#guardsymposium2026
@GuardConsortium

GUARD CONSORTIUM

ADVANCED UROTHELIAL CARCINOMA · 2026

Beyond Enfortumab Vedotin – Pembrolizumab

Second- and third-line treatment in advanced urothelial carcinoma: what real-world data and the 2026 guidelines now allow us to say.

Urbano Anido Herranz, MD · September 2026

Disclosures

Stocks

Novavax, Biomea Fusion, Candel Therapeutics, Personalis

Consultant or advisory board

Novartis, Ipsen, AstraZeneca, Merck, Pfizer, Astellas, Bayer, Janssen, Recordati, MSD

Travel support

Ipsen, Bayer, Merck, Pfizer, Novartis, AstraZeneca

Honoraria

Novartis, Ipsen, Astellas, Bayer, BMS, Pfizer, Roche, AstraZeneca, Merck, Eisai, Rovi, Priothera

Contents

01 The first line has moved the problem

02 Real-world evidence after EV + pembrolizumab

03 Biomarker-directed options

04 Sequencing in practice

01

The first line has moved the problem

GUARD CONSORTIUM

EV + pembrolizumab has displaced platinum from first line

Objective response

67.7%

With 29.1% complete responses, against 44.4% with platinum-based chemotherapy.

Median PFS

12.5 mo

Versus 6.3 months with chemotherapy in the EV-302 comparator arm.

Median OS

33.6 mo

Versus 15.9 months — the largest survival gain seen in this disease.

Powles T, et al. N Engl J Med. 2024;390:875–888.

The therapeutic bottleneck has moved to second line

The question

The question is no longer which treatment follows platinum, but how to sequence platinum, targeted agents and new ADCs after EV and pembrolizumab.

The evidence

No prospective trial has been designed in this setting; the evidence available today is almost entirely retrospective.

The constraint

Attrition is the constraint: across real-world sequences only a minority of patients ever start a third line, so agents kept in reserve are frequently never used.

Moinard-Butot F, et al. STATES-Bladder. Urol Oncol. 2026;44:111036.

EAU 2026 addresses the post-EV setting explicitly

Platinum doublet

Cisplatin or carboplatin with gemcitabine after EV plus a checkpoint inhibitor — weak recommendation, in the absence of prospective trials.

Erdafitinib

Strong recommendation in tumours with susceptible FGFR3 alterations, on the strength of the THOR trial.

Trastuzumab deruxtecan

After exposure to EV, immunotherapy and platinum in HER2 IHC 3+; may be considered in IHC 2+.

EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer, 2026 — metastatic disease.

02

Real-world evidence after EV + pembrolizumab

GUARD CONSORTIUM

Six cohorts describe the same second line

COHORT	2L, N / N	TREATMENT AFTER EV+P	OUTCOMES
UNITE, ASCO GU 2026	68 of 377	Platinum 39% · SG 21% · erdafitinib 10% · T-DXd 9%	ORR 24%, mPFS 2.8 mo, mOS 9.0 mo
Flatiron Health 2026	118 of 757	Carboplatin 35% · cisplatin 13% · EV re-challenge 13%	rwOS 7.1 / 8.3 / 8.5 mo; “other” 14.0 mo
MSKCC 2026	46 of 236	Carboplatin n=34 · cisplatin n=12	ORR 49%, mPFS 5.0 mo, mOS 12 mo
PrecisionQ, USA 2026	46 of 406	Chemotherapy in 32 of 46	TTNT from 1L 9.7 mo
GUARDIANS, Germany	60 of 468	Platinum predominant; also FGFRi, vinflunine, taxanes, SG, T-DXd	Same pattern outside the USA
Athens cohort, ASCO 2026	10 of 62	Platinum	mPFS after platinum 6.1 mo

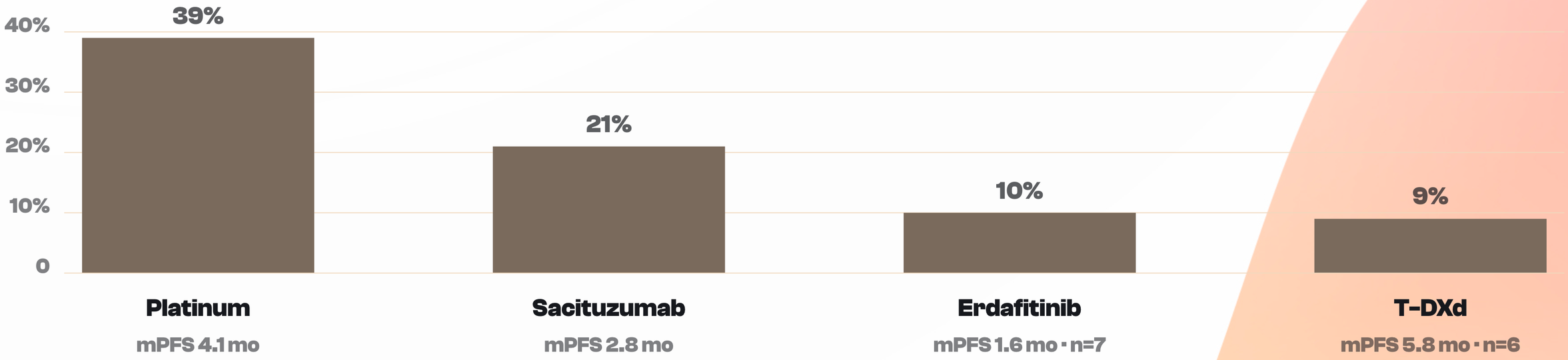
> “Across real-world datasets, platinum chemotherapy is emerging as the predominant second-line strategy after EV + pembrolizumab.”

49%

Objective response to platinum after EV and pembrolizumab in the MSKCC cohort: 46 of 236 patients treated, median DOR 5.2 months, mPFS 5.0 months, mOS 12 months. No difference between cisplatin and carboplatin, on a sample far too small to claim equivalence.

Sternschuss M, et al. ESMO Open. 2026;11(8):108318.

UNITE shows what is used, not what works best



Share of second-line treatments in the cohort, with median PFS below each bar. Group sizes are minute: this figure describes practice, not comparative efficacy.

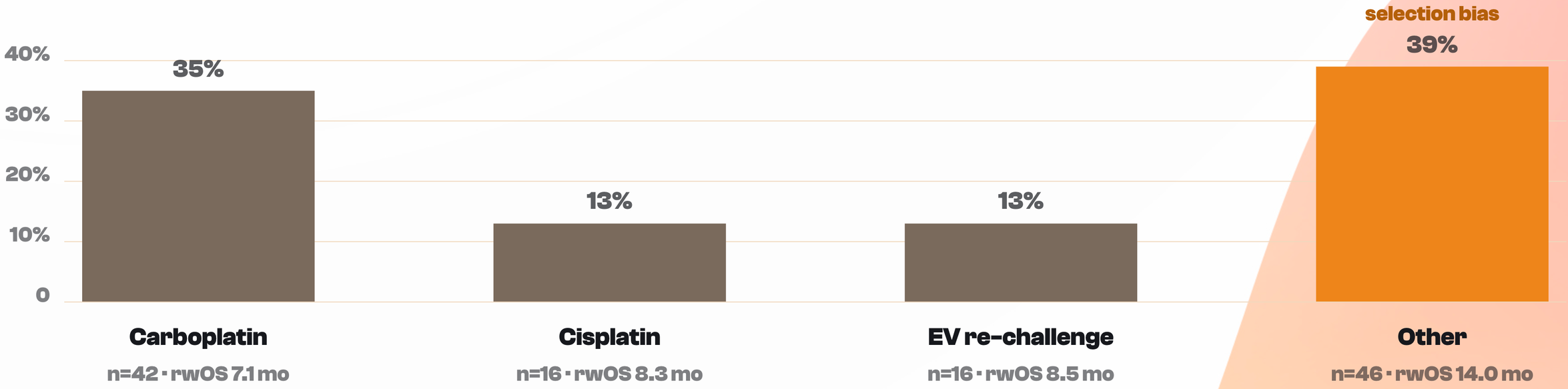
Jiang CY, et al. J Clin Oncol. 2026;44(suppl 7):705.

#guardsymposium2026

@GuardConsortium

GUARD CONSORTIUM

The Flatiron “other” group reflects selection, not superiority



Share of second-line treatments in the cohort, with median real-world OS below each bar. The “other” group pools biomarker-selected patients — erdafitinib 11, T-DXd 11, sacituzumab 10 — and cannot be compared causally with the platinum arms. Gebrael G, et al. Bladder Cancer. 2026.

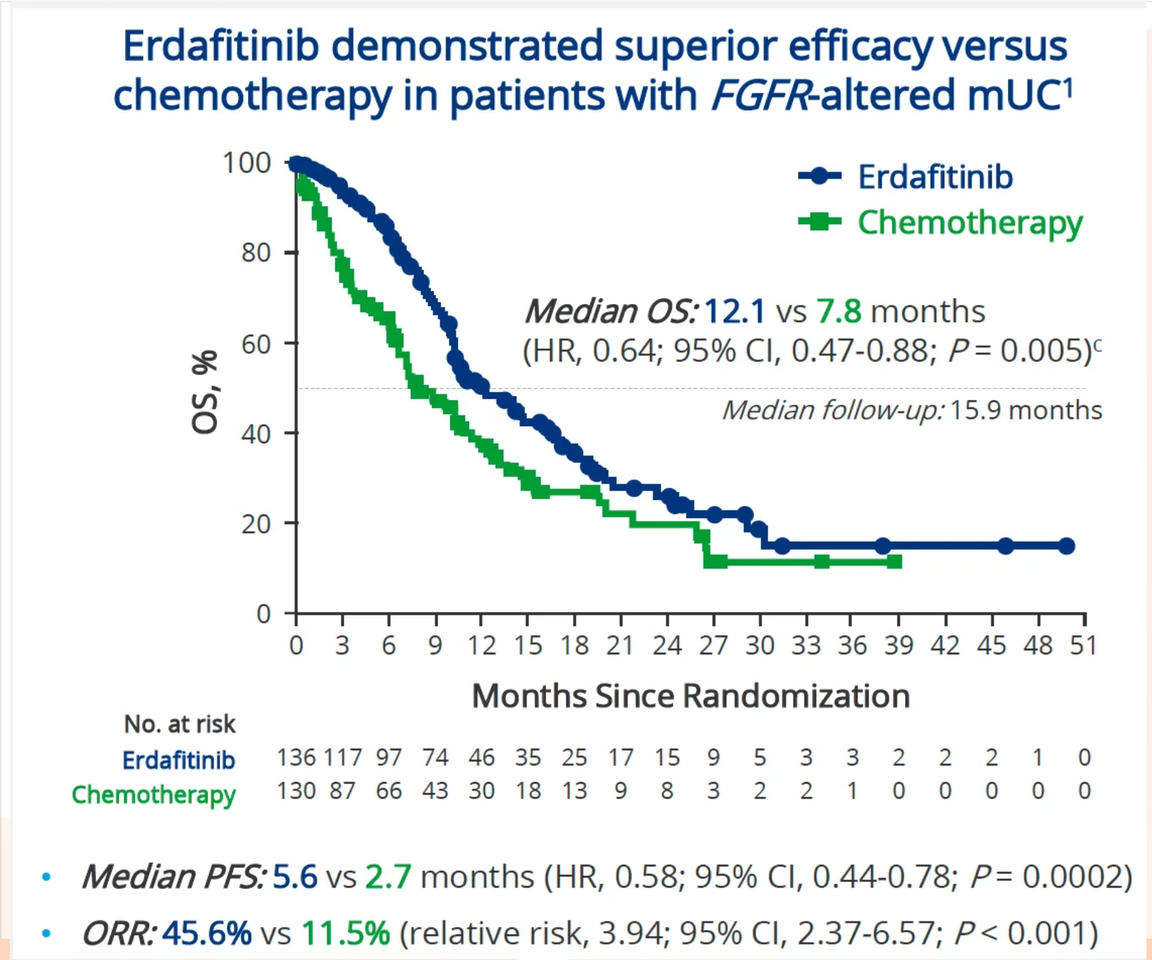
03

Biomarker-directed options

GUARD CONSORTIUM

Erdafitinib retains activity after enfortumab vedotin

- UNITE, FGFR3-altered: erdafitinib before EV, ORR 33% and mPFS 7.5 months; after EV, ORR 31% and mPFS 4.0 months.
- THOR, after anti-PD-1/L1: OS 12.1 versus 7.8 months, HR 0.64; mPFS 5.6 versus 2.7 months.
- Approved in Europe for FGFR3-altered disease after a PD-1/PD-L1-containing line.
- Request FGFR3 before second line is needed, not at rapid progression.

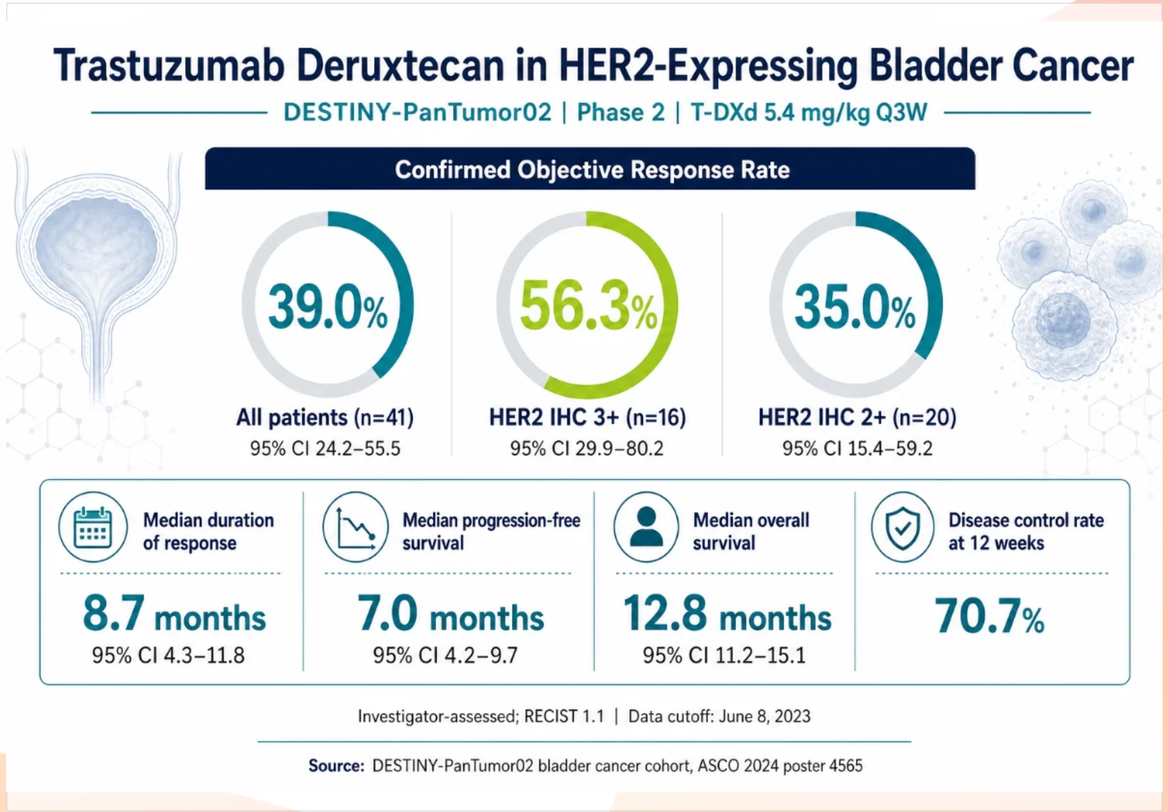


#guardsymposium2026
@GuardConsortium

GUARD CONSORTIUM

HER2 testing belongs in the initial profiling panel

- DESTINY-PanTumor02 bladder cohort: 41 patients with HER2-expressing urothelial carcinoma, ORR approximately 39% in a heavily pretreated population.
- EAU 2026 recommends T-DXd after EV, checkpoint inhibitor and platinum in HER2 IHC 3+, and allows it to be considered in IHC 2+.
- The European label covers HER2 IHC 3+ solid tumours previously treated and without satisfactory alternatives.



#guardsymposium2026
@GuardConsortium

GUARD CONSORTIUM

Sacituzumab govitecan has lost its place after EV

- MSKCC, 82 patients treated after EV: ORR 11%, mPFS 2.1 months, mOS 6.0 months.
- UNITE, 107 patients after EV: ORR 18%, mPFS 3.2 months, mOS again 6.0 months.
- TROPiCS-04 was negative and the US urothelial indication was withdrawn; EAU 2026 already records that withdrawal.
- Its remaining interest is historical, investigational or dependent on local availability.

Sternschuss M, et al. ESMO Open. 2025;10:105305 · UNITE, PMID 41152111 · EAU 2026, summary of changes.

“Platinum → avelumab after prior pembrolizumab: biologically plausible, clinically unproven.”

— 9 of 46 platinum-treated patients in the MSKCC cohort received avelumab; beyond that, a three-case series

04

Sequencing in practice

GUARD CONSORTIUM

A practical algorithm for 2026

First line

EV + pembrolizumab

At progression, FGFR3 and HER2 status should already be available.

Second line

FGFR3 wild-type

Gemcitabine–cisplatin if genuinely cisplatin-fit; gemcitabine–carboplatin if cisplatin-ineligible.

FGFR3-altered

Erdafitinib or platinum. No prospective comparison exists; platinum is reasonable in rapidly progressing visceral disease.

Third line

Erdafitinib if unused · T-DXd if HER2 IHC 3+ · clinical trial whenever possible

Taxane, vinflunine or other palliative chemotherapy in selected patients. EV re-challenge only in highly selected cases; avelumab after platinum remains investigational.

Four randomised trials will answer this

TRIAL · NCT	PHASE · N	ENTRY AFTER EV+P	COMPARISON	PRIMARY	SPAIN
TROPION-Urothelial03 · NCT07129993	2/3 · 630	Progression during/after 1L EV+P; platinum-eligible	Dato-DXd + carbo/cis *vs* gemcitabine + carbo/cis	PFS-BICR + OS	No sites
IZABRIGHT-Bladder01 · NCT07106762	2/3 · 470	Progression on/after immunotherapy; platinum-eligible; ≤2 lines	Iza-bren, bispecific EGFR×HER3 ADC, *vs* platinum chemotherapy	PFS-BICR + OS	11 sites
TroFuse-031 · NCT07419295	3 · 590	Prior anti-PD-(L)1 **and** platinum **and** EV; ≤2 lines	Sac-TMT *vs* investigator's choice non-platinum chemotherapy	OS	8 sites
SG + pembrolizumab, NCI · NCT06524544	3 · 320	Anti-PD-(L)1-resistant, primary resistance excluded; prior EV mandatory	SG + pembrolizumab *vs* physician's choice chemotherapy	OS	US only

An anti-TROP2 ADC or any topoisomerase I payload used off-trial closes four of these protocols at once. Mature data 2029–2030.

TROPION-Urothelial03 adds Dato-DXd to the platinum we already give

SPONSOR
Daiichi Sankyo with AstraZeneca

PHASE · N
Phase 2/3 · 630

DESIGN
Randomised, open-label, two parts

OPENS — READS OUT
Sep 2025 — Jun 2029

SITES
Global; none in Spain

POPULATION
la/mUC progressing during or after first-line EV+P

→

KEY SELECTION
Platinum candidate: cisplatin if fit, carboplatin only if ineligible. No other prior line for advanced disease

→ **R** open-label

EXPERIMENTAL
Dato-DXd + carboplatin or cisplatin
TROP2 ADC, deruxtecan payload

CONTROL
Gemcitabine + carboplatin or cisplatin
Split-dose cisplatin allowed if CrCl 40–60

→

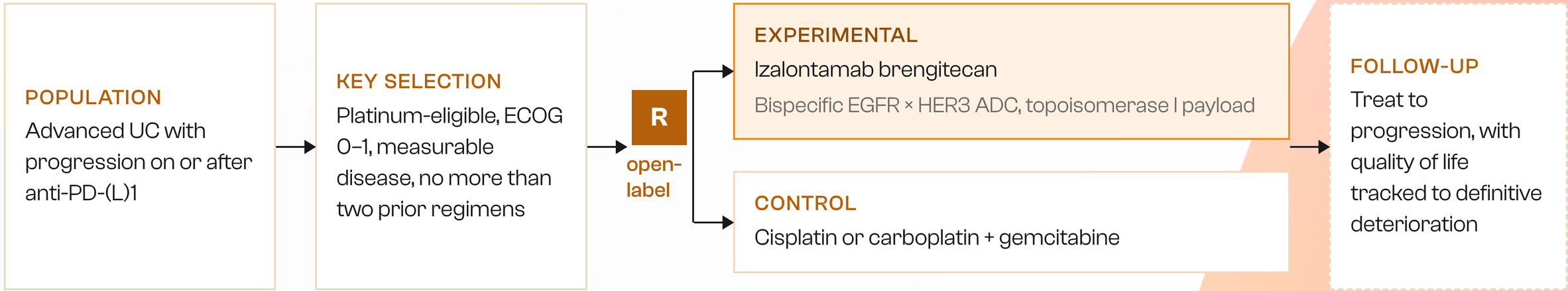
FOLLOW-UP
Treat to progression; part B opens conditional on the part A read

PRIMARY — ORR IN PHASE 2; BICR PFS AND OS CO-PRIMARY IN PHASE 3

> **Excludes** any other prior line, prior anti-TROP2 ADC and any history of ILD. The only trial defined by EV+P as the sole prior line, so it answers the second-line question directly — but it excludes the patient EV itself has made platinum-unfit.

IZABRIGHT is the trial with the widest Spanish footprint

SPONSOR	PHASE · N	DESIGN	OPENS — READS OUT	SITES
Bristol-Myers Squibb	Phase 2/3 · 470	Randomised, open-label	Sep 2025 — Jan 2029	163, of them 11 in Spain



PRIMARY — RECOMMENDED PHASE 3 DOSE, THEN BICR PFS AND OS CO-PRIMARY

Excludes platinum within 12 months, prior EGFR or HER3 ADC and any prior topoisomerase I inhibitor. Defined by prior immunotherapy, not prior EV: it will pool post-EV-P patients with the classic platinum → anti-PD-(L)1 pathway.

TroFuse-031 requires platinum first, so in Europe it is a third-line trial

SPONSOR	PHASE · N	DESIGN	OPENS — READS OUT	SITES
MSD	Phase 3 · 590	Randomised, open-label	Apr 2026 — Jul 2029	90, of them 8 in Spain

POPULATION
la/mUC with radiographic progression on the immediately preceding line

KEY SELECTION
Prior anti-PD-(L)1 *and* platinum *and* EV, all three. ECOG 0–1, no more than two prior lines

R
open-label

EXPERIMENTAL
Sacituzumab tirumotecan
TROP2 ADC, topoisomerase I payload

CONTROL
Investigator's choice single-agent non-platinum chemotherapy

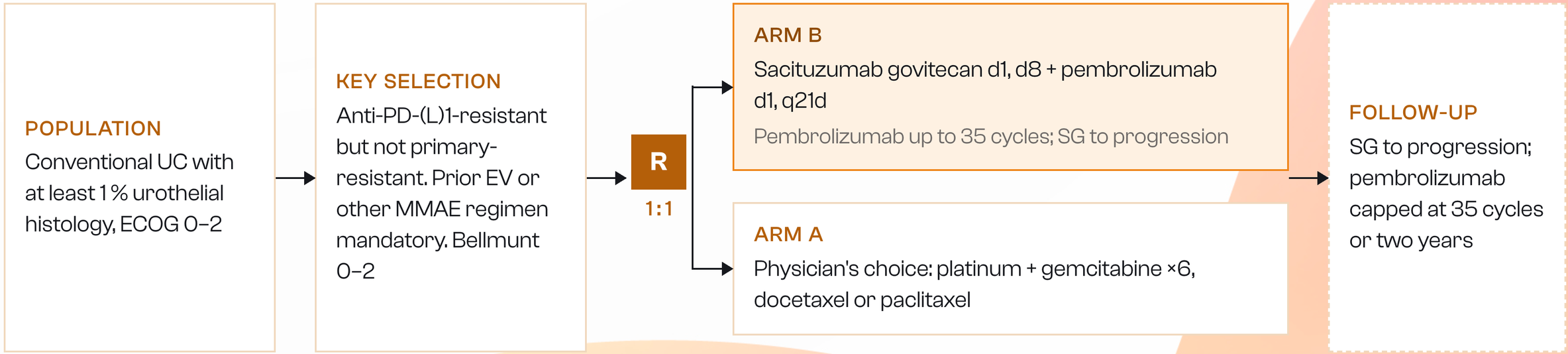
FOLLOW-UP
Treat to progression, with EORTC QLQ-C30 at every cycle

PRIMARY — OVERALL SURVIVAL

Excludes prior anti-TROP2 or topoisomerase I payload ADC, CNS metastases and severe dry eye or blepharitis. Prior platinum is mandatory, so second line straight after EV+P does not qualify.

The NCI trial re-challenges with pembrolizumab, in a highly selected cohort

SPONSOR	PHASE · N	DESIGN	OPENS — READS OUT	SITES
National Cancer Institute	Phase 3 · 320	Randomised 1:1, open-label	Dec 2025 — Dec 2030	United States only

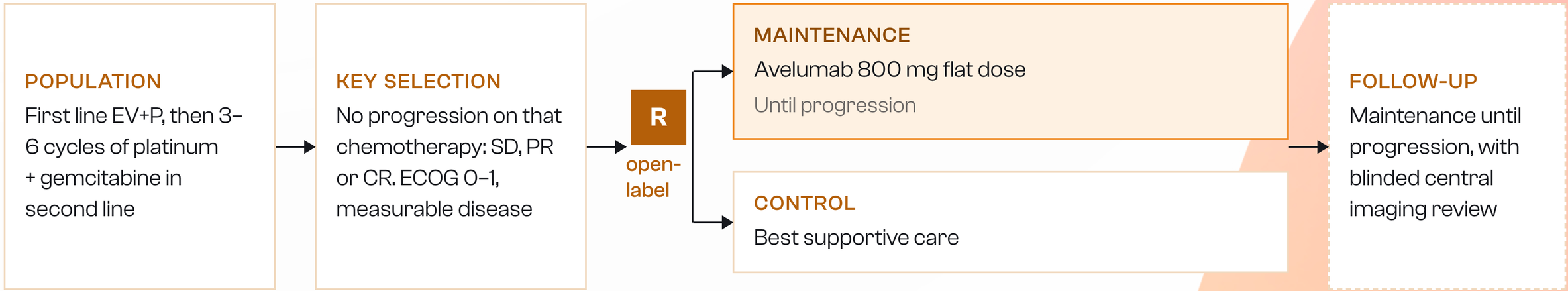


PRIMARY — OVERALL SURVIVAL

Excludes progression within 12 weeks of the first anti-PD-(L)1, prior grade ≥ 3 immune toxicity and prior anti-TROP2 ADC. A susceptible FGFR3 alteration obliges a prior FGFR inhibitor: the trial orders the sequence rather than randomising it.

AVESEC revisits maintenance immunotherapy after pembrolizumab

SPONSOR	PHASE · N	DESIGN	OPENS — READS OUT	SITES
GOIRC, Italy	Phase 2 · 144	Randomised, open-label	Jun 2026 — not stated	19, all in Italy



PRIMARY — 12-MONTH PFS BY BLINDED CENTRAL REVIEW

Excludes progression on second-line chemotherapy and prior grade ≥ 3 checkpoint-inhibitor toxicity. The only trial carrying the JAVELIN Bladder 100 paradigm into the post-EV-P setting.

A single-arm trial finally measures what we already do by default

SPONSOR	PHASE · N	DESIGN	OPENS — READS OUT	SITES
Fox Chase Cancer Center	Phase 2 · 55	Single-arm, two-stage	Jul 2025 — Jan 2030	Single centre, Fox Chase

POPULATION
Ia/mUC with exactly one prior line: EV+P

→

KEY SELECTION
Platinum-naive for advanced disease, ECOG 0–2. May start within 28 days of the last EV-P dose

→

SINGLE ARM
Gemcitabine 1,000 mg/m² d1, d8 + carboplatin AUC 5 d1, q21d

To progression · CT or MRI every 9 weeks

→

STAGE 1 · N = 19
Futility analysis; the trial stops here if response is insufficient

→

STAGE 2 · TO N = 55
Full accrual, with blood and ctDNA correlatives

PRIMARY — BEST OVERALL RESPONSE BY RECIST 1.1

> **Excludes** prior platinum for advanced disease and CrCl ≤ 20 mL/min. Not a new drug but a benchmark: it calibrates the control arms of TU03, IZABRIGHT and the NCI trial against current default practice.

Zanzalintinib is the only non-ADC, oral strategy on the list

SPONSOR	PHASE · N	DESIGN	OPENS — READS OUT	SITES
Investigator-initiated, with Exelixis	Phase 2 · 44	Single-arm, open-label	Oct 2026 — not stated	United States only

POPULATION
Predominant UC after 1–3 prior lines that must include EV and anti-PD-(L)1

→

KEY SELECTION
No prior VEGF inhibitor, ECOG 0–2. Prior platinum permitted but not required

→

SINGLE ARM
Zanzalintinib 60 mg once daily, oral, to progression

VEGFR / MET / AXL inhibitor

→

IMAGING
Every 8 weeks for three assessments, then every 12 weeks

→

ANALYSIS · N = 44
Full accrual, with PFS, duration of response and OS as secondary

PRIMARY — OBJECTIVE RESPONSE RATE

> **Excludes** any prior VEGF inhibitor, more than three prior lines, LVEF below 50 % and QTcF above 480 ms. The option for the patient who has exhausted the ADCs or cannot take another intravenous schedule.

Messages to take home

01 EV + pembrolizumab has moved the bottleneck to second line.

02 **Platinum dominates real-world second line: ORR 49%, mPFS 5.0 mo, mOS 12 mo.**

03 No evidence that cisplatin beats carboplatin here; choose on fitness.

04 Sequencing is no longer only “by line” — test FGFR3 and HER2 early.

05 Third line is biomarker-directed: erdafitinib, T-DXd, and trials for the rest.

ADVANCED UROTHELIAL CARCINOMA · 2026

Thank you

Questions welcome

Urbano Anido Herranz, MD

GUARD CONSORTIUM