VGO NORTE INTERNATIONAL GU DEBATES

Treating Bladder Cancer in 2030: What does the future hold?

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Bladder Cancer Advocacy Network
BCAN
Leading the way to awareness and a cure

UNIVERSITY of WASHINGTON

FRED HUTCH
CURES START HERE™

Disclosures in last 2 years

Company	Nature of Financial Relationship
Acrivon Therapeutics; ALX Oncology; Genentech; Gilead; Merck KGaA; MSD	research funding to institution
AstraZeneca; Astellas Pharma, Bristol-Myers Squibb; Daiichi Sankyo; Gilead; Janssen; Merck KGaA; MSD; Pfizer; Replimune; Foundation Medicine; Eli Lilly; Urogen; Tyra Biosciences; Natera; Ottimo Pharma; Bayer; 7 Hills Pharma	consulting

Gaps & unmet needs in NMIBC

“Need for effective intravesical alternatives when BCG fails”

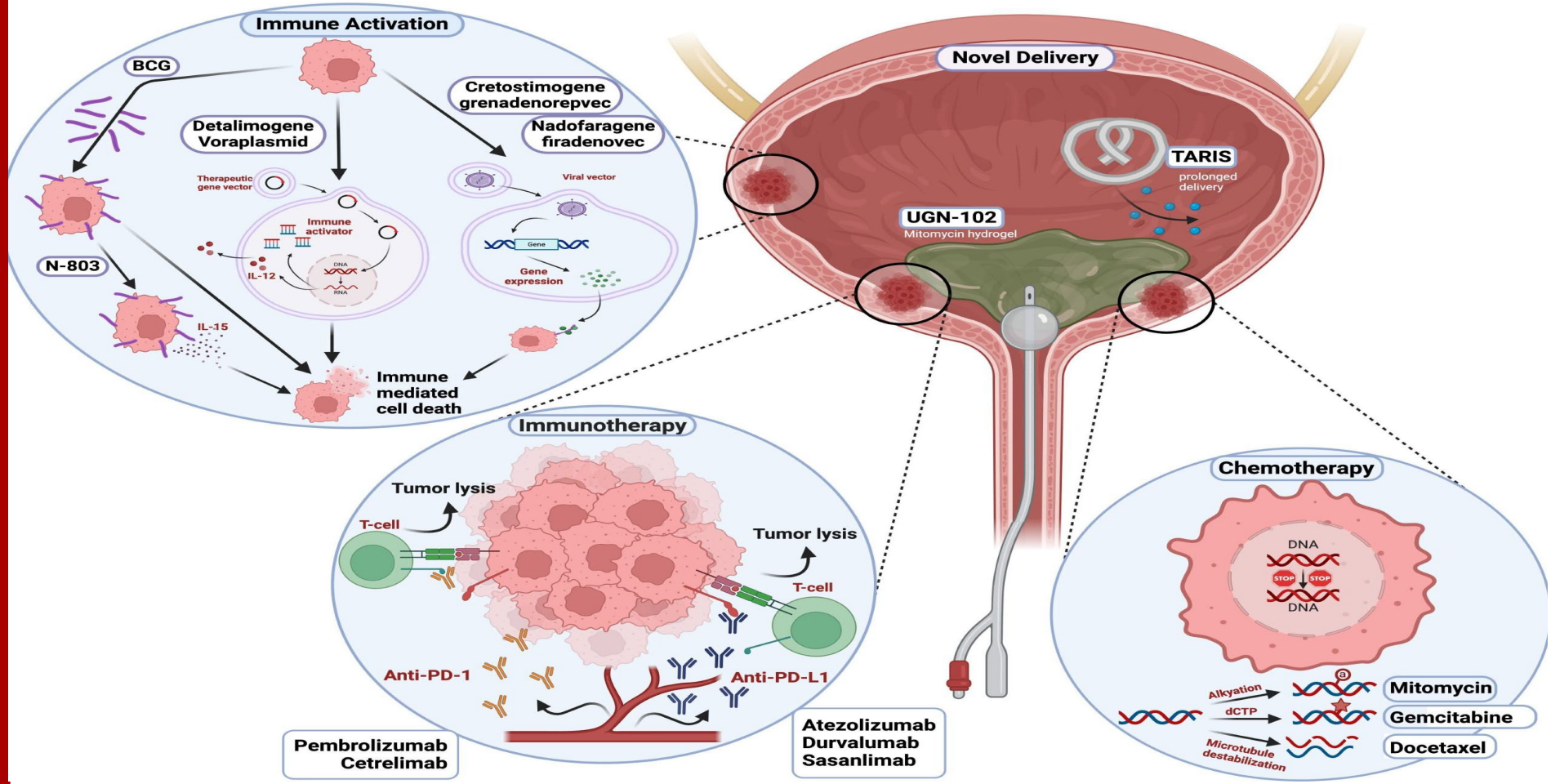
“Need better access to experienced medical oncologists”

Systemic vs local toxicity

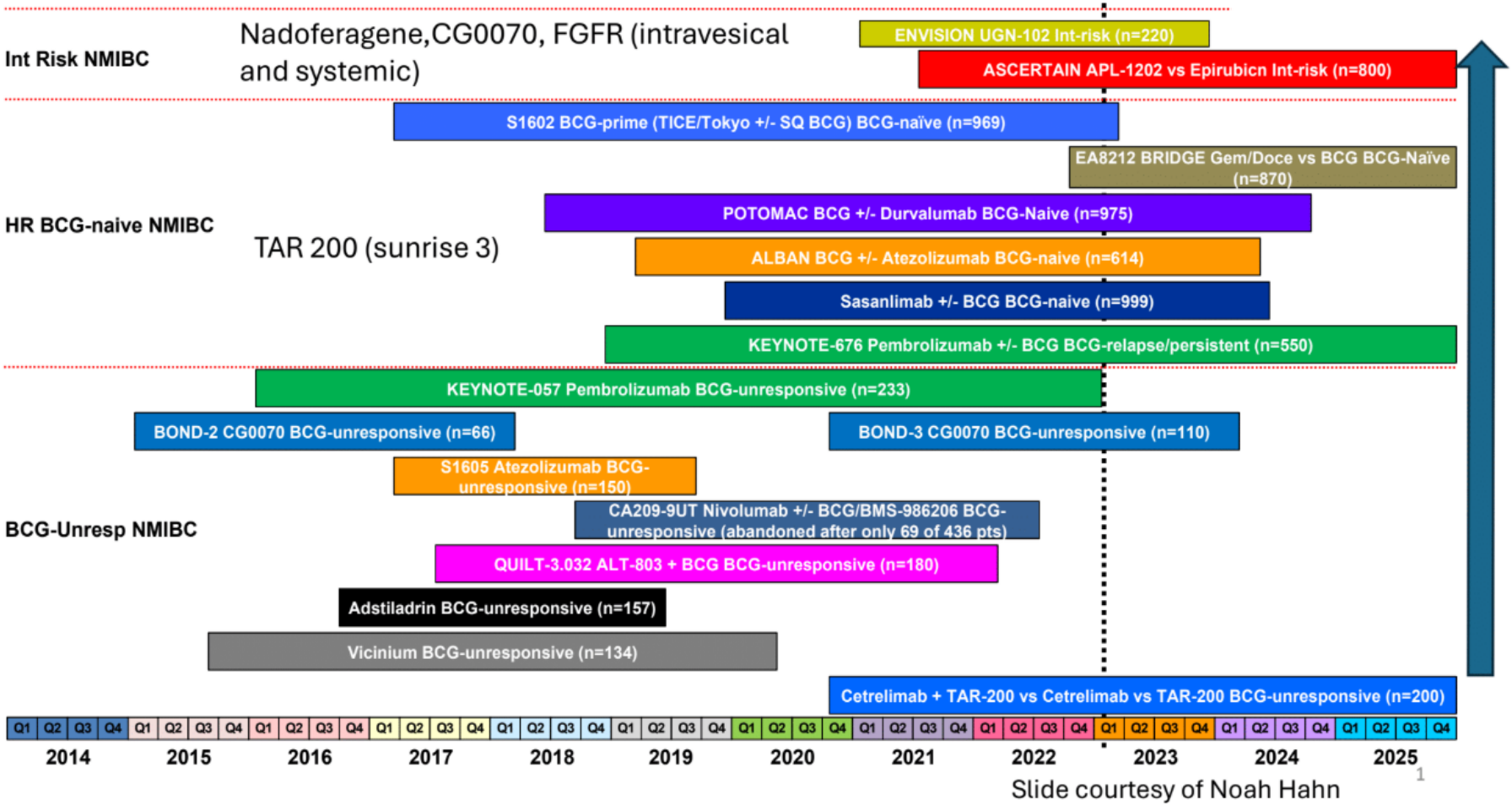
Administration burden

Supply (BCG) availability

Mechanisms are expanding



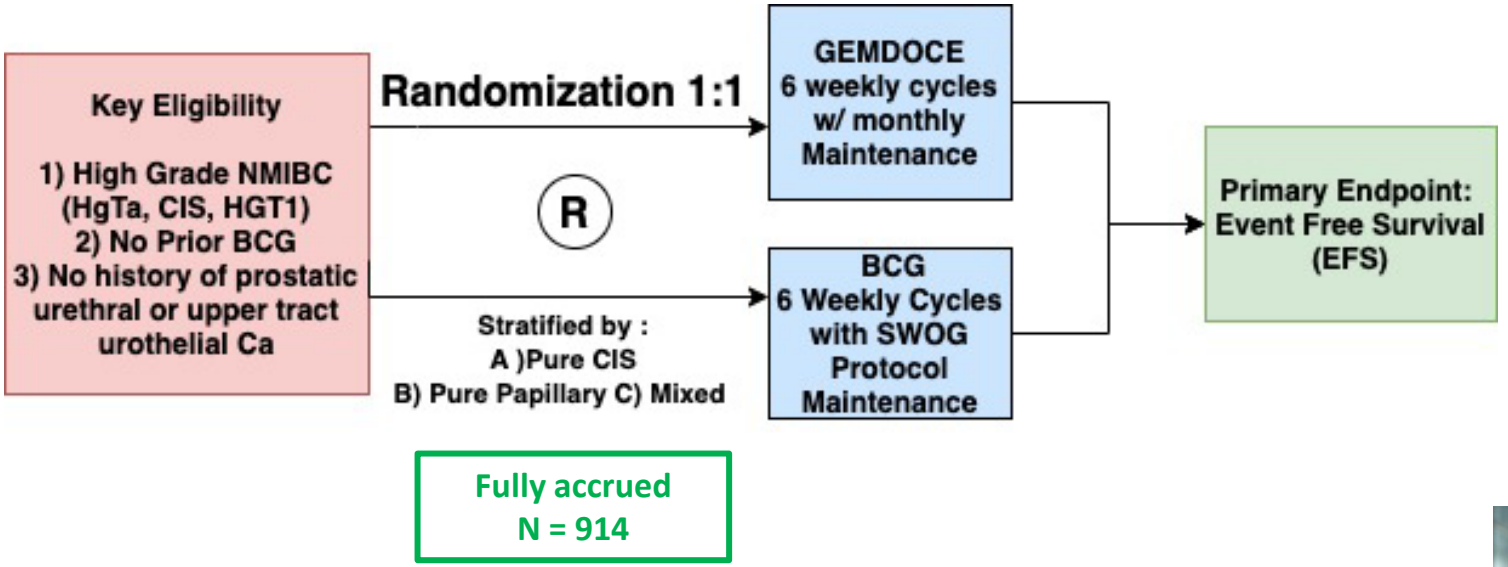
Where is the future?



Slide courtesy of Noah Hahn

EA8212 BRIDGE

Objective: To assess whether event-free survival is non-inferior for GemDoce vs standard BCG for pts with BCG-naïve high-grade NMIBC (PI: Max Kates)

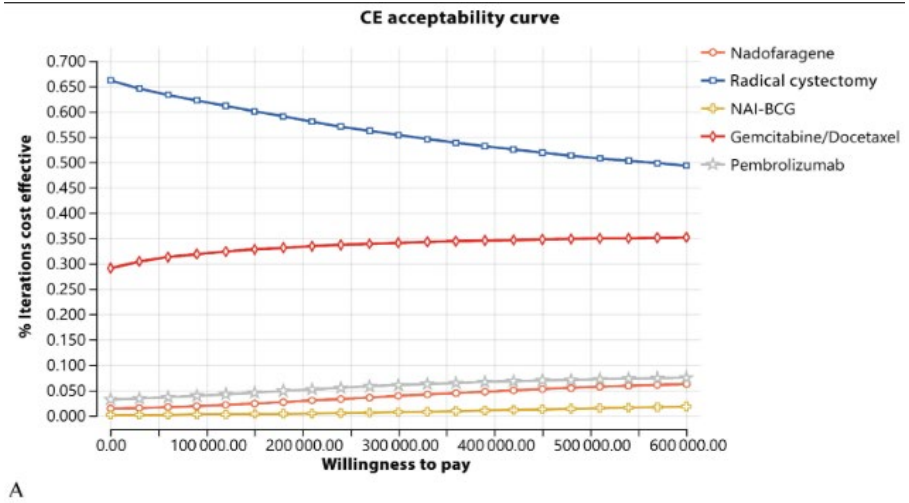




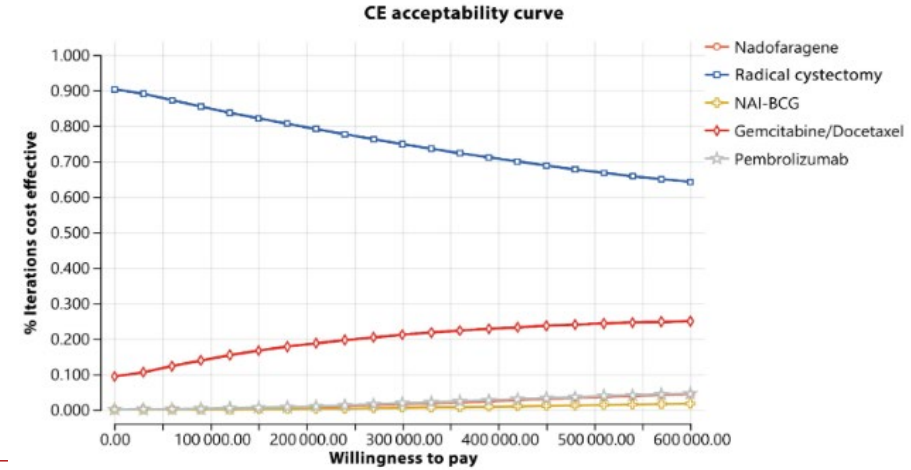
Costs are compounding

Therapy	Average Retail Price (USD)
Gemcitabine[1]	$26 per 1, 26.3ML of 1GM/26.3ML
Docetaxel[2]	$158 per 2, 1 ML 20MG/ML, vials
Pembrolizumab[3]	$22,674 per dose
Nadofaragene[4]	$60,000 per dose
Nogapendekin[5]	$35,800 per dose
TAR-200	$70,000 per dose

Slide courtesy of Dr Tyson



A



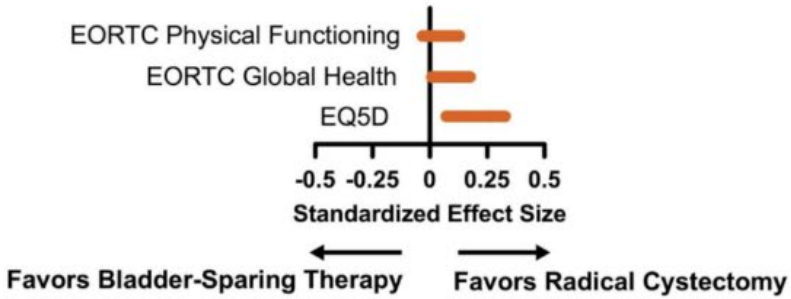
B

CISTO study (Gore et al. JCO 2025)

Results: Patient Characteristics

	BST (n = 371)	RC (n = 199)	P-value
Age, mean (SD)	**72.4 (8.3)**	**69.6 (9.1)**	**<0.001**
Age ≥ 75, n (%)	**150 (40%)**	**62 (31%)**	**0.03**
Female, n (%)	78 (21%)	39 (20%)	0.74
White, n (%)	332 (89%)	182 (91%)	0.56
Partnered, n (%)	**288 (78%)**	**170 (86%)**	**0.03**
Urban residence, n (%)	**323 (87%)**	**156 (78%)**	**0.008**
Comorbidity Index, mean (SD)	1.4 (5.0)	1.1 (4.5)	0.50
Cancer severity at enrollment			
Stage T1, n (%)	**110 (30%)**	**113 (57%)**	**<0.001**
Concomitant CIS, n (%)	**165 (45%)**	**108 (55%)**	**0.02**

Results: General Quality of Life



Summary of 12-Month Outcomes

Favors BST	No Difference	Favors RC
Bowel health Sexual health	Physical functioning • Overall • By age Role functioning Social functioning Urinary health	Physical functioning • Patients w/ CIS • Unpartnered Cognitive functioning Mental health Financial health
Progression-free survival	Cancer-specific survival Overall survival	Recurrence-free survival

AUA 2025: Dr John Gore

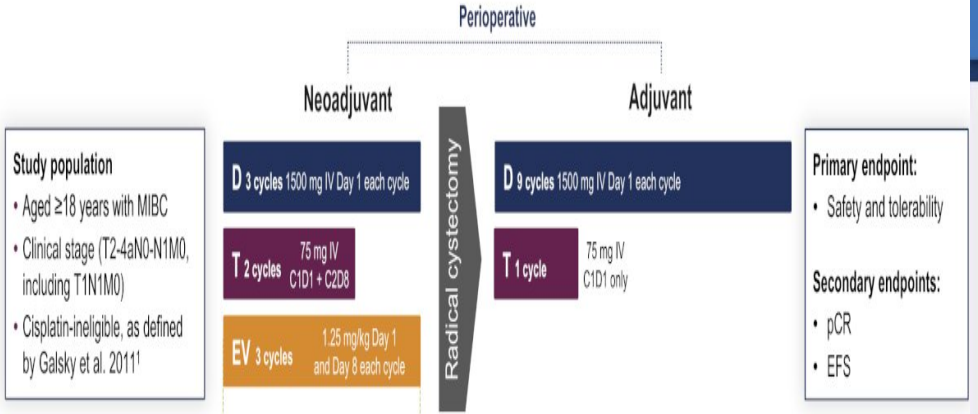
Future of NMIBC

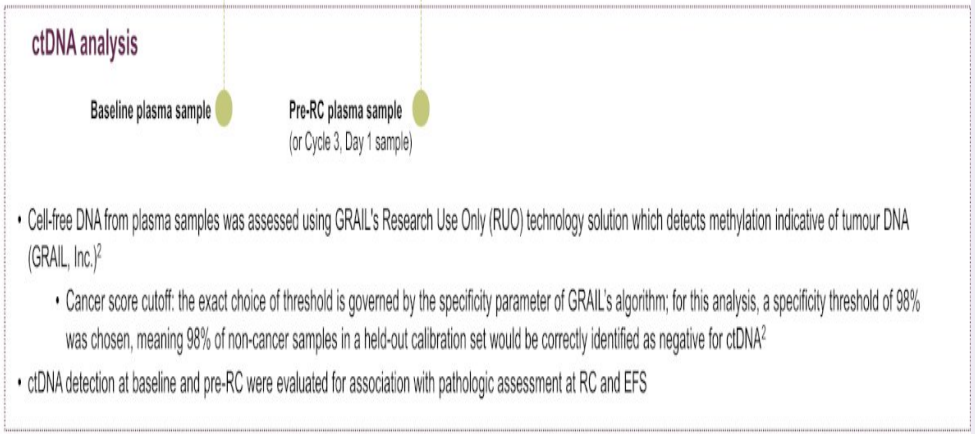
- BCG-naïve: awaiting data from ongoing phase 3 trials, e.g. BRIDGE, Sunrise 3 (TAR-200), V940-011 (vaccine)
- Urine cell-free DNA/RNA for risk stratification, response assessment, detection of residual disease & local urinary tract recurrence

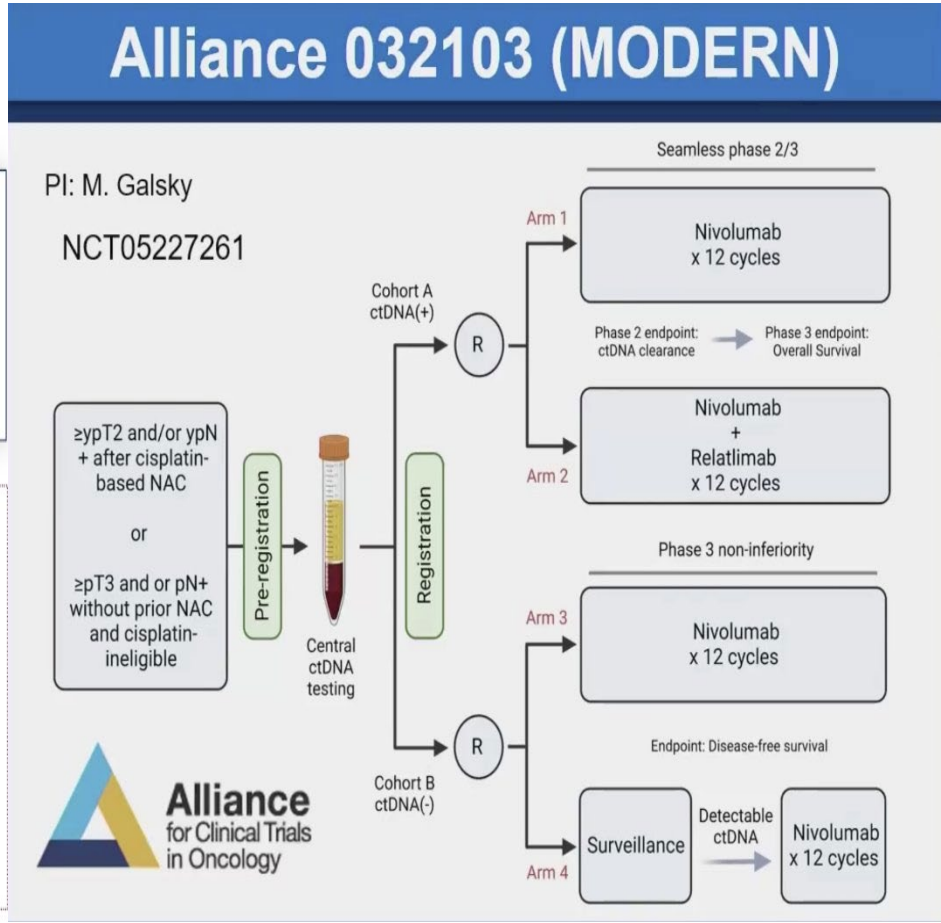
-very promising data -> awaiting assay optimization & assessment of clinical utility in clinical trials & RWD

- Predictive biomarkers of response (genomics, AI, etc.): need to assess clinical utility in trials (BRIDGE, etc.)

Future of MIBC



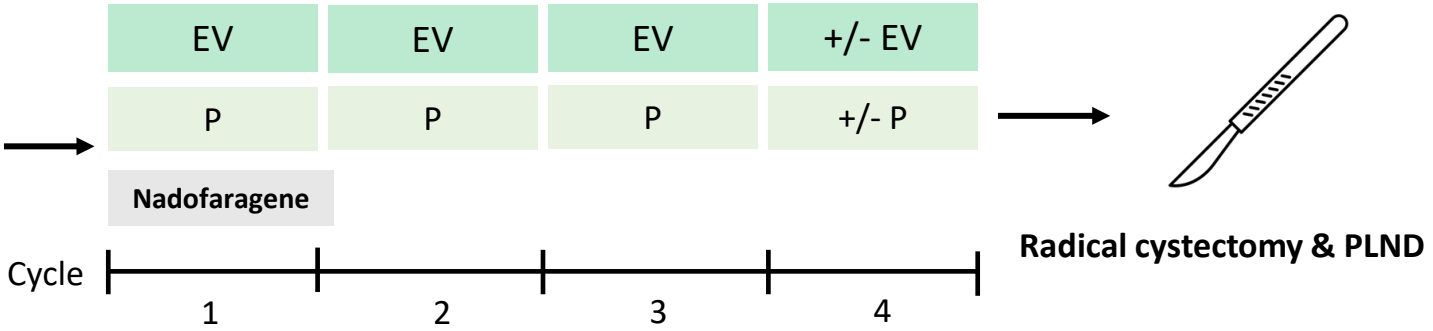




Can we combine systemic & intravesical therapy in MIBC? Pilot trial at UW/Fred Hutch: potential future implications for bladder preservation?

Population:

- Pts with MIBC who plan to undergo neoadjuvant EV/P -> radical cystectomy/PLND

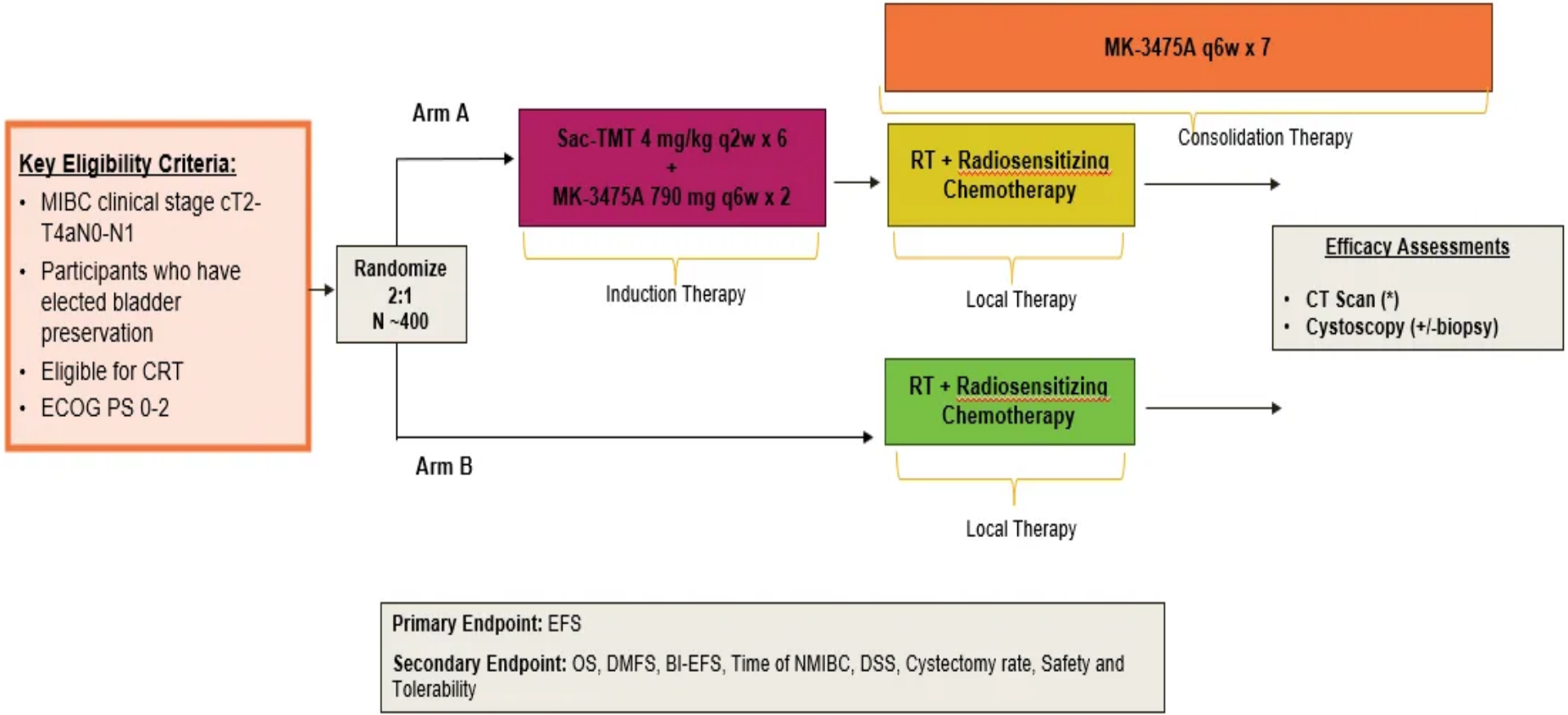


Feasibility: % **of pts who receive nadofaragene and complete ≥ 2 cycles of EV-P in the neoadjuvant period followed by radical cystectomy / PLND (≤ 10 weeks of last neoadjuvant dose)**

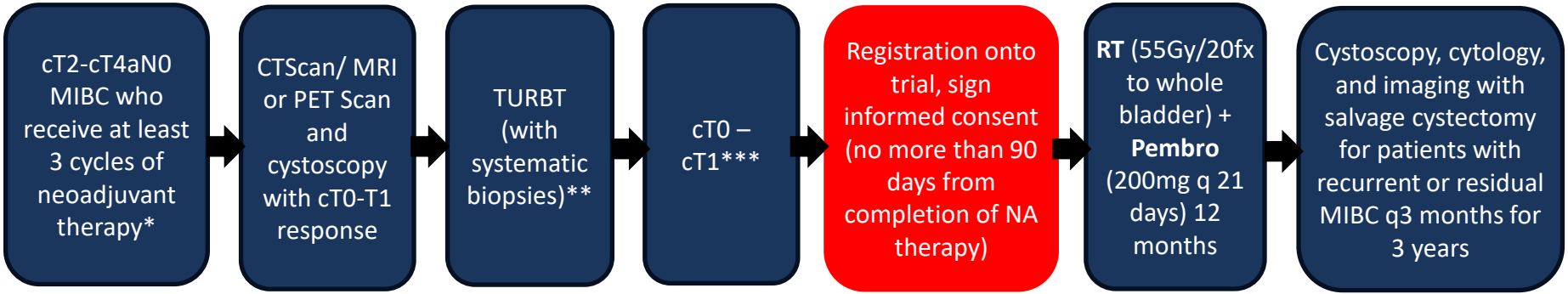
Safety (≥ G3 TRAEs; CTCAE v6.0)

Pathologic Response
-complete response (ypT0N0) on RC
-downstaging (≤ypT1N0) on RC

Trofuse-055: do we need neoadjuvant systemic therapy prior to chemo-RT as part of TMT?



Can we offer bladder preservation without cytotoxic radio-sensitizing chemotherapy after downstaging with systemic neoadjuvant therapy? S2427/BRIGHT trial



*Pts who receive NAC as the NAT must have ≥3 cycles of NCCN-approved regimen
**Pts found to have >T1 clinical stage on TURBT will proceed to SOC radical cystectomy
***Diffuse CIS excluded (>3 cm area of contiguous CIS or >3 separate locations of CIS on TURBT (dome/posterior/left/right/trigone)

S1806: Phase III Trial of Concurrent Chemoradiation With or Without Atezolizumab for Localized Muscle Invasive Bladder Cancer

-Cisplatin 35 mg/m2 weekly
-5-FU (500 mg/m2 x 5 days 1st & 4th week during RT) & mitomycin-C (day 1)
-Gemcitabine 27 mg/m2 twice per week

CRT (concurrent chemoradiation)

cT2-T4N0M0 stratified by:
- Chemotherapy regimen
- Radiation field
- Performance status
- Clinical stage

Randomized 1:1
475 patients

CRT+ Atezo x9

Primary endpoint
BIEFS*

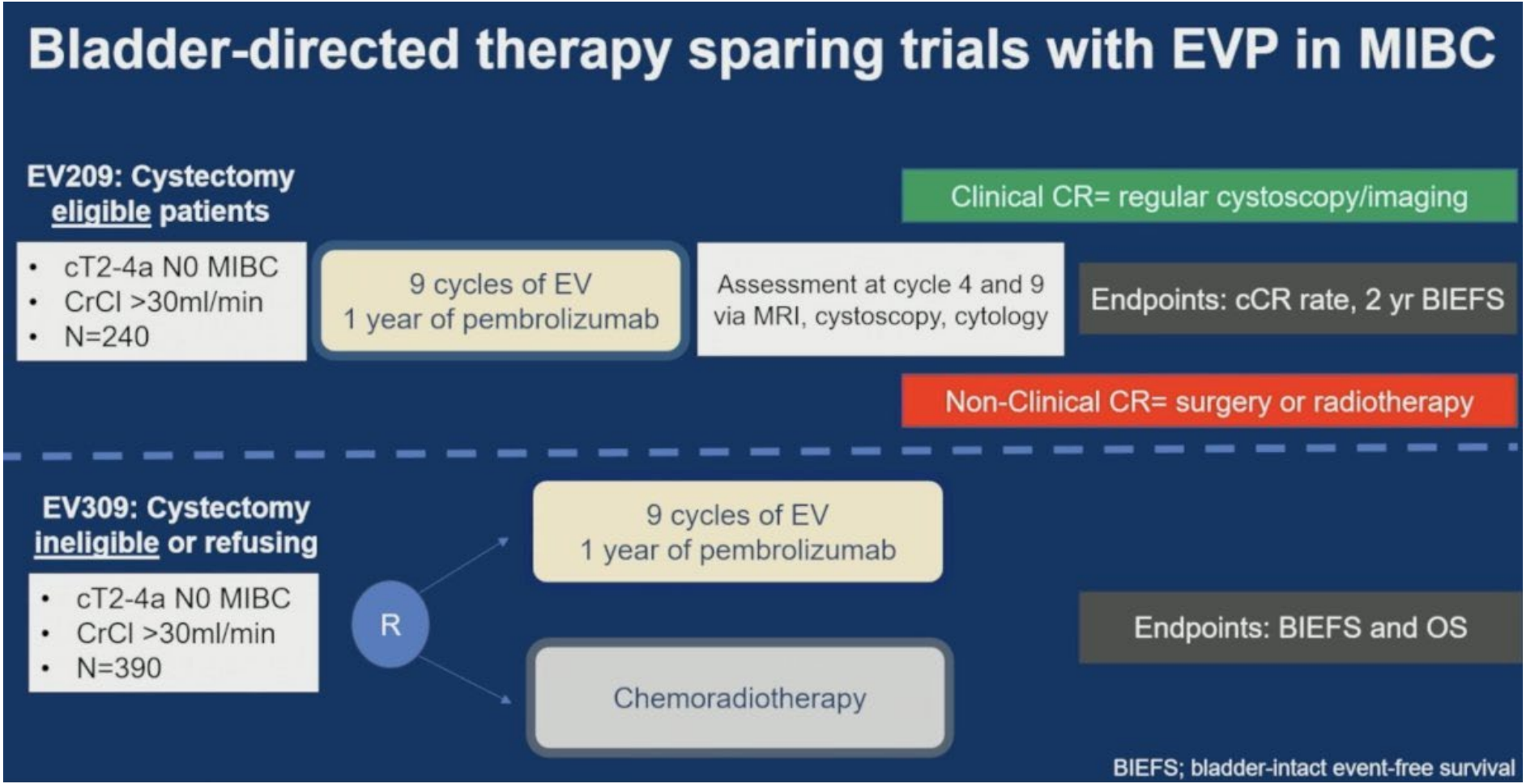
Secondary end point
- OS at 5 years
- Clinical response at 5 months
- DSS
- MFS
- Toxicity at 1 & 2 years
- NMIBC recurrence
- Cystectomy rate
- Global QoI

TM endpoints
- MRE 11
- DDR alterations
- Immune-related biomarkers

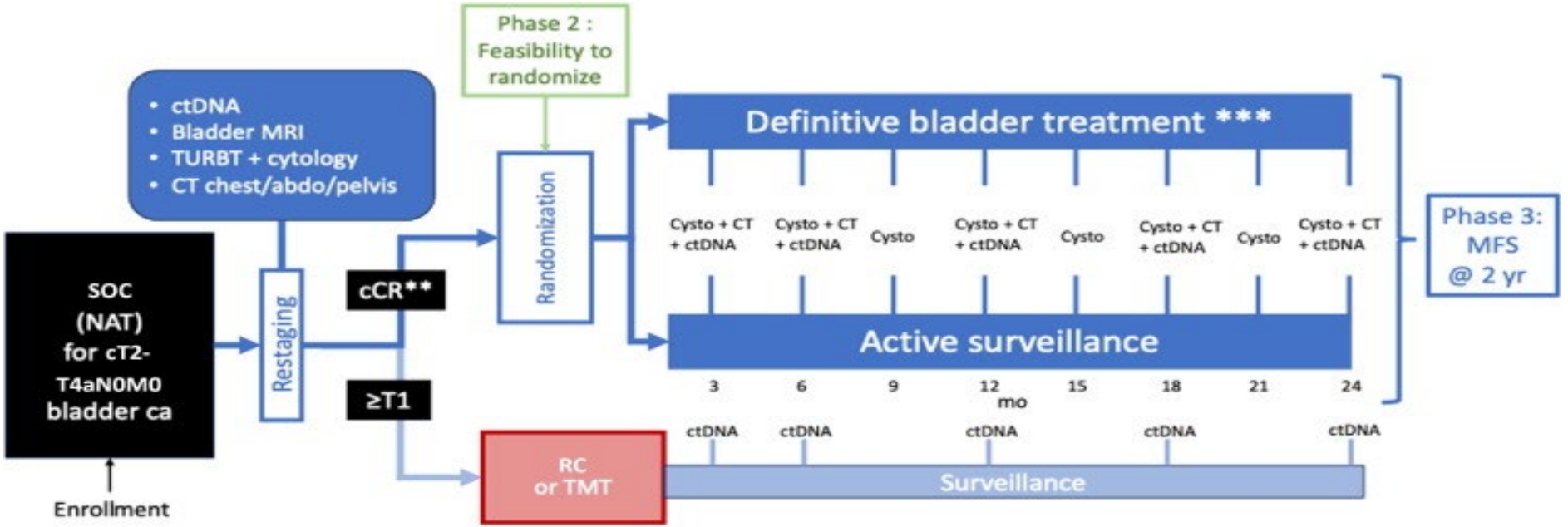
*BIEFS (bladder intact event-free survival): muscle-invasive recurrence in bladder, regional pelvic soft tissue or LN recurrence, distant mets, bladder cancer or toxicity-related death or cystectomy

Singh et al. *JCO* 2020;38(6_suppl):TPS586

Can we cure pts with MIBC using systemic therapy alone?



Can we cure pts with MIBC using systemic therapy alone? NEOBLAST trial



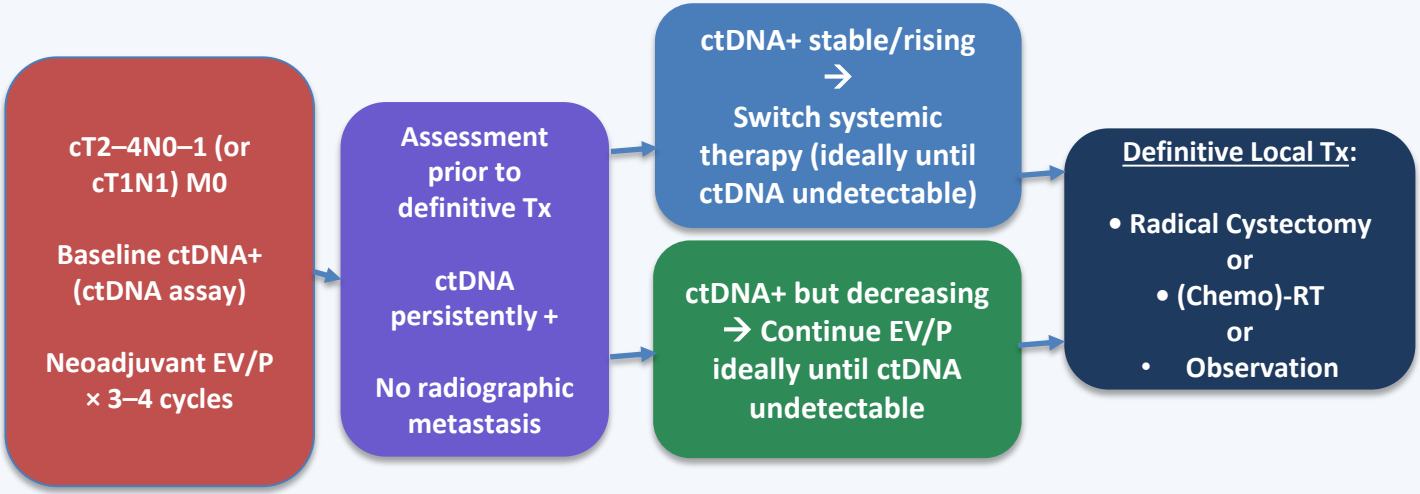
**Definition of cCR:
- Negative MRI (VI-RADS 0–2)
- Negative repeat TURBT (< cT1, no extensive CIS)
- Negative ctDNA
- No mets (negative conventional CT/MRI or PET-CT)

Exploratory: Negative utDNA

[a] NAT = any SOC regimen approved at time of enrollment (Cisplatin, EV, IO, etc.)
[b] Patient/investigator's choice; Radical cystectomy or TMT

Can we use ctDNA-guided treatment for MIBC?

- *Urothelial histology pure or mixed with any % subtype/variant if primary urothelial (excluding small cell histology)*
- *No other active or recent cancer that can interfere with study assessments*
- *Eligible for EV/P per provider assessment*



Suzanne Cole



Confidential slide

Goal: Avoid definitive local treatment in pts with high rate of recurrence/progression based on ctDNA+

Can we enroll pts with pure or predominant non-conventional urothelial histology in a large neoadjuvant therapy trial?

Inclusion Criteria

- **cT2-T4a, cN0-1, M0 (cT1N1 permitted)**
- **Radical cystectomy candidate**
- **No active autoimmune disease / no current/recent systemic immunosuppressive therapy**
- **Predominant subtype histology (pure or >50% subtype) on TURBT**

EV/P x 4

Endpoints

Primary: Cohort-specific pathologic complete response pCR (*ypT0N0*)

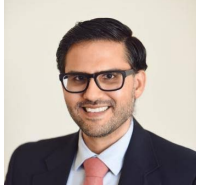
Secondary (cohort specific):
Event-free survival
Overall survival
ctDNA clearance
Safety (all pts)

Exploratory:
Translational studies with tissue, blood, urine

Seven Different cohorts (capped at 32/arm):

- **UC with squamous features**
- **Pure squamous**
- **UC with glandular features**
- **Pure adenocarcinoma**
- **Plasmacytoid**
- **Sarcomatoid**
- **Micropapillary**

Ali Khaki



Adjuvant therapy at the discretion of investigator
(will not affect primary endpoint of ypT0N0)

Confidential slide

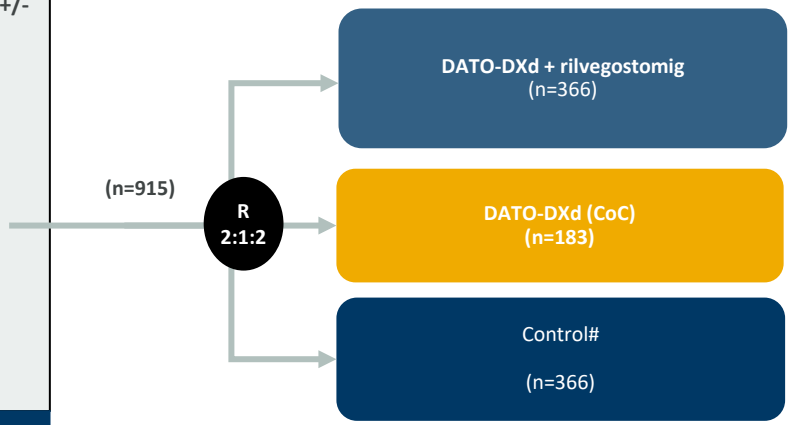
Can we switch therapy in the adjuvant setting based on path stage? TROPION-Urothelial04

Core

Patient population

- Histologically confirmed MIUC completed neoadjuvant chemo+/-IO or naïve to neoadjuvant & post-radical surgery
- Randomization within 4 months of radical surgery (must have recovered from all surgical complications <G1)
- High risk
  - ≥ypT2 or ypTanyN+ with prior neoadjuvant therapy
  - ≥ pT3 or pTanyN+ (naïve)
- Include UTUC

Stratification factors
- Prior neoadjuvant therapy: prior IO vs IO-naïve
- Pathological stage: T2N0 vs >T2 or N+
- Tumor location: Bladder vs upper tract



Endpoints

Primary
- DFS

Secondary endpoints
- OS
- DSS
- Distant MFS
- NUT-RFS
- Safety
- PRO
- PK & immunogenicity

Exploratory endpoints
- ctDNA

Treatment dose and duration

Dato-DXd	6mg/kg IV Q3W for 9 cycles (~ 6m), can be extended based on investigator assessment of tolerability up to 1y
Rilve	750 mg IV Q3W 17 cycles or up to 1 yr whichever occurs first
Nivo (SOC)	240 mg IV Q2W OR 480 mg IV Q4W up to 1 yr
Durva (SOC) per local approval	1500 mg IV Q4W up to 8 cycles
EV + pembro (P) (SOC) per local approval	EV 1.25 mg/kg D1, D8 Q3W 6 cycles +P 200 mg IV Q3W 14 cycles

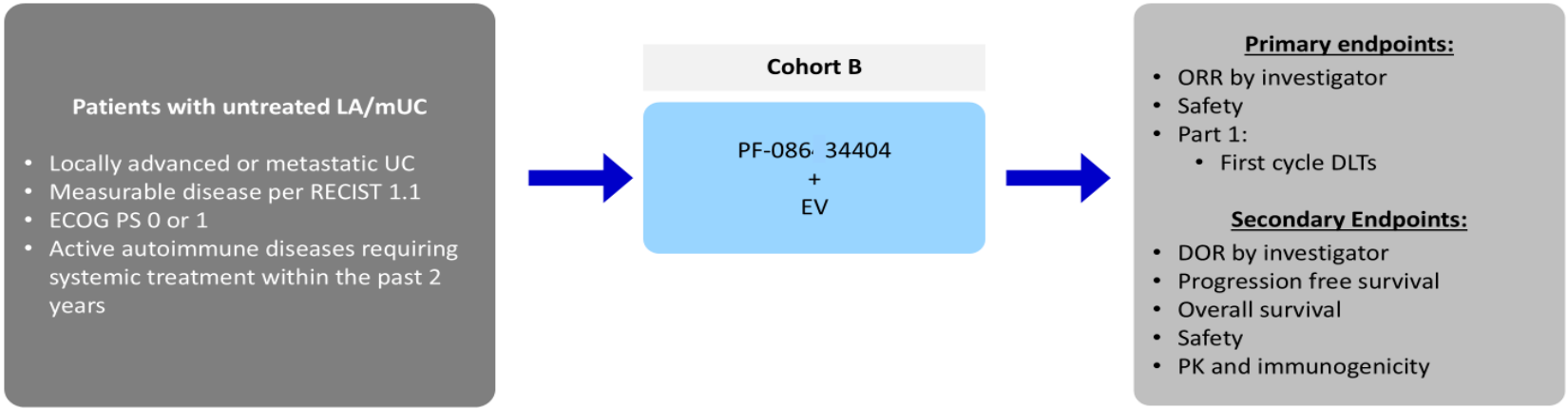
DFS=disease-free survival; DSS=disease-specific survival; MFS=metastatic free survival; NUTRFS=non-urothelial tract recurrence-free survival; OS=overall survival; PRO=patient reported outcomes

#Control arm choice based on neoadjuvant treatment received & local approvals / reimbursement of regimen (EV/P or durvalumab or nivolumab)

Future of metastatic UC: is there a role for PD-1/VEGF bispecific?

Symbiotic-GU-06 Cohort B: Phase 1/2 Study Design in Previously Untreated Locally Advanced/Metastatic Urothelial Cancer (NCT07421700)

Recruiting



DOR: Duration of response; **ECOG PS:** Eastern Cooperative Oncology Group performance status; **EV:** Enfortumab vedotin;; **LA:** Locally advanced; **mUC:** Metastatic urothelial cancer; **ORR:** Objective response rate; **PK:** Pharmacokinetics; **RECIST v1.1**: Response evaluation criteria in solid tumors 1.1; **UC:** Urothelial cancer
https://clinicaltrials.gov/study/NCT07421700. Accessed February 19, 2026.

Symbiotic-GU-06 Cohort A: Phase 1/2 Design in Previously Treated Locally Advanced/Metastatic Urothelial Cancer (NCT07421700)

Recruiting

Previously treated patients with LA/mUC

- Locally advanced or metastatic UC
- Measurable disease per RECIST 1.1
- ECOG PS 0-1
- No active autoimmune disease requiring systemic treatment within past 2 years

Cohort A

PF-08634404 monotherapy

Primary Endpoints:

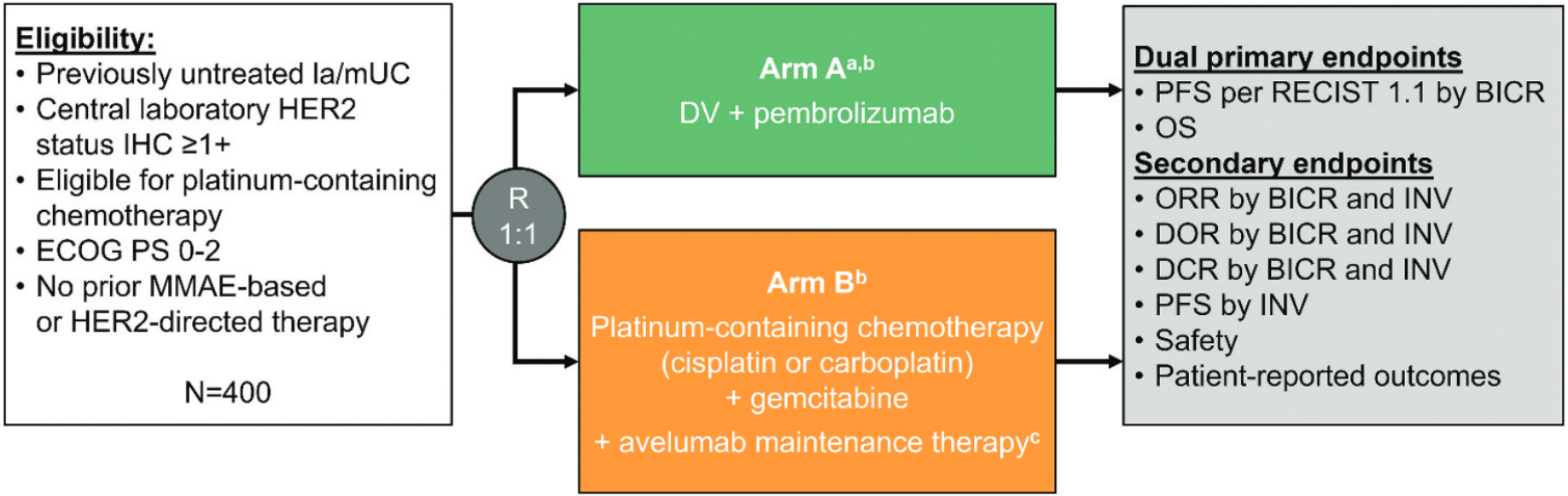
- ORR by investigator
- TEAEs & SAEs

Secondary Endpoints:

- DOR by investigator
- Safety
- Progression-free survival
- Overall survival
- PK & immunogenicity

DOR: Duration of response; **ECOG PS:** Eastern Cooperative Oncology Group performance status; **IO:** Immunotherapy; **LA:** Locally advanced; **mUC:** Metastatic urothelial cancer; **ORR:** Objective response rate; **PK:** Pharmacokinetics; **PRO:** Patient reported outcome; **Q3W:** Every 3 weeks; **RECIST v1.1**: Response evaluation criteria in solid tumors 1.1; **SAE**: serious adverse event; **TEAE**: treatment-emergent adverse event; **UC:** Urothelial cancer
https://clinicaltrials.gov/study/NCT07421700. Accessed June 19, 2026.

SGNDV-001: Phase 3 DV/P vs Gem/Platinum->Ave



Powles Future Oncol. 2025;21(21):2705-12

Is there a role for triplet therapy in metastatic UC?

16:00 - 17:30 Mini Oral session 1 : GU tumours, renal & urothelial

CHAIRS: LAURENCE ALBIGES, SHILPA GUPTA, STEFANIE ZSCHÄBITZ

Conclusions

Data is from GU-ASCO 2025 presentation and will be updated in 2 weeks

- LY3866288 200 mg BID was selected as the RP2D
- LY3866288 demonstrates
  - Promising preliminary efficacy in patients with *FGFR3*-altered metastatic urothelial carcinoma treated with ≥200 mg BID
    - 41% (16/39) of patients with an activating *FGFR3* mutation or fusion had a confirmed response with a 90% DCR
    - 50% (6/12) of patients who previously received an FGFR inhibitor had a confirmed response
  - Favorable safety profile
    - Diarrhea was the most common TEAE and was predominantly low grade and manageable
    - High grade FGFR-1, 2, and 4 mediated AEs (e.g. nail/skin disorders and ocular toxicity) typical of pan-FGFR inhibitors were very rare
- XX% (xx/5) had PRs in the B5 cohort evaluating LY3866388 in combination with enfortumab vedotin and pembrolizumab
- FORAGER-2, a global, registrational study investigating vepugratinib in combination with enfortumab vedotin and pembrolizumab in 1L mUC will be enrolling (NCT#####)

DRAFT DATA

Alexandra Drakaki, MD.
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Alexandra Drakaki

Phase I study of LY3866288, a potent, highly isoform-selective FGFR3 inhibitor in FGFR3-altered advanced solid tumors (FORAGER-1): Dose optimization

KARLSRUHE AUDITORIUM - HALL 5.2

Is there a role for triplet therapy in metastatic UC?

TROPHY-U-01 cohort 7: ESMO'26: Sweis, Grivas et al.

Histologically documented, previously untreated, locally advanced unresectable or metastatic urothelial cancer:

- Measurable disease by CT/MRI per RECIST 1.1
- Provision of archival tumor tissue or fresh biopsy
- No prior systemic therapy for locally advanced or metastatic UC
- ECOG PS 0-1

SG + EV + ZIM
Safety lead-in

SG RP2D + EV + ZIM
Stage 1 expansion

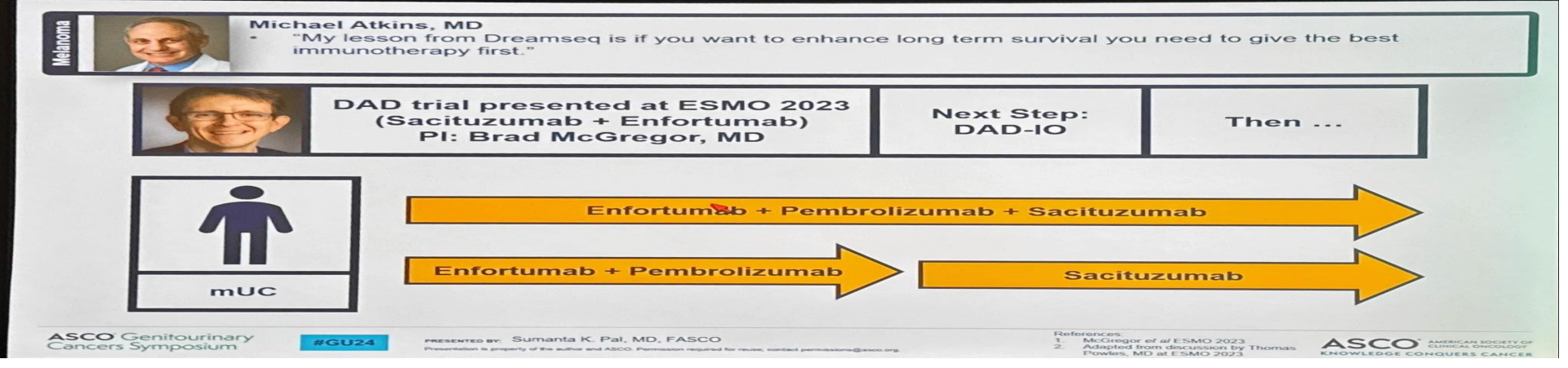
Endpoints

Primary

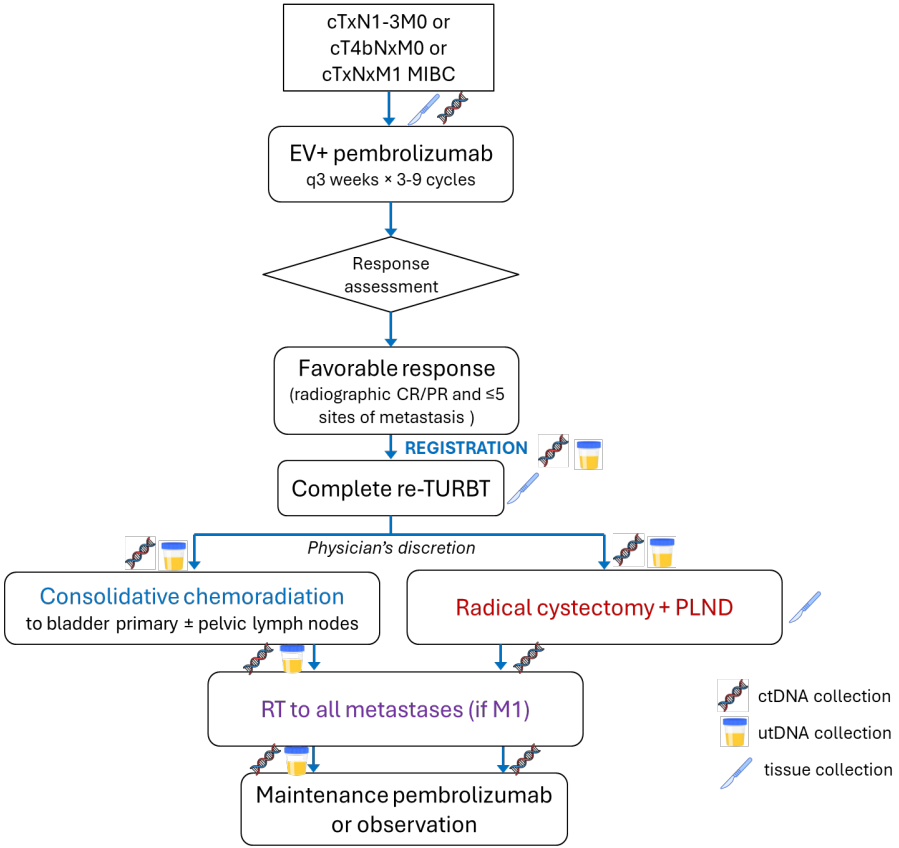
- **Safety / tolerability**
- **Confirmed ORR (INV, RECIST 1.1)**

Secondary[d]

- **DOR, CBR, PFS (INV, RECIST 1.1)**
- **OS**



Is there a role for consolidative radiation or cystectomy after response to EV/P? REINFORCE (phase I/II pilot feasibility trial)



Key inclusion criteria:

- Histo-pathologically confirmed cTxN1-3M0 or cT4bNxM0 or cTxNxM1 MIBC; If M1, pts need to have ≤5 sites of metastasis after EV-P
- Candidates for RT
- All sites of metastasis amenable to SBRT
- ECOG PS 0-2
- Adequate organ function

Key exclusion criteria:

- Prior RT to pelvis or overlap of current proposed RT field with prior RT field precluding delivery of full-dose RT
- Intracranial metastasis
- Any small cell, >50% plasmacytoid or sarcomatoid histology

Primary endpoint:
Feasibility/completion rate of protocol-defined treatment

Secondary endpoints:

- 1-year PFS
- ≥G3 AEs attributed to chemoRT or MDT
- QOL

Exploratory endpoints:

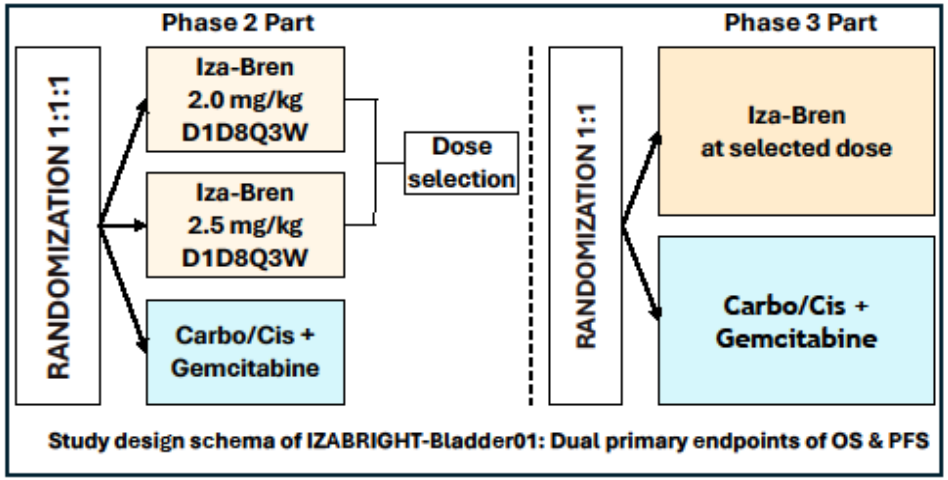
- Role of ctDNA & utDNA as MRD biomarkers, longitudinal dynamics
- Change in tumor clonal heterogeneity over time

Single institutional trial at UW/Fred Hutch (~20 pts)

IZABRIGHT-Bladder01: EGFRxHER3 bispecific ADC for IO-experienced mUC

IZABRIGHT-Bladder01: ESSENTIAL DETAILS

DESIGN	Global randomized Phase 2/3 trial (n=470) • Phase 2 for dose selection (n=90) • Confirmatory Phase 3 (n=380)
INDICATION	• mUC which has progressed on or after anti-PD(L)-1 in locally advanced or metastatic setting, either in combination with or sequential to at least one additional systemic therapy (e.g., PBC or ADC) • Maximum of 2 prior lines of therapy
INTERVENTION	IV Iza-Bren D1D8Q3W (EGFRxHER3 bispecific ADC)
CONTROL	Platinum of choice (Cis or Carbo) + Gemcitabine
ENROLLMENT	October 2025 – October 2028



Study design schema of IZABRIGHT-Bladder01: Dual primary endpoints of OS & PFS

IZABRIGHT-Bladder01: CLINICAL OPPORTUNITY FOR PARTICIPANTS AND SITES

BROAD PATIENT POPULATION	• Broad eligibility: 1L- 3L mUC with disease progression on or after anti-PD(L)-1-based treatment in either the locally advanced or metastatic setting
FAVOURABLE CONTROL ARM	• Control arm of study is standard of care PBC: (Cis or Carbo) + Gemcitabine
CONVINCING EARLY EFFICACY DATA	• cORR was 37.9% in patients with 2L-3L mUC following prior anti-PD(L)-1-based treatment[1] • Median duration of response of 11.3 months[1]
DIFFERENTIATED ADC SAFETY PROFILE	• Very low risk of ILD with Iza-Bren (0.1% G3 ILD AE rate observed in solid tumor trials (n=1,416))[1]

1 IZABRIGHT-Bladder01 Stable Draft Protocol (pages 31 and 39)

Confidential

TroFuse-031 phase 3 trial

Eligibility
- Pts must have received prior platinum chemotherapy, anti-PD-(L)1 therapy & EV, either in combination or as monotherapy
- Pts must have progressed to the immediately prior line of therapy
- ECOG PS 0-1

R 1:1

N=590

Sac-TMT 4 mg/kg Q2W

until PD or unacceptable toxicity

Investigator choice of chemotherapy (docetaxel 75 mg/m2, paclitaxel 175/m2, or vinflunine 320 mg/m2) Q3W until PD or unacceptable toxicity

Stratification factors:
- Presence of liver metastases (yes vs no)
- Number of prior lines (1 vs 2 lines)
- Geographic region (North America vs Western Europe vs ROW)

Enrollment caps:
- Pts with liver metastasis capped at ~20%
- Pts receiving vinflunine on control arm capped at ~35%
- Pts without prior EV/P capped at ~60%

Primary Endpoint: OS
Key Secondary Endpoints: PFS by investigator, ORR by investigator, safety

EA8231 phase 3 trial: role for ICI rechallenge?

N=320 **1:1 randomization**

Metastatic or locally advanced / unresectable UC

1. ECOG PS 0-2
2. Anti-PD(L)1 therapy required in any disease setting AND no tumor progression on prior anti-PD(L)1 therapy within 12 weeks of prior ICI initiation
3. Prior exposure to EV unless contraindicated
4. ≥1 lines of systemic therapy for advanced disease [*FGFR3*-altered tumors must have received FGFR inhibitor unless contraindicated]

Stratification Factors:

- ❑ Bellmunt score (0-1 vs 2)
- ❑ Prior lines of therapy (≤2 lines vs >2 lines)
- ❑ Prior exposure to platinum-based chemo (*yes* vs *no prior exposure & platinum-eligible per physician discretion* vs *no prior exposure & platinum-ineligible per physician discretion*)
- ❑ Duration of prior anti PD-(L)1 therapy (≤6 vs >6 months)

ARM A: TPC (Therapy per Physician Choice) -SOC

- ❑ Platinum-based doublet [up to 6 cycles]
  - ❑ Carboplatin + Gemcitabine
  - ❑ Cisplatin + Gemcitabine
- ❑ Docetaxel [treatment until progression or unacceptable toxicity]
- ❑ Paclitaxel [treatment until progression or unacceptable toxicity]

ARM B: Sacituzumab (SG) + Pembrolizumab

- ❑ SG 10 mg/kg on Days 1/8 + Pembrolizumab 200mg Day 1 (q21-day cycle) [SG until progression or unacceptable toxicity; Pembrolizumab up to 35 cycles]

G-CSF prophylaxis strongly recommended with SG

Chair: Monika Joshi, MD, MRCP
Co-chair: Petros Grivas, MD, PhD, FASCO

Primary endpoint:
Overall survival

Secondary endpoints:

1. PFS
2. ORR
3. Clinical benefit rate (CR/PR/SD)
4. QoL/PRO
5. Duration of Tx
6. Safety/toxicity

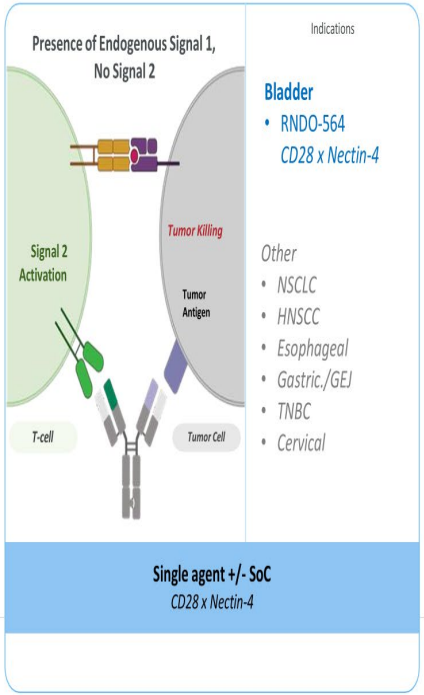
Correlative biomarkers:

1. NGS: DNA/RNA tumor tissue
2. TROP2 IHC
3. PD-L1 IHC
4. TMB/MSI status
5. ctDNA in blood
6. Urine biomarker

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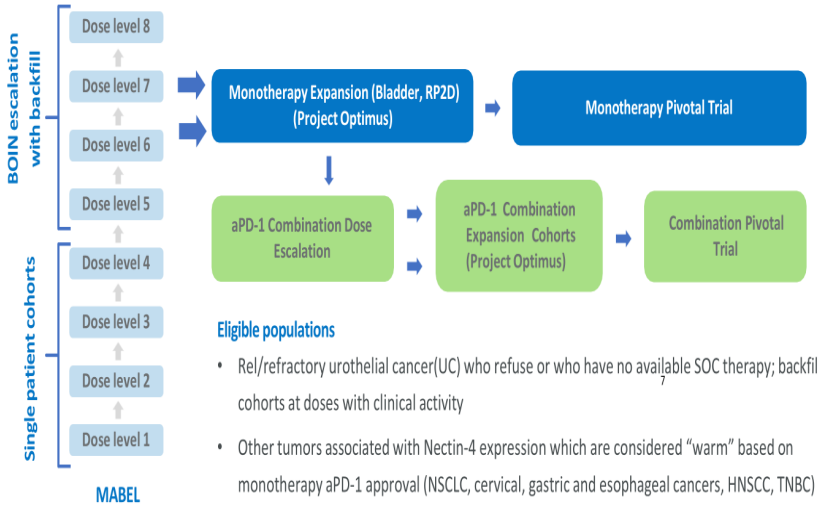
Is there a role for co-stimulatory bispecific antibodies?

RNDO-564 hypothesis: Nectin-4 targeted CD28 costimulation will be active in immune-primed tumors



RNDO-564 Phase 1/1b study schema

An Open-Label, Multicenter, Phase 1/1b Study of RNDO-564 as Monotherapy and in Combination with Pembrolizumab in Adult Participants with Relapsed/Refractory Locally Advanced or Metastatic Urothelial Cancer and other Tumors Associated with Nectin-4 Expression



Eligible populations

- Rel/refractory urothelial cancer(UC) who refuse or who have no available SOC therapy; backfill cohorts at doses with clinical activity
- Other tumors associated with Nectin-4 expression which are considered "warm" based on monotherapy aPD-1 approval (NSCLC, cervical, gastric and esophageal cancers, HNSCC, TNBC)
- Expansion cohorts for pts with non-UC indications planned, based on emerging data

The future is bright…

- Bispecific ADCs (many targets and/or many payloads?)
- Bispecific T cell engagers & CAR-T cells (requires infrastructure)
- Vaccines (“*off-the-shelf*/shared antigens & personalized/neoantigens)
- Radioligands, e.g. Nectin4-targeting
- Targeted therapies based on additional targets/biomarkers
- Multi-omics drug development & optimal patient selection
- “Digital twins” / AI-based technology / germline & somatic testing
- Precision oncology pathways in EMR / virtual tumor boards
- We need to eliminate disparities & ensure equitable access to care!

What about using AI?

Prediction ≠ Clinical Utility

- Retrospective/cohort models ✓
- External validation emerging
- Prospective implementation ?
- AI-guided outcome trials ✕

The future is not only about better prediction; it is about better informed/shared decisions

✓ Earlier prediction / better prognosis

✓ Personalize surveillance/therapy

✓ Integrate multimodal data

✓ Prove clinical benefit & utility

Building Trust: What We Actually Need

Four pillars for trustworthy AI in cardio-oncology

1 BETTER EVIDENCE

- Prospective + randomized validation
- Patient-centered outcomes

2 LIFECYCLE MONITORING

- Pre-deployment evaluation
- Real-world monitoring
- Recalibration and updates

3 TRANSPARENCY

- Training data
- Limitations
- Intended population

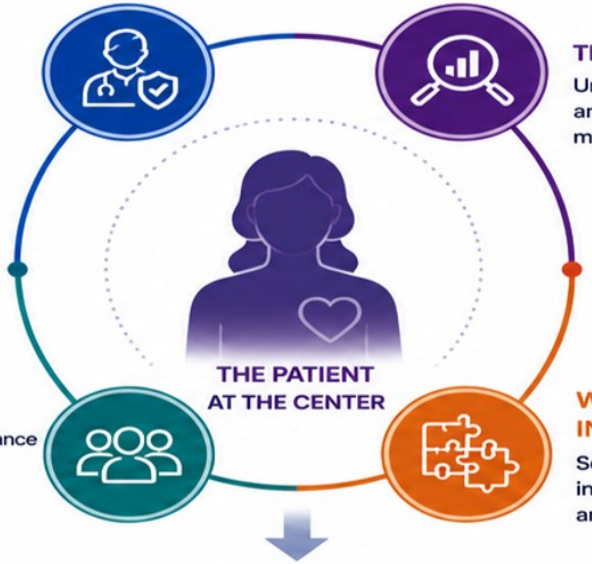
4 EQUITY

- Representative datasets
- Subgroup performance reporting

Trust is built longitudinally—not at deployment.

Trustworthy AI → Better Care

Human-centered by design. Built for patients.



TRUSTWORTHY AI

BETTER CARE • BETTER DECISIONS • BETTER OUTCOMES

The future is not just intelligent—it must be trustworthy.

What does it take to **trust** AI enough to act on it?



Today: promising prediction

Tomorrow: trustworthy clinical implementation

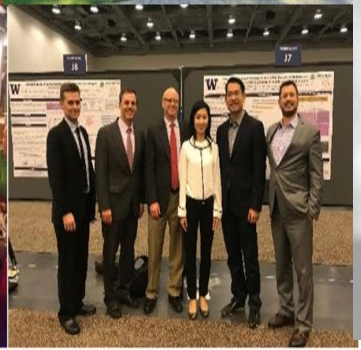
THANK YOU ☺

Patient & families!

Collaborators, sponsors, institutions, foundations, colleagues, research, admin & clinical staff: TEAMS! @PGrivasMDPhD pgrivasmdphd












As you set out for Ithaka
hope the voyage is a long one,
full of adventure, full of discovery.
Laistrygonians and Cyclops,
angry Poseidon – don't be afraid of them:
you'll never find things like that on your way
as long as you keep your thoughts raised high,
as long as a rare excitement
stirs your spirit and your body.