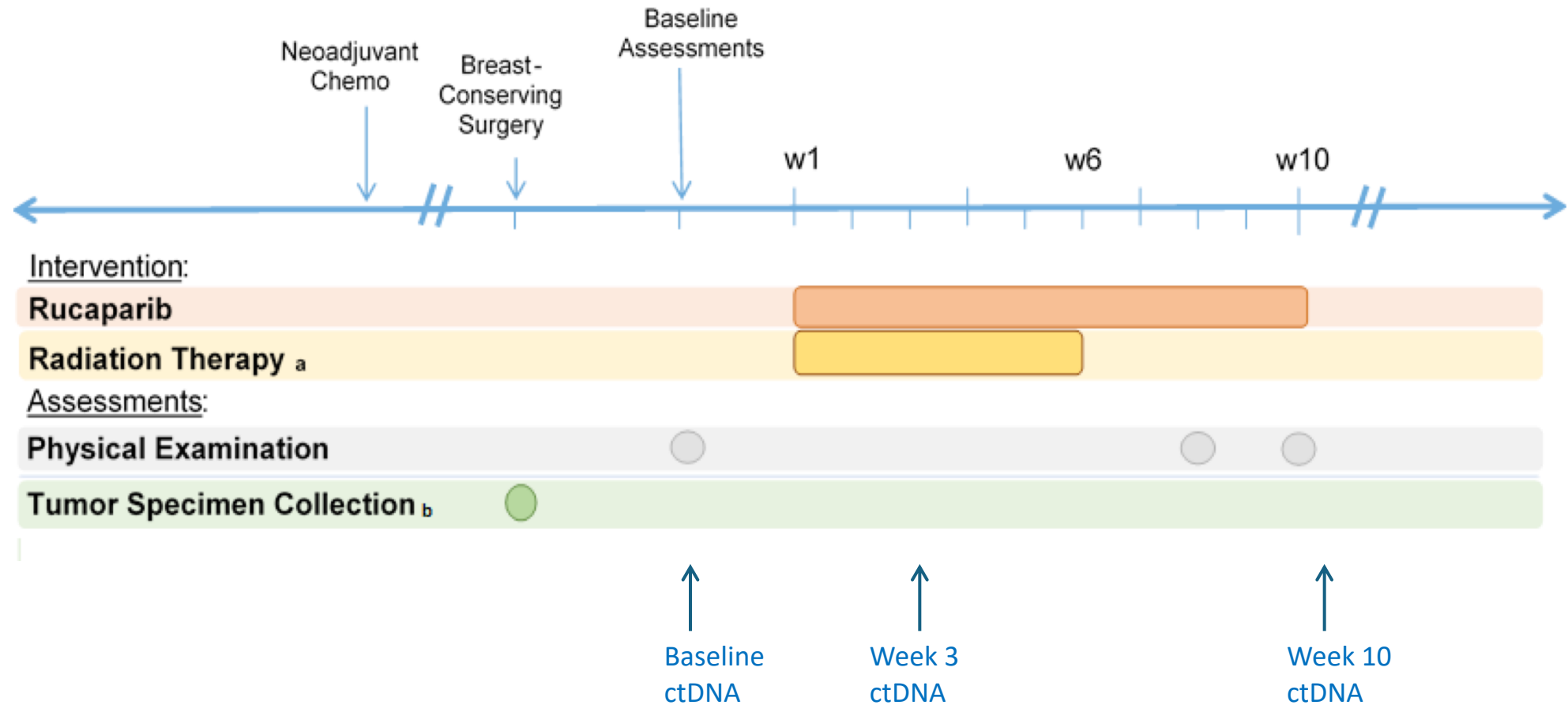
^bOther refers to non-brain distant recurrence sites, which were classified per clinical identification.

Background: Rucaparib

- Rucaparib (CO-338) is a small molecule inhibitor of PARP being developed for cancers associated with homologous recombination deficiency (HRD).
- Rucaparib has been shown to potently inhibit PARP-1, PARP-2, and PARP-3 and has demonstrated activity in a background of *BRCA1* and *BRCA2* mutations in both clinical and nonclinical studies.
- Rucaparib has also been shown to decrease tumor growth in mouse xenograft models of human cancer with or without deficiencies in *BRCA*.



A Phase I Study of Rucaparib Administered Concurrently with Postoperative Radiotherapy in Patients with Triple Negative Breast Cancer with an Incomplete Pathologic Response Following Neoadjuvant Chemotherapy



Primary Objective

- Determine the maximum tolerated dose of rucaparib that can be administered concurrently with standard doses of radiotherapy to the breast +/- regional nodes.
- Dose limiting toxicities (DLT) will be defined as toxicities probably or definitely related to the study drug observed during the 70 days that include the 6 weeks of radiotherapy and rucaparib concurrently and an additional 4 weeks of maintenance rucaparib, as follows:
 - Confluent moist desquamation, defined as the presence of a single, contiguous region of moist desquamation that exceeds 25 cm² in area
 - Absolute Neutrophil Count <1,000/mm³, with or without fever; or platelet count <50,000/mm³; or hemoglobin <8.0 g/dl.
 - Any Grade ≥3 by the NCI CTCAE version 4.03 non-hematologic toxicity
 - Any toxicity requiring a radiotherapy dose delay exceeding 5 business days

Stats

- TITE-CRM design using defined dose-limiting toxicity (DLT).
- The acute observation period for toxicity is defined as 10 weeks, which includes the 6-week rucaparib and radiotherapy treatment course and a 4-week post RT rucaparib maintenance period.
- The target rate for dose-limiting toxicity is 30%.
- Target accrual = 30 patients over 2 years.

MTD / primary endpoint on 18-002 (n=30)

Dose Escalation Schedule	
Dose Level	Dose of Rucaparib administered concurrently with 60 Gy of radiation therapy to the breast & regional nodes
Dose Level -1	300 mg BID
Dose Level 0	400 mg BID
Dose Level 1	500 mg BID
Dose Level 2	600 mg BID

← 3/5 DLT

← 1/2 DLT

Dose Escalation Schedule	
Dose Level	Dose of Rucaparib administered concurrently with radiation therapy to the breast / chest wall +/- regional nodes
Dose Level -4	200 mg QD
Dose Level -3	300 mg QD
Dose Level -2	200 mg BID
Dose Level -1	300 mg BID
Dose Level 0	400 mg BID
Dose Level 1	500 mg BID
Dose Level 2	600 mg BID

← 0/6 DLT

← 3/15 DLT MTD

← 1/2 DLT

MTD on MSK 18-002

Dose Level	Dose of Rucaparib	Patients at Dose Level	DLTs observed
Dose Level -4	200 mg QD	6	0
Dose Level -3	300 mg QD (MTD)	15	3
Dose Level -2	200 mg BID	2	1
Dose Level -1	300 mg BID	5	3
Dose Level 0	400 mg BID	2	1

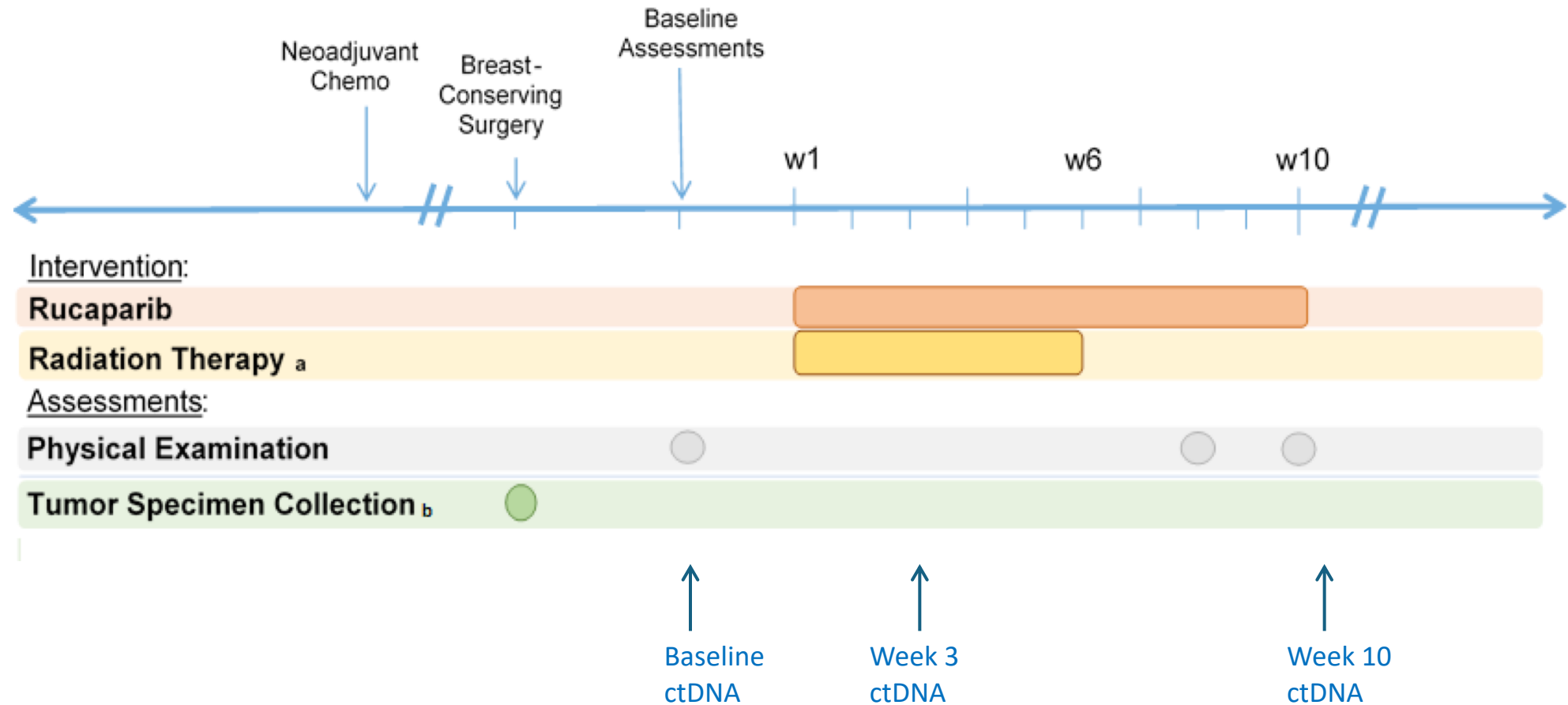
AEs on 18-002

	Grade 1	Grade 2	Grade 3	DLT
Radiation dermatitis	8 (27%)	15 (50%)	7 (23%)	6 (20%)*
Fatigue	17 (57%)	7 (23%)	0	0
Neutropenia / lymphopenia	0	1 (3%)	3 (10%)	2 (7%)*
Lymphedema	7 (23%)	2 (7%)	0	0
Nausea/vomiting	17 (57%)	0	0	0
Diarrhea	6 (20%)	1 (3%)	0	0
Dyspepsia	5 (17%)	0	0	0
Dizziness	4 (13%)	0	0	0
Fibrosis / induration	6 (20%)	1 (3%)	2 (6%)	0
Pain	11 (36%)	7 (23%)	0	0
Pleuritic pain	1 (3%)	1 (3%)	1 (3%)	0
Peripheral neuropathy	5 (17%)	1 (3%)	0	0
Anorexia	4 (14%)	0	0	0
Constipation	4 (13%)	0	0	0
Joint range of motion	8 (27%)	0	0	0
Pruritis	6 (20%)	3 (10%)	0	0
Telangiectasia	3 (10%)			
Skin hyper or hypopigmentation	18 (60%)	0	0	0
Change in taste	6 (20%)	1 (3%)	0	0
Breast atrophy	1 (3%)	2 (7%)	0	0
Other	10 (33%)	7 (23%)	0	0
Total	148	48	13	8

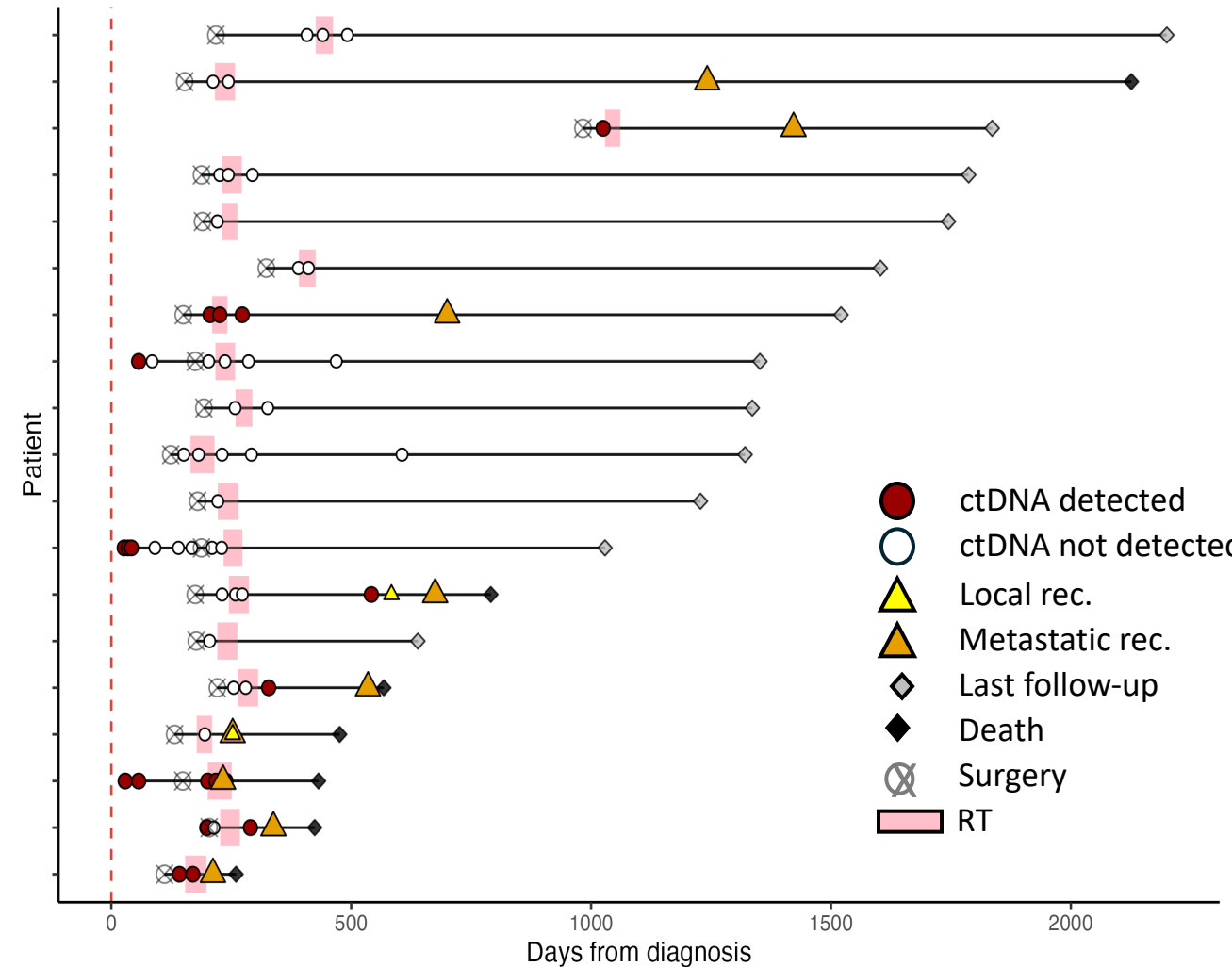
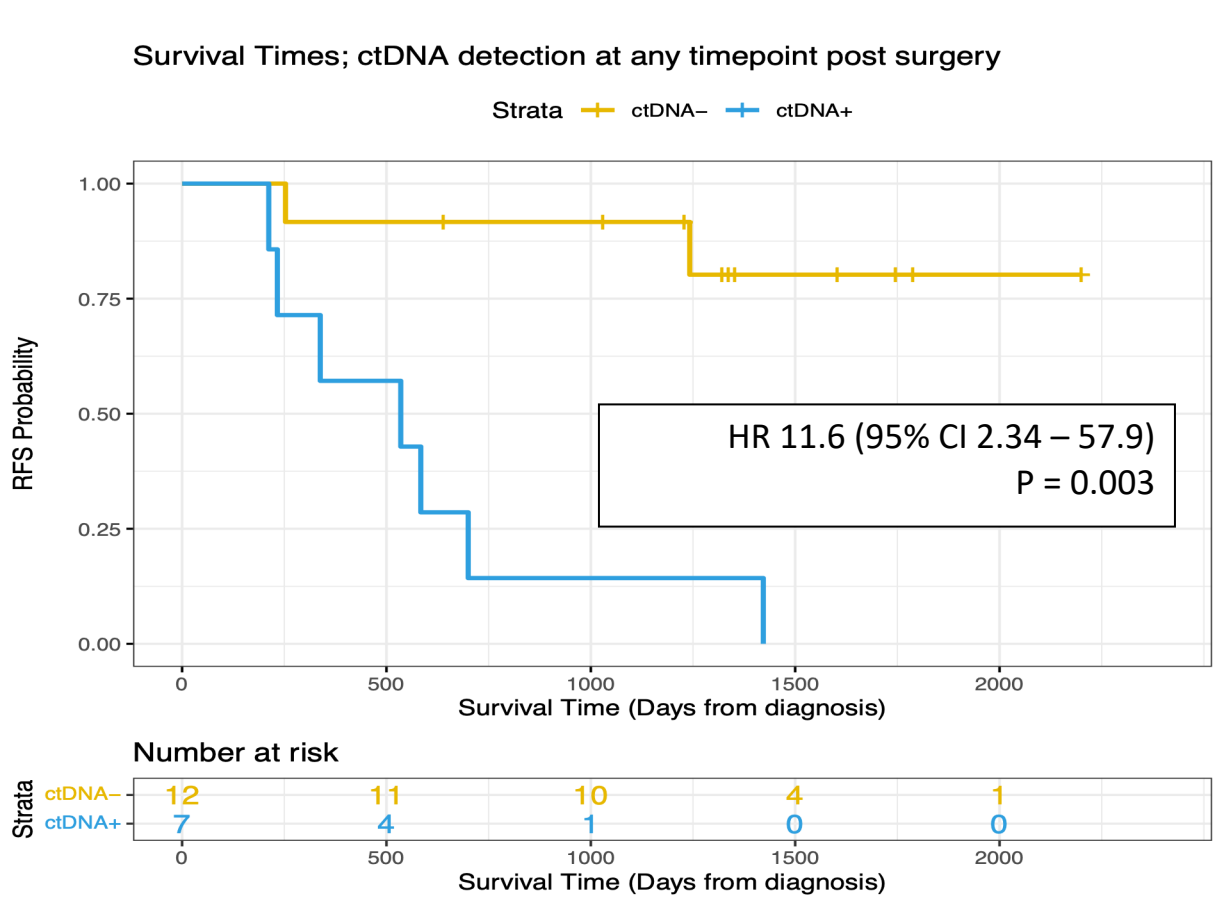
Additional results from 18-002 (n=30)

- Median age of enrolled patients was 50 (range 31-75).
- Median clinical tumor size before neoadjuvant chemotherapy (NAC) was 5 cm (range 1.3-8) and 19 patients were clinically node positive.
- 5 BRCA1/2 mutants
- Fourteen women had lumpectomy while the remainder had mastectomies, of which all but 5 had reconstructions
- Two patients progressed during the study period. 3 additional “hyperprogressors”, total 5 patients who progressed during treatment or within 90 days.
- With a median follow-up of 20 months, there were 2 local-regional recurrences (1 isolated) and 11 distant metastases.

A Phase I Study of Rucaparib Administered Concurrently with Postoperative Radiotherapy in Patients with Triple Negative Breast Cancer with an Incomplete Pathologic Response Following Neoadjuvant Chemotherapy



ctDNA as a correlate for outcomes in 18-002

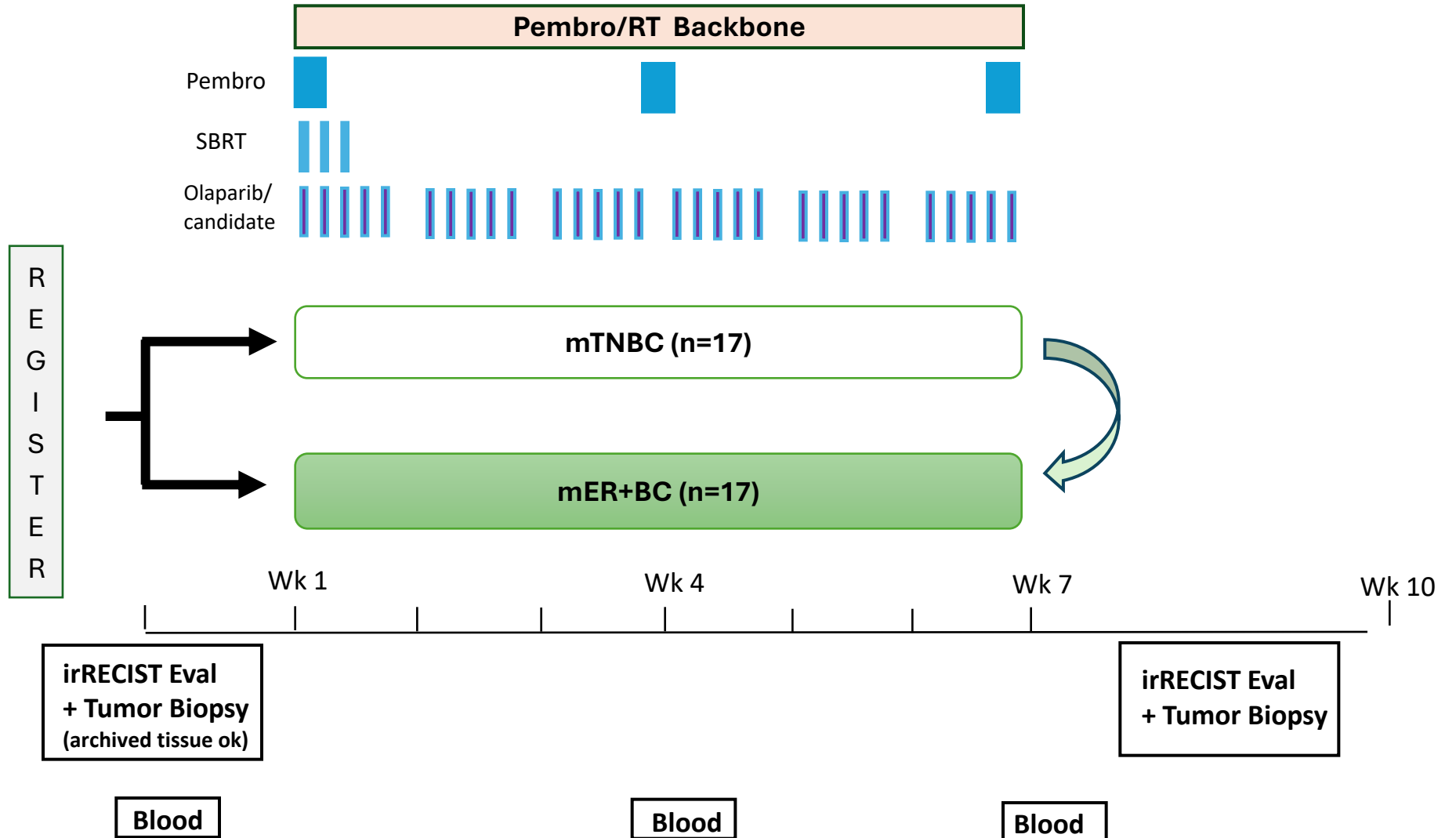


MISP 58597 / MSK 20-505

Study Population

- Metastatic triple-negative breast cancer (mTNBC)
- Prior ICI or PD-L1 negative
- ≤3 lines of prior lines for metastatic disease
- ≥ 2 measurable sites of disease

- **Metastatic ER+ breast cancer (mER+BC)**
- Any number of prior lines for metastatic disease
- ≥ 2 measurable sites of disease



Endpoints

- The primary endpoint is ORR in the non-targeted, unirradiated lesion(s), as defined by RECIST v.1.1 criteria at 8 weeks after the first dose of pembro/first fraction of RT.
- Secondary endpoints are to assess the ORR by irRECIST, safety and toxicity, progression-free survival (PFS), and overall survival (OS).
- Exploratory endpoints are to characterize the immunologic response via blood and tissue-based biomarkers. Safety will be continuously monitored throughout the study.

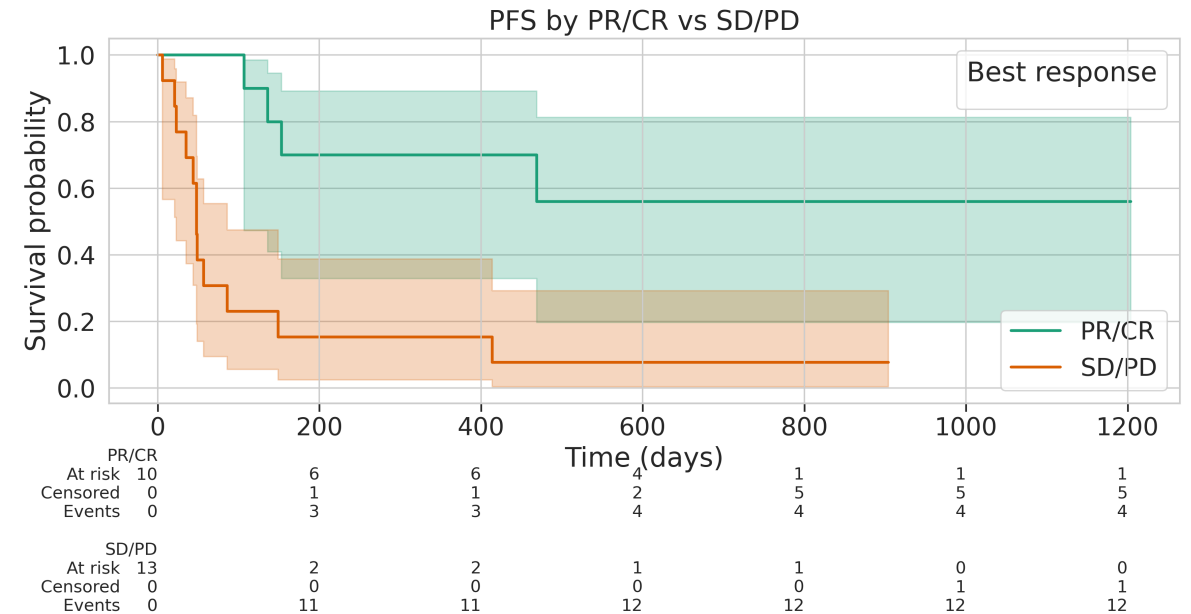
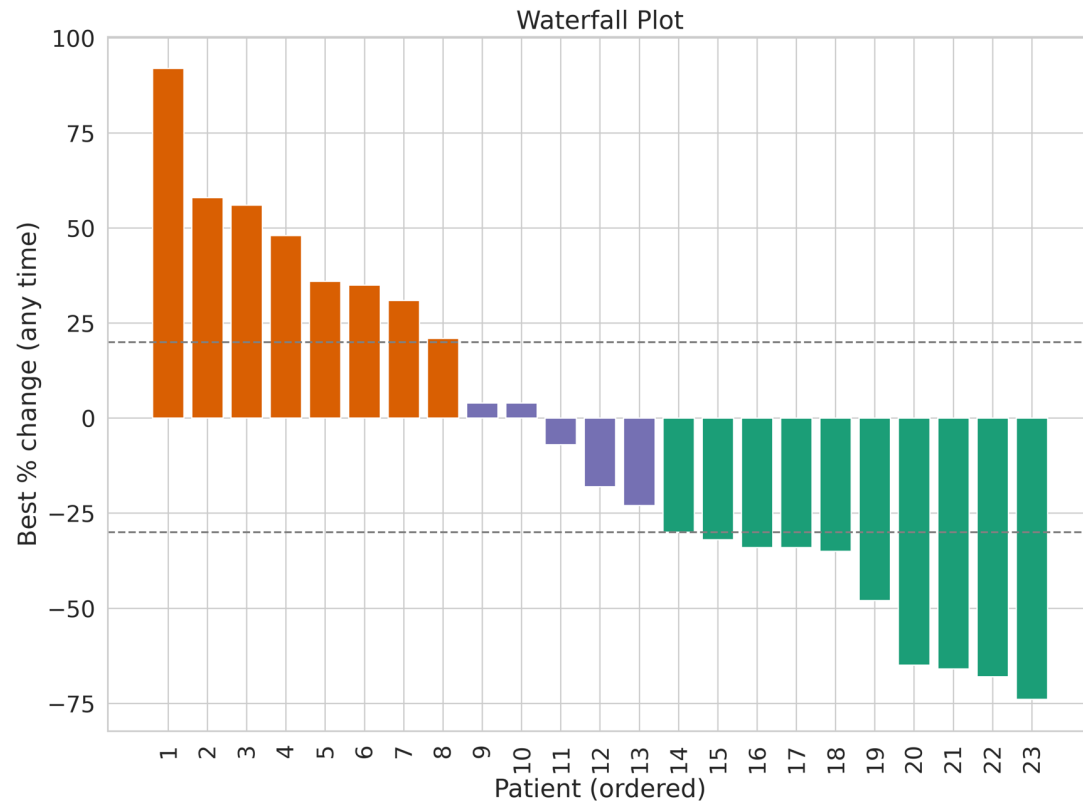
Statistics continued

- For each arm, 9 patients will be enrolled in the first stage. If there is no PR or CR, the study will be terminated. Otherwise, 8 additional patients will be accrued for a total of 17. The null hypothesis will be rejected if ≥ 3 responses are observed in 17 patients.

Response assessment totals from 20-505

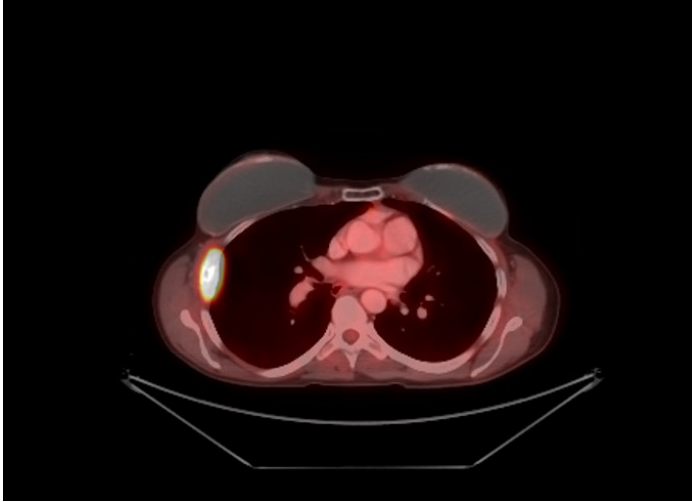
Response	All	TNBC	ER+
Progressive Disease	11	6	5
Stable Disease	5	3	2
Partial Response	7	3	6
Complete Response	0	0	0
Total	25	12	13

Clinical outcomes from 20-505

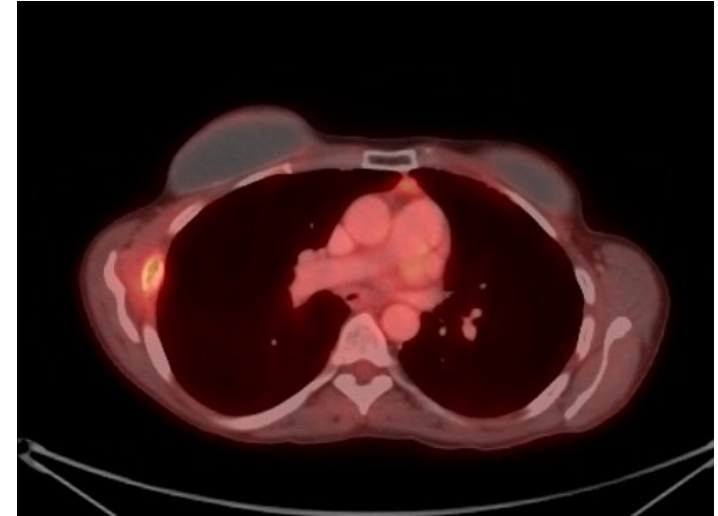


Patient 8

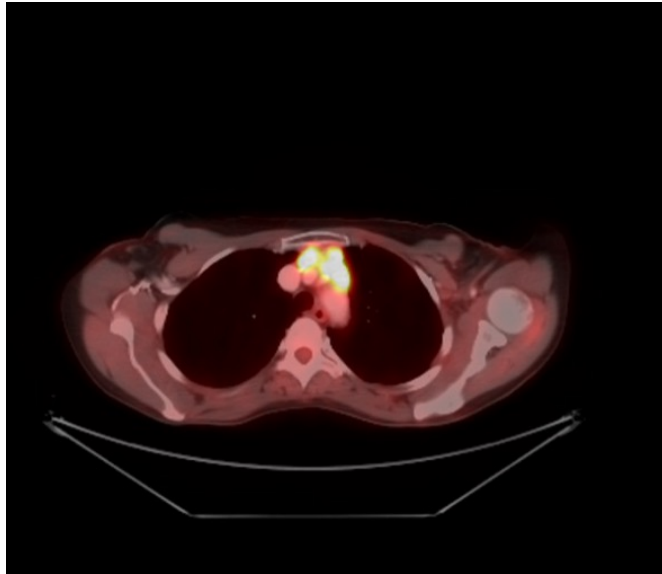
9/28/2022
Irradiated



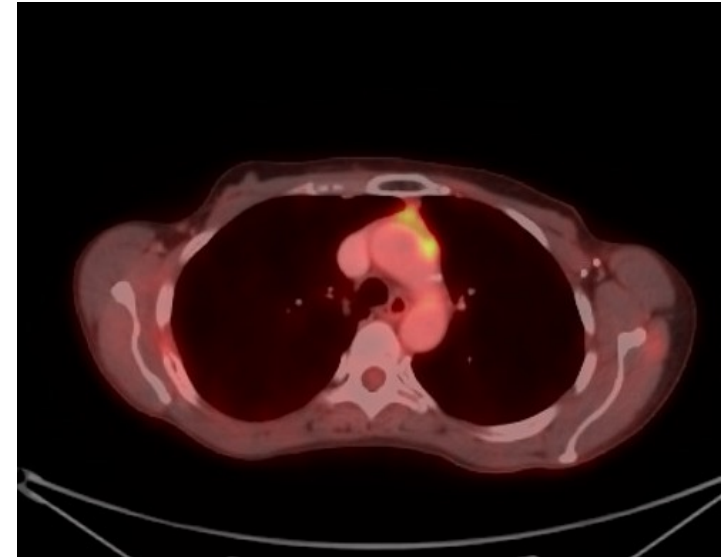
12/21/2022
Irradiated



9/28/2022
Unirradiated



12/21/2022
Unirradiated

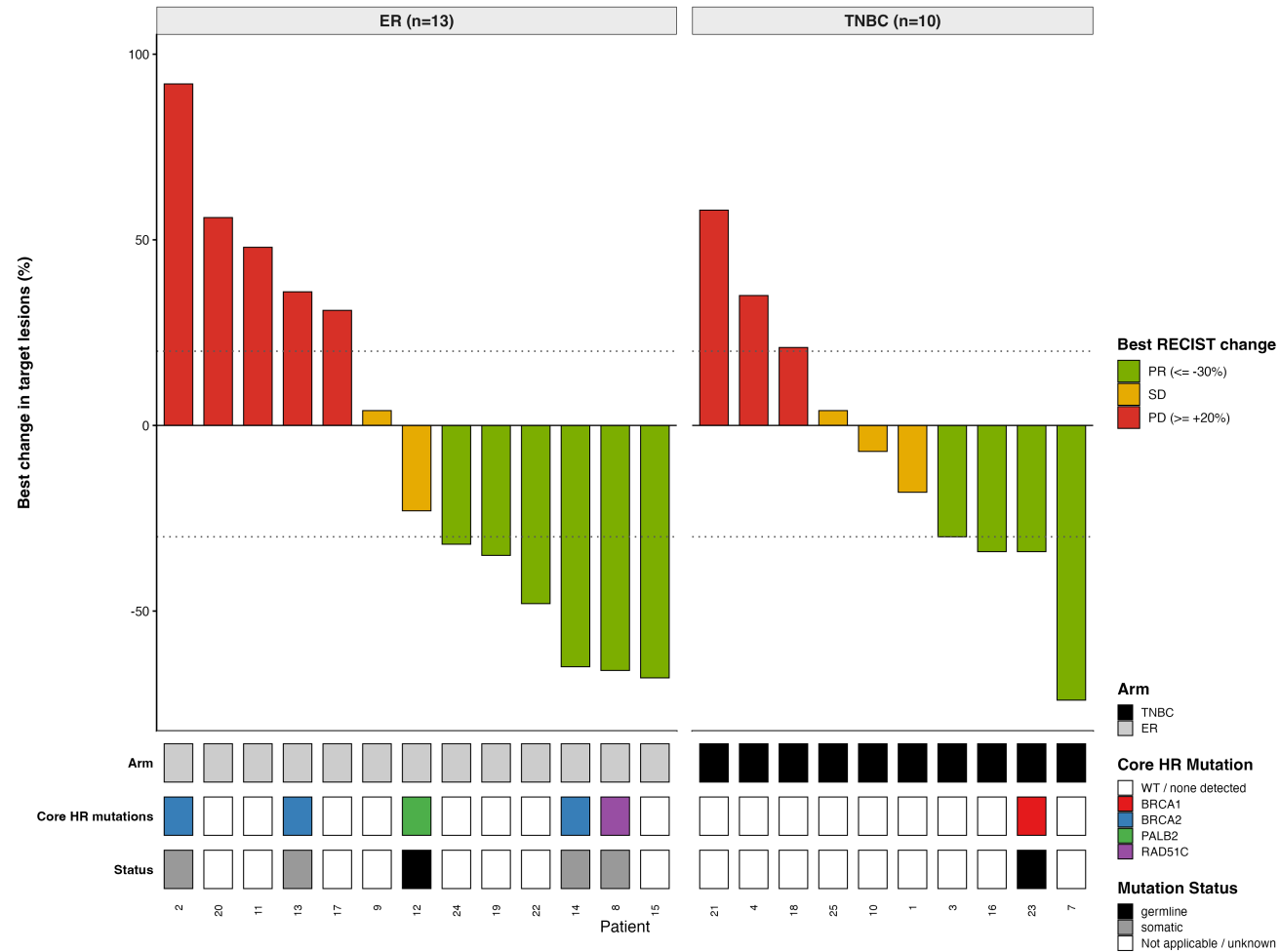


Continued clinical benefit until 3/23 with multiple brain metastases (mixed extracranial picture)

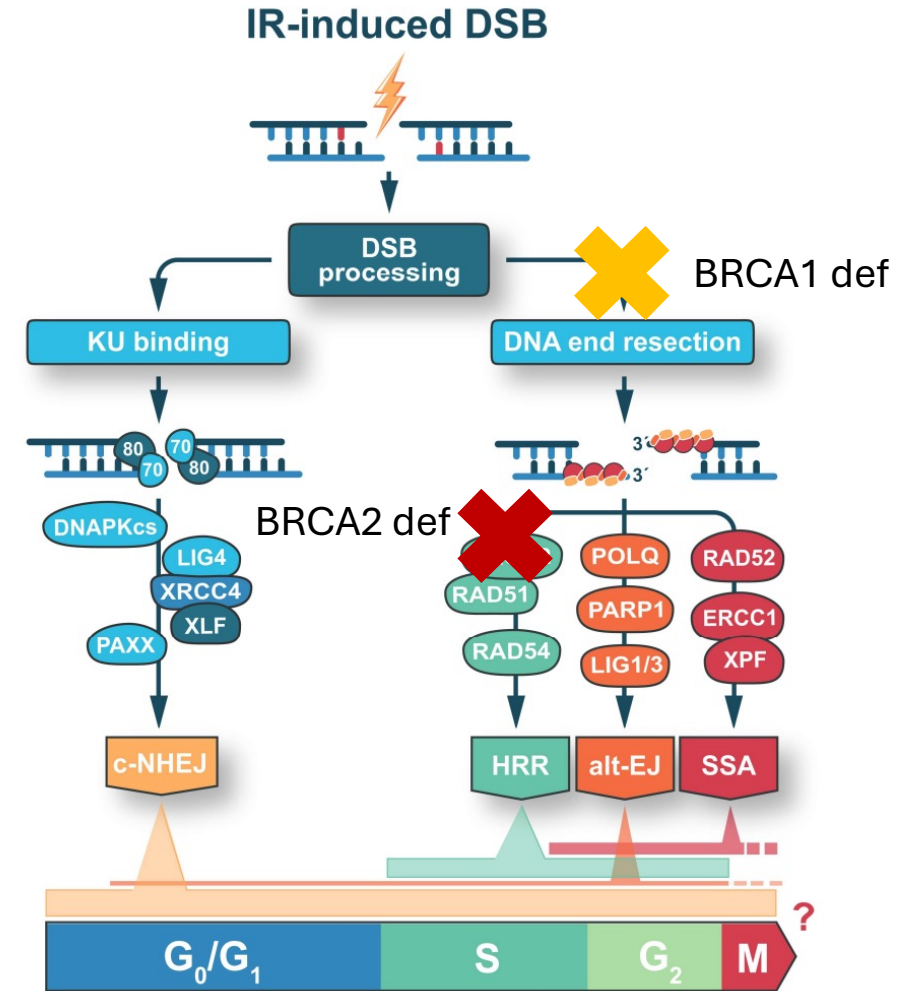
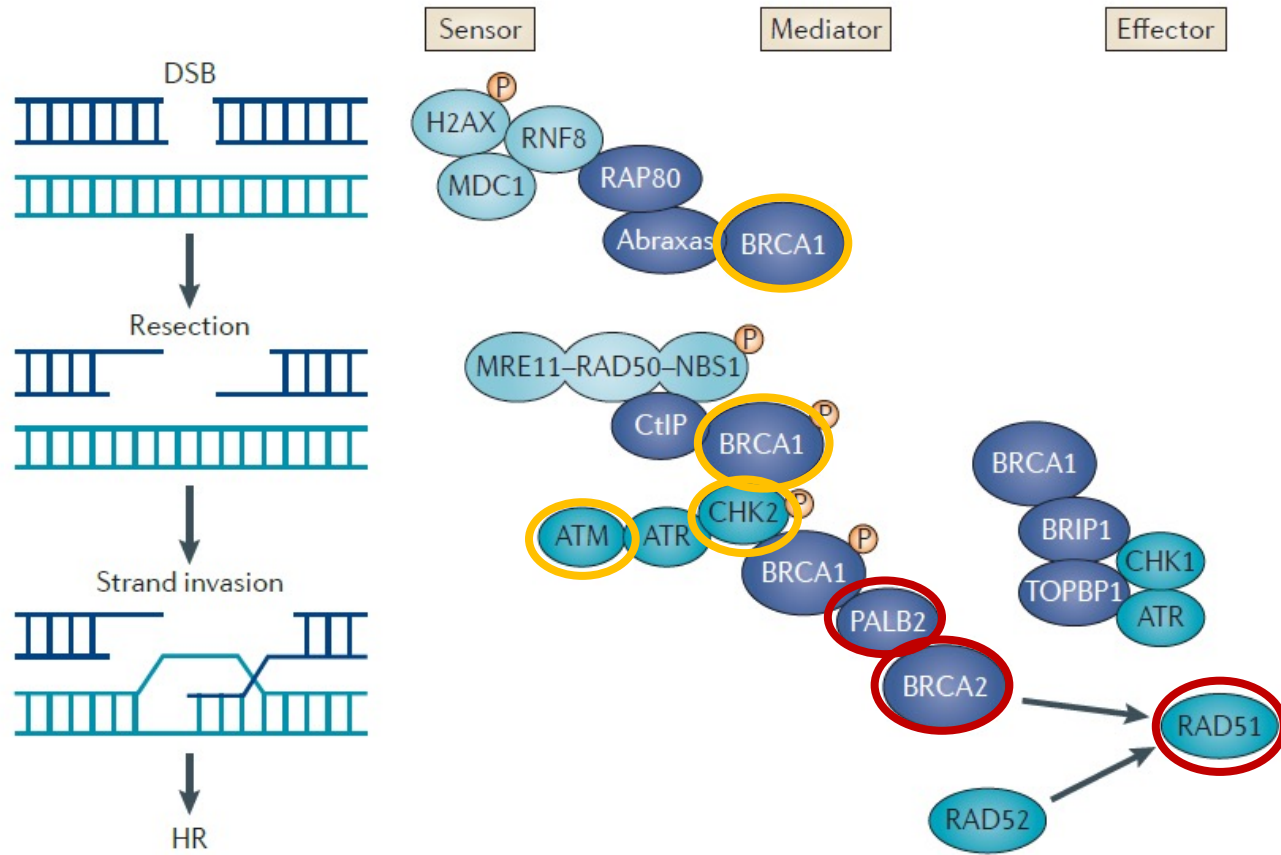
Patient ID	Cohort	Scan Results	
1	TNBC	Stable disease	
2	ER+	Progressive Disease	
3	TNBC	Stable disease	
4	ER+	Progressive Disease	
5	TNBC	Progressive Disease	
6	TNBC	Progressive Disease	
7	TNBC	Partial Response	gERCC3 frameshift, pathogenic
8	ER+	Complete Response	sRAD51C p.P21T oncogenic(recurrent hotspot) (22 TMB, MSS)
9	ER+	Stable disease	
10	TNBC	Progressive Disease	
11	ER+	Progressive Disease	
12	ER+	Partial Response	g&s PALB2 frameshift
13	ER+	Progressive Disease	
14	ER+	Partial Response	BRCA2 mutation by Guardant
15	ER+	Stable disease	
16	ER+	Progressive Disease	
17	TNBC	Partial Response	
18	TNBC	Progressive Disease	
19	TNBC	Progressive Disease	
20	TNBC	Partial Response	
21	TNBC		



Clinical outcomes from 20-505 by subtype



Upstream and downstream pathway of HR



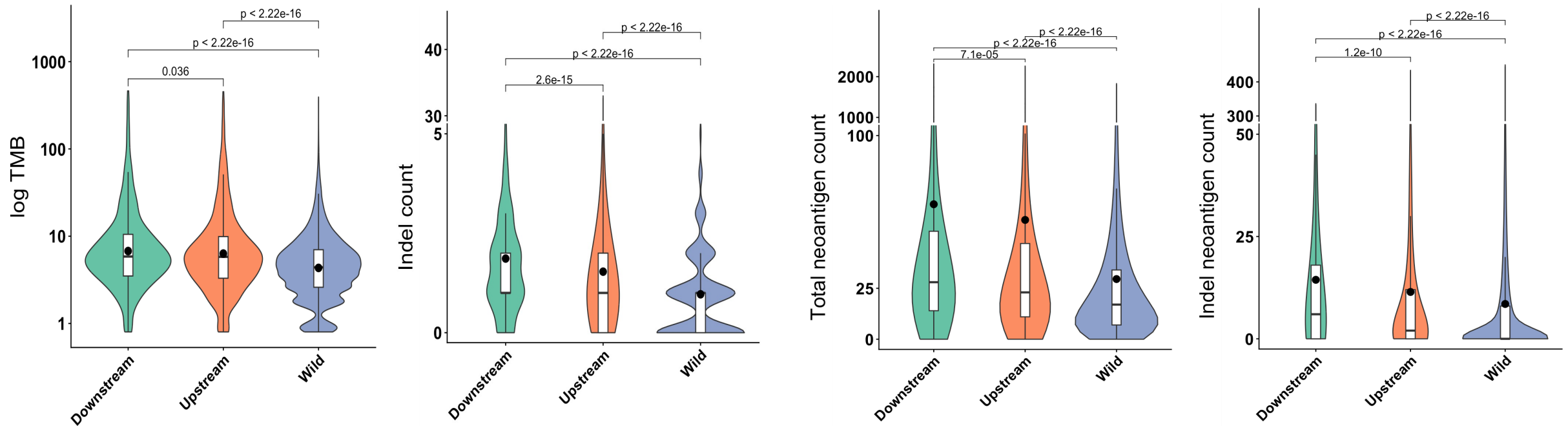
Hypothesis

- BRCA2 and BRCA2-like tumors (“downstream HRD”) have a distinct tumor microenvironment and may derive greater benefit from immune-checkpoint blockade (ICB).

Total indels and indel-derived neoantigens are higher in downstream HRD

MSK-IMPACT, n = 39,270

- Upstream (ATM, CHEK2, BRCA1), n = 2,092
- Downstream (BRCA2, PALB2, RAD51C), n = 1,049

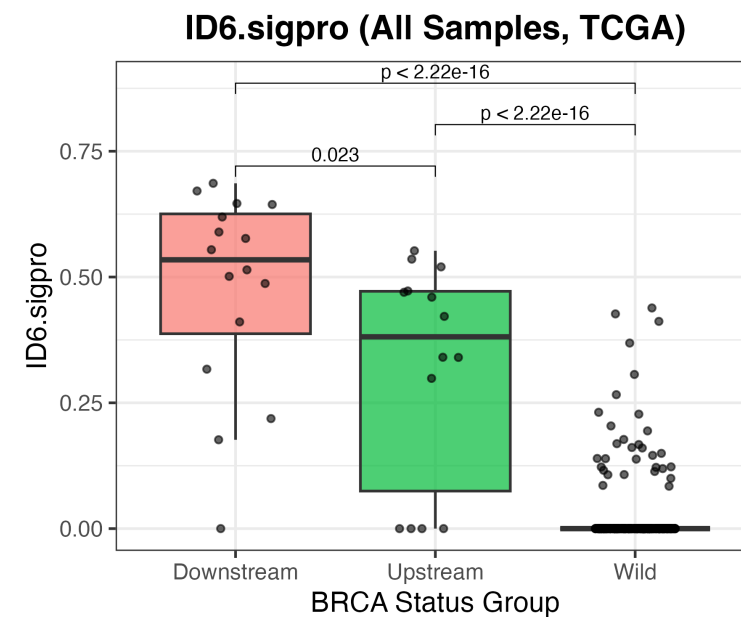
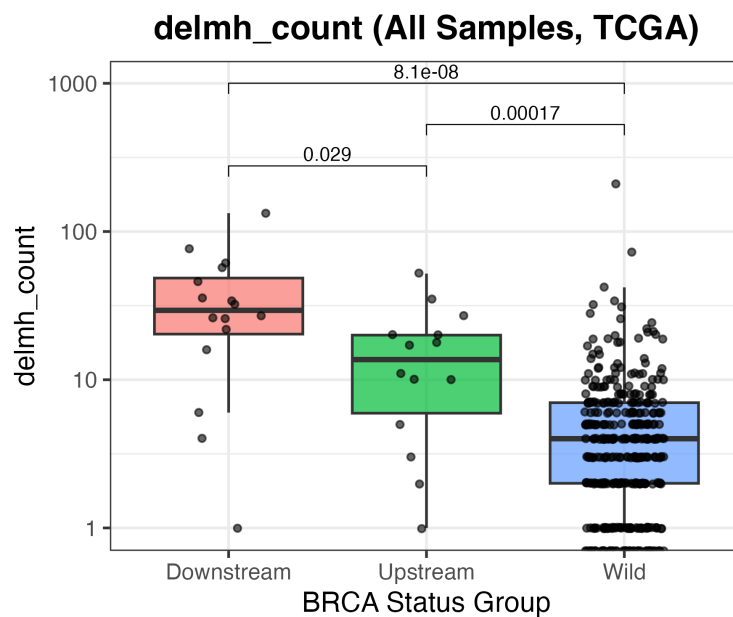
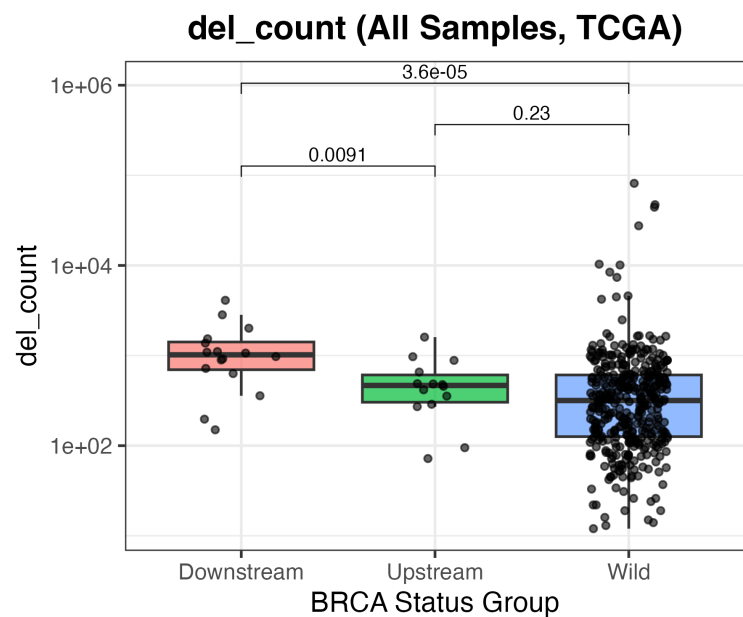


WGS analysis suggests greater MMEJ dependence in downstream HRD

TCGA, n=769

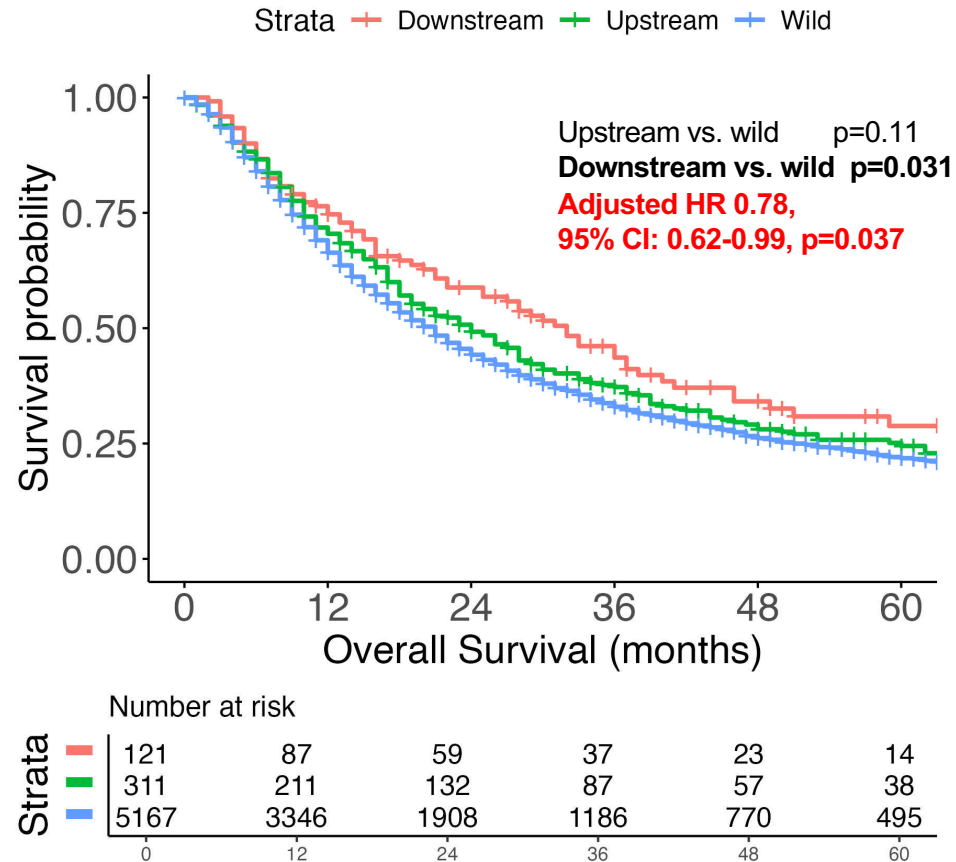
Upstream (BRCA1), n =14

Downstream (BRCA2, PALB2, RAD51C), n = 16

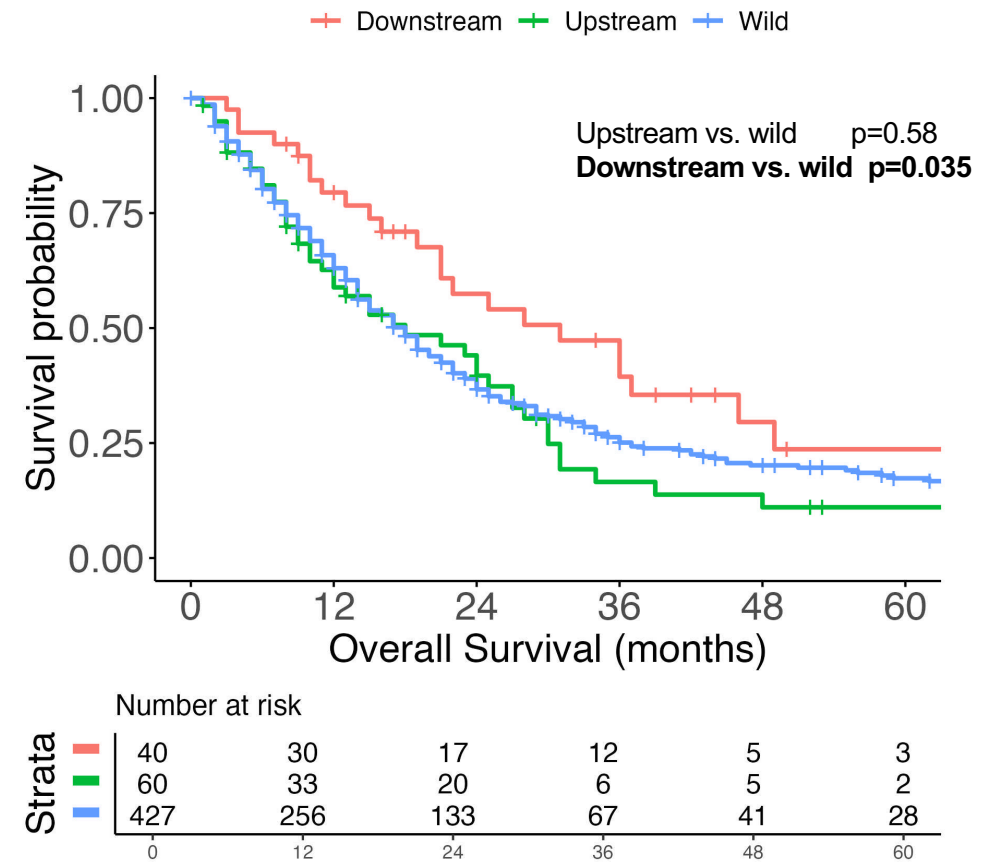


Patients with downstream HRD benefit more from ICB

All patients of MSK-IMPACT cohort

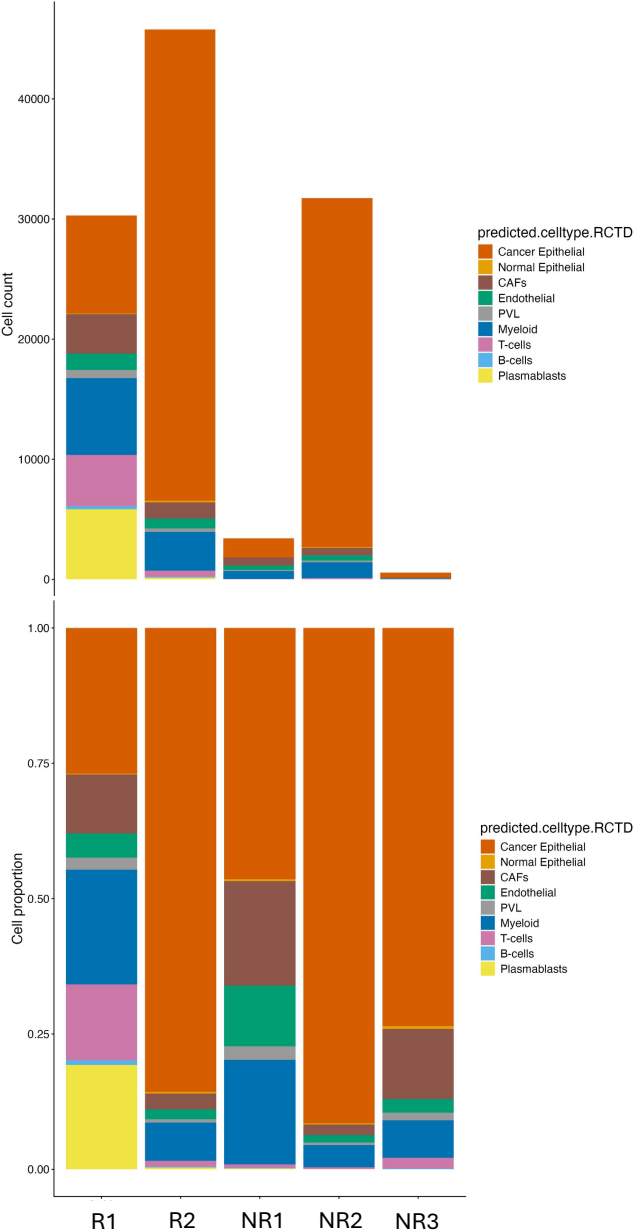
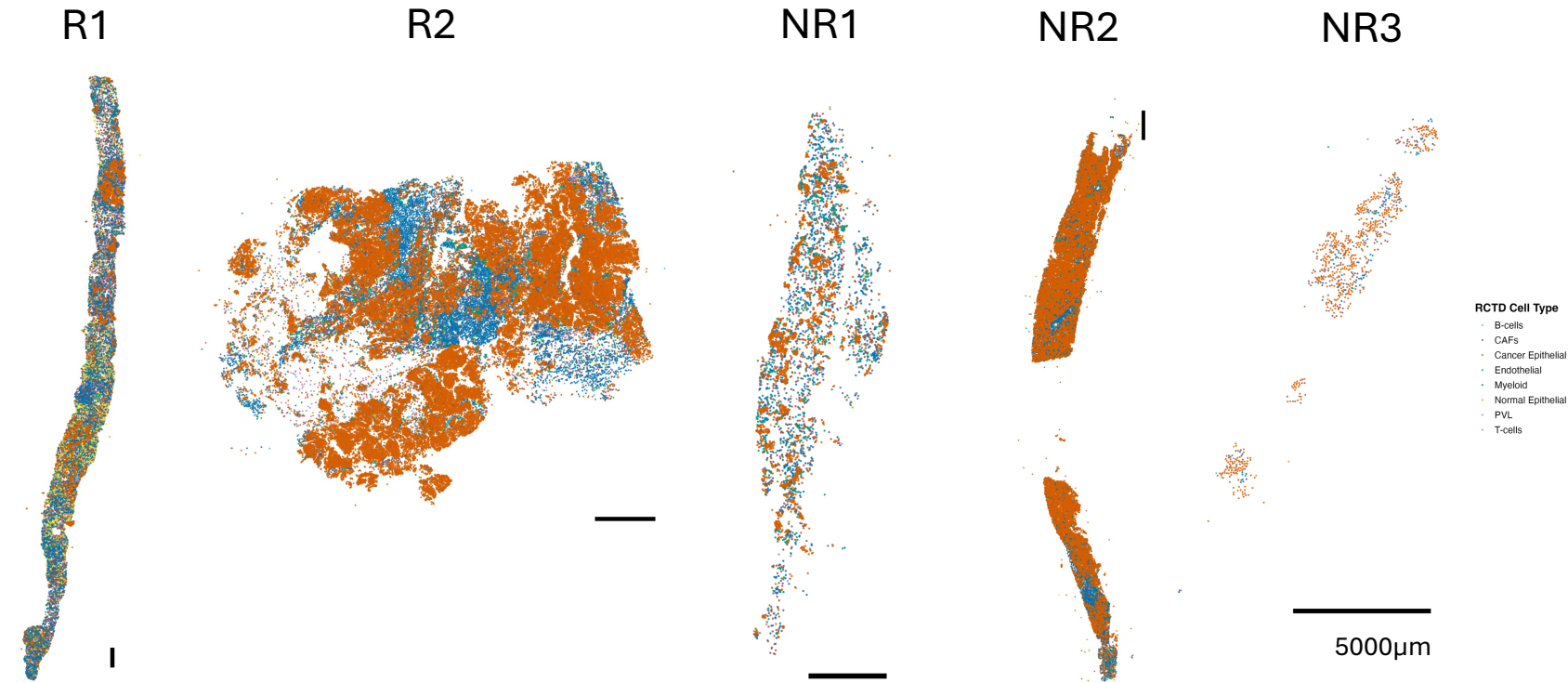


Breast, Ovarian, Pancreas, and Prostate cancer (BOPP)

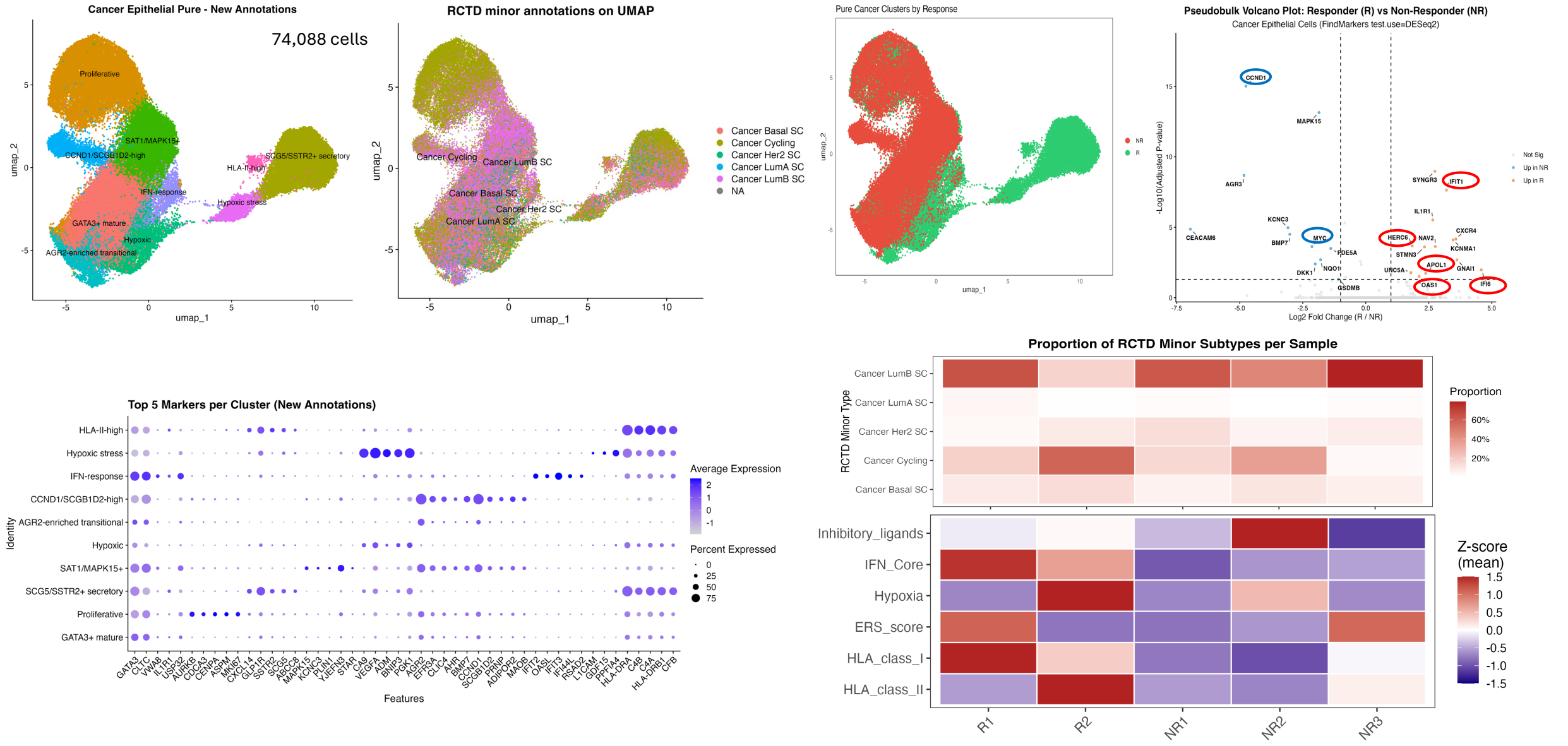


Xenium-based spatial transcriptomic analysis of responders and non-responders

ID	Best Response	PFS (month)	Subtype	Biopsy Site	Germline HR mutations	Somatic HR mutations	TMB
R1	CR	4.6	ER+ PR- HER2 (1+)	Mediastinal Lymph node	No	RAD51C	22
R2	PR	11.4	ER+ PR- HER2 (0)	Lung	Unknown	BRCA2	5.8
NR1	PD	2.8	ER+ PR- HER2 (1+)	Liver	No	No	4.1
NR2	PD	3.3	ER+ PR- HER2 (0)	Liver	No	BRCA2	9.9
NR3	SD	3.9	ER+ PR+ HER2 (0)	Chest wall	No	NA	NA



HLA and ISG programs are reduced in tumor cells from non-responders



Summary

- Downstream HRD was associated with higher TMB, higher indel burden, and mutational features suggestive of MMEJ, and with improved outcomes after ICB.
- At single-cell resolution, preneoplastic breast tissue from BRCA1 and BRCA2 mutation carriers showed distinct immune states.
- BRCA1 was associated with more suppressive myeloid features, whereas BRCA2 showed greater antigen-presentation activity and higher CD8+ T-cell cytotoxicity.
- In Xenium analysis of trial specimens, responder tumors were enriched for T cells with APC/HLA-active myeloid/tumor-cell niches, whereas non-responder tumors were markedly T-cell-depleted with dominant hypoxic niches.

NGS and how it may affect local therapy / radiation therapy in breast cancer patients

Possible read outs enabled by
NGS

↓

LOF
mutations in
key alleles

↓

Signature analysis/
inferences for HRD

↓

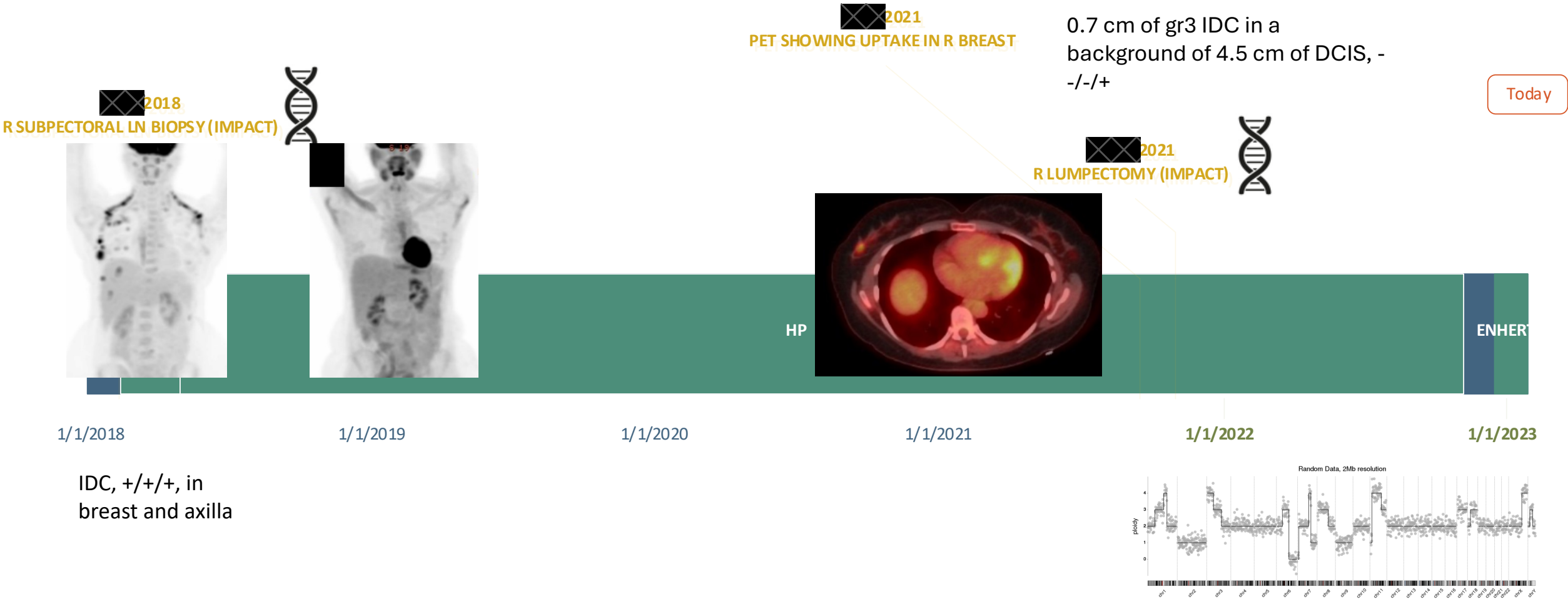
Phylogeny
inferences

↓

ctDNA read
outs in limited
disease

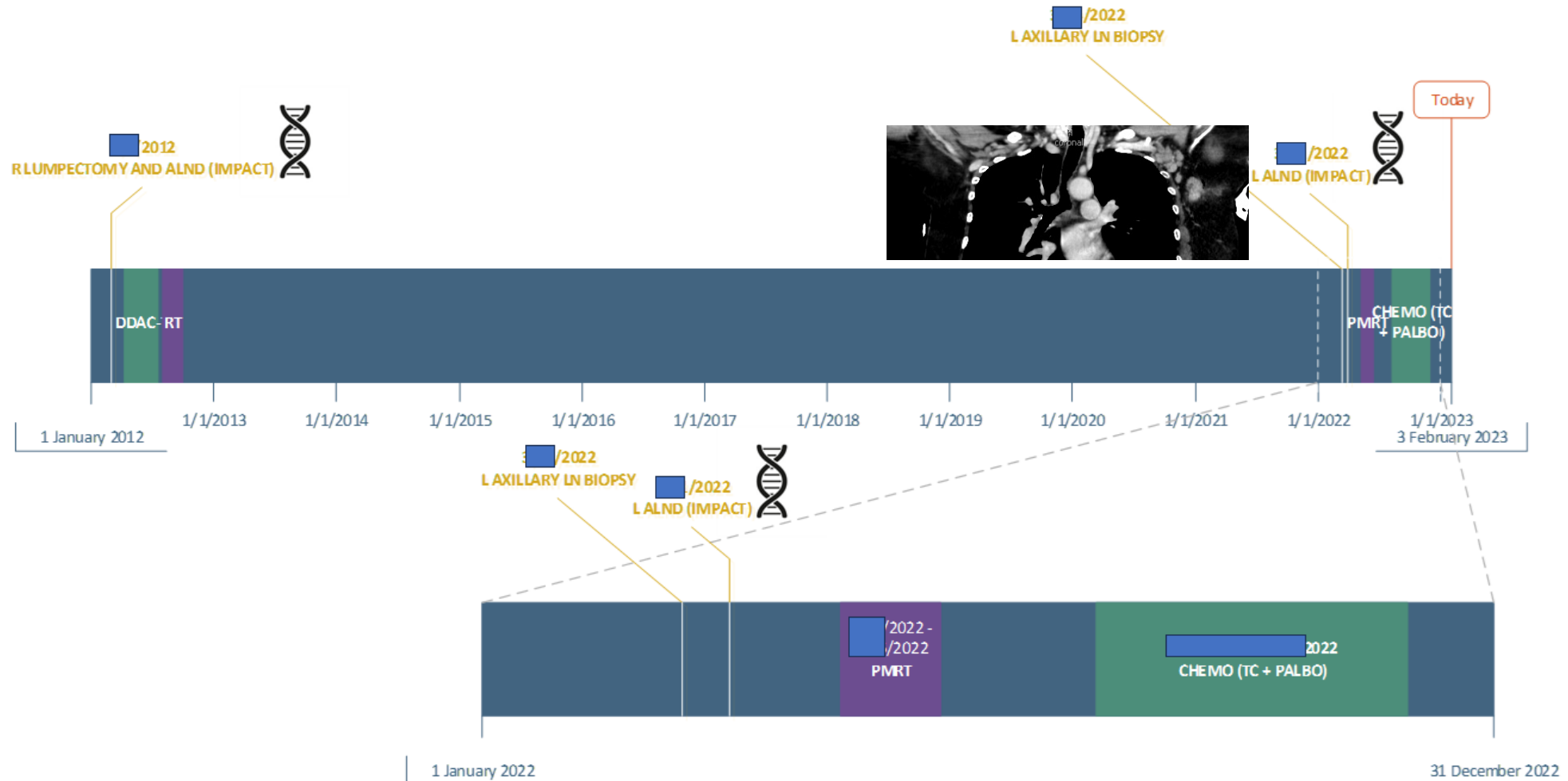
NGS to resolve tumor phylogeny

46 year old woman with de novo Her2+ MBC



NGS to resolve tumor phylogeny

58 year old woman with contralateral axillary disease 10 years after initial diagnosis.



NGS and how it may affect local therapy / radiation therapy in breast cancer patients

Possible read outs enabled by
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↓

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↓

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↓

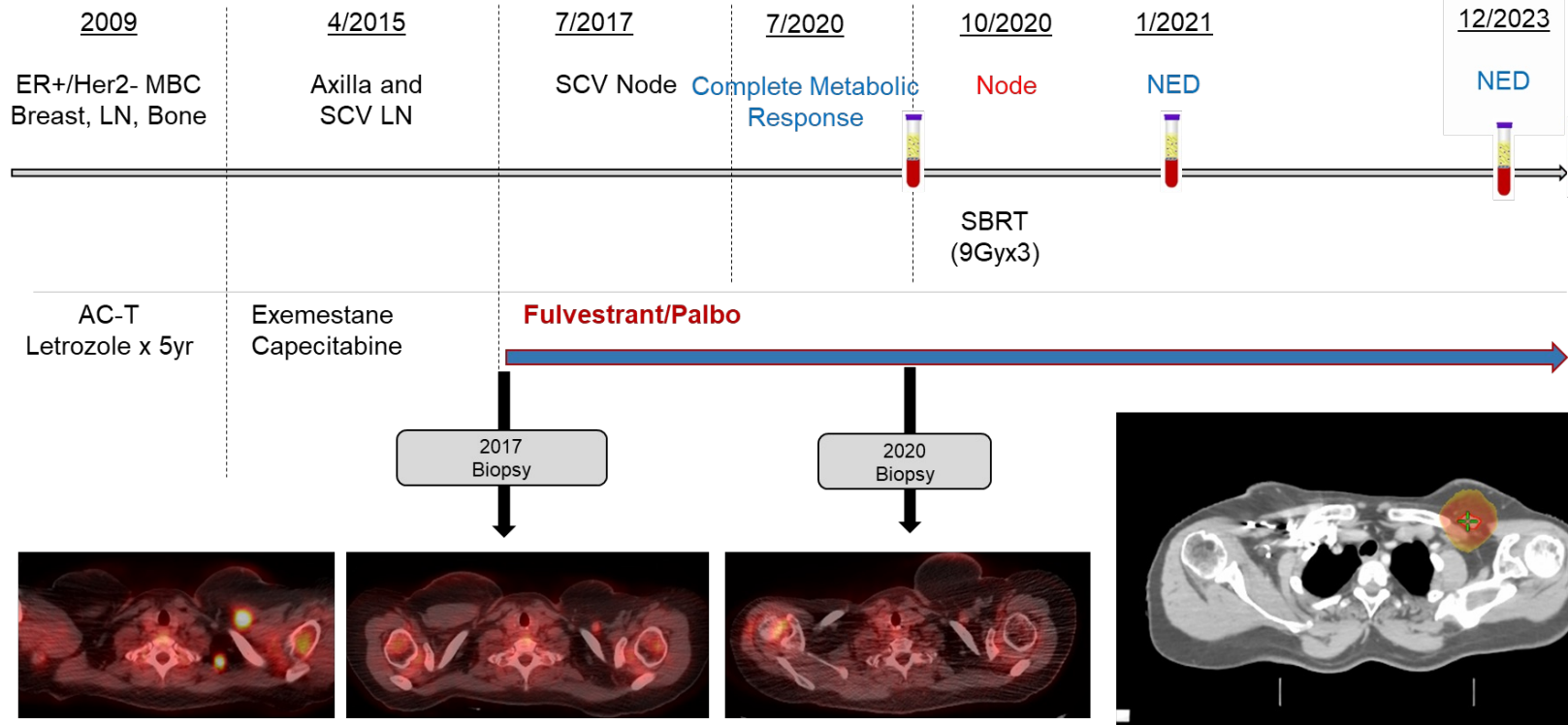
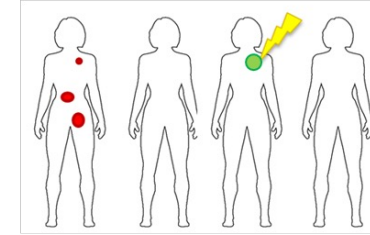
Phylogeny
inferences

↓

ctDNA read
outs in limited
disease

Role of SBRT for Solitary Progression

67F gBRCA2 ER+/Her2- MBC to Breast, LN, Bone



Role of SBRT for Solitary Progression

22-259 (AIM-B): SBRT to Ablate Isolated Disease on Systemic Therapy to improve PFS in Metastatic Breast Cancer

Eligibility:

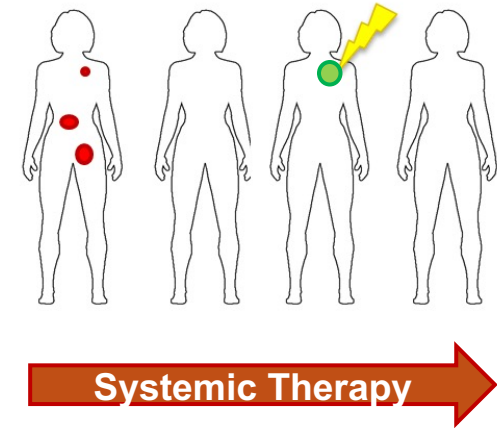
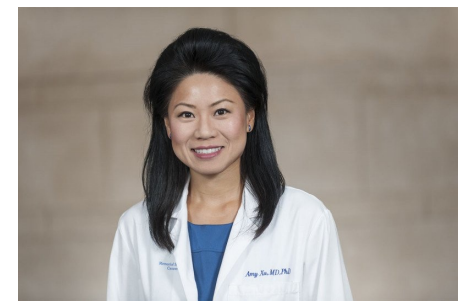
- Sustained response [CR or stable] to systemic therapy for ≥ 6 months
- Isolated site of progression, biopsy mandated (clinical, IMPACT testing)

Interventions:

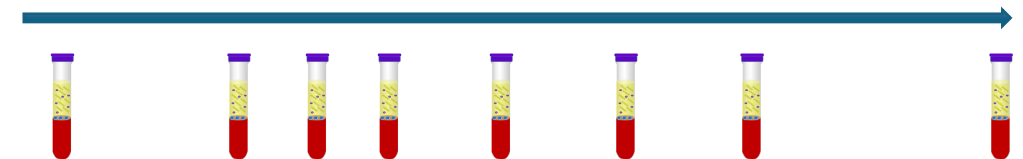
- SBRT to isolated site of progression (non randomized)
- Continue same systemic therapy

Endpoints:

- 1°: Progression Free Survival (3 month PFS 50% $\rightarrow$ 80%)
- 2°: Time to next line systemic therapy, OS, toxicity, local control (PERCIST)
- Exploratory:* Rate of ctDNA clearance 3 months following SBRT



Serial ctDNA monitoring



Summary

- The proliferation of NGS may allow tailored approaches to :
 - Dose de-escalation in the palliative setting
 - Combination drug + RT studies in high risk contexts
 - Phylogeny inferences that affect treatment indications and volumes
 - Selective use of RT in metastatic patients
- Breast cancer directed radiotherapy is still highly relevant!