World Conference On
Genitourinary Cancers

2025 NASHVILLE, TN

ROLE OF PRECISION MEDICINE IN GU CANCERS

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Rogel Cancer Center

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August 23, 2025

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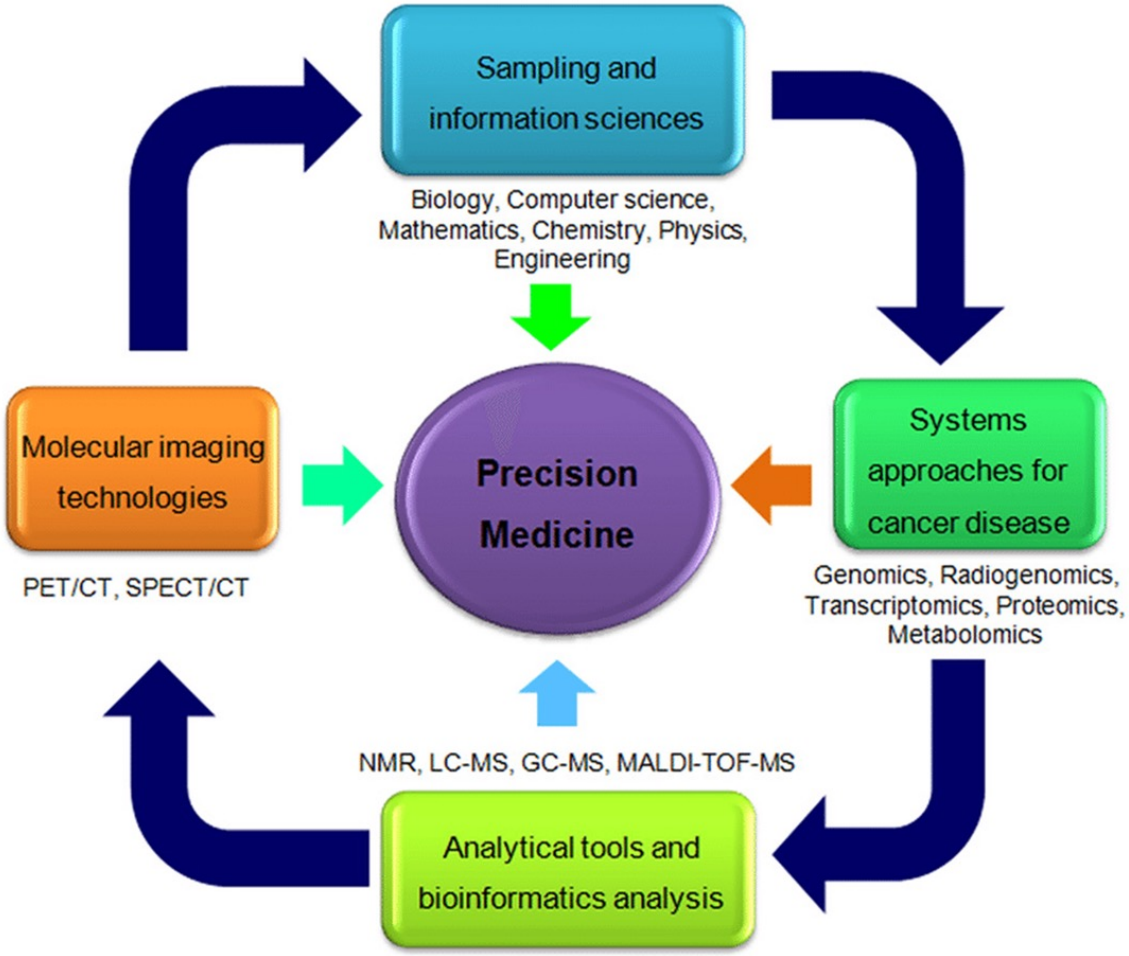
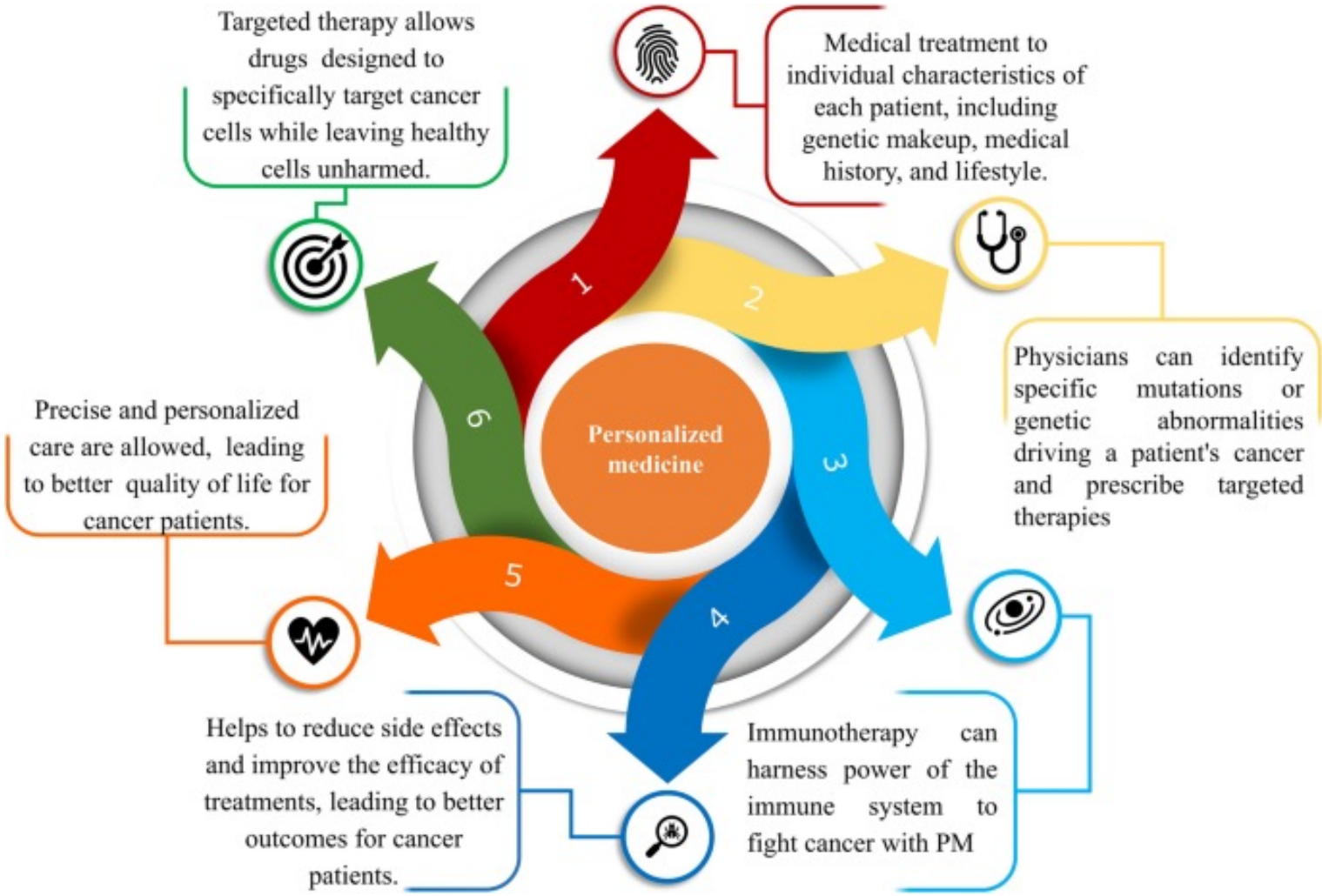
Precision Medicine

- **Precision medicine** refers to the integration of molecular and genomic profiling to guide diagnosis, prognosis, and individualized therapy selection.

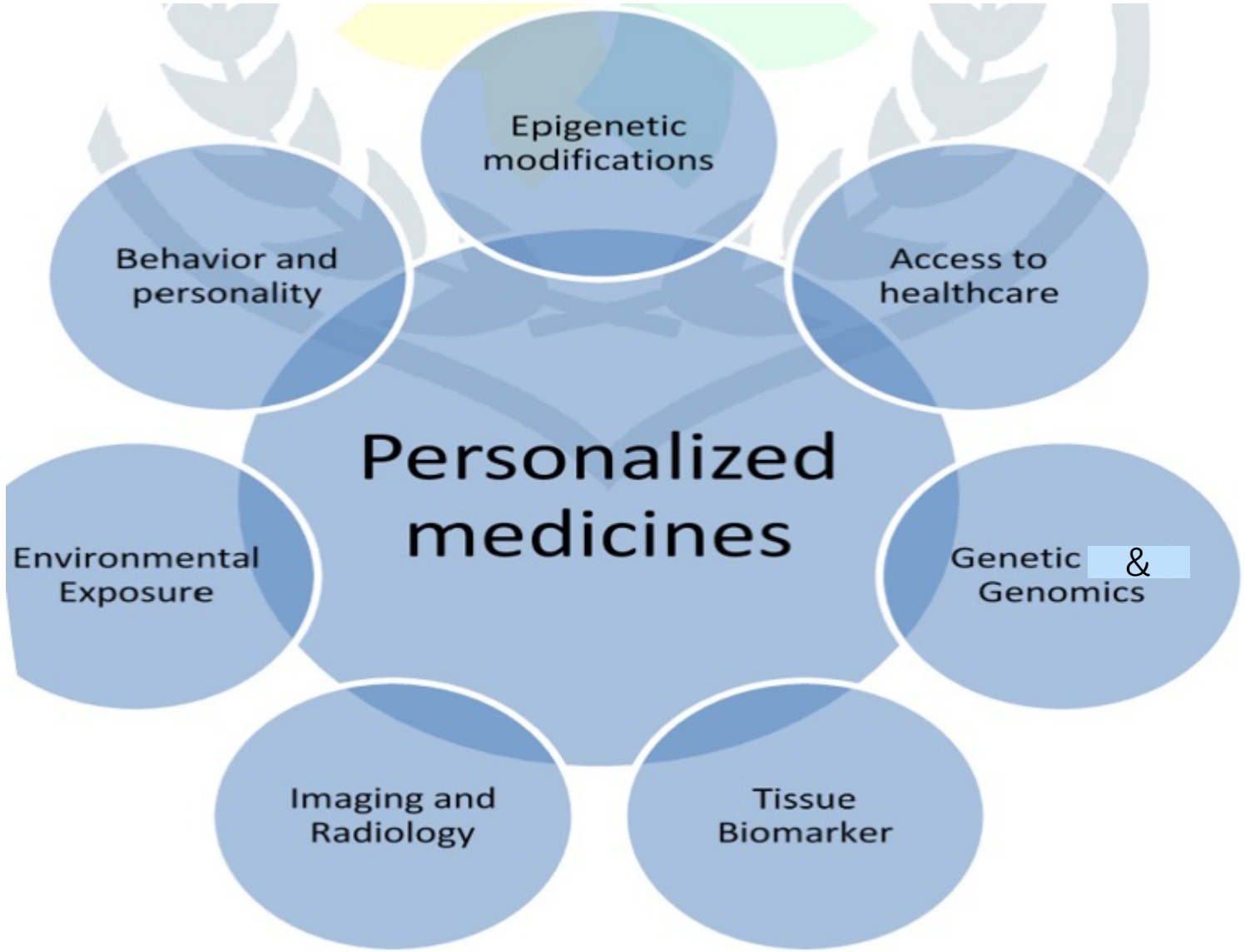


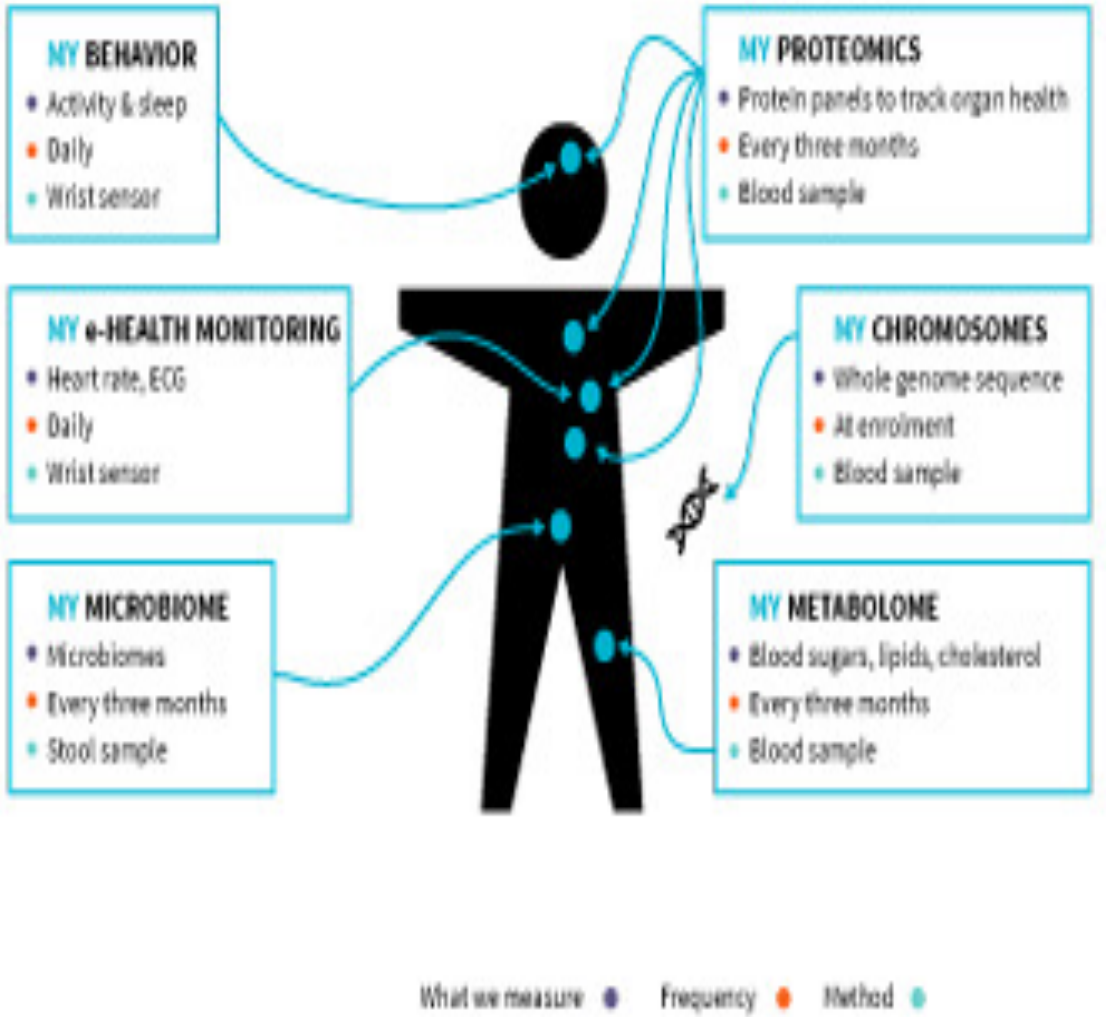
Multiple Ways of Achieving Precision!



Precision Medicine

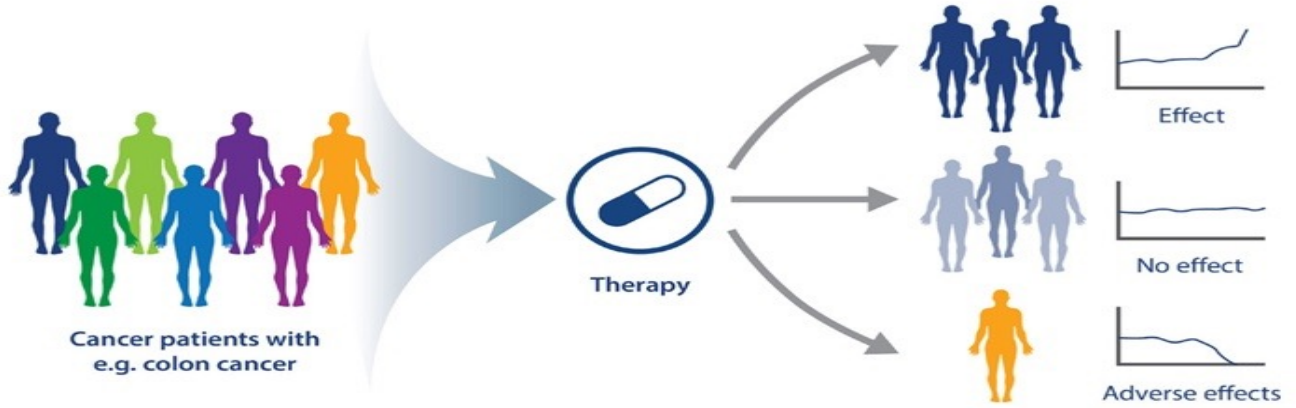
- One biomarker
- Biomarker panel
- Use of AI to evaluate a host of undefinable factors
- Clinical factors
- Pharmacogenomics
- Minimal residual Disease
- Imaging Markers




MY BEHAVIOR
Activity & sleep
Daily
Wrist sensor
MY PROTEOMICS
Protein panels to track organ health
Every three months
Blood sample
MY e-HEALTH MONITORING
Heart rate, ECG
Daily
Wrist sensor
MY CHROMOSOMES
Whole genome sequence
At enrolment
Blood sample
MY MICROBIOME
Microbiomes
Every three months
Stool sample
MY METABOLOME
Blood sugars, lipids, cholesterol
Every three months
Blood sample
What we measure
Frequency
Method

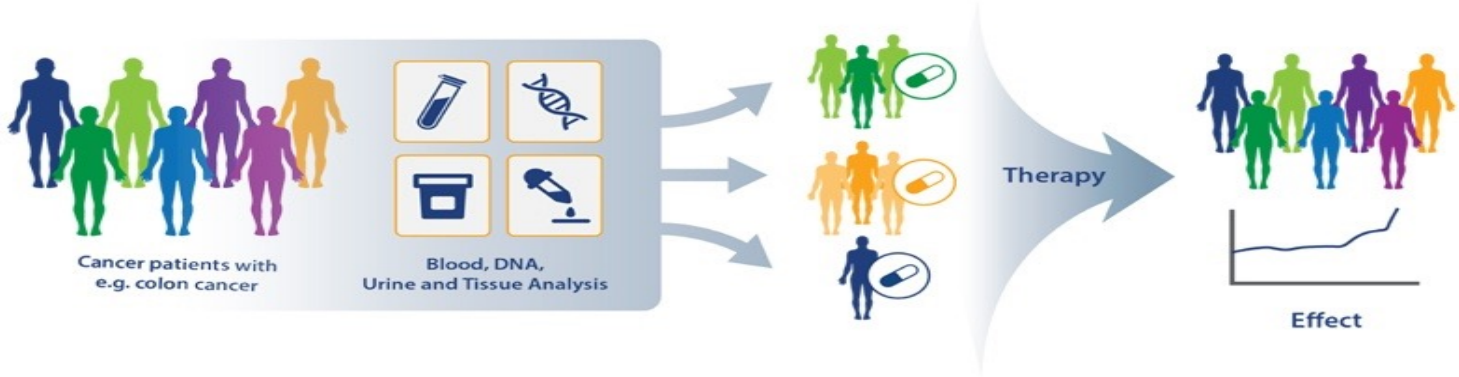
Current Medicine

One Treatment Fits All



Future Medicine

More Personalized Diagnostics



Prostate Cancer

Met CRPC:

- HRR mutations: PARP inhibitors
- SPOP mutations may predict response to androgen receptor pathway inhibitors in metastatic hormone-sensitive disease.
- **TMB > 10 – Immunotherapy**
- **PTEN loss: capivasertib**
- RB loss: neuroendocrine features

Urothelial Cancer

- Use of FGFR3 mutation status to select patients for FGFR inhibitors (e.g., erdafitinib)
- PD-L1 expression, microsatellite instability (MSI), and tumor mutational burden (TMB) to guide immune checkpoint inhibitor therapy (e.g., pembrolizumab, dostarlimab)
- Molecular subtyping of bladder cancer (luminal, basal, neuroendocrine-like) further refines therapeutic stratification.
- Antibody Drug Conjugates

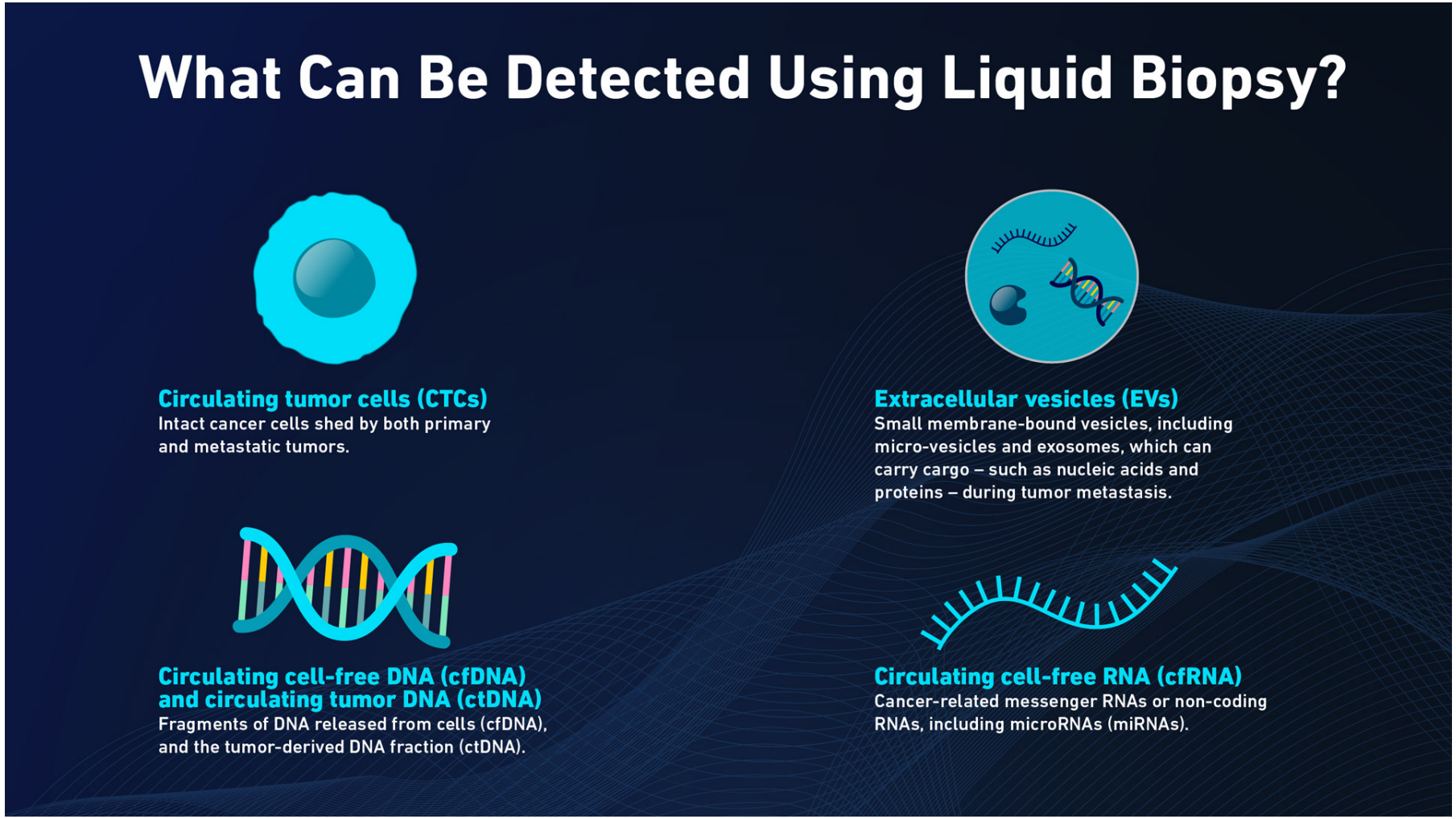
Renal Cancer

- **RCC : Prognostic** PBRM1, and BAP1 though routine clinical use of targeted therapies based on these markers is still evolving.
- **VHL-HiF inhibitors such as Belzutifan, casdatifan**
- **Kim-1- Prognostic with immune therapy and post nephrectomy**
- For testicular germ cell tumors, **microRNA profiling** is emerging as a superior diagnostic and prognostic tool compared to conventional serum markers.

Pharmacogenomics: Optimizing Therapy

- Needs focused development
- Wide open research field
- Requires collaboration with dedicated pharmacology faculty with interest in this field
- Can be a powerful tool for translational clinical trial
- Requires universal collection of tissue and blood sample
- Can help define efficacy and toxicity

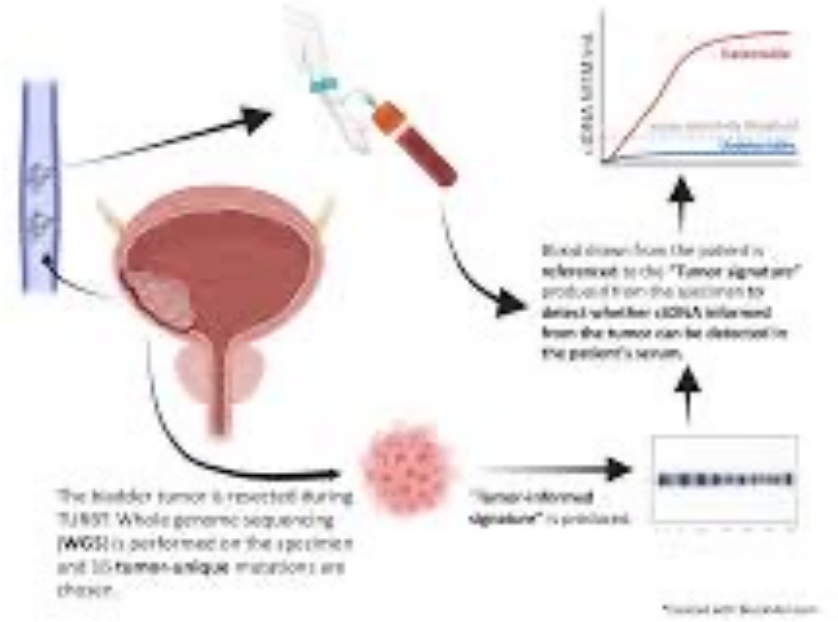
MRD vs Liquid Biopsy: ctDNA is one component



Application of ctDNA in Urothelial Cancer

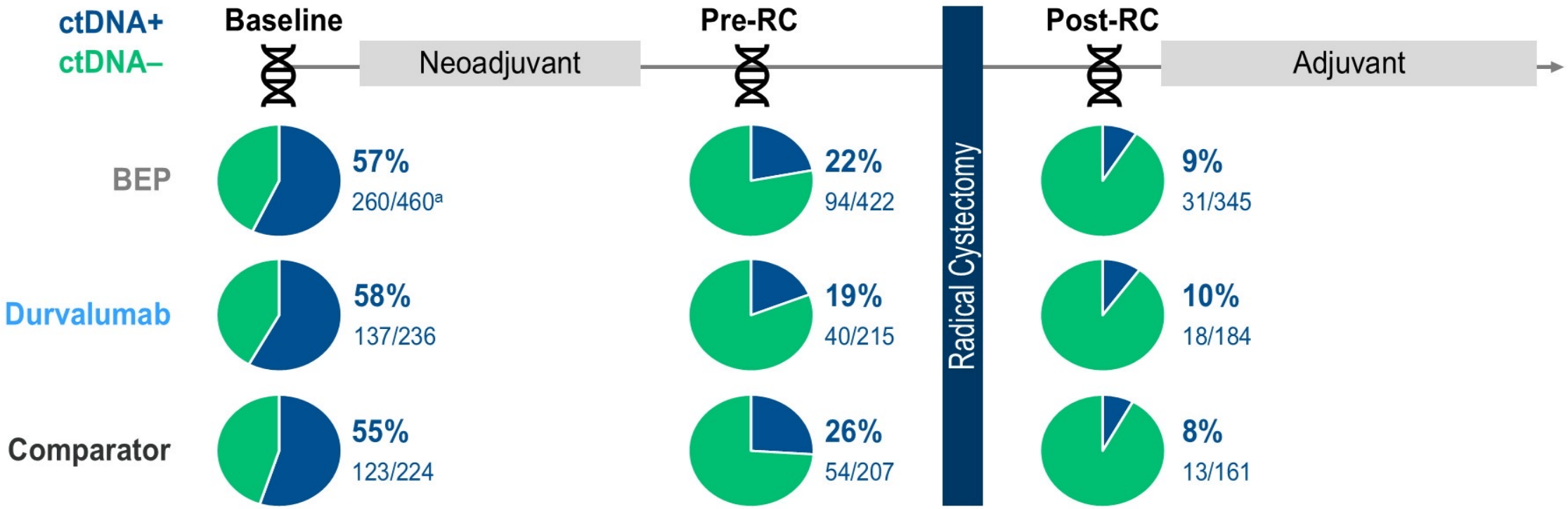
Monitoring with ctDNA for bladder cancer

- Risk-stratify patients with MIBC
- Predict disease recurrence early, before traditional imaging methods
- Predict and monitor treatment response to inform clinical decisions



NIAGARA: ctDNA Detection Rates

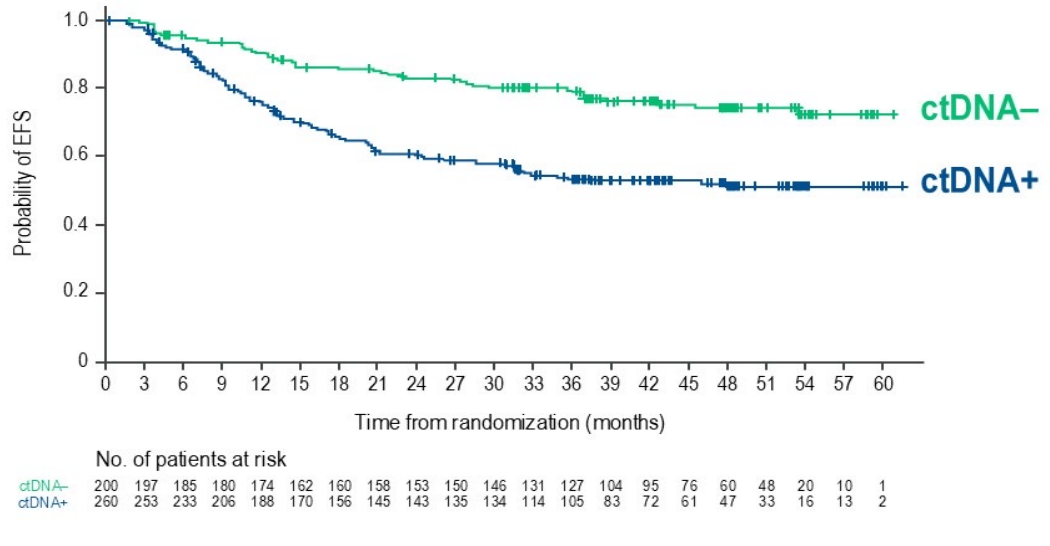
ctDNA+ rates decreased after neoadjuvant treatment and radical cystectomy



NIAGARA Baseline: ctDNA Detection Was Prognostic for EFS

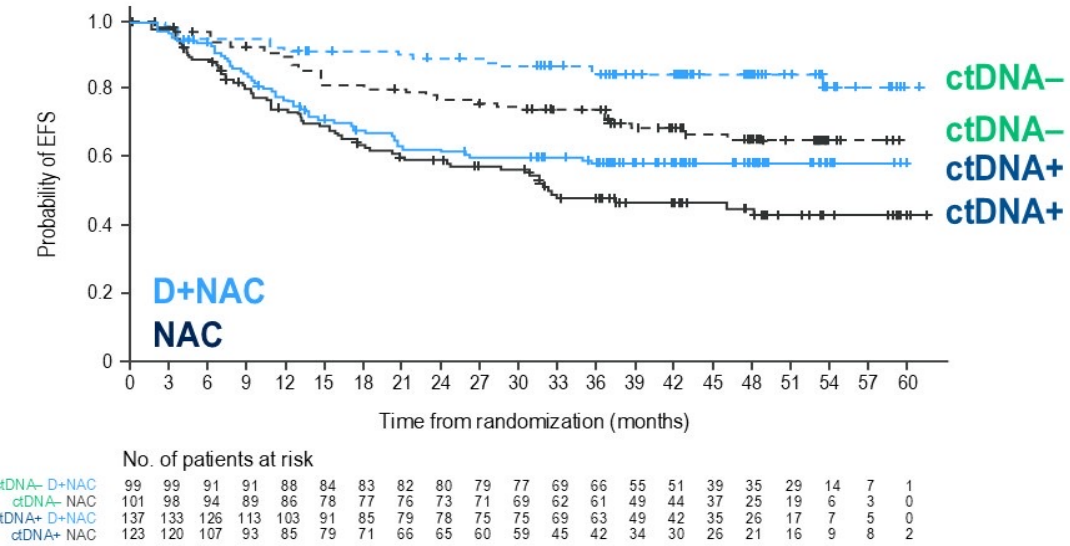
Perioperative D+NAC provided EFS benefit to patients with ctDNA+ or ctDNA– status

EFS (combined arms)



ctDNA– vs ctDNA+	**HR, 0.42** (95% CI, 0.30–0.60)

EFS (per arm)



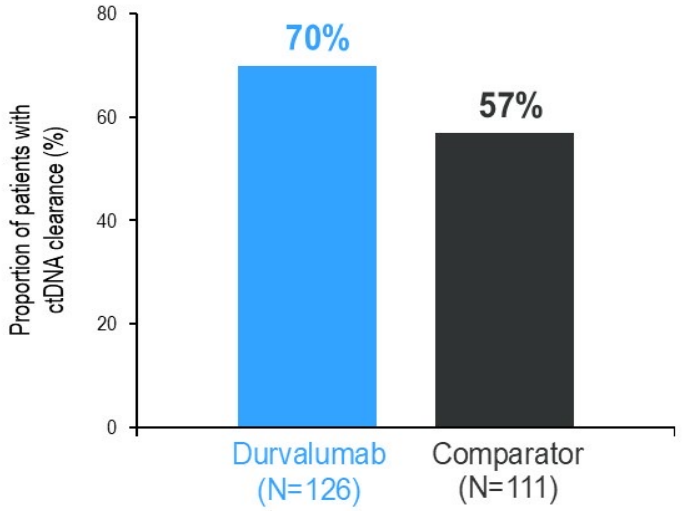
ctDNA–: D+NAC vs NAC	**HR, 0.45** (95% CI, 0.24–0.84)
ctDNA+: D+NAC vs NAC	**HR, 0.73** (95% CI, 0.51–1.05)

Durvalumab arm = D+NAC; Comparator arm = NAC

- **BEP baseline ctDNA+ = 57%**

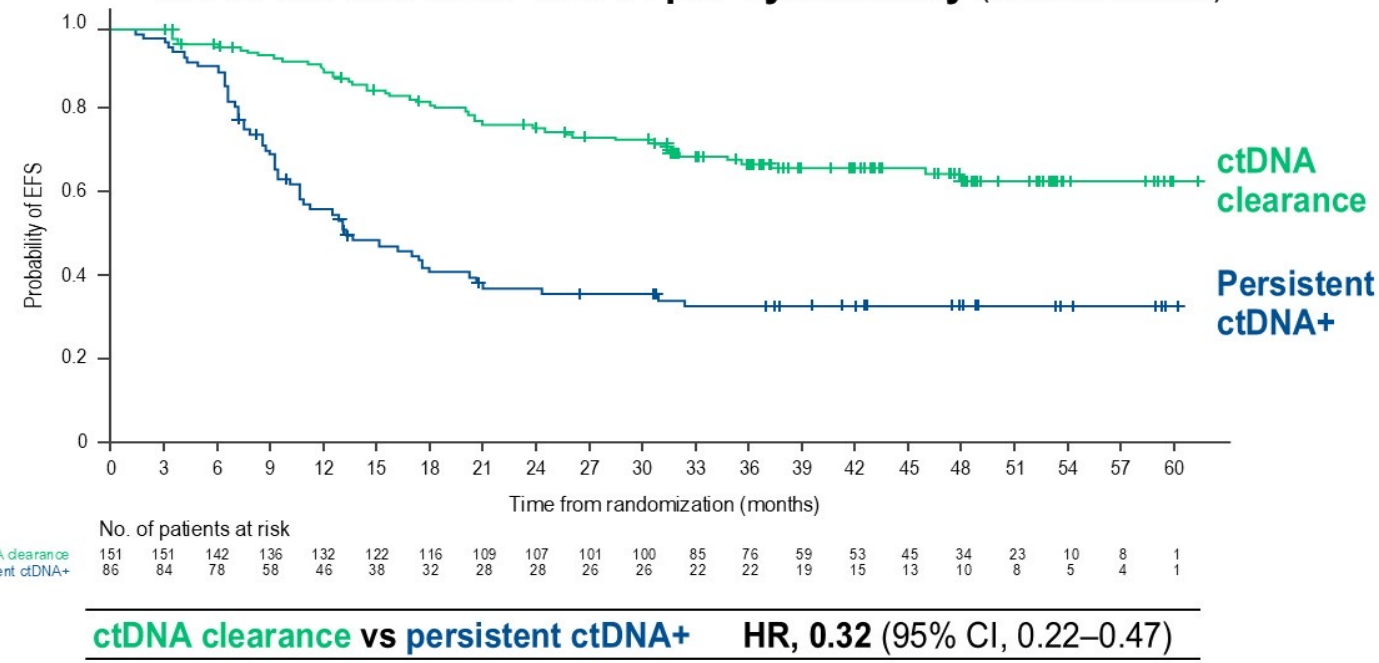
NIAGARA Neoadjuvant Treatment: ctDNA Clearance Was Higher in the Durvalumab Arm and Prognostic for EFS

ctDNA clearance from baseline to pre-cystectomy



Patients that were ctDNA+ at baseline and had a pre-RC ctDNA sample

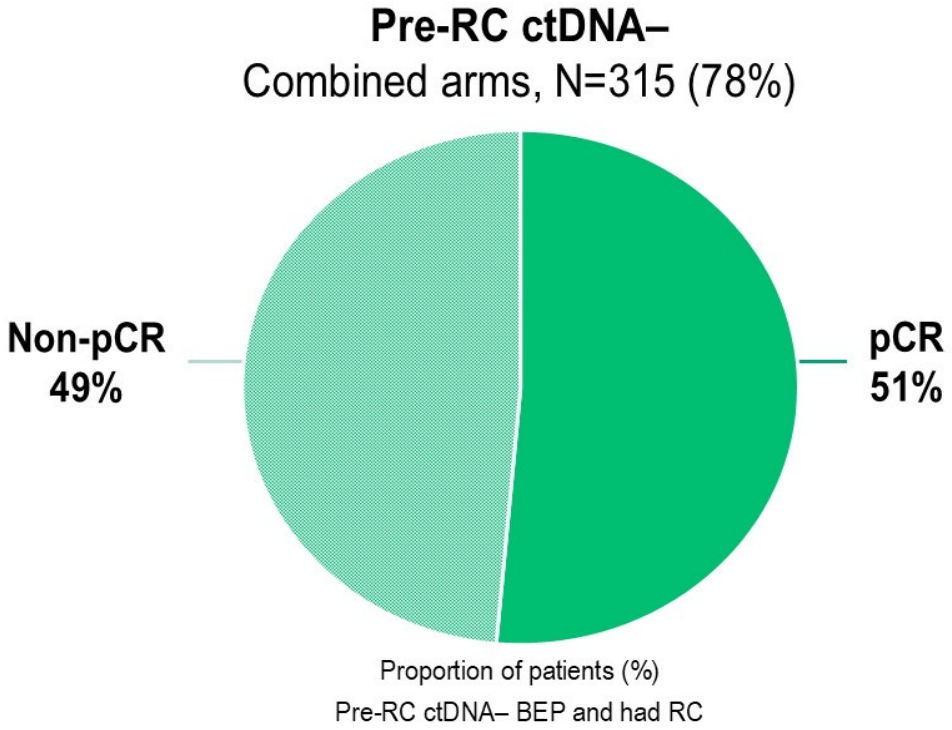
EFS in the baseline ctDNA+ population that did or did not clear ctDNA pre-cystectomy (combined arms)

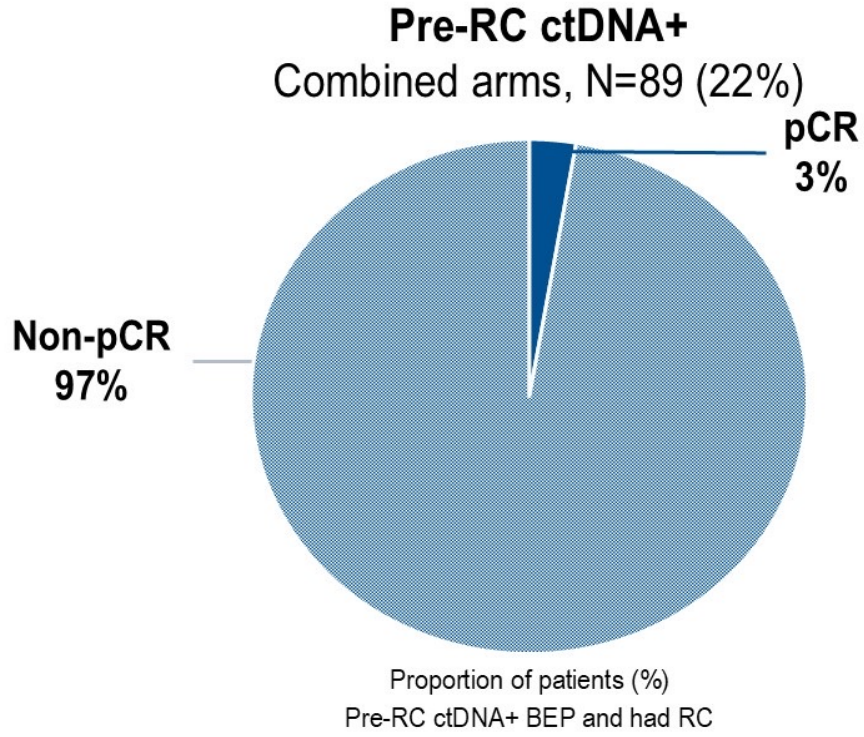


ctDNA clearance vs persistent ctDNA+ **HR, 0.32** (95% CI, 0.22–0.47)

- **BEP with baseline ctDNA+ and evaluable sample pre-RC = 237 patients**

NIAGARA Pre-Cystectomy: Relationship Between ctDNA Detection and Pathological Complete Response



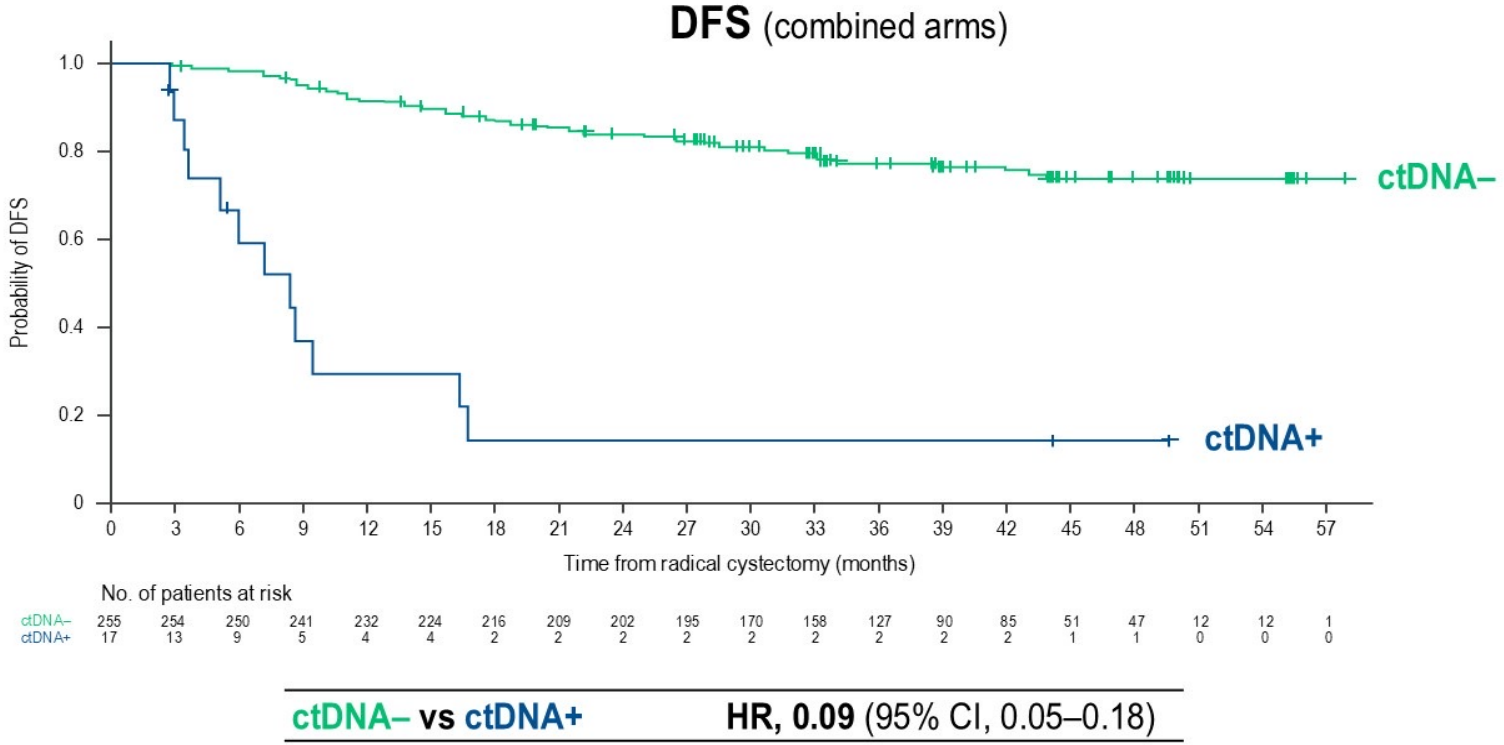


ctDNA– status was not associated with pCR

ctDNA+ status was highly correlated with non-pCR

- **BEP pre-cystectomy ctDNA+ = 22%**

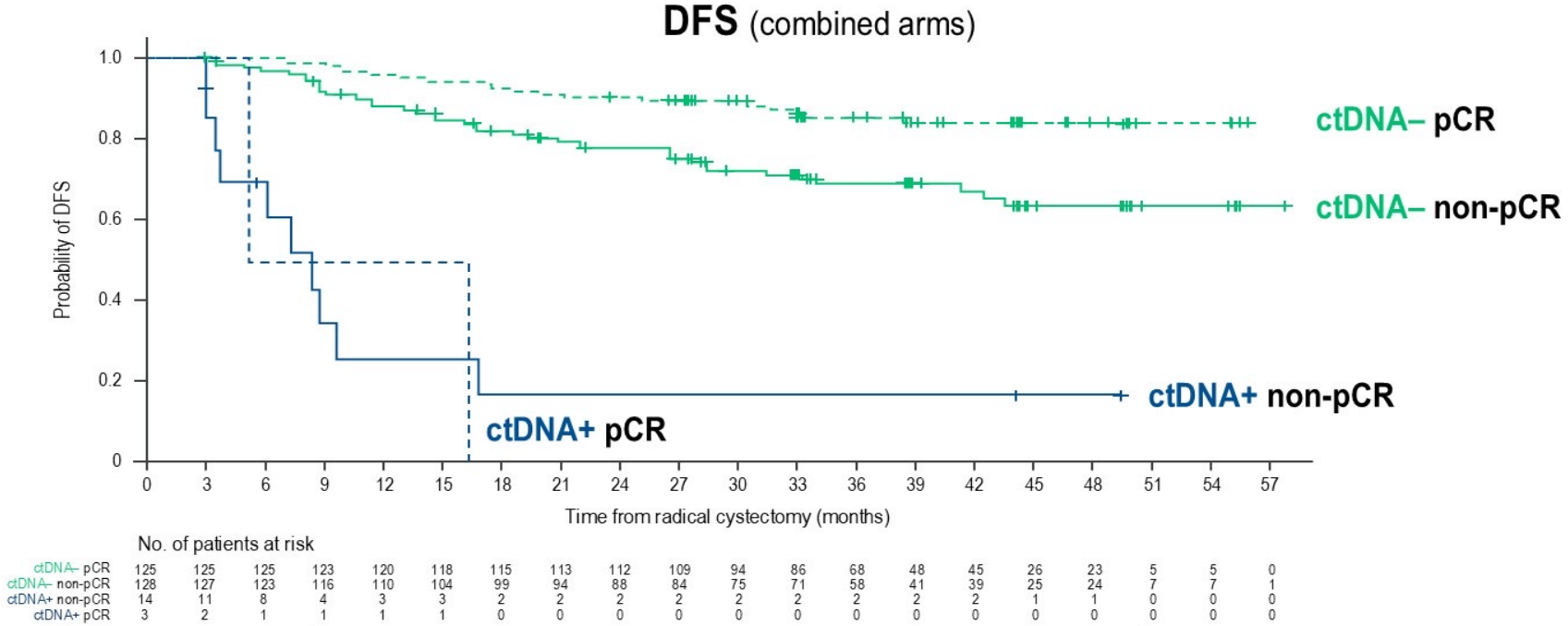
NIAGARA Post-Cystectomy: ctDNA Detection Was Prognostic for DFS



- **BEP post-cystectomy ctDNA+ = 9%**

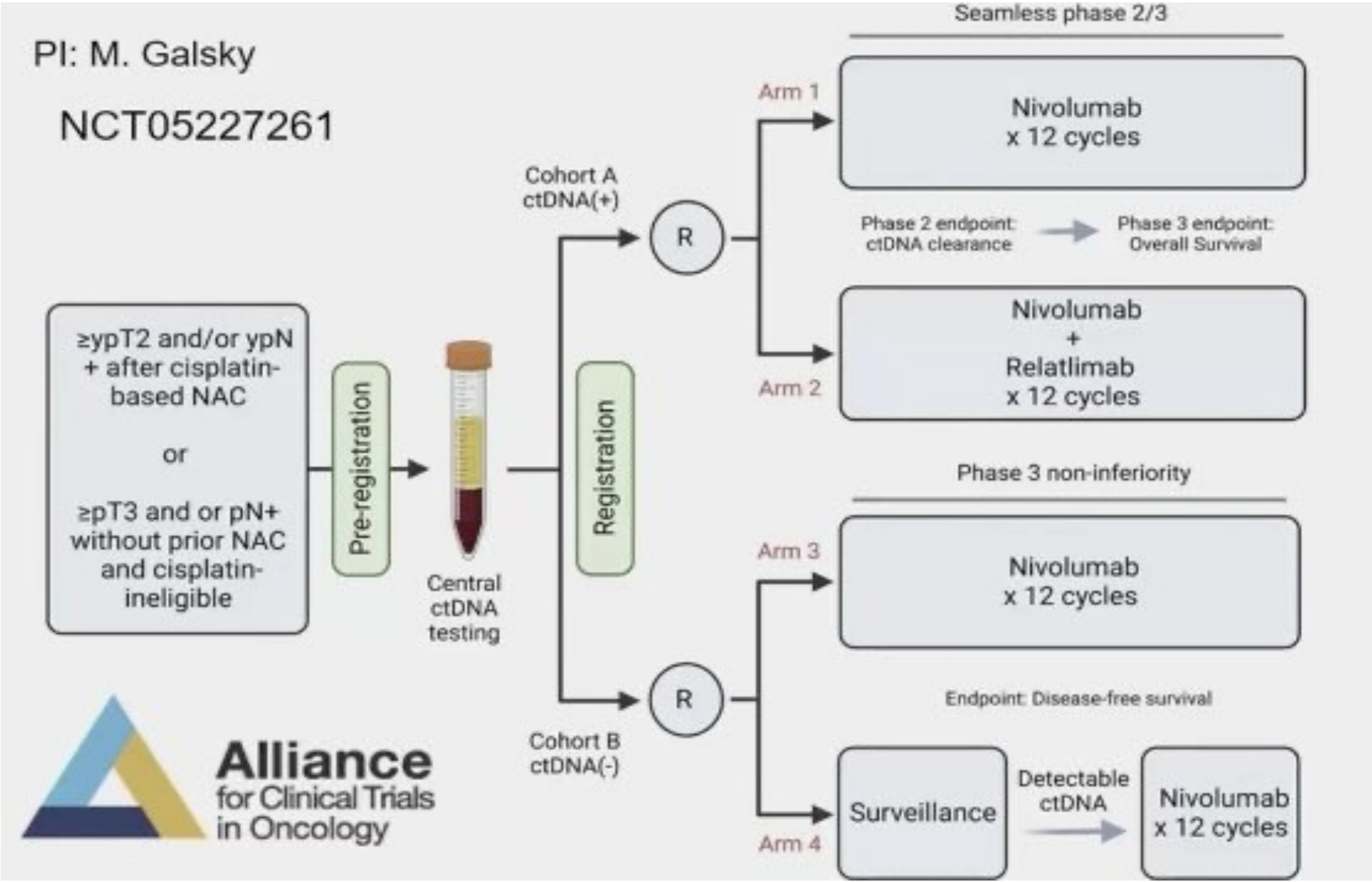
NIAGARA Post-Cystectomy: DFS by ctDNA Detection and pCR

In the ctDNA– population, patients with pCR had better DFS prognosis



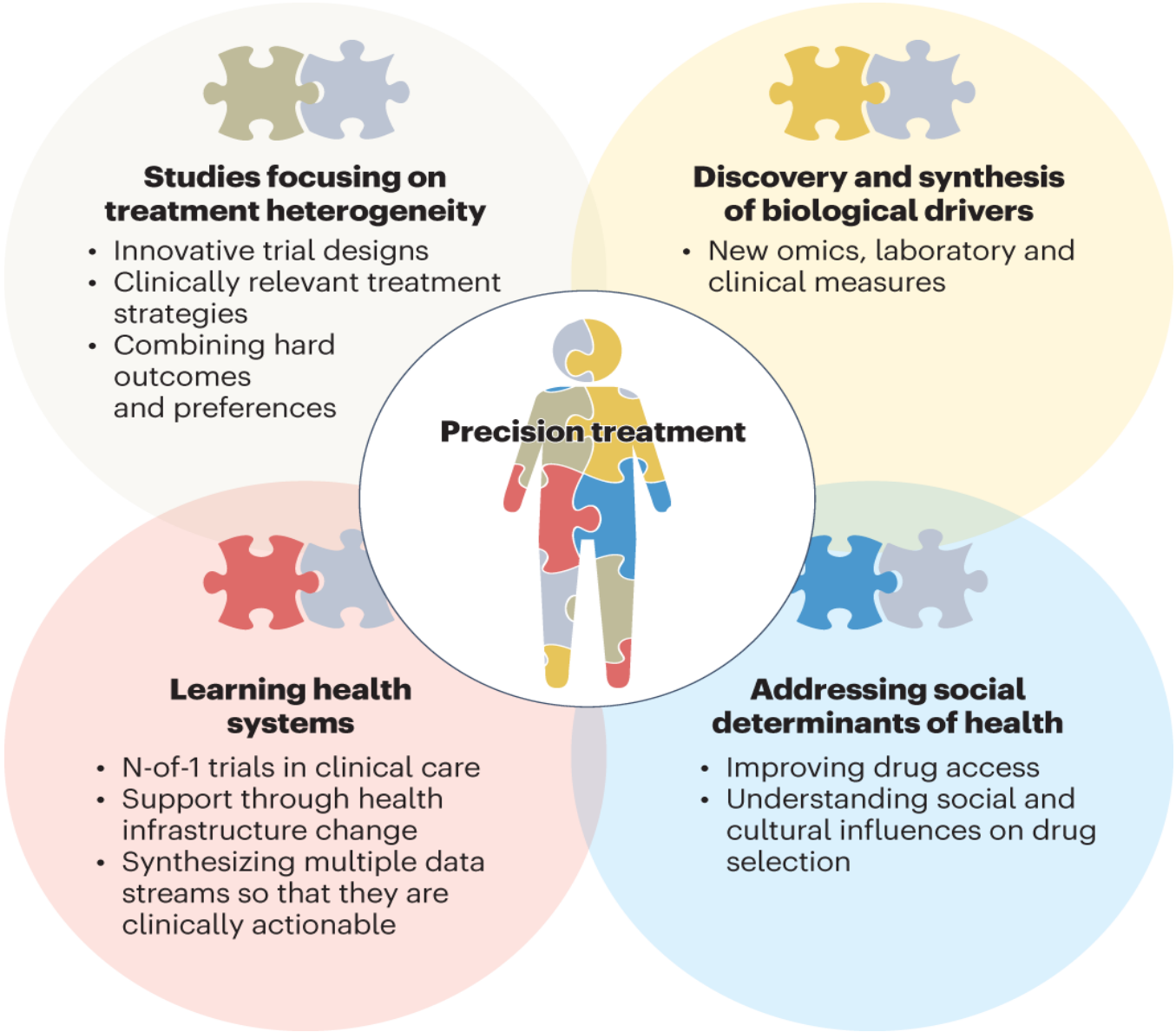
ctDNA–: pCR vs non-pCR	**HR, 0.41** (95% CI, 0.23–0.72)
ctDNA+: pCR vs non-pCR	HR not calculated[a]

MODERN TRIAL-Led by ALLIANCE group

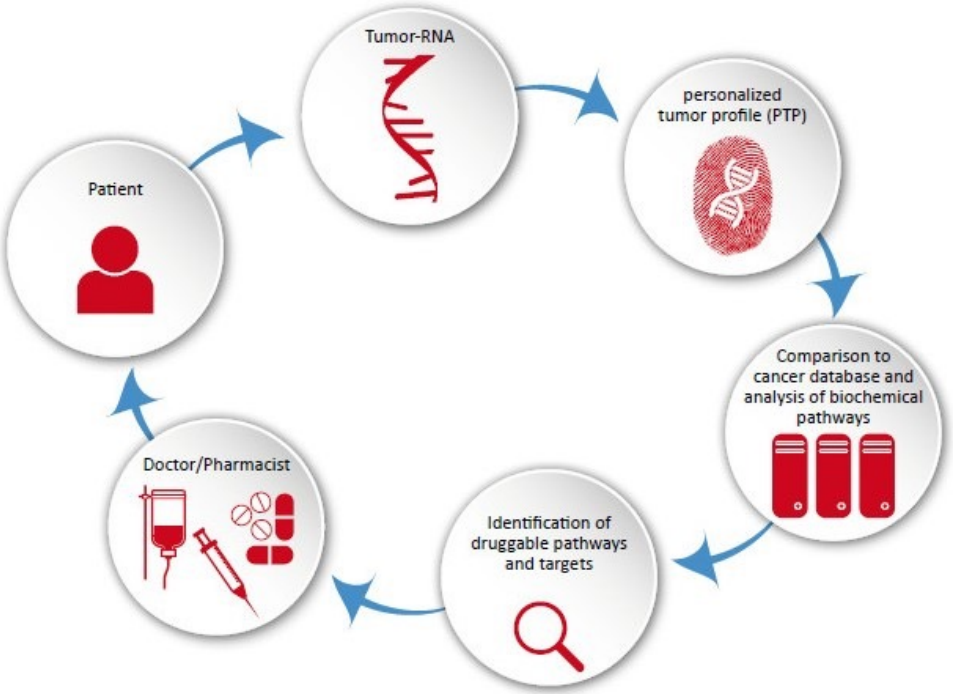


Conclusions and Impact

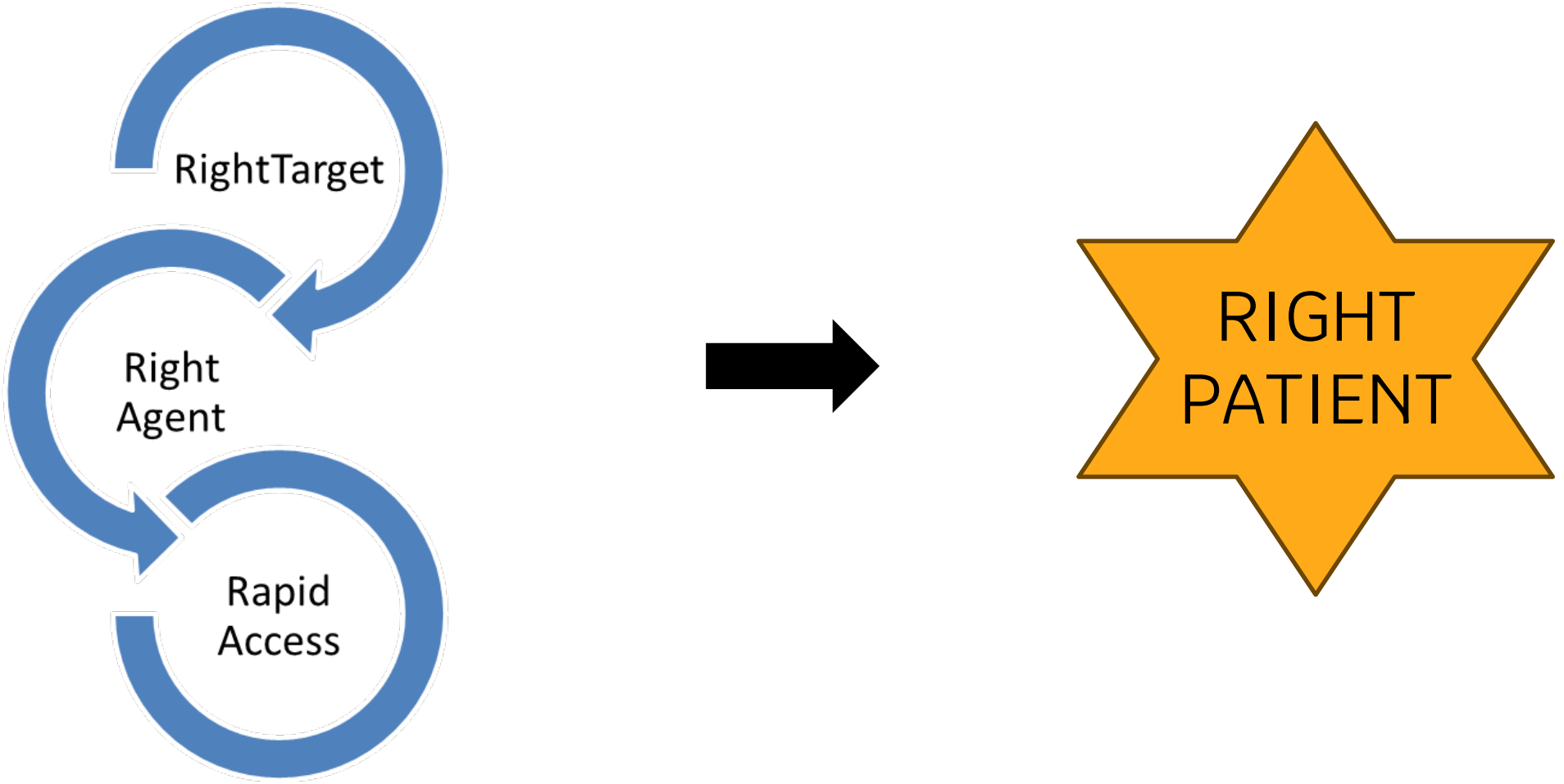
- Sifting the Evidence: separating the important ones ; corn from the husk
- Enables enriched trials that are far more successful
- N of 1 trials is where the future lies
- Individual therapy plans with AI applications are the future!



Detecting +Matching = Precision Medicine



3 Rs of Precision Medicine



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TRIALS IN PROGRESS IN EARLY-STAGE THERAPEUTICS

Elisabeth Heath, MD
Chair, Department of Oncology
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August 23, 2025

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Therapies Targeting CLDN6

- Tight junction protein claudin 6 (CLDN6) plays a role in regulation of epithelial and endothelial cell proliferation and differentiation
- CLDN6 is one of 27 CLDN family proteins with 4 transmembrane domains
- CLDN6 binds with signal proteins and activates cell adhesion signals and regulate activity of nuclear receptors
- CLDN6 is overexpressed in multiple cancers including testicular cancer (non-seminoma) while being absent in normal adult tissues

Adra N et al. Invest new Drugs 2022; 10.1007/s10637-022-01276-w.

ASP1650

- Chimeric-mouse/human-IgG1 antibody directed against CLDN6
- Phase II trial of ASP1650 in patients with relapsed/refractory GCT
- In 19 patients, 17 were non-seminoma
- No DLTs reported
- RP2D of 1500 mg/m2 every 2 weeks
- Results show lack of efficacy with no particular or complete response observed
- 71.6% mean percent membrane staining for CLDN6

Adra N et al. Invest new Drugs 2022; 10.1007/s10637-022-01276-w.

Novel CLDN6-Targeted Agents in Early Phase Studies

THERAPY	TYPE	DISEASE TYPE	CLINICAL TRIALS #
DS-9606 (Daiichi Sankyo)	CLDN6-directed ADC with modified pyrrolobenzodiazepine (PBD) payload	Testicular cancer	NCT05394675
TORL-1-23 (TORL Biotherapeutics)	CLDN6-directed ADC with MMAE payload	Testicular cancer	NCT05103683
BNT211 (BioNTech)	CAR-T in combination with CAR vaccine	Testicular cancer	NCT04503278
BNT142 (BioNTech)	MRNA encoded, bispecific antibody targeting CLDN6 and CD3	Testicular cancer	NCT5262530)

DS-9606

- Humanized anti-CLDN6 ADC with payload of a modified PBD
- Phase I of DS-9606 in patients with metastatic solid tumors with CLDN6 expression
- In 53 patients, 36% ovarian cancer, 21% germ cell tumors, and others
- No DLTs reported
- MTD 0.15 mg/kg dose IV q 3 weeks
- Among 7 with germ cell tumors, 2 had PRs, remained on treatment for more than 6 months, and most had reduction of tumor markers
- Overall confirmed ORR 15%

Patel MR et al. Ann Oncol. 2024;35(suppl 2):S488-S489. doi:10.1016/j.annonc.2024.08.677.

TORL-1-23

- Humanized anti-CLDN6 ADC with payload of MMAE
- Phase I of TORL-1-23 in patients with metastatic solid tumors with CLDN6 expression
- In 30 patients, 14 ovarian cancer, 1 testicular cancer, and others
- No DLTs reported
- Dose expansion 2.4 mg/kg dose IV q 3 weeks
- Ovarian cancer patients had ORR of 50%
- Overall confirmed ORR 33%
- Phase II trial in ovarian cancer underway, unknown testicular cancer results

Konecny GE et al. Ann Oncol. 2024;35(suppl 2):S551. doi:10.1016/j.annonc.2024.08.783.

BNT112

- Autologous CAR-T cell therapy targeting CLDN6 in combination with CAR vaccine
- Phase I of BNT112 in patients with metastatic solid tumors with CLDN6 expression (at least 50% by IHC)
- In 74 patients, 25 testicular cancer patients
- Overall ORR 24%
- Patients who received CAR-T and CAR vaccine had ORR 58%
- Toxicity: Grade 3 or higher in 66.7%
- Planned Phase II trial in testicular cancer withdrawn

Konecny GE et al. Ann Oncol. 2024;35(suppl 2):S551. doi:10.1016/j.annonc.2024.08.783.

BNT142

- Novel lipid nanoparticle (LNP)-encapsulated mRNA encoding the anti-CLDN6/CD3 bispecific antibody RoboMab02.1 (mRNA-encoded T-cell engager)
- Intravenous administration leads to BNT142 RNA-LNPs to be taken up by liver cells and translated into RiboMab02.1
- Phase I/II reported by Yap et al. For weekly BNT142-01
- 65 patients enrolled (10 testicular, 44 ovarian, 5 NSCLC)
- 23% of grade 3 adverse events including cytokine release syndrome, elevation of AST/ALT, and fever
- Confirmed disappointing overall response rate of 5%

Yap T et al. 10.1200/JCO.2025.43.16_suppl.2501.

Ongoing CLDN6-Targeted Agents in Early Phase Studies

THERAPY	TYPE	DISEASE TYPE	CLINICAL TRIALS #
CTIM-76 (Context Therapeutics)	Humanized T cell engaging bispecific antibody targeting CLDN6	Testicular cancer	NCT06515613
SAIL66 (Chugai Pharmaceutical)	Trispecific T-cell engager (TCE) targeting CLDN-6, CD3 and CD137	Testicular cancer	NCT05735366
QLS5132 (Qilu Pharmaceutical)	Antibody Drug Conjugate targeted to CLDN6 with topoisomerase I inhibitor payload	Testicular cancer	NCT06932094
XmAb541 (Xencor)	Bispecific T-cell engager targeting CLDN6 and CD3	Testicular cancer	NCT06276491

Therapies Targeting DLL3

- DLL3 is an inhibitory Notch ligand upregulated in small cell lung cancer and other neuroendocrine neoplasms

Table 1 | Tumor specimens evaluated with DLL3 immunohistochemistry

Organ site	Tumor type	Total cases (n)	Positive >= +1 n (%)	Total H-score median (range)	Membrane H-score median (range)
Lung					
	SCLC	17	16 (94%)	95 (0–175)	20(0–70)
	LCNEC	20	16 (80%)	100 (0–180)	20(0–115)
	Mixed histology	8	5 (63%)	90 (0–175)	35 (0–75)
Uterine cervix					
	SCNEC	10	9 (90%)	137.5 (0-190)	25 (0–42)
	LCNEC	4	4 (100%)	58.5 (0–115)	11.5 (0–65)
	Combined	7	5 (71%)	25 (0-185)	6 (0–90)
Bladder					
	SCC	19	14 (74%)	70 (0-210)	0 (0–80)
Skin					
	Merkel cell carcinoma	33	32 (97%)	140 (0-190)	26(0–70)
Thyroid					
	Medullary thyroid carcinoma	74	20 (27%)	0 (0–235)	0 (0–90)
Head and Neck					
	NEC	19	12 (63%)	9 (0-230)	4(0–52)
Prostate					
	AVPC-NEC	16	12 (75%)	115 (0–250)	1.5 (0–160)
	AVPC-non-NEC	10	0 (0%)	0	0

Serrano AG et al. npj Precision Oncology | (2024) 8:268.

Neuroendocrine Carcinomas of the Prostate

THERAPY	TYPE	DISEASE TYPE	CLINICAL TRIALS #
177Lu-DTPA-SC16.56 (MSKCC)	Antibody targeting DLL3 delivering targeted beta radiation	Neuroendocrine Prostate Cancer	NCT06941480
MRT-2359 (Monte Rosa Therapeutics)	Oral, first in class molecular glue degrader targeting GSPT1	Neuroendocrine Prostate Cancer	NCT05546268
HPN328 (Harpoon Therapeutics)	Trispecific T-cell engager targeting DLL3 and CD3 with albumin binding domain to extend half life and Given with atezolizumab or Ifinatamab Deruxtecan (ADC targeting B7-H3)	Neuroendocrine Prostate Cancer	NCT04471727

Therapies Targeting CD70

- CD70 is a type II transmembrane protein in the tumor necrosis factor (TNF) superfamily, expressed in activated lymphocytes, including B cell, T cells, NK cells, and mature dendritic cells
- CD70 overexpressed in clear cell and sarcomatoid renal cell carcinoma (lower in papillary subtype)
- CD70 expression is increased in metastatic lesions compared to primary clear cell renal cell carcinoma

Huang RR et al. Clinic Genitourinary Cancer; April 2024, Pages 347-353.

Emerging Targets in Renal Cell Carcinoma

THERAPY	TYPE	DISEASE TYPE	CLINICAL TRIALS #
ADI-270 (Adicet Therapeutics)	Engineered gamma-delta Chimeric Receptor [CAR] Vδ1 T Cell product Targeting CD70	Renal Cell Carcinoma	NCT06480565
CD70-Binding Chimeric Antigen Receptor	Peripheral blood lymphocytes transduced with a CD70-binding chimeric antigen receptor to people with CD70 expressing cancers	Renal Cell Carcinoma	NCT02830724
CTX131 (CRISPR Therapeutics AG)	Allogeneic CD70- directed CAR-T cell immunotherapy comprised of allogeneic T cells that are genetically modified ex vivo using CRISPR-Cas9 gene editing components	Renal Cell Carcinoma	NCT05795595

Therapies Targeting PPAR

- PPARg is a transcription factor driving the luminal differentiation and growth of muscle invasive bladder cancer
- Phase I trial of FX-909 evaluating bladder cancer and other cancers such as colon, pancreatic and lung cancer
- First in class transcription factor targeting agent

Iyer G et al. 2024 ASCO GU Conference, TPS709.

Summary

- **Testicular Cancer**
  → *Consider enrollment in CLDN6-targeted trials*
  - **CLDN6** is a cancer-testis antigen absent in normal tissues and overexpressed in germ cell tumors
  - Multiple platforms in development: **CAR-T cells**, **bispecific antibodies**, **RNA vaccines**
- **Neuroendocrine Prostate Cancer**
  → *Consider DLL3-targeted immunotherapy trials*
  - **DLL3** is selectively expressed in small cell/neuroendocrine tumors
  - Therapeutic agents in development include **T-cell engagers** and **ADC platforms**
- **Renal Cell Carcinoma**
  → *Consider CD70-targeted clinical trials*
  - **CD70** is highly expressed in clear cell RCC and certain lymphomas
  - Emerging therapies: **CAR-T cells**, **ADC**, and **T-cell engagers** in early-phase studies
- **Urothelial Cancer**
  → *Consider PPARγ-targeted therapies for luminal subtypes*
  - **PPARγ** is a transcription factor driving luminal UC; **FX-909** is a first-in-class inverse agonist
  - Phase 1 trials enrolling biomarker-selected patients (e.g., **PPARG)**

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FIT FOR TREATMENT? ASSESSING PHYSIOLOGIC RESERVE IN GU CANCER MANAGEMENT

Stephanie A. Berg, DO

Dana-Farber Cancer Institute, Lank Center for GU Oncology

August 23, 2025

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Presentation Outline

- Define frailty and physiologic reserve in GU oncology
- Review validated assessment tools and implications for treatment
- Explore integration into clinical decision-making and trial design

Background and Rationale

- **Frailty**: a *multidimensional syndrome* characterized by *diminished physiologic reserve and decreased resiliency*, resulting in *increased vulnerability* to stressors such as cancer and its treatments.

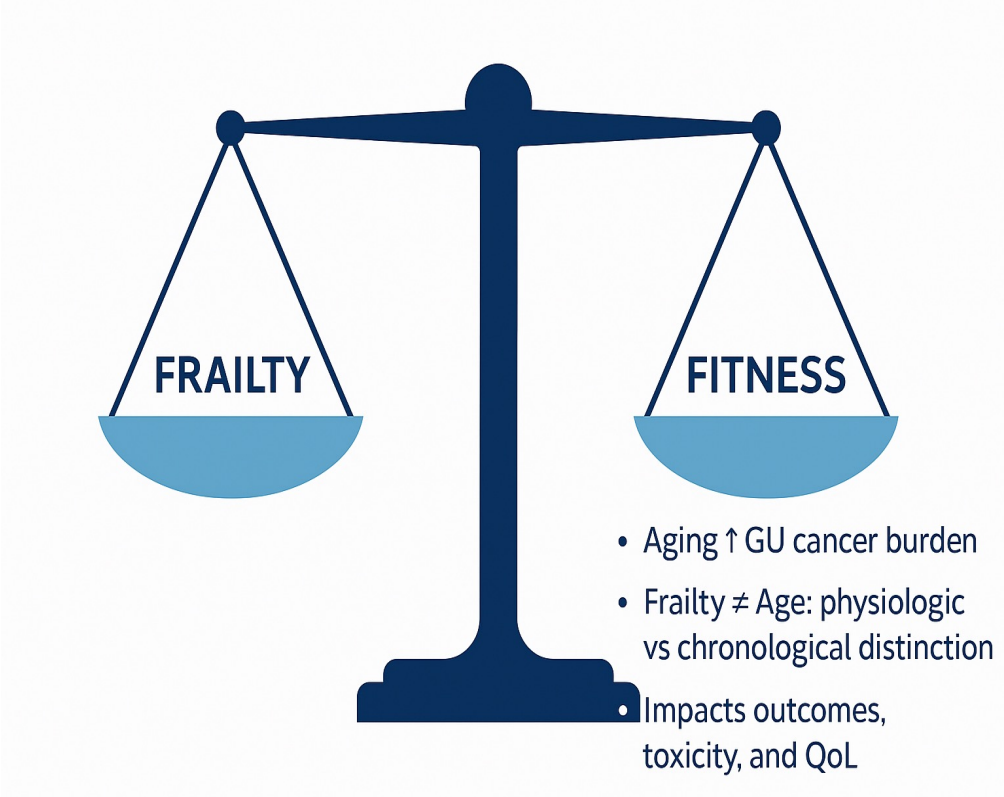
- In oncology, frailty is identified using either the frailty phenotype (e.g., **Fried criteria**: unintentional weight loss, exhaustion, low physical activity, slowness, and weakness) or the cumulative deficit model (e.g., Rockwood frailty index), which tallies accumulated deficits across multiple domains

Background and Rationale

- **Frailty**: distinct from chronological age and is independently associated with increased risk of chemotherapy intolerance, postoperative complications, functional decline, and mortality in older adults with cancer

Background and Rationale

- **64% of bladder**, **70% of prostate**, and **58% of kidney cancers** occur in patients ≥ 65 years[1]
- Chronological age underestimates vulnerability: **up to 30% of older GU patients are "frail"** by screening tools, despite ECOG 0-1 PS[2]
- Frailty linked to 2-3× higher postoperative complications and GU surgery 1.8-fold increased mortality[3]



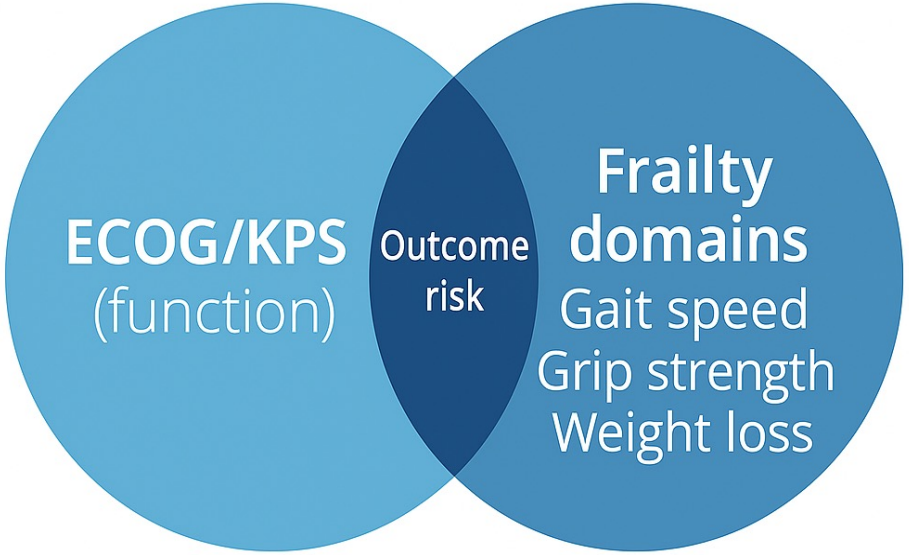
1) SEER: Cancer stat facts: Bladder, prostate, kidney. https://seer.cancer.gov/statfacts. Accessed July 2025
2) Ann Oncol. 2014;25(9):1770–1775
3) Ann Surg Oncol. 2022;29(7):4690–470

Frailty Across GU Tumor Types

- **Bladder Cancer**: Radical cystectomy ± NAC → frailty predictive of complications
- **Prostate Cancer**: ADT, radical prostatectomy → assess sarcopenia and cognitive status
- **Renal Cell Carcinoma**: Role in cytoreduction and systemic therapy choices (immune checkpoint inhibitors, VEGFR-TKI)

Frailty ≠ ECOG: What Are We Really Measuring?

- ECOG 0–1 or KPS >70% = covers ~80% of candidates but misses 30% with diminished reserve
- Frailty domains (Fried phenotype) are multidimensional and capture:
  - Physical Gait speed < 0.8 m/s (AUC 0.92 for frailty)
  - Physical Grip strength < 20 kg women, < 30 kg men
  - Nutritional/Unintentional weight loss ≥ 5% in 6 months



Both predict survival, but frailty adds vulnerability to toxicity

Quick, Validated, Actionable: Frailty Tools at the Bedside

Tool	Domains Covered	Time to Administer	Clinical Utility
G8	Nutrition, mobility, cognition	5–7 minutes	Quick screening pre-operative (cystectomy, prostatectomy, nephrectomy)
CARG	Chemotherapy toxicity risk	10–15 minutes	Personalizing chemo plans for bladder & prostate; ? Renal (TKI/IO)
Fried	Physical frailty criteria (5 items)	~10 minutes	Ideal for prehabilitation enrollment
eFI/CGA	Comprehensive geriatric domains (8 items)	30–60+ minutes	In-depth profiling for trial stratification and complex cases

What the Data Says: Frailty Predicts More Than We Think

Metric	Fit Performance	Frail Performance	Effect Measure
Median Overall Survival[1]	60 months	**24 months**	HR 2.4; p < 0.001
2-year Event-Free Survival	70%	40%	—
Grade ≥ 3 Toxicity[2]	50%	**65%**	OR 1.8 (95% CI 1.2–2.7)
Pathologic CR (post-NAC) prehab[3]	28%	**38%**	+10% absolute improvement
Median Hospital Stay post-RC (prehab)[4]	—	—	-1.5 days (p = 0.03)

1) J Urol. 2020;204(4):786–794
2) J Clin Oncol. 2004;22(24):4320–4326
3) J Urol. 2017;197(1):130–136
4) J Surg Oncol. 2018;118(2):287–295

Toward Frailty-Informed Research

Wearable Type	Metrics	Body Location	Trial/Study Example
IMUs & Accelerometers	Gait speed, stride/stance time	Thighs, shins, feet, trunk	Instrumented gait analysis in 133 older adults (1)
Consumer Activity Trackers	Steps, PA time/intensity, sedentary	Wrist (ActiGraph, Fitbit)	Systematic review of 29 studies (2)
Smartbands & Smart Garments	HR, RR, BP, temp, posture, sleep	Wrist, torso (textile-embedded)	NCT05173870 pilot monitoring pre-frailty (3)
Actigraphy Devices	Circadian amplitude, stability	Wrist	BWH cohort, rest-activity rhythms predicting frailty (4)

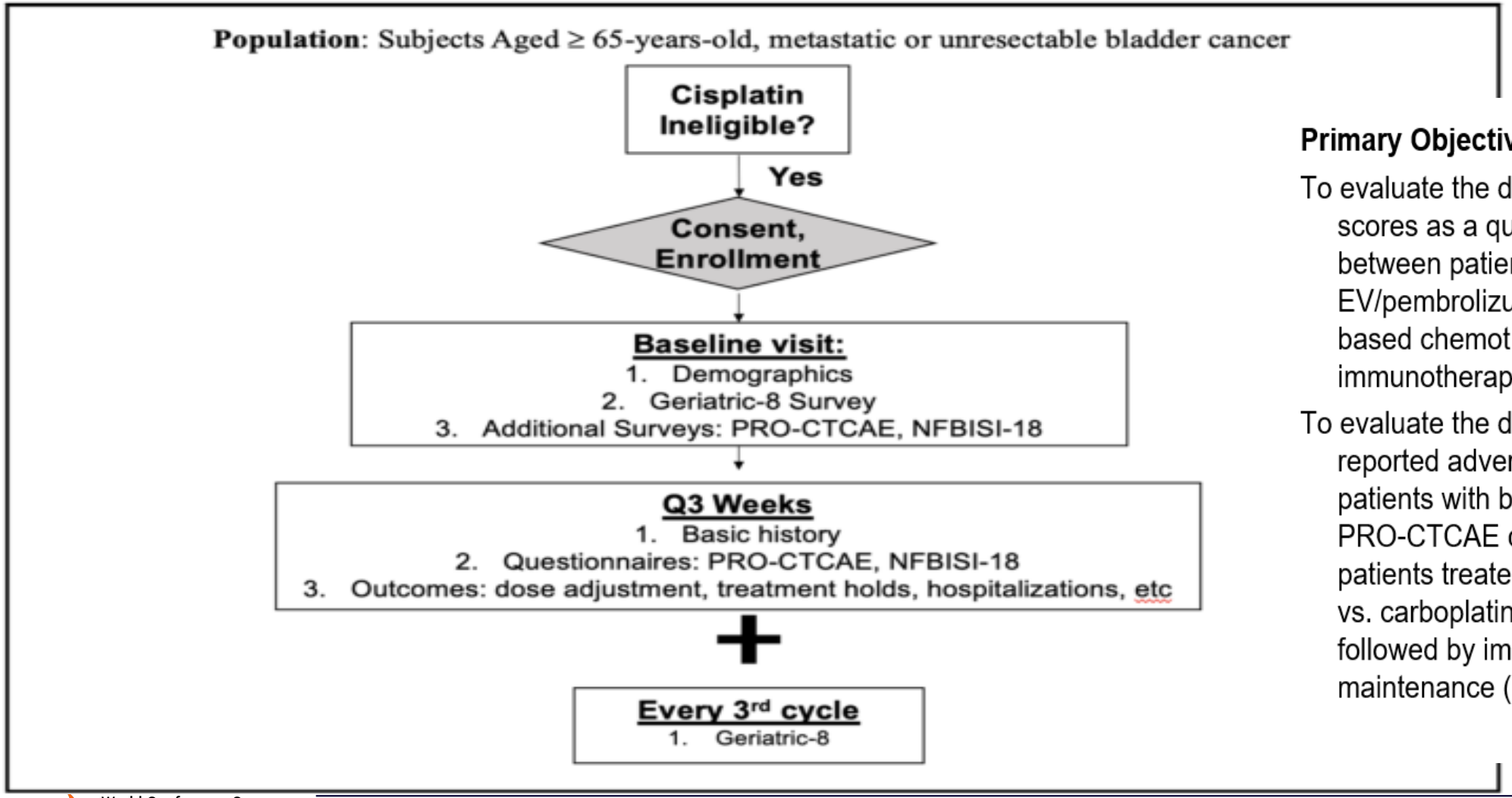
1) *Applied Sciences*. 2020; 10(23):8451
2) *J NeuroEngineering Rehabil* **18**, 112 (2021)
3) https://ichgcp.net/clinical-trials-registry/NCT05173870
4) *Nat Commun* **14**, 7219 (2023

Integrating FIT into Clinical Workflow

1. **Treatment tailoring**: Omitting NAC in frail cystectomy candidates reduced 30-day mortality from 8%→4%
2. **Prehabilitation** (RC): 4-week exercise/nutrition program improved 6-min walk distance by +42 m ($p < 0.01$)
3. **Resource allocation**: Frail patients triaged to ICU beds post-op showed 25% fewer unexpected transfers
4. **Shared decision-making**: Structured frailty report (CGA-based) increased patient satisfaction scores by 15%

1) Cancer. 2008 Jun 1;112(11):2637–43.
2) J Urol. 2017;197(1):130–136.
3) Ann Surg Oncol. 2019;26(12):3941–3950
4) J Geriatr Oncol. 2019;10(4):499–505

Embedding Frailty into Trial Design



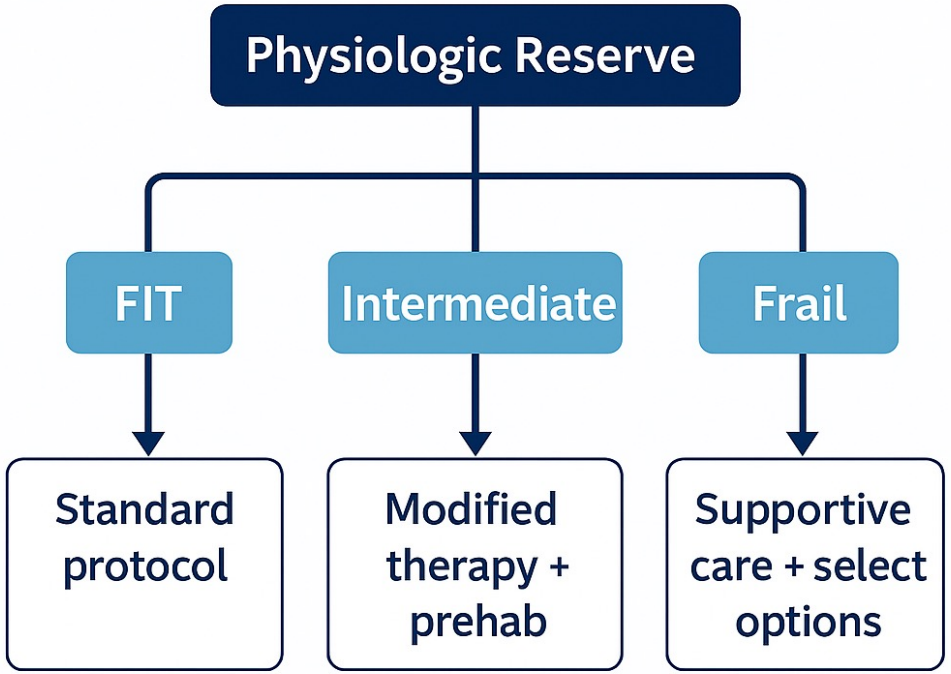
Primary Objectives:

To evaluate the difference in NFBISI-18 scores as a quality-of-life measurement between patients treated with EV/pembrolizumab vs. carboplatin-based chemotherapy followed by immunotherapy maintenance (SM).

To evaluate the difference in patient reported adverse events relevant to patients with bladder cancer (via the NCI PRO-CTCAE questionnaire) between patients treated with EV-pembrolizumab vs. carboplatin-based chemotherapy followed by immunotherapy maintenance (SM).

From Screening to Strategy: FIT in Action

✅ Screen all GU patients ≥ 65 years
✅Use a rapid tool (G8/CARG) for initial triage
✅ Offer prehabilitation to intermediate–frail
✅ Engage geriatrics early for frail
✅ Collaborate across disciplines

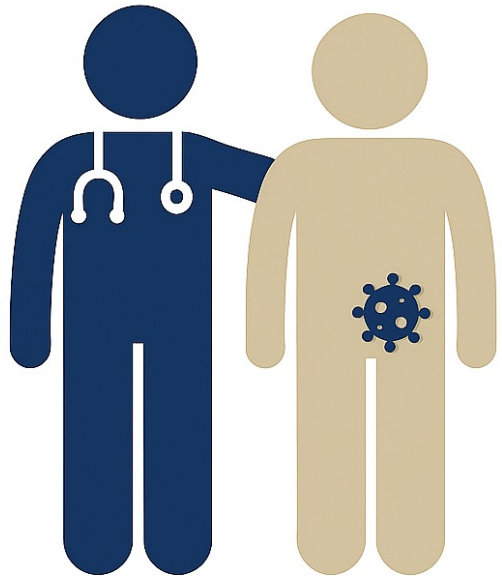


Nutrition/ Weight Loss	Single item from the G8 and MNA	Weight loss during the past 3 months? 0= weight loss greater than 3 kg (6.6 lbs) 1= does not know 2= weight loss between 1 and 3 kg (2.2 and 6.6 lbs) 3= no weight loss (range 0-3)	Score of 0	• Discuss concerns related to nutrition and how treatments impact nutrition • Consider information for **nutritional supplements**, liberalize calorie-restricted diets; small frequent meals, high protein/ calorie snacks. • **Consider referrals:** 1) nutritionist, 2) dentist if poor dentition or denture issues: 3) speech therapy if difficulty with swallowing; 4) meals-on-wheels. • Use caution with emetogenic regimen, aggressive anti-emetic use. Refer to physical/occupational therapy for functional impairments affecting food intake; Consider medications to stimulate for loss of appetite
Social Support	Medical Outcomes Survey (MOS) Social support 8 item Question #17	Instrumental items 1-4 Emotional items 5-8	Any instrumental item with none, a little, or some of the time Any emotional item with none, a little, or some of the time	• Discuss adequacy and availability of social support at home • Discuss who the patient can contact in case of an emergency • Confirm documented health care proxy is in the medical record • Consider referral or information on: 1) social worker 2) visiting nurse service or 3) home health aide • Order lifeline emergency service.

Cognitive Function	Mini-cog	1 point for each word recall 2 points for clock draw if normal, 0 if abnormal Total of 5 points (range 0-5.	Score: 0-2 high likelihood of cognitive impairment	• Provide explicit **written instructions** for appointments and treatments • Elicit input from confidant on cognition; Assess decision-making capacity; Elicit health care proxy info; Cognitive specialist (neurologist/ geriatrician) referral; OT referral for cognitive rehabilitation; consider neuropsychological testing
Geriatric Assessment Screening Tool*	Geriatric-8 (G-8)	8-items (age food intake, weight loss, mobility, BMI, neuropsych issue, prescription drugs, health self-assessed)	Score: 0-14 recommend completing a full geriatric assessment evaluation	• Administer the PGA or another GA and implement the recommendations based on the results (see above)
Risk of Chemotherapy Toxicity**	CARG Toxicity Tool: www.mycarg.org Go to the "Chemo-Toxicity Calculator" under CARG TOOLS	11-items (sociodemographics, tumor/treatment variables, laboratory test results [hemoglobin, creatinine clearance], and geriatric assessment variables)	Score: 0-5 Low Risk 6-9 Intermediate Risk 10-23 High Risk	• For Intermediate/High Risk patients, consider administering the full PGA and implement the recommendations noted above based on the results • Consider the following cancer treatment modifications, particularly for intermediate/ high risk patients and considering non-curative treatment settings: 1) consider single agent rather than doublet therapy; 2) modify dosage (e.g., 20% dose reduction with possible escalation); 3) modify treatment schedule. • Consider more frequent toxicity checks (weekly or every other week)

Key Takeaways

- Frailty screening ≠ delay — it informs **precision**
- Physiologic reserve drives toxicity, recovery, and survival
- Frailty tools complement PS
- Prehabilitation is a proven modifier of risk
- Future trials must embed frailty metrics prospectively



Treat the patient, not just the tumor

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PALLIATIVE CARE AND DECISION-MAKING FOR GU MALIGNANCIES

Elizabeth Wulff, MD, Associate Professor of Medical Oncology and Palliative Medicine, University of Kansas Medical Center

August 23, 2025

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Palliative Care

CAPC Definition:

> ". . . Specialized health care for people living with a serious illness. This type of care is focused on providing relief from symptoms and stress of a serious illness. The goal is to improve quality of life for both the patient and the family."

Other features:

- Interdisciplinary team: physicians, nurses, social workers, chaplains
- Provided alongside conventional care, **including care with curative intent**
- Appropriate at **any age** and for **any stage** in a serious illness

Primary vs Specialty Palliative Care

Specialty palliative care

- Specialist clinicians and organizations that provide expert consultation and/or co-management.

Primary palliative care

- Core skills and competencies required of all health care professionals.

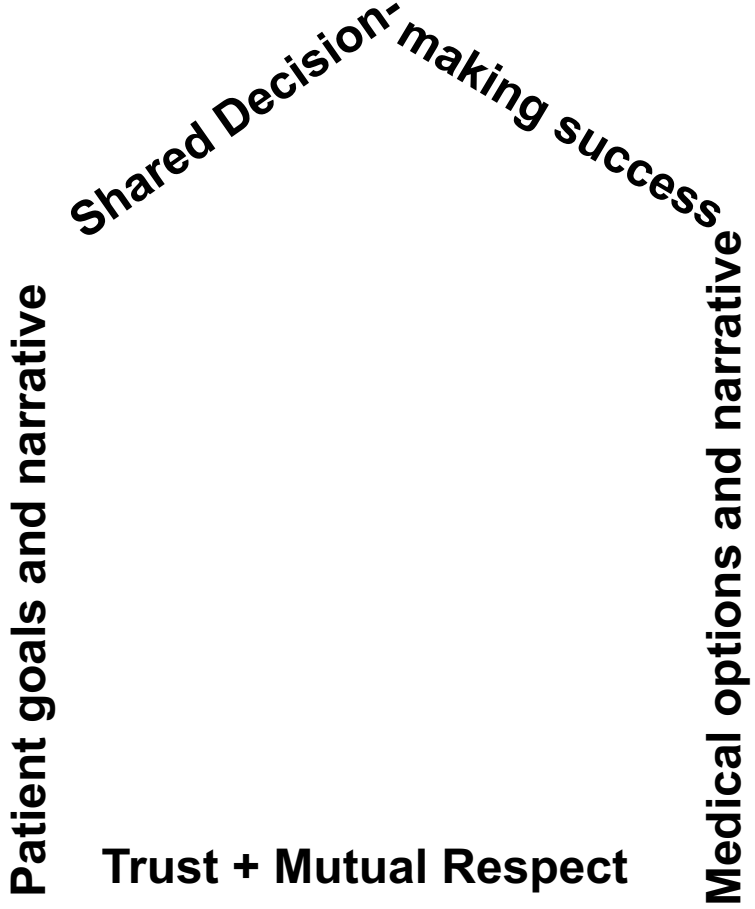
Why is Primary Palliative Care Needed?

You already know this one . . .

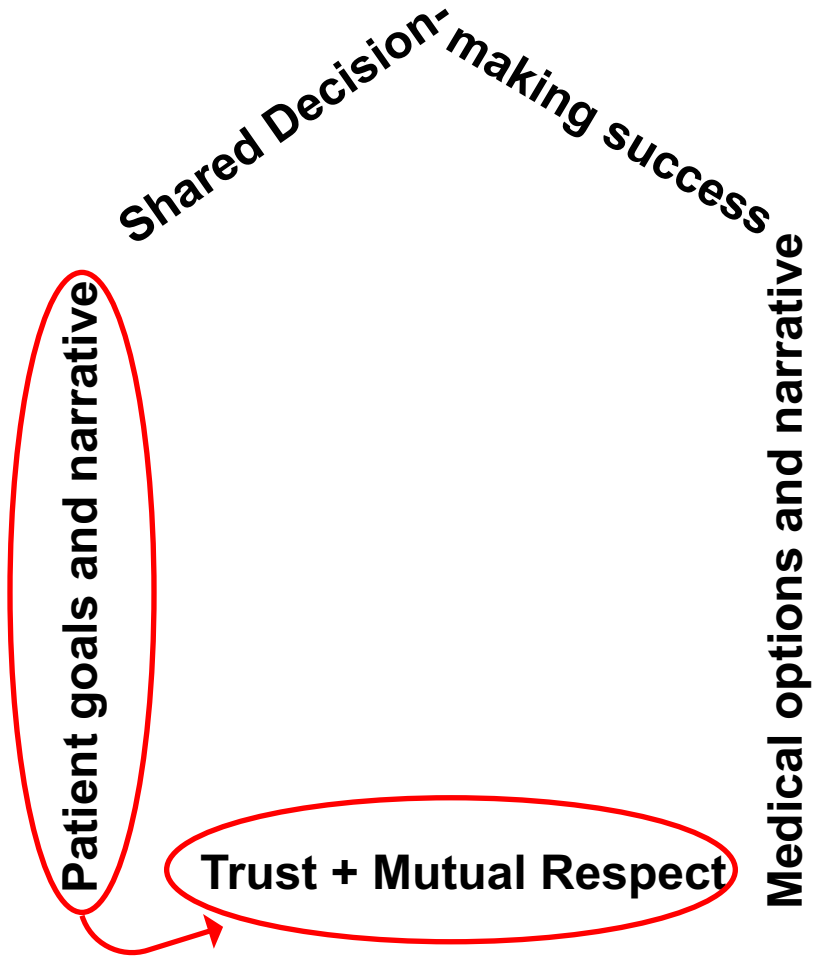
- Your patients are frail
- Your patients have comorbidities
- The stakes are high with modern cancer therapies

Data-driven primary palliative care techniques can help you navigate decision-making.

Primary Palliative Care Principles (PPCP): Goals of care



Bhang TN, Iregui JC. The House Model: An Updated Visual Framework for Goals of Care Conversations. J Palliat Med. 2019 Aug;22(8):880. doi: 10.1089/jpm.2019.0193. PMID: 31380716.



Bhang TN, Iregui JC. The House Model: An Updated Visual Framework for Goals of Care Conversations. J Palliat Med. 2019 Aug;22(8):880. doi: 10.1089/jpm.2019.0193. PMID: 31380716.

What really are goals of care (GOC)?

GOC Defined

Multidimensional description of a patient's values and how they intersect with medical care

- Decision making preferences
- Fears/goals
- Views on trade-offs
- Wishes for family involvement
- Prognostic information

Barriers

- Time
- Emotional discomfort/awkwardness
- Prognostication challenges
- Patient factors (anger, denial, anxiety)
- Satisfaction scores?

Mack JW, Cronin A, Taback N, et al. End-of-life care discussions among patients with advanced cancer: a cohort study. *Ann Intern Med*. 2012;156(3):204-210.
Mack JW, Cronin A, Keating NL, et al. Associations between end-of-life discussion characteristics and care received near death: a prospective cohort study. *J Clin Oncol*. 2012;30(35):4387-4395.

Three Key Techniques to Assess GOC

- Ask-tell-ask
- “Tell me more”
- Summarize

Ask-tell-ask

What:

Technique for assessing and delivering medical knowledge

When:

All the time!

How:

Ask the patient what they understand about something

Tell them something they need to know

Ask what this meant to them (read: what they understood)

Repeat PRN!

Clinical vignette: GOC

A patient has been referred to you to discuss intermittent Enzalutamide +/- androgen-deprivation therapy for high-risk biochemical recurrence.

Clinical vignette: ask-tell-ask

Physician: (Ask) “I know that your urologist referred you to me to talk about how your PSA is rising after your prostatectomy and then your radiation PSA. What did she tell you about what’s going on?”

Patient: “She said that you were going to talk to me about doing treatment with medicine. She said it’s something that you deal with all the time.”

Physician: (Tell) “That’s right. Your PSA is rising, but you can’t get more radiation or surgery, so hormonal therapy is a treatment option in this situation. (Ask) When you hear something like that, what goes through your mind?”

“Tell me more”

What:

A prompt to help patients or caregivers explore/explain their thoughts about something.

When:

Whenever you need a patient to explain their perspective.

If you need clarity.

How:

Step 1: Say “Tell me more.”

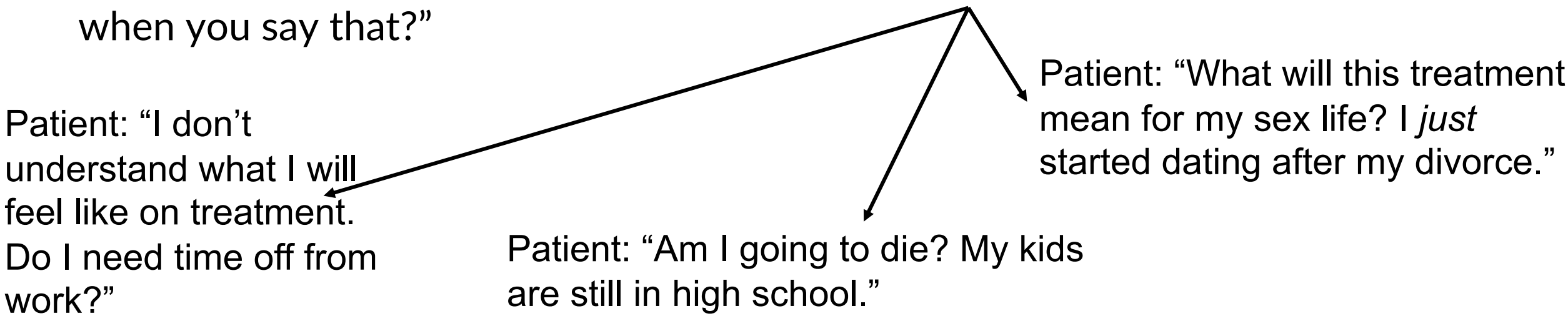
Step 2: Listen to what the patient responded and consider repeating steps 1 and 2. Done!

“Tell me more,” cont.

As a reminder, you just asked “When you hear [that hormonal therapy is a treatment in this scenario], what goes through your mind?”

Patient (distressed): “I just don’t understand what this means for me.”

You: “Thank you so much for sharing your perspective, I can tell you’re weighing a lot of factors. Could you please tell me more about what you mean when you say that?”



Summarize

What:

A way to synthesize a conversation, check your understanding about what the patient said, and reinforce to the patient that they were understood.

When:

After you've led the patient through a series of ask-tell-asks and "tell me mores."

Can be helpful if need a moment to gather your thoughts.

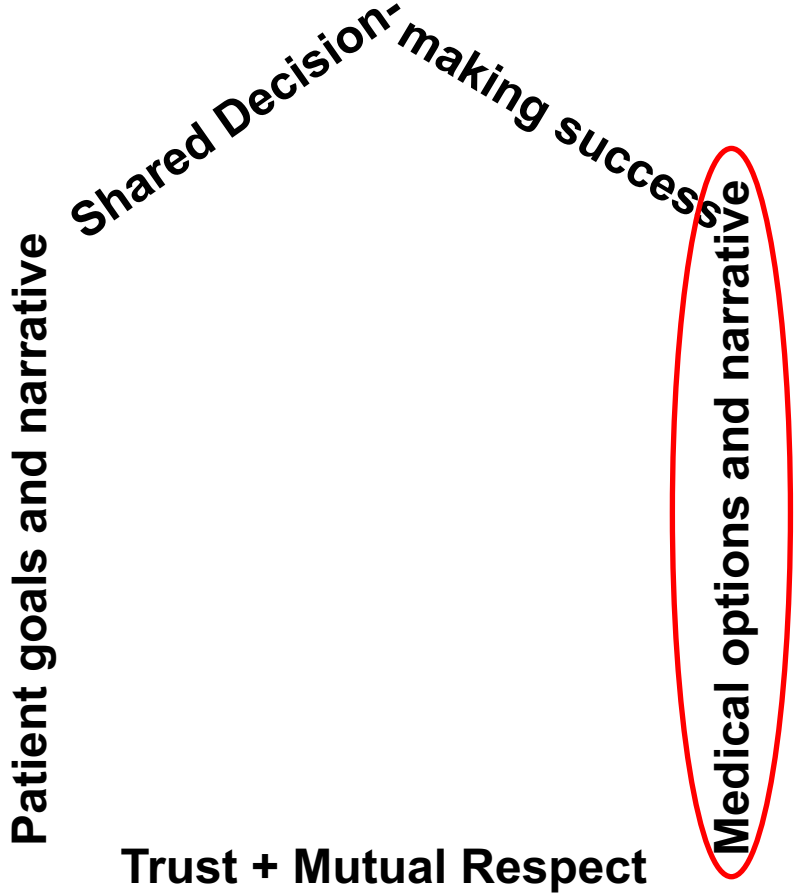
(Also helps to regain some ownership of the conversation if the conversation has taken a tangent.)

Summarize, cont.

How:

- Consider starting with a statement of respect for what the patient shared
  - NURSE model
    - **N**ame it: “It sounds like you are…”
    - **U**nderstanding: “This helps me understand…”
    - **R**especting: “I’m grateful for/impressed with/moved by what you have shared…”
    - **S**upporting: “We will continue to walk with you…
    - **E**xploring: “Can you tell me more about…”
- Give a brief synopsis
- Consider ending with a question (“Did I understand you correctly?” “Does that sound right?”)

PPCP: Cultivation of Prognostic Awareness

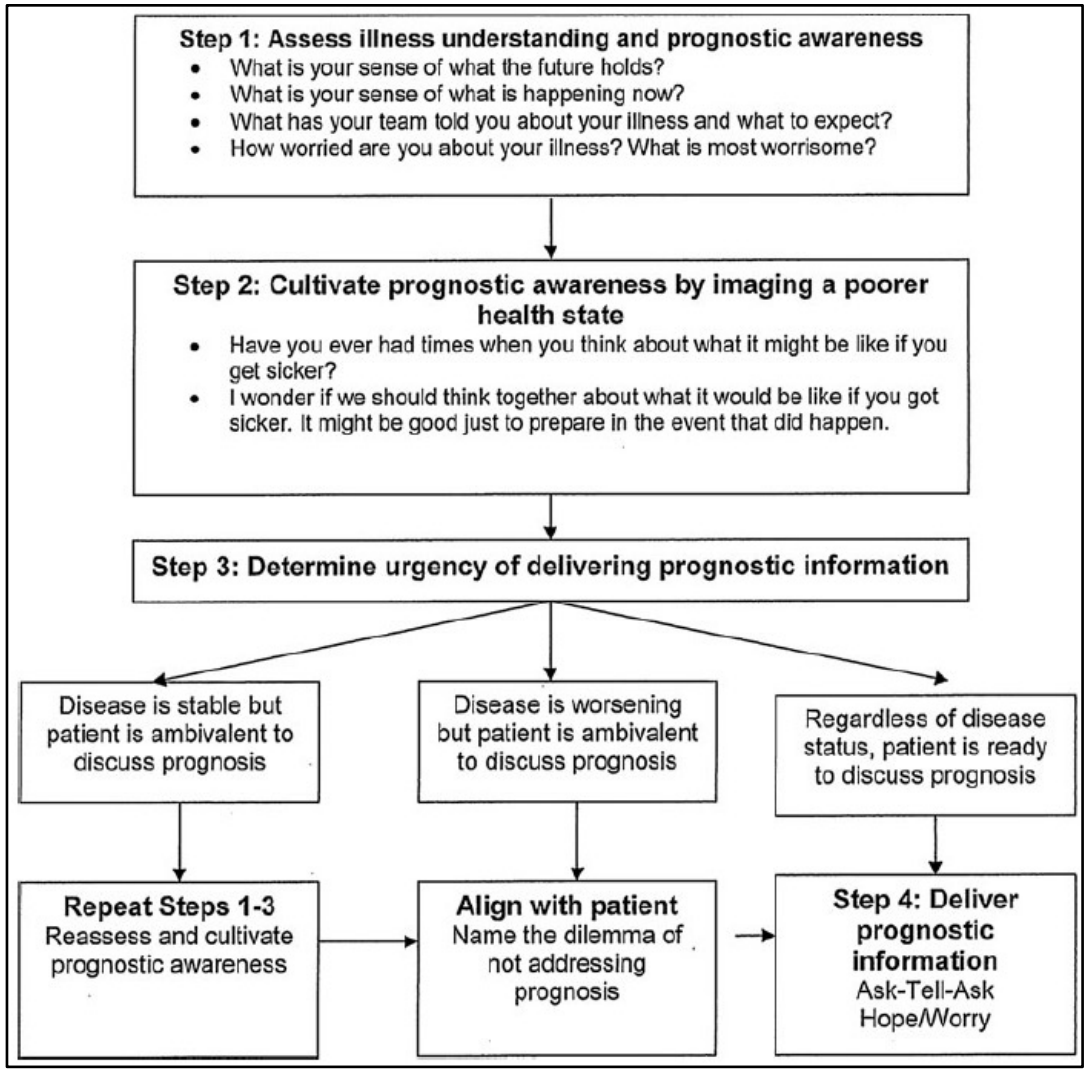

Shared Decision- making success
Patient goals and narrative
Medical options and narrative
Trust + Mutual Respect

Cultivation of Prognostic Awareness

Helping patients understand what you understand about their expected medical trajectory and outcomes

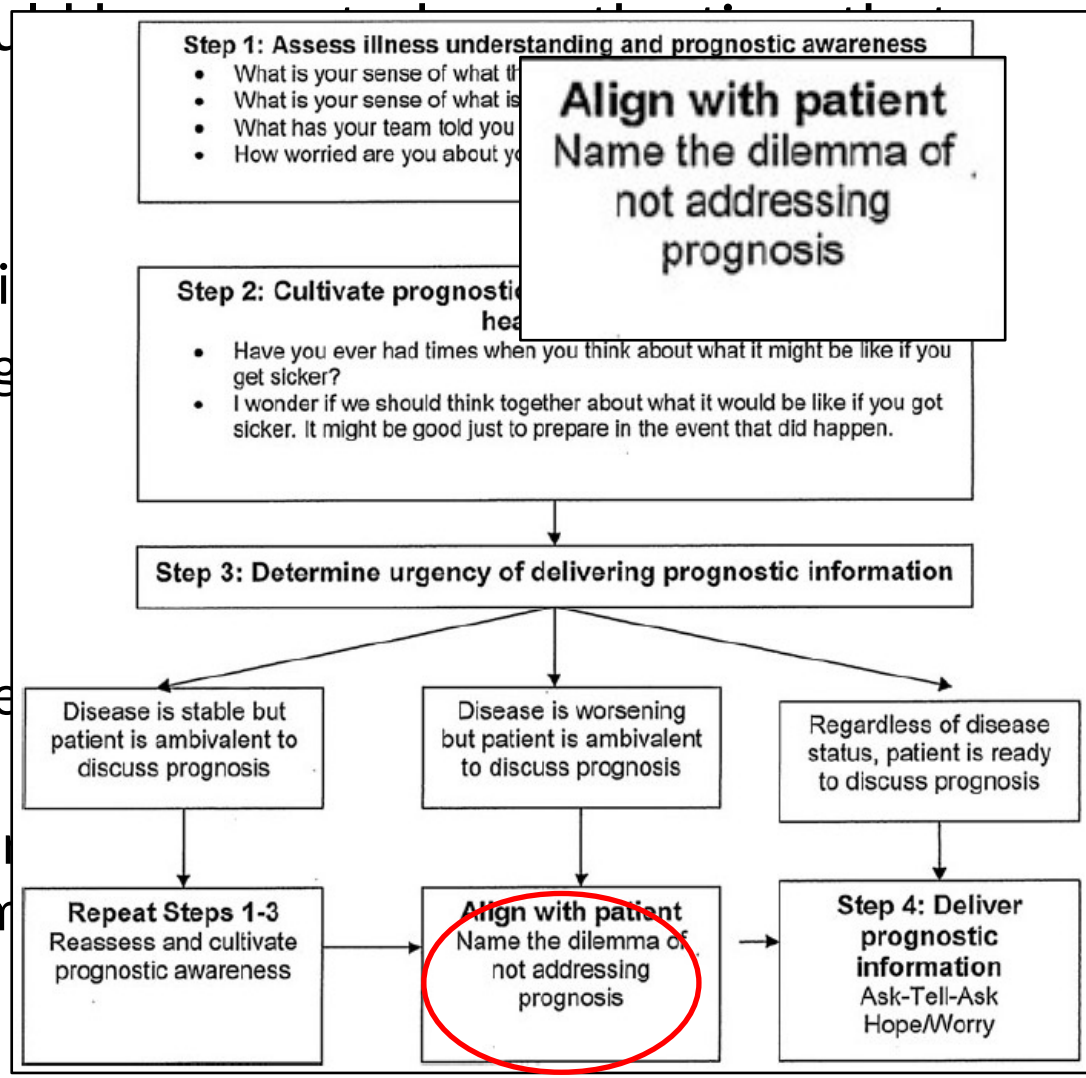
Cultivating Prognostic Awareness

- Patients don't always share in our understanding/expectations about their cancer outcomes, which can impede shared decision-making
- It is possible bridge this gap, with these steps
  - Assess their illness understanding
  - Invite them to imagine a worse health state and discuss theoretical plans in that state
  - Deliver prognostic information

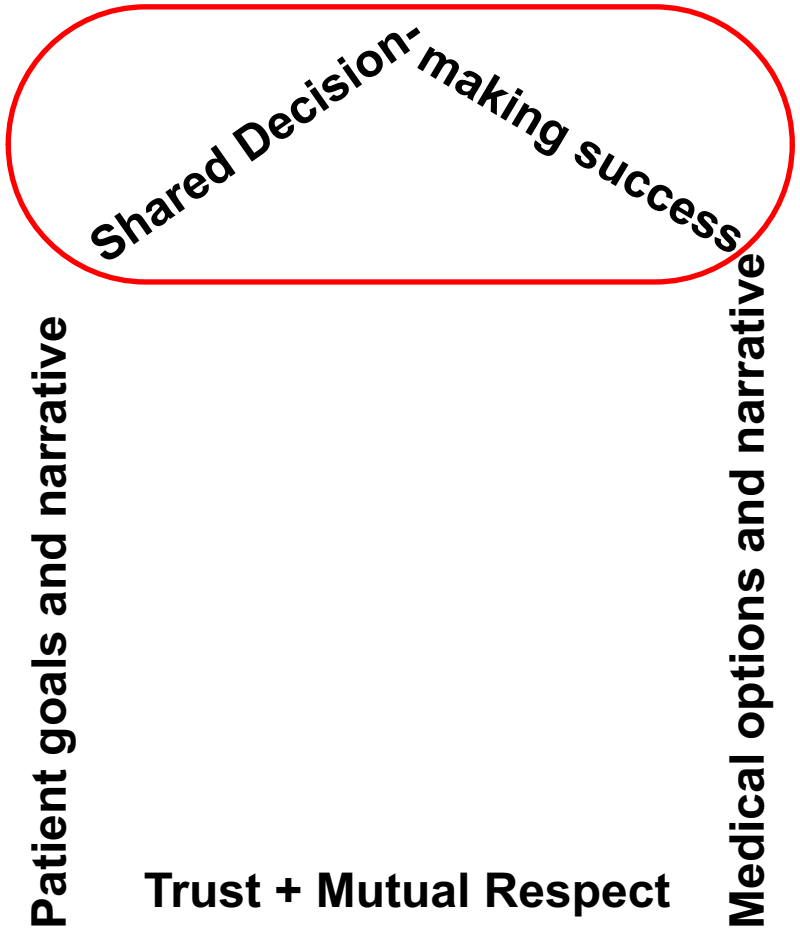


Cultivating, cont.

- Aligning and naming the dilemma can and shou
  you work with a patient.
- Aligning:
  - Verbally naming the patient's stated belief or prioriti
  - "I can tell you're really hopeful this treatment is going
    last treatment we did."
- Naming the dilemma:
  - "I'm worried" statements
  - ". . . But I'm concerned that the treatment may not be
    much worse."
  - ". . . I wouldn't have prescribed that treatment if I wer
    you've lost 15 pounds in two months, which makes m



PPCP:
Shared Decision-Making


Shared Decision-making success
Patient goals and narrative
Trust + Mutual Respect
Medical options and narrative

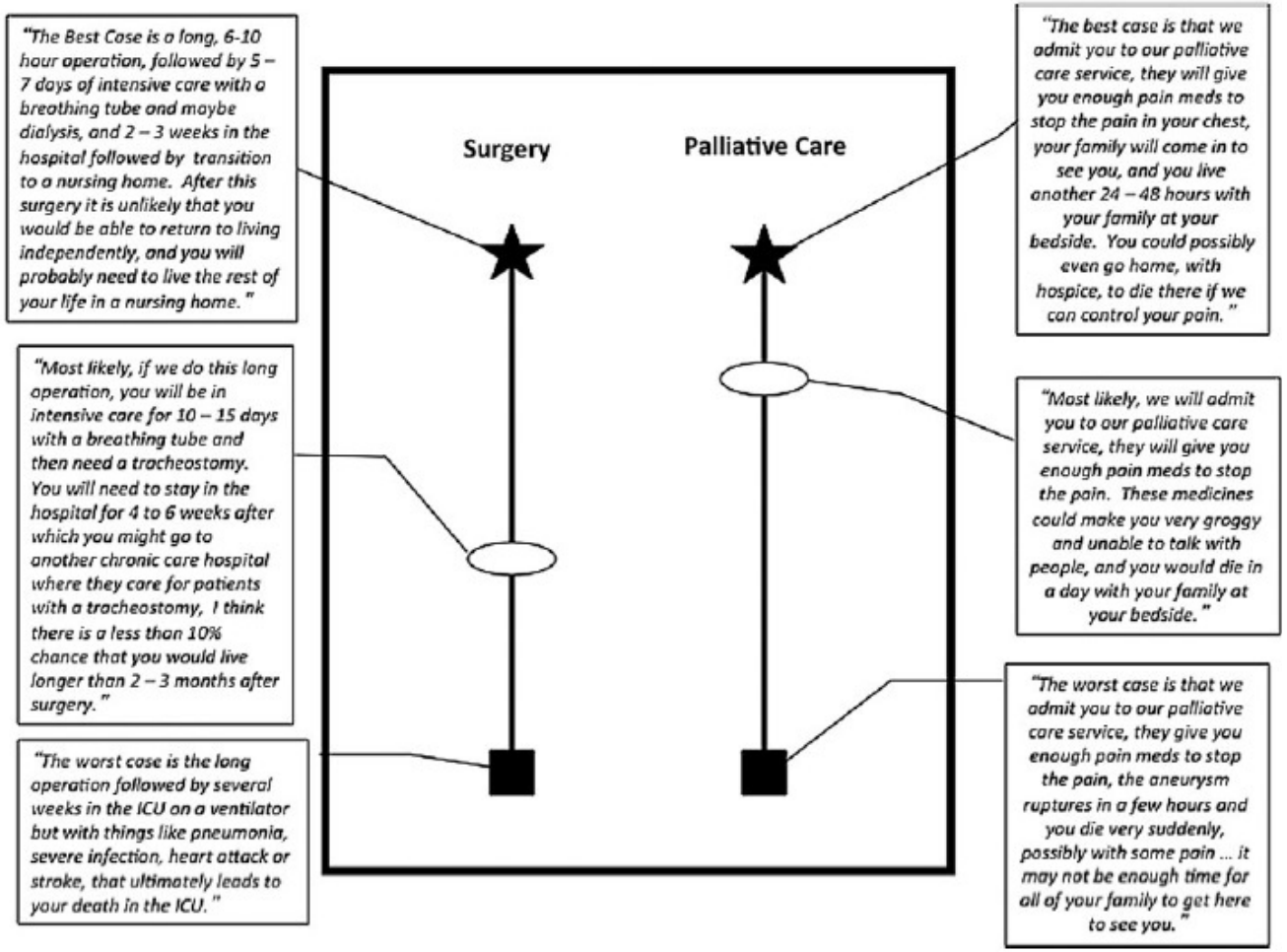
Best Case Scenario/Worst Case Scenario

BCS/WCS is a validated communication tool for surgical decision-making but also works well for decision-making about systemic cancer therapy.

- Steps:
  - Describe two treatment options and the best, worst, and most likely outcomes for both treatments
    - Illustrate on a simple line diagram

Schwarze ML, Kehler JM, and Campbell TC. Nativating high risk procedures with more than just a street map. J Pall Med. 16:10. 2013

BCS/WCS



- This tool uses a visual component, which is drawn in real time during the discussion
- Draw a vertical line with a star at the top and a box at the bottom.
  - Describe the star (best case scenario)
  - Describe the box (worst case scenario)
  - Draw a circle or mark on the line to indicate where they'll likely fit, and describe the most likely scenario

Schwarze ML, Kehler JM, and Campbell TC. Nativating high risk procedures with more than just a street map. J Pall Med. 16:10. 2013

Clinical vignette – BCS/WCS

- 74-year-old gentleman with history of resected pT2b, WHO grade 2 clear cell renal cell carcinoma without sarcomatoid features.
- 12-month imaging reveals three new lung nodules (1.5 cm RUL, 0.9 cm RLL, 1.8 cm LLL)
- He is asymptomatic and considers himself a “go getter;” surveillance is not psychologically acceptable to him.
- Tumor conference discussion determines that the treatment options include
  - Stereotactic radiation
  - Systemic therapy with standard frontline regimen

Stereotactic Radiation

Best case
"You go through a short course of radiation and have mild fatigue, but it resolves quickly. Your cancer is controlled long-term."

Most likely scenario
"You go through a short course of radiation, which causes mild tiredness, but it resolves within 2 weeks. Scans within 12 months show more new cancer spots, which could cause stress or even pain depending on where they are, and we go through the same decision process again.

Worst case
"You go through a short course of radiation and it goes well, but on your first post-radiation scan you have growing cancer, and it has spread to bone, which causes pain. The pain makes it harder to tolerate your medicine treatment, but you still can and it still helps."

Standard Systemic Therapy

Best case
"Your cancer responds to treatment and goes all the way on scans. You have some treatment-related side effects, but they can be managed well enough that you can stay on treatment.

Most likely scenario
"Your cancer shrinks but doesn't go away. You have side effects that require medication to manage them on an ongoing basis, and your treatment plan needs changes at different times to manage side effects. You can still do your hobbies, but you have to make adjustments because of some of the side effects."

Worst case
"You have severe treatment-related side effects, which result in you going to the hospital and taking long-term steroids. The steroids cause side effects while you take them. Your cancer still benefits from treatment, but you do have less energy than you did before you started treatment, even when you're done with steroids. Your cancer still benefits."

Conclusions

- Data-driven strategies for primary palliative care can improve quality of life for you and your patients.
- Ask-tell-ask, “tell me more,” and summarizing can help elucidate goals of care.
- “I’m worried” statements can meaningfully cultivate prognostic awareness.
- Consider the best case/worst case scenario to help support patients in decision-making.

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IMPLEMENTING PATHWAYS IN AN EVOLVING LANDSCAPE

Lisa Raff, PharmD, MSPharm, BCPS, BCOP
Vice President of Pharmacy Services, OneOncology

August 23rd, 2025

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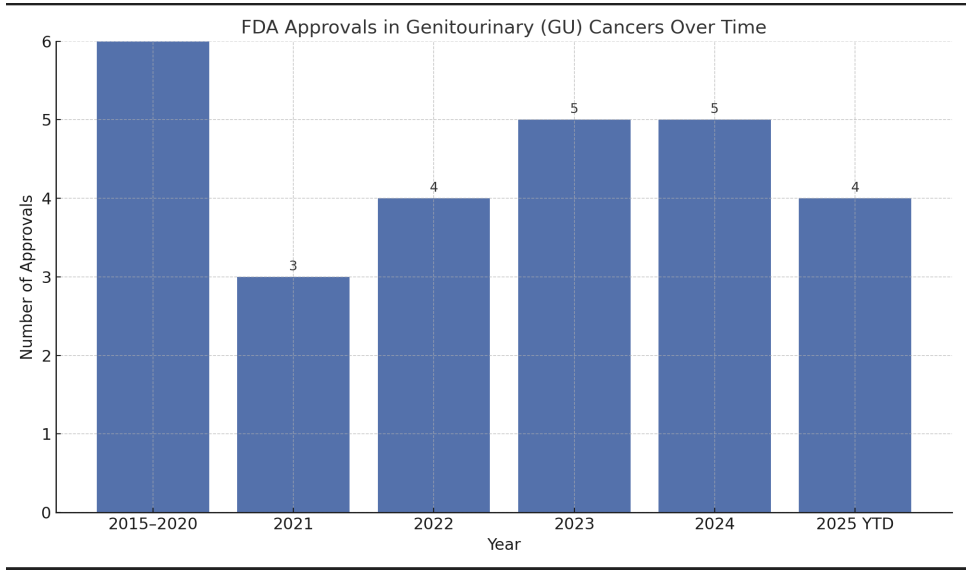
Pathways in Genitourinary Malignancies

Ability to Adapt to a Rapidly Changing Treatment Landscape Across GU Malignancies

Bispecifics, radioligand & targeted therapies and ADCs are reshaping GU treatment paradigm

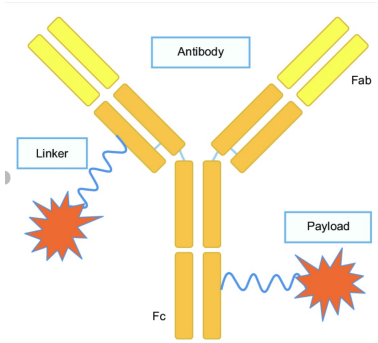
- **From 2023 to mid-2025 there have been over 10 new approvals or label expansions in GU cancer:**
  - ✓ Including 3+ ADCs, radioligand therapy, and immunotherapy
  - ✓ This pace is double the average GU oncology approval rate from the 2015–2020 period

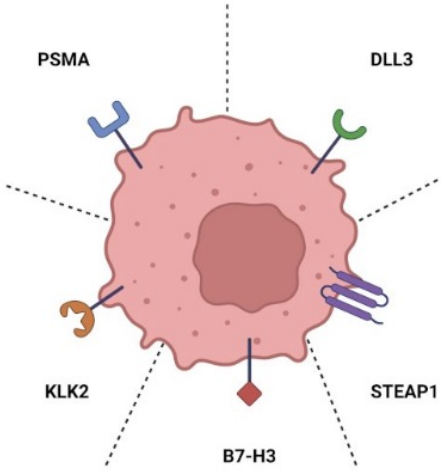


Pathways in Genitourinary Malignancies

An estimated 10 to 15 FDA approvals are anticipated in the genitourinary treatment landscape by the end of 2027

- Rapid Expansion of ADC Pipeline: 10+ ADCs in GU cancers are in Phase I/II now, several already in registrational studies
- Radioligand Therapies: Expansion of PSMA-targeted therapies and new ligands in development
- Broader integration of checkpoint blockade strategies across treatment settings
- Biomarker-Driven Therapies: FGFR, HER2, CDH6, PSMA, and B7-H3 being heavily explored





Pathways in Genitourinary Malignancies

Ability to adapt to a rapidly changing treatment landscape across GU malignancies

- Pathways must be nimble in incorporating emerging data, real-world insights, and expert consensus to help guide busy medical oncologists in daily treatment decisions
- Pathways act as clinical roadmaps, enabling evidence-based, consistent, and efficient care
- Use of an embedded clinical decision support tool streamlines documentation, supports patient access, and helps to drive adherence and adoption of novel therapies at the time of treatment decision
- Pathways are dynamic platforms that integrate precision oncology, real-time clinical data and must absorb new evidence and realign standard regimens rapidly

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IMPROVING COMMUNICATION IN A MULTIDISCIPLINARY ENVIRONMENT

Kelvin A. Moses, MD, PhD, FACS
Associate Professor of Urology
Vanderbilt University Medical Center

August 23, 2025

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Agenda

- Multidisciplinary teams in GU cancer
- Who’s on your team
- Best practices for communication

Multidisciplinary Teams in GU Cancer

- Increasingly complex approach to cancer
- Screening and diagnosis
- Advanced imaging techniques
- Combined systemic therapy and surgical care
- Genetic profiling and counselling
- Addressing patient reported outcomes
- Survivorship
- Taking account of social determinants of health

Goals of Multidisciplinary Care

- Simplify the treatment decision-making process for the patient by including the entire team in one place
  - “One Stop Shop”
- Deliver high quality care through collaborative discussion with Medical Oncology, Radiation Oncology, Physician Extenders, Patient Navigator, and Patient/Family
- Provide consistency with a team approach
- Encourage participation in clinical trials
- Improve patient satisfaction and potentially impact overall survival

Identifying your team

Assets and Obstacles

Effective Communication for the Multi-D Team

- Open communication
- Nonpunitive environment
- Clear direction
- Clear and known roles and tasks for team members
- Respectful atmosphere
- Shared responsibility for team success
- Appropriate balance of member participation for the task at hand
- Acknowledgment and processing of conflict
- Clear specifications regarding authority and accountability
- Clear and known decision-making procedures
- Regular and routine communication and information sharing
- Enabling environment, including access to needed resources
- Mechanism to evaluate outcomes and adjust accordingly

O'Daniel and Rosenstein, Chapter 33, Professional Communication and Team Collaboration.
Patient Safety and Quality: An Evidence-Based Handbook for Nurses.
Hughes RG, editor. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008 Apr.

Potential Obstacles to Effective Communication

- Personal values and expectations
- Personality differences
- Hierarchy
- Disruptive behavior
- Culture and ethnicity
- Generational differences
- Gender
- Historical interprofessional and intraprofessional rivalries
- Differences in language and jargon
- Differences in schedules and professional routines
- Varying levels of preparation, qualifications, and status
- Differences in requirements, regulations, and norms of professional education
- Fears of diluted professional identity
- Differences in accountability, payment, and rewards
- Concerns regarding clinical responsibility
- Complexity of care
- Emphasis on rapid decision-making

O'Daniel and Rosenstein, Chapter 33, Professional Communication and Team Collaboration. Patient Safety and Quality: An Evidence-Based Handbook for Nurses. Hughes RG, editor. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008 Apr.

Models for a Successful Prostate Cancer MDC

Medical Oncology/Radiation Oncology

Weekly Tumor Board

Nuclear Medicine

Specialty Pharmacy

Payment assistance, oral medications mailed

Medical Genetics

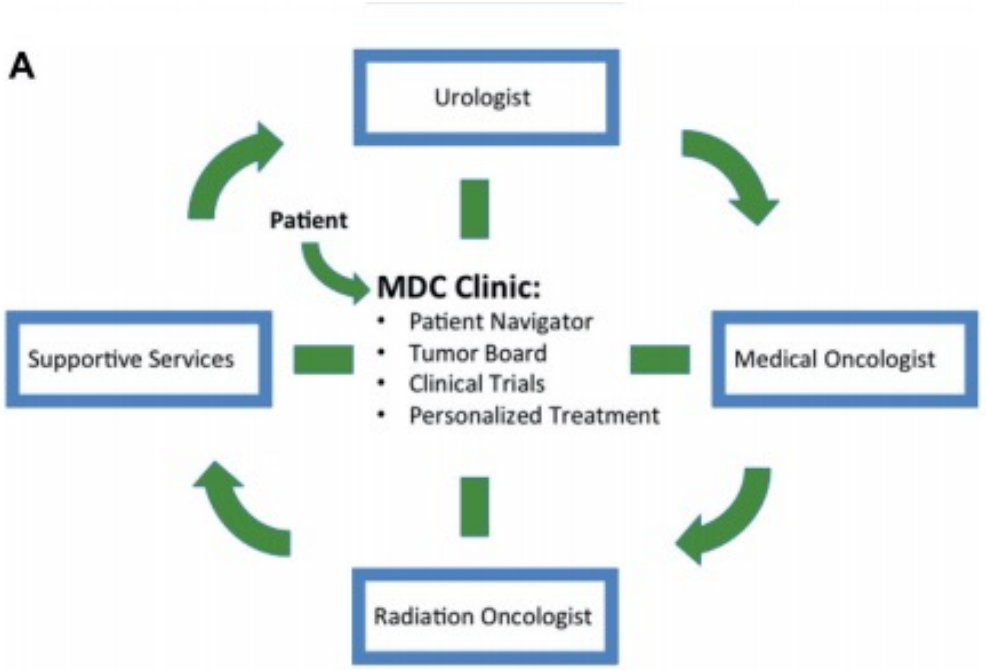
Counseling and germline/somatic testing

Apheresis Location

For sipuleucel-T (American Red Cross)

Palliative Care/Hospice

Industry Partners (Clinical Trials)



Virtual MDC Models

1. Same day/different clinic
2. Different day/different clinic

Stratton, Moeller and Cookson, Urol Pract 2016

Kelvin A. Moses
Urology

Tarek Absi
CT Surgery

Kara Siegrest
Cardiac Anesthesia

C. Louis Garrard
Vascular

Sekhar Padmanabhan
HPB

Amy Luckenbaugh
Urology

Eric Quintana
CT Surgery

Brian Rini
Medical Oncology

The Renal Cell Gang

Experienced urologist
Liver surgeon (liver mobilization and control of the vena cava)
Vascular surgeon (caval reconstruction/patch)
Cardiac anesthesiologist (hemodynamic management/intra-operative TEE)
Cardiac surgeon (sternotomy, right heart veno-venous bypass, and cardiopulmonary bypass +/- circulatory arrest)

Dan Joyce
Urology

My Suggestions

- Set an agenda
- Utilize EHR and technology, but don’t forget to meet in person as often as possible
- Stay abreast of emerging therapies
- Center the patient
- Treat lack of consensus as an opportunity to learn and adjust

Summary

- Multidisciplinary care is the standard for management of genitourinary cancer, particularly for advanced disease
- Effective communication is needed to make decisions and act in an efficient manner
- Team commitment comes from top-down and bottom-up, but the team leader needs to demonstrate skill in team building and maintenance
- When possible, engage in team building to foster an environment of trust and respect, accountability, situational awareness, open communication, assertiveness, shared decision-making, feedback, and education
- Our patients rely on multidisciplinary teams for optimal treatment and outcomes

O'Daniel and Rosenstein, Chapter 33, Professional Communication and Team Collaboration.
Patient Safety and Quality: An Evidence-Based Handbook for Nurses.
Hughes RG, editor. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008 Apr.

World Conference On
Genitourinary Cancers

2025 NASHVILLE, TN

THANK YOU!

Kelvin.a.moses@vumc.org

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World Conference On
Genitourinary Cancers
2025 NASHVILLE, TN

DEFINING MRD

Alan Tan, MD - Vanderbilt University Medical Center

August 23, 2025

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@alantanmd

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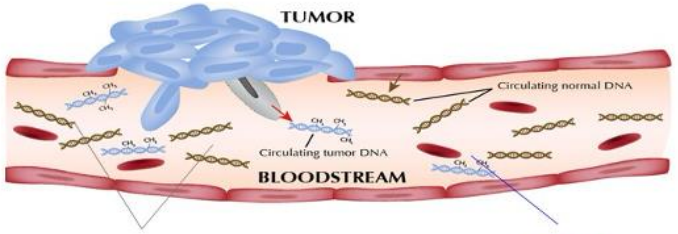
Circulating tumor DNA (ctDNA)



cfDNA

circulating free DNA

DNA-lipoprot complexes

Breakdown of bacteria, virus, blood cells

Spontaneous release of DNA from healthy cells

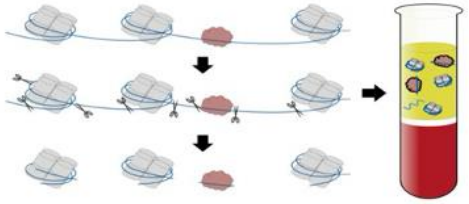
ctDNA

circulating tumor DNA

Necrotic cells

Apoptosis

Active release



DNA fragments (<146bp)

Urine cfDNA
from renal clearence

- Highly tumor specific
- Early detection/screening
- Actionable genomic alterations
- Disease monitoring (MRD, prognosis)

cfDNA half life: <2 hours → real time monitoring of tumor burden

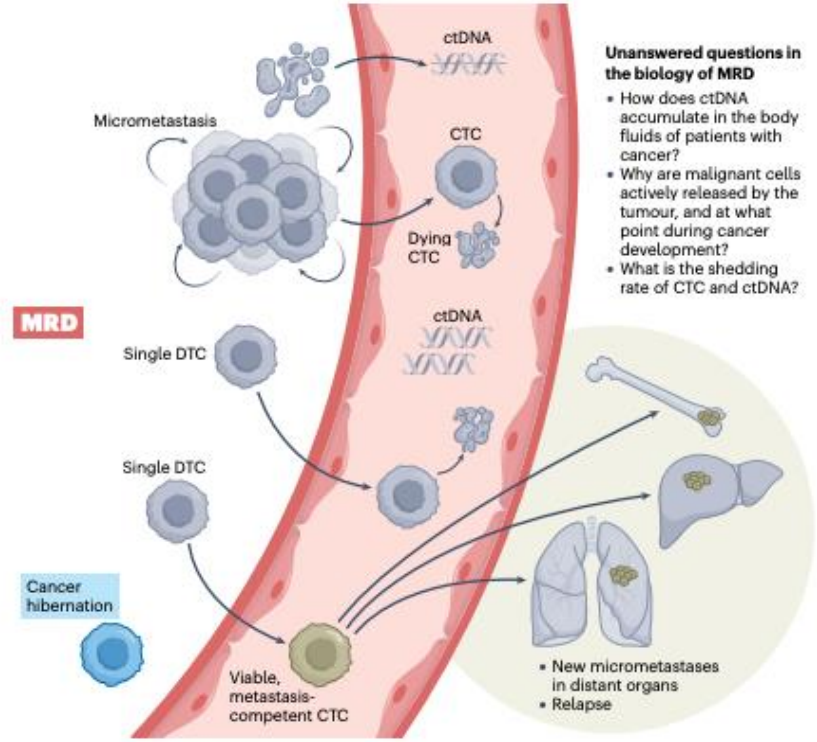
Leary et al, Sci Transl Med, 2012

Minimal Residual Disease (MRD)

Microscopic tumor burden remaining in the body after treatment in patients who have no clinical evidence of disease

These residual cells can persist locally, circulate in the bloodstream as circulating tumor cells (CTCs), or reside in distant organs as disseminated tumor cells (DTCs) or micrometastases

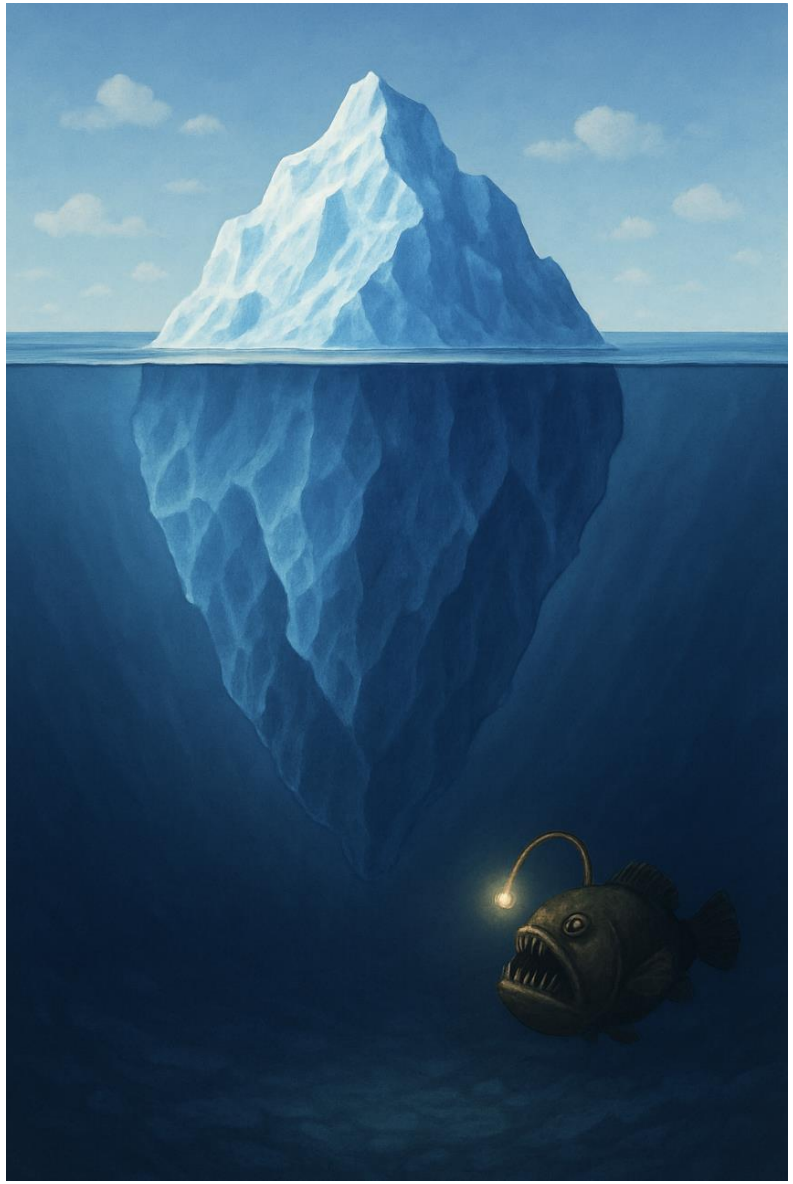
MRD detection after completion of local therapy could identify which patients will recur and allow personalization of adjuvant therapy



Pantel et al. – Nature Reviews Clin Onc 2025

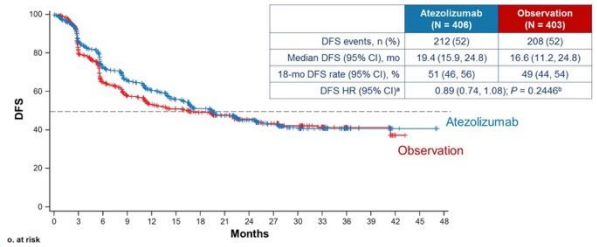
ctDNA MRD: Tumor-Informed vs. Tumor-Naive

	Tumor Informed	Tumor Naïve
Adequate specimen	Limitation – UTUC, bone mets, no Nx	Not required
Sensitivity	Better LOD (.01 to <1ppm)	Less sensitive
Specificity	Very good Screens out CHIP	Very good CHIP needs filter algorithm, epigenomics and fragmentomics improve
Emerging Variants/biomarkers	No	Yes
Turnaround time	Slower ~ 4-6 weeks for baseline, subsequent 1 week	7-10 days
Key Applications	• MRD • Assess treatment response • Serial monitoring	• MRD • Assess heterogeneity, actionable alterations, resistance • Serial monitoring

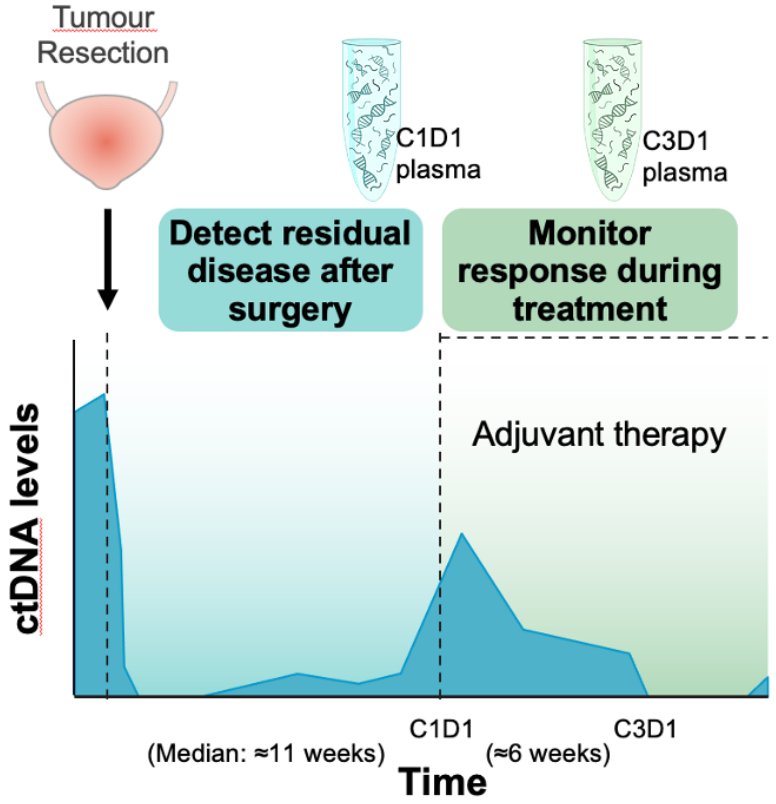


Tumor-Informed ctDNA

Evaluation of ctDNA in IMvigor010



	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); $P = 0.2446$[b]	



1. Tumour tissue and germline material were sequenced (whole exome sequencing)
2. Up to 16 mutations for personalised mPCR ctDNA assay were identified for each patient
3. Plasma samples were sequenced to ≈100,000×
4. If ≥2 mutations were detected, sample was defined as ctDNA(+)
5. MRD sample timepoint before adjuvant treatment (C1D1) was collected
6. On-treatment sample (C3D1; week 6) was also collected

C, cycle; D, day; mPCR, multiplex polymerase chain reaction; MRD, molecular residual disease.

Powles et al. IMvigor010 ctDNA
https://bit.ly/2IxYIIE

IMVIGOR 010

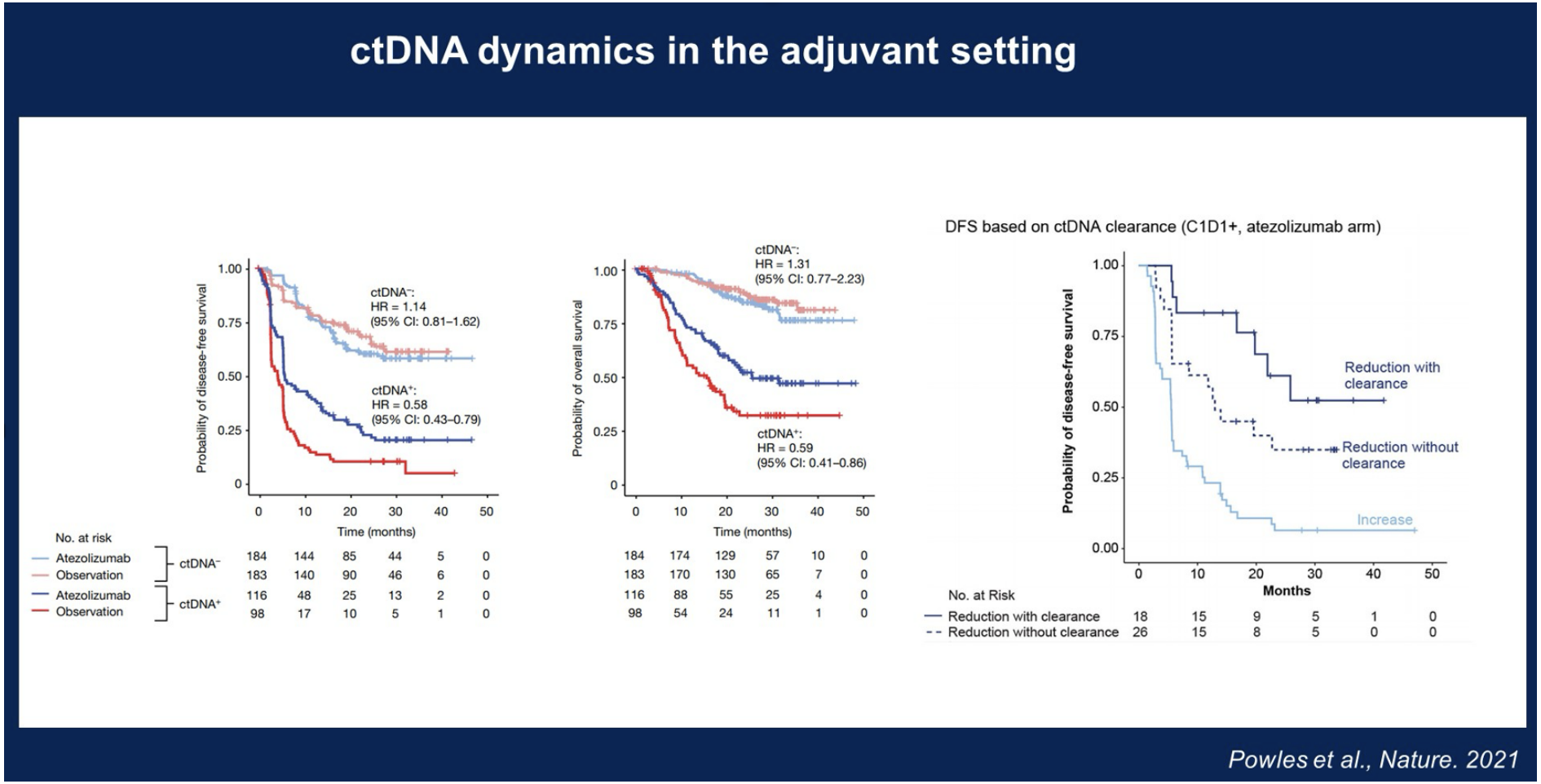

ctDNA dynamics in the adjuvant setting
Probability of disease-free survival
ctDNA⁻: HR = 1.14 (95% CI: 0.81–1.62)
ctDNA⁺: HR = 0.58 (95% CI: 0.43–0.79)
Time (months)
No. at risk
Atezolizumab
Observation
Atezolizumab
Observation
ctDNA⁻
ctDNA⁺
184 144 85 44 5 0
183 140 90 46 6 0
116 48 25 13 2 0
98 17 10 5 1 0
Probability of overall survival
ctDNA⁻: HR = 1.31 (95% CI: 0.77–2.23)
ctDNA⁺: HR = 0.59 (95% CI: 0.41–0.86)
Time (months)
184 174 129 57 10 0
183 170 130 65 7 0
116 88 55 25 4 0
98 54 24 11 1 0
DFS based on ctDNA clearance (C1D1+, atezolizumab arm)
Probability of disease-free survival
Reduction with clearance
Reduction without clearance
Increase
Months
No. at Risk
Reduction with clearance 18 15 9 5 1 0
Reduction without clearance 26 15 8 5 0 0
Powles et al., Nature. 2021

Figure 1. IMvigor011 Study Design

Screening

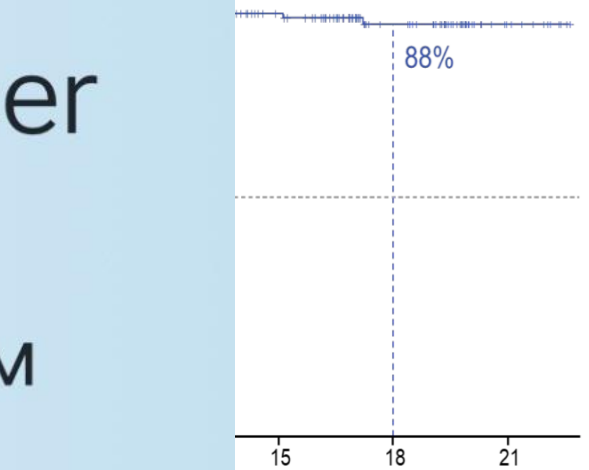
Key eligibility

- High-risk MIBC
  - ypT2-T4a or ypN+ and M0 at cystectomy for patients with prior NAC
  - pT3-T4a or pN+ and M0 at cystectomy for patients without prior NAC
- No post-surgical radiation or AC
- If no prior NAC given, patient had to refuse or be ineligible for cisplatin-based AC
- No evidence of residual disease
- Tumour sample available for WES[a] and PD-L1[b] status

6-14 wee
post cyst
with lymp
dissectio

ctDNA–, circulating tumor DNA negative; ctDNA+, circulating tumor DNA positi
[a] Evaluable WES data for development of a personalised multiplex PCR (mPCR
[b] Per the VENTANA SP142 IHC assay.
[c] Every 6 weeks up to 36 weeks and q12w (every 12 weeks) up to 21 months.
[d] q12w up to Week 84 or until 21 months from date of cystectomy, whichever o
[e] ctDNA positivity is defined as ≥2 mutations per ctDNA mPCR assay. Patients
cystectomy and no evidence of disease recurrence within 28 days of treatmer
[f] Imaging and blood draws q9w (every 9 weeks) starting at Week 9 up to Week
[g] Assessed q9w up to Year 3; less often up to Year 6.

Relapse in the persistently ctDNA-ve
om IM011



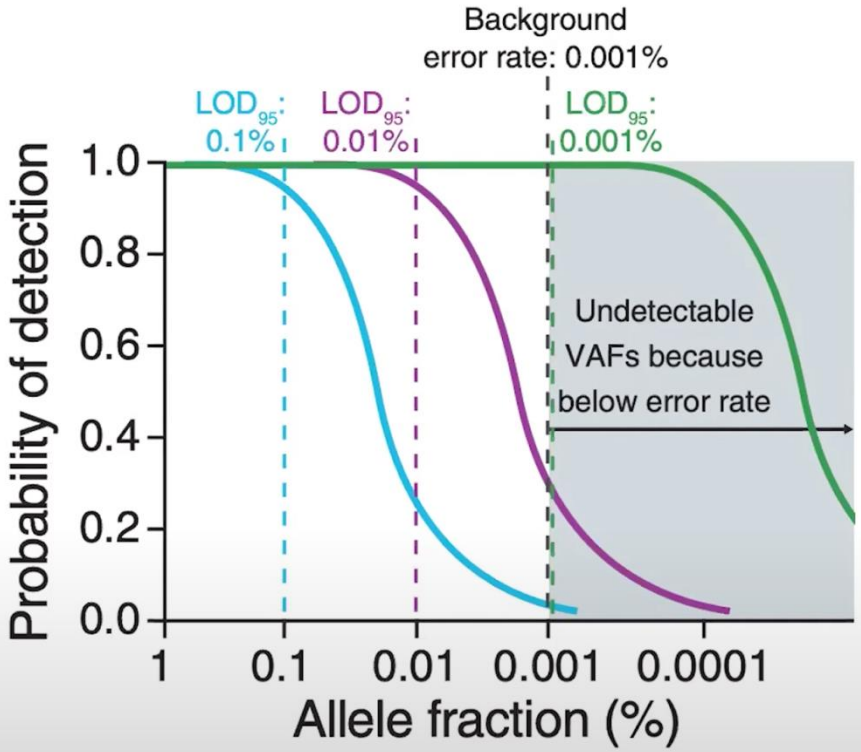
AUGUST 18, 2025

IMvigor011 Bladder Cancer Trial Achieves Positive Results, with Signatera™ Strongly Predicting Adjuvant Immunotherapy Benefit

Powles, Thomas, Zoe June Ass
Urothelial Carcinoma." *Nature*

ant Immunotherapy in

How to increase sensitivity of ctDNA MRD



Track more mutations

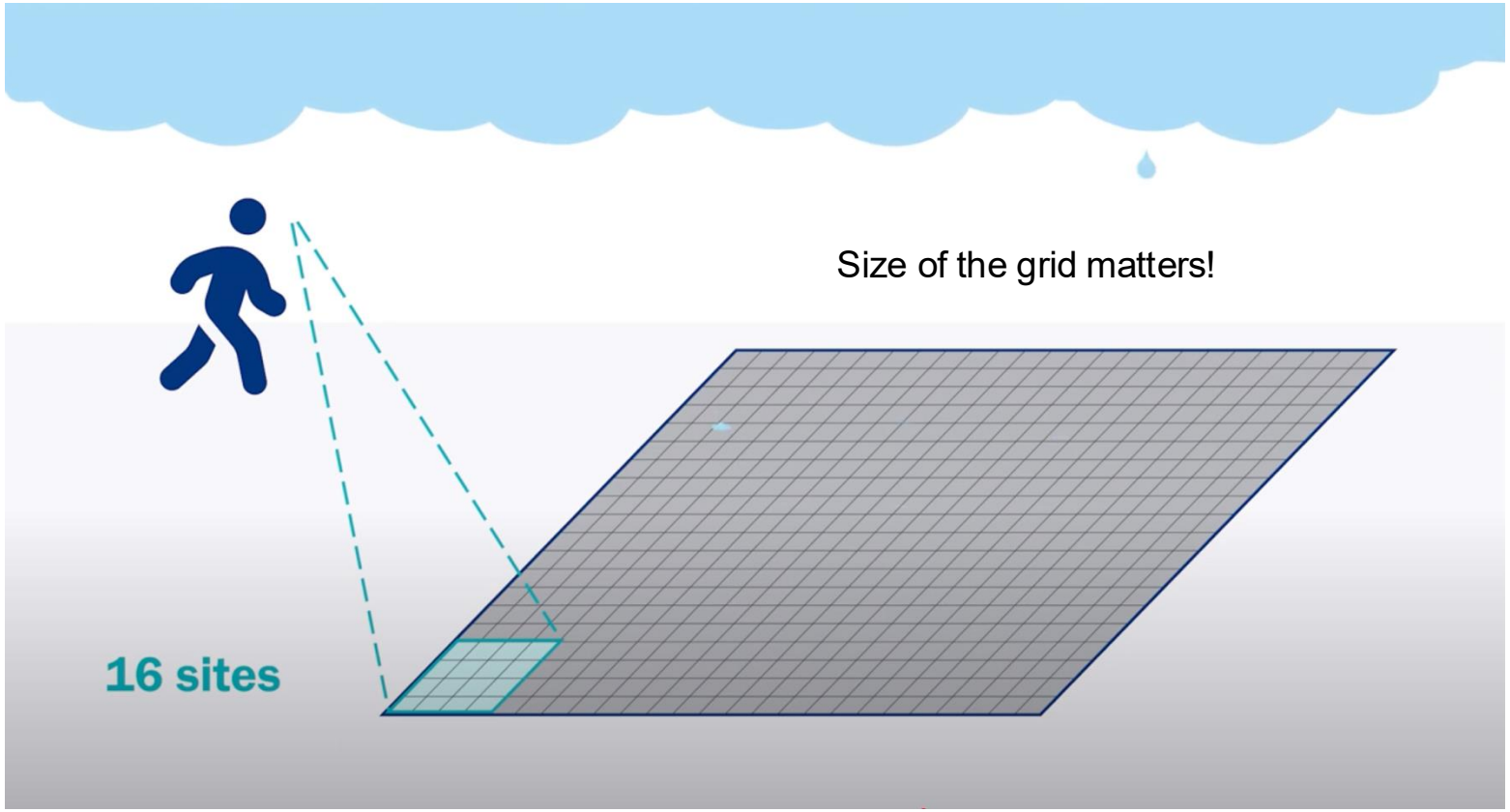
And

Decrease background error rate

* Longitudinal monitoring

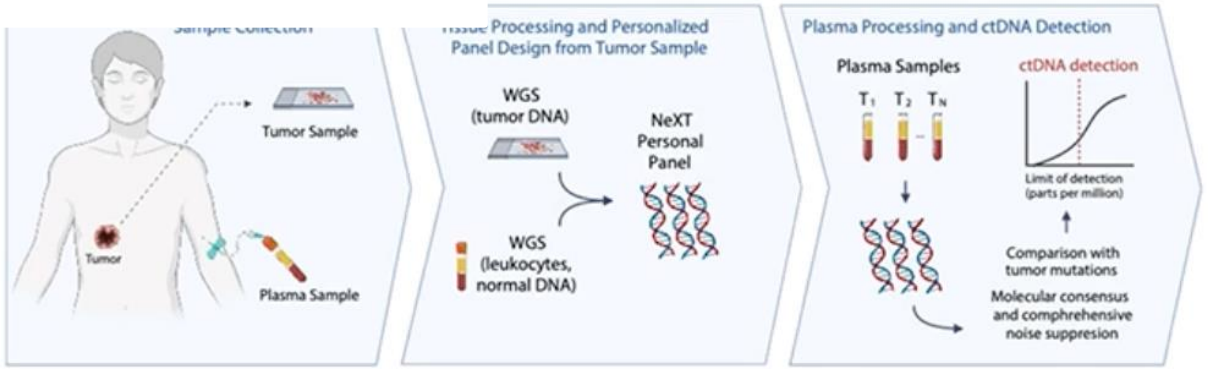
Moding et al. Cancer Discov. 2021

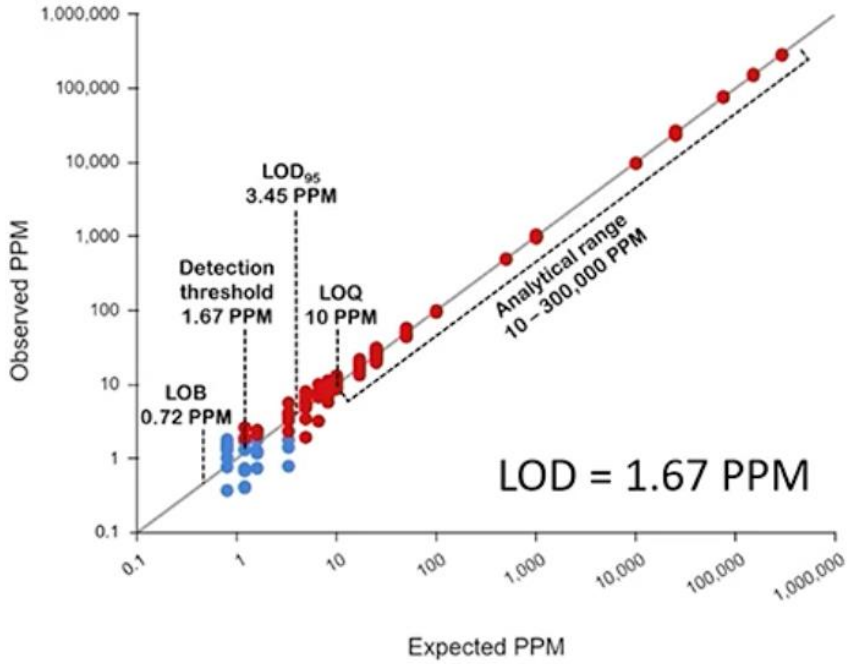
Is it Raining ctDNA?



- Better quantification (more raindrops detected)
- More precise with smaller tumors

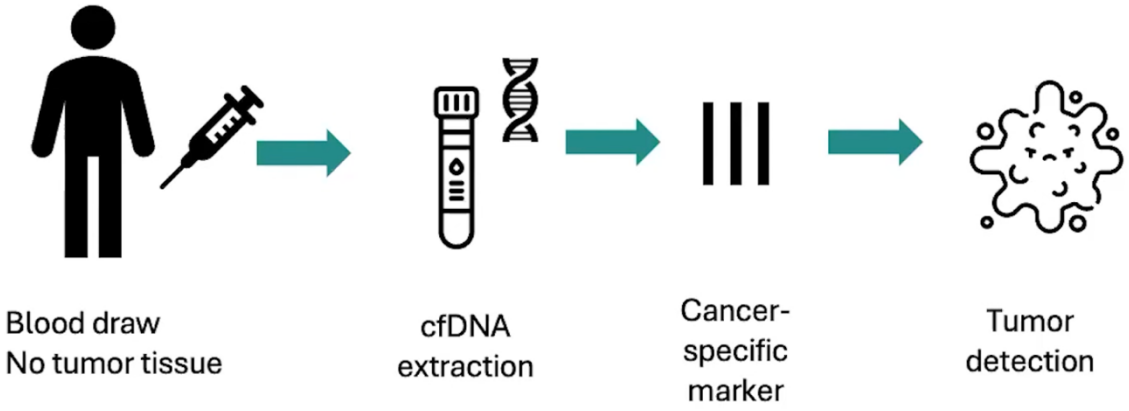
Pushing the limit of detection: Increasing # of variants





Whole Genome Sequencing up to ~1800 Variants

Northcott J et al, *Oncotarget* 2024



Tumor-Naive ctDNA

BARCELONA 2024 ESMO congress

Circulating Tumour DNA (ctDNA) Clearance With Neoadjuvant Durvalumab (D) + Tremelimumab (T) + Enfortumab Vedotin (EV) for Cisplatin-Ineligible Muscle-Invasive Bladder Cancer (MIBC) From the Safety Run-in Cohort of the Phase 3 VOLGA Trial

Alexandra Drakaki,[1] Thomas Powles,[2] Ying Wang,[3] Manojkumar Bupathi,[4] Monika Joshi,[5] Mark Fleming,[6] Alfonso Gómez de Liaño,[7] Rafael Morales-Barrera,[8] Roberto Pili,[9] Suliman Boulos,[10] Yashaswi Shrestha[11]

[1]Division of Hematology/Oncology, David Geffen School of Medicine, Los Angeles, CA, USA; [2]Genitourinary Oncology, Barts Cancer Institute, Queen Mary University of London, London, UK; [3]Oncology Data Science, AstraZeneca, Waltham, MA, USA; [4]Medical Oncology, Rocky Mountain Cancer Centers, Littleton, CO, USA; [5]Department of Medicine/Division of Hematology and Oncology, Penn State Cancer Institute, Hershey, PA, USA; [6]US Oncology Research, Virginia Oncology Associates, Norfolk, VA, USA; [7]Medical Oncology, Complejo Hospitalario Universitario Insular-Materno Infantil, Las Palmas, Spain; [8]Medical Oncology Department, Vall d'Hebron Institute of Oncology and University Hospital, Universitat Autonoma de Barcelona, Barcelona, Spain; [9]Division of Hematology/Oncology, Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY, USA; [10]Oncology, AstraZeneca, Cambridge, UK; [11]Translational Medicine, AstraZeneca USA, Gaithersburg, MD, USA

1970MO

Presenter: Alexandra Drakaki, MD, PhD, UCLA, USA

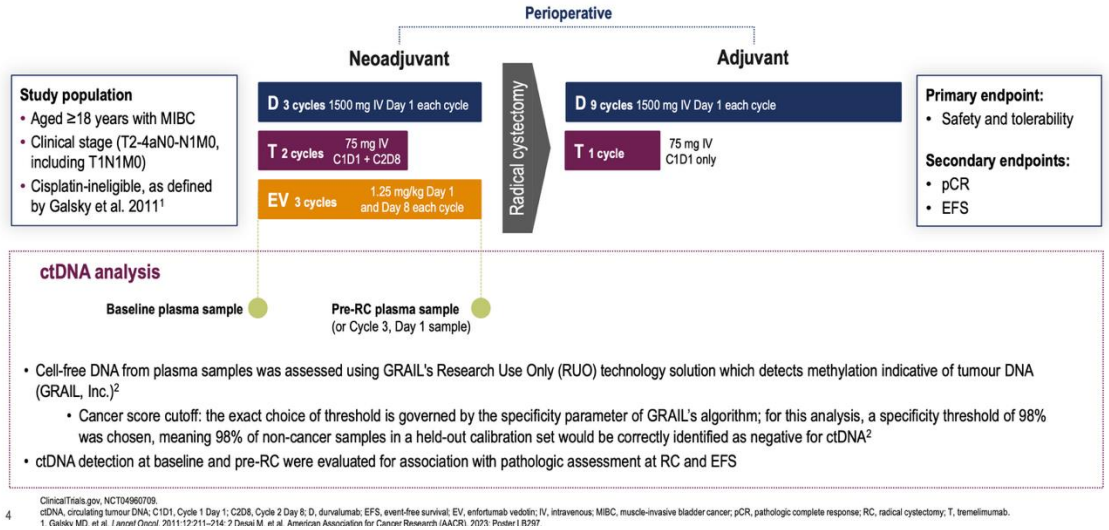
1

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Cystectomy	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N
Clinical stage at baseline	T2	>T2	T2	T2	T2	T2	T2	T2	T2	T2	T2	>T2	T2	>T2	T2	T2	>T2
Pathological assessment at RC			pCR				Downstaged			No change		Upstaged			NA	NA	NA
Baseline ctDNA status	+	+	+	+	+	–	–	–	–	+	+	+	+	+	–	–	NS
Pre-RC ctDNA status	–	–	–	–	–	–	NS	–	–	–	–	+	+	+	–	NS	NS

ctDNA clearance

- At baseline, the overall ctDNA-positive rate was 62.5% (10/16 patients) and the overall ctDNA-negative rate was 37.5% (6/16 patients)
- After neoadjuvant treatment, the pre-RC ctDNA-negative rate was 78.6% (11/14 patients)
- A total of 7 out of 10 patients had ctDNA clearance (baseline ctDNA positive, then pre-RC ctDNA negative)

VOLGA safety run-in design and ctDNA analysis

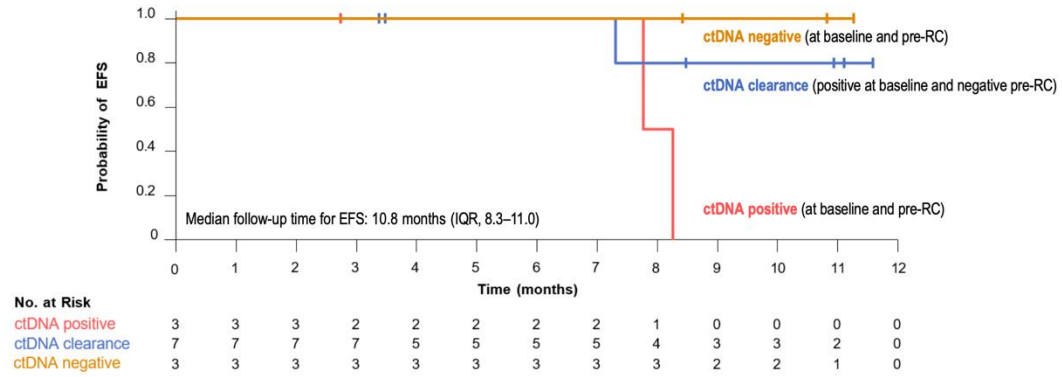


- Cell-free DNA from plasma samples was assessed using GRAIL's Research Use Only (RUO) technology solution which detects methylation indicative of tumour DNA (GRAIL, Inc.)[2]
  - Cancer score cutoff: the exact choice of threshold is governed by the specificity parameter of GRAIL's algorithm; for this analysis, a specificity threshold of 98% was chosen, meaning 98% of non-cancer samples in a held-out calibration set would be correctly identified as negative for ctDNA[2]
- ctDNA detection at baseline and pre-RC were evaluated for association with pathologic assessment at RC and EFS

ClinicalTrials.gov, NCT04960709.
ctDNA, circulating tumour DNA; C1D1, Cycle 1 Day 1; C2D8, Cycle 2 Day 8; D, durvalumab; EFS, event-free survival; EV, enfortumab vedotin; IV, intravenous; MIBC, muscle-invasive bladder cancer; pCR, pathologic complete response; RC, radical cystectomy; T, tremelimumab.
1. Galsky MD, et al. Lancet Oncol. 2011;12:211–214. 2. Desai M, et al. American Association for Cancer Research (AACR). 2023; Poster LB297

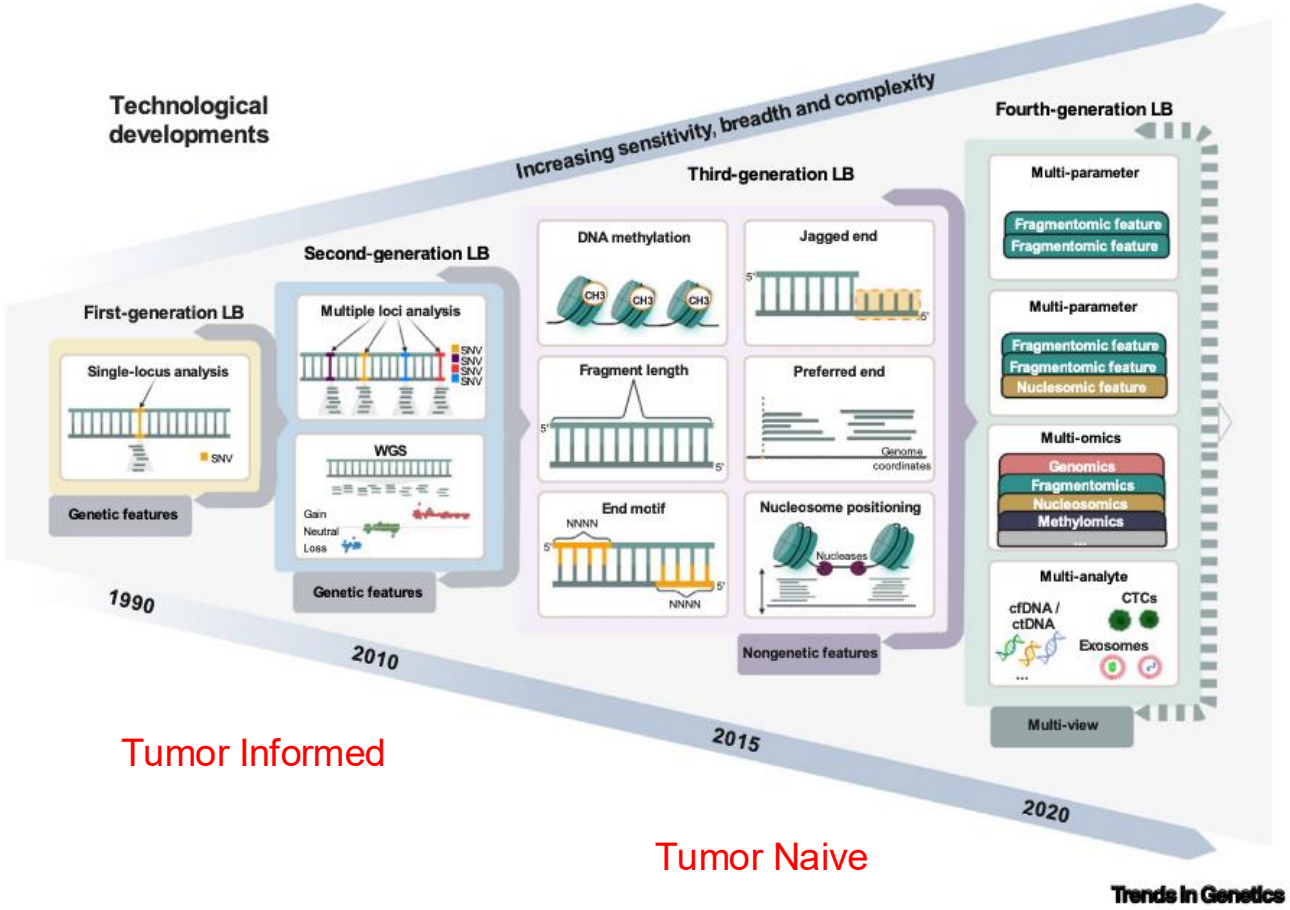
4

ctDNA clearance and its association with EFS



- EFS was assessed in 13 patients who completed RC; 10 were ctDNA-positive at baseline, and 3 were ctDNA-negative at baseline
- **Longer EFS was observed in the ctDNA clearance and ctDNA negative groups compared with the ctDNA positive group**

Next Generation MRD with Machine Learning



T. Moser et al., Trends in Genetics, 2023

Conclusions

- **Tumor informed have best sensitivity and optimal for detecting MRD at very low levels, < 1 PPM**

- **Next generation tumor informed tests increase sensitivity by tracking more variants (up to 5000) and filtering background**

- **Tumor naïve assays have rapid turnaround and capture tumor evolution but are currently less sensitive. Methylation, Fragmentomics, and scanning entire genome poised to improve sensitivity and specificity**

Thank You

@alantanmd

alan.tan@vumc.org

World Conference On
Genitourinary Cancers
2025 NASHVILLE, TN

Using ctDNA to Measure MRD in Bladder Cancer

Elizabeth R. Plimack, MD, MS, FASCO
Deputy Director
Professor of Medical Oncology
Fox Chase Cancer Center

@ERPlimackMD

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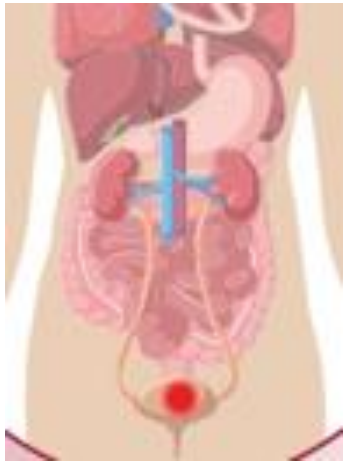
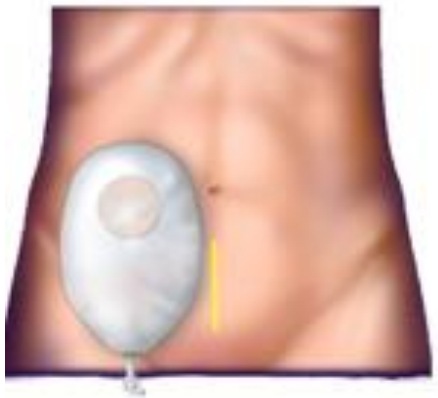
Clinical Scenarios of MRD using ctDNA



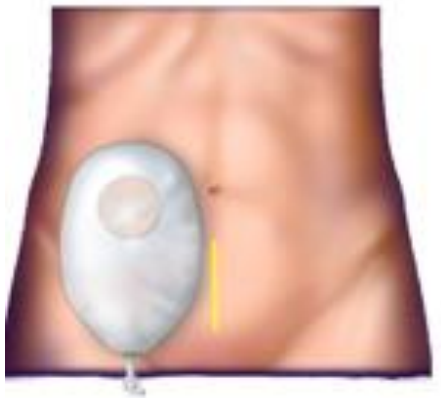
Neoadjuvant

Determining chances of pT0 after NAC for the purposes of bladder preservation



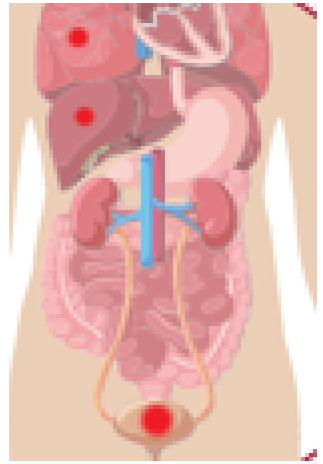
Adjuvant

Determining risk of recurrence / potential for benefit in the adjuvant setting



Surveillance

Post curative treatment (with imaging)

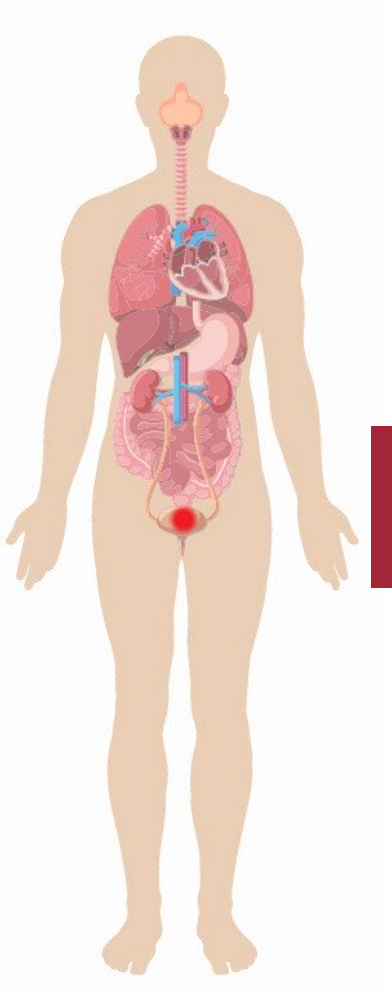


Metastatic

Confirmation of CR, monitoring disease progression (with imaging)

MIBC Current Standard of Care:

Neoadjuvant



Systemic therapy

?ctDNA -

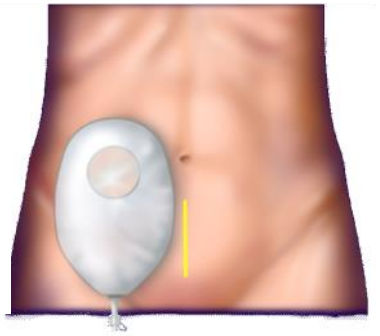
No residual disease

Unnecessary Surgery

?ctDNA +

Residual disease in bladder

Curative Surgery



?ctDNA +

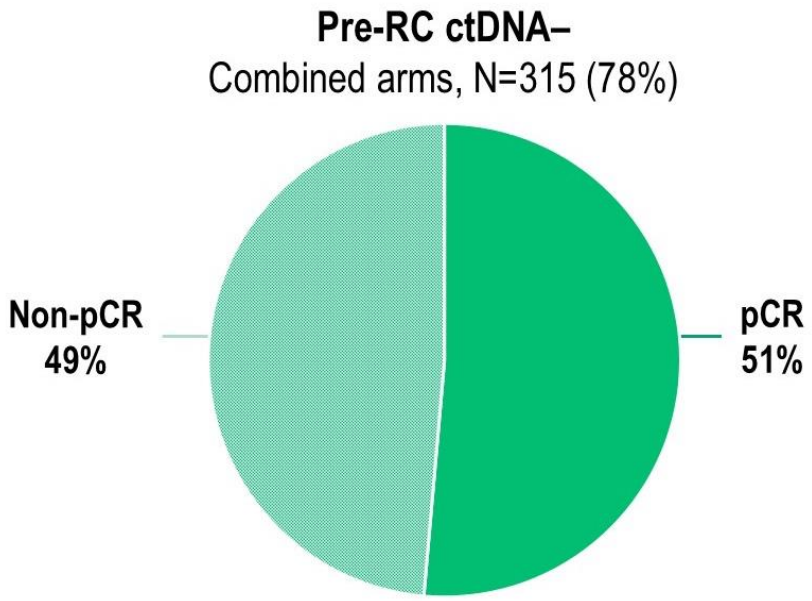
Subclinical metastases beyond the bladder

Futile Surgery

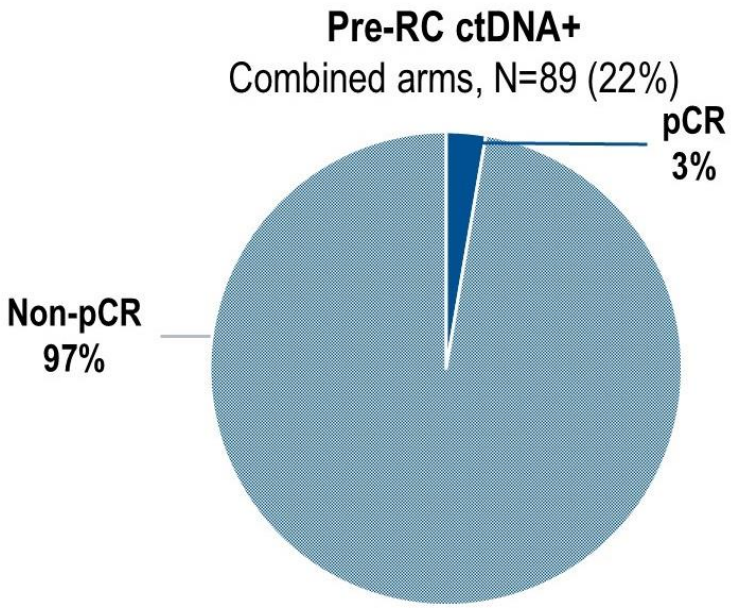
Surgery For All

NIAGARA [Gem Cis Durva Neoadjuvant]
Post NAC/Pre-Cystectomy ctDNA Detection and Pathological Complete Response

Neoadjuvant



ctDNA-
status was not associated
with pCR



ctDNA+
status was highly correlated
with non-pCR

Comparing accuracy of favorable biomarker results post NAC with pCR at cystectomy

Neoadjuvant

Negative ctDNA post NAC (Durva GC) pre cystectomy

n=315

Powles et al. ASCO 2025

VIRADS 0-3 (negative) post NAC pre cystectomy

n=68

Necchi A ...Brembilla G. BJU International. 2024

Negative TURBT with mapping biopsies post NAC pre cystectomy

n=31

Zibelman M, ...Kutikov A. J Urol. 2021;205(6):1605-11

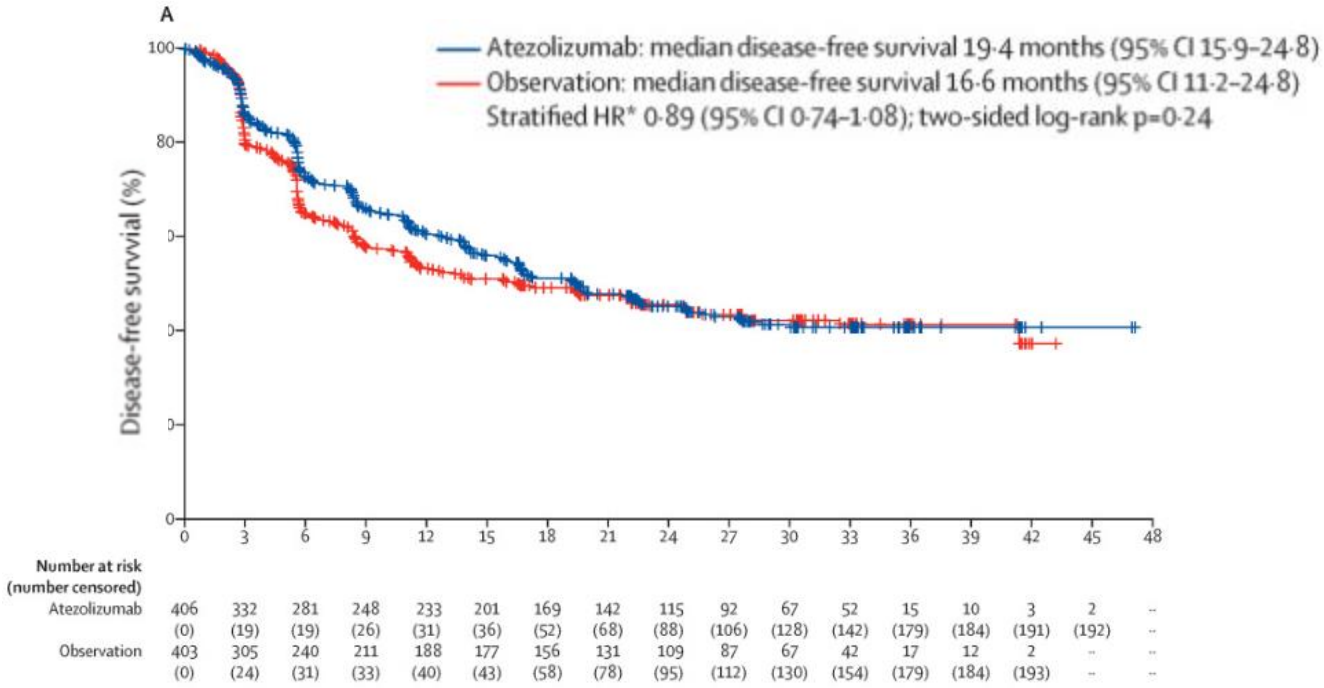
Mutation present in pre NAC (ddMVAC or GC) TURBT tissue: ATM RB1 FANCC ERCC2

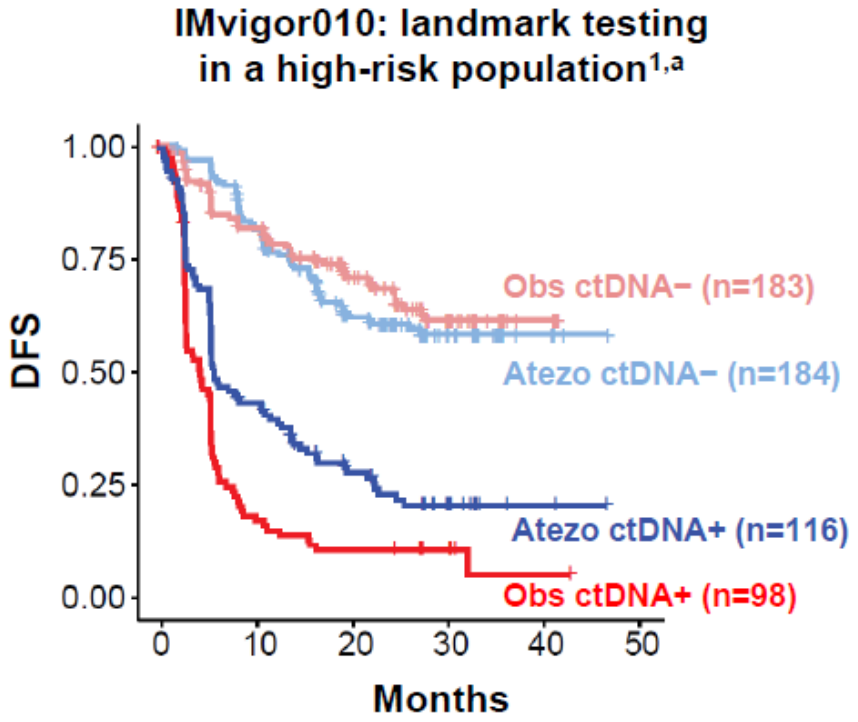
n=56

Plimack ER, ...McConkey DJ.. Eur Urol. 2024.

Adjuvant: Can ctDNA be used, in conjunction with pathologic stage, to better select patients for adjuvant therapy?

Adjuvant

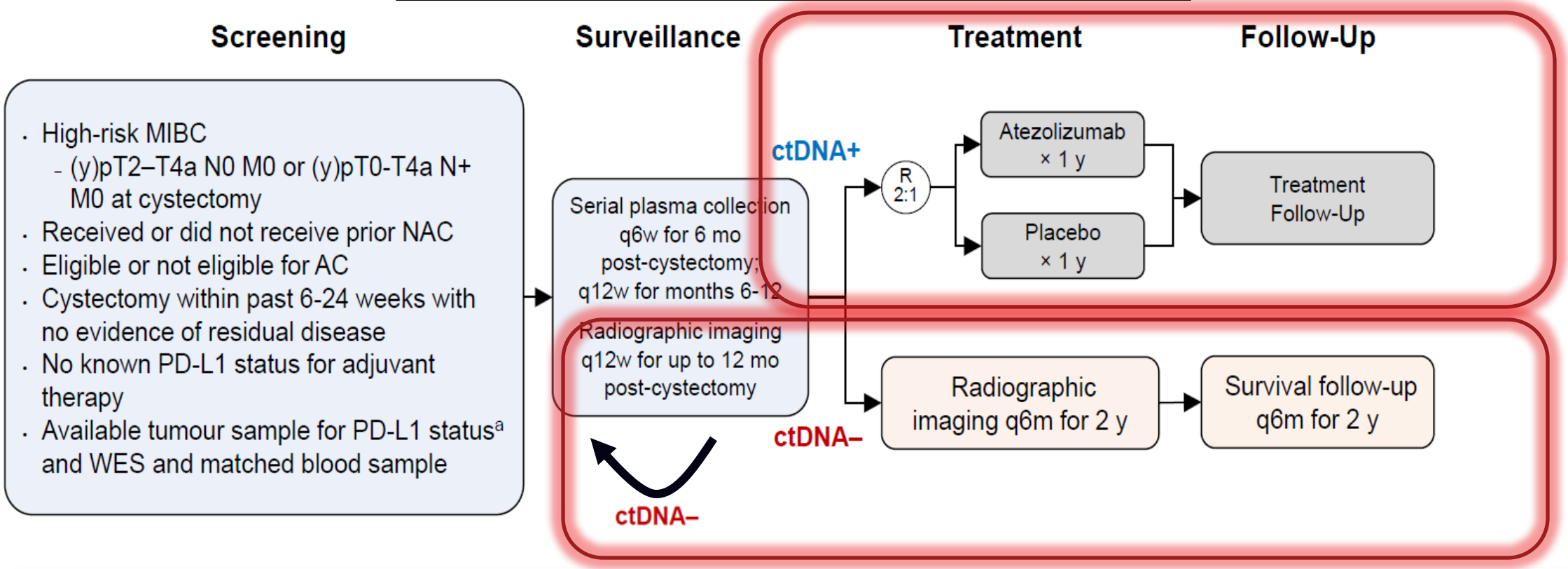




Adjuvant: Can ctDNA be used, in conjunction with pathologic stage, to better select patients for adjuvant therapy?

Adjuvant

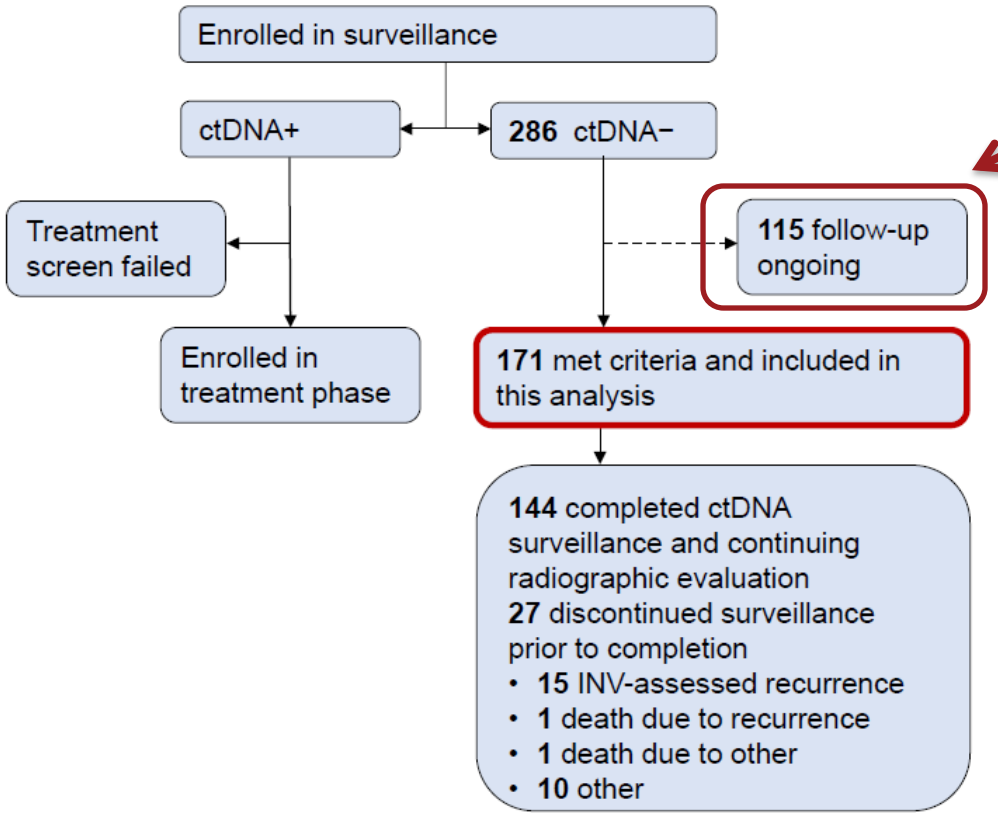
Risk adapted adjuvant therapy: IMvigor011

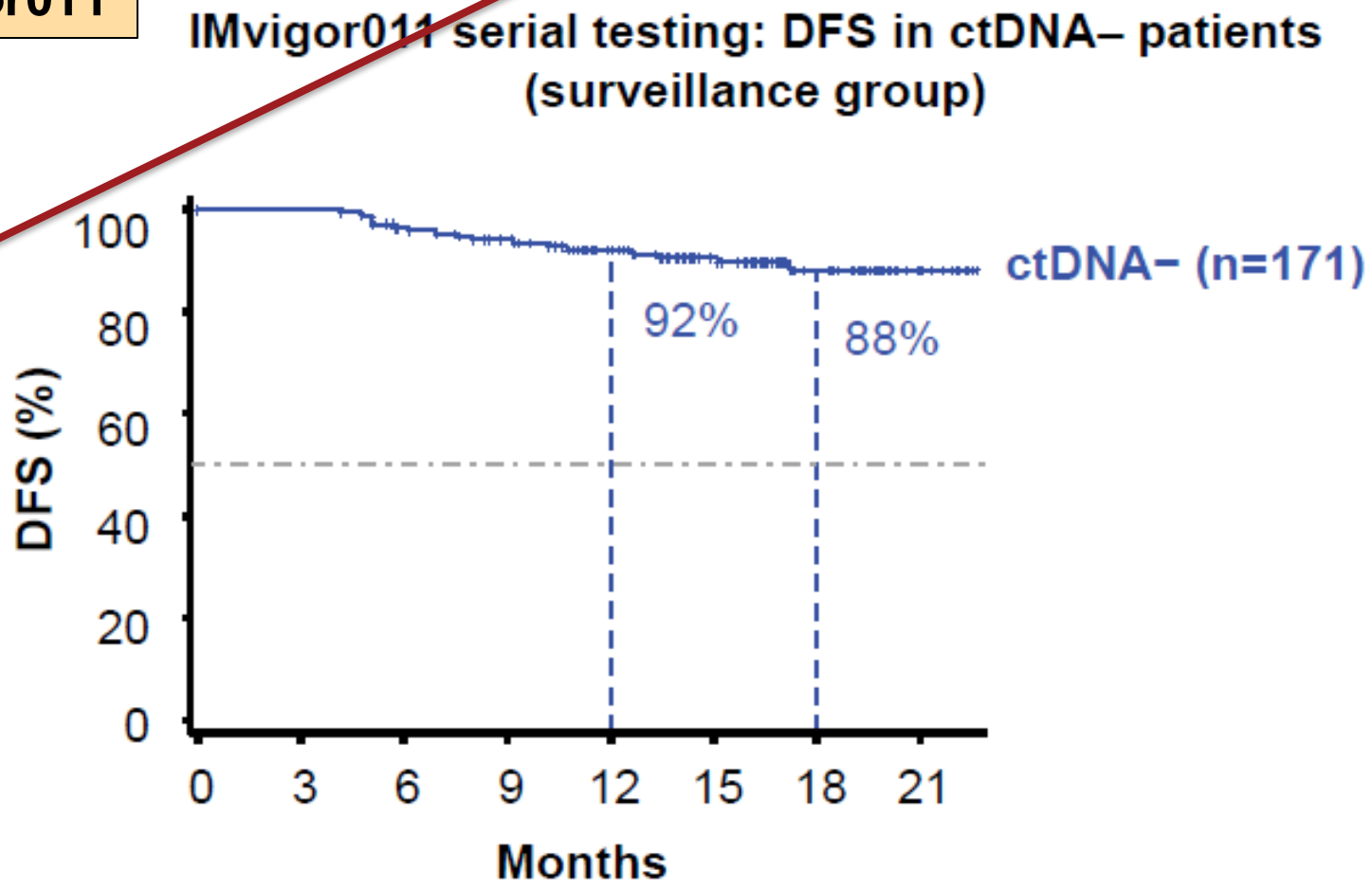


August 18 2025: *Signatera-positive patients treated with atezolizumab had statistically significant and clinically meaningful improvements in disease-free survival and overall survival*

12 month serially negative ctDNA negative patients do well – but at least 12% still relapse

Risk adapted adjuvant therapy: IMvigor011



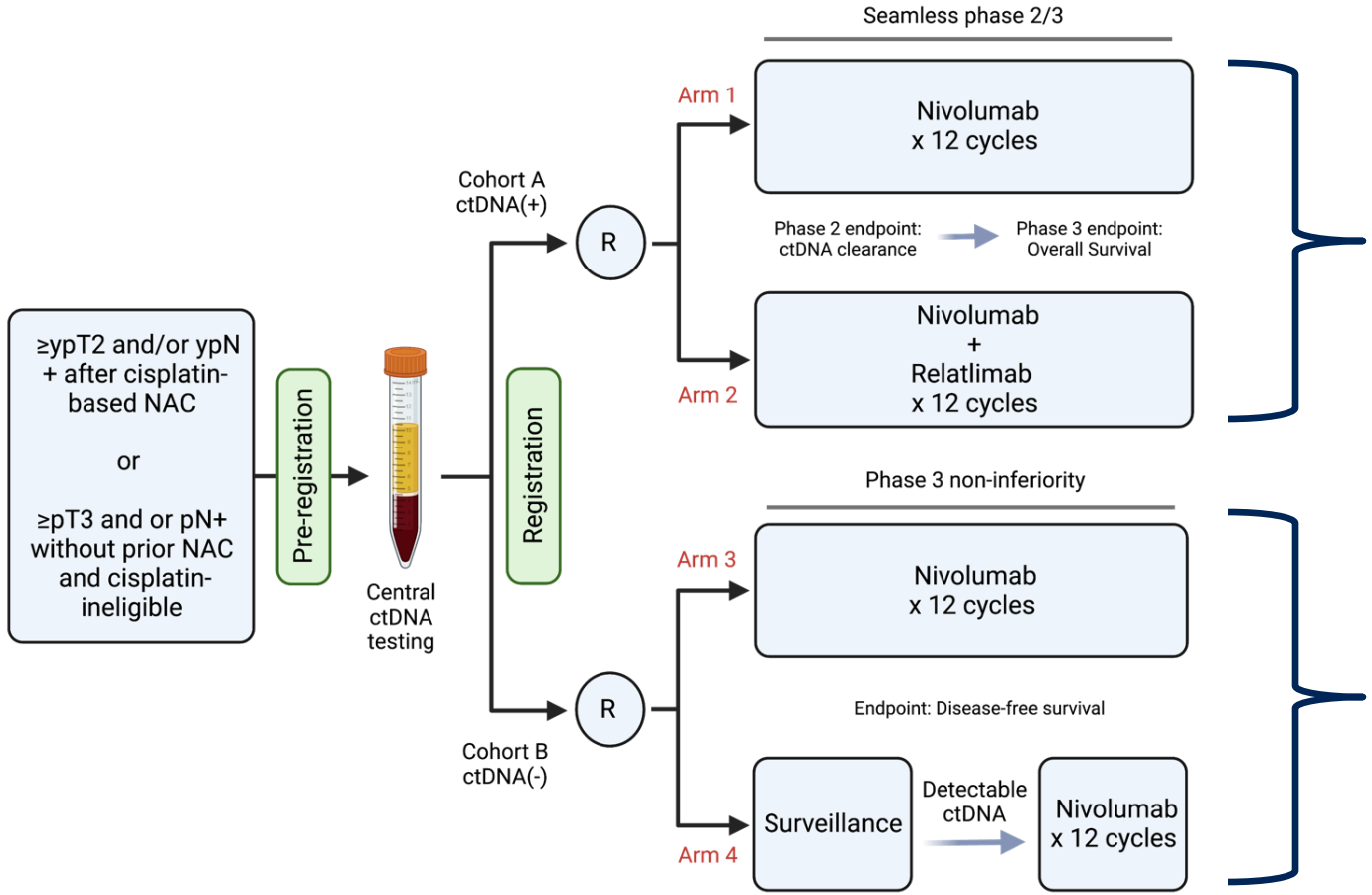


Powles T, Bellmunt T, Jensen JB, et al. EAU 2024, Paris, France. April 5-8, 2024.

Adjuvant: Can ctDNA be used, in conjunction with pathologic stage, to better select patients for adjuvant therapy?

Adjuvant

Risk adapted adjuvant therapy: MODERN

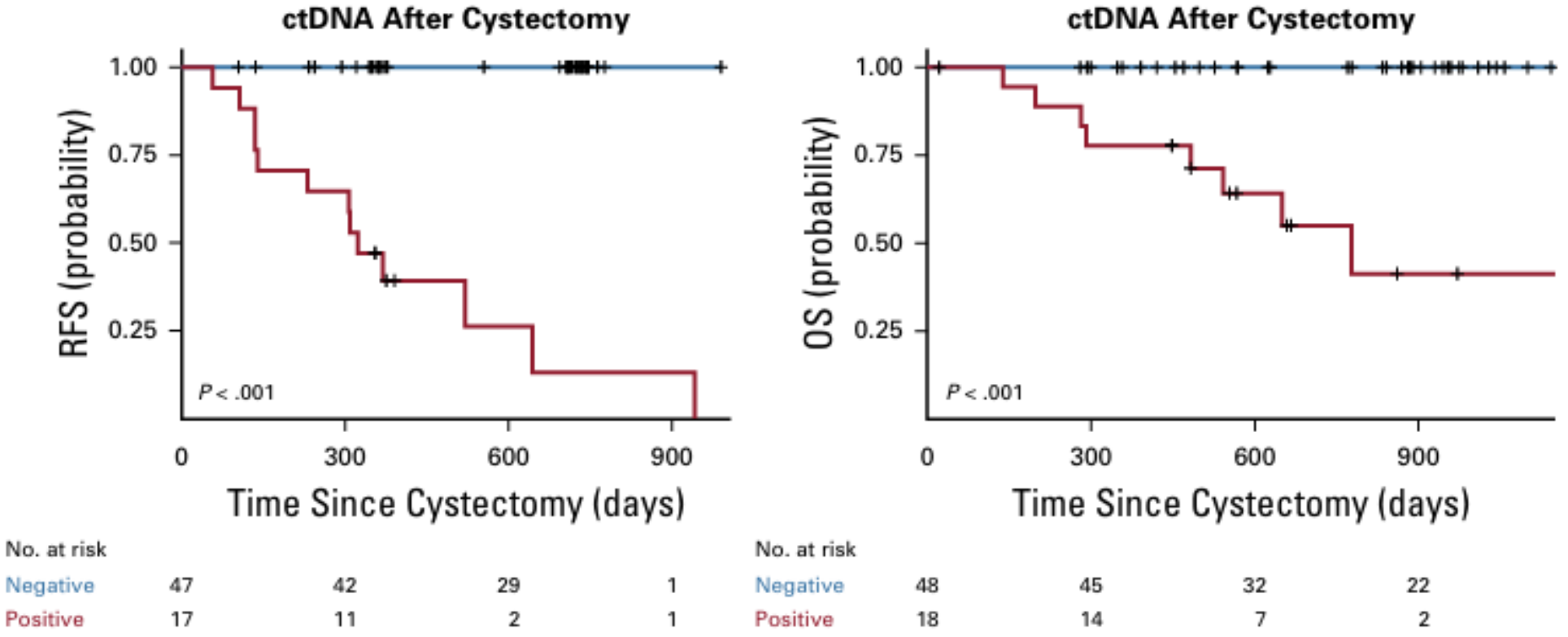


Does escalation (adding relatlimab) Improve OS in ctDNA positive?

Does nivolumab provide any DFS benefit in ctDNA negative?

2019 Danish group showed 100% (!) RFS for post cystectomy ctDNA negative

Surveillance

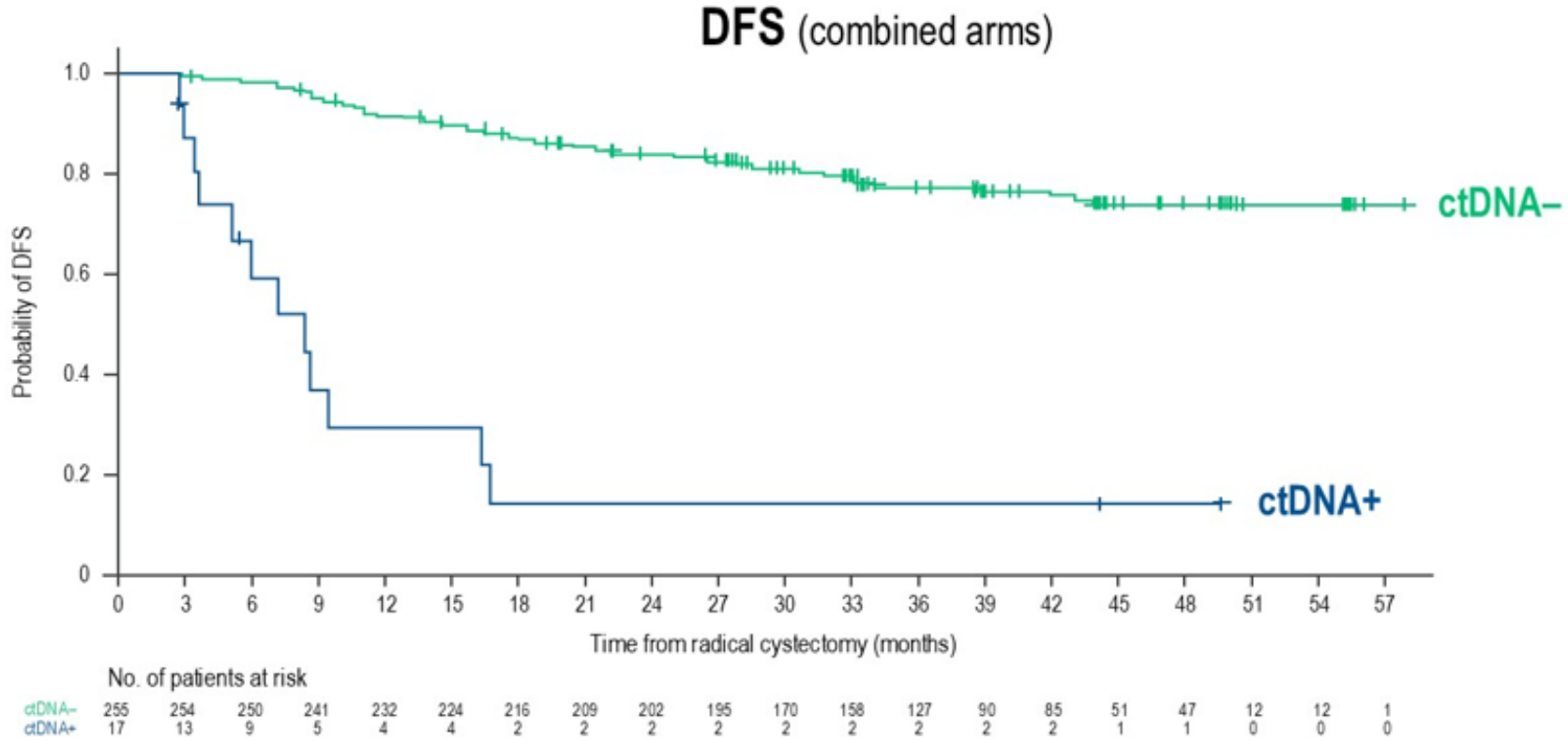


Christensen E, Birkenkamp-Demtröder K, Sethi H, et al. Early detection of metastatic relapse and monitoring of therapeutic efficacy by ultra-deep sequencing of plasma cell-free DNA in patients with urothelial bladder carcinoma. *J Clin Oncol.* 2019;37(18):1547-1557. doi:10.1200/JCO.18.02052

2025 Larger prospective studies show rate ~80%

Surveillance

NIAGARA Post-Cystectomy ctDNA- vs ctDNA+



ctDNA– vs ctDNA+ HR, 0.09 (95% CI, 0.05–0.18)

Powles T, et al. ASCO 2025

Metastatic Disease: ctDNA does not closely correlate with imaging

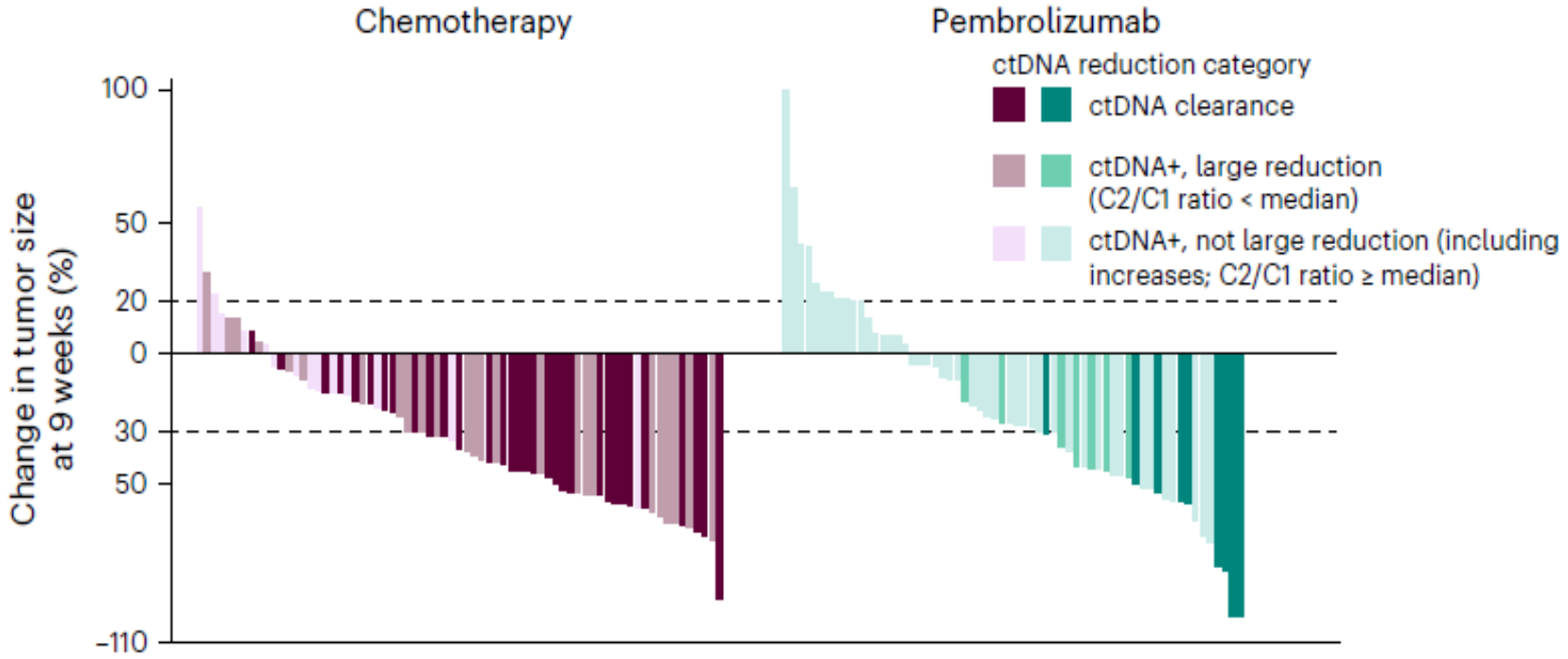
Metastatic

KEYNOTE-361 Study Design (NCT02853305)

- **Locally advanced unresectable or metastatic urothelial carcinoma**
- **No prior systemic therapy for advanced disease**

R (1:1:1)

- Pembrolizumab + Gemcitabine + Platinum for ≤6 cycles → Pembrolizumab for ≤6 cycles
- Pembrolizumab for ≤35 cycles
- Gemcitabine + Platinum for ≤6 cycles



Powles, T., Chang, YH., Yamamoto, Y. *et al.* Pembrolizumab for advanced urothelial carcinoma: exploratory ctDNA biomarker analyses of the KEYNOTE-361 phase 3 trial. *Nat Med* **30**, 2508–2516 (2024). https://doi.org/10.1038/s41591-024-03091-7

World Conference On
Genitourinary Cancers
2025 NASHVILLE, TN

WHAT'S DIFFERENT WITH MRD IN PROSTATE?

Michael Schweizer, MD
University of Washington / Fred Hutch Cancer Center

August 23, 2025

Accredited by
PIM Postgraduate Institute for Medicine
Professional Excellence in Medical Education

Twitter: @MikeSchweizerMD

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Minimal Residual Disease and Prostate Cancer

MRD status is not routinely used or well defined in prostate cancer… may refer to:

- **Pathologic assessment of disease burden post-prostatectomy… usually in context of neoadjuvant trials**

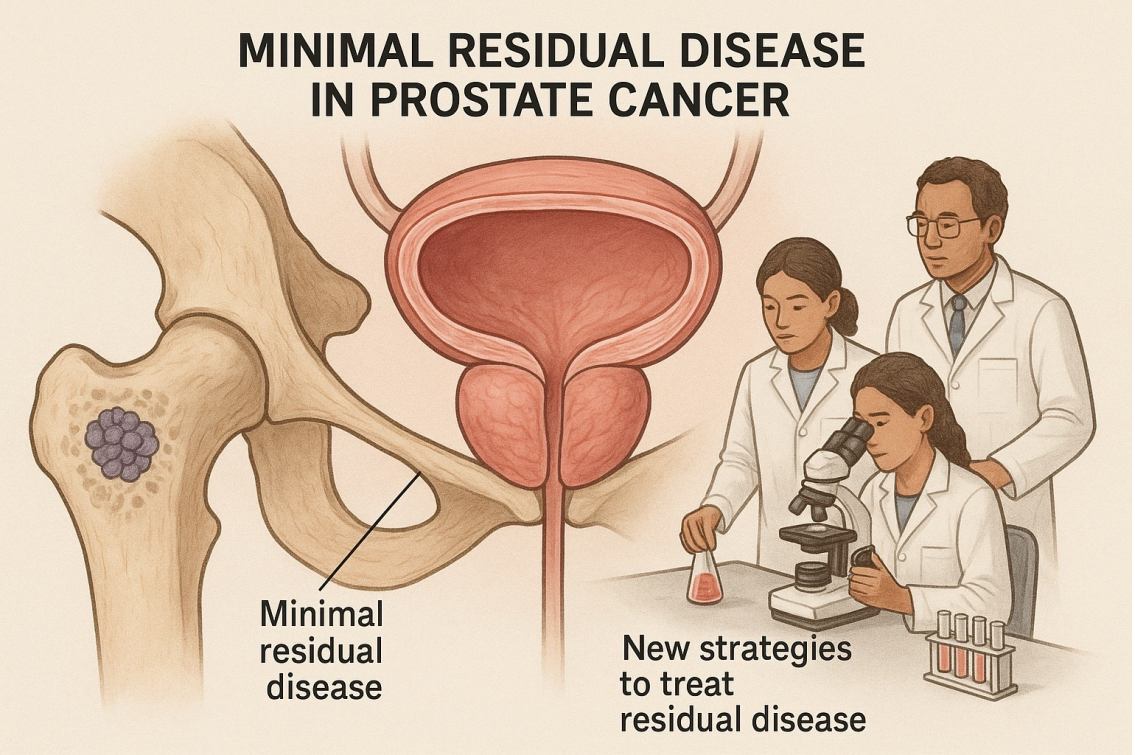
  or

- **Residual microscopic disease after local therapy: PSA vs ctDNA**

  or

- **Residual low volume disease on next-gen imaging… next talk**

Michael Schweizer, MD



”Generate an image to depict minimal residual disease in prostate cancer… Add some scientists”

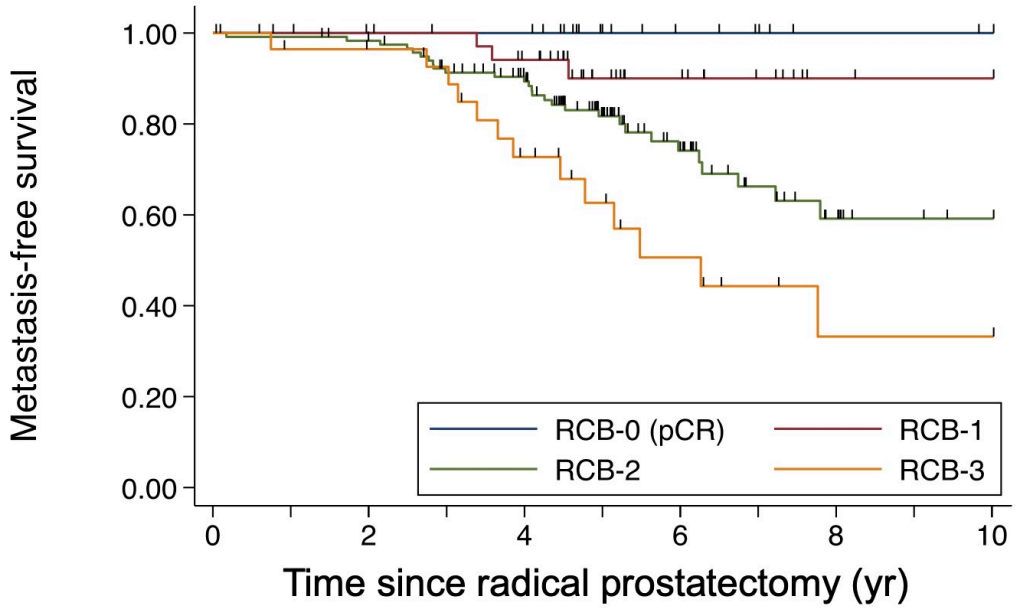
MRD: Neoadjuvant Studies

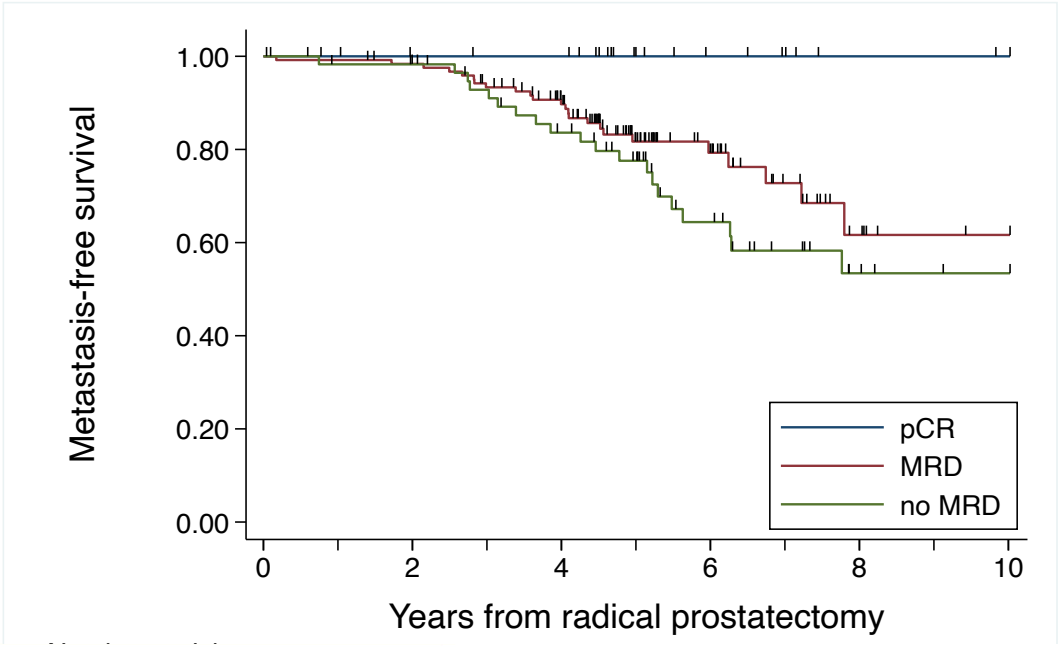
- **Neoadjuvant trials testing ADT have historically shown pathologic complete response (pCR) rates of ~5%[1-4]**
- **pCR up to ~10% with contemporary androgen receptor (AR) pathway inhibitors (ARPI) with an addition ~10% with minimal residual disease[5,6]**
- **MRD: Most studies define as ≤5mm residual tumor in the longest cross-section at RP**

Variable	ELAP, No. (%)	EL, No. (%)
No. of patients	50	25
ypT stage		
T0	5 (10)	2 (8)
T2	20 (40)	9 (36)
T3a	16 (32)	7 (28)
T3b	9 (18)	7 (28)
Pathology N stage		
N0	45 (90)	22 (88)
N1	5 (10)	3 (12)
Positive surgical margins		
No	41 (82)	22 (88)
Yes	9 (18)	3 (12)
Extracapsular extension		
No	27 (54)	12 (48)
Yes	23 (46)	13 (52)
Positive seminal vesicle invasion		
No	41 (82)	18 (72)
Yes	9 (18)	7 (28)
Pathologic response		
pCR	5 (10)	2 (8)
MRD (≤ 5 mm)*	10 (20)	2 (8)
pCR or MRD	15 (30)	4 (16)
Downstaging	3 (6)	1 (4)
Stable staging	10 (20)	5 (20)
Upstaging	21 (42)	15 (60)
Unevaluable†	1 (2)	—
Median total tumor volume, mL (range)	0.6 (0-10.4)	0.8 (0-10.1)
Median cellularity, % (range)	5 (0-60)	7 (0-50)
Median RCB, cm^3 (range)	0.03 (0-4.0)	0.05 (0-5.0)

1. Klotz LH, et al. The Journal of urology 2003;170:791-4.
2. Gleave ME, et al. The Journal of urology 2001;166:500-6; discussion 6-7.
3. Labrie F, et al. Urology 1997;49:56-64.
4. van der Kwast TH, et al. Urology 1999;53:523-9.
5.. Ravi, et al. E Urol. 87 (2025) 643 – 650
6. McKay, et al.. J Clin Oncol. 2019 Apr 10;37(11):923-931

Residual Cancer Burden Post-prostatectomy



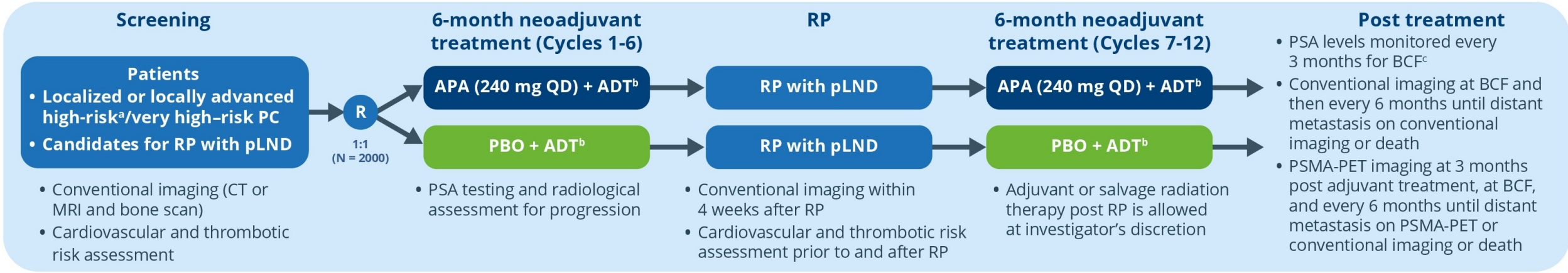


	Hazard ratio (95% CI)	*p* value
Prostate-specific antigen (per 1-unit increment, log-transformed)	1.30 (0.96–1.77)	0.094
cT3–4 stage (vs cT1–2)	2.58 (1.38–4.82)	0.003
Gleason 9–10 (vs 7–8)	2.29 (1.20–4.36)	0.012
Residual cancer burden (per 1-unit increment)	1.21 (1.01–1.47)	0.039

CI = confidence interval.

Ravi, et al. E Urol. 87 (2025) 643 – 650

Phase 3 PROTEUS Trial



Primary end points (assessed by blinded independent central review)

- **pCR rate**
- **MFS**: Time from randomization to date of first occurrence of radiographic distant metastasis on conventional imaging, histopathologic finding of distant metastasis, or death from any cause, whichever occurs first

Secondary end points

- **PSA-free survival**
- **PFS**

Additional end points

- Overall survival
- Second PFS
- Time to castration-resistant PC
- Time to BCF
- Time to testosterone recovery
- Time to first subsequent therapy (including reinitiation of ADT)
- % of patients with no evidence of disease on PSMA-PET imaging
- % of patients receiving postoperative RT
- Patient-reported outcomes
- MFS based on PSMA-PET or conventional imaging
- Failure-free survival[f]

Safety

- Based on periodic physical examination, vital signs, and clinical laboratory tests at clinic visits

Kibel, et al. J Clin Oncol 40, 2022 (suppl 6; abstr TPS285)

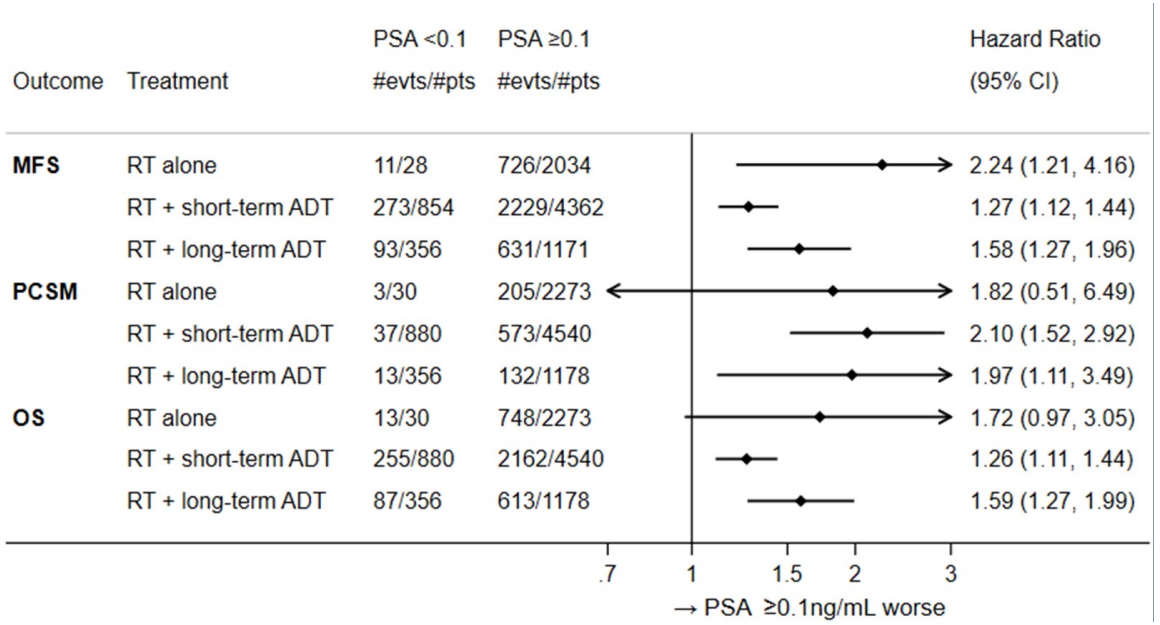
Early relapse monitoring: ctDNA vs PSA

PSA

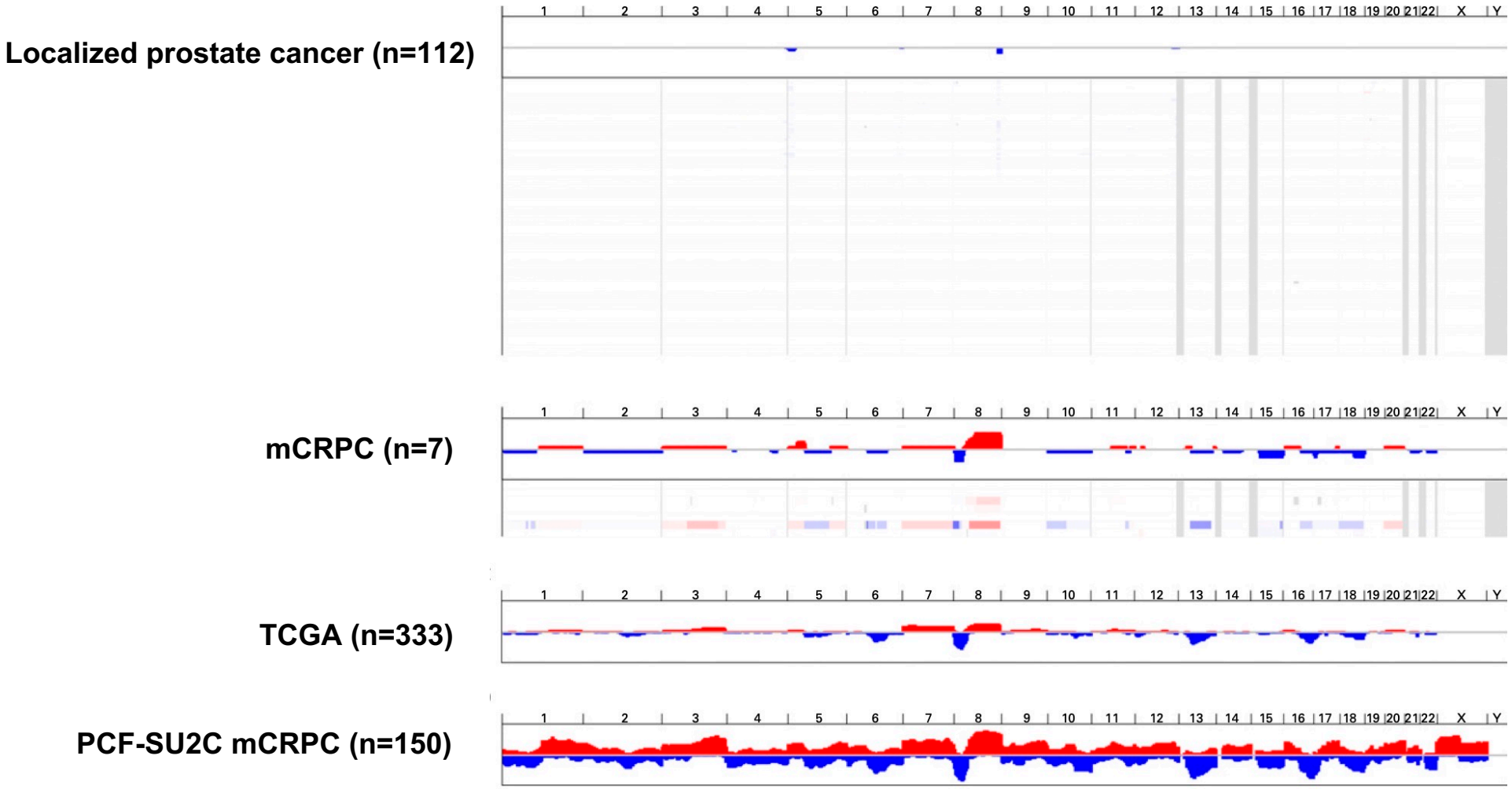
- **Pros: cheap, results in real time, clinically actionable and likely prognostic post-definitive therapy**
- **Cons: may not be elevated in aggressive prostate cancer variants, lags clinically relevant endpoints (i.e. PFS, OS)**

ctDNA

- **Pros: Can also provide actionable genomic data (in metastatic setting)**
- **Cons: Not sensitive in non-metastatic setting**

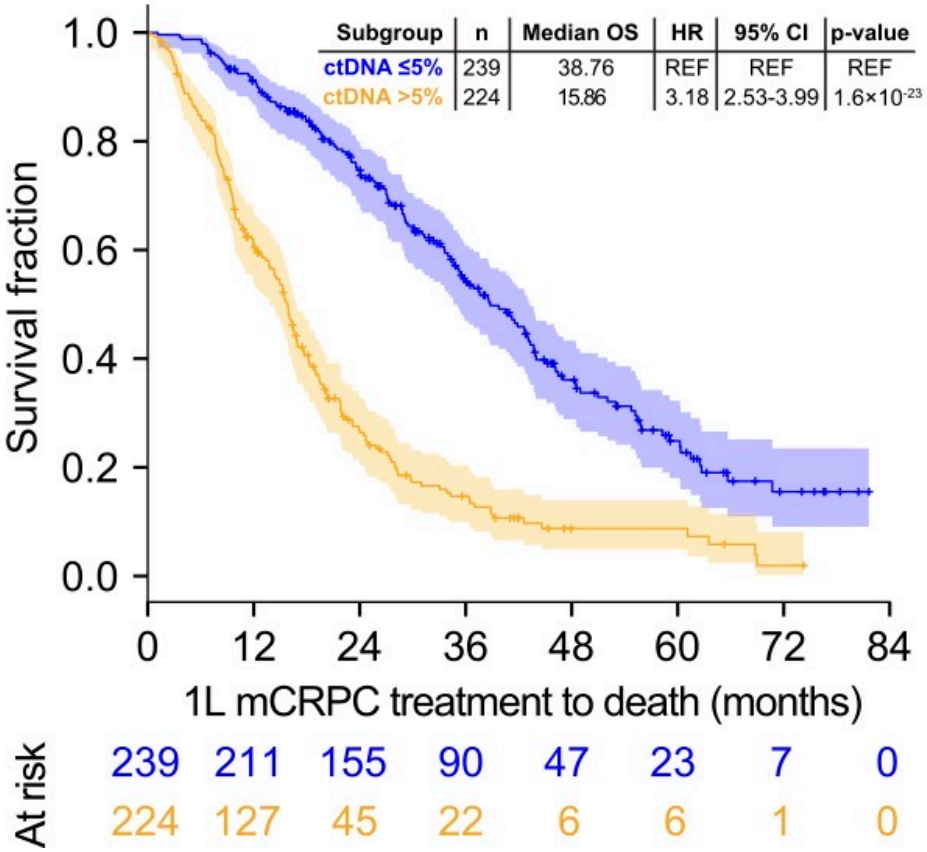


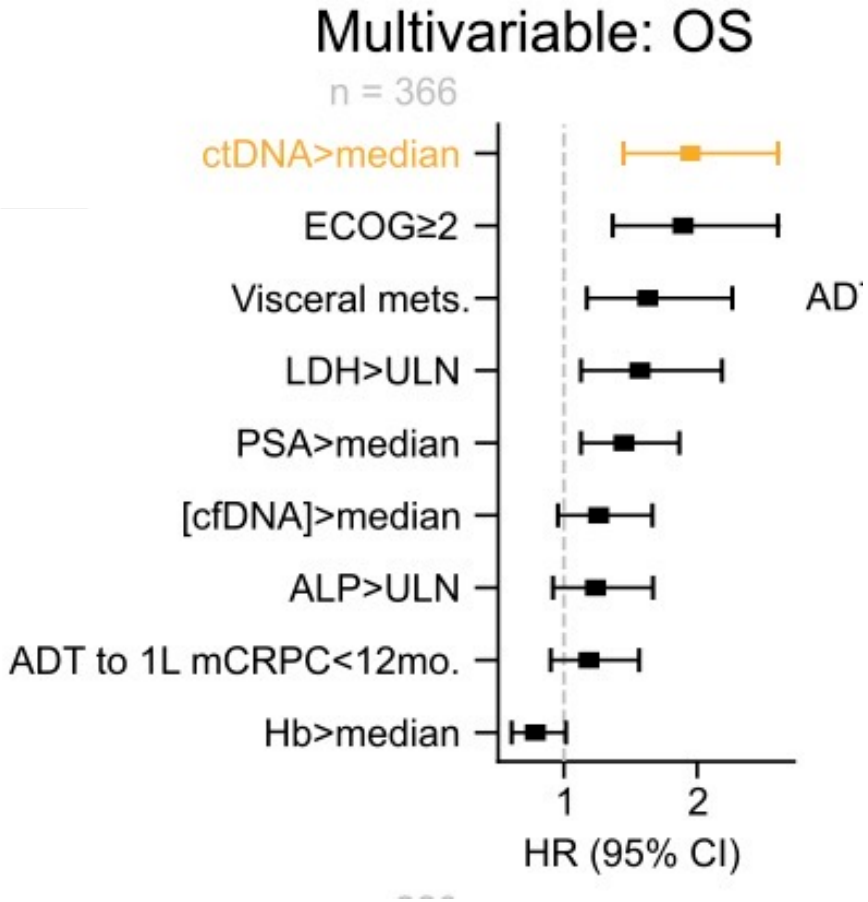
ULP Whole-genome Sequencing of ctDNA



Hennigan, et al. JCO Precis Oncol. 2019:3:PO.19.00176

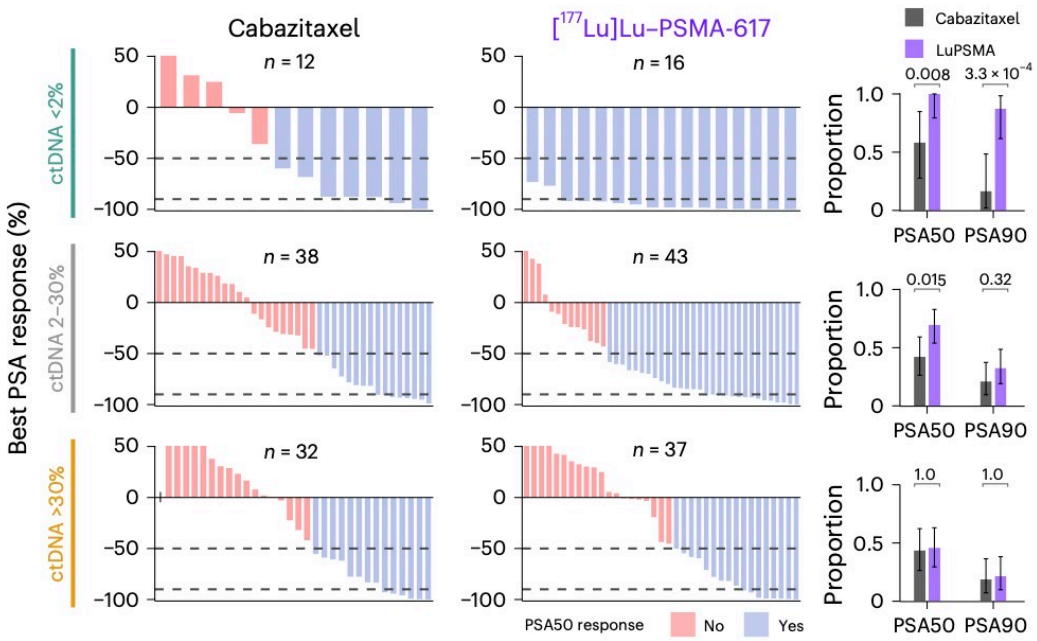
ctDNA fraction in mCRPC is prognostic

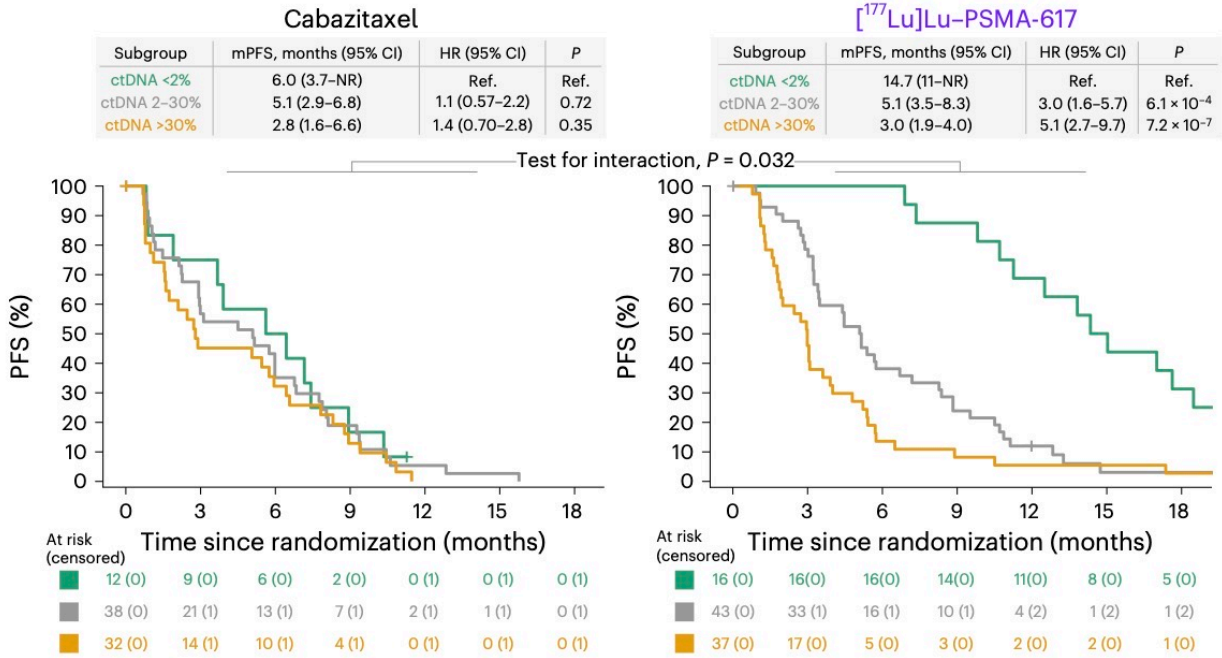




Fonseca, et al. Nat Commun. 2024 Feb 28;15(1):1828.

ctDNA fraction in mCRPC is prognostic





Subgroup	mPFS, months (95% CI)	HR (95% CI)	P
ctDNA <2%	6.0 (3.7–NR)	Ref.	Ref.
ctDNA 2–30%	5.1 (2.9–6.8)	1.1 (0.57–2.2)	0.72
ctDNA >30%	2.8 (1.6–6.6)	1.4 (0.70–2.8)	0.35

Subgroup	mPFS, months (95% CI)	HR (95% CI)	P
ctDNA <2%	14.7 (11–NR)	Ref.	Ref.
ctDNA 2–30%	5.1 (3.5–8.3)	3.0 (1.6–5.7)	6.1×10^{-4}
ctDNA >30%	3.0 (1.9–4.0)	5.1 (2.7–9.7)	7.2×10^{-7}

Kwan, et al. Nat Med. 2025 May 27. doi: 10.1038/s41591-025-03704-9

Summary

- MRD status in neoadjuvant trials appears to correlate with outcomes… more prospective data needed
- PSA is sensitive for early relapse… hard to beat in practice
- ctDNA lacks sensitivity in the non-metastatic setting

World Conference On
Genitourinary Cancers
2025 NASHVILLE, TN

EMERGING DATA IN IMAGING MRD: PSMA PET AND BIOCHEMICAL RECURRENCE (BCR)

Ravi A. Madan
National Cancer Institute

August 23, 2025

Accredited by
PIM Postgraduate Institute for Medicine
Professional Excellence in Medical Education

@Dr_RaviMadan

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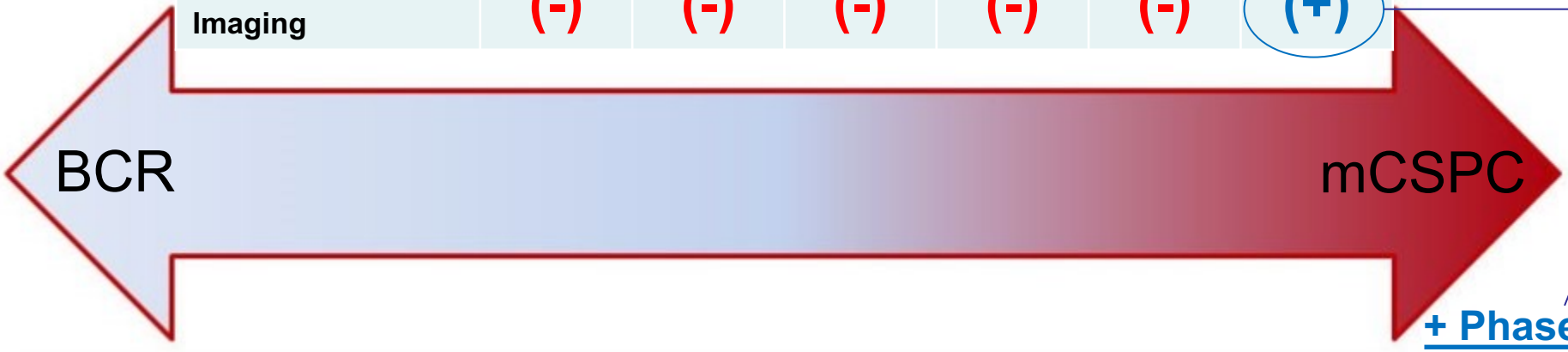
PART OF THE LOCKWOOD GROUP

PSMA PET and the *Continuum* of BCR to mCSPC

PET Imaging	(-)	(-)	(+)	(+)	(+)	(+)
Conventional Imaging	(-)	(-)	(-)	(-)	(-)	(+)



Negative Data for ADT
ELAAT/TOAD trial
(Loblaw et al, ASCO 2018)

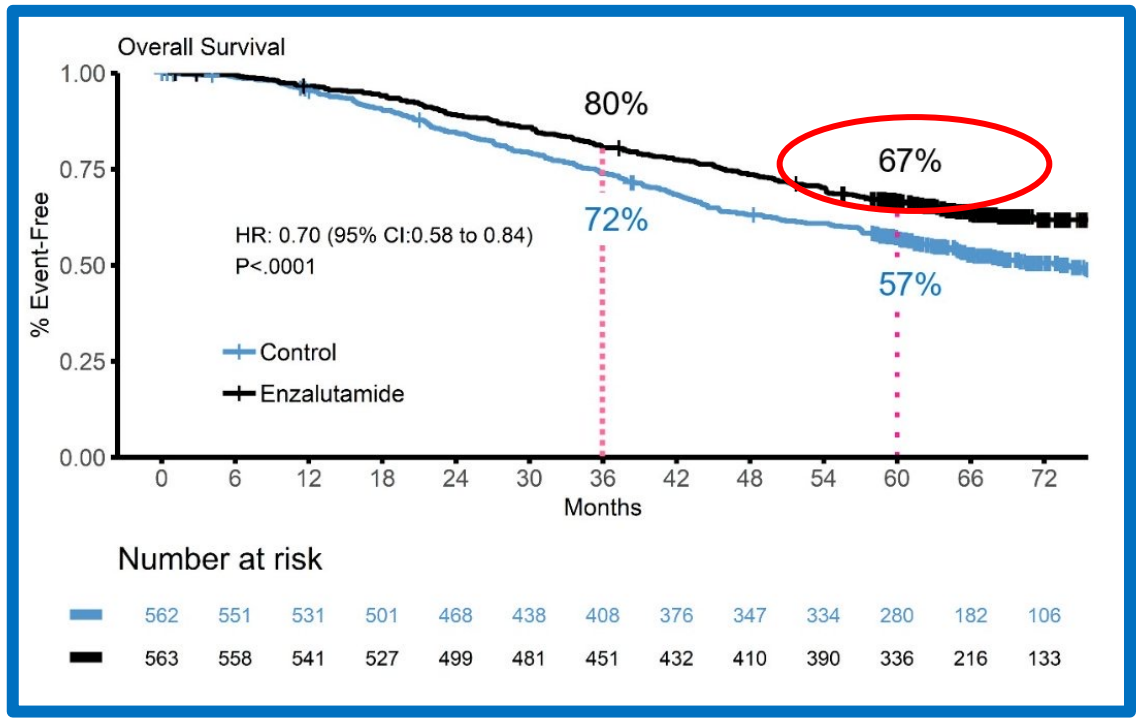
TAX3503: ADT + Docetaxel
(Morris, MJ et al. Eur Urol Oncol, 2021)

+ Phase 3*
CHAARTED
ENZAMET
LATTITUDE
PEACE1
(*PET Imaging Not Evaluated)
Recurrent Pts a Minority

Adapted from Kase AM et al, Cancers 2022

But the Proof is in The Pudding
BCR ≠ mCSPC

mCSPC
ENZAMET:
ADT +/-Enzalutamide
Davis, I et al. ASCO, 2022



BCR
EMBARK:
ADT +/-Enzalutamide
Freedland, SJ et al. NEJM, 2023

- ADT + Enza = 92% at 5 years
- Enza Monotherapy = 90% at 5 years
- ADT alone = 87% at 5 years
- Median age is 71 years old!

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Brief Correspondence

Clinical and Genomic Differences Between Advanced Molecular Imaging-detected and Conventional Imaging-detected Metachronous Oligometastatic Castration-sensitive Prostate Cancer

Philip Sutera[a], *Yang Song*[b,c], *Kim Van der Eecken*[d,e], *Amol C. Shetty*[b,c], *Keara English*[a], *Theresa Hodges*[b,c], *Jinhee Chang*[c], *Valérie Fonteyne*[f], *Zaker Rana*[c], *Lei Ren*[c], *Adrianna A. Mendes*[g], *Nicolaas Lumen*[f], *Louke Delrue*[h], *Sofie Verbeke*[e], *Kathia De Man*[i], *Daniel Y. Song*[a,j,k], *Kenneth Pienta*[j,k], *Felix Y. Feng*[l], *Steven Joniau*[m], *Tamara Lotan*[g], *Barton Lane*[n], *Ana Kiess*[a], *Steven Rowe*[o], *Martin Pomper*[a,j,k,o], *Theodore DeWeese*[a], *Matthew Deek*[p], *Christopher Sweeney*[q], *Piet Ost*[d,r,†,*], *Phuoc T. Tran*[a,c,†,*]

"Patients with CIM-omCSPC had significantly higher Gleason grade group (p = 0.032), higher prostate-specific antigen at omCSPC diagnosis (8.0 vs 1.7 ng/ml; p < 0.001), more frequent pathogenic TP53 mutations (28% vs 17%; p = 0.030), and worse 10-yr OS (85% vs 100%; p < 0.001)."

OS Benefit from EMBARK *Likely* to be Biomarker Driven

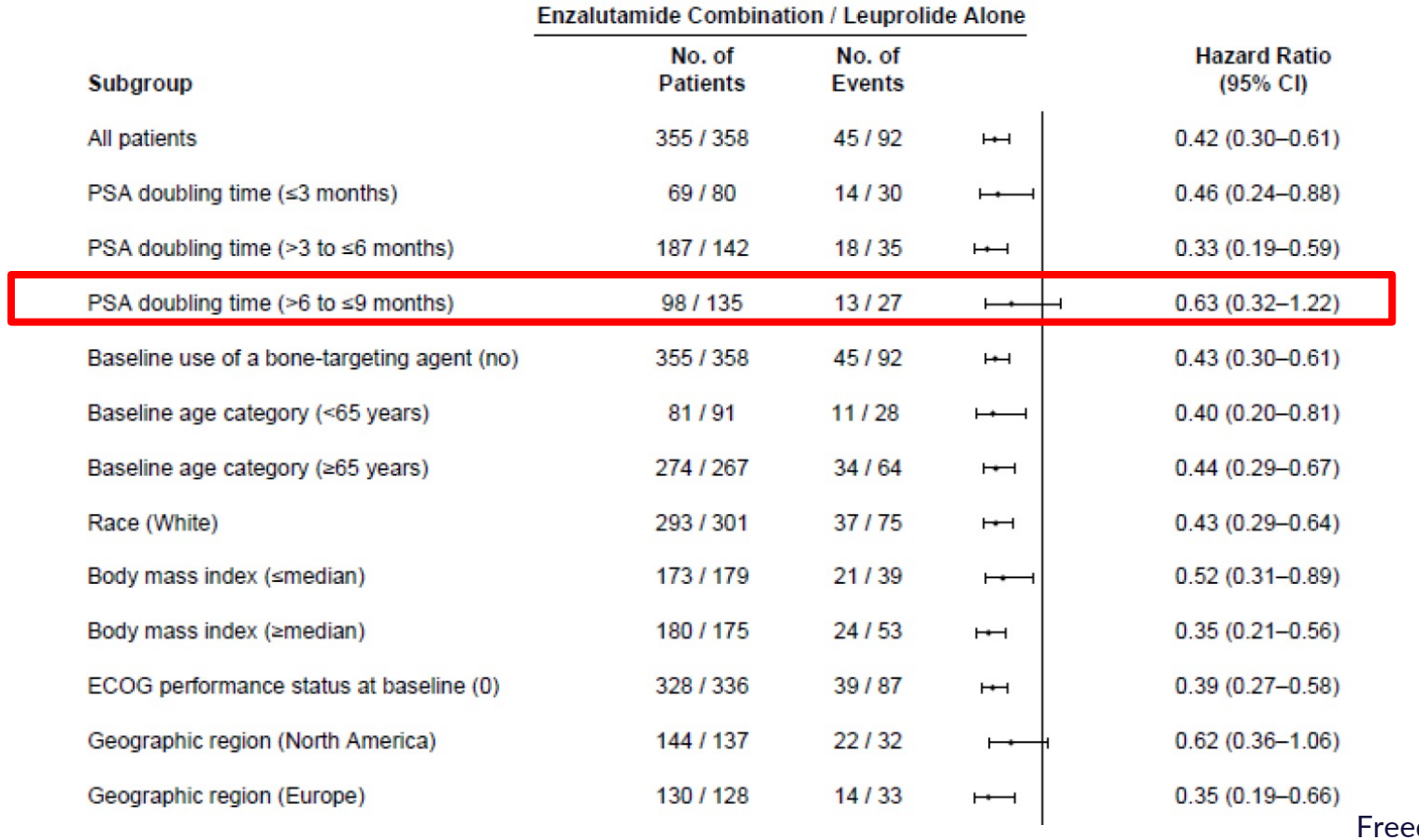
- ADT + Enza = 92% at 5 years
- Enza Monotherapy = 90% at 5 years
- ADT alone = 87% at 5 years
- Median age is 71 years old!

Freedland, SJ et al. NEJM, 2023

OS Benefit from EMBARK *Likely* to be Biomarker Driven

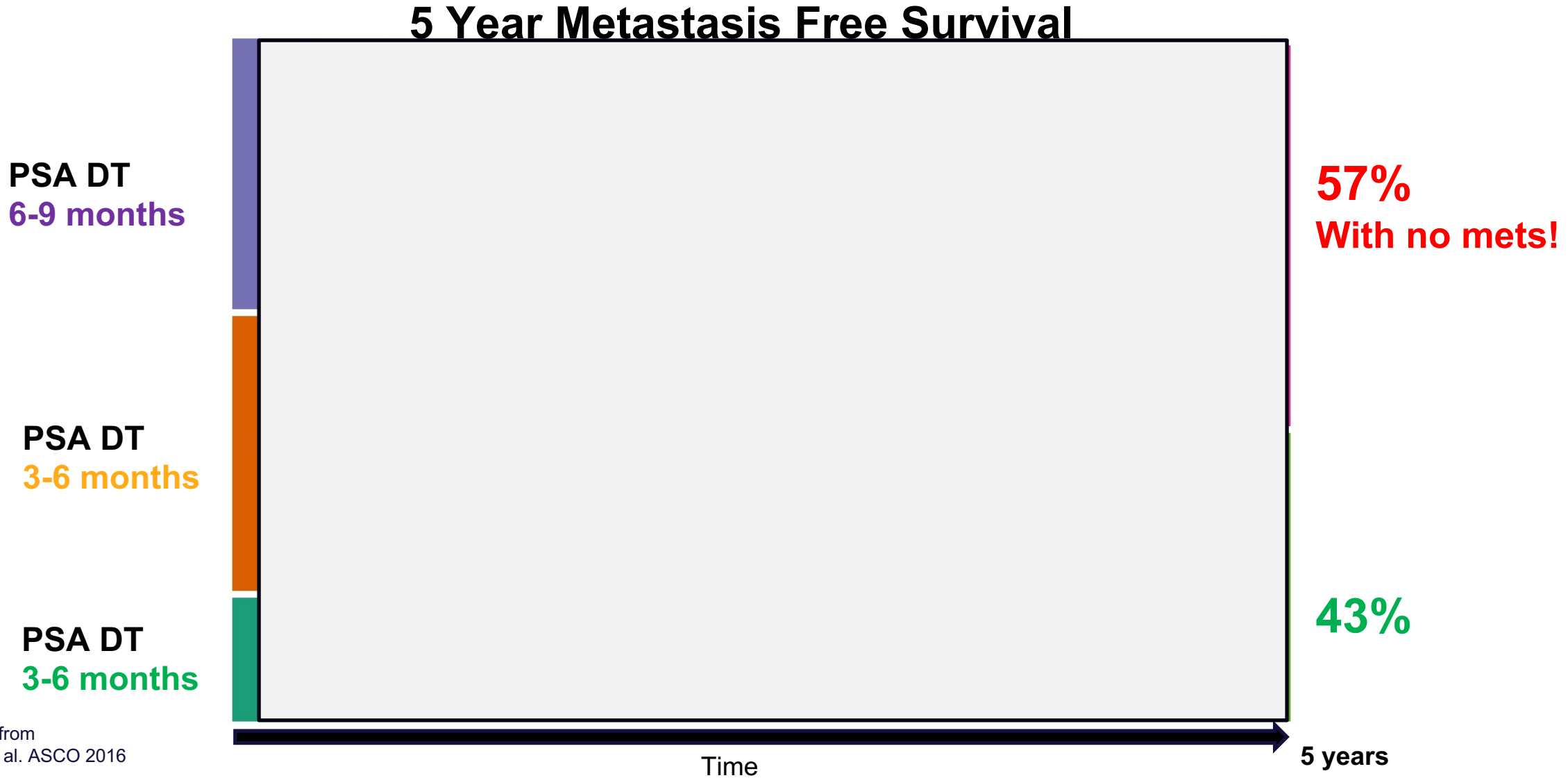
Figure S3. Metastasis-free Survival for Pre-specified Subgroups Enzalutamide Combination vs. Leuprolide Alone (ITT Population).*

Subgroup	Enzalutamide Combination / Leuprolide Alone: No. of Patients	Enzalutamide Combination / Leuprolide Alone: No. of Events	Hazard Ratio (95% CI)
All patients	355 / 358	45 / 92	0.42 (0.30–0.61)
PSA doubling time (≤3 months)	69 / 80	14 / 30	0.46 (0.24–0.88)
PSA doubling time (>3 to ≤6 months)	187 / 142	18 / 35	0.33 (0.19–0.59)
PSA doubling time (>6 to ≤9 months)	98 / 135	13 / 27	0.63 (0.32–1.22)
Baseline use of a bone-targeting agent (no)	355 / 358	45 / 92	0.43 (0.30–0.61)
Baseline age category (<65 years)	81 / 91	11 / 28	0.40 (0.20–0.81)
Baseline age category (≥65 years)	274 / 267	34 / 64	0.44 (0.29–0.67)
Race (White)	293 / 301	37 / 75	0.43 (0.29–0.64)
Body mass index (≤median)	173 / 179	21 / 39	0.52 (0.31–0.89)
Body mass index (≥median)	180 / 175	24 / 53	0.35 (0.21–0.56)
ECOG performance status at baseline (0)	328 / 336	39 / 87	0.39 (0.27–0.58)
Geographic region (North America)	144 / 137	22 / 32	0.62 (0.36–1.06)
Geographic region (Europe)	130 / 128	14 / 33	0.35 (0.19–0.66)



Freedland, SJ et al. NEJM, 2023

MFS with NO Therapy Based on Johns Hopkins Data



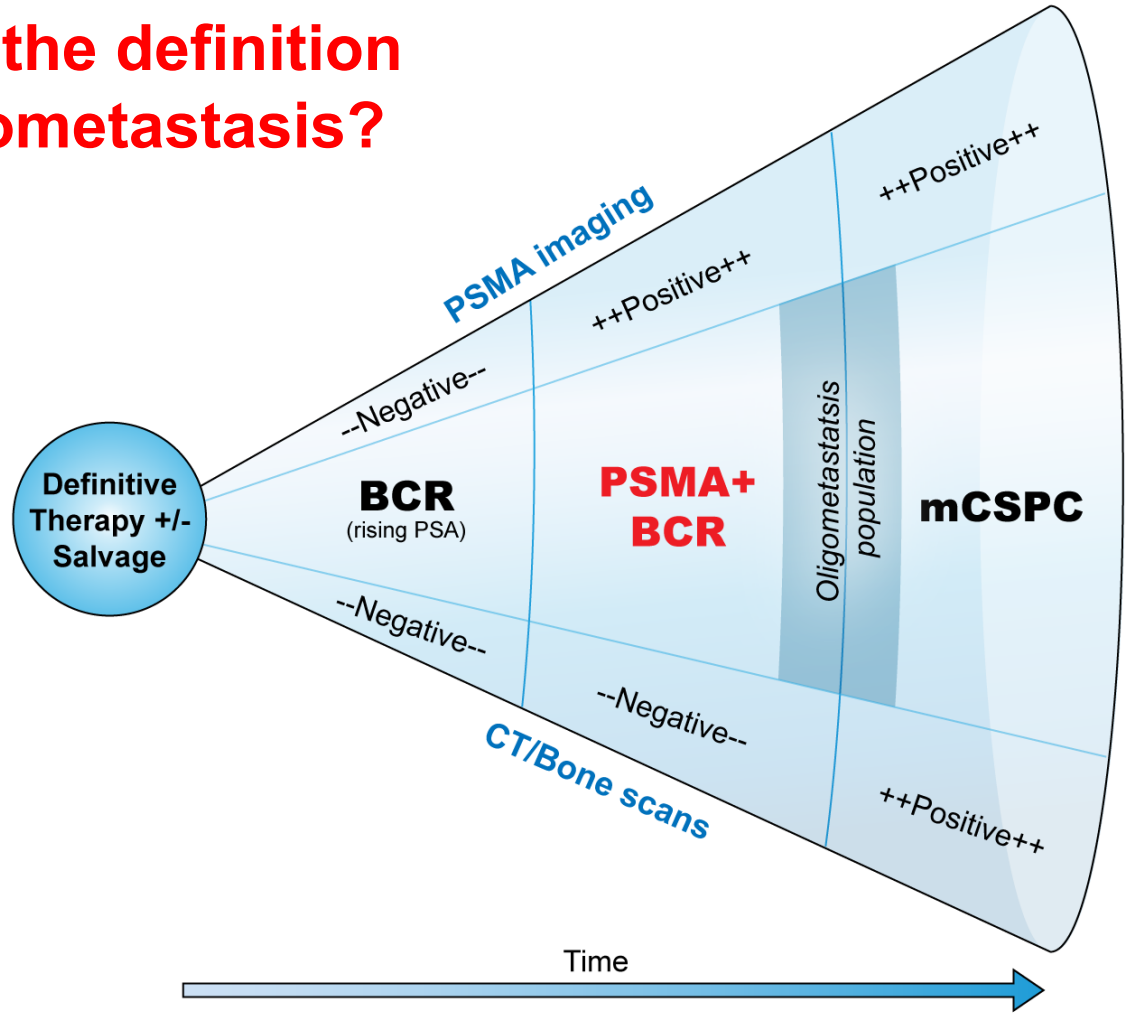
Based on Data from
Suzman, DL. et al. ASCO 2016

Is there Data Supporting SBRT to “Oligometastasis”?

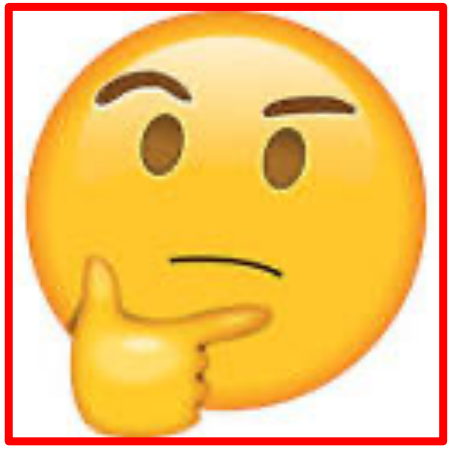
What is the definition of Oligometastasis?

ADT?

Baseline PSA DT?



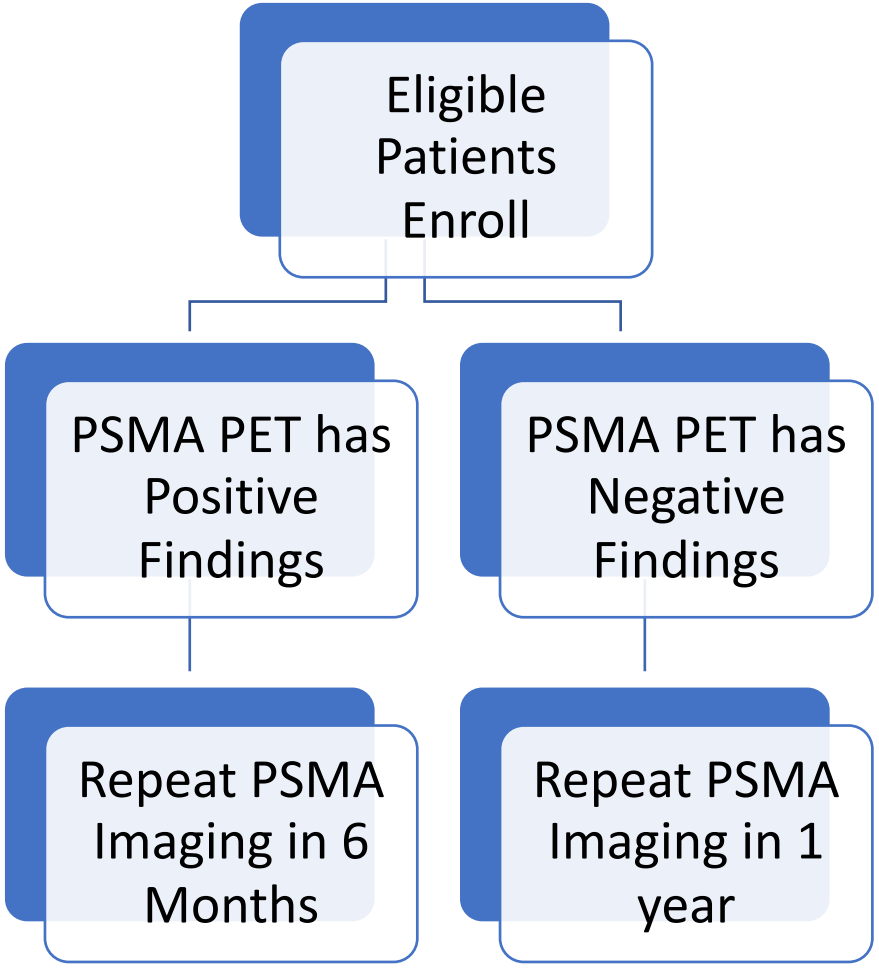
ADT+ ARPI?



Eugonadal PFS Benefit?

Figure from Einstein DJ et al., in review.

Prospective PSMA Monitoring Study: NCT05588128



- Enroll up to 350 pts
- 5 Year of Follow-up

Inclusion Criteria

- History of primary treatment for prostate cancer (either surgery or radiation).
- PSA ≥ 0.50
- Testosterone >100

Exclusion Criteria

- Evidence of soft tissue disease on CT scan
- Evidence of bone lesions on Tc99 bone scan
- Prostatectomy within 1 year before entering the study

Total Enrollment over 140 pts

Patient Characteristics at Baseline

	N= 86 patients	
Median Age	71 years	range 48-92
Median PSA	3.05 ng/ml	range 0.5-71.6
Median PSA Doubling Time	11.1 months	range 1.2 – 132.4
Patients with PSA DT ≤ 6 months	25 (29%)	
Negative PSMA	10 (12%)	
Positive PSMA	76 (88%)	
Prostate Only	17 (20%)	
Beyond Prostate	59 (68%)	
1 Lymph node	17 pts	
2-3 Lymph nodes	9 pts	
4+ Lymph Nodes	23 pts	
Bone Findings	7 pts	
Serosal Findings	4 pts	

Prospective Monitoring of Prostate Specific Membrane Antigen Positive Biochemically Recurrent Prostate Cancer (PSMA+ BCR): Preliminary Data from 6-Month PSMA Follow-up

Madan RA et al. ASCO 2025

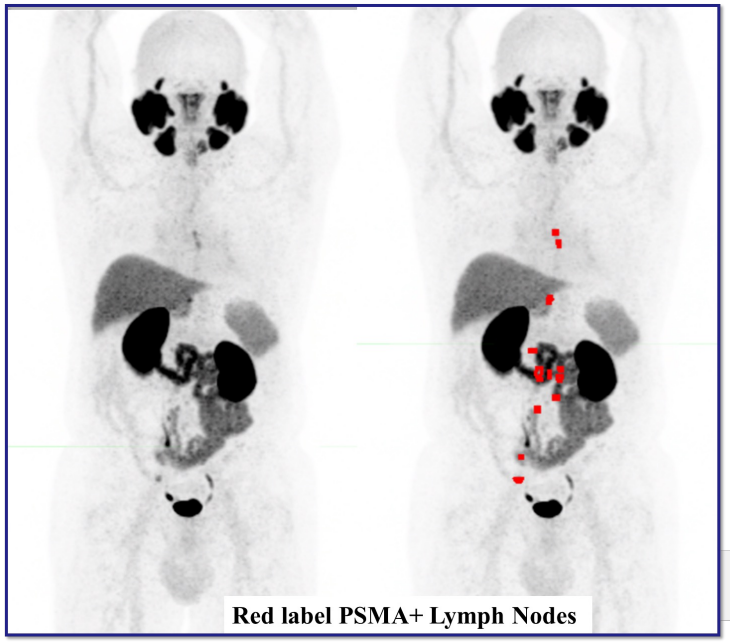
Results of 6-Month Follow-Up of 76 PSMA+ BCR Patients

	PSMA+ Prostate Only (n=17)	PSMA+ Beyond Prostate (n=59)
Patients Selecting Intermittent ADT	0	1
Patients Selecting Radiation Alone	1	4
Patients Selecting NCI Protocol (no ADT)	0	4
Patients Selecting Monitoring without Therapy	16	50
Patients with Metastatic Progression at 6 months	**0**	**1**

*Metastatic progression defined on CT and/or Bone Scan

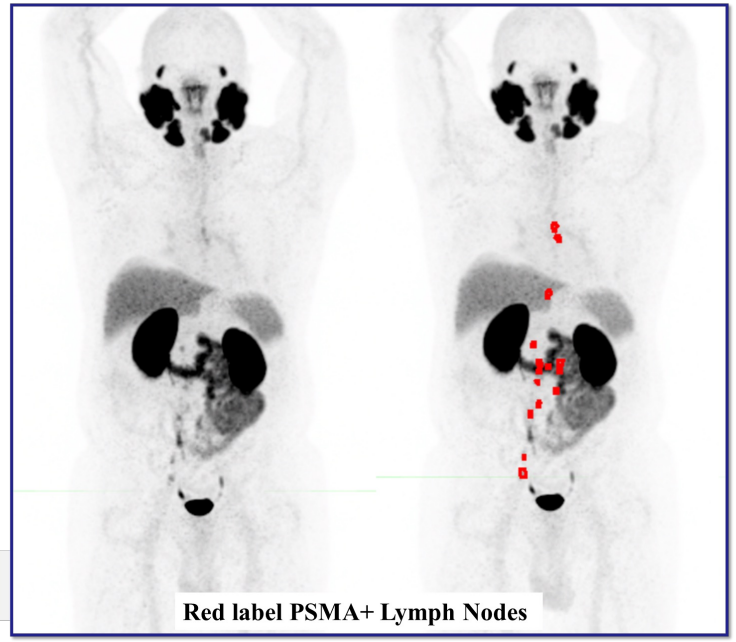
Madan RA et al. ASCO 2025

PSMA+ BCR is an Indolent Disease State That Frequently can be Monitored for Years without Therapy



Baseline

- 71 year old male
- Gleason 3+4, Treated with RT+ ADT in 2008
- Enrollment PSA=6.2 ng/ml, T= 351 ng/dL
- Enrollment PSA DT is 13.7 months
- Initial PSMA shows 10+ LNs, all less than 1.0 cm



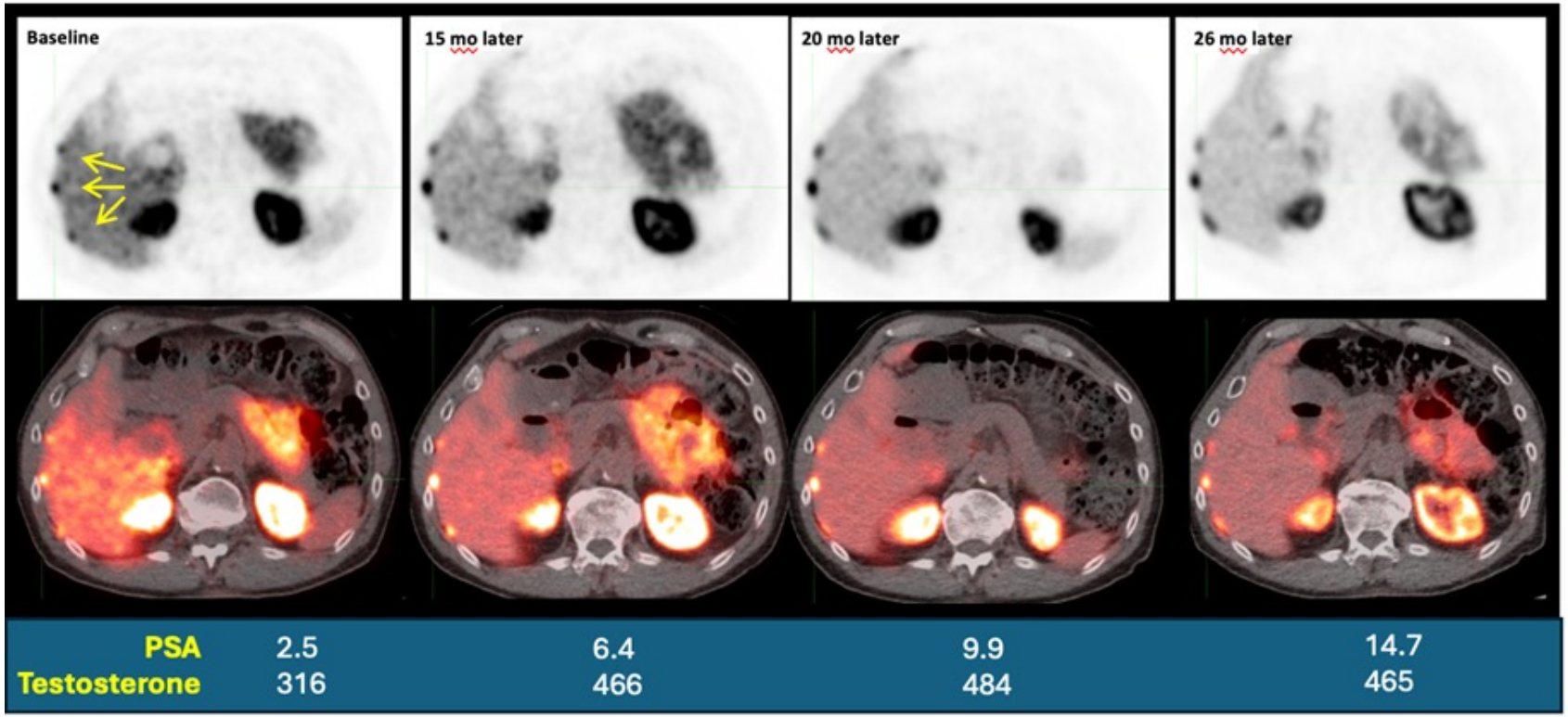
6 Month Follow-up

- PSA = 8.5 ng/ml, T= 266 ng/dL
- Nodes remain less than 1.0 cm
- No treatment

Madan RA et al. ASCO 2025

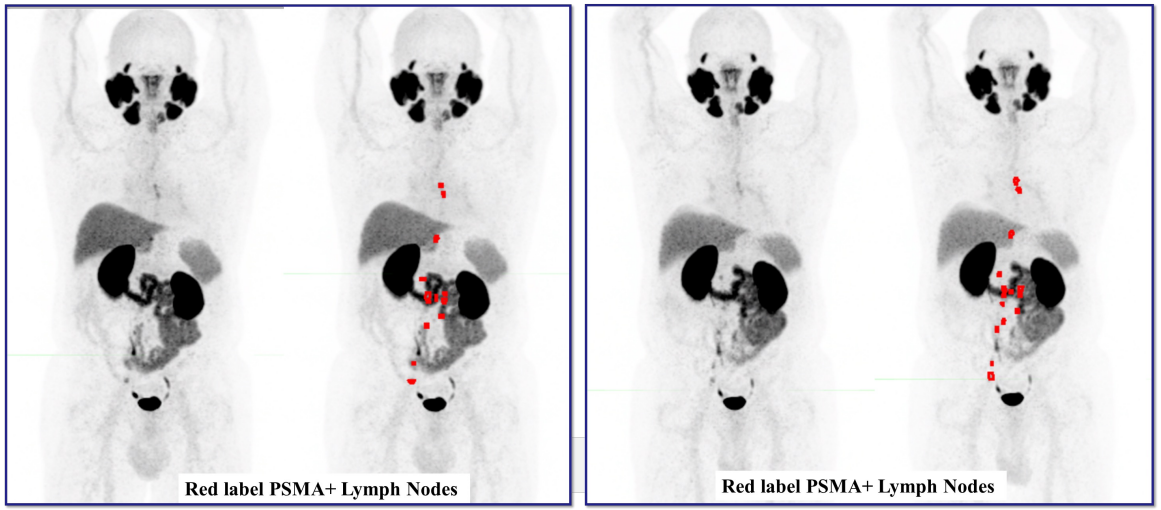
PSMA+ BCR is an Indolent Disease State That can be Monitored for Years without Therapy

PSMA PET/CT imaging of a BCR patient with three PSMA (+) lesions on the liver serosal surface.



Abel ML et al. Nature Rev Urol, *in press*.

PSMA+ BCR is an Indolent Disease State That can be Monitored for Years without Therapy



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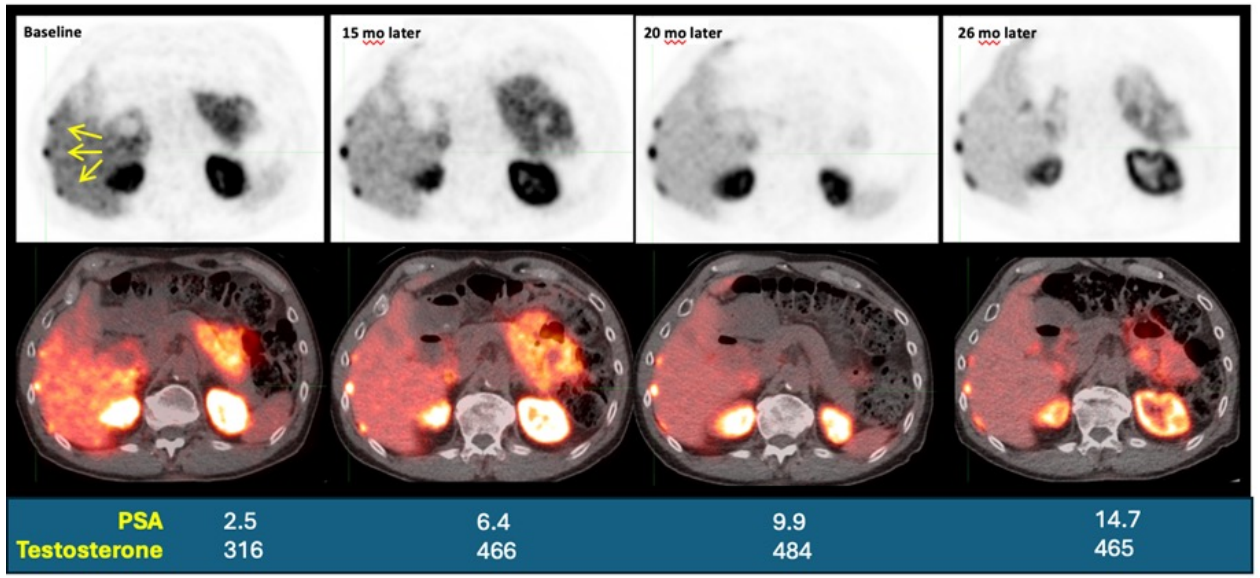
- No treatment

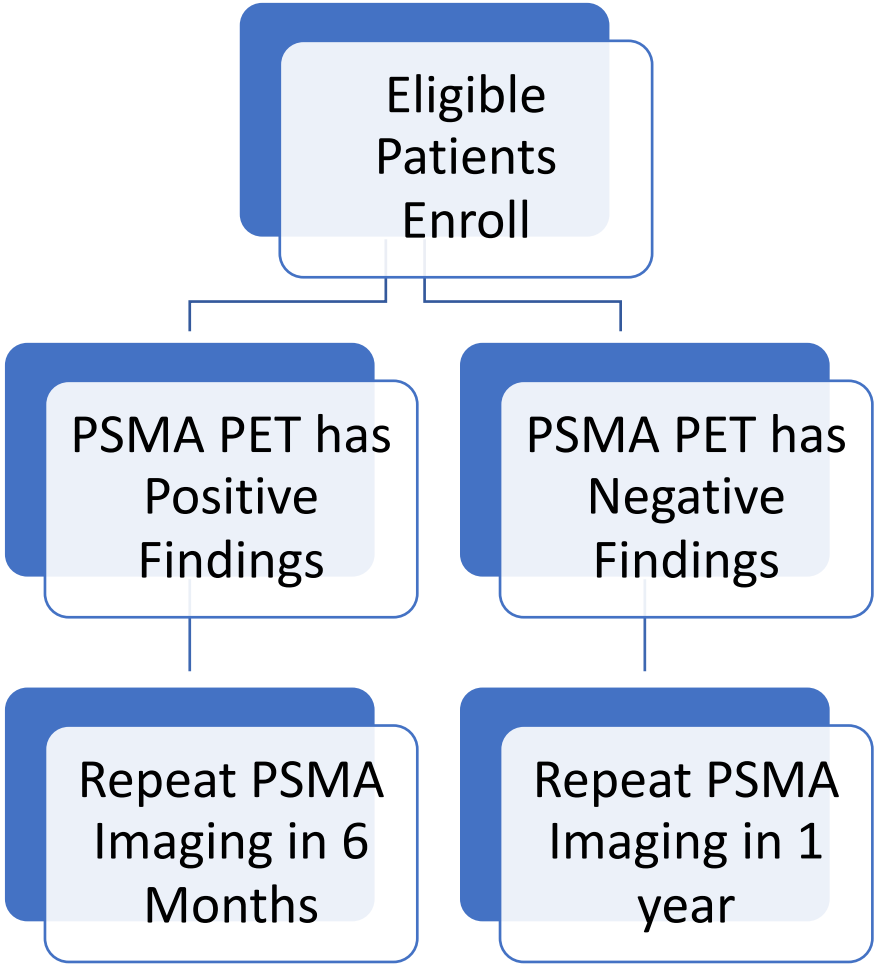
Madan RA et al. ASCO 2025



Abel ML et al. Nature Rev Urol, *in press*.

THANK YOU!!!

Prospective PSMA Monitoring Study: NCT05588128



- Enroll up to 350 pts
- 5 Year of Follow-up

Inclusion Criteria

- History of primary treatment for prostate cancer (either surgery or radiation).
- PSA ≥ 0.50
- Testosterone >100

Exclusion Criteria

- Evidence of soft tissue disease on CT scan
- Evidence of bone lesions on Tc99 bone scan
- Prostatectomy within 1 year before entering the study

World Conference On
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2025 NASHVILLE, TN

HOW CAN WE BETTER MEASURE MRD IN KIDNEY CANER?

Brian Rini, MD
Vanderbilt Ingram Cancer Center

Accredited by
PIM Postgraduate Institute for Medicine
Professional Excellence in Medical Education

@brian_rini
@uromigos

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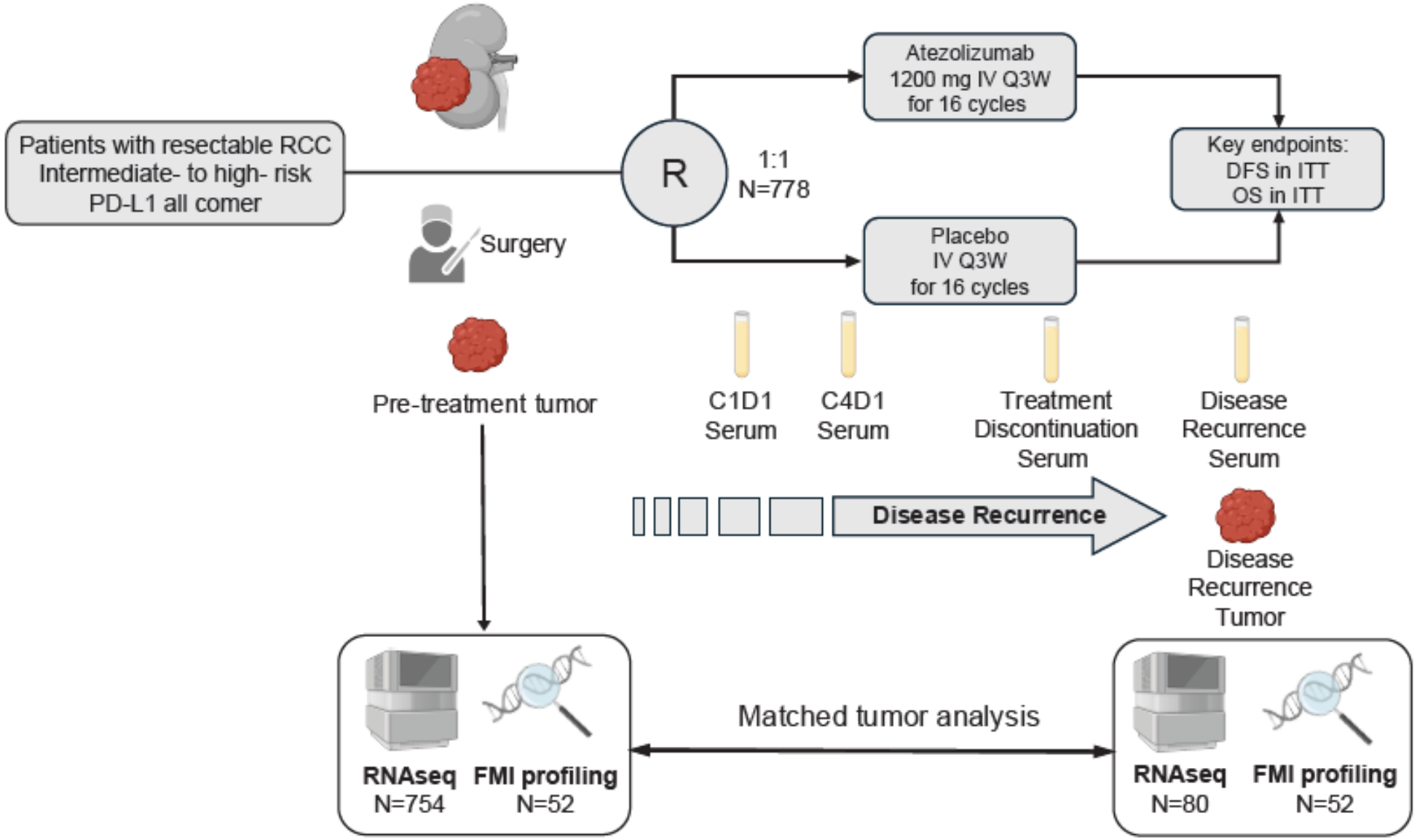
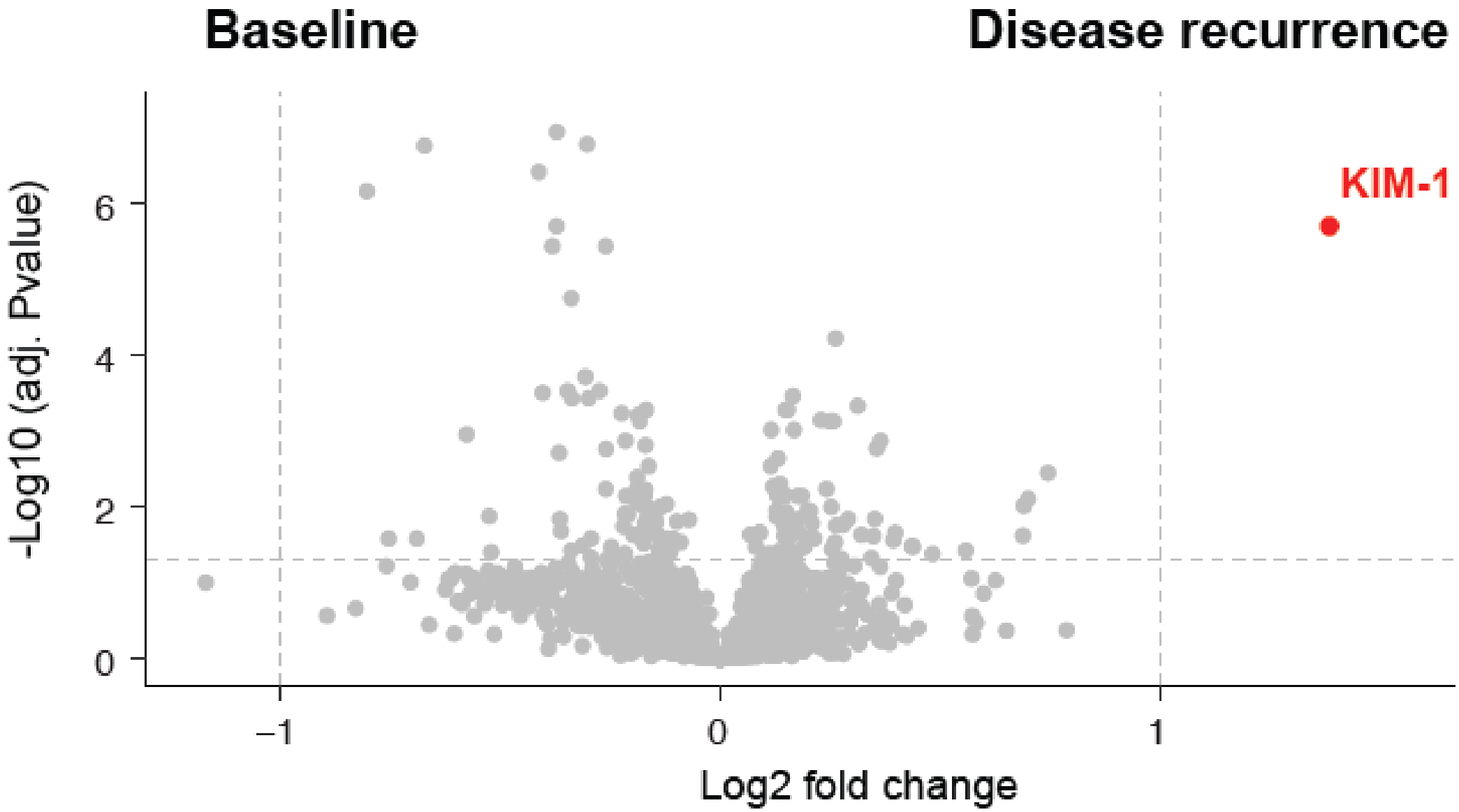


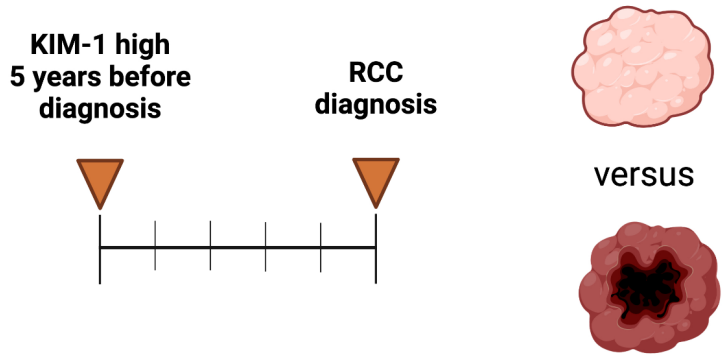
Rini et al. (submitted)


Baseline
Disease recurrence
KIM-1
-Log10 (adj. Pvalue)
6
4
2
0
−1
0
1
Log2 fold change

KIM-1 is a blood biomarker associated with RCC outcomes in multiple clinical settings

Pre-nephrectomy

- Higher KIM-1 is associated with higher RCC risk
- Pre-nephrectomy KIM-1 is associated with metastasis-free survival (MFS) and OS



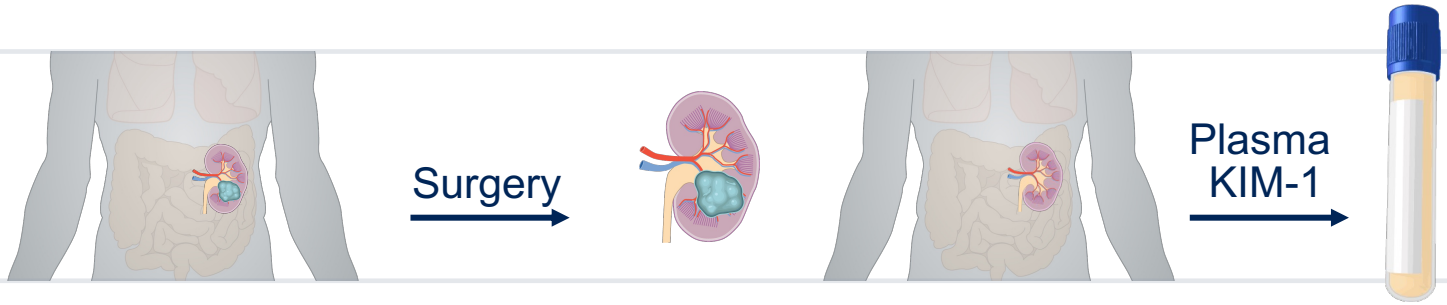
- Elevated up to five years before RCC diagnosis
- Discriminates benign versus malignant tumors

Scelo et al, *CCR* 2018
Xu et al, JCO 2024
Steiner et al, *Eur Urol Focus* 2025

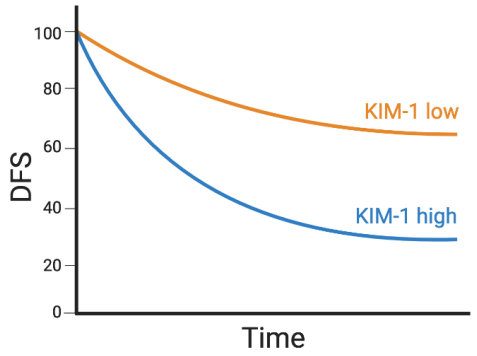
David McDermott, MD, Beth Israel Deaconess Medical Center, Harvard Medical School

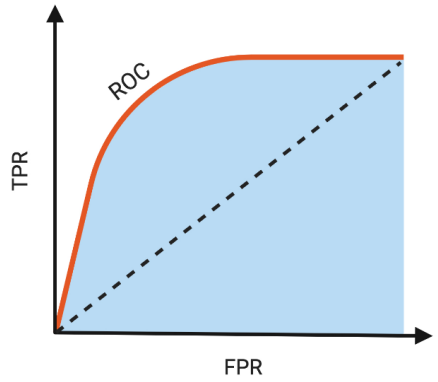
KIM-1 is a blood biomarker associated with RCC outcomes in multiple clinical settings

Adjuvant



Post-nephrectomy KIM-1 is associated with minimal residual disease and worse disease-free survival (DFS) and OS (ASSURE, CheckMate-914, IMmotion-010)



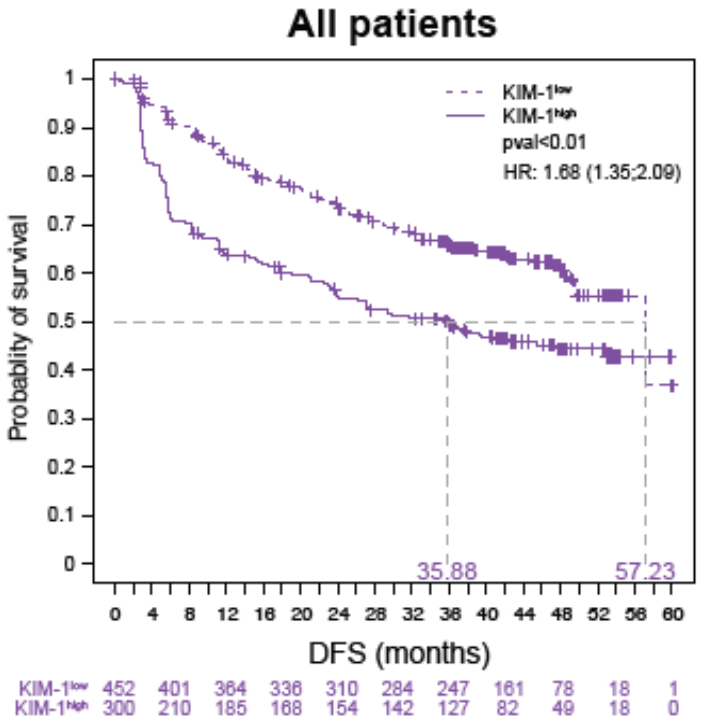


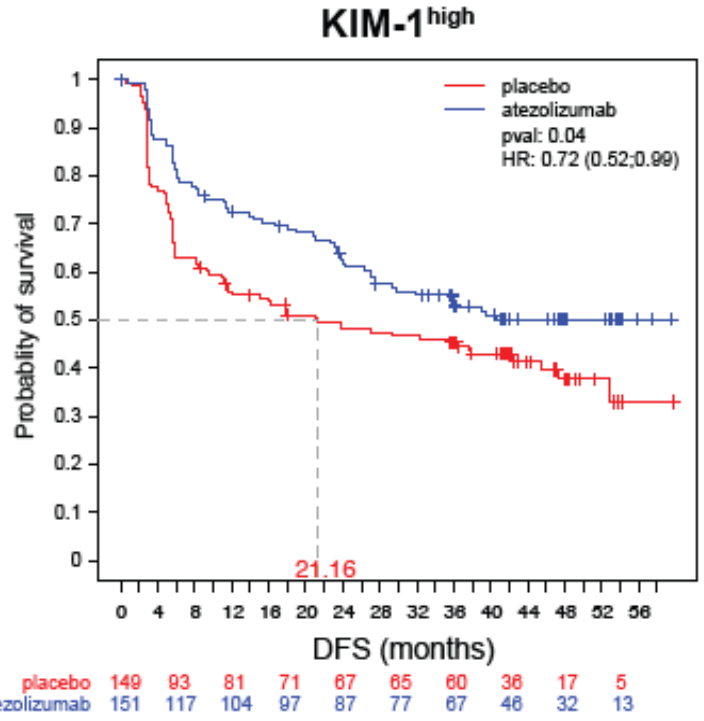
- Marker for recurrence risk
- KIM-1 increases in patients with disease recurrence
- Improves concordance when added to clinical prognostic models

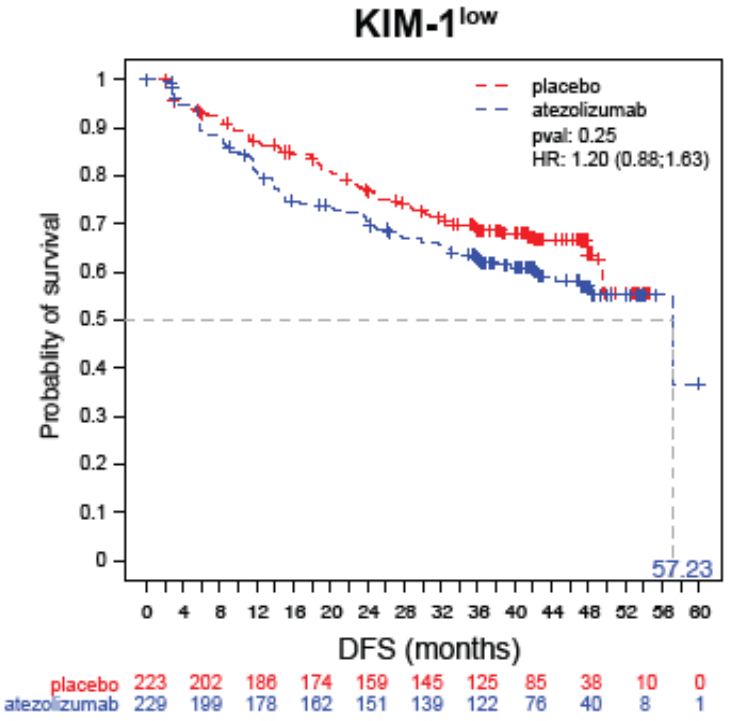
Xu et al, *CCR* 2021
Vemula et al, *CR* 2024
Albiges et al, *JCO* 2024
Steiner et al, *Eur Urol Focus* 2025

David McDermott, MD, Beth Israel Deaconess Medical Center, Harvard Medical School

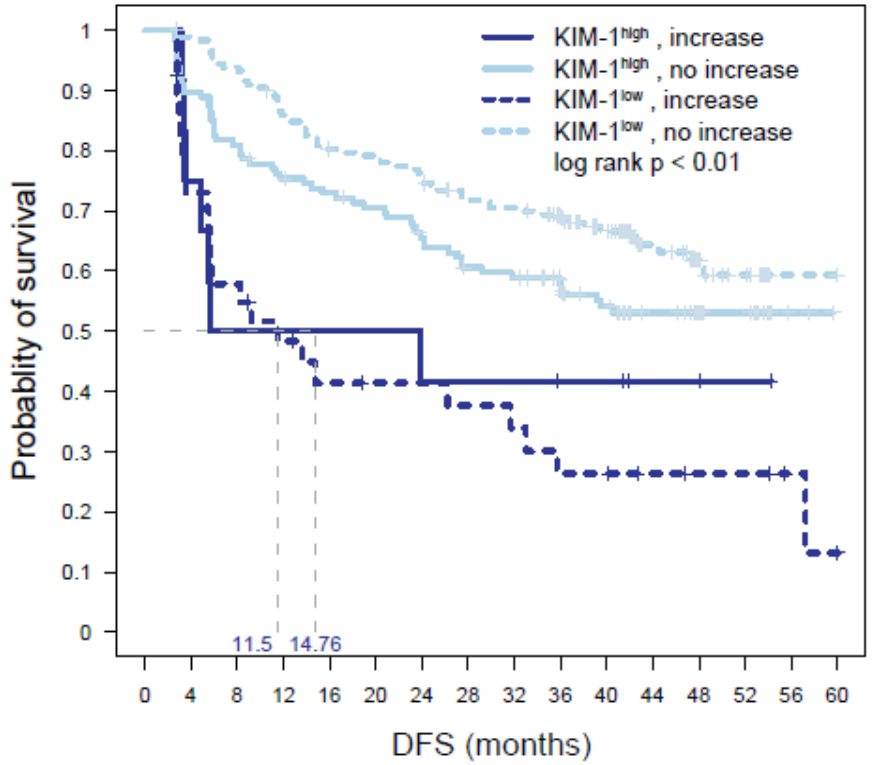
IMmotion 010: Post-nephrectomy KIM-1 Level is both Prognostic and Predictive







Atezolizumab

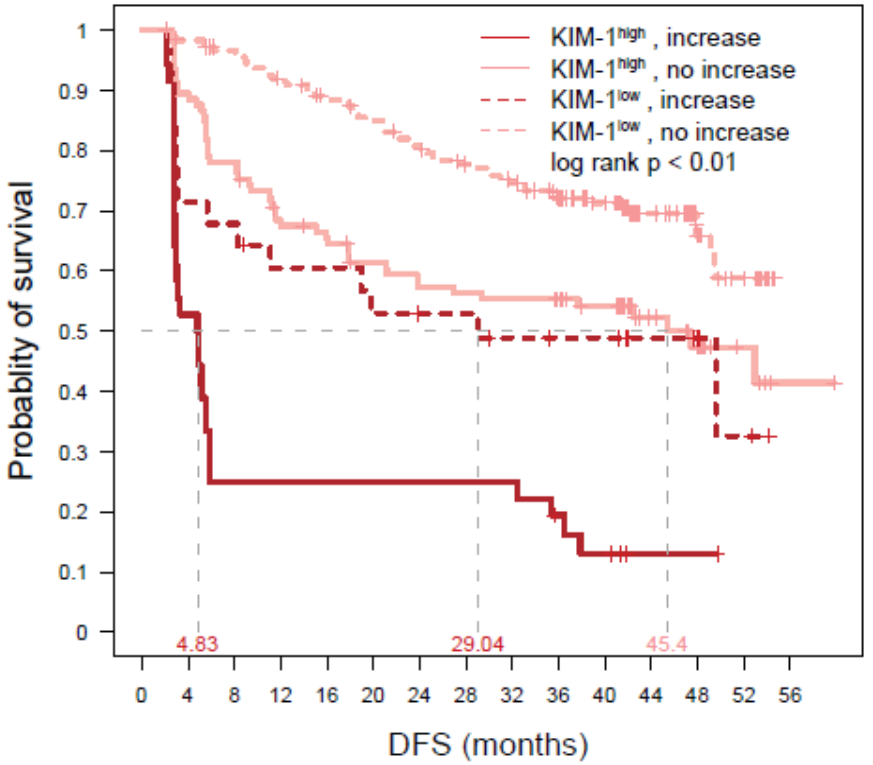


KIM-1high, increase	12	9	6	6	6	6	5	5	5	4	4	2	2	1	0	0
KIM-1high, no increase	126	113	102	94	90	86	79	72	70	62	54	38	29	21	3	0
KIM-1low, increase	34	24	19	15	12	11	11	10	9	7	7	5	4	4	2	1
KIM-1low, no increase	179	176	167	152	141	138	132	123	121	108	91	51	34	18	1	0

Time (months)

Baseline	On-treatment	n	Median DFS	HR (95% CI)
KIM-1high	Increase	12	14.8	1.68 (0.77, 3.69)
	No increase	126	NE	
KIM-1low	Increase	34	11.5	3.56 (2.21, 5.75)
	No increase	179	NE	

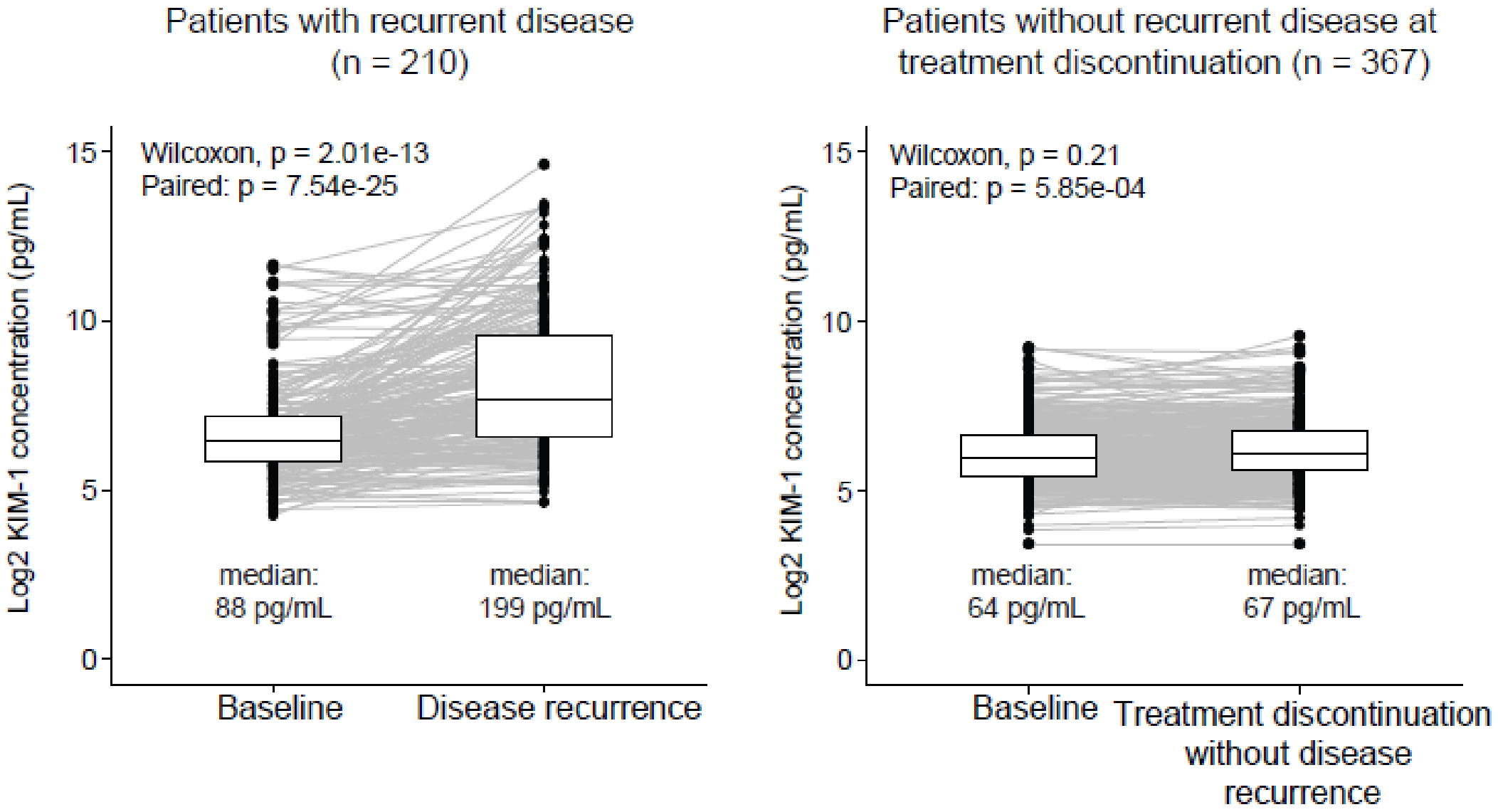
Placebo



KIM-1high, increase	36	19	9	9	9	9	9	9	9	6	4	1	1	0	0	
KIM-1high, no increase	105	94	82	70	66	60	56	55	54	52	46	24	16	8	3	
KIM-1low, increase	28	20	19	16	16	14	13	13	11	10	10	6	4	2	0	
KIM-1low, no increase	179	174	168	158	149	143	134	126	120	108	94	60	33	22	0	

Time (months)

Baseline	On-treatment	n	Median DFS	HR (95% CI)
KIM-1high	Increase	36	4.8	3.53 (2.24, 5.58)
	No increase	105	45.4	
KIM-1low	Increase	28	29.0	2.51 (1.42, 4.44)
	No increase	179	NE	


Patients with recurrent disease
(n = 210)
Wilcoxon, p = 2.01e-13
Paired: p = 7.54e-25
Log2 KIM-1 concentration (pg/mL)
15
10
5
0
median:
88 pg/mL
median:
199 pg/mL
Baseline
Disease recurrence
Patients without recurrent disease at
treatment discontinuation (n = 367)
Wilcoxon, p = 0.21
Paired: p = 5.85e-04
Log2 KIM-1 concentration (pg/mL)
15
10
5
0
median:
64 pg/mL
median:
67 pg/mL
Baseline
Treatment discontinuation
without disease
recurrence

Longitudinal Testing of Circulating Tumor DNA in Patients With Metastatic Renal Cell Carcinoma

Arnab Basu, MD, MPH[1]; Cherry Au, MD[2]; Ajitha Kommalapati, MD[1]; Hyndavi Kandala, MD[1]; Sumedha Sudhaman, PhD[3]; Tamara Mahmood, MS, PA[3]; Carcia Carson, PhD[3]; Natalia Pajak, MSPAS, PA-C[3]; Punashi Dutta, PhD[3]; Mark Calhoun, PhD[3]; Meenakshi Malhotra, PhD[3]; Adam C. ElNaggar, MD[3]; Minetta C. Liu, MD[3]; James Ferguson III, MD, PhD[1,4]; Charles Peyton, MD[1,4]; Soroush Rais-Bahrami, MD, MBA[1,4,5]; and Alan Tan, MD[6]

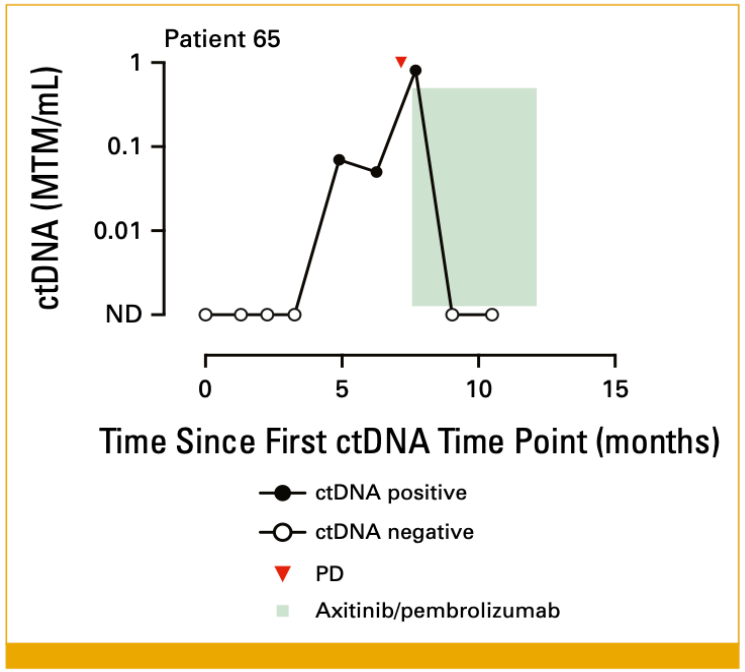


FIG 3. Patient-specific plot highlighting serial ctDNA monitoring with radiologic findings in patients with metastatic RCC during surveillance. ctDNA, circulating tumor DNA; MTM, mean tumor molecules; ND, not detected; PD, progressive disease; RCC, renal cell carcinoma.

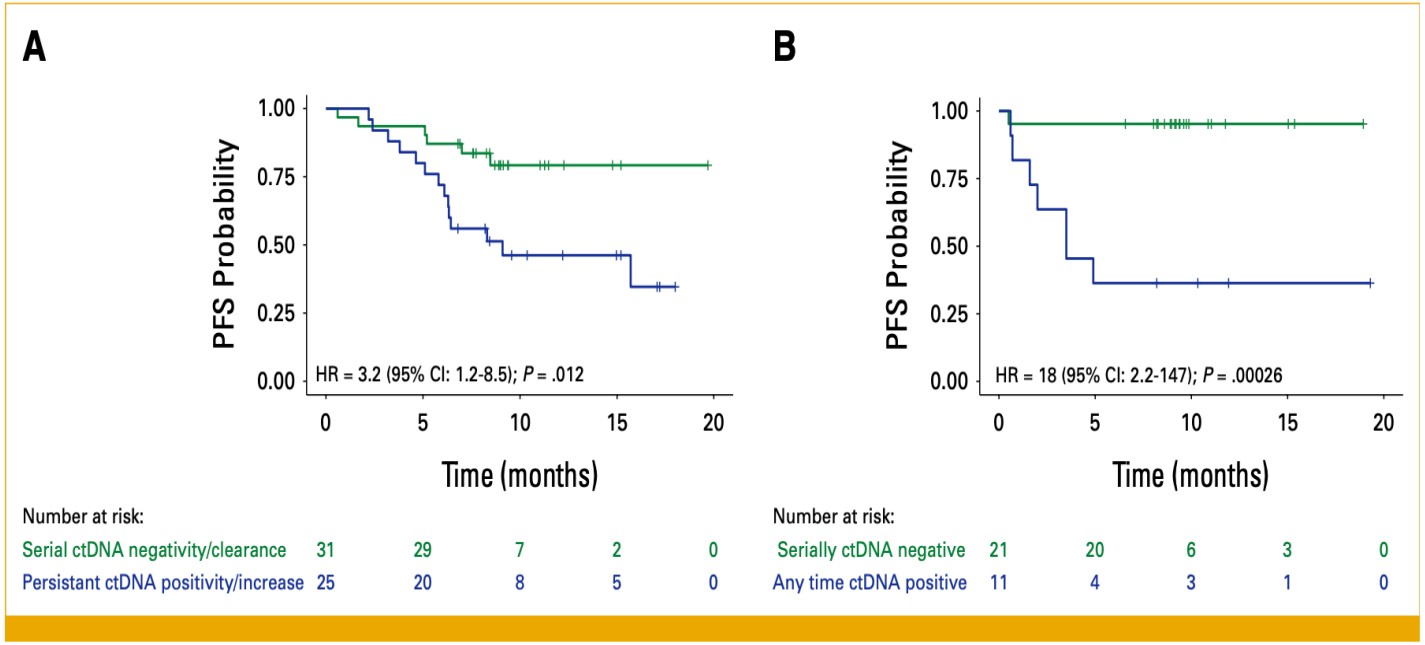


FIG 2. ctDNA status and dynamics are associated with PFS in patients with RCC. Kaplan-Meier estimates for PFS stratified by ctDNA dynamics/status. (A) TRM by ctDNA dynamics included all patients in the TRM setting with two consecutive ctDNA time points preceding the first progression event or end of follow-up in patients who did not progress (n = 56). Four patients from the TRM cohort did not have a second time point before a PFS event. (B) Association of longitudinal ctDNA status (before or at the time of PFS) in the surveillance cohort and PFS (n = 32). HRs and 95% CIs were calculated using the Cox proportional hazard model. *P* values were calculated using the two-sided log-rank test. ctDNA, circulating tumor DNA; HR, hazard ratio; PFS, progression-free survival; RCC, renal cell carcinoma; TRM, treatment response monitoring.

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Personalized ctDNA Adaptive Intermittent SystEmic TKI for Renal Cell Carcinoma (PRECISE-TKI-RCC)

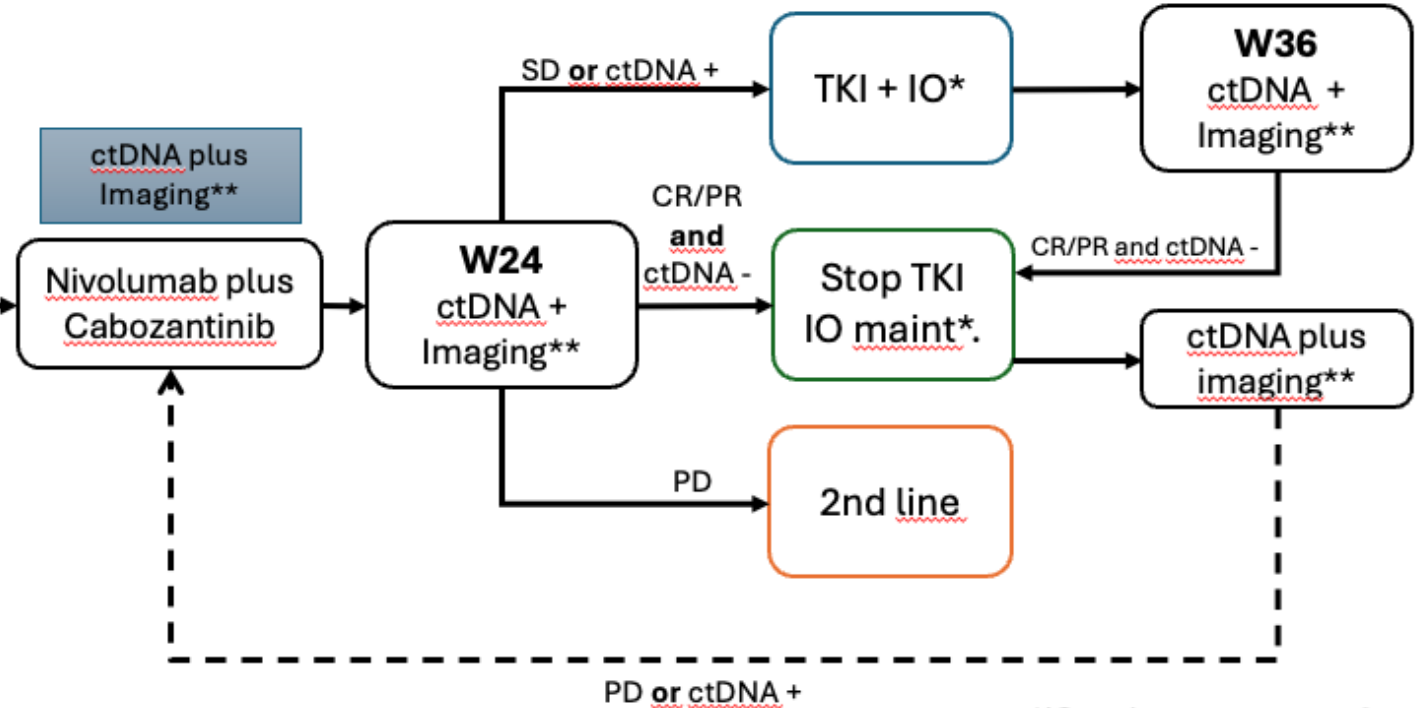
Phase II

Key Eligibility Criteria

- KPS ≥ 70%
- Newly-diagnosed mccRCC
- No prior systemic therapy
- Tumor sample available for WES

1º EP:
Rate of patients without progression 12 weeks after the cabozantinib interruption

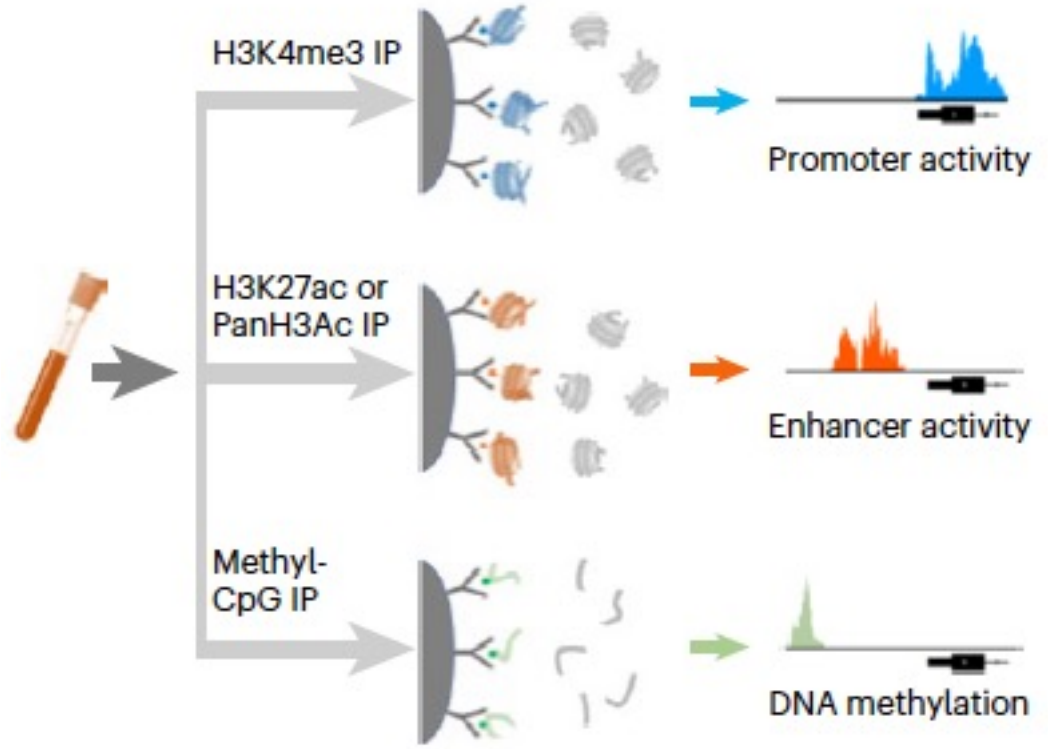
2º EP:
PFS
TKI-Free interval
ctDNA detection rate
ctDNA clearance at 24w
Concordance ctDNA and RECIST 1.1



*IO maintenance up to 2 yrs maximum

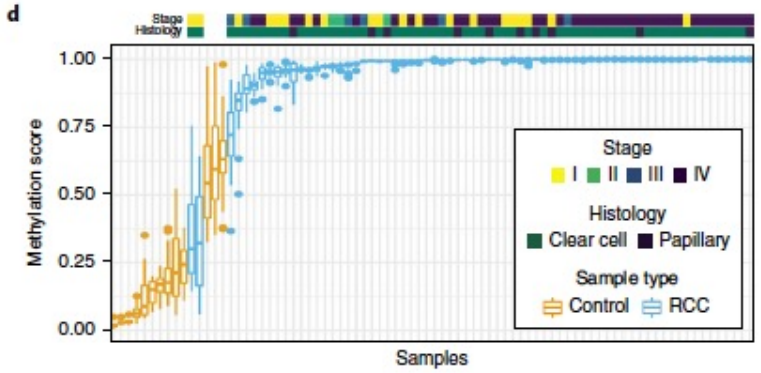
** ctDNA performed q4w and images q12w

Liquid biopsy epigenomic profiling: Multiple assays from a single tube



Novel ctDNA assay, no tumor tissue necessary

DNA methylation can discriminate between renal cell carcinoma and normal control patients



Other epigenetic marks (H3K27ac and H3K4me3) are being developed to infer gene expression and tumor biology from liquid biopsy samples (e.g., resistance mechanisms)

Baca et al., Nat Med 2023; Nuzzo et al., Nat Med 2020

Slide courtesy of Scott Haake, MD, PhD

KCRC Kidney Cancer RESEARCH CONSORTIUM

Perform multicenter, tissue rich, transformative clinical trials

Seed money from DOD

Circulating tumor cells

ctDNA

	Total enrolled	Baseline	Restaging #1	Restaging #2	TOP	2-years
MD-Andeson Cancer Center (Univeristy of Texas)	40	33	17	10	0	2
Rogel Cancer Center (Univeristy of Michigan)	30	26	16	13	1	0
Abramson Cancer Center (Penn Medicine)	24	24	17	14	1	0
Simmons Cancer Center (UT Southwestern)	16	16	5	1	0	0
Tennessee Valley VA (Nashville, TN)	3	3	3	3	0	2
Beth Israel Deaconess Medical Center (Boston, MA)	11	6	3	1	1	0
Ingram Cancer Center (VUMC)	56	55	42	27	4	2
Total	180	163	103	69	7	6

UT Southwestern Medical Center

Penn Medicine

VANDERBILT UNIVERSITY MEDICAL CENTER

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®

UNIVERSITY OF MICHIGAN HEALTH MICHIGAN MEDICINE

Beth Israel Deaconess Medical Center

DukeHealth

Conclusions

- **MRD assays in RCC could help inform clinically-relevant questions including de-escalation of therapy (intermittent approaches, stopping drug(s) at a given timepoint and/or after consolidative approaches).**

- **KIM-1 is a promising MRD candidate with accumulating evidence for prognostic and predictive potential.**

- **ctDNA assays are being increasing applied to RCC including in the metastatic setting.**

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CASE BASED APPROACH TO PARP INHIBITORS IN PROSTATE CANCER

Chandler Park MD FACP
Co-Director GU clinical trials at Norton Cancer Institute
Advisory Dean/Clinical Professor
University of Louisville School of Medicine

August 23, 2025

X: CParkMD LinkedIN: ChandlerParkMD

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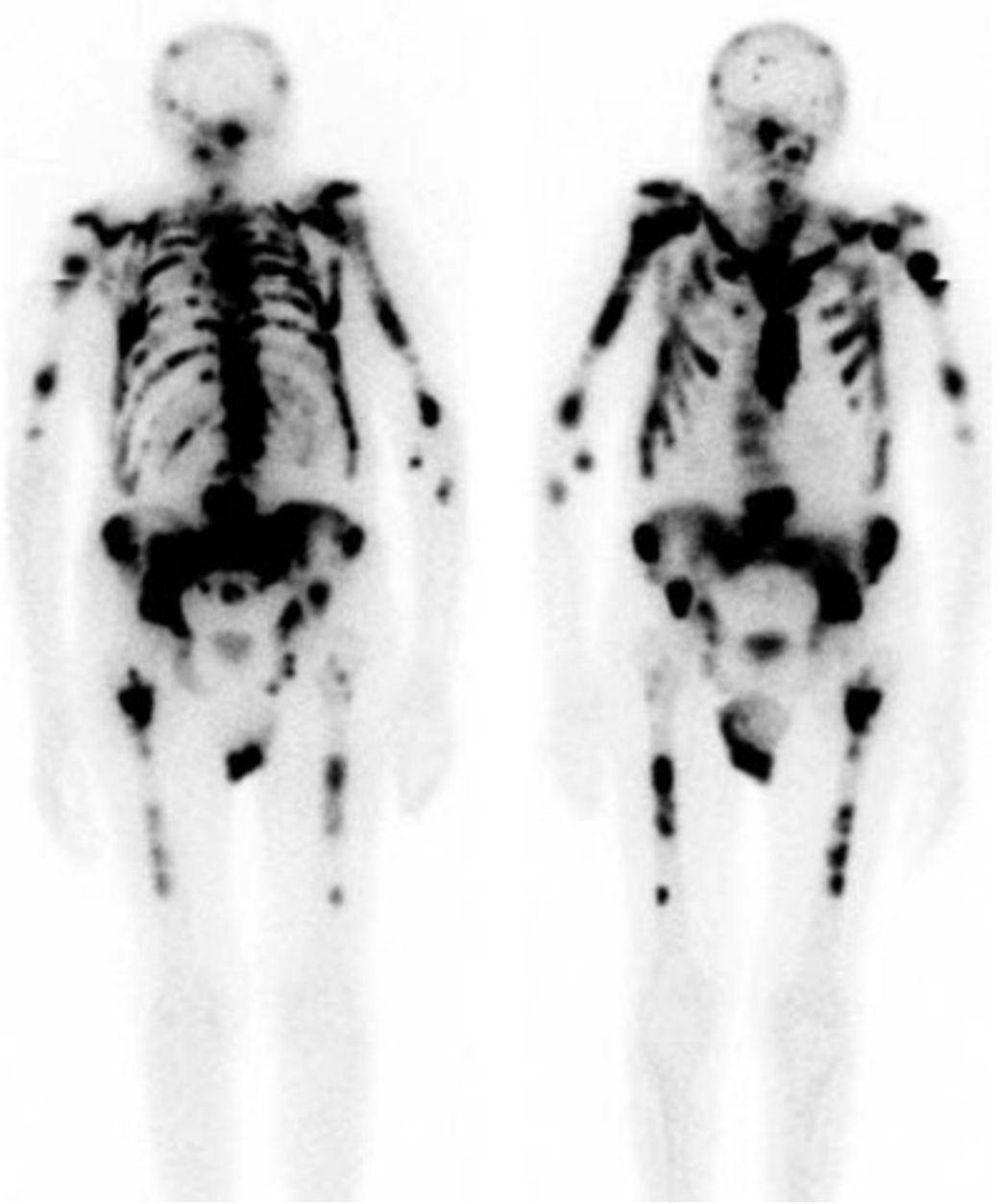
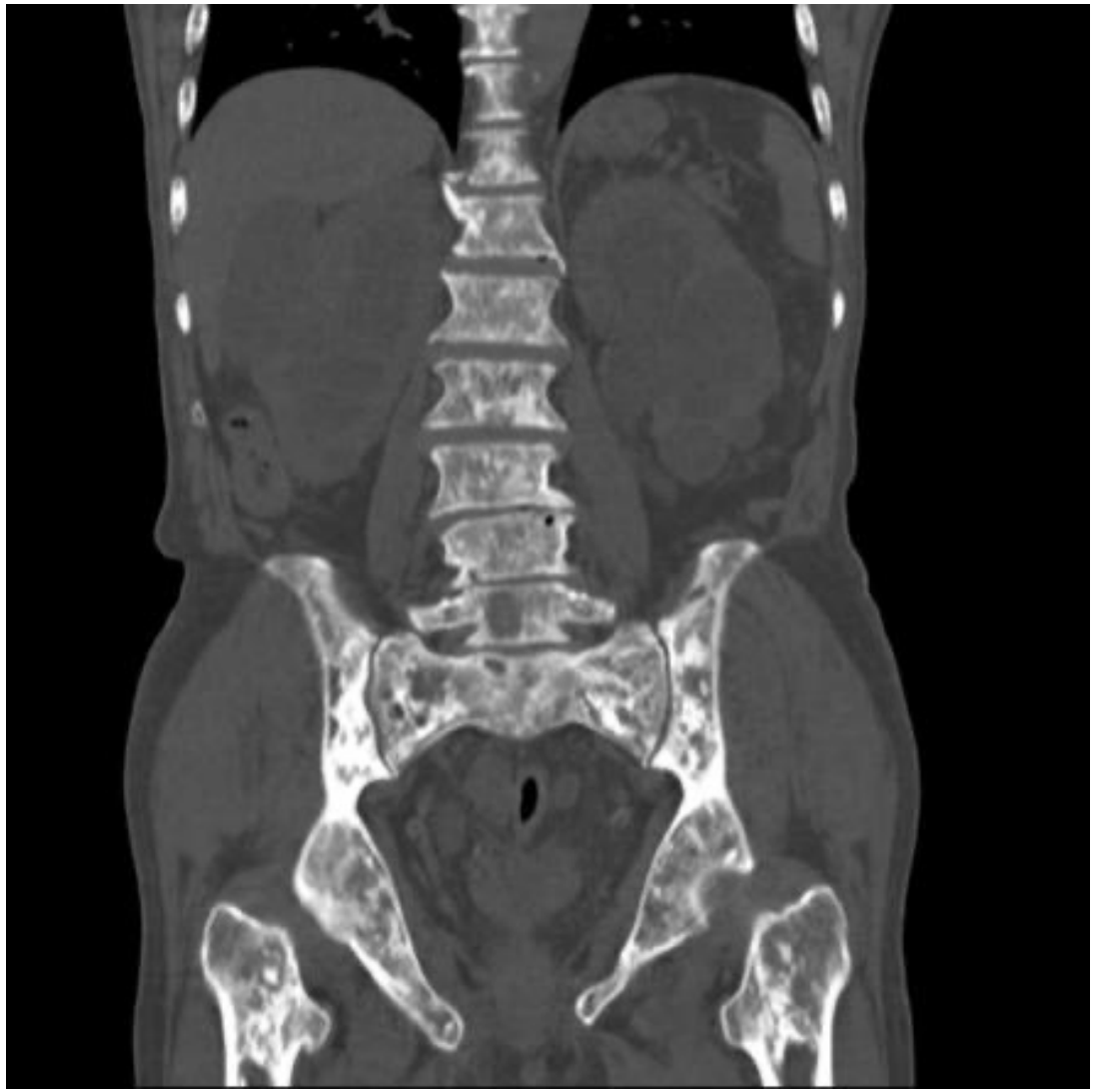
Case

A 74-year-old man presents to ER with severe back pain that is worsened at night.

- CT Chest. Abdomen, and Pelvis showed diffuse metastatic osteoblastic lesions in the majority of the appendicular and axial bones. CT also showed multifocal hepatic and extensive pelvic adenopathy. Bone scan showed a super scan.
- CT guided live biopsy returned as Prostate Adenocarcinoma. Gleason 4+5=9. PSA 550. CBC and CMP Normal.
- Patient underwent germline and somatic mutation studies. Germline studies: BRCA2.
- Patient underwent a PSMA PET/CT scan showed diffuse metastatic uptake with mean SUV 45





Doublet vs Triplet Therapy for mHSPC?

The NEW ENGLAND JOURNAL of MEDICINE

Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer

Authors: Matthew R. Smith, M.D., Ph.D., Maha Hussain, M.D., Fred Saad, M.D., Karim Fizazi, M.D., Ph.D., Cora N. Sternberg, M.D., E. David Crawford, M.D., Evgeny Kopyltsov, M.D., Chandler H. Park, M.D., Boris Alekseev, M.D., Álvaro

Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer

Authors: Kim N. Chi, M.D., Neeraj Agarwal, M.D., Anders Bjartell, M.D., Byung Ha Chung, M.D., Andrea J. Pereira de Santana Gomes, M.D., Robert Given, M.D., Álvaro Juárez Soto, M.D., Axel S. Merseburger, M.D., Mustafa Özgüroğlu,

Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

Authors: Karim Fizazi, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fein, M.D., Nobuaki Matsubara, M.D., Alfredo Rodriguez-Antolin, M.D., Ph.D., Boris Y. Alekseev, M.D., Mustafa Özgüroğlu, M.D., Dingwei Ye, M.D., Susan Feyerabend,

Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer

Authors: Ian D. Davis, M.B., B.S., Ph.D., Andrew J. Martin, Ph.D., Martin R. Stockler, M.B., B.S., Stephen Begbie, M.B., B.S., Kim N. Chi, M.D., Simon Chowdhury, M.B., B.S., Ph.D., Xanthi Coskinas, M.Med.Sc., Mark Frydenberg, M.B., B.S.,

Treatment

- **What treatment would I consider in this patient with high volume and high-risk metastatic hormone sensitive prostate cancer?**

- **ARASENS, TITAN, LATITUDE, ARCHES/ENZAMET, ARANOTE ?**

- **AMPLITUDE?**

- **PSMAddition?**

- **PTEN mutation? CAPItello-281?**

Personalized treatment era for 1st line metastatic hormone sensitive prostate cancer?

World Conference On
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2025 NASHVILLE, TN

CASE-BASED APPROACH TO KIDNEY CANCER

Hans Hammers, MD, PhD
Professor of Medicine
UT Southwestern, Dallas, TX

08/23/2025

@HHammersMD on X

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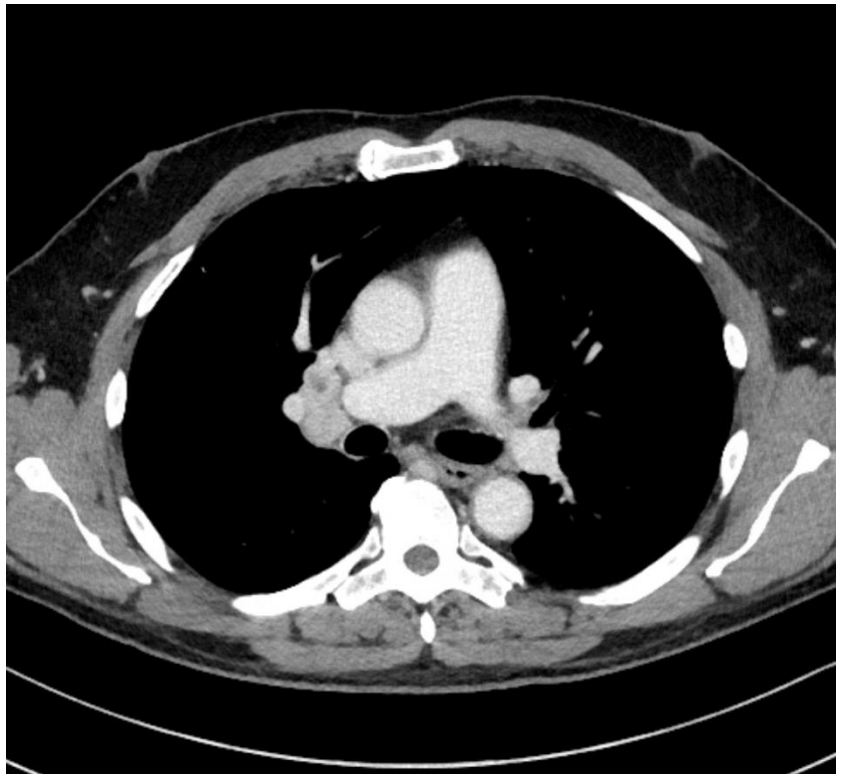
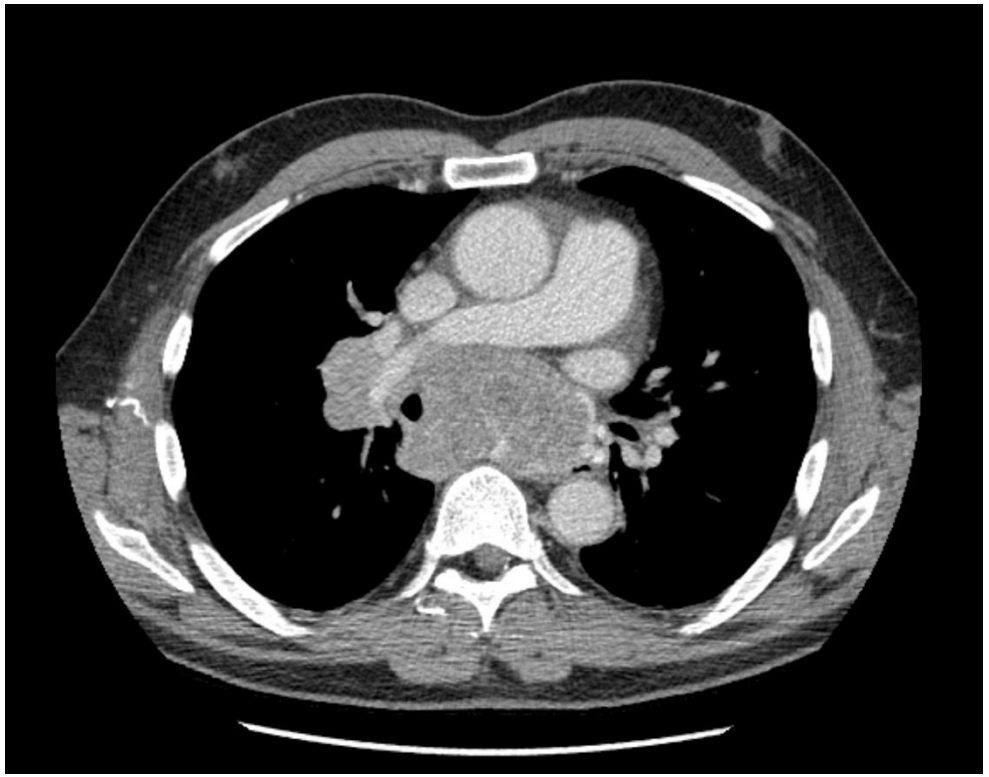
Cases



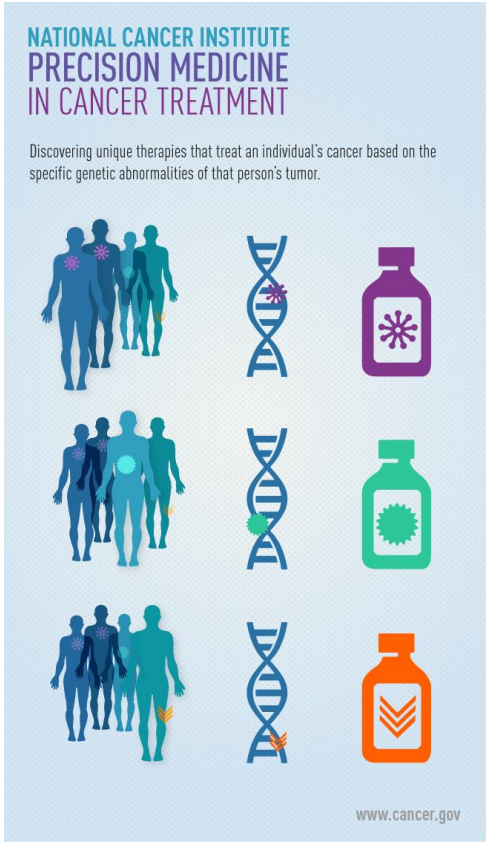
Charles
63 yo s/p Nx, recurrent R hilar LAD within 1 year, no lab abn, no Sx



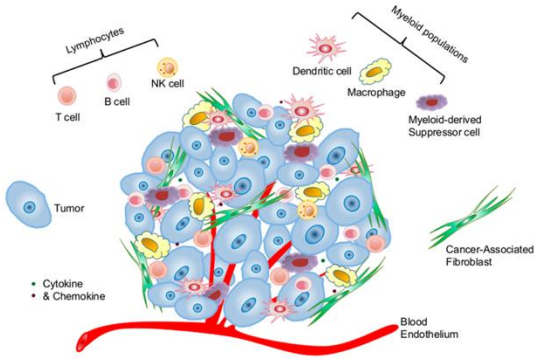
John
72 presents with Stage IV disease with mediastinal LAD, bone mets, hypercalcemia, anemia and chest pressure/SOB

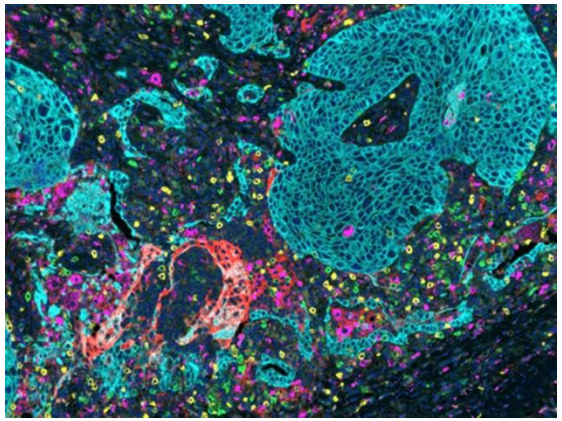
Predictive Biomarkers – Complicated in ccRCC

NO Driver Mutations



Tumor Microenvironment. IO / Blood Vessels



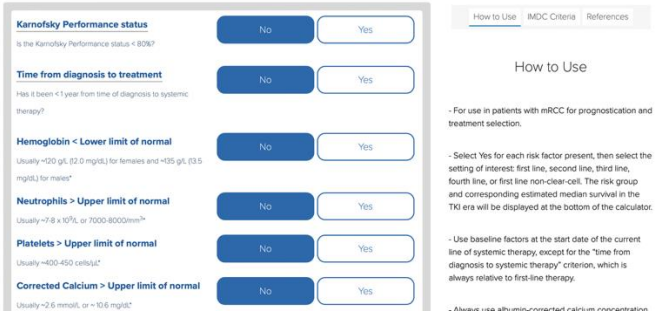


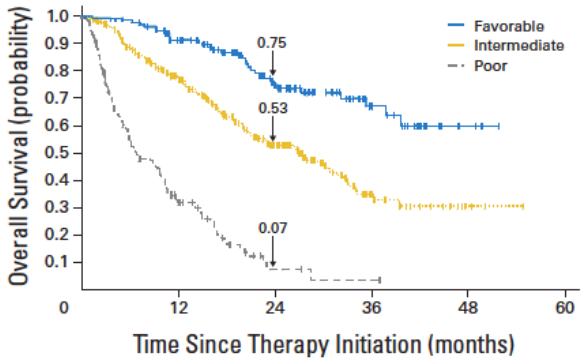
IMDC Risk Criteria

International mRCC Database Consortium

WORKING TOGETHER AGAINST KIDNEY CANCER

IMDC Risk Calculator | Instructions





NCCN Update 2025

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Kidney Cancer

NCCN Guidelines Index
Table of Contents
Discussion

New preferred regimen designations

PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV (M1 OR UNRESECTABLE T4, M0) OR RELAPSED DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	**Preferred Regimens**	**Other Recommended Regimens**	**Useful in Certain Circumstances**
Favorable[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Ipilimumab + nivolumab[b]	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Pazopanib • Sunitinib	• Active surveillance[1,2,3] • Axitinib (category 2B)
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Ipilimumab + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B)

NEW: All Risk Groups = All Treatment Options

Final Results of First-line IO Combination Trials in mRCC (ITT population)

	CheckMate 214 (Ipi/Nivo)[1] (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro)[2] (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo)[3] (n=323 vs n=328)	CLEAR (Len/Pembro)[4] (N=355 vs n=357)
OS HR mOS, months	**0.71** 52.7 vs 37.8	**0.84** 47.2 vs 40.8	**0.79** 46.5 vs 35.5	**0.79** 53.7 v. 54.3
Landmark OS	**42%** at 6 years **31%** at 9 years	**42%** at 5 years	**41%** at 5 years	**66%** at 3 years
PFS HR mPFS, months	**0.88** **12.4** vs 12.3	**0.69** **15.7** vs 11.1	**0.58** **16.4** vs 8.3	**0.47** **23.9** vs 9.2
Landmark PFS	**26%** at 6 years **23%** at 8 years	**18%** at 5 years	**14%** at 5 years	**37%** at 3 years
ORR, %	**40** vs 33	**61** vs 40	**56** vs 27	**71** vs 37
CR, %	**12** vs 3	**12** vs 4	**14** vs 5	**18** vs 4
Median f/u	**9.3 years**	**5.6 years**	**5.6 years**	**4.2 years**
Primary PD	**18%**	**12%**	**7%**	**5%**

X adapted from @Brian_Rini

PD1-CTLA4 | PD1-VEGF

	CheckMate 214 (Ipi/Nivo)[1] (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro)[2] (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo)[3] (n=323 vs n=328)	CLEAR (Len/Pembro)[4] (N=355 vs n=357)
OS HR mOS, months	**0.71** 52.7 vs 37.8	**0.84** 47.2 vs 40.8	**0.79** 46.5 vs 35.5	**0.79** 53.7 v. 54.3
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Landmark PFS	**26%** at 6 years **23%** at 8 years	**18%** at 5 years	**14%** at 5 years	**37%** at 3 years
ORR	**40%**		**60%**	
CR, %	**12** vs 3	**12** vs 4	**14** vs 5	**18** vs 4
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X adapted from @Brian_Rini

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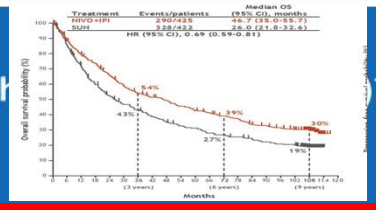
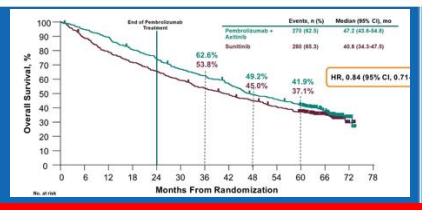
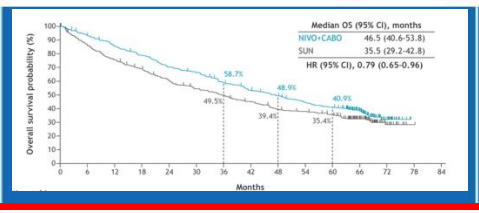
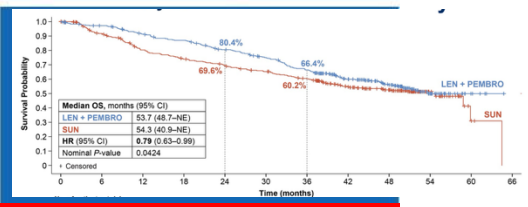
PD	**20%**		**5-10%**	

X adapted from @Brian_Rini

PD1-CTLA4

PD1-VEGF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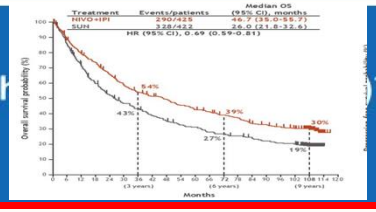
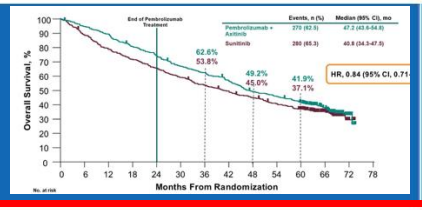
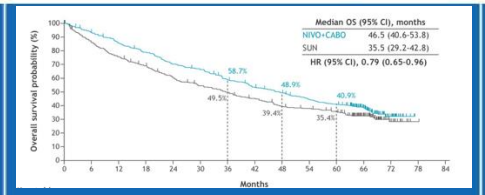
X adapted from @Brian_Rini

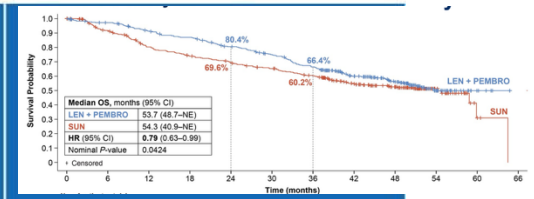
PD1-CTLA4

PD1-VEGF









OS HR	**0.7**		**0.8**	
Landmark OS	**42%** at 6 years **31%** at 9 years	**42%** at 5 years	**41%** at 5 years	**66%** at 3 years
5 yr PFS	**31%**	**18%**	**14%**	**?**
Landmark PFS	**26%** at 6 years **23%** at 8 years	**18%** at 5 years	**14%** at 5 years	**37%** at 3 years
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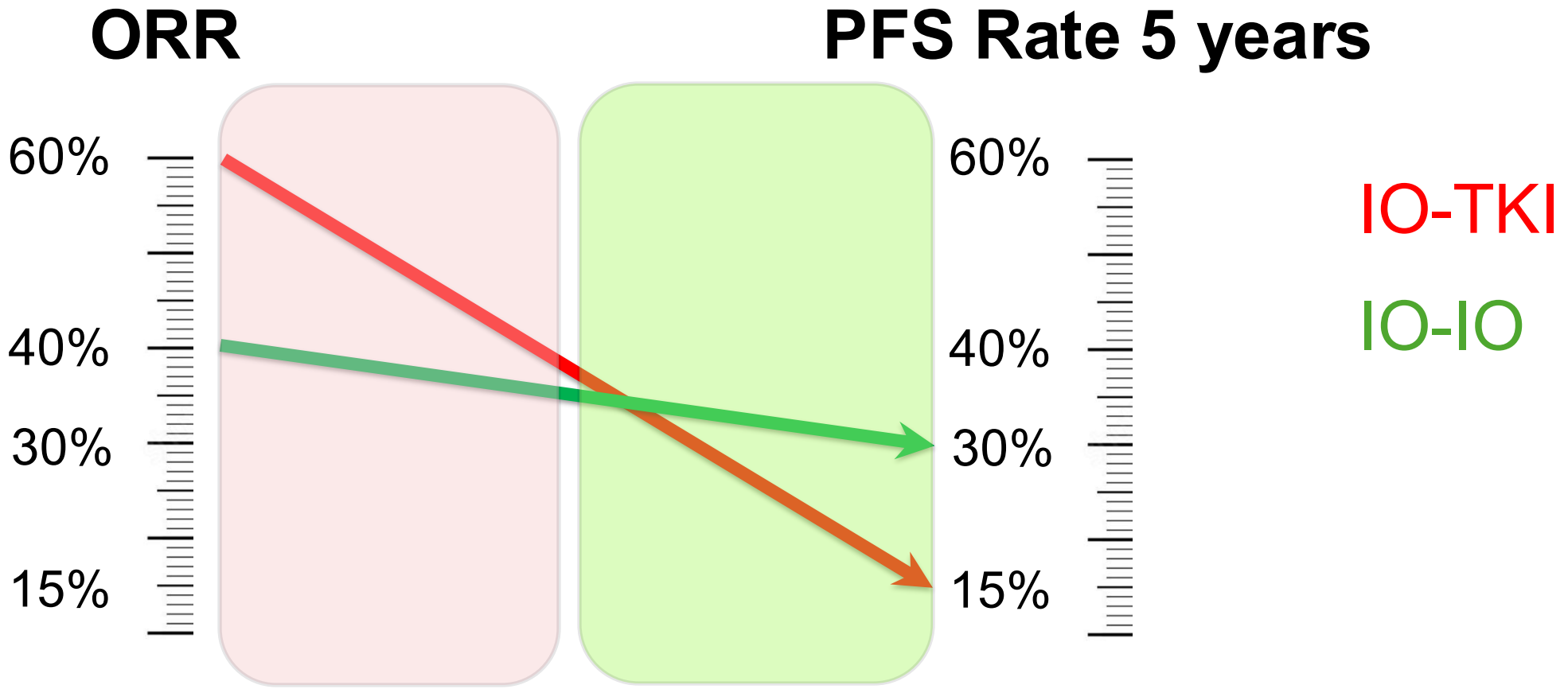
X adapted from @Brian_Rini

IO-IO vs IO-TKI



CONCLUSIONS:

With time the **Dust Has Settled:**

- *IMDC not useful* to select patients
- Ask: **Does the patient need a TKI**? (PD risk)
- For **long term outcome**: I prefer **PD1/CTLA4** (OS curves, HR, PFS rates, TFS)
- **VEGF TKIs do NOT enhance Immunotherapy**

THANK YOU!

World Conference On
Genitourinary Cancers
2025 NASHVILLE, TN

MUSCLE-INVASIVE BLADDER CANCER SYSTEMIC THERAPY AND OUTCOMES

Jacqueline T. Brown, MD
Winship Cancer Institute of Emory University

August 23, 2025
twitter: jackiebrown_MD

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PIM Postgraduate Institute for Medicine
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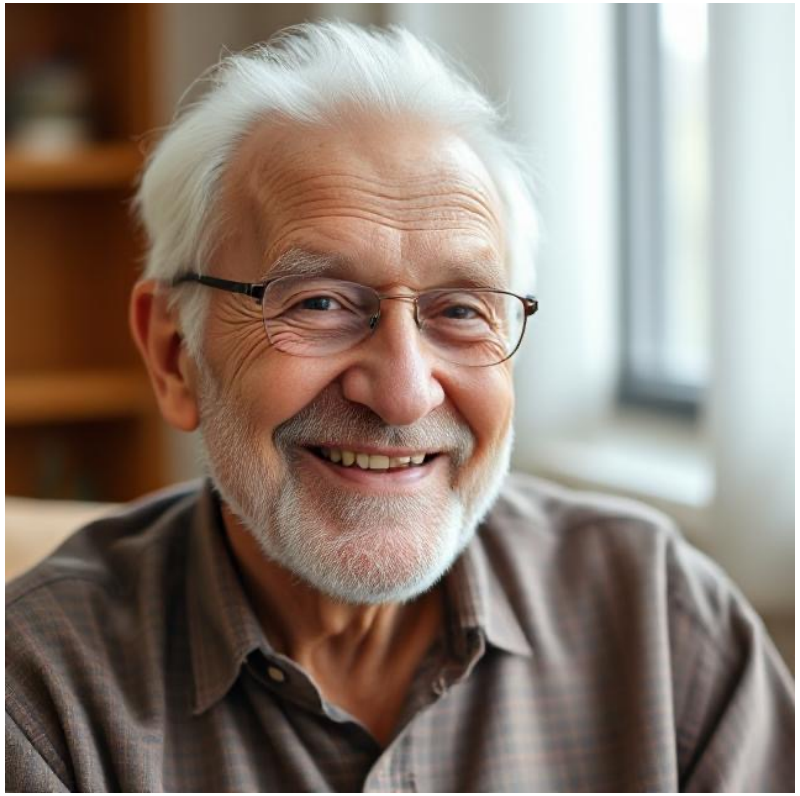
BEN

- 74yo with recently diagnosed MIBC
- TURBT shows high-grade urothelial carcinoma with invasion into the muscularis propria
- Cross-sectional imaging shows
  - Mild L hydronephrosis with hazy perivesical stranding
  - Prominent L external iliac lymph node with mild FDG avidity on subsequent PET
  - No clear metastatic disease
- Ben's renal function is at his baseline – CrCl of 52 mL/min



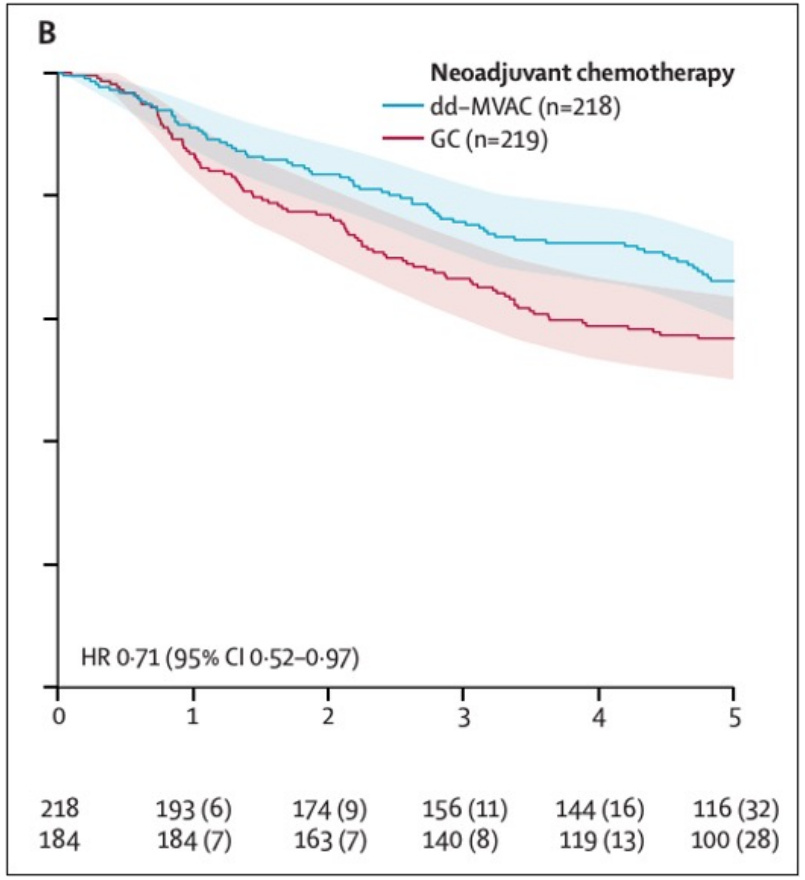
Considerations in treating Ben / MIBC in August 2025

- Fitness and renal function – neoadjuvant ddMVAC vs gem/cis
- Role for IO – as perioperative “sandwich” (NIAGARA) vs risk adapted approach based on response to neoadjuvant therapy (CHECKMATE-274)
- ctDNA – Do we send it? What do we do with it when it comes back?
- Bladder-sparing approaches: CRT now, but what’s next?

Choosing a chemotherapy backbone – ddMVAC vs GC

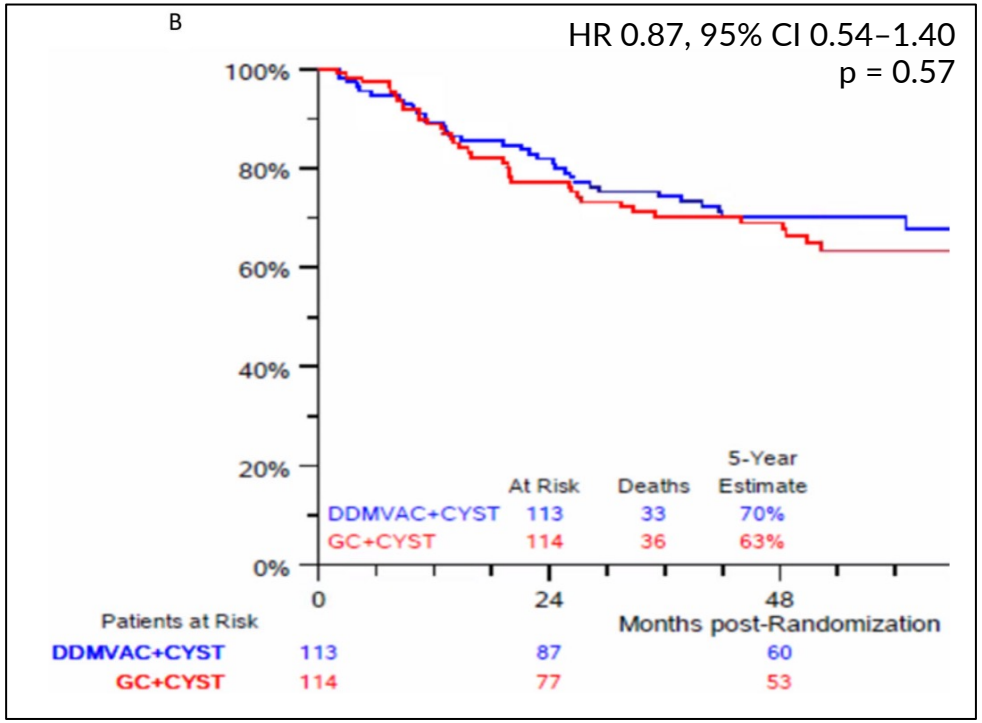
VESPER: ddMVAC x 6 vs GC x 4

N = 437



COXEN: ddMVAC x 4 vs GC x 4

N = 227

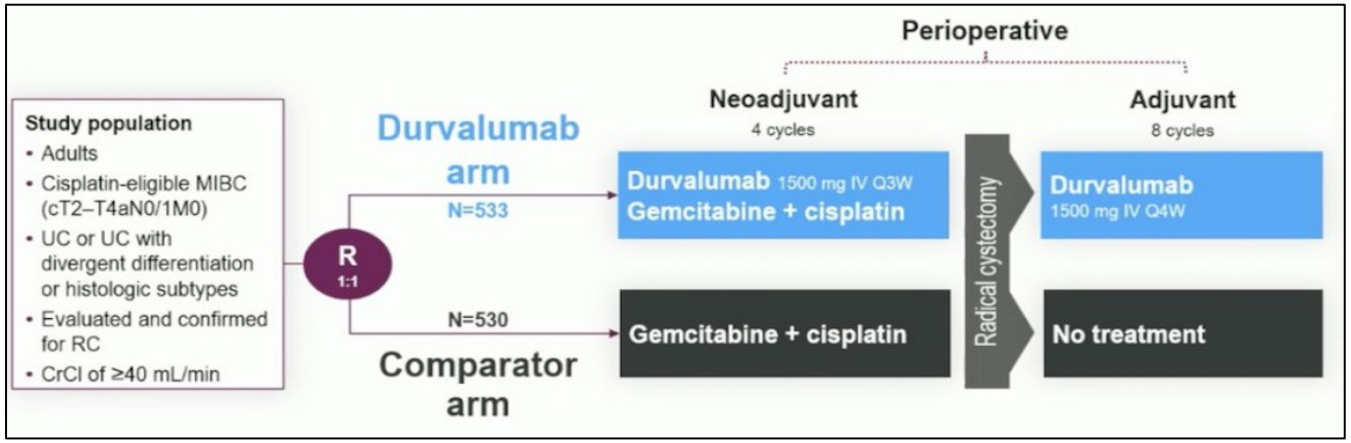


(get cisplatin in however you can)

Pfister, C. (2024). Lancet Onc 25(2): 255-264.
Flaig, T. (2023). Eur Urol 84(3): 341-347.

Does everyone need IO? And in what phase of treatment?

NIAGARA: perioperative durvalumab for all ("sandwich")

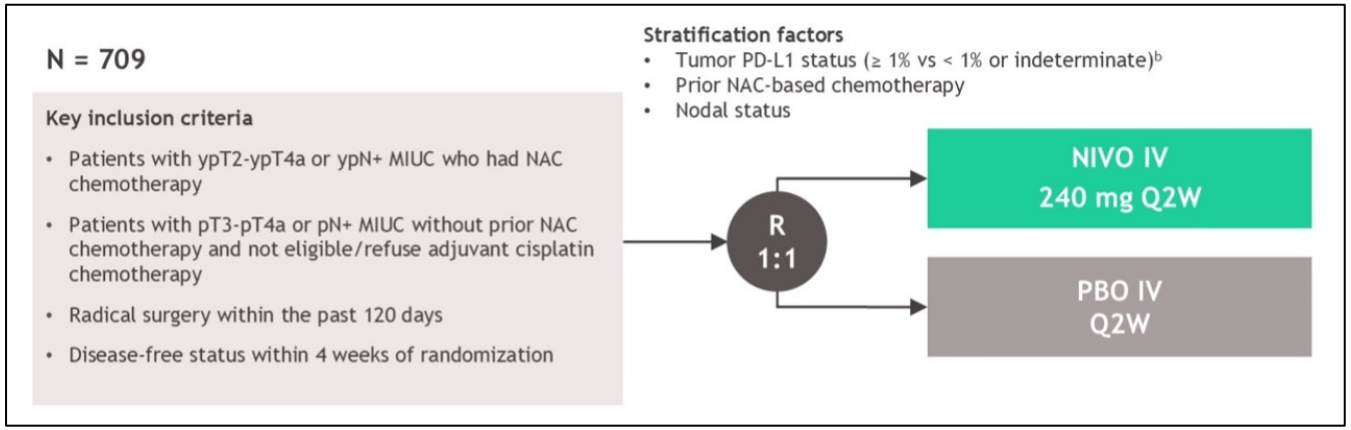


✓ **EFS:** HR 0.68 (95% CI 0.56-0.82)

✓ **OS:** HR 0.75 (95% CI 0.59-0.93)

✗ What about ddMVAC pts? Overtreatment with adjuvant for all?

CHECKMATE-274: adjuvant nivolumab in >= ypT2



✓ **DFS:** HR 0.63 (95% CI 0.51-0.78), P<0.001)

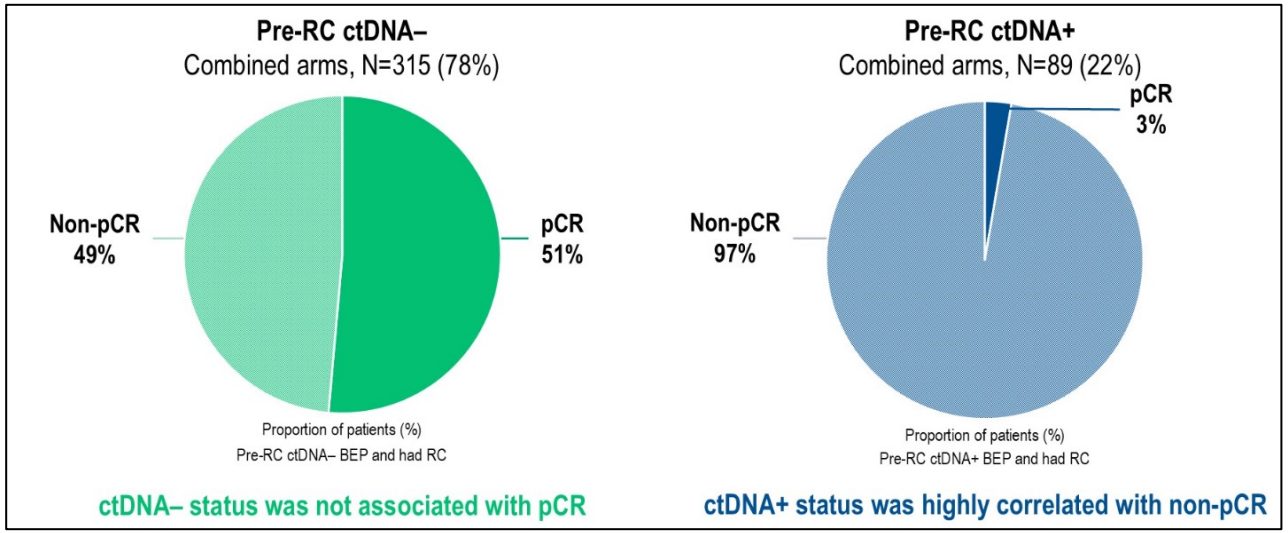
✓ **OS:** HR 0.70 (95% CI 0.55-0.90), P=0.01

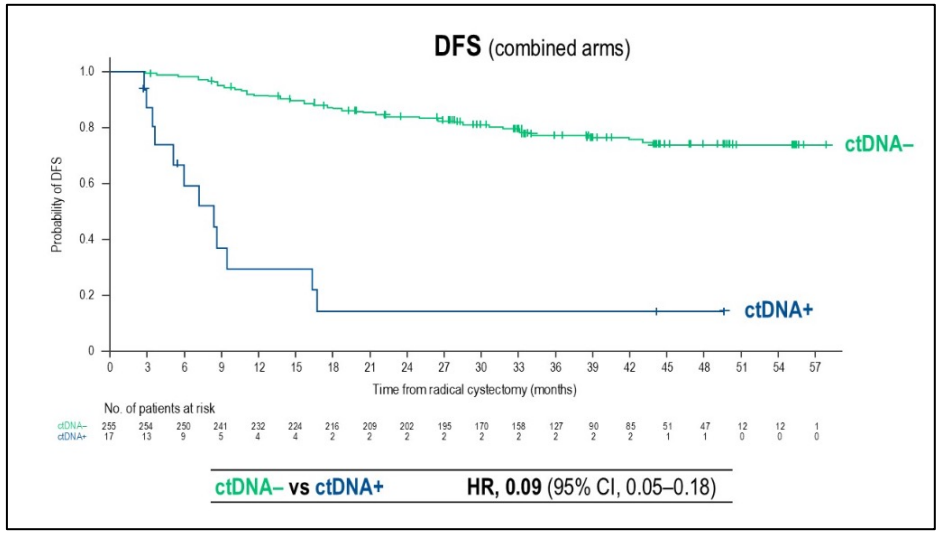
✗ IO addition to NAC improved ctDNA clearance (13%) and pCR (10%)

Powles, T. (2024). NEJM 391: 1173-1786.
Milowsky, M. GU ASCO 2025.
Powles, T. ASCO 2025.

Circulating tumor DNA (ctDNA) is a prognostic biomarker

NIAGARA

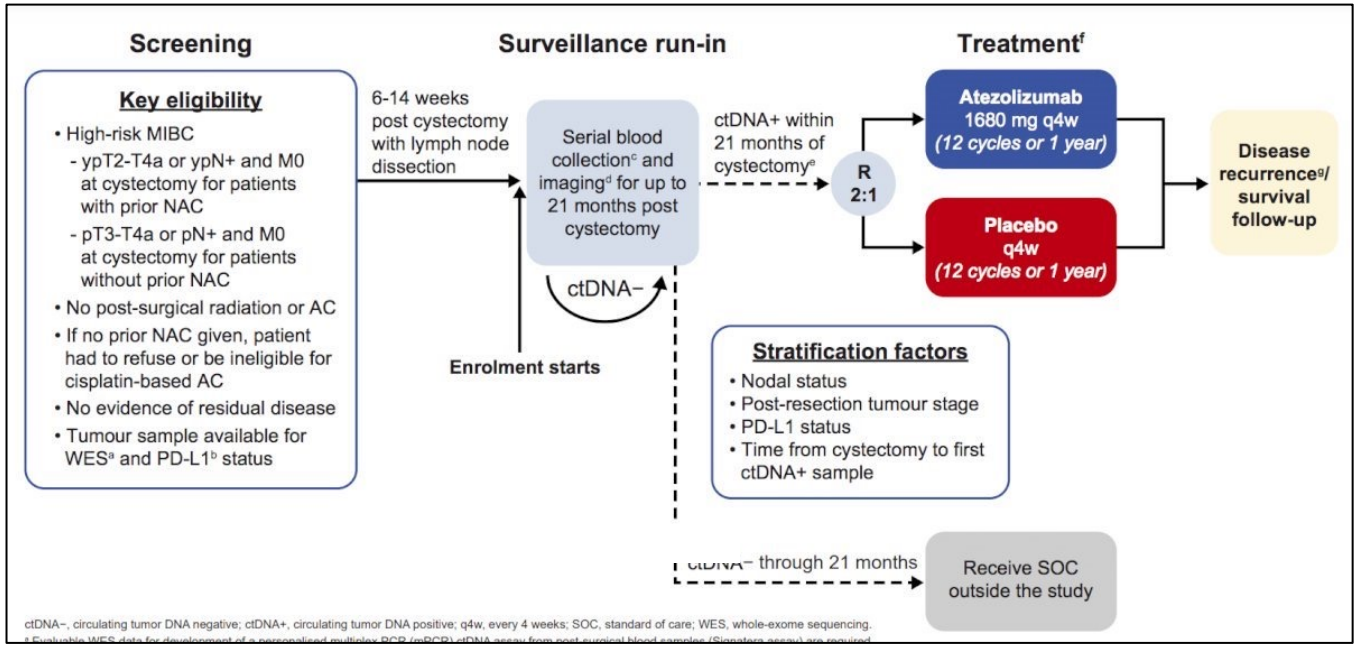




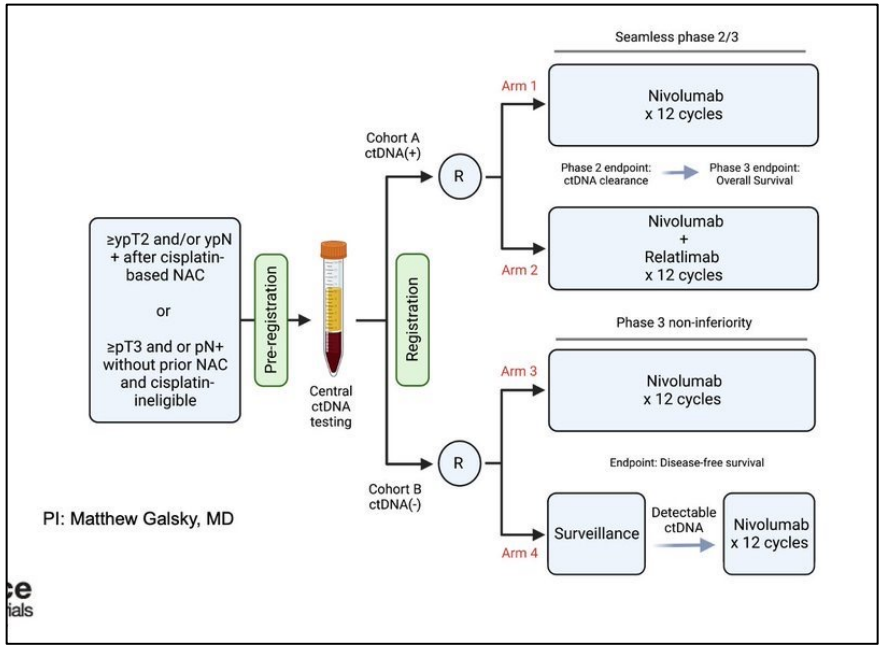
Powles, T. ASCO 2025.

But will ctDNA be predictive?

IMVIGOR-011 Active, not recruiting



MODERN/A032103 Recruiting

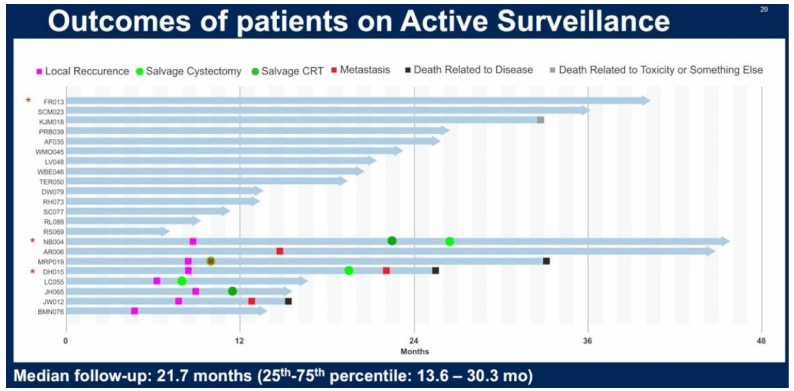


The future

Bladders can be spared

RETAIN-2
ddMVAC + nivo x 3 in DDR mut
Ghatalia, ASCO GU 2025

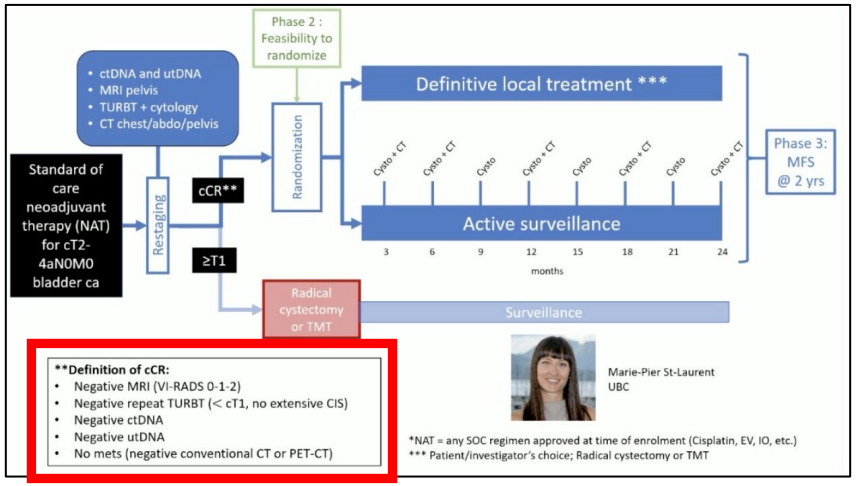
Active, not recruiting



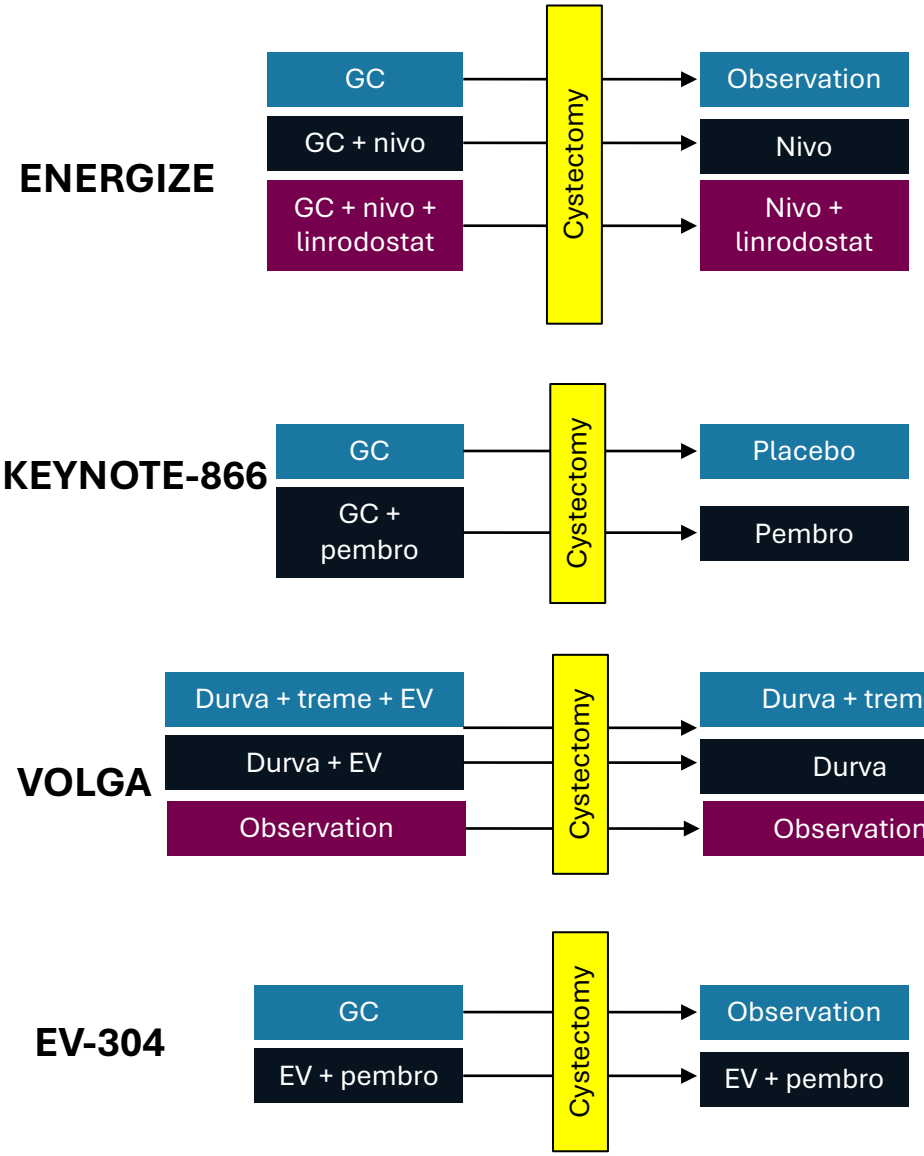
In those with a stringent definition of pCR

NEO-BLAST
St-Laurent, ASCO GU 2025

Recruiting



Who receive excellent systemic therapy



Thank you!

World Conference On
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EMERGING TREATMENTS IN UROTHELIAL CARCINOMA

Karine Tawagi, MD,
Genitourinary Oncology, Assistant Professor of Medicine, UIC
Program Director, Hematology/Oncology Fellowship, UIC

8/23/25

Twitter/X: drkarinetawagi

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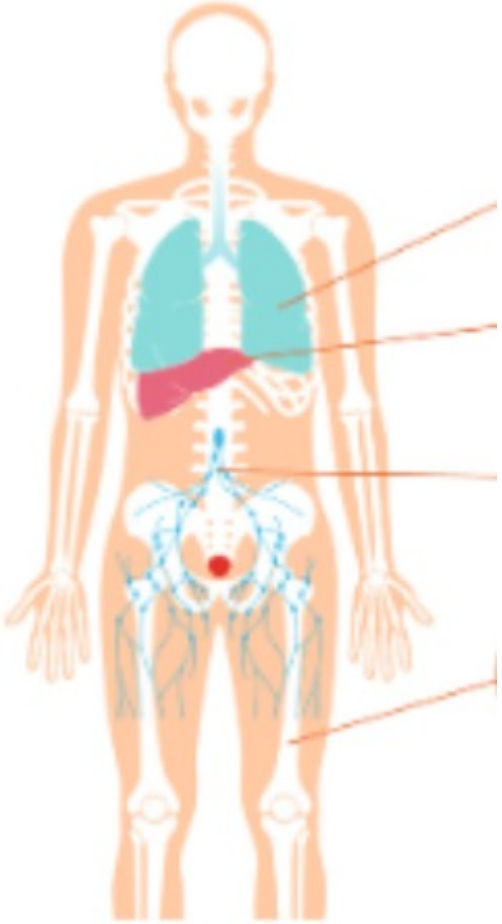
Outline – Emergencing Therapies in UC: ADCs

1. Intravesical ADCs
2. Novel combination therapies
    - Novel approved ADC + IO combinations
    - ADCs + RT
    - Triplet therapy (Double ADC)
    - EV + Erdafitinib
    - EV + Cabozantinib
3. Novel ADCs in development
    - Nectin-4
    - Trop-2
    - Her-2
    - Other targets



1. Intravesical ADCs

Phase I EV104

High-risk BCG-unresponsive NMIBC

Primary endpoint: AEs

→ **Intravesical EV Induction then maintenance**

Phase II: NCT06187506

Very high risk, HER2 +ve NMIBC

Primary endpoint: 3m-CR, EFS

→ **Disitimab Vedotin + BCG**

Abstract 775, TPS894

Phase I/II TroFuse-027

Intermediate-risk NMIBC

Primary endpoint: AEs

→ **Intravesical Sacituzumab Tirumotecan**

Phase II: NCT06630871

High or very high risk, HER2 2/3+ NMIBC

Primary endpoint: 3m-CR, EFS

→ **DV + Tislelizumab + reTURBT**

TPS895

What's the optimal treatment duration and management of relapse?

2. Novel Combination Therapies: ADCs + IO

13

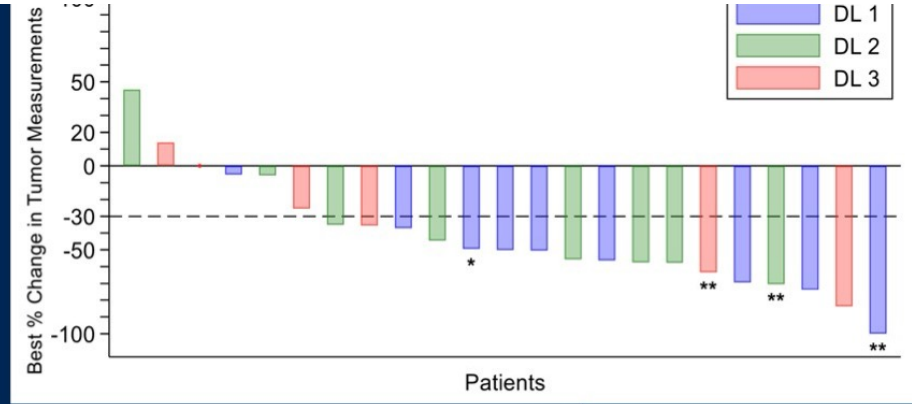
Selected Ongoing Trials of ADCs + Immunotherapy in mUC					
Treatments	**Alias**	**Ph**	**Population**	**Primary Endpoint**	**NCT Number**
DV + Pembrolizumab	DV-001	III	1st line HER2+	PFS, OS	NCT05911295
DV + Toripalimab		III	1st line HER2+	PFS, OS	NCT05302284
Zelenectide Pevedotin + Pembro	DURAVELO-2	III	1st line	PFS	NCT06225596
EV + SG + Pembrolizumab	DAD-IO	II	1st line	ORR	NCT04724018
Datopotamab-DXd + Volrustomig or Rilvergostomig	TROPION-Pan Tumor 03	II	1st or 2nd line	ORR, AEs	NCT05489211
SG + Avelumab	JAVELIN Bl. Medley	II	1st line	PFS, AEs	NCT05327530
EV + Pembro + Sacituzumab TMT or investigational agents	KEYMAKER-U04	I/II	1st line	ORR, PFS	NCT05845814
EV or SG + Atezolizumab	MORPHEUS-UC	Ib/II	Post-platinum	ORR	NCT03869190
SG + Zimberelimab (aPD-1) + Domvanalimab (aTIGIT)	TROPHY-U01 Cohort 7	I/II	1st line	ORR	NCT03547973
BGB-C354 (B7-H3 ADC) + Tislelizumab		I	Later line	AEs, ORR	NCT06422520

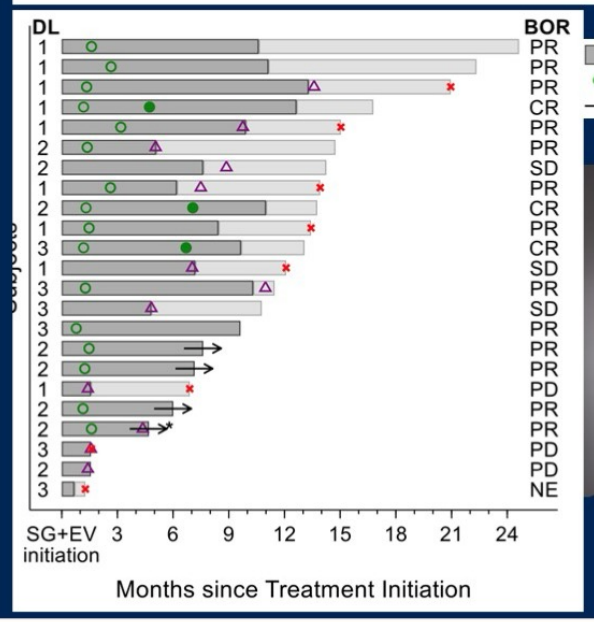
2. Novel Combination Therapies: Triplet (Double ADC) Combinations

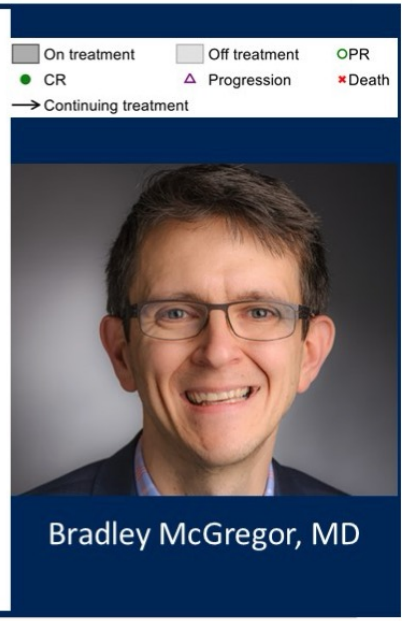
ADC + ADC
Dual Antibody Drug Trial (DAD)

- Enfortumab Vedotin + Sacituzumab Govitecan
- 3rd line (post-platinum, post IO)
- RP2D: EV 1.25mg/kg, SG 8mg/kg
- 70% ORR, durable responses
- Role for adding PD-1?
  - "The DAD-IO" trial

McGregor et al ESMO 2023







Bradley McGregor, MD

ASCO Genitourinary Cancers Symposium #GU25

PRESENTED BY: Terry Friedlander, MD

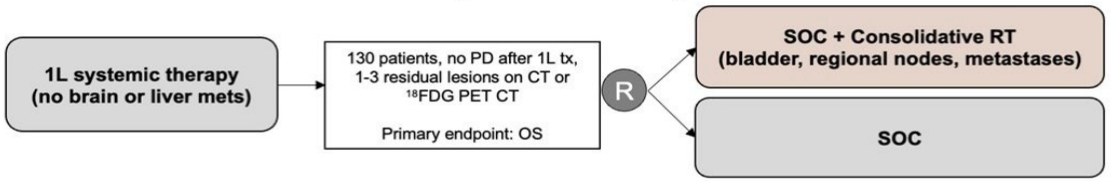
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

2. Novel Combination Therapies: ADCs + RT

ADC + Radiation Therapy

Ongoing Trials in mUC: Consolidative RT

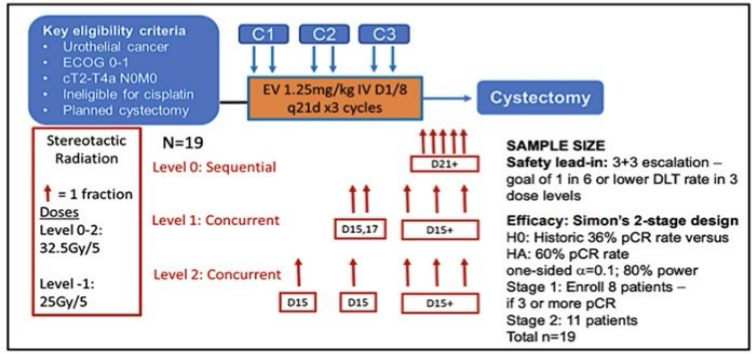
Phase II BLAD RAD01/GETUG-AFU V07 (PI: Jonathan Khalifa)



Khalifa J Clin Oncol 39, 2021 (suppl 15; abstr TPS4588). Presented at ASCO 2021

Courtesy of Maria Jiang, MD

Phase I/II STAR-EV: EV + RT (Tian Zhang)



Other select trials in MIBC with radiation

NCT05879653, PEVRAD	Phase II, n=30	EV + RT	Japan	PI: Takashi Kobayashi
NCT05833867	Phase I, n=20	SG + adaptive RT	USA	PI: Shilpa Gupta
NCT06470282	Phase I/II, n=47	EV + Pembro + RT	USA	PI: Vadim Koshkin
NCT05979740	Phase II, n=6	RC48 + Toripalimab + RT	China	PI: Haige Chen

ASCO Genitourinary Cancers Symposium #GU25

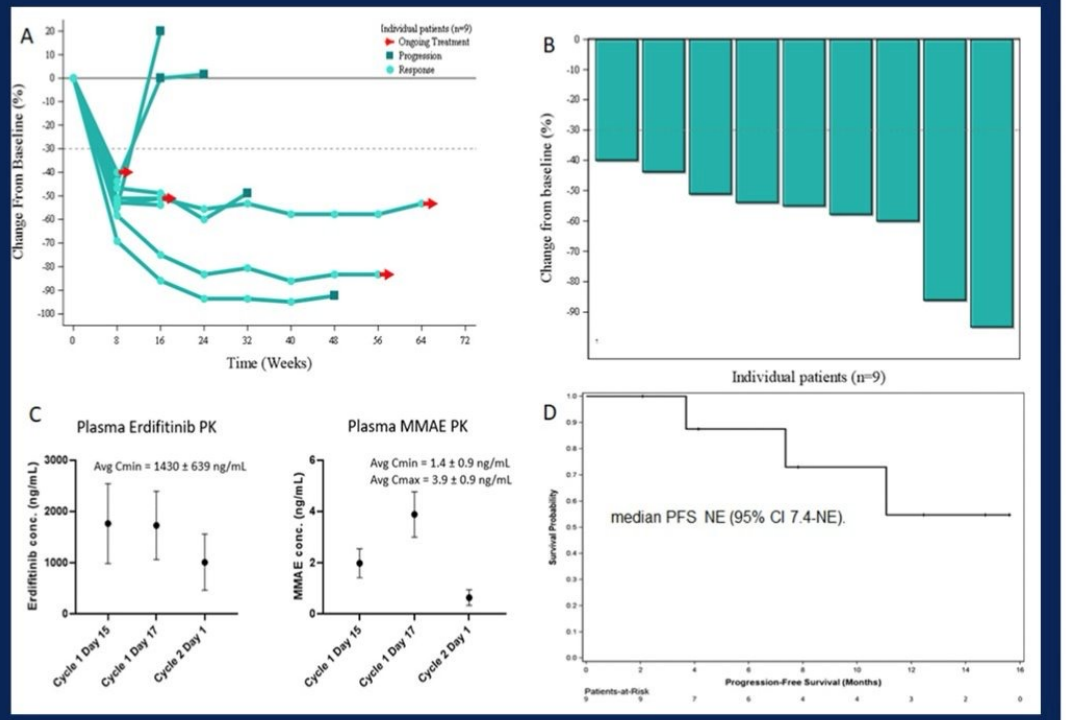
PRESENTED BY: Terry Friedlander, MD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

2. Novel Combination Therapies: Erdafitinib + EV

Phase Ib Trial of Erdafitinib + EV in mUC with FGFR2/3 alterations

Rohit Jain, MB BS MD



AE TERM	Any Grade n (%)	≥Grade 3 n (%)
Hyperphosphatemia	9 (100.0%)	
Mucositis oral	9 (100.0%)	
AST increased	8 (88.9%)	
Hypercalcemia	8 (88.9%)	
Diarrhea	7 (77.8%)	1 (11%)
Rash maculo-papular	6 (66.7%)	2 (22%)
Fatigue	6 (66.7%)	
Hypoalbuminemia	6 (66.7%)	
Hypomagnesemia	6 (66.7%)	
PPE syndrome	6 (66.7%)	3 (33%)
Eye disorders: CSR/RPED/Positive Amsler Grid	6 (66.7%)	
Peripheral sensory neuropathy	6 (66.7%)	
Alopecia	5 (55.6%)	
Anemia	5 (55.6%)	1 (11%)
Dry eye	5 (55.6%)	
Nail change/ loss/Paronychia	5 (55.6%)	1(11%)
Dry mouth	5 (55.6%)	
Hyponatremia	5 (55.6%)	
Hypophosphatemia	5 (55.6%)	
Lymphocyte count decreased	5 (55.6%)	2 (22%)
Anorexia	4 (44.4%)	1 (11%)
Creatinine increased	4 (44.4%)	
Dysgeusia	4 (44.4%)	
Nausea	4 (44.4%)	1 (11%)
ALT increased	3 (33.3%)	
Dry skin	3 (33.3%)	
Dysphagia	3 (33.3%)	
Pruritus	3 (33.3%)	
Weight loss	3 (33.3%)	
Blurred vision	2 (22.2%)	
Edema limbs	2 (22.2%)	
Gait disturbance	2 (22.2%)	
Hyperglycemia	2 (22.2%)	
Hyperkalemia	2 (22.2%)	
Hypokalemia	2 (22.2%)	1 (11%)
Serum amylase increased	2 (22.2%)	
Urinary tract infection	2 (22.2%)	2 (22%)
Vomiting	2 (22.2%)	1 (11%)

Jain et al GU ASCO 2024, Clark-Garvey et al CCR Volume 30, Issue 10, Supplement 15, May 2024

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2. Novel Combination Therapies: Cabozantinib + EV

EV + Cabozantinib Phase I/II trial

Jacqueline Brown, MD

Mehmet Bilen MD

Figure 1. Best overall responses (n=9)

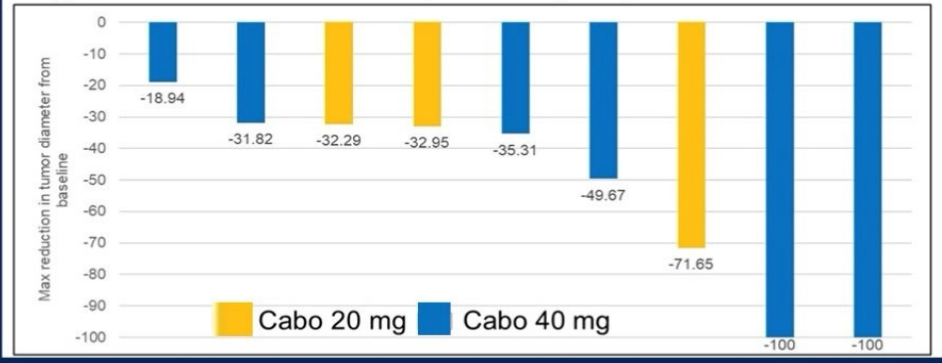

Table 3. Treatment-related adverse events and dose reductions

Cabo dose (mg)	20		40			n (%)
Grade	1/2	3	1/2	3	4	
Skin rash / HFS	4	1	1	1		7 (63.6)
Elevated ALT	3	1	1			5 (45.5)
Fatigue	2			2		4 (36.4)
Eye irritation	2		2			4 (36.4)
Hypophosphatemia	1	2	1			4 (36.4)
Elevated AST	3		1			4 (36.4)
Constipation	2		2			4 (36.4)
Hyponatremia		2	1			3 (27.3)
Anorexia	2		1			3 (27.3)
Mucositis	2		1			3 (27.3)
Sensory neuropathy	2	1				3 (27.3)
Motor neuropathy	3					3 (27.3)
Insomnia	2		1			3 (27.3)
AKI		2		1*		3 (27.3)
Dehydration	1	1*				2 (18.2)
Dyspepsia	2					2 (18.2)
Arthralgia	2					2 (18.2)
Alopecia	2					2 (18.2)
Anemia	1		1			2 (18.2)
Nausea	2					2 (18.2)
Hypomagnesemia	1		1			2 (18.2)
Pruritis			2			2 (18.2)
Febrile neutropenia		1			1*	2 (18.2)
Edema	2					2 (18.2)
SVC syndrome				1*		1 (9.1)
Proteinuria	1					1 (9.1)
Hypertriglyceridemia			1			1 (9.1)
Hyperglycemia			1			1 (9.1)
Dose reductions due to treatment-related AEs						
40 mg	3 (100%)					
20 mg	7 (63.6%)					

*Treatment-related SAE

Brown et al ASCO 2024

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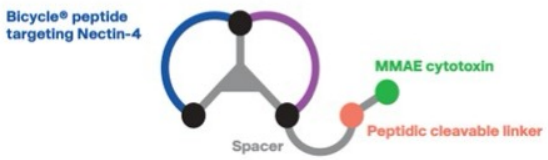
3. Novel ADCs in Development

Nectin-4

BT8009 (Zelenectide pevedotin)



Phase I/II Duravelo trial:
n=45 mUC, 3L+, EV-naive[1]

BT8009 5mg/m² q1w	
ORR	45%
DoR	11.1 mo

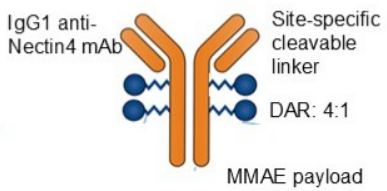
PN only G1/G2, no ≥G3

BAT8007[3], LY4101174[4] LY4052031[5], SHR-A2102[6]

topo I inhibitor payloads

Abstract 657, TPS900

9MW2821



Phase I/II trial (UC cohort):
n=37 mUC, 2L+ [2]

9MW2821 1.25mg/kg d1,8,15 q4w	
ORR	62.2%
mPFS	8.8 mo

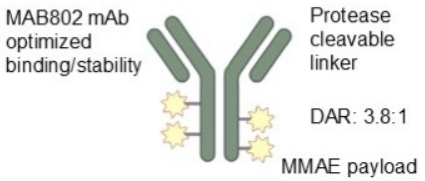
CRB-701 (SYS6002)[7]

site-specific cleavable linker

Abstract 807

HER-2

MRG002



Phase II trial:
n=43 mUC, 2L+, IHC 2/3+[8]

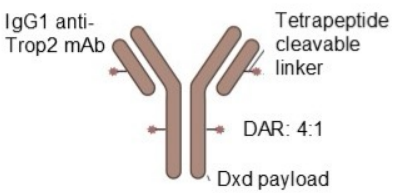
MRG002 2.6 or 2.2g/m² q3w	
ORR	53.4%
mPFS	6.4 mo

Phase I/II trial:
n=38 mUC, 1L+, IHC 1-3+[9]

MRG002 + Pucotenlimab	
ORR	63.6%
PFS at 12mo	71%

Trop2

Datopotamab Deruxtecan



Phase I TROPION-PanTumor-01
n=40 mUC cohort, 2L+[10]

Dato-Dxd 6mg/kg q3w	
ORR	27.5%
mPFS	6.9 mo

Abstract 663

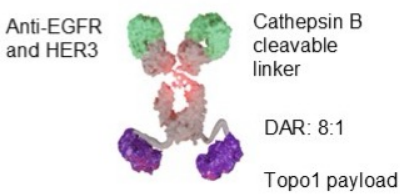
Sacituzumab Tirumotecan

topo I payload

Abstract 796

EGFR/HER3

BL-B01D1 Bispecific



Phase II BL-B01D1-201
n=27 mUC, 2L+[11]

BL-B01D1 2.2 mg/kg d1,8 q3w	
ORR	40.7%
PFS at 6 mo	62.4%

Patritumab Deruxtecan[12]

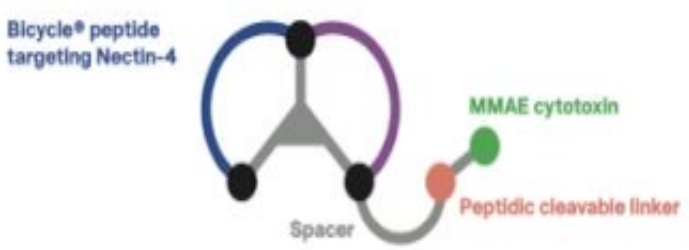
HER3 ADC

[1]Torras et al. ESMO 2024. [2]Zhang, ASCO 2024. [3]Jiang, ASCO 2024. [4]Rosenberg. AACR 2024; [5]Sagar AACR 2024; [6]Tang. GU ASCO 2025; [7]Ye. GU ASCO 2024. [8]Qu. Eur J Cancer. 2024; [9]Cui. ESMO 2024. [10]Meric-Bernstam. GU ASCO 2025. [11]Ye. ESMO 2024. [12]Powles. ESMO 2024

3. Novel ADCs in Development: Zelenectide pevedotin

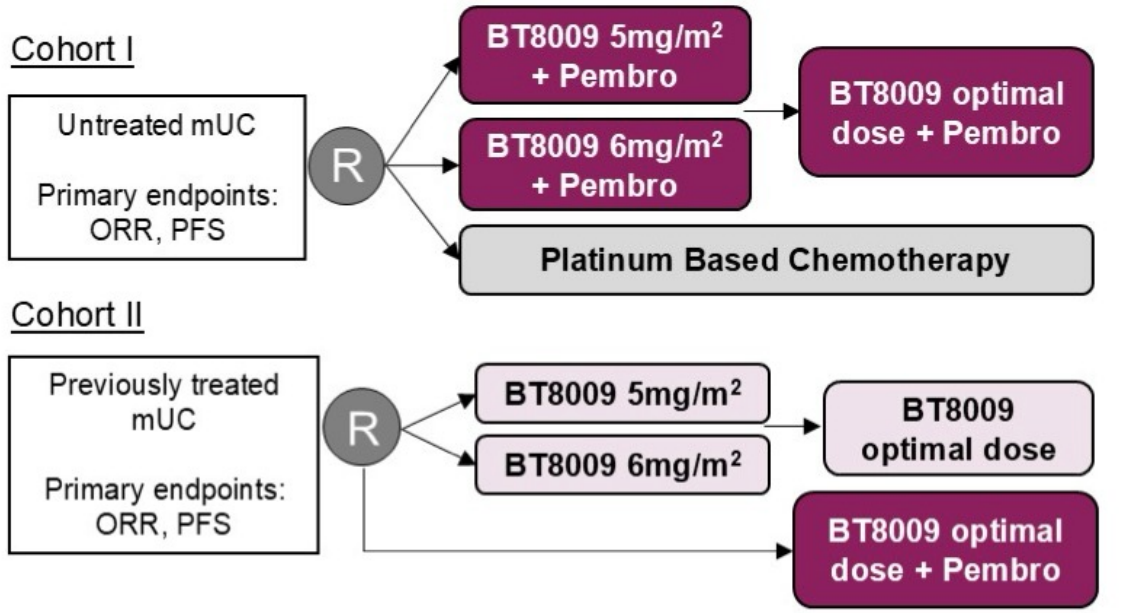
Bicycle-toxin conjugate w/ smaller scaffold may penetrate tumors that evade bulky ADCs

BT8009 (Zelenectide pevedotin)



Duravelo-1: Urothelial Cancer Patients (Post-Platinum/ICI, no EV) Treated with BT8009 Monotherapy (N=38)	
ORR	45%
Disease Control Rate	61%
Median DoR	11.1 months
Peripheral Neuropathy Rate	36%

Phase II/III DURAVELO-2: BT8009 +/- Pembrolizumab



Platinum chemo control arm in the EVP era?

3. Novel ADCs in Development: Other Nectin-4 agents

- **Optimizing payloads:**
  - **Shift from tubulin inhibitors (e.g., MMAE) to topoisomerase I inhibitors (e.g., exatecan)**
- **Better tumor cell penetration and bystander effect**
- **Improved linkers:**
  - **More stable in circulation**
  - **Controlled payload release in tumor microenvironment**
- **Increased Drug-to-Antibody Ratio (DAR):**
  - Enhances cytotoxic payload delivery without increasing toxicity

- LY4191174: topo I payload w/ dfft toxicities, optimizing linker payload stability, increasing drug-antibody ratio (DAR)
- SYS6002: mAB backbone prolonged half-life w/ lower dose frequency, more uniform DAR
- SHR-A2102: IgG1 mAb against nectin-4, a cleavable linker, and a topoisomerase I inhibitor payload

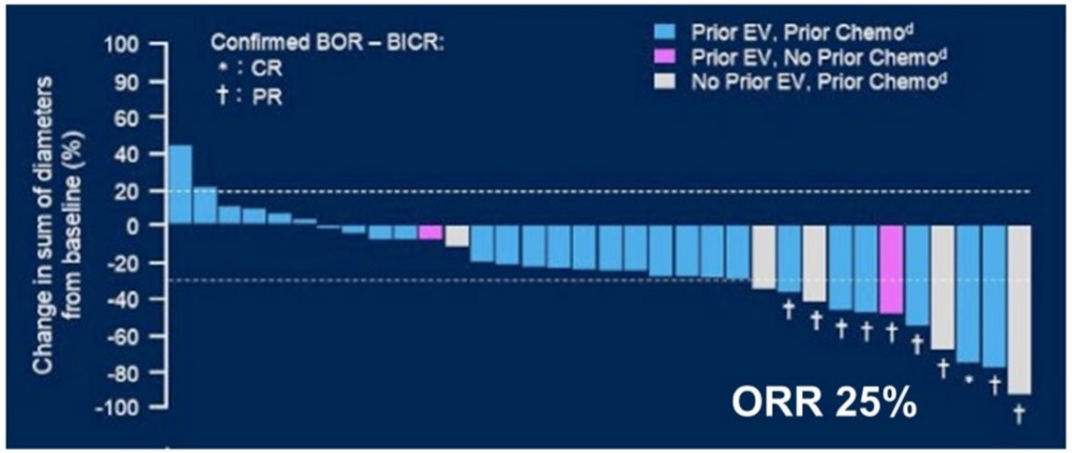
Conclusions

- **SHR-A2102 showed a tolerable and manageable safety profile in patients with advanced or metastatic urothelial carcinoma.**
  - Common TRAEs were hematological toxicities and gastrointestinal toxicities;
  - Incidences of TRAEs leading to dose reduction (8.6%) and treatment discontinuation (2.5%) were relatively low;
  - 6 mg/kg of SHR-A2102 had fewer toxicities, compared with 8 mg/kg.
- **Promising anti-tumor activity was observed at 6 and 8 mg/kg Q3W.**
  - ORR: 41.9% at 6 mg/kg; 50.0% at 8 mg/kg;
  - Median DoR: 7.6 months at 6 mg/kg; 5.5 months at 8 mg/kg;
  - Median PFS: 5.8 months at 6 mg/kg; 5.8 months at 8 mg/kg.
- **6 mg/kg Q3W was established as the recommended dose for SHR-A2102 monotherapy for pretreated advanced or metastatic urothelial carcinoma.**

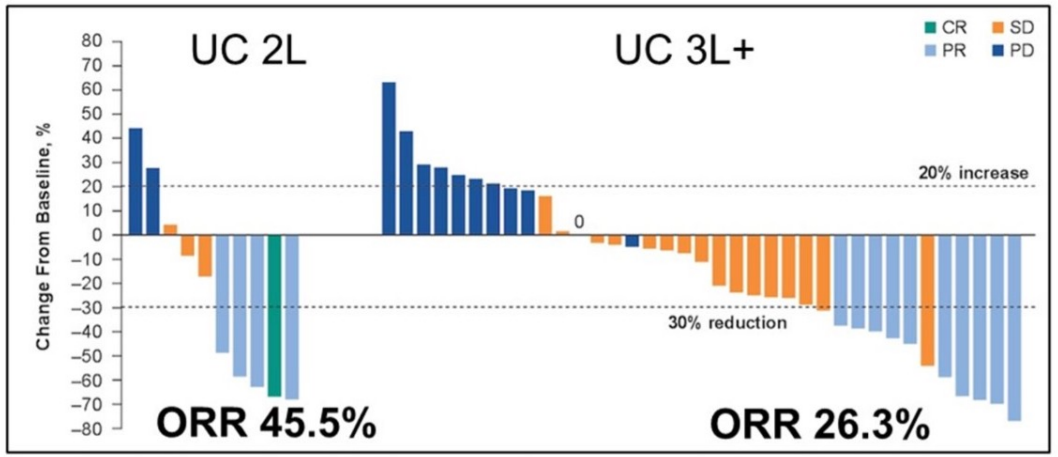
3. Novel ADCs in Development: Trop-2

Is Trop-2 the target that we thought it was in mUC?

Humanized TROP-2–targeting immunoglobulin linked to a potent exatecan-derived topo-I payload via a tetrapeptide-based plasma-stable, selectively cleavable linker



Novel TROP-2–targeting ADC which uses a proprietary novel, irreversible hydrolysable linker with a belotecan-derivative topo-I payload



I would argue yes based on ASCO GU 2025, but time will tell

1. Meric-Bernstam F, et al. ASCO GU 2025.
2. Ye D, et al. ASCO GU 2025.

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3. Novel ADCs in Development: HER-2

14

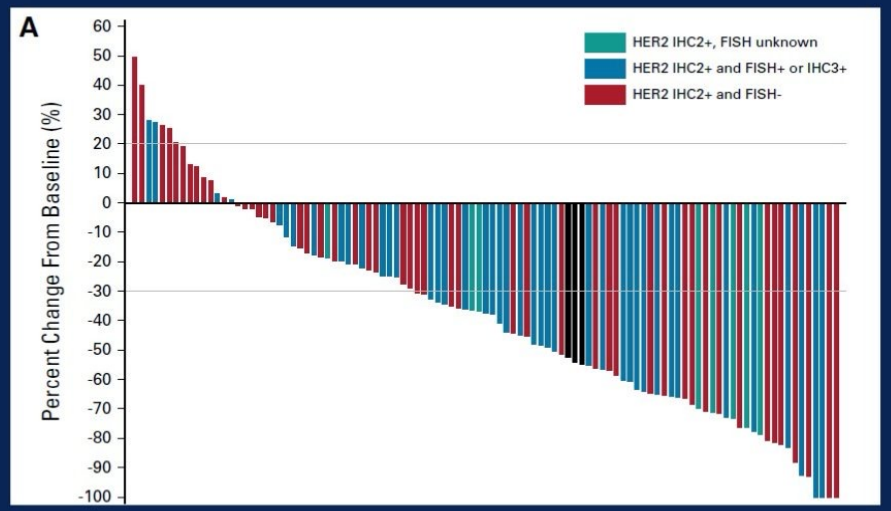
Disitamab Vedotin in Patients with HER2–3+ or 2+ Locally Advanced or Metastatic UC

Two phase II, open-label, multicenter,

Single-arm studies (RC48-C005 and RC48-C009)

Patients with HER2 IHC 3+ or 2+locally advanced or metastatic UC who have progressed on at least one previous line of systemic chemotherapy

- confirmed ORR by BIRC was 50.5% (95% CI, 40.6 to 60.3).
- Median PFS of 5.9 months and the median OS of 14.2 months

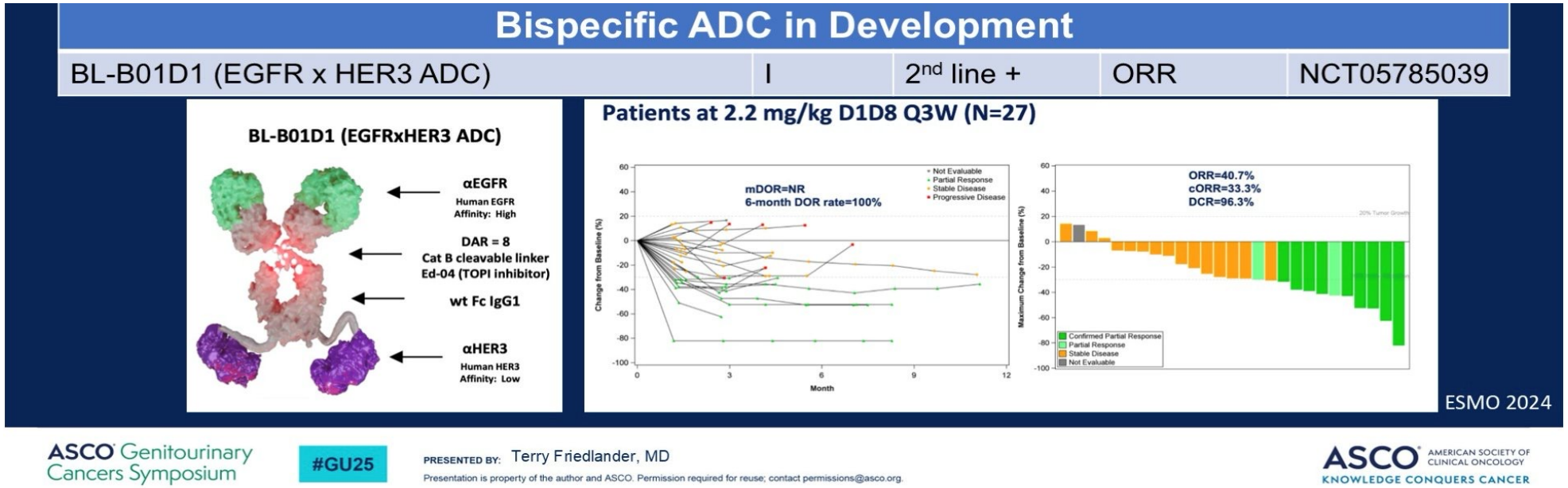


DV is now in Phase III trials in front line

Sheng et al JCO 2023

- Phase Ib/II trial + Toripalimab
- 61% of whom were treatment-naïve
- HER2 overexpression (defined as IHC 2+ or 3+) in 59%
- Confirmed ORR was 73.2% (95% CI, 57.1 to 85.8) for IIT and 76.0% for treatment-naïve patients

3. Novel ADCs in Development: Novel Targets



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- B7-H3 ADC: over-expressed even after nectin-4 loss
- SLITRK6 ADC: tumor antigen retained on tumor biopsies frommetastatic foci

Closing Thoughts / Remaining Questions

- **Precision ADC development:**
  - Moving to earlier disease stages, more bladder-sparing approaches, increased cure rates
  - Tailor to molecular profile (e.g., HER2, Nectin-4, TROP2 expression)
    - Defined activity for lower expressing e.g. HER2 and/or mutated
  - Novel payloads
  - Combination with IO to enhance response and durability
- **Key questions moving forward:**
  - What is the ideal antigen threshold?
  - Appropriate patient selection to enhance efficacy, minimized toxicity, inform cost and payor decisions
  - How do we best sequence or combine ADCs?

THANK YOU.

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World Conference On
Genitourinary Cancers
2025 NASHVILLE, TN

EMERGING APPROACHES TO PROSTATE CANCER

Benjamin Garmezy, MD

Associate Director of Genitourinary Research, Sarah Cannon Research Institute

Co-Chair, Genitourinary Research Executive Committee, Sarah Cannon Research Institute

GU Medical Oncologist, SCRI Oncology Partners, Nashville Tennessee

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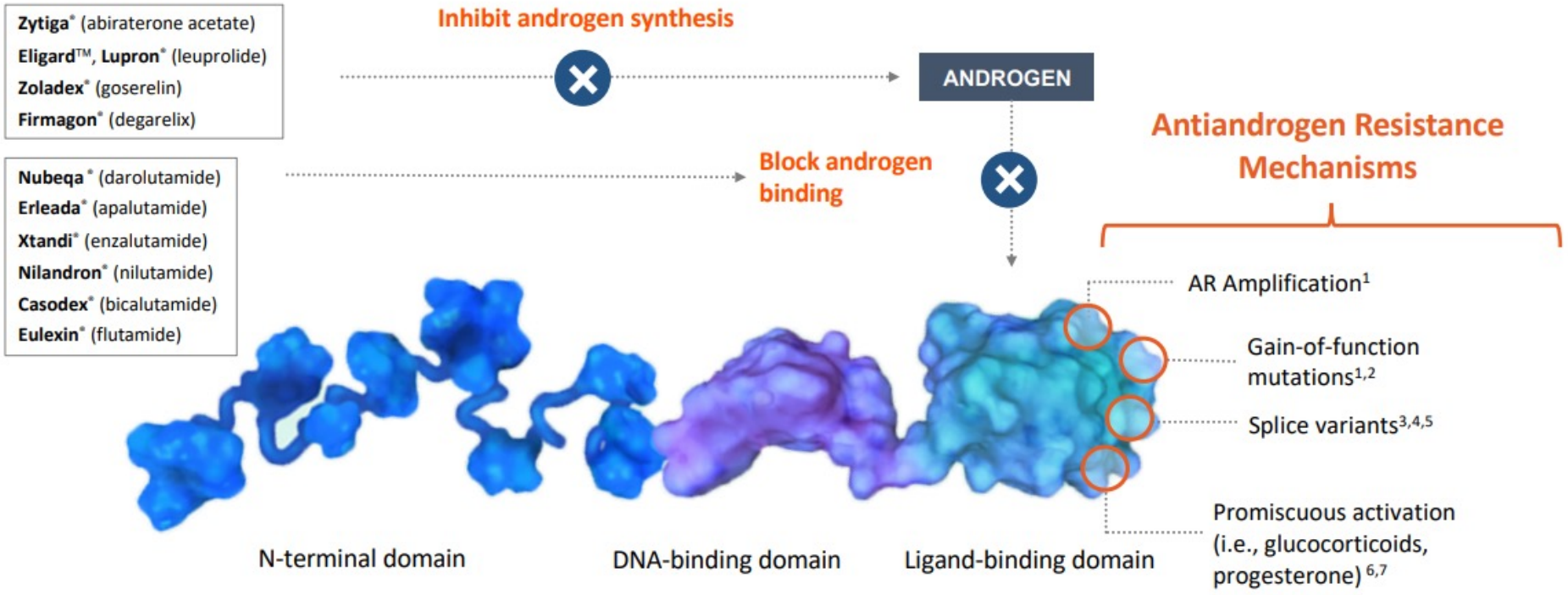
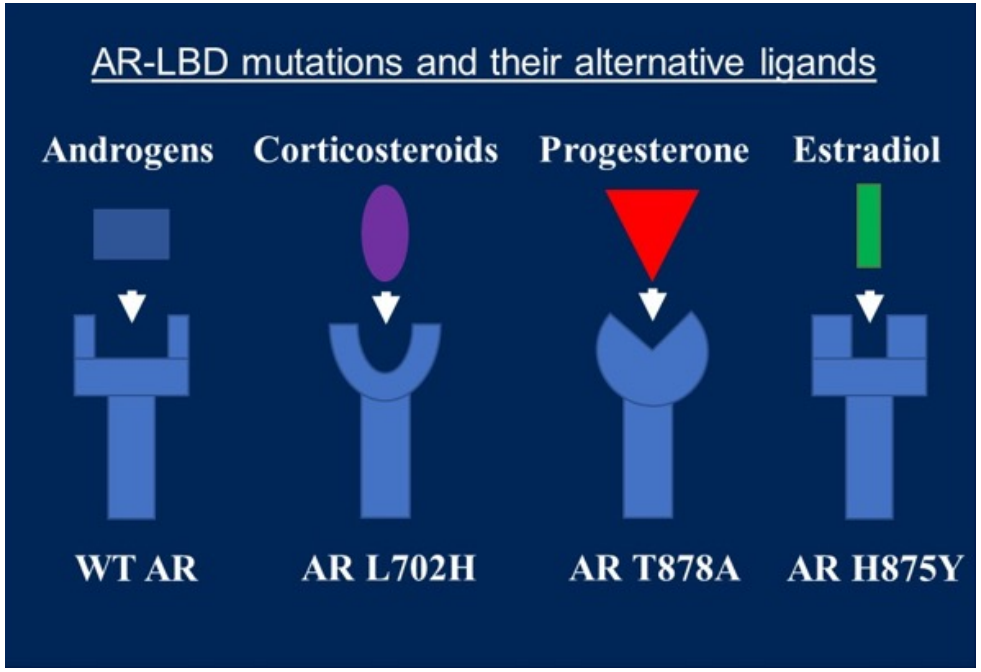
Moving Beyond AR Inhibition

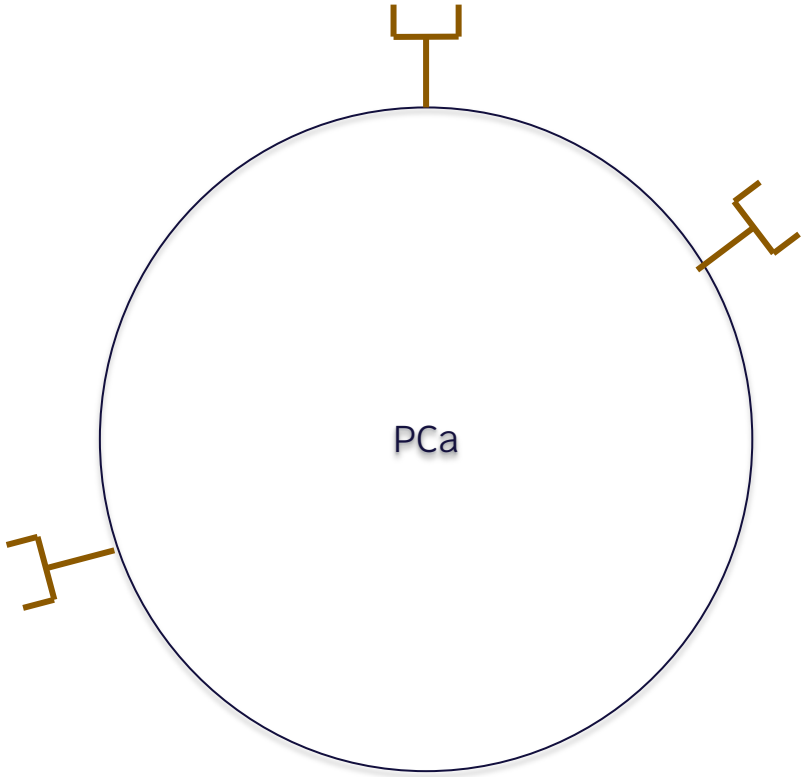


- All current antiandrogens function through the ligand-binding domain of the androgen receptor
- Known antiandrogen resistance mechanisms develop at the ligand binding domain

ESSA Corporate Presentation 2021.
1. Azad AA, et al. Clin Cancer Res. 2015.
2. Joseph JD, et al. Cancer Discov. 2013.
3. Antonarakis ES. et al. NEJM. 2014.
4. Mostagehel, EA. et al. AI Clin Cancer Res. 2011.
5. Chen, EJ. et al. Clin Cancer Res. 2015.

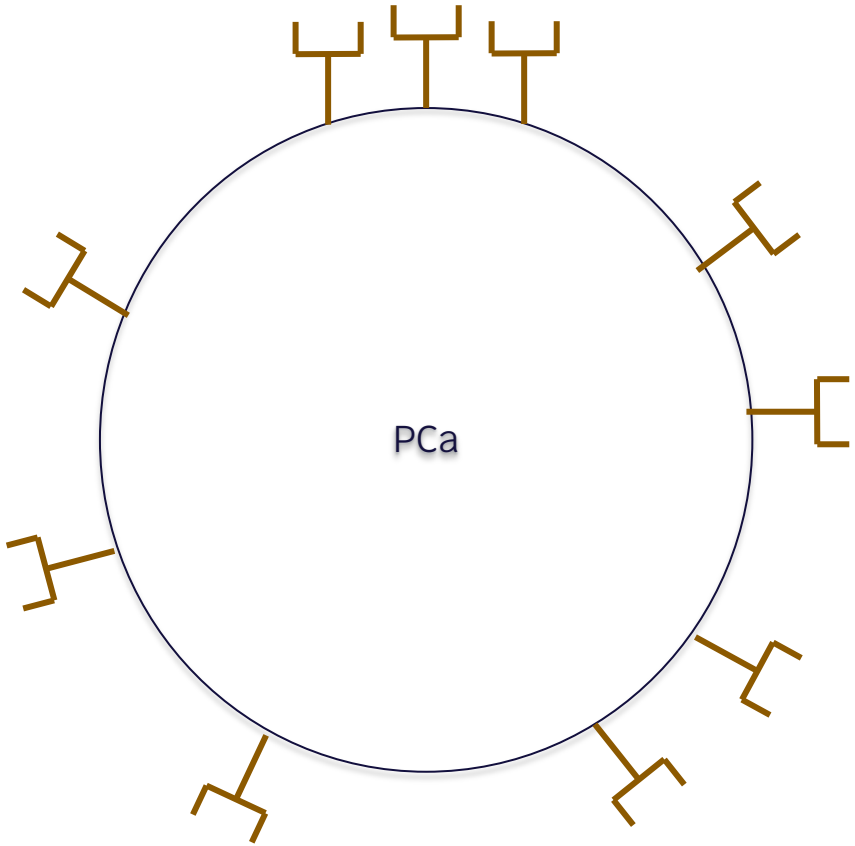
One Mechanism of ARPI Resistance: Ligand Binding Domain Alterations



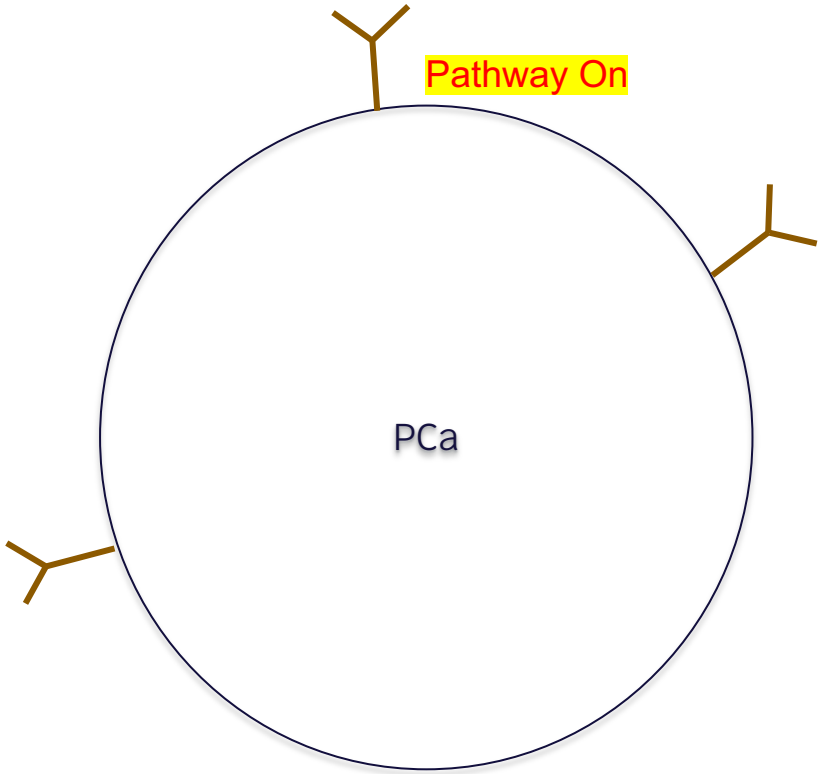


Fizzazi, et al. GU ASCO 2022

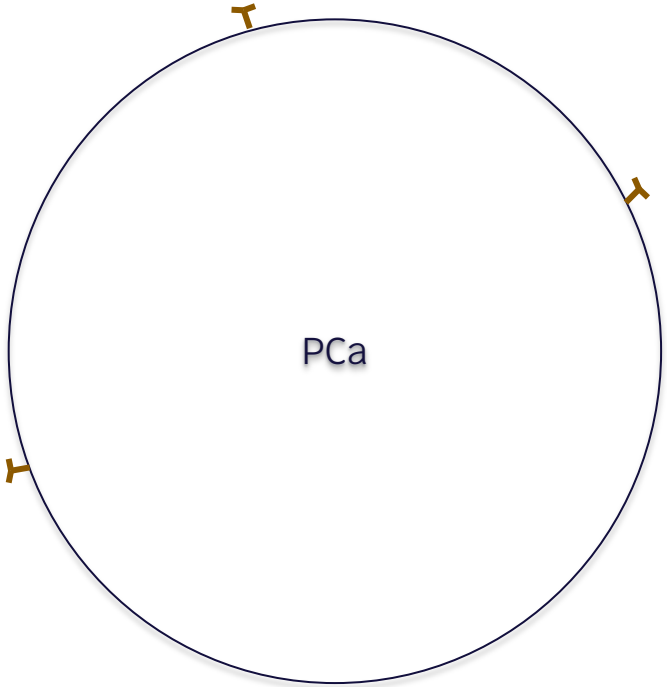
Ligand Binding Domain Alterations



AR Amplifications

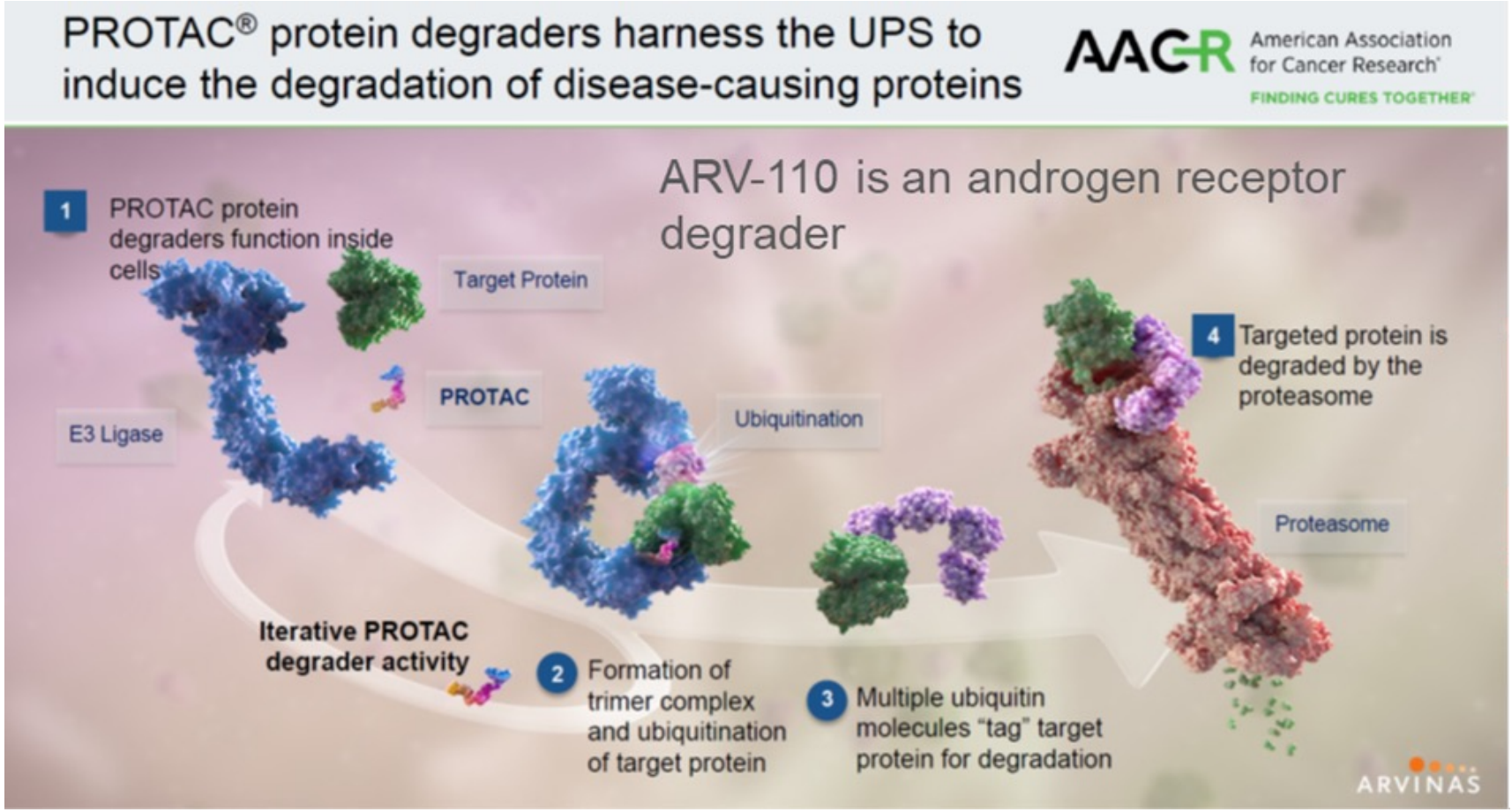


AR LBD Mutations



AR Truncations/Splice

PROTACs



Snyder, et alAACR 2021.

Overcoming LBD Mutations

Androgen Receptor Degraders

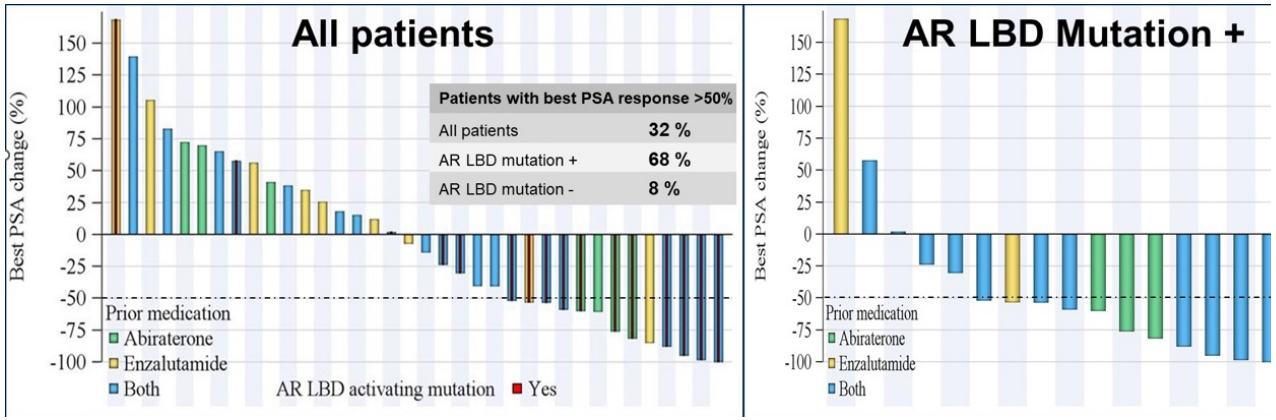
- Bavedegalutamide (ARV-110)
- Luxdegalutamide (ARV-766/JSB-462)
- Gridegalutamide (BMS-986365)
- GDC-2992
- HP-518
- *And many more!*

Adrenal Biosynthesis Inhibitors

- Opevesotat (MK-5684)

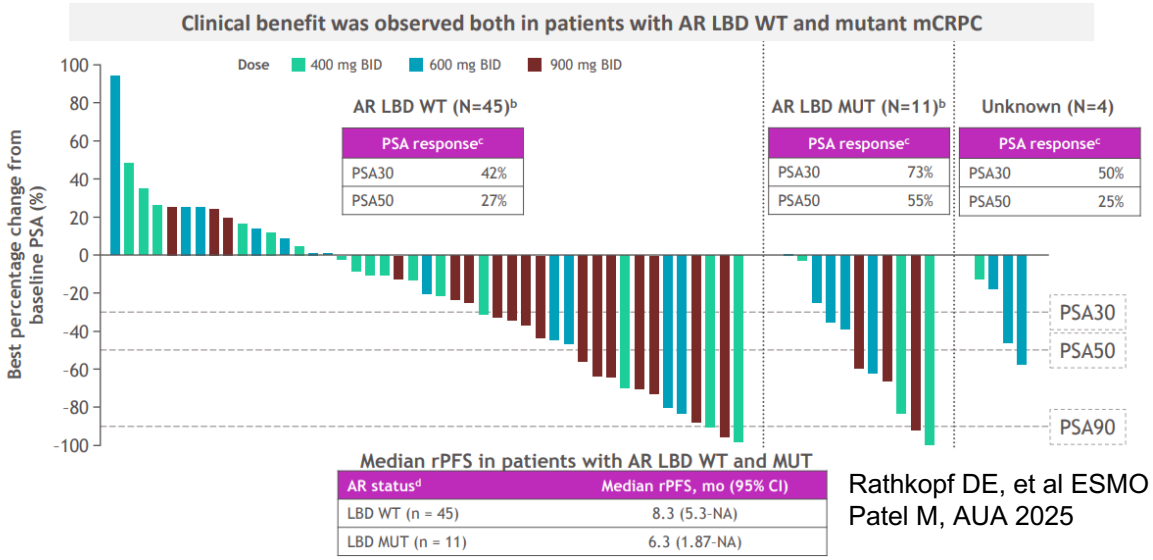
Snyder, et al AACR 2021.

Opevesostat



Fizazi K, et al. GU ASCO 2022

Gridegalutamide

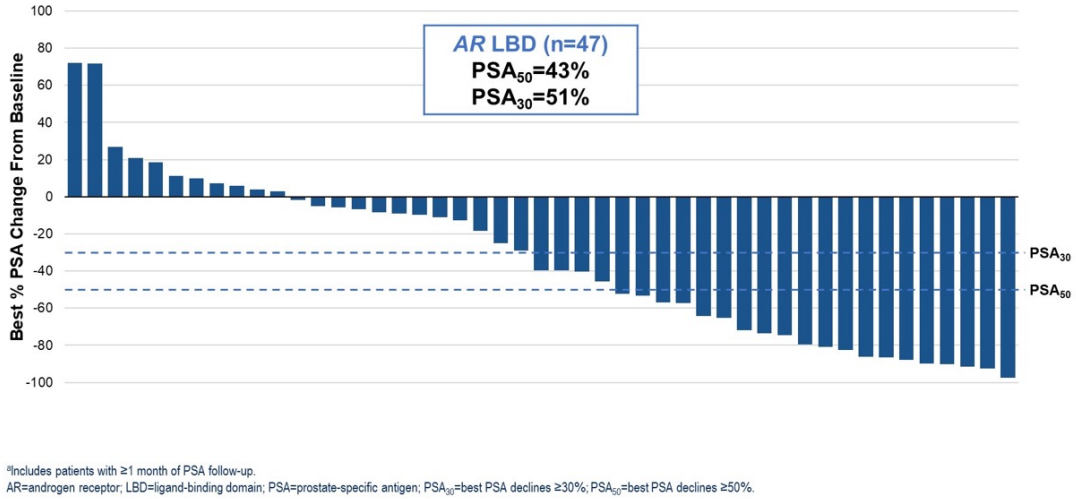


Rathkopf DE, et al ESMO 2024
Patel M, AUA 2025

Bavedegalutamide

Gao X, et al. GU ASCO 2022

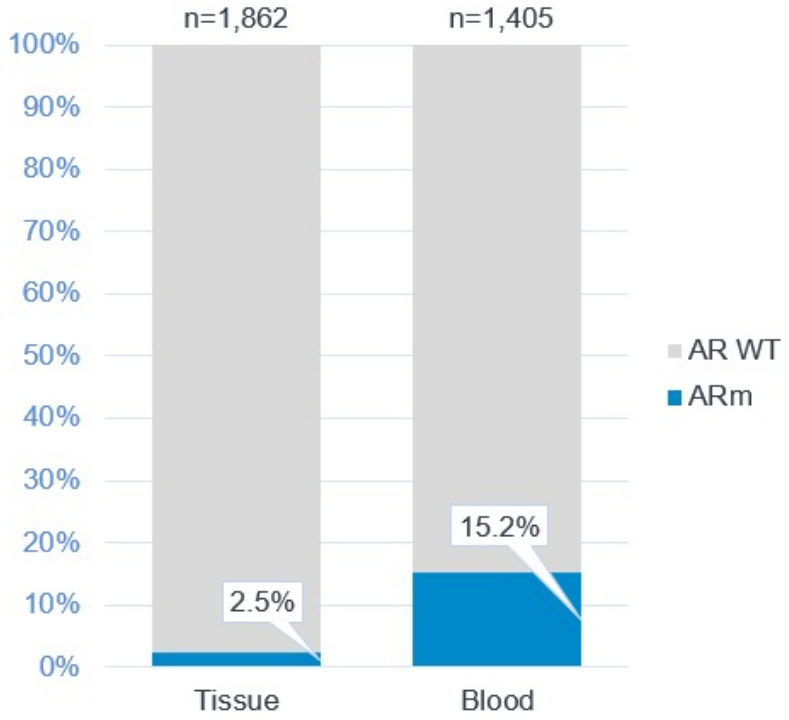
Luxdegalutamide



aIncludes patients with ≥1 month of PSA follow-up.
AR=androgen receptor; LBD=ligand-binding domain; PSA=prostate-specific antigen; PSA_{30}=best PSA declines ≥30%; PSA_{50}=best PSA declines ≥50%.

Petrylak D, et al. ASCO 2024

AR Mutation Prevalence: SCRI Network DATA



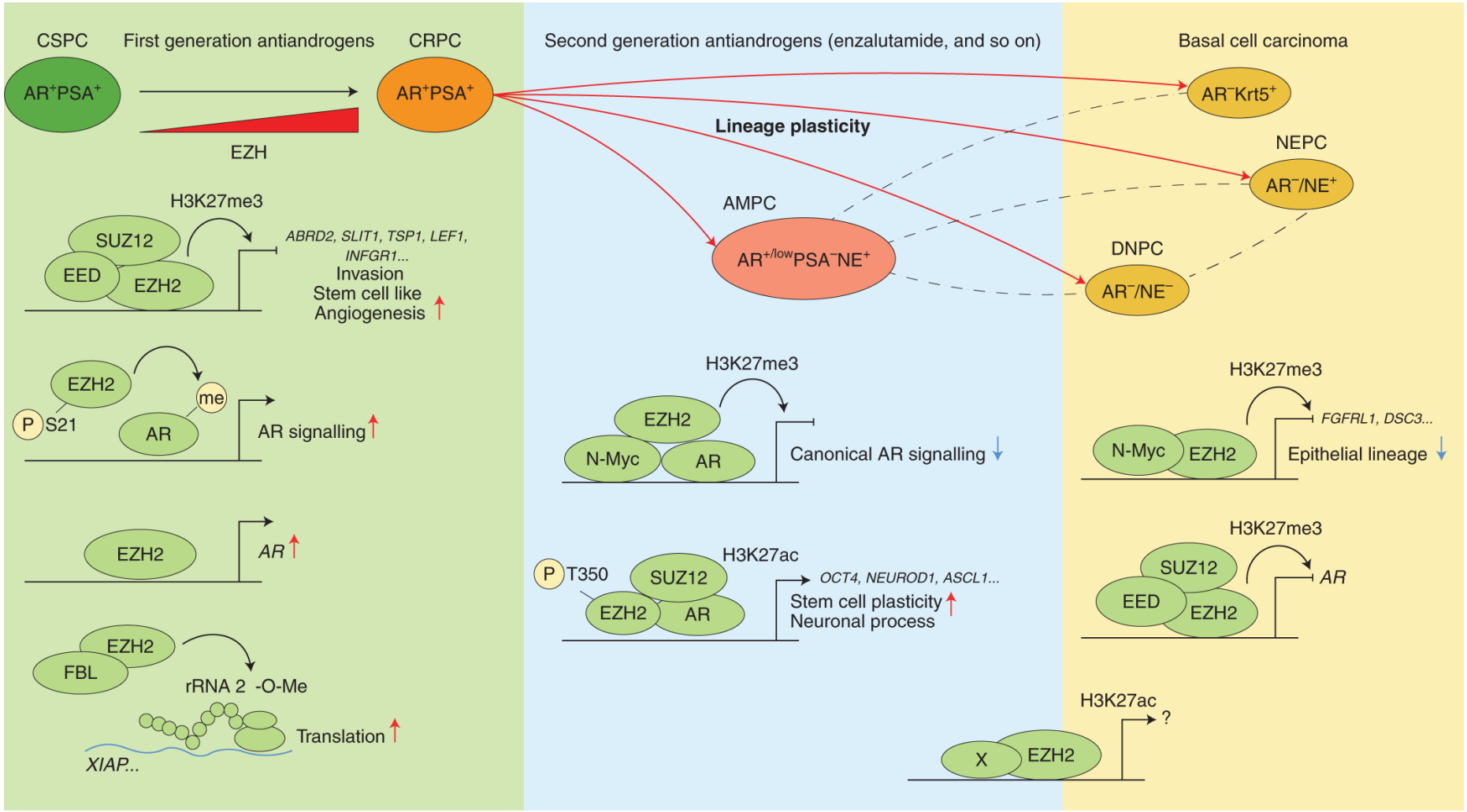
- High frequency of AR mutations by blood-based NGS
  - Potentially from point in care
  - Potentially from sampling tumor heterogeneity)
- High frequency of multiple AR mutations
  - Particularly with blood-based NGS
- Same distribution of specific AR mutations from blood and tissue

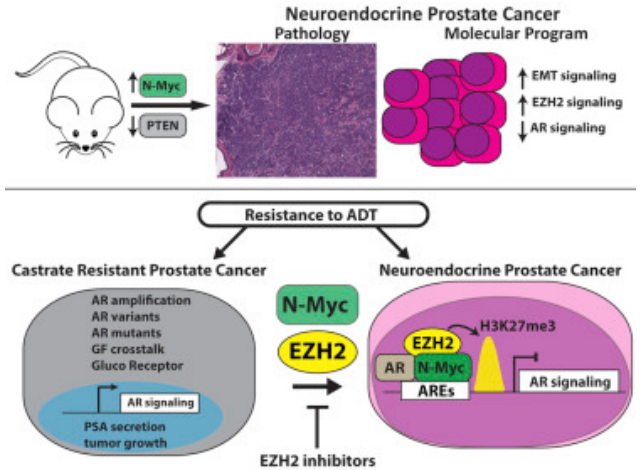
AR mutation type	ARm	
	N	%
At Least 1 Alteration	306	100.0
Multiple Alterations	156	51.0
Missense	304	99.3
R630Q	4	1.3
C687Y	1	0.3
L702H	156	51.0
V716M	14	4.6
R727H	1	0.3
W742C	25	8.2
W742L	10	3.3
M750V	1	0.3
M750L	1	0.3
R775C	1	0.3
F827L	1	0.3
H875Y	70	22.9
F877L	15	4.9
T878A	115	37.6
T878S	13	4.2
S889G	4	1.3
D891H	3	1.0
Copy Number Unknown	36	11.8
Copy Number Amplification	45	14.7

	ARm/ Tissue		ARm/ Blood		
Variable	N	%	N	%	p-value
At Least 1 Alteration	46	100.0	213	100.0	1.0000
Multiple Alterations	14	30.4	112	52.6	0.0088
Missense	45	97.8	212	99.5	0.3242
R630Q	2	4.3	2	0.9	0.1461
C687Y	0	0.0	1	0.5	1.0000
L702H	18	39.1	112	52.6	0.1064
V716M	5	10.9	8	3.8	0.0599
R727H	0	0.0	1	0.5	1.0000
W742C	2	4.3	19	8.9	0.3868
W742L	1	2.2	6	2.8	1.0000
M750L	0	0.0	1	0.5	1.0000
M750V	0	0.0	1	0.5	1.0000
F827L	0	0.0	1	0.5	1.0000
H875Y	9	19.6	51	23.9	0.5702
F877L	2	4.3	11	5.2	1.0000
T878A	15	32.6	82	38.5	0.5047
T878S	0	0.0	11	5.2	0.2216
S889G	0	0.0	2	0.9	1.0000
D891H	0	0.0	2	0.9	1.0000
Copy Number Amplification	5	10.9	30	14.1	0.8118

Sturgill, ASCO GU 2025

EZH2/PRC2 in Prostate Cancer

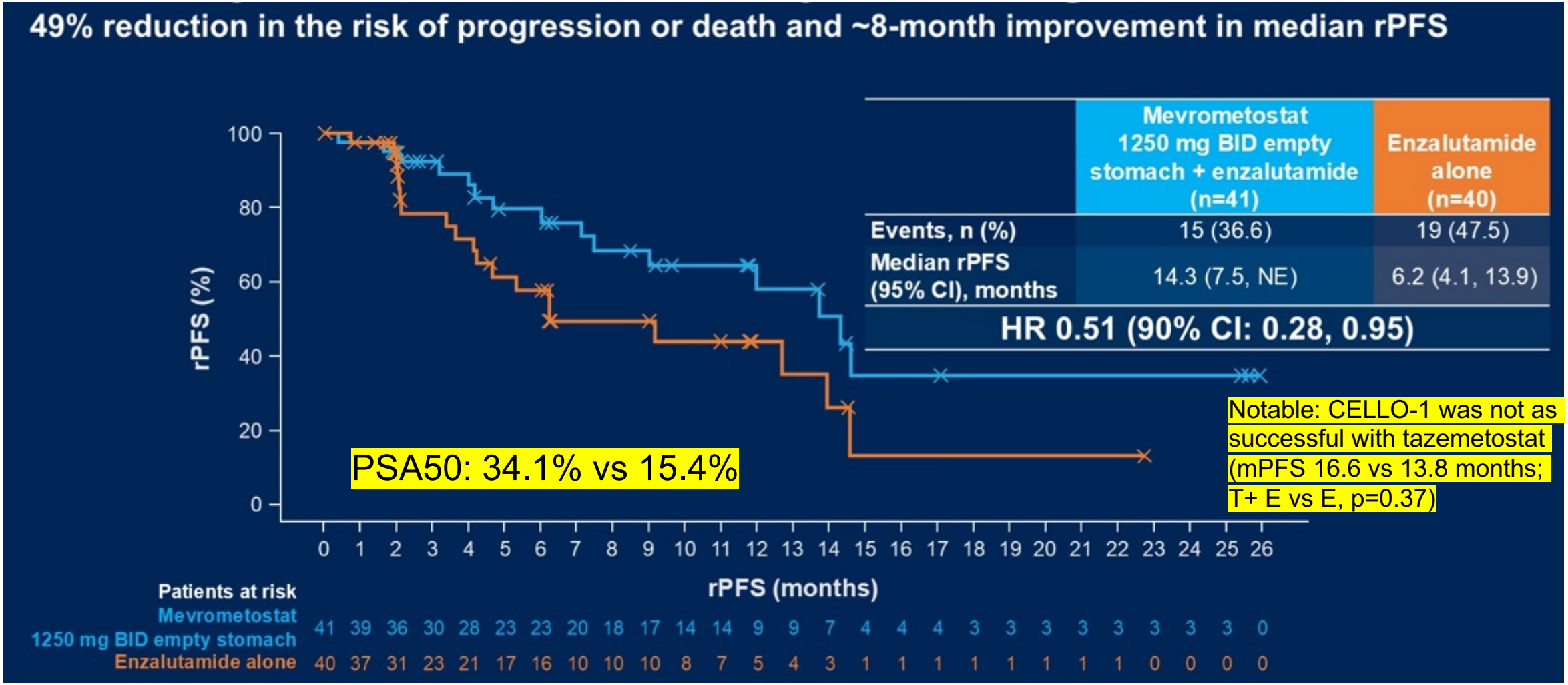




Dardenne E et al. Cancer Cell 2016.

Xin L. Nature Cell Biology, 2021.

Mevrometostat (EZH2i) + Enzalutamide

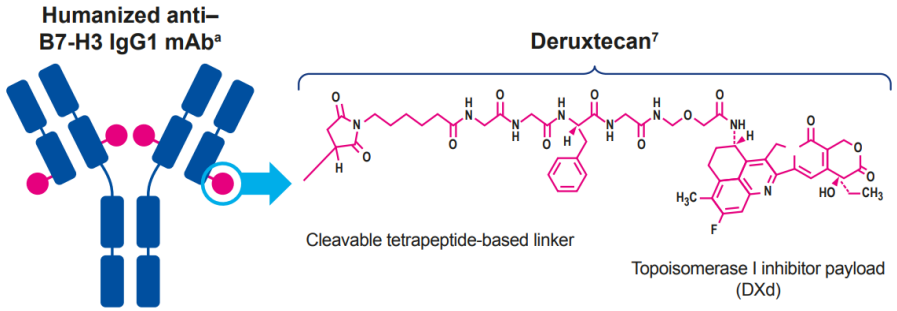


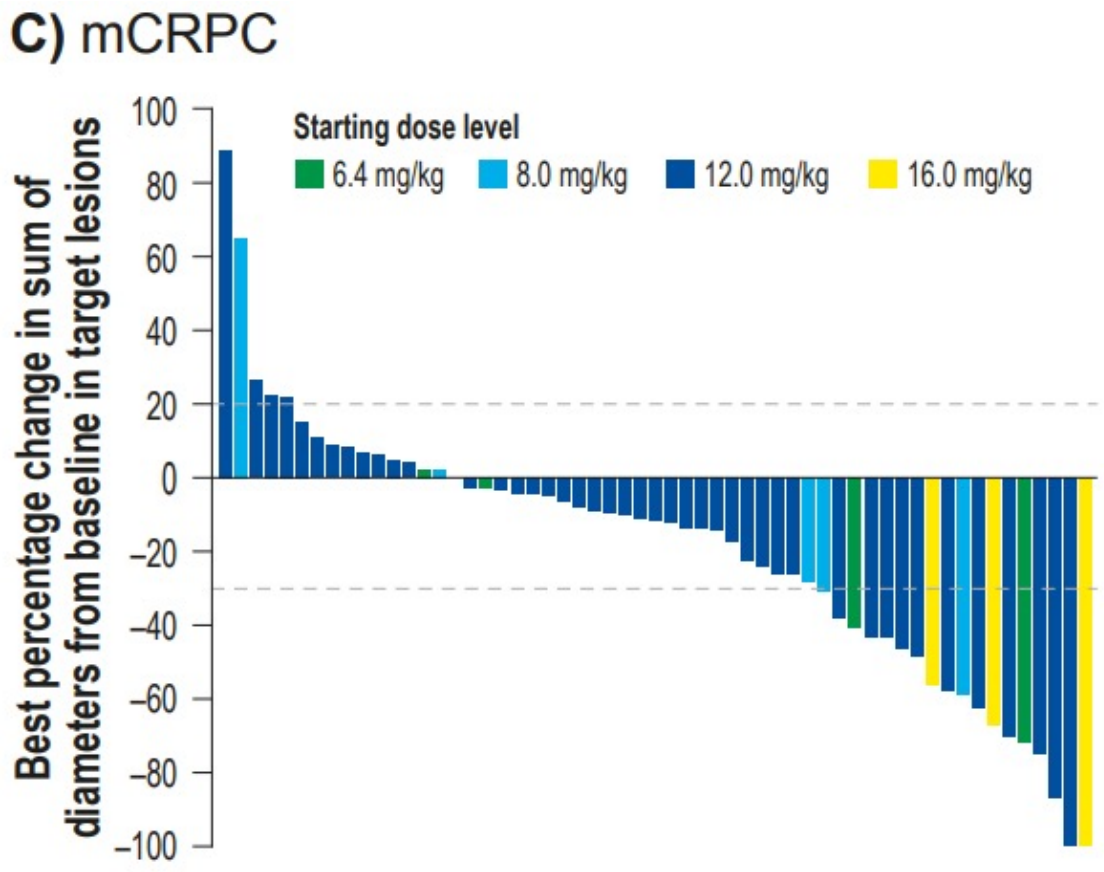
ORIC-944 is another PRC2 inhibitor in clinic

Schweizer MT, ASCO 2024
Schweizer MT, GU ASCO 2025

Antibody Drug Conjugates

Ifinatamab Deruxtecan (I-DXd; DS-7300)





	mCRPC
Efficacy population (≥4.8 mg/kg)	**n=73**
Confirmed ORR, n (%; 95% CI)[a]	15 (25.4; 15.0–38.4)
Confirmed PR, n (%)	15 (25.4)
Confirmed ORR in patients with liver mets at baseline (27/59, 45.8% of mCPRC efficacy population ≥4.8 mg/kg), n (%)	9 (33.3)
TTR, median (95% CI), months[a]	1.4 (1.2–2.6)
DOR, median (95% CI), months[a]	6.4 (3.0–10.0)
Median PFS, months (95% CI)[b]	5.3 (4.1–6.9)
Median OS, months (95% CI)[b]	13.0 (10.3–16.0)
Follow-up, median (95% CI), months[b]	16.6 (14.5–18.6)
Safety population (all doses)	**n=75**
Number of prior systemic regimens, median (range)	6 (1–11)
Taxane, n (%)	61 (81.3)
NHA, n (%)	72 (96.0)

Phase 3: Ideate-Prostate01; randomizing against Docetaxel

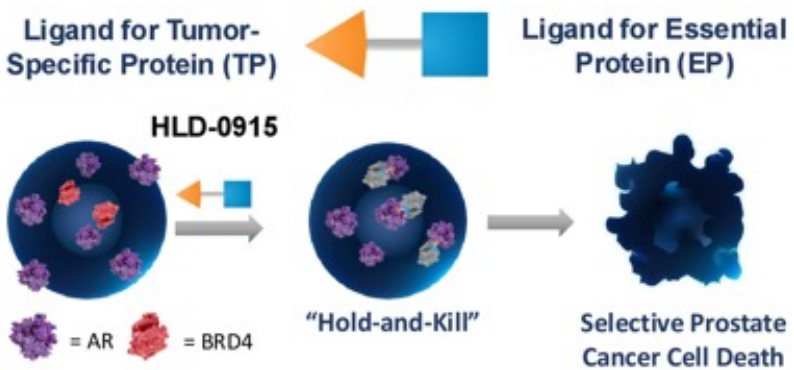
Patel M. ESMO 2023

Antibody Drug Conjugate Targets

- B7H3
- PSMA
- STEAP1
- TROP2
- CD46
- KLK2/hk2
- DLL3 (NEPC/Small Cell)
- SEZ6 (NEPC/Small Cell)
- *And more…*

What about a RIPTAC? (Regulated Induced Proximity Targeted Chimera)

HLD-0915 is a Novel RIPTAC™ Therapeutic

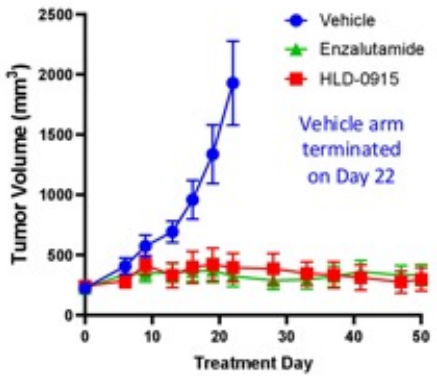


- RIPTACs rely on AR expression; AR does not need to be a driver
- Forms a tumor specific, proapoptotic ternary complex that causes BRD4 loss of function (LoF)
- BRD4 inactivation (cMYC/HEXIM1/TXNIP) closely tracks trimer complex formation in tumors

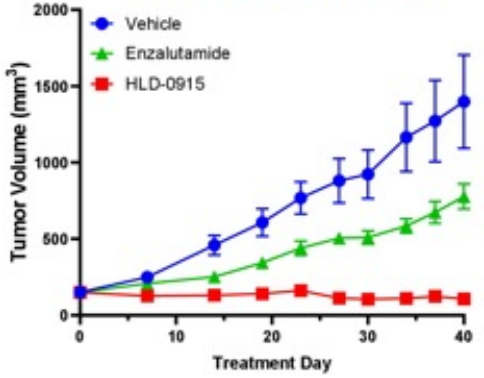
HLD-0915 has a Robust Efficacy Profile Across Multiple Preclinical CRPC Models

Tumor regressions observed in enzalutamide-insensitive models with PSA declines

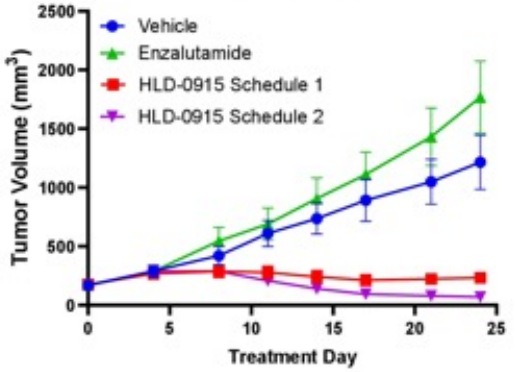
Castrate LNCaP Model
(AR^{T878A}, enzalutamide sensitive)



Castrate VCaP Model
(AR^{amp}, V7+, $TP53^{R248W}$, low enzalutamide sensitivity)



Castrate LNCaP95 Model
(AR^{T878A}, V7+, androgen independent, enzalutamide resistant)



ADC-like: Tumor-selectve cell death independent of oncogenic driver -> potential for activity across resistance mechanisms

Kayser-Bricker KJ, ASCO 2025 TPS5115

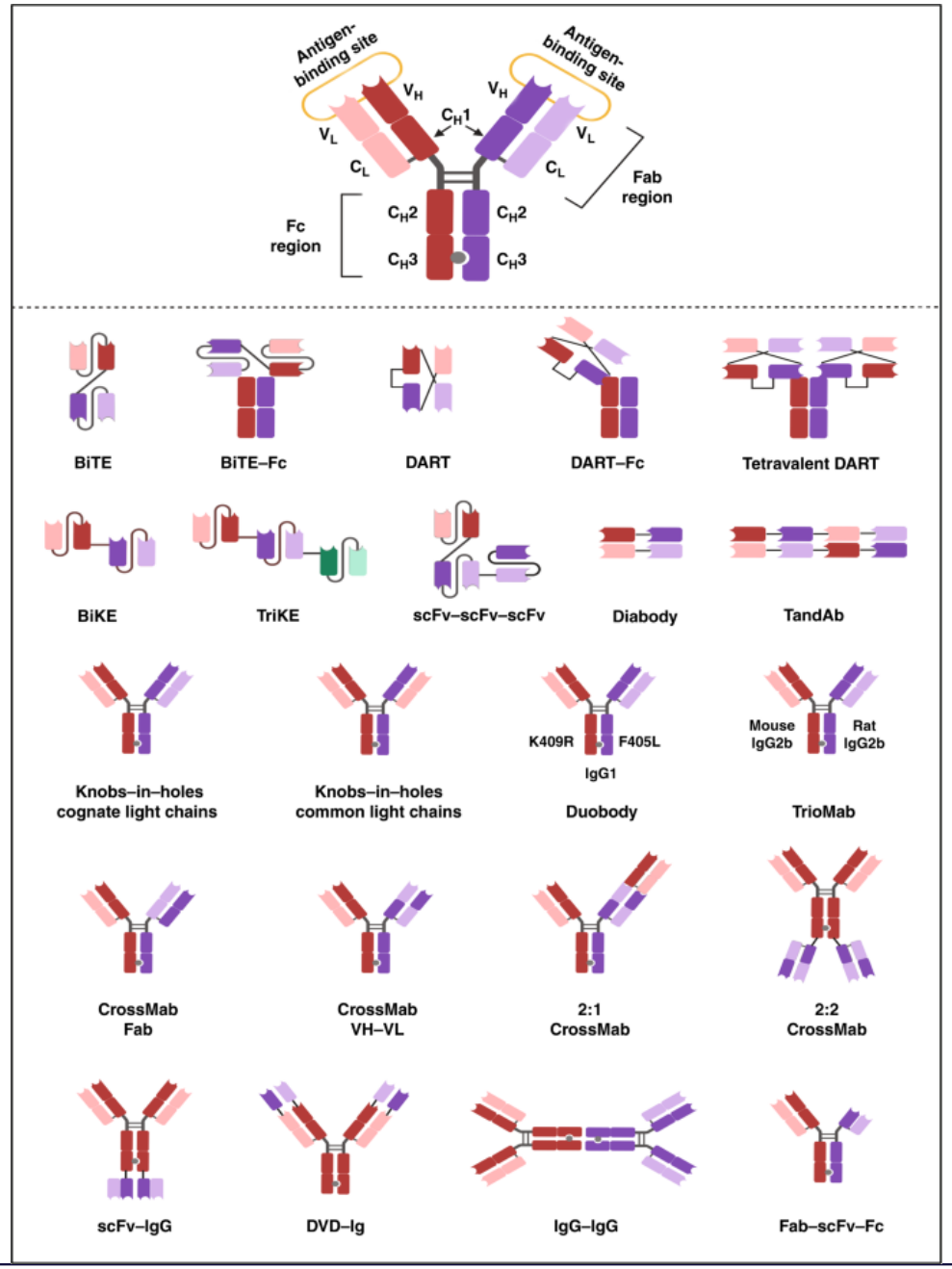
ADC Targets ⟶ T-Cell Engager Targets

- B7H3 -> Phase 1
- PSMA -> Phase 1
- STEAP1 -> Xaluritamig (Phase 3)
- TROP2 -> In development
- CD46 -> ?
- KLK2/hk2 -> Pasritamig (Phase 3)
- DLL3 (NEPC/Small Cell) -> *Tartalamab*, *(others in phase 1/2: HPN328)*
- SEZ6 (NEPC/Small Cell) -> ?
- *And more…*

T Cell Engagers

Increasing Complexity:

- Changes in the relative binding affinity
- Masking (tumor-associated proteases)
- “2+1” Design
- “Crossmab Design
- Fc addition (prolong half life)
- IV vs Subcutaneous
- Costimulatory Signals
- Combination trials
- *And more…*



Sing A, et al. *British Journal of Cancer*, 2021.

Other Exciting Therapies (a small selection)

Targeting HRR/DDR:

- PARP1 selective, PARG, ATR, DNA Polymerase θ

Molecular Glue Technology

- AR, AR-V7, GSPT1, BRD4

Novel Radioligand Conjugates and Targets (thinking beyond Lutitium-177)

- Actinium-225 (alpha), Thorium-227 (alpha), CU-67 (beta)

CAR-T

- PSMA, PSCA, STEAP1, STEAP2

Thank you!

ben.garmezy@scri.com

@BGarmezy

World Conference On
Genitourinary Cancers
2025 NASHVILLE, TN

EMERGING APPROACHES IN KIDNEY CANCER

Eric Jonasch, MD- UT MD Anderson Cancer Center

August 22nd 2025

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PIM Postgraduate Institute for Medicine
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RCC Therapeutic Options- It's Been a Journey

RCC Therapeutic Options- It's Been a Journey

But there are new treatments on the horizon

RCC Therapeutic Options- It's Been a Journey

Cytokines

TKIs

Checkpoint Blocking Antibodies

But there are new treatments on the horizon

HIF2 Alpha Inhibitors

Immune Signaling Modulators

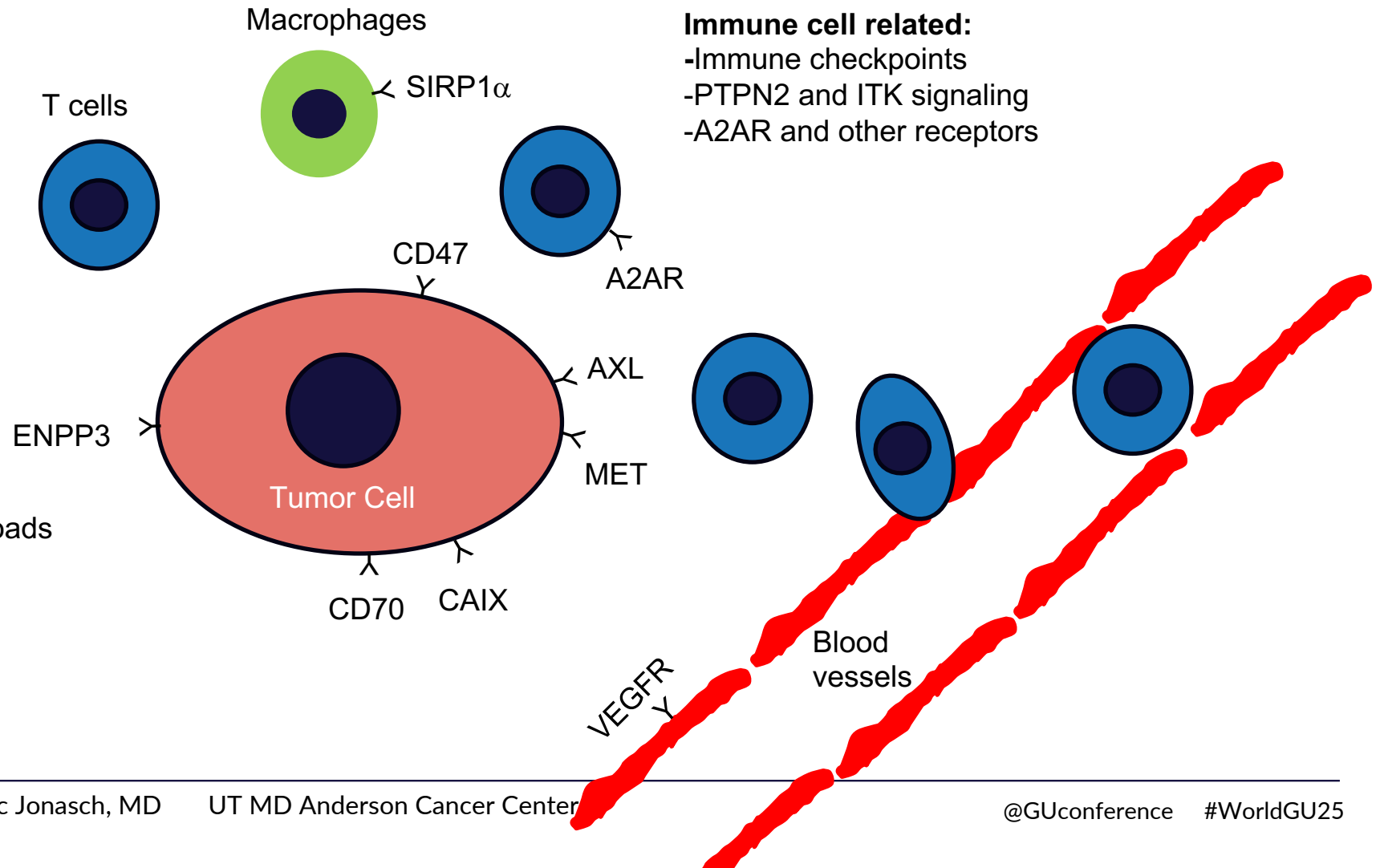
Bispecific Antibodies

ADCs/ Radioligands

Cellular Therapies

RCC Therapeutic Options- Modulating the Microenvironment

Tumor cell autonomous:
-intracellular signaling (HIF)
-cell surface receptor signaling
-cell surface receptor directed payloads



Immune cell related:
-Immune checkpoints
-PTPN2 and ITK signaling
-A2AR and other receptors

HIF2α Inhibitors

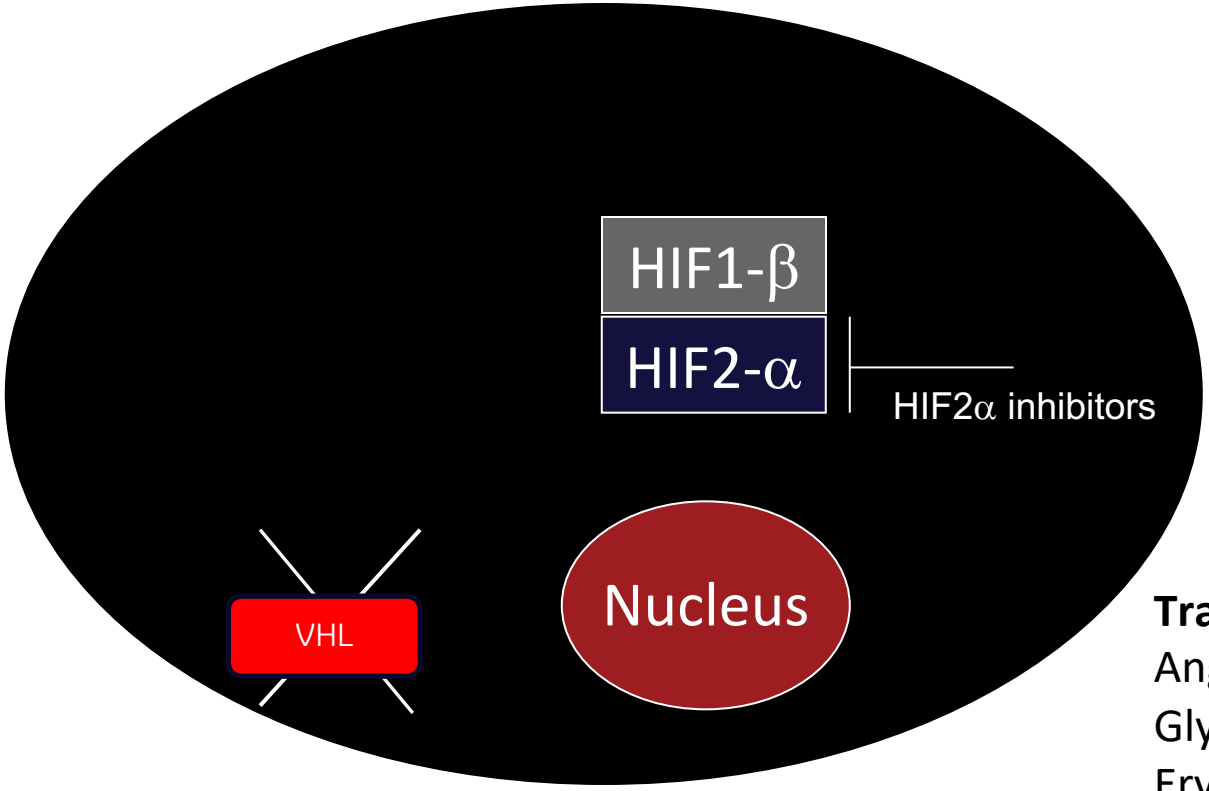
Belzutifan, Casdatifan

-Single agent?

-Together with a TKI?

-Together with an IO agent?

-Do effector T-cells like this?



Multiple studies underway or completed:
-LITESPARK 003
-LITESPARK 11
-LITESPARK 12
-PEAK 1
-EVOLVE
-ARC20

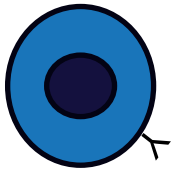
Transcription of:
Angiogenic factors
Glycolysis regulators
Erythropoietin
DNA repair proteins

Immune Signalling Modulators

A2AR Inhibitor (Corvus)

PTPN2 Inhibitor (Calico)

ITK Inhibitor (Corvus)



Can these agents prevent or overcome T-cell exhaustion?

Bispecific Antibodies

Volrustomig
PD-1xCTLA-4

Ivonescimab
PD-1xVEGF-A

Cadonilimab
PD-1xCTLA-4

BNT327/PM8002
PD-1xVEGF-A

IO/IO

IO/VEGF

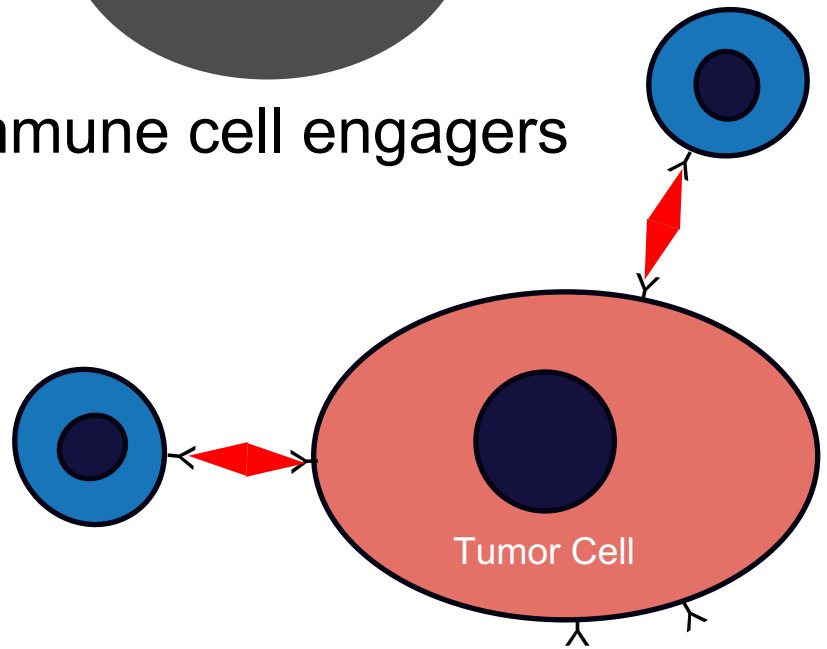
Incyte
CD70xCD3

JNJ87890387
ENPP3xCD3

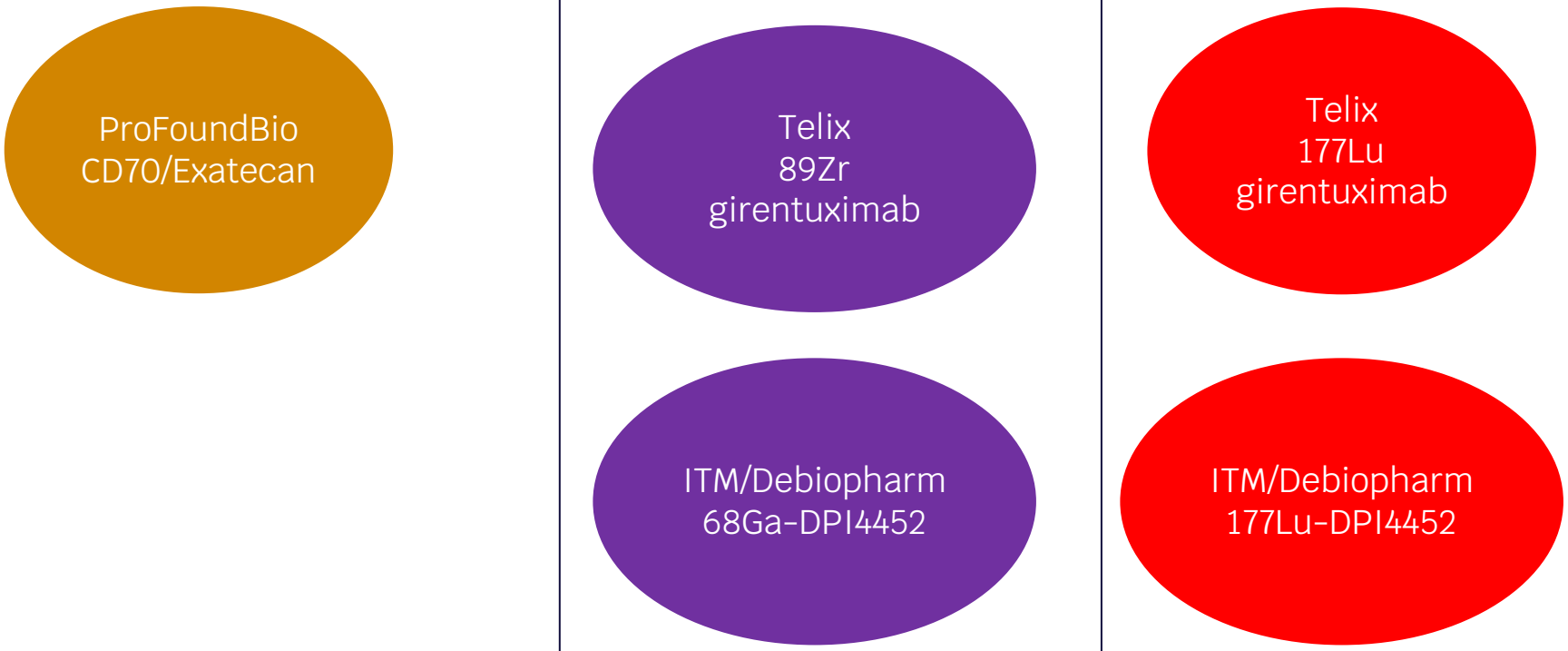
XmAb819
ENPP3xCD3

XmAb819
ENPP3xSIRP1α

Immune cell engagers



Antibody/Small Molecule Conjugates



Should we use beta or alpha emitters?

Should we use antibodies or small molecules?

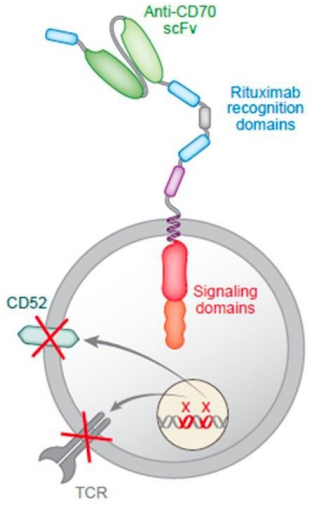
What is optimal half-life for either?

CAR-T Therapy

CAR-T therapy: Auto or Allo?

Which target? CAIX? CD70? ENPP3? More than one?

Armored or not?



TRAVERSE Phase 1b Study Design (NCT04696731)

Key Eligibility Criteria

- Aged ≥18 years with advanced or metastatic ccRCC
- Disease progression after PD-1 axis and VEGF targeted therapies
- CD70 positive by IHC on archival or fresh tumor tissue
- ECOG 0-1
- Adequate pulmonary, cardiac, renal, hepatic, and hematologic function

Phase 1b[a] treatment

Day -5 to Day -3: Standard Lymphodepletion Flu/Cy

Day 0: ALLO-316 80×10⁶ CAR+ cells

Follow up through M60: Safety and efficacy assessments

Phase 1b Endpoints

- Primary
  - TEAEs
- Secondary
  - ORR, CRR, DOR, TTR, PFS, OS, CAR T expansion kinetics

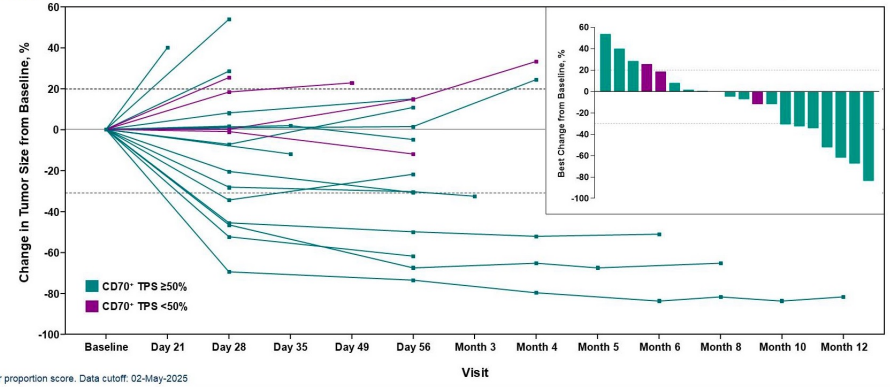
[a]Phase 1a evaluated escalating doses of both ALLO-316 and various lymphodepletion regimens in a 3+3 design.
CAR, chimeric antigen receptor; ccRCC, clear cell renal cell carcinoma; CRR, complete response rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; Flu/Cy, fludarabine 30 mg/m² and cyclophosphamide 500 mg/m² daily for 3 days; IHC, immunohistochemistry; M, month; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival; TEAE, treatment-emergent adverse events; TTR, time to response; VEGF, vascular endothelial growth factor.

2025 ASCO ANNUAL MEETING #ASCO25 PRESENTED BY: Dr. Samer A. Srour

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Tumor Responses Occur Early and Are Sustained Following a Single Infusion of ALLO-316

Among CD70⁺ TPS ≥50% patients, 44% (7/16) had >30% reduction in diameter of baseline target lesions



TPS, tumor proportion score. Data cutoff: 02-May-2025

2025 ASCO ANNUAL MEETING #ASCO25 PRESENTED BY: Dr. Samer A. Srour

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Summary

We have several new therapeutics approaches!

How do we prioritize development of these agents?

What are our clinical unmet needs and will this help us define our approach?

Thank You!

World Conference On
Genitourinary Cancers
2025 NASHVILLE, TN

HARNESSING RESISTANCE TO IMMUNOTHERAPY APPROACHES IN KIDNEY CANCER

David A. Braun | Yale Cancer Center

08.23.25

@BraunMDPhD

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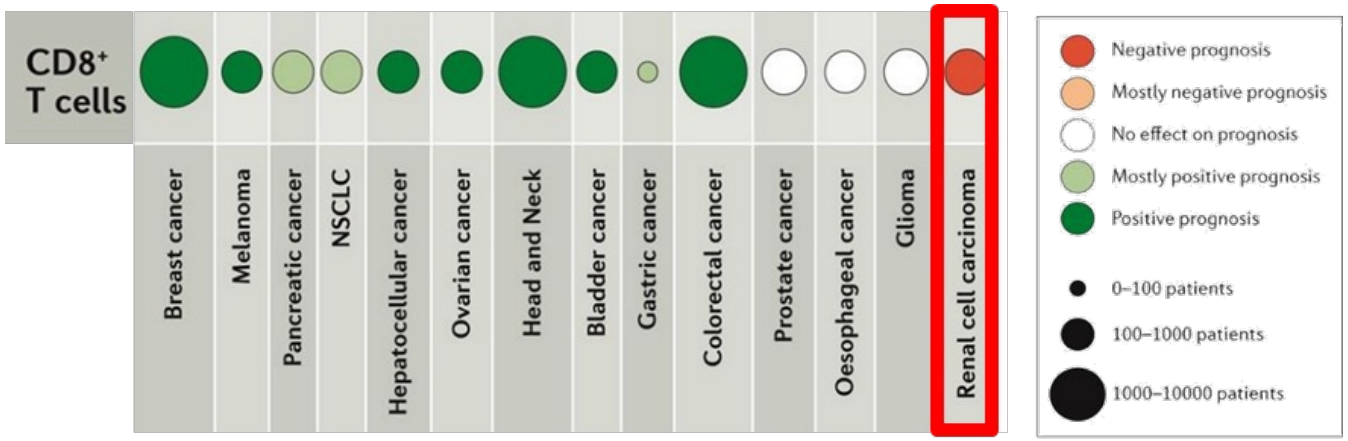
RCC is distinct from other immunotherapy-responsive solid tumors

High CD8⁺ T cell infiltration is historically associated with a *worse prognosis*

(Fridman *Nat Rev Clin Oncol* 2017)



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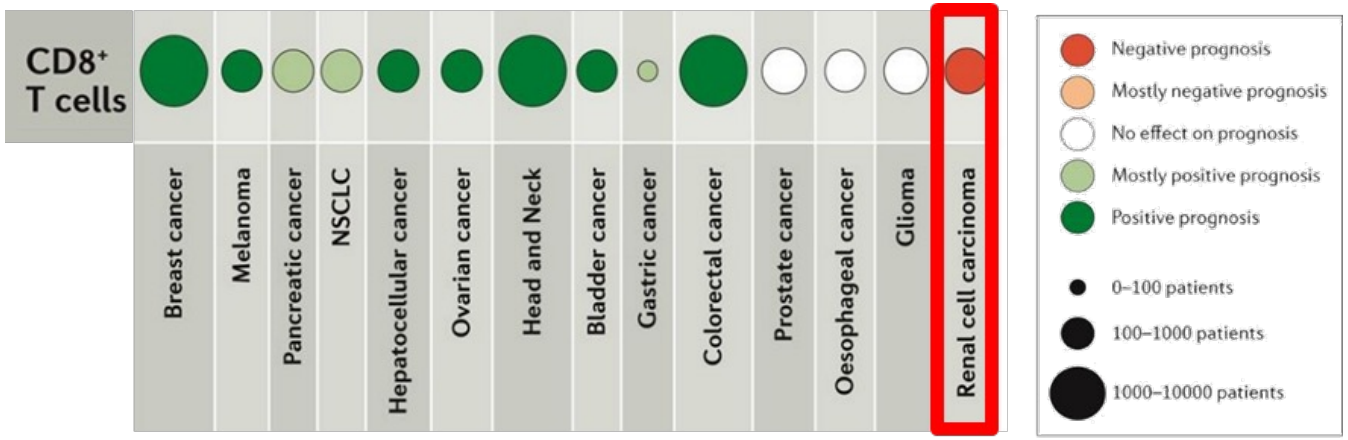
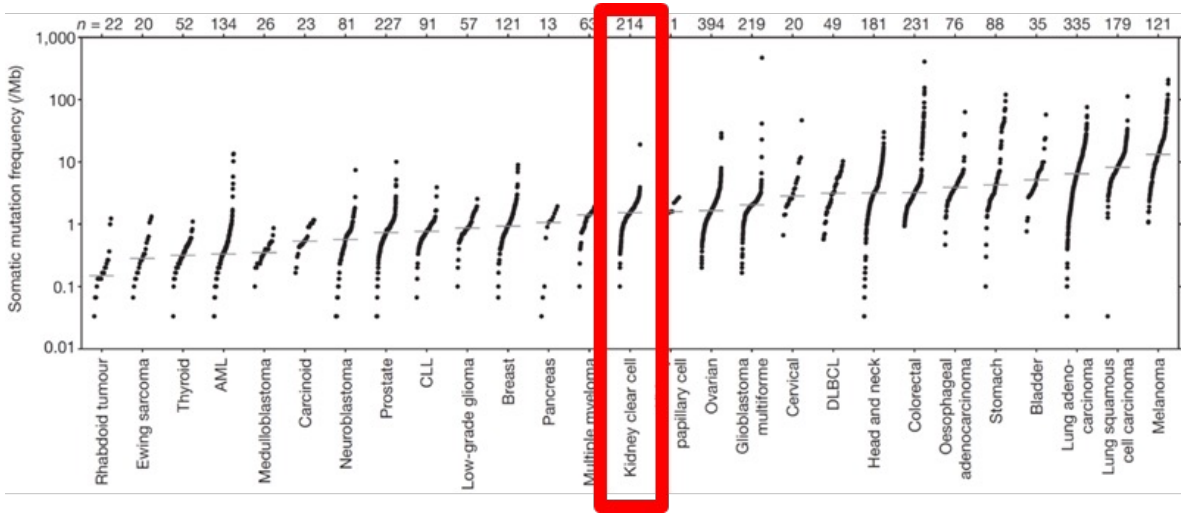
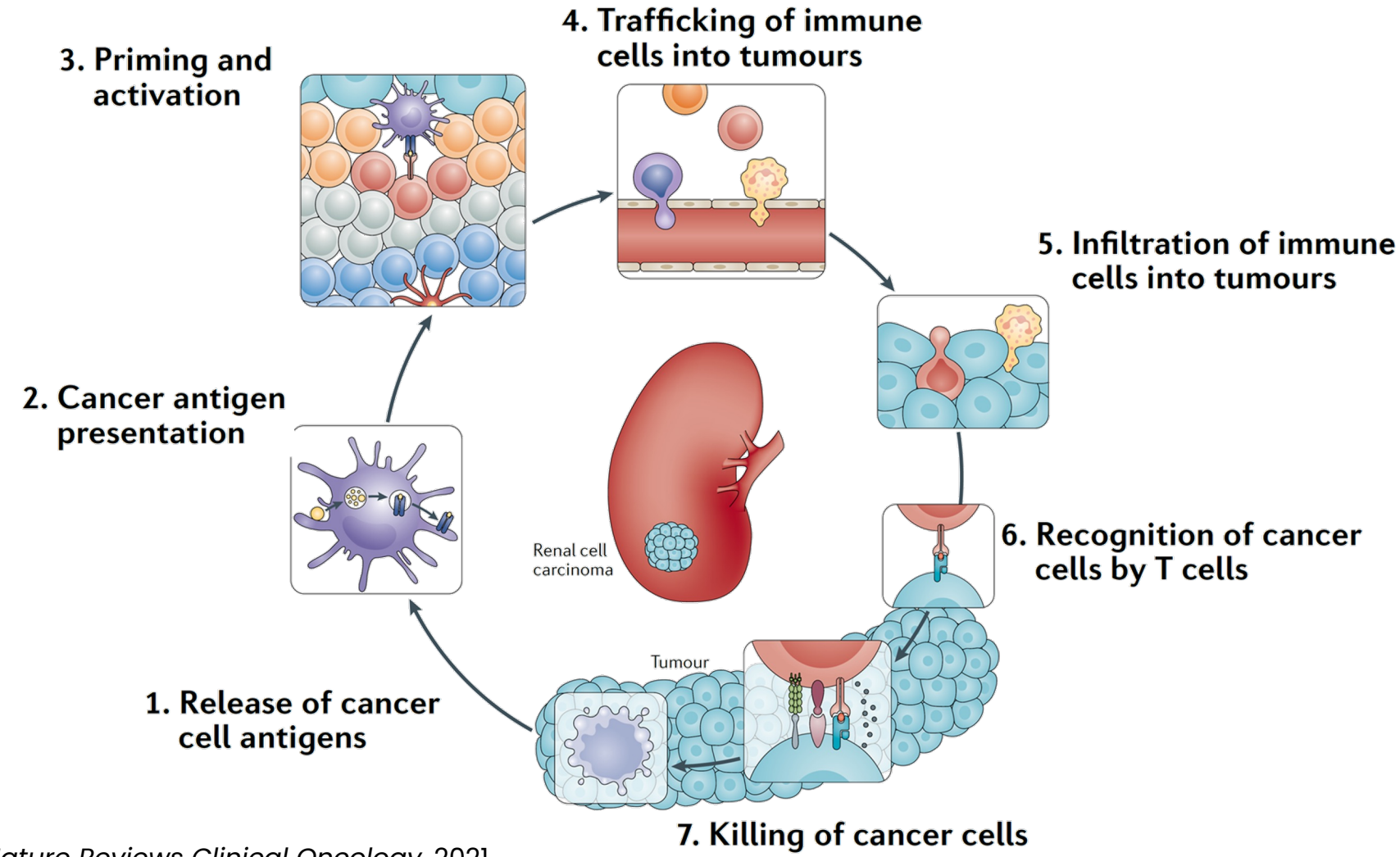


Clear cell renal cell carcinoma (ccRCC) has a modest mutation burden compared to other immunotherapy-responsive tumors
(Lawrence *Nature* 2013)

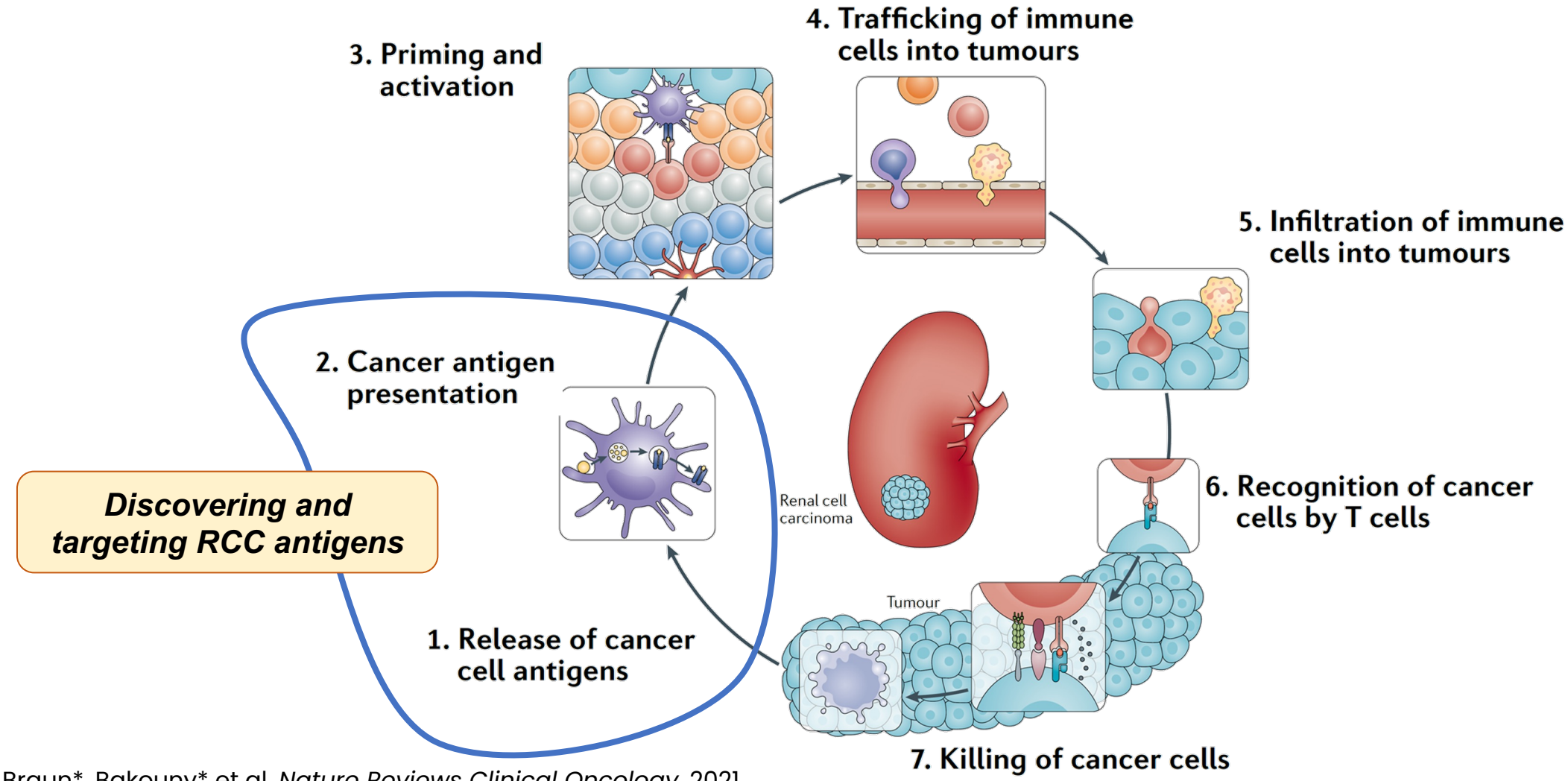


RCC: a model for the cancer-immunity cycle



Braun*, Bakouny* et al. *Nature Reviews Clinical Oncology*, 2021

RCC: a model for the cancer-immunity cycle

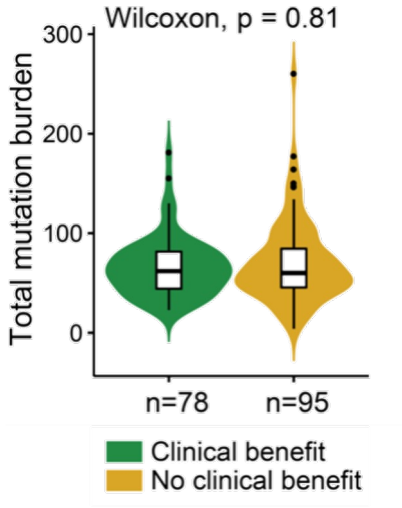


Discovering and targeting RCC antigens

Braun*, Bakouny* et al. *Nature Reviews Clinical Oncology*, 2021

Do neoantigens matter in RCC?

TMB is not associated with ICI response in RCC…



Braun et al. *Nature Medicine*, 2020

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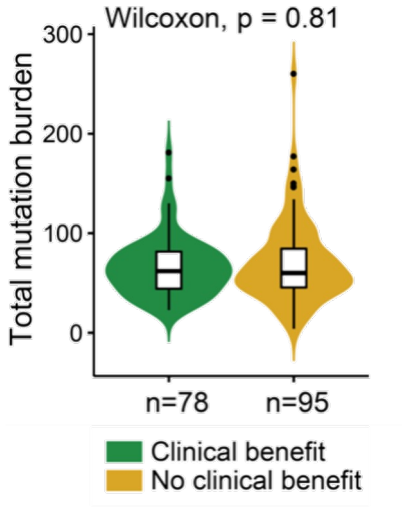
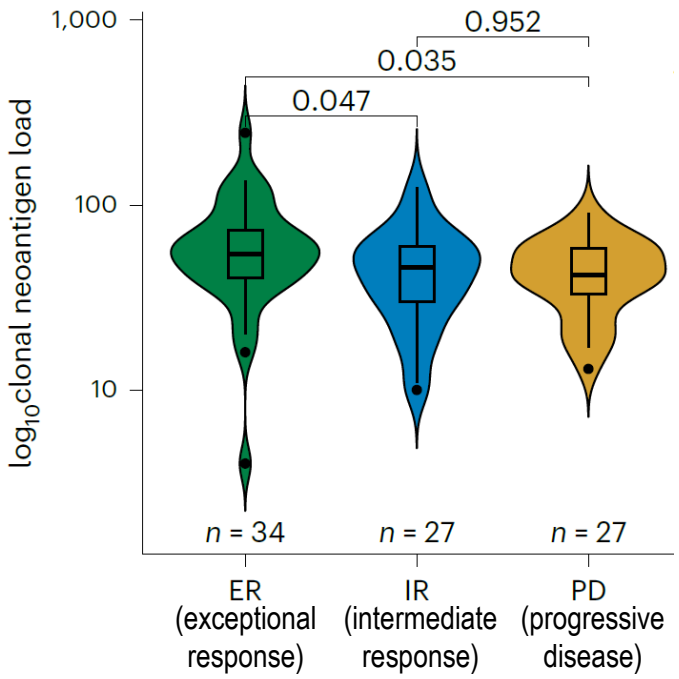
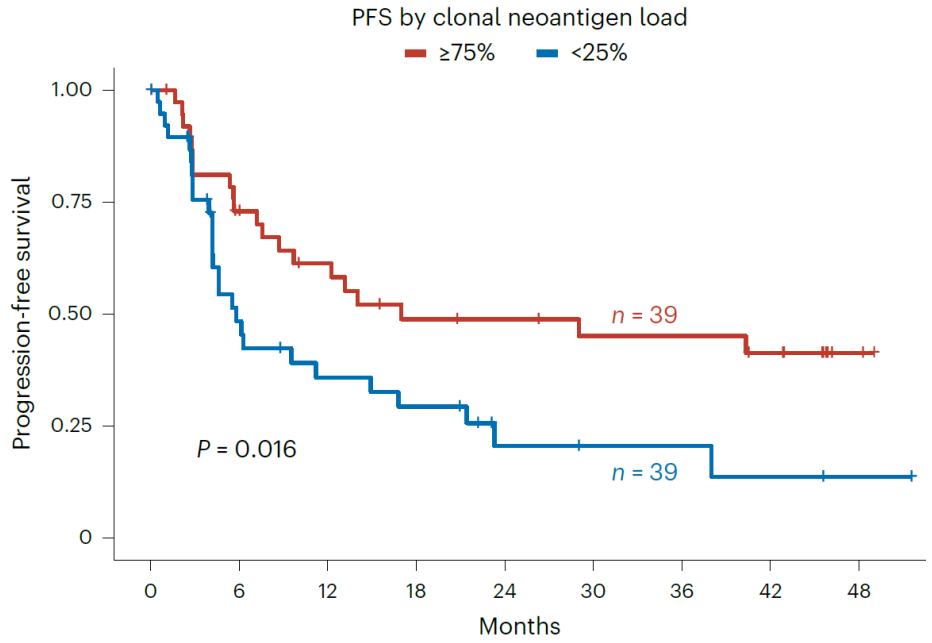


But clonal neoantigens are increased in exceptional response with ICI

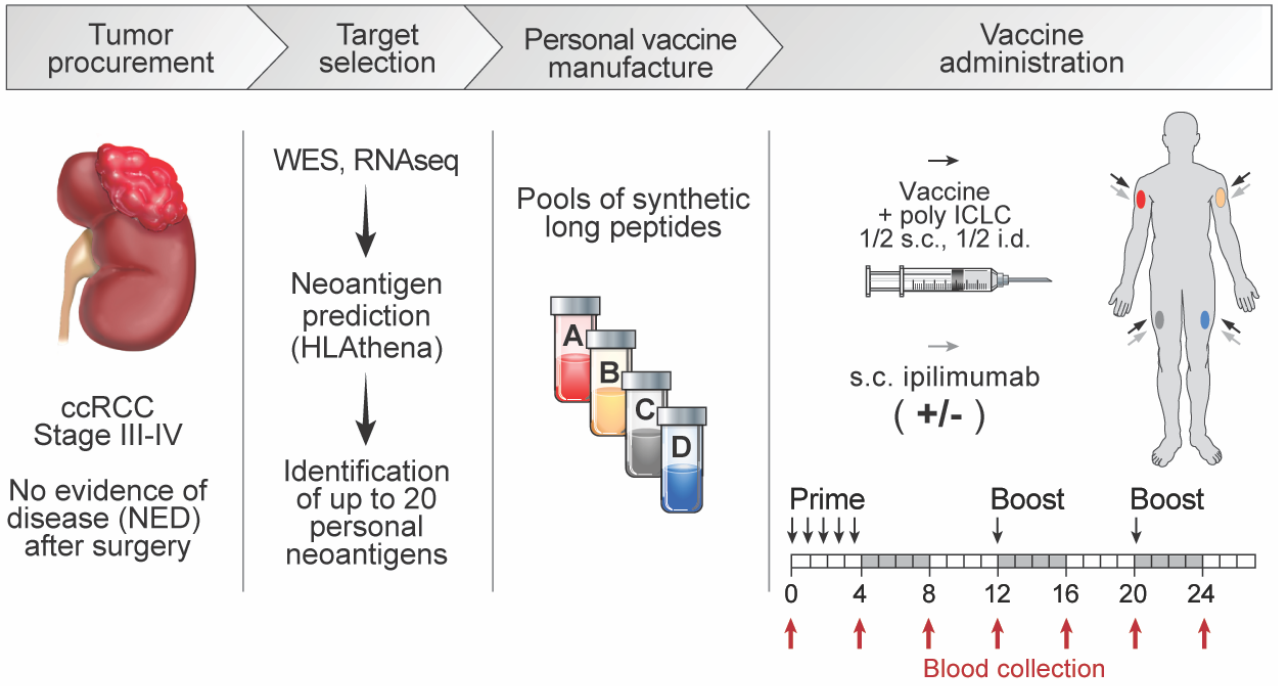




Braun et al. *Nature Medicine*, 2020; Jammihal*, Saliby*…Choueiri*, Braun*, Shukla*, *Nature Cancer*, 2025

Targeting neoantigens in RCC

Personalized cancer vaccine



Braun et al. *Nature*, 2025; with T. Choueiri, D. Keskin, P. Ott, C. Wu

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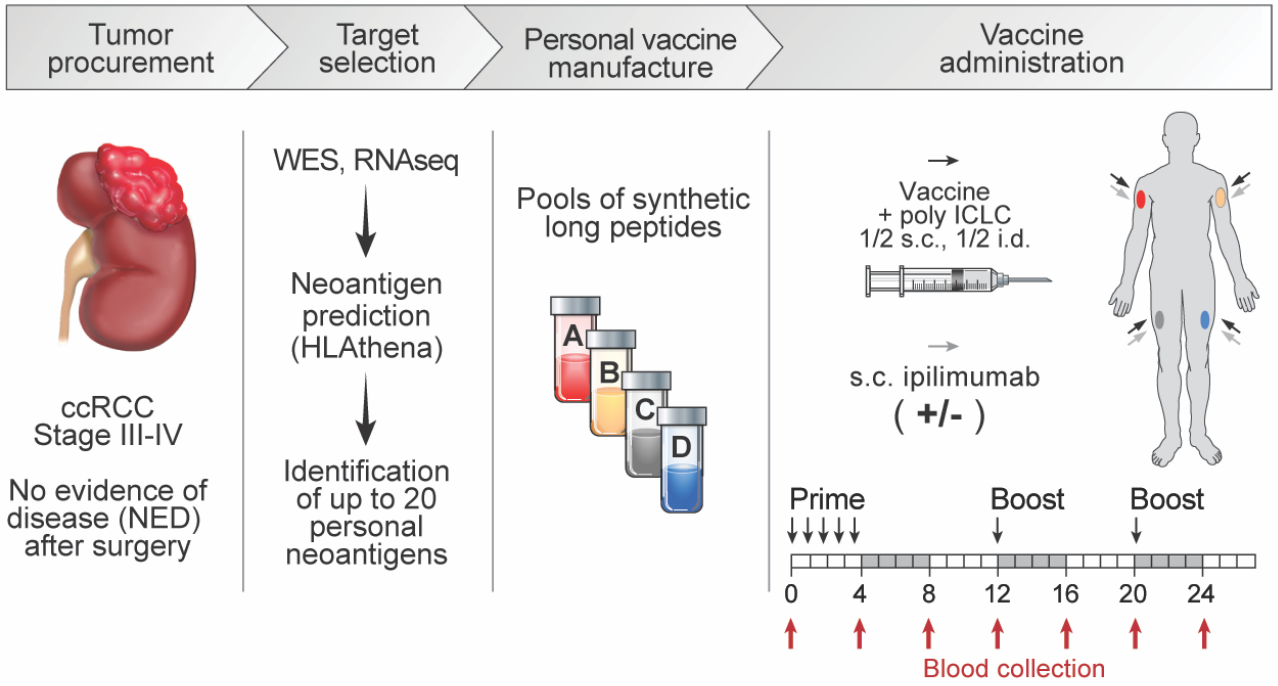
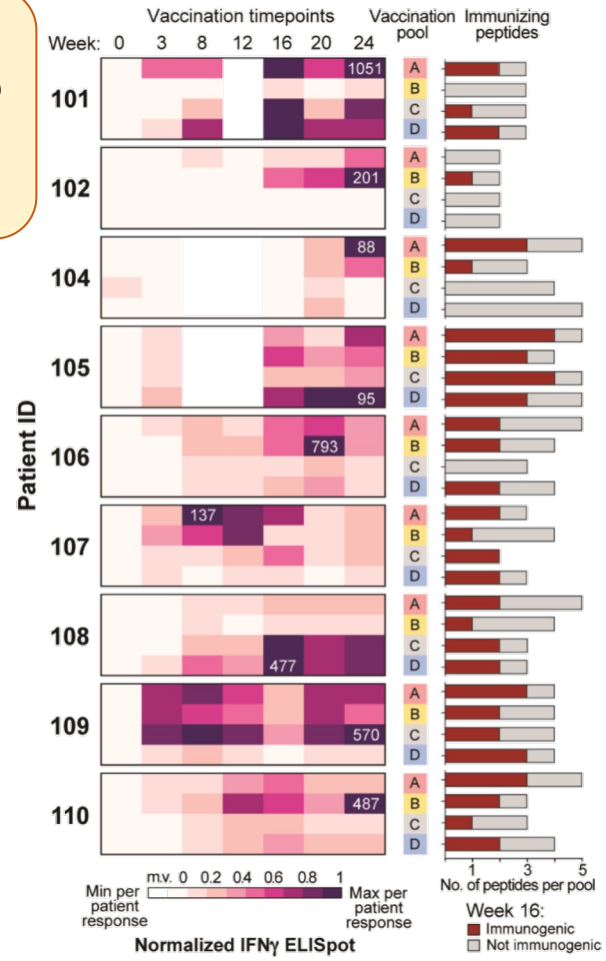


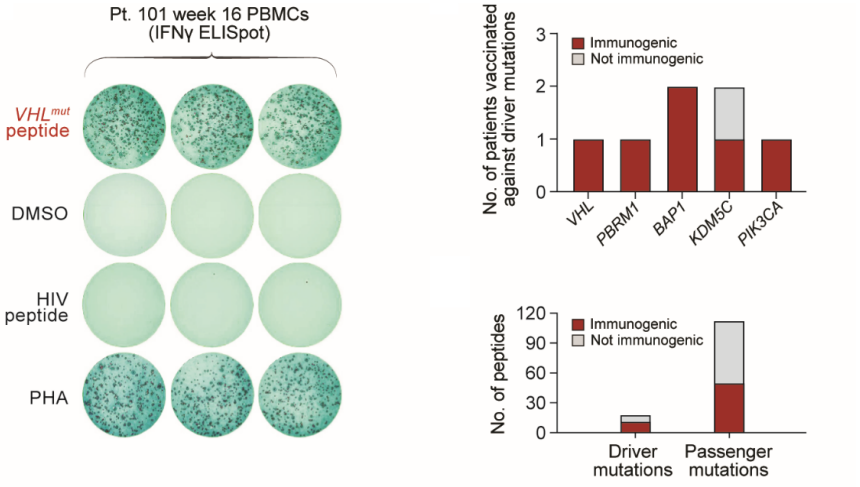
Vaccination generates immune response in ALL patients



Braun et al. *Nature*, 2025; with T. Choueiri, D. Keskin, P. Ott, C. Wu

Neoantigen vaccine durably expands T cell clonotypes and leads to anti-tumor reactivity

Vaccination against driven mutations generates immune responses



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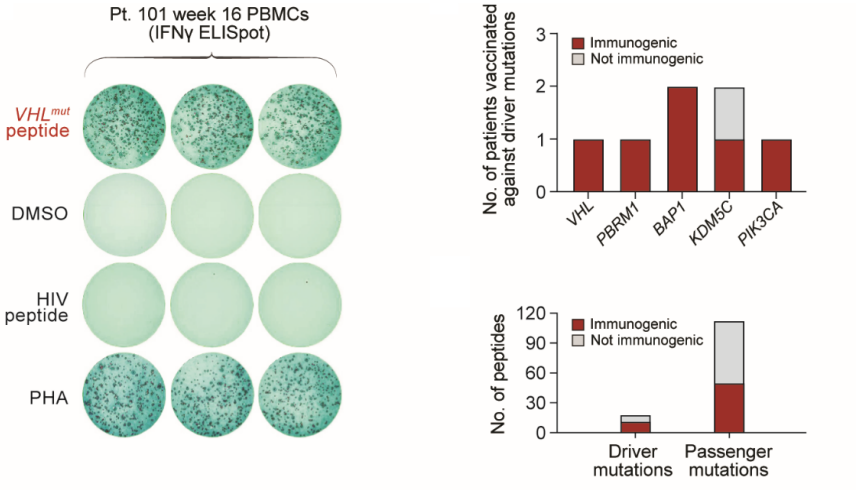
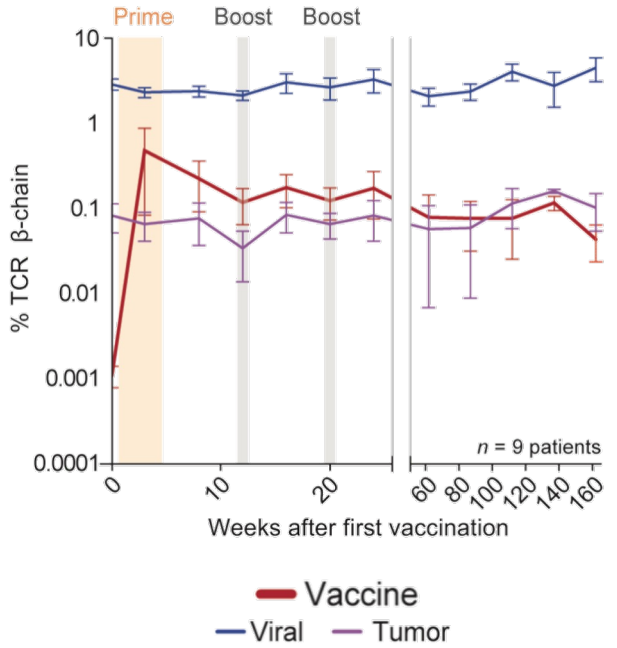
Durable T cell expansion





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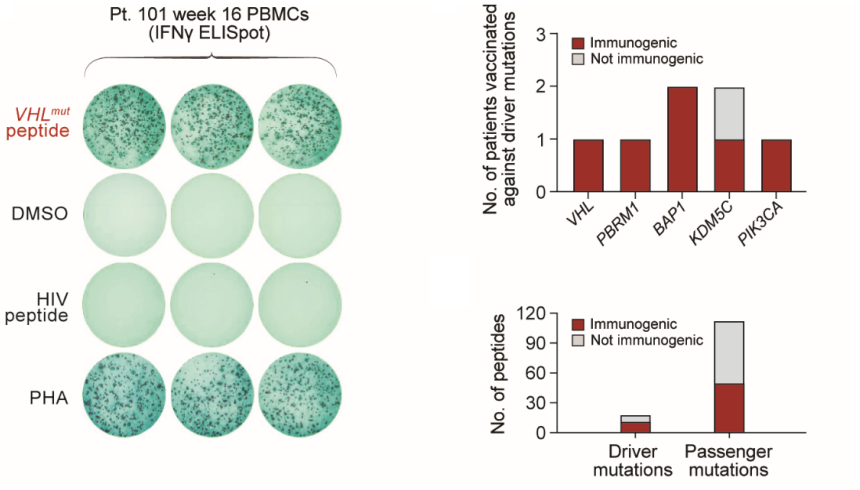
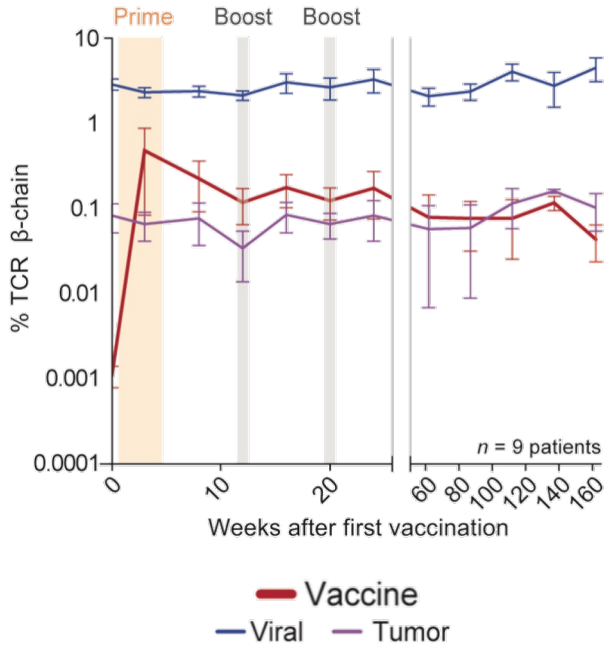
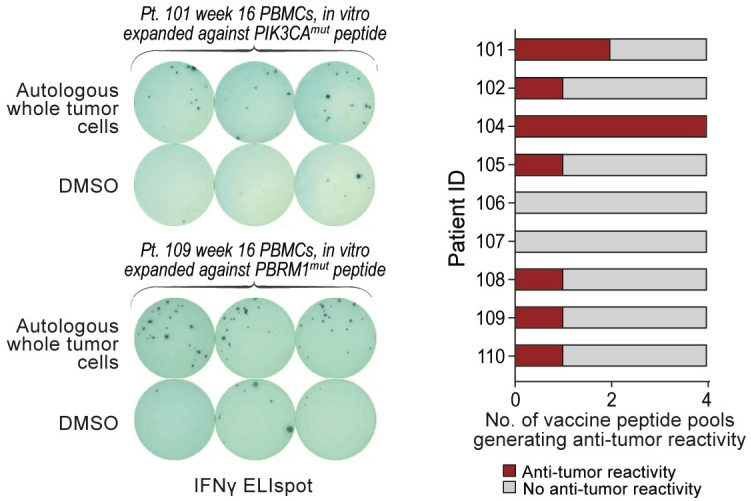


Durable T cell expansion

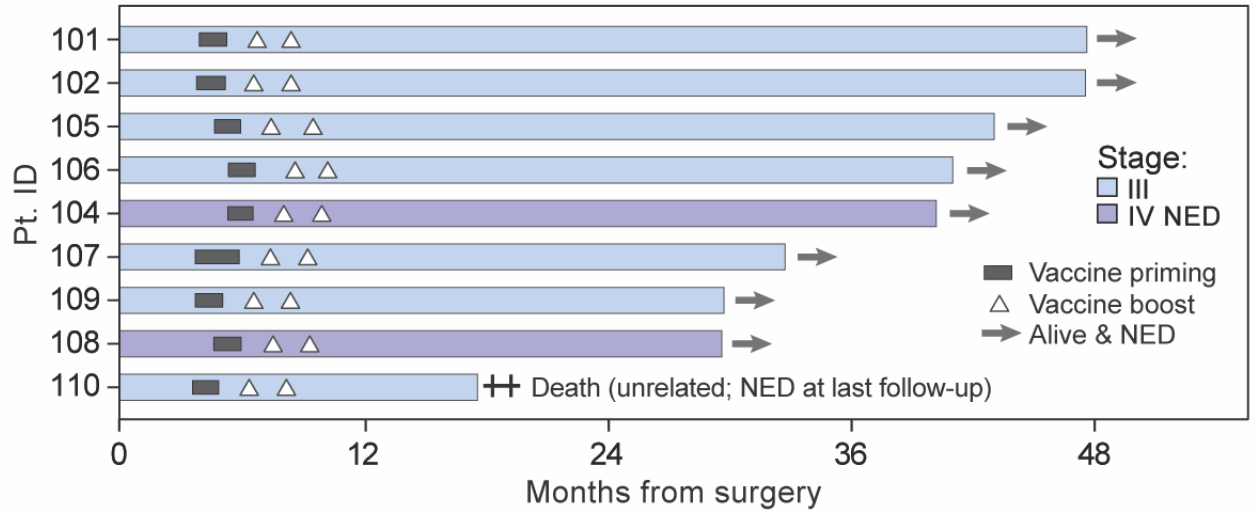


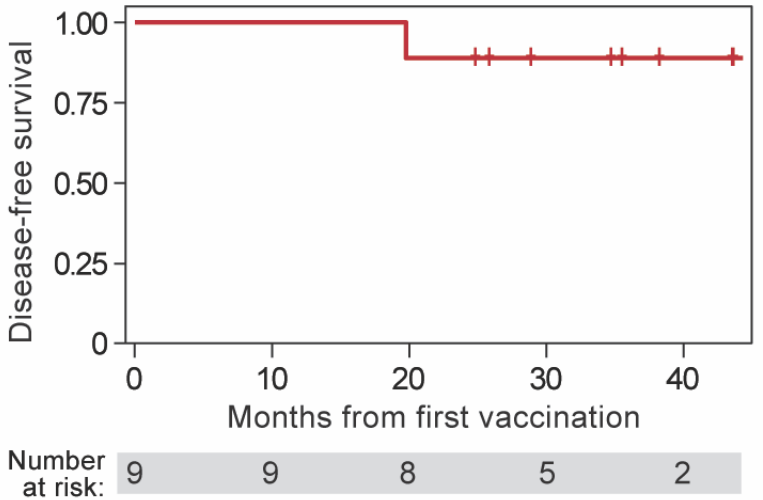
Vaccination expands tumor-reactive T cells



Braun et al. *Nature*, 2025; with T. Choueiri, D. Keskin, P. Ott, C. Wu

No disease recurrences following neoantigen vaccination (only n = 9)





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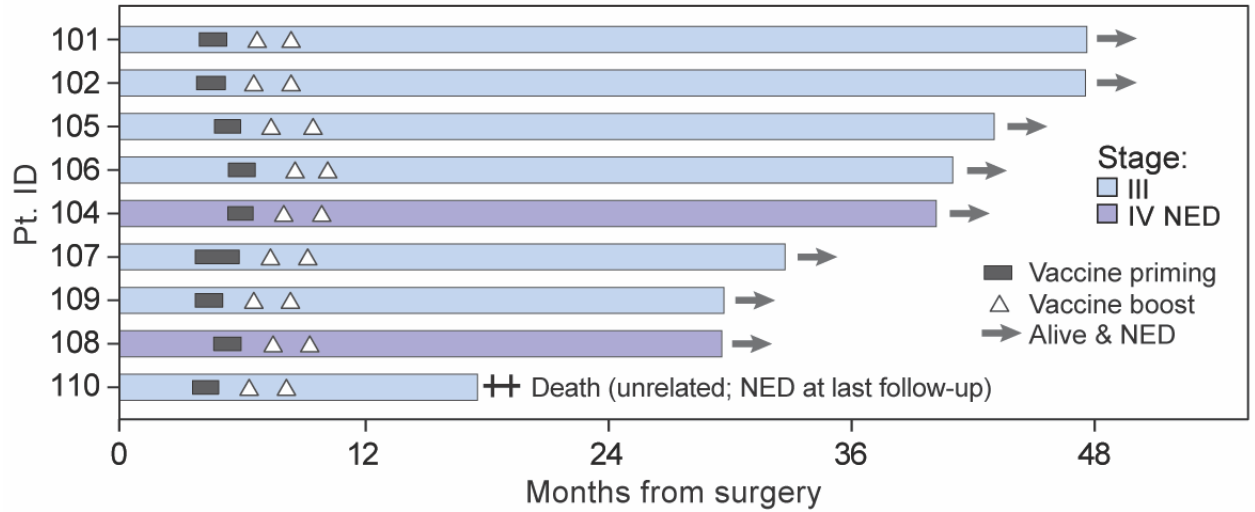
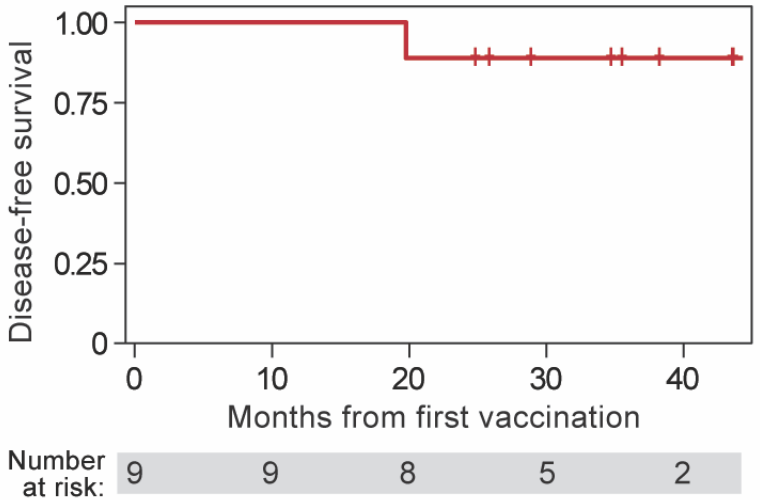
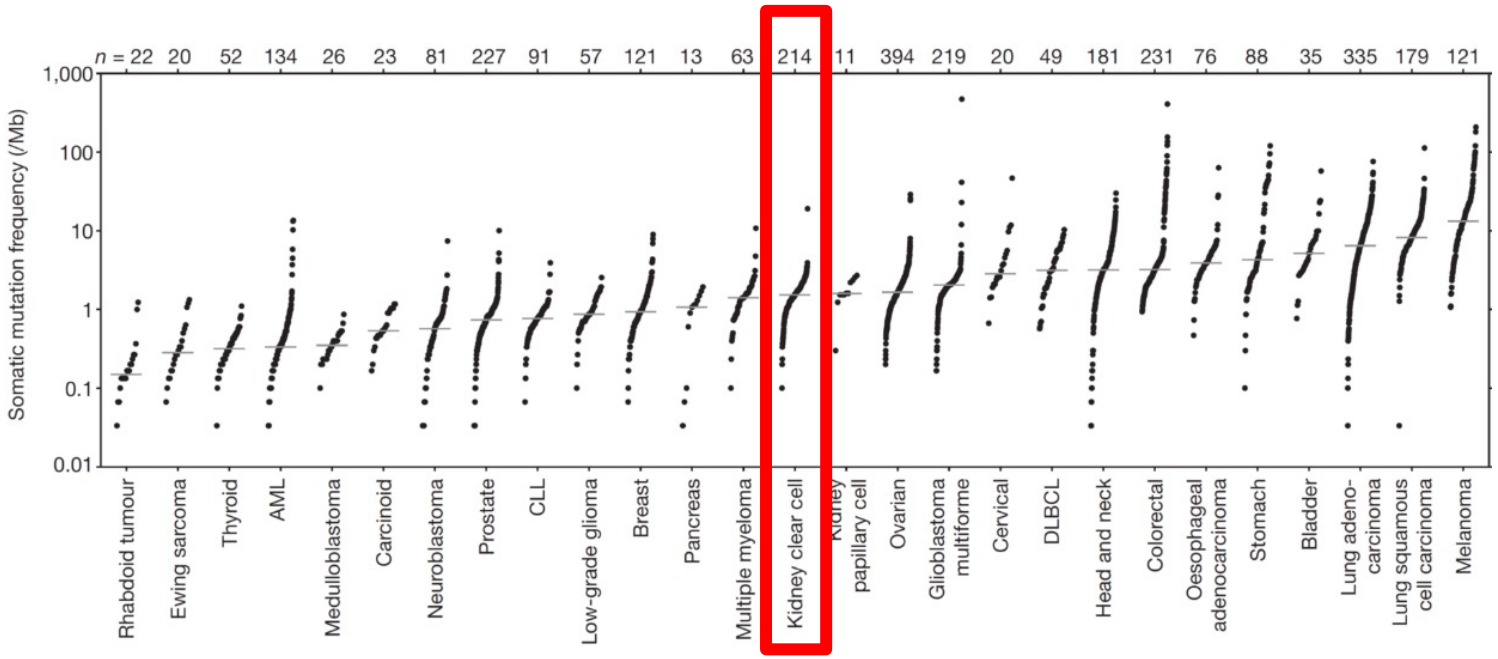


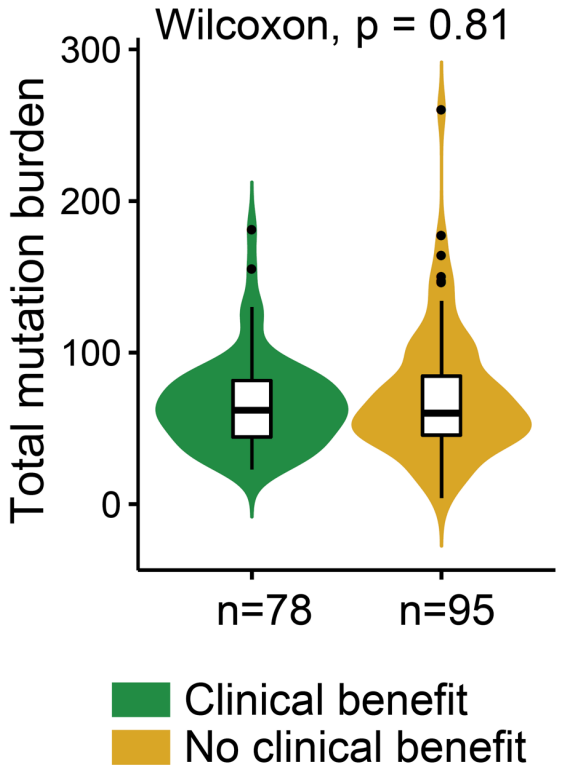


Phase II INTerpath-004 (~270 pts) now fully accrued

Braun et al. *Nature*, 2025; with T. Choueiri, D. Keskin, P. Ott, C. Wu

Neoantigens are not the only CD8+ T cell target in RCC

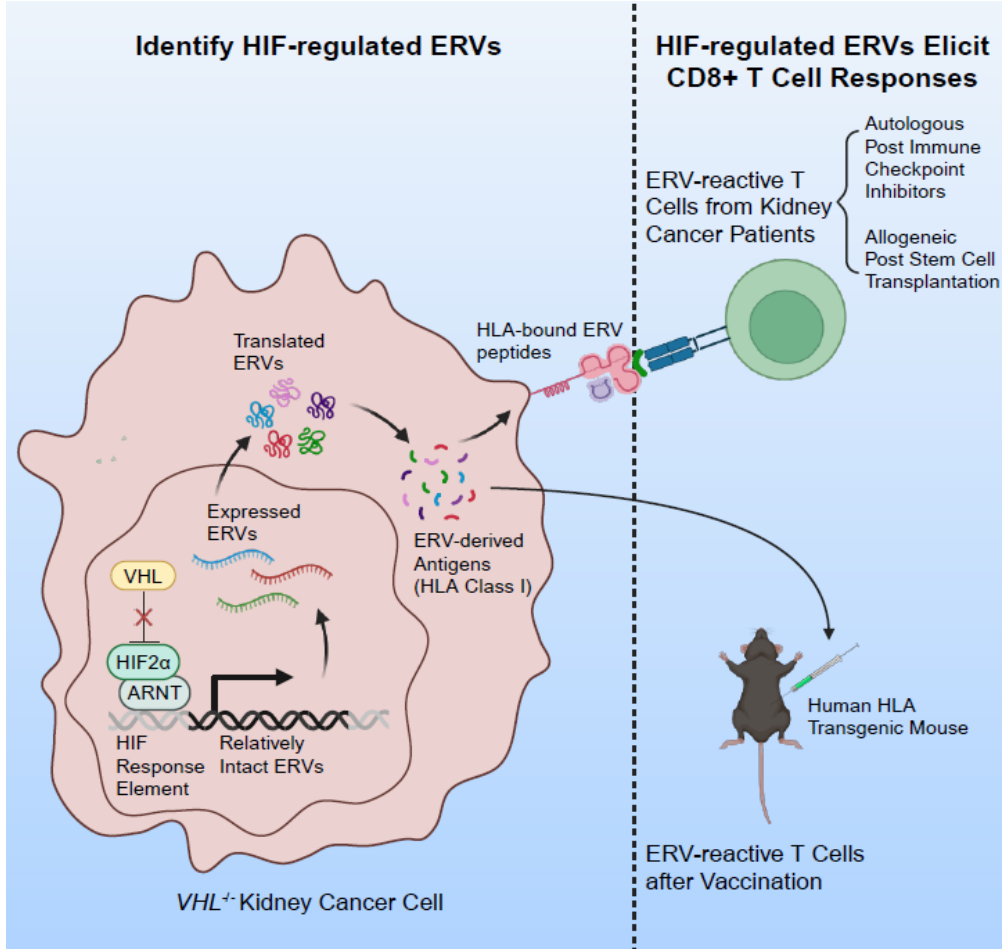




Neoantigens are not the only drivers of immunity in RCC

Lawrence, *Nature*, 2013; Braun et al. *Nature Medicine*, 2020

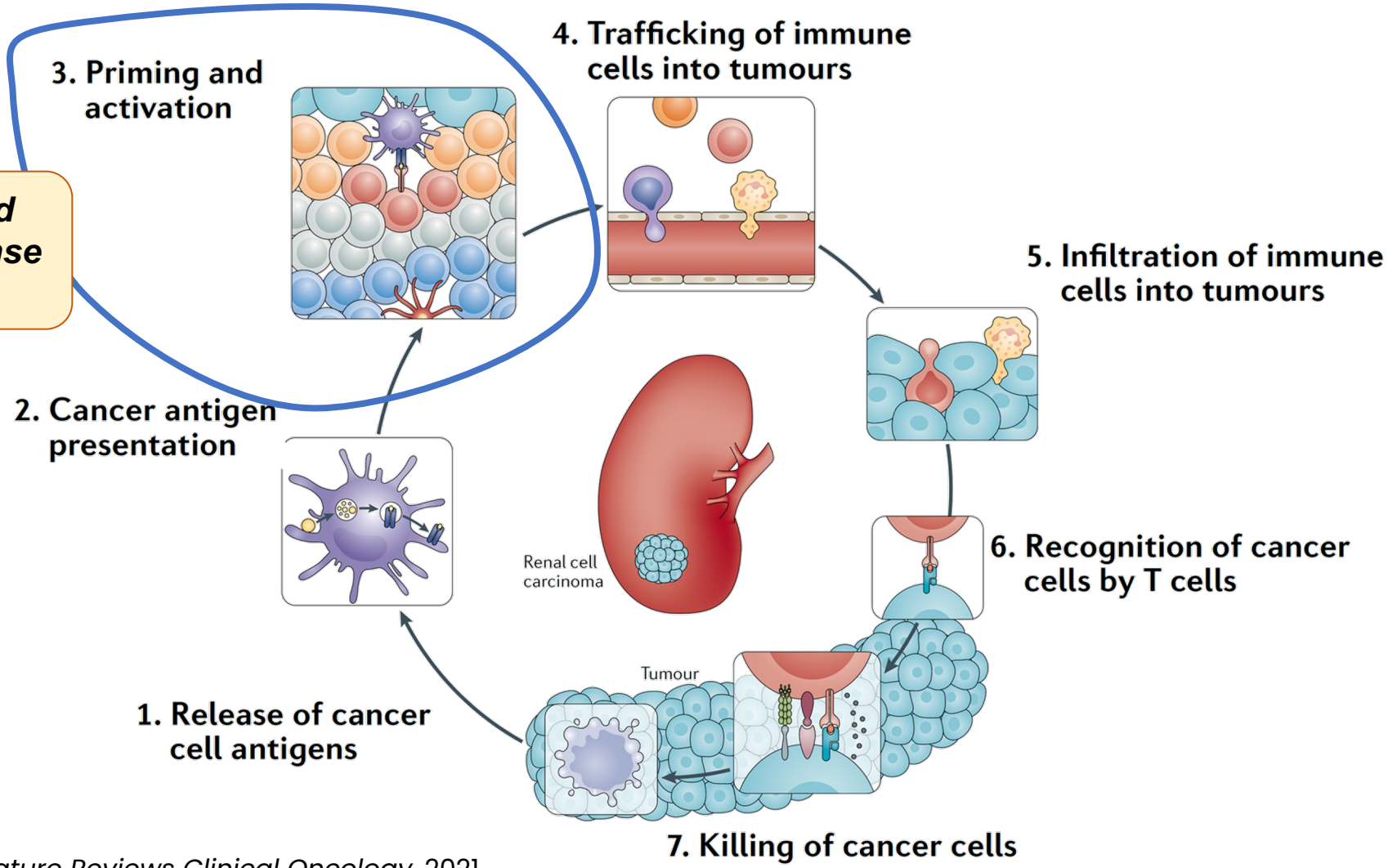
Endogenous retroviruses (ERVs) are expressed, form antigens, and can elicit T cell responses in RCC



Jiang*, Braun*, Klauser*, *Cell*, 2025; with S. Carr, D. Keskin, C. Wu, and W. Kaelin

RCC: a model for the cancer-immunity cycle

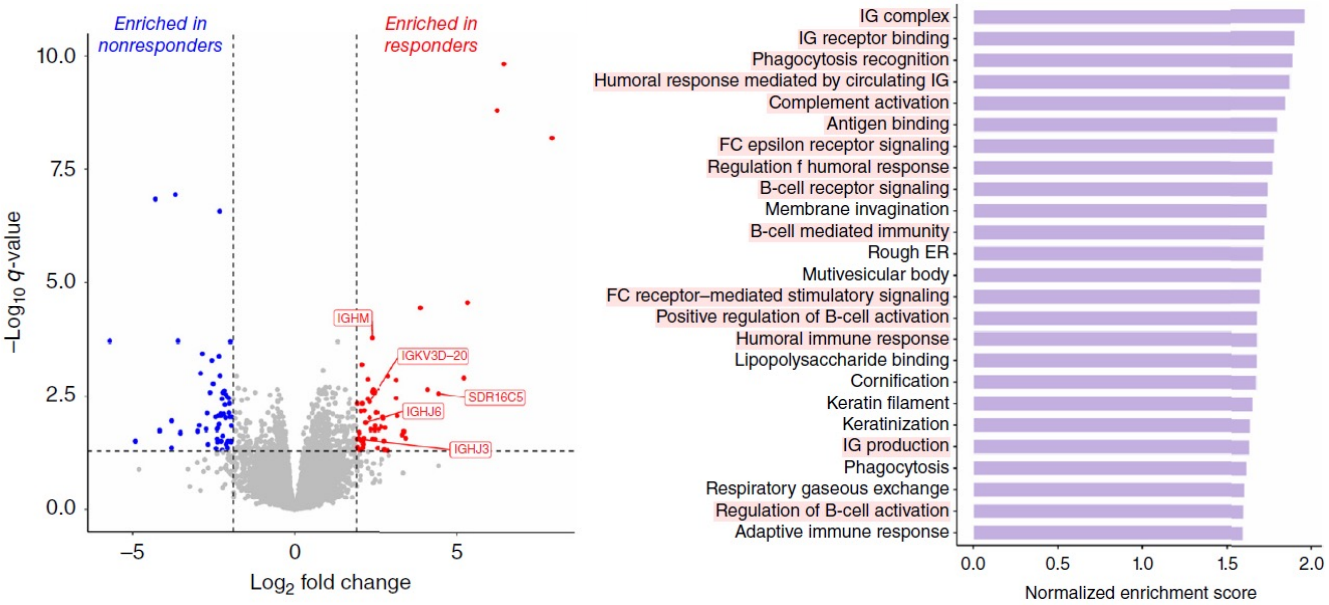
TLS associated with ↑ IO-response in RCC



Braun*, Bakouny* et al. *Nature Reviews Clinical Oncology*, 2021

Tertiary lymphoid structures (TLS) are associated with ↑↑↑IO response in RCC

B cell genes/signatures enriched in αPD-1 response (HCRN GU16-260)



Hugaboom*, Wirth*, Street*…Atkins*, Wu*, Braun*, *Cancer Discovery*, 2025

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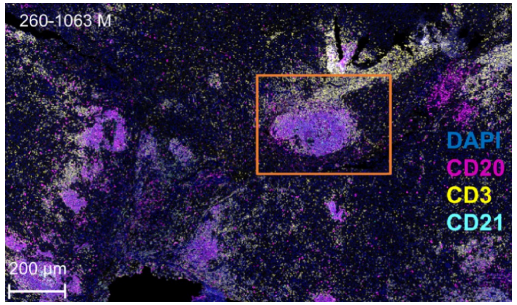

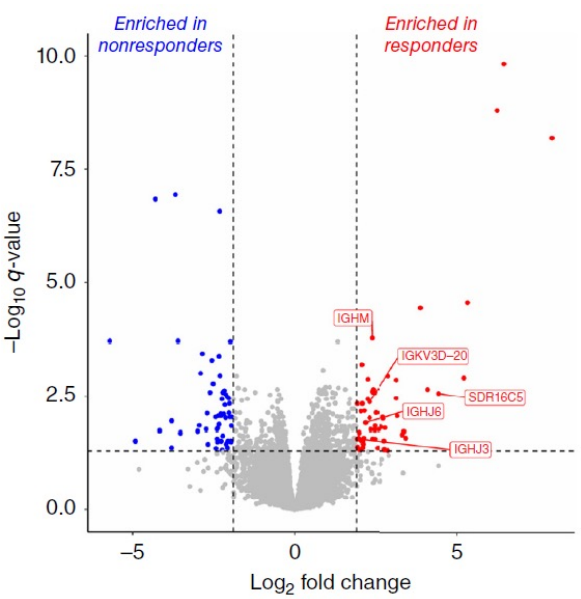

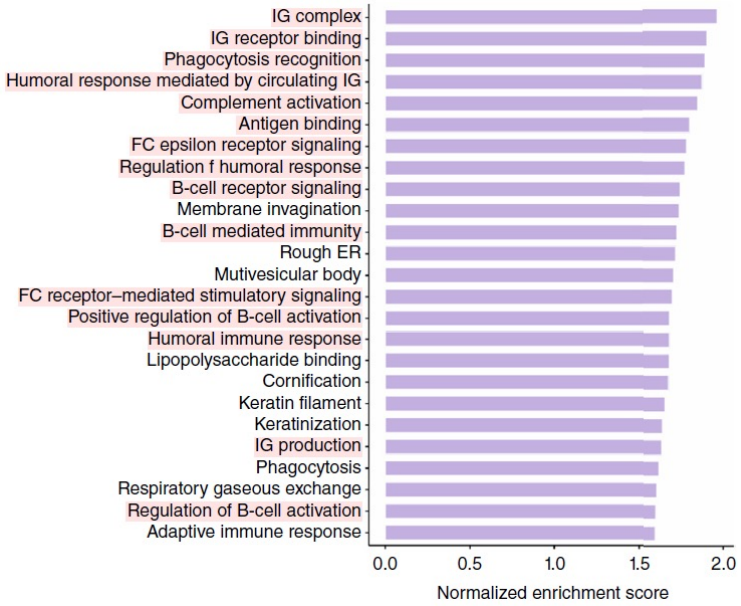

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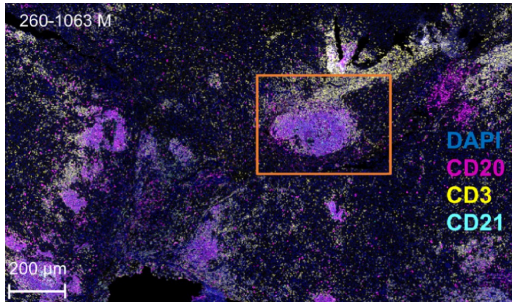
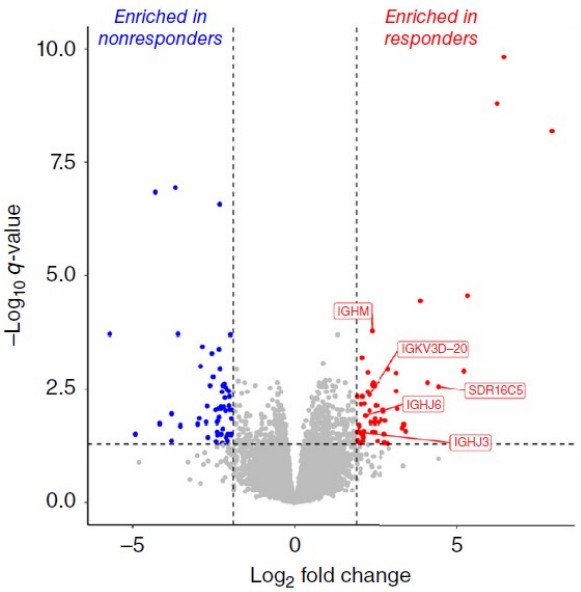
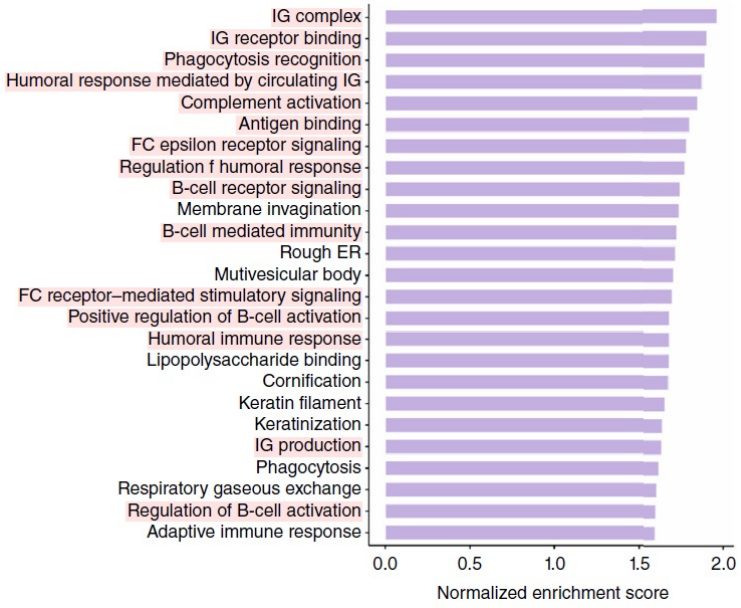
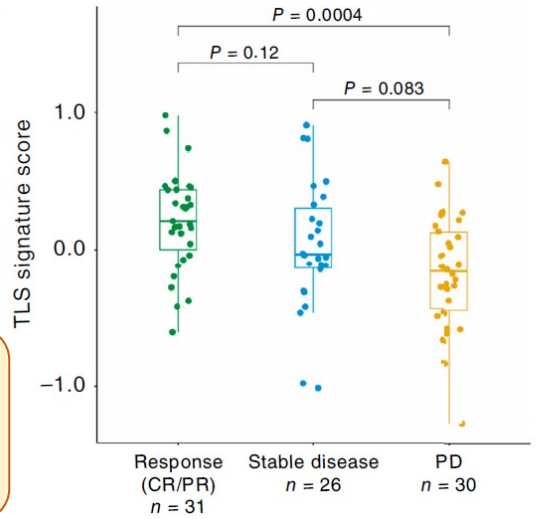
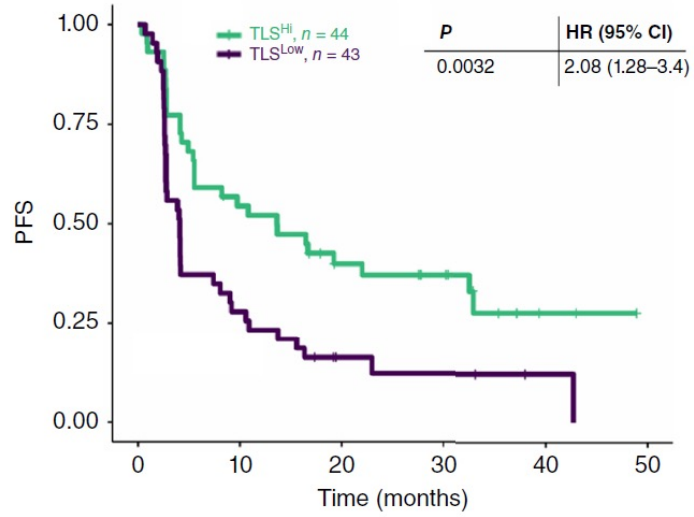






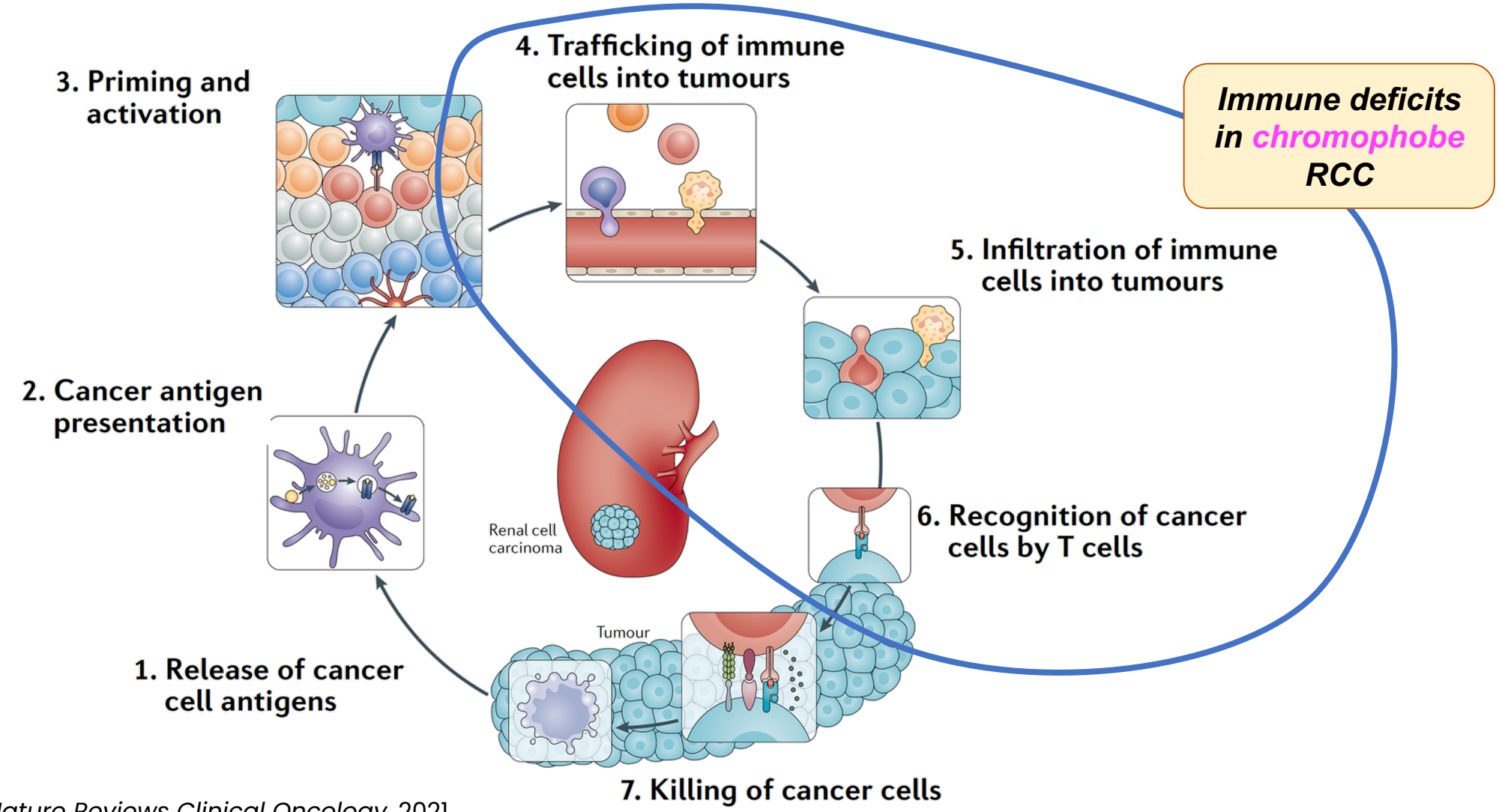
TLS are associated with improved outcomes with IO





Hugaboom*, Wirth*, Street*…Atkins*, Wu*, Braun*, *Cancer Discovery*, 2025

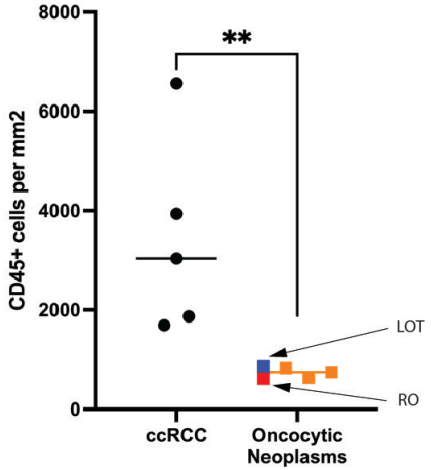
RCC: a model for the cancer-immunity cycle

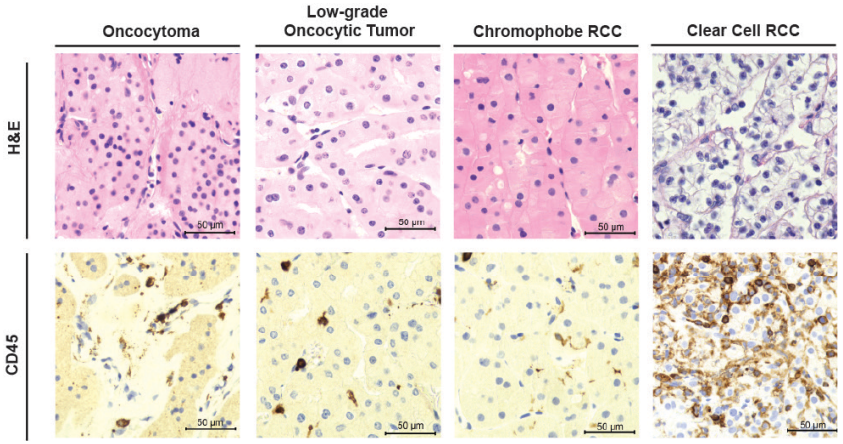


Braun*, Bakouny* et al. *Nature Reviews Clinical Oncology*, 2021

CD8+ T cell do not traffic to or infiltrate into chromophobe RCC

Chromophobe RCC has low immune cell infiltration





Labaki...Van Allen*, Shukla*, Choueiri*, Henske*, Braun*, *Journal of Clinical Oncology*, 2025.

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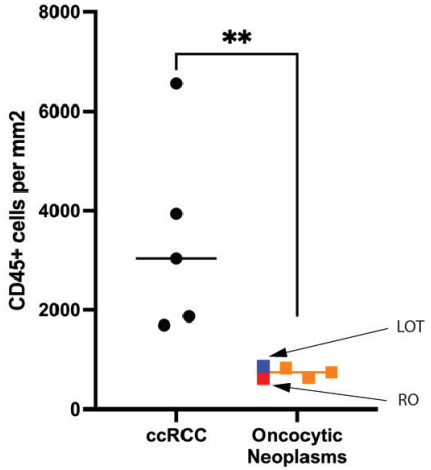
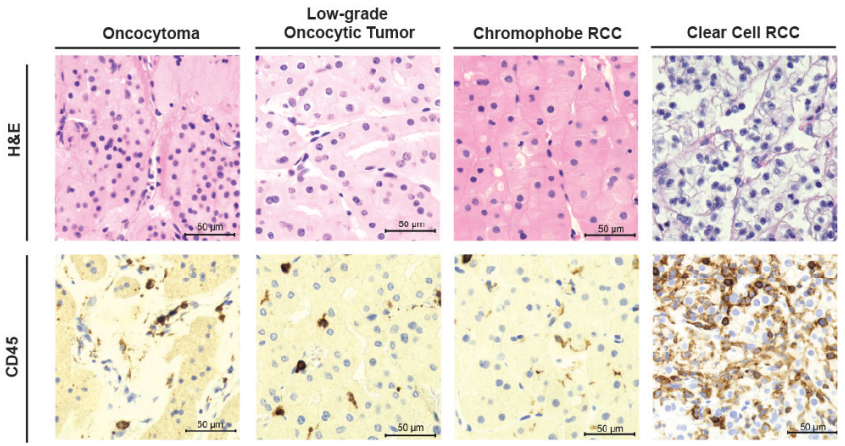
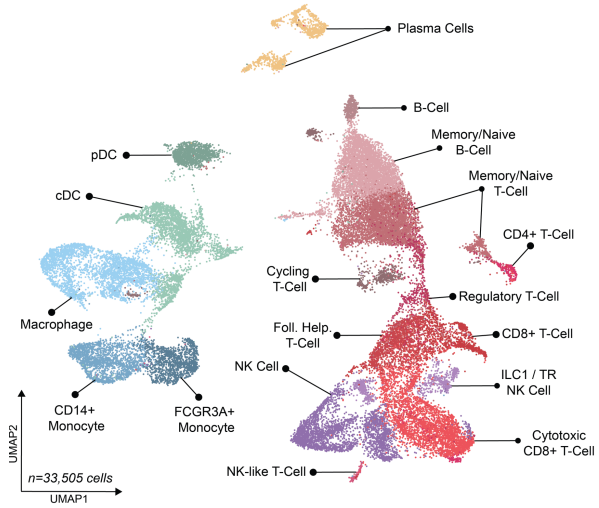
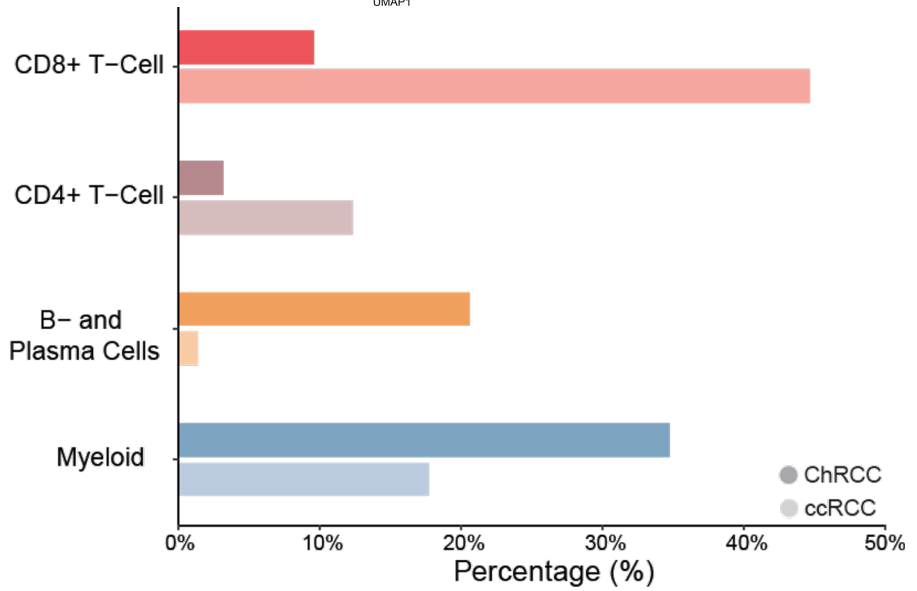




Among infiltrating immune cells, very few are CD8+ T cells

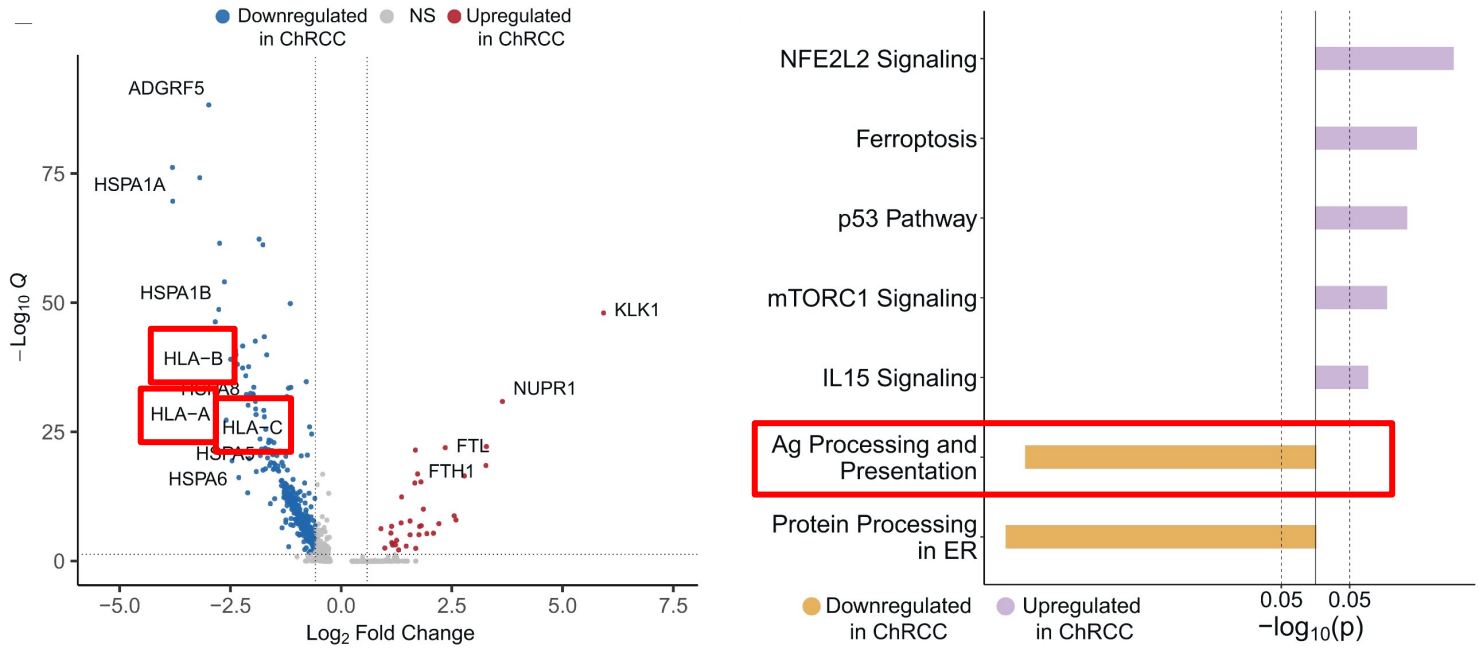




Labaki...Van Allen*, Shukla*, Choueiri*, Henske*, Braun*, *Journal of Clinical Oncology*, 2025.

Chromophobe RCC evades CD8+ T cell detection

Chromophobe RCC tumor cells downregulate HLA class I and other antigen-presenting machinery)



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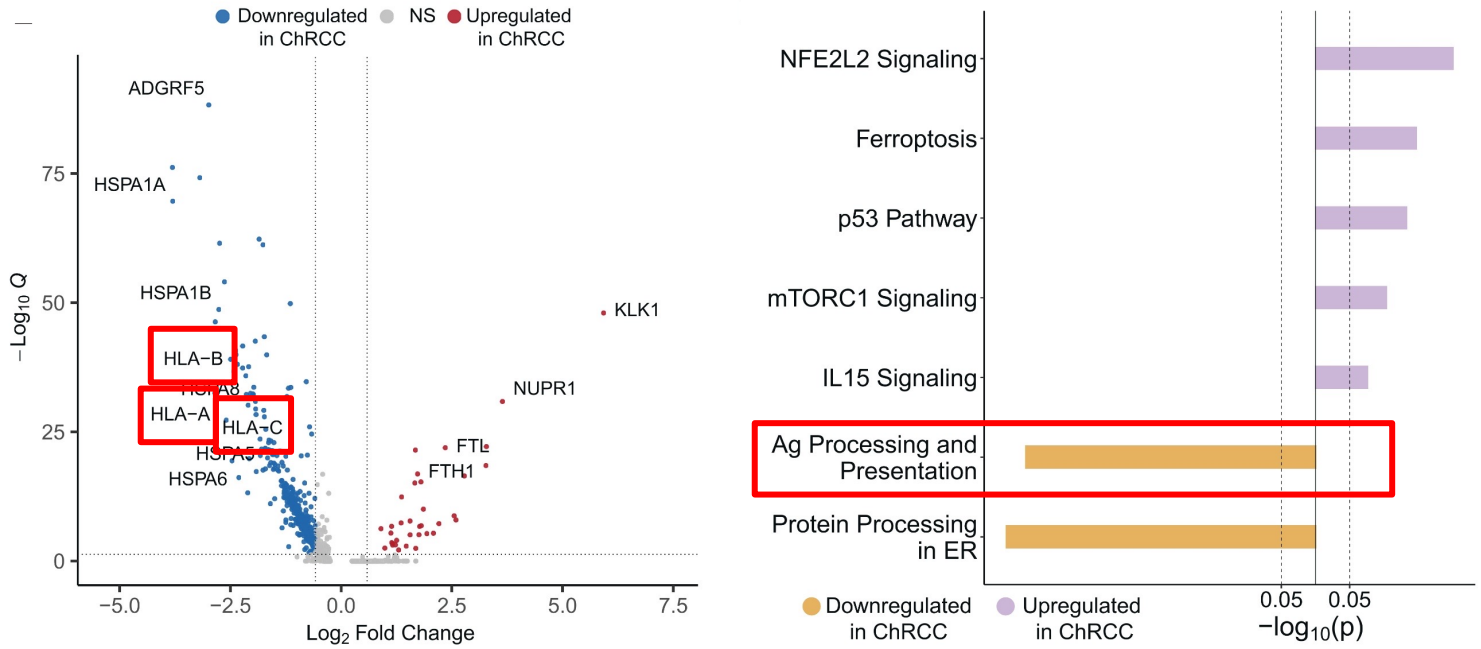
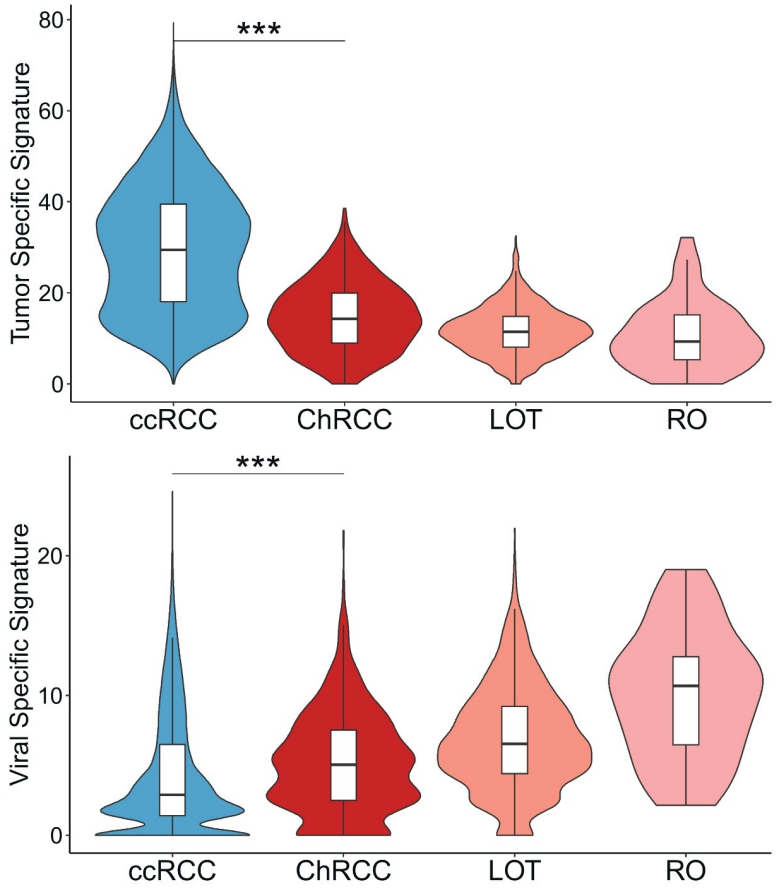


Tumor-infiltrating CD8+ T cells are largely bystanders



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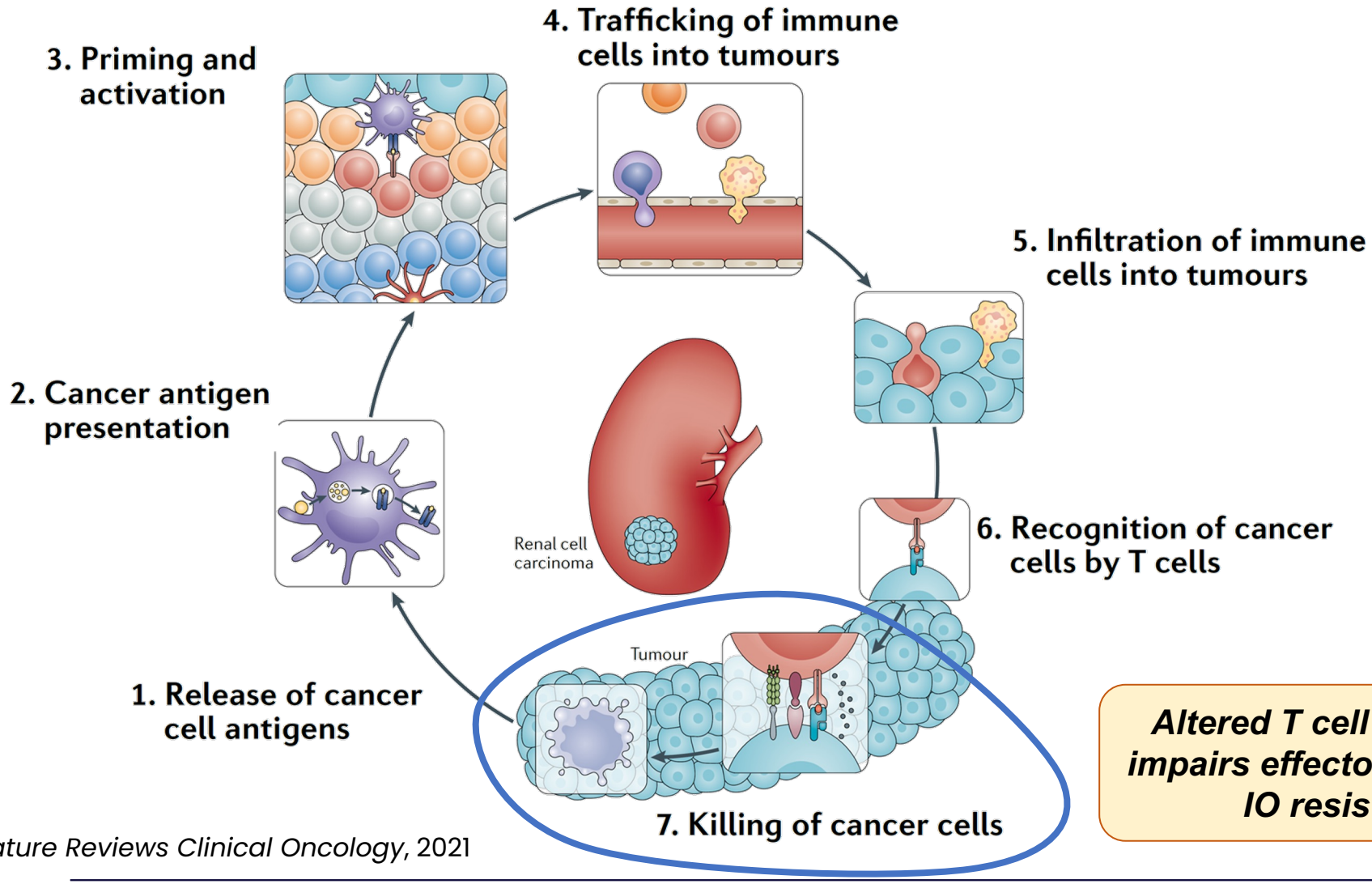
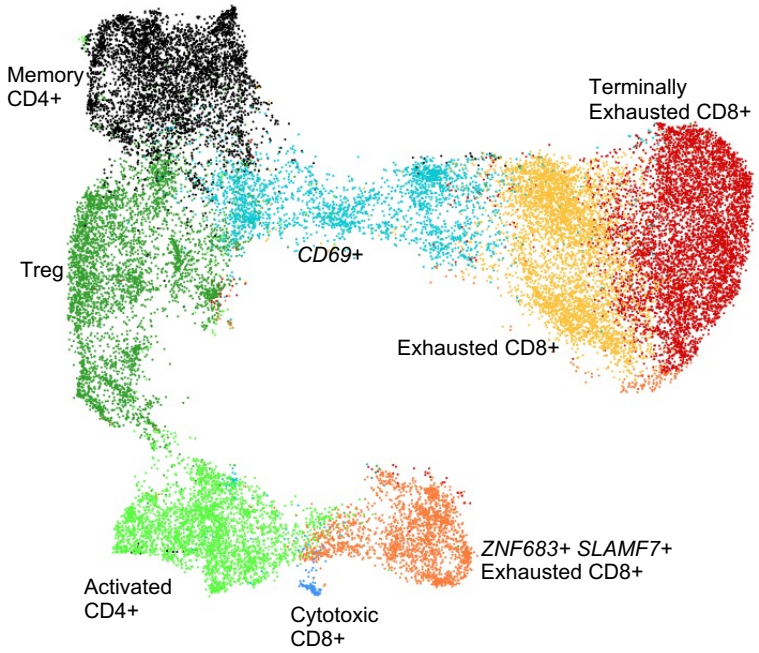


Altered T cell phenotype impairs effector function → IO resistance

Braun*, Bakouny* et al. *Nature Reviews Clinical Oncology*, 2021

ZNF683+ SLAMF7+ exhausted CD8+ T cells are enriched in tumors resistant to PD-1 blockade

scRNA-set of T cells from RCC treated with αPD-1 (HCRN GU16-260)



Hugaboom*, Wirth*, Street*...Atkins*, Wu*, Braun*, *Cancer Discovery*, 2025

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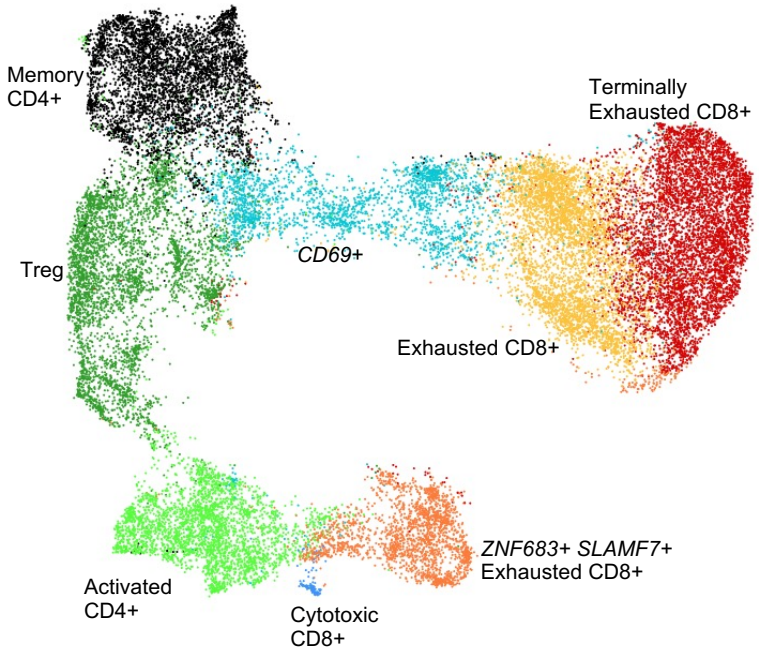
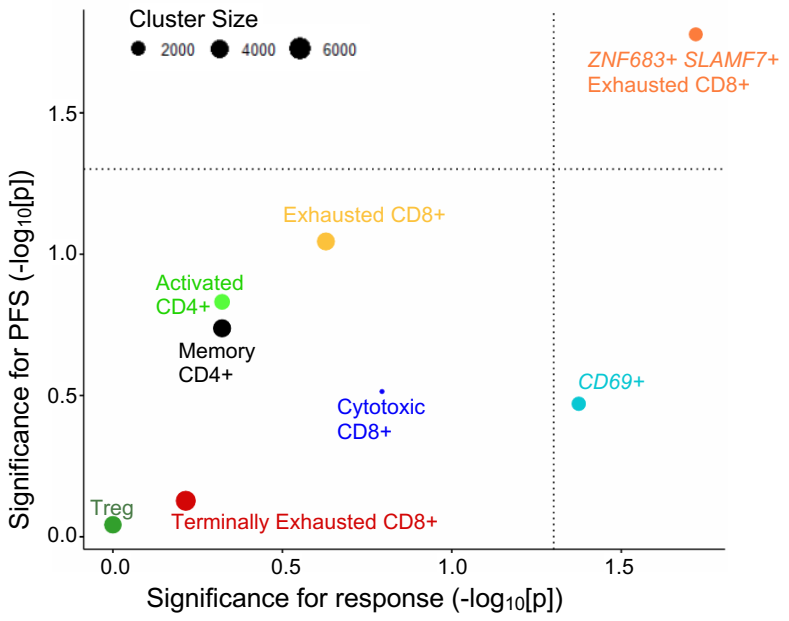
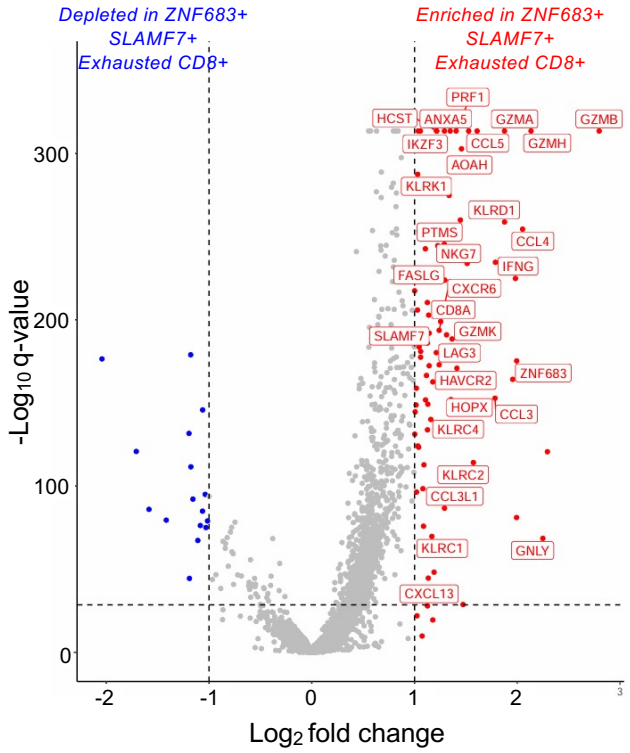
ZNF683+ SLAMF7+ Exhausted CD8+ associated with resistance to anti-PD-1







Hugaboom*, Wirth*, Street*...Atkins*, Wu*, Braun*, *Cancer Discovery*, 2025

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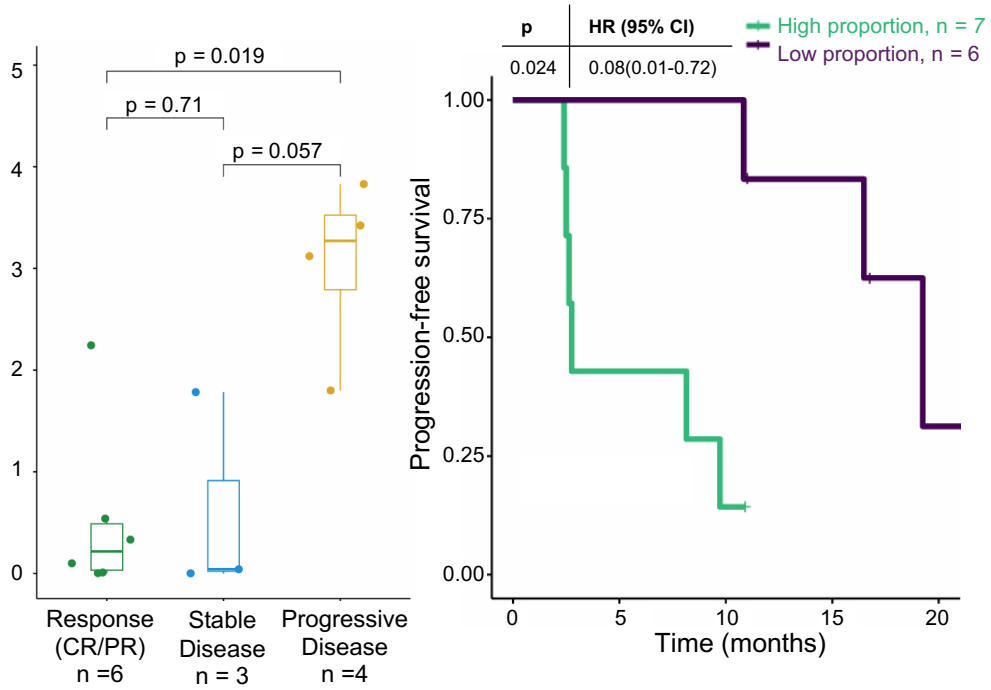
Discovery cohort (scRNA-seq)



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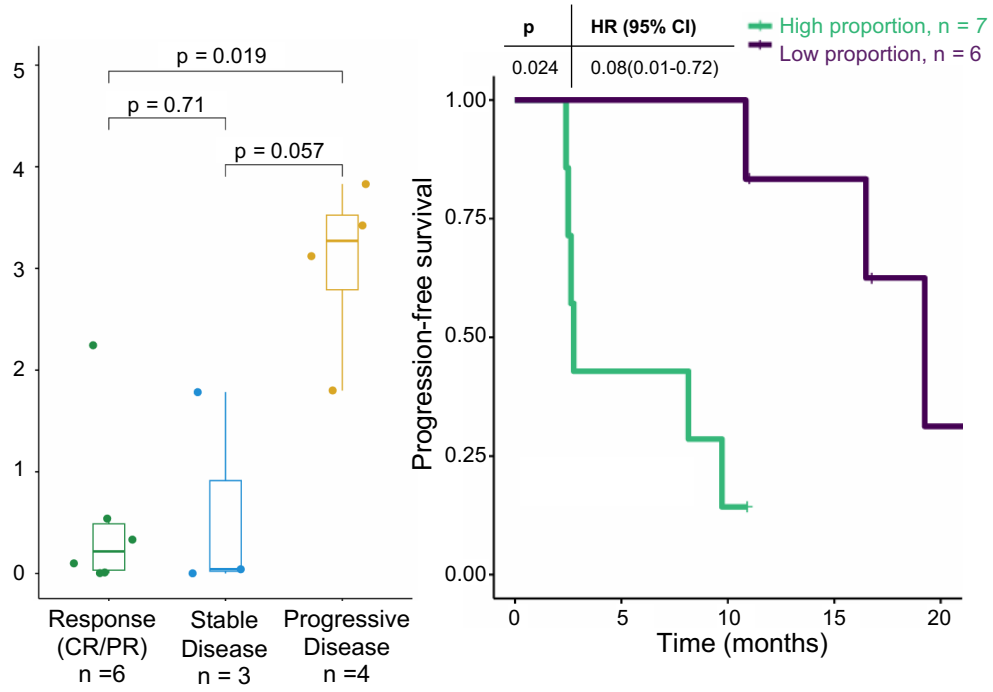
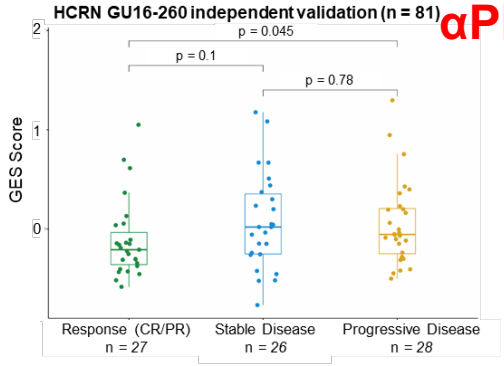
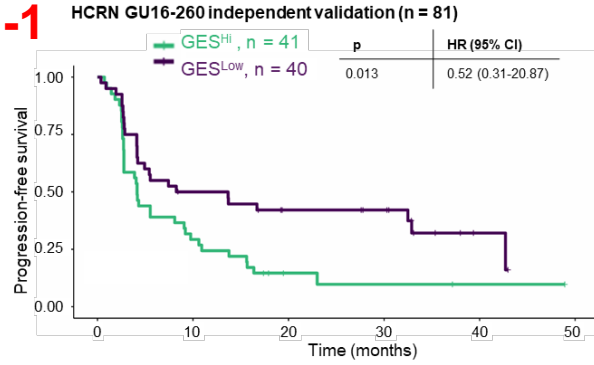
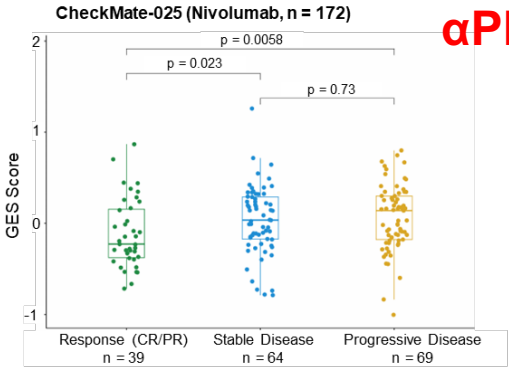
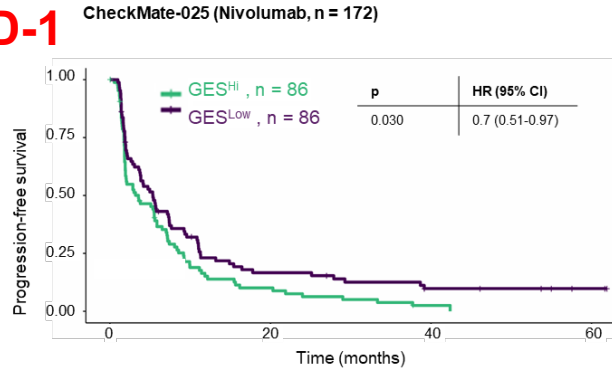


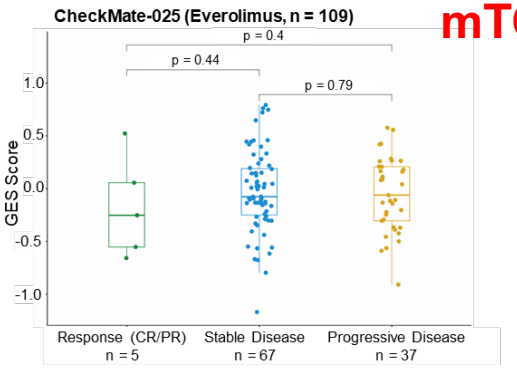
Validation (bulk RNA-seq)

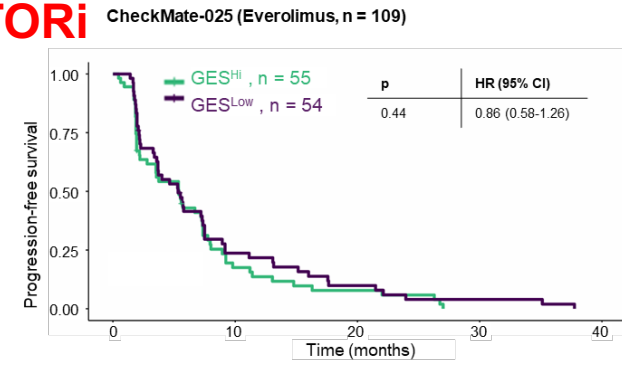












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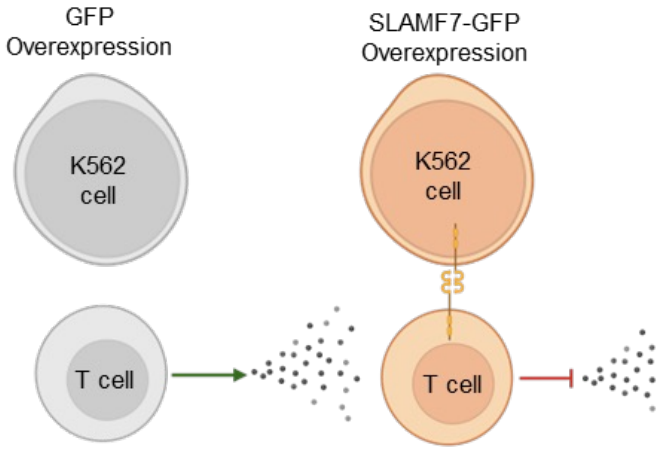
SLAMF7 directly impairs T cell function

Experimental set-up: Overexpress SLAMF7 on heathy T Cells



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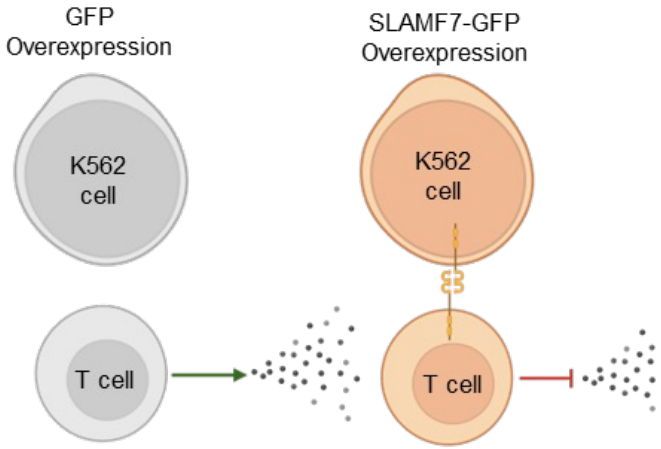

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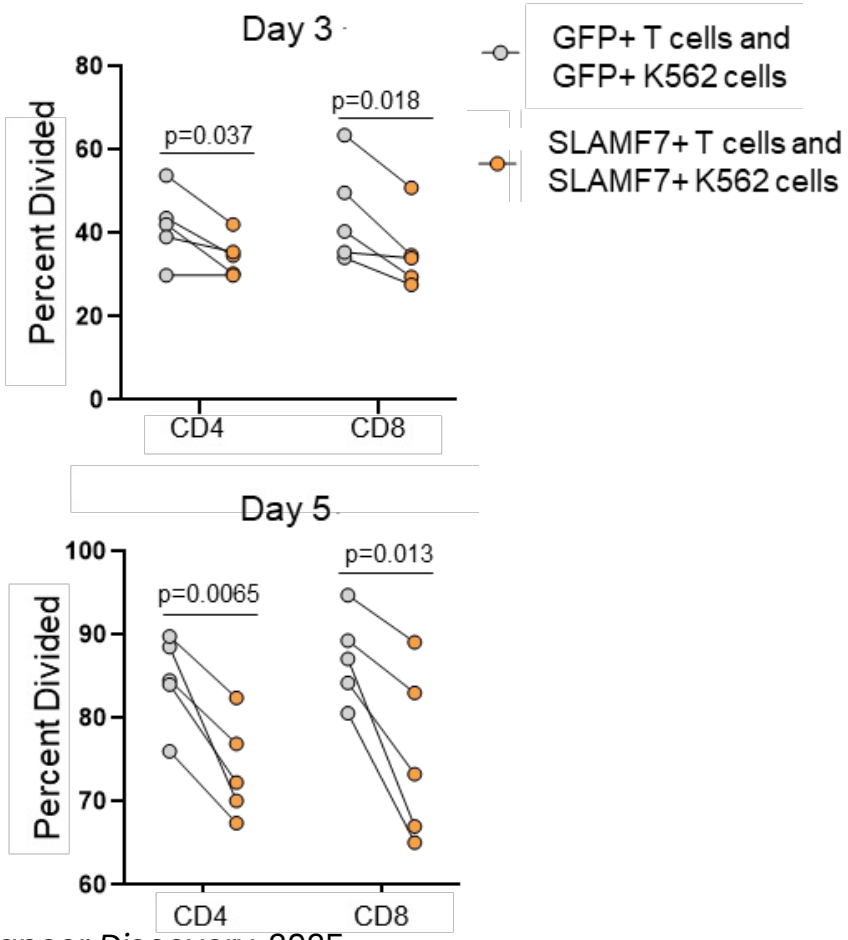

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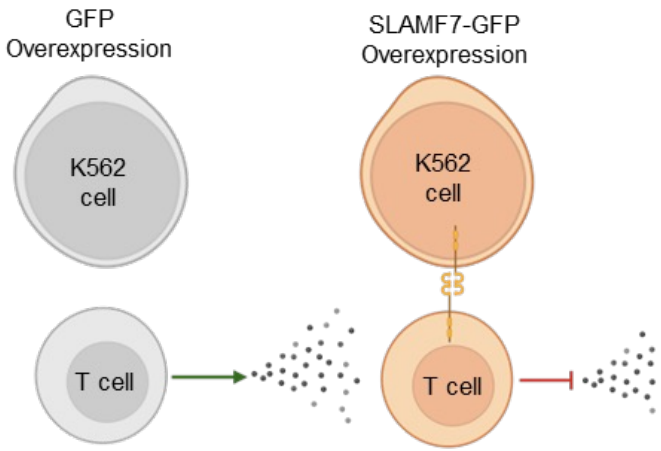

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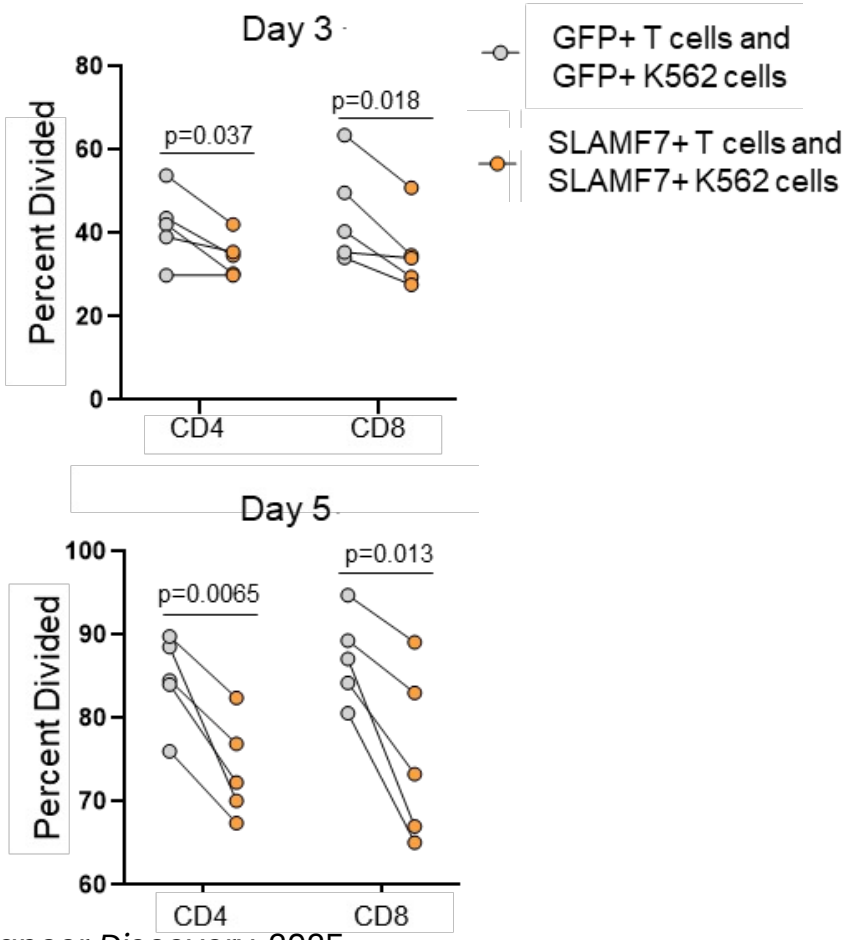
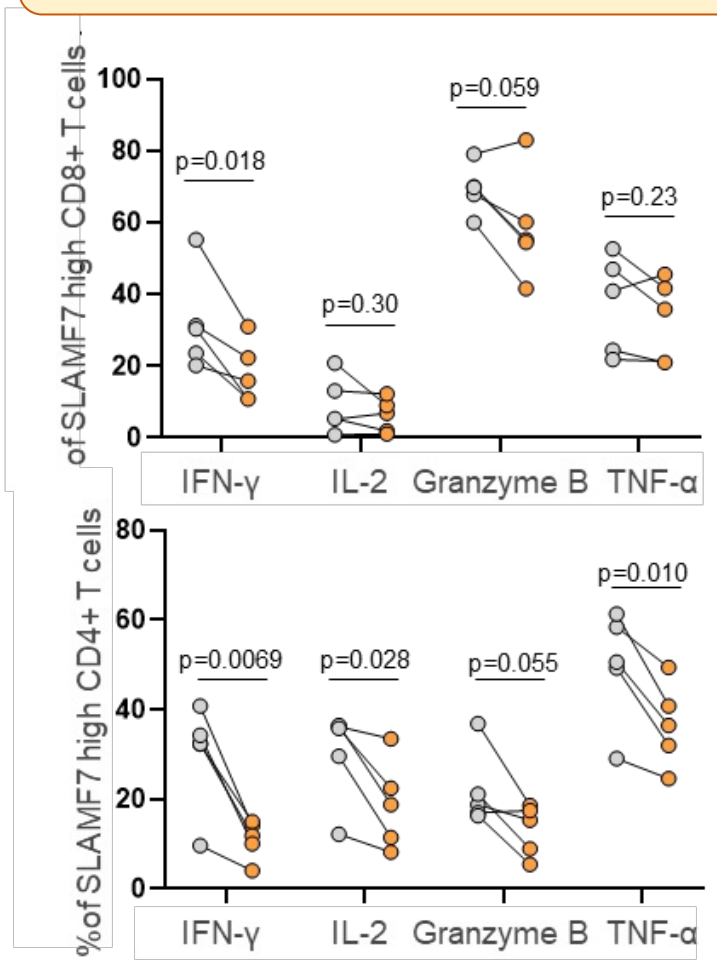


SLAMF7 inhibits IFNγ and granzyme-B production

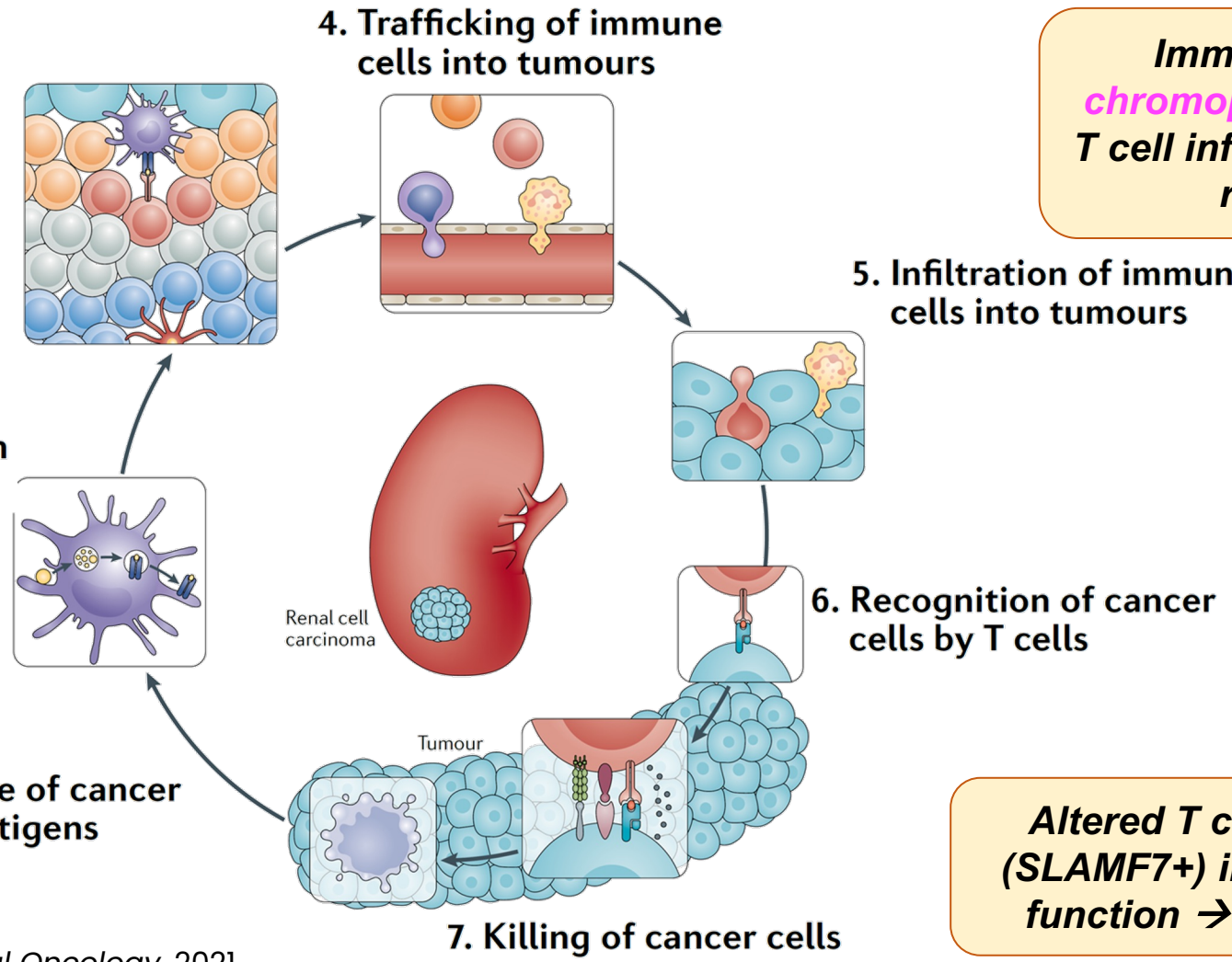


Hugaboom*, Wirth*, Street*...Atkins*, Wu*, Braun*, *Cancer Discovery*, 2025

RCC: a model for the cancer-immunity cycle

TLS associated with ↑ IO-response in RCC

Immune deficits in chromophobe RCC impair T cell infiltration and tumor recognition



Neoantigens and ERVs are targetable RCC antigens

Altered T cell phenotype (SLAMF7+) impairs effector function → IO resistance

Braun*, Bakouny* et al. *Nature Reviews Clinical Oncology*, 2021

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- Zachary Yochum

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- Sabina Signoretti
- Catherine Wu
- Patrick Ott
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- Eli Van Allen
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- Michael Hurwitz
- Harriet Kluger
- Mario Sznol
- Marcus Bosenberg
- Pat Kenney
- Fed Ghali
- Wen-Shen Tan
- Debo Adeniran
- Peter Humphrey
- Jeff Ishizuka

Patients and their families

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CDMRP Department of Defense

CRI Cancer Research Institute™

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DOD KC190128