3rd Annual Southern California Genitourinary Cancer Research Forum

Panel: Bladder Studies (NMIBC; MIBC; Metastatic, 1st; Metastatic; Salvage)

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Speakers:

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This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

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- *No relevant financial relationships with any ineligible companies.*

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

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The off-label/investigational use of Nexus ADC for Nectin-4, Vepugratinib, Relatlimab/Nivolumab (MODERN trial), Dato-DXD.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Making sure underserved populations are particularly addressed.*
- *Disparities in access to care.*
- *Responses in different populations.*
- *Potential health disparities in delivery of bladder cancer care.*
- *The care of women with bladder cancer.*
- *The lack of understanding of sexual function in women following treatment for bladder cancer and the barriers in discussing this with this patient population.*

Non-Muscle Invasive Bladder Cancer

Case presentation

A 74-year-old man presents with **painless gross hematuria**. Cystoscopy and TURBT reveal **a 4-cm papillary bladder tumor**, with final pathology demonstrating **high-grade T1 urothelial carcinoma**. Given **high-risk NMIBC**, further risk-adapted clinical trial options are considered.

- High-risk non-muscle invasive bladder cancer, treatment naïve.

Keck Medicine of USC

ResQ132EX: Expanded Access use of Recombinant Bacillus Calmette-Guerin in Non-Muscle Invasive Bladder Cancer study.

Recombinant BCG (rBCG) Expanded Access Program (EAP)

NCT06810141

Promising rBCG Clinical Trials – SAKK 06/14 Phase 2

STUDY DESIGN

- Multicenter, open-label, single arm, Phase II European study investigating **intravesical VPM1002BC (rBCG) in patients with recurrent IR or HR NMIBC after conventional BCG therapy**
- Enrolled n=40 patients with recurrent HG NMIBC after ≥5 BCG instillations (induction) ± BCG maintenance (n=27 any CIS)
- Primary endpoint: Recurrence Free Rate (RFR) @ 60 wks (1 yr)
  - Positive cytology or cystoscopy required histological proof of recurrence
- rMBCG dose: 1-19.2x10^8 CFU/50mL saline solution
- Dosing schedule: 6 weekly instillations of VPM1002BC followed by 3 weekly instillations at 3, 6, and 12 months

RESULTS

- Safety: No ≥Grade 4 AEs, 14.3% Grade 1 TRAEs, 54.8% Grade 2 TRAEs, 4.8% Grade 3 TRAEs
- Tolerability: Well-tolerated; 95% received >4 instillations during induct
- Efficacy: 49% 1 yr RFR, 47% 2 yr RFR, 44% 3 yr RFR (met primary endpoint with stable durability)
  - Progression Free Rate: 77% @ 1, 2, and 3 yrs
  - 56% CIS patients had CR @ 12 weeks with 1.1 yr mDoR (upper bound not reach
  - OS Rate: 93% @ 1 yr, 78% @ 2 yrs & 3 yrs

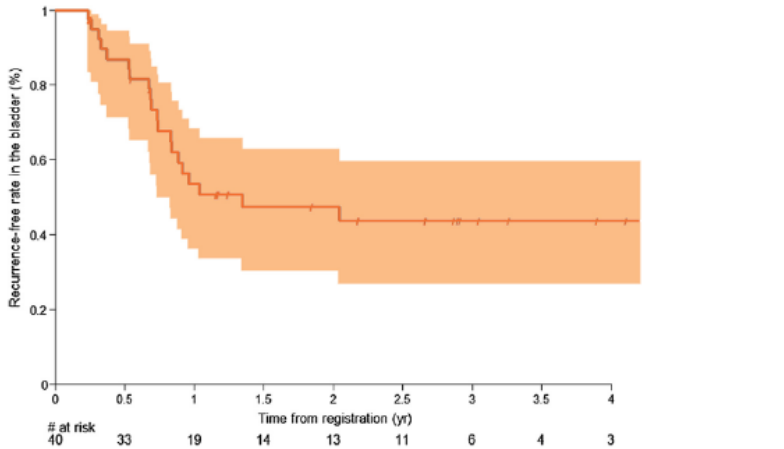


Fig. 2 – Kaplan-Meier plot for time to recurrence in the bladder for the full analysis set (median follow-up 2.9 yr, 95% confidence interval 2.7–3.3).

Table 5 – Treatment-associated adverse events in the treatment phase

Adverse event	Patients, *n* (%)		
	Grade 1	Grade 2	Grade 3
Vertigo		1 (2.4)	
Gastrointestinal disorders	2 (4.8)		
Fatigue	2 (4.8)	3 (7.1)	
Fever	2 (4.8)	1 (2.4)	
Frequency, urgency	7 (16.7)	5 (11.9)	
Malaise		1 (2.4)	
BCG-induced systemic inflammatory reaction		1 (2.4)	
Cold		1 (2.4)	
Genitourinary infection		14 (33.3)	2 (4.8)
Alanine aminotransferase increased		1 (2.4)	
Neuralgia		1 (2.4)	
Haematuria	2 (4.8)		
Macrohaematuria	1 (2.4)		
Urinary retention	1 (2.4)		
Urinary tract obstruction	1 (2.4)	1 (2.4)	
Urinary tract pain	6 (14.3)	1 (2.4)	
Vaginal pain		1 (2.4)	
Skin affection	3 (7.1)	2 (4.8)	
Thromboembolic event		1 (2.4)	

CFU = Colony Forming Units, CR
Complete Response, mDoR = Me
Duration of Response; OS = Over
Survival, IR = Intermediate Risk,
High Risk

Source: Rentsch et al., 2022, European Urology Oncology

Key Protocol Instructions

Keck Medicine of USC

2.1. Study Design

All treatment decisions, and all post treatment follow-up, will be made according to the institutions' standard of care.

3.1.1. Inclusion Criteria and Contraindications

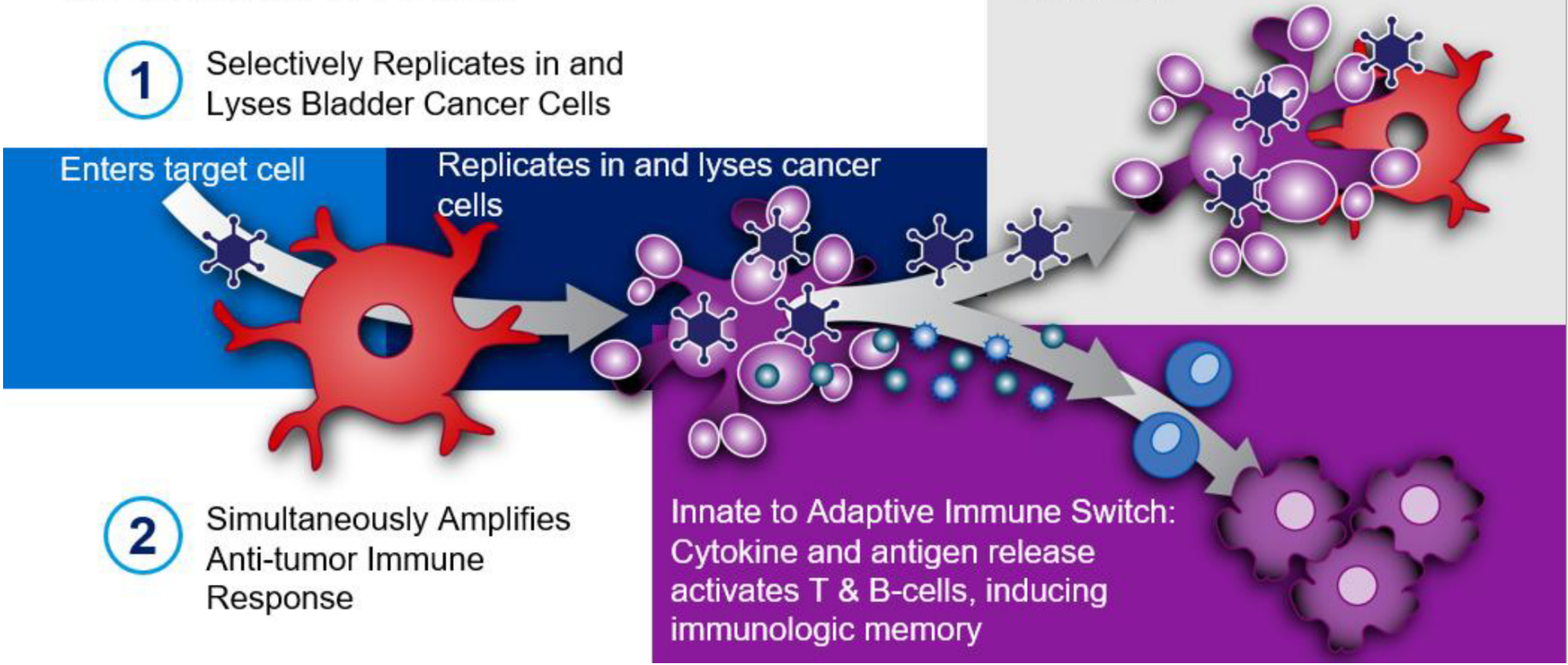
Participants must meet the inclusion criteria and contraindications determined by the standards of their institution per the TICE BCG label. In BCG naïve subjects with NMIBC, enrollment should occur only if TICE BCG is unavailable.

5.1. Procedures and Evaluations

The procedures and evaluations to be performed in this study will be according to the institution's standard of care per the standard of care of approved TICE BCG.

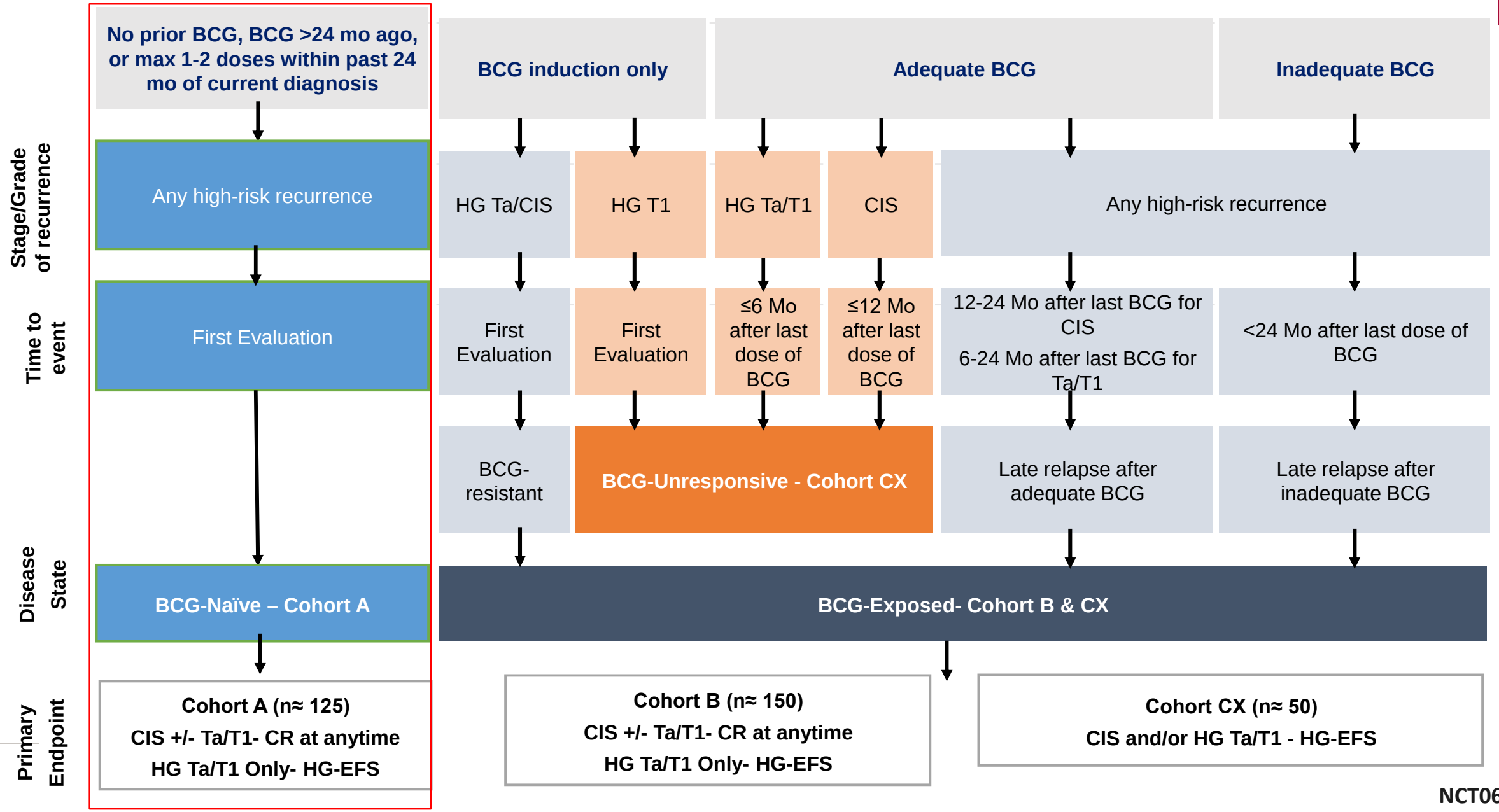
Oncolytic Immunotherapy: Cretostimogene Grenadenorepvec's Dual Mechanism of Action

1 Selectively Replicates in and Lyses Bladder Cancer Cells



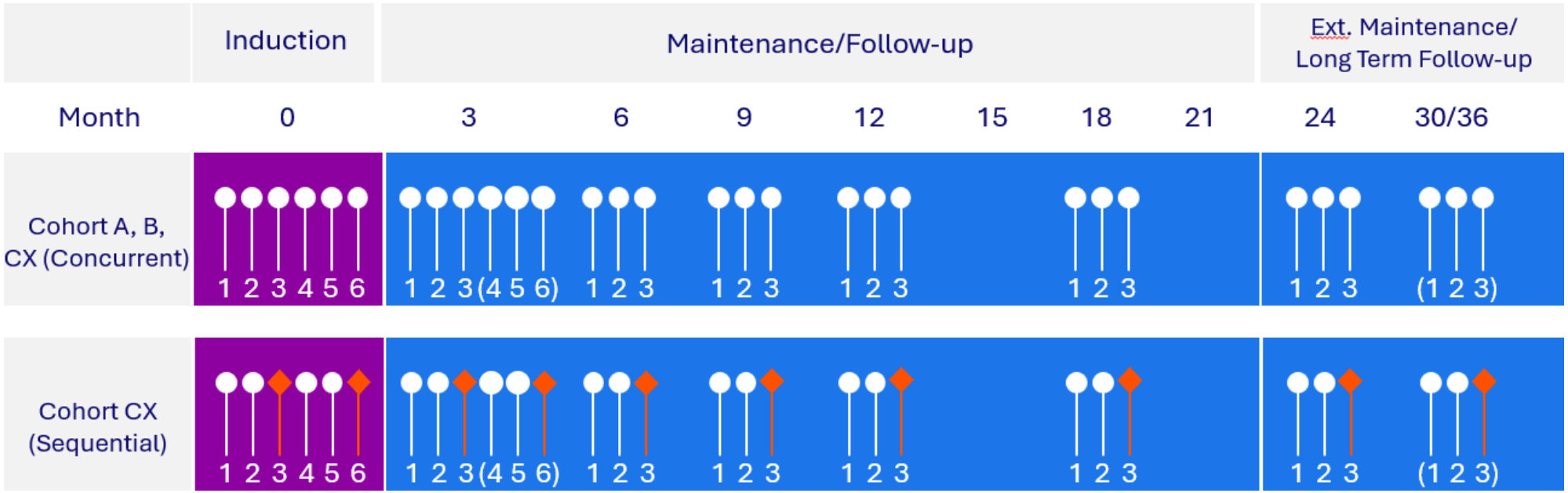
2 Simultaneously Amplifies Anti-tumor Immune Response

CORE-008: Phase 2, Multi-Cohort Trial in HR NMIBC



NCT06567743

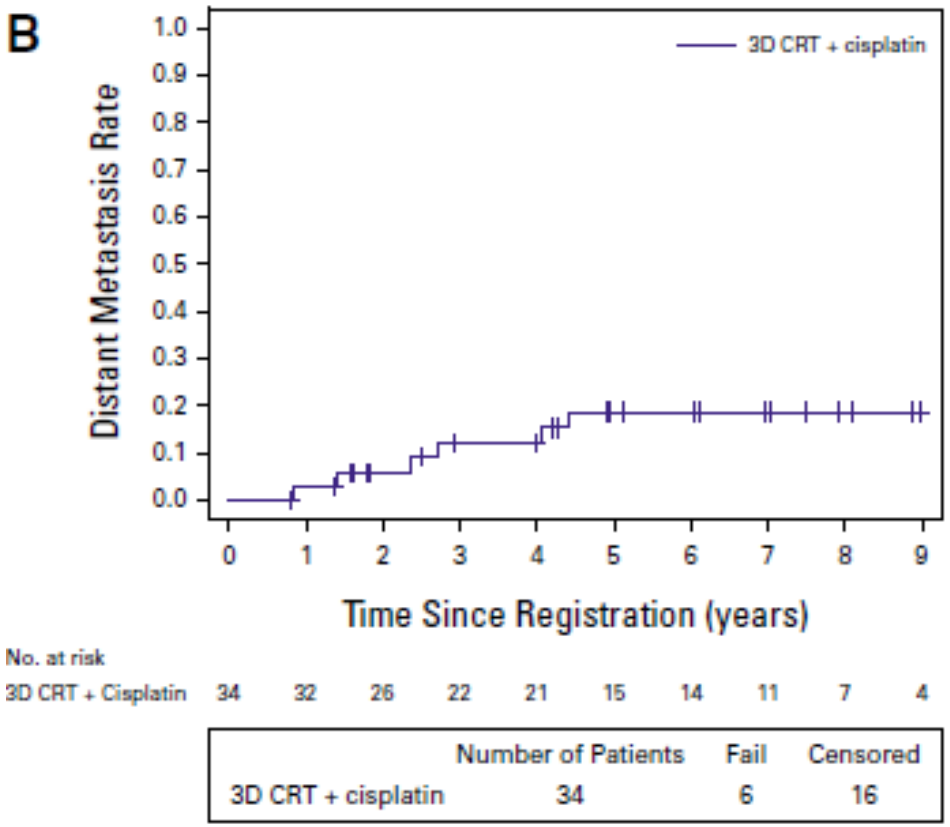
Treatment & Assessment Schedule



- Re-induction allowed for patients with HG Ta and/or CIS at Month 3
- Randomized 1:1 (Original 5-step [Arm 1] or Optimized 2-step [Arm 2] administration)
- Cystoscopy & Cytology every 3 months with mandatory mapping biopsies at 12 Mo
- CT/MRU every 6 months
- Treatment is optional in Year 3

NRG GU014: PARRC

RTOG 0926



NRG-GU014

Schema

Cystectomy Recommended High Risk T1 Urothelial Carcinoma

↓

STRATIFY

- disease history (de novo vs. recurrent)
- histology (urothelial or mixed vs. non-urothelial)

RANDOMIZE*

Arm 1	**Arm 2**
Bladder-directed radiotherapy + Concurrent Chemotherapy**	Bladder-directed radiotherapy + Pembrolizumab x 9 cycles

*Randomization is 1:1

** Chemotherapy is physician's choice regimens below:

- Cisplatin
- Gemcitabine
- Mitomycin-C
- 5-Fluorouracil

NCT06770582

3-year freedom from cystectomy 88%

Case presentation

A 68-year-old man with a history of **high-grade NMIBC previously treated with BCG** presents with persistent urinary urgency and positive urine cytology. Repeat cystoscopy and TURBT **reveal CIS**, without evidence of muscle-invasive disease. He is interested in exploring bladder-preserving clinical trial options.

- High-grade non-muscle invasive bladder cancer, BCG refractory

ABLE-22: Safety and efficacy evaluation of nadofaragene firadenovec-vncg alone or in combination with chemotherapy or immunotherapy — a randomized, open-label, phase 2 study

Siamak Daneshmand,[1] Stephen Boorjian,[2] Joshua Meeks,[3] Trinity Bivalacqua,[4] Yair Lotan,[5] Wassim Kassouf,[6] Girish Kulkarni,[7] Paolo Gontero,[8] Peter Albers,[9] Jørn S. Jakobsen,[10] Kristian Juul[10]

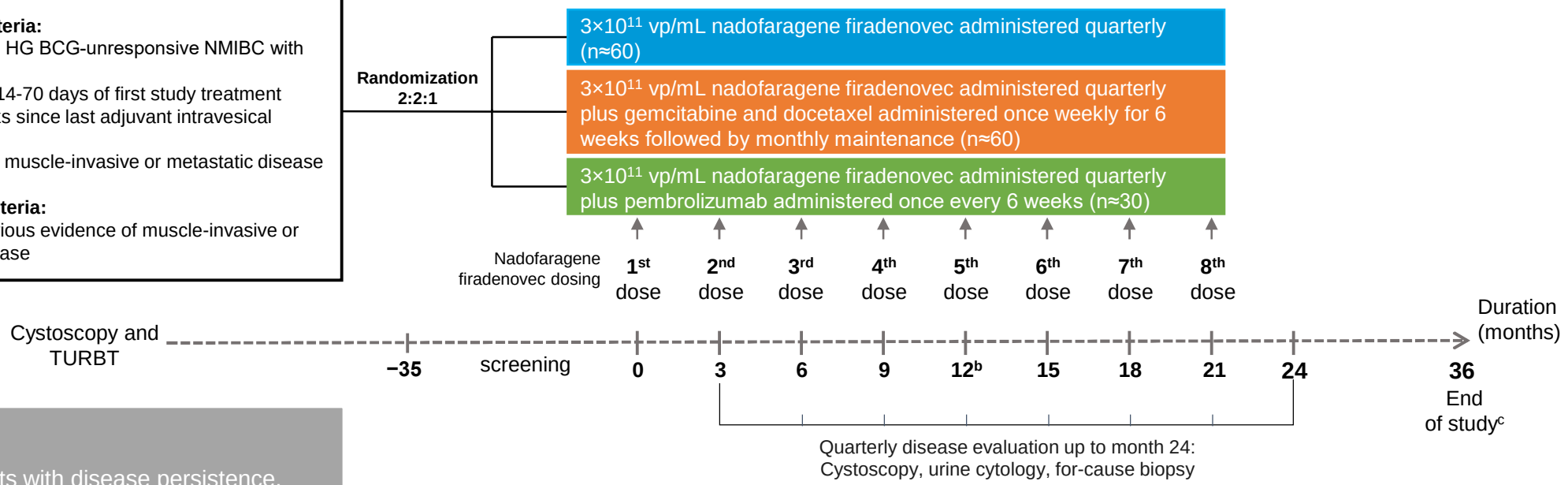
[1]Keck School of Medicine of USC, Los Angeles, CA, USA; [2]Mayo Clinic, Rochester, MN, USA; [3]Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [4]Hospitals of the University of Pennsylvania, Philadelphia, PA, USA; [5]University of Texas Southwestern Medical Center, Dallas, TX, USA; [6]McGill University Health Centre, Montreal, QC, Canada; [7]University of Toronto, Toronto, ON, Canada; [8]Medical University of Turin, Turin, Italy; [9]Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany; [10]Ferring Pharmaceuticals A/S, Copenhagen, Denmark

ABLE-22: Study Design

N≈150

Key inclusion criteria:
- ≥ 18 years with HG BCG-unresponsive NMIBC with CIS ± Ta/T1
- TURBT within 14-70 days of first study treatment
- At least 8 weeks since last adjuvant intravesical therapy[a]
- No evidence of muscle-invasive or metastatic disease

Key exclusion criteria:
- Current or previous evidence of muscle-invasive or metastatic disease



Re-induction:

- In participants with disease persistence, re-induction will be offered once at month 3 followed by maintenance treatment in absence of recurrence or progression

BCG, Bacillus Calmette-Guérin; CIS, carcinoma in situ; HG, high-grade; NMIBC, non–muscle-invasive bladder cancer; TURBT, transurethral resection of bladder tumor; vp, viral particle.
[a]Excluding a single postoperative dose of a cytotoxic agent following TURBT or BCG therapy within ≥5 weeks before biopsy required for study entry.
[b]Continued treatment after month 12 will be offered in absence of disease recurrence or progression following first instillation.
[c]Data will be collected annually up to month 36 from participants who have completed the month 24 assessment visit or who have discontinued treatment due to disease recurrence or progression.

NCT06545955

Muscle Invasive Bladder Cancer

Case presentation

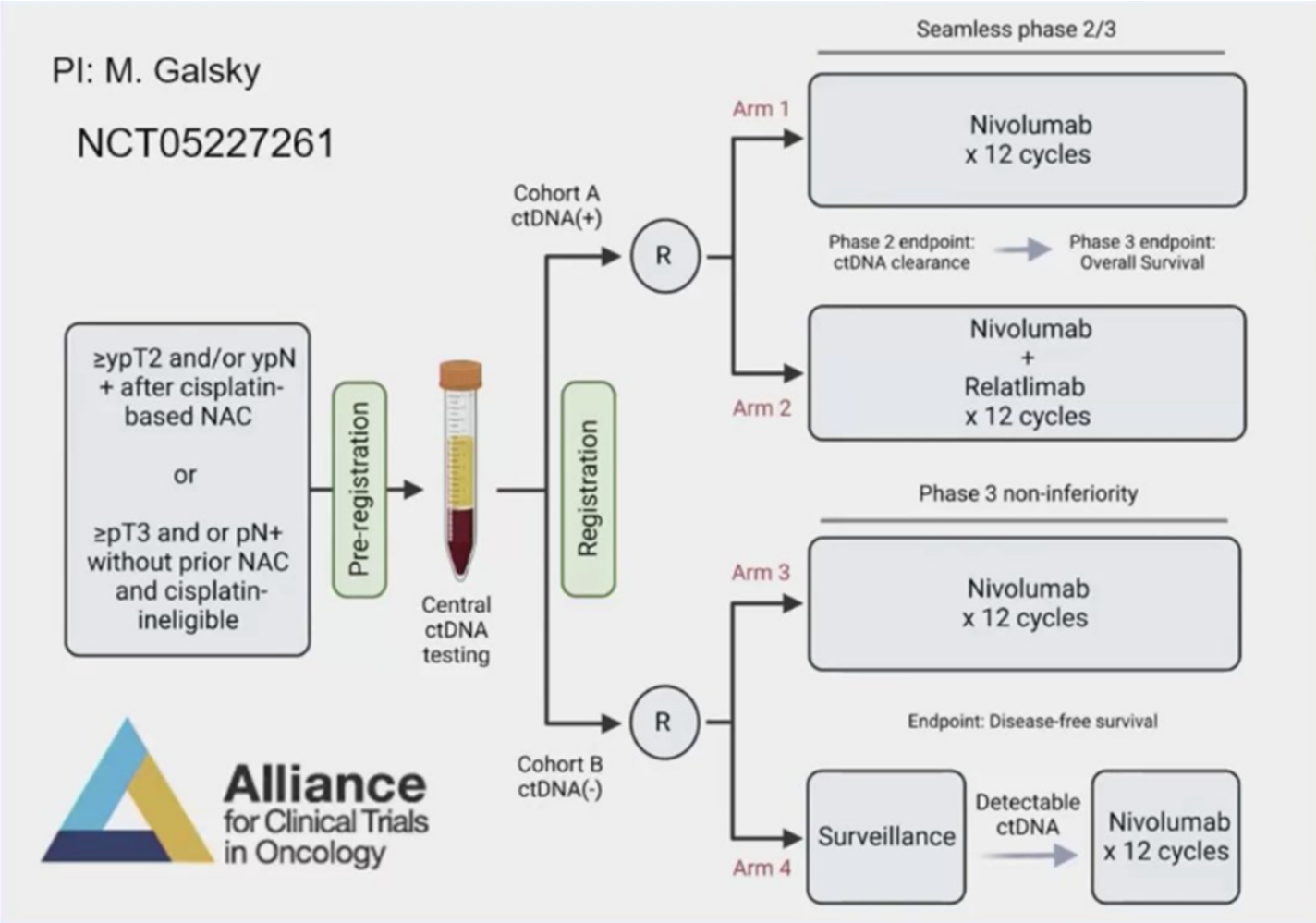
A 62-year-old woman with **cT2 muscle-invasive** disease receives **four cycles of neoadjuvant cisplatin/gemcitabine** and subsequently undergoes radical cystectomy with pelvic lymph node dissection. Pathologic evaluation demonstrates **residual disease**. She is considered for adjuvant therapy clinical trials aimed at improving long-term outcomes.

- Muscle-invasive bladder cancer, s/p NAC and cystectomy + PLND

MODERN: An Integrated Phase 2/3 and Phase 3 Trial of MRD-Based Optimization of ADjuvant ThErapy in URothelial CaNcer

UCLA

UC San Diego Health



*patients with pT2N0 (distinct from ypT2N0) will be eligible IF ctDNA (+)

NCT05987241

Case presentation

A 62-year-old woman with **cT2 muscle-invasive** bladder cancer is evaluated in a multidisciplinary clinic. While a surgical candidate, she wishes to pursue **bladder-sparing approaches**. Clinical trials exploring non-cystectomy treatment strategies are discussed.

- Muscle-invasive bladder cancer, treatment naïve

NRG GU015: RANDOMIZED PHASE III TRIAL ADAPTIVE RADIATION AND CHEMOTHERAPY FOR MUSCLE INVASIVE BLADDER CANCER (ARCHER) ARCHER

Schema

REGISTRATION
Confirm eligibility*

STRATIFICATION
1. Clinical stage (T2 vs. T3)
2. Type of Radiosensitizing Chemotherapy planned**
3. Neoadjuvant therapy (yes vs. no)

RANDOMIZATION
(1:1)

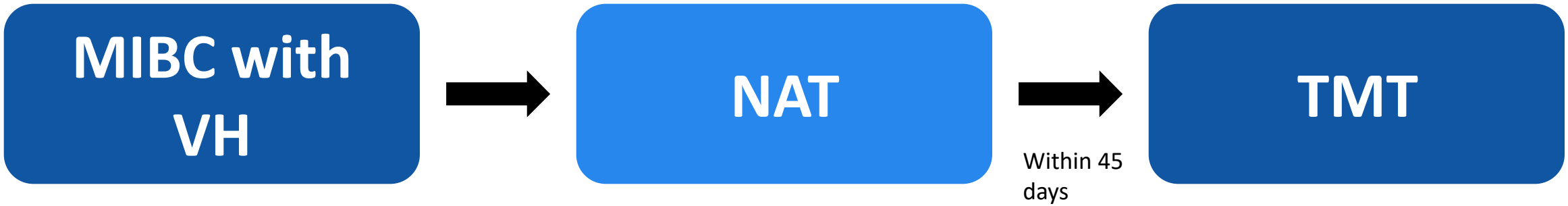
ARM 1
4 weeks radiosensitizing chemotherapy + hypofractionation
(55 Gy/20 Fractions)

ARM 2
4 weeks radiosensitizing chemotherapy + SBRT (ultra-hypofractionation) (32.5 Gy/5 Fractions)

*See protocol section 3.1 for details
**Types of chemotherapy regimens are:
- Cisplatin
- Gemcitabine
- Mitomycin-C/5-Fluorouracil

NCT07097142

Cedars-Sinai VH IIT



HCRN GU22-598: Enfortumab vedotin plus pembrolizumab with Risk Adapted Individualized Bladder Sparing

Key Eligibility Criteria
- Clinically localized MIBC.
- Clinical stage cT2-3N0M0.
- Undergone a standard of care maximal TURBT ≤ 60 days prior C1D1.
- Eligible RC and PLND.

→ **TURBT** →

Clinical restaging
- Cystoscopy
- Biopsies
- Urine cytology
- MRI

→ **Clinical complete response** → **No cystectomy / EV + Pembrolizumab**

→ **No clinical complete response** → **Cystectomy**

Endpoints:
Primary: clinical complete response rate
Secondary: Safety / RFS / MFS / OS.

NCT06809140

S2427: Combining Immunotherapy and Radiation Therapy to Help Patients Avoid Bladder Removal After Treatment Shrinks Muscle Invasive Bladder Cancer (BRIGHT)

cT2-cT4aN0 MIBC who receive at least 3 cycles of neoadjuvant therapy* → CT Scan/ MRI or PET Scan and cystoscopy with cT0-T1 response → TURBT (with systematic biopsies)** → cT0 – cT1*** → Informed consent and Registration to S2427 within 90 days after the last dose of NAT → RT (55Gy/20fx to whole bladder) + Pembro (200mg q 21 days) for 12 months → Cystoscopy, cytology, and imaging with salvage cystectomy for patients with recurrent or residual MIBC q3 months for 3 years

* Patients who receive NAC as the NAT must have at least 3 cycles of cis-based regimen

** Patients found to have >T1 disease on TURBT will proceed to SOC cystectomy

*** Diffuse CIS patients will be excluded (>3 cm area of contiguous CIS or >3 separate locations of CIS on TURBT (dome/posterior/left/right/trigone)

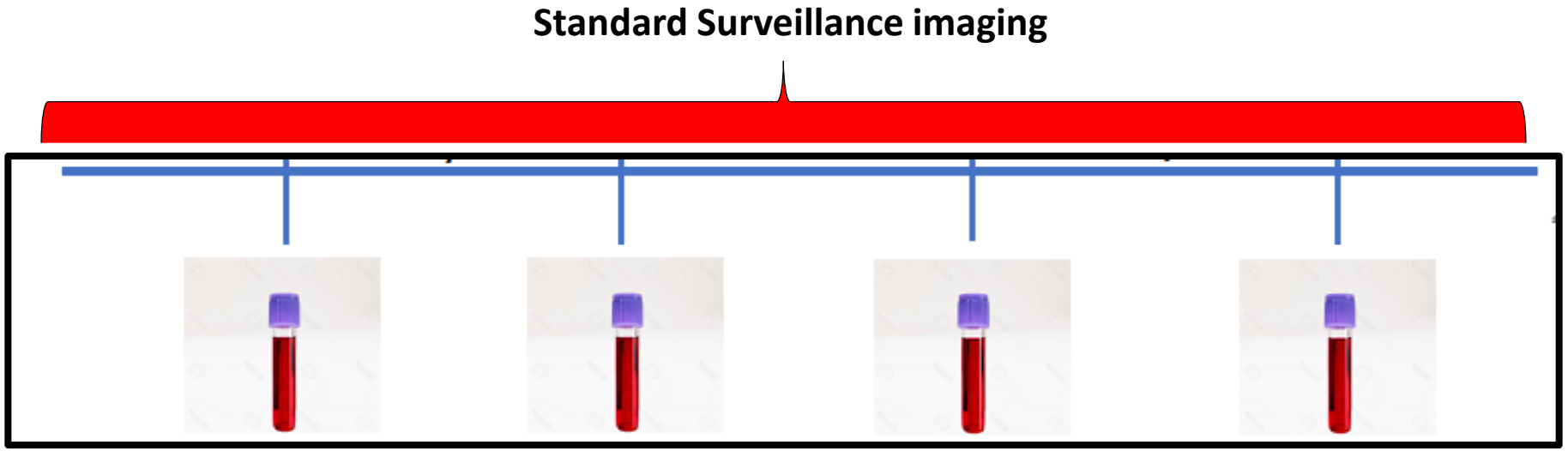
NCT07061964

ORACLE: Observation of ResiduAl Cancer with Liquid Biopsy for Evaluation

UC San Diego Health

Guardant Health Reveal ctDNA Assay for 11 cancer types, including bladder cancer and upper tract urothelial carcinoma

- Blood collection at SOC time points



Primary Endpoint: Distant RFS

Secondary Outcomes: Sensitivity, positive predictive value, lead time

NCT05059444

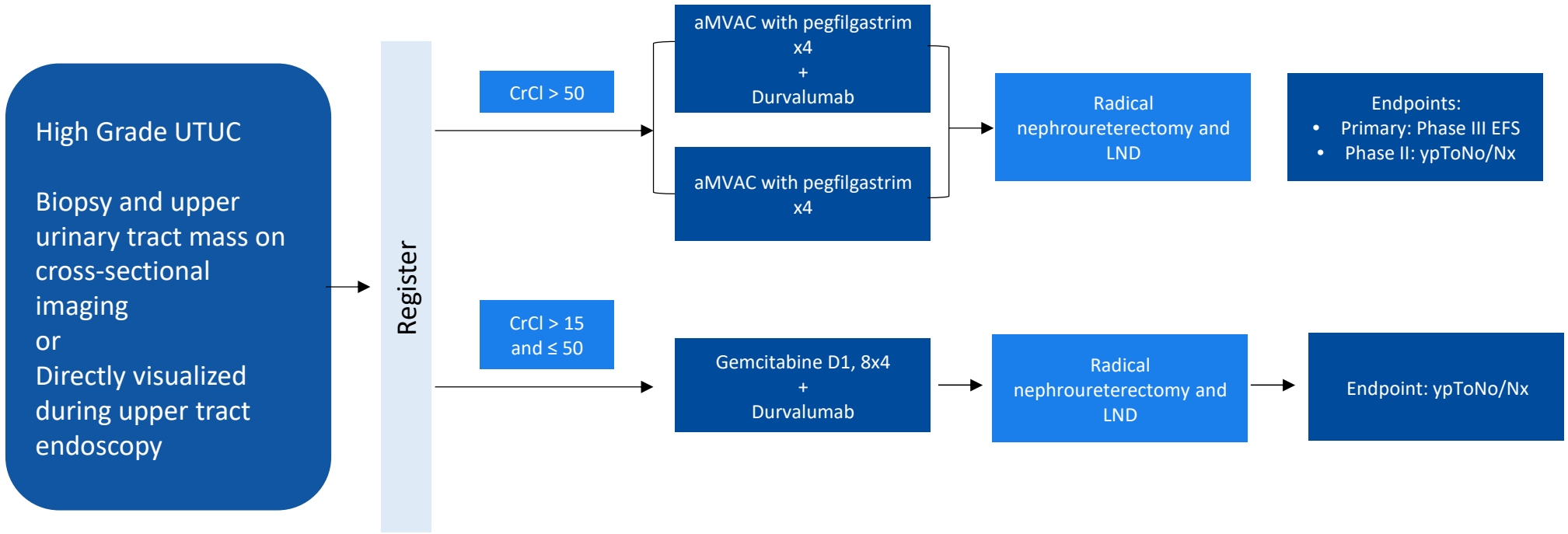
Case presentation

A 71-year-old man presents with hematuria and is found to have a **mass in the right renal pelvis.** Ureteroscopy and biopsy confirm **high-grade urothelial carcinoma** with features consistent with **T2 disease**. Staging demonstrates no evidence of metastatic disease. He has no history of muscle-invasive bladder cancer.

- High-grade upper tract urothelial carcinoma, treatment naïve

EA8192 Phase II/III– Cisplatin eligible / Phase II single-arm – Cisplatin ineligible

UC San Diego Health



Cisplatin Eligible Arm						
Total N	Accrual (mos)	Additional Follow-up (mos)	Events at full information	HR	One-sided type I error	Power
220	44	40	171	0.67	0.05	84%
Phase II portion - Target pCR rate 28% vs. null 14%						

PRIMARY: Pathological outcomes (pT0N0/Nx)

KEY SECONDARY: OS, EFS, DFS, Safety/tolerability

EXPLORATORY: QOL/Health status utility, Safety, PK, Immunogenicity (anti-drug antibodies), relationship between biomarkers in blood and tumor tissue and efficacy, safety, PK, or other biomarker endpoints.

NCT04628767

EA8192 Phase II/III– Cisplatin eligible / Phase II single-arm – Cisplatin ineligible

UC San Diego Health

INCLUSION CRITERIA:

1. High Grade UTUC
    1. Biopsy
    2. Cytology/imaging
    3. Visualized mass and cytologyHistologically confirmed metastatic clear cell
2. **Creatinine clearance ≥30 ml/min**

- **(LVEF) ≥ 50%**
- **No metastasis (LN) < 1 cm**
- **No neuropathy > grade 2**

EXCLUSION CRITERIA:

1. No metastases
2. No secondary cancers
3. No concomitant bladder cancer
4. No history of recent MIBC status post chemo/cystectomy

Advanced/Metastatic Disease

Case presentation

A 69-year-old man presents with metastatic urothelial carcinoma of the bladder. Next-generation sequencing of tumor tissue reveals **HER2 expression and an *FGFR3* alteration**, prompting consideration of biomarker-driven systemic therapy and clinical trial options.

- Metastatic bladder cancer, HER2+ and *FGFR3* alteration present

REJOICE-PanTumor01: A Phase 2, Multicenter, Open-Label, Pan-Tumor Trial to Evaluate Efficacy and Safety of Raludotatug Deruxtecan (R-DXd) in Participants with Advanced/Metastatic Solid Tumors

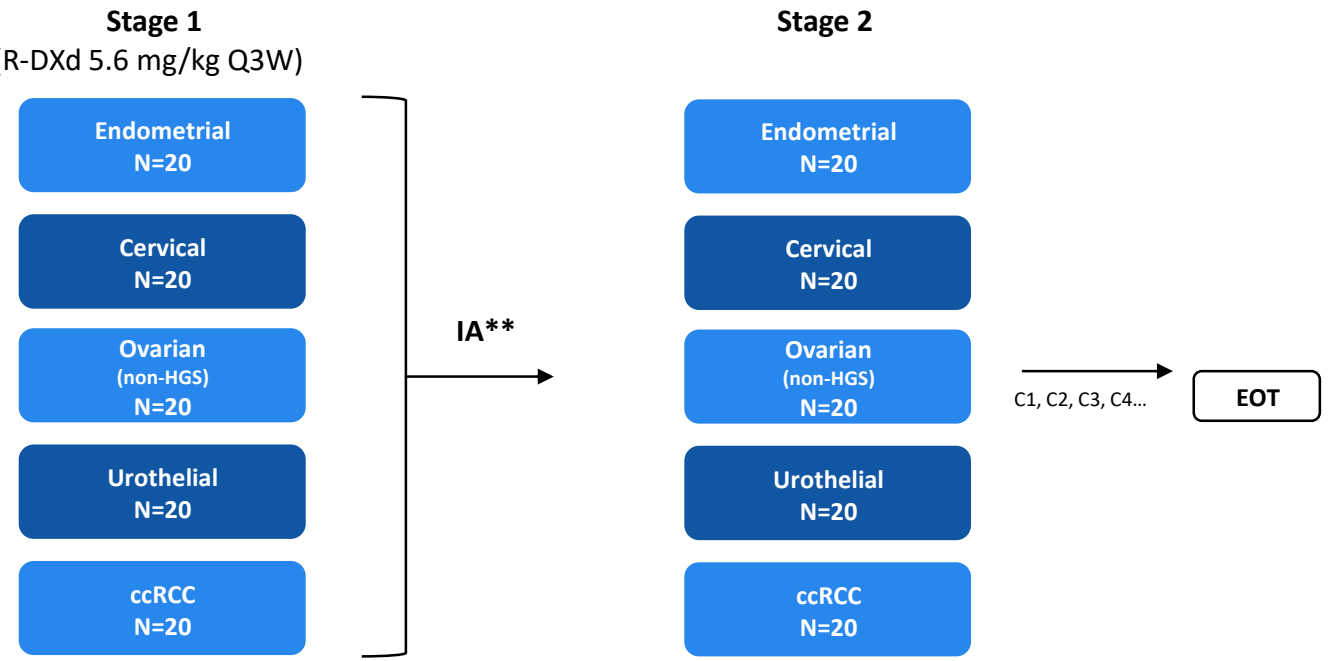
UCI

Screening (≤28D)

Target population

- Recurrent/metastatic solid tumors
- ECOG PS 0-1
- Measurable disease
- No selection based on target expression

Treatment*



Follow up

- Safety (FU 40D)
- LTSFU (Q90D)

Primary Endpoints

- ORR (by investigator assessment per RECIST 1.1 except ccRCC cohort)
- DCR (by investigator assessment per RECIST 1.1 ccRCC cohort only)
- Safety and tolerability

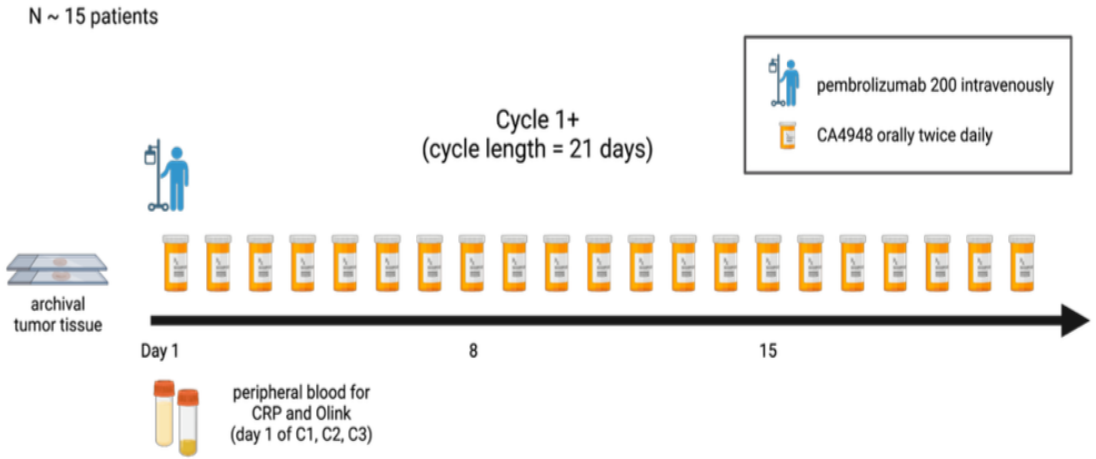
Secondary Endpoints

- ORR (ccRCC cohort only), DCR (except ccRCC cohort), PFS, DoR, and TTR (by investigator assessment per RECIST 1.1)
- PK, ADA

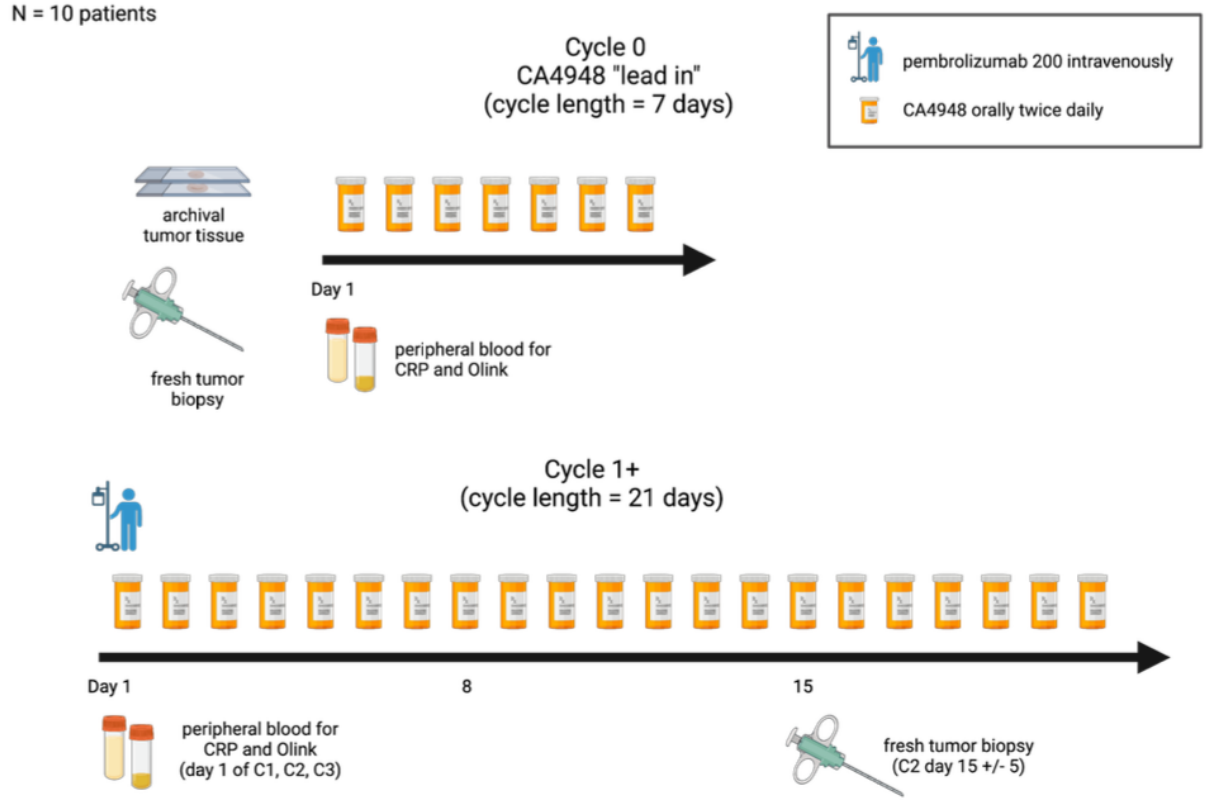
NCT06660654

Phase 1 Trial of CA-4948 in Combination with Pembrolizumab to Overcome Resistance to PD-1/PD-L1 Blockade in Metastatic Urothelial Cancer

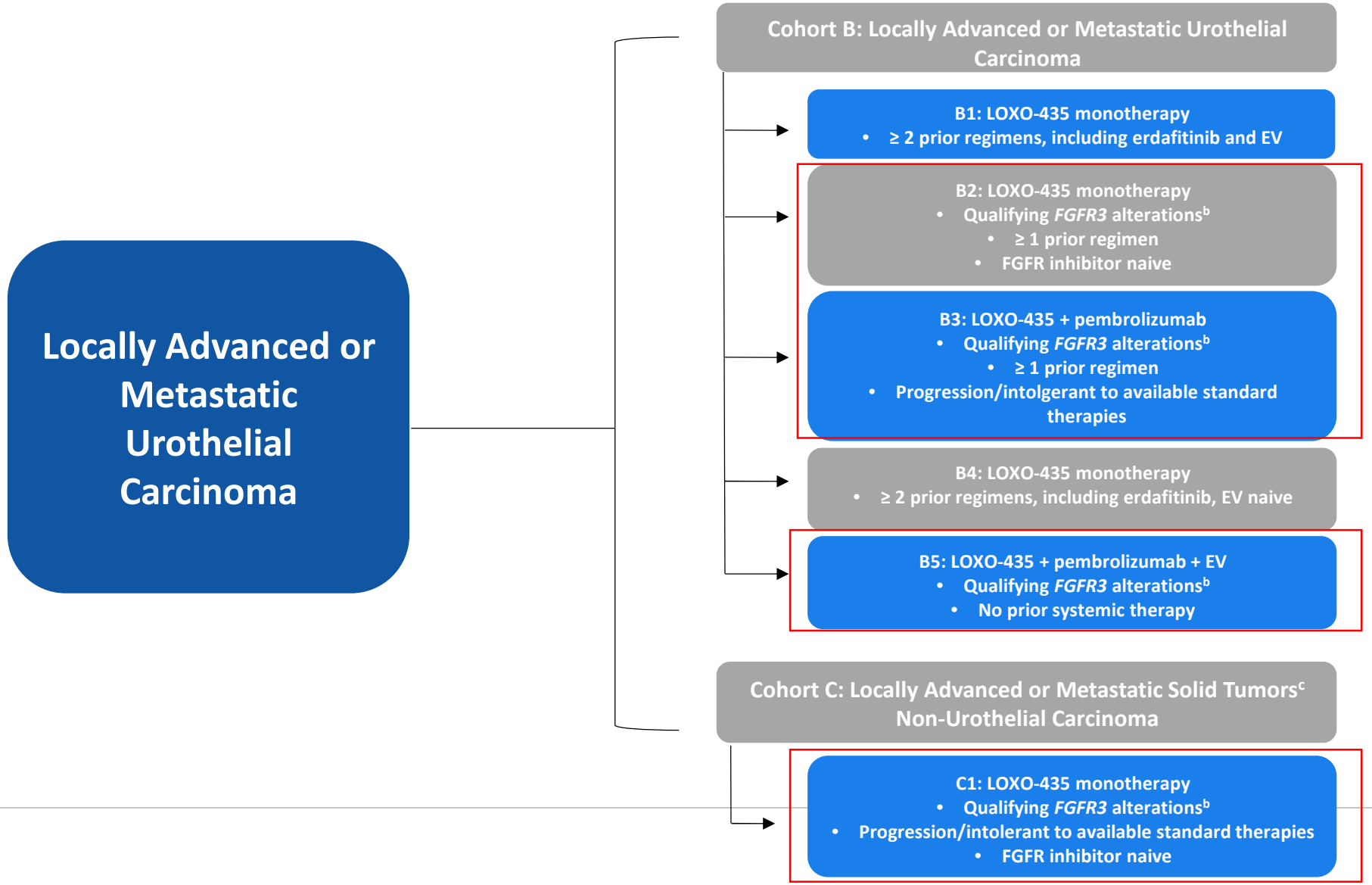
Dose Escalation



Dose Expansion

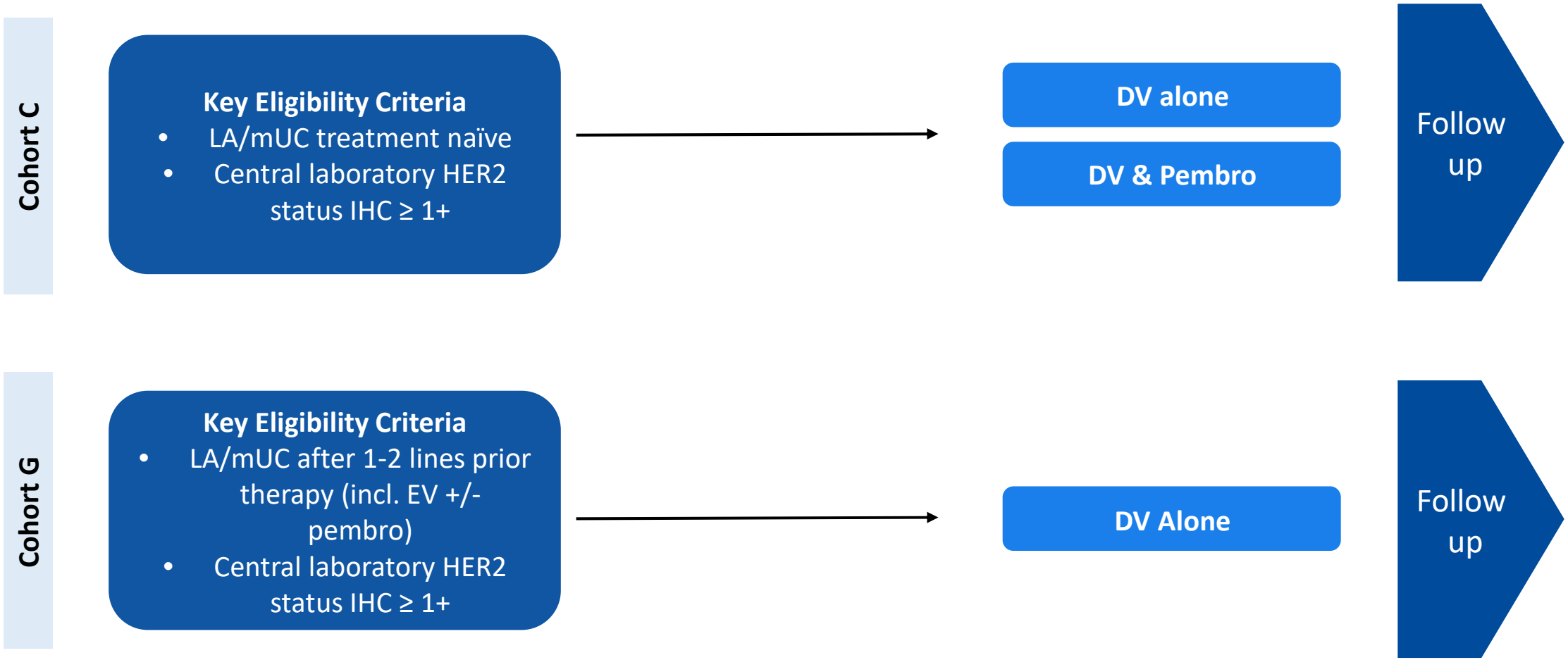


FORAGER-1: A Phase I, Open-Label, Multicenter Study of LOXO-435 in Locally Advanced or Metastatic Solid Tumors Including Urothelial Cancer with FGFR3 Alterations



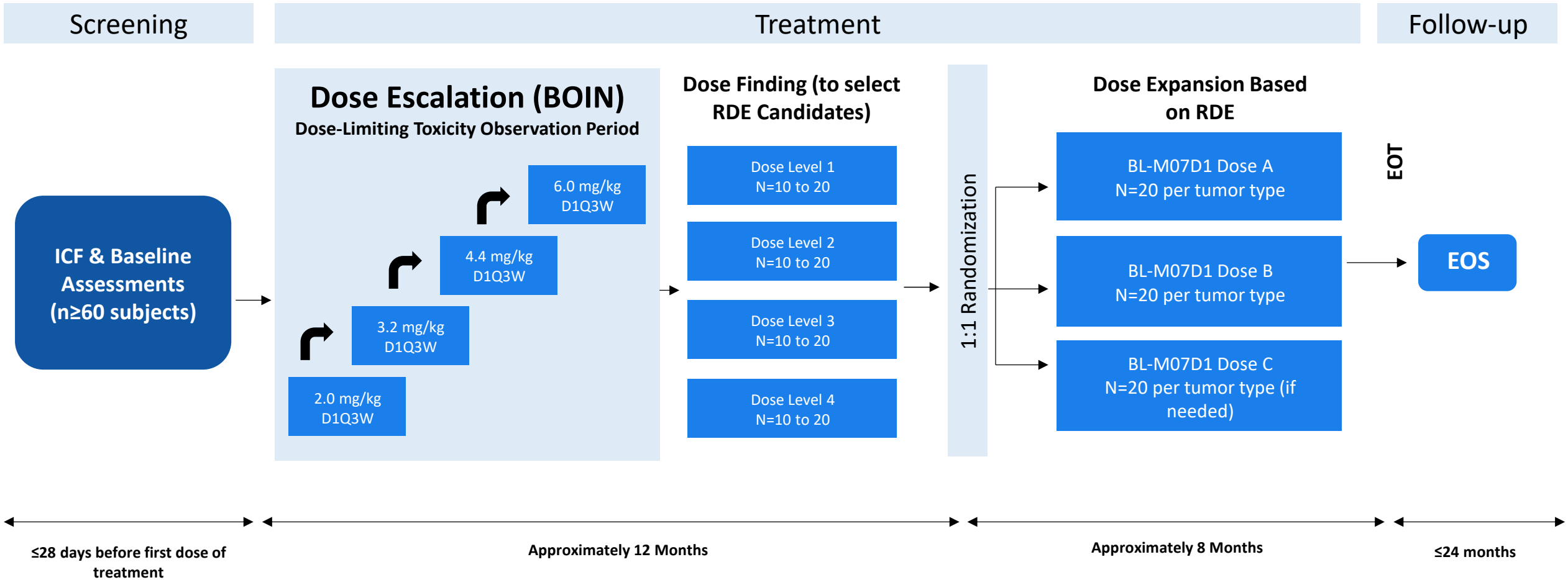
NCT05614739

Phase 2 study of disitamab vedotin (RC48 ADC) with pembrolizumab vs chemotherapy in patients with locally advanced or metastatic urothelial carcinoma that expresses HER2



NCT04879329

BL-M07D1 in Subjects with HER2 Expressing Advanced Malignant Solid Tumors



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