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COUNTRY

DATE

Biology of breast cancer

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Disclosures

- Speaker's fee Lilly
- I had to make selections and could not present everything

Outline

- Predictive and resistance markers for:
  - Antibody-drug conjugates
  - Immunotherapy
  - Endocrine therapy
- Immune landscape & microenvironment
- Liquid biopsies
- Lobular breast cancer

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Predictive and resistance markers for:

- Antibody-drug conjugates (ADCs)
- Immunotherapy
- Endocrine therapy

ADCs

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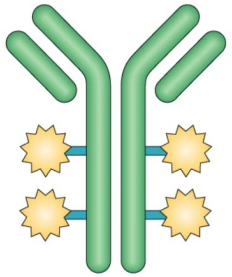
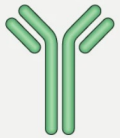
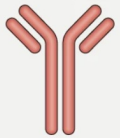
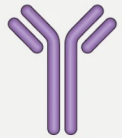
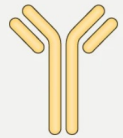
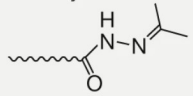
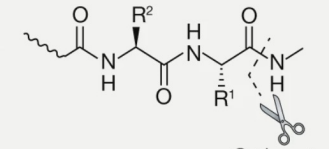
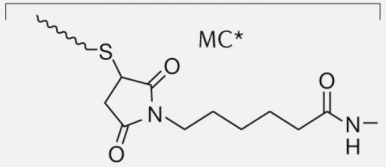
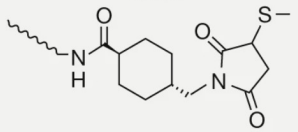
a



b

	IgG1	IgG2	IgG3	IgG4
Antibodies				
Serum half-life	21 days	21 days	7–21 days	21 days
C1q binding	Yes	Yes	Yes	No
Fcγ avidity	High	Low	High	Moderate

	Cleavable			Non-cleavable
Linkers	Hydrazone 	Disulfide 	Dipeptide 	MC*  MCC* 
	Acid cleavable	Reducible	Protease cleavable	

Payloads	 Auristatins	 Maytansinoids	 Calicheamicins	 Camptothecins
	Anti-microtubule	Anti-microtubule	DNA cleavage	Topoisomerase 1 inhibition

- Target/antigen density
- Effective internalization of the antibody
- Heterogeneity of expression ➔ can be overcome with bystander effect
- Normal tissue expression
- Good target does not guarantee good ADC

Drago *et al.* Nat Clin Onc Rev 2021

Open questions

- Is expression of target associated with biological differences (many abstracts re HER2-low)?
- Heterogeneity of expression of the targets in the metastatic setting?
- Predictors of therapeutic response and mechanisms of *de novo* and acquired resistance?

Low HER2- A separate entity? Published Data and SABCS News: a pathologist's perspective

David L. Rimm MD-PhD
Anthony N Brady Professor of Pathology
Departments of Pathology and Medicine (Oncology)

San Antonio Breast Cancer Symposium®, December 6-10, 2022

Recommended presentations!

HER2 Low: A separate entity? PRO

Giuseppe Curigliano, MD PhD
Istituto Europeo di Oncologia, IRCCS and University of Milano, Milan, Italy

San Antonio Breast Cancer Symposium®, December 6-10, 2022

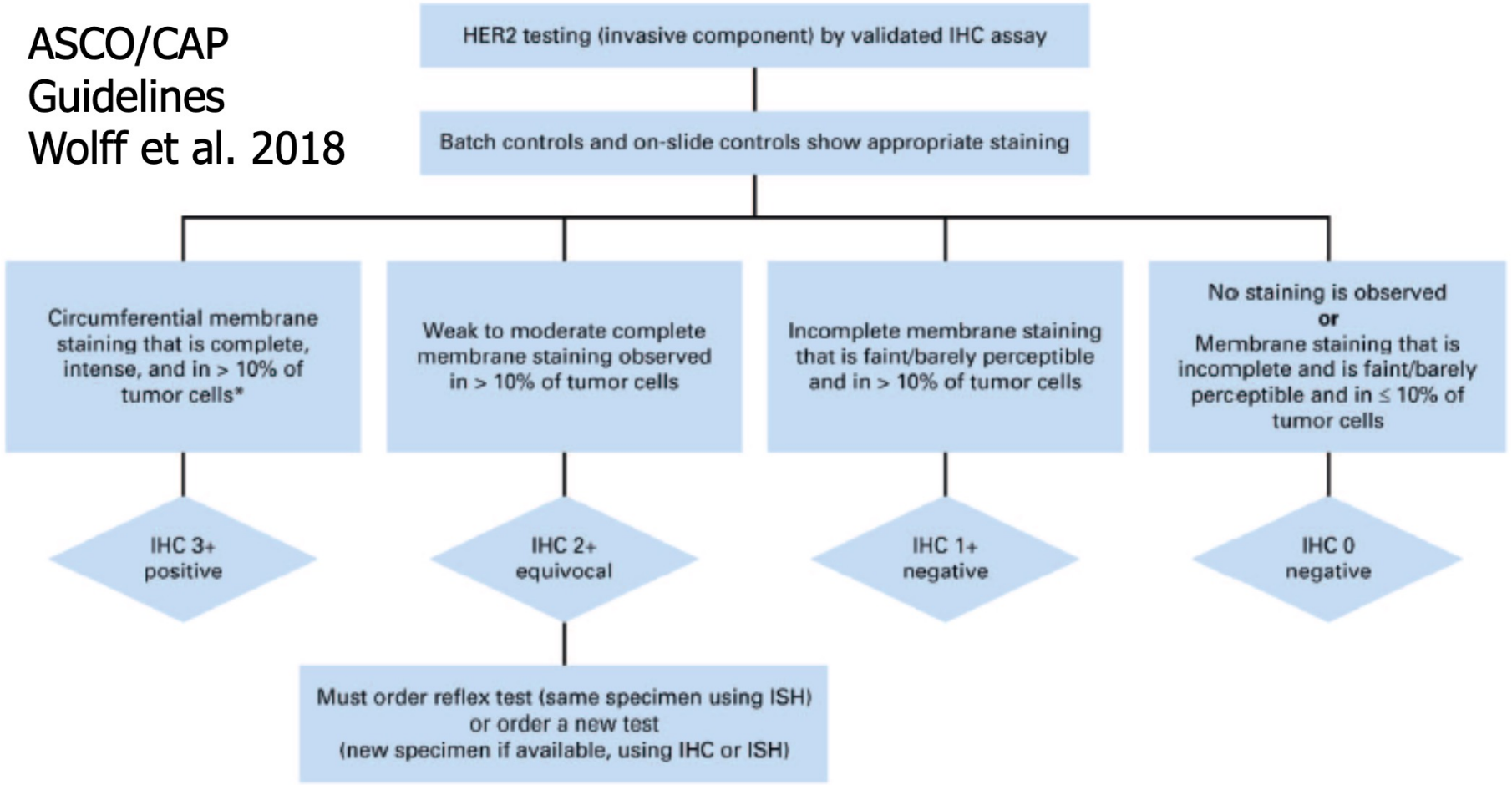
HER2-LOW: A SEPARATE ENTITY?

NO

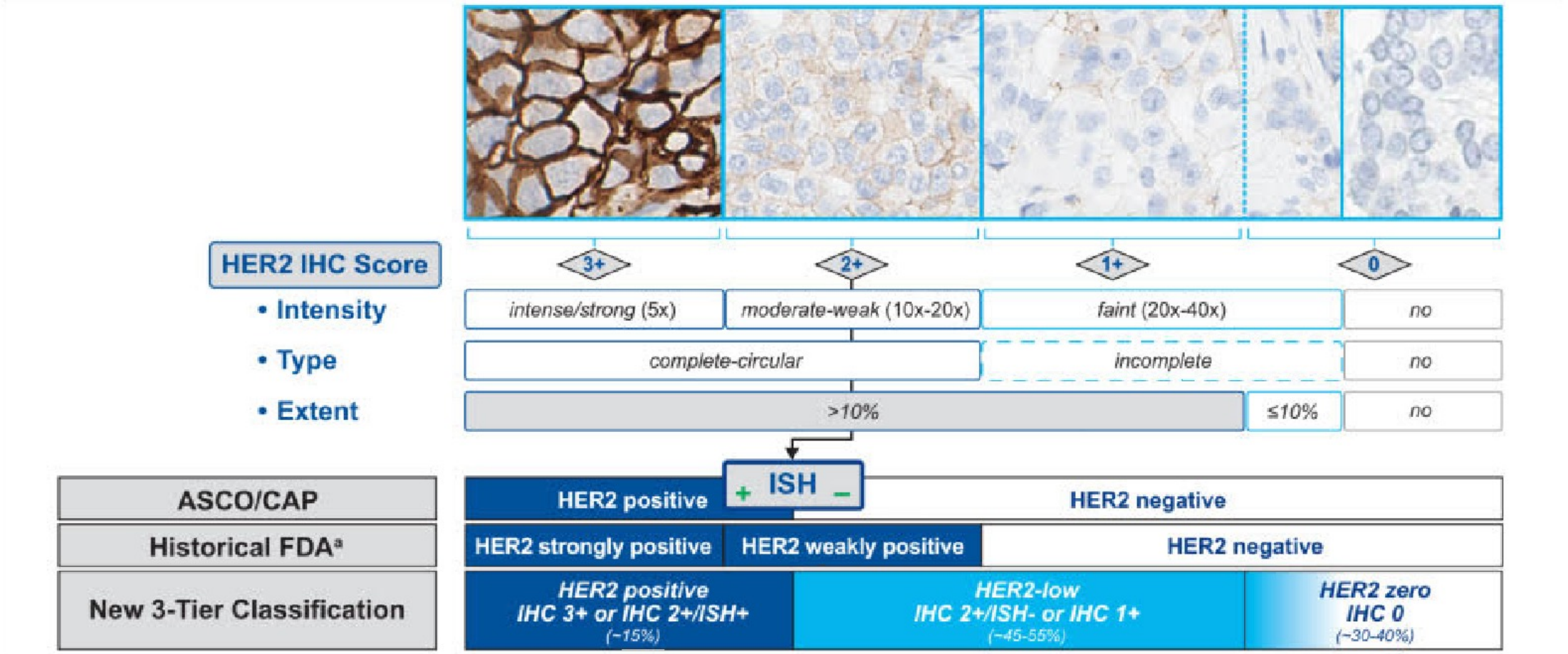
Sara M. Tolaney
Dana-Farber Cancer Institute

Assessement of HER2-low

ASCO/CAP Guidelines Wolff et al. 2018



Assessement of HER2-low



Rûschoff G et al. (HER2-13)

Assessement of HER2-low

77 pathologists completed pre-training or real-world scoring in 14 countries
(n = 49 for 4B5, n = 28 for HcT)

74 pathologists completed post-training scores
(n = 48 for 4B5, n = 26 for HcT).

Table. Summary of Pathologist Concordance and Interobserver Variability

Test: Scoring Criteria	Concordance κ analysis and ORA (%)	
	Baseline	After training
Ventana 4B5:		
ASCO/CAP[a]	0.96 (98.9)	0.97 (99.4)
Historical FDA[b]	0.82 (92.4)	0.81 (92.2)
New Class[c]	0.75 (82.8)	0.79 (84.9)
HercepTest:		
ASCO/CAP[a]	0.84 (94.3)	0.85 (94.7)
Historical FDA[b]	0.72 (88.3)	0.75 (89.8)
New Class[c]	0.81 (84.1)	0.82 (85.3)

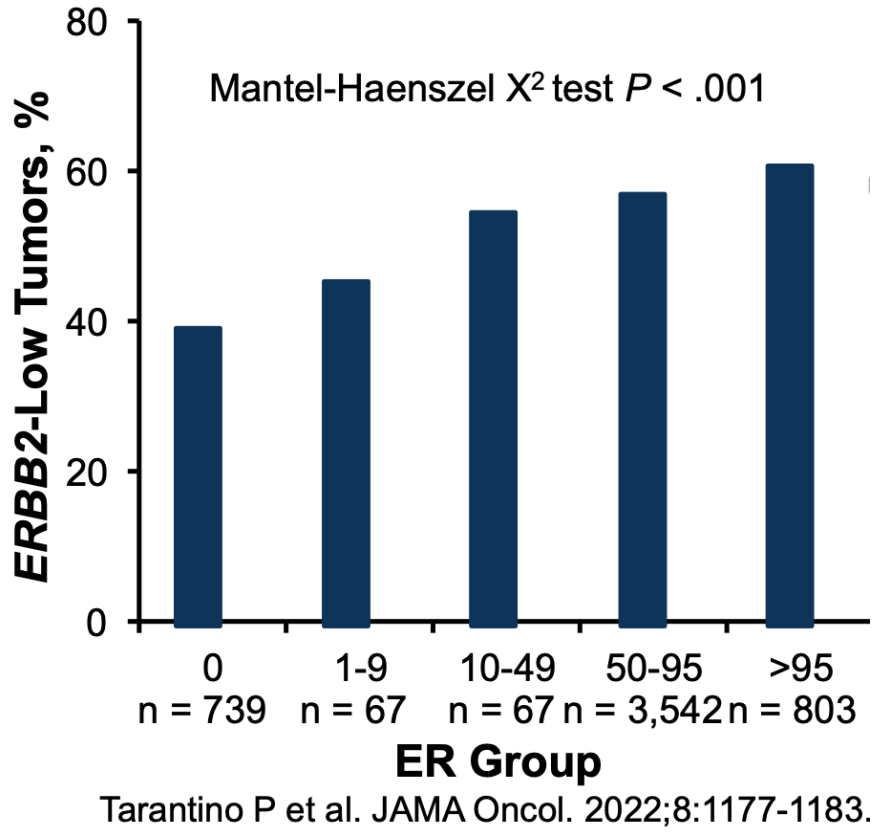
Overall score concordance with a new category of HER2-low was above the 80% ORA benchmark for both 4B5 and HcT and is higher than previously reported (Fernandez et al. JAMA Oncol 2022)

Rûschoff G et al. (HER2-13)

Debate is still open, but many reasons to suggest that HER2low is NOT a separate clinical or biological entity (S. Tolaney)

- Does not have unique clinical-pathologic features
- Not associated with a different prognosis
- Not associated with different benefit to therapy
- Not biologically distinct
- Not biologically stable or consistent

Differences that have been reported are mainly related to ER expression since % of HER2-low is associated with ER



Tarantino P et al. JAMA Oncol. 2022;8:1177-1183.

+ also shown in:

Peiffer D et al. (HER2-11)

Geukens G et al. (HER2-16)

No differences in clinical characteristics seen when considering HR+ and HR- BC separately

	HR-positive		HR-negative		Total[a] (N=789)
	HER2-low (n=394)	HER2 IHC 0 (n=160)	HER2-low (n=84)	HER2 IHC 0 (n=75)	
Female, n (%)	394 (100.0)	159 (99.4)	83 (98.8)	75 (100.0)	787 (99.7)
Age at index date, median (range), years[b]	60 (31-97)	59 (28-90)	57 (31-80)	52 (35-92)	58 (28-97)
Age ≥45 years at index date, n (%)	271 (68.8)	116 (72.5)	53 (63.1)	45 (60.0)	491 (62.2)
Race, n (%)					
Asian	97 (24.6)	42 (26.3)	17 (20.2)	28 (37.3)	185 (23.4)
White	158 (40.1)	59 (36.9)	49 (58.3)	35 (46.7)	366 (46.4)
Other[c]/not reported/missing	139 (35.3)	59 (36.9)	18 (21.4)	12 (16)	238 (30.1)
Time from initial BC diagnosis to index date, median (range), years[b]	2 (0-33)	2 (0-21)	2 (0-17)	1.5 (0-22)	2 (0-33)
Metastatic/locally advanced at index date, n (%)[b]					
Locally advanced	7 (1.8)	2 (1.3)	0	2 (2.7)	11 (1.4)
Metastatic	293 (74.4)	129 (80.6)	60 (71.4)	62 (82.7)	550 (69.7)
Both	10 (2.5)	6 (3.8)	2 (2.4)	2 (2.7)	20 (2.5)
Not reported/missing	84 (21.3)	23 (14.4)	22 (26.2)	9 (12.0)	208 (26.4)

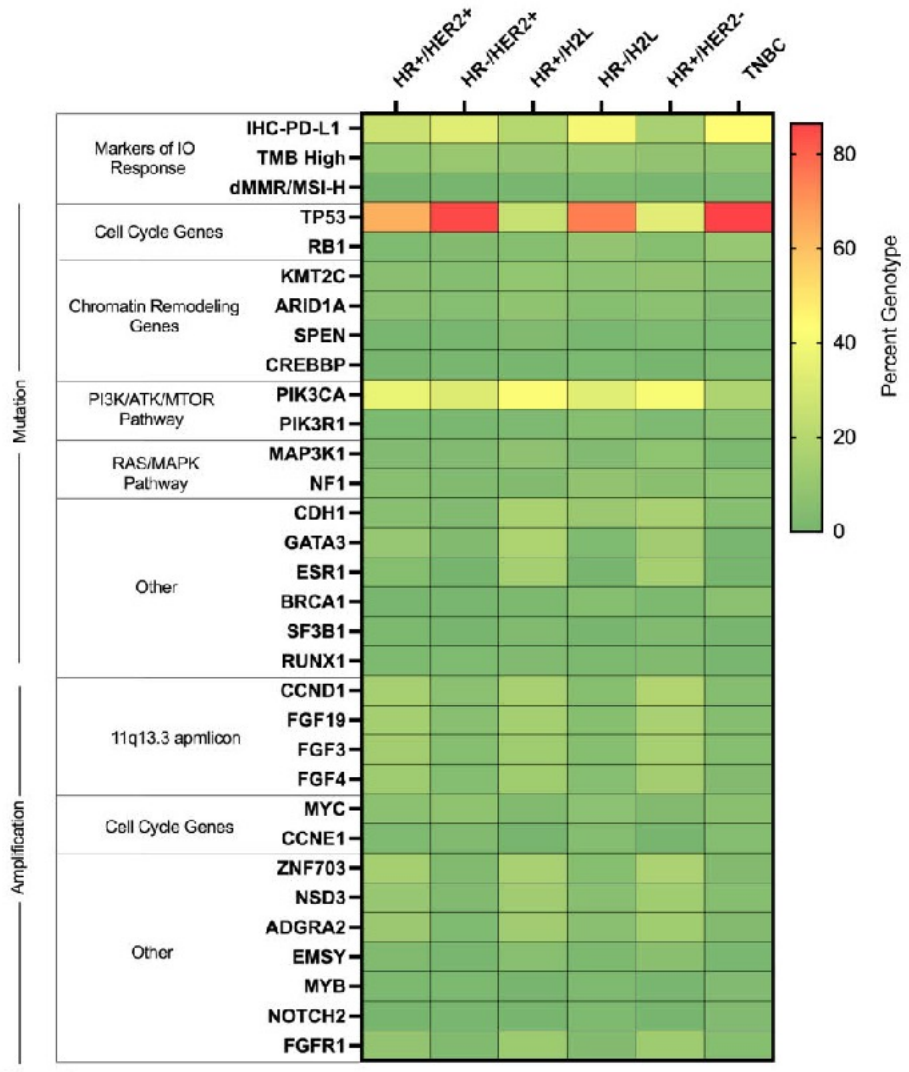
BC, breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry.
[a]Includes patients with missing HR status; [b]Index date was the date of earliest metastatic BC diagnosis identified during the patient selection period. For patients without metastasis during the patient selection period, the earliest date of unresectable diagnosis during patient selection period was used as the index date; [c]Includes Black or African American, American Indian or Alaska Native, and other.

Viale G et al. (HER2-15)

No differences in genomics seen (3 concordant abstracts)

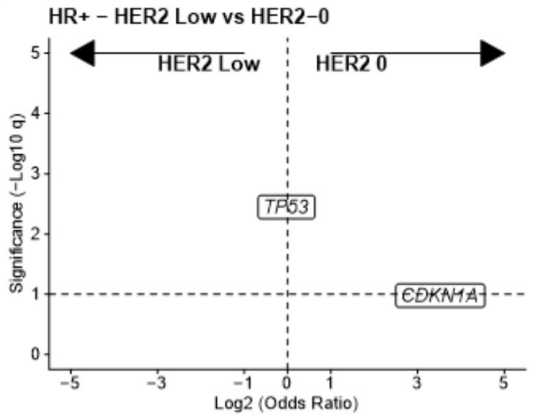
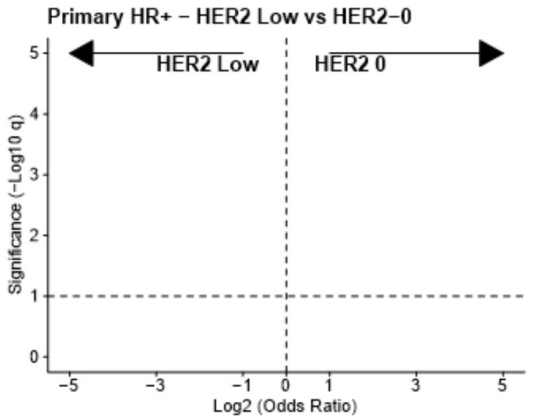
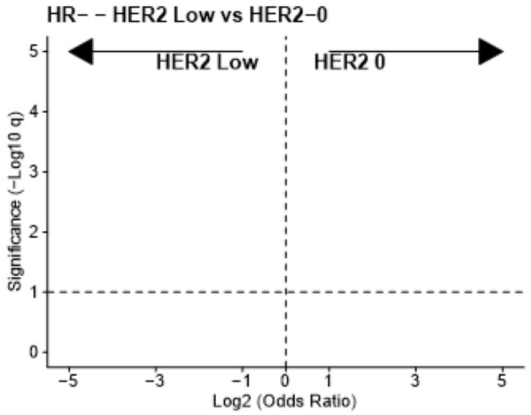
Caris Life Science Database (> 11,000 pts):

- mutations/amplifications/TMB based on targeted seq
- PD-L1 by IHC



Bansal R et al. (HER2-12)

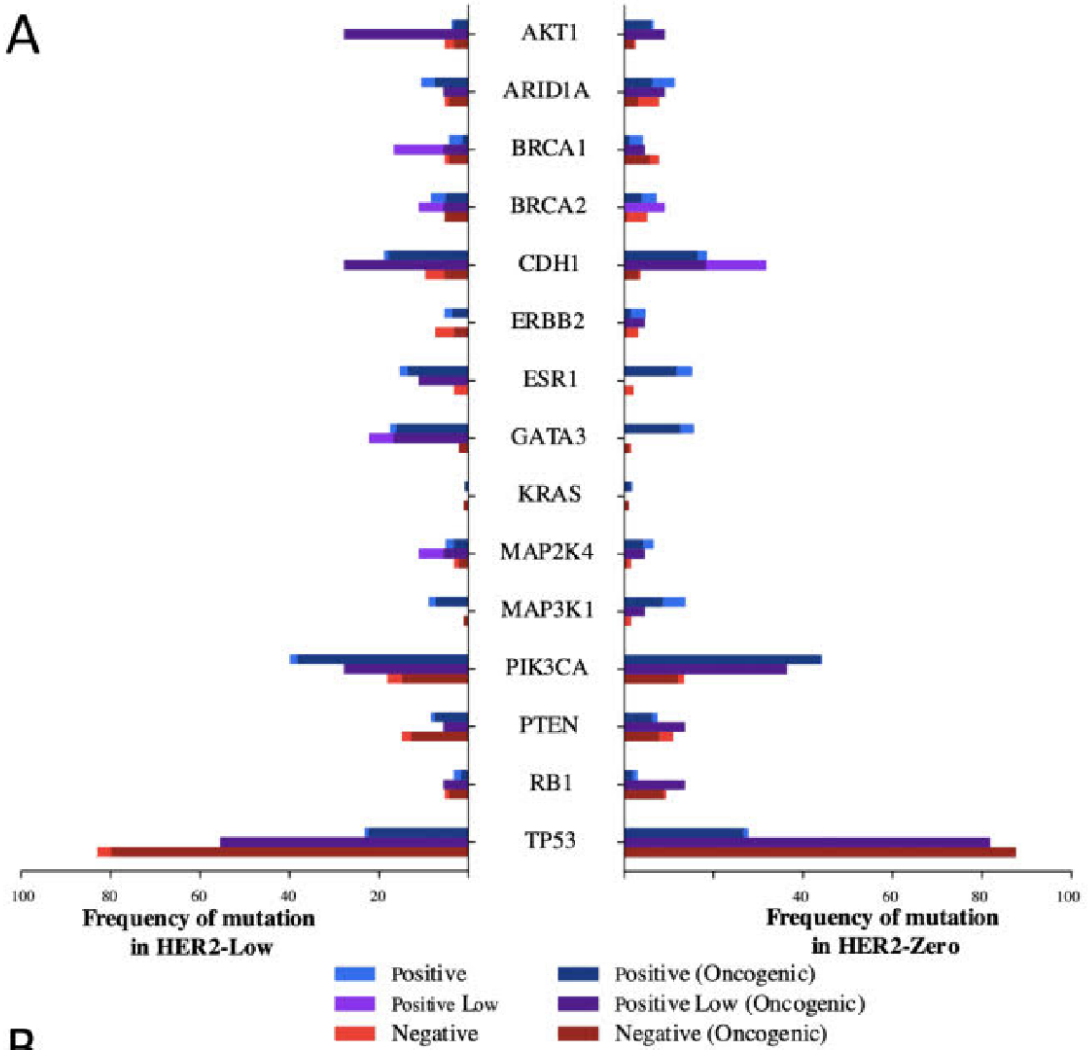
No differences in genomics seen (3 concordant abstracts)

	Primary	Mets
HR+		
HR-		

Marra A et al. (HER2-07)

No differences in genomics seen (3 concordant abstracts)

> 1,000 pts with MBC treated at Da-Farber for which NGS data were available



No difference seen in TMB neither

Tarantino P et al. (HER2-05)

Open questions

- Is expression of target associated with biological differences?
- Heterogeneity of expression of the targets in the metastatic setting?
- Predictors of therapeutic response and mechanisms of *de novo* and acquired resistance?

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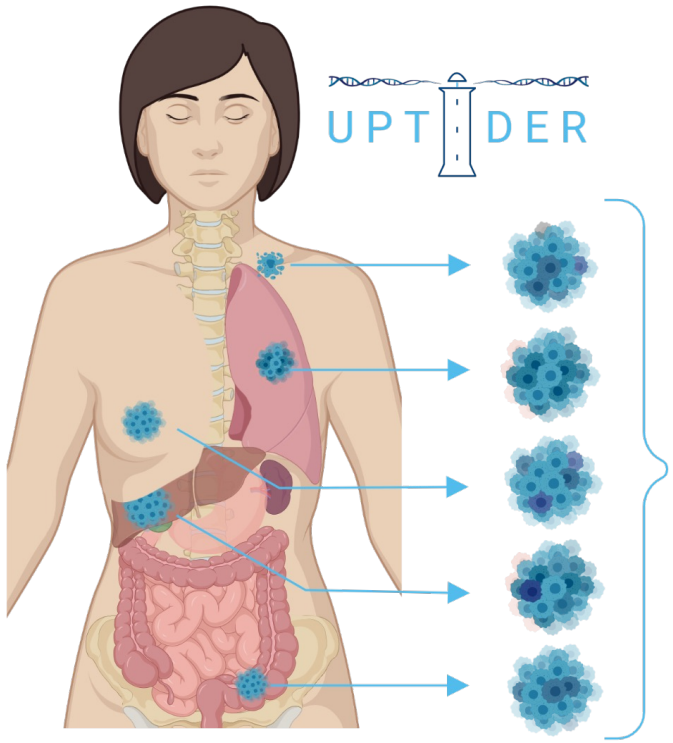
Tissue donation

Does HER2-status on one metastatic or primary biopsy reflect a patient's HER2-profile?

10 patients with *HER2*-non-amplified metastatic breast cancer



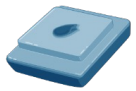
At autopsy

257 metastases

(median: 25/patient, range: 9-41)

8 breast tumour samples

Clinical archives



Longitudinal/during life

5 metastases

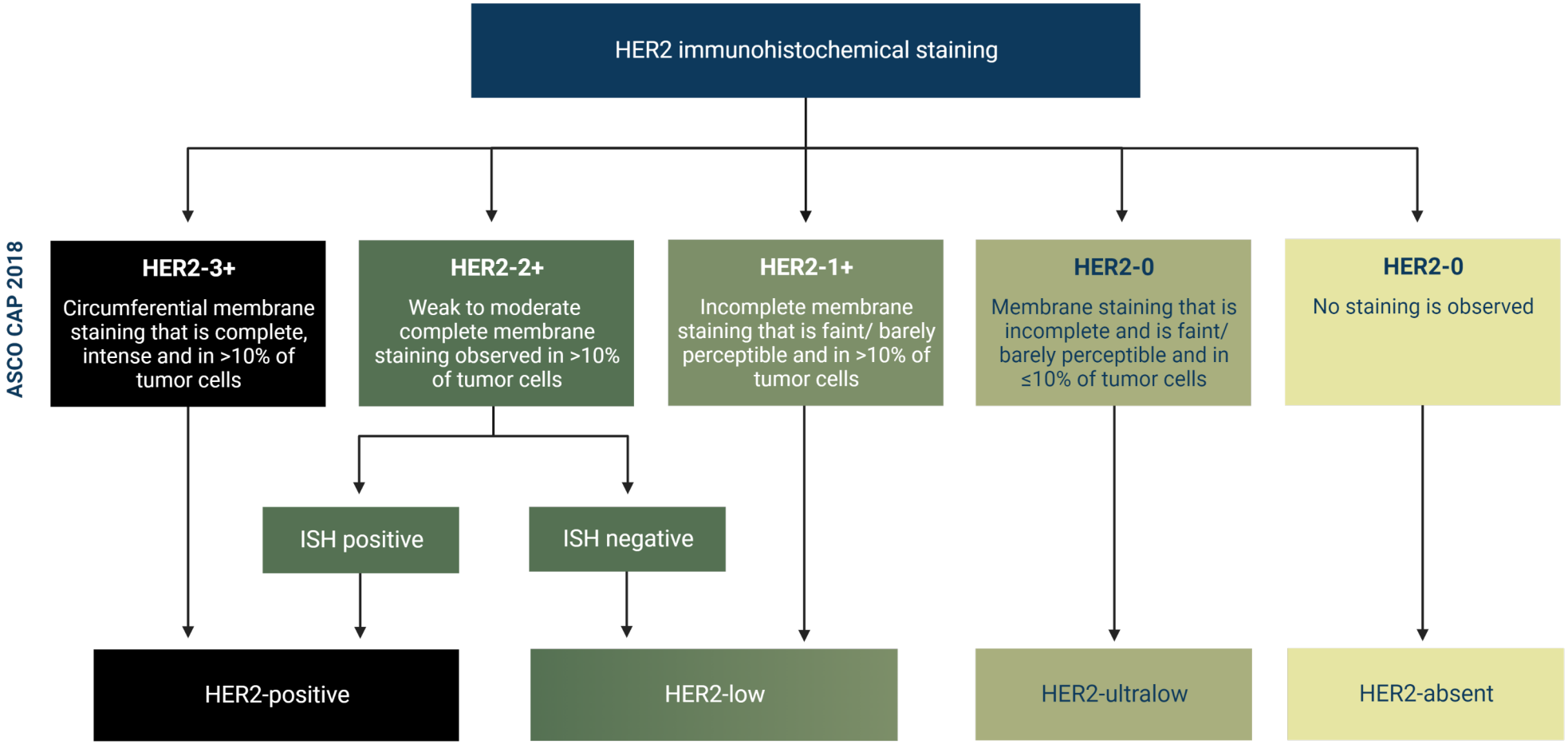
30 breast tumour samples

6 axillary lymph node samples

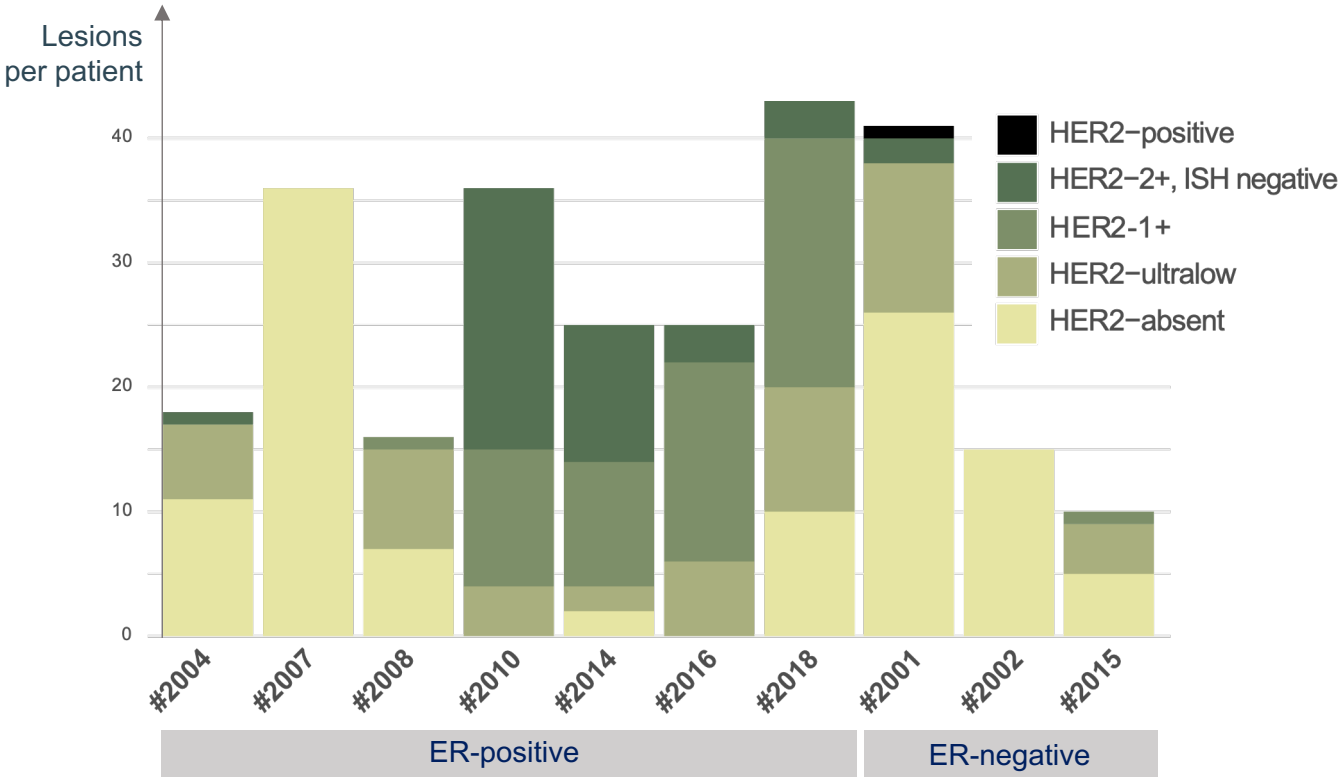
306 samples

HER2-scoring
ER-scoring

HER2-16

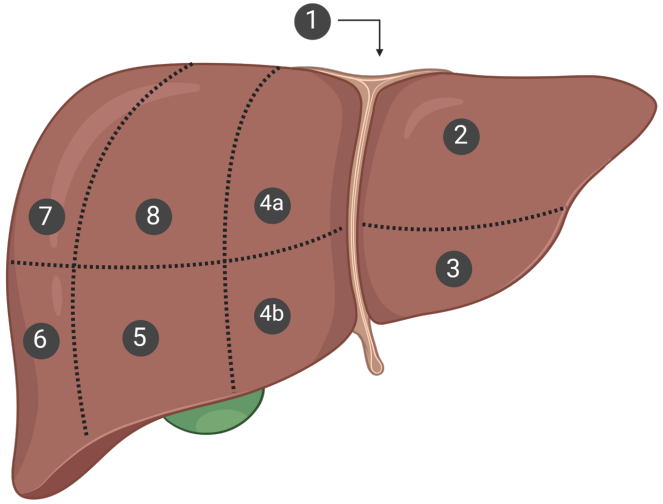


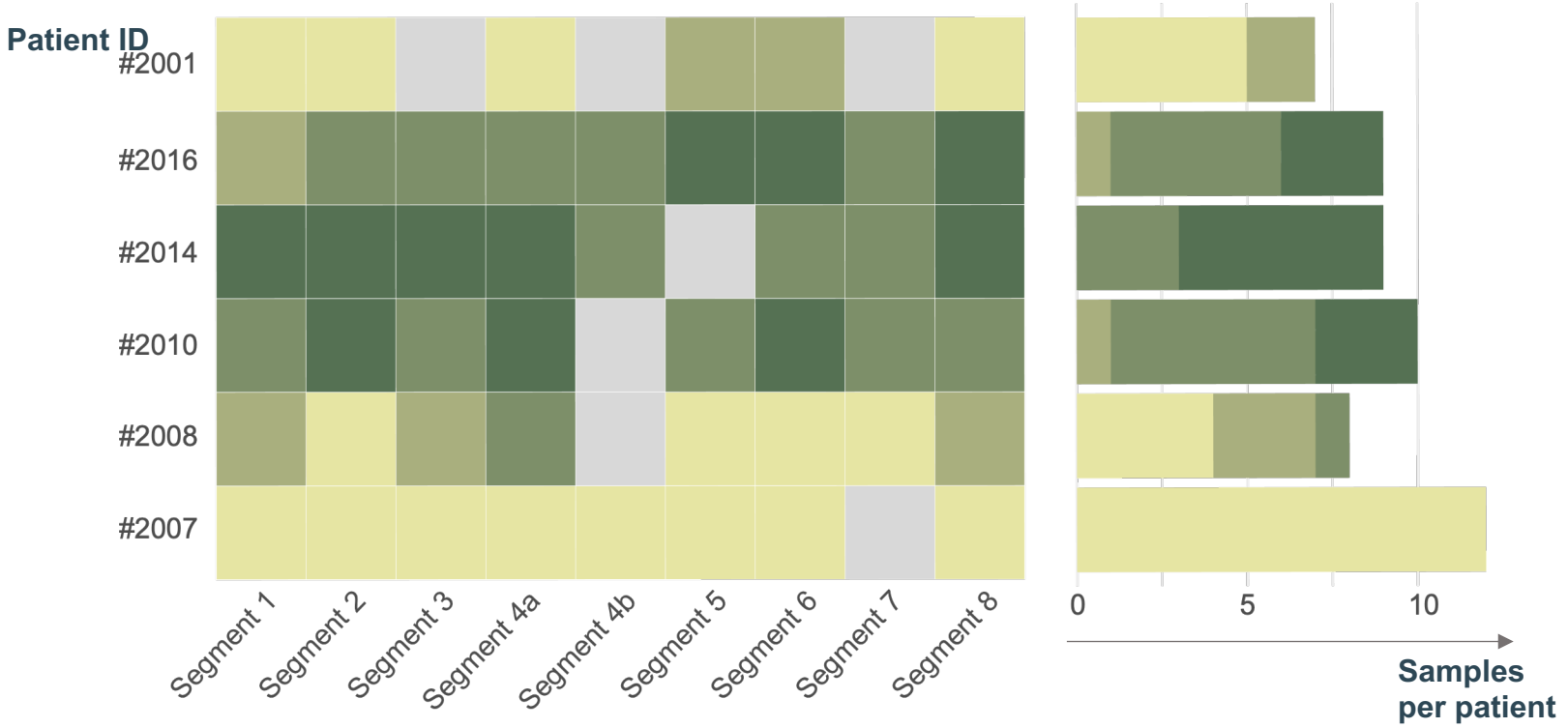
Intra-patient heterogeneity of HER2 scores



1. HER2-low and HER2-zero lesions coincide in 8/10 patients
2. HER2-status of different metastases was highly variable within one patient
3. Half of HER2-zero lesions observed was HER2-ultralow

Intra-organ heterogeneity





These results put into question the assessment of a patient's HER2-low status from a single biopsy at any point in time for benefit of T-DXd

Open questions

- How to best assess the presence of the antibody target?
- Heterogeneity of expression of the targets in the metastatic setting?
- Predictors of therapeutic response and mechanisms of *de novo* and acquired resistance?

RESEARCH BRIEF

Parallel Genomic Alterations of Antigen and Payload Targets Mediate Polyclonal Acquired Clinical Resistance to Sacituzumab Govitecan in Triple-Negative Breast Cancer

James T. Coates[1,2], Sheng Sun[1,2], Ignaty Leshchiner[3], Nayana Thimmiah[1], Elizabeth E. Martin[3], Daniel McLoughlin[1], Brian P. Danysh[3], Kara Slowik[3], Raquel A. Jacobs[3], Kahn Rhrissorrakrai[4], Filippo Utro[4], Chaya Levovitz[4], Elyssa Denault[1], Charlotte S. Walmsley[1], Avinash Kambadakone[2,5], James R. Stone[2,5], Steven J. Isakoff[1,2], Laxmi Parida[4], Dejan Juric[1,2], Gad Getz[1,2,3,6], Aditya Bardia[1,2], and Leif W. Ellisen[1,2,7]

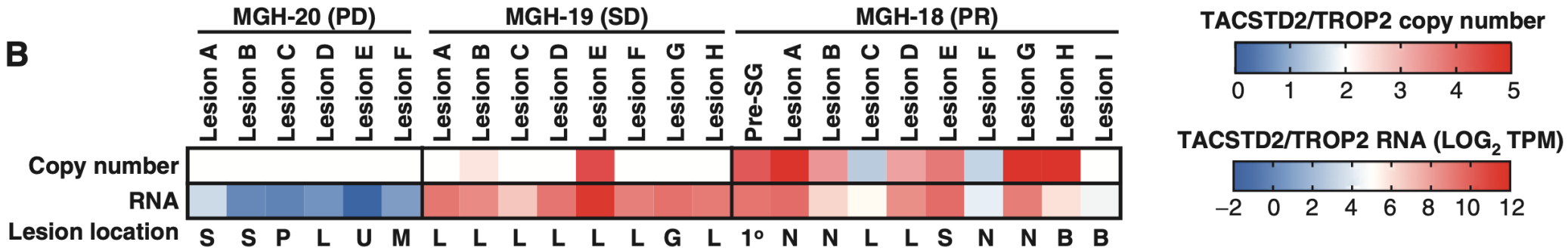
ABSTRACT Sacituzumab govitecan (SG), the first antibody–drug conjugate (ADC) approved for triple-negative breast cancer, incorporates the anti-TROP2 antibody hRS7 conjugated to a topoisomerase-1 (TOP1) inhibitor payload. We sought to identify mechanisms of SG resistance through RNA and whole-exome sequencing of pretreatment and postprogression specimens. One patient exhibiting *de novo* progression lacked TROP2 expression, in contrast to robust TROP2 expression and focal genomic amplification of *TACSTD2/TROP2* observed in a patient with a deep, prolonged response to SG. Analysis of acquired genomic resistance in this case revealed one phylogenetic branch harboring a canonical $TOP1^{E418K}$ resistance mutation and subsequent frameshift *TOP1* mutation, whereas a distinct branch exhibited a novel $TACSTD2/TROP2^{T256R}$ missense mutation. Reconstitution experiments demonstrated that $TROP2^{T256R}$ confers SG resistance via defective plasma membrane localization and reduced cell-surface binding by hRS7. These findings highlight parallel genomic alterations in both antibody and payload targets associated with resistance to SG.

SIGNIFICANCE: These findings underscore TROP2 as a response determinant and reveal acquired SG resistance mechanisms involving the direct antibody and drug payload targets in distinct metastatic subclones of an individual patient. This study highlights the specificity of SG and illustrates how such mechanisms will inform therapeutic strategies to overcome ADC resistance.

A

Participant ID	Molecular subtype	Age at diagnosis	Days on IMMU-132	Days from last dose SG to death	Treatments before SG	Treatments after SG	Lesions sequenced at autopsy	Best response (per RECIST)	Extent of best response (%)
MGH-18	TNBC	41	253	138	2	2	9	PR	–45.0
MGH-19	TNBC	59	150	305	5	4	8	SD	–21.9
MGH-20	TNBC	62	34	56	4	1	6	PD	+78.0

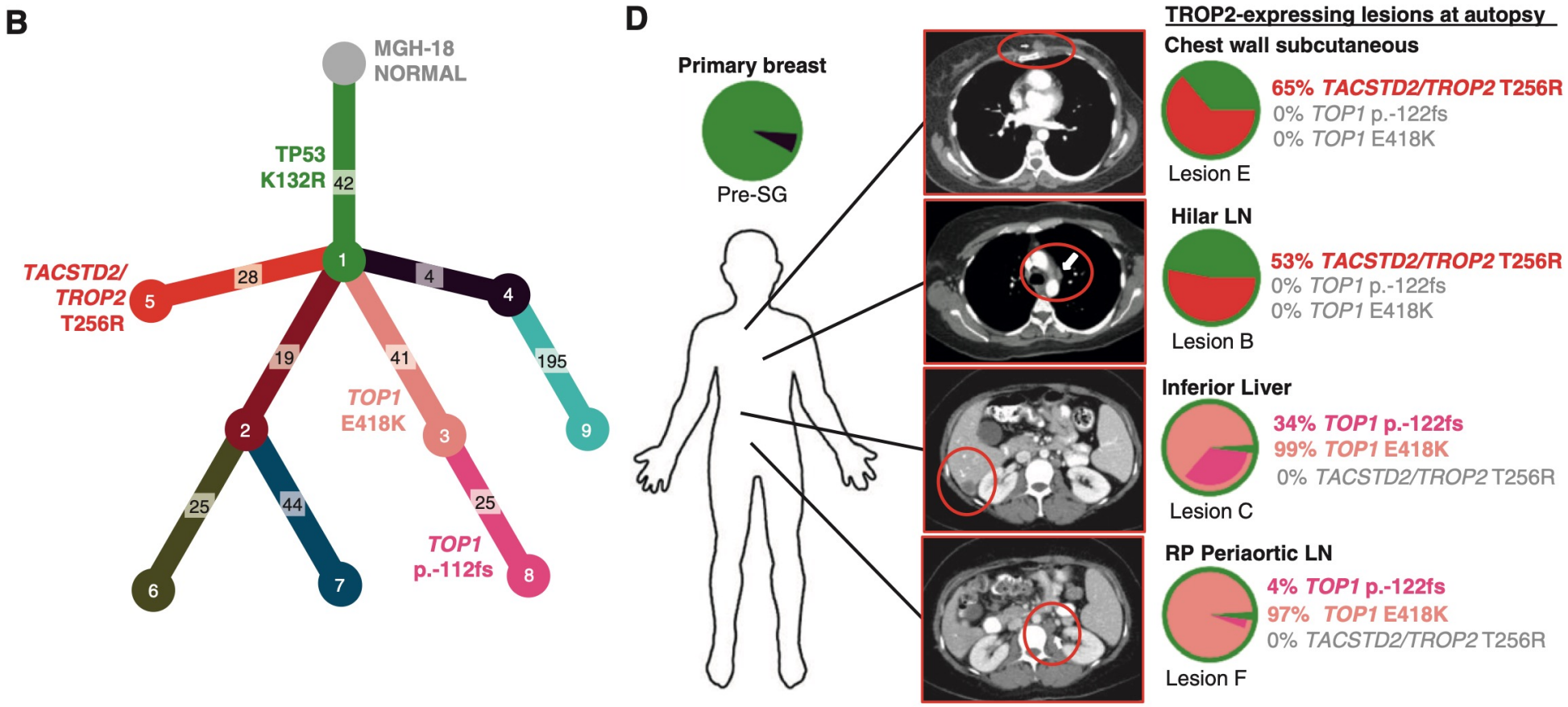
B



- 3 patients with metastatic TNBC treated with SG and heterogeneous responses
- All eventually died and autopsy was performed

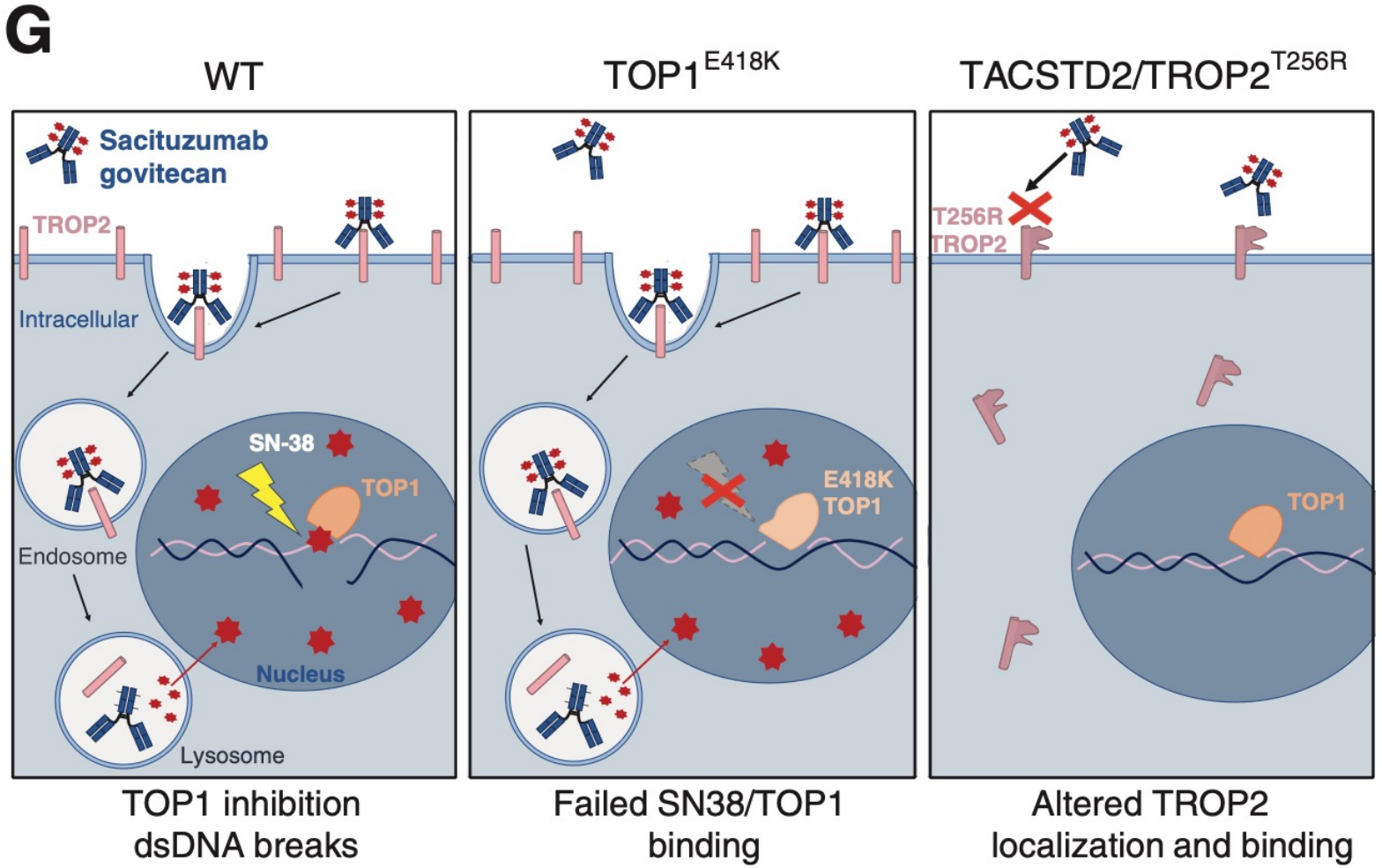
- Pt with de novo resistance (MHG-20) ➔ NO expression of TROP2 (mRNA & IHC)

Coates *et al.* Can Disc 2021



Mutually-exclusive genomic alterations of *TACSTD1/TROP2* and *TOP1*

Coates *et al.* Can Disc 2021



- Which is the frequency of these mechanisms of resistance?
- One metastatic biopsy is not enough ➔ intra-patient inter-metastasis heterogeneity
- Will we see similar mechanisms of resistance to other ADCs?

Coates *et al.* Can Disc 2021

Predictive and resistance markers for:

- Antibody-drug conjugates (ADCs)
- Immunotherapy
- Endocrine therapy

PD4-05 (Wu SY et al.): Integrated multi-cohort profiling identifies CCL19+ dendritic cells to potentiate It efficacy in TNBC

It’s not only about CD4 or CD8 cells

- ICI only benefit a subset of patients with early and metastatic TNBC

➔**biomarkers needed**

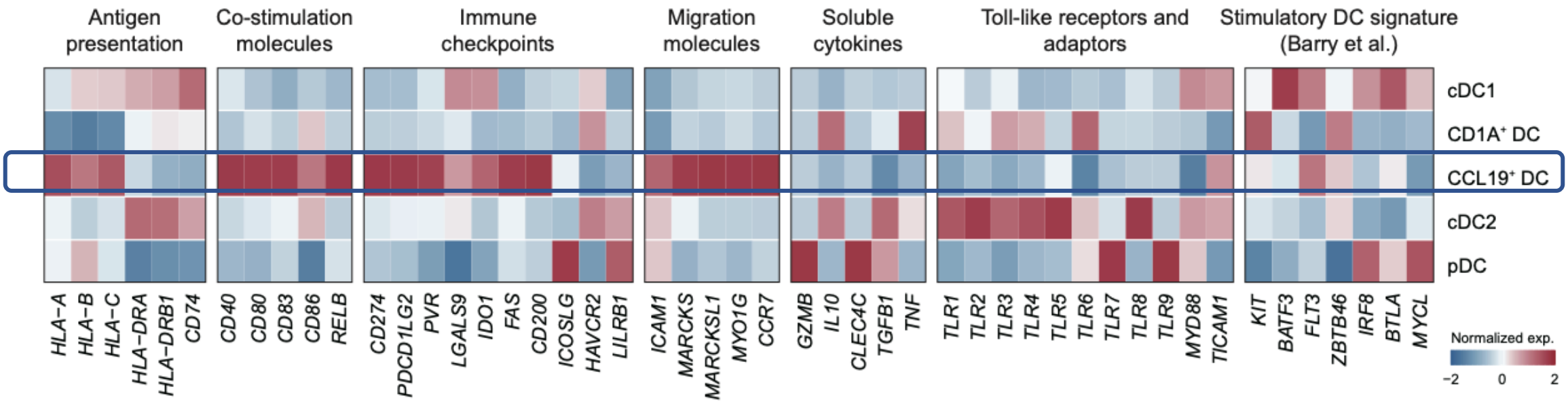
- **Dendritic cells (DCs)**:
  - Key antigen-presenting cells specialized in orchestrating adaptive T cell response
  - Heterogeneous group of cells
  - Understudied in BC in the context of ICI

Aims:

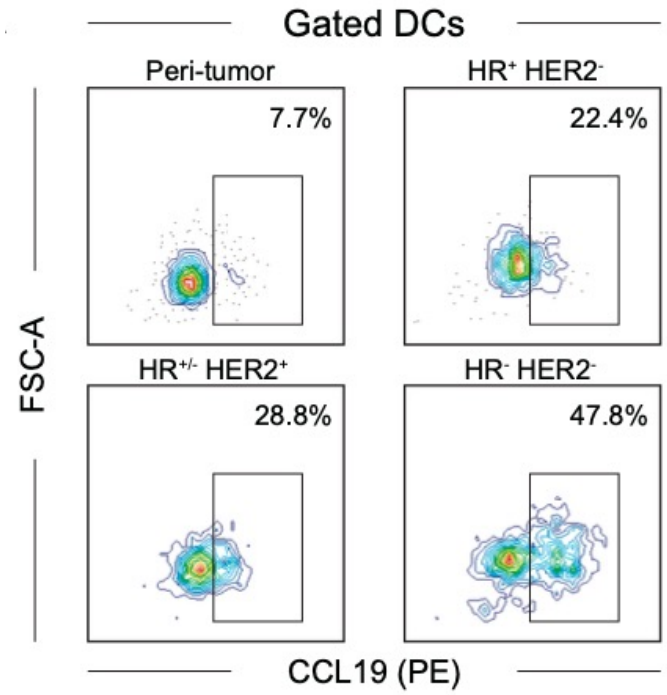
1) Exploring **DC diversity** in TNBC

2) Investigate whether a DC subpopulation could be associated with the **efficacy of ICI**

Identification of DC clusters through re-analysis of existing scRNA-seq data



Prevalence of CCL19+ DC: higher in TNBC

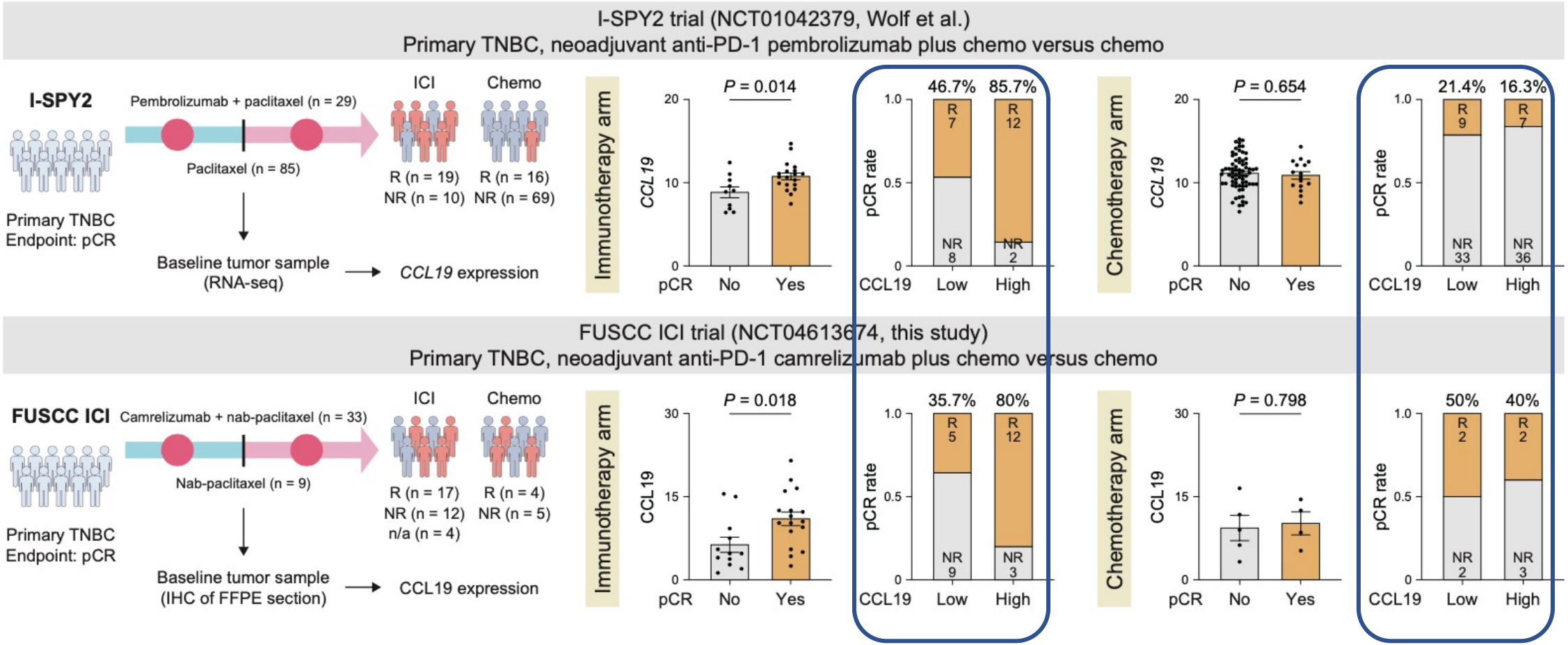


FUSCC mRNA (n = 360)	CCL19+ DC sig. Low	CCL19+ DC sig. High	*P* value
Tumor size (mm)			
≤ 20	64 (35.8)	67 (37.2)	
> 20	115 (64.2)	113 (62.8)	0.773
Lymph nodes			
none	113 (62.8)	102 (57.3)	
1-3	42 (23.3)	53 (29.8)	
4-9	13 (7.2)	16 (9.0)	
> 9	12 (6.7)	7 (3.9)	0.844
Molecular subtype			
IM	8 (4.4)	79 (43.9)	
MES	18 (10.0)	20 (11.1)	
LAR	61 (33.9)	35 (19.5)	
BLIS	93 (51.7)	46 (25.6)	< 0.001***

FUSCC mIHC (n = 186)	CCL19+ DC IHC Low	CCL19+ DC IHC High	*P* value
Tumor size (mm)			
≤ 20	24 (25.8)	35 (37.6)	
> 20	69 (74.2)	58 (62.4)	0.083
Lymph nodes			
none	58 (62.4)	50 (53.8)	
1-3	22 (23.7)	29 (31.2)	
4-9	9 (9.7)	6 (6.5)	
> 9	4 (4.3)	8 (8.6)	0.323
Molecular subtype			
IM	7 (7.5)	33 (35.5)	
MES	9 (9.7)	10 (10.8)	
LAR	25 (26.9)	18 (19.4)	
BLIS	52 (55.9)	32 (34.4)	< 0.001***

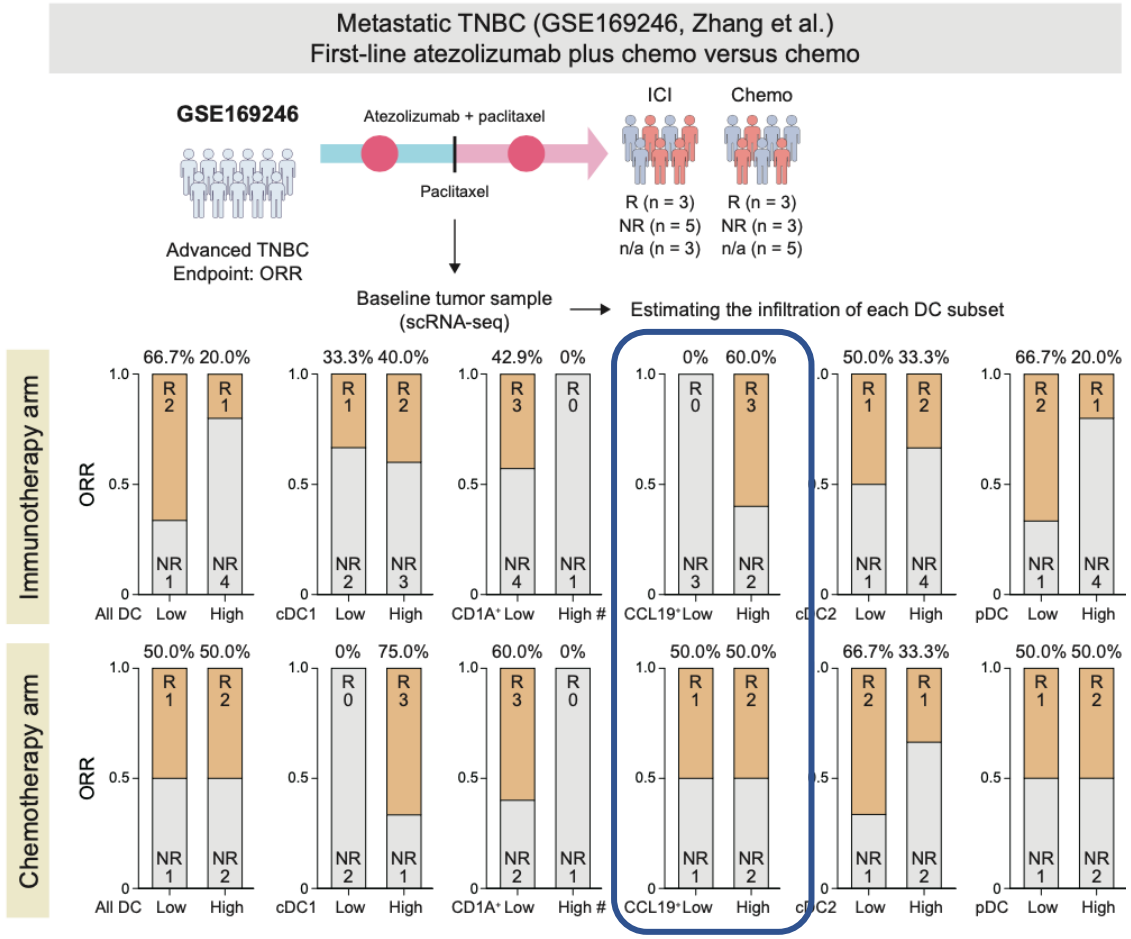
- Higher prevalence of CCL19+ DCs in TNBC as compared to other molecular subgroups.
- Within TNBC, higher prevalence within the immunomodulatory subtype.

Response to IT (early setting)

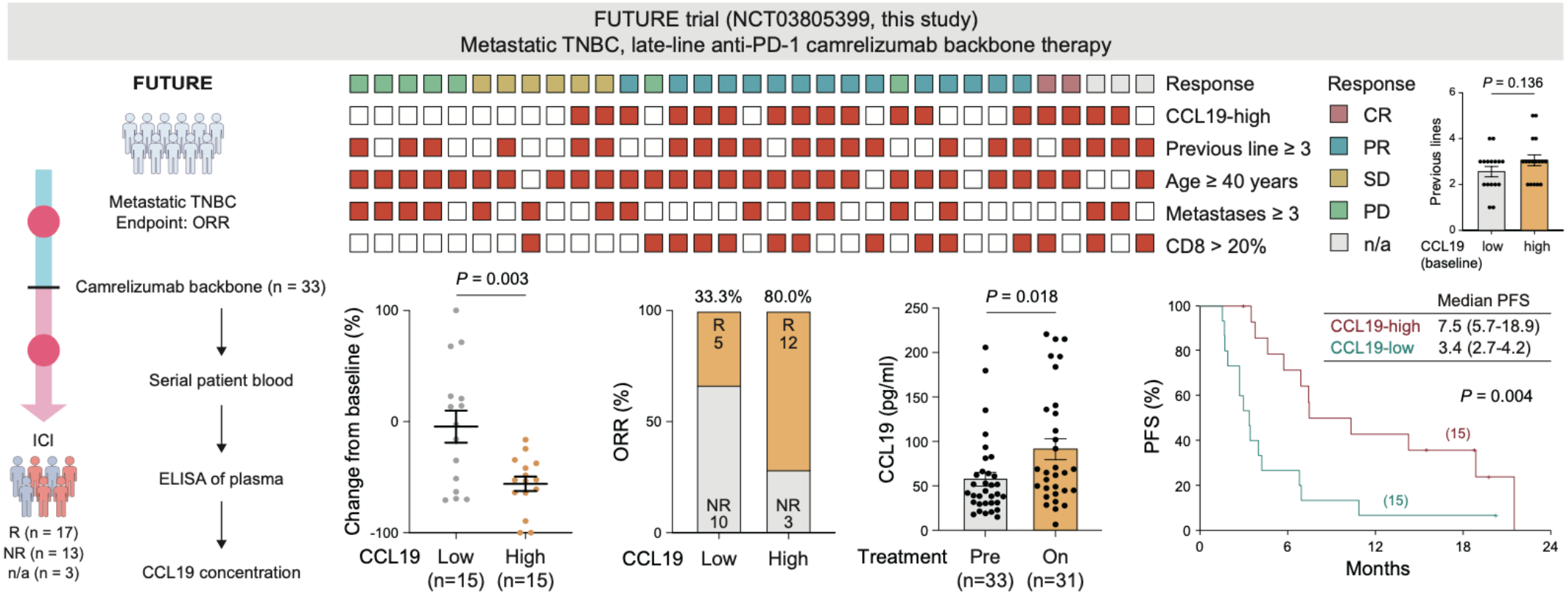


CCL19 is associated with response to neoadjuvant ICI +chemotherapy but not with response to neoadjuvant chemotherapy alone.

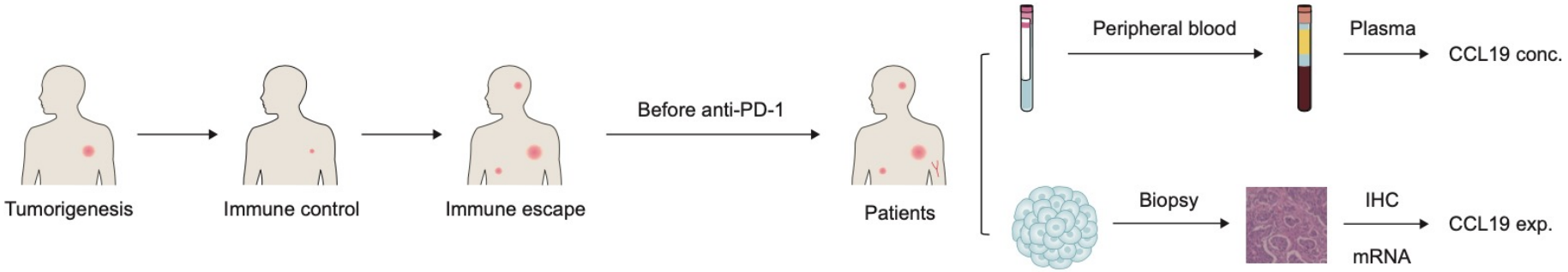
Response to IT (metastatic setting)



Response to IT (metastatic setting- CCL19 in plasma)



Flow chart of measuring baseline CCL19 level to facilitate patient stratification upon ICI therapy in the clinic



- Distinct population of CCL19+ DCs potentiates ICI-response in TNBC
- Baseline CCL19, as measured in tumor or plasma, is associated with efficacy of ICI in patients with early and metastatic TNBC

Predictive and resistance markers for:

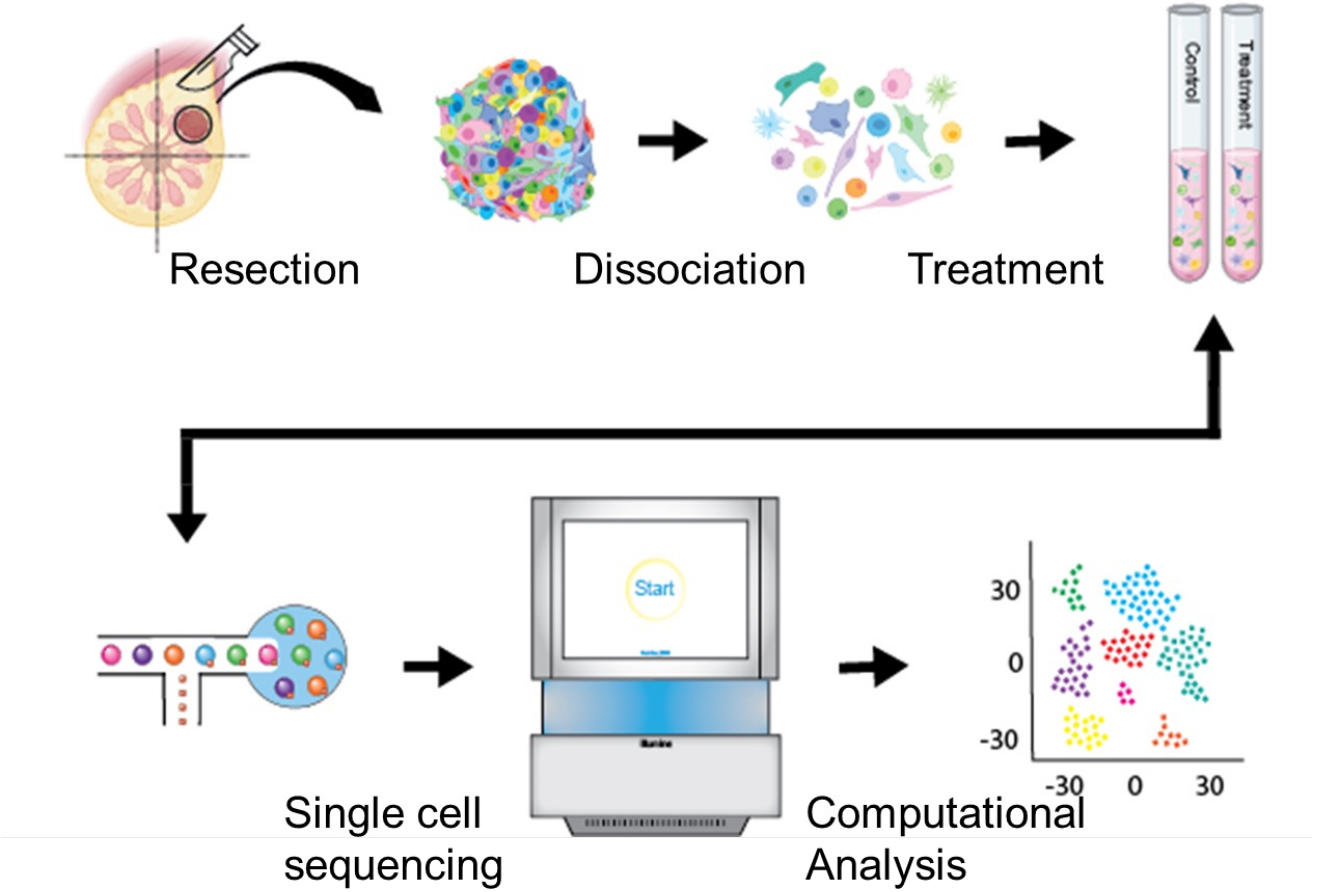
- Antibody-drug conjugates (ADCs)
- Immunotherapy
- Endocrine therapy

PD4-08 (Kim H et al.): A novel single cell model of Tamoxifen response in primary human breast tumors

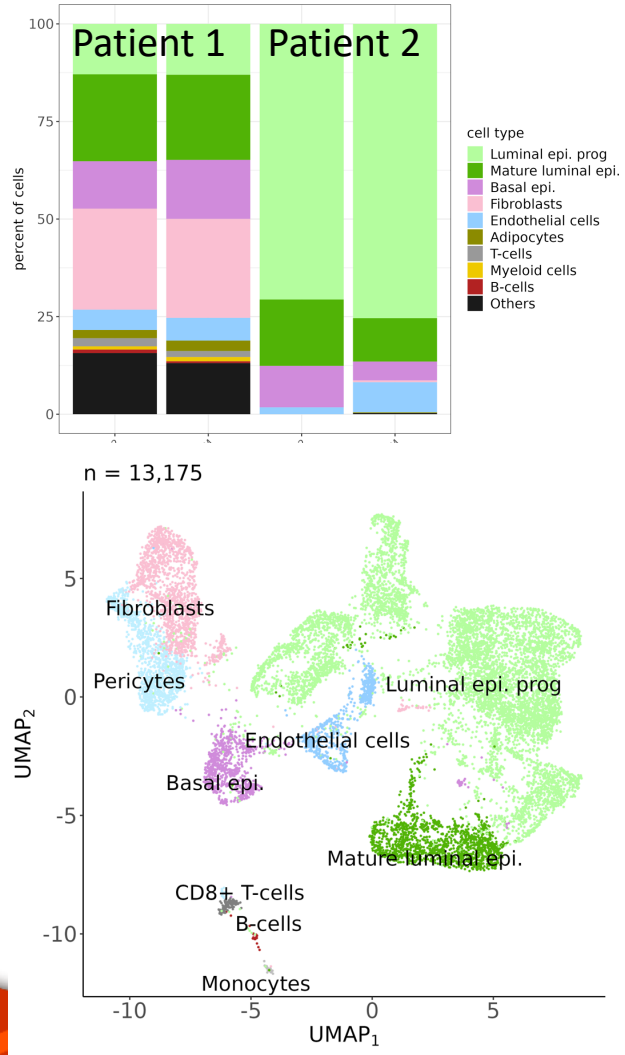
OR-to-lab pipeline to test drug sensitivity

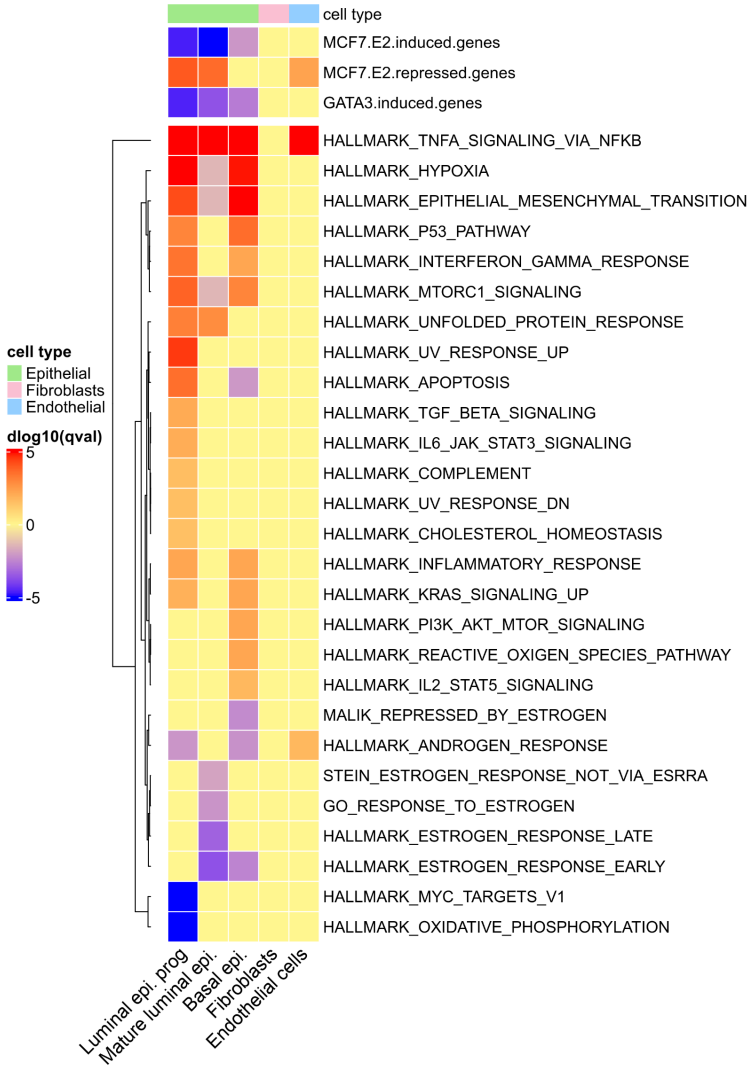
Aims:

1) To create an OR-to-lab pipeline to test treatment effect
2) To identify mechanisms of resistance/sensitivity to Tamoxifen



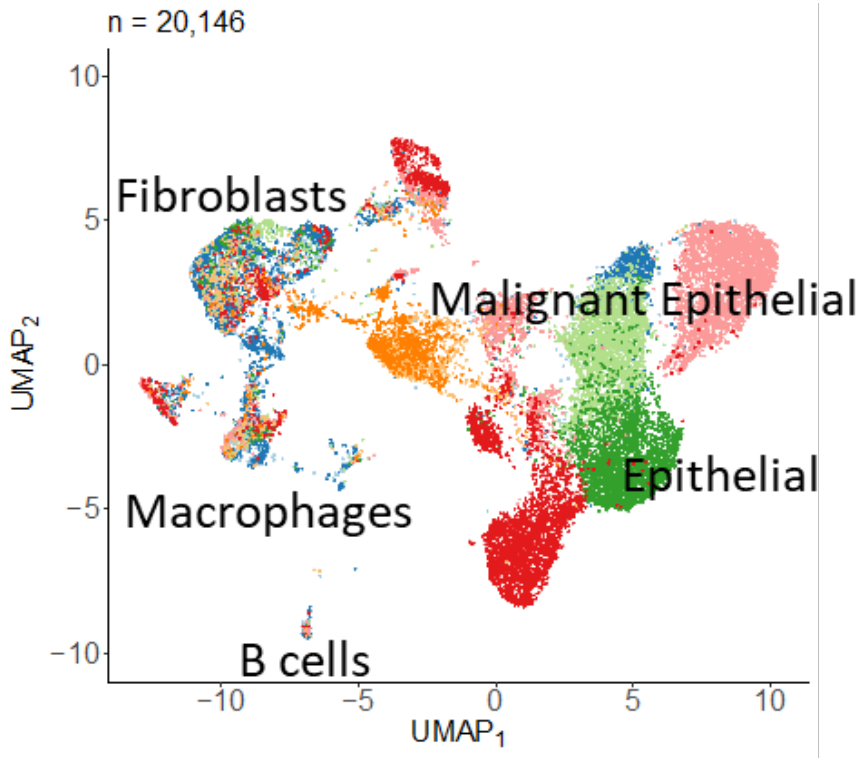
Results on two normal breast samples

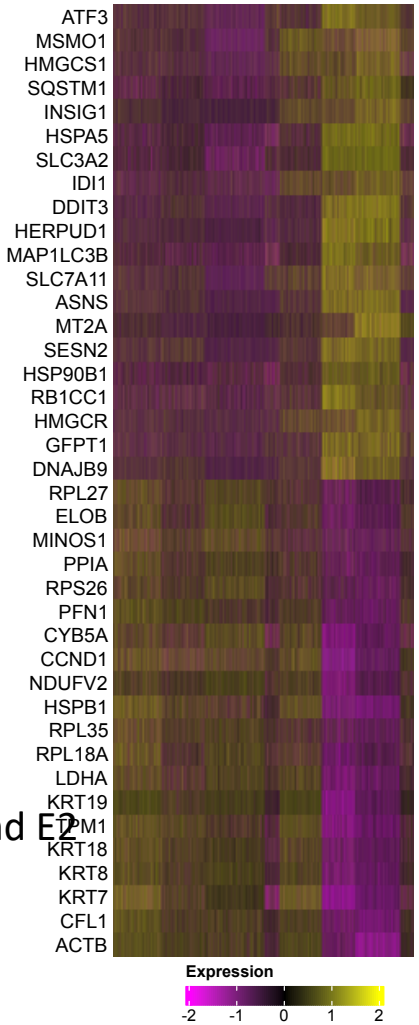




- Changes mainly seen in the **epithelial cells** (especially in luminal progenitor cells)
- With Tamoxifen: robust depletion of estrogen- induced genes & enrichment of estrogen-repressed genes

Results on two breast cancer samples





- Down regulation of canonical GATA3 and E2 induced genes
- Upregulation of EGFR/MAPK, RAS, and HDAC target signatures

- OR-to-lab pipeline developed to test effect of tamoxifen on human normal breast and ER+ breast cancer samples.
- Single-cell analyses have the potential to identify cell subpopulations in human samples from patients with ER+ breast cancer.
- Changes mainly visible in tumor epithelial cells, highlighting changes in different processes.
- Approach could be expanded to other tumor types & therapies.

Immune landscape & microenvironment

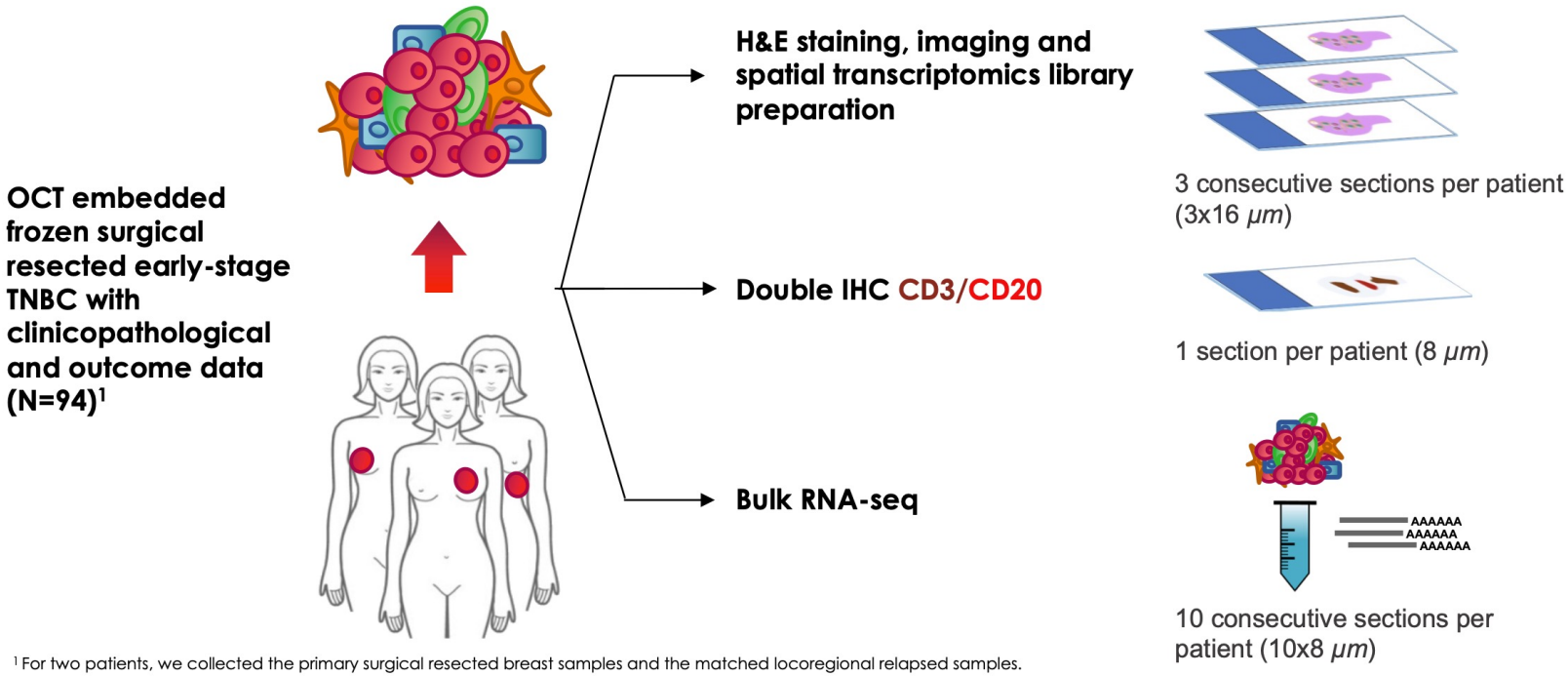
- TNBC
- HER2-/Immune-/DR- subtype

PD4-01 (Wang X et al.): Spatial transcriptomics reveals a substantial heterogeneity in TNBC tumor and stroma compartments with potential clinical implications

TNBC characterization & re-classification using ST

Aims

- To characterize the **spatially resolved transcriptome** of cancer cells, their nearby and distant microenvironment and **their interactions**;
- To assess the role of **intratumor heterogeneity** and tumor **microenvironment** in predicting **clinical outcomes**



[1] For two patients, we collected the primary surgical resected breast samples and the matched locoregional relapsed samples.

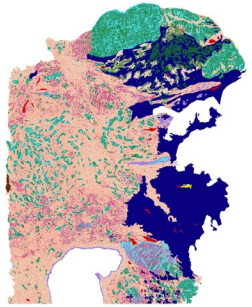
Moprohological annotations & association with subtypes

Morphological annotations

17 morphological annotations

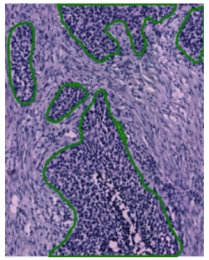
- Tumor
- Stroma cell
- Lymphocyte
- Low TILs (<30%) stroma
- High TILs (≥30%) stroma
- Acellular stroma
- Fat tissue
- Necrosis
- In situ
- Lymphoid nodule
- Vessels
- Lactiferous duct
- Nerve
- Heterologous element
- Tumor region
- Whitespace
- Artefact

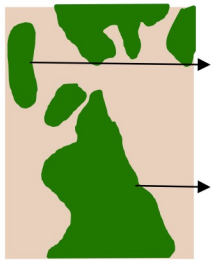
Manual delineation +/- machine learning using QuPath *version 0.2.3.*



Contribution of each morphological annotation

Tumor patches

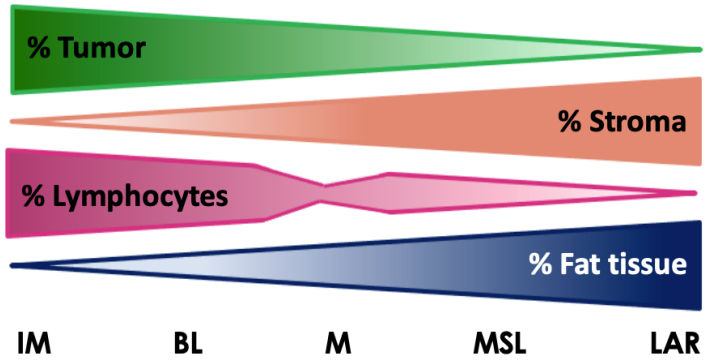


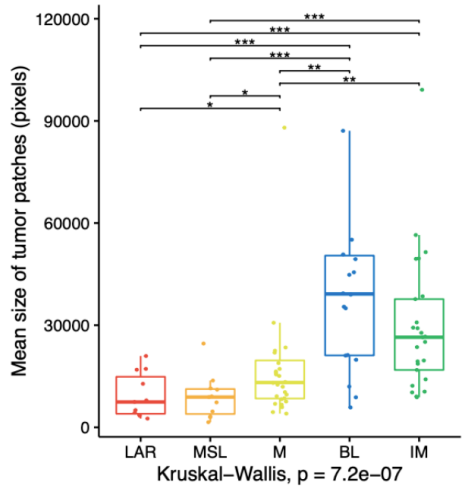


A small tumor patch

A large tumor patch

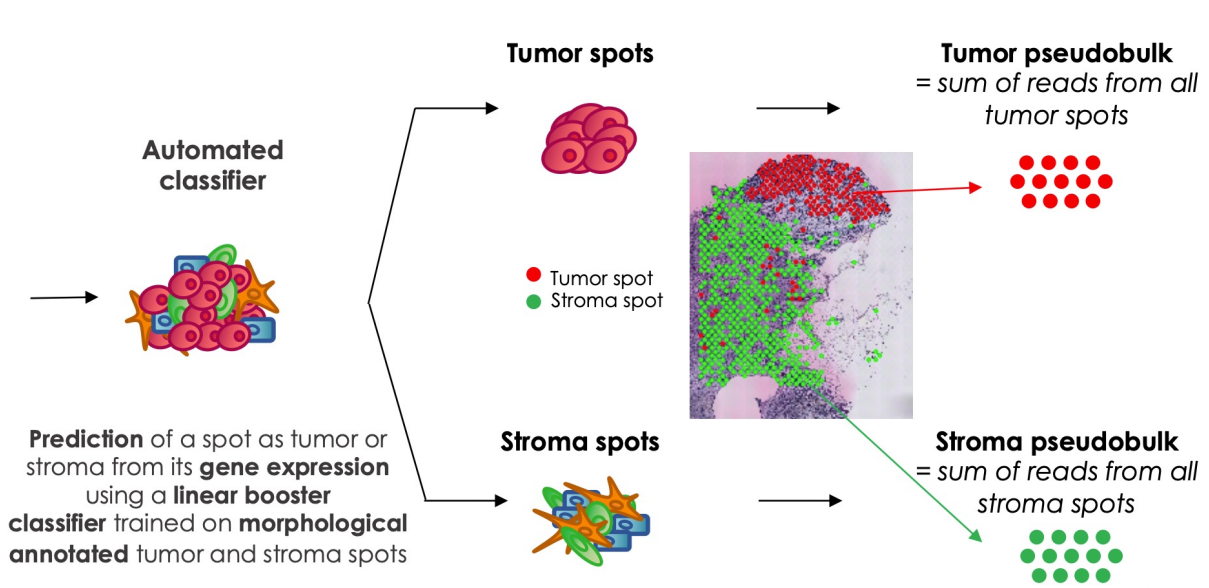
Number, size (pixels), diversity of size (described by evenness)

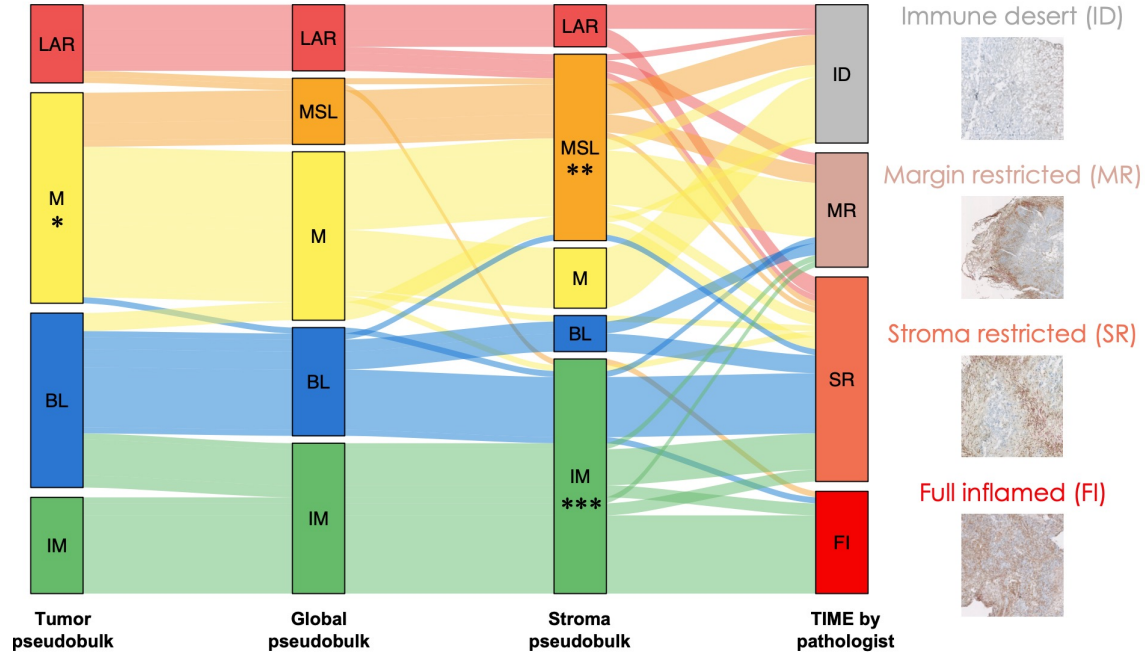




Basal like (BL), Immunomodulatory (IM), Luminal Androgen Receptor (LAR), Mesenchymal (M), Mesenchymal stem like (MSL)

Separate tumor & stroma classification of TNBC

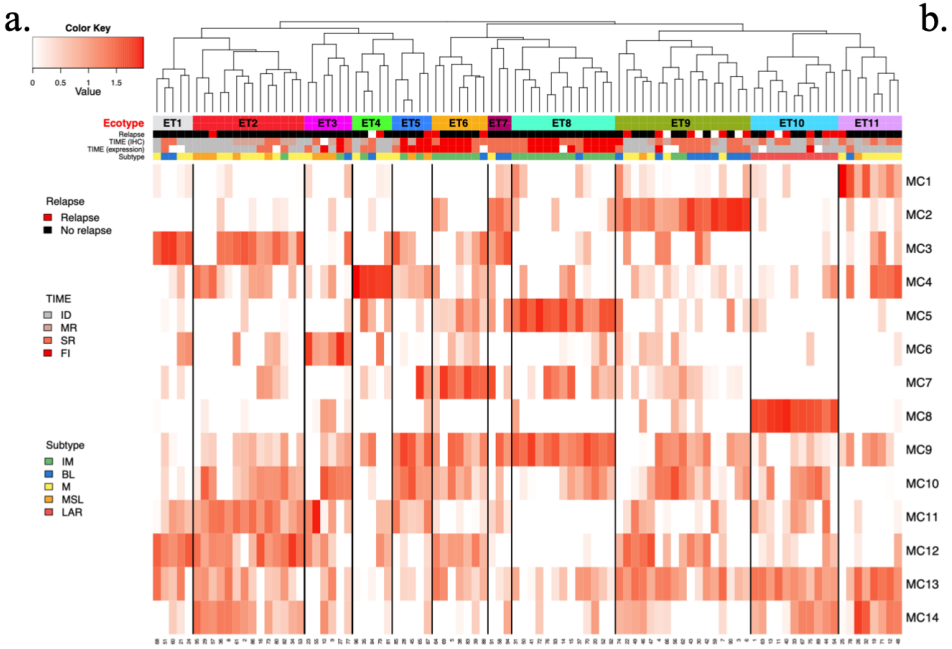




Basal like (BL), Immunomodulatory (IM), Luminal Androgen Receptor (LAR), Mesenchymal (M), Mesenchymal stem like (MSL)

New classification of TNBC- “11 ecotypes”

a.



b.

Ecotype	Name	Characteristics
ET1	Proliferative	High proliferation, ERBB2 expression
ET2	Mesenchymal stromal	EMT, angiogenesis, low proliferation
ET3	Mixed	Stroma, moderate immune infiltration (NKT cells), low proliferation
ET4	Immuno-depleted	Low immune infiltration, low apoptosis, low stroma (CAF)
ET5	Immuno-angiogenic	High immune infiltration, apoptosis, angiogenesis, low proliferation
ET6	Immuno-proliferative	Th1 cells enriched immune infiltration, EMT
ET7	Stromal proliferative	High proliferation, PI3K/AKT/mTOR, EMT
ET8	Pure immunogenic	High immune infiltration
ET9	Basal cycling	Moderate proliferation, EMT, MYC target, NECTIN4 expression
ET10	LAR	AR expression, ER signaling, fatty metabolism
ET11	Mesenchymal proliferative	High proliferation, low immune infiltration, GPNMB expression

- Substantial morphological differences across the five TNBC subtypes.
- Different contribution of stroma/tumor compartments to molecular subtypes.
- Different contribution of pairs of molecular subtypes from stroma/tumor compartment to TIME classification.
- Definition of new ‘ecotypes’.
- Potential clinical relevance to be further investigated.

Liquid biopsies

- Marker of disease recurrence
- ctDNA evaluation in other body liquids

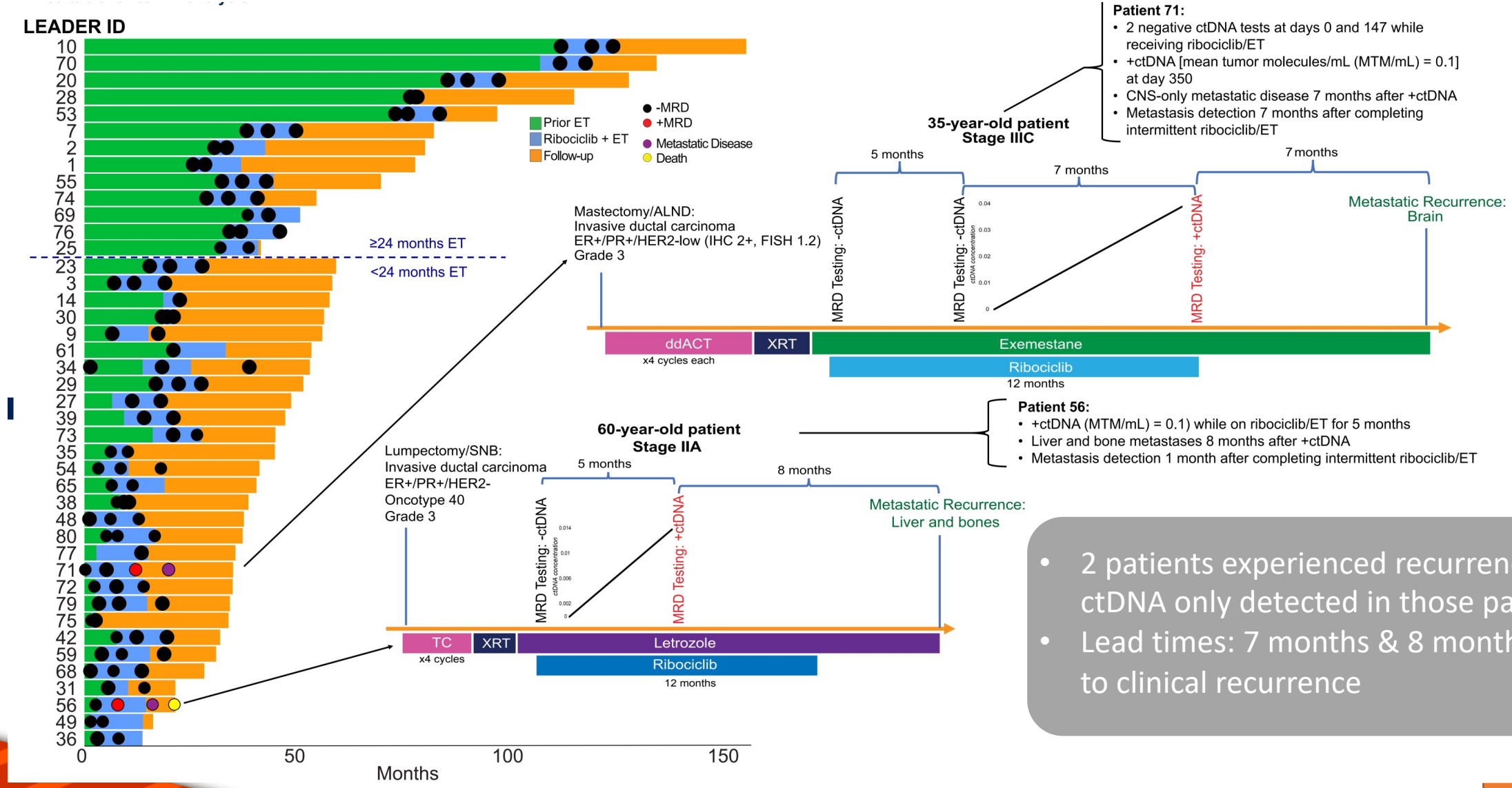
PD17-03 (Medford *et al*.): Cell-free DNA monitoring in a phase II study of adjuvant endocrine therapy with CDK 4/6 inhibitor ribociclib for *localized HR+/HER2- breast cancer* (LEADER)

PD17-02 (Bailleux et al.): ctDNA Molecular Response based on breast cancer driver mutations predicts progression in aromatase inhibitor-sensitive first line treatment of oestrogen receptor-positive (*ER+) HER2-negative (HER2-) advanced breast cancer*

PD17-01 (Ma *et al.*): Genomic analysis of circulating tumor DNA (ctDNA) from patients with HR+, *HER2-mutant metastatic breast cancer* (MBC) enrolled in SUMMIT: mechanisms of acquired resistance to neratinib + fulvestrant + trastuzumab (N+F+T)

Monitoring of recurrence in pts with early BC

- Patients with **stage 1-3 ER+ BC**
- **LEADER trial:** prospective phase II trial evaluating the addition of the CDK4/6 inhibitor ribociclib in patients with 1 remaining year of adjuvant ET
- **Translational objective:** ctDNA monitoring to predict recurrences
- **Signatera™ assay** (WES of primary tumor and then selection of 16 genes to be evaluated in blood)- 42 patients.



- 2 patients experienced recurrence: ctDNA only detected in those patients
- Lead times: 7 months & 8 months prior to clinical recurrence

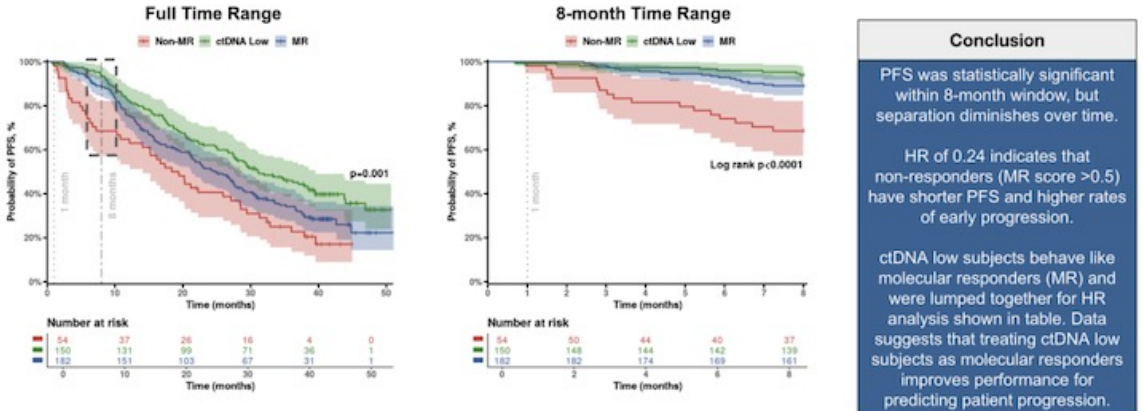
Monitoring of recurrence in pts with advanced BC

- Patients with **advanced ER+ BC**
- **PADA-1 trial:** to assess clinical utility of sequential analysis of ctDNA for emerging *ESR1* mutations to trigger an early switch from AI plus palbociclib to fulvestrant plus palbociclib treatment. The study included 1,017 patients and was positive on its primary end-point.
- **Translational objective:** analyze the predictive value of 4-week molecular response (MR) for patient progression.
- **Guardant360 Response:** (1) evaluation of alterations in 74 genes, (2) restriction to 11 BC driver genes- 372/1,017 (37%) patients

1) ctDNA low: responders
2) Molecular responders (MR)
3) Non-MR

All genes

Guardant360 Response Predicts Patient Progression



Conclusion

PFS was statistically significant within 8-month window, but separation diminishes over time.

HR of 0.24 indicates that non-responders (MR score >0.5) have shorter PFS and higher rates of early progression.

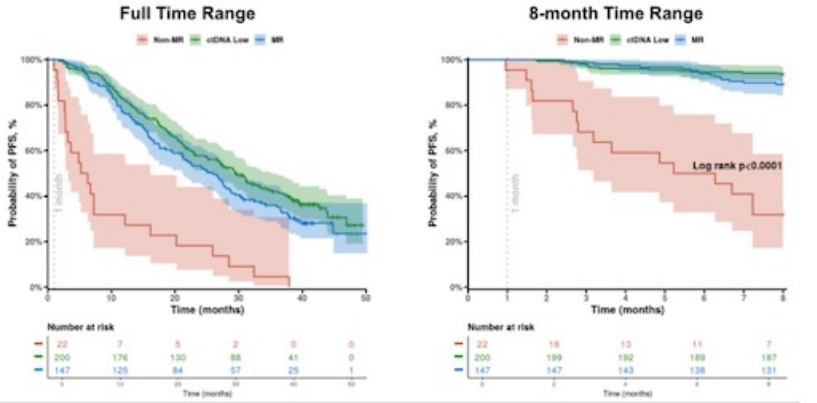
ctDNA low subjects behave like molecular responders (MR) and were lumped together for HR analysis shown in table. Data suggests that treating ctDNA low subjects as molecular responders improves performance for predicting patient progression.

	Full time range HR (95% CI); p-value	8-month HR (95% CI); p-value
MR + ctDNA Low vs Non-MR	0.61 (0.44 - 0.85), p<0.01	0.24 (0.13 - 0.43), p=0.0001

Figure: Molecular responders (MR) defined by a cutoff of 50% decrease in ctDNA (MR < 0.5) and molecular non-responders (Non-MR) by MR > 0.5. Cut-off optimization based on prior publications and verified to perform well/optimally in this cohort. ctDNA Low is defined by no somatic mutations at either time point, or somatic mutations detected at levels below the limit for quantifying change in ctDNA level.

11 BC driver genes

Predictive Ability of Custom Breast Cancer Gene List to Identify Non-Responders by ctDNA



Conclusion

When MR is calculated with a curated list of breast cancer driver mutations only, the number of molecular non-responders identified decreased from 55 to 22, but that sub-group has a higher chance of early progression (**PPV=68%**) compared to the original MR algorithm (**PPV = 31%**).

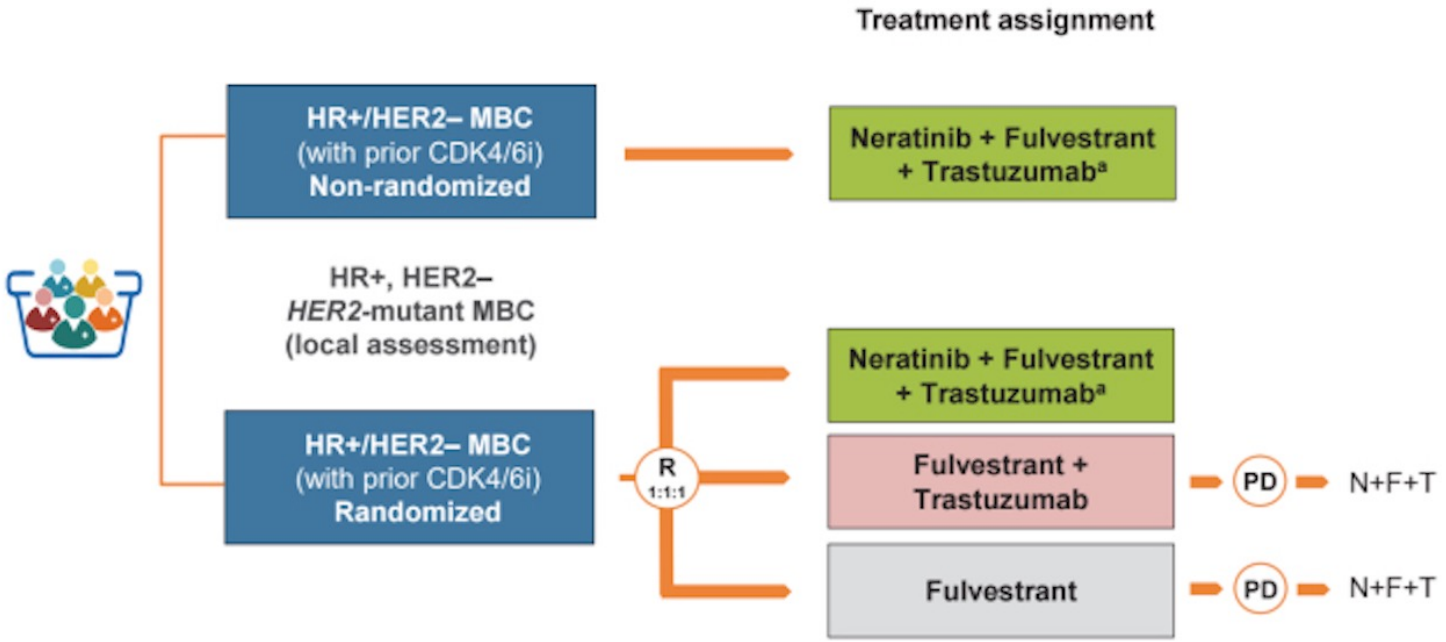
HR of 0.08 indicates that non-responders (MR score >0.5) have shorter PFS and higher rates of early progression.

	Full time range HR (95% CI); p-value	8-month HR (95% CI); p-value
MR + ctDNA Low vs Non-MR	0.23 (0.14 - 0.35), p < 0.001	0.08 (0.04 - 0.17), p<0.001

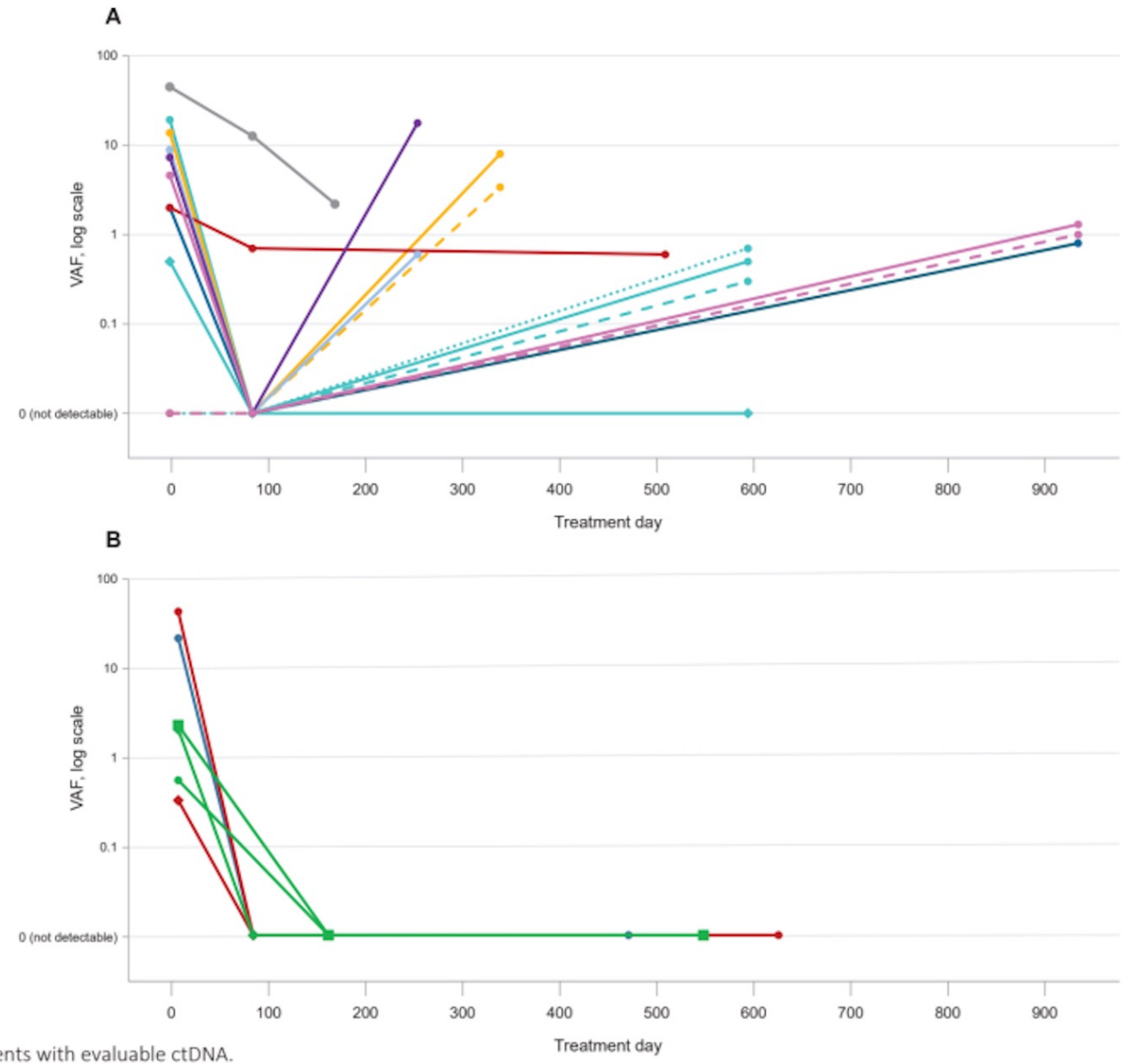
Figure: Molecular responders (MR) defined by a cutoff of 50% decrease in driver-only ctDNA (MR < 0.5) and molecular non-responders (Non-MR) by MR > 0.5. Cut-off optimization based on prior publications and verified to perform well/optimally in this cohort. ctDNA Low is defined by no somatic mutations at either timepoint, or somatic mutations detected at levels below the limit for quantifying change in ctDNA level. Driver mutations selected based on known breast cancer driver mutations (PIK3CA, GATA3, TP53, AKT1, ERBB2, BRCA2, BRCA1, ATM, ESR1, PALB2, RB1).

- Changes in ctDNA fraction during the first weeks of treatment are predictive of long term clinical benefit on an individual patient basis, particularly **during the first year of therapy.**
- The identification of patients at **high risk for early clinical failure** at the onset of treatment may allow for therapy escalation and/or change.

Mechanisms of acquired resistance to neratinib, fulvestrant & trastuzumab



Objective: to evaluate VAF of *HER2* mutations at 3 timepoints, as well as genomic landscape in patients who responded to NFT



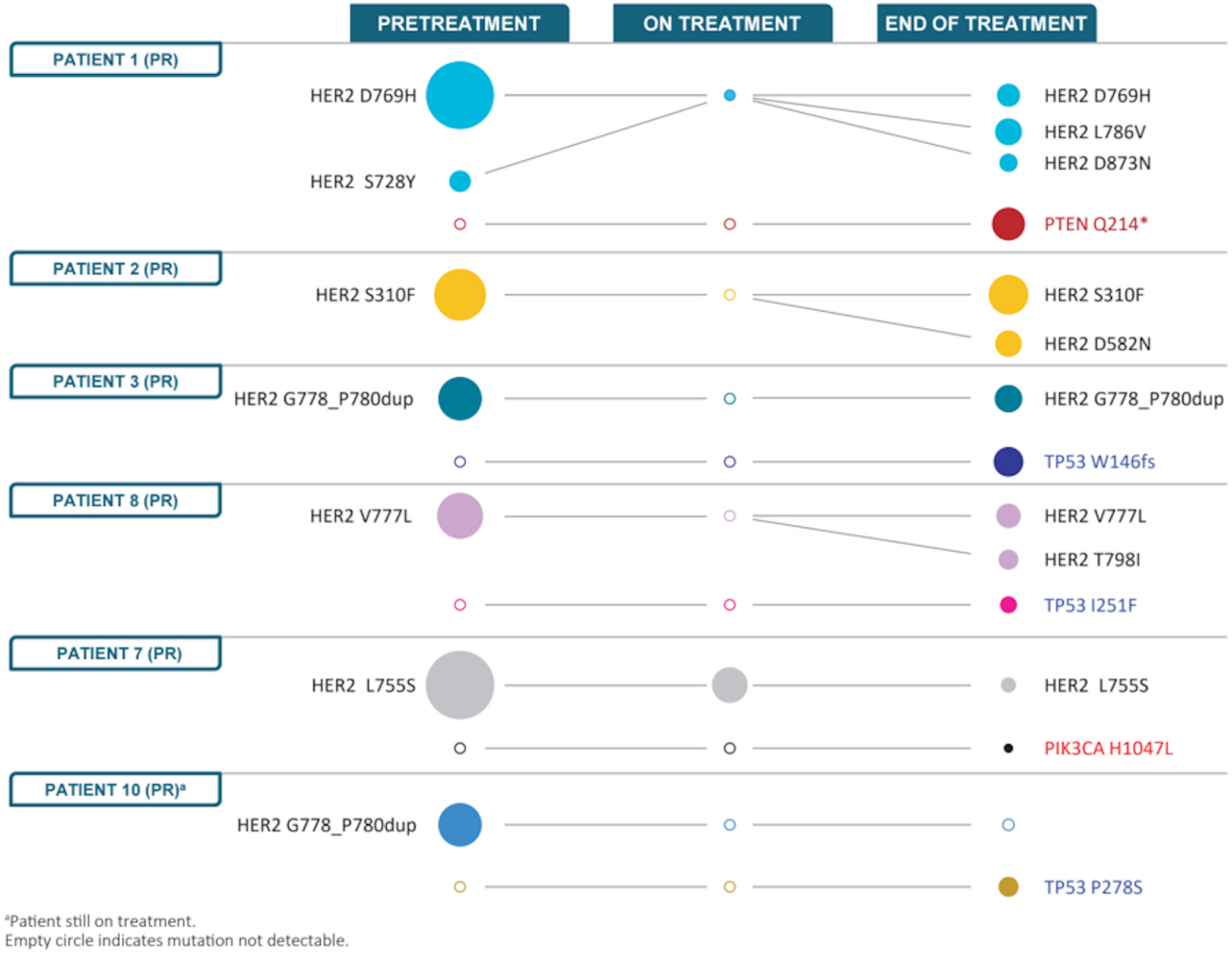
[a]Patients with evaluable ctDNA.
Dashed lines indicate emergent mutations.

Patient 1 (PR) D769H
D873N
L786V
S728Y
Patient 2 (PR) D582N
S310F
Patient 3 (PR) G778_P780dup
Patient 4 (PR) L755S
Patient 5 (PR) V777L
Patient 6 (PR) Y772_A775dup
Patient 7 (PR) L755S
Patient 8 (PR) V777L
T798I

- Patients with Partial Response (PR) who progressed after treatment
- Blood draw at inclusion, on treatment & at progression

Patient 10 (PR) G778_P780dup
Patient 13 (PR) T862A
I767M
Patient 14 (CR) G776V
L1109I
S310F

- Patients who remained on treatment
- Blood draw at inclusion, on treatment & at last FU



[a]Patient still on treatment.
Empty circle indicates mutation not detectable.

- *HER2* mutation VAF in ctDNA decreases upon treatment and increase upon progression
- Mutations that emerged upon progression: novel *HER2* mutations, and mutations in *PIK3CA*, *TP53* and *PTEN*
- Dual HER2 tergeting + endocrine treatelnt cannot prevent the emerge of novel *HER2* mutations

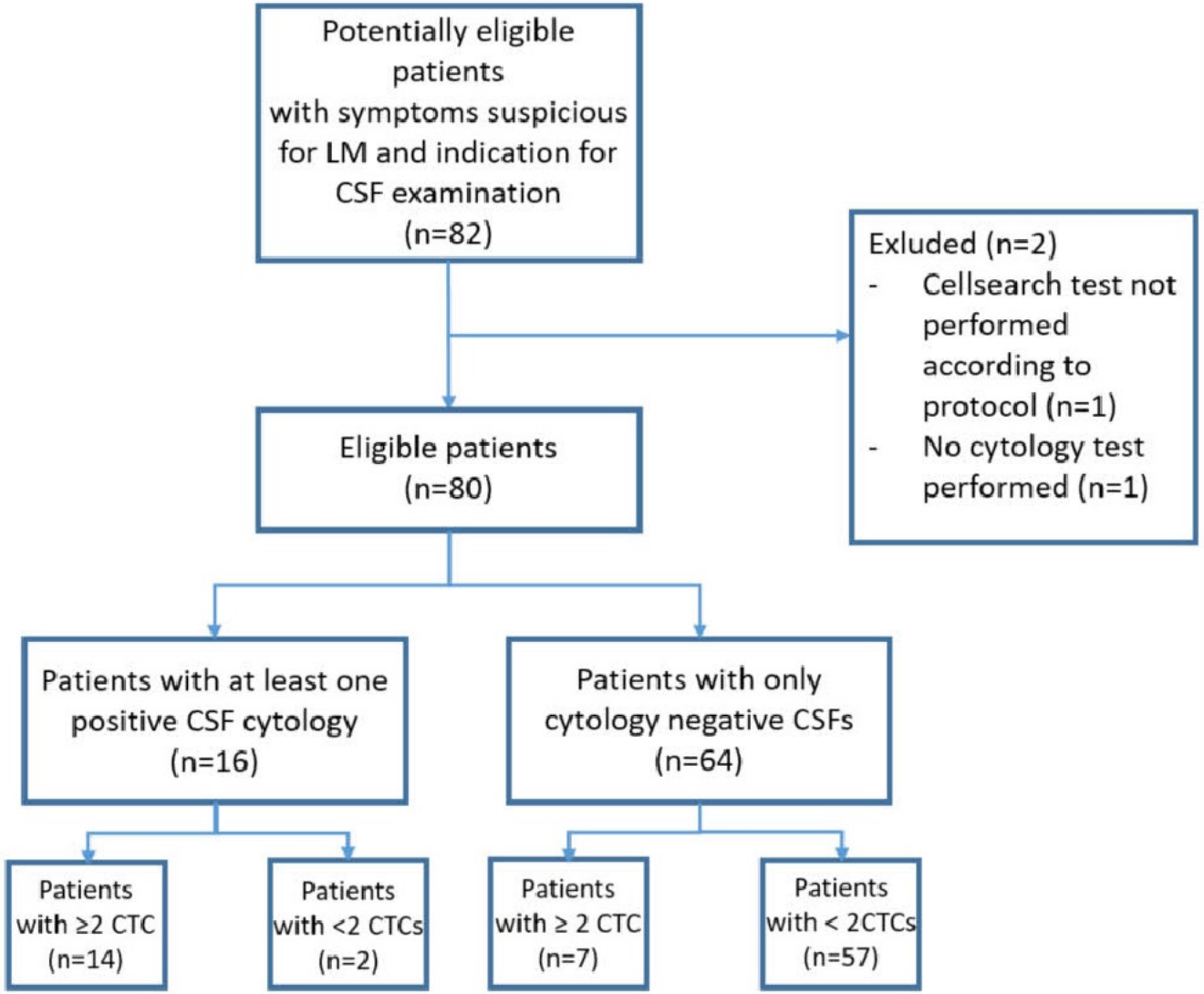
Liquid biopsies

- Marker of disease recurrence
- ctDNA evaluation in other body liquids

P1-05-03 (Jongbloed *et al.*): Optilizing detection of leptomeningeal metastases in breast cancer
P5-05-06 (Richard *et al.*): ctDNA detection in seven different types of body liquids in patients with metastatic breast cancer

Optimizing detection of leptomeningeal metastases (LM)

Aim:
To prospectively compare cytology (current gold standard for CSF analysis in diagnosing LM) with CTC enumeration and ctDNA detection in CSF



Optimizing detection of leptomeningeal metastases

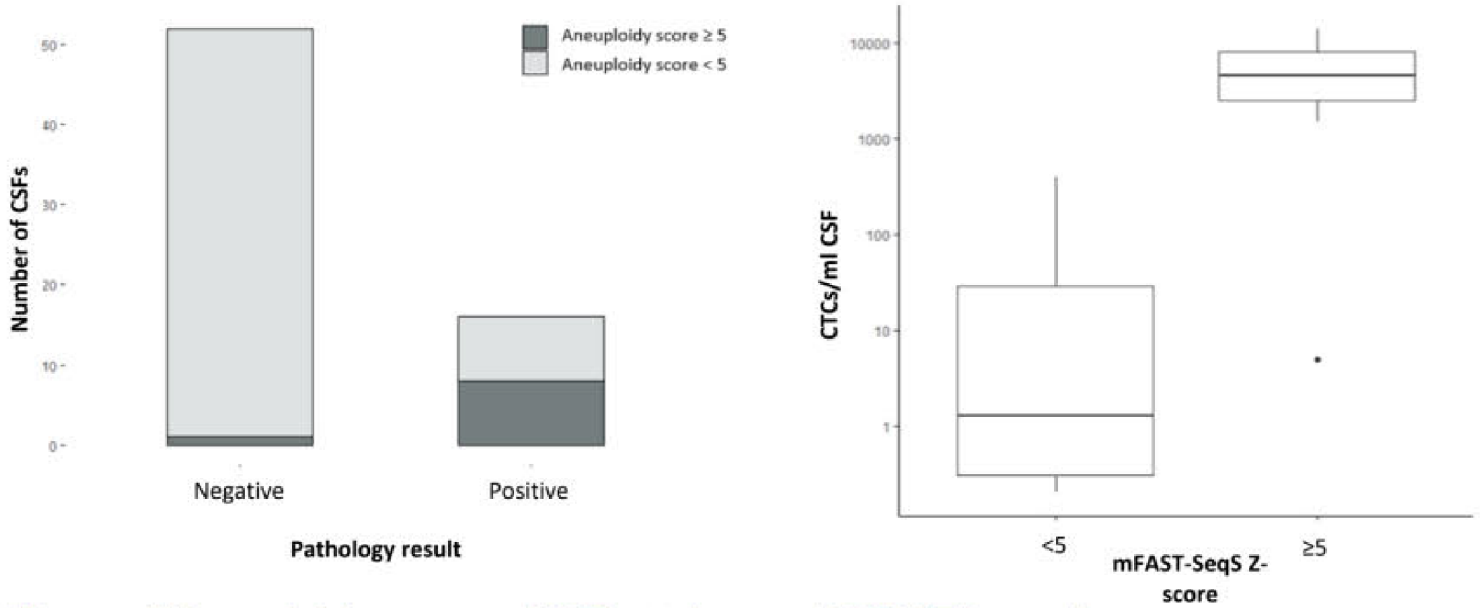


Figure 5 Aneuploidy score and CSF cytology and CSF CTCs results.
Left: mFAST-SeqS (aneuploidy) Z-score per cytology result.
Right: Number of CTCs in CSF with mFAST-SeqS (aneuploidy) Z-score ≥5 vs. mFAST-SeqS (aneuploidy) Z-score <5.

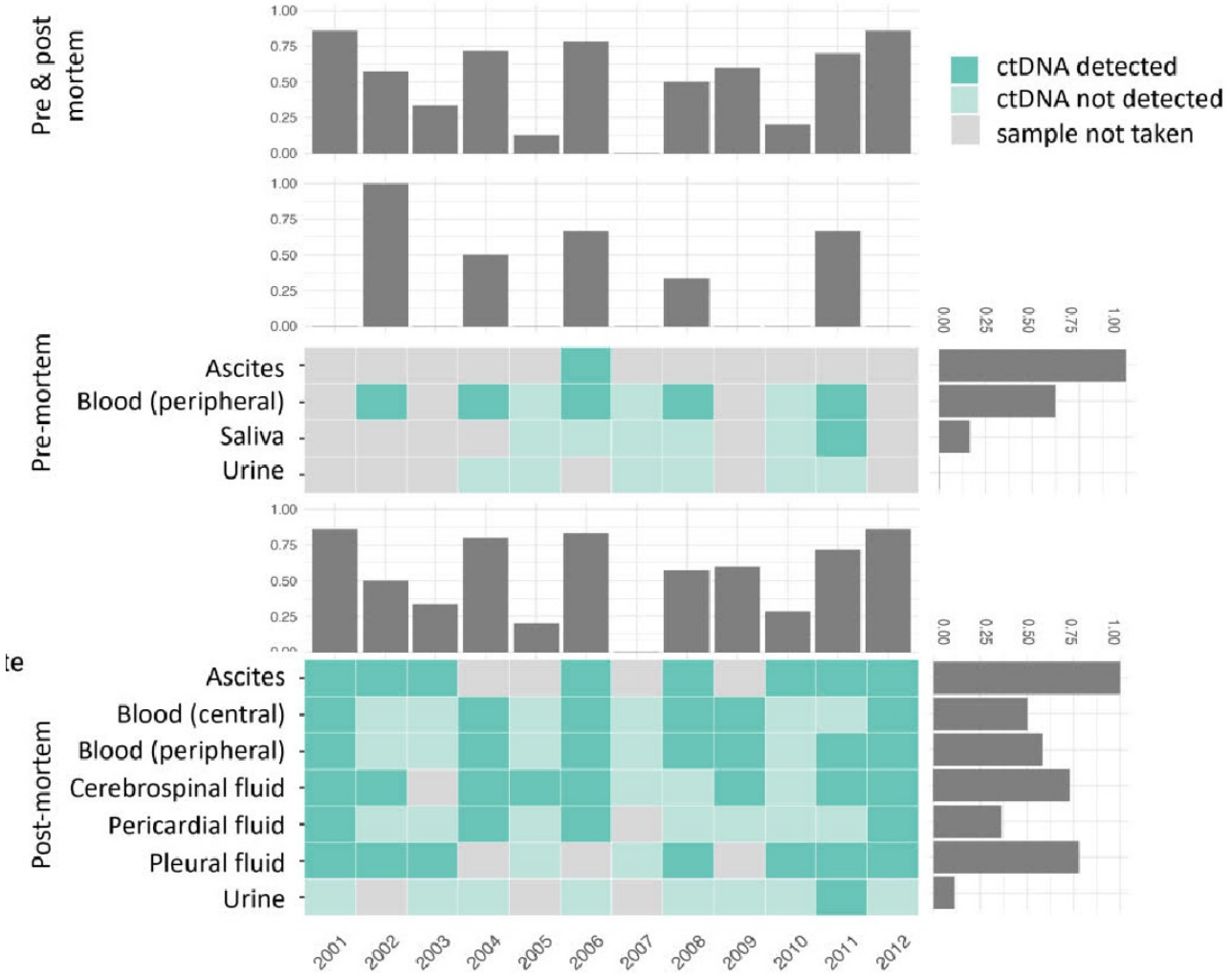
- CTC detection could even improve timely diagnosis of LM in patients with breast cancer.
- However, the added value of ctDNA seems less evident (maybe aneuploidy only is not enough?).

Detecting ctDNA in multiple body liquids

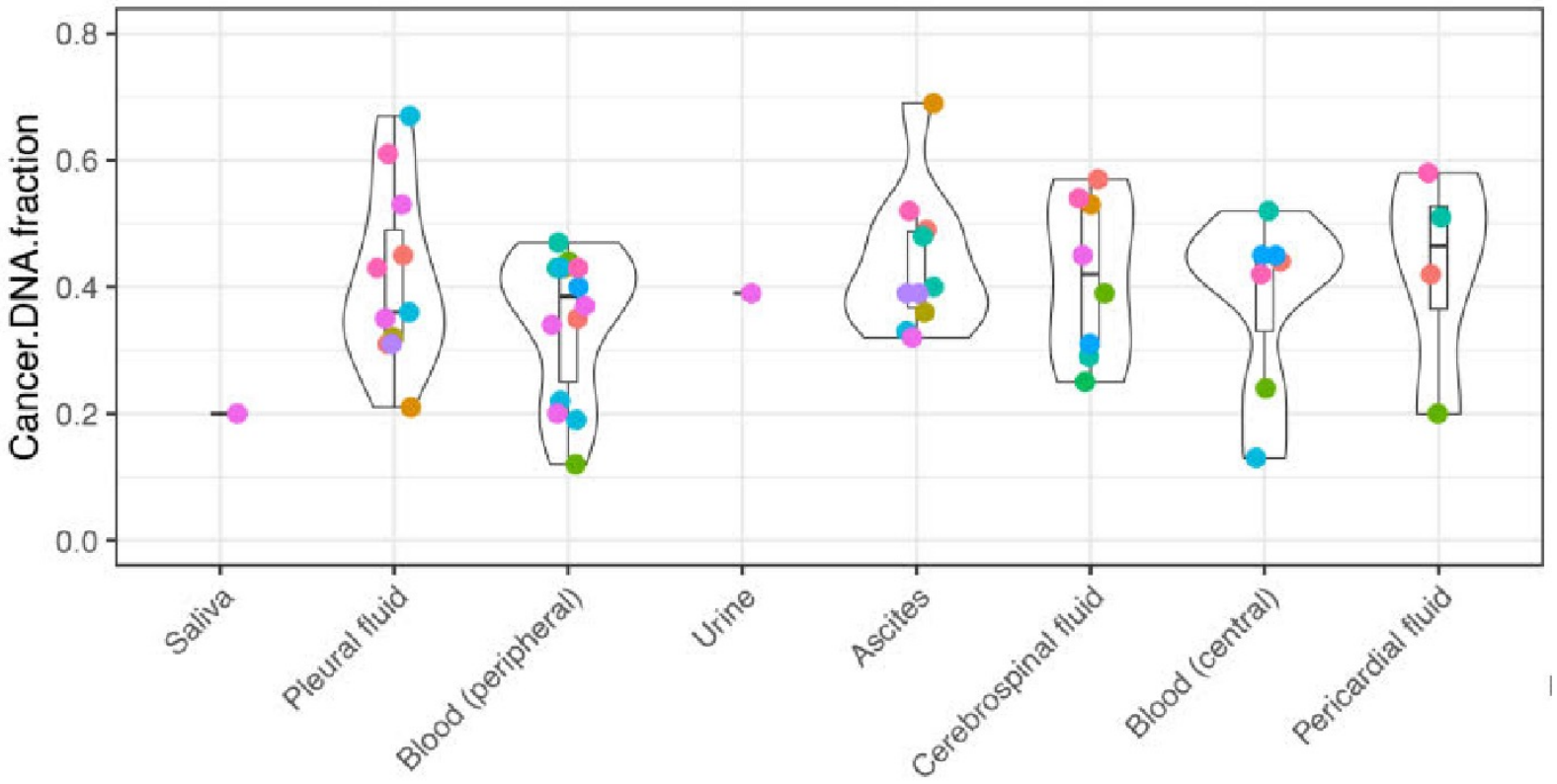
Aims:

(i) Investigate whethere ctDNA can be detected in different types of body liquids,

(ii) Assess whether the levels of ctDNA in a given liquid are associated with metastases in specific organs.



Detecting ctDNA in multiple body liquids



- ctDNA was detected in all liquid types, but not in all patients.
- Presence of ctDNA in a given liquid associated with metastases in surrouding organs.
- For some patients, ctDNA not detected in blood while detected in other liquid(s)

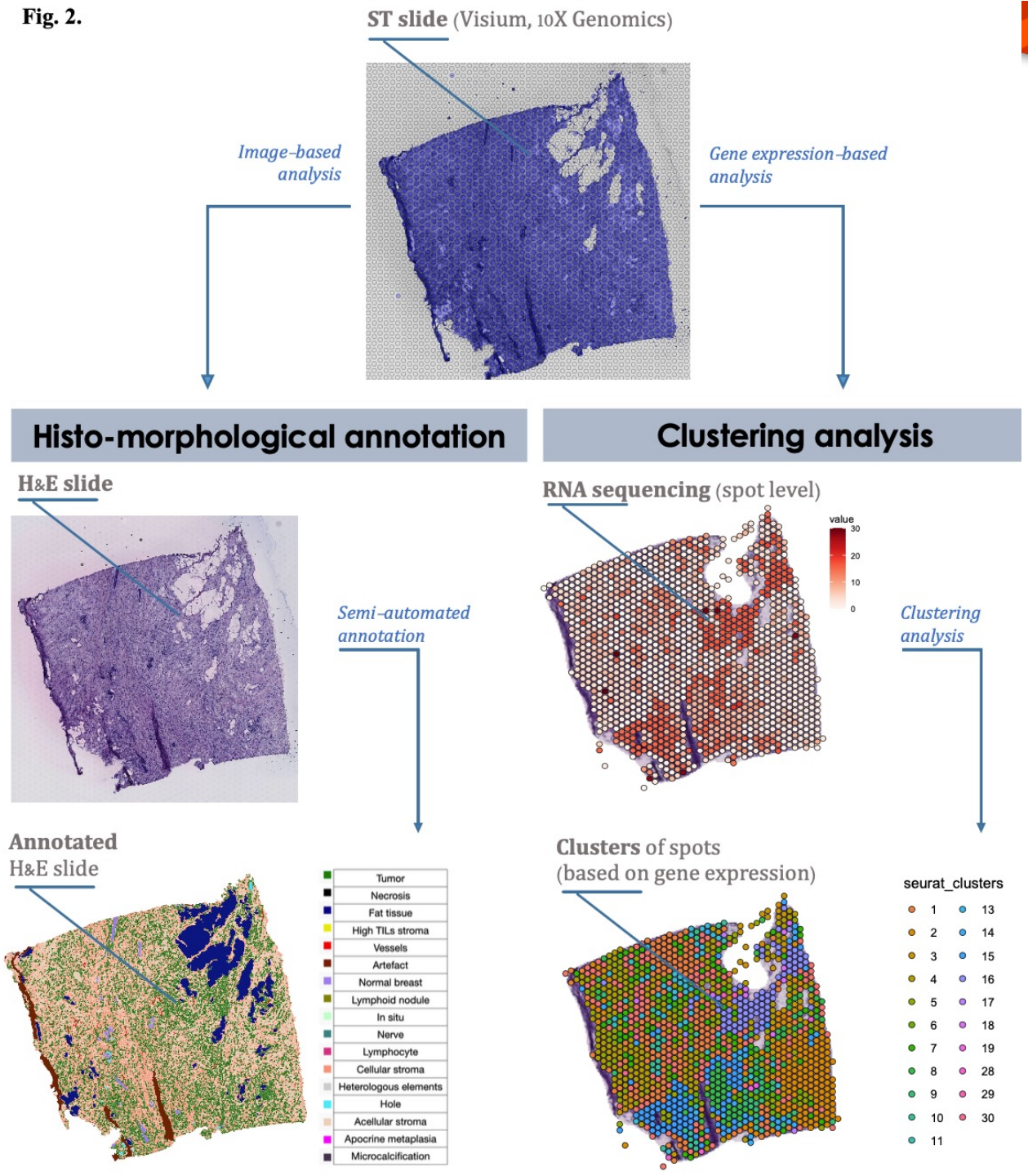
Lobular breast cancer (ILC)

P2-21-01 (Serra M et al.): Decoding Inter- and Intra-Tumor Heterogeneity in Lobular Breast Cancer Using Spatial Transcriptomics and Clustering Analysis
PD04-07 (Shah OS et al.): Uncovering molecular heterogeneity of mixed ductal and lobular carcinoma using digital spatial profiling
P3-05-08 (Hensing WL et al.): Prevalence and prognosis of ER-loss in advanced invasive lobular carcinoma
P3-05-40 (Van Baelen et al.): Association of BMI with clinicopathological features and survival in patients with primary invasive lobular breast cancer
P5-14-01 (Desmedt et al.): Transcriptomic insights into lobular breast cancer biology: a retrospective analysis of the MINDACT clinical trial

Intra and inter-tumor ILC heterogeneity

Aims:

1. To characterize spatial heterogeneity of ILC
2. To investigate the potential prognostic relevance

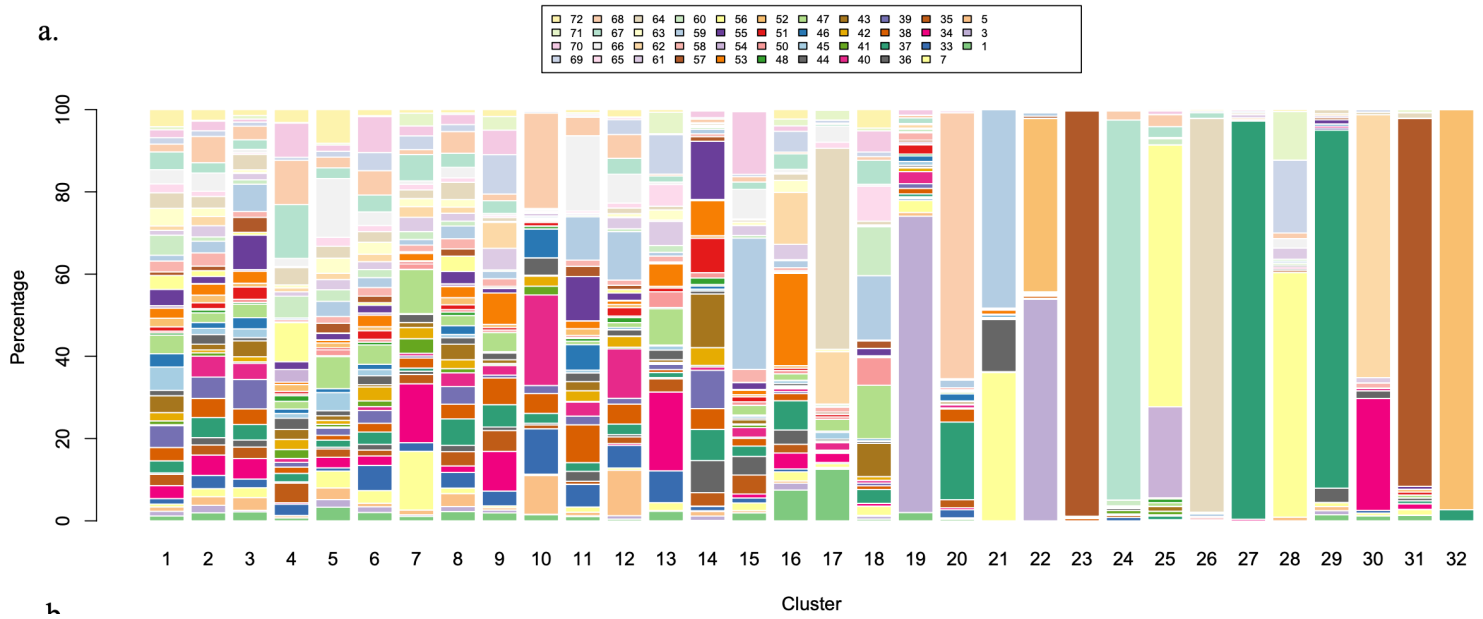


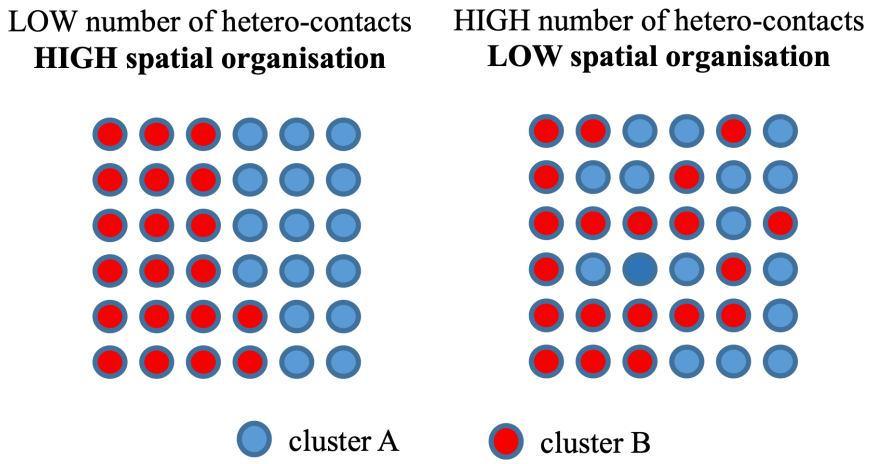
PD2-21-01

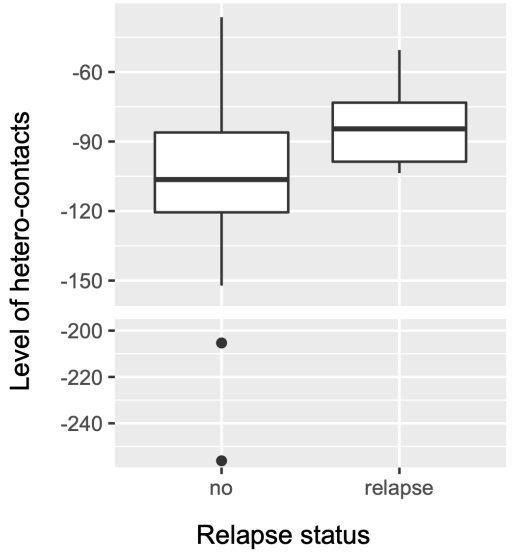
Table 1.

	ST cohort	Grade			Tumor stage	
	Tot	G1	G2	G3	T1	T2-3
N. of samples	43	5	34	4	24	19
	Nodal status		**Disease relapse**			
	N0	N+	No	Yes		
N. of samples	30	13	34	9		

Identification of 32 clusters across all patients

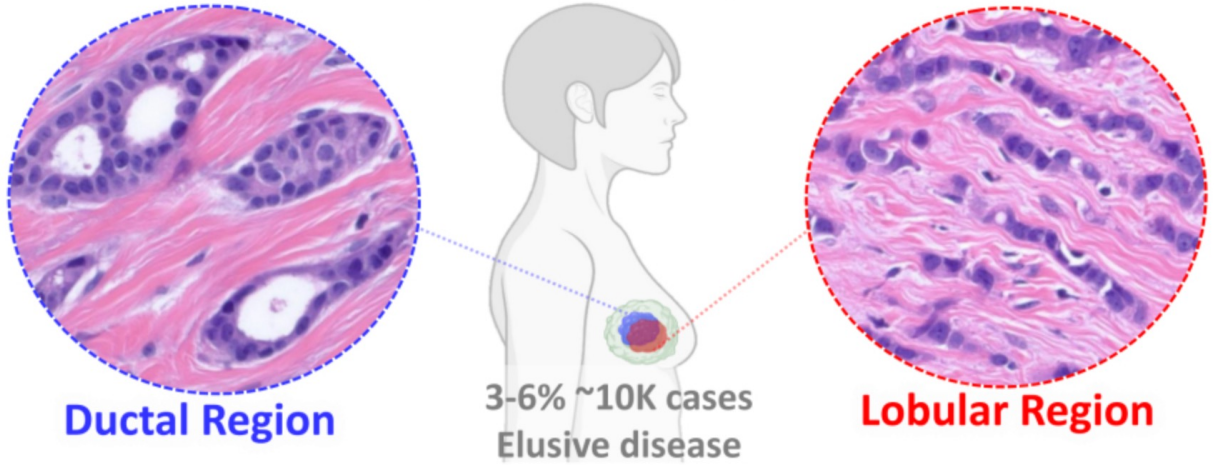






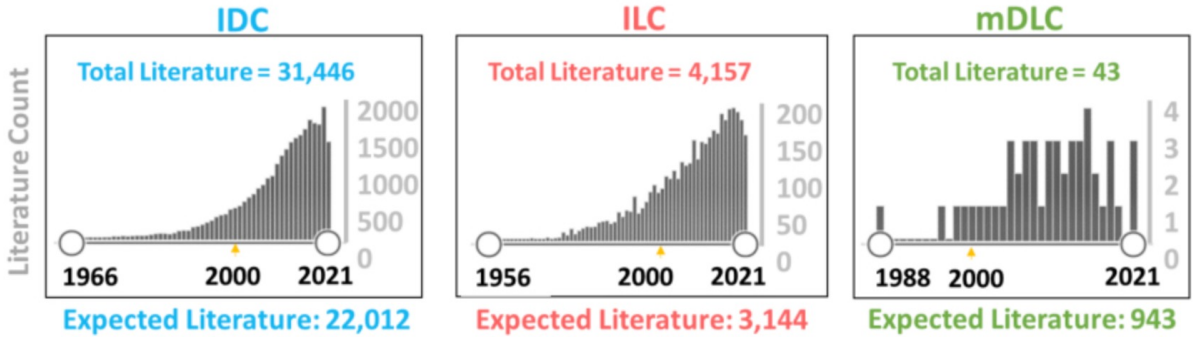
- Intra-tumor heterogeneity: presence of different clusters represented by different pathway within a patient.
- Inter-ILC heterogeneity.
- Difference in spatial organization of the clusters could have a prognostic relevance, i.e. more disorganized tumors associated with worse prognosis.

Mixed ductal and lobular breast cancer

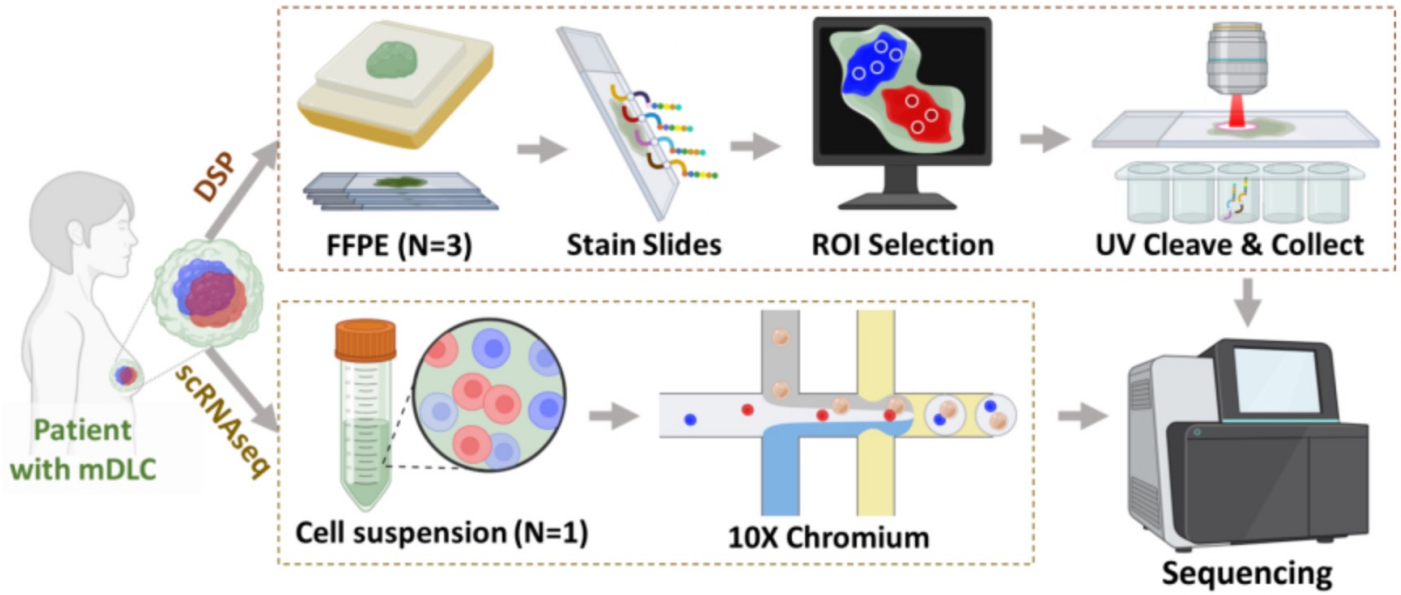


Admix of ductal and lobular regions
Limited molecular characterization
Limited clinical management guidelines

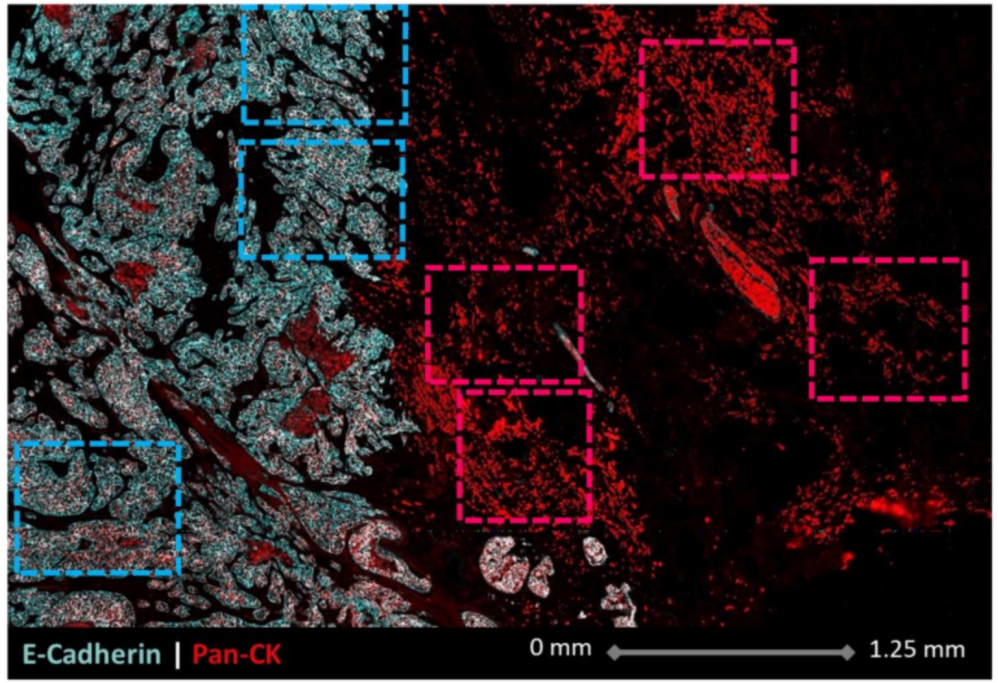
Given disease incidence, mDLC are understudied



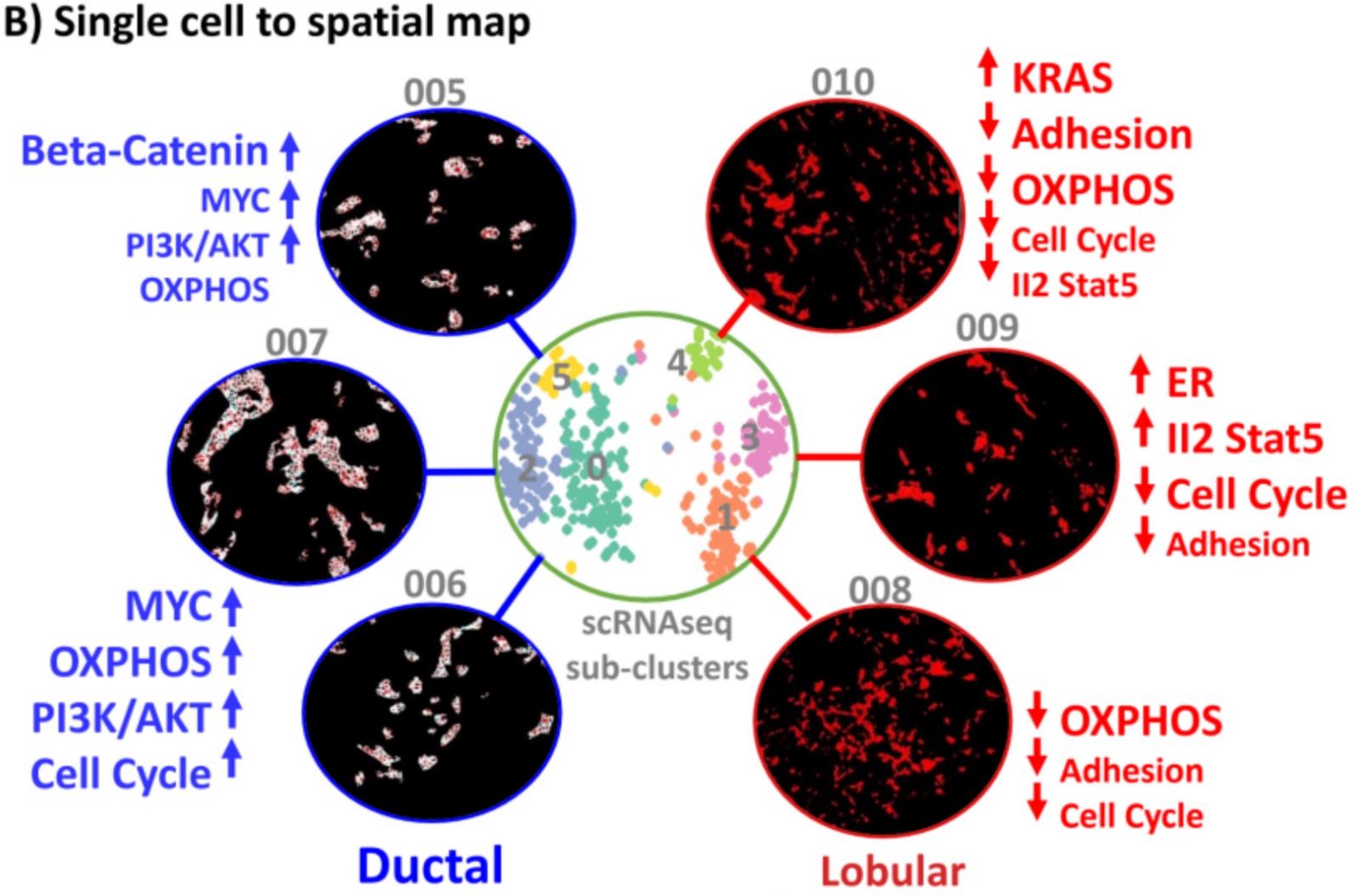
Mixed ductal and lobular breast cancer



Selecting Regions of Interest (ROI)



Mixed ductal and lobular breast cancer

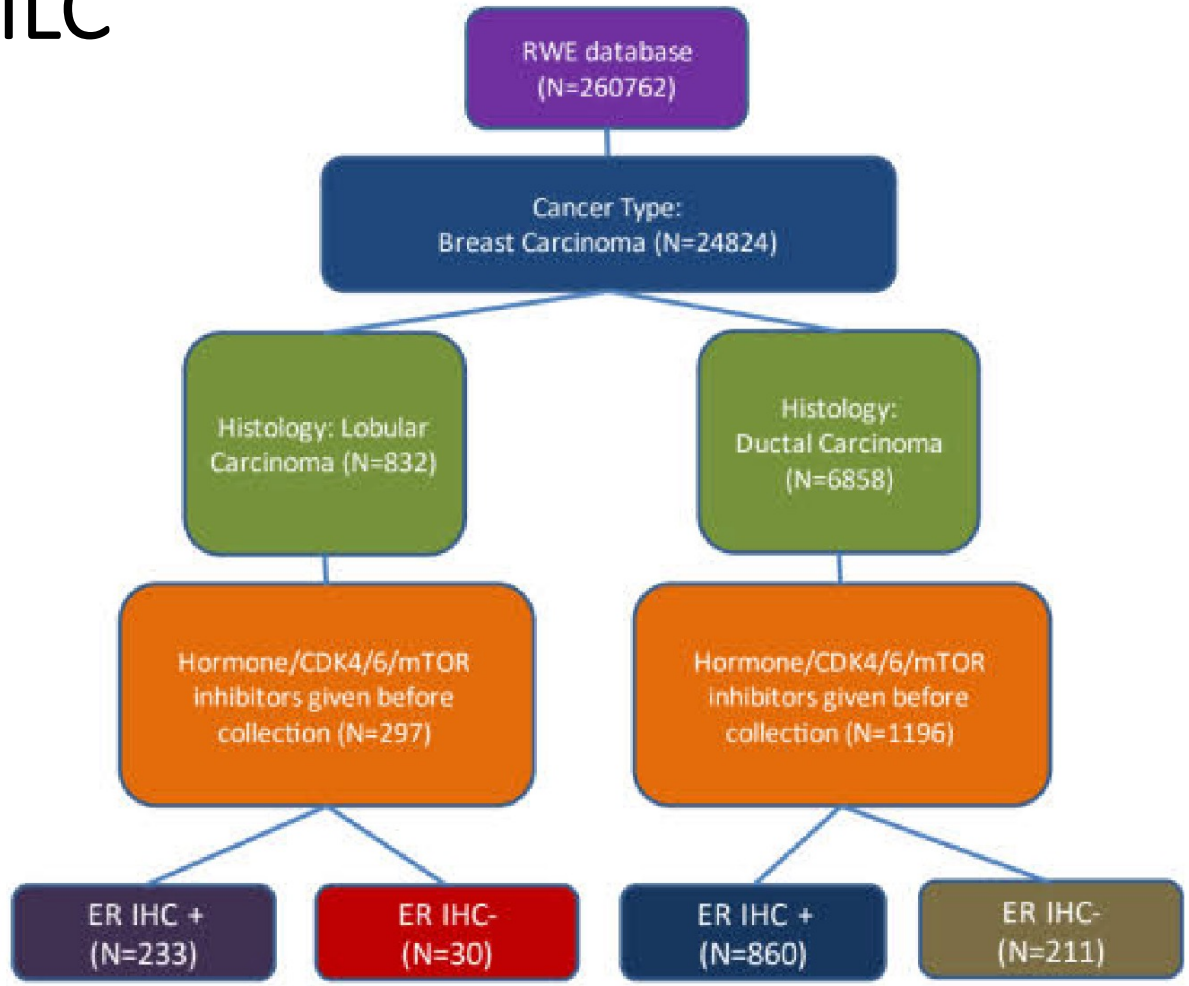


- Many differences observed between the two histologic subypes, but also within each subtype
- Some findings are counterintuitive to what is know re IDC/ILC
- Results need to be confirmed on a larger nr of samples

ER-loss in metastatic ILC

Aims:

Define prevalence & clinical relevance of ER-loss in patients with metastatic ILC, using large real-world dataset



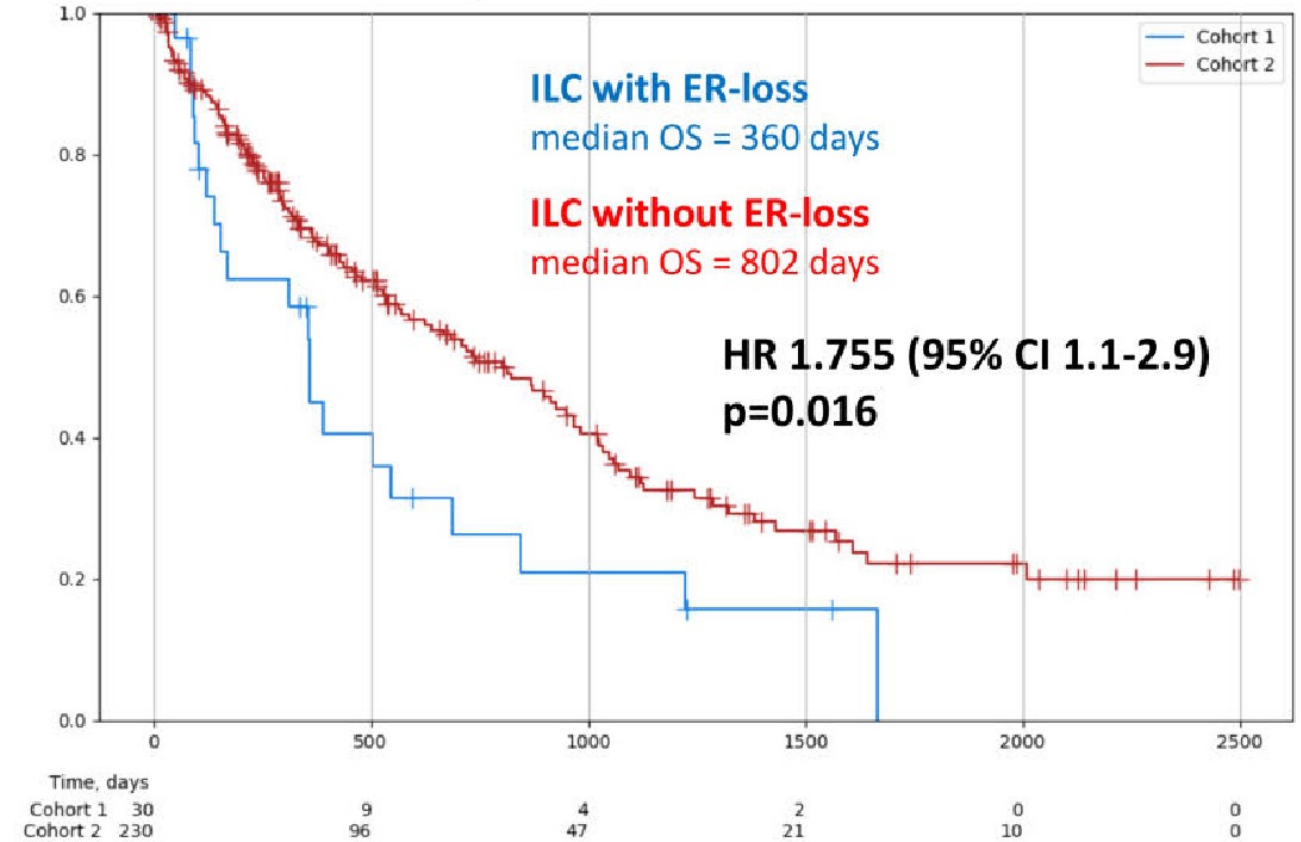
ER loss: 11.4%

ER loss: 19.6%

ER-loss in metastatic ILC

Overall Survival for ILC with or without ER loss*

Time of tissue collection to last patient contact



No multivariable analysis provided

- ER-loss seems to be less frequent in patients ILC as compared to NST (only 1 met evaluated)
- ER-loss associated with worse OS both in patients with ILC and NST

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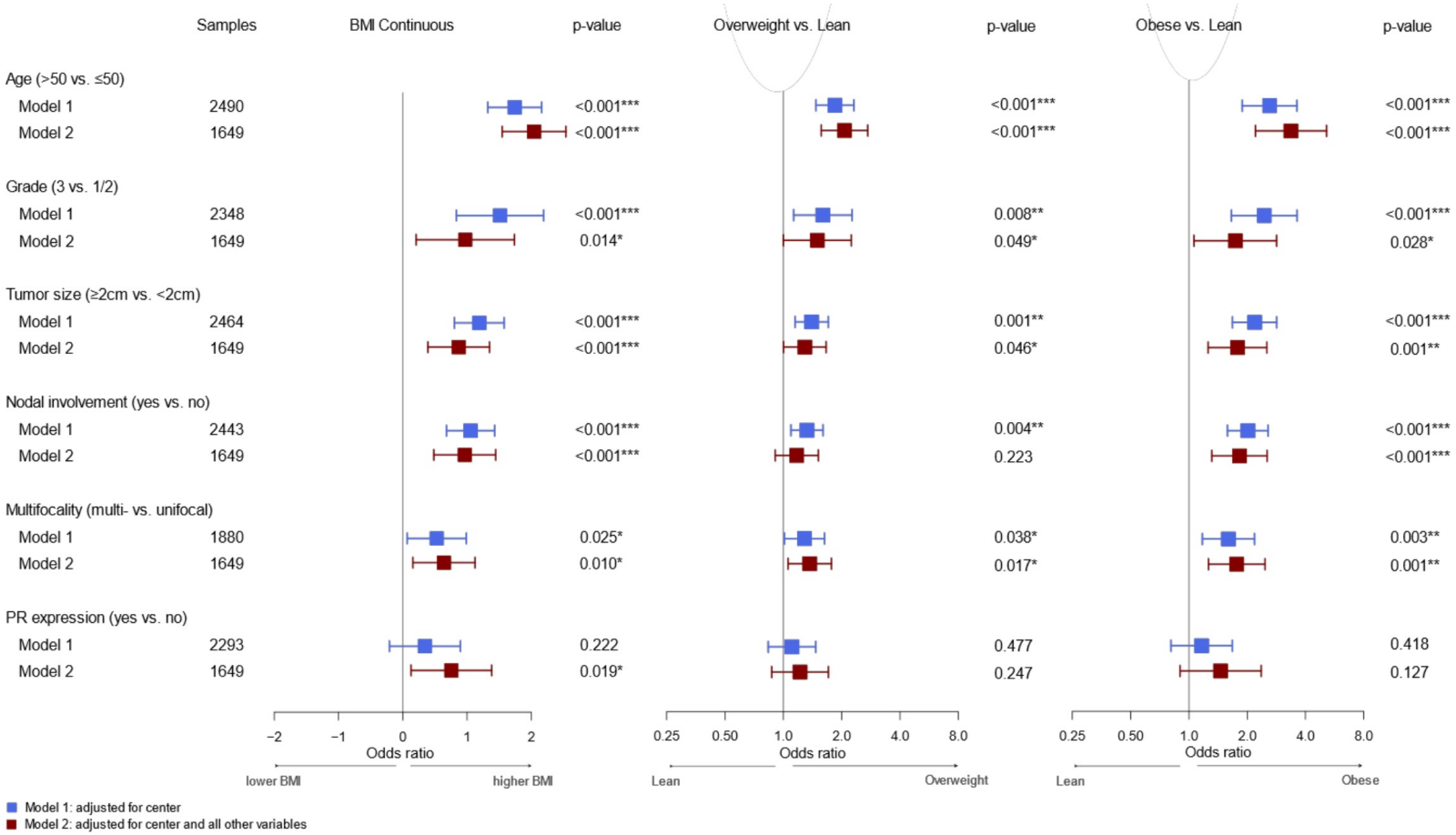
ILC & BMI

Aims:

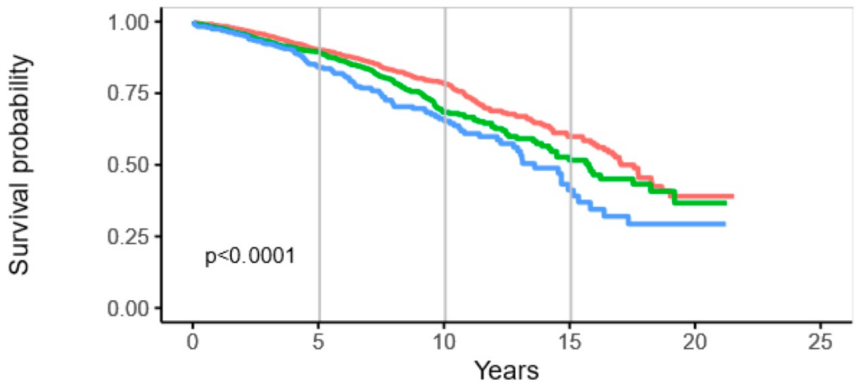
Investigate in large multi-centric retrospective series of 2,900 pts with primary ILC, the association of BMI with:

1. clinicopathological features of ILC
2. prognosis

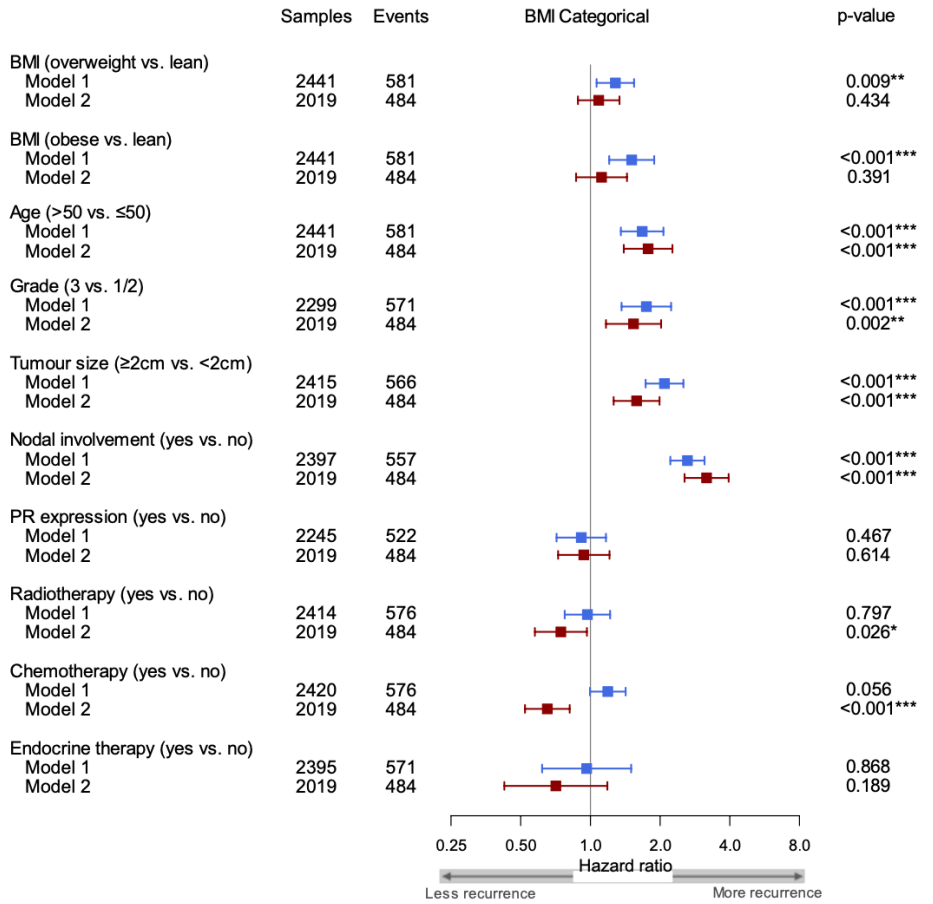


P3-05-40

ILC & BMI



Number at risk (number censored)						
Lean	384 (0)	969 (294)	390 (778)	89 (1023)	9 (1083)	0 (1092)
Overweight	701 (0)	474 (159)	180 (371)	48 (479)	2 (517)	0 (519)
Obese	356 (0)	215 (92)	84 (188)	20 (234)	3 (246)	0 (249)
Cumulative number of events						
Lean	3	121	216	272	292	292
Overweight	3	68	150	174	182	182
Obese	1	49	84	102	107	107



- Association of worse prognostic factors such as higher grade, larger tumour size, nodal involvement with higher BMI.
- No statistical evidence for a prognostic role for BMI in the multivariable analyses.
- Prognostic effect might be mediated through its association with these clinicopathological variables.

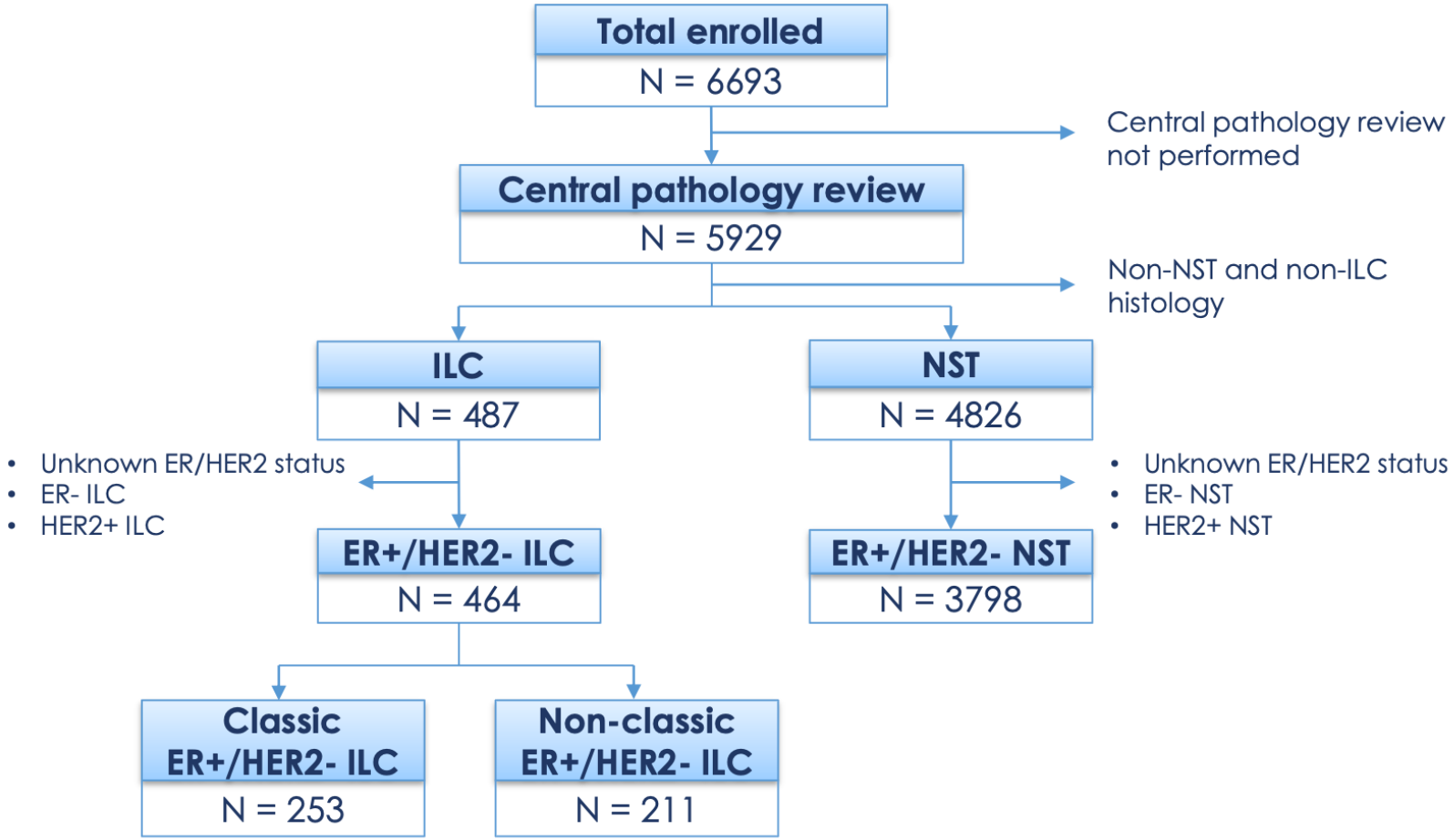
Retrospective analysis transcriptomic data MINDACT

Aims

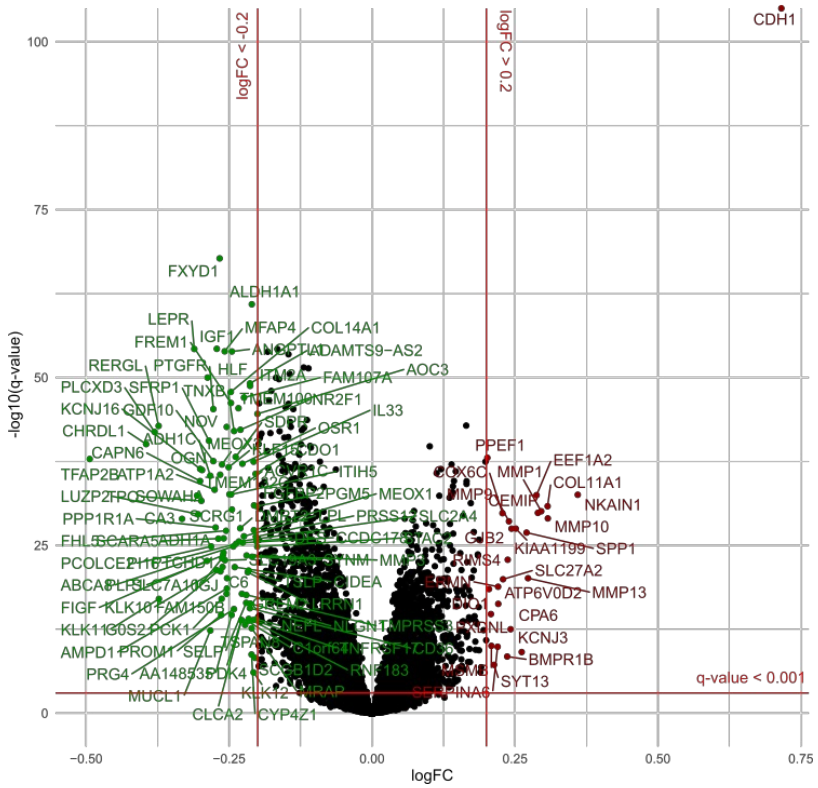
Transcriptomic differences between:

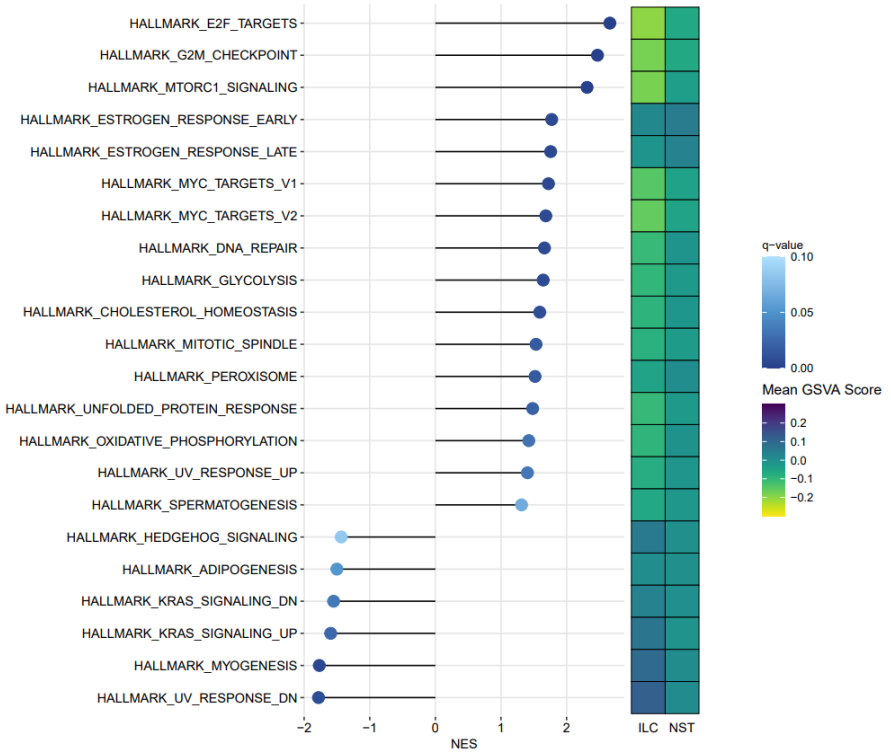
1. ER+/HER2- NST versus ER+/HER2- ILC

2. Recurring and non-recurring ER+/HER2- ILC in the subgroup of patients with a low clinical and low genomic (cL/gL) risk



Transcriptomic differences ER+/HER2- ILC vs NST





ILC presents differences in lipid metabolism and in the extracellular matrix, a decreased ER- signaling and increased PI3K/Akt signaling.

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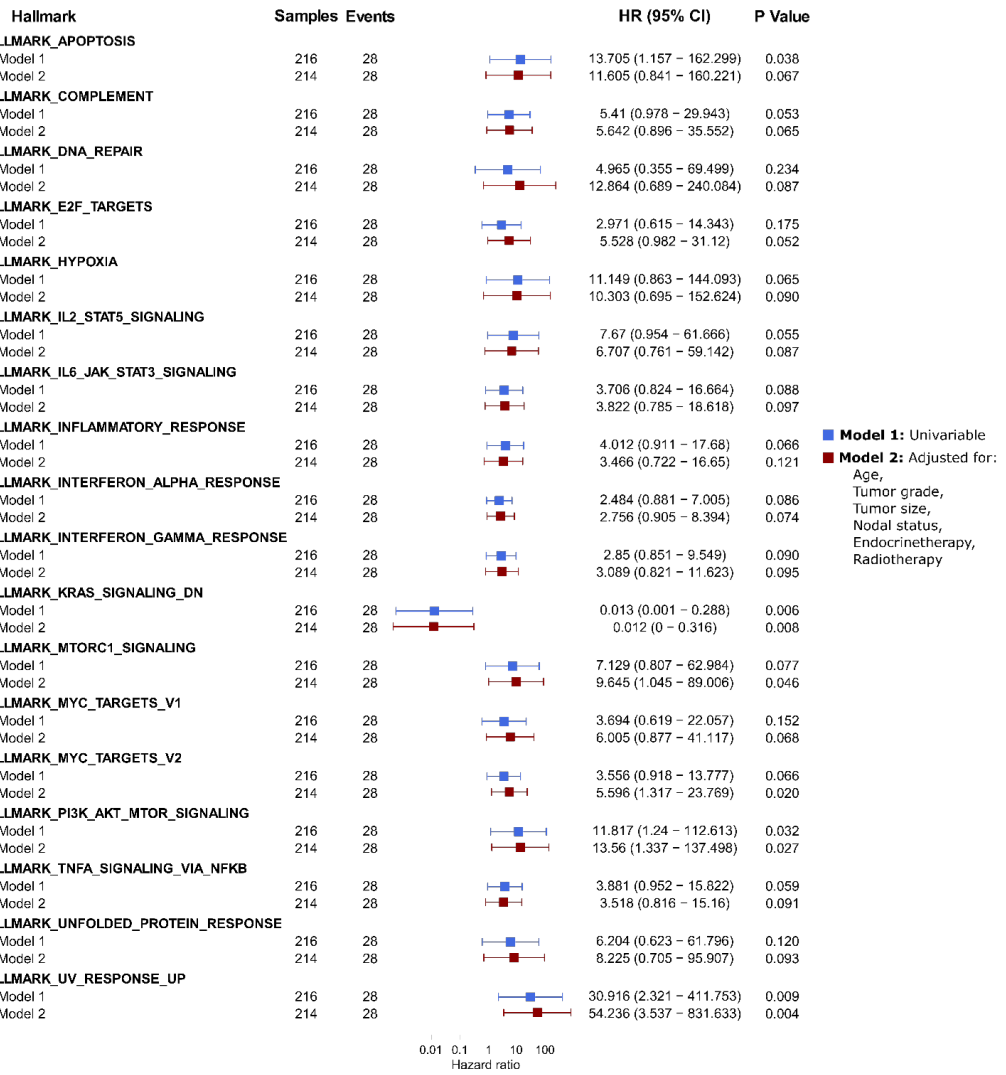
ER+/HER2- ILC with low clinical AND genomic risk from pts who did or did not relapse



1.Marked transcriptomic differences were identified between ER+/HER2- NST and ILC.

2. Enrichment of hallmarks related to apoptosis, inflammatory response, hypoxia and oncogenic signaling (PI3K/Akt, c-Myc) is associated with worse survival in patients with cL/gL ILC.

Conclusive remarks

- Research scene dominated by the ADCs (detection of target, prediction of response/resistance, identification of new targets etc)
- Documentation of intra-tumor heterogeneity increases with the use of newer technologies/ clinical implication to be further investigated
- Multitechnical and multidisciplinary approaches to investigate therapy resistance/sensitivity
- Liquid biopsies: still an area under intense clinical investigation (what to look for, which liquids, for which purpose)
- Novel insights into ILC

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Thank you very much for your attention!

Questions: christine.desmedt@kuleuven.be