SITC-IBCG Guidelines
Locally advanced/Metastatic Urothelial Cancer

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Disclosures

Consultant: Merck, Pfizer, EMD Sorono, Astellas, Seattle Genetics, Gilead Sciences, Natera, Guardant Health, Foundation Medicine, Bayer, Bristol Myers Squibb

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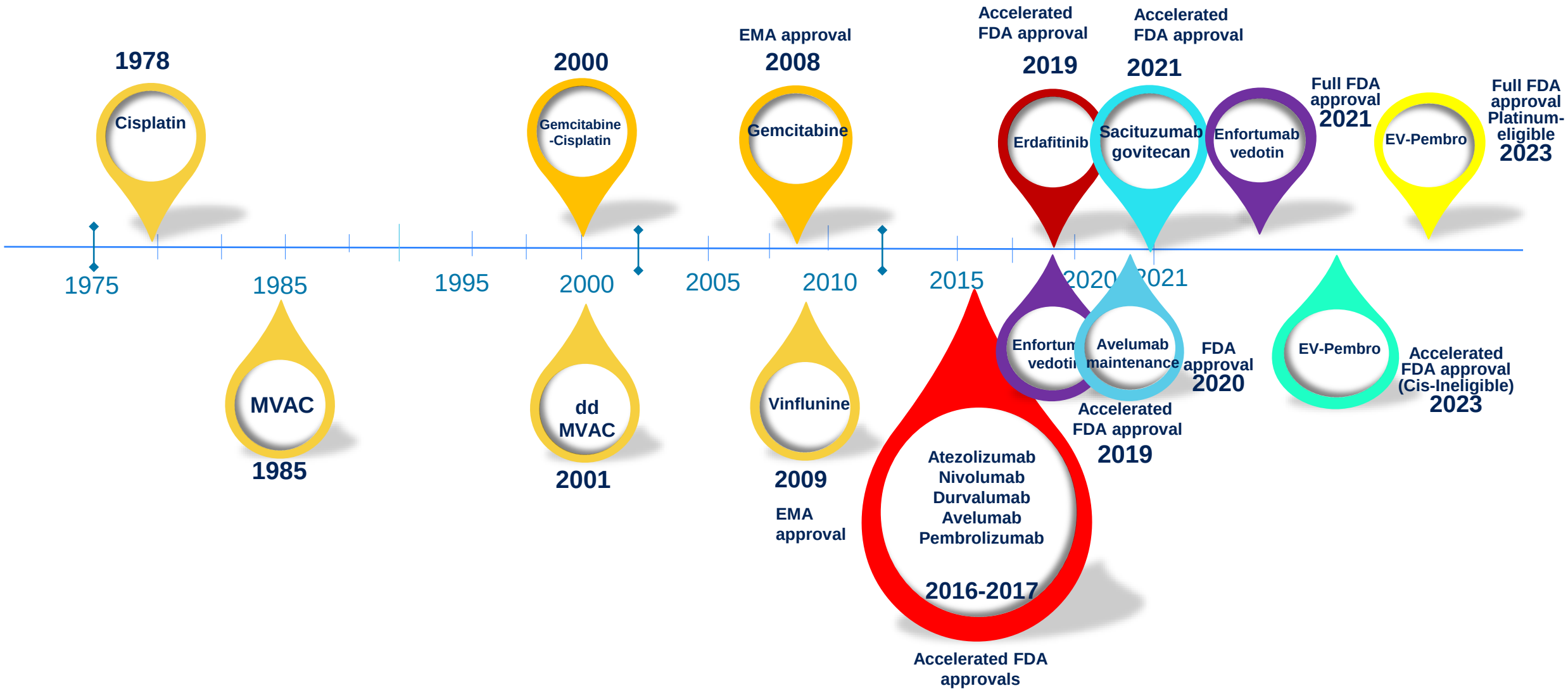
Stocks: Moderna, BionTech, Nektar Therapeutics

Therapy Advances in Locally Advanced/Metastatic UC (la/mUC)



Research Hypothesis for Phase III trials in 1L la/mUC
Gold Standard: Improvement in Overall Survival (OS)

- Primary Endpoint: OS
  - Progression-free survival (PFS) can be considered a primary endpoint in phase 2 trials
- Secondary Endpoints:
  - PFS
  - Objective Response Rates (ORR)
  - Safety/Toxicity
  - Biomarkers of response
  - Quality of life (QOL) assessment

Trial considerations

- Stratification Factors
  - Visceral metastases
  - ECOG PS

- Patient Population
  - Stage IV (T4bN0M0, AnyT N1-3 M0, AnyT AnyN M1)
  - Categorized into cisplatin-eligible/ineligible
  - Consider re-challenge if >/= 12 months have elapsed from prior use of therapy in non-metastatic setting
- Imaging
  - CT/MRI preferable, avoid FDG-PET/CT for response assessment

Platinums had been the unbeaten backbone of 1L therapy in la/mUC prior to 2023

- Gemcitabine-Cisplatin: Median OS ~ 14 months, ORR 49%
- ddMVAC: Median OS ~ 15 months, ORR 70%
- Gemcitabine-Carboplatin: Median OS~ 13 months ORR 43%
- Gem-Cis/Carbo followed by avelumab maintenance: Median OS~24 months
- 1L trials need platinum chemotherapy as adequate control arm

Von der Maase H et al. JCO 2005 Sternberg CN Eur J Cancer 2006, Galsky MD Lancet 2020, Flannery K et al. Future Oncol 2019, Powles T et al. NEJM 2021

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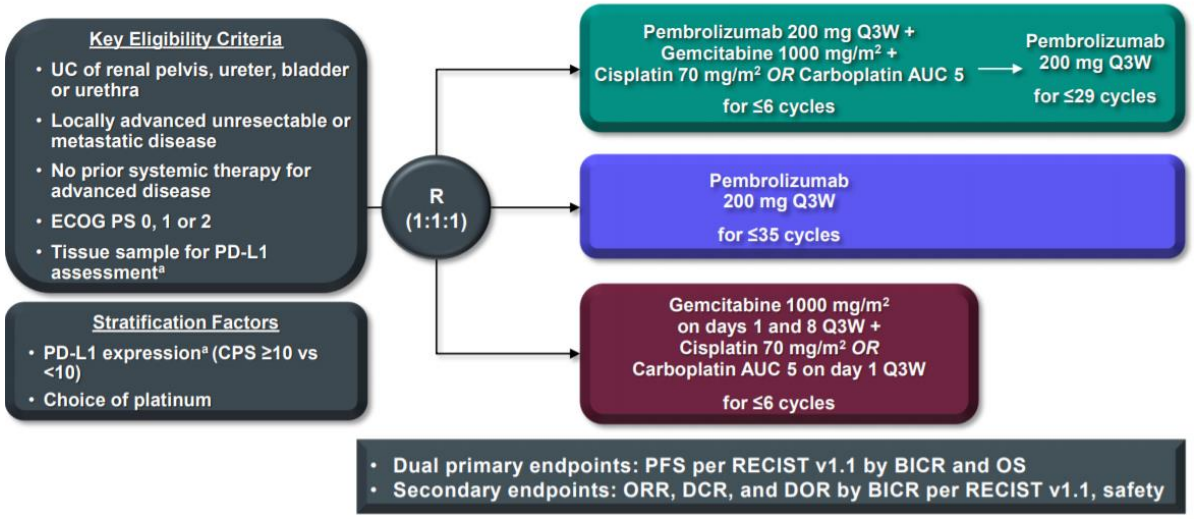
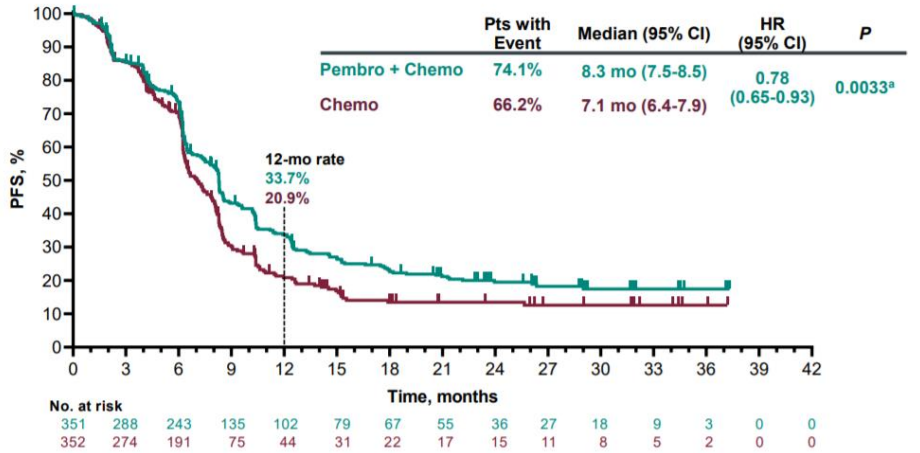
1L Platinum chemotherapy plus pembrolizumab vs chemotherapy (KEYNOTE-361)

KEYNOTE-361 Study Design (NCT02853305)

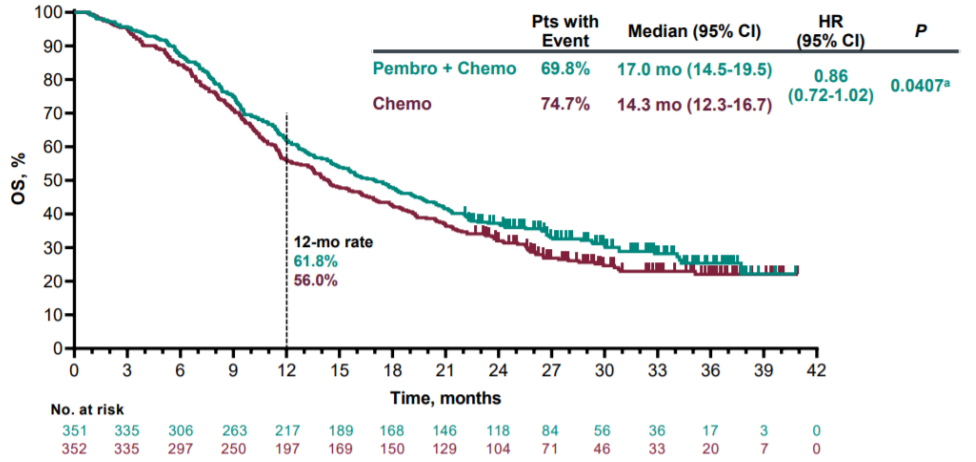


N=1010

PFS by BICR: Pembro + Chemo vs Chemo, ITT Population (Primary Endpoint)



OS: Pembro + Chemo vs Chemo, ITT Population



Powles T et al. Lancet 2021

1L Platinum chemotherapy plus atezolizumab/placebo (IMvigor130)

IMvigor130 study design

- Locally advanced or mUC
- No prior systemic therapy in the metastatic setting
- ECOG PS ≤ 2
- 1L platinum-eligible
- N = 1200
- Randomised 1:1:1

→ **Arm A** Atezo + plt/gem

→ **Arm B** Atezo monotherapy

→ **Arm C** Placebo + plt/gem

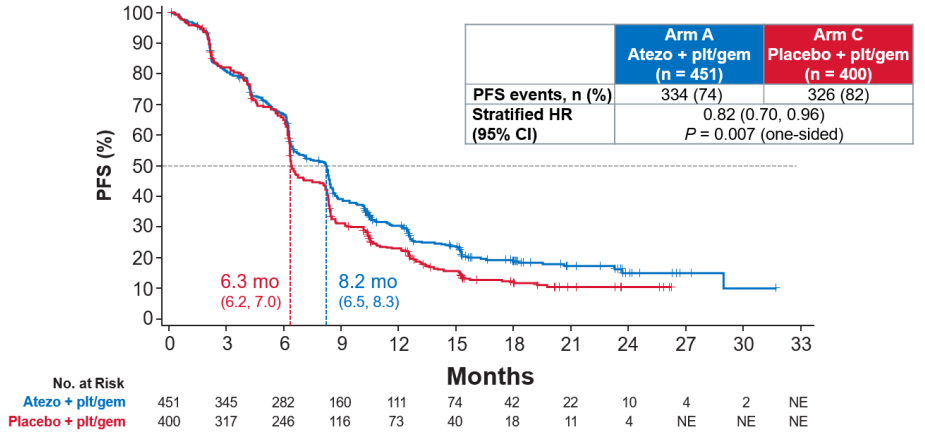
Stratification factors:
- PD-L1 IC status (IC0 vs IC1 vs IC2/3)
- Bajorin risk factor score including KPS < 80% vs ≥ 80% and presence of visceral metastases (0 vs 1 vs 2 and/or patients with liver metastases)
- Investigator choice of plt/gem (cisplatin + gem or carboplatin + gem)

Co-primary endpoints:
- INV-assessed PFS[a] and OS (Arm A vs C)
- OS (Arm B vs C, hierarchical approach)

Key secondary endpoints:
- INV-ORR[a] and DOR
- PFS[a] and OS (Arm B vs C; PD-L1 IC2/3 subgroup)
- Safety

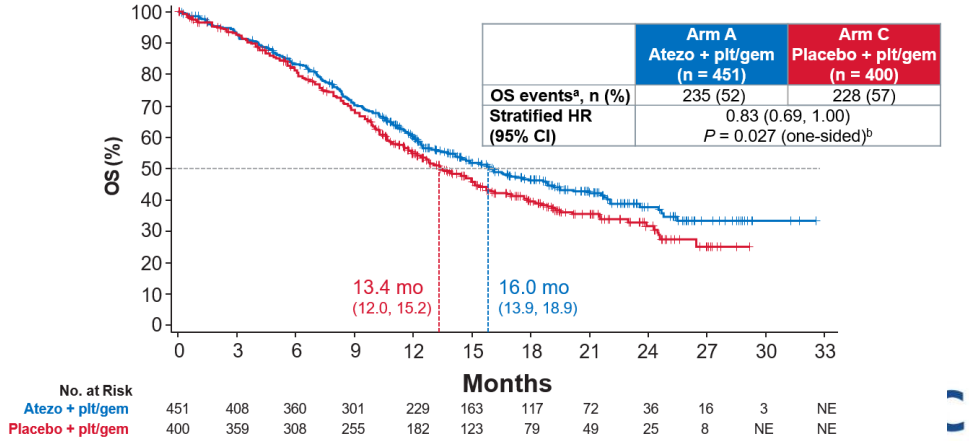
[a] per RECIST 1.1.

Final PFS: ITT (Arm A vs Arm C)



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
PFS events, n (%)	334 (74)	326 (82)
Stratified HR (95% CI)	0.82 (0.70, 0.96) *P* = 0.007 (one-sided)	

Interim OS: ITT (Arm A vs Arm C)



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
OS events[a], n (%)	235 (52)	228 (57)
Stratified HR (95% CI)	0.83 (0.69, 1.00) *P* = 0.027 (one-sided)[b]	

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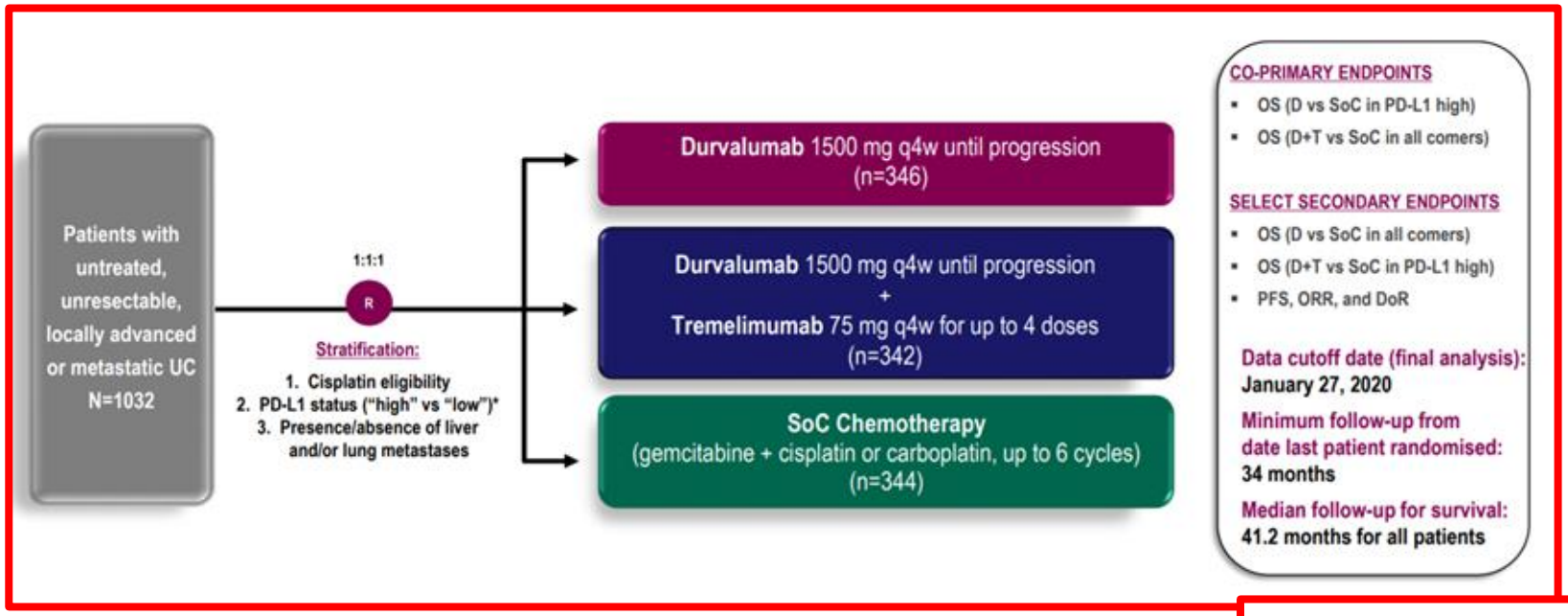
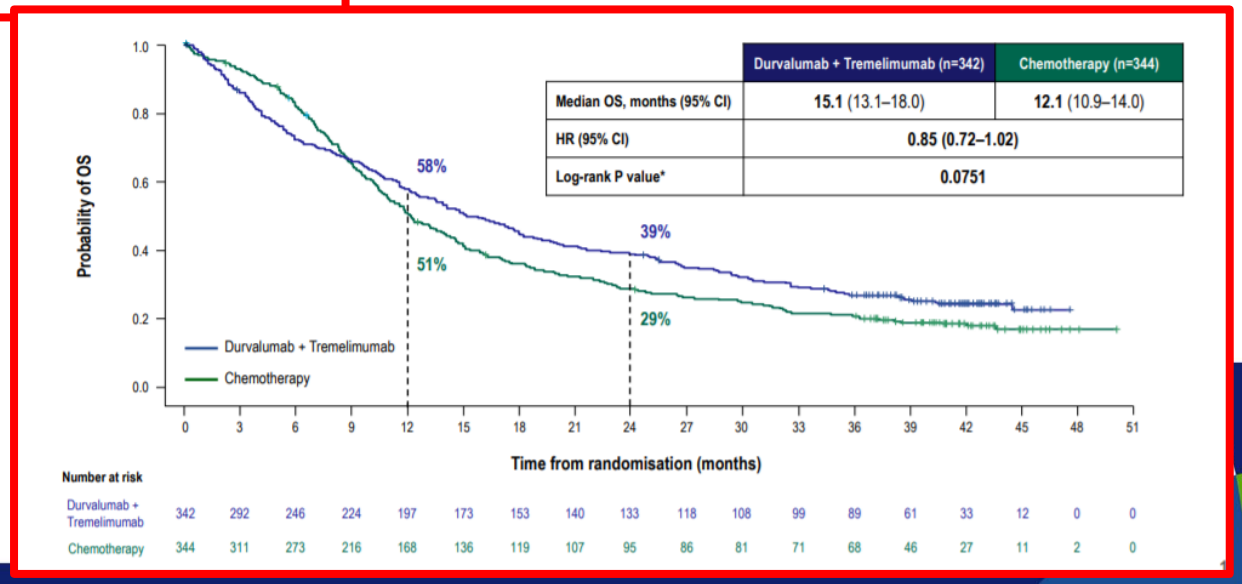
Galsky MD et et al. Lancet Oncology 2020

1L Durvalumab +/- tremelimumab vs platinum chemotherapy (DANUBE)

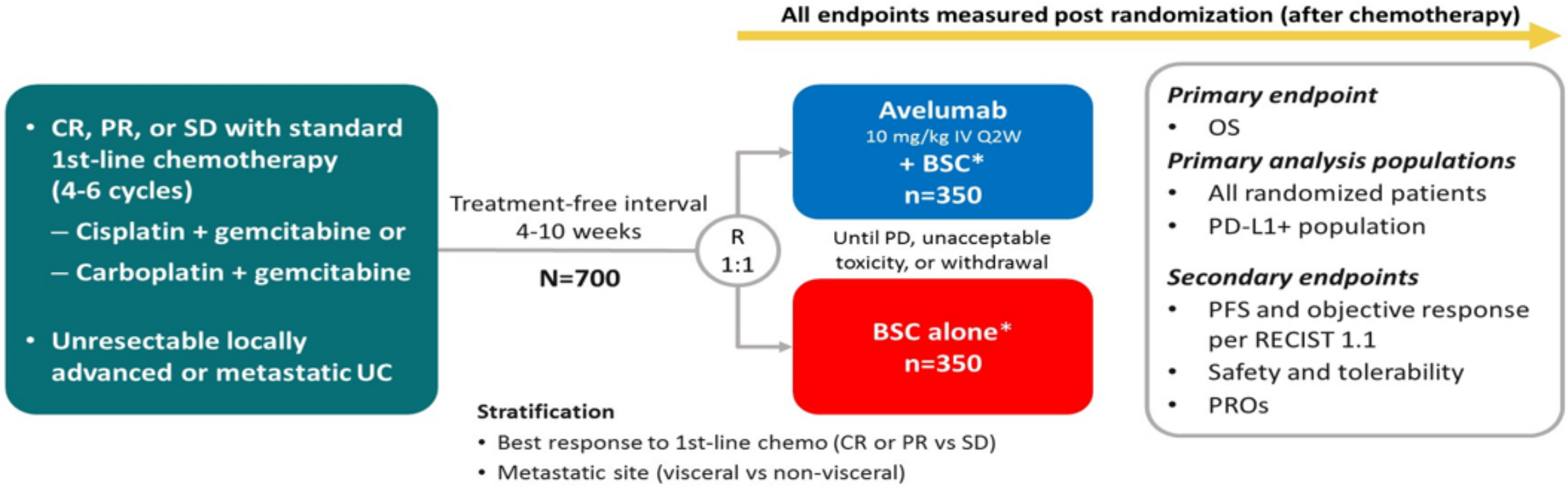




Powles T et al. *Lancet*. 2020

JAVELIN Bladder 100- “Switch Maintenance” Strategy after 1L platinum-based chemotherapy

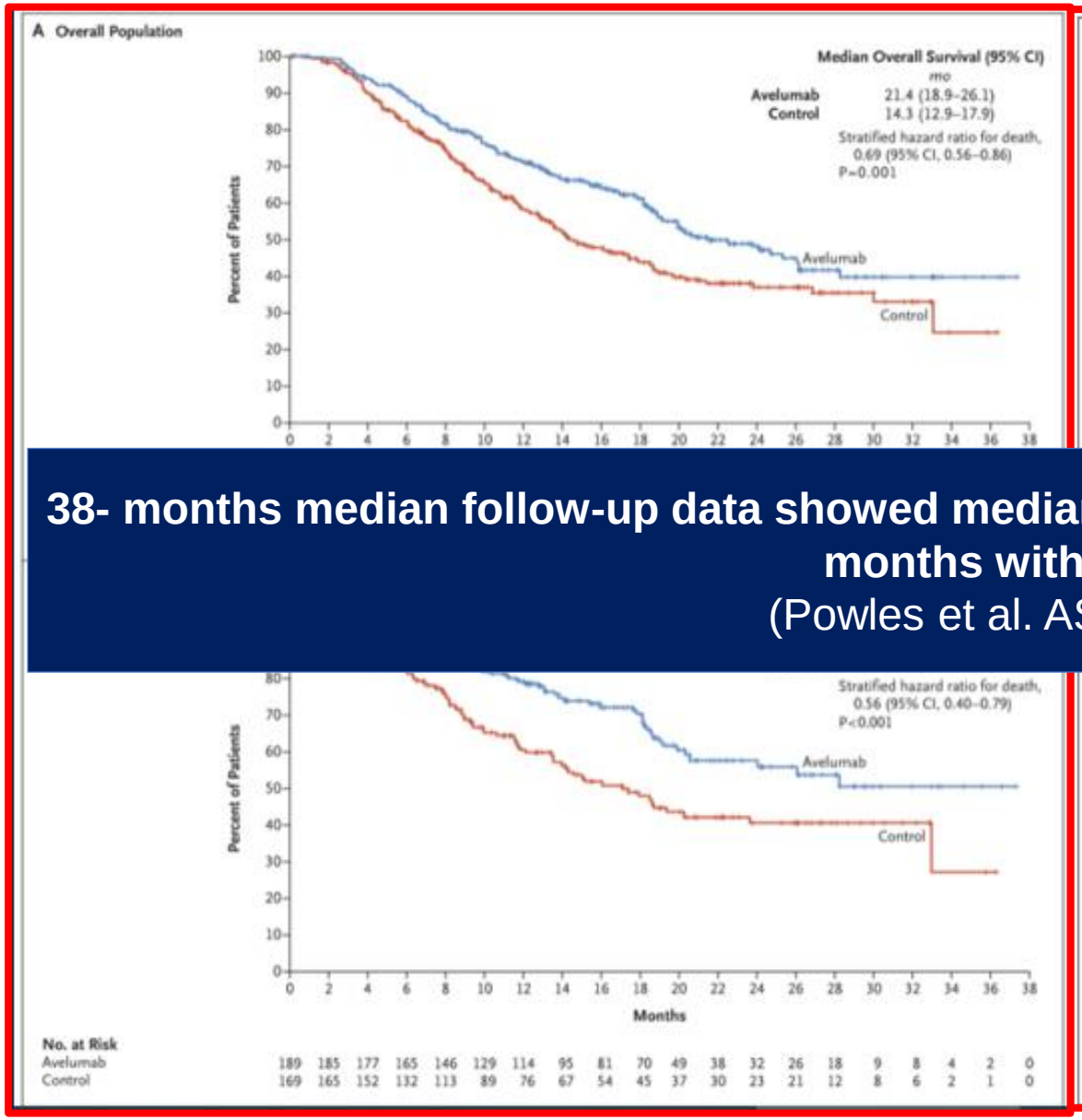
JAVELIN Bladder 100 study design (NCT02603432)

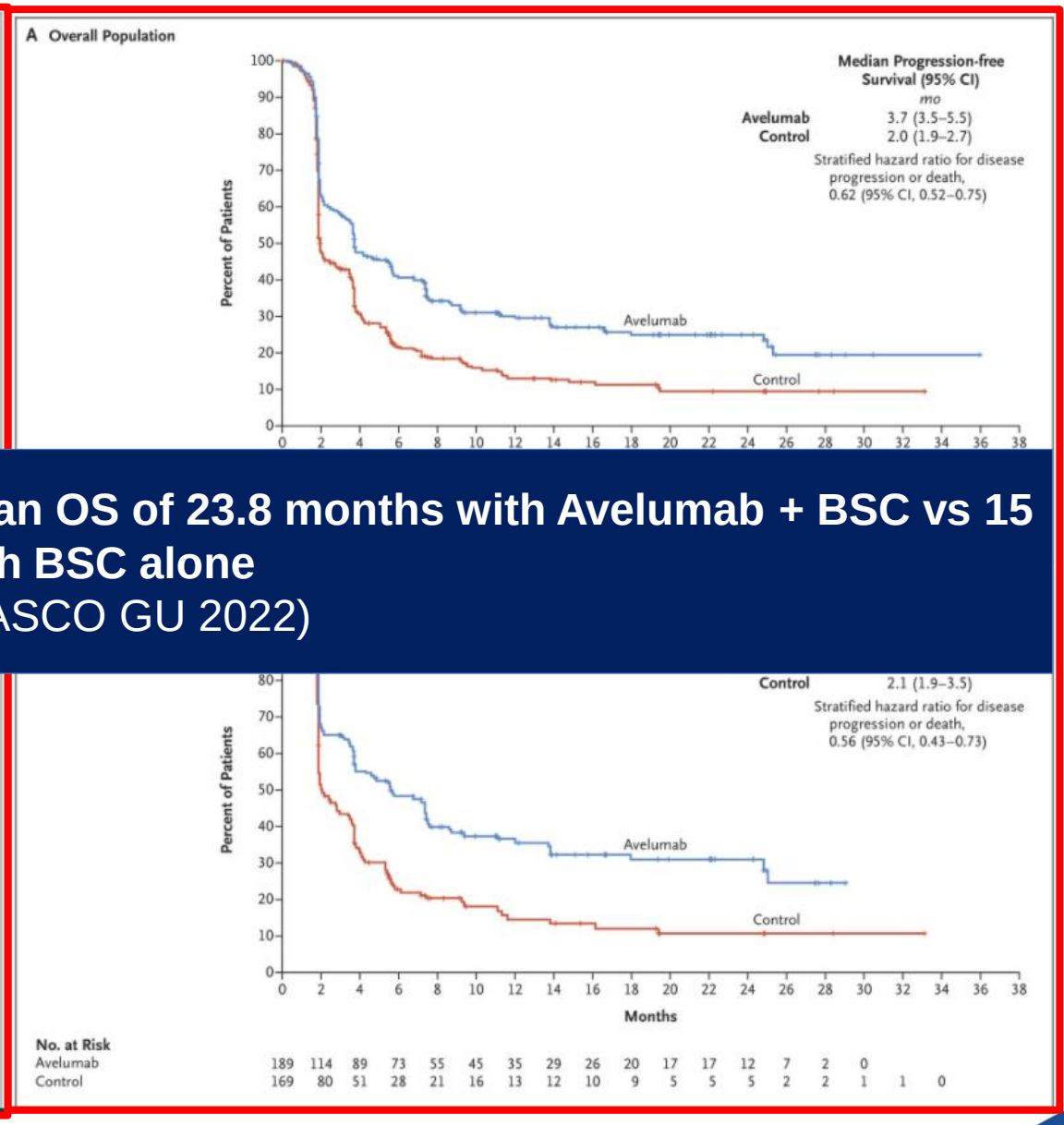


PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

Thomas Powles et al. NEJM 2020

Maintenance avelumab improves OS and PFS





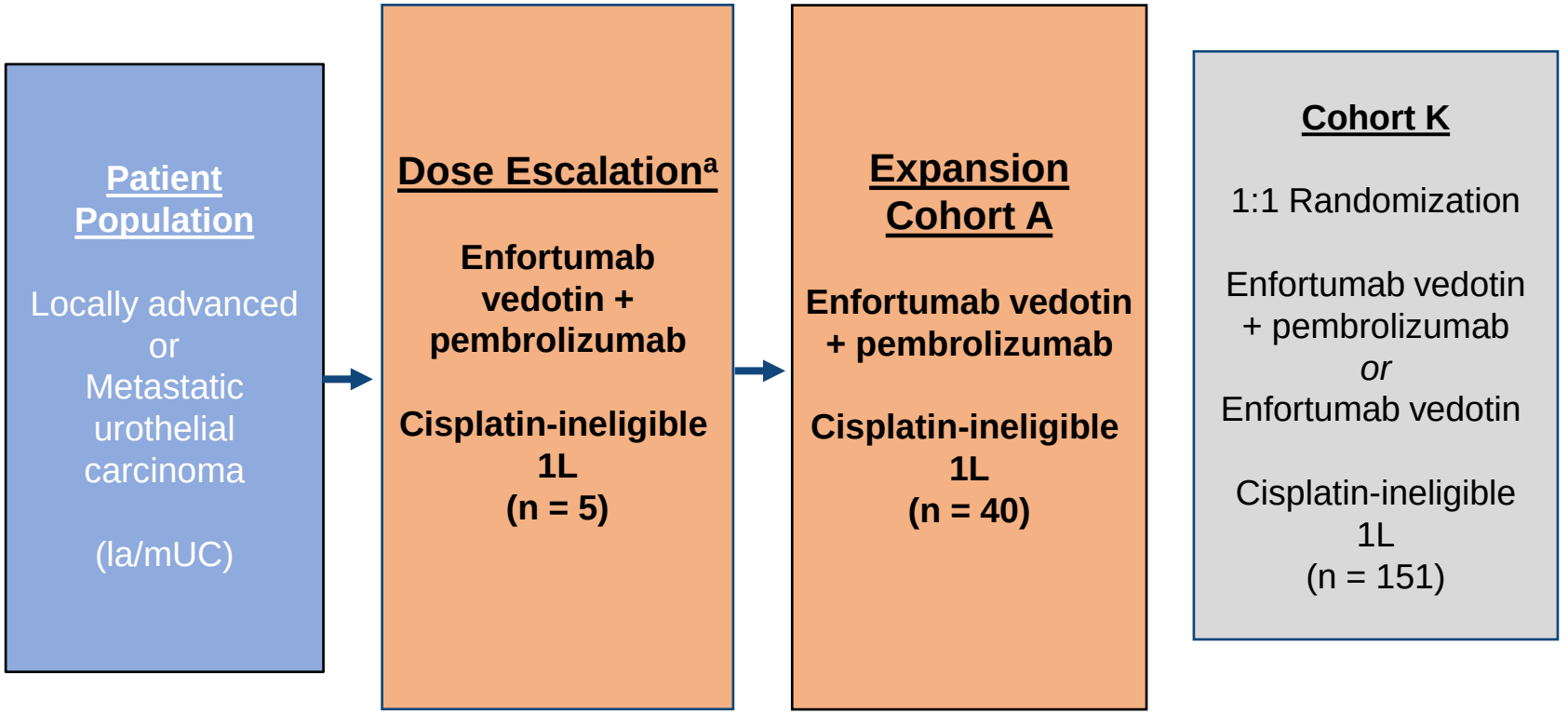
38- months median follow-up data showed median OS of 23.8 months with Avelumab + BSC vs 15 months with BSC alone
(Powles et al. ASCO GU 2022)

Thomas Powles et al. NEJM 2020

1L Enfortumab vedotin and pembrolizumab in patients with la/mUC

Study Design – EV+P Cohorts

EV-103 is an open-label, multiple cohort, phase 1b/2 study



- **Dosing:** EV 1.25 mg/kg IV on Days 1 and 8, and P 200 mg IV on day 1 of every 3-week cycle
- **Primary endpoints:** AEs, lab abnormalities
- **Key secondary endpoints:** confirmed ORR, DOR, DCR, and PFS per RECIST v1.1 by BICR[b] and investigator; OS, plasma/serum PK of EV

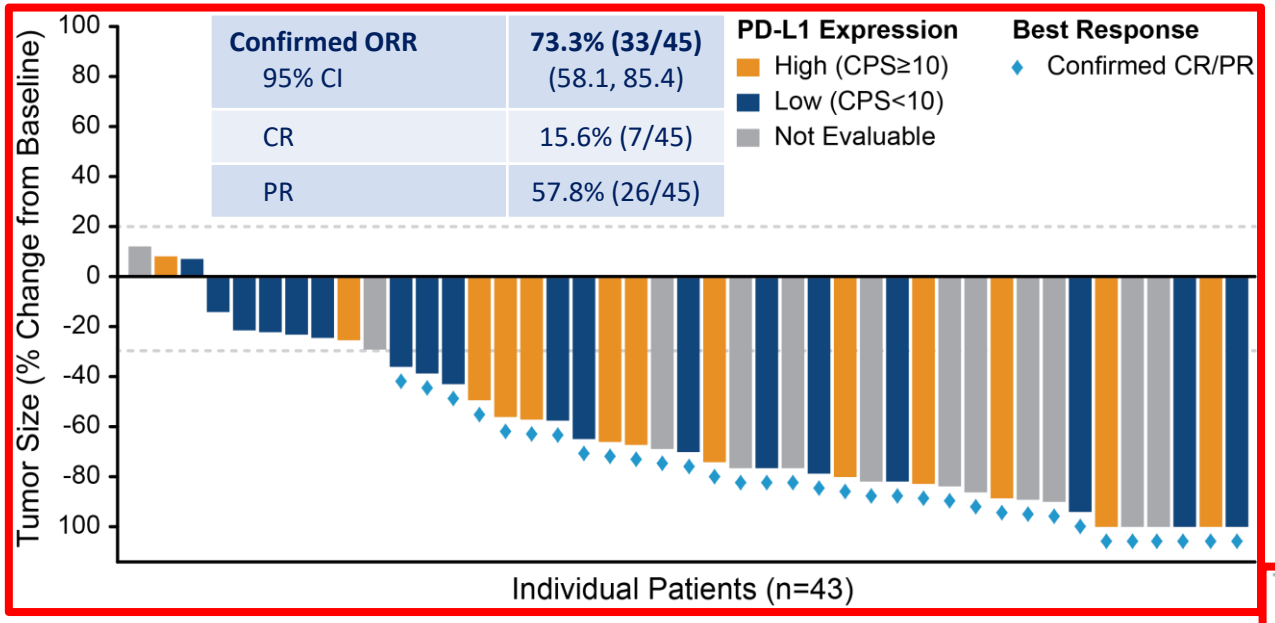
AE = adverse events; BICR = blinded independent central review; DCR = disease control rate; DOR = duration of response; EV = enfortumab vedotin; ORR = objective response rate; OS = overall survival; P = pembro; PFS = progression-free survival; PK = pharmacokinetics; 1L = first-line

Exploratory endpoints: biomarkers of activity including baseline PD-L1 status and Nectin-4 expression; **Dose Escalation/Cohort A** completed enrollment in Jan 2019; **Data cutoff** was 16 Sep 2022

[a]Patients assigned to EV 1.25 mg/kg + pembro and for whom study treatment was administered as 1L therapy

[b]The efficacy endpoints per RECIST v1.1 by BICR are presented for the first time herein. Results by investigator assessment have been previously published (Hoimes CJ, et al. JCO 2022).

EV103 Dose escalation and Cohort A



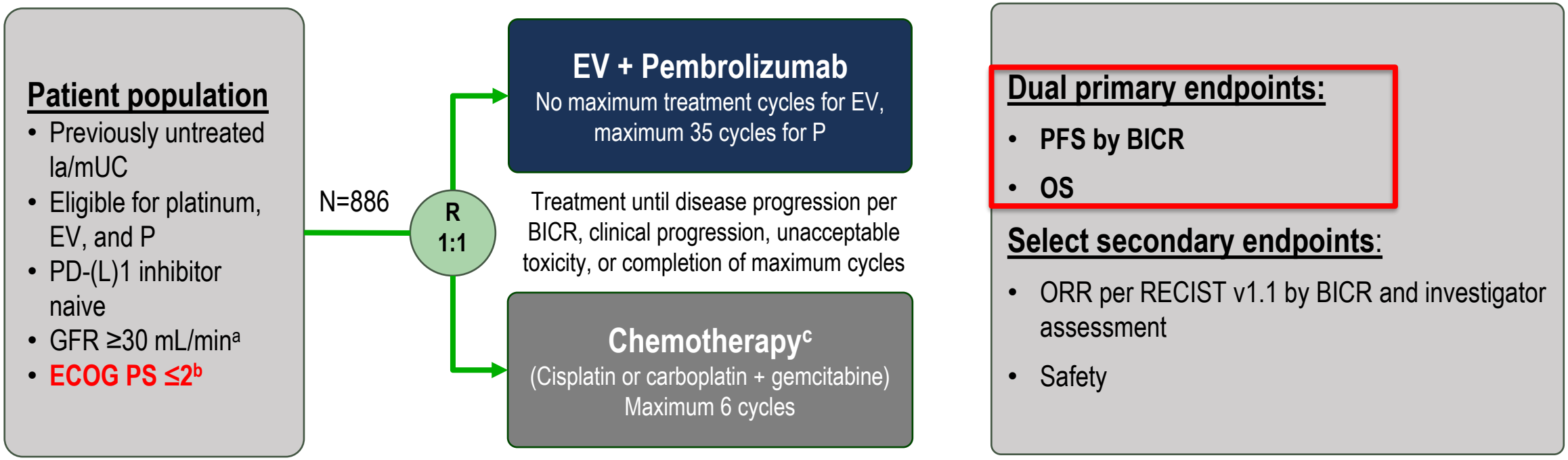
Hoimes C et al. JCO 2022

EV103 Cohort K (Randomized Ph 2)

	EV+P (N=76)	EV Mono (N=73)
Confirmed ORR, n (%) (95% CI)	49 (64.5) (52.7, 75.1)	33 (45.2) (33.5, 57.3)
Best overall response, n (%)		
Complete Response	8 (10.5)	3 (4.1)
Partial Response	41 (53.9)	30 (41.1)
Stable Disease	17 (22.4)	25 (34.2)
Progressive Disease	6 (7.9)	7 (9.6)
Not Evaluable	3 (3.9)	5 (6.8)
No Assessment	1 (1.3)	3 (4.1)
Median time to objective response (range), mos	2.07 (1.1, 6.6)	2.07 (1.9, 15.4)
Median number of treatment cycles (range)	11.0 (1, 29)	8.0 (1, 33)

O'Donnell P et al. JCO 2023

EV-302/KEYNOTE-A39 (NCT04223856)



Stratification factors: cisplatin eligibility (eligible/ineligible), PD-L1 expression (high/low), liver metastases (present/absent)

Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol-defined; patients received 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and P (200 mg; IV) on Day 1

Statistical plan for analysis: the first planned analysis was performed after approximately 526 PFS (final) and 356 OS events (interim); if OS was positive at interim, the OS interim analysis was considered final

Data cutoff: 08 Aug 2023; FPI: 7 Apr 2020, LPI: 09 Nov 2022

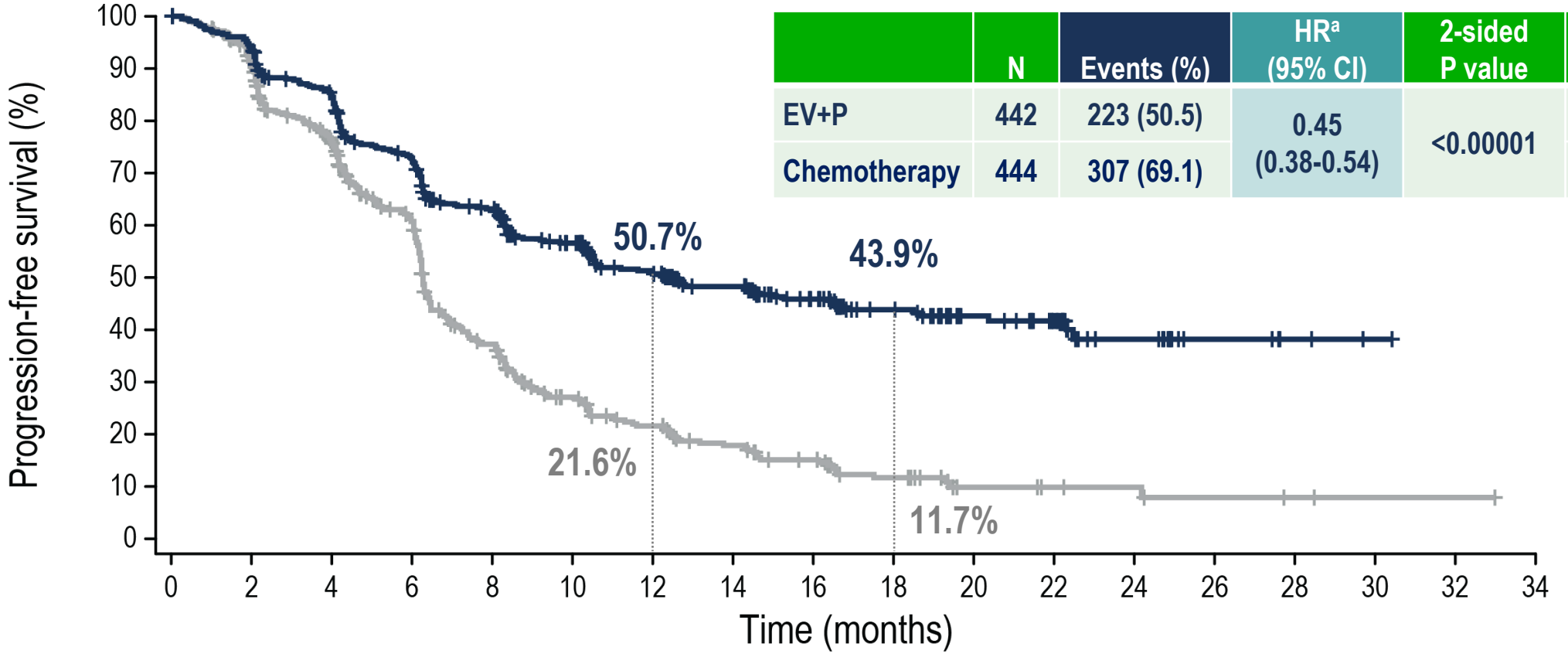
BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; ORR, overall response rate; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors
[a]Measured by the Cockcroft-Gault formula, Modification of Diet in Renal Disease, or 24-hour urine
[b]Patients with ECOG PS of 2 were required to also meet the additional criteria: hemoglobin ≥10 g/dL, GFR ≥50mL/min, may not have NYHA class III heart failure
[c]Maintenance therapy could be used following completion and/or discontinuation of platinum-containing therapy

Powles T et al. NEJM 2024

Progression-Free Survival per BICR

Risk of progression or death was reduced by 55% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mPFS (95% CI), months
EV+P	442	223 (50.5)	0.45 (0.38-0.54)	<0.00001	12.5 (10.4-16.6)
Chemotherapy	444	307 (69.1)			6.3 (6.2-6.5)



N at risk

EV+P	442	409	361	303	253	204	167	132	102	73	45	33	17	6	3	1
Chemotherapy	444	380	297	213	124	78	56	41	30	19	8	6	5	3	2	1	1

Data cutoff: 08 Aug 2023

PFS at 12 and 18 months as estimated using Kaplan-Meier method
HR, hazard ratio; mPFS, median progression-free survival
[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm

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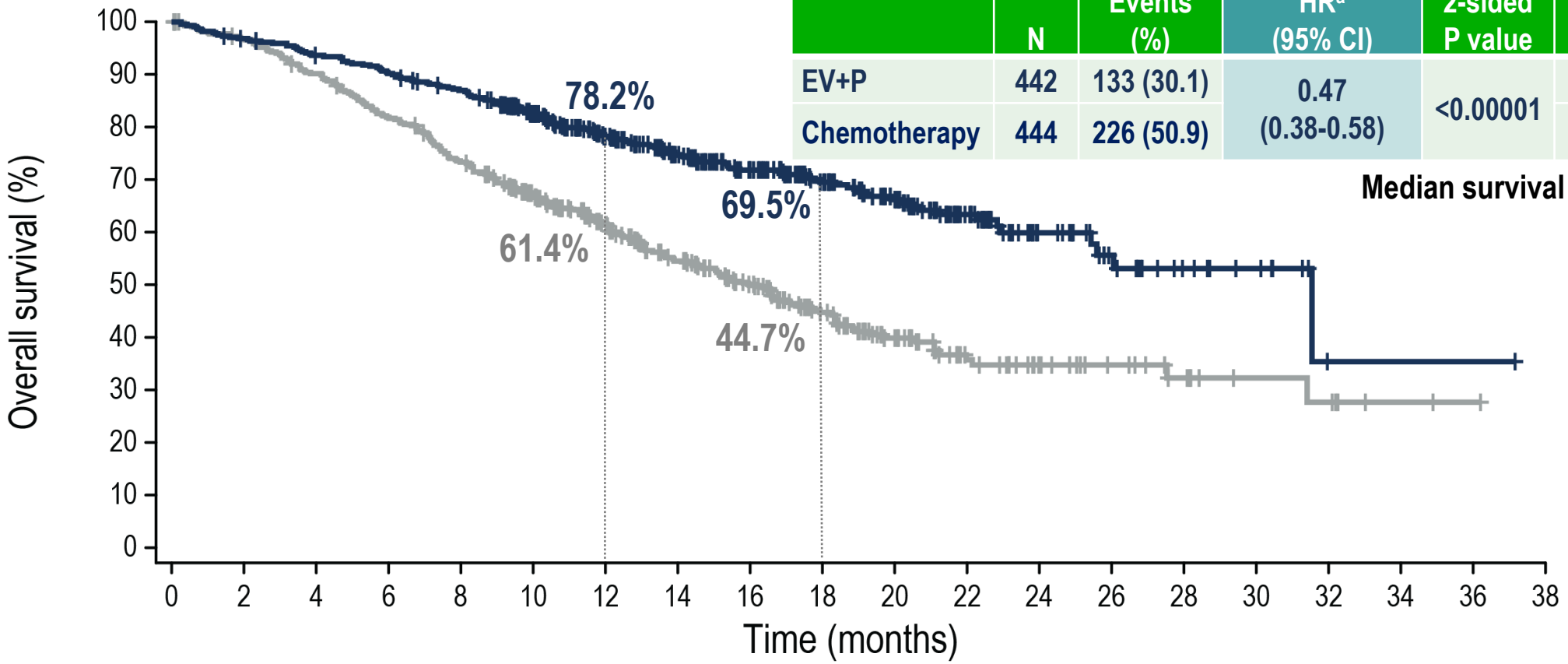
Powles T et al. NEJM 2024

Overall Survival

Risk of death was reduced by 53% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mOS (95% CI), months
EV+P	442	133 (30.1)	0.47 (0.38-0.58)	<0.00001	31.5 (25.4-NR)
Chemotherapy	444	226 (50.9)			16.1 (13.9-18.3)

Median survival follow-up: 17.2 months



N at risk

EV+P	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

Data cutoff: 08 Aug 2023

OS at 12 and 18 months was estimated using Kaplan-Meier method
mOS, median overall survival; NR, not reached
[a]Calculated using stratified Cox proportional hazards model. A hazard ratio <1 favors the EV+P arm

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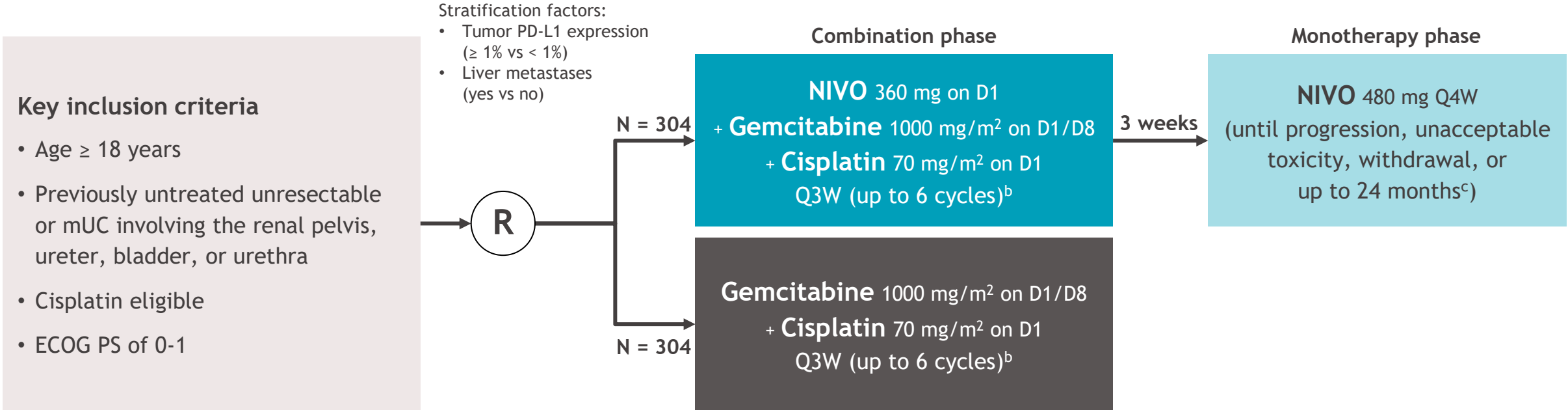
Powles T et al. NEJM 2024

1L Gemcitabine-Cisplatin and Nivolumab in cisplatin-eligible patients with la/mUC

Study design

- NIVO + gemcitabine-cisplatin vs gemcitabine-cisplatin in cisplatin-eligible patients[a]

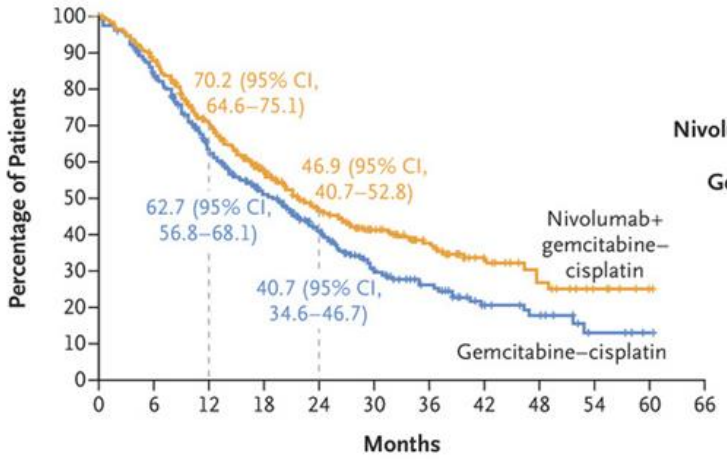


Median (range) study follow-up, 33.6 (7.4–62.4) months

Primary endpoints: OS, PFS per BICR
Key secondary endpoints: OS and PFS by PD-L1 ≥ 1%,[d] HRQoL
Key exploratory endpoints: ORR per BICR, safety

MS van der Heijden et al. NEJM 2023

A Overall Survival



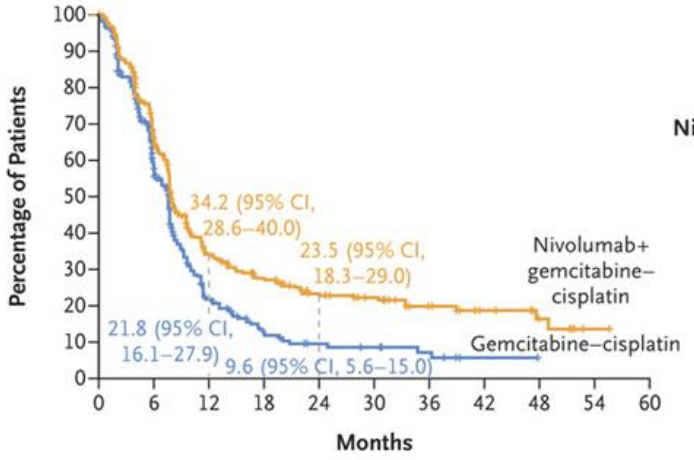
	No. of Events/ No. of Patients	Median Overall Survival (95% CI)
		mo
Nivolumab+Gemcitabine–Cisplatin	172/304	21.7 (18.6–26.4)
Gemcitabine–Cisplatin	193/304	18.9 (14.7–22.4)

Hazard ratio for death, 0.78 (95% CI, 0.63–0.96)
P=0.02

No. at Risk

Nivolumab+gemcitabine–cisplatin	304	264	196	142	97	69	48	25	15	7	2	0
Gemcitabine–cisplatin	304	242	166	122	82	49	33	17	13	4	1	0

B Progression-free Survival



	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)
		mo
Nivolumab+Gemcitabine–Cisplatin	211/304	7.9 (7.6–9.5)
Gemcitabine–Cisplatin	191/304	7.6 (6.1–7.8)

Hazard ratio for disease progression or death, 0.72 (95% CI, 0.59–0.88)
P=0.001

No. at Risk

Nivolumab+gemcitabine–cisplatin	304	179	82	57	41	31	19	11	6	1	0
Gemcitabine–cisplatin	304	119	35	17	10	8	5	1	0	0	0

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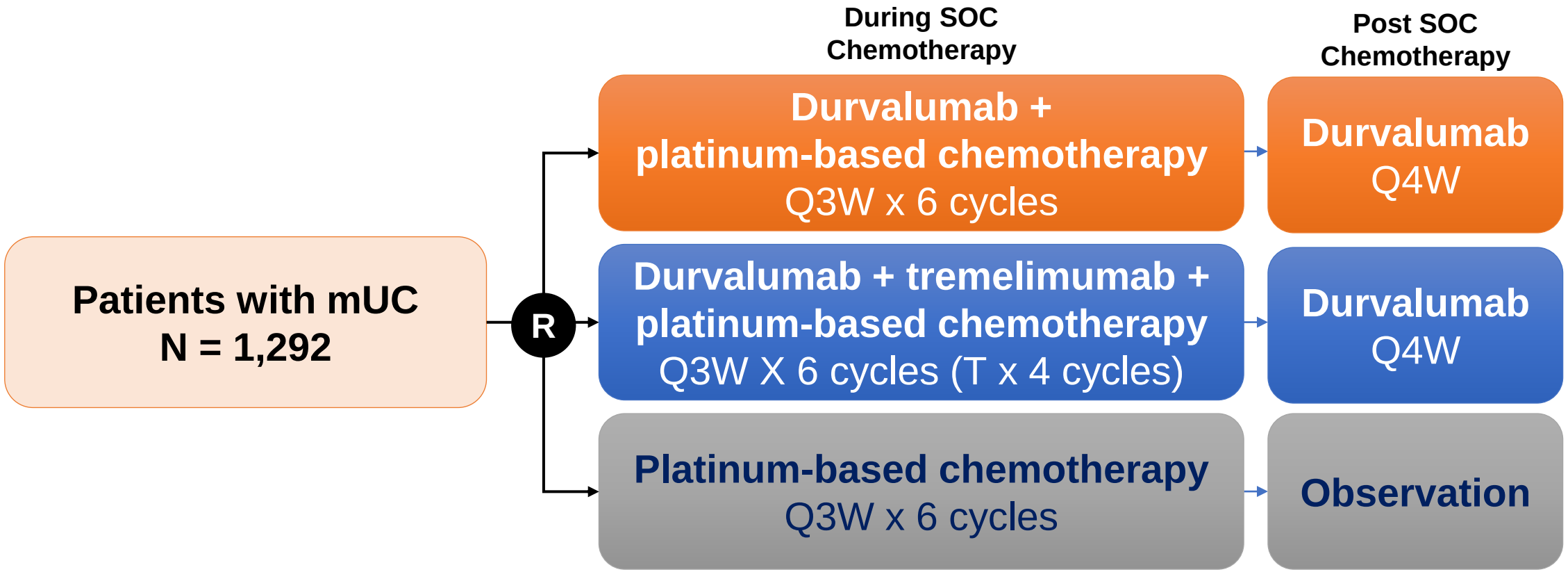
MS van der Heijden et al. NEJM 2023

1L Chemotherapy vs Chemo +IO (NILE)



- **Co-primary endpoints:** OS in PD-L1+ (arm 1 vs arm 3)
- **Select secondary endpoints:** OS, OS 24 mo, PFS, ORR

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Second-line therapy and beyond in la/mUC

- Single-arm signal finding trials
  - Can use ORR as primary endpoint (but misses RECIST 1.1 non-measurable disease)
  - Avoid PFS as primary endpoint

- Randomized phase 3 trials
  - Primary endpoint should be OS (time from date of randomization to death from any cause)
  - Patients still alive are censored at the last date known to be alive
- Adequate control arm post EV progression
  - Sacituzumab govitacen, taxane, vinflunine or erdafitinib (select patients)

Pembrolizumab in platinum-refractory la/mUC (KEYNOTE-045)

Initial efficacy was maintained at 2-, 3-, and 5-years follow-up

5-year follow-up	Pembrolizumab ITT n = 270	Chemotherapy ITT n = 272
ORR, % (95% CI)	21.9 (17.1-27.3)	11.0 (7.6-15.4)
Best response, n (%)		
CR	27 (10.0)	8 (2.9)
PR	32 (11.9)	22 (8.1)
SD	47 (17.4)	92 (33.8)
PD	129 (47.8)	90 (33.1)
NA[a]	31 (11.5)	51 (18.8)
NE[b]	4 (1.5)	9 (3.3)

Pembrolizumab vs Investigator's choice chemotherapy
OS: 10.1 mo vs 7.2 mo
DOR: 29.7 mo vs 4.4 mo

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Bellmunt J et al. N Engl Med. 2017;Fradet Y et al. Ann Oncol. 2019; Necchi A et al. Ann Oncol. 2019; Bellmunt J et al. ASCO 2021 Abstract 4532

EV in mUC patients with prior platinum/IO la/mUC (EV-301)

EV-301 Open-Label Phase 3 Trial Design

Key eligibility criteria:

- Histologically/cytologically confirmed UC, including with squamous differentiation or mixed cell types
- Radiographic progression or relapse during or after PD-1/L1 treatment for advanced UC
- Prior platinum-containing regimen for advanced UC[b]
- ECOG PS 0 or 1

1:1 randomization with stratification[a]

Enfortumab vedotin (N=301)
1.25 mg/kg on Days 1, 8, and 15 of each 28-day cycle

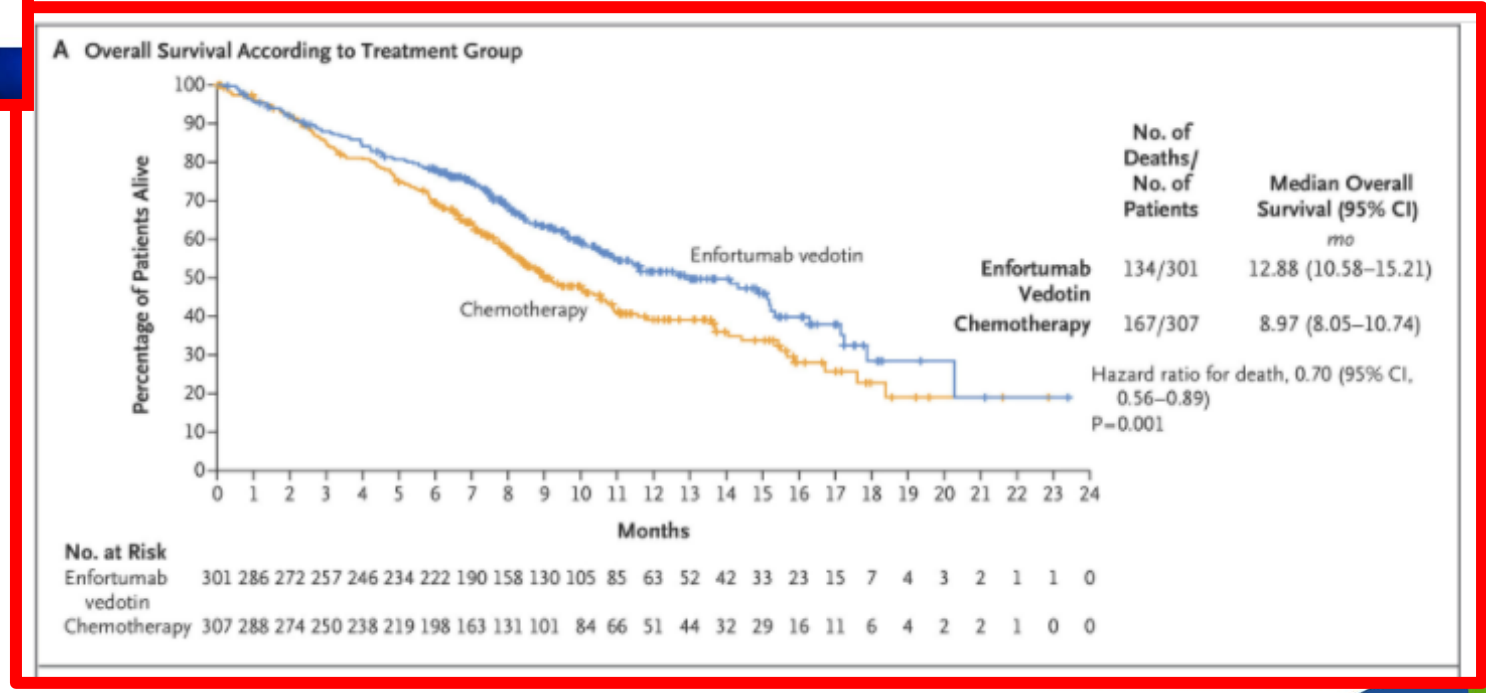
Preselected Chemotherapy (N=307)[c]
Docetaxel 75 mg/m² or Paclitaxel 175 mg/m² or Vinflunine[d] 320 mg/m² on Day 1 of each 21-day cycle

Primary endpoint: Overall survival

Secondary endpoints:
- Progression-free survival
- Disease control rate
- Overall response rate
- Safety

Investigator-assessed per RECIST v1.1

[a]Stratification variables were ECOG performance status (0 or 1), regions of the world (United States, western Europe, or rest of world), liver metastasis (yes or no).
[b]If used in the adjuvant/neoadjuvant setting, progression must be within 12 months of completion.
[c]Investigator selected prior to randomization.
[d]In countries where approved; overall proportion of patients receiving vinflunine capped at 35%.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1/L1, programmed cell death protein-1/programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; UC, advanced urothelial carcinoma.



Powles T et al. NEJM 2021

Erdafitinib is a Pan-FGFR Inhibitor With Activity in Metastatic Urothelial Carcinoma

- ***FGFRalt*** are observed in **~20% of advanced or mUC** and may function as oncogenic drivers[1,2]

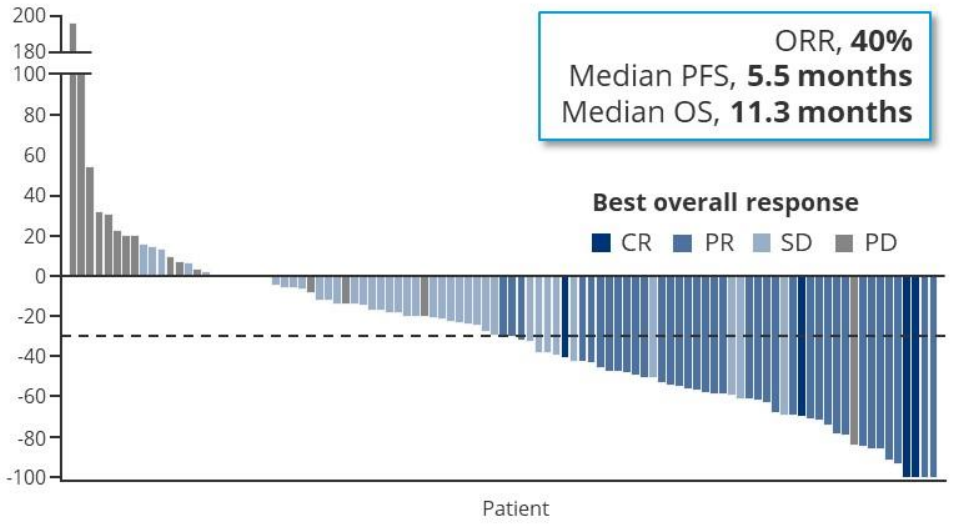
Erdafitinib is an oral selective pan-FGFR tyrosine kinase inhibitor[3]

  - Erdafitinib was granted accelerated approval in the United States and is approved in 17 other countries to treat locally advanced or mUC in adults with susceptible *FGFR3/2alt* who have progressed after platinum-containing chemotherapy[4-6]

- **THOR** is a confirmatory, randomized phase 3 study:

  - Cohort 1 assessed whether erdafitinib improved survival over chemotherapy in patients with *FGFRalt* mUC who progressed on or after ≥1 prior treatment that included anti–PD-(L)1

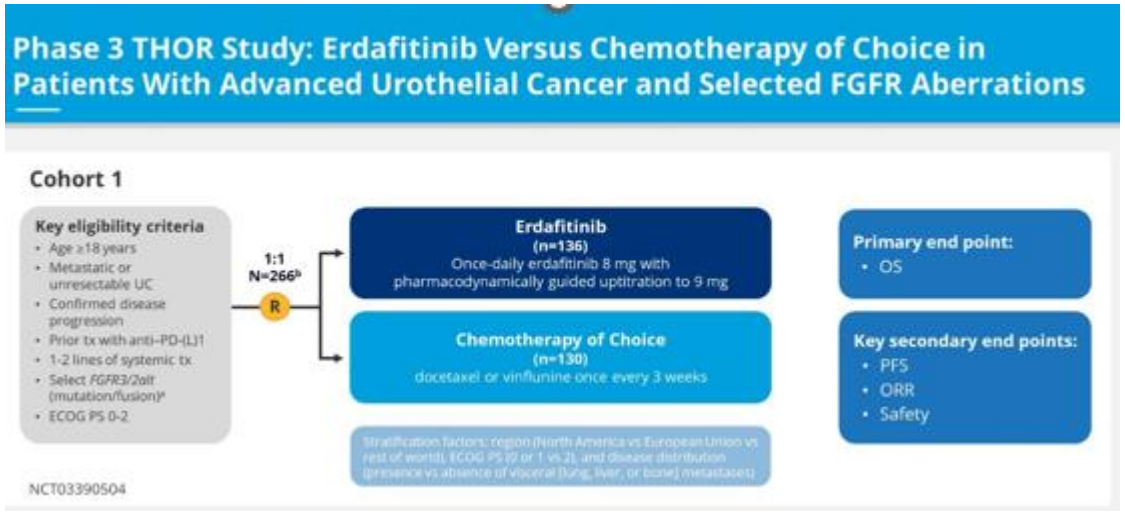
In the single-arm phase 2 BLC2001 trial, erdafitinib showed a benefit in patients with *FGFR-altered* advanced urothelial cancer[4]



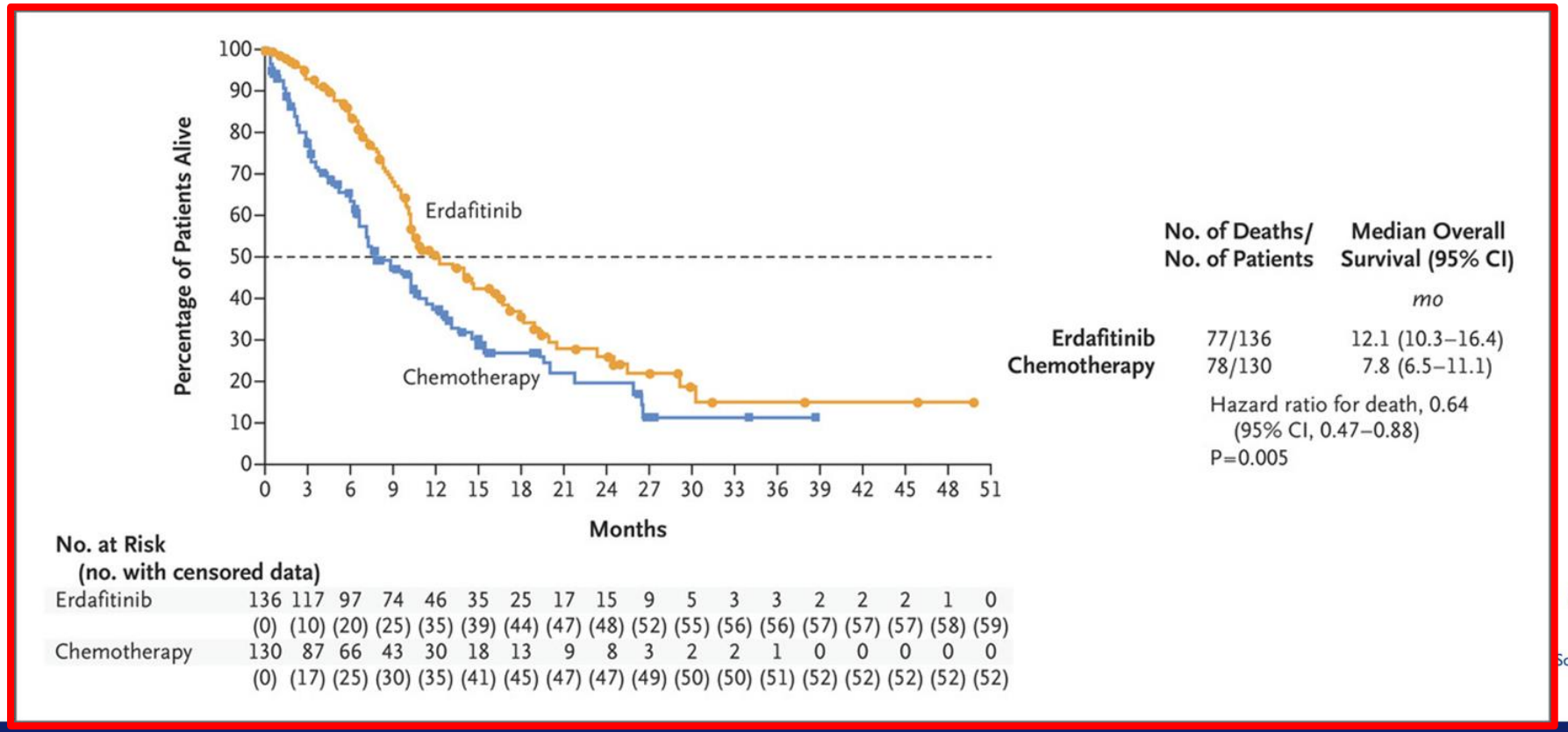
Patients received erdafitinib 8 mg/d with pharmacodynamically guided uptitration to 9 mg/d.

FGFR, fibroblast growth factor receptor; *FGFRalt*, *FGFR* alterations; mUC, metastatic urothelial carcinoma; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival.
[a]Patients received erdafitinib 8 mg/d with pharmacodynamically guided uptitration to 9 mg/d.

1. Necchi A, et al. *Eur Urol Focus*. 2019;5:853-586; 2. di Martino E, et al. *Future Oncol.* 2016;12:2243-2263; 3. Perera TPS, et al. *Mol Cancer Ther.* 2017;16:1010-1020; 4. Loriot Y, et al. *N Engl J Med.* 2019;381:338-348; 5. BALVERSA® (erdafitinib) [package insert]. Horsham, PA: Janssen Products, LP; 2023; 6. Siefker-Radtke AO, et al. *Lancet Oncol.* 2022;23:248-258.

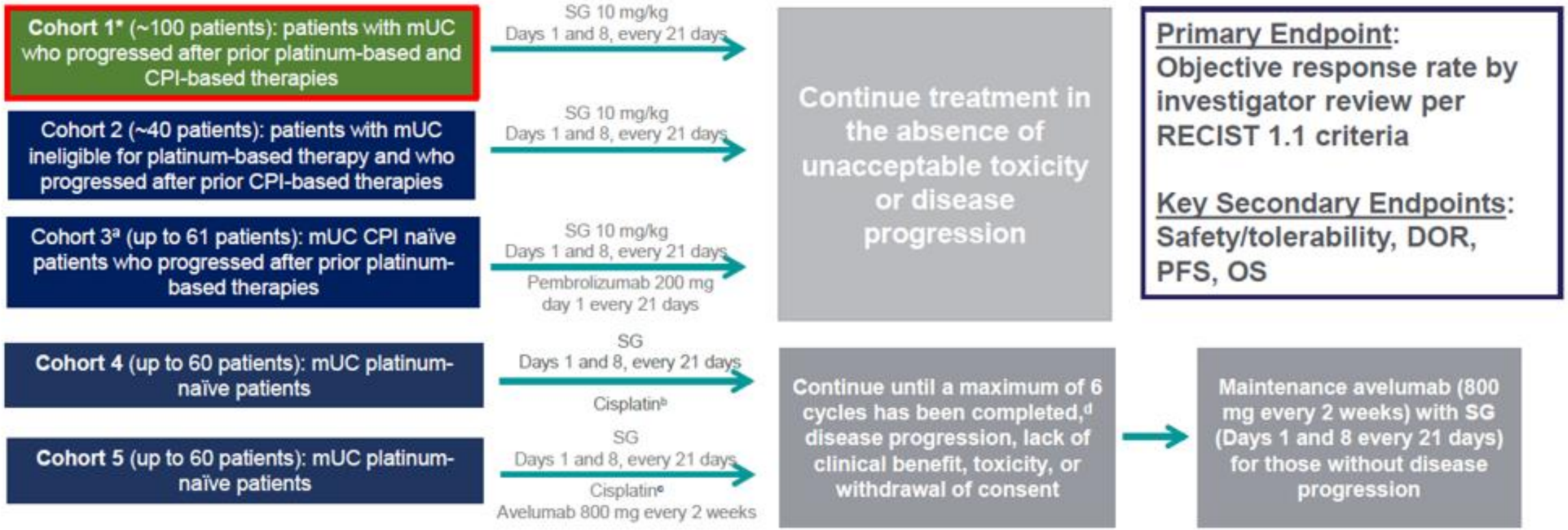


ASCO Annual Meeting 2023 Slide use permitted by Dr. Yohann Loriot



Loriot, Y et al. NEJM 2023

Sacituzumab govitecan (SG) in la/mUC
TROPHY-U-01: Multi-cohort Phase 2 trial



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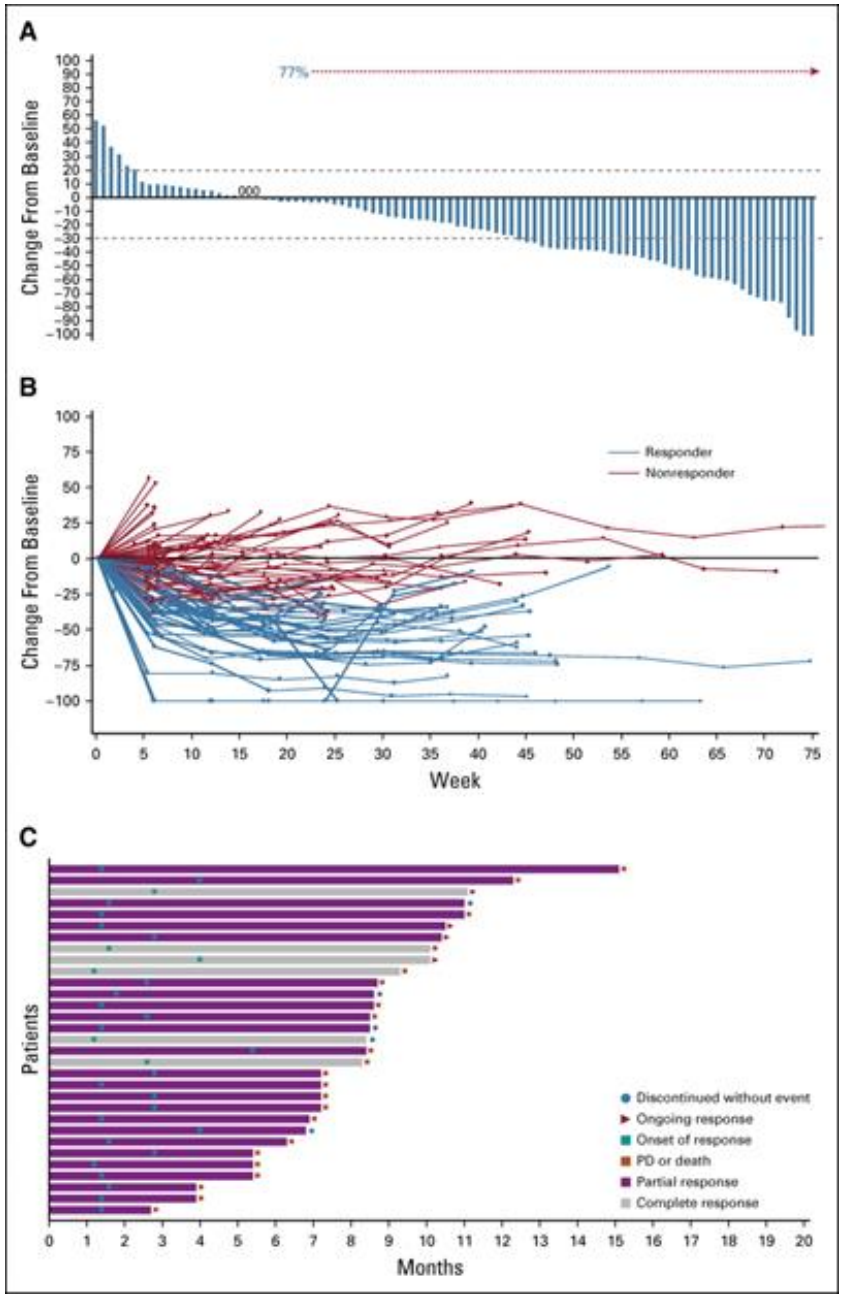

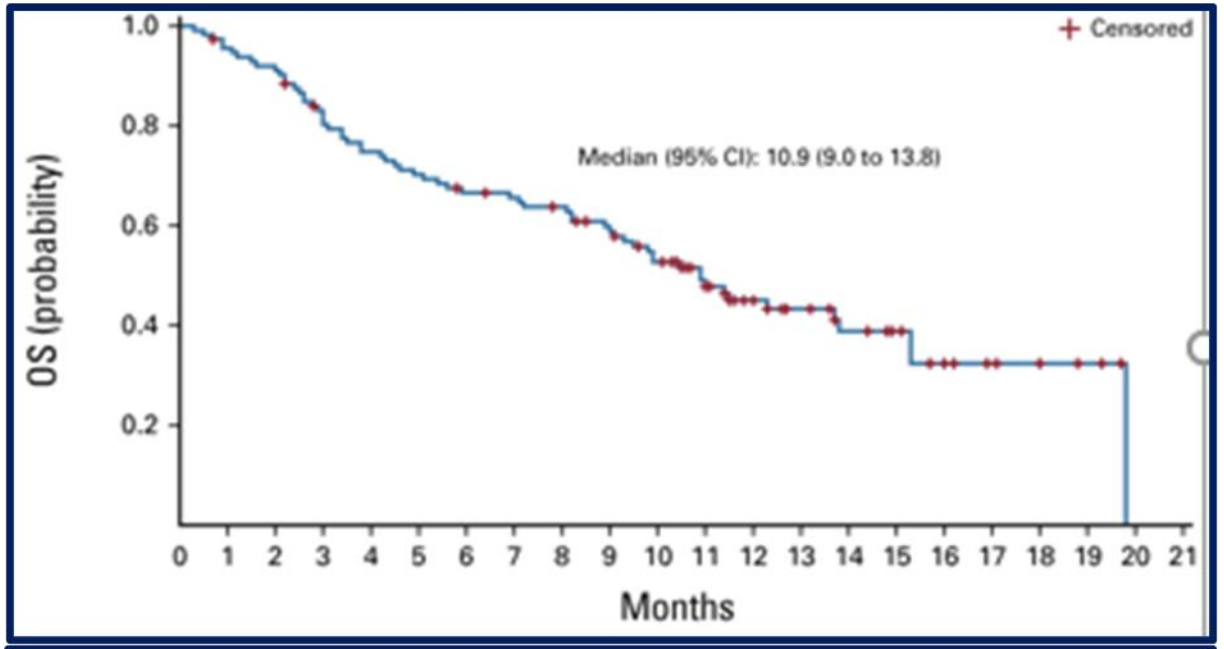

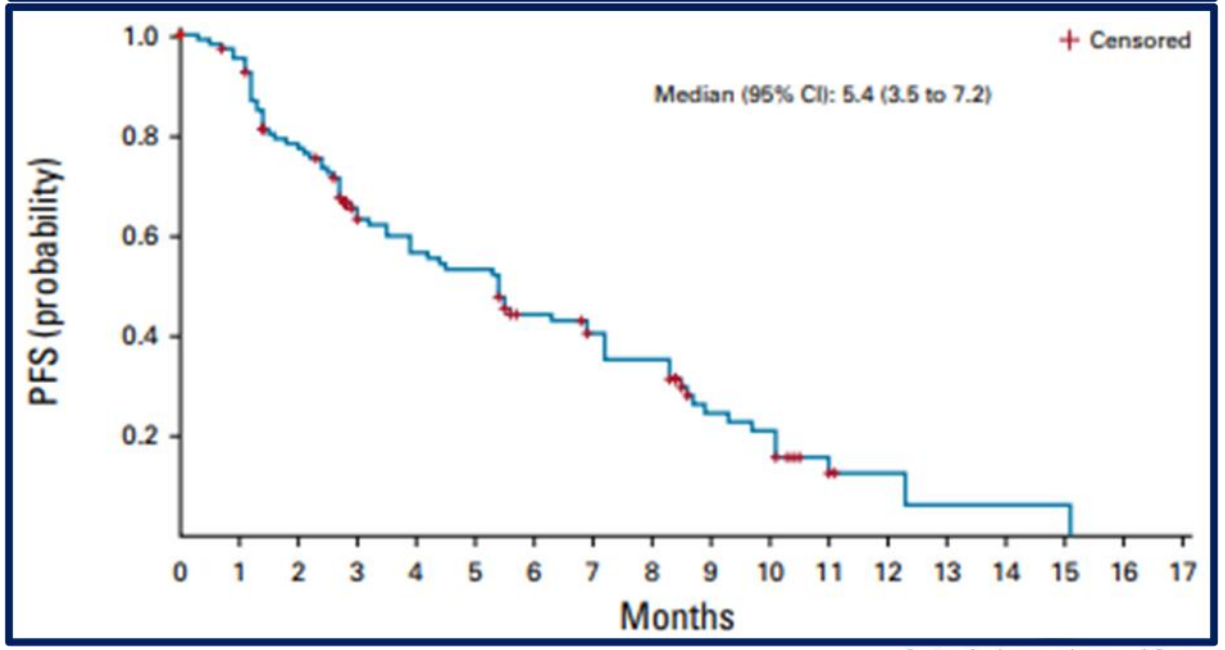

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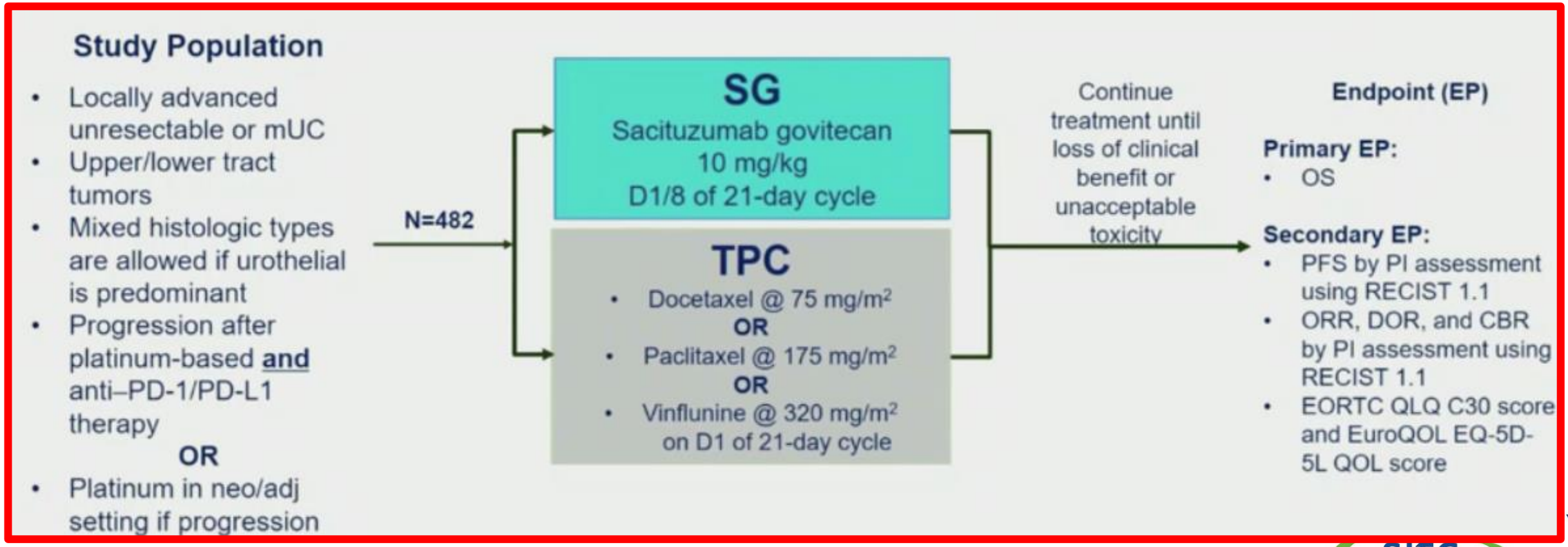
Tagawa ST, JCO 2021

TROPics-04- Phase 3 trial of SG vs chemotherapy



SITC-IBCG Panel Recommendations for Clinical Trial Endpoints

- **Primary Endpoint: OS**
  - ✓Progression-free survival (PFS) can be considered a primary endpoint in phase 2 trials
- **Secondary Endpoints:**
  - ✓PFS
  - ✓Objective Response Rates (ORR)
  - ✓Safety/Toxicity
  - ✓Biomarkers of response
  - ✓Quality of life (QOL) assessment
- **Adequate control arm for 1L la/mUC**
  - ✓EV-Pembro should be the control arm in future trials since it will replace platinums in 1L setting
- **Adequate control arm post EV progression**
  - ✓Sacituzumab govitacen, taxane, vinflunine or erdafitinib (select patients)
- **Need to validate biomarkers and novel imaging**

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Thank You!

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