2nd Annual Southern California Genitourinary Cancer Research Forum

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

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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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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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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.

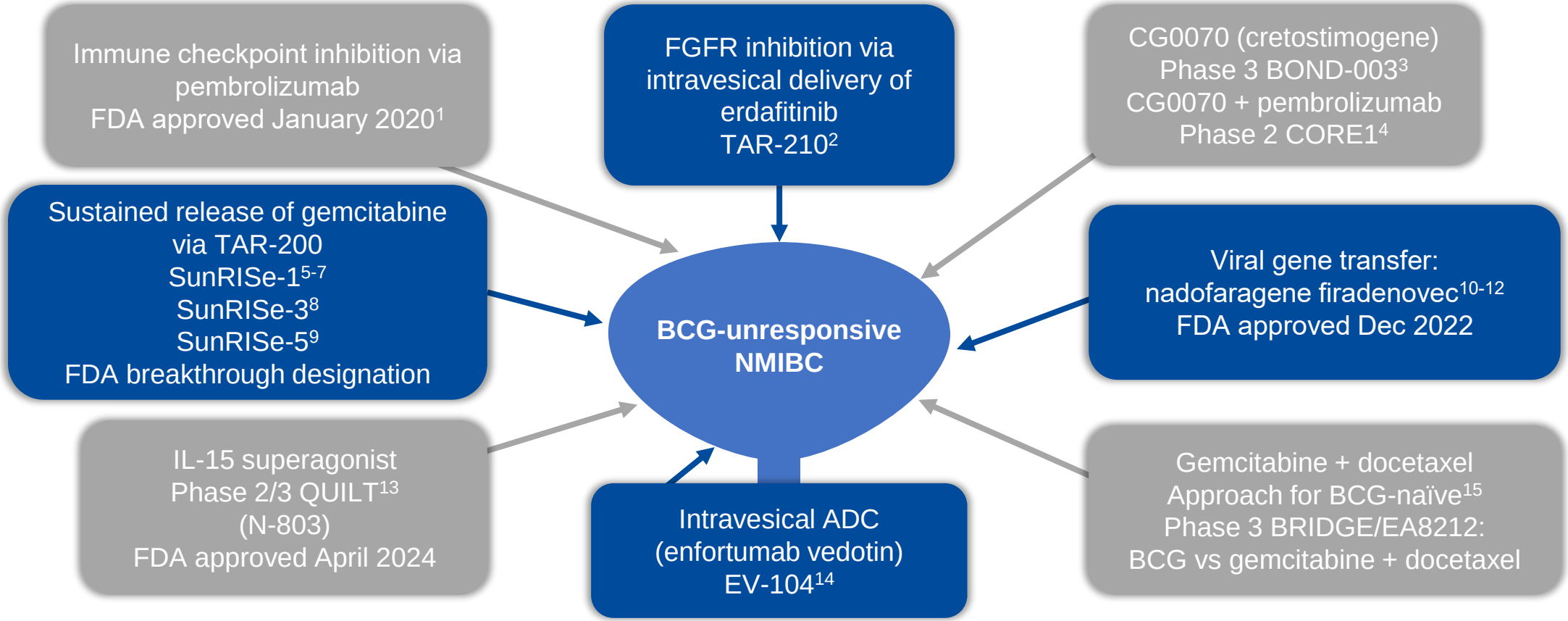
EXEMPTION:

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:

- *Barriers to cross cultural inclusion in clinical trials.*
- *Disparities in care of under-represented patients.*
- *Gender differences in bladder cancer.*
- *Address tertiary care practice and how that may differ from a community practice setting.*

Snapshot of Treatment Approaches for High-Risk NMIBC Unresponsive to BCG



1. Balar AV et al. *Lancet Oncol*. 2021;22:919-930. 2. Vilaseca A et al. AUA 2024. Abstract PD48-02. 3. Tyson MD et al. AUA 2024. Abstract P2-02.
4. Li R et al. *J Clin Oncol*. 2022;40(suppl 16). Abstract 4597. 5. Daneshmand S et al. AUA 2023. LBA 02-03. 6. Necchi A et al. ESMO 2023. LBA105.
7. van der Heijden MS et al. ESMO 2024. Abstract LBA85. 8. https://clinicaltrials.gov/study/NCT05714202. 9. Porten S et al. SUO 2024. Abstract 134
10. Boorjian SA et al. *Lancet Oncol*. 2021;22:107-117. 11. Narayan VM et al. *Front Oncol.* 2024;14:1359725 12. Boorjian SA et al. EAU 2024. Abstract A0583.
13. Chamie K et al. *NEJM Evid*. 2022;2. 14. Kamat AM et al. *J Clin Oncol.* 2023;41(suppl 16). Abstract 4596. 15. McElree IM et al. *J Urol*. 2022;208:589-599.

Case Presentation

- A 68-year-old man presents with recurrent Ta, low-grade (G1) NMIBC. His previous TURBT one year ago confirmed Ta LG disease, and he was treated with intravesical chemotherapy (no BCG) but no maintenance therapy. On follow-up cystoscopy, he has a single recurrent lesion (2.5 cm) on the lateral bladder wall.

➡ **Intermediate-risk NMIBC (recurrent Ta LG lesion)**

➡ **Tissue sent for molecular testing showed an FGFR3 fusion.**

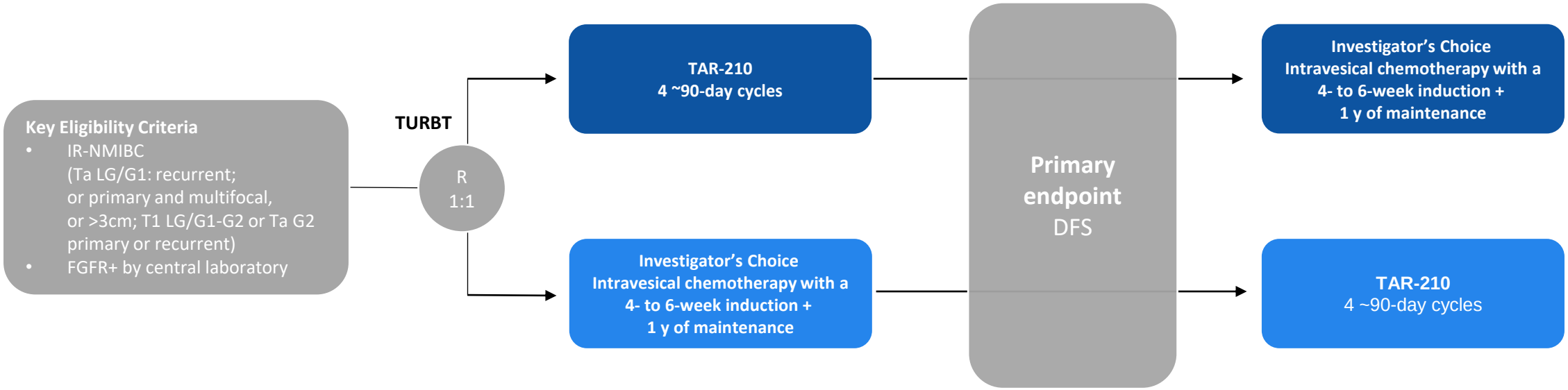
a) Intravesical BCG (Induction + 1-Year Maintenance)

b) Intravesical Gemcitabine

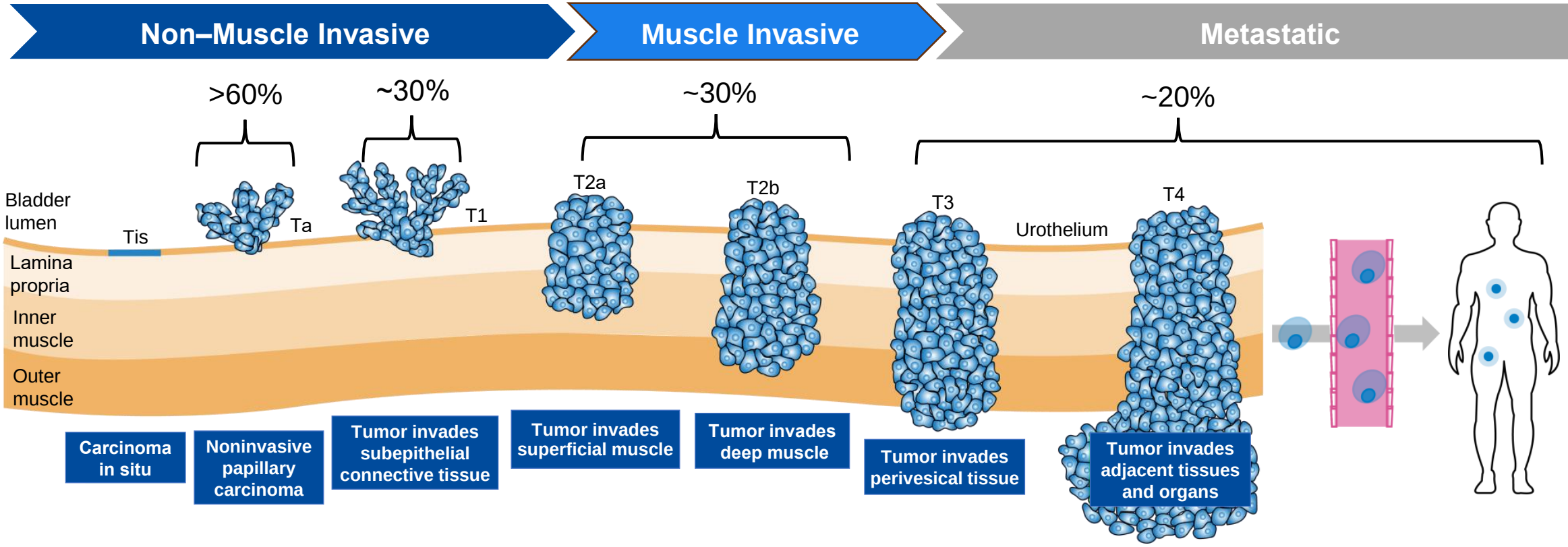
c) Intravesical Mitomycin C

d) FGFR-targeted clinical trial (e.g., MoonRISe-1 – TAR-210 intravesical erdafitinib)

MoonRISe-1: TAR-210 vs IV chemotherapy in IR NMIBC with susceptible FGFR alterations



FGFR Mutations Are Frequently Observed in Bladder Cancer



FGFR inhibitors can be effective across the disease spectrum

Knowles MA et al. *Nat Rev Cancer*. 2015;15:25-41.

Case Presentation

- A **69-year-old man** presents with **painless hematuria**. Cystoscopy reveals a **multifocal bladder tumor**, and TURBT confirms **high-grade Ta disease with concomitant CIS**. Muscularis propria is present and uninvolved. He has **no prior intravesical therapy.**

→ **High-risk NMIBC (high-grade Ta + CIS, BCG-naïve)**

a) BCG induction + maintenance for up to 3 years

b) Intravesical gemcitabine + docetaxel (Clinical trial: BRIDGE)

c) N-803 + BCG (Clinical trial: QUILT-2.005)

d) Radical cystectomy

NMIBC – 1st Line

BRIDGE

ECOG-ACRIN
Cancer Research Group

EA8212
Version Date: January 12, 2023

Schema

Key Eligibility
1. High Grade NMIBC (HgTa, CIS, HGT1)
2. No prior BCG
3. No history of prostatic urethral or upper tract urothelial cancer

Stratification Factors

TURBT tumor stage:
1. Pure CIS
2. Pure Papillary (HgTa or HGT1) disease
3. Concurrent CIS and papillary disease (CIS+HgTa or CIS+HGT1)

RANDOMIZATION

Arm A: GEMDOCE[1]

Frequency
- Intravesical GEMDOCE once a week for six consecutive weeks during Induction followed by monthly GEMDOCE instillations during Maintenance for 2 years

Dosing
- Gemcitabine 1g in sodium chloride 0.9% 50 mL followed by
- Docetaxel 40mg in sodium chloride 0.9% 50 mL

Arm B: BCG[1]

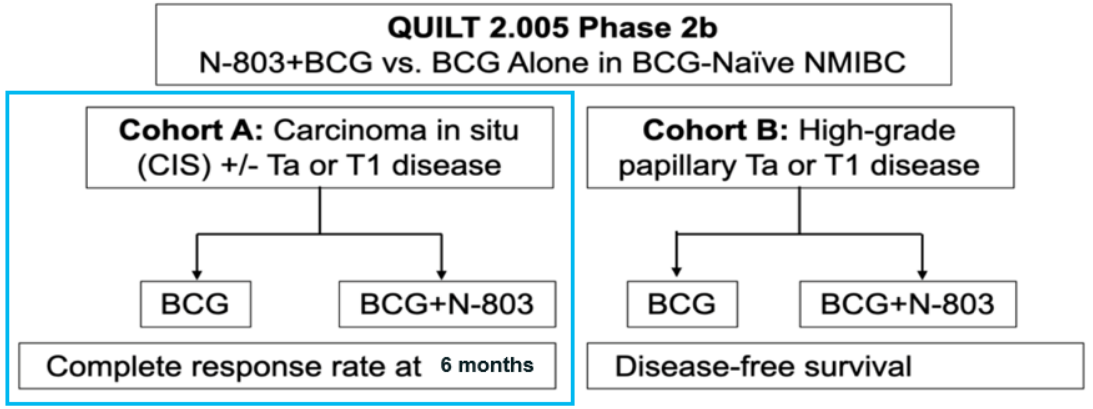
Frequency
- Intravesical BCG once a week for six consecutive weeks during Induction followed by BCG instillations during Maintenance once a week for 3 consecutive weeks at months 3, 6, 12, 18, 24, 30 and 36 months

Dosing
- BCG 50 mg in sodium chloride 0.9% 50 mL

Follow-Up

Accrual = 870

QUILT 2.005



Case Presentation

- A 73-year-old man was diagnosed with high-grade CIS NMIBC and underwent TURBT, followed by BCG induction (6 doses) and started planned 36-month maintenance therapy according to standard guidelines. At his 12-month cystoscopy, a suspicious lesion was found. Confirmatory pathology after TURBT showed recurrent high-grade CIS. Muscularis propria was well represented and not compromised.

➡ **BCG-unresponsive NMIBC (High-grade recurrent CIS)**

a) Radical cystectomy with pelvic lymph node dissection (PLND)

b) Intravesical chemotherapy (Gemcitabine + Docetaxel)

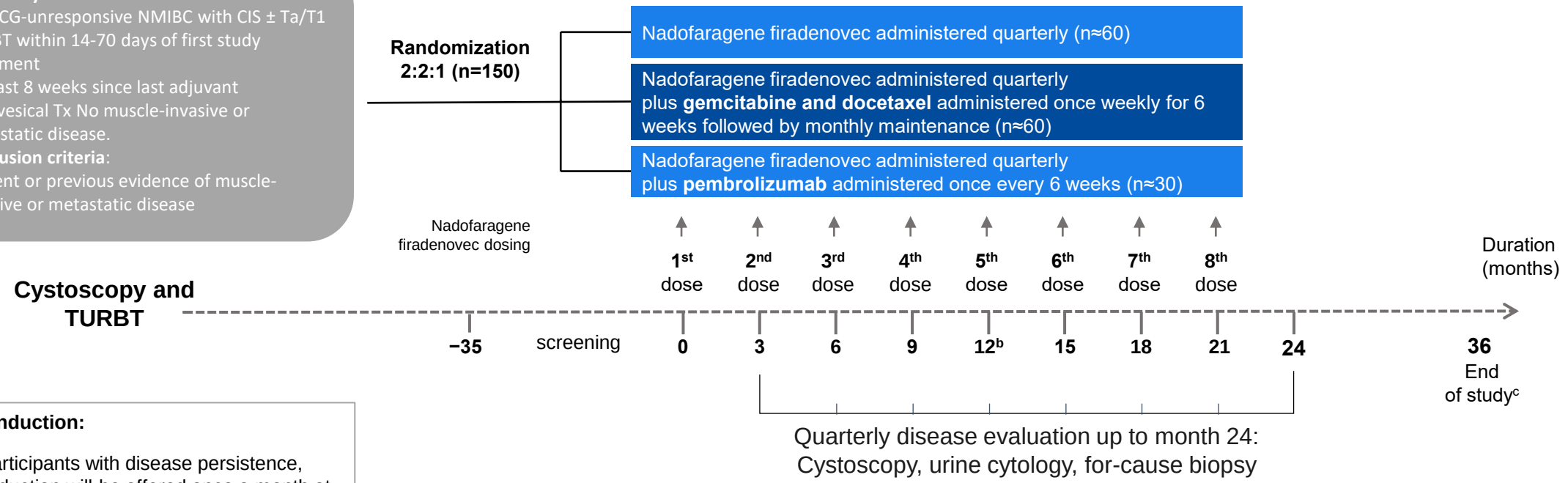
c) Pembrolizumab

d) Nadofaragene firadenovec

ABLE-22

Key Eligibility Criteria
- 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 Tx No 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 a month at month 3 followed by maintenance treatment in the absence of recurrence or progression.

Case Presentation

- A 65-year-old man presents with gross hematuria and a 5 cm sessile bladder mass on CT urogram. Cystoscopy confirms a broad-based, sessile tumor, concerning for muscle invasion, but he has not yet undergone TURBT. Given the tumor characteristics, he is referred for multi-parametric MRI to assess muscle invasion before TURBT.

- ➡ **Bladder mass concerning for MIBC, pre-TURBT evaluation**

a) TURBT for histologic confirmation and staging

b) Multi-parametric MRI (mpMRI) for non-invasive assessment of muscle invasion

c) Clinical trial evaluating mpMRI vs. TURBT for initial staging

Outcomes with Multi Parametric MRI Compared to Diagnostic Transurethral Resection of Bladder Tumor (TURBT) in Patients with Suspected Muscle-Invasive Bladder Cancer – a Pilot Study.

Endpoints:
Primary: Incidence of concordance between VI-RADS score 4 and 5 bladder tumors on mpMRI and pathologic muscularis propria invasion (pT2) on TURBT.
Secondary: Time from initial cystoscopy to performing each diagnostic test / Time to initiation of cancer-directed therapy / Incidence of repeat TURBT / Patient-assessed quality of life with each diagnostic test / Incidence of adverse events related to each diagnostic test / PFS / Financial toxicity of each diagnostic test.

NCT06335667

Case Presentation

- A 69-year-old man was diagnosed with muscle-invasive bladder cancer (MIBC) after undergoing TURBT for gross hematuria. Pathology confirmed cT2 disease, with no evidence of lymph node involvement on imaging. He is otherwise fit for radical cystectomy but is interested in bladder-sparing options.

➡ **Muscle-invasive bladder cancer (cT2N0M0), fit for cystectomy**

a) Trimodal therapy (TMT): TURBT followed by chemoradiation

b) HCRN GU22-598: Enfortumab vedotin + pembrolizumab with risk-adapted bladder preservation

c) SWOG/NRG 1806: Chemoradiation + atezolizumab for bladder preservation

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** →

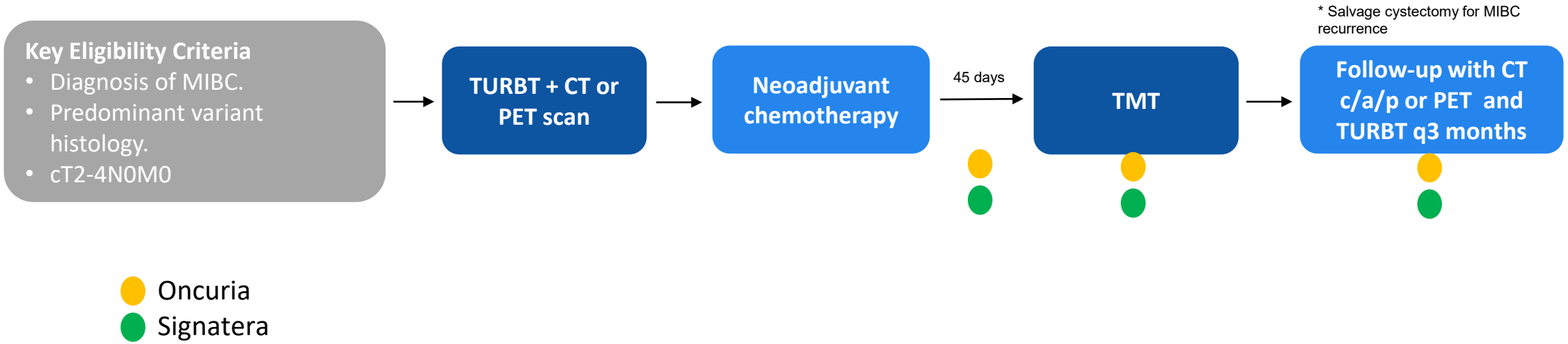
Clinical restaging
- Cystoscopy
- Biopsies
- Urine cytology
- MRI

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

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

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

Bladder Preservation for Patients with Muscle Invasive Bladder Cancer (MIBC) with Variant Histology



Endpoints:
Primary: Feasibility of initiating TMT within 45 days of NAC +/- IO completion.
Secondary: 3-year bladder intact EFS / PFS / MFS / Rate of salvage cystectomy
Exploratory: Oncuria and Signatera and their ability to detect relapse/recurrence in this patient population over a 3-year follow-up period after TMT.

3 new bladder preservation trials

2 NRG trials

- T1 NMIBC SBRT vs conventional fractionation
- T2-T4aN0M0 MIBC TMT

1 SWOG trial

- Response adapted post-NAC in T2-T4aN0M0 MIBC

Case Presentation

- A 70-year-old man with muscle-invasive bladder cancer (MIBC) underwent radical cystectomy with pelvic lymph node dissection (PLND) after receiving neoadjuvant chemotherapy (NAC) with gemcitabine and cisplatin. Final pathology revealed pT3N0 disease, indicating high-risk residual disease.

- ➡ **Muscle-invasive urothelial carcinoma (ypT3N0)**

a) Adjuvant nivolumab

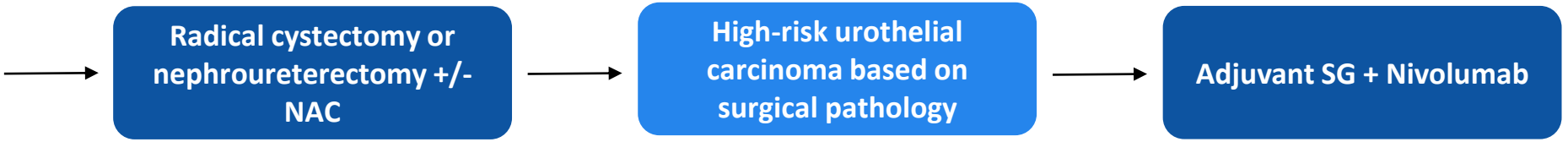
b) Observation with surveillance

c) Clinical trial of adjuvant sacituzumab govitecan + nivolumab

Adjuvant sacituzumab govitecan (SG) plus nivolumab in patients with muscle-invasive urothelial carcinoma at high-risk for recurrence

Key Eligibility Criteria

- Muscle-invasive UC of bladder or upper tract.
- s/p curative-intent surgery within 180 days prior to study therapy initiation.
- Ineligible or refuse platinum-based adjuvant chemotherapy.
- If prior NAC, must have pT2-T4 / pN+ disease on surgical pathology; if w/o NAC, then pT3-T4 /pN+ disease.

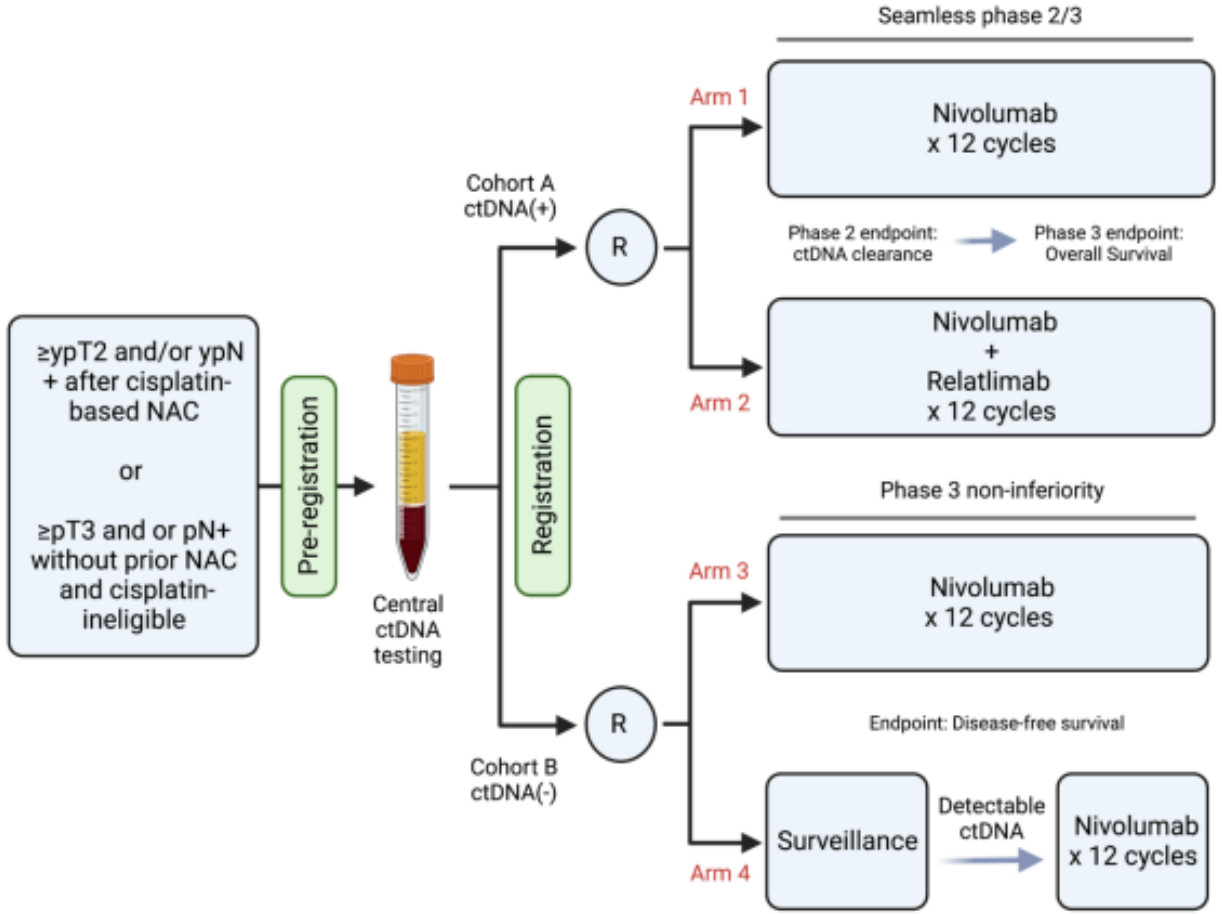


NCT06682728

Sacituzumab govitecan: TROP-2 directed antibody-drug conjugate.

Endpoints:
Primary: Investigator-assessed DFS at 6 month.
Secondary: DFS / Distant metastasis-free survival (MFS) / OS / Incidence of grade 3 or higher adverse events / Rate of ctDNA clearance in baseline ctDNA positive patients / Exploratory biomarker analysis.

MODERN – ctDNA directed adjuvant therapy for MIBC



R = Randomization. 1 cycle = 28 days.

Figure 7. Schema of A032103

Case Presentation

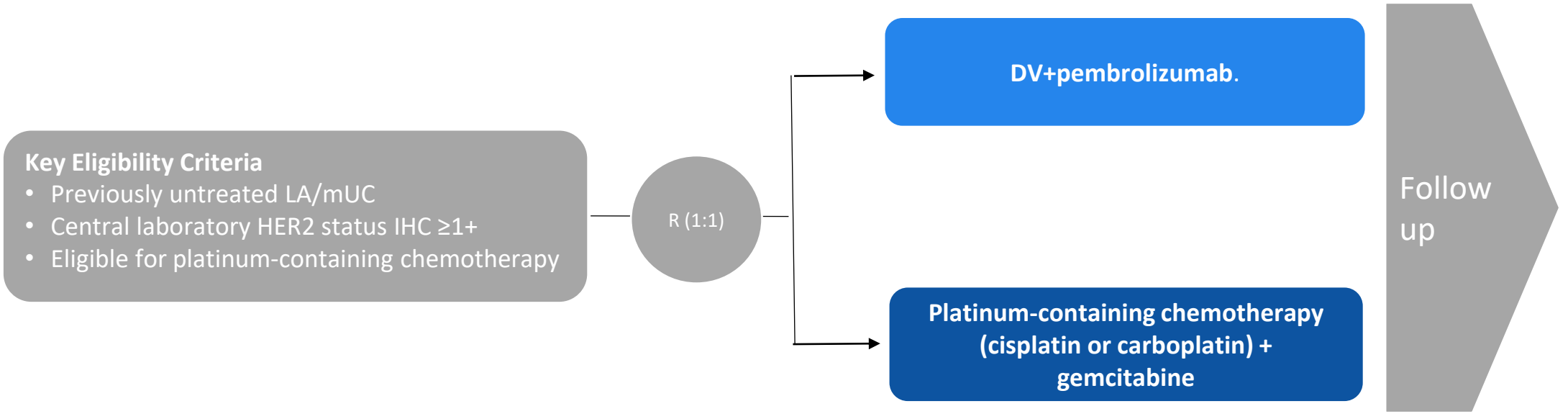
- A 72-year-old man presents with new-onset hematuria and weight loss. CT imaging reveals a bladder mass with multiple pulmonary nodules. TURBT confirms urothelial carcinoma with HER2 2+ expression. He is cisplatin-eligible with no overt comorbidities and is now being evaluated for first-line treatment options.
- ➡ **Metastatic urothelial carcinoma (mUC), HER2 2+**
- ➡ **Cisplatin-eligible, previously untreated**

a) Gemcitabine + Cisplatin → Avelumab maintenance

b) Enfortumab vedotin + Pembrolizumab

c) Disitamab vedotin + Pembrolizumab or other HER2-targeted clinical trials

Phase 3 study of disitamab vedotin with pembrolizumab vs chemotherapy in patients with previously untreated locally advanced or metastatic urothelial carcinoma that expresses HER2 (DV-001)



Disitimab vedotin: HER2 directed antibody-drug conjugate.

Endpoints:
Primary: PRFS by BICR and OS.

Case Presentation

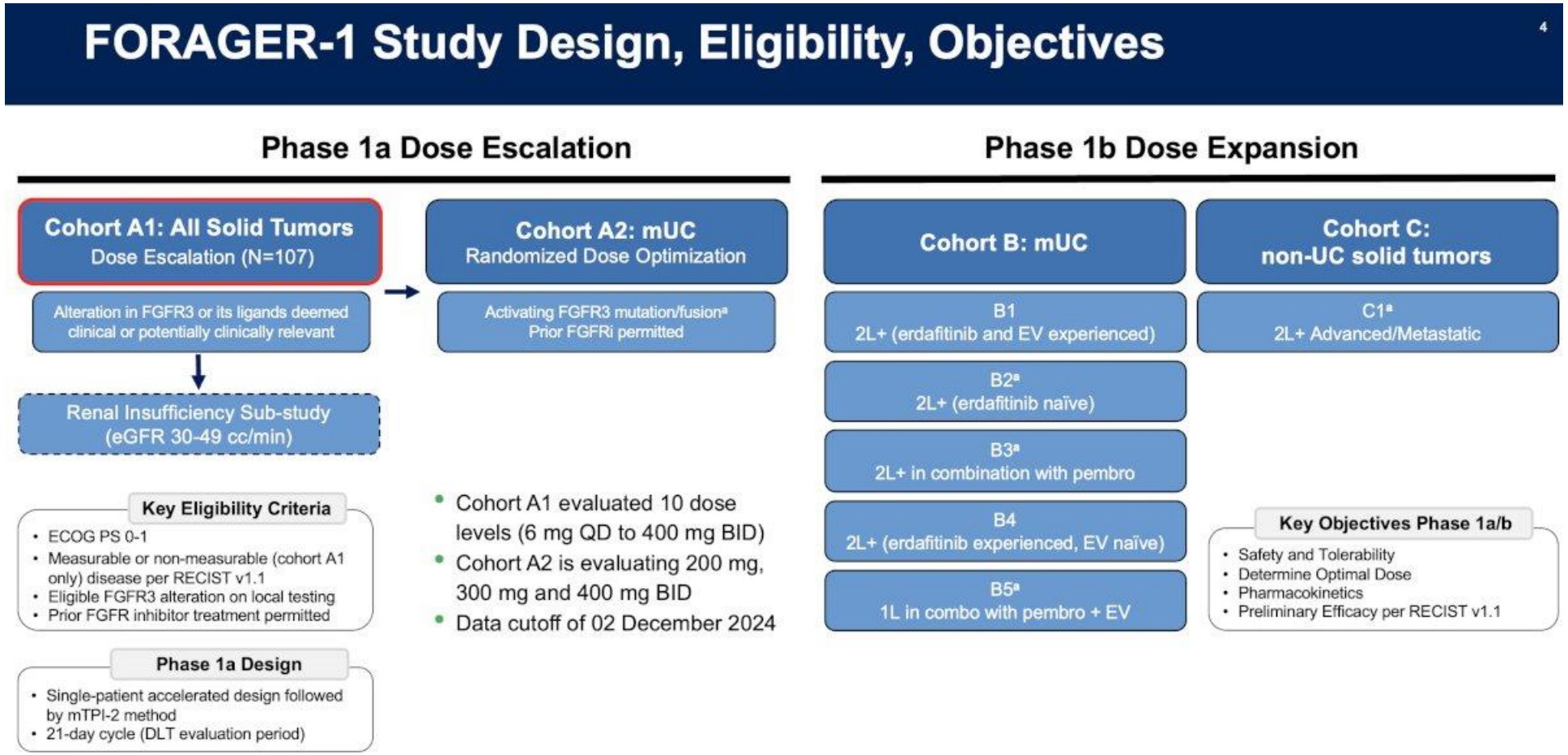
- A 74-year-old man with metastatic urothelial carcinoma (mUC) and an FGFR3 fusion was previously treated with first-line enfortumab vedotin plus pembrolizumab, achieving partial response. Upon progression, he received erdafitinib, with stable disease for six months before further progression. Repeat molecular testing reveals a secondary FGFR3 resistance mutation, and he is now being evaluated for further treatment options.
- ➡ **Metastatic urothelial carcinoma (mUC) with FGFR3 alteration**
- ➡ **Prior FGFR inhibitor exposure, secondary resistance mutation detected**

a) Sacituzumab govitecan

b) Single-agent chemotherapy (e.g., paclitaxel, docetaxel, or vinflunine)

c) LOXO-435 (Clinical trial: selective FGFR3 inhibitor for resistant mutations)

A first-in-human phase 1 study of LOXO-435, a potent, highly isoform-selective FGFR3 inhibitor in advanced solid tumors with FGFR3 alterations



LOXO-435: FGFR3 inhibitor.

Case Presentation

- A 66-year-old woman was diagnosed with metastatic urothelial carcinoma (mUC) and received first-line gemcitabine and cisplatin, achieving partial response. She then started switch-maintenance avelumab but experienced disease progression after 10 months. She was treated with eight doses of enfortumab vedotin (EV), achieving partial response, but treatment was discontinued due to grade 2 neuropathy. After four months without therapy, she developed new pulmonary and hepatic metastases and remains ECOG 1.

➡ **Progressive mUC following standard treatments**

a) Sacituzumab govitecan

b) Re-exposure to enfortumab vedotin (EV) at a reduced dose despite prior neuropathy

c) Single-agent chemotherapy (e.g., paclitaxel, docetaxel, or vinflunine)

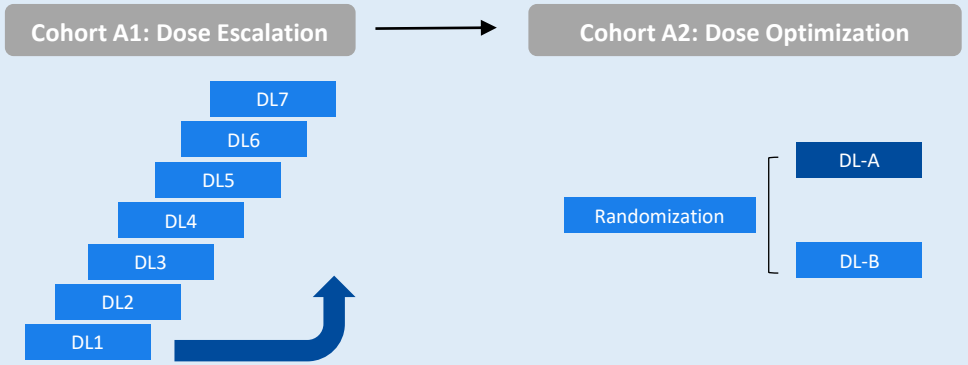
d) Clinical trial of a novel ADC or combination therapy

LY4052031

Phase 1a: Dose Escalation and Optimization

Key Eligibility Criteria:

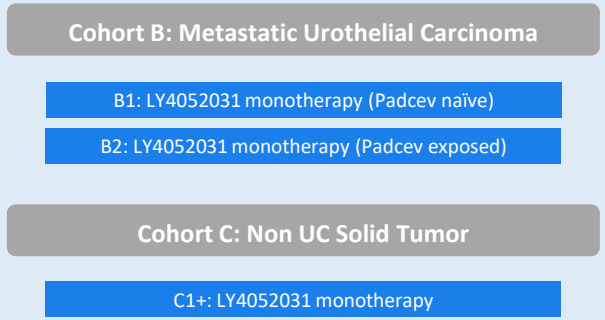
- Tumor types: UC, TNBC, NSCLC, Ovarian, Cervical, HNSCC, Esophageal, Pancreatic, and Prostate.
- Received SOC therapies or refused/ineligible SOC therapy.
- Non-measurable disease permitted only in Phase 1a dose escalation cohort.
- CrCl ≥ 50 ml/min



Phase 1b: Dose Expansion

Key Eligibility Criteria:

- Received at least 1 L of therapy (some disease types may require receiving all available SOC therapies or ineligible/refusing SOC therapy).
- Measurable disease.



1. Dosing schedule IV Q3 weeks.
2. 2-3 patients per dose level. Allow backfill up to 20 patients per select DL.
3. May have randomized dose optimization cohort if dose escalation data suggestive. Dose levels may be any monotherapy DL cleared by dose escalation step.
4. May include renal insufficiency sub-study on any monotherapy DL cleared by dose escalation step.
5. Sponsor may elect to begin phase 1b cohort 1C prior to identifying the RP2D/optimal dose.