GUARD CONSORTIUM

GUARD SYMPOSIUM

6-7 JULIO 2023

GU-Alliance for Research and Development

#guardsymposium2023

@GuardConsortium

TALLER
NUEVAS ESTRATEGIAS - ADCs

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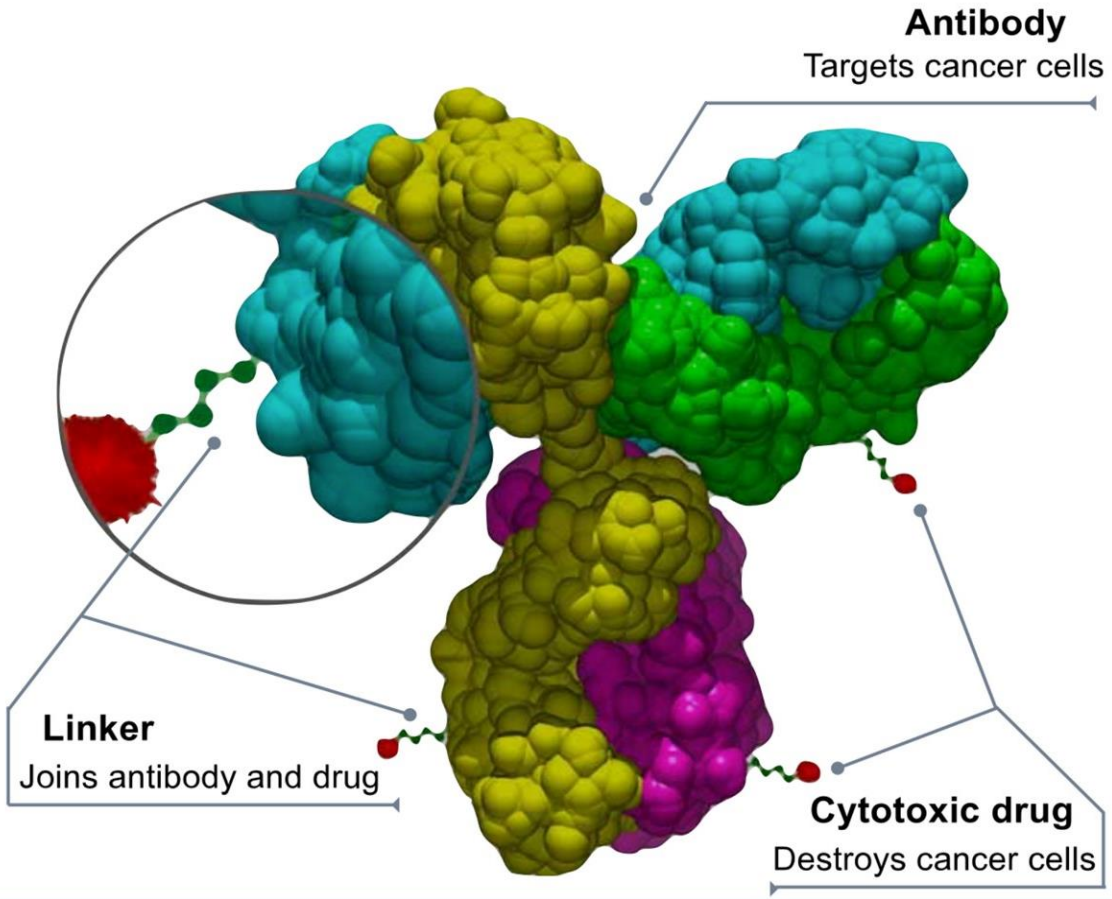


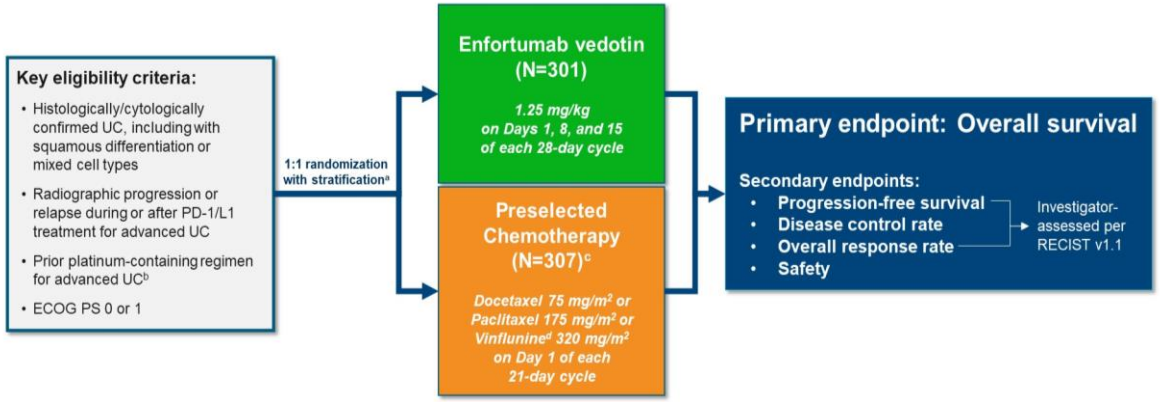
ANTIGEN SHOULD BE EXPRESSED BY TUMOR CELLS

ANTIGEN SHOULDN'T BE EXPRESSED BY NORMAL TISSUE (TOXICITY)

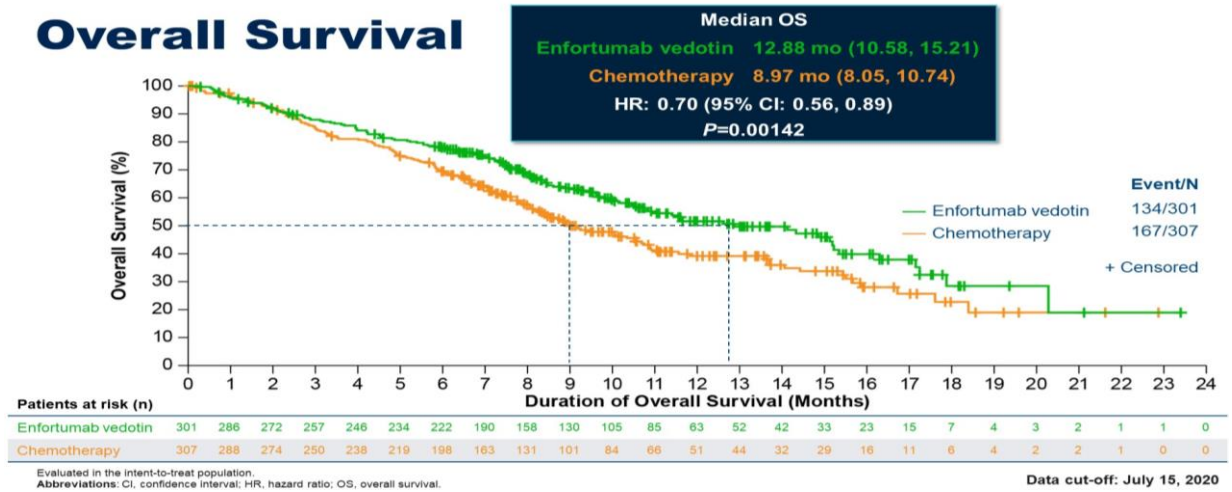
TUMOR SHOULD BE SENSITIVE TO THE CHOSEN CYTOTOXIC DRUG

LINKER SHOULD BE STABLE (AVOID SYSTEMIC TOXICITY)

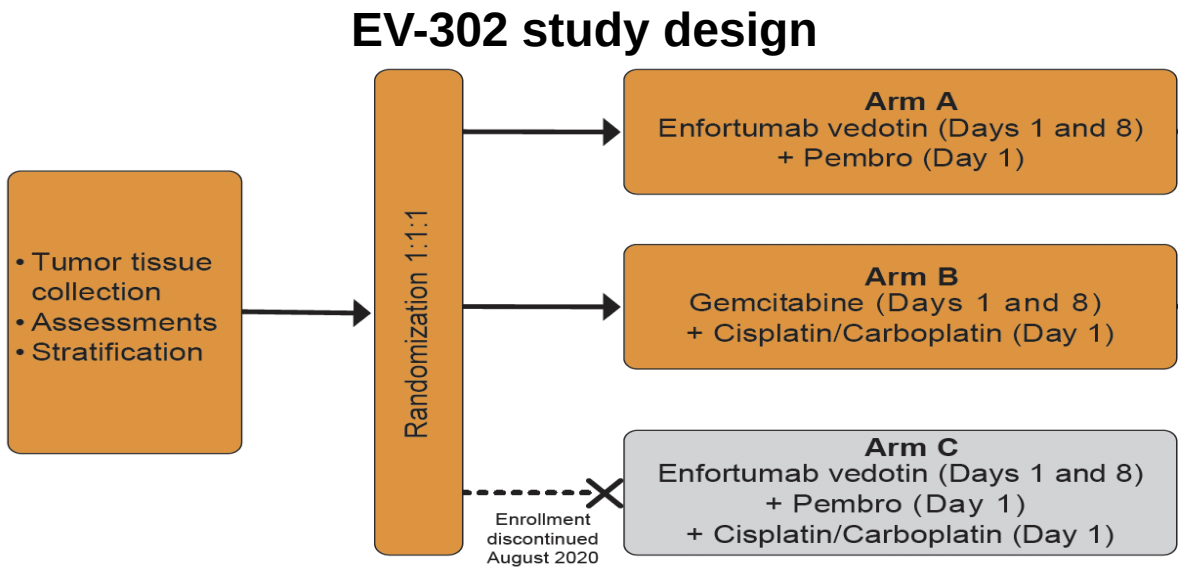
EV-301 Open-Label Phase 3 Trial Design

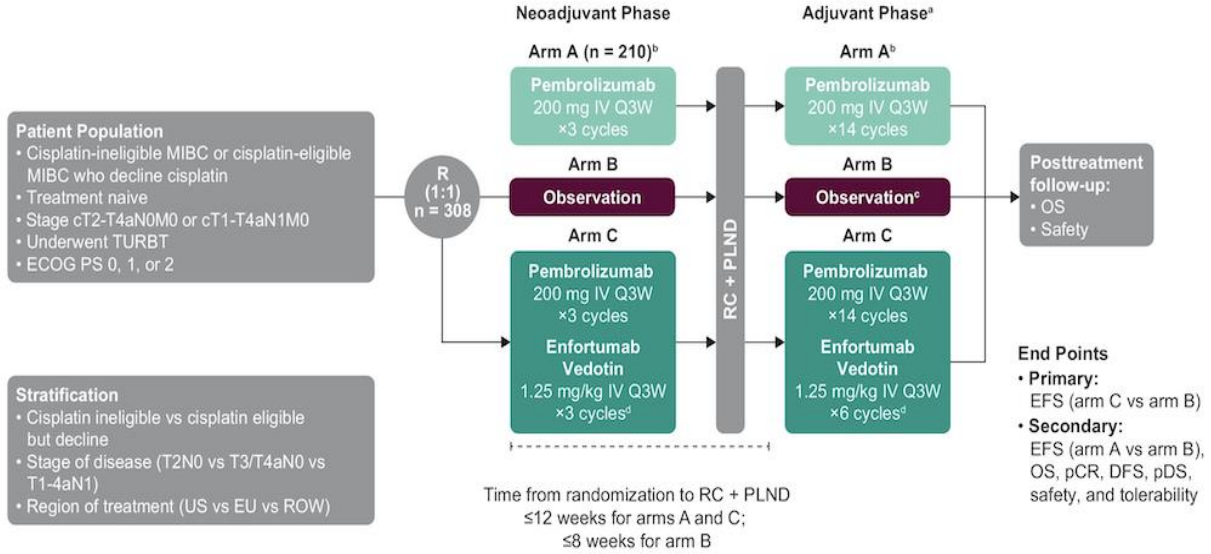


Overall Survival



EV-302 study design





TROPiCS-04 Study Design

TROPiCS-04 Urothelial Cancer

Study Population

- Locally advanced unresectable or mUC
- Upper/lower tract tumors
- Mixed histologic types are allowed if urothelial is predominant
- Progression after platinum-based **and** anti–PD-1/PD-L1 therapy

OR

- Platinum in neo/adj setting if progression within 12 months and subsequent CPI

N=482

SG
Sacituzumab govitecan
10 mg/kg
D1/8 of 21-day cycle

TPC
- Docetaxel @ 75 mg/m²
OR
- Paclitaxel @ 175 mg/m²
OR
- Vinflunine @ 320 mg/m² on D1 of 21-day cycle

Continue treatment until loss of clinical benefit or unacceptable toxicity

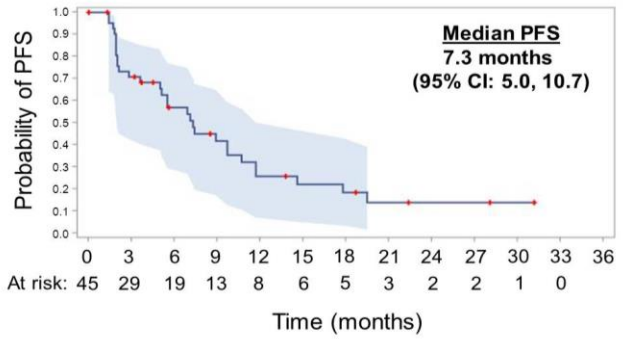
Endpoint (EP)

Primary EP:
- OS

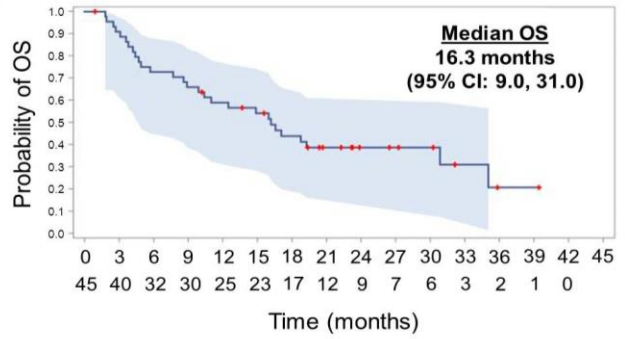
Secondary EP:
- PFS by PI assessment using RECIST 1.1
- ORR, DOR, and CBR by PI assessment using RECIST 1.1
- EORTC QLQ C30 score and EuroQOL EQ-5D-5L QOL score

Progression-Free and Overall Survival*

Progression-Free Survival



Overall Survival



Cohort 1[a] (~100 pts): Pts (≥18 years) with mUC who progressed after prior PT- and CPI-based therapies	SG 10 mg/kg D1 and D8, every 21 D
Cohort 2 (~40 pts): Pts with mUC who progressed after CPI therapy and were PT-ineligible at the start of study	SG 10 mg/kg D1 and D8, every 21 D Continue treatment in the absence of unacceptable toxicity or disease progression
Cohort 3 (up to 61 pts): CPI-naïve pts with mUC who progressed after prior PT-based therapies	SG 10 mg/kg D1 and D8, every 21 D + Pembrolizumab 200 mg D1 every 21 D
Cohort 4 (up to 57 pts): Pts with cis-eligible, treatment-naïve LA or mUC	Induction: cis+SG (6 cycles); Maintenance: (1) SG+avelumab; (2) SG+zim
Cohort 5[b] (~158 pts): Pts with LA or mUC who completed 1L cis + gem without progression	Arms: (1) SG+zim; (2): avelumab; (3): zim
Cohort 6 (up to 226 pts): Pts with cis-ineligible, treatment-naïve LA or mUC	Arms: (1) SG; (2) SG+zim; (3) SG+zim+dom; (4) carbo+gem+avelumab maintenance

DS8201-A-U105 Study Design

Key Eligibility Criteria

- HER2-expressing advanced/metastatic BC or UC (centrally confirmed)
- ECOG PS 0 or 1
- ≥1 measurable lesion per RECIST v1.1
- No prior T-DXd or I-O
- To be eligible for part 1, patients must meet additional cohort specific criteria of part 2

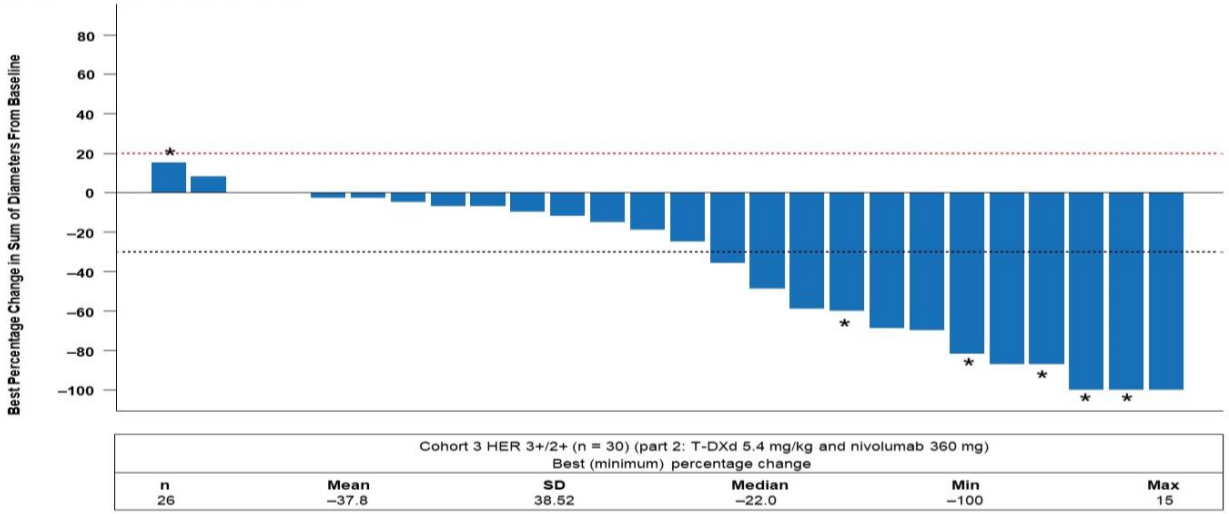
Part 1: Dose Escalation

- T-DXd 3.2 mg/kg + Nivolumab 360 mg Q3W[a] n = 4
- T-DXd 5.4 mg/kg + Nivolumab 360 mg Q3W[a] n = 3

→ RDE[b]

Part 2: Dose Expansion

- Cohort 1: HER2-positive (IHC 3+ or IHC 2+/ISH+) BC after T-DM1 n = 29
- Cohort 2: HER2 low (IHC 1+ or IHC 2+/ISH-) BC after standard treatment n = 16
- **Cohort 3: HER2 high (IHC 3+/2+) UC after chemotherapy n = 30**
- **Cohort 4: HER2 low (IHC 1+) UC after chemotherapy n = 4**



Eligibility:

- LA/mUC
- Previously untreated
- Eligible for platinum
- Central lab HER2 status ≥ IHC 1+

(n=700)

R 1:1

DV + Pembrolizumab
*Treatment until progression

Cisplatin/Carboplatin + Gemcitabine
X 4-6 cycles

Stratification Factors:

- Cisplatin eligible vs. ineligible
- PD-L1 expression
- HER2 status
- Geographical Region

Dual-Primary Endpoints

- **PFS by BICR**
- **OS**

* DV 2.0 mg/kg Q2W until disease progression and pembrolizumab 400 mg Q6W for up to 18 cycles

** **Crossover to the experimental arm will not be permitted for subjects in the control arm)**

Toxicity (*ADC*)	Severity	Management of Toxicity
Skin reactions (*EV*)	Suspected SJS or TEN	Immediately withhold EV and refer to specialized care Permanently discontinue in confirmed cases
	Grade 2	Withhold until ≤grade 1 Consider referral to specialized care Consider dose reduction if rechallenging after grade 2 toxicity
Hyperglycemia (*EV*)	Blood glucose >13.9 mmol/L (>250 mg/dL)	Withhold until elevated blood glucose has improved to ≤13.9 mmol/L (≤250 mg/dL) Resume treatment at the same dose
Peripheral neuropathy (*EV*)	Grade 2	Withhold until ≤grade 1 For first occurrence, resume treatment at the same dose level. Consider dose reduction for rechallenge after recurrences
	Grade ≥3	Permanently discontinue
Pneumonitis (*trastuzumab deruxtecan*, *trastuzumab emtansine*)	Grade ≥2	Referral to pulmonary, CT thorax, PFT if pneumonitis/ILD suspected Permanently discontinue
Ocular toxicity (*EV*)	Grade ≥2	Consider referral to specialized care Consider topical ophthalmic corticosteroids

Abbreviations: ADC, antibody-drug conjugate; CT, computed tomography; EV, enfortumab vedotin; ILD, interstitial lung disease; PFT, phenylalanine mustard, fluorouracil, tamoxifen; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

ANTI NECTINA-4

ENFORTUMAB:
1L ENF.MTS
PERIOPERATORIO

ANTI TROP-2

SACITUZUMAB:
PERIOP (F.II) +/- PEMBRO

DATOPOTOMAB:

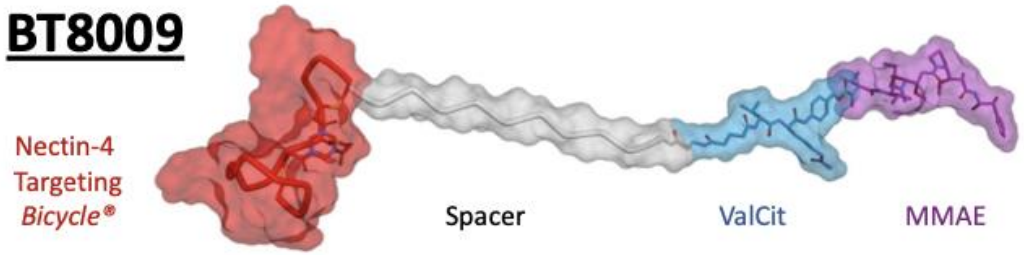
ANTI HER-2

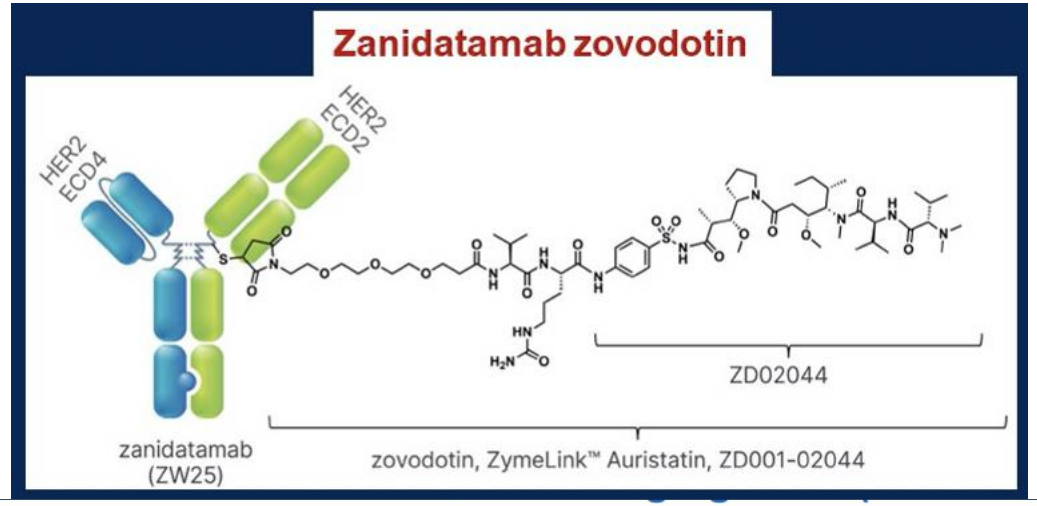
DISITAMAB:
1L ENF.MTS

TRASTU-DERUXTECÁN

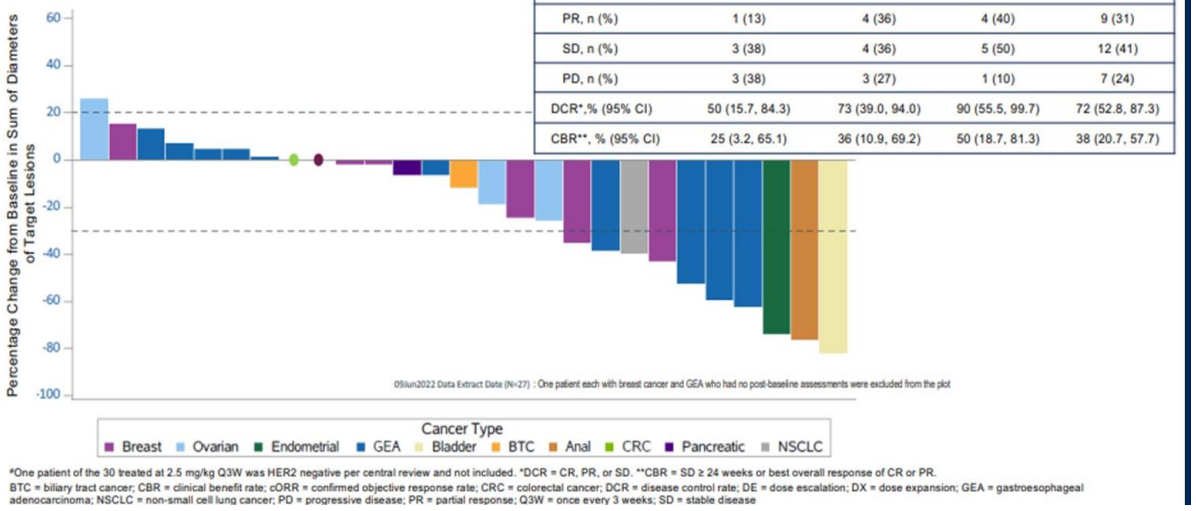
First-in-Human Study with a *Bicycle®* Toxin Conjugate targeting Nectin-4 with an MMAE cytotoxic payload. Patient enrollment ongoing.

BT8009





	Breast (n=8)	GEA (n=11)	All Other (n=10)	Total (N=29)#
cORR, % (95% CI)	13 (0.3, 52.7)	36 (10.9, 69.2)	40 (12.2, 73.8)	31 (15.3, 50.8)
PR, n (%)	1 (13)	4 (36)	4 (40)	9 (31)
SD, n (%)	3 (38)	4 (36)	5 (50)	12 (41)
PD, n (%)	3 (38)	3 (27)	1 (10)	7 (24)
DCR*,% (95% CI)	50 (15.7, 84.3)	73 (39.0, 94.0)	90 (55.5, 99.7)	72 (52.8, 87.3)
CBR**, % (95% CI)	25 (3.2, 65.1)	36 (10.9, 69.2)	50 (18.7, 81.3)	38 (20.7, 57.7)



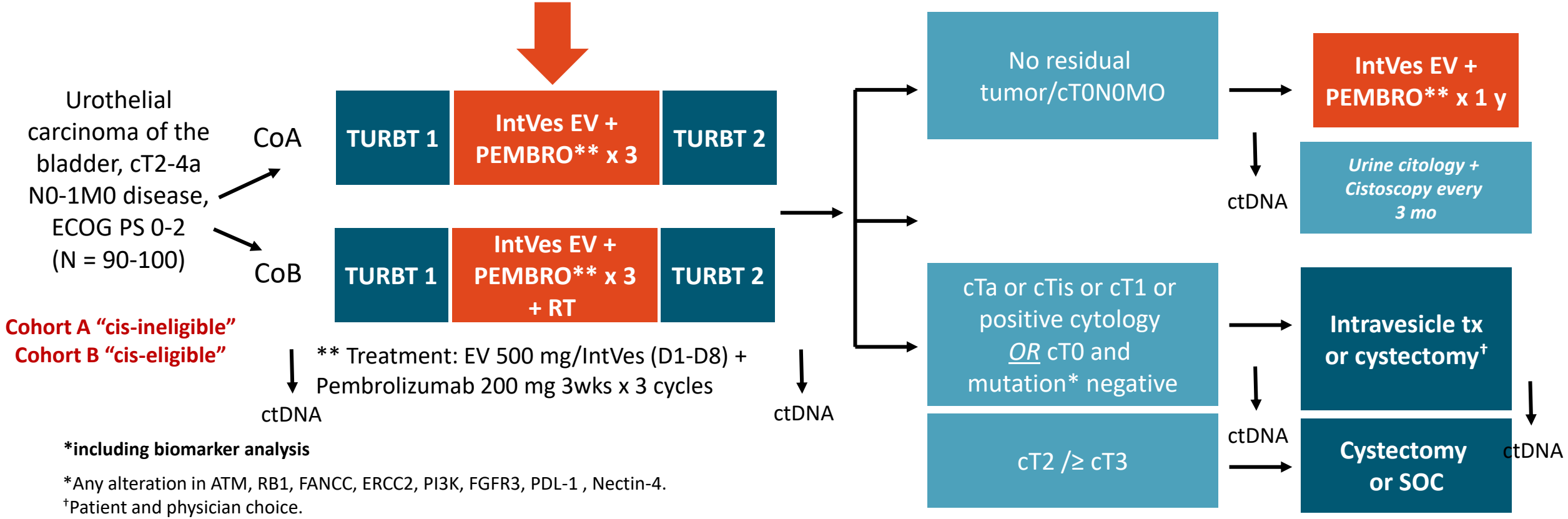
*One patient of the 30 treated at 2.5 mg/kg Q3W was HER2 negative per central review and not included. *DCR = CR, PR, or SD. **CBR = SD ≥ 24 weeks or best overall response of CR or PR.
BTC = biliary tract cancer; CBR = clinical benefit rate; cORR = confirmed objective response rate; CRC = colorectal cancer; DCR = disease control rate; DE = dose escalation; DX = dose expansion; GEA = gastroesophageal adenocarcinoma; NSCLC = non-small cell lung cancer; PD = progressive disease; PR = partial response; Q3W = once every 3 weeks; SD = stable disease

PROYECTOS - PROPUESTAS EN DESARROLLO

- Análisis de los pacientes en uso compasivo de Enfortumab-vedotín en España
- Elaboración de consenso sobre manejo de toxicidad por ADCs

Perioperative IntraVesical-EV + IV PEMBRO +/- RT for Bladder cancer as part of Risk-adapt Bladder-Sparing approach

- Single-arm, open-label proof of concept trial

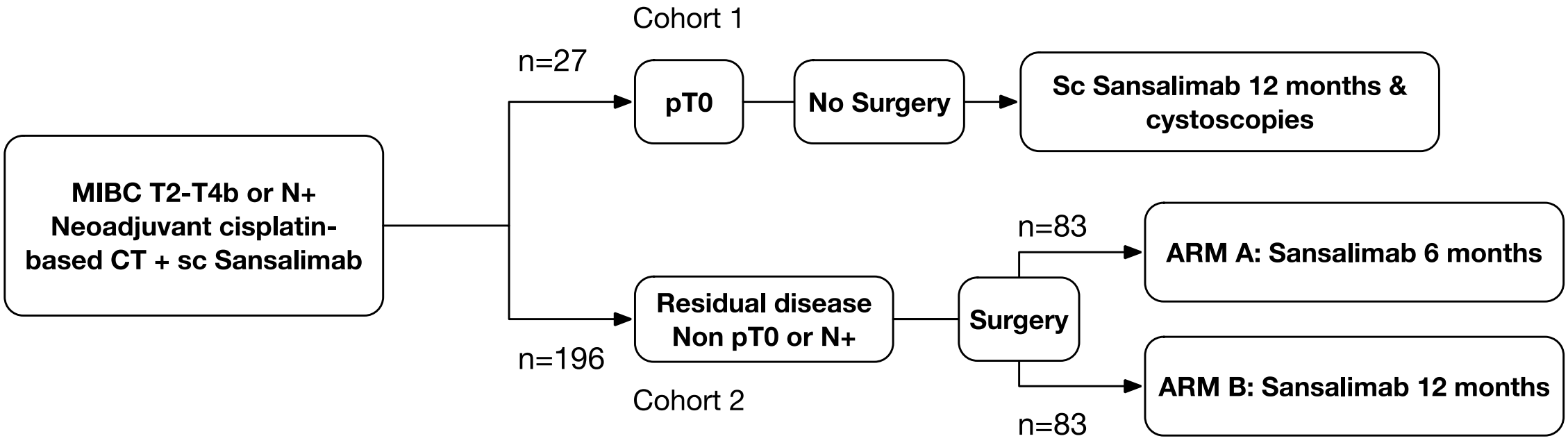


***including biomarker analysis**

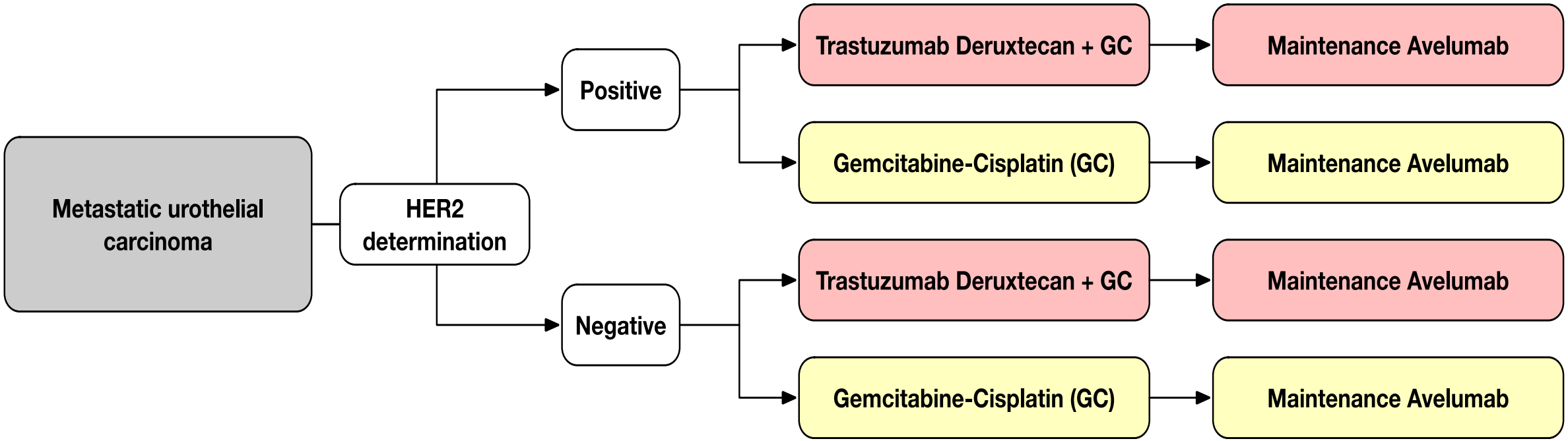
*Any alteration in ATM, RB1, FANCC, ERCC2, PI3K, FGFR3, PDL-1 , Nectin-4.
†Patient and physician choice.

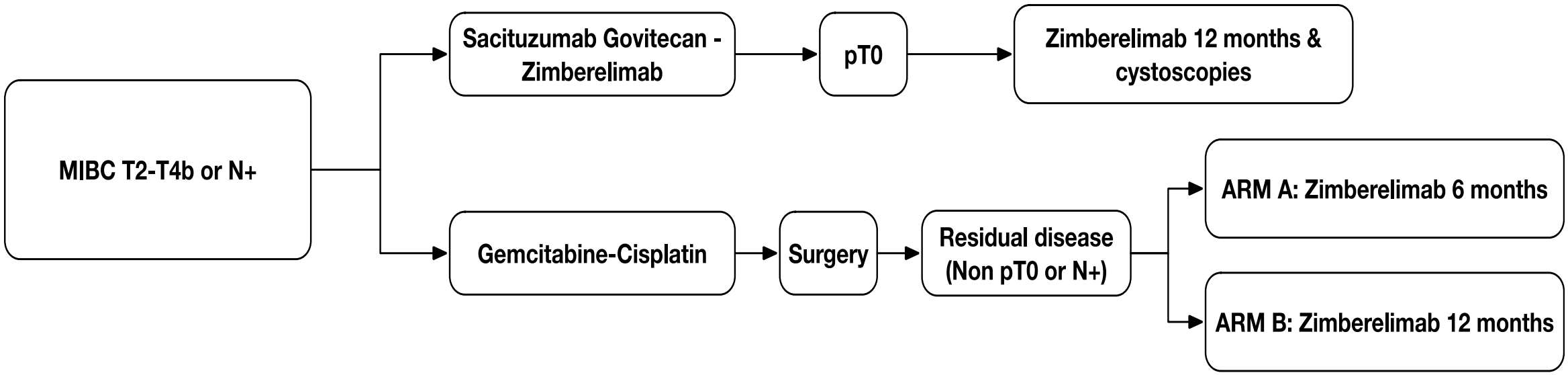
- Primary endpoint:** pCR by sequential TURBT, mets and local relapsed 2 years-disease free survival (Secondary endpoints:, safety, TTF, OS)

Phase II trial



Primary Endpoint: 2 years DFS outside bladder


Metastatic urothelial carcinoma
HER2 determination
Positive
Negative
Trastuzumab Deruxtecan + GC
Gemcitabine-Cisplatin (GC)
Trastuzumab Deruxtecan + GC
Gemcitabine-Cisplatin (GC)
Maintenance Avelumab
Maintenance Avelumab
Maintenance Avelumab
Maintenance Avelumab


MIBC T2-T4b or N+
Sacituzumab Govitecan - Zimberelimab
pT0
Zimberelimab 12 months & cystoscopies
Gemcitabine-Cisplatin
Surgery
Residual disease (Non pT0 or N+)
ARM A: Zimberelimab 6 months
ARM B: Zimberelimab 12 months

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