UCSF Helen Diller Family Comprehensive Cancer Center

How Clinical Trials in Metastatic Breast Cancer are Shaping the Future in Early Stage Disease

Hope S. Rugo, MD
Professor of Medicine and Winterhof Family Distinguished Professor of Breast Oncology
Director, Breast Oncology and Clinical Trials Education
University of California San Francisco Comprehensive Cancer Center
San Francisco, CA USA

Key Recent Lessons Learned From MBC Trials

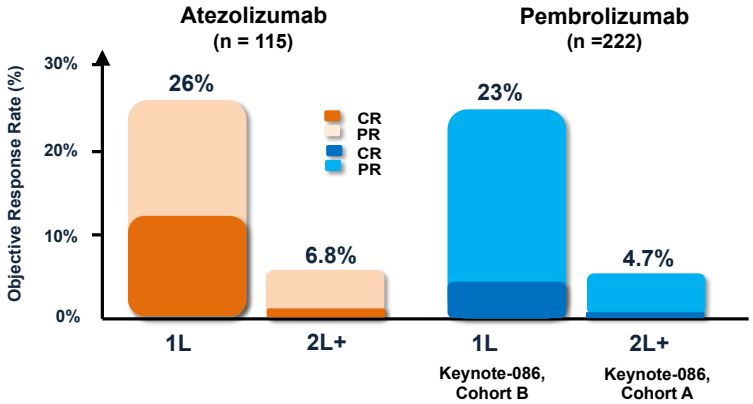
Data that has and is shaping trials in early-stage disease: a snapshot of HER2- Disease

- Immunotherapy
  - From TNBC to biologic subsets
- Antibody drug conjugates
  - Combinations
  - Targets and toxciity
- ctDNA
  - Targeting therapy to biologic subsets
- Individualizing therapy: neoadjuvant before post-neoadjuvant therapy

Immunotherapy

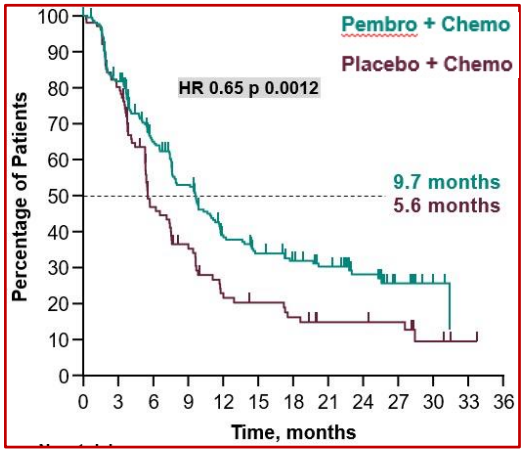
- **TNBC: metastatic to early-stage disease**
  - Prior treatment and rapid relapse is associated with poor response to immunotherapy
  - PD-L1 is clearly an imperfect marker: the addition of pembrolizumab to neoadjuvant/adjuvant therapy improves both pCR and EFS regardless of expression
- **Challenges moving forward**
  - Improve the efficacy of immunotherapy
    - Novel combinations: ADCs, immune targets
  - Improve biomarkers
    - Understanding resistance before increased resistant clonal expansion
      - We can't rescue rapidly developing resistant disease
    - Who needs more or less therapy?
  - HR+ disease: a new frontier?

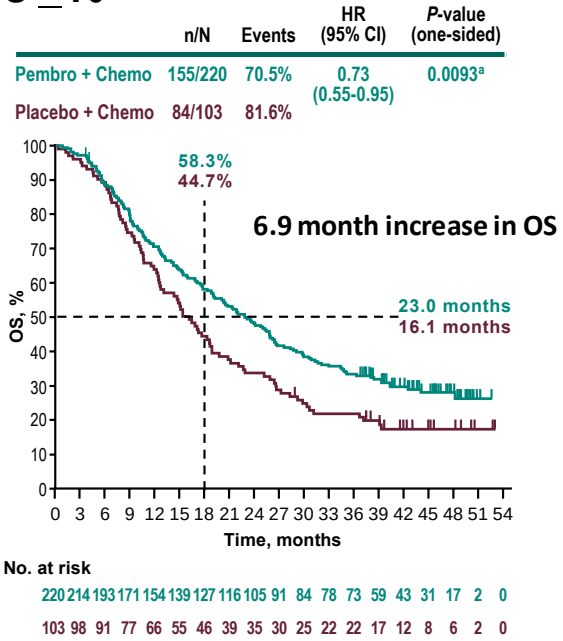
Monotherapy ORR for Metastatic TNBC: Line of Therapy Matters



First-line in Combination with Chemotherapy Improves PFS and OS in PD-L1+ Disease

PD-L1 CPS ≥10

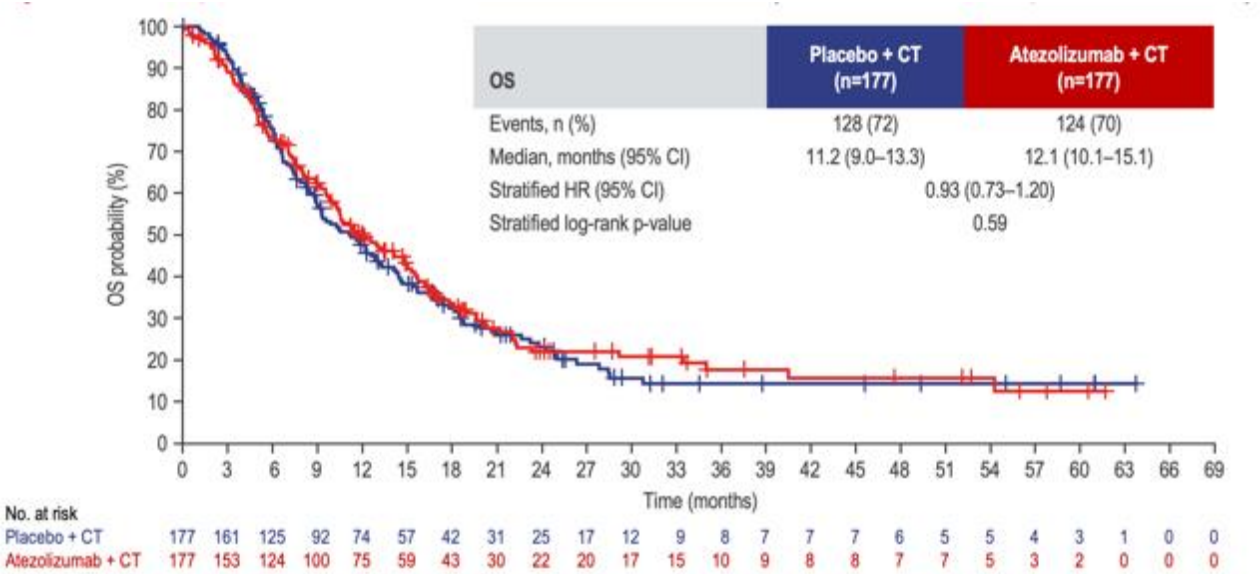




Emens et al, JAMA Onc 2018; Adams et al, Ann Onc 2018, Cortes et al, NEJM 2022

Rapid Development Of Resistant Disease

Impassion132: No improvement in OS in PD-L1+ TNBC



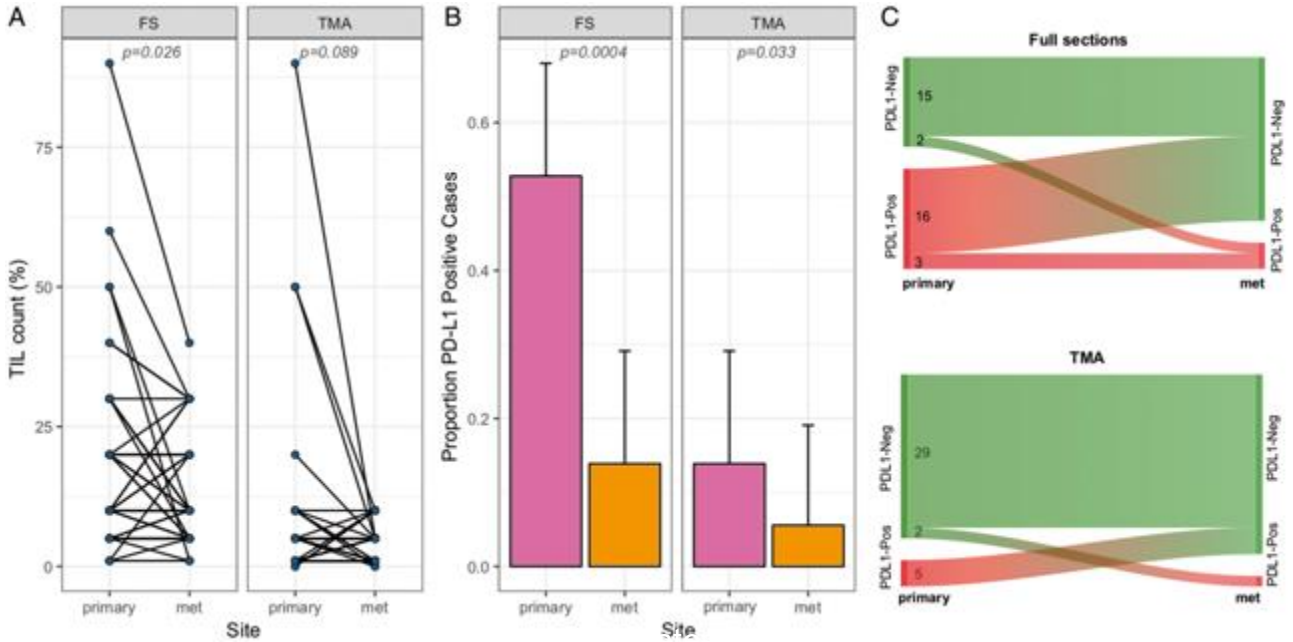
Patients with recurrent disease <12 months from adjuvant Rx

PFS ~4 mo

OS ~12 mo

Dent et al, ESMO BC 2024

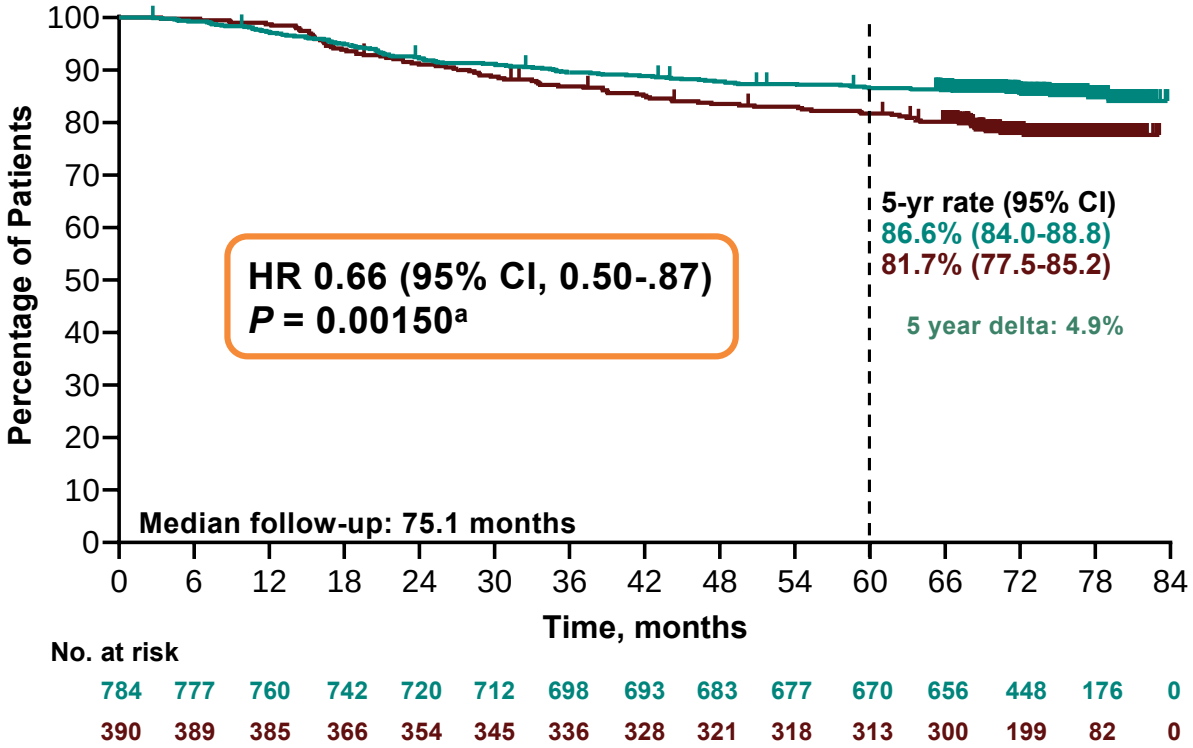
Immunologic Differences Between Primary and Metastatic Tumor Samples



Percent TIL counts in full sections and TMAs.

Szekely, et al (Pusztai), Ann Oncol 2018

Key Secondary Endpoint: Overall Survival



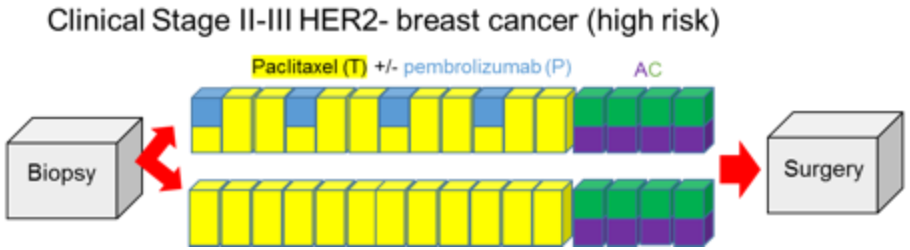
	Pts w/ Event
Pembro + Chemo/Pembro	14.7%
Placebo + Chemo/Placebo	21.8%

67.3% information fraction[a]

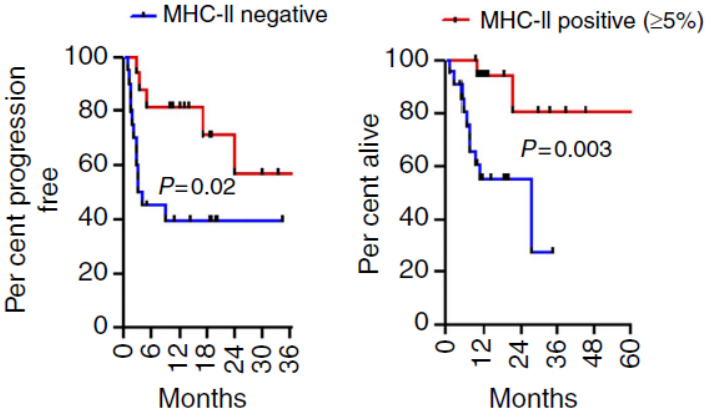
Schmid et al, ESMO 2024

HLA-DR/MHC Class II

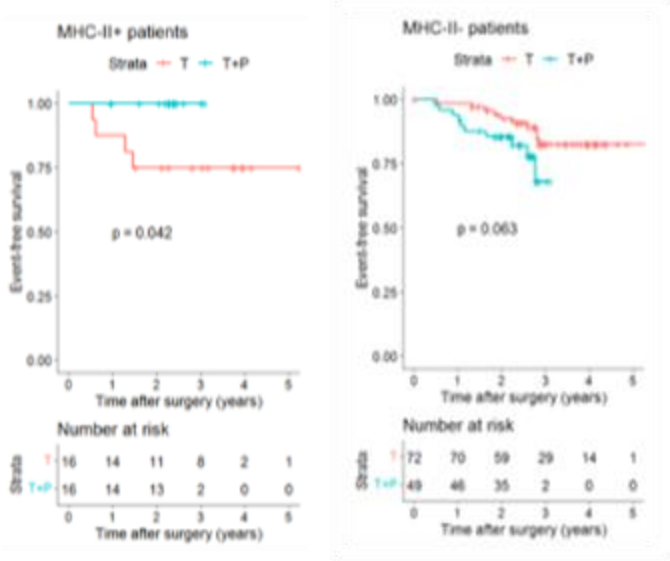
- Predicts benefit from immune checkpoint inhibitors in melanoma and lymphoma
- Ongoing analyses in early stage TNBC in pre-op setting



Gonzalez-Ericsson et al, ISPY2 team CCR, 2021



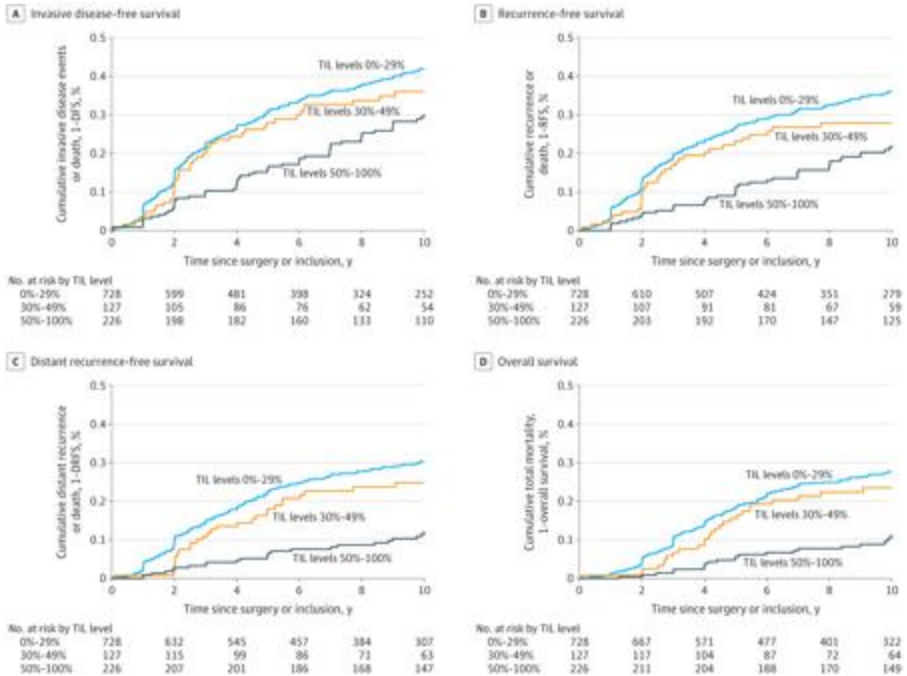
Johnson DB, …, Balko, Nature Communications 2016



TILS as a Prognostic Biomarker – decrease therapy?

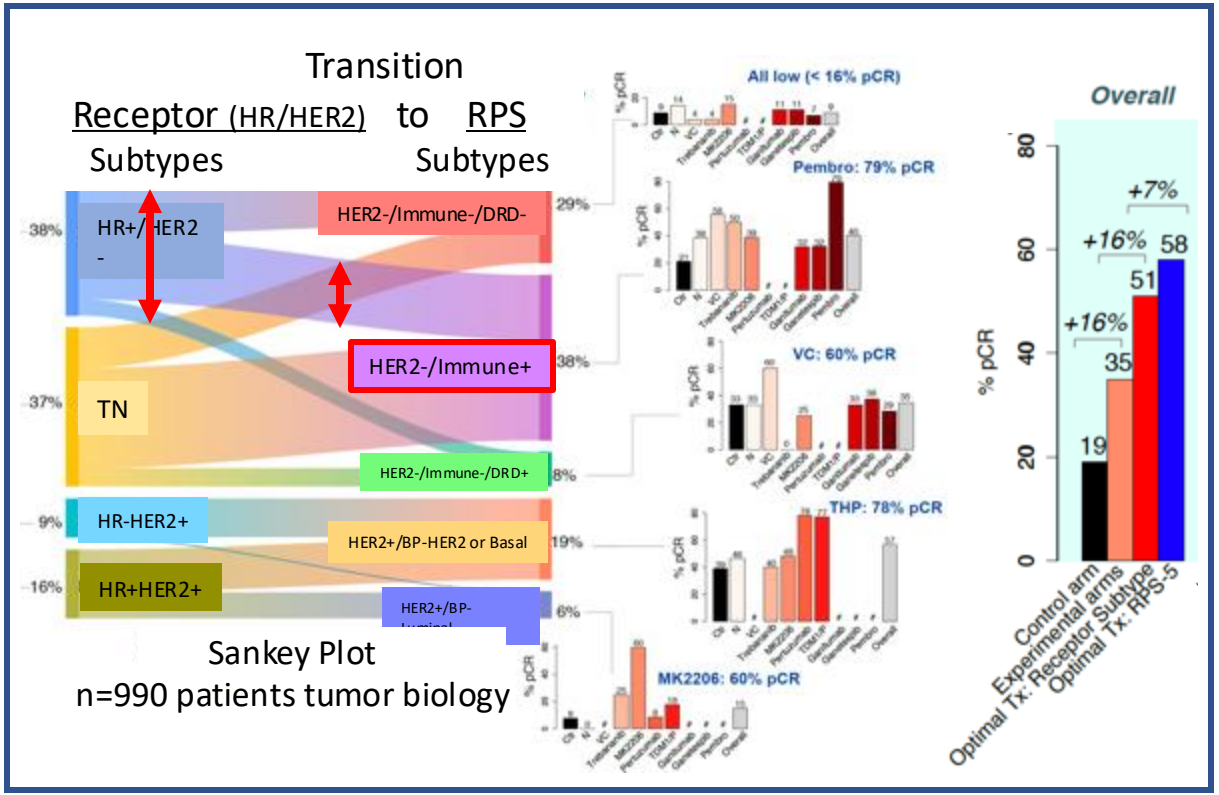
- Retrospective international study
  - 1966 patients with TNBC diagnosed between 1979-2017
    - Treatment with surgery with/without RT, no chemotherapy
    - 55% stage I, median age 56, median TIL 15% (IQR, 5%-40%)
      - TILs ≥50%: 21% TILS <30%: 66%
- 5 year DRFS and OS for stage I TNBC
  - TIL ≥50%:
    - DRFS 94% (95% CI, 91%-96%)
    - OS 95% (95% CI, 92%-97%)
  - TIL <30%:
    - DRFS 78% (95% CI, 75%-80%)
    - OS 82% (95% CI, 79%-84%)
- Median FU 18 years
  - Each 10% higher TIL increment was independently associated with improved iDFS, RFS and OS
- **Could TILs help stratify treatment based on risk?**
  - >1% TILS predicted benefit from nivolumab in Checkmate 7FL

Mortality Events for the Stage I TNBC Subset Using Prespecified TIL Thresholds



Leon-Ferre et al, JAMA 2024 Apr 2;331(13):1135-1144.doi: 10.1001/jama.2024.3056

I-SPY Developed Response Predictive Subtypes



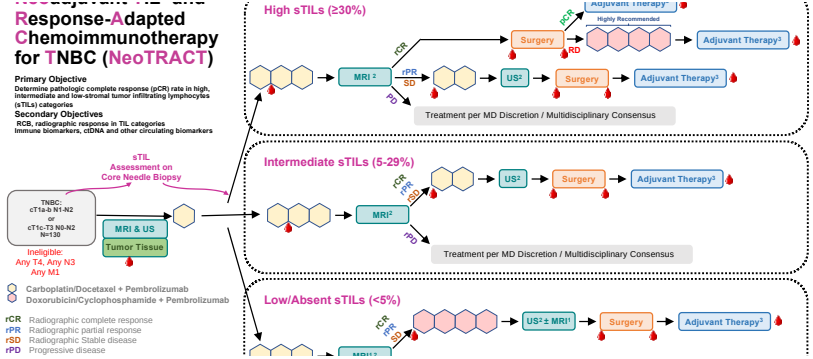
Wolf, Yau, Esserman, van 't Veer et al; 2022 Cancer Cell

Increase Response Prediction (first n=990 patients, 9 arms + control):

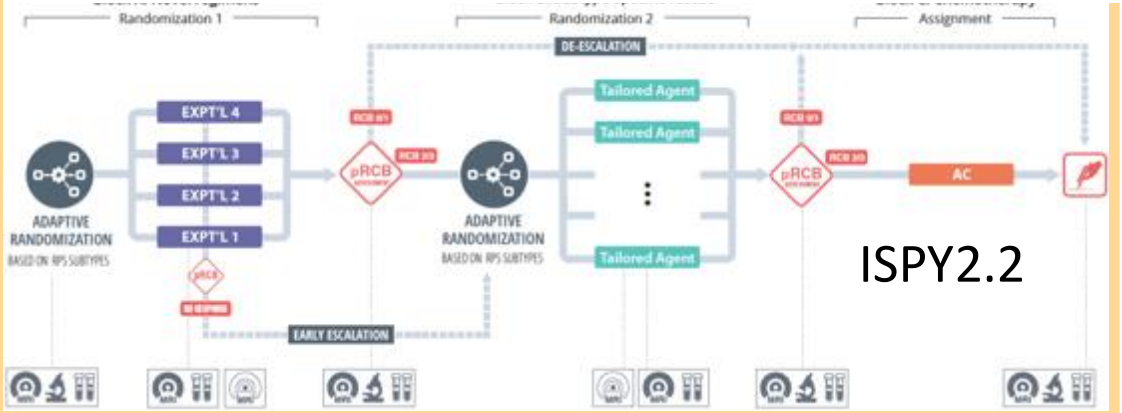
1) Standard Chemotherapy without subtype selection 20-25%
2) Receptor subtype with preferred/optimal targeted agent ~50%
3) Response Predictive Subtypes with preferred targeted agent predicted ~60-70% (ongoing)
4) Goal > 90% of patients have pCR (associates w 95% 5yr DRFS)

Next Steps in the Neoadjuvant Setting

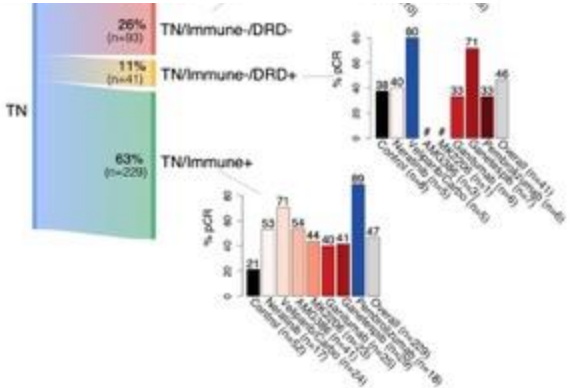
Stratify treatment based on TILS



ISPY2.2: Individualize therapy based on biology/biomarkers and response in the neoadjuvant setting; test new agents first



ISPY2.2

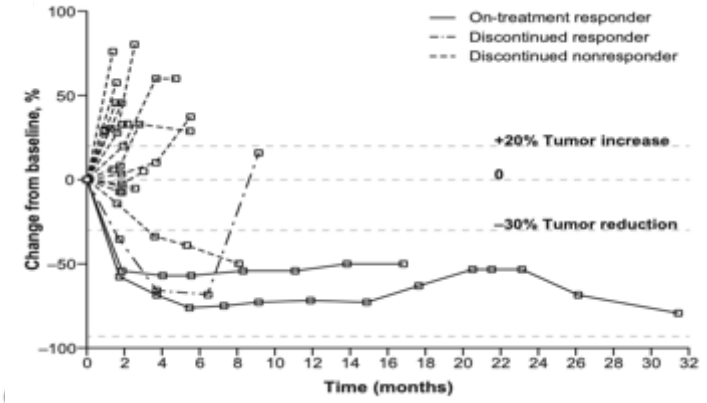


Yee D et al. 2022 ASCO Abstract 591; Wolf, Yao et al, CCR 2022.

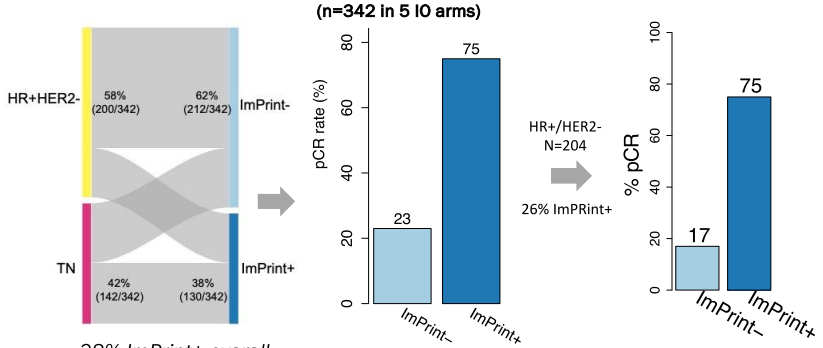
Immunotherapy: What Did We Learn In HR+ Disease?

Refining who benefits

- Keynote 028
  - Heavily pre-treated HR+/HER2- metastatic disease
  - 19.4% PD-L1 positive: 25 treated with pembrolizumab alone
    - ORR 12%, CBR 20% BUT DOR 12 months
- I-SPY2
  - Mammaprint high risk ≥stage II HR+/HER2- disease
    - pCR higher in high-2, basal-like disease and in IMPRINT positive



I-SPY2: Overall HER2- and HR+:
IMPRINT Prevalence and Performance with Immunotherapy



- *38% ImPrint+ overall*

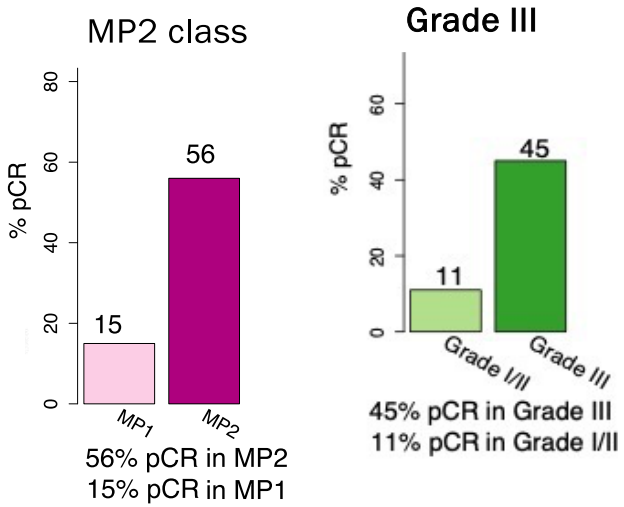
Wolf, Yau, et al, ASCO 2023, AACR 2024; Huppert et al, ASCO 2022

- ***75% pCR in ImPrint+***
- ***23% pCR in ImPrint-***

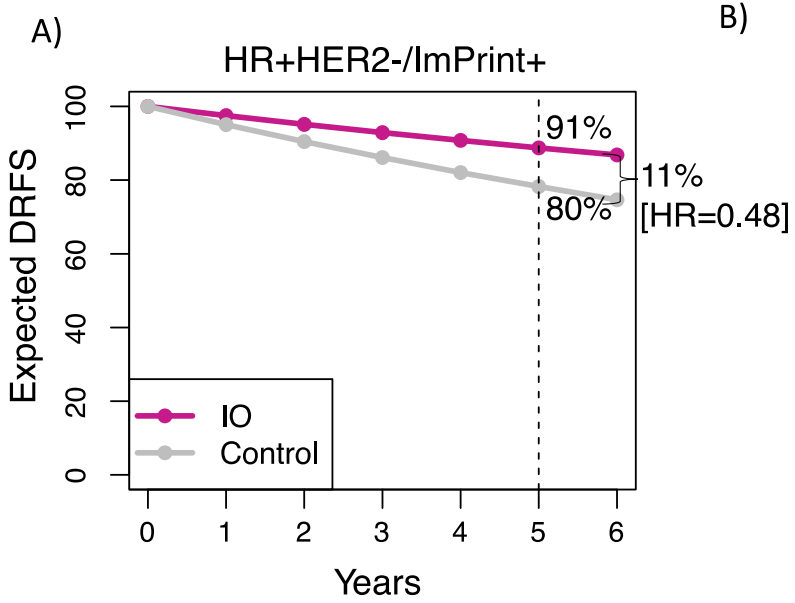
- *75% pCR in ImPrint+*
- *17% pCR in ImPrint-*

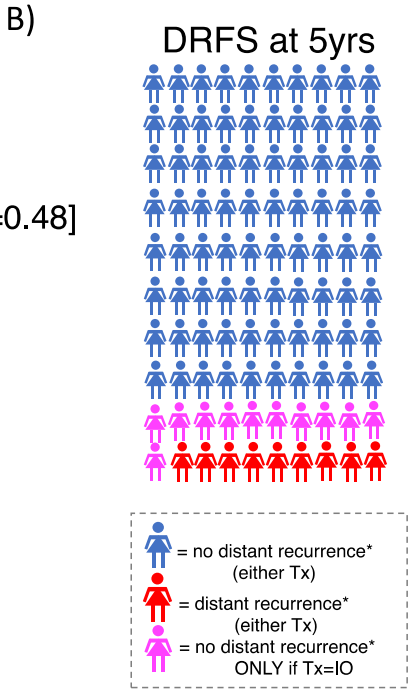
Rugo et al, CCR 2018; Wolf, Yao et al, AACR 2024

IMPRINT: Better PPV than MP2 and Grade



HR+HER2-/Imprint+: Predicted Distant RFS Advantage For IO Over Control





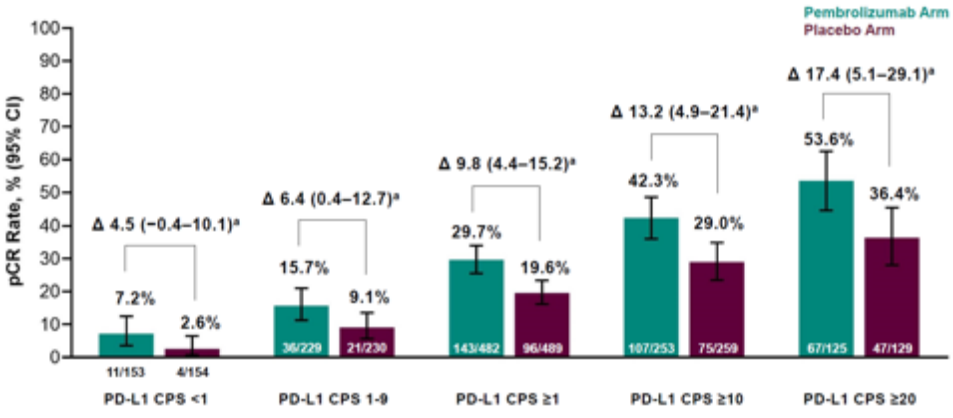
- Based on the pCR rates in the IO vs. control (75% vs. 33%), the predicted DRFS of HR+HER2-/ImPrint+ patients are 91% vs 80% at 5 years, respectively.

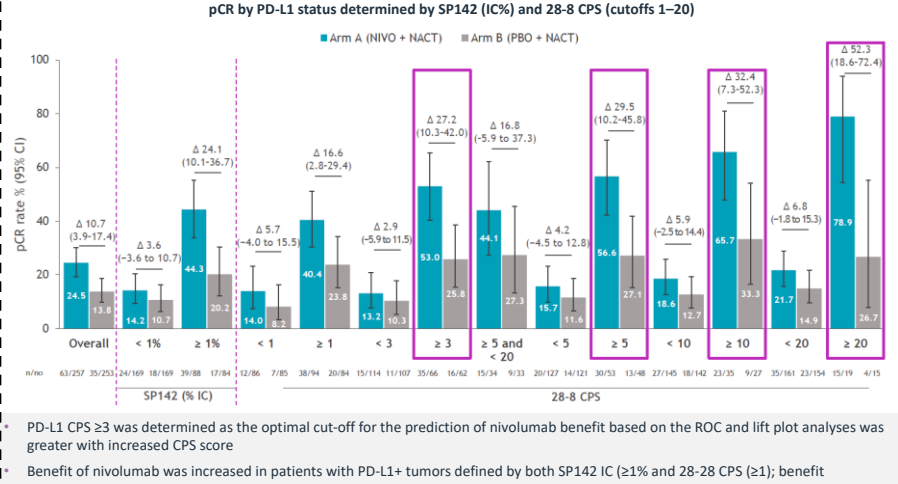
Wolf, Yau, et al, AACR 2024

KEYNOTE-756 and CheckMate 7FL: pCR by PD-L1 Expression in High Risk HR+ Disease

All grade 3, centrally confirmed, at least stage II

pCR rate by PD-L1 expression





- PD-L1 CPS ≥3 was determined as the optimal cut-off for the prediction of nivolumab benefit based on the ROC and lift plot analyses was greater with increased CPS score
- Benefit of nivolumab was increased in patients with PD-L1+ tumors defined by both SP142 IC (≥1% and 28-28 CPS (≥1); benefit

In addition to PD-L1 expression, ER expression plays a clear role in response to IO

Data cutoff: May 25, 2023 (first planned interim analyses)
O'Shaughnessy J, et al. SABCS 2023. Abstract GS01-02

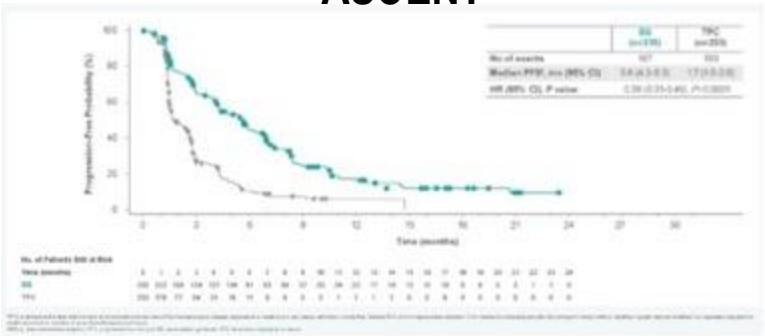
Loi S, et al. SABCS 2023. Abstract GS01-01

Antibody Drug Conjugates

A revolution in chemotherapy delivery

Sacituzumab govitecan in mTNBC

ASCENT

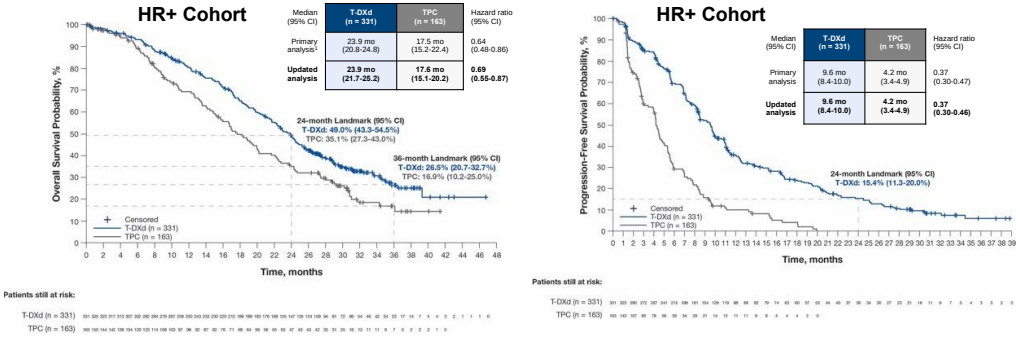


Bardia et al. *NEJM*, 2021; Modi et al, NEJM 2022

Trastuzumab deruxtecan in mHR+/HER2low

Destiny Breast-04

Updated OS and Investigator Assessed PFS in HR+/HER2 Low MBC



Primary Analysis (BICR)

OS	HR+ T-DXd (n=331)	HR+ TPC (n=163)
Median OS, months	23.9	17.5
HR (95% CI); *P* value	HR 0.64 (0.48-0.86); 0.0028	

PFS	HR+ T-DXd (n=331)	HR+ TPC (n=163)
Median PFS, months	10.1	5.4
HR (95% CI); *P* value	0.51 (0.40-0.64); <0.0001	

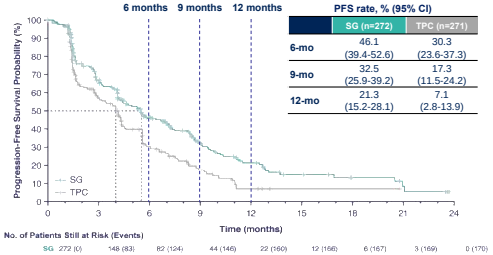
Modi S et al. *N Engl J Med*. 2022;387(1):9-20. Modi S. 2023 ESMO Congress. Abstract 3760.

TROP2 ADCS: Broad Efficacy

TROPiCS-02 for HR+/HER2- Disease: PFS & OS in the ITT Population

PFS[1]

BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2-7.0)	4.0 (3.1-4.4)
Stratified HR (95% CI)	0.66 (0.53-0.83)	
Stratified Log Rank *P* value	*P*=.0003	



PFS rate, % (95% CI)	SG (n=272)	TPC (n=271)
6-mo	46.1 (39.4-52.6)	30.3 (23.6-37.3)
9-mo	32.5 (25.9-39.2)	17.3 (11.5-24.2)
12-mo	21.3 (15.2-28.1)	7.1 (2.8-13.9)

OS[2,3]

	SG (n=272)	TPC (n=271)
Median OS, mo (95% CI)	14.5 (13.0-16.0)	11.2 (10.2-12.6)
Stratified HR (95% CI)	0.79 (0.65-0.95)	
Nominal *P* value	*P*=.0133	

OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-mo	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-mo	25.7 (20.5-31.2)	21.1 (16.3-26.3)

SG demonstrated a statistically significant improvement in PFS and OS vs TPC

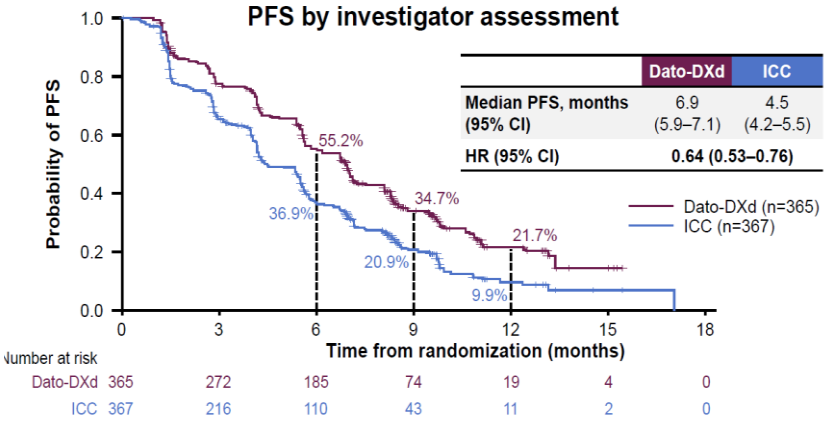
Median follow-up was 10.2 months.
BICR, blinded independent central review; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376. Adapted from Rugo HS, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol. 2022.* doi: 10.1200/JCO.22.01002. Reprinted with permission from American Society of Clinical Oncology. 2. Rugo H, et al. ESMO 2022. Oral LBA76. 3. Tolaney et al, ASCO 2023. Abstract 1003; Rugo et al, Lancet 2023

No new toxicity signals compared to ASCENT

Rugo et al, Lancet 2023

TROPION-Breast01: PFS

PFS by investigator assessment



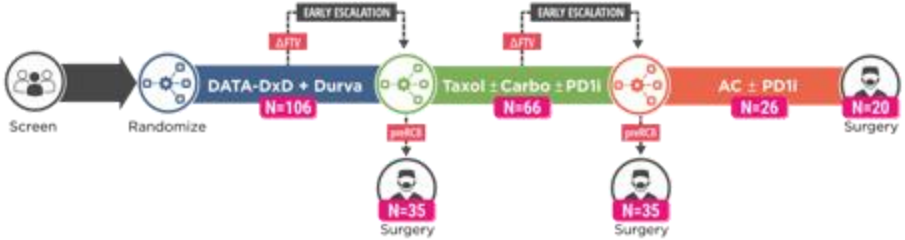
	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.9–7.1)	4.5 (4.2–5.5)
HR (95% CI)	0.64 (0.53–0.76)	

Bardia A, et al. SABCS 2023. Abstract GS02-01

23 Sept 2024: No OS benefit: Role of ADC sequencing

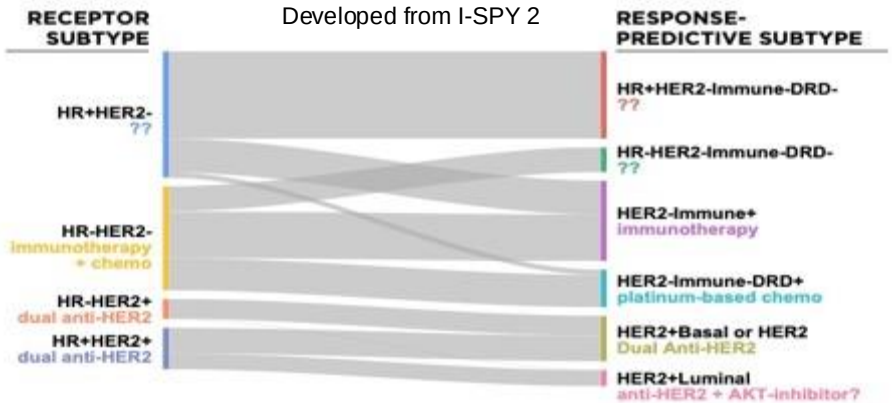
Can We Optimize Neoadjuvant Systemic Treatment?

Dato-DXd + Durva Schema



Primary Endpoint: pCR

Block B: Based on RPS (Response Predictive Subtypes)

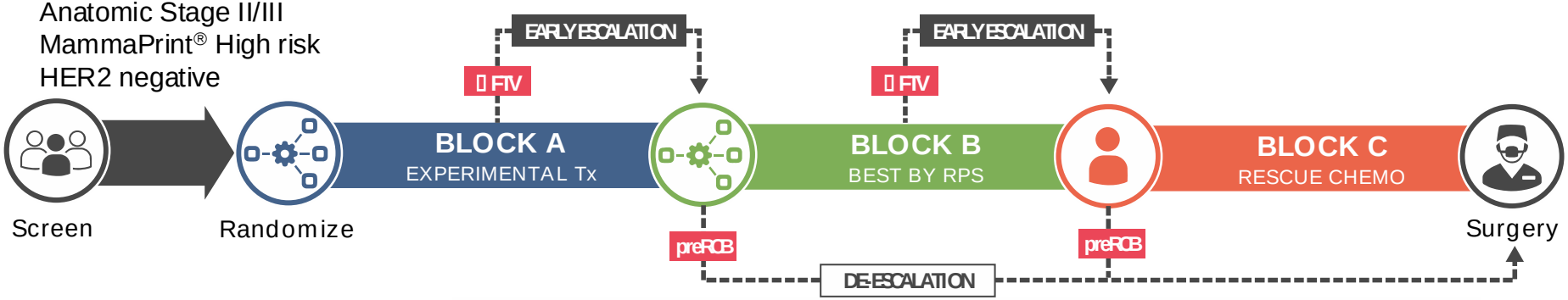


- RPS developed from ~990 I-SPY2 patients across 9 arms
- Reflects predicted sensitivity to immune, DNA damage repair deficiency, HER2-targeting agents
- Used to inform I-SPY 2.2 Block B agent drug assignments/ randomization
- In Dato+Durva arm (HER2-)
  - 38% of HR+ are immune+
  - 49% of HR- are immune+

Shatsky et al, ASCO 2024; Adapted from Cortes, ASCO 2024

I-SPY 2.2 Design Features: Multiple Sequential Regimens

Eligibility for Dato+Durva arm:
Anatomic Stage II/III
MammaPrint® High risk
HER2 negative



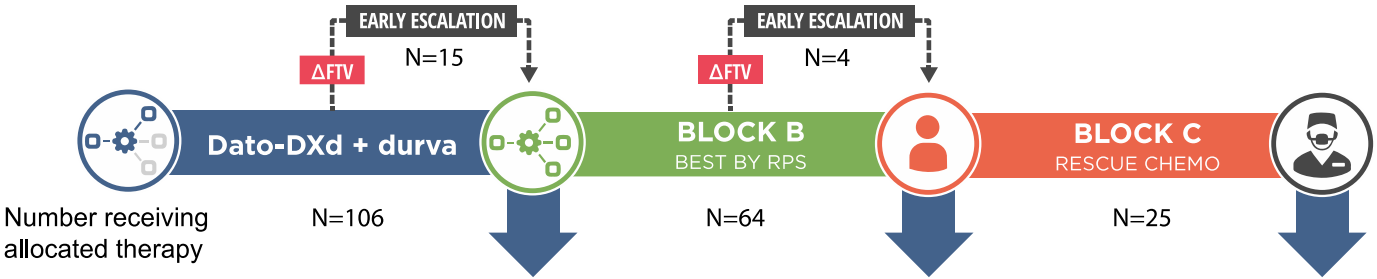
Treatment Assignments/Randomization	*based on Response Predictive Subtype (RPS)*	
HR+ HER2- Immune- DRD-	Taxol	AC
HR- HER2- Immune- DRD-:	Taxol + Carbo + Pembro	AC + Pembro
HER2- Immune+:	Taxol + Carbo + Pembro	AC + Pembro
HER2- Immune- DRD+:	Taxol + Carbo + Pembro	AC + Pembro
HER2- Immune- DRD+:	Taxol + Carbo	AC + Pembro

Comparator arm: Dynamic control

Specific to each subtype identified from previously tested I-SPY2 agents between March 2010 and April 2022 (e.g. paclitaxel -> AC ; paclitaxel + pembrolizumab -> AC ; paclitaxel + veliparib + carboplatin -> AC)

Trivedi et al, ESMO 2024 and Shatsky et al, Nat Med 2024

Timing of pCR in Immune+ and HR- subtypes



				Total
Num exiting block	42	39	25	**106**
Num pCR after block	25	22	6	**53**

	After Block A	After Block B	After Block C	Total
HER2-Immune+ (N=47)				
N achieving pCR	20	14	3	37
Cumulative % of total observed pCR	54%	92%	100%	
HR-HER2-* (N=64)				
N achieving pCR	21	15	3	39
Cumulative % of total observed pCR	54%	92%	100%	

* Excludes 1 patient who did not receive pembrolizumab in Block B

ISPY2.2: Key Takeaways

The ISPY 2.2 Dato + Durva treatment strategy resulted in an overall pCR rate of 50%

- The highest pCR rate was seen in Immune+ (79%) followed by HR- (62%) subtypes
  - > 50% of pCRs achieved by Block A alone and >90% achieved by Block B
  - Many patients were able to avoid taxane and/or anthracycline treatment
- In HR-/Immune-/DRD-, the modeled pCR rate for the treatment strategy outperformed the dynamic control

TB04 Study Design: Ph3 Dato-DXd + Durva in Neoadjuvant/Adjuvant TNBC

TROPION-Breast04

Neoadjuvant | Surgery | Adjuvant

Key Eligibility Criteria

- Histologically confirmed Stage II or III unilateral or bilateral primary invasive breast cancer.
- TNBC (ER and PR < 1%) or hormone receptor-low breast cancer (ER and/or PR 1% to < 10%, neither hormone receptor may be ≥ 10%), and HER2-negative.
- No evidence of distant disease.
- No prior surgery, radiation, or systemic anticancer therapy.
- ECOG PS 0 or 1.
- Adequate hematologic and organ function.

Stratification factors:

- Lymph node status (positive versus negative)
- Tumour stage (cT1 to cT2 versus cT3 to cT4
- Hormone receptor status (hormone receptor-negative [ER and PR < 1%] versus hormone receptor-low (ER and/or PR 1% to < 10%, neither hormone receptor may be ≥ 10%])
- Geographic region (US/Canada/Europe/Australia versus Rest of World).

1:1

Experimental Arm

Dato-DXd + durvalumab
Q3W x 8 (24 weeks)

→ Durvalumab x 9 cycles +/- chemotherapy [a, b, c]

Control Arm

Pembrolizumab + carboplatin + paclitaxel
Q3W x 4 (12 weeks)

→

Pembrolizumab + doxorubicin or epirubicin + cyclophosphamide
Q3W x 4 (12 weeks)

→ Pembrolizumab x 9 cycles +/- chemotherapy [a, c, d]

Dual primary endpoints:
pCR and EFS

Secondary endpoints:
OS, DDFS, safety and tolerability, PROs, PK, immunogenicity

Exploratory endpoints include but are not limited to:
TROP2, PD-L1

a. Endocrine therapy is permitted for participants with hormone receptor-low tumours. No adjuvant CDK4/6 inhibitor (eg, abemaciclib, ribociclib).
b. Adjuvant chemotherapy may be given in combination with durvalumab for participants with residual disease. Chemotherapy options at discretion of investigator, either: doxorubicin/epirubicin + cyclophosphamide, followed by paclitaxel + carboplatin; doxorubicin/epirubicin + cyclophosphamide followed by paclitaxel; carboplatin + paclitaxel; capecitabine.
c. Olaparib may be administered to participants who are g*BRCA*-positive with residual disease.
d. Adjuvant capecitabine may be given in combination with pembrolizumab for participants with residual disease, at the discretion of investigator.

PI: Heather McArthur
NCT06112379

Antibody Drug Conjugates: Does Expression of the Target Receptor Matter?

TROPiCS-02: Sacituzumab govitecan in HR+/HER2- MBC

PFS

	Status	Median PFS, months (95% CI)		HR (95% CI)
		SG	TPC	
Trop-2	H-score <100	5.0 (4.1, 6.0) n=96	4.0 (2.7, 5.6) n=96	**0.79** (0.56, 1.12)
	H-score ≥100	5.8 (4.0, 8.3) n=142	4.1 (2.3, 4.5) n=128	**0.61** (0.45, 0.83)

OS

	Status	Median OS, months (95% CI)		HR (95% CI)
		SG	TPC	
Trop-2	H-score <100	14.9 (12.7, 18.1) n=96	11.3 (10.0, 13.3) n=96	**0.78** (0.57, 1.06)
	H-score ≥100	14.4 (12.7, 17.0) n=142	11.2 (9.9, 12.7) n=128	**0.82** (0.63, 1.08)

DESTINY BREAST-04: Trastuzumab deruxtecan in HR+ HER2low MBC

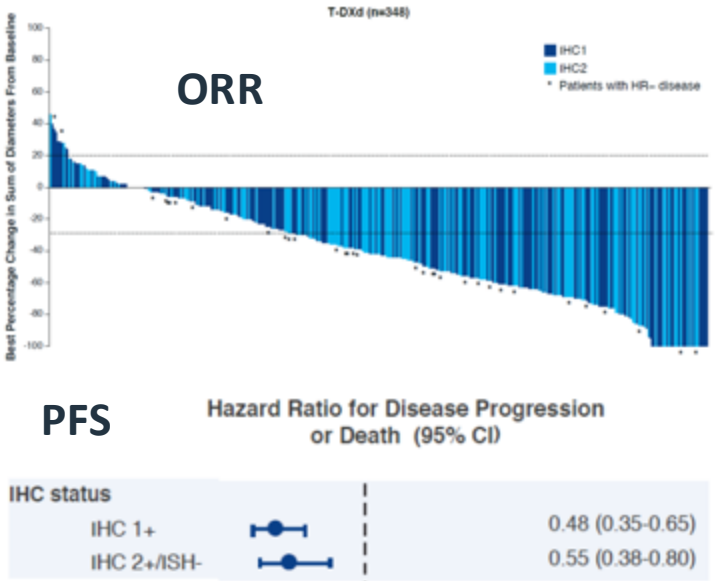


Figure modified from supplemental material

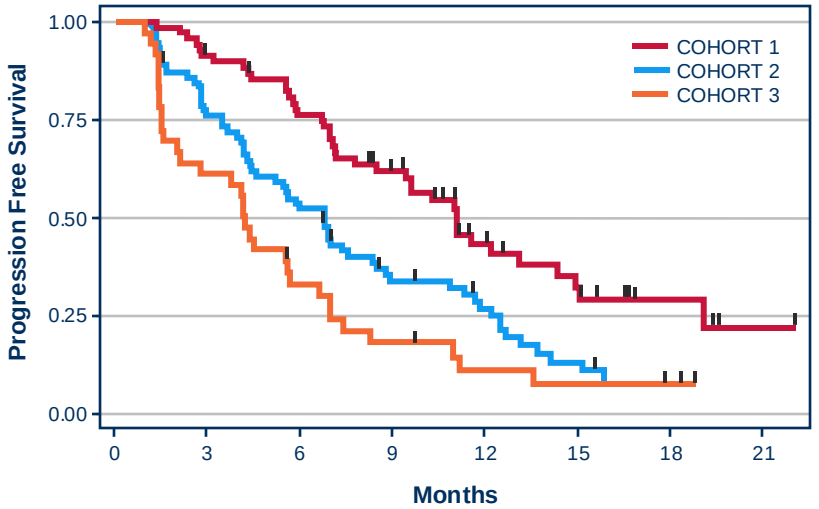
Tolaney et al. ASCO 2023. Abstract 1003; updated from Rugo et al, ESMO 2022 and Rugo et al, SABCS 2022; Rugo et al, Lancet 2023; Modi NEJM 2022, SABCS 2022

DAISY: PFS According to HER2 Expression[1]

NCT04132960

Data cut-off: Oct 19, 2021	Cohort 1 HER2 IHC 3+ or IHC 2+/ISH+ (n=68)	Cohort 2 HER2 IHC 2+/ISH- or IHC 1+ (n=72)	Cohort 3 HER2 IHC 0 (n=37)
Median PFS (mths) (95% CI)	11.1 (8.5–14.4)	6.7 (4.4-8.3)	4.2 (2-5.7)
HR (95% CI)	0.53 (0.34-0.84)	1.00	1.96 (1.21-3.15)
***p*-value**		***p* <0.0001**	

	Median PFS	Median OS
(HR+)	4.5 months	11.6 months
(HR-)	2.1 months	10.3 months



COHORT 1	68	61	50	34	18	11	4	1
COHORT 2	72	54	37	21	15	6	2	0
COHORT 3	37	22	11	6	3	2	1	0

THE PFS IS DEFFERENT BETWEEN THE THREE COHORTS *p* <0.0001

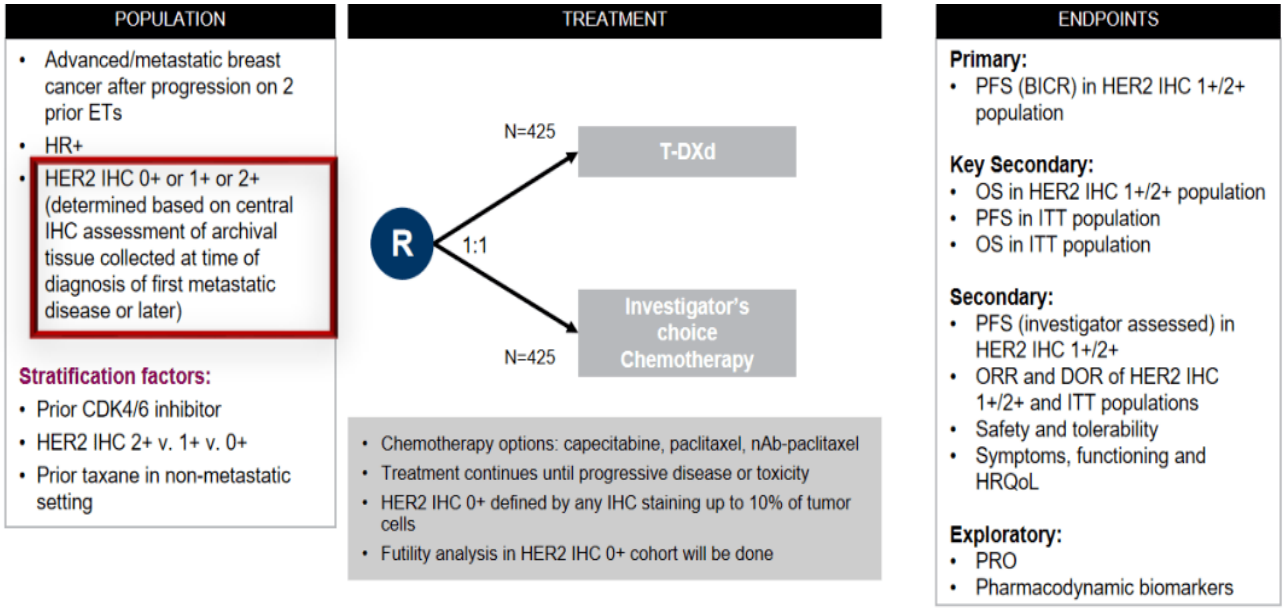
Median follow-up: 15.6 months

1. Mosele F, et al. Nat Med. 2023;29(8):2110-2120. doi:10.1038/s41591-023-02478-2

Testing Trastuzumab Deruxtecan in HER2 'Ultralow' DESTINY-Breast06

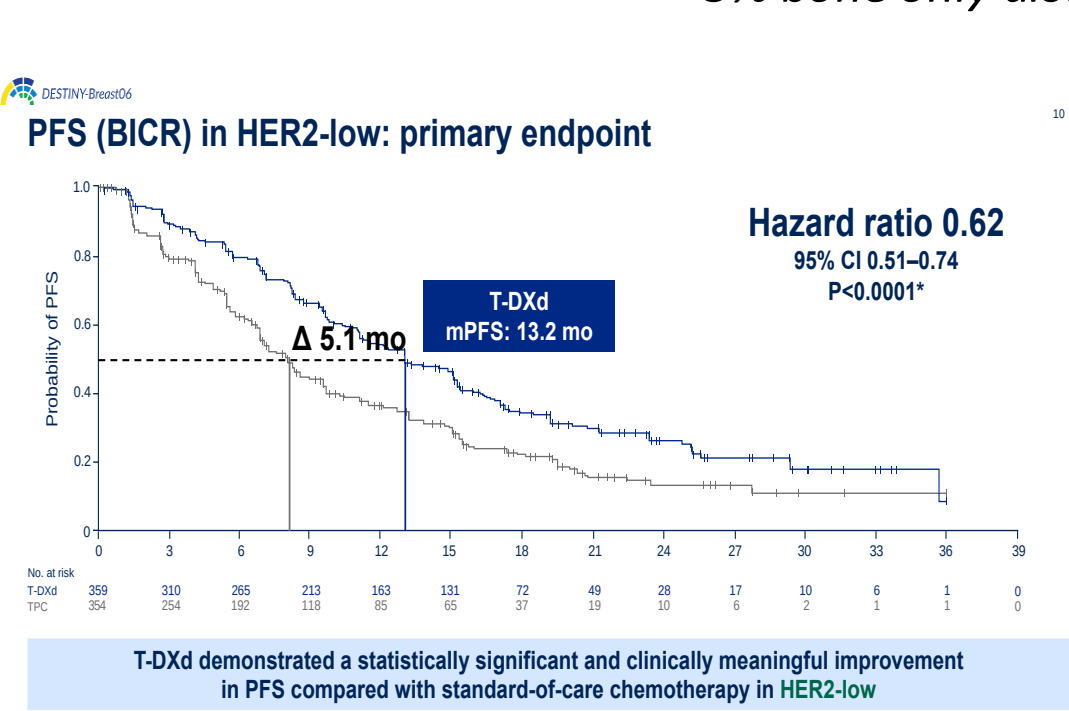
Key differences with DB-04:

- Includes IHC0 (ultralow, n=150)
- Larger (n=850)
- Restricted to HR+ disease
- Chemo-naïve patients

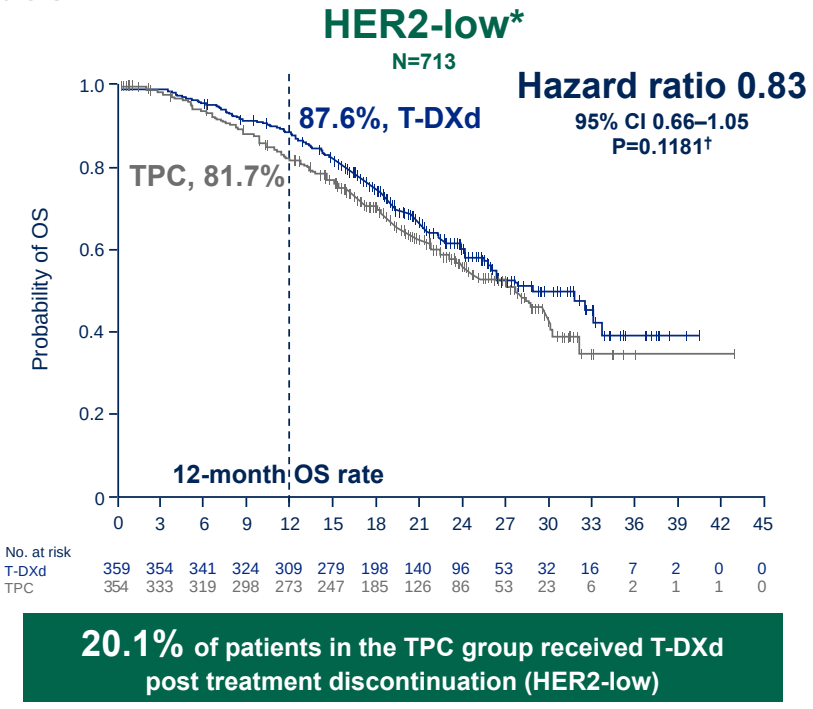


Destiny Breast-06: PFS and OS in HER2-Low

3% bone only disease



T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

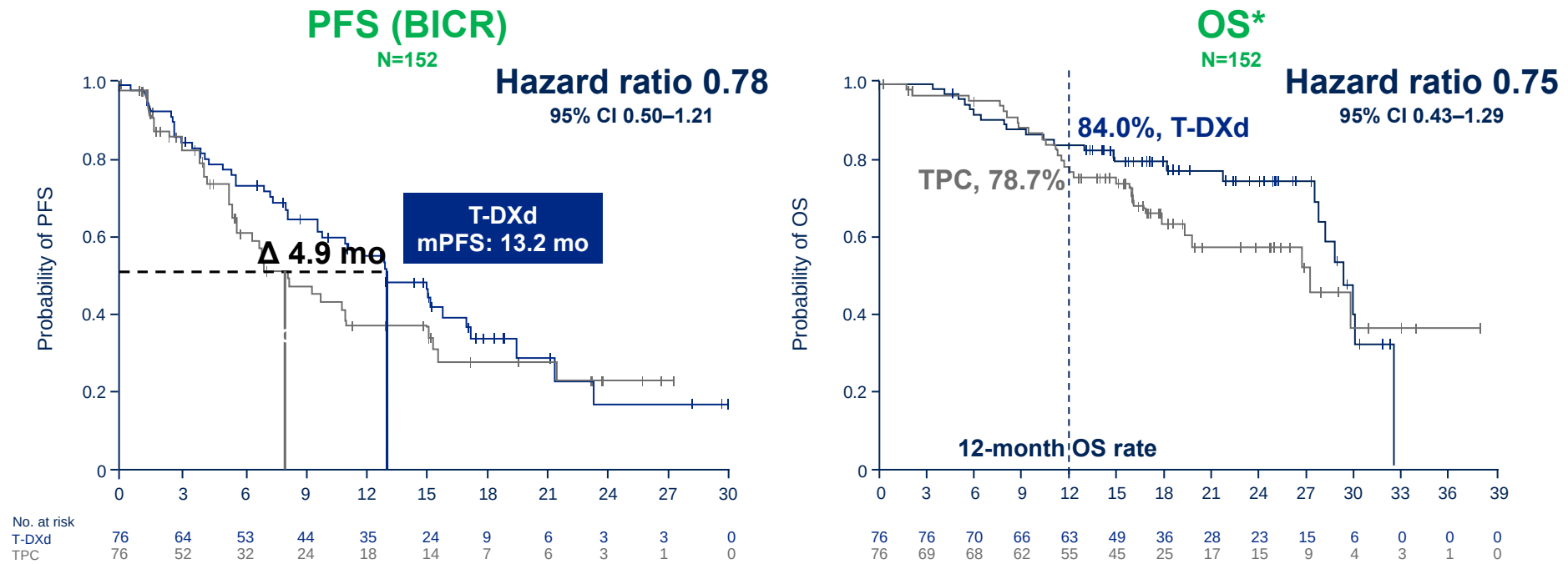


20.1% of patients in the TPC group received T-DXd post treatment discontinuation (HER2-low)

Curigliano et al, ASCO 2024 LBA

Destiny Breast-06: PFS and OS in HER2-ultralow

Prespecified Exploratory Analyses



PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

Curigliano et al, ASCO 2024 LBA

ASCENT and TROPiCS-02: Safety Outcomes by UGT1A1 Status

UGT1A1

- ✓ Variants affect enzymatic function, causing reduced metabolic capacity
- ✓ Over 50% of individuals may harbor an UTG1A1 polymorphism, dependent on genetic ancestry

	ASCENT		TROPiCS-02	
SG patients (n=250)	UTG1A1 Status n(%)	Dose Intensity (%)	UTG1A1 Status n(%)	Dose Intensity (%)
*1/*1 (wt)	113 (44)	99.8	104 (38)	99
*1/*28	96 (37)	99.5	119 (44)	98
*28/*28	34 (13)	99.8	25 (9)	94

Grade ≥3 TEAEs Overall (%)	SG (n=268)
Neutropenia	52
Diarrhea	10
Anemia	8
Febrile neutropenia	6

	ASCENT			TROPiCS-02		
Grade ≥3 TEAEs By UTG1A1 Status (%)	*1/*1 (wt)	*1/*28	*28/*28	*1/*1 (wt)	*1/*28	*28/*28
Neutropenia	53	47	59	45	57	64
Diarrhea	10	9	15	6	13	24
Anemia	4	6	15	6	8	8
Febrile neutropenia	3	5	18	6	7	4
Growth factor for neutropenia (initiated on/after first dose) overall 54%						
				33	49	11

ASCENT: Treatment discontinuation due to TRAEs more common in *28 homozygous genotype

Nelson et al. *Cancers.* 2021;13:1566.
Rugo et al. *npj Breast Cancer.* 2022;8:98.
Marmé et al. *Annals of Oncol.* 2023;8(1suppl_4):101223-101223.
Rugo et al, Lancet 2023

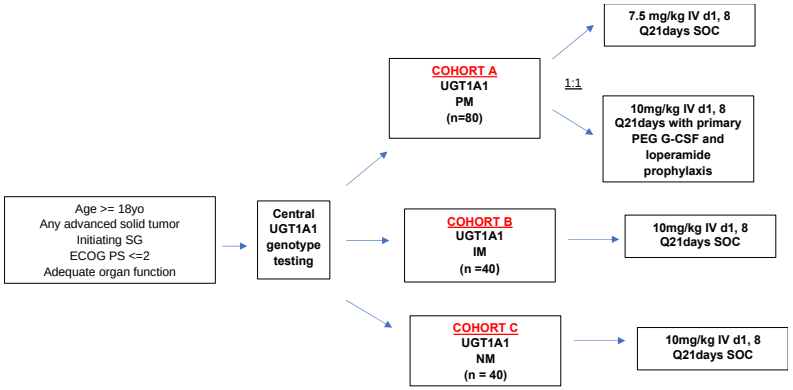
UNDERSTANDING UGT1A1 POLYMORPHISMS

An opportunity to maximize efficacy and minimize toxicity

Predicted UGT1A1 Phenotypes Based on Commonly Observed Diplotypes						
Predicted UGT1A1 Phenotype	Frequently Reported Diplotypes [Less Commonly Investigated Diplotypes] β					
Normal metabolizer (NM)	*1/*1 [*1/*36, *36/*36]					
Intermediate metabolizer (IM)	*1/*28, *1/*6 [*1/*37, *6/*36, *28/*36, *36/*37]					
Poor metabolizer (PM)	*6/*6, *6/*28, *28/*28 [*6/*37, *28/*37, *37/*37]					
UGT1A1 Phenotype Frequencies among Racial/Ethnic Groups μ						
UGT1A1 Phenotype	African American/Afro-Caribbean	Central/ South Asian	East Asian	European	Latino	Sub-Saharan African
NM	2%	29%	50%	13%	4%	32%
IM	20%	50%	42%	46%	33%	49%
PM	78%	21%	8%	41%	63%	19%

Ryan et al, Cancers 2021

OPTIM-SG: Alliance Trial Concept

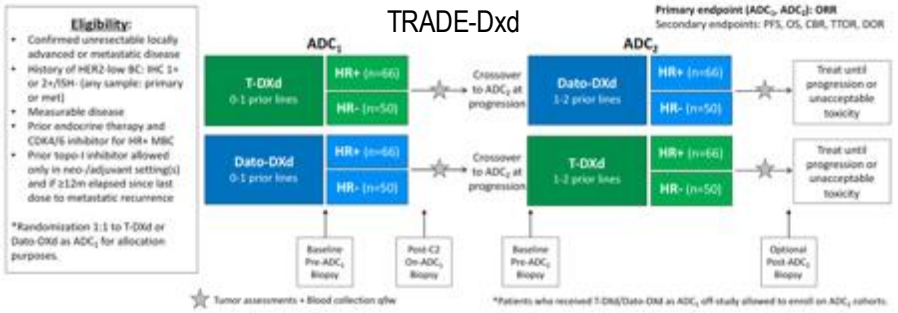


- *UGT1A1 PM: *28*28, *6*6, *37*37 ,*6*28, *6*37, *28*37*
- *UGT1A1 IM : *28*1 *6*1, *36*1, *37*1, *37*36, *6*36, *28*36 AND UGT1A1 NM: *36*36, *1*1*

Sagar Sardesai, Daniel Hertz, Maryam Lustberg

Next Steps for ADCS

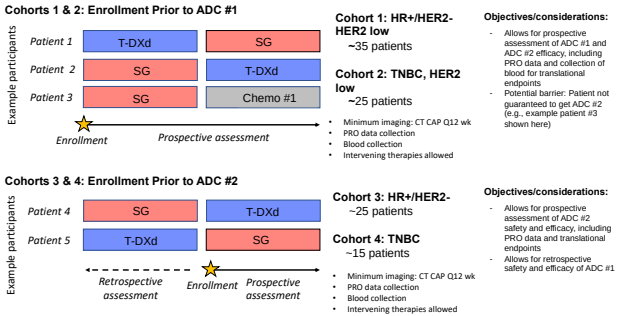
- First-line
- Rapidly move to the early-stage setting
  - Post-neoadjuvant
  - Neoadjuvant
- Understanding sequencing
- Mechanisms of resistance
- Combination therapy
- New antibodies, new payloads



PI: Ana Garrido-Castro

Registry sequencing study

PI: Laura Huppert



SERIES Study. PI: Reshma Mahtani

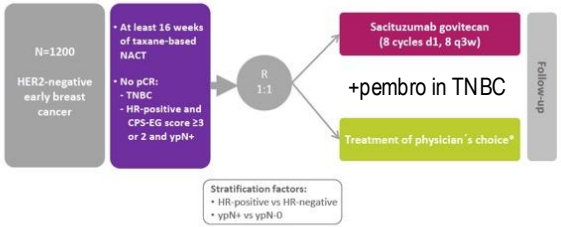
ASCENT-03 (NCT05382299): PD-L1 negative
N=540

First-line therapy
- PD-L1 neg TNBC
- TNBC Rxd with IO in early stage

→ Sacituzumab govitecan

→ TPC: paclitaxel, nab-paclitaxel, gem/carbo

GBG: SASCIA Post-Neoadjuvant Trial
NCT04595565



TROPION-Breast02 (n=625)
NCT05374512

PD-L1 negative

Key eligibility criteria:
- Locally recurrent inoperable or metastatic TNBC
- No prior chemotherapy or targeted systemic therapy for metastatic breast cancer
- Not a candidate for PD-1 / PD-L1 inhibitor therapy
- Measurable disease as defined by RECIST v1.1
- ECOG PS 0 or 1
- Adequate hematologic and end-organ function

Stratification factors:
- Geographic location
- DFI (*de novo* vs DFI >12 months)

1:1

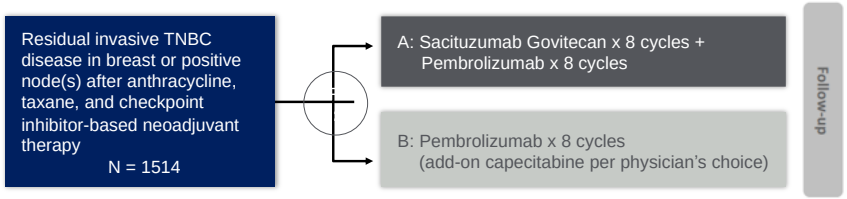
→ Dato-DXd

→ Investigator's choice of chemotherapy

Neoadjuvant TNBC
TROPION Breast04 (n=1728)
NCT06112379
Dato/durva

NeoSTAR
SG/pembro
Laura Spring

Phase III Trial: Optimice-RD/ASCENT-05
Residual disease in TNBC



PI: Sara Tolaney; Alliance Foundation Trial

Ascent-07:
First-line Chemotherapy in HR+

Key eligibility criteria:
- HR+/HER2* negative, locally advanced and unresectable, or metastatic breast cancer
- Eligible for first chemotherapy for advanced mBC
- Progressed after 1 or more ET for mBC, or relapsed within 12 months of completing adjuvant ET or while receiving adjuvant ET
- No prior treatment with a topoisomerase I inhibitor
- Measurable disease per RECIST v1.1
- Prior CDK 4/6i not required (no prior CDK 4/6i capped at 30%)

N = 654
2:1 randomization

→ Sacituzumab govitecan 10 mg/kg IV Days 1 and 8, every 21 days

→ Treatment of physician's choice (capecitabine, paclitaxel, nab-paclitaxel)

Stratification:
- Duration of prior CDK 4/6i in metastatic setting (none/≤12 mos vs >12 mos)
- HER2 IHC (HER2 IHC 0 vs HER2 IHC-low ([IHC 1+; 2+/ISH-])
- Geographic region (US/CAN/EU vs. ROW)

Primary Endpoint
- PFS by BICR

Key Secondary Endpoints
- OS
- ORR by BICR
- TTDD to Physical functioning

Secondary Endpoints
- PFS by investigator
- ORR by investigator
- DOR
- Safety

TROPION Breast03 (n=1075)
NCT05629585

N=1075
Stage I-III TNBC
Residual disease after at least 6 cycles of neoadjuvant chemotherapy

→ R 1:1:1

→ Datopotamab deruxtecan x 8 cycles Durvalumab x 9 cycles

→ Datopotamab deruxtecan x 8 cycles

→ Capecitabine x 8 cycles OR Pembrolizumab x 9 cycles OR Cape + Pembro

Sacituzumab Tirumotecan (sac-TMT)

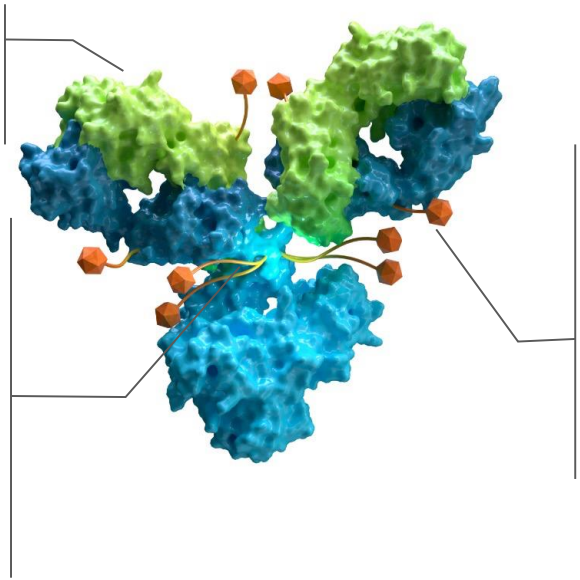
Sac-TMT is a TROP2 ADC developed with a proprietary Kthiol (pyrimidine-thiol) linker conjugated to a novel topoisomerase I inhibitor at DAR 7.4. The features of sac-TMT lead to release of the payload both in the tumor microenvironment (TME) and inside tumor cells, achieving a balance between the safety and efficacy of the ADC.

Antibody

- hRS7, a recombinant humanized anti-TROP2 antibody with high affinity

Linker

- **Kthiol conjugation:** irreversible coupling to improve stability of ADC
- **Payload release:** intracellular enzymatic cleavage and extracellular hydrolysis in TME
- **Balanced stability:** balance between efficacy and safety to expand therapeutic window

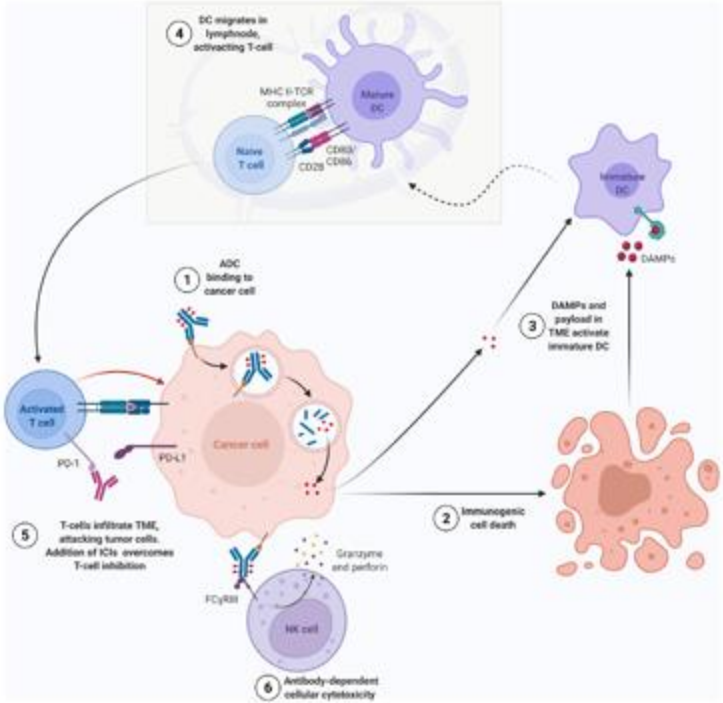


Payload

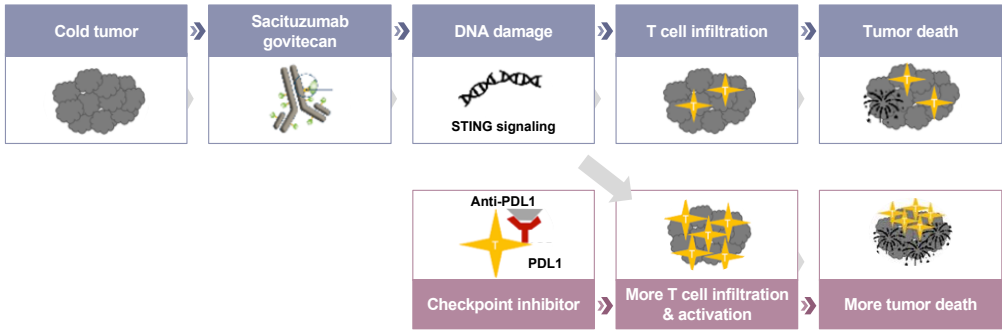
- **Novel topo I inhibitor** (belotecan derivative named T030), highly active
- Average **DAR: 7.4** (range:7–8)
- **Bystander effect**
- Methylsulfonyl derivatization enhances linker stability and toxin permeability

ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio; TME, tumor microenvironment; TROP2, trophoblast cell surface antigen 2.

Rationale For Combining Immunotherapy and ADCS



Hypothesis: ADCs like SG induce DNA damage and result in STING activation, with enhanced efficacy in combination with pembrolizumab



Courtesy Sara Tolaney

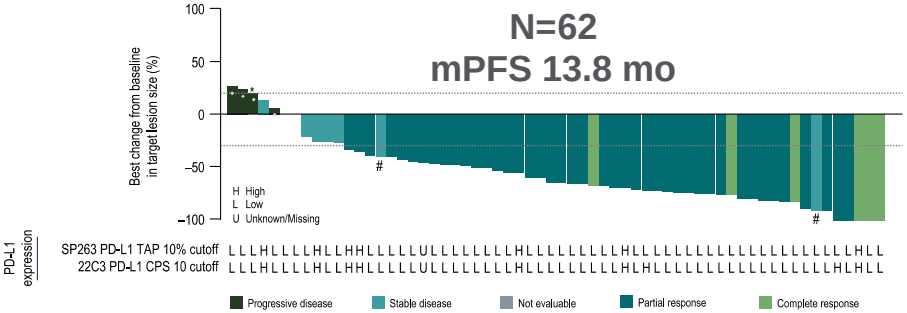
Nicolo E et al, Cancer Treatment Reviews 2022

ADCs plus Checkpoint Inhibitors: 1st line mTNBC

Dato-DXd + Durvalumab in the Begonia Trial

Confirmed ORR was **79%** (49/62; 95% CI, 66.8–88.3) with 6 CR and 43 PR

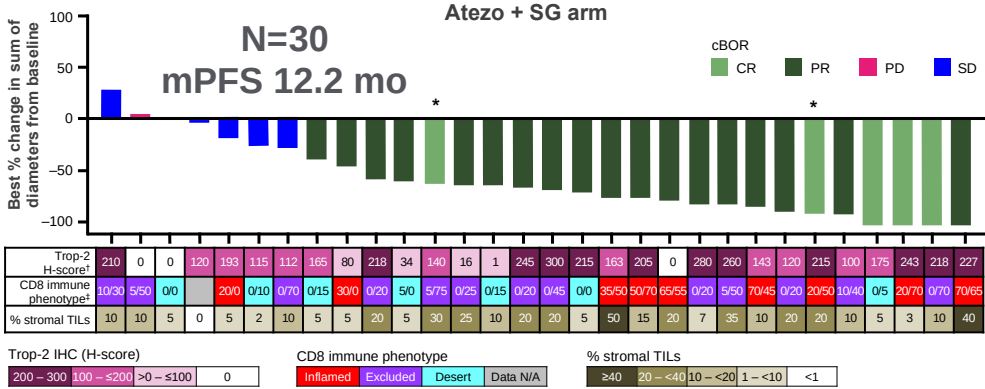
- Antitumour responses were observed regardless of PD-L1 expression level as assessed by 2 separate PD-L1 assays and scoring methods



Schmid et al, ESMO 2023

Sacituzumab Govitecan + Atezolizumab in the Morpheus-PAN BC Trial (PD-L1+)

Confirmed ORR 76.7%, 5 CR, 18 PR



Schmid et al, ESMO BC 2024

ASCENT-04 (NCT05382286): PD-L1 positive

N=570

1L mTNBC PD-L1+

- Previously untreated, inoperable, locally advanced, OR metastatic TNBC
- PD-L1+ (CPS ≥10, IHC 22C3 assay)
- PD-L1 and TNBC status centrally confirmed
- Prior anti-PD-(L)1 allowed in the curative setting
- ≥6 months since treatment in curative setting

1:1

N=570
(≤25% *de novo*)

SG + pembrolizumab
(SG: 10 mg/kg IV on days 1 and 8 of 21-day cycles; Pembro: 200 mg IV on day 1 of 21-day cycles)

TPC chemotherapy + pembrolizumab
(Pembro dosed as above. TPC: gem 1000 mg/m² with carbo AUC 2 IV on days 1 and 8 of 21-day cycles OR paclitaxel 90 mg/m² IV on days 1, 8, and 15 of 28-day cycles OR nab-paclitaxel: 100 mg/m² IV on days 1, 8, and 15 of 28-day cycles)

TROPION Breast05 (n=625)

NCT06103864

Key Eligibility Criteria

- Previously untreated locally recurrent inoperable or metastatic TNBC
- ECOG PS 0 or 1
- Measurable disease as defined by RECIST 1.1
- Adequate haematologic and end-organ function
- PD-L1 centrally confirmed
- PD-L1 positive by 22C3 assay CPS ≥ 10 IHC
- No systemic steroids
- No active autoimmune diseases
- No active brain metastases
- DFI ≥ 6 months since treatment in curative setting
- Prior PD-1/PD-L1 treatment for early stage TNBC allowed

Stratification Factors

- DFI history (de novo versus prior DFI 6 to 12 months[a] versus prior DFI > 12 months)
- Geographic location (US/Canada/Europe versus Dato-DXd Monotherapy Enrolling Countries versus Rest of World)
- Prior PD-1/PD-L1 treatment for early stage TNBC (yes versus no)

N=625
1:1:1[c]

Arm 1
Dato-DXd
6.0 mg/kg IV Q3W
+
Durvalumab
1120 mg IV Q3W
(n=275)

Arm 2
Investigator's Choice Chemotherapy[b]
+
Pembrolizumab
200 mg IV Q3W
(n=275)

Arm 3
Dato-DXd
6.0 mg/kg IV Q3W
(n=75)[d]

Primary endpoint:
PFS (BICR)

Key secondary endpoint:
OS

Secondary endpoints including:
PFS (inv), ORR, DoR, CBR, TTD, PRO, Safety, Tolerability, PK, and Immunogenicity

Exploratory endpoints including:
TROP2

[a] DFI 6 to 12 months capped at 20%.
[b] Chemotherapy options include paclitaxel (90 mg/m² IV on days 1, 8, and 15, Q4W), nab-paclitaxel (100 mg/m² IV days 1, 8, and 15, Q4W) or gemcitabine 1000 mg/m² IV + carboplatin AUC 2 IV days 1 and 8 Q3W.
[c] Once approximately 75 participants are randomised to Arm 3, this cohort will close, and all countries will continue with a 1:1 randomisation strategy for Arms 1 and 2.
[d] In selected countries only.

SACI-IO TNBC and HR+: Sacituzumab govitecan +/− pembrolizumab in 1L PD-L1− mTNBC and HR+

Garrido-Castro/Tolaney

mTNBC

- No prior chemo
  No prior PD-1/L1
- PD-L1 <1% by SP-142
  ER ≤5%
  PR ≤5%
  HER2-
- Stable brain mets
- Exclude prior: PD-1/L1, SG, Irinotecan

mHR+/HER2-

- ≥ 1 Hormonal
- 0-1 Prior Chemo
- Exclude prior: PD-1/L1, SG, Irinotecan

N=110

1:1

N=110

Sacituzumab govitecan
10 mg/kg IV d1, 8 q21 days
+
pembrolizumab
200 mg/kg d1 q21 days

Sacituzumab govitecan
10 mg/kg d1,8 q21 days

Endpoints
Primary
- PFS

Secondary
- OS, ORR
- Duration and time to objective response, time to progression, CBR
- Safety and tolerability

80% power to detect PFS improvement from 5.5 months (Arm B) to 8.5 months (Arm A)

Stay tuned ASCO 2024: Saci-IO in HR+ PD-L1 negative

TROFUSE 010: PD-L1-

Sacituzumab tirumotecan in HR+

N=1200

Key inclusion criteria:

- Unresectable locally advanced or metastatic centrally-confirmed **HR+/HER2-** breast cancer
- Disease recurrence on/after **CDK4/6i** (in the early or metastatic setting)

Key exclusion criteria:

- Previously treated with **chemotherapy** in metastatic setting
- Disease **recurrence** within **6 months** after completion of adjuvant/neoadjuvant chemotherapy

Stratification Factors:
1) PD-L1 status (CPS<1 vs CPS 1-9 vs CPS≥10)
2) TROP2 expression (low+medium vs high)
3) Geographical Region (WE vs NA vs ROW)

R
3:3:2

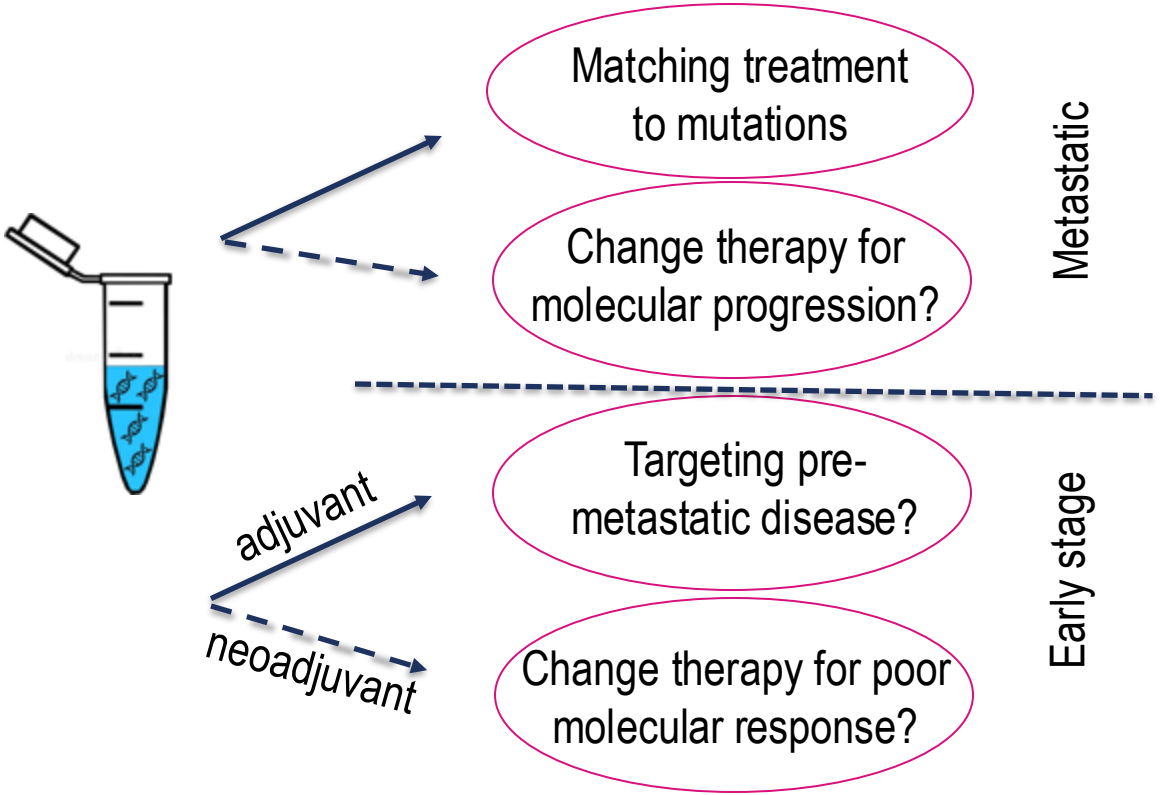
Arm A: MK-2870

Arm B: MK-2870 + Pembrolizumab

Arm C: TPC*

*Treatment of Physician's Choice:
Paclitaxel/ Nab-Paclitaxel/ Capecitabine/ Liposomal Doxorubicin

MOVING FORWARD WITH ctDNA



- Multiple ctDNA assays
  - Agnostic versus tumor informed assays
    - Sensitive vs specific
  - Exploratory markers
    - Orphan noncoding RNA (oncRNA)
    - ER/HER2
    - Epigenetics

TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
HR-positive/ HER2-negative[w]	*PIK3CA* activating mutation	NGS, PCR (Blood or tumor tissue if blood negative)	Alpelisib + fulvestrant[x]	Category 1	Preferred second- or subsequent-line therapy
HR-positive/ HER2-negative[y]	*PIK3CA or AKT1* activating mutations or *PTEN* alterations	NGS, (Blood or tumor tissue if blood negative)	Capivasertib + fulvestrant[y]	Category 1	Preferred second- or subsequent-line therapy in select patients[y]
HR-positive/ HER2-negative[z]	*ESR1* mutation	NGS, PCR (Tumor tissue or blood)	Elacestrant[z]	Category 2A	Other recommended regimen
Any	Germline *BRCA1* or *BRCA2* mutation	Germline sequencing	Olaparib Talazoparib	Category 1	Preferred
Any	*NTRK* fusion	FISH, NGS, PCR (Tumor tissue or blood)	Larotrectinib[aa] Entrectinib[aa]	Category 2A	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, NGS, PCR, (Tumor tissue)	Pembrolizumab[bb,cc] Dostarlimab-gxly[dd]	Category 2A	
Any	TMB-H (≥10 mut/Mb)	NGS (Tumor tissue or blood)	Pembrolizumab[bb,cc]	Category 2A	
Any	*RET*-fusion	NGS (Tumor tissue or blood)	Selpercatinib[ee]	Category 2A	

[w] For HR-positive/HER2-negative breast cancer, assess for PIK3CA mutations with tumor or liquid biopsy to identify candidates for alpelisib plus fulvestrant. PIK3CA mutation testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy). If liquid biopsy is negative, tumor tissue testing is recommended.

[x] The safety of alpelisib in patients with Type 1 or uncontrolled Type 2 diabetes has not been established.

[y] In adult patients with *PIK3CA* or *AKT1* activating mutations, or for *PTEN* alterations after disease progression or recurrence after ≥1 prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor.

[z] For postmenopausal or premenopausal patients receiving ovarian ablation or suppression or adult males with ER-positive, HER2-negative, *ESR1*-mutated disease after progression on one or two prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor. Assess for ESR1 mutations at progression following prior lines of endocrine therapy.

[aa] Larotrectinib and entrectinib are indicated for the treatment of solid tumors that have an NTRK gene fusion without a known acquired resistance mutation and have no satisfactory alternative treatments or that have progressed following treatment.

[bb] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

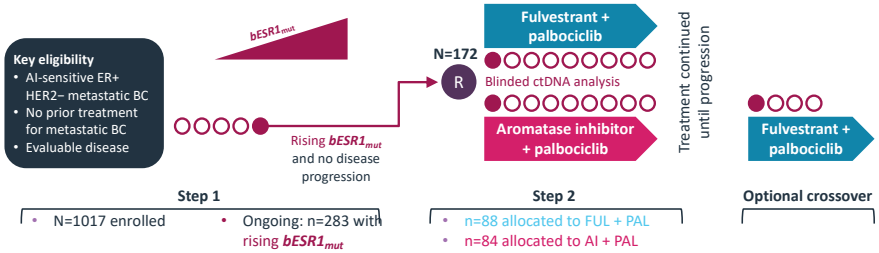
[cc] Pembrolizumab is indicated for the treatment of patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, or TMB-H tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.

[dd] Dostarlimab-gxly is indicated for adult patients with MSI-H/dMMR unresectable or metastatic tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

[ee] Selpercatinib is indicated for adult patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

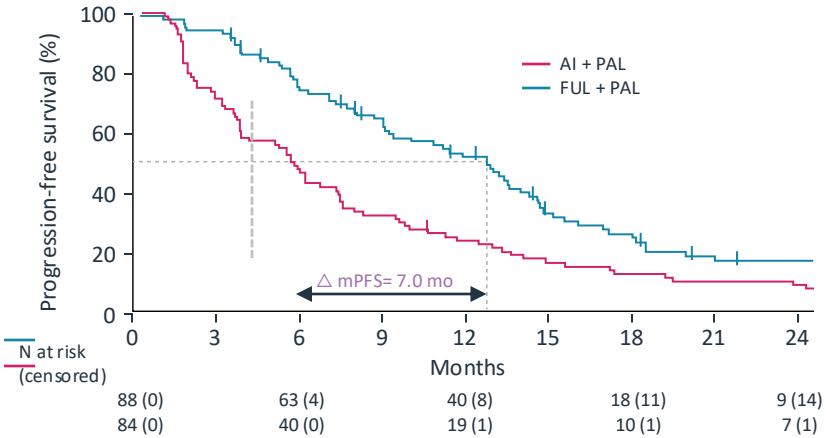
PADA-1: Change Therapy Based on mESR1



	ASCO 2023 analysis[2]		2021 analysis[1]	
	FUL + PAL	AI + PAL	FUL + PAL	AI + PAL
mPFS, months (95% CI)	12.8 (9.3–14.7)	5.8 (3.9–7.5)	11.9	5.7
HR (95% CI)	0.54 (0.38, 0.75)		0.61	
Optional crossover (n=49) mPFS (95% CI)	3.5 (2.4, 5.4)			

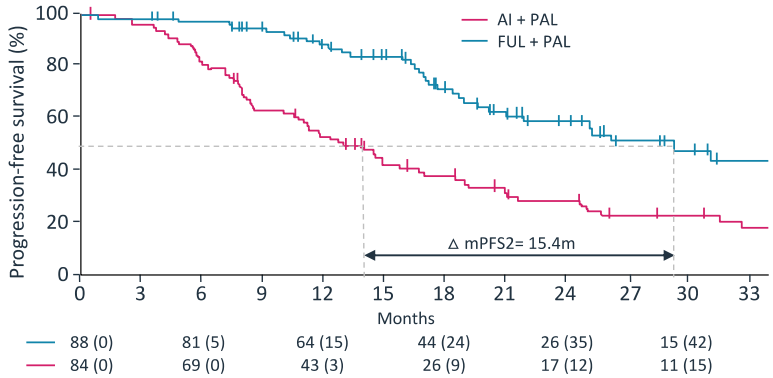
Updated PFS results (primary endpoint)

Data cutoff June 2022: Median F/U 28.2 mo; N=152 PFS events



PFS2, from randomization

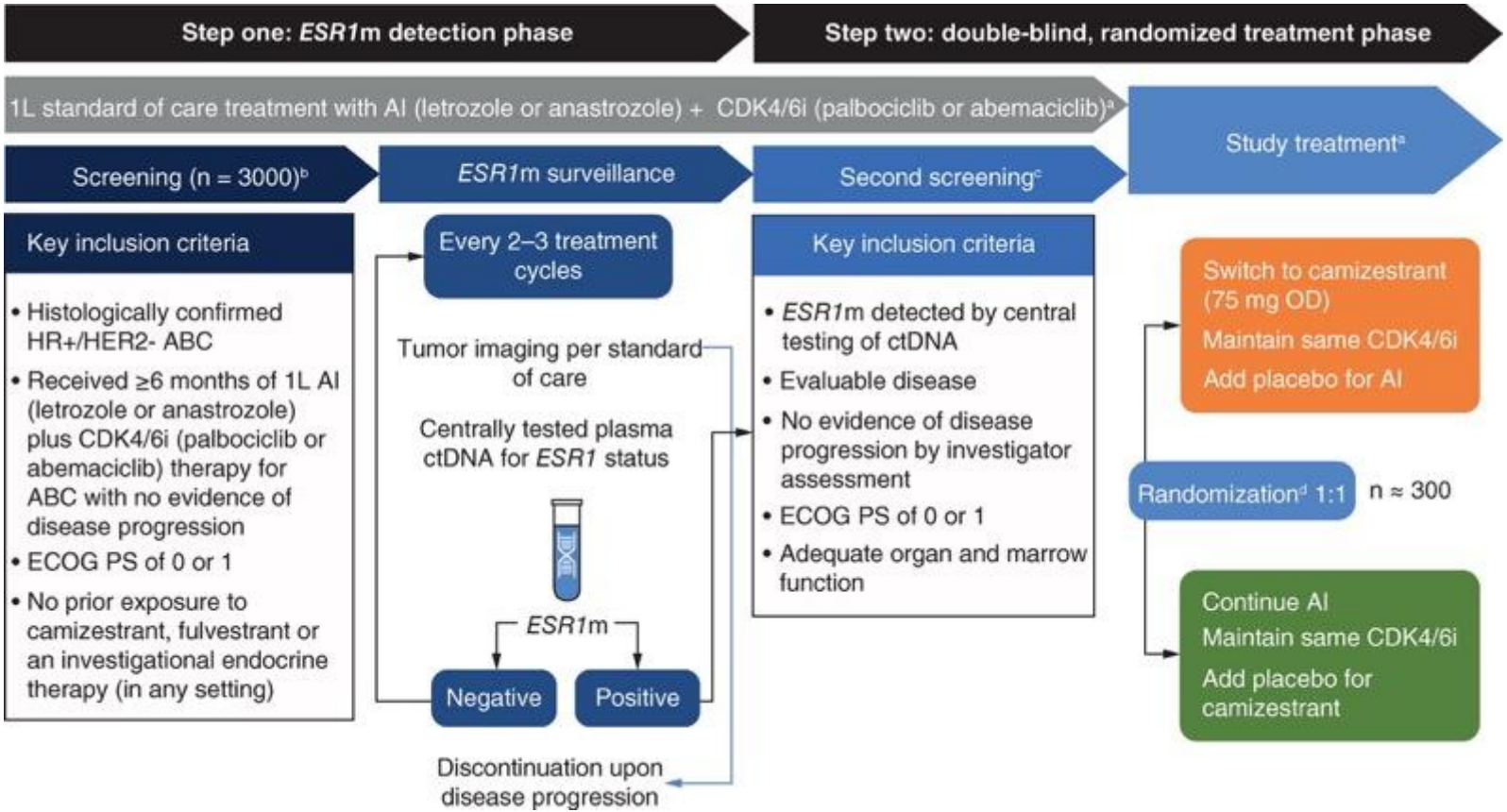
Data cutoff June 2022: N=93 PFS2 events (54% maturity)



	FUL + PAL	AI + PAL
mPFS2, months (95% CI)	29.4 (21.9, NR)	14.0 (11.0, 18.6)
HR (95% CI)	0.37 (0.24, 0.56)	

1. Bidard, et al. Lancet Oncol 2022; 2. Bidard FC, et al. ASCO 2023. Abstract 1002

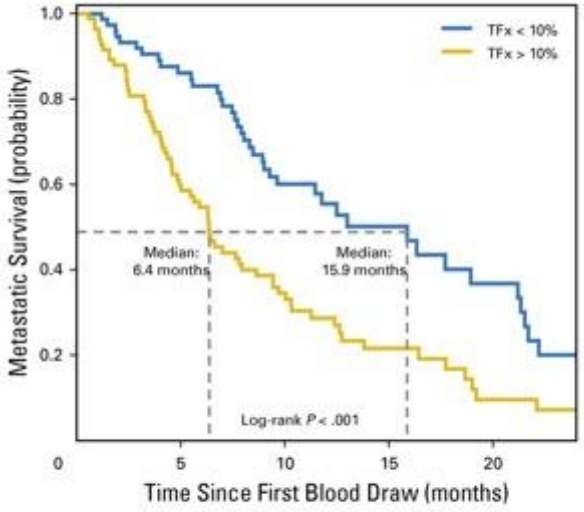
SERENA-6: Switching ET to camizestrant in pts with *ESR1*^{mut} ctDNA



PIs: N Turner & F Bidard

Metastatic Disease

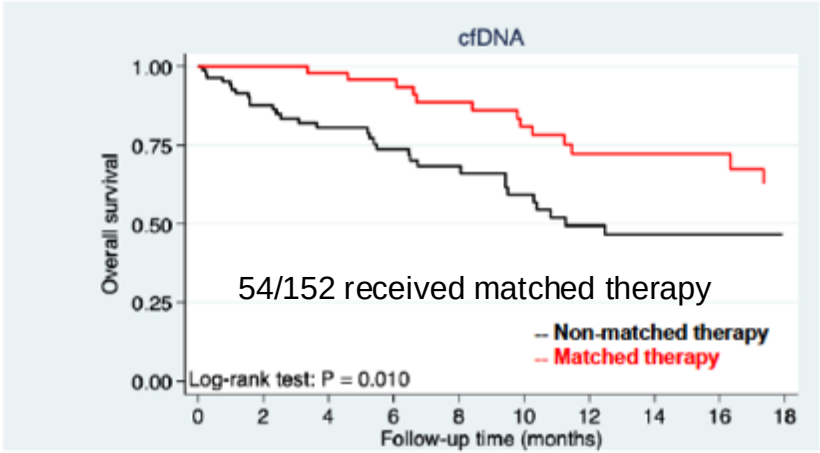
ctDNA Fraction is Associated with Survival



Stover et al. JCO 2018

No. at risk				
Fx < 10%	75	57	34	16
Fx > 10%	83	48	25	11

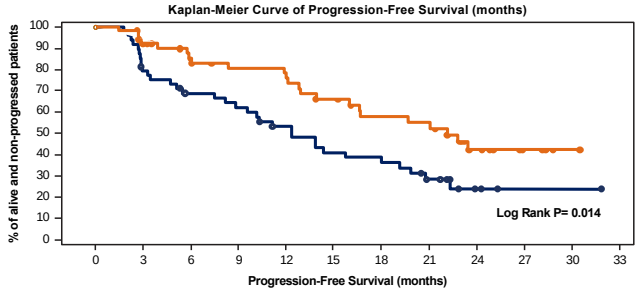
Survival is Improved with Matched Therapy vs. Non-Matched Therapy Based on cfDNA Actionable Mutation Results



Vidula et al. CCR 2021

ctDNA Clearance at C2D1 Associated with Improved Outcomes: BioItaLEE Study

Arpino, et al. *ASCO.* 2022.



Patients at risk												
VAF cleared at C2D1	55	45	38	33	31	26	21	19	10	4	1	0
VAF not cleared at C2D1	50	38	31	28	22	17	15	9	3	1	1	0

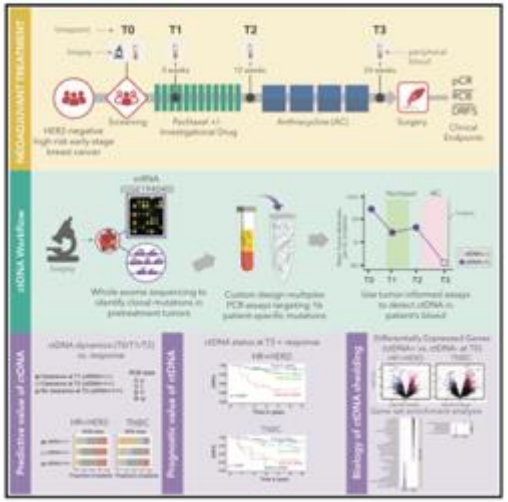
FAIM study: ctDNA clearance guided therapy (NCT04920708)

Article

Cancer Cell

Clinical significance and biology of circulating tumor DNA in high-risk early-stage HER2-negative breast cancer receiving neoadjuvant chemotherapy

Graphical abstract



Authors

Mark Jesus M. Magbanua, Lamorna Brown Swigart, Ziad Ahmed, ..., Angela M. DeMichele, Hope S. Rugo, Laura J. van 't Veer

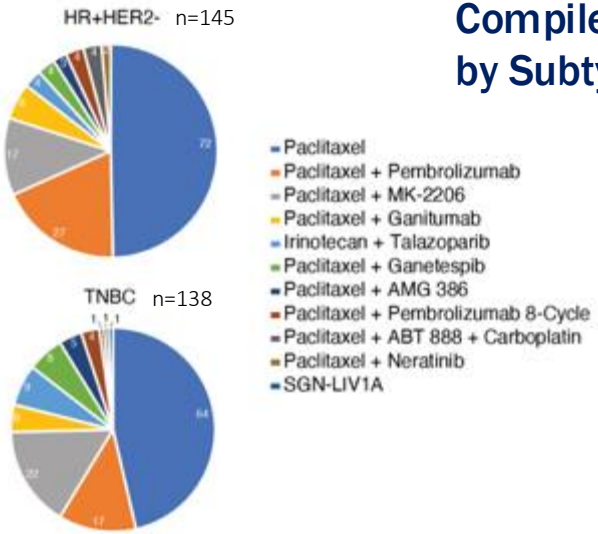
Correspondence

mark.magbanua@ucsf.edu

In brief

Magbanua et al. examine the dynamics of ctDNA in plasma of high-risk early-stage breast cancer patients receiving neoadjuvant chemotherapy. Understanding the predictive and prognostic value of ctDNA and biology of ctDNA shedding in different breast cancer subtypes can inform the use of ctDNA for treatment selection to improve patient outcomes.

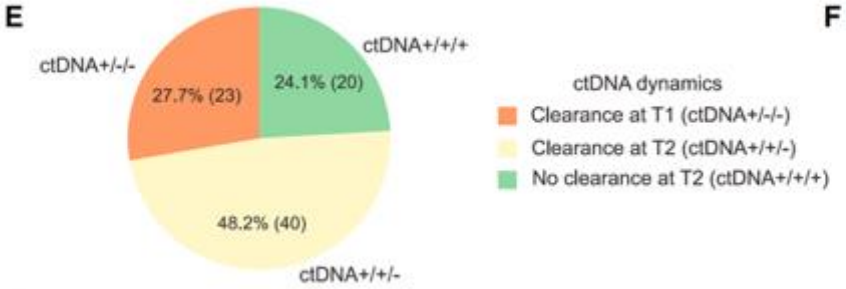
Circulating Tumor DNA (exploratory biomarker):
Personalized 16 tumor mutated specific fragments
Serial liquid biopsies: 283 pts various treatment arms



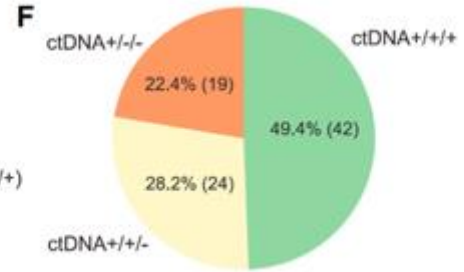
Magbanua et al, Cancer Cell, 2023
https://doi.org/10.1016/j.ccell.2023.04.008

I-SPY2: ctDNA as a Biomarker of Response & Resistance for Early-Stage Disease Decrease During Treatment Predicts pCR

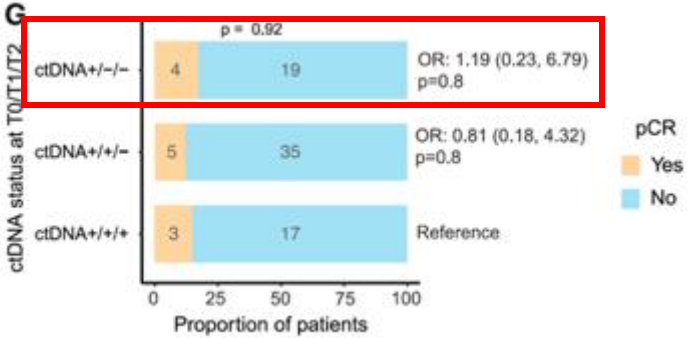
HR+/HER2-

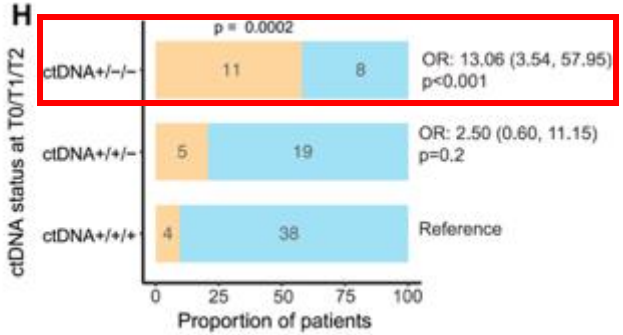


Triple Negative



Compiled Series by Subtype





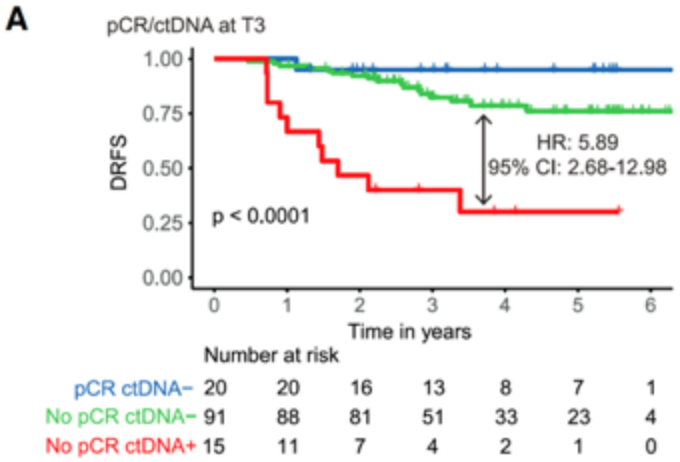
Early Clearance (T1) Strong Predictor of Response (pCR)

Magbanua et al, Cancer Cell, 2023
https://doi.org/10.1016/j.ccell.2023.04.008

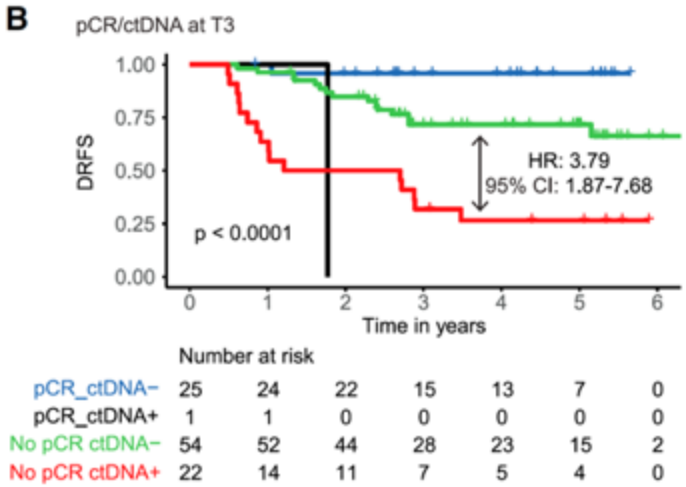
ctDNA as a Biomarker of Response and Resistance for Early-Stage Disease Non-Clearance at Surgery Predicts Risk of Recurrence

Compiled Series by Subtype

HR+/HER2-



Triple Negative

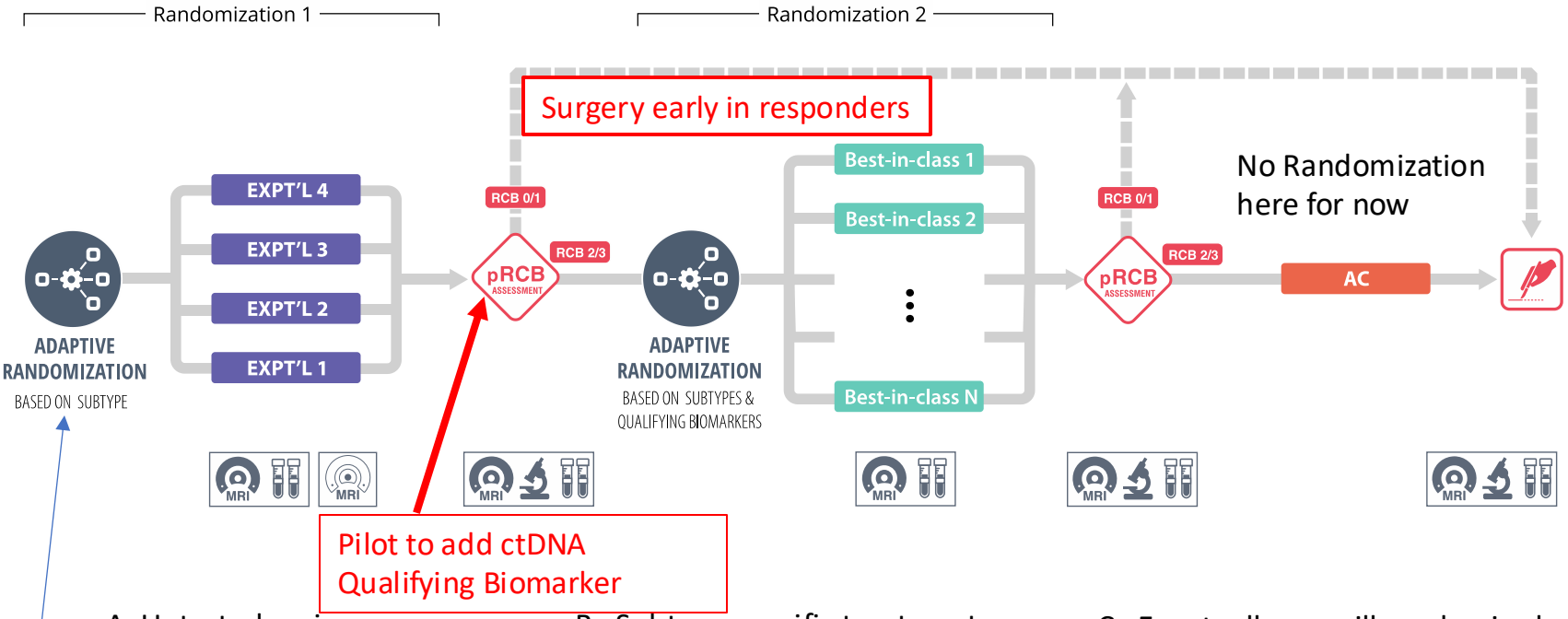


ctDNA status at surgery adds to survival prediction

Magbanua et al, Cancer Cell, 2023
https://doi.org/10.1016/j.ccell.2023.04.008

I-SPY 2.2: Sequential Multiple Assignment Randomized Trial (SMART) design

Get Effective New Therapies to Patients Early, Before Development of Resistance
Utilize Biology of Tumors and Early Response Prediction Personalize Treatment



A. Untested regimens

B. Subtype specific treatments

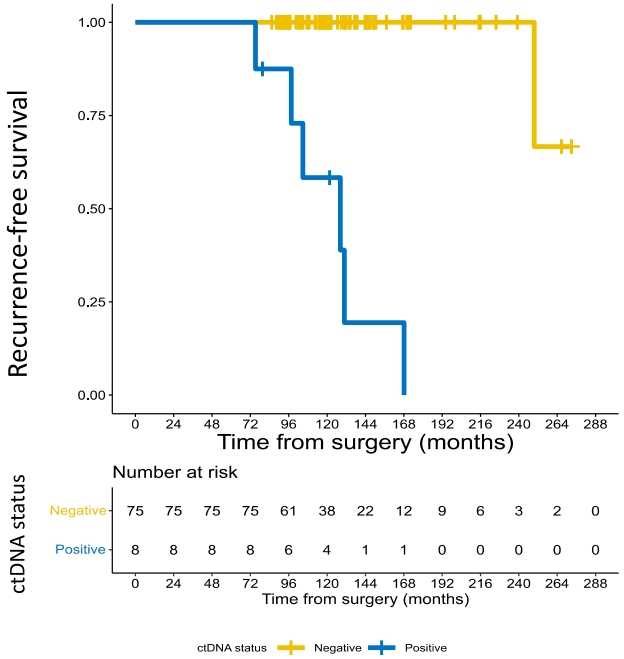
C. Eventually we will randomize here as well

Response Predictive Subtypes; Wolf et al, Cancer Cell 2022

How To Optimize Therapy From Here?

Development of resistance starts in the early-stage setting

- Next steps
  - Biomarkers to determine optimal first therapy
  - ctDNA to determine early signs of resistance
  - Rapid change of therapy before development of metastatic disease
- This could be accomplished in the neoadjuvant setting for more proliferative, chemotherapy sensitive disease and in the adjuvant setting for more indolent disease
  - The challenge in indolent disease is low ctDNA positivity
    - 10% (8/83) with detectable ctDNA after 5 years
    - Median lead time ~12 months, 6/10 with metastatic recurrence (2 without recurrence)
    - Repeated assays required



Lipsyc-Sharf et al. JCO. 2022.

Multiple Trials In This Space

Change in therapy based on ctDNA in high-risk ER+/HER2- early-stage disease

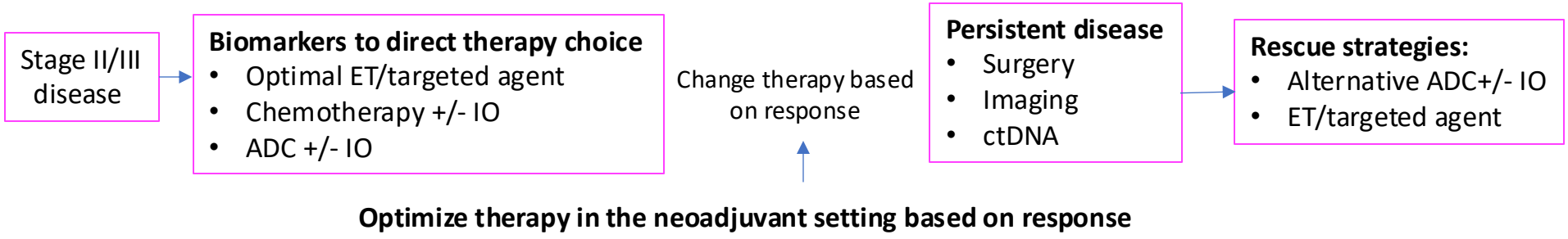
Does change in therapy based on detection of ctDNA in early-stage disease change outcome?

- TRAK-ER (NCT04985266)
- DARE (NCT04567420)
  - Low positive results are challenging
  - Focus on highest risk disease
    - Defined as higher burden of disease at treatment start

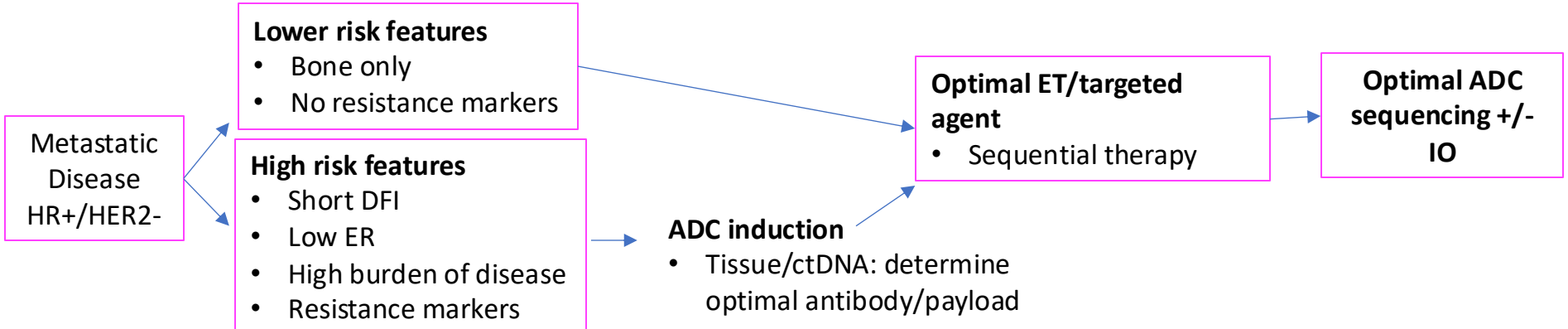
Does intensified surveillance to identify the first signs of metastatic disease change outcome?

- SURVIVE (NCT05658172)
  - Randomized therapy for HER2+ and ER+ cohorts, +ctDNA and M0

Roadmap for the Future? HER2- Breast Cancer



Optimize biomarkers, understand optimal ET, targeted agents, ADC?



Thank you!

- To move forward, we learn from the past and present – but only as a collaborative international community
- Thank you to my remarkable and treasured colleagues and friends who I learn from every day – and who create passion in our work together
- Thank you to our patients, without whom we would not be able to move the needle forward
- Thank you to my mother – without whom I would not have focused on breast cancer, and to my amazing family without whose support I could not have pursued my dreams
- Here's to the next generation of researchers, who truly represent the future

“Success is not final, failure is not fatal: It is the courage to continue that counts.”

—Winston Churchill

THANK YOU!