

# MLS Nashville: Bladder and Prostate Cancer Updates in 2024

**Benjamin Garmezy, MD**

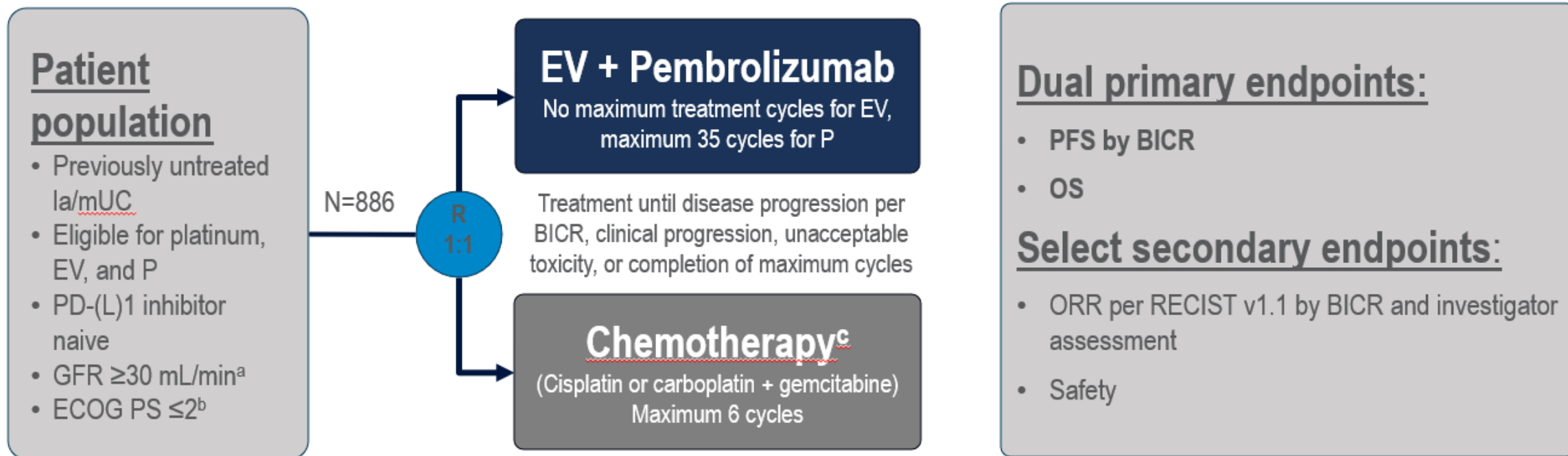
Associate Program Director of Genitourinary Research, SCRI  
Co-Chair, GU Executive Research Committee, SCRI  
GU Medical Oncologist and Phase 1 Physician, SCRI Oncology Partners, Nashville, TN

June 22, 2024

**SCRI** Sarah Cannon  
Research Institute

# Metastatic Urothelial Carcinoma

# EV-302: Enfortumab Vedotin + Pembrolizumab

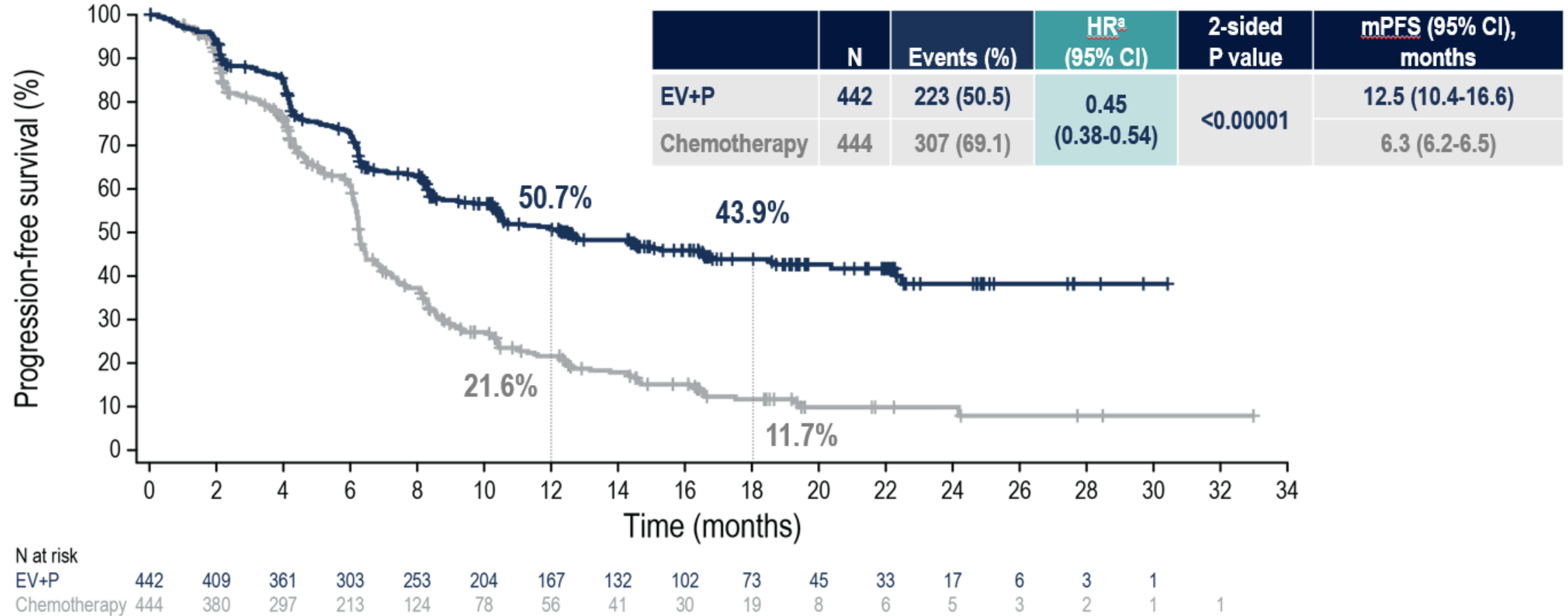


Stratification factors: cisplatin eligibility (eligible/ineligible), PD-L1 expression (high/low), liver metastases (present/absent)

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

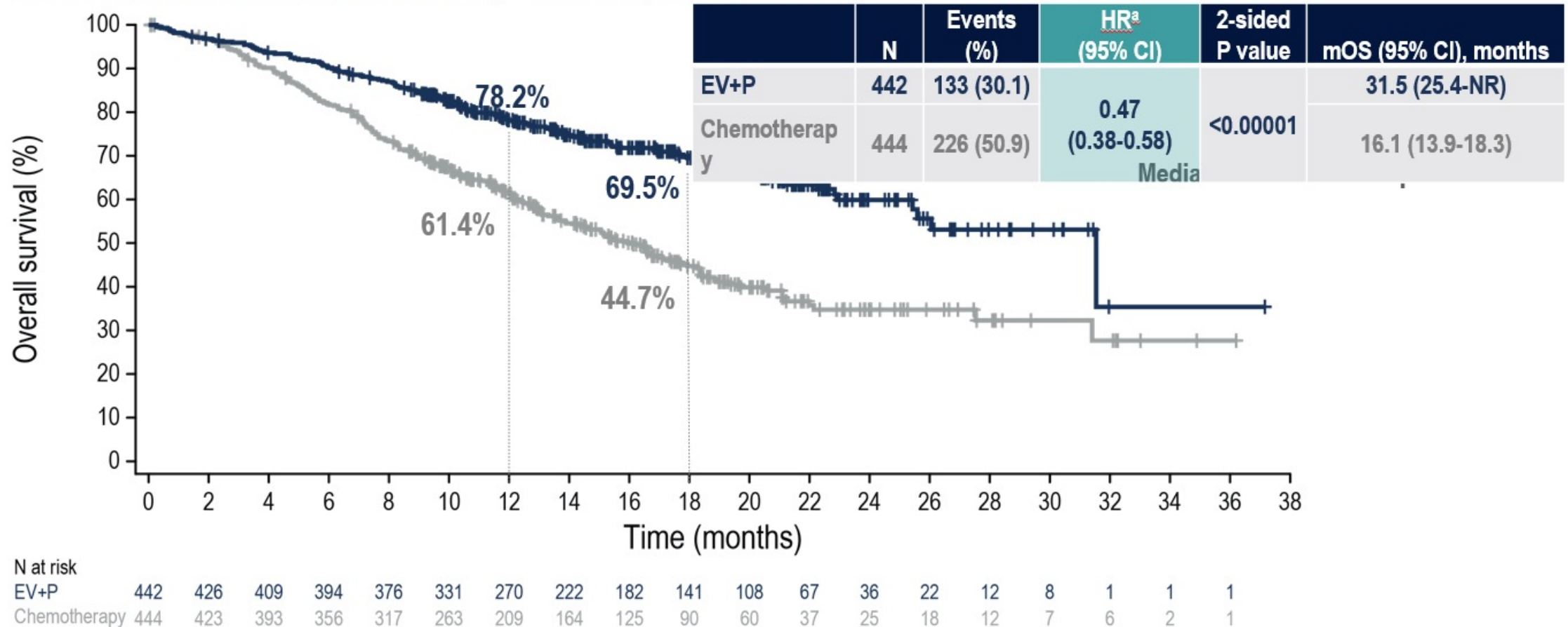
# EV-302: Progression-Free Survival per BICR

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



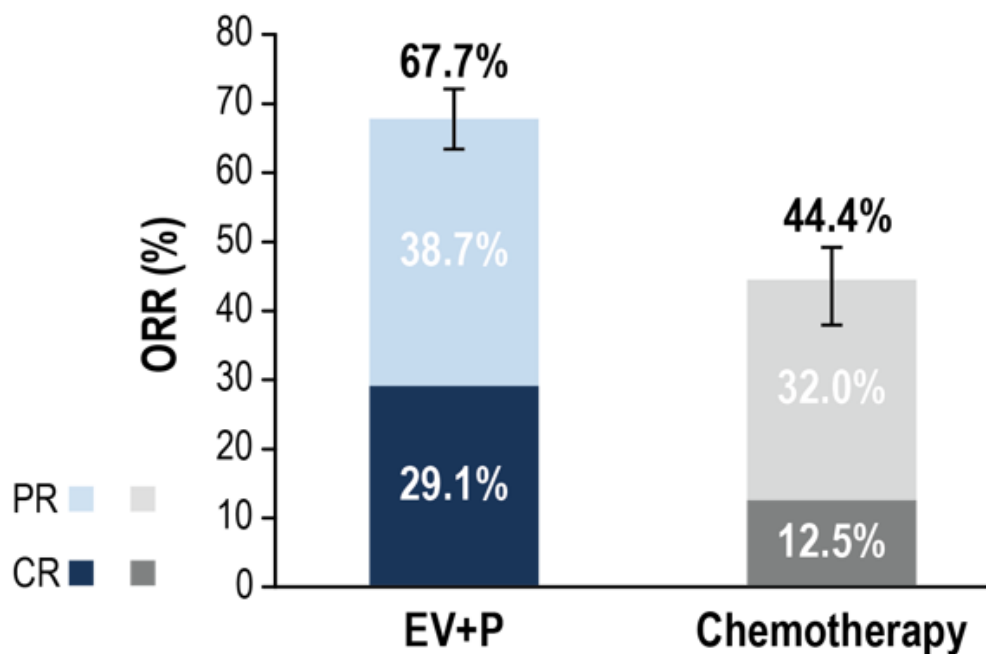
# EV-302: Overall Survival per BICR

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



# EV-302: Overall Response per BICR

Significant improvement in objective response rate was observed with EV+P

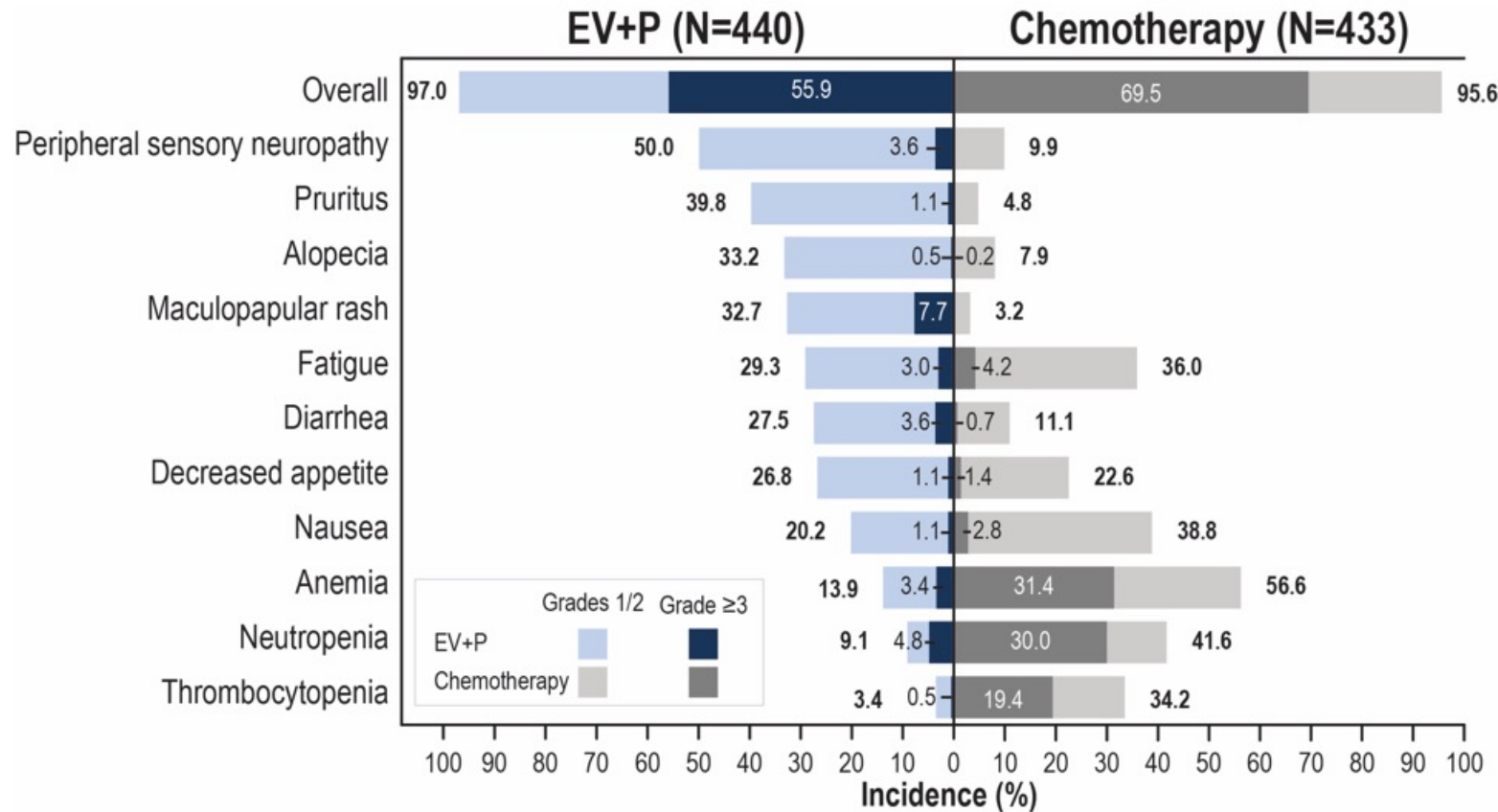


Median DOR (95% CI)	EV+P	Chemotherapy
	NR (20.2, NR)	7.0 (6.2, 10.2)

	EV+P (N=437)	Chemotherapy (N=441)
Confirmed ORR, n (%) (95% CI)	296 (67.7) (63.1-72.1)	196 (44.4) (39.7-49.2)
2-sided P value	<0.00001	
Best overall response <sup>a</sup> , n (%)		
Complete response	127 (29.1)	55 (12.5)
Partial response	169 (38.7)	141 (32.0)
Stable disease	82 (18.8)	149 (33.8)
Progressive disease	38 (8.7)	60 (13.6)
Not evaluable/No assessment <sup>b</sup>	21 (4.8)	36 (8.2)

# EV-302: Treatment-Related Adverse Events

Grade  $\geq 3$  events were 56% in EV+P and 70% in chemotherapy



Serious TRAEs:

- 122 (27.7%) EV+P
- 85 (19.6%) chemotherapy

TRAEs leading to death (per investigator):

EV+P: 4 (0.9%)

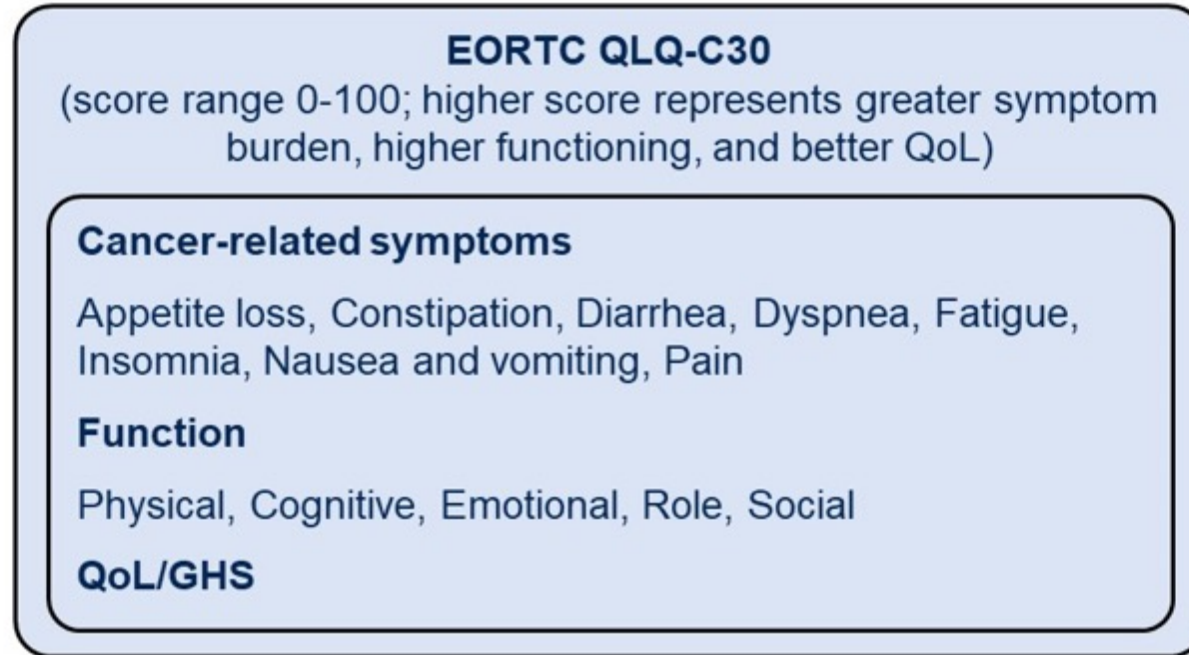
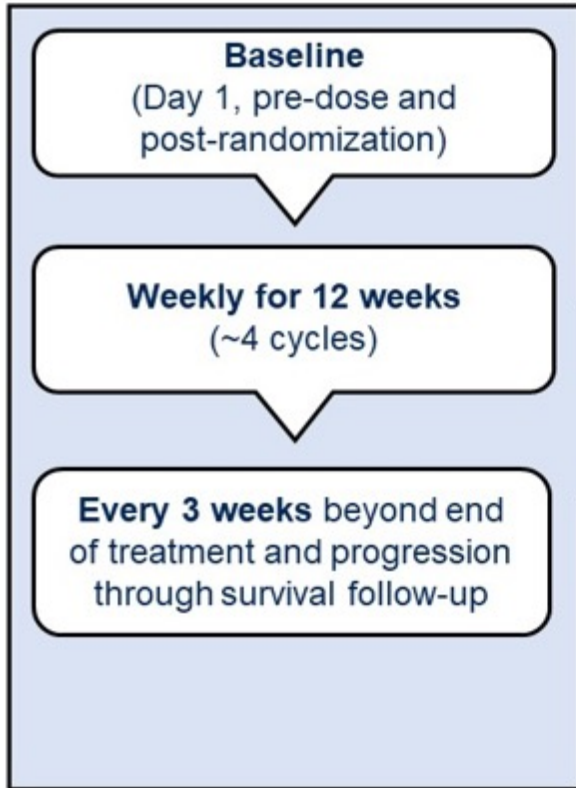
- Asthenia
- Diarrhea
- Immune-mediated lung disease
- Multiple organ dysfunction syndrome

Chemotherapy: 4 (0.9%)

- Febrile neutropenia
- Myocardial infarction
- Neutropenic sepsis
- Sepsis

Median number of cycles (range): 12.0 (1,46) for EV+P; 6.0 (1,6) for chemotherapy

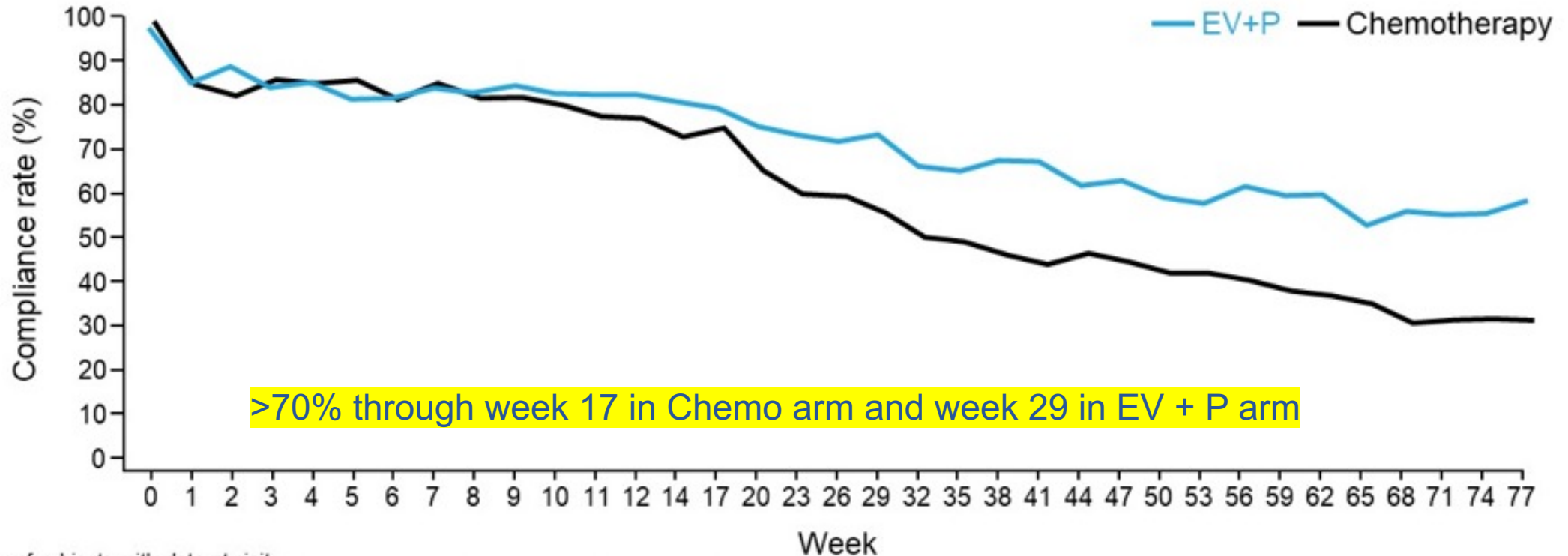
# EV-302: PRO Collection (ASCO 2024 Update)



- TTPP and mean change from baseline in worst pain (BPI-SF Question 3) at week 26 were pre-specified endpoints included in the hierarchical statistical testing plan.
- Pre-specified descriptive analyses included change from baseline and time to confirmed deterioration (TTCD).
- Patients with moderate/severe pain at baseline were a pre-specified subgroup of interest.



# EV-302: PRO Collection (ASCO 2024 Update)



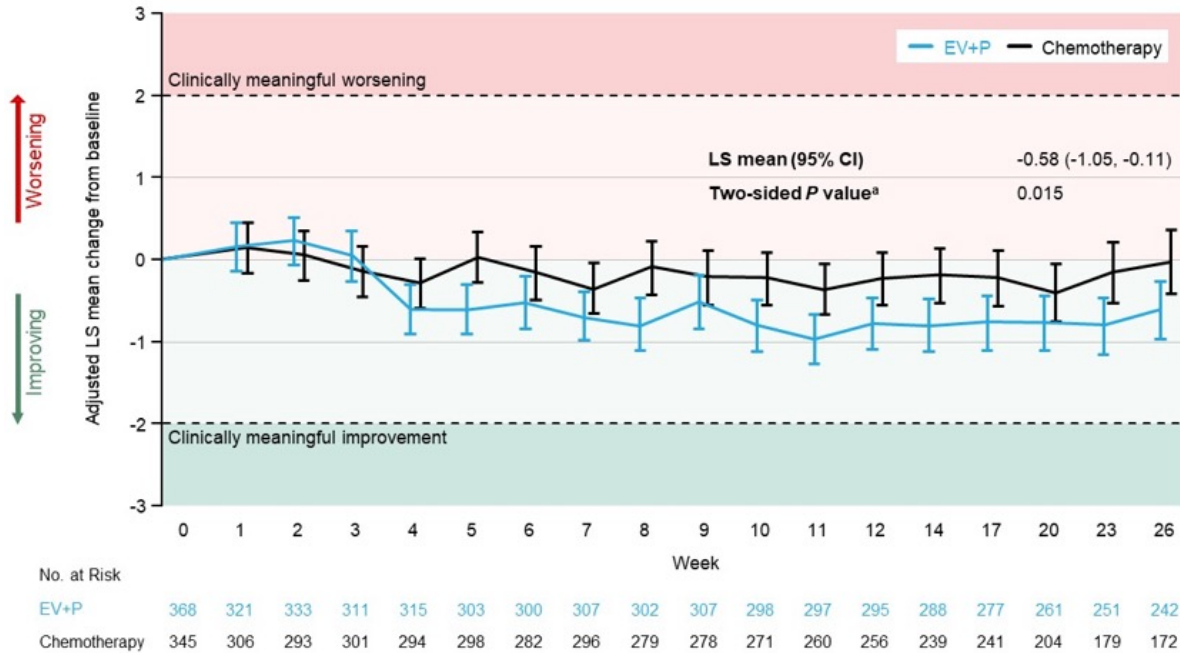
No. of subjects with data at visit

EV+P	365	321	330	311	314	300	300	306	301	307	299	296	296	289	278	261	252	241	241	215	210	212	205	177	166	150	138	139	127	117	95	95	88	82	77
Chemotherapy	350	300	288	300	294	296	282	294	279	278	271	260	256	239	240	204	179	172	158	135	127	116	104	98	89	78	70	63	54	49	42	34	32	29	26

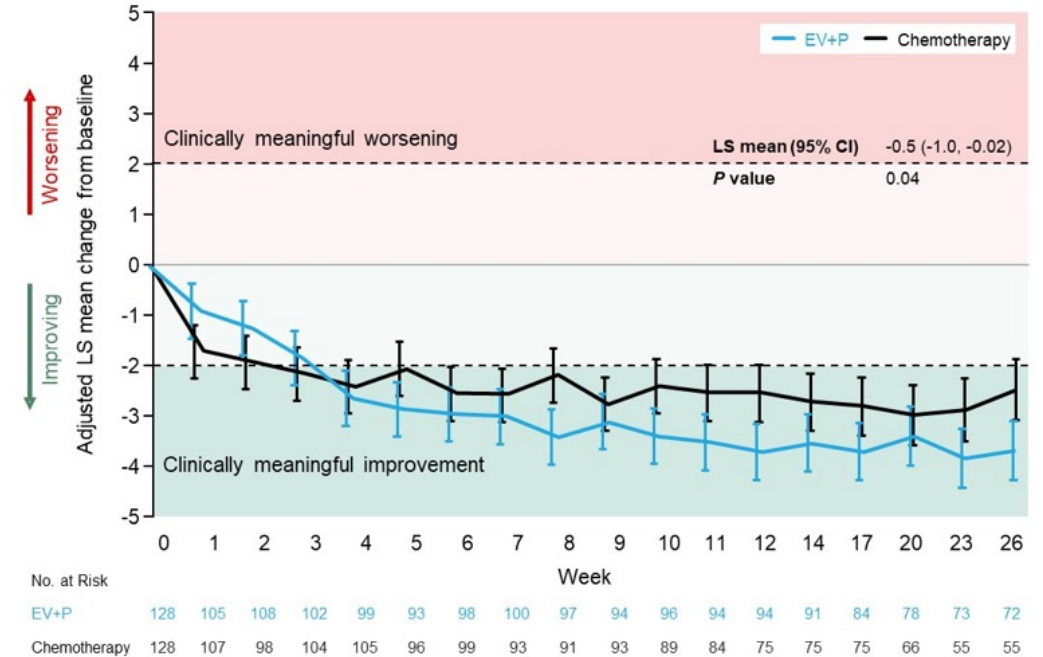
No. of subjects who are expected to have PRO assessments

EV+P	376	376	373	371	369	368	367	365	364	363	361	359	359	357	350	348	343	336	330	326	323	314	306	285	265	254	239	226	213	196	180	170	160	148	132
Chemotherapy	355	355	352	351	348	347	347	347	343	342	340	337	334	329	322	314	300	291	285	270	261	252	238	212	201	186	168	157	142	133	121	112	103	92	84

# EV-302: Change in Worst Pain (BPI-SF)

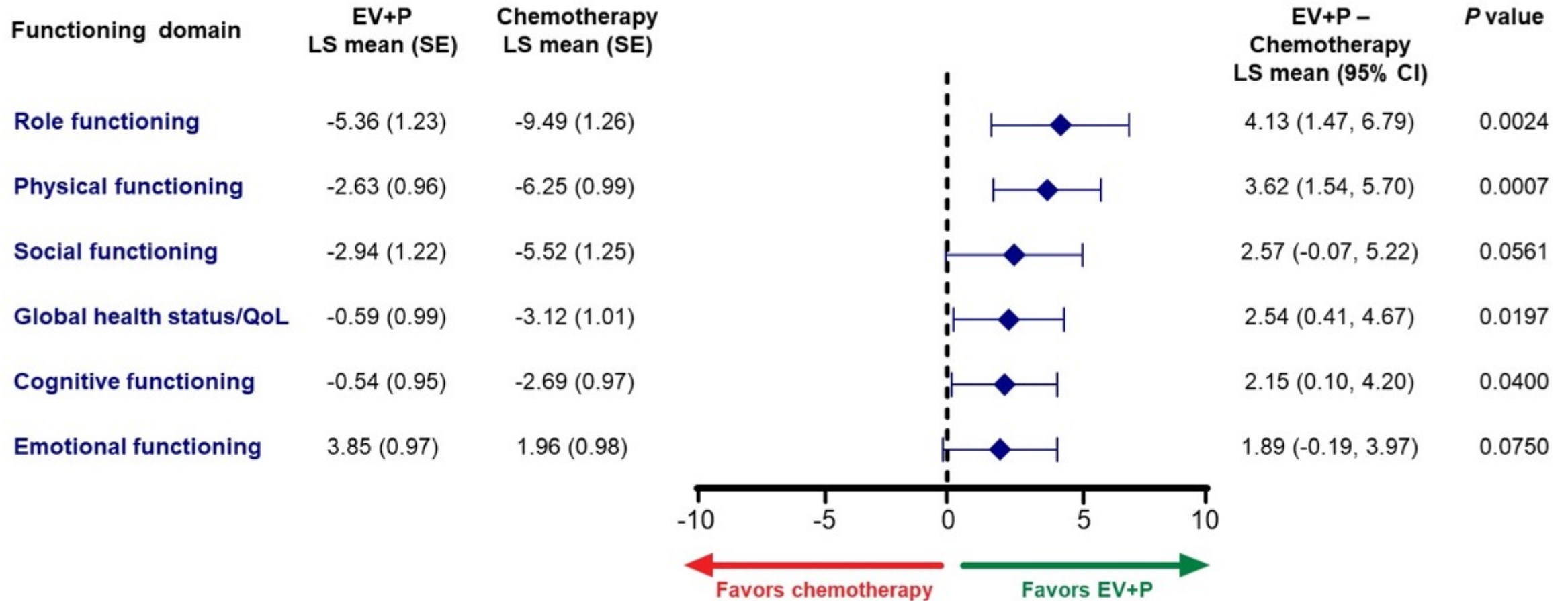


All Patients



Patients with Moderate/Severe Pain at Baseline

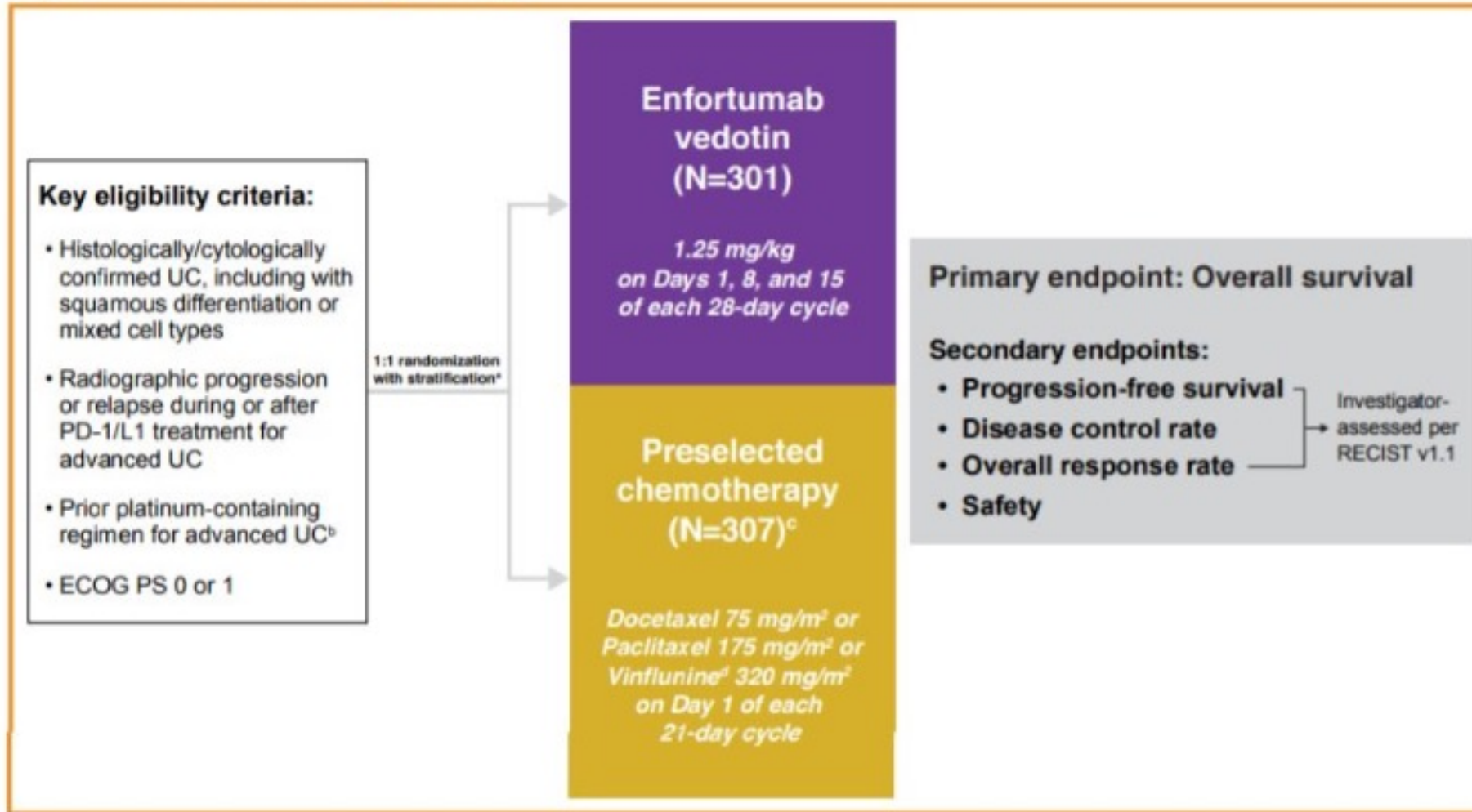
# EV-302: EORTC QLQ-C30 Functioning Domains



Based on change from baseline during the first 26 weeks

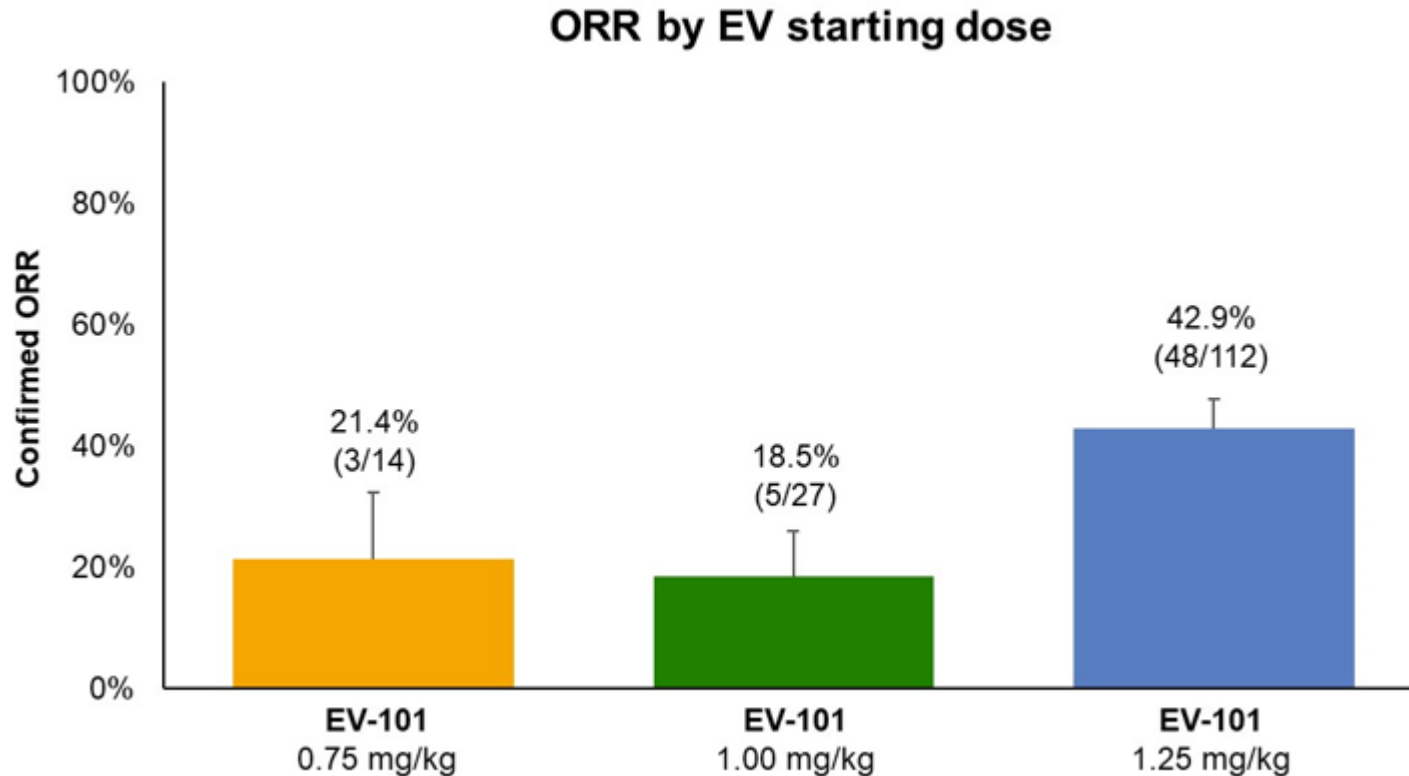
# Effect of Enfortumab Exposure

Figure 1. EV-301 Study Design



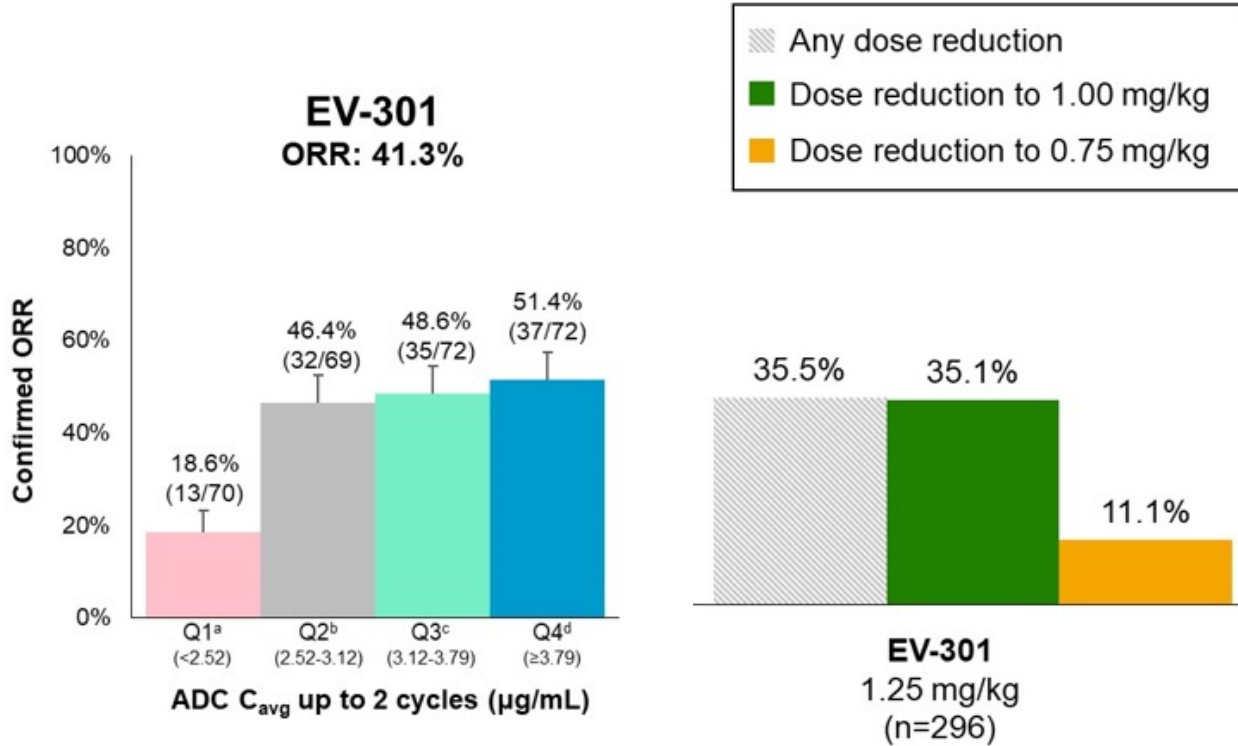
# Effect of Enfortumab Vedotin Exposure

(monotherapy, EV-101 Phase 1 Study)



# Effect of Enfortumab Vedotin Exposure

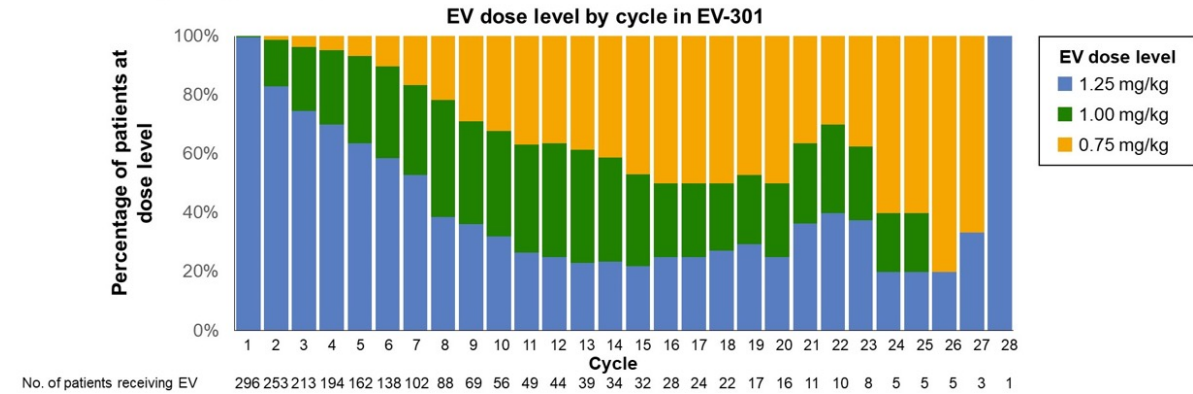
(monotherapy, EV-301 Phase 3 Study)



Response Rate

Dose Reductions

The majority of patients in EV-301 maintained EV 1.25 mg/kg through Cycle 7; dose reductions were more frequent in later cycles

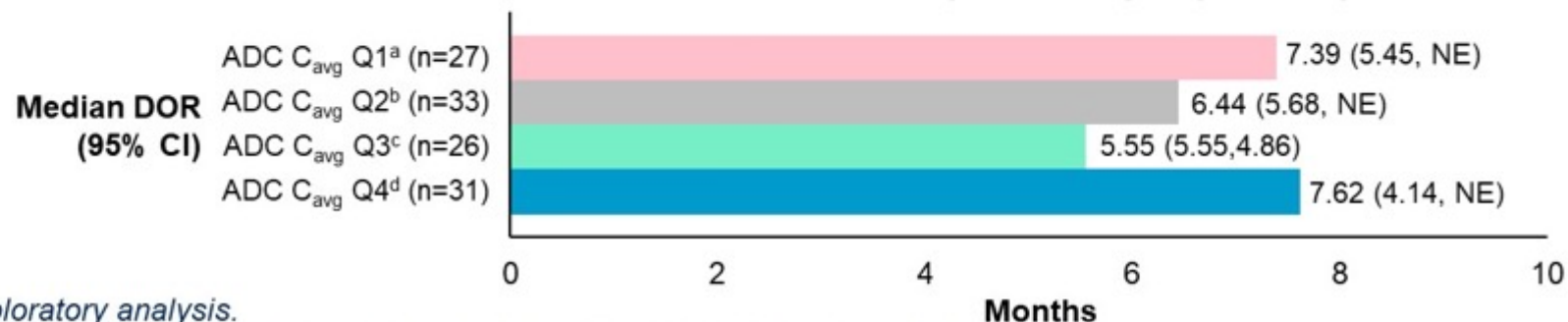


Dose Level by Cycle

# EV-301: Durable Responses even with Modifications

	ADC C <sub>avg</sub> Q1 <sup>a</sup> (n=74)	ADC C <sub>avg</sub> Q2 <sup>b</sup> (n=74)	ADC C <sub>avg</sub> Q3 <sup>c</sup> (n=74)	ADC C <sub>avg</sub> Q4 <sup>d</sup> (n=74)
Median EV ADI (mg/kg/4 week) <sup>e</sup> (range)	2.37 (1.15, 3.77)	2.96 (1.57, 3.82)	3.26 (2.36, 3.86)	3.59 (2.50, 3.93)
Any EV dose delay (%)	59.5	58.1	44.6	26.4
Any EV dose reduction (%)	54.1	39.2	28.4	20.3
To 1.0 mg/kg	52.7	39.2	28.4	20.3
To 0.75 mg/kg	21.6	14.9	6.8	1.4
Median time to EV dose reduction (range), mo	2.02 (0.79, 9.27)	2.96 (0.95, 12)	3.06 (0.72, 6.64)	2.79 (0.89, 9.04)

Median DOR for responders by exposure quartile



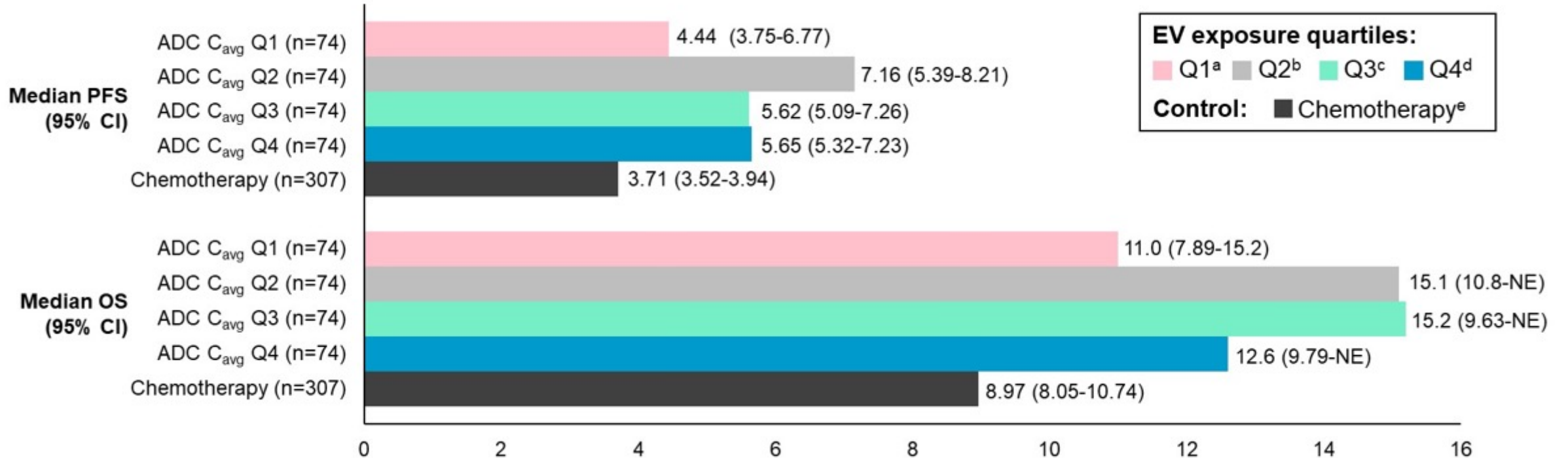
## EV-301:<sup>1</sup>

ORR: 41%

Median time to response:  
1.9 months (range: 1.1-5.7)

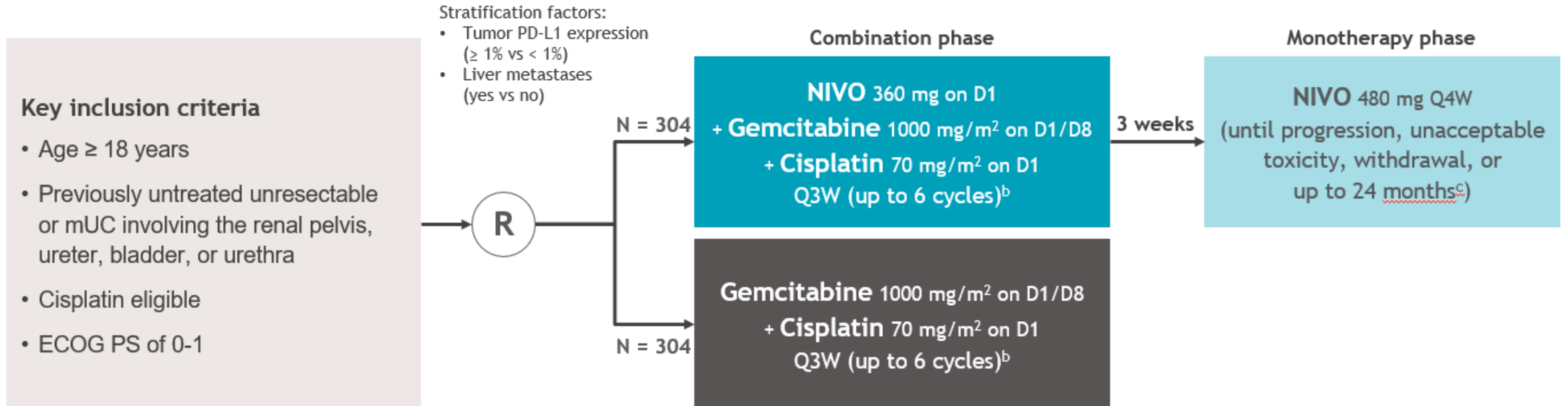
All data presented are from a post hoc, exploratory analysis.

# EV-301: Survival Benefit vs Chemotherapy





# CM-901: Nivolumab + Gemcitabine/Cisplatin vs GC



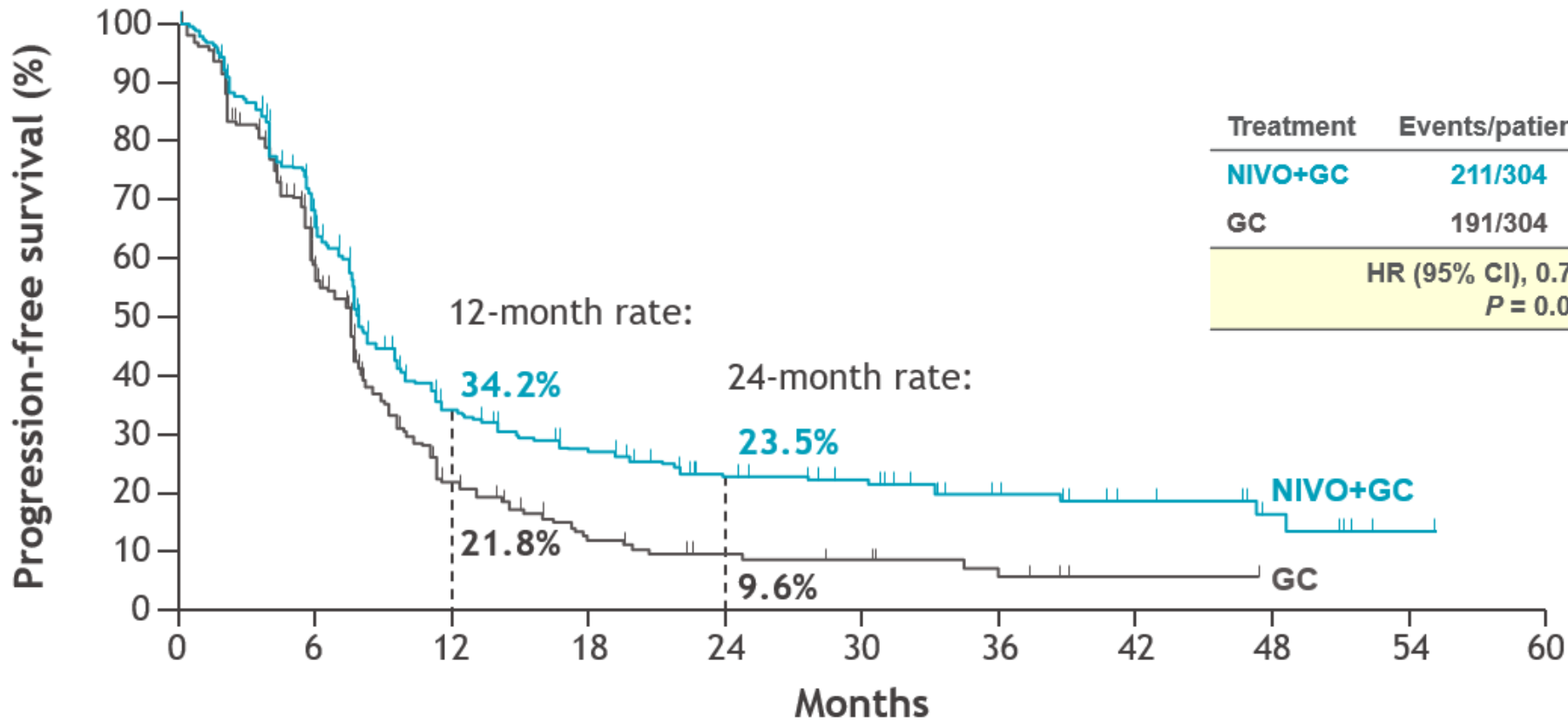
Median (range) study follow-up, 33.6 (7.4-62.4) months

Primary endpoints: OS, PFS per BICR

Key secondary endpoints: OS and PFS by PD-L1  $\geq$  1%,<sup>d</sup> HRQoL

Key exploratory endpoints: ORR per BICR, safety

# CM-901: PFS per BICR

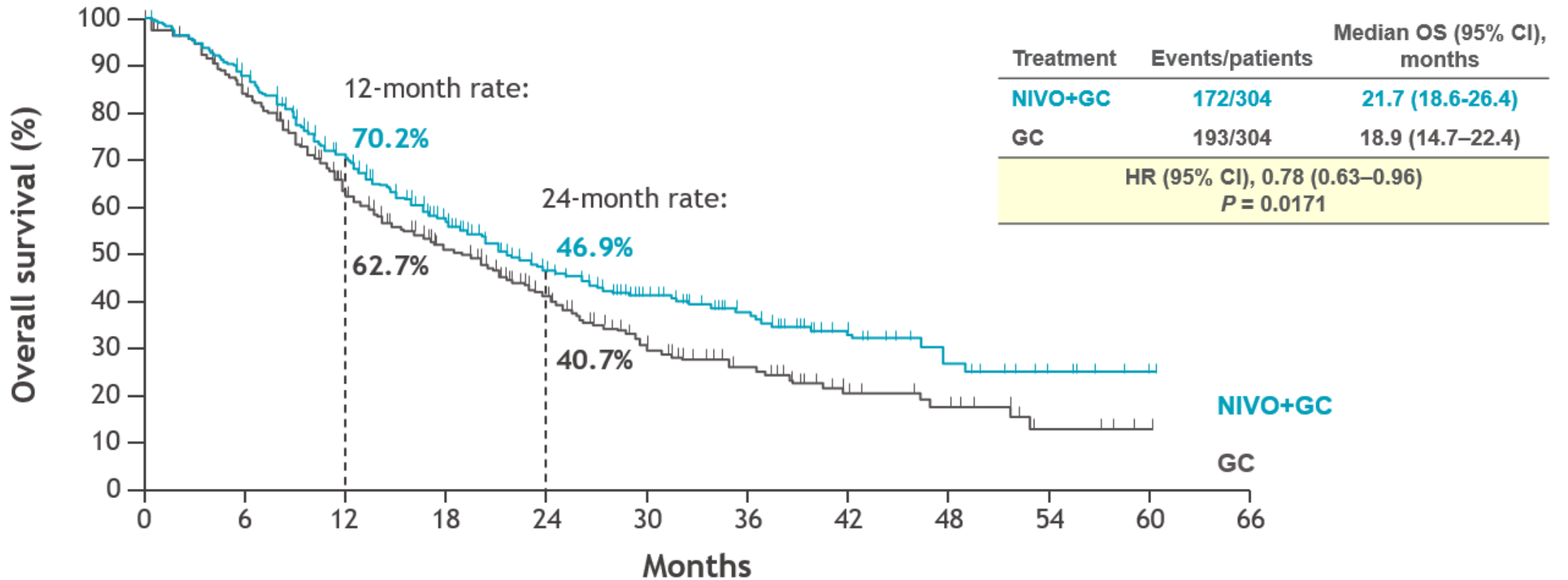


Treatment	Events/patients	Median PFS (95% CI), months
<b>NIVO+GC</b>	<b>211/304</b>	<b>7.9 (7.6-9.5)</b>
<b>GC</b>	<b>191/304</b>	<b>7.6 (6.1-7.8)</b>
<b>HR (95% CI), 0.72 (0.59-0.88)</b> <b>P = 0.0012</b>		

No. at risk

<b>NIVO+GC</b>	<b>304</b>	<b>179</b>	<b>82</b>	<b>57</b>	<b>41</b>	<b>31</b>	<b>19</b>	<b>11</b>	<b>6</b>	<b>1</b>	<b>0</b>
GC	304	119	35	17	10	8	5	1	0	0	0

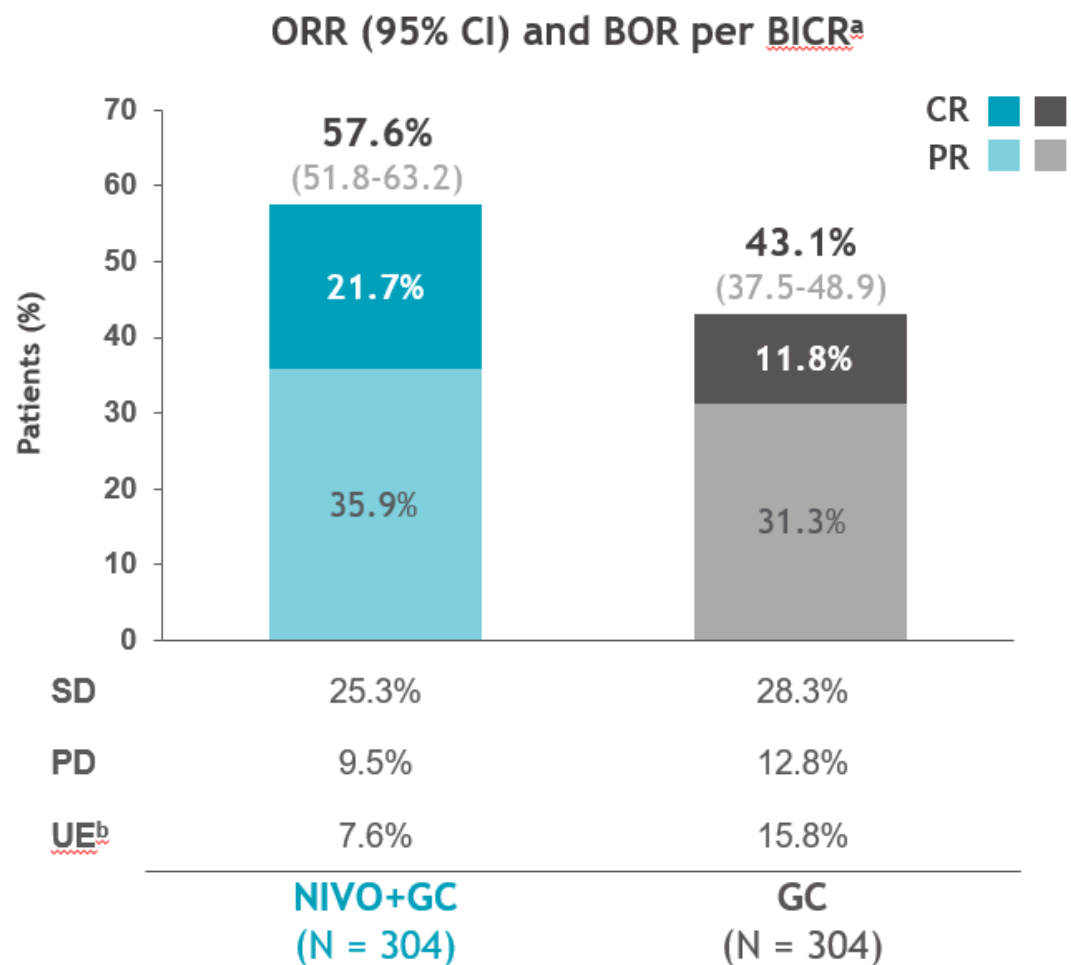
# CM-901: Overall Survival



No. at risk

<b>NIVO+GC</b>	<b>304</b>	<b>264</b>	<b>196</b>	<b>142</b>	<b>97</b>	<b>69</b>	<b>48</b>	<b>25</b>	<b>15</b>	<b>7</b>	<b>2</b>	<b>0</b>
GC	304	242	166	122	82	49	33	17	13	4	1	0

# CM-901: Objective Response Rate

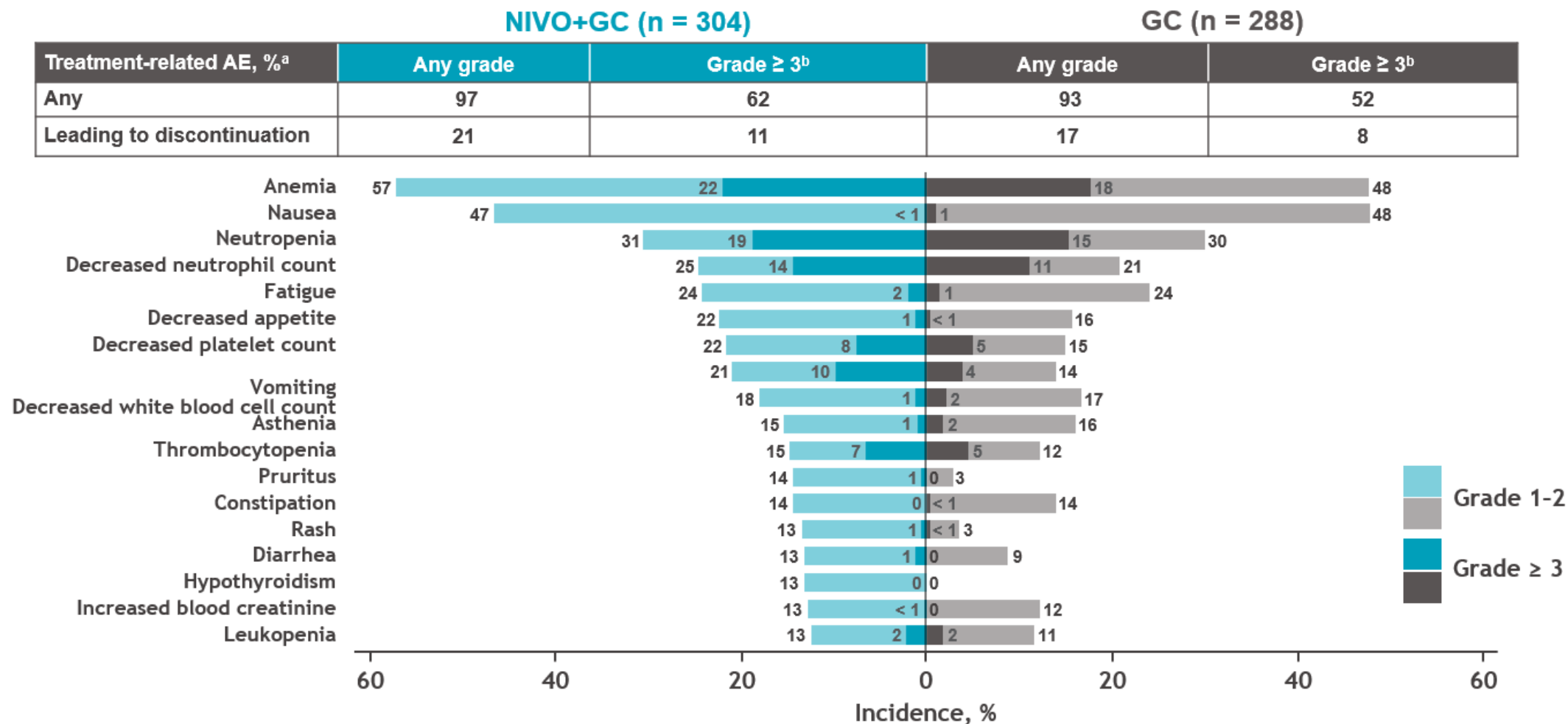


## Time to and duration of responses

	NIVO+GC (n = 175)	GC (n = 131)
Any objective response <sup>c</sup>		
Median TTR (Q1-Q3), months	2.1 (2.0–2.3)	2.1 (2.0–2.2)
Median DoR (95% CI), months	9.5 (7.6–15.1)	7.3 (5.7–8.9)

	NIVO+GC (n = 66)	GC (n = 36)
Complete response <sup>d</sup>		
Median TTCR (Q1-Q3), months	2.1 (1.9-2.2)	2.1 (1.9-2.2)
Median DoCR (95% CI), months	37.1 (18.1-NE)	13.2 (7.3-18.4)

# CM-901: Treatment-related adverse events

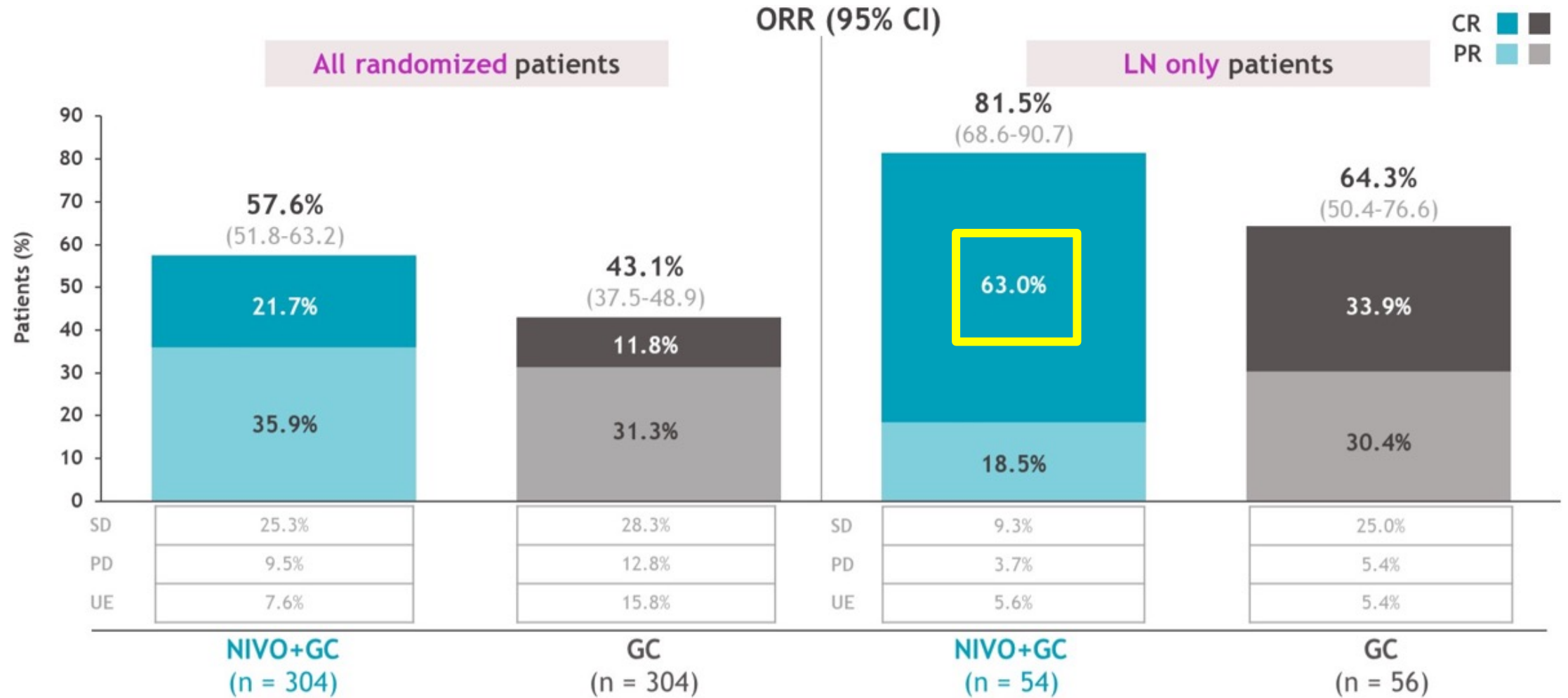


# CM-901: ASCO 2024 Update (Lymph Node Only)

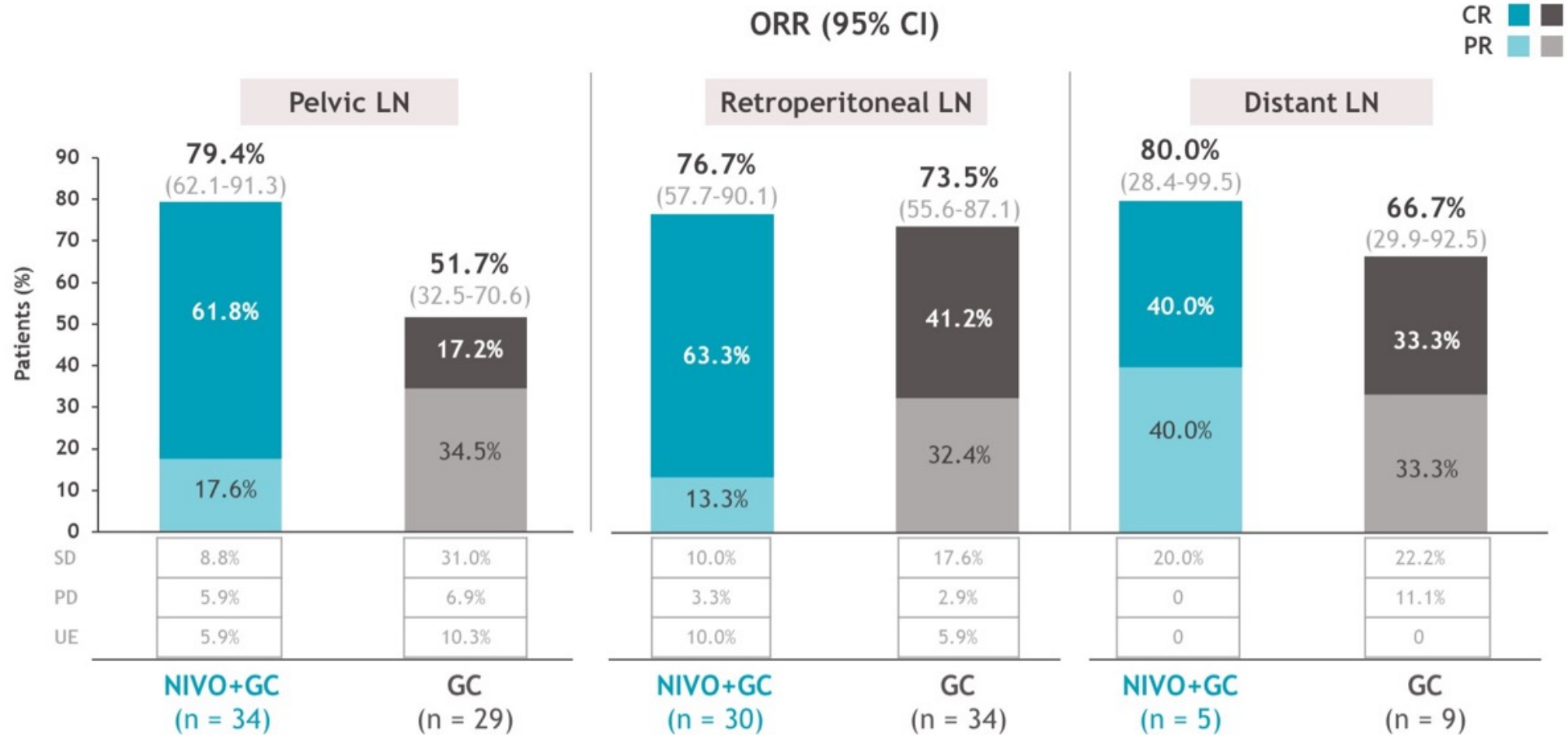
	All randomized patients		Patients with CR	
	NIVO+GC (N = 304)	GC (N = 304)	NIVO+GC (N = 66)	GC (N = 36)
Median age (range), years	65.0 (32-86)	65.0 (35-85)	65.0 (33-81)	63.5 (36-80)
Male sex, n (%)	236 (78)	234 (77)	53 (80)	31 (86)
<b>Race</b>				
White	211 (69)	225 (74)	47 (71)	27 (75)
Black or African American	0	2 (< 1)	0	0
American Indian or Alaska Native	1 (< 1)	1 (< 1)	0	1 (3)
Asian	75 (25)	63 (21)	16 (24)	6 (17)
Other	17 (6)	13 (4)	3 (5)	2 (6)
<b>LN only disease,<sup>a</sup> n (%)</b>	<b>54 (18)</b>	<b>56 (18)</b>	<b>34 (52)</b>	<b>19 (53)</b>
<b>Disease stage at study entry, n (%)</b>				
Stage III	37 (12)	28 (9)	9 (14)	5 (14)
Stage IV	265 (87)	274 (90)	56 (85)	31 (86)
Not reported	2 (< 1)	2 (< 1)	1 (2)	0
<b>PD-L1 status, n (%)</b>				
≥ 1%	112 (37)	109 (36)	28 (42)	11 (31)
< 1%	192 (63)	195 (64)	38 (58)	25 (69)
<b>Subsequent anticancer therapy received</b>	<b>108 (36)</b>	<b>156 (51)</b>	<b>23 (35)</b>	<b>15 (42)</b>

- Of the 608 total patients randomized, 102 (16.8%) achieved a CR
- Approximately 50% of patients with CR had LN only mUC vs approximately 20% of all randomized patients

# CM-901: LN-Only Response Rates

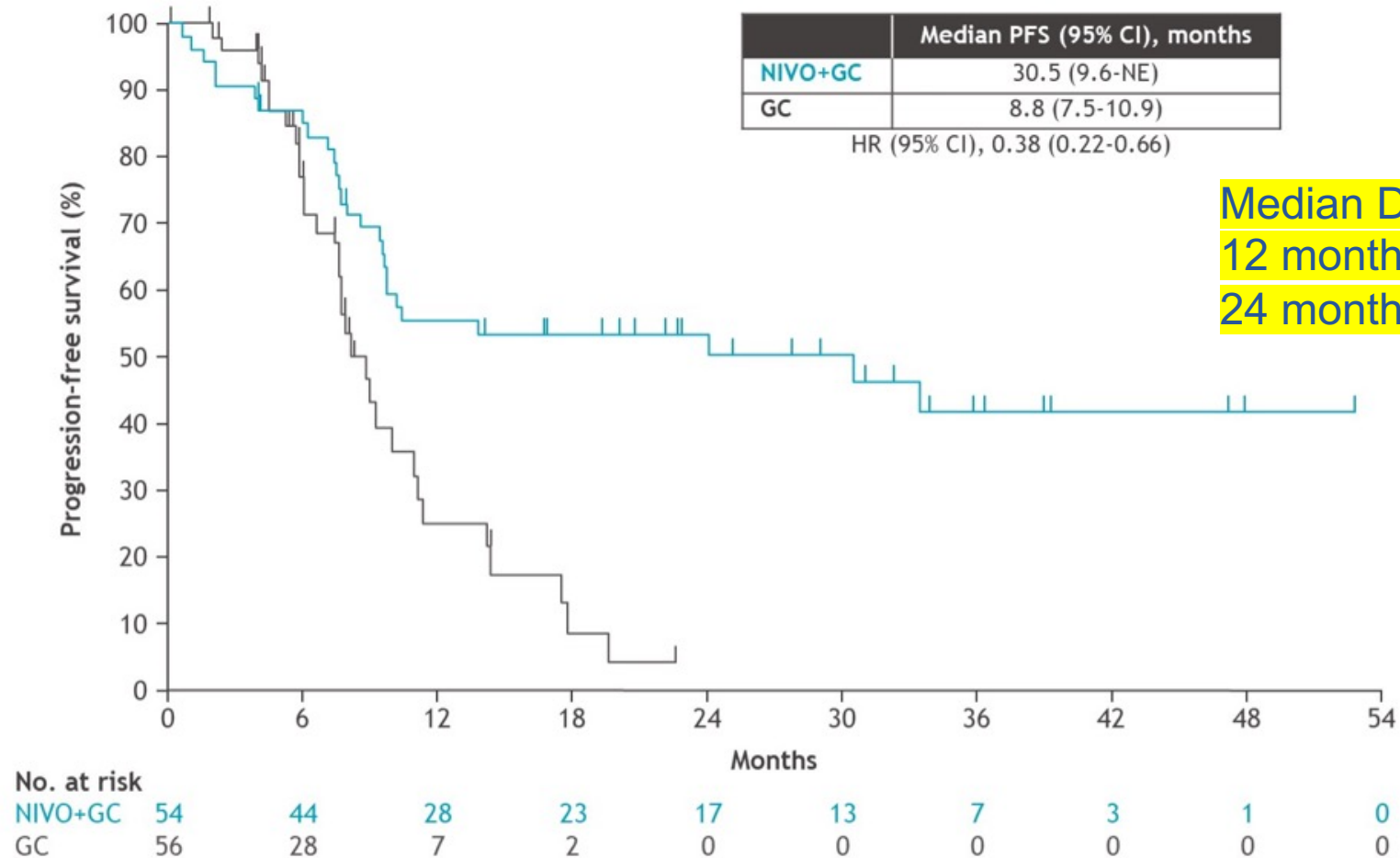


# CM-901: LN-Only Response Rates



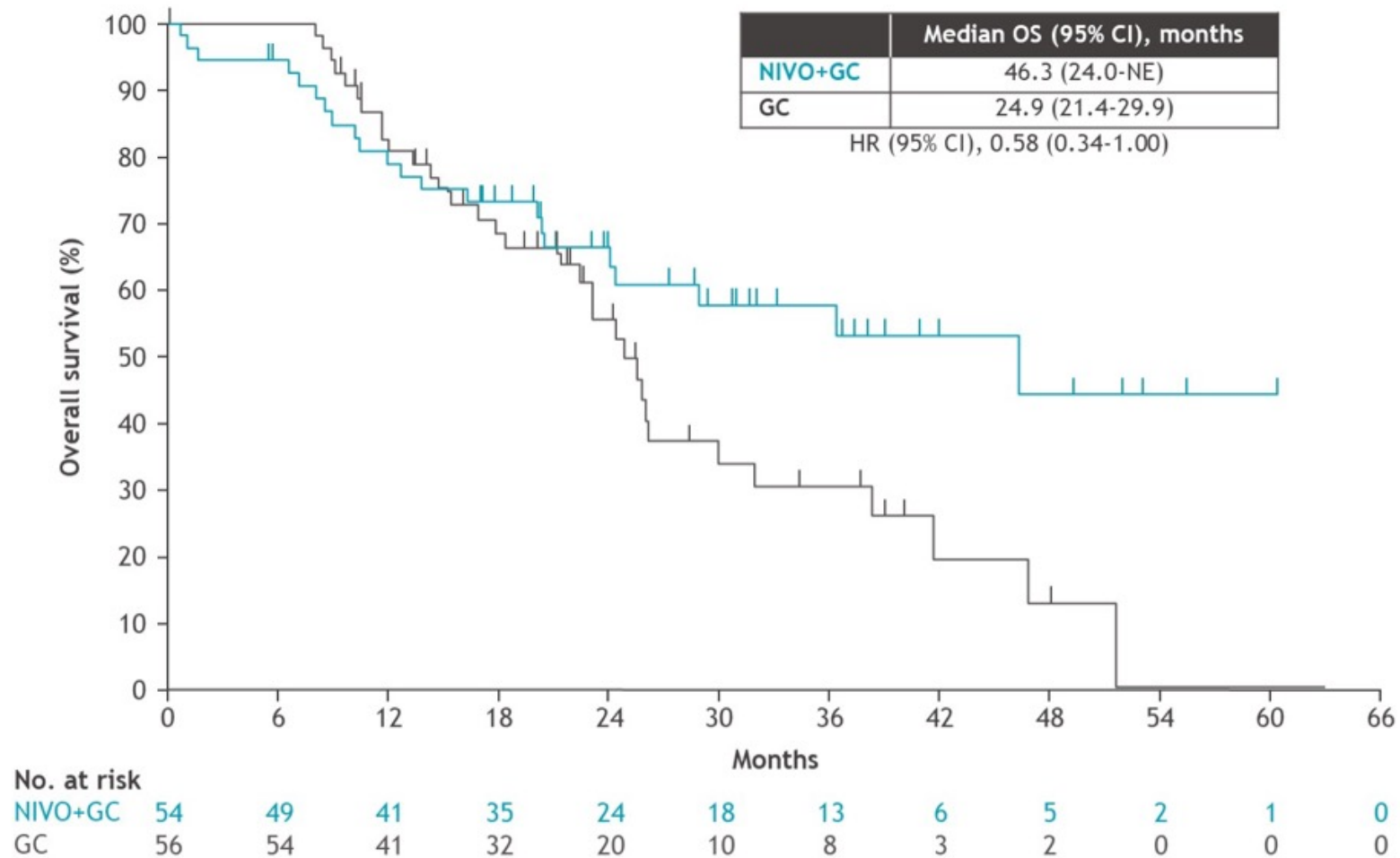


# CM-901: LN-Only Progression Free Survival



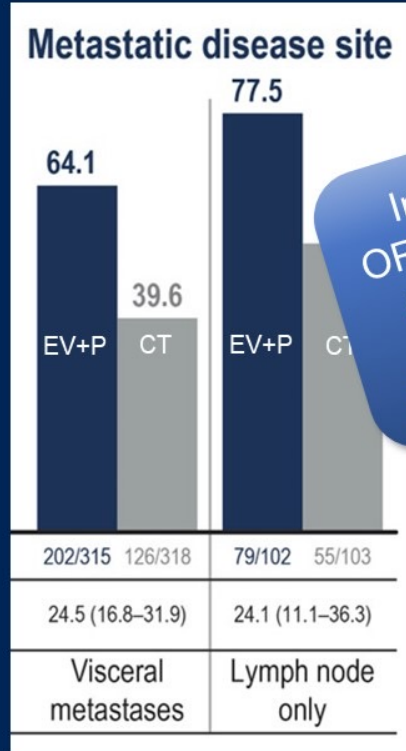
Median Duration of CR: NR vs 8.7 months  
 12 month CR Rate: 70% (vs 32%)  
 24 month CR Rate: 65% (vs 0%)

# CM-901: LN-Only Overall Survival

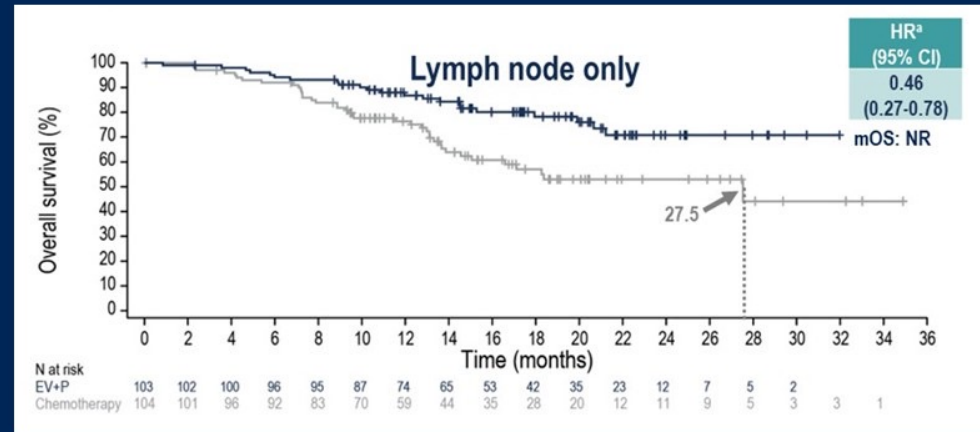


# How EV+P performed in lymph node-only aUC patients?

## Objective Response Rate



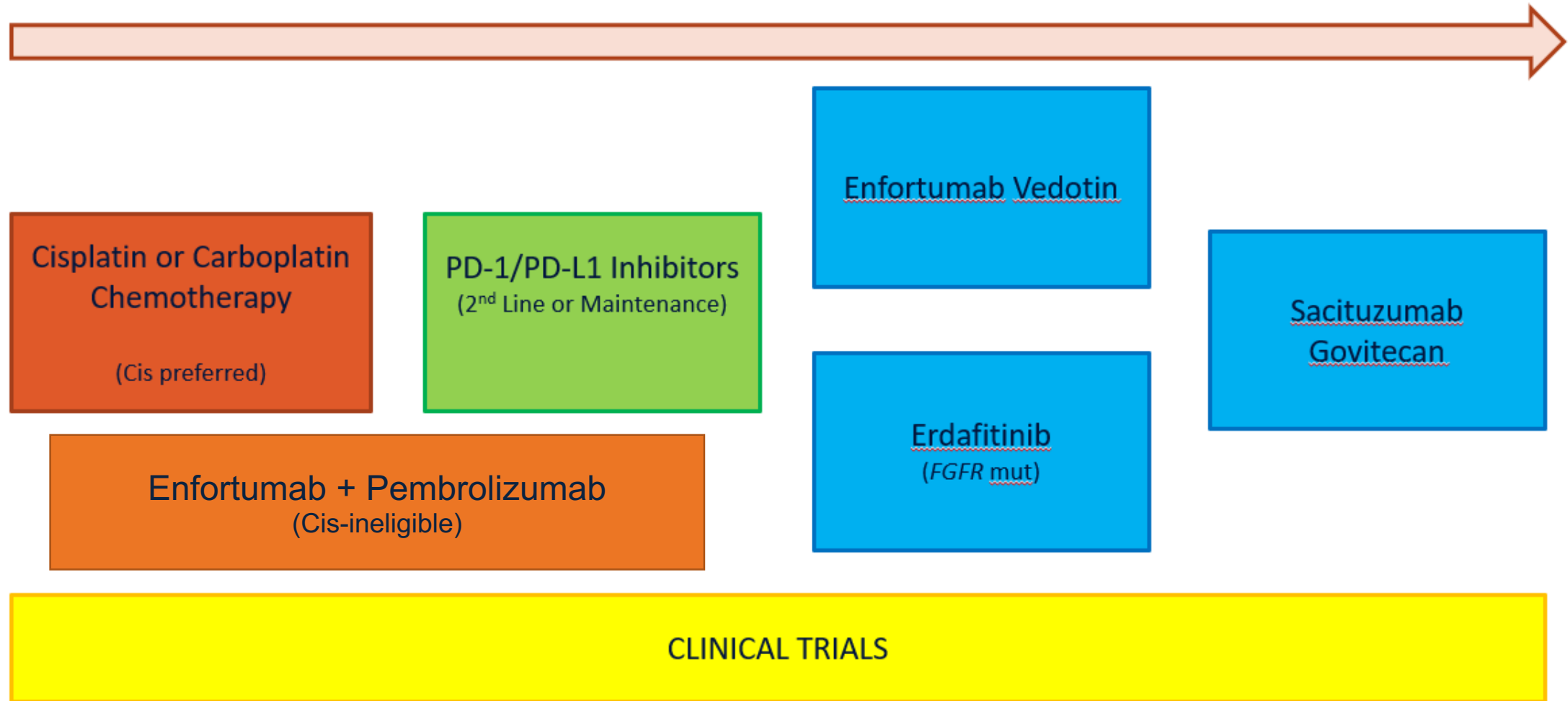
In comparison, ORR in lymph node only disease for Nivo + CG is 81.5% (63% CRR)



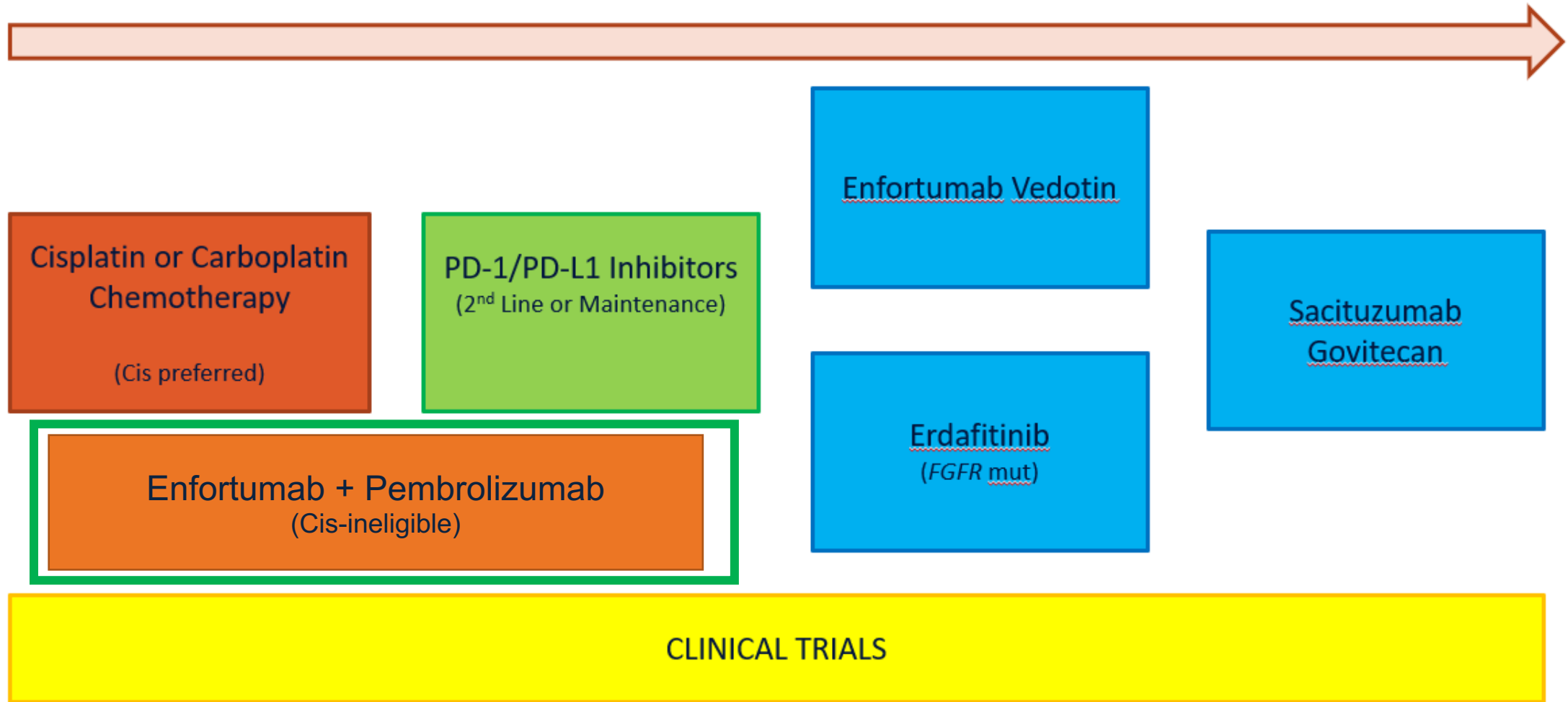
Subgroup	mOS, months (Events/N)		Hazard Ratio (95% CI)
	EV+P	Chemotherapy	
Overall	31.5 (133/442)	16.1 (226/444)	0.47 (0.38–0.58)
Metastatic disease site			
Visceral metastases	25.6 (108/318)	13.6 (182/318)	0.47 (0.37–0.60)
Lymph node only	NR (22/103)	27.5 (39/104)	0.46 (0.27–0.78)

1. Van der Heijden MS, et al. *J Clin Oncol* 2024;42(Suppl. 4):LBA530.

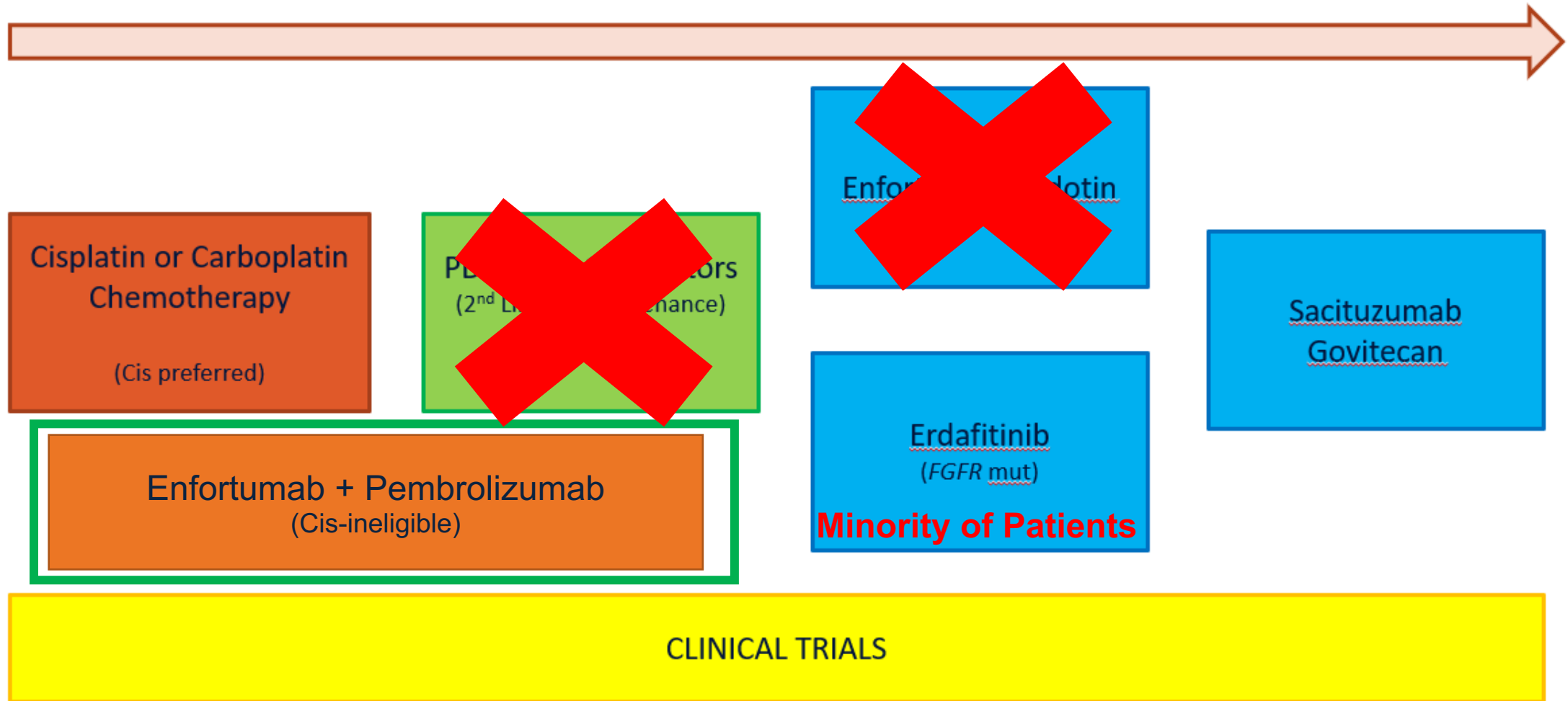
# Metastatic Urothelial Carcinoma



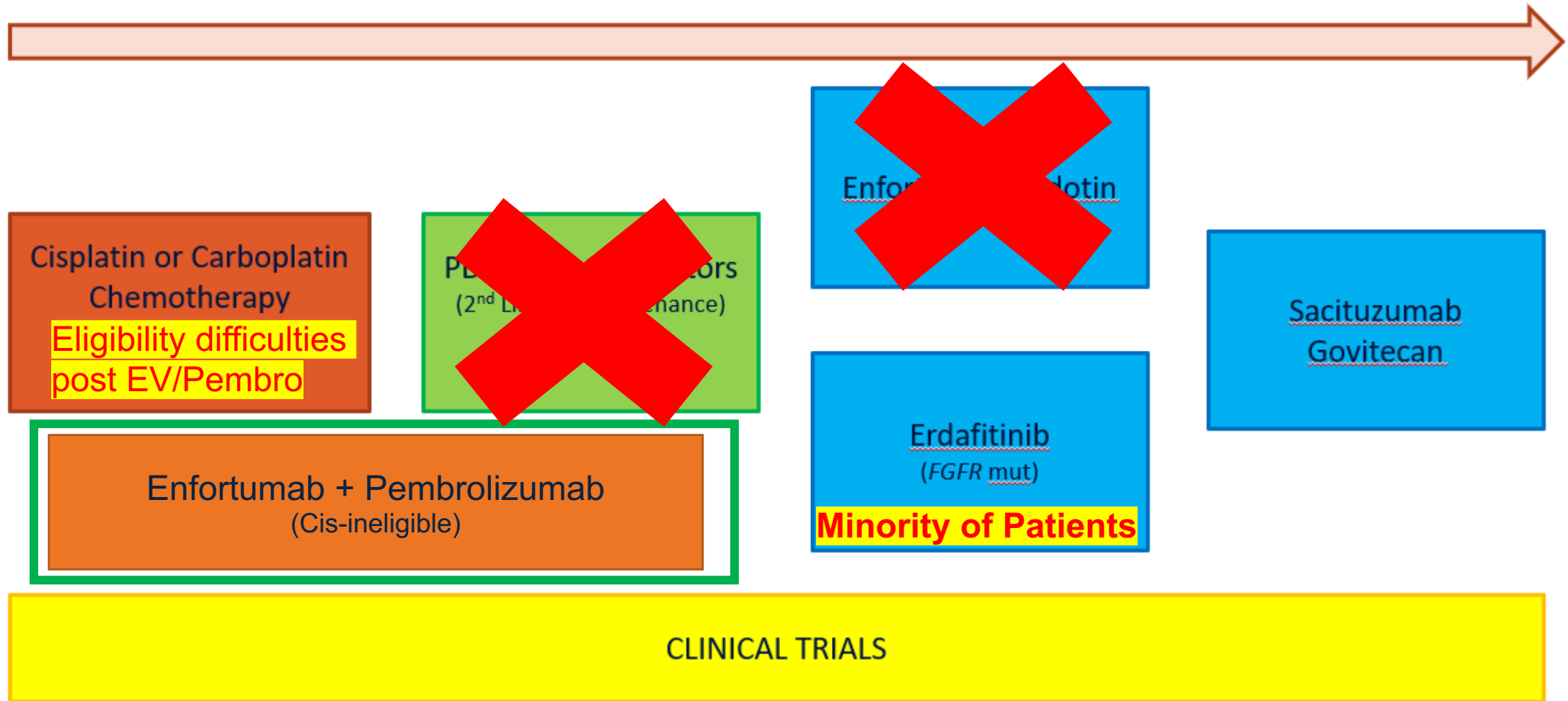
# Metastatic Urothelial Carcinoma



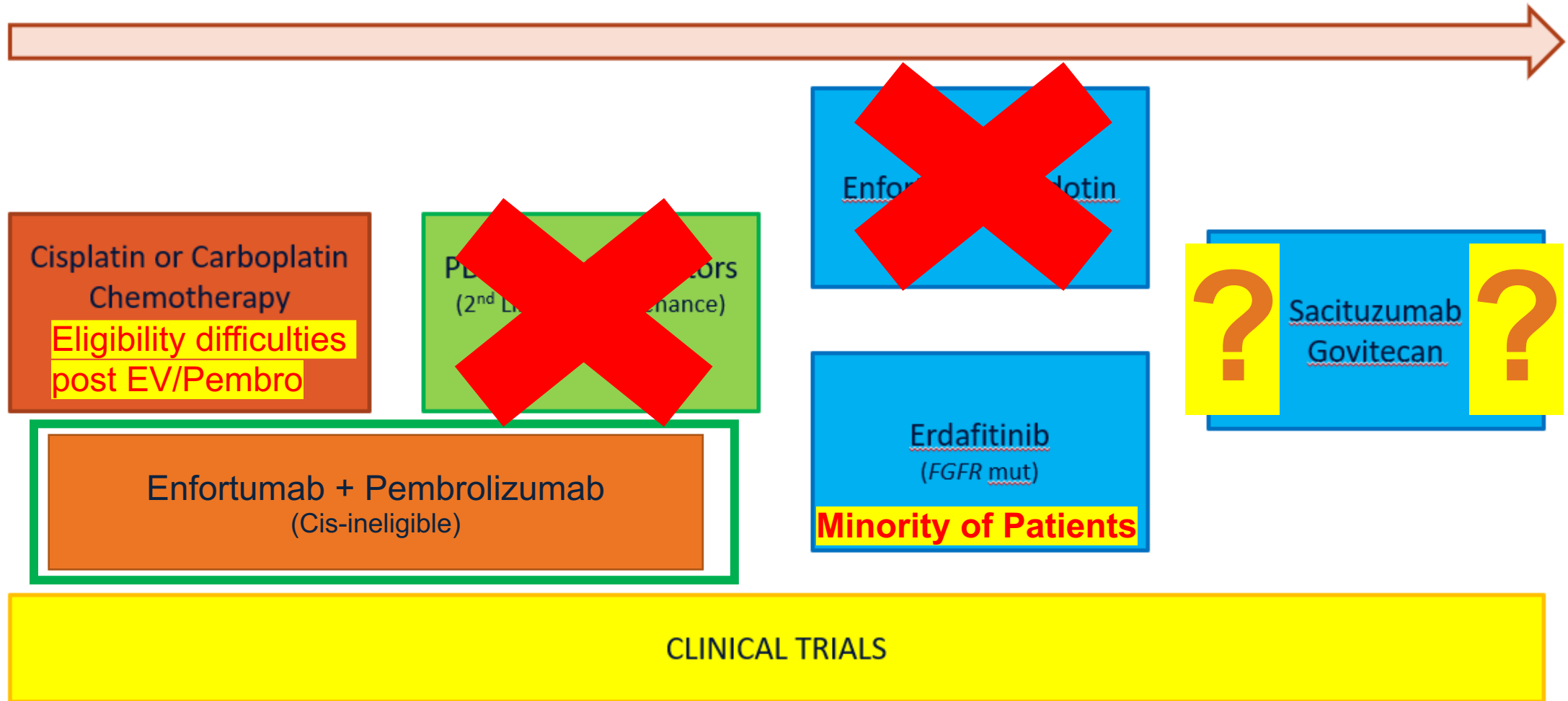
# Metastatic Urothelial Carcinoma



# Metastatic Urothelial Carcinoma



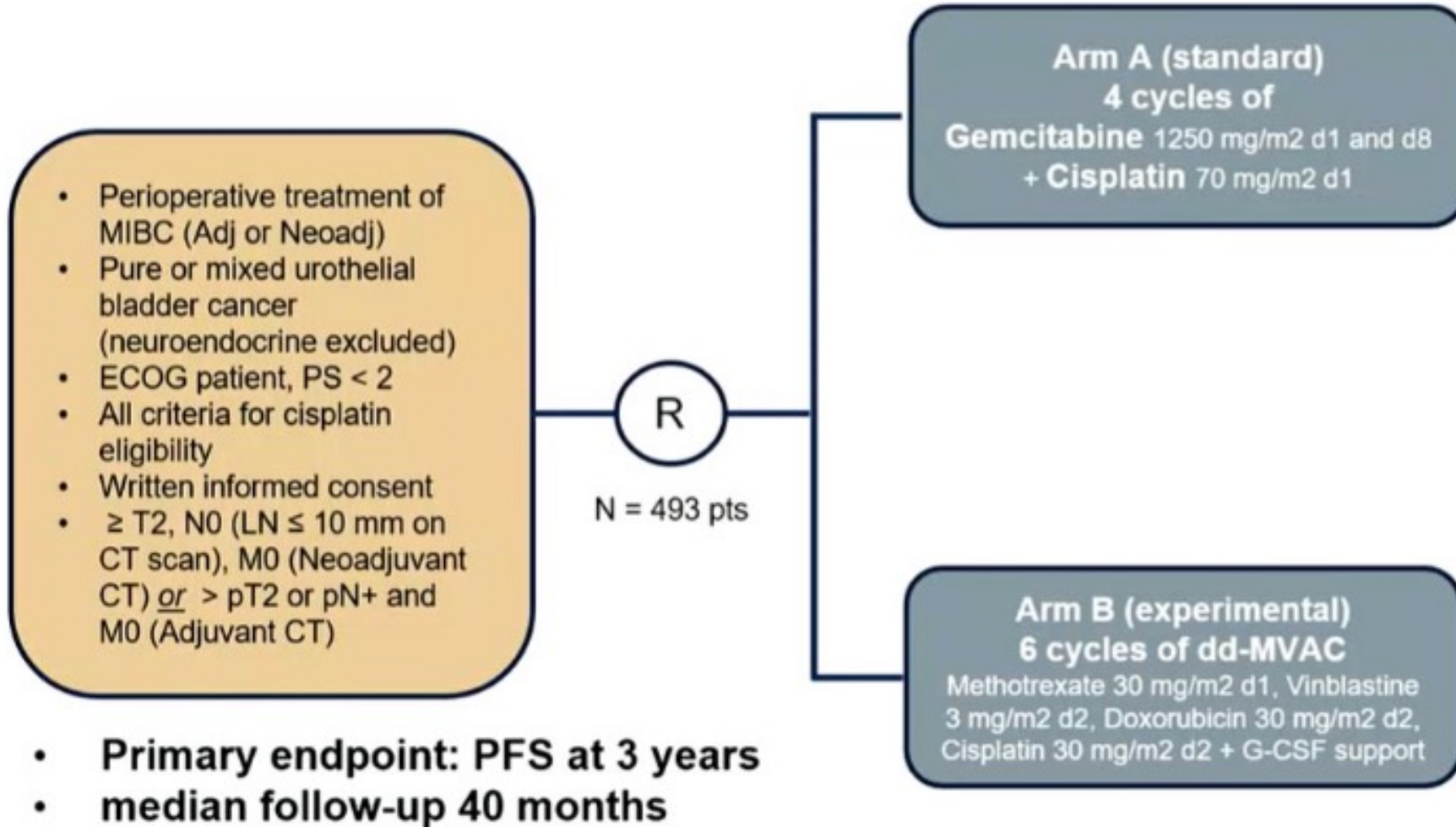
# Metastatic Urothelial Carcinoma



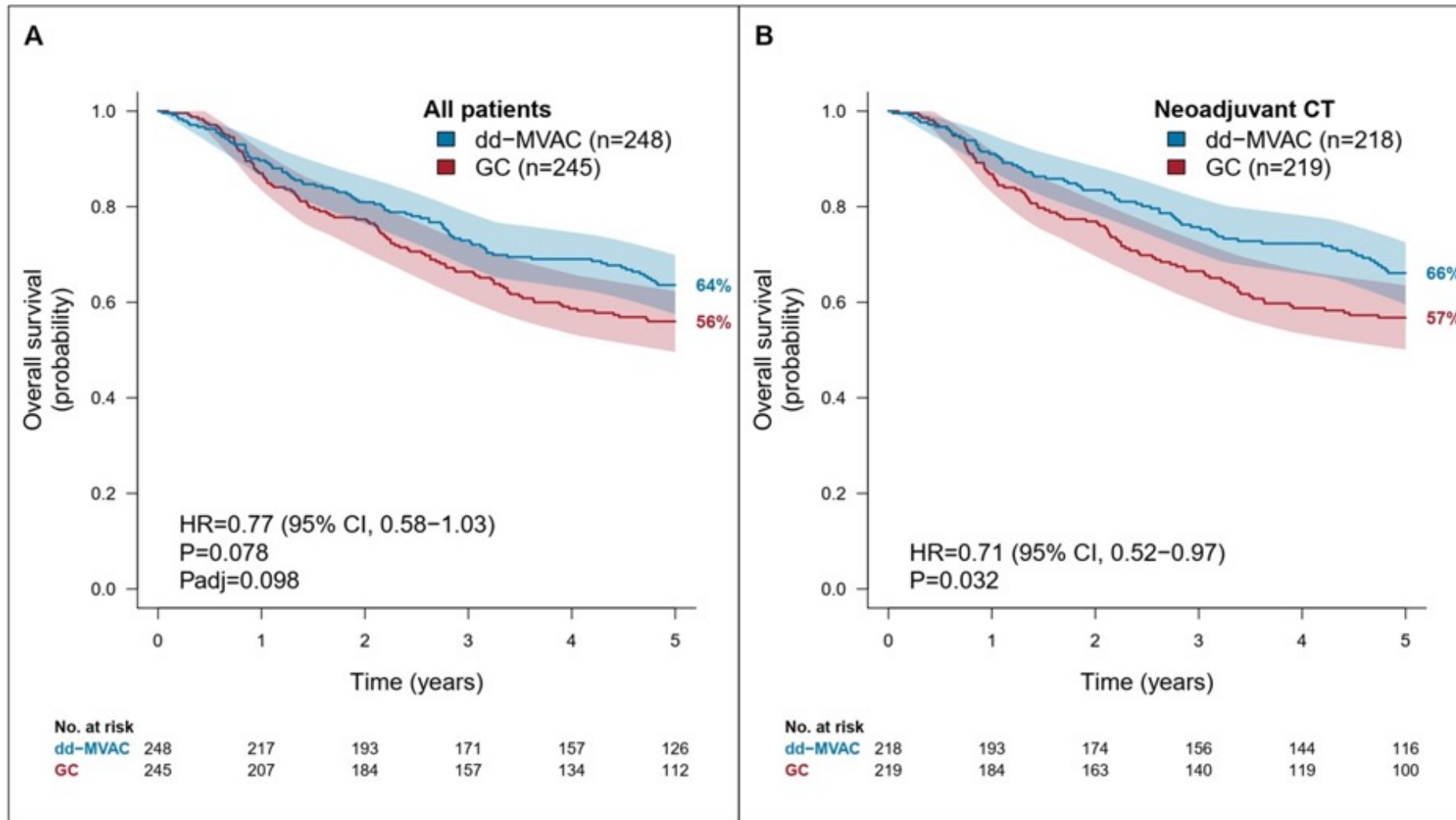


# Perioperative Urothelial Carcinoma

# GETUG/AFU V05 VESPER Phase III Trial



# GETUG-AFU VESPER: Perioperative Chemo



# AURA: Phase II Neoadjuvant Avelumab + Chemo

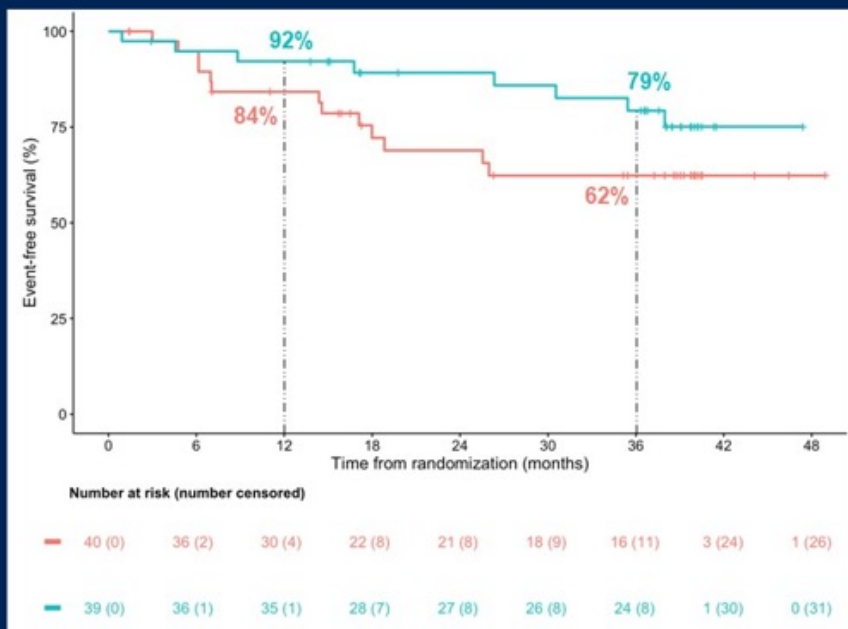


Primary endpoint was pCR

# AURA: Phase II Neoadjuvant Avelumab + Chemo

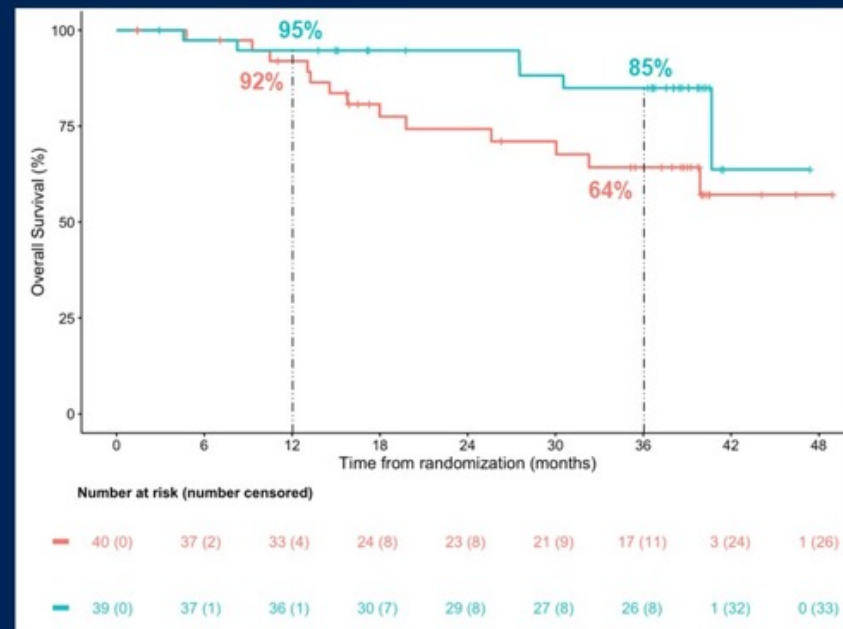
## Survival in the cisplatin-eligible cohort

Event-free survival



— ddMVAC-A  
— GC-A

Overall survival



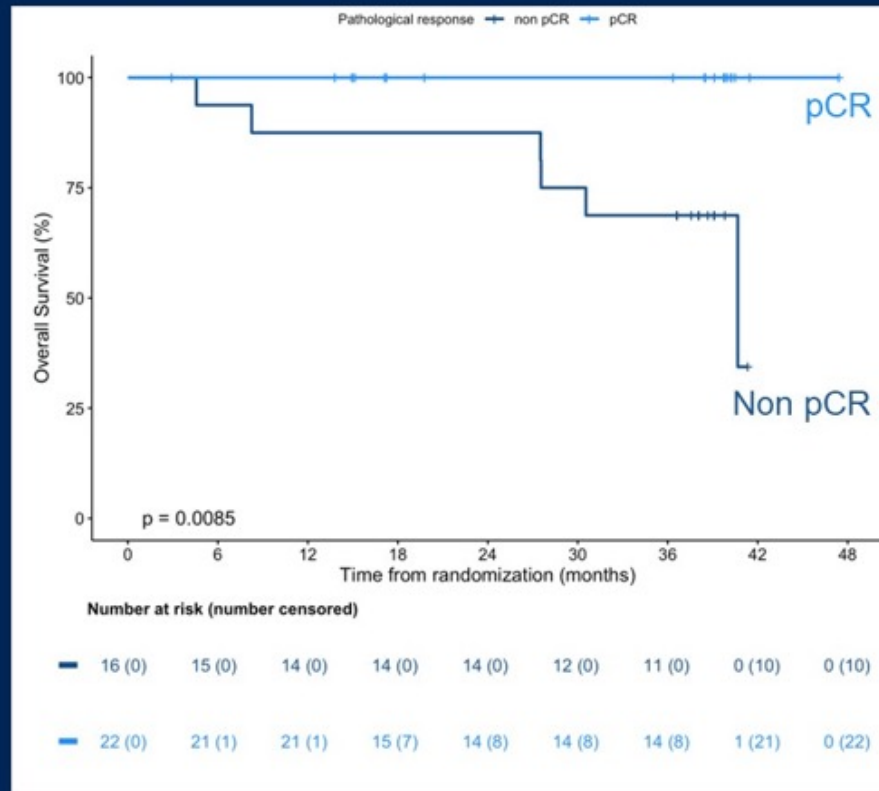
12-month EFS	92% ddMVAC-A 84% GC-A
Preliminary 36-month EFS	79% ddMVAC-A 62% GC-A

12-month OS	95% ddMVAC-A 92% GC-A
Preliminary 36-month OS	85% ddMVAC-A 64% GC-A

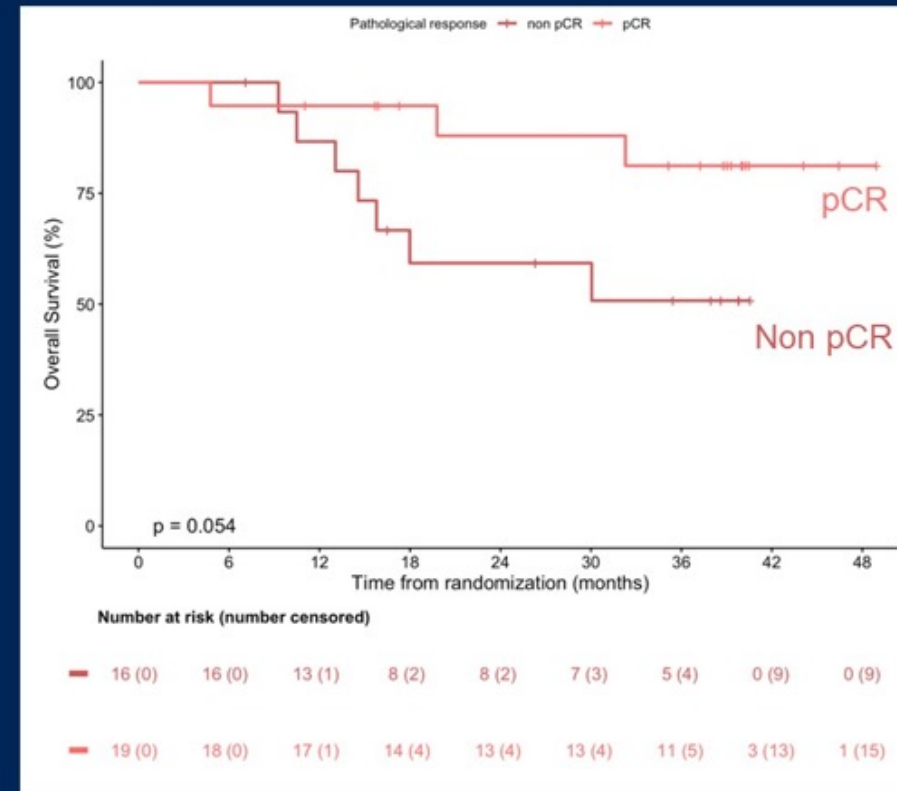
# AURA: Phase II Neoadjuvant Avelumab + Chemo

Overall survival in the cisplatin-eligible cohort according to pCR

ddMVAC-A arm



GC-A arm



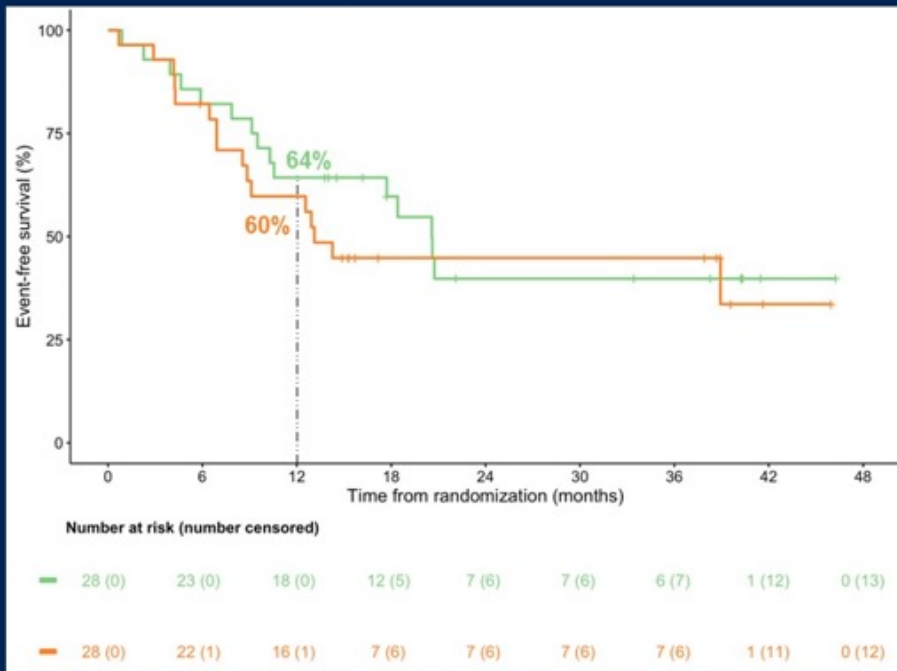
Achieving a pCR is associated with longer overall survival

# AURA: Phase II Neoadjuvant Avelumab + Chemo

## Survival in the cisplatin-ineligible cohort

9

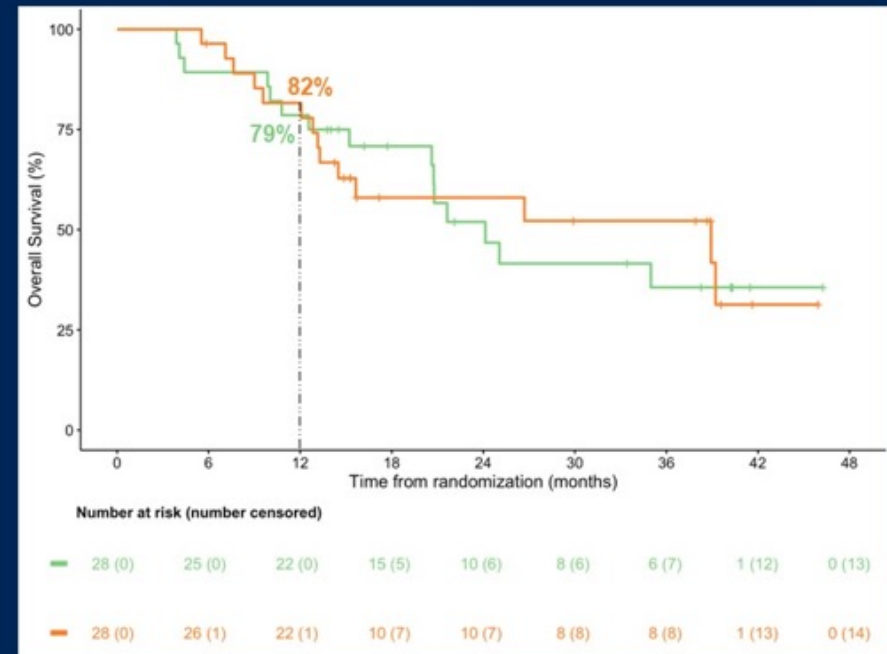
### Event-free survival



12-month EFS

64% A  
60% PG-A

### Overall survival



12-month OS

79% A  
82% PG-A

# Metastatic Prostate Cancer



# CYCLONE 2: Abiraterone +/- Abemaciclib in mCRPC

## Key Eligibility Criteria

### mCRPC

- Metastatic disease on bone/CT/MRI scan
- Radiographic and/or PSA progression during continuous ADT/post orchiectomy

### Visceral metastases were allowed

- Including liver metastases

### ECOG PS 0-1

- Symptomatic patients are eligible
- Adequate organ function

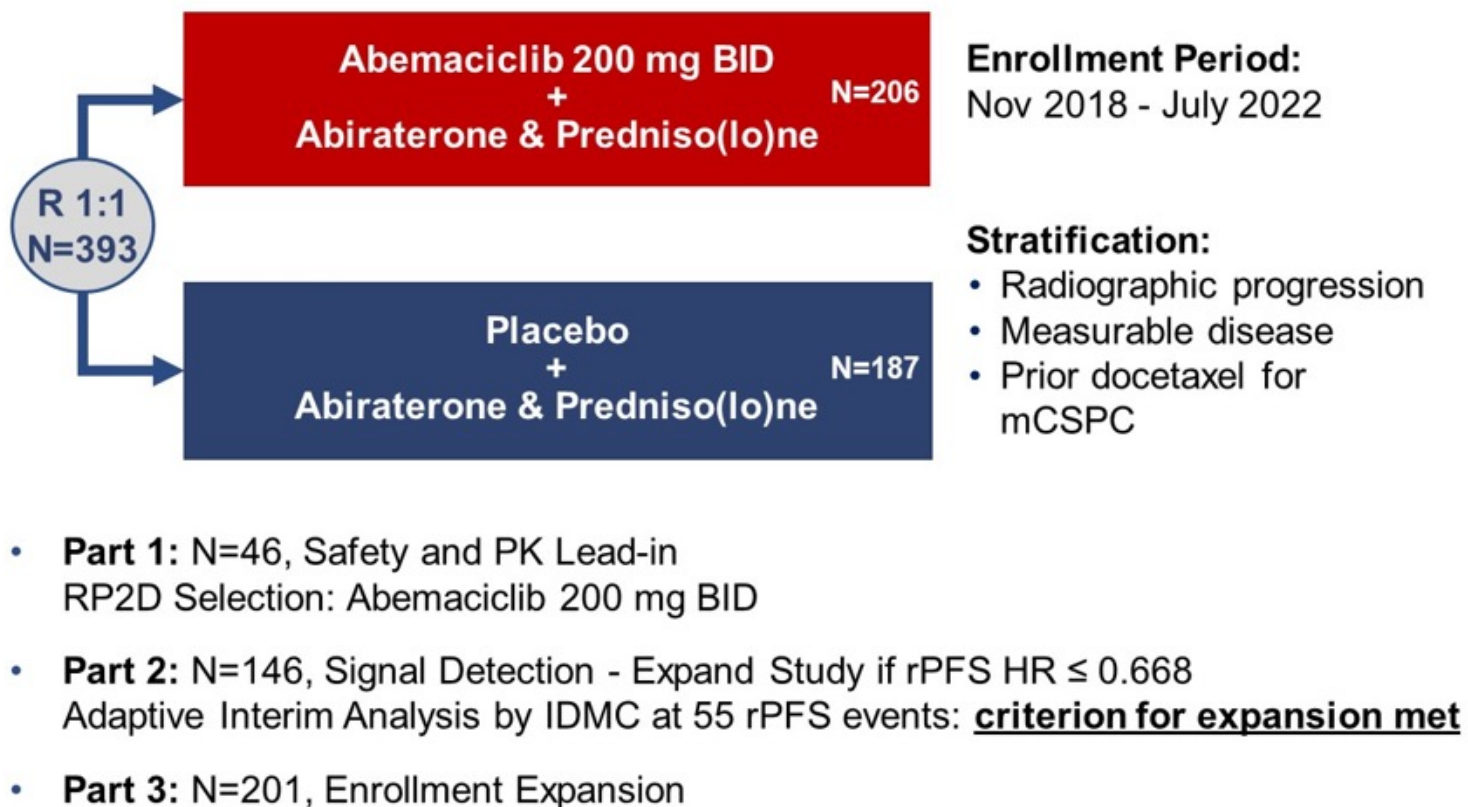
### On-study requirement

- Continuous ADT

### Excluded prior therapies

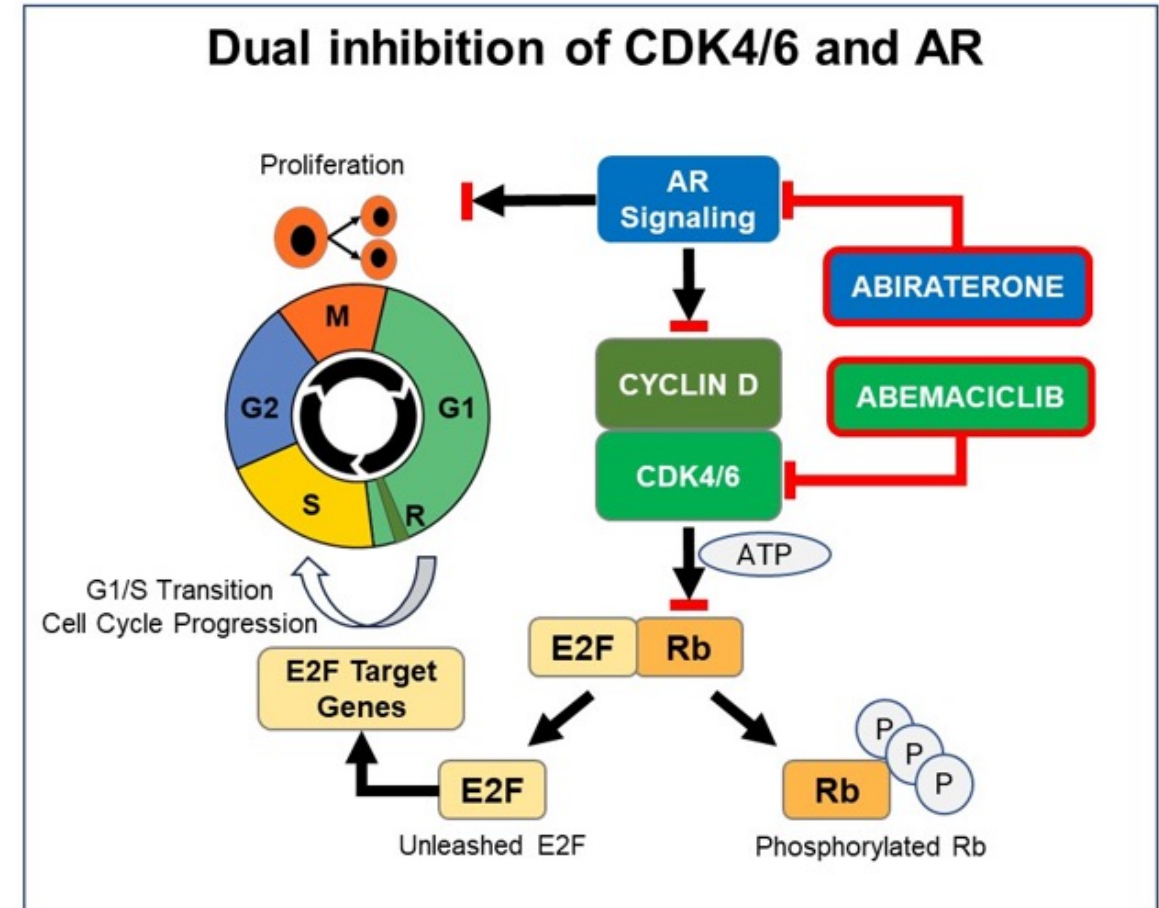
- CDK4/6i
- ARPI
- Chemotherapy for mCRPC (prior docetaxel for mCSPC is permitted)

## Phase 2/3 Seamless Study Design



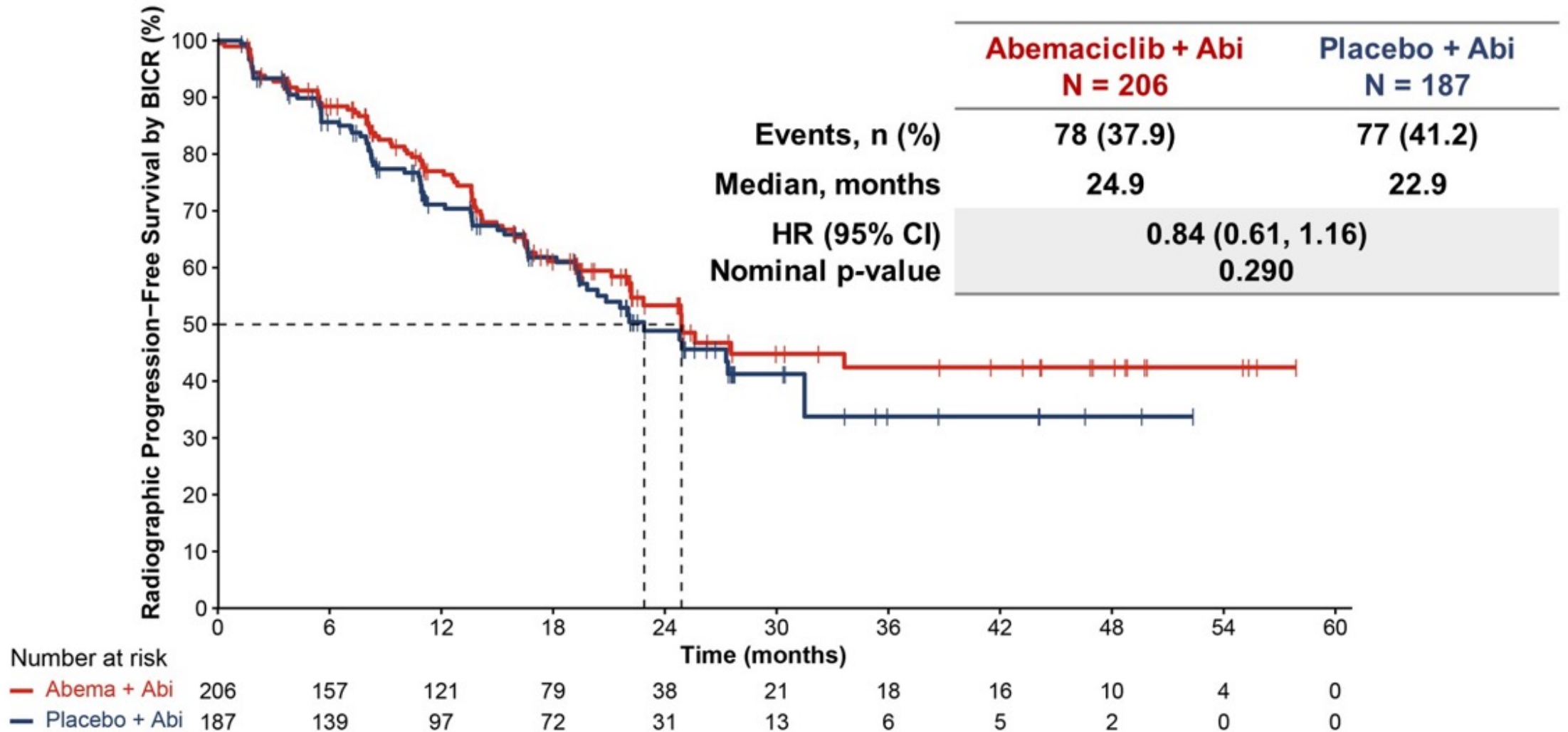
# CYCLONE 2: Abiraterone +/- Abemaciclib in mCRPC

- Abemaciclib is an oral, continuously dosed, cyclin-dependent kinase 4/6 (CDK4/6) inhibitor indicated for the treatment of metastatic and high-risk early-stage HR+, HER2- breast cancer<sup>1</sup>
- AR signaling activates CDK4/6 to sustain proliferation of prostate cancer cells<sup>2</sup> and upregulation of cyclin D1 is a potential mechanism of resistance to AR signaling therapy<sup>3</sup>
- Abemaciclib induces cell cycle arrest and tumor growth inhibition in prostate cancer models<sup>4</sup> and showed signals of clinical activity in heavily pretreated patients with mCRPC (CYCLONE 1)<sup>5</sup>
- The addition of CDK4/6 blockade with abemaciclib may maximize the depth and duration of efficacy of AR pathway inhibition in the treatment of mCRPC

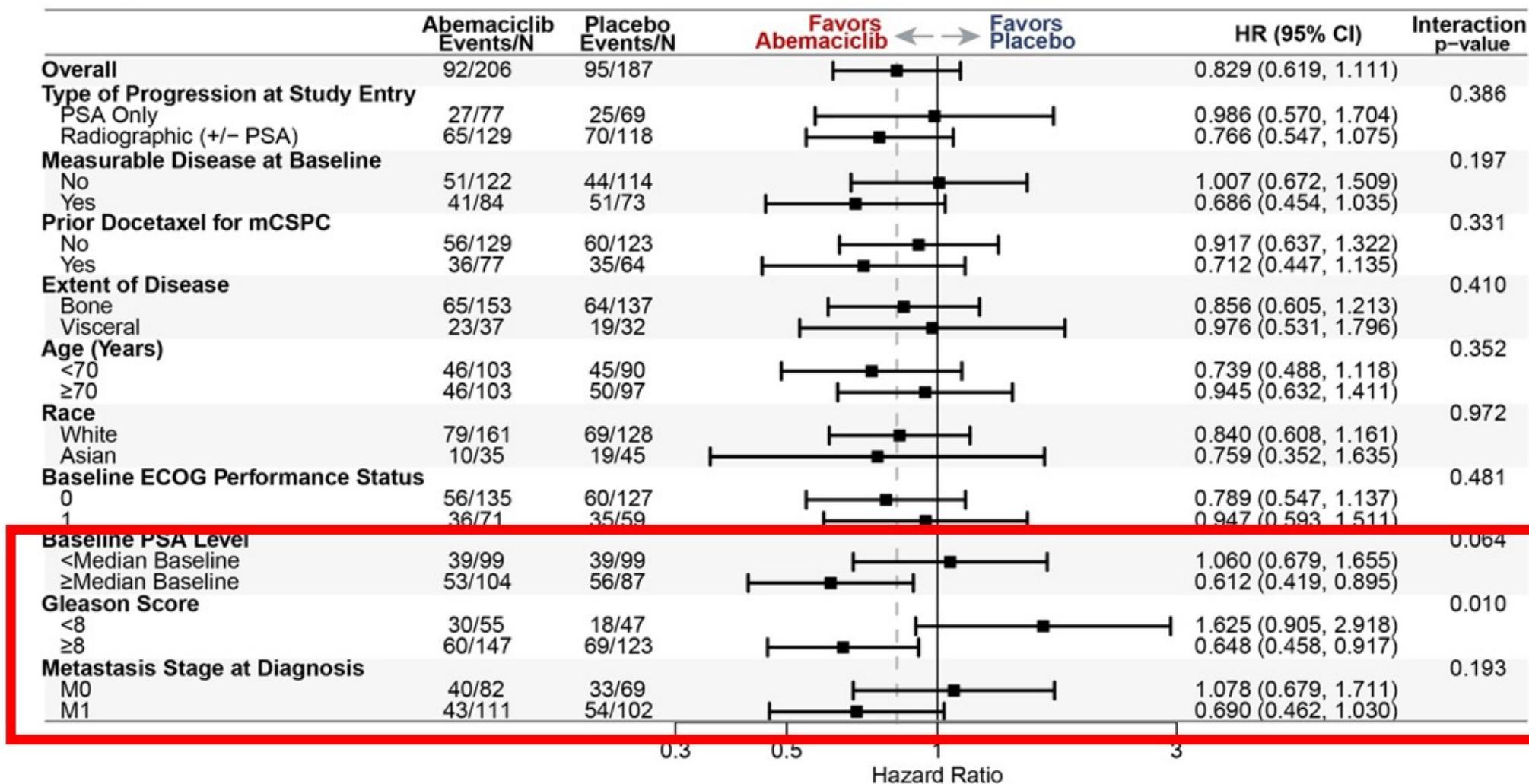


1. Abemaciclib [package insert]. Indianapolis, IN; Eli Lilly and Company; 2021; 2. Xu Y, et al. Can Res. 2006;66(15):7783-92; 3. Pal SK, et al. Cancer. 2018;124(6):1216-1224; 4. Torres-Guzmán, et al. Cancer Res. 2020;80(16):4850; 5. Agarwal N. et al. Clin Cancer Res. 2024

# CYCLONE 2: Radiographic PFS by Central Review

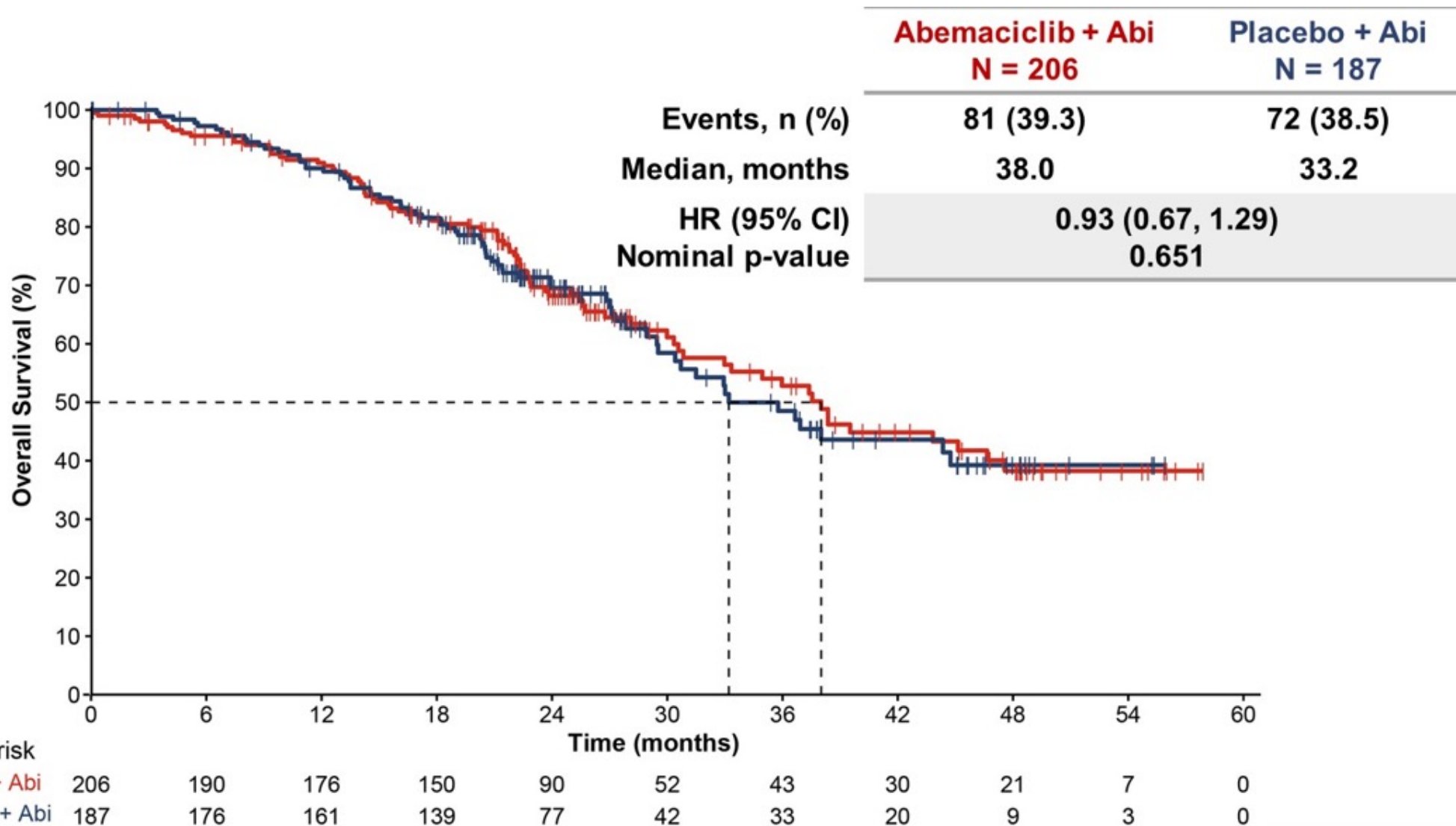


# CYCLONE 2: Radiographic PFS

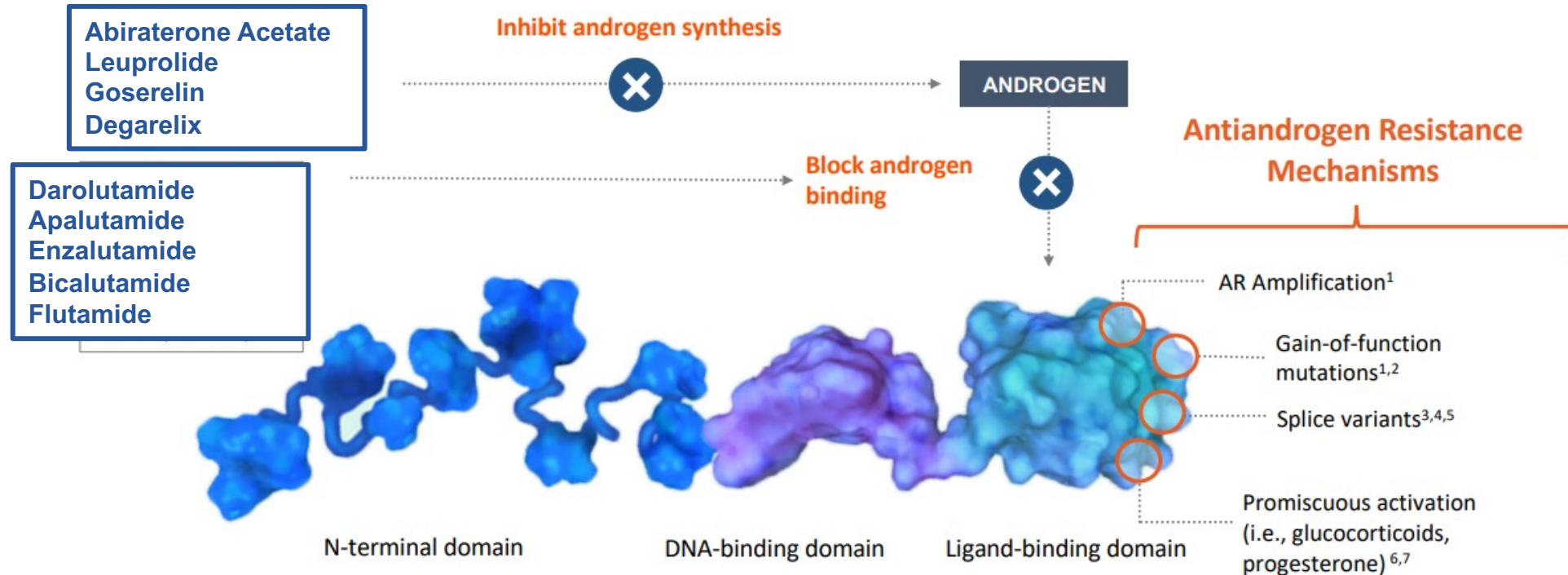


Trends for numerically greater treatment effect in poor prognosis subgroups

# CYCLONE 2: Overall Survival

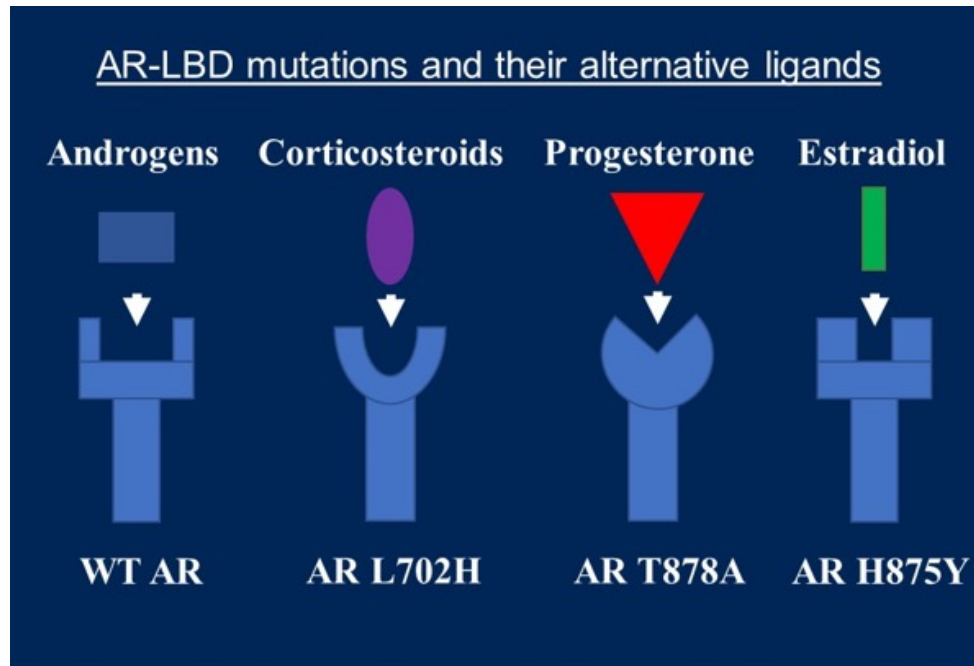


# Current Novel Antiandrogen Therapies Only Target the Androgen Receptor Ligand Binding Domain

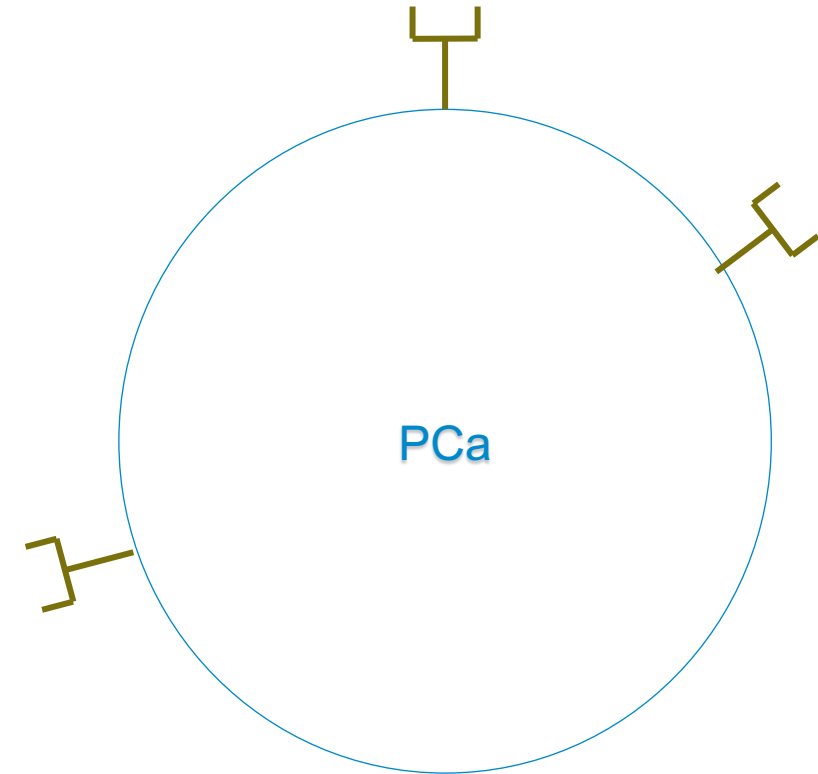


- All current antiandrogens function through the ligand-binding domain of the androgen receptor
- Known antiandrogen resistance mechanisms develop at the ligand binding domain

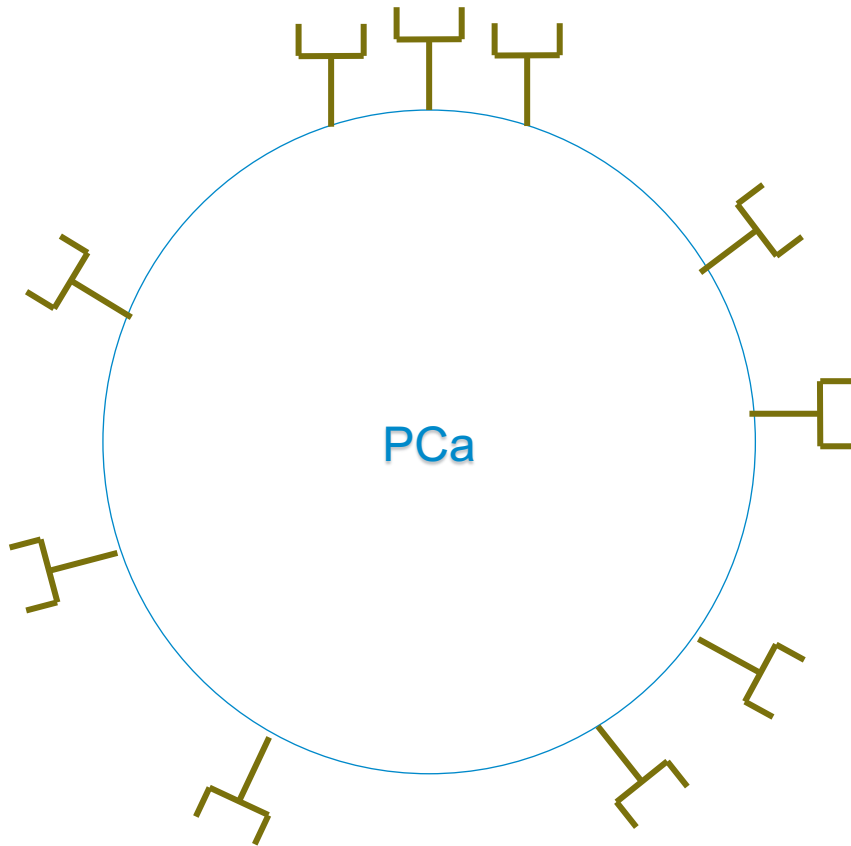
# Further Hormone Manipulation in Prostate Cancer



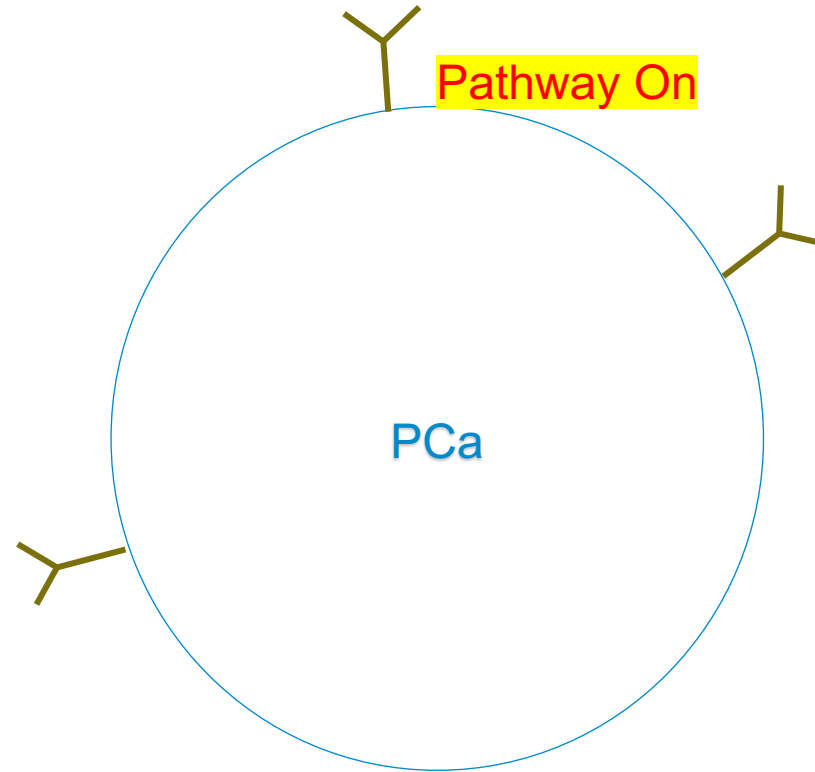
Fizzazi, et al. GU ASCO 2022



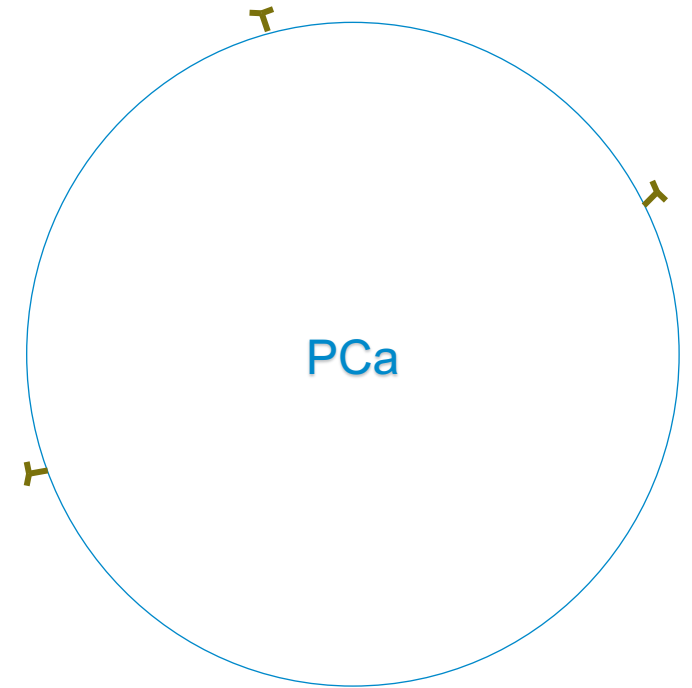
# Further Hormone Manipulation in Prostate Cancer



**AR Amplifications**



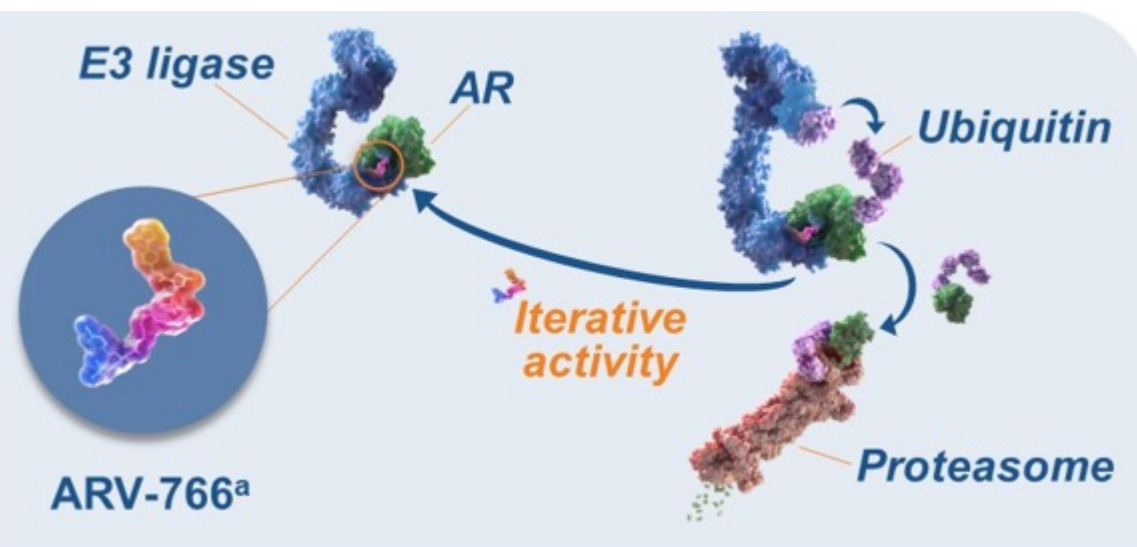
**AR LBD Mutations**



**AR Truncations/Splice**



# ARV-766: Androgen Receptor Degradator



- ~20% of men with mCRPC will develop AR LBD mutations (amino acids 671-920)
  - L702H, H875Y, T878A are most common (poor prognosis)

## Phase 1 dose escalation (part A)

### Key eligibility criteria

- Progressive mCRPC
- Ongoing ADT
- $\geq 2$  prior systemic therapies (including  $\geq 1$  ARPI)

### Treatment

- Ascending doses of ARV-766 (20–500 mg orally QD)

### Primary objective

- Safety and tolerability of ARV-766 to select RP2Ds

## Phase 2 cohort expansion (part B)

### Key eligibility criteria

- Progressive mCRPC
- Ongoing ADT
- 1–3 prior ARPIs
- $\leq 2$  prior chemotherapy regimens

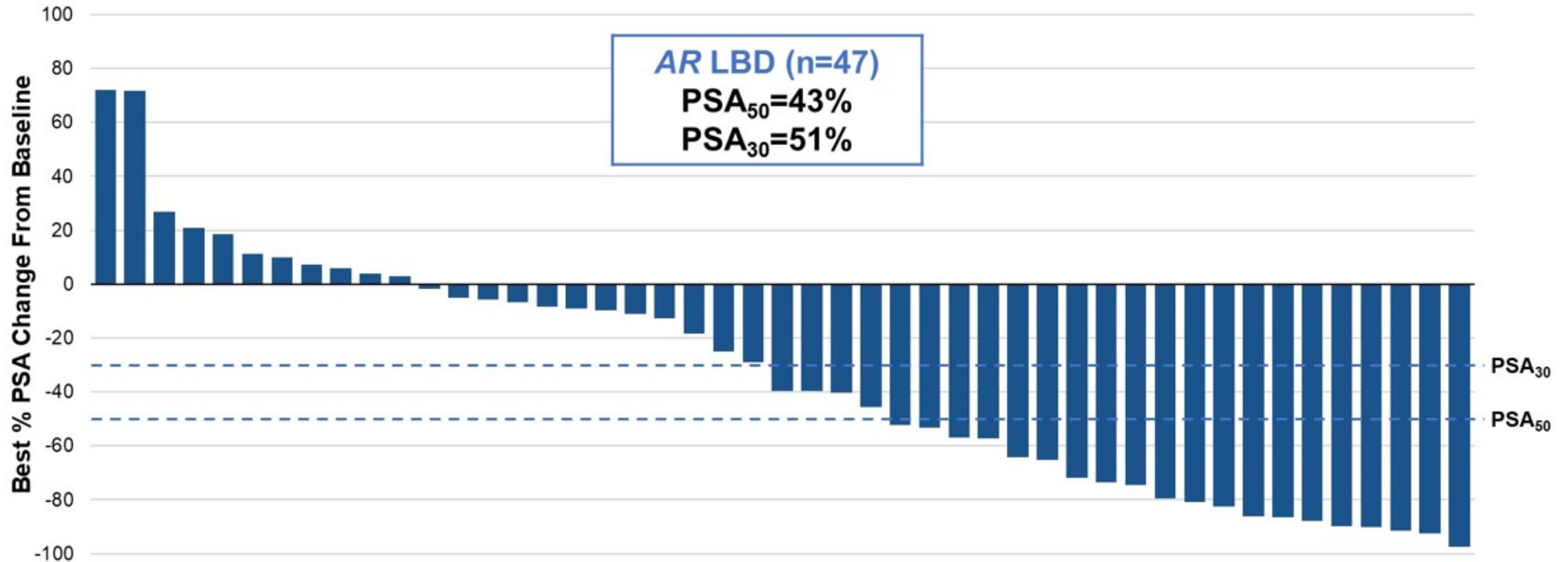
### Treatment

- ARV-766 100 mg or 300 mg orally QD (1:1 randomization)

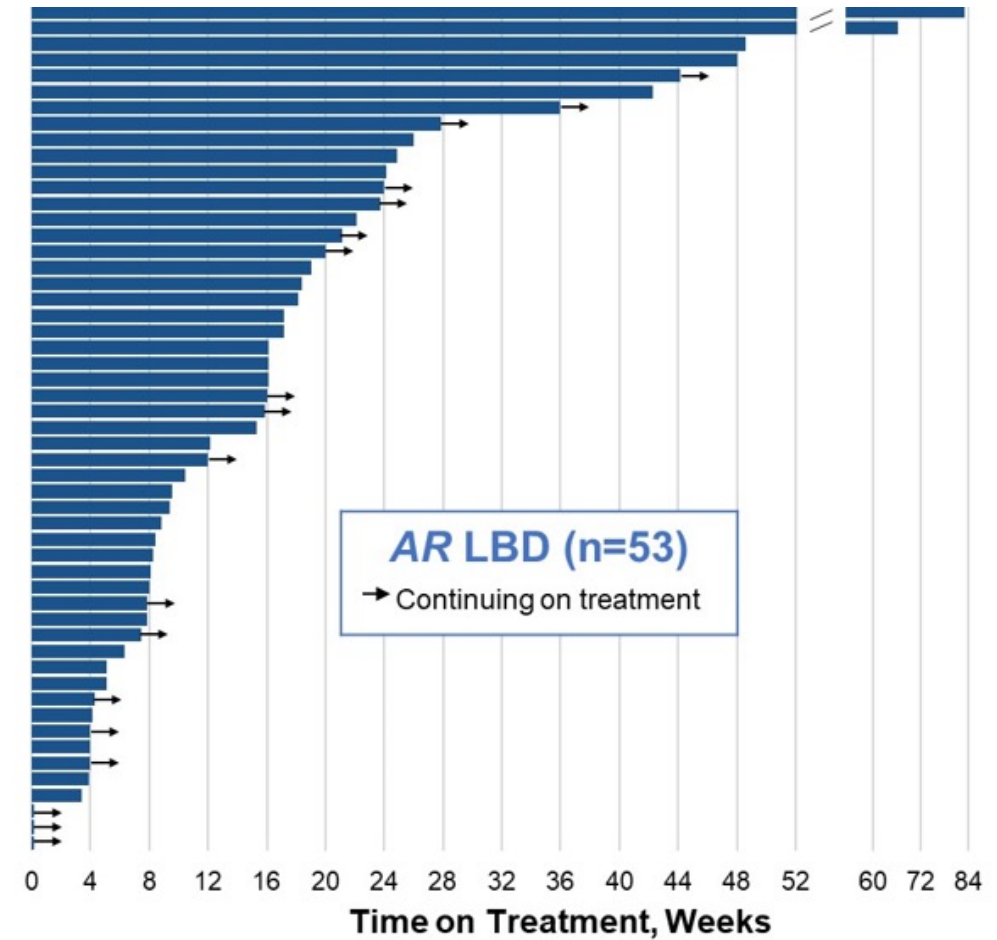
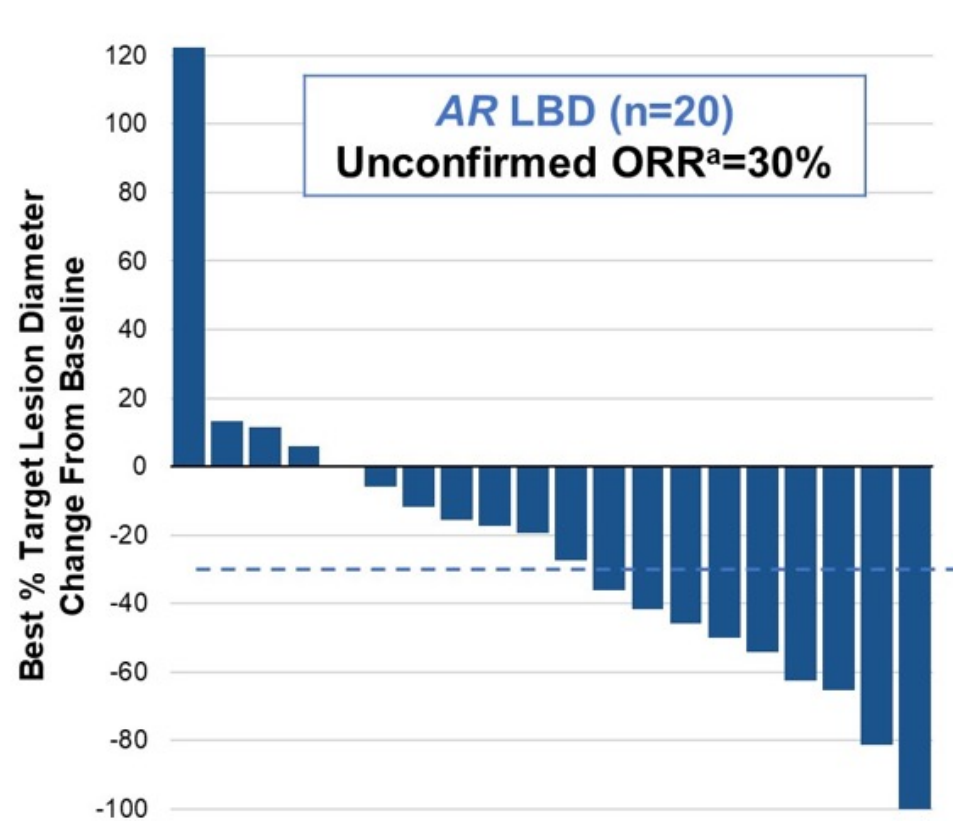
### Primary objective

- Evaluate the antitumor activity of ARV-766

# ARV-766: Best PSA Declines in Patients with AR LBD Mutations



# ARV-766: Tumor Response and Treatment Duration (LBD mut)



<sup>a</sup>Per PCWG3/RECIST; includes patients with measurable disease at baseline and  $\geq 1$  on-treatment scan.

AR=androgen receptor; LBD=ligand-binding domain; ORR=objective response rate; PCWG3=Prostate Cancer Working Group 3; RECIST=Response Evaluation Criteria in Solid Tumors.

# Thank you!

[ben.garmezy@scri.com](mailto:ben.garmezy@scri.com)