

Value of biomarkers in therapeutic decision making. Is it time for ctDNA?

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COI

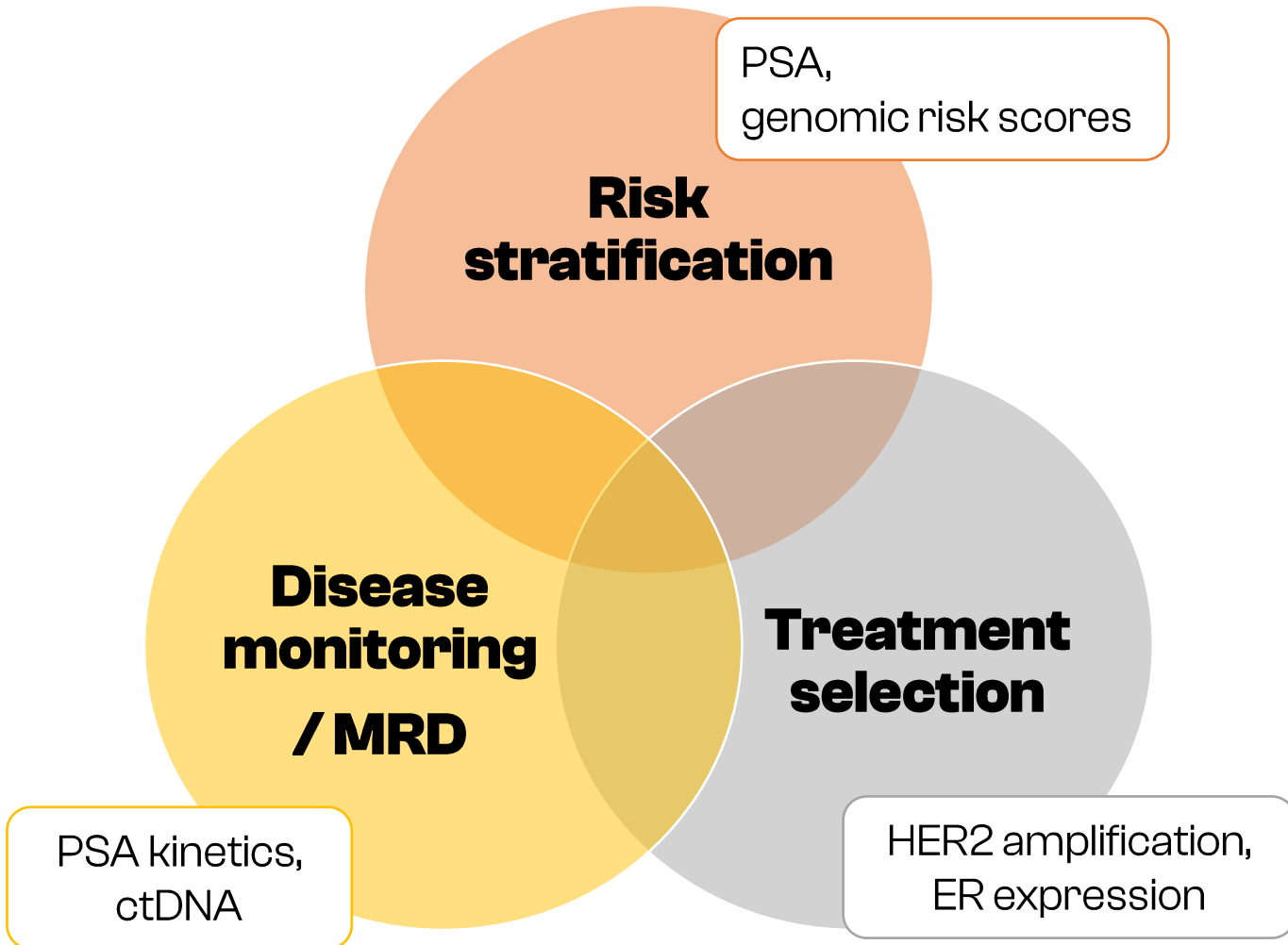
Honoraria: Merck, Roche, Pfizer, Ipsen

Travel/accommodation: Bristol Myers Squibb, Roche, Merck, Astra Zeneca

#guardsymposium2026
X @GuardConsortium



Integrating biomarkers into bladder cancer



NMIBC

Can we improve risk stratification?
Can biomarkers select intravesical therapy?

MIBC

Can we predict response to chemo?
Can biomarkers help us preserve the bladder?

Can biomarkers guide treatment decision? Escalation vs omission?

DNA Alterations

FGFR3

ADC targets

PD-L1
Immune signatures

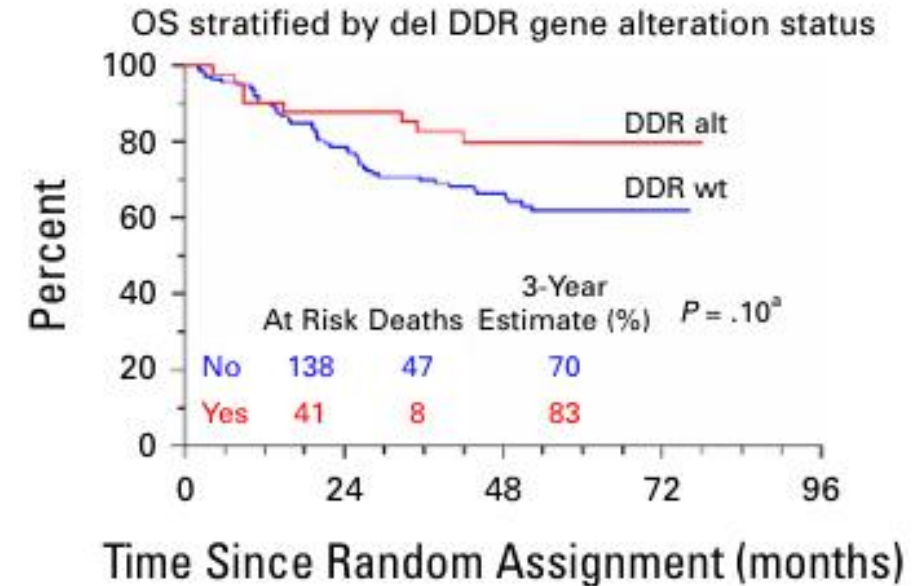
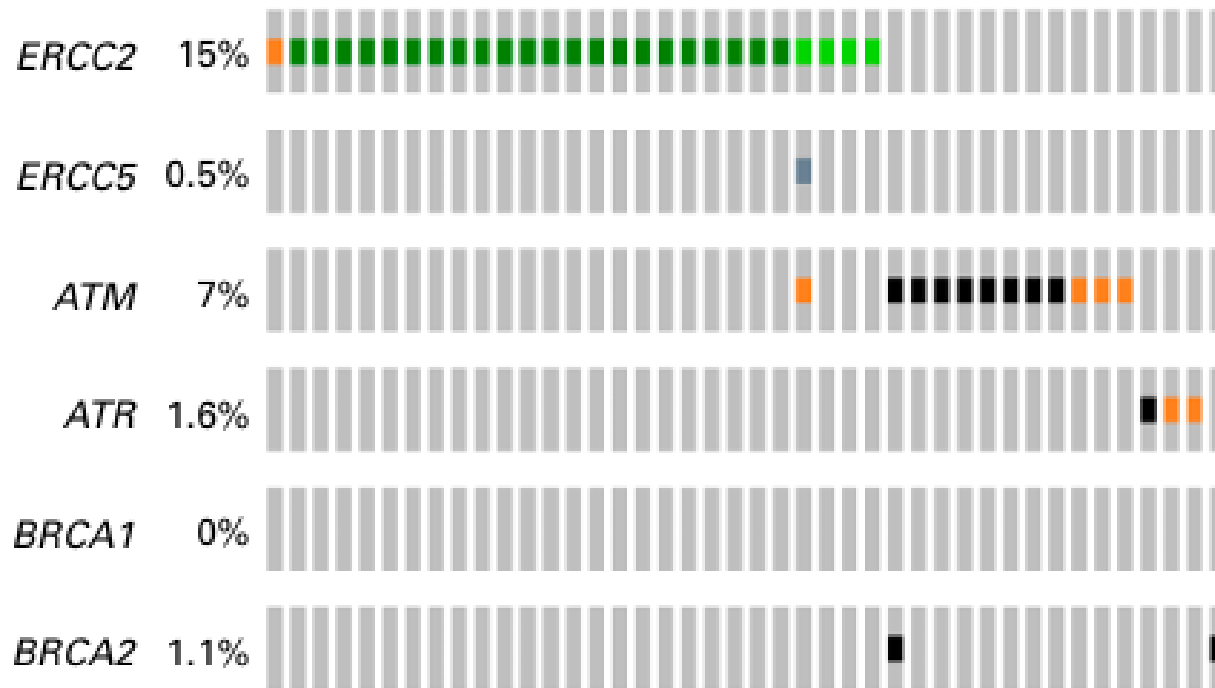
DNA Alterations

FGFR3

ADC targets

Immune signatures
PD-L1

DDR alterations associate with response but do not guide neoadjuvant treatment



Patients at risk

	0	24	48	72	96
No	138	118	99	84	65
Yes	41	36	34	32	25

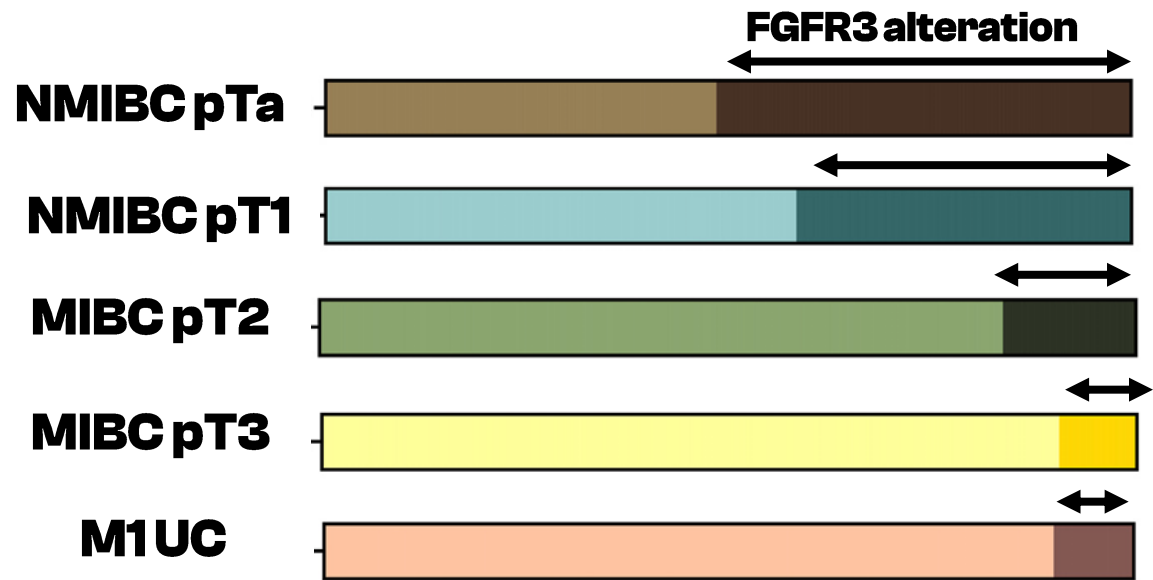
DNA Alterations

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FGFR3 can be targetable throughout the disease

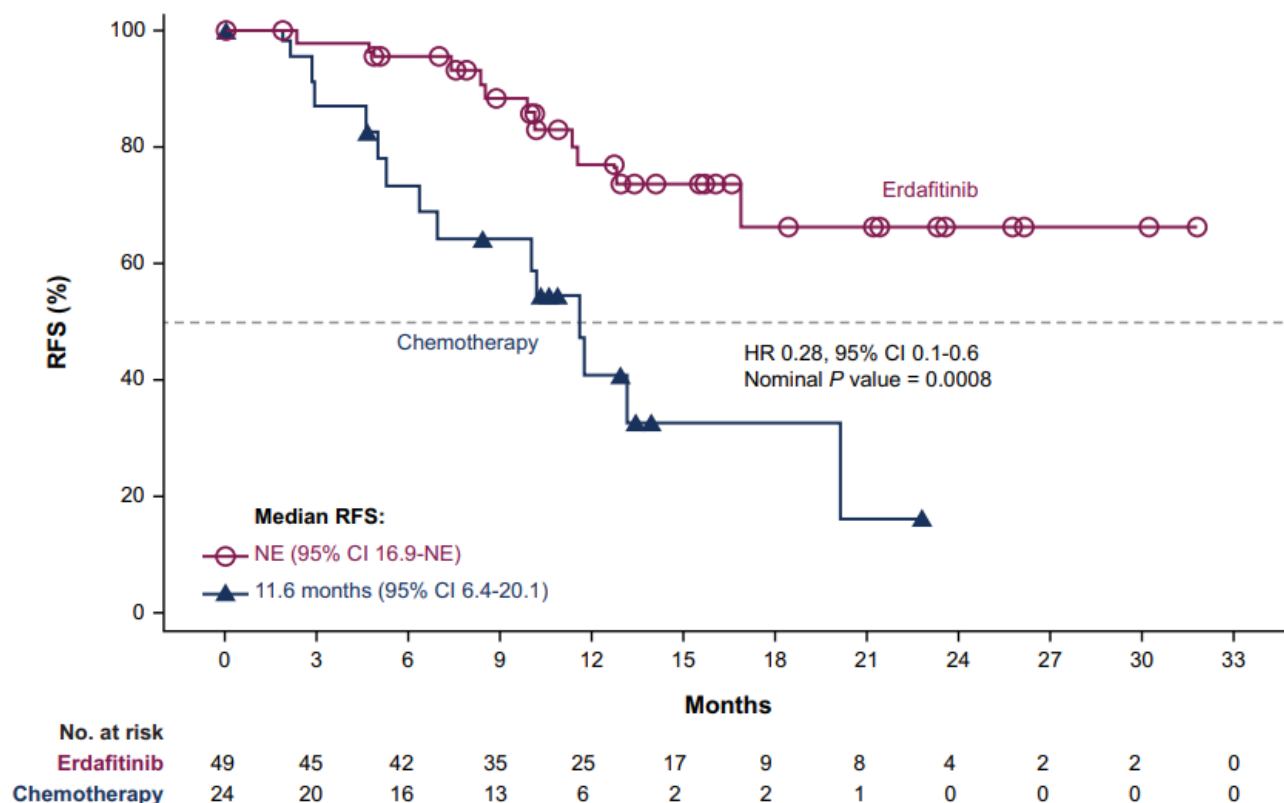


FGFR3 alterations are most frequent in **NMIBC** and decline with increasing stage and grade

Different studies, different platforms, different definitions of eligible alterations...

	Erdafitinib (BCL2001) ¹⁻³		Infigratinib (BGJ398) ⁴⁻⁶	Pemigatinib (FIGHT-201) ⁷	Futibatinib ⁸⁻¹⁰	Rogaratinib (FORT-1) ¹¹	Zoligratinib (Debio-1347) ¹²
Phase	II	III ¹³	Ib	II	I (dose expansion)	II/III	II
Primary Endpoint	ORR 40%	ORR 46% OS (HR 0,64)	ORR 25.4%	ORR 17.8% (A-CD) ORR 23.3% (A-ID)	ORR 15.8%	ORR 20.7%	ORR
Method	Central confirmation (RT-PCR)	Local (NGS tissue/ blood) Central (RT-PCR)	DNA (and cfDNA)	DNA	DNA	RNAscope + exploratory analysis of FGFR3 DNA alterations	RNA sequencing
- FGFR3 mut - FGFR3 fus - FGFR1 - FGFR2 - FGFR4 - Others							
% positive for FGFR alteration	9.5%	16.6% (central) 15.8% (any)	68% (cfDNA)	17%	69%	25% (DNA)	57%

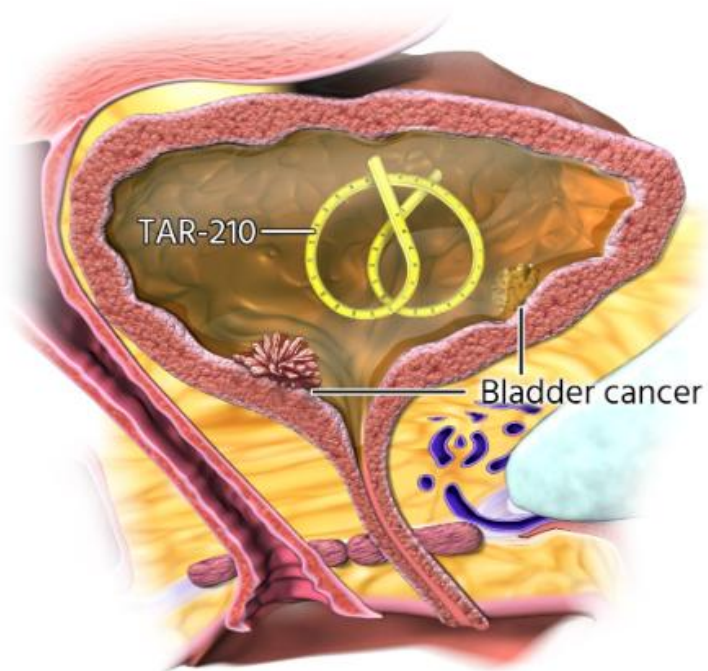
Oral erdafitinib showed activity in FGFR-altered NMIBC after BCG (THOR-2 cohort 1)



Clinical activity was limited by the tolerability of long-term systemic therapy

29% discontinued treatment due to adverse events

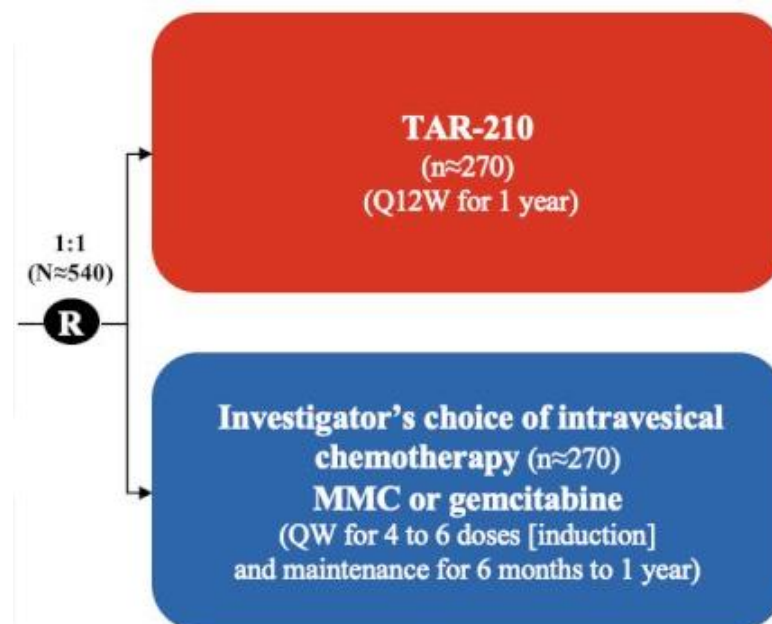
TAR-210 delivers FGFR3 inhibition directly to the bladder (MoonRISe-1)



IR NMIBC:

- Ta LG/grade 1 (recurrent or primary)
- Ta LG/grade 2 (primary or recurrent)

FGFR2/3 alterations by central or local tissue or urine testing



Intravesical erdafitinib may retain FGFR activity while reducing systemic toxicity

DNA Alterations

FGFR3

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Immune signatures

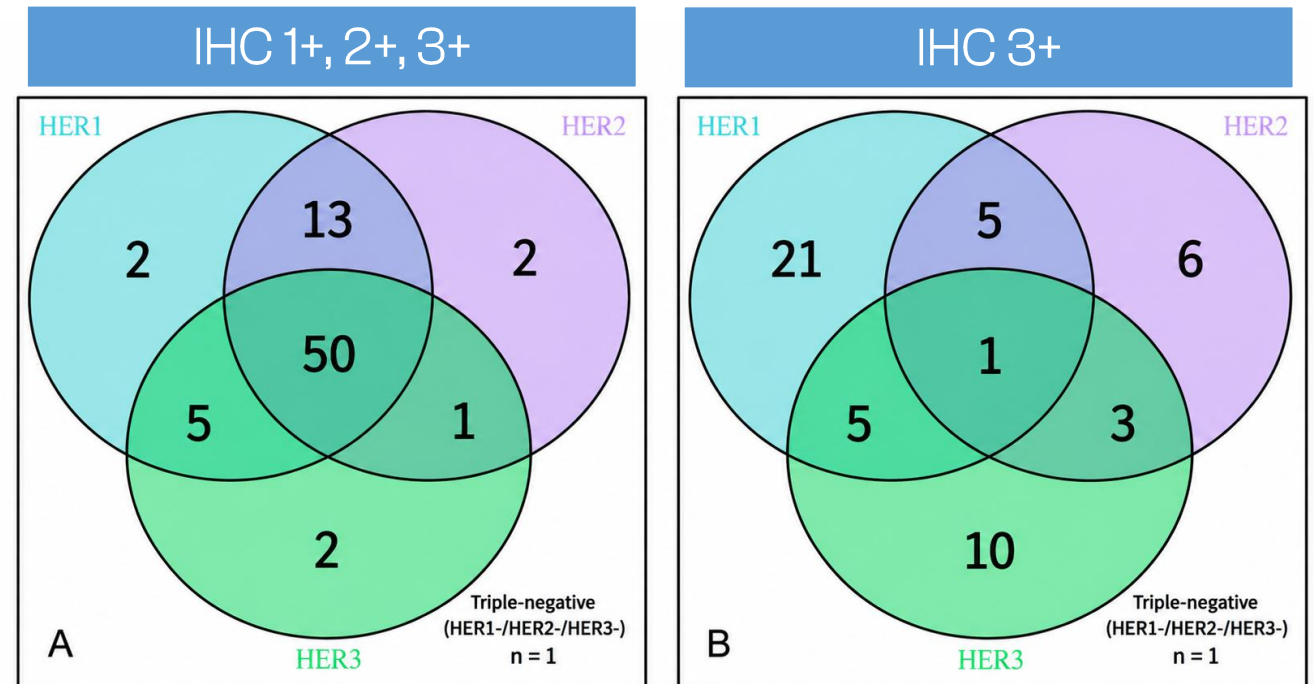
How much HER2 expression is enough?

HER2 as a delivery address

ADC binding → internalisation → payload release



Bystander effect extending activity
beyond HER2 high disease



HER2 is not an isolated target, frequently co-expressed

Amplification and membranous Nectin-4 may stratify EV benefit

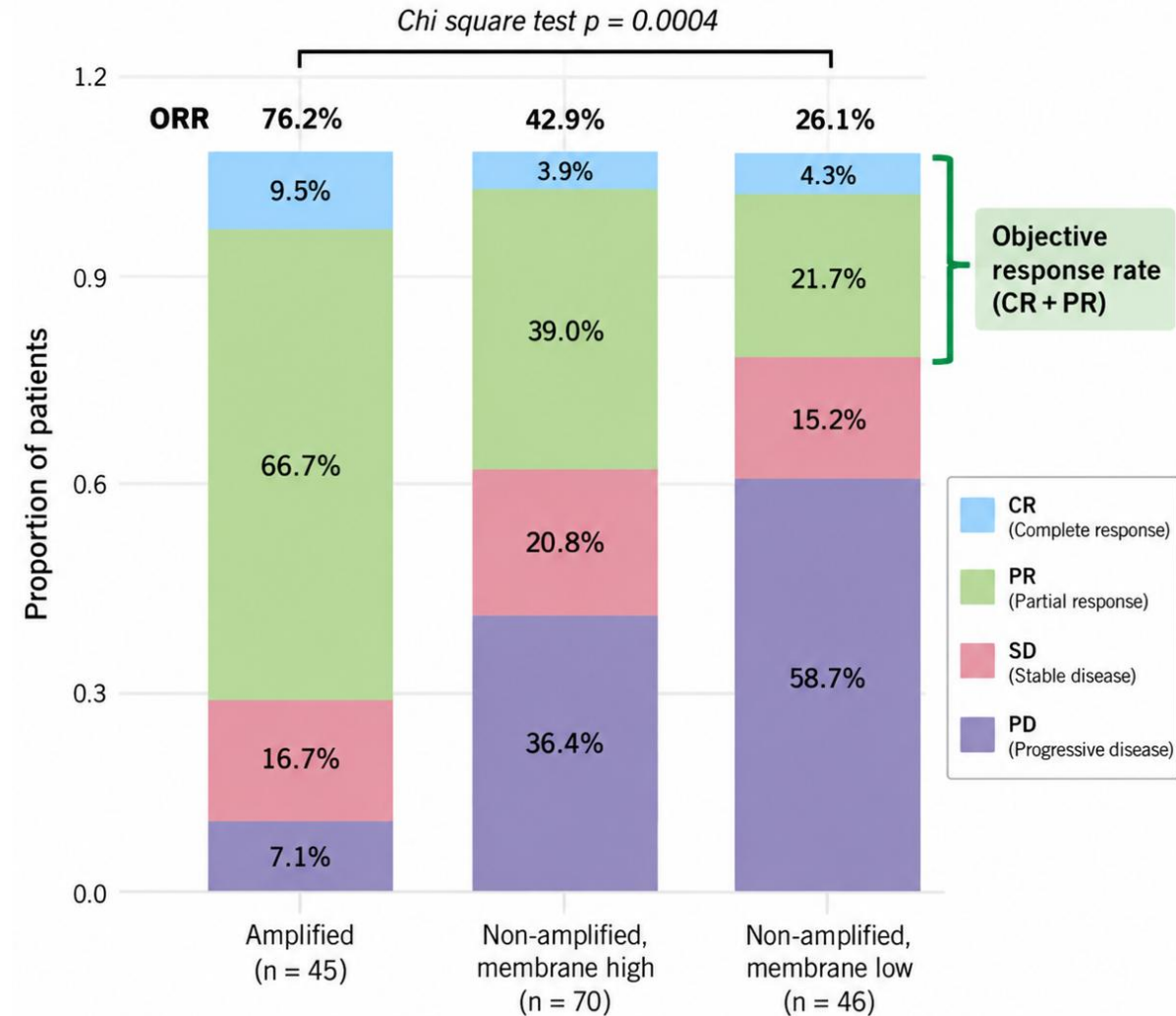
ORR

76% — NECTIN4 amplified

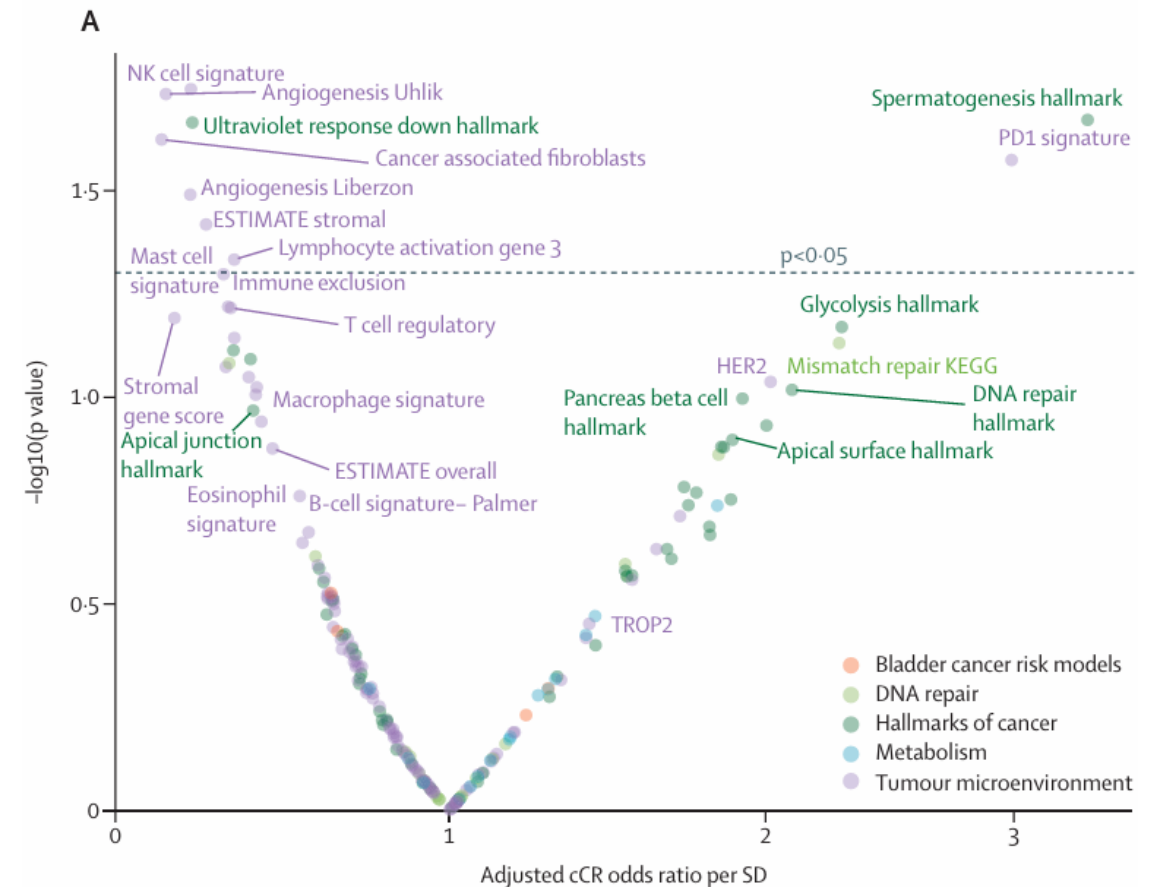
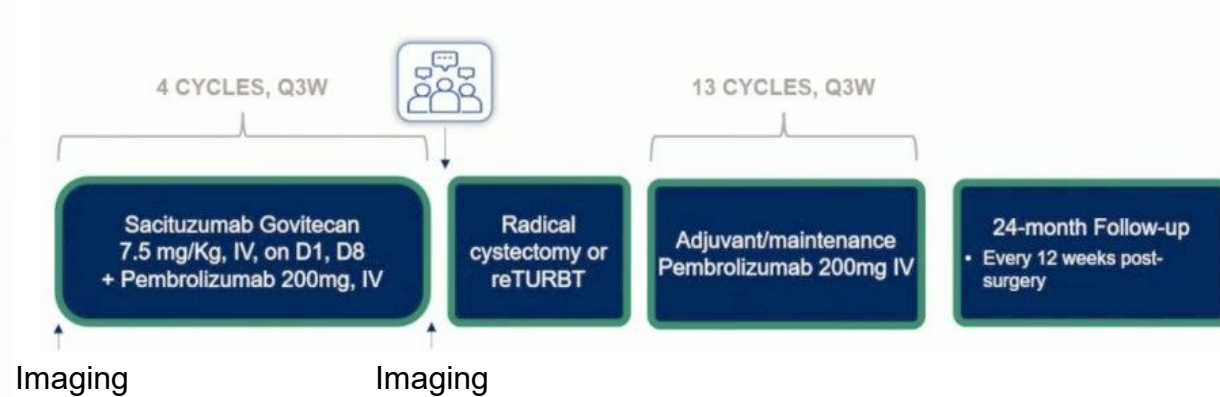
43% — Non-amplified / membrane-high

26% — Non-amplified / membrane-low

Both genomic status and membrane localisation matter



SURE-02 brings TROP-2 ADC therapy into bladder preservation



DNA Alterations

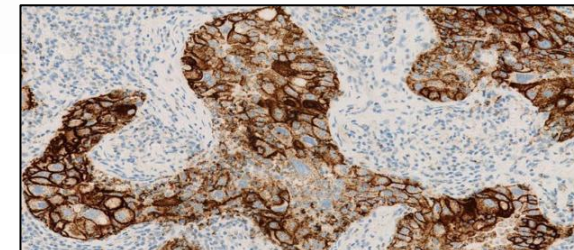
FGFR3

ADC targets

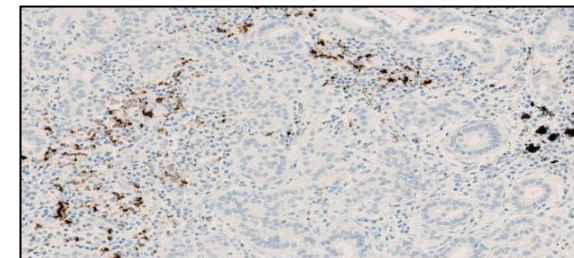
PD-L1
Immune signatures

PD-L1 is not a single biomarker

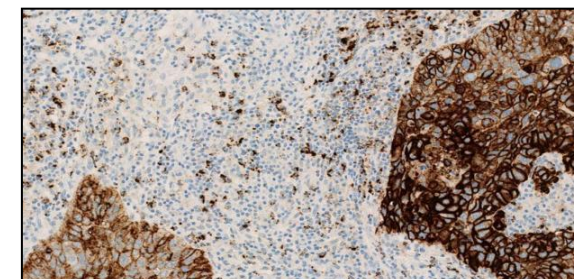
	EFS	OS	HR	PD-L1	HR (PD-L1+)
CheckMate 274	✓	✗	0.83 (0.67-1.02)	TC ≥ 1%	0.56 (0.36-0.86)
IMvigor010	✗	✗	0.91 (0.73-1.13)	IC ≥ 5%	1.04 (0.74-1.46)
AMBASSADOR	✓	✗	0.98 (0.76-1.26)	CPS ≥ 10	1.09 (0.77-1.54)



Staining in tumour cells

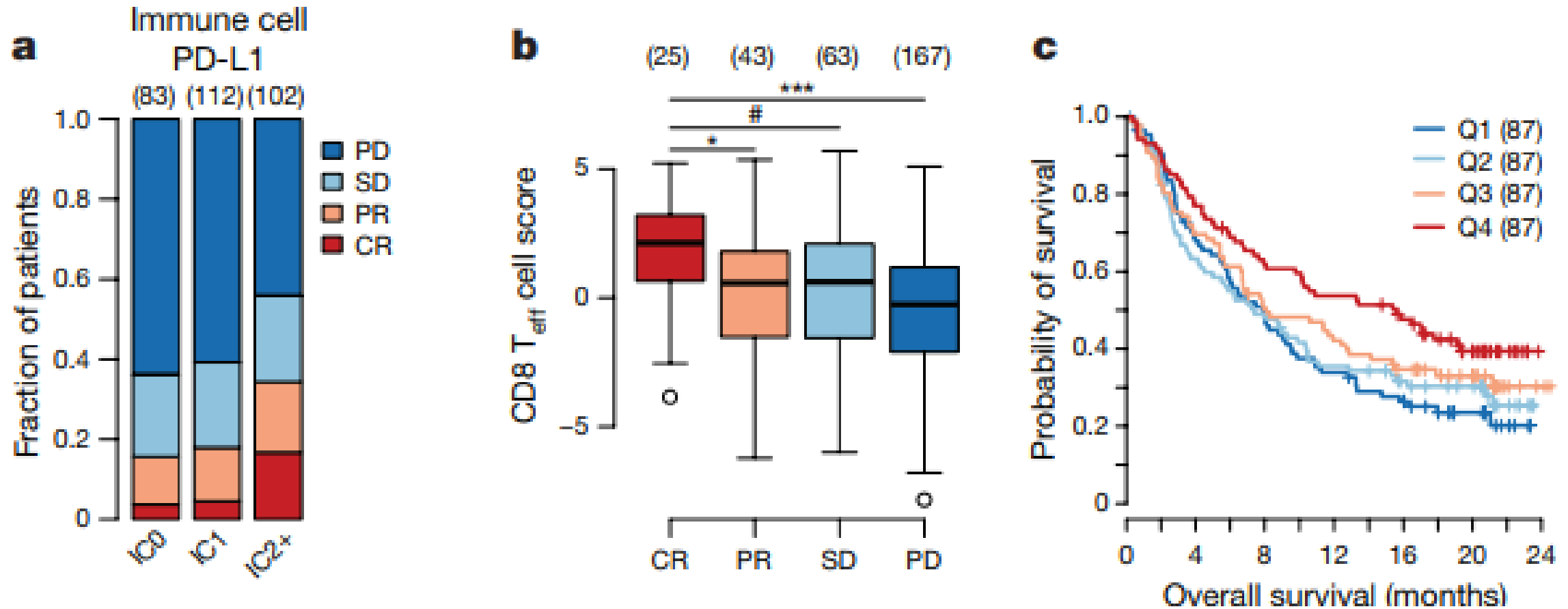


Staining in immune cells

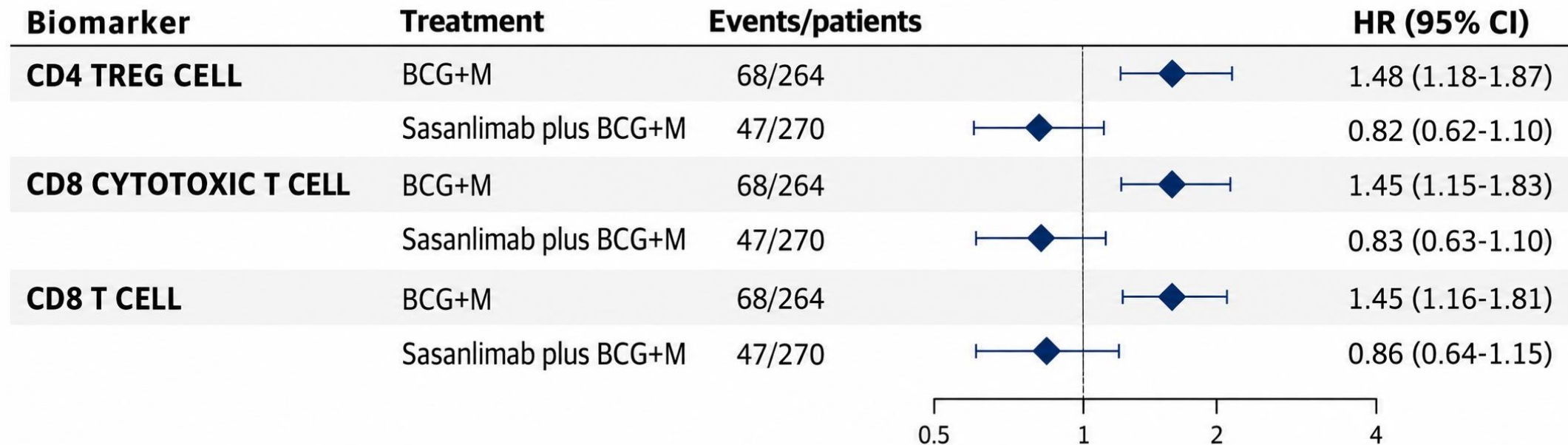


Staining in tumour cells and immune cells

T-cell infiltration identifies patients more likely to benefit from PD-L1 blockade



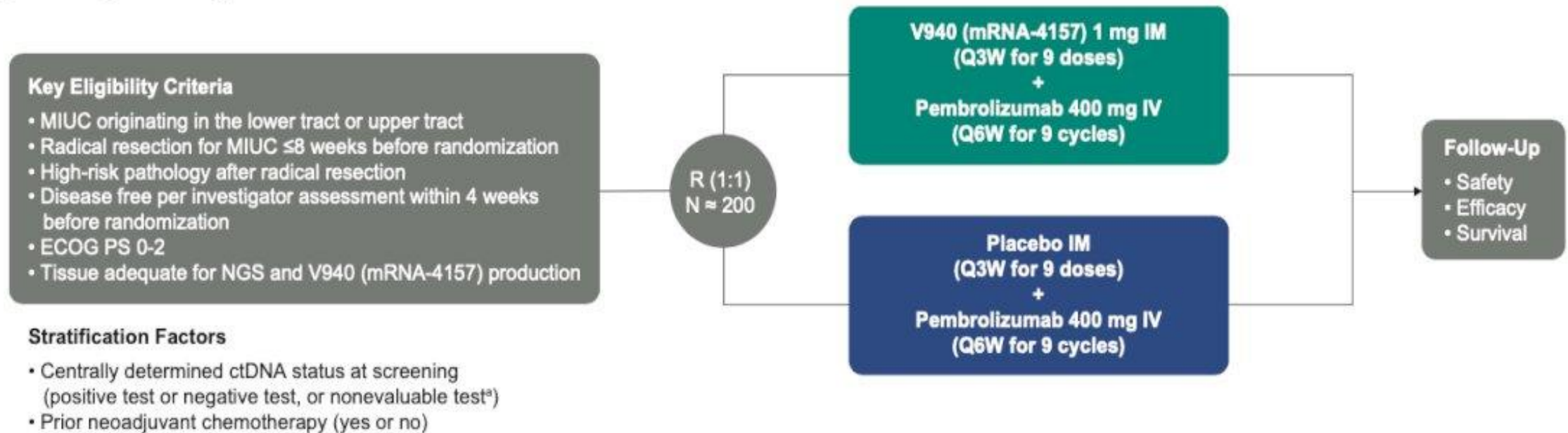
High T-cell and immune signatures predict poor outcomes with BCG, but not with sasanlimab



Not all immunotherapies are the same

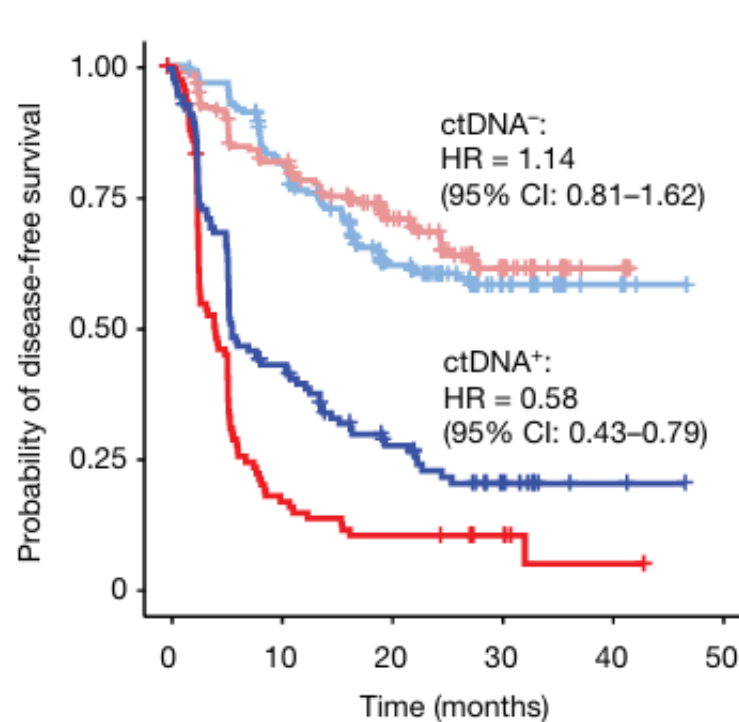
Different immunotherapies need different immune biomarkers

Study design and patients

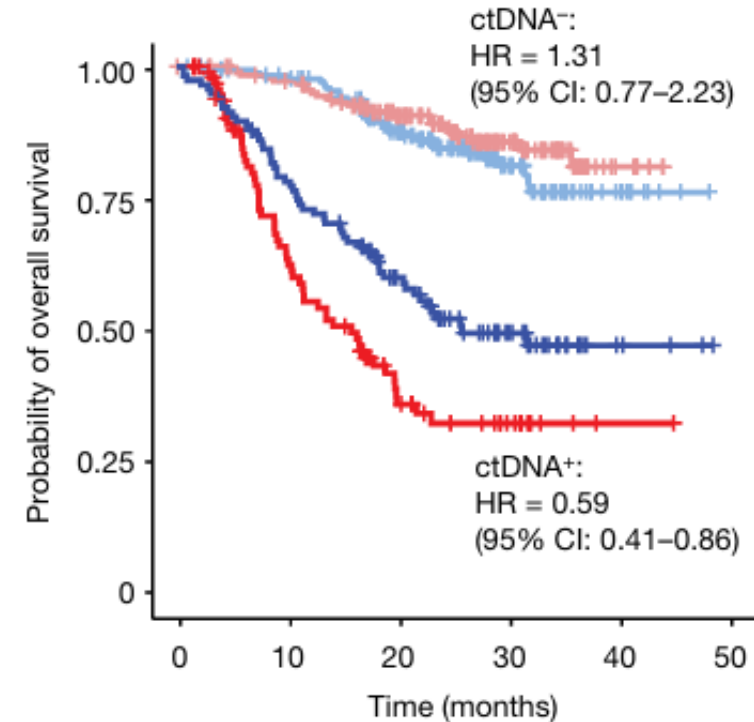


The absence of an inhibitory TME might be associated with better outcomes

IMvigor010 ctDNA identifies a high-risk population which benefits from adjuvant atezolizumab



No. at risk		Time (months)					
— Atezolizumab	— Observation	ctDNA ⁻	184	144	85	44	5
			183	140	90	46	6
— Atezolizumab	— Observation	ctDNA ⁺	116	48	25	13	2
			98	17	10	5	1



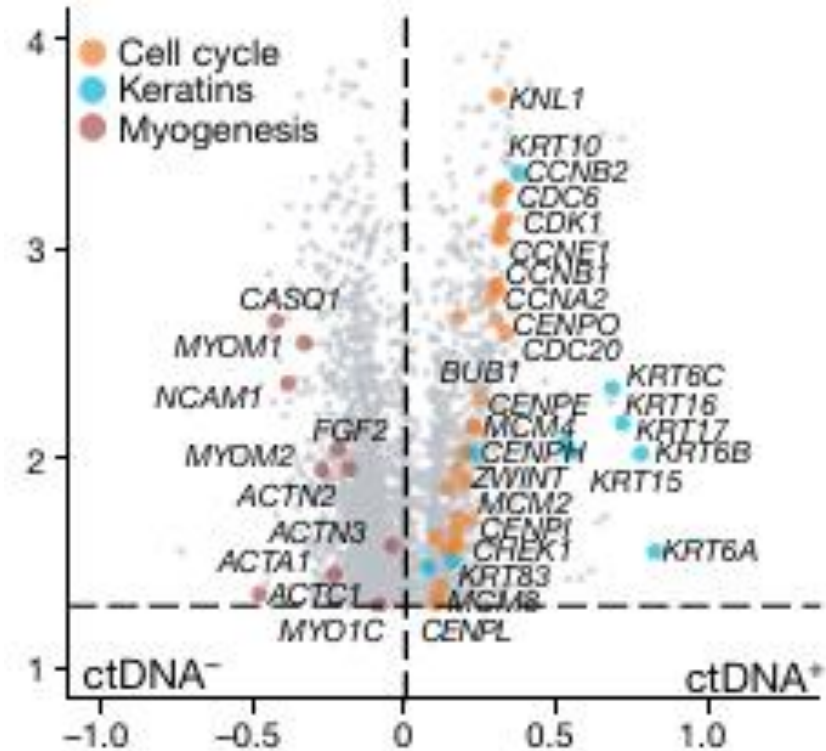
184	174	129	57	10	0
183	170	130	65	7	0
116	88	55	25	4	0
98	54	24	11	1	0

ctDNA+ and ctDNA- have differential gene expression

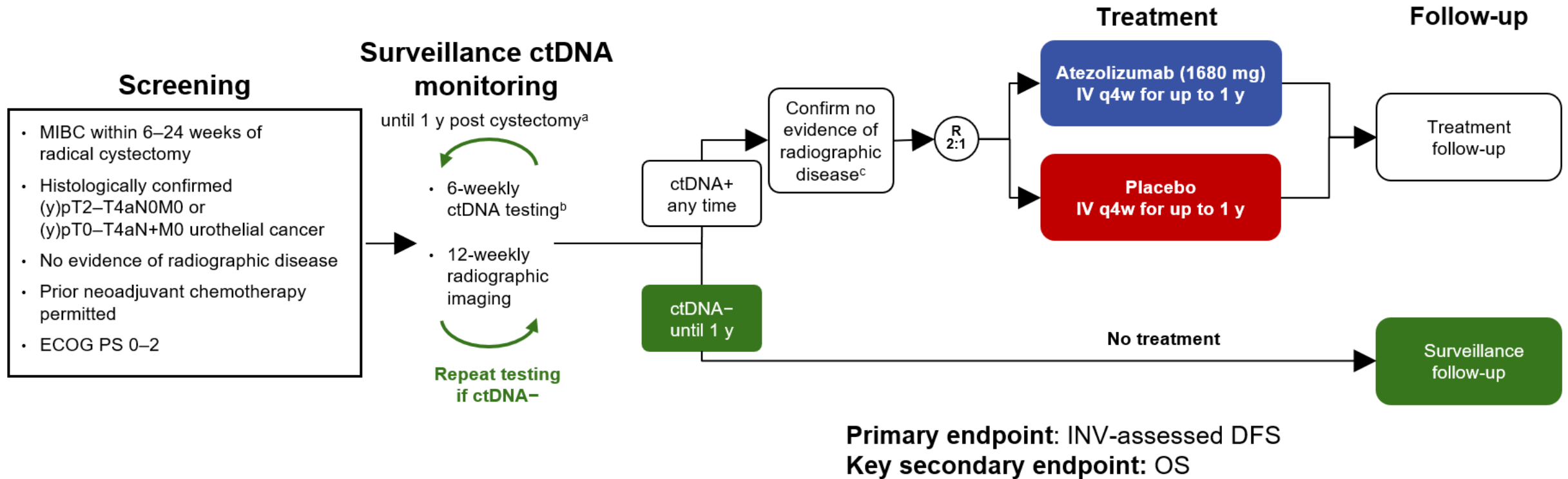
In **ctDNA+** : cell-cycle and keratin genes

Non-relapse: immune response signatures and basal squamous genes features

Relapse: angiogenes and fibroblast TGF β signalling

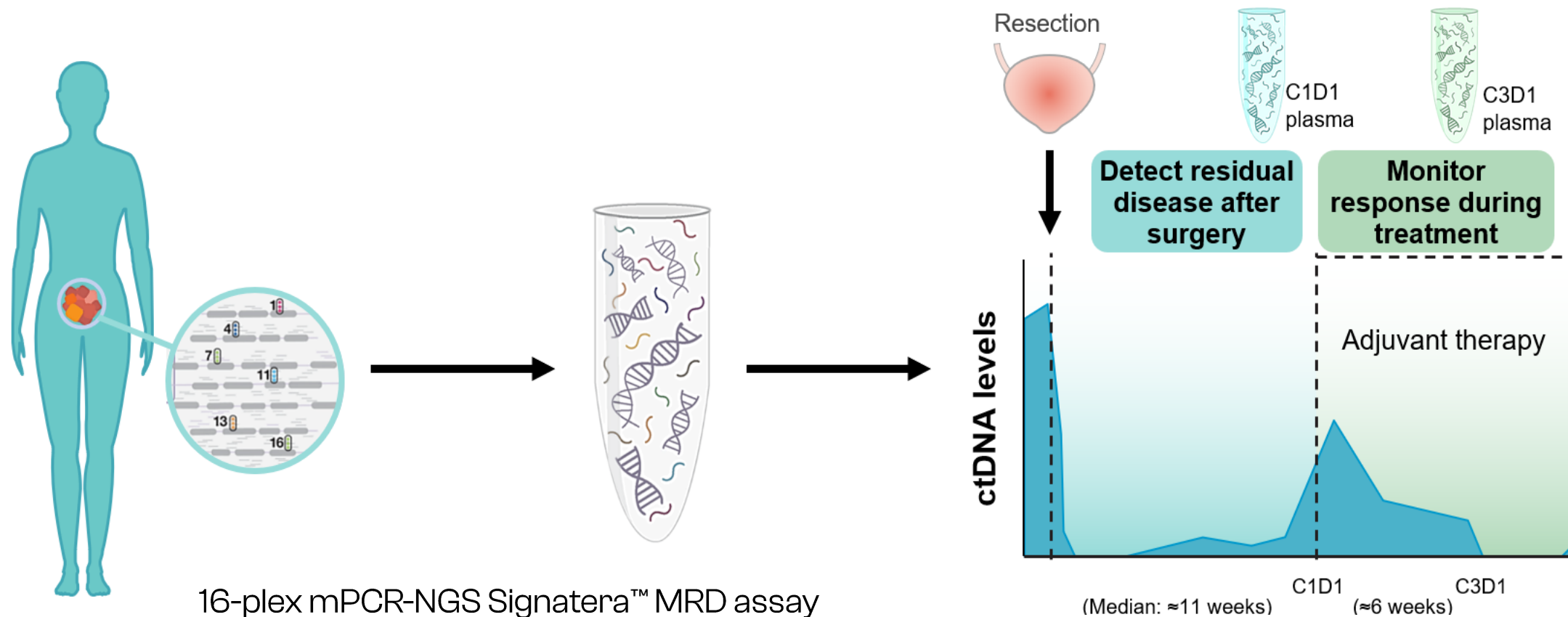


IMvigor011 prospectively tests ctDNA-guided adjuvant therapy

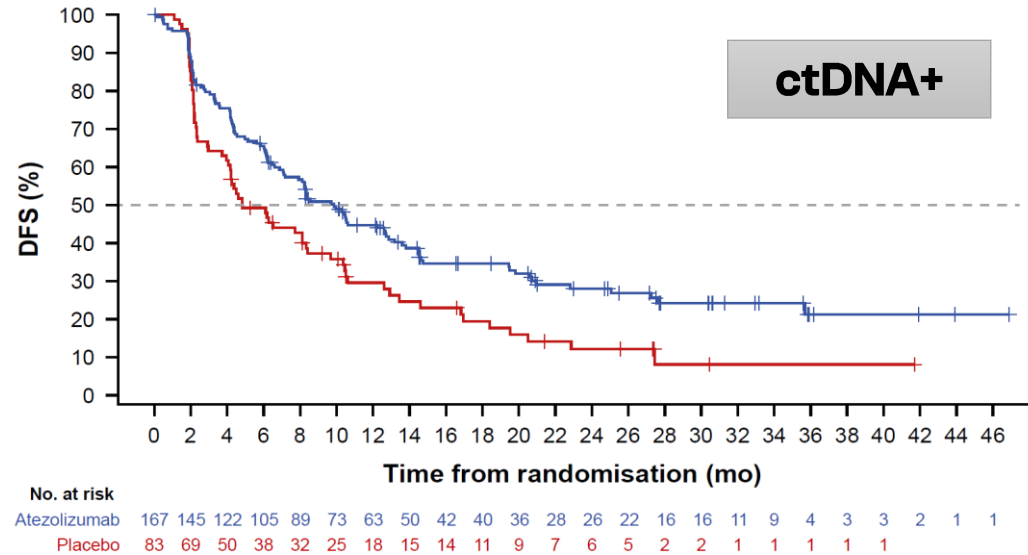


Serial ctDNA identifies molecular relapse before radiological recurrence

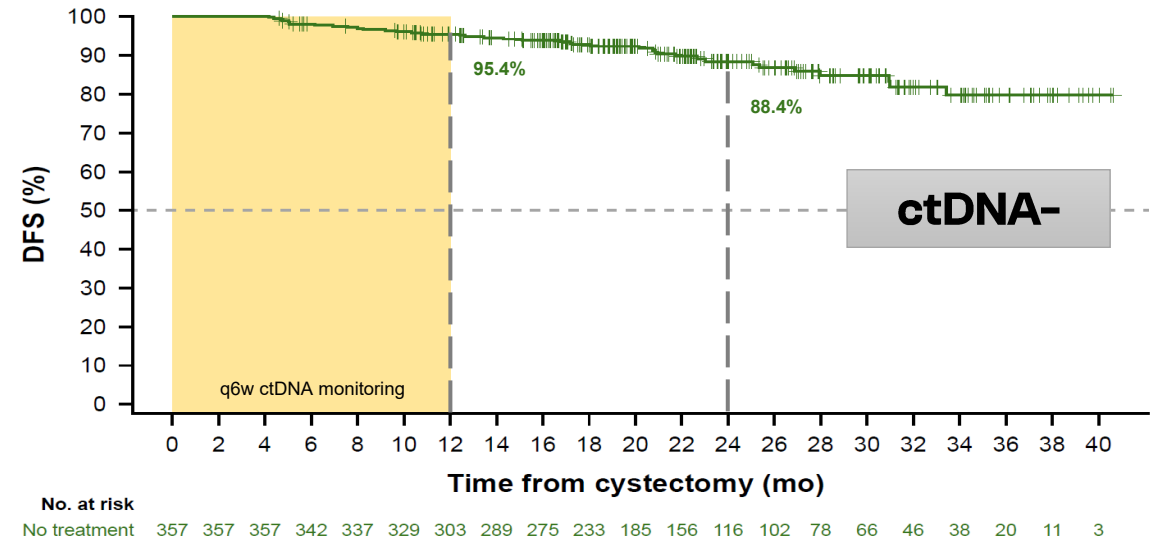
Tumour-informed ctDNA tracks molecular residual disease



IMvigor011 makes ctDNA clinically actionable



ctDNA positive post-cystectomy:
early treatment beneficial



ctDNA negative: spared unnecessary therapy

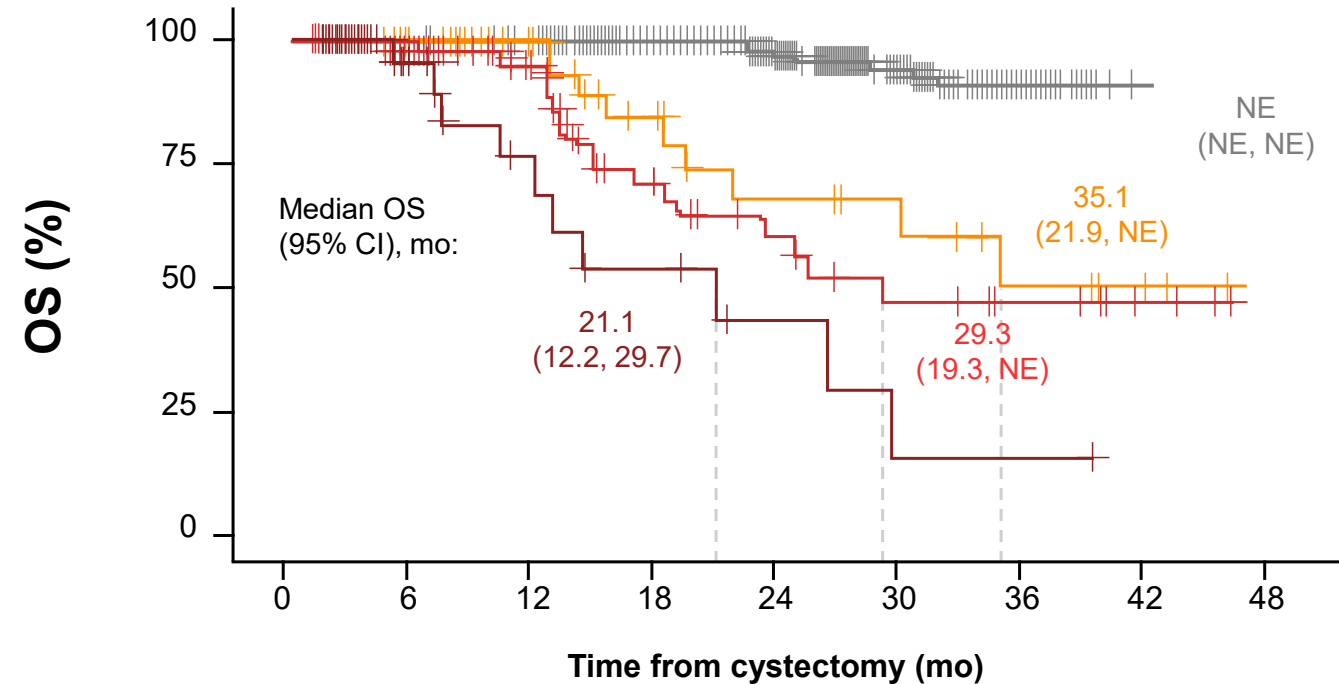
Molecular relapse precedes clinical relapse

ctDNA can be defined as positive/negative but we can also look at ctDNA blood concentration levels

Higher concentration = worse outcomes

Parallels between ctDNA and PSA

Should the highest ctDNA positive patients be treated with more aggressive therapies (EVP)?



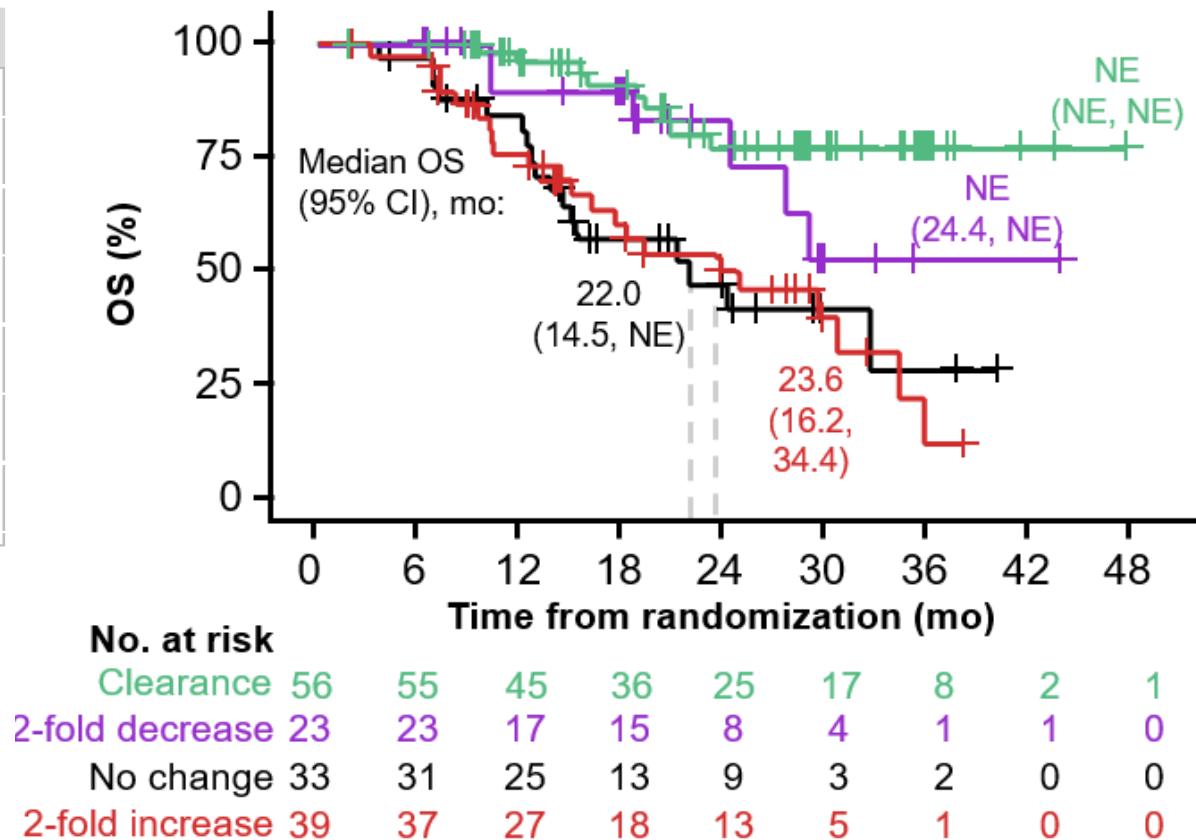
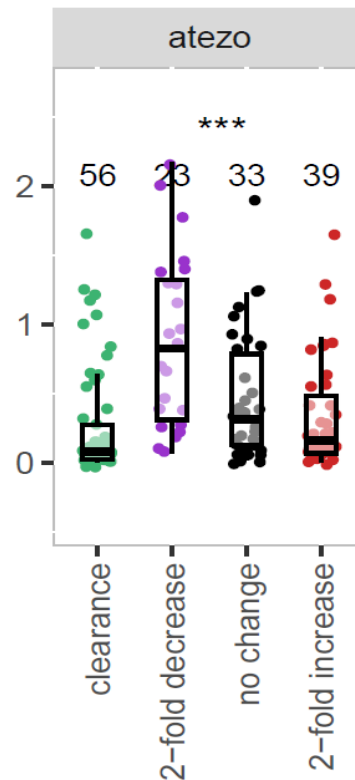
No. at risk	0	6	12	18	24	30	36	42	48
ctDNA-	357	345	319	250	138	79	26	0	0
>0.1-≤3 MTM/mL	56	40	30	18	11	9	5	3	0
>3 MTM/mL	99	59	40	23	15	10	7	3	0
>3 MTM/mL	57	18	10	6	3	1	1	0	0

With sequential samples, we can measure ctDNA reduction and clearance

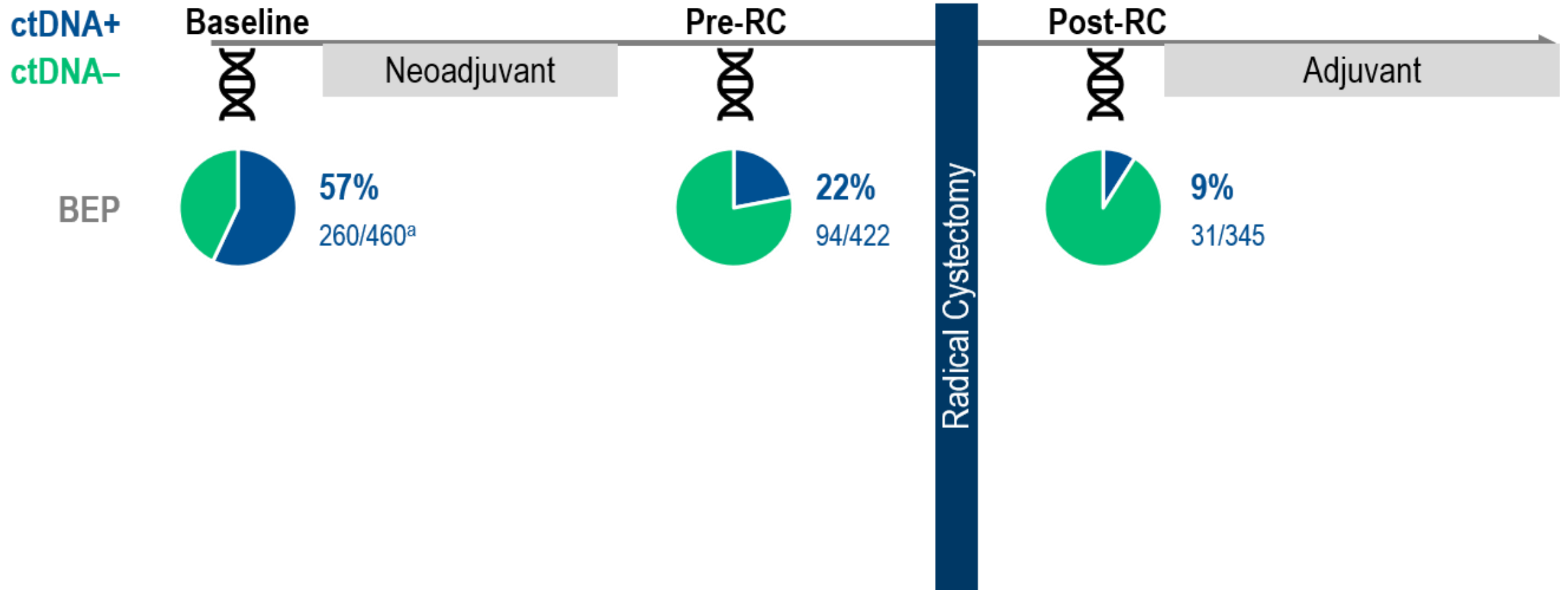
ctDNA as a continuous variable

Clearance =
improved outcomes

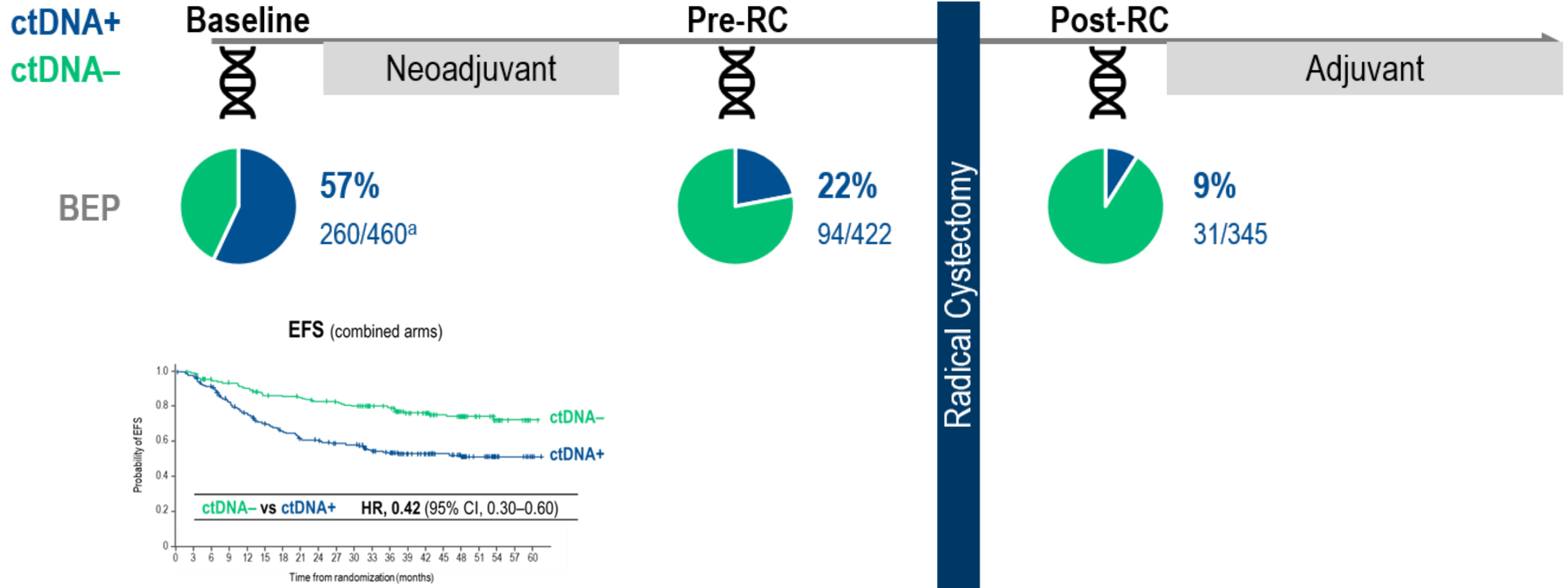
Deepest responders =
best outcomes



NIAGARA ctDNA analysis at key timepoints:



NIAGARA ctDNA analysis at key time points:



NIAGARA ctDNA analysis at key time points:

ctDNA+
ctDNA–

BEP

Baseline



57%
260/460^a

Neoadjuvant

Pre-RC



22%
94/422

Post-RC

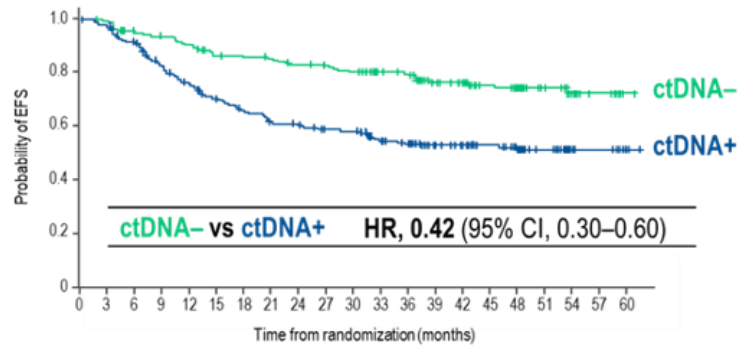


9%
31/345

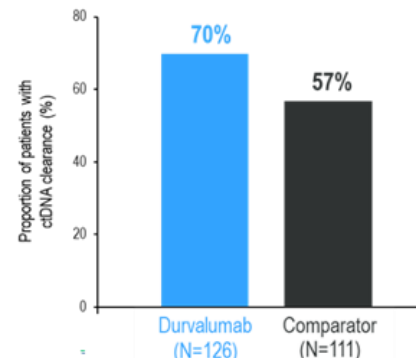
Adjuvant

Radical Cystectomy

EFS (combined arms)



ctDNA clearance from baseline
to pre-cystectomy



HR, 0.32 (95% CI, 0.22–0.47)

NIAGARA ctDNA analysis at key time points:

ctDNA+
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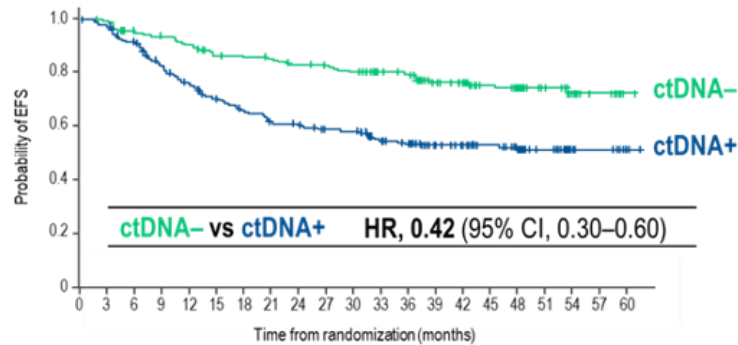


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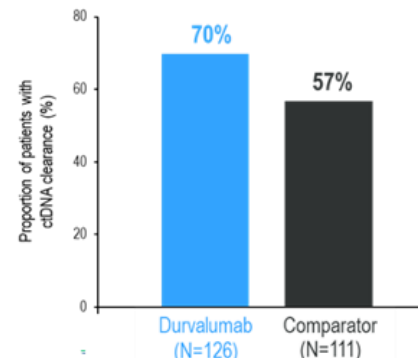
Adjuvant

Radical Cystectomy

EFS (combined arms)

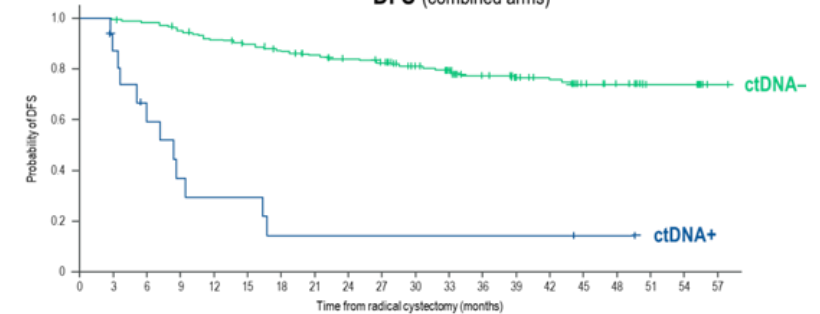


ctDNA clearance from baseline
to pre-cystectomy



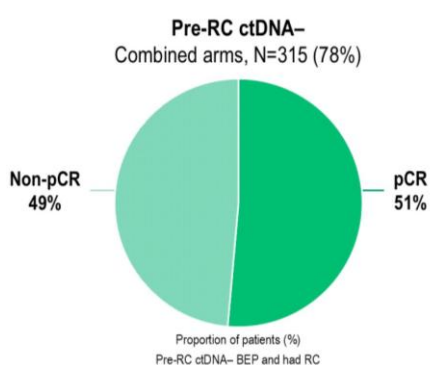
HR, 0.32 (95% CI, 0.22–0.47)

DFS (combined arms)

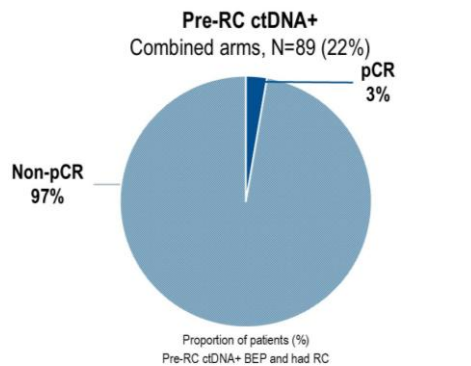


ctDNA and utDNA can potentially compliment one another, which will be useful in the bladder sparing trials

ctDNA

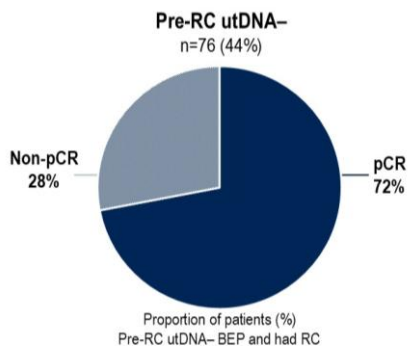


ctDNA- status was not associated with pCR

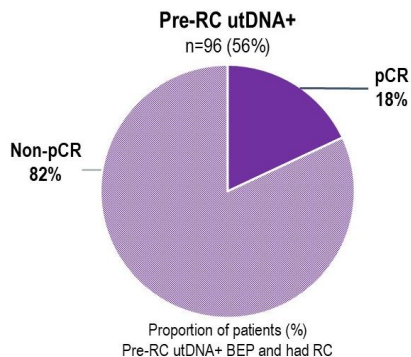


ctDNA+ status was highly correlated with non-pCR

utDNA



utDNA- status at pre-RC is associated with higher likelihood of pCR



utDNA+ status at pre-RC is associated with higher likelihood of non-pCR

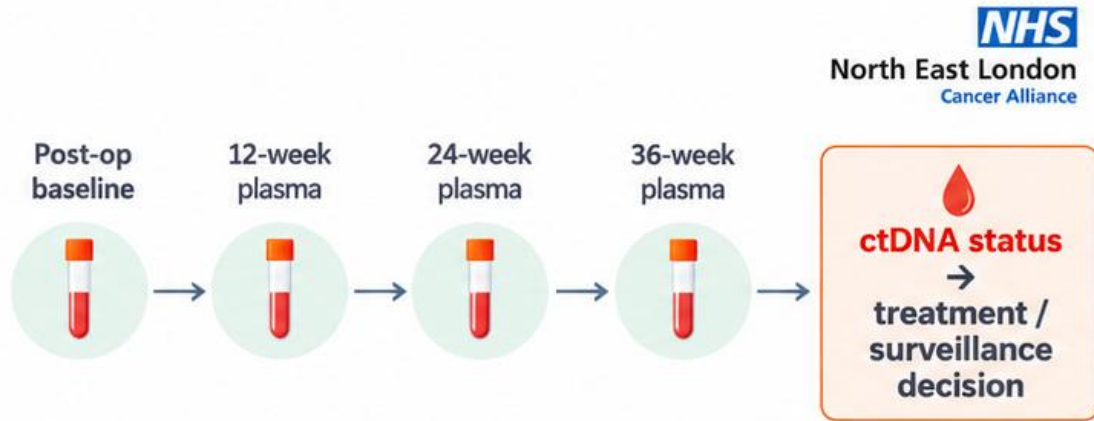
Assessing complete response after NACT:

ctDNA is helpful in those who are positive

utDNA is helpful in those who are negative

ctDNA in clinical practice

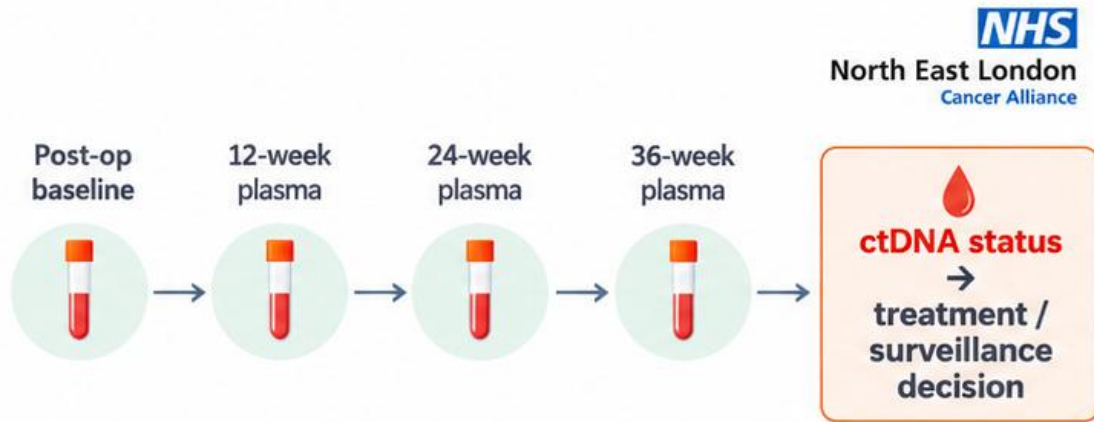
Real-world implementation: NHS pilot



-  **40 patients** with bladder cancer
-  Post-operative plasma ctDNA testing at up to **4 timepoints**
-  Assessing impact on **adjuvant treatment** and **surveillance decisions**

ctDNA in clinical practice

Real-world implementation: NHS pilot



-  **40 patients** with bladder cancer
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Investigator-sponsored studies

IST 1: ctDNA/utDNA-guided adjuvant study in UTUC

✓ High-risk UTUC
(pT2-pT4 and/or
N+,M0)
✓ Post-radical
nephrou

N=100
Sac-TMT 12 cycles
Pembrolizumab 9 cycles

Primary Endpoints:
1) ctDNA clearance
at 18W
2) 2-year DFS

Baseline post-op
ctDNA/utDNA
(Signatera assay) →  On-treatment
(12-18W)
ctDNA/utDNA

IST 2: ctDNA dynamics in EV rechallenge

CONCLUSIONS

- **Tissue biomarkers refine biology, but rarely select treatment alone (exception: FGFR3 inhibition and HER2)**
- **Different immune therapies need different immune biomarkers**
- **Post-cystectomy ctDNA is prognostic and correlates with molecular residual disease but it's not predictive**
 - o In IM011, it was predictive of response to atezolizumab (because patients at risk were selected)
- **ctDNA is not binary: burden, timing and kinetics matter**
- **In bladder-preservation strategies, a 2-compartment approach (ctDNA and utDNA) may be needed**

¡Gracias!

