IV GO NORTE INTERNATIONAL GU DEBATES
OCTOBER 2nd - 3rd 2025
#GonorteGUDebates

The use of genomic and transcriptomic biomarkers to help identifying responders in the perioperative setting

REAL LAB

cnio stop cancer

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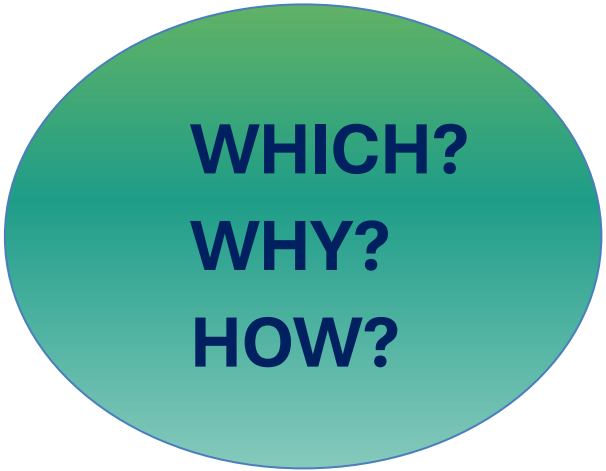
No biomarker is clinically approved to guide perioperative treatment decisions

Promising biomarkers exist — but none are yet ready for routine clinical use

The key questions are:



Plasma ctDNA

vs

Baseline

Neoadjuvant

Cystectomy

Relapse

Higher ctDNA → pCR

ABACUS
(Atezolizumab)
Eur Urol 2022

NABUCCO
(Ipi+Nivo)
Nature Medicine 2023

Aarhus University Hospital
(Chemo)
Clinical Cancer Research 2023

ctDNA clearance → pCR → PFS

ABACUS
(Atezolizumab)
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NABUCCO
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Nature Medicine 2023

Aarhus University Hospital
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Clinical Cancer Research 2023

ctDNA → PFS

ABACUS
(Atezolizumab)
Eur Urol 2022

VOLGA
(Durva+Treme+EV)
Annals of Oncology 2023

ctDNA as Biomarker for Neoadjuvant Treatment in Bladder Cancer

- Most solid biomarker in the neoadjuvant setting
- ~40% undetectable ctDNA at baseline
- ctDNA dynamics predict pCR/relapse
- Needs prospective validation & standardization
    - Assay design (tumor-informed vs tumor-naïve)
    - Cut-offs and timing
- Cost burden

DNA Damage Repair genes

Controversial predictive value of mutations in DNA Damage Response genes to NAC:

ERCC1/2, *ATM*, *RB1*, *FANCC*

Van Allen et al. *Cancer Discovery* 2024

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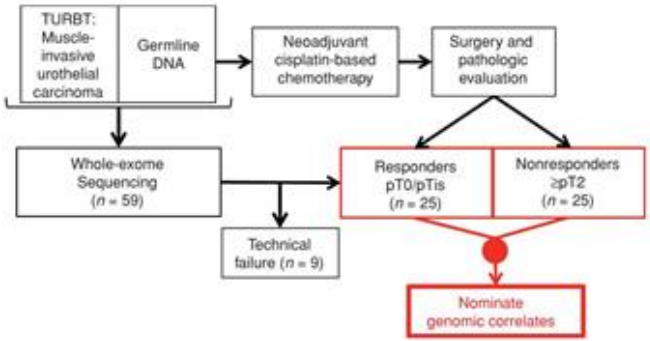


exomes sequencing
n=58

Van Allen et al. *Cancer Discovery* 2014

DNA Damage Repair genes

ERCC2 mutations predict response to NAC with limited negative predictive value

SWOG S1314-cohort

Table 2 – Association of gene variant with pathologic complete response (pT0) [a]

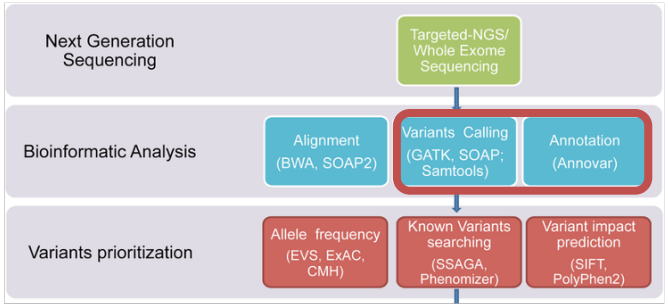
Gene	Variant?	*n*/*N* (%) with pT0	Sensitivity (95% CI) Specificity (95% CI) PPV (95% CI) NPV (95% CI)	Odds ratio (95% CI) [b] Two-sided *p* value	AUC [c]
Mutation in one or more of the 4 genes: *ATM*, *ERCC2*, *FANCC*, or *RB1*	Yes	27/56 (48)	0.79 (0.66, 0.93) 0.59 (0.48, 0.71)	5.36 (2.05, 14.02) 0.001	0.71
	No	7/49 (14)	0.48 (0.35, 0.62) 0.86 (0.73, 0.94)		
ATM	Yes	14/25 (56)	0.41 (0.25, 0.58) 0.85 (0.76, 0.93)	4.23 (1.60, 11.2) 0.004	0.66
	No	20/80 (25)	0.56 (0.35, 0.76) 0.75 (0.64, 0.84)		
ERCC2	Yes	12/18 (67)	0.35 (0.19, 0.51) 0.92 (0.82, 1.00)	5.47 (1.80, 16.6) 0.003	0.65
	No	22/87 (25)	0.67 (0.41, 0.87) 0.75 (0.64, 0.83)		
FANCC	Yes	0/4 (0)	0.00	Too few variants	
	No	34/101 (34)	0.94 (0.89, 1.00) 0.00 (0.00, 0.60) 0.66 (0.56, 0.75)		
RB1	Yes	12/25 (48)	0.35 (0.19, 0.51) 0.82 (0.73, 0.91)	2.31 (0.91, 5.86) 0.08	0.62
	No	22/80 (28)	0.48 (0.28, 0.69) 0.73 (0.61, 0.82)		

AUC = area under the curve; CI = confidence interval; NPV = negative predictive value; OR = odds ratio; PPV = positive predictive value.
[a] AUC for clinical stage alone = 0.55.
[b] OR adjusted for stratification factor T2 versus T3–4a in the logistic model.
[c] AUC including clinical stage + respective variant in the model.

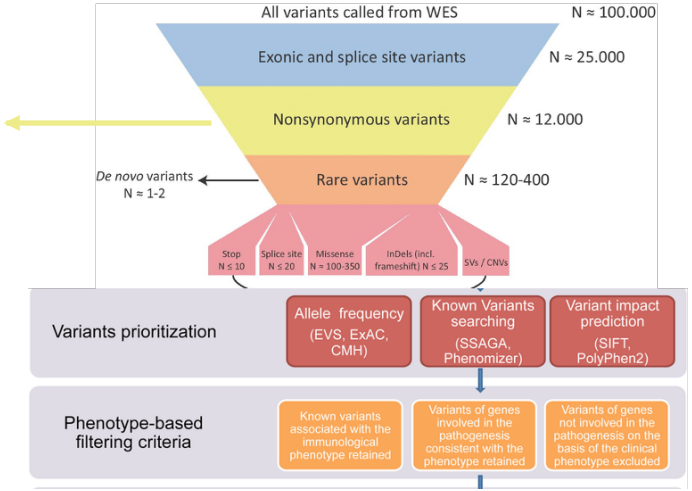
~ 10% non-synonymous mutations in MI-BLCA

Plimack Eur et al. *Eur Urol* 2024

Variant calling and filtering means scanning through countless DNA changes and carefully narrowing them down to the rare few that truly impact health

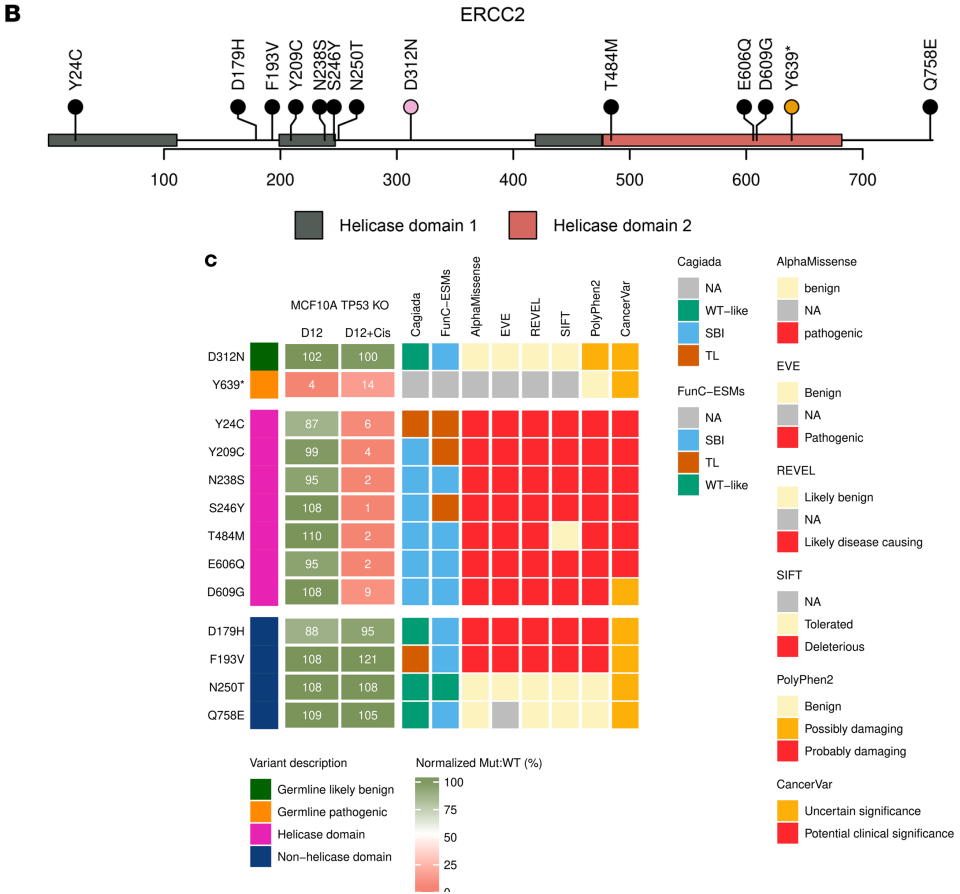


TMB data



The Oncomine™ Comprehensive Assay Plus and similar automated, standardized workflows streamline the entire NGS process, but the data they generate are still subject to the same biases and limitations inherent to sequencing.

Functional impact of the detected variants



Challenges in Variant filtering

Börcsök J. *et al*. JCI 2025

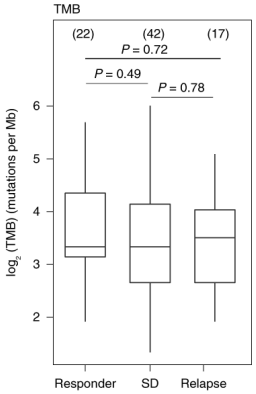
Controversial TMB for immunotherapy response in the neoadjuvant setting

Association observed in some trials, but not reliable for patient selection
Need for standardized methods and cutoffs (8–20 mut/Mb)

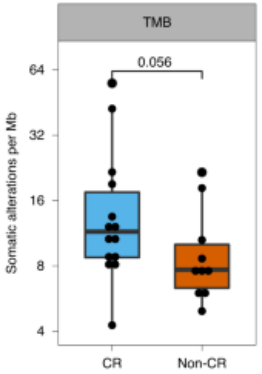
PURE-01, NABUCCO

ABACUS

ABACUS



NABUCCO



Challenges of genetic variants and TMB as predictive biomarkers

Sample type: fresh vs. Paraffin

Somatic vs germline

Sequencing approaches need standardization:

- WGS, exomes, **commercial panels**
- Sequencing depth
- Analysis bioinformatic pipelines: variant callers
- Variant filtering settings: functional impact of the mutant alleles

Plus:

Study design factors

Treatment & endpoints

Molecular Subtypes

Conflicting Evidence: Molecular Subtypes and Response to Chemo and ICI

Chemotherapy

Basal–squamous subtype

Poorer responses: Taber et al., *Nat Commun* 2020

Improved survival in NAC-treated cohort: Seiler et al., Eur Urol 2017
McConkey et al., Eur Urol 2017

Non-luminal tumors:

Greatest benefit from NAC: Lotan et al., J Urol 2022

Immunotherapy

PURE-01: No association between molecular subtype and pembrolizumab response.

Molecular Subtypes

Conflicting Evidence: Molecular Subtypes and Response to Chemo and ICI

Classification issues

At least six published classification systems (TCGA, Lund, consensus, etc.)

Different sequencing methods (RNA-seq vs panels, FFPE vs frozen) → inconsistent calls

Cut-off thresholds & algorithms vary

Tumor biology

Intratumoral heterogeneity (different regions, mixed histologies)

Temporal evolution: subtypes may shift with therapy

Continuum rather than discrete categories

Apart from:

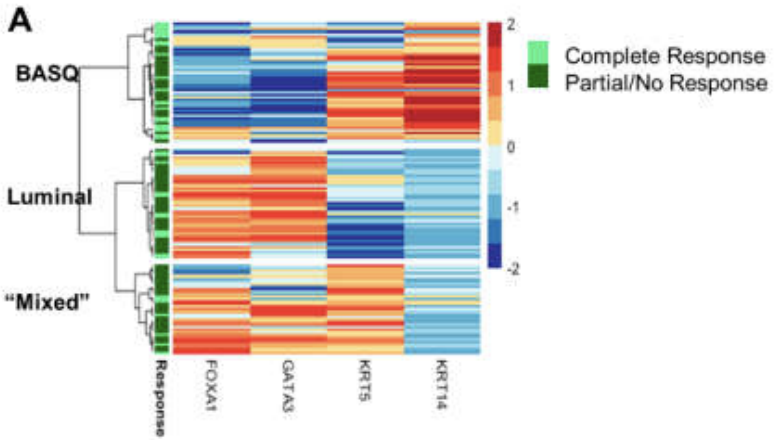
Study design factors

Treatment & endpoints

Integrated clinical-taxonomic-gene expresión-signature

Retrsopective study: a predictive signature for response to NAC that integrates the expression of three genes with clinicopathological characteristics and taxonomic subtypes.

Immunohistochemistry-Based Taxonomical Classification

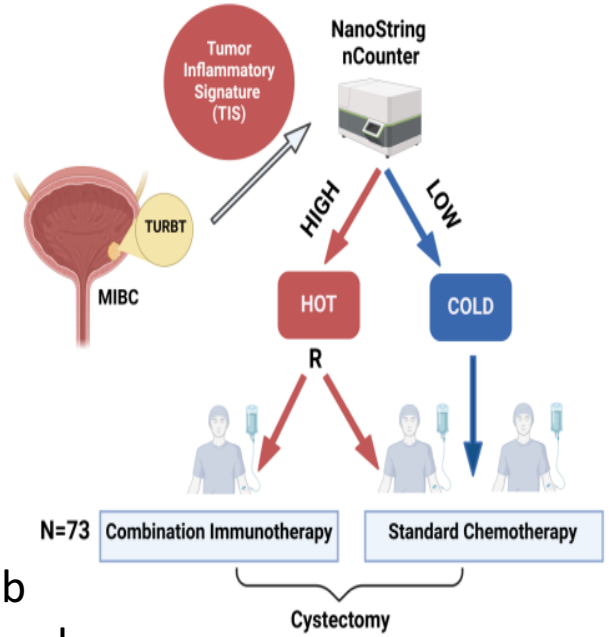


Model	Variables included	LASSO-selected genes included	AUC
(1) Clinical score	cTNM Hydronephrosis Histological type	–	0.56
(2) Clinical score plus taxonomic subtype	cTNM Hydronephrosis Histological type BASQ vs luminal/mixed	–	0.58
(3) Clinical score plus taxonomic subtype plus gene expression	cTNM Hydronephrosis Histological type BASQ vs luminal/mixed Eight selected genes	*RAD51* *IFNγ* *CHEK1* *CXCL9* *c-Met* *KRT14* *HERC2* *FOXA1*	0.65
(4) Clinical score plus taxonomic subtype plus gene expression	cTNM Hydronephrosis Histological type BASQ vs luminal/mixed Three selected genes	*RAD51* *IFNγ* *CHEK1*	0.71

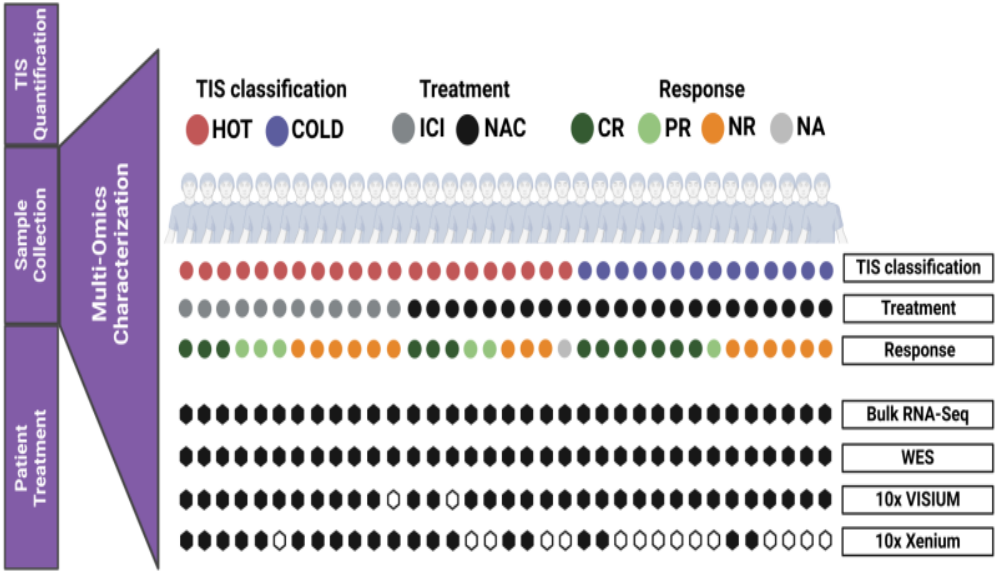
Albert Font et al. *Cancers* 2020

Albert Font et al. *Frontiers in Oncology* 2023

Spatial Biomarkers DUTRENEO



durvalumab
tremelimumab

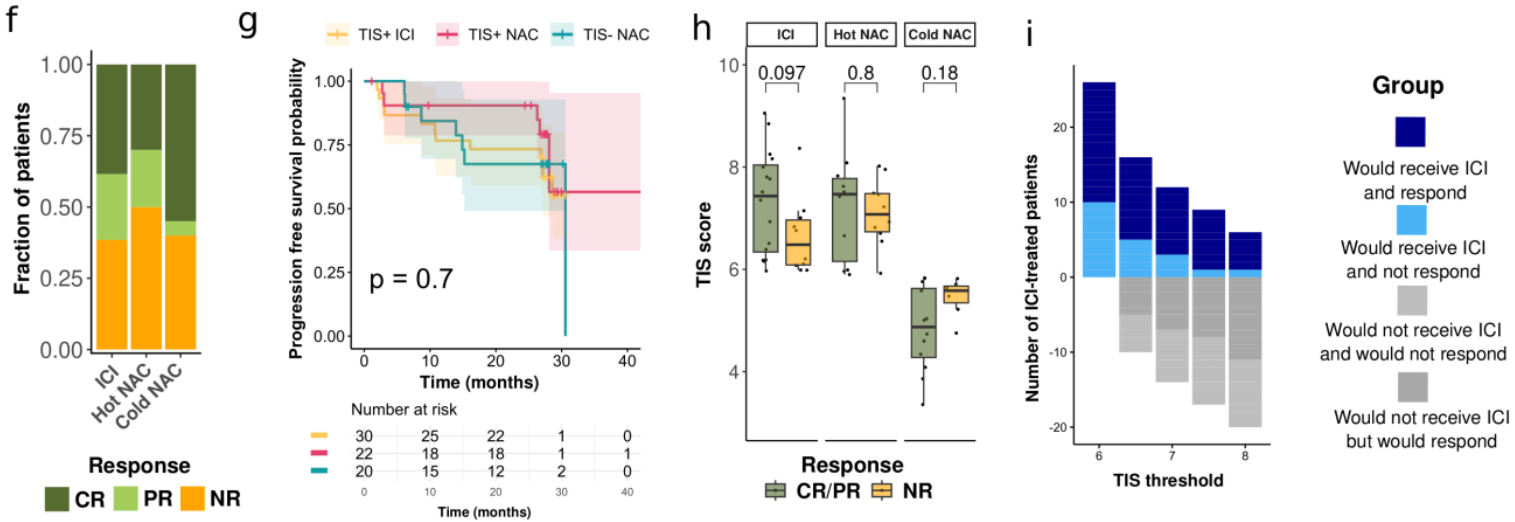


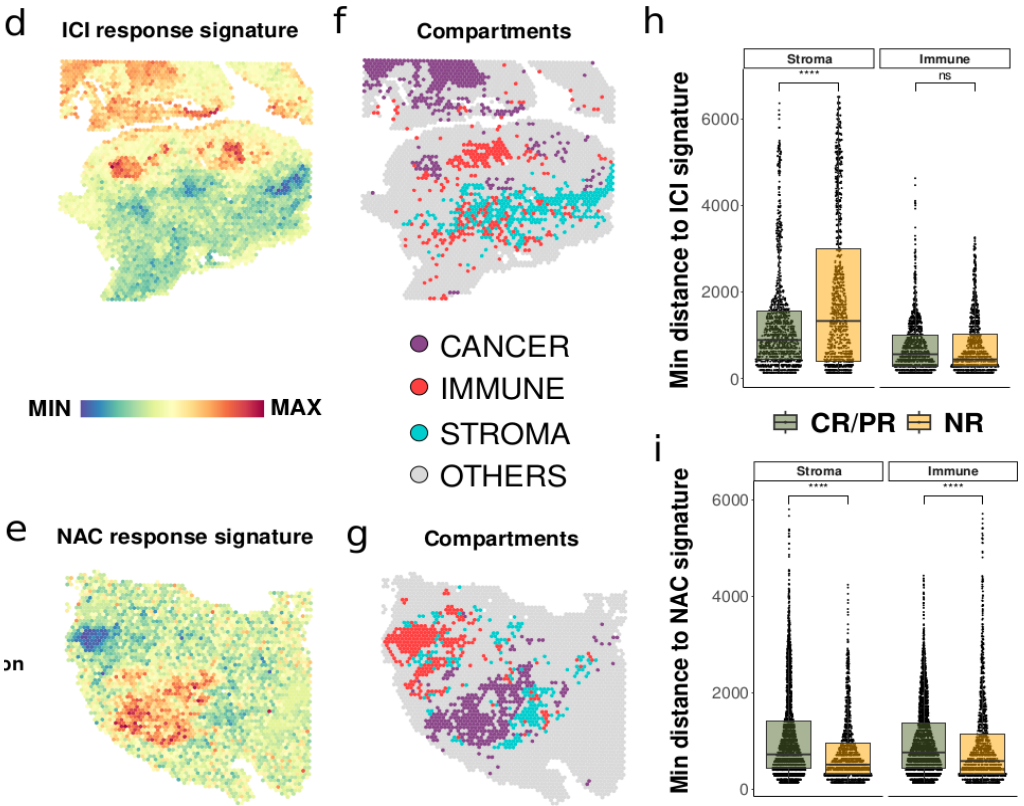
Fundación JOSEP CARRERAS contra la leucemia

REAL LAB

Enrique Grande, Mustafa Sibai et al. medRxiv 2025

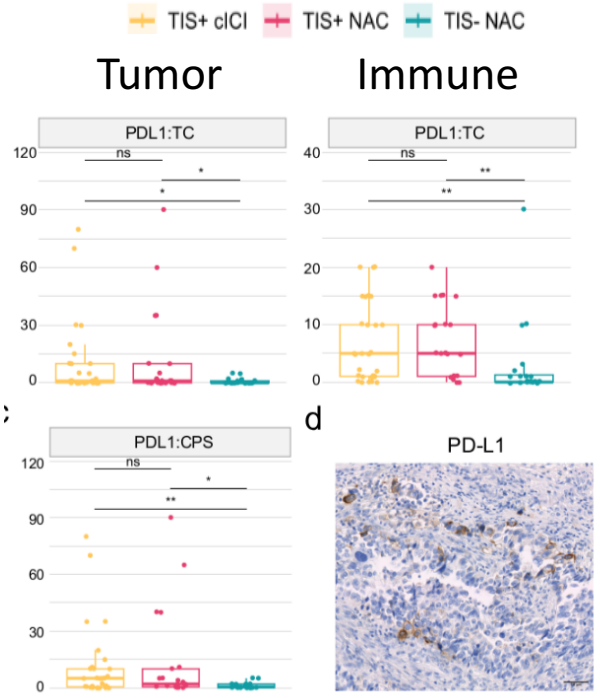
There was no statistically significant difference in the primary endpoint between patients with hot tumours treated with ICI and those treated with NAC

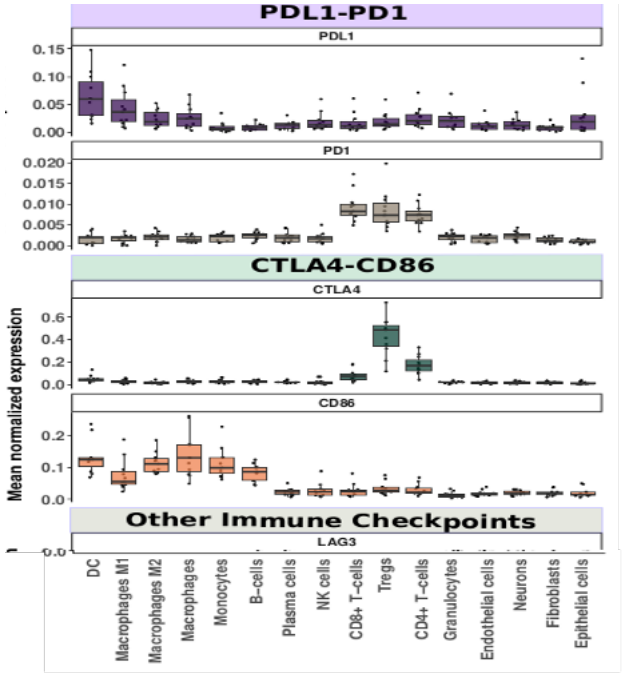


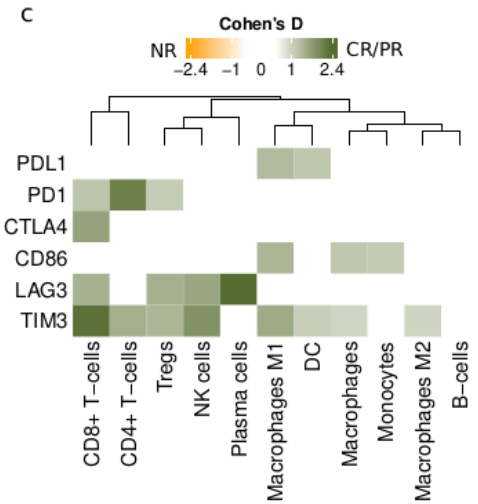


35 pre-treatment spatial transcriptomics

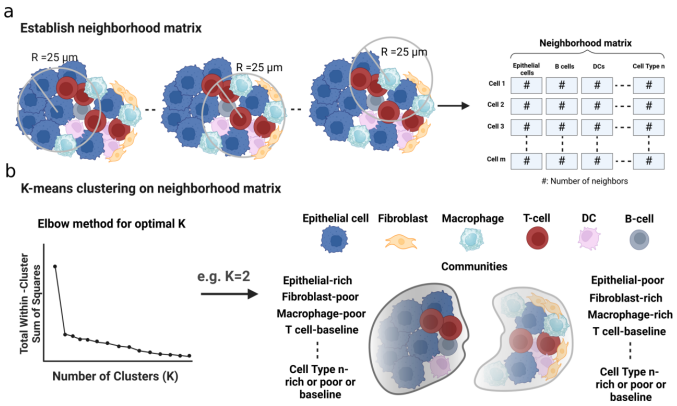
PD-L1 alone did not predict ICI response, but broader immune features distinguished responders from non-responders

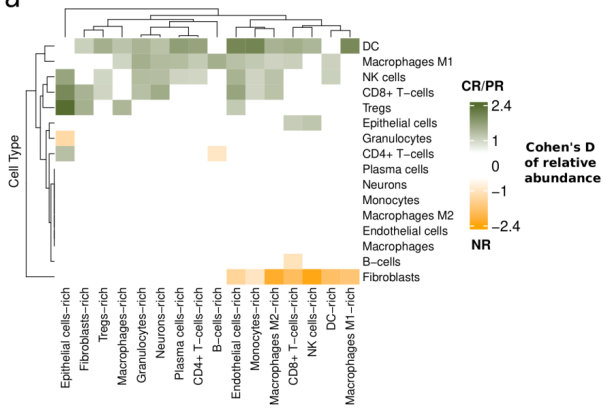


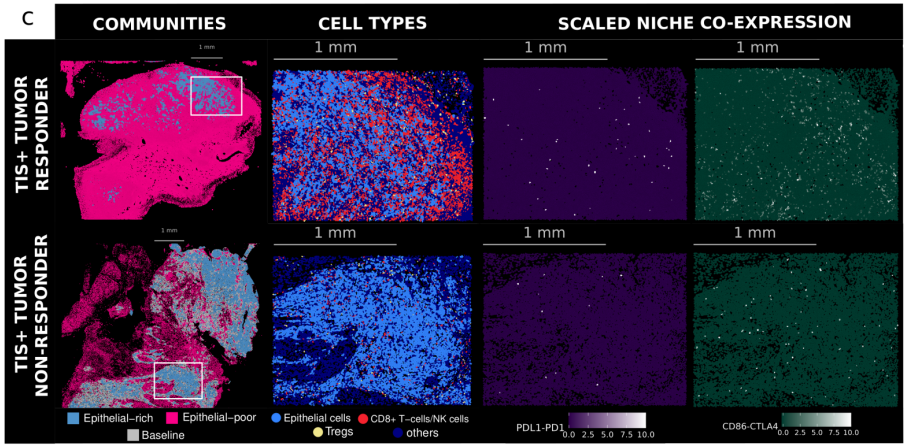




Cancer cell neighborhoods differed between ICI responders and non-responders.







The challenge now is progressing from discovery studies, through robust large retrospective and prospective cohorts, toward truly conclusive data.

The neoadjuvant setting offers the best opportunity for biomarker development.

Several biomarkers correlate with response, but lack of measurement standardization and cut-offs limits clinical use.

Need for the increasing use of more quantitative assays.

Spatial biology is informative, but needs translation into clinically accessible toolss-

AI will be key for image-based biomarker analysis.

Patient heterogeneity demands multimodal biomarker approaches: AI facilitate multimodal biomarkers integration

Increasing future complexity (ICI + chemo, ADCs, multimodal approaches)

Needed: prospective studies with predefined (and possibly multiple) cut-offs, standardized methods, and rigorous multimarker validation supported by solid retrospective data.