Kidney and Bladder Cancer: Targeted, Immuno & Other Strategies

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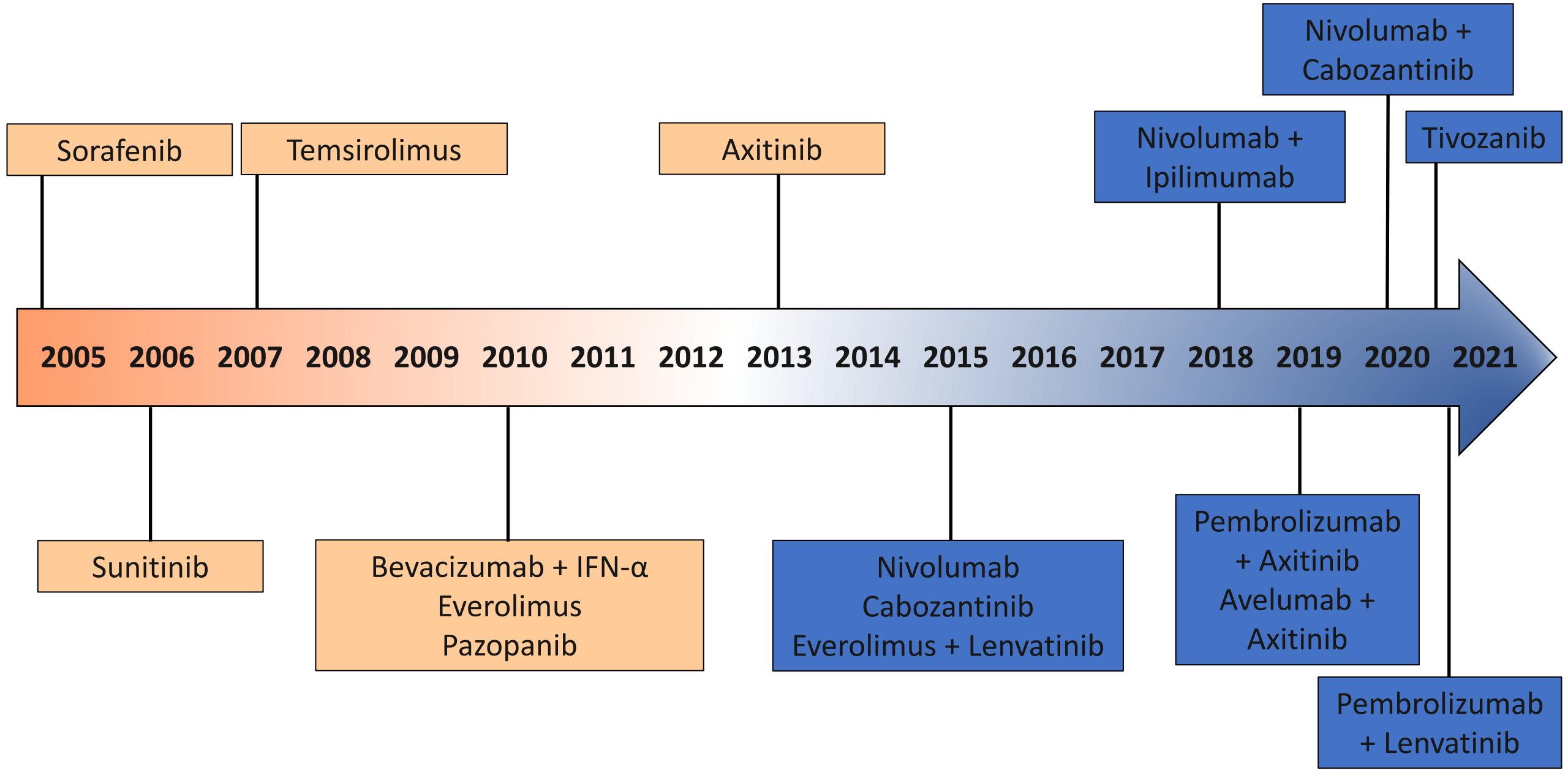
Outline

- Renal Cell Carcinoma
- Urothelial Carcinoma

Treatment Landscape of Metastatic RCC

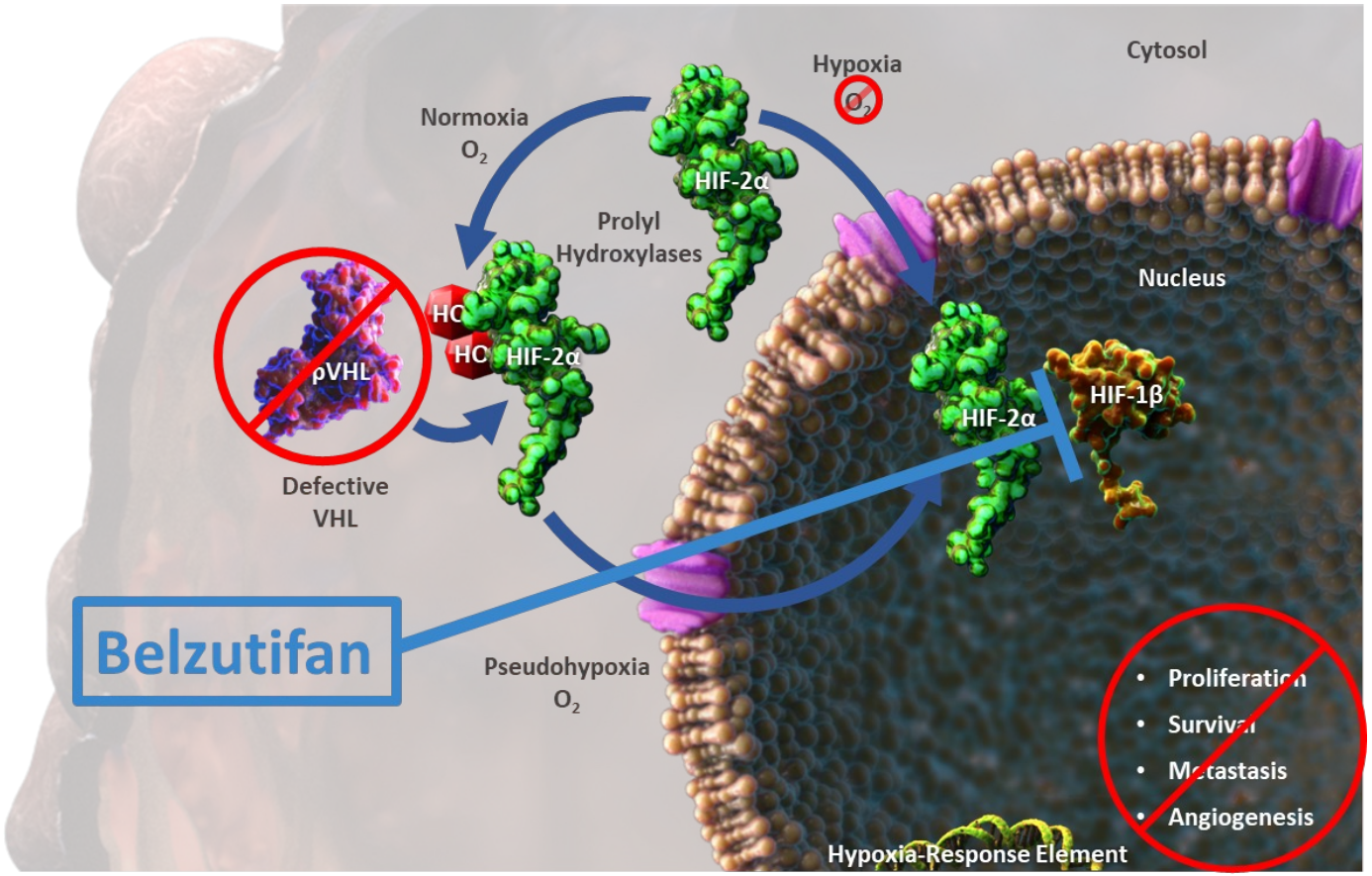


Refractory Setting

HIF-2α Inhibition in Renal Cell Carcinoma

- The HIF pathway is central to the pathophysiology of clear cell renal cell carcinoma (ccRCC) and von Hippel-Lindau (VHL) disease

- Belzutifan, a model of bench to bedside development, is a first-in-class oral HIF-2α inhibitor that blocks heterodimerization with HIF-1β and downstream oncogenic pathways[1,2]
  - Approved in the US for certain VHL disease-associated RCC, pNET and CNS-HB
  - Demonstrated clinical activity in pretreated advanced ccRCC[2-5]



CNS-HB, central nervous system hemangioblastoma; pNET, pancreatic neuroendocrine tumor; VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor.

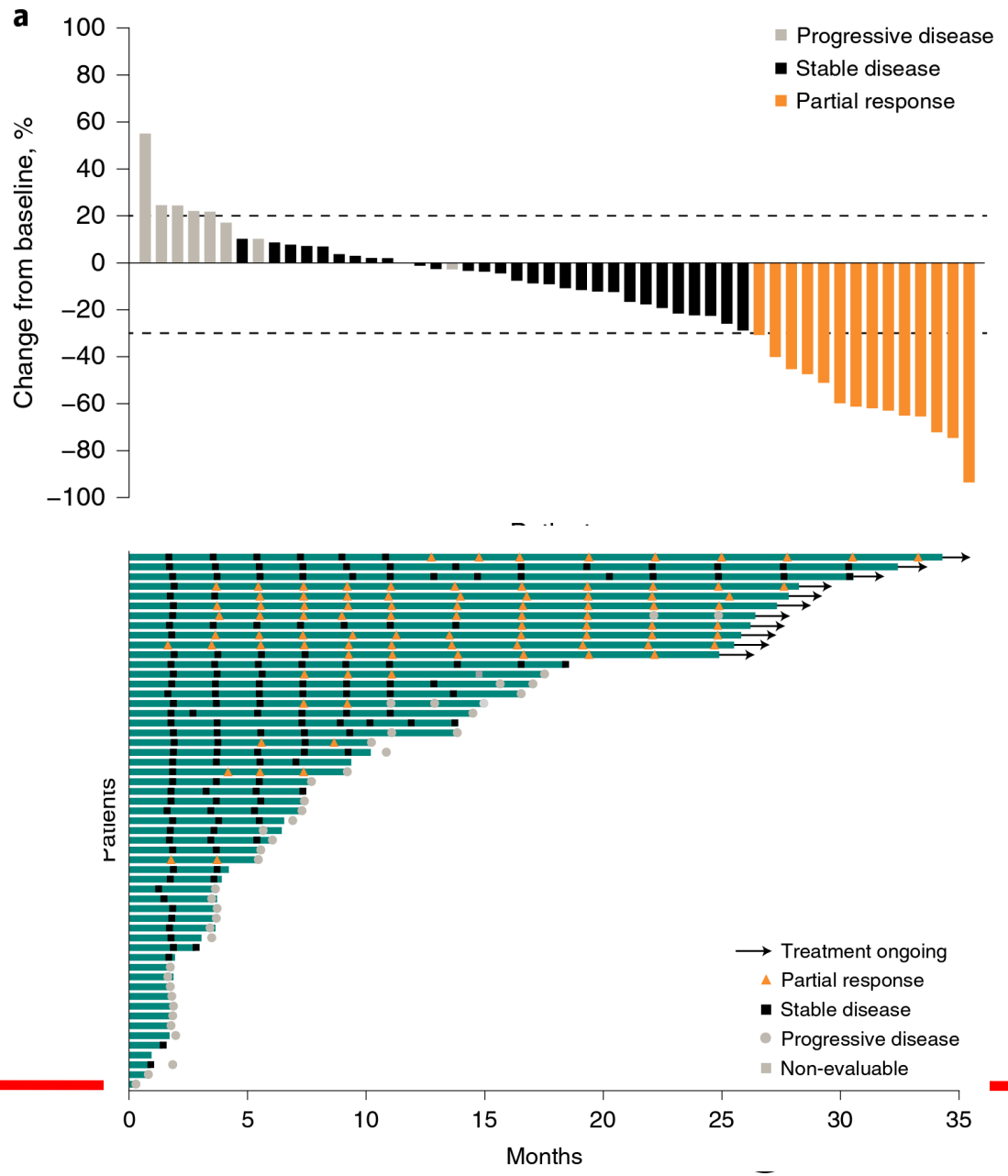
1. Jonasch et al. *New Eng J Med* 2021;385:2036-2046; 2. Choueiri et al. *Nat Med* 2021;27:802-805; 3. Agarwal et al. ESMO 2023; Presentation 1881O; 4. Choueiri et al. *Lancet Oncol* 2023;24:553-562; 5. Choueiri et al. ESMO 2023; Presentation LBA87.

Albiges et al, ESMO 2023

Belzutifan in Refractory RCC (Choueiri T et al, Nature 2021)

Study Population
Advanced RCC
≥1 prior line of therapy (median, 3)
Any risk group (intermediate, 73%)

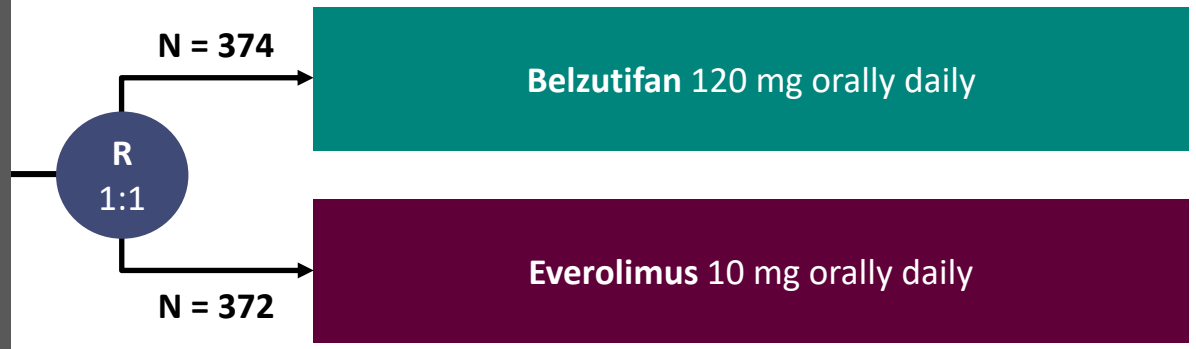
	Belzutifan (Phase 1/2 Trial)
N	55
Median (range) treatment line	3 (1-9)
Median follow-up	28 months
ORR	25% (14 confirmed PRs)
Disease control rate	80%
Median PFS (overall)	14.5 months
Median DOR	NR
Most common AEs	Anemia (76%) and fatigue (71%)
Most common grade 3 AEs	Anemia (27%) and hypoxia (16%)



LITESPARK-005 Study (NCT04195750)

Key Eligibility Criteria

- Unresectable, locally advanced or metastatic clear cell RCC
- Disease progression after 1-3 prior systemic regimens, including ≥1 anti–PD-(L)1 mAb and ≥1 VEGFR-TKI
- Karnofsky Performance Status score ≥70%



Stratification Factors

- IMDC prognostic score[a]: 0 vs 1-2 vs 3-6
- Prior VEGF/VEGFR-targeted therapies: 1 vs 2-3

Dual Primary Endpoints:

- PFS per RECIST 1.1 by BICR
- OS

Key Secondary Endpoint:

- ORR per RECIST 1.1 by BICR

Other Secondary Endpoints Include:

- DOR per RECIST 1.1 by BICR
- Safety
- Time to deterioration in FKSI-DRS and EORTC QLQ-C30 GHS/QoL

[a] Based on the number of present risk factors according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC).
BICR, blinded independent central review; DOR, duration of response; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index – Disease-Related Symptoms; GHS, global health status; mAb, monoclonal antibody; QoL, quality of life.

Albiges et al, ESMO 2023

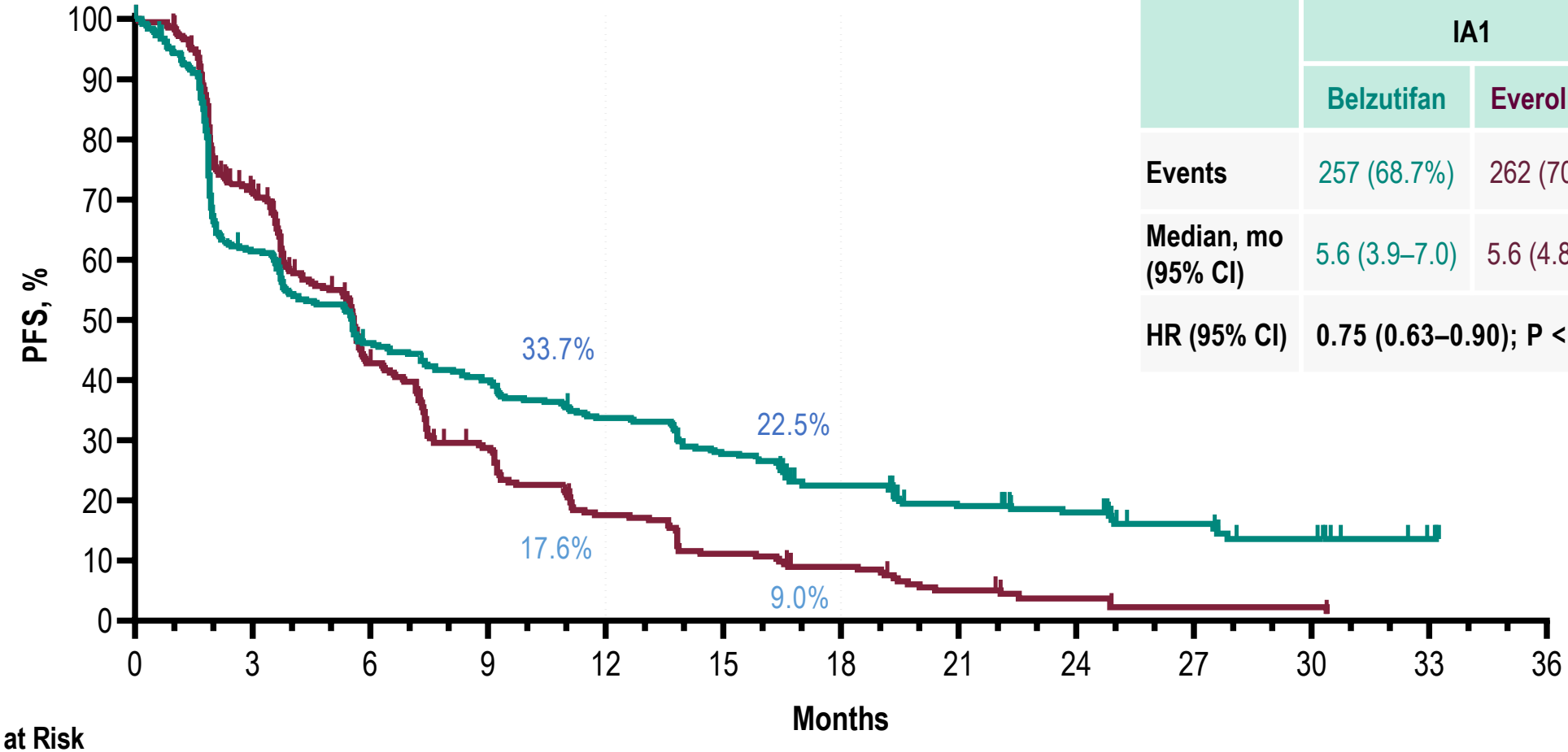
Baseline Characteristics

	Belzutifan (N = 374)	Everolimus (N = 372)
Age, median (range), yrs	62 (22–90)	63 (33–87)
Male	79.4%	76.3%
KPS score[a]		
90/100	63.6%	64.5%
70/80	36.1%	35.2%
IMDC risk categories		
Favorable	21.1%	22.3%
Intermediate	66.6%	65.6%
Poor	12.3%	12.1%
Sarcomatoid features		
Yes	11.2%	8.3%
No/Unknown/Missing	88.8%	91.7%
Prior nephrectomy	69.8%	69.6%
# Prior VEGF/VEGFR-TKIs		
1	50.0%	51.1%
2-3	50.0%	48.9%
# Prior lines of therapy[b]		
1	12.3%	14.0%
2	42.0%	44.6%
3	45.2%	40.3%

[a] 0.3% pts in each arm had a missing KPS score. [b] 0.5% of pts in the belzutifan arm and 1.1% in the everolimus arm had 4 prior lines of therapy (protocol violation). Data cutoff date for IA2: June 13, 2023.

Primary Endpoint: PFS per RECIST 1.1 by BICR

Kaplan-Meier Estimate of PFS at IA2



	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	257 (68.7%)	262 (70.4%)	289 (77.3%)	276 (74.2%)
Median, mo (95% CI)	5.6 (3.9–7.0)	5.6 (4.8–5.8)	5.6 (3.8–6.5)	5.6 (4.8–5.8)
HR (95% CI)	0.75 (0.63–0.90); P <.001*		0.74 (0.63–0.88)	

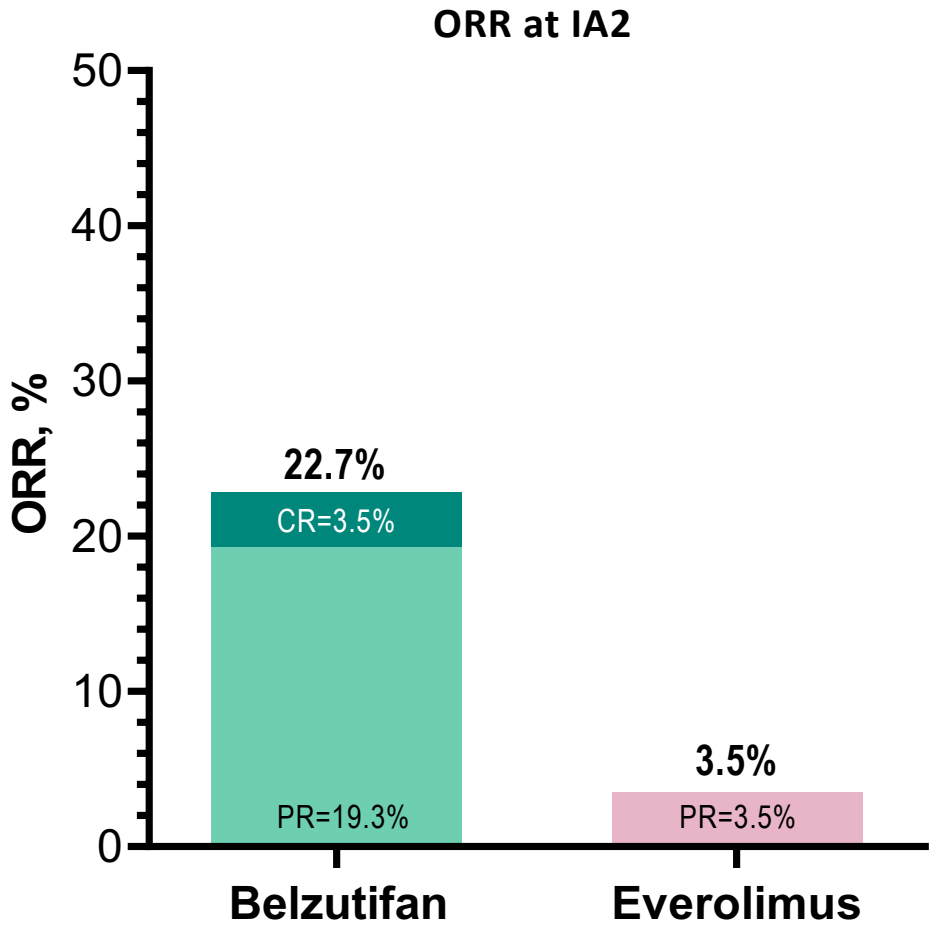
No. at Risk

Belzutifan	374	218	156	135	113	93	66	45	35	21	14	4	0
Everolimus	372	226	113	70	41	26	19	10	5	2	2	0	0

Albiges et al, ESMO 2023

Key Secondary Endpoint: ORR by BICR per RECIST 1.1

	Belzutifan (N = 374)	Everolimus (N = 372)
	IA1	
ORR, % (95% CI)	**21.9% (17.8–26.5)**	**3.5% (1.9–5.9)**
Estimated difference in % (95% CI)	**18.4 (14.0–23.2); P <.00001***	
CR	2.7%	0
PR	19.3%	3.5%
SD	39.3%	65.9%
PD	33.7%	21.5%
Non-evaluable[a]	1.3%	2.2%
No assessment[b]	3.7%	7.0%
	IA2	
ORR, % (95% CI)	**22.7% (18.6–27.3)**	**3.5% (1.9–5.9)**
Estimated difference in % (95% CI)	**19.2 (14.8–24.0)**	



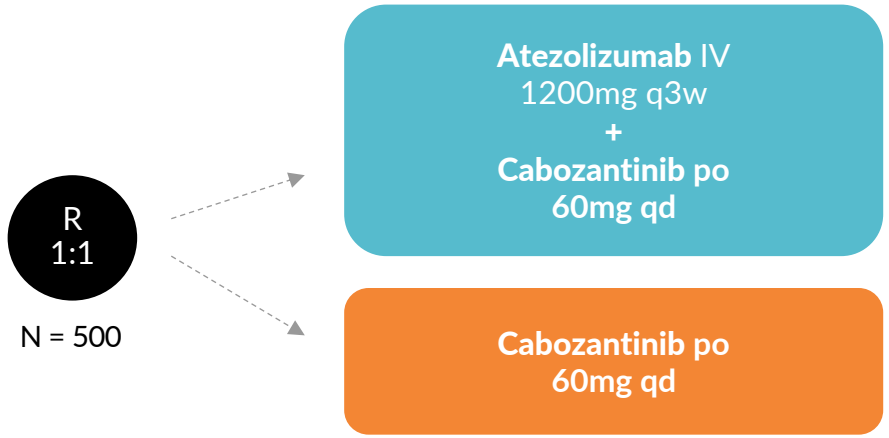
Albiges et al, ESMO 2023

[a] Insufficient data for response assessment per RECIST 1.1. [b] No post-baseline assessment available.
* denotes statistical significance. CR, complete response; PR, partial response. Data cutoff date for IA1: November 1, 2022. Data cutoff date for IA2: June 13, 2023.

Salvage PD-L1 Inhibitor is not superior to TKI alone

CONTACT-03

- Histologically confirmed advanced, metastatic ccRCC or nccRCC
- Radiographic progression during or following ICI treatment



No crossover allowed

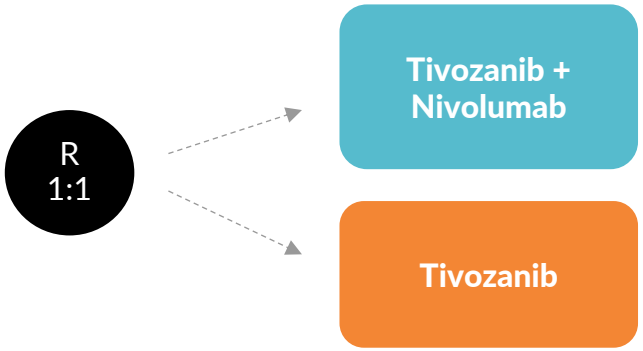
Negative Trial

Treatment until progression

- Primary endpoint: PFS, OS
- Secondary endpoint: PFS, ORR, DoR, Safety and Tolerability

TINIVO-2

- Histologically/cytologically confirmed recurrent/ metastatic RCC
- ECOG PS 0 or 1
- Progressed following immediate prior immunotherapy treatment in first or second line
- Stratified by IMDC and prior TKI



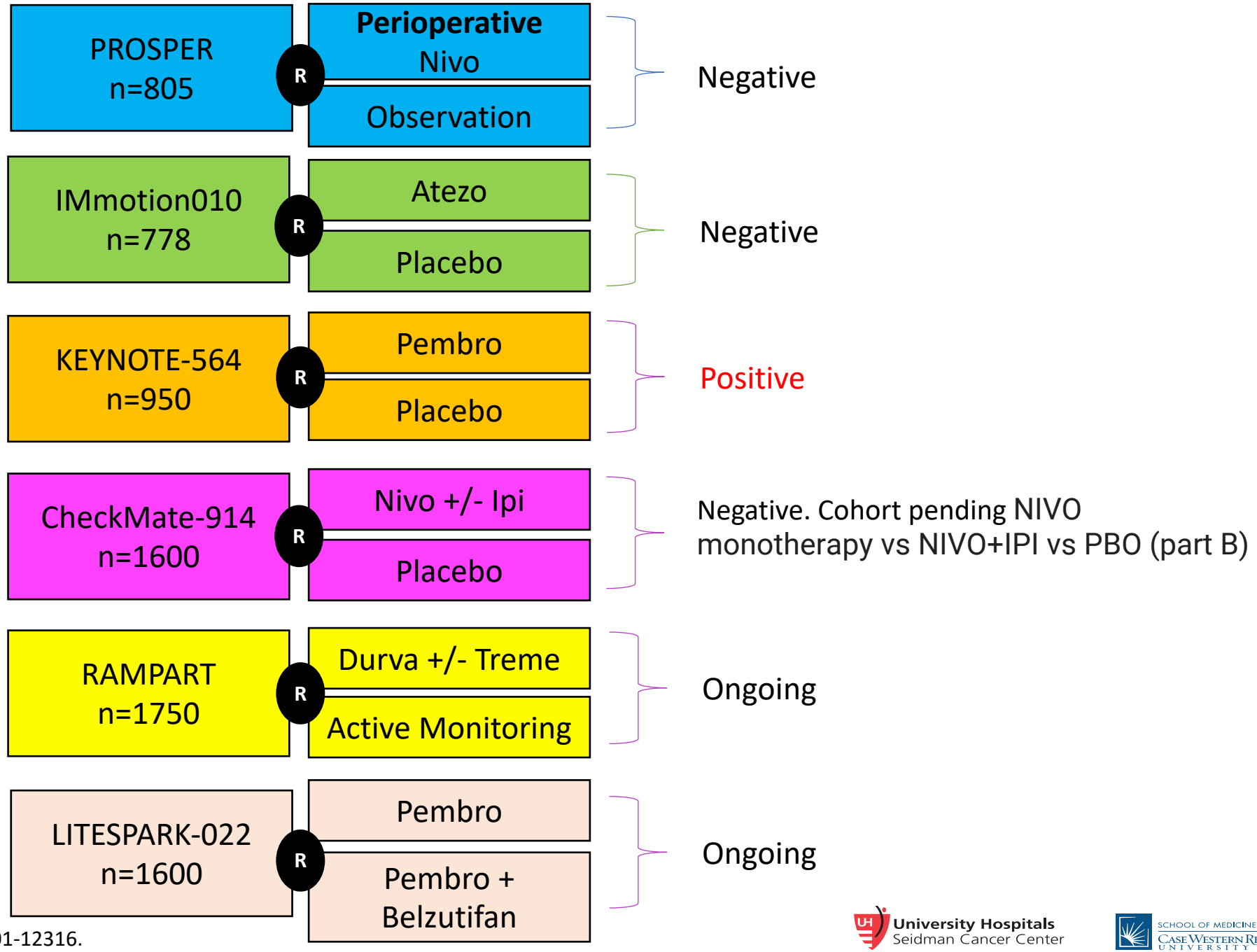
Completed enrollment
Spring 2023

Treatment until progression

- Primary endpoint: PFS
- Secondary endpoint: OS, ORR, DoR, Safety and Tolerability

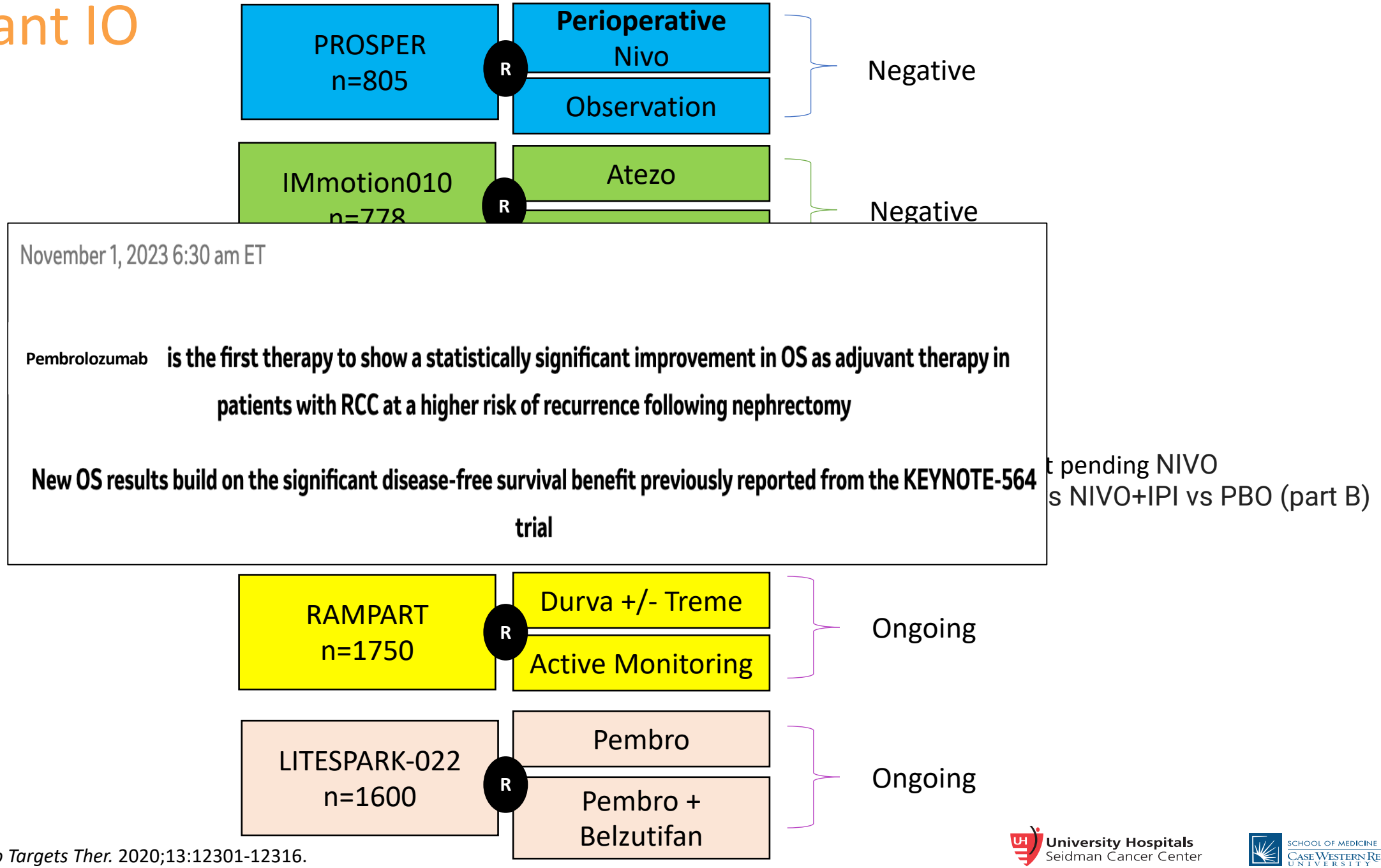
Adjuvant

Adjuvant IO Trials



Tacconi EMC, et al. *Onco Targets Ther.* 2020;13:12301-12316.

Adjuvant IO Trials



Tacconi EMC, et al. *Onco Targets Ther.* 2020;13:12301-12316.

Urothelial Carcinoma

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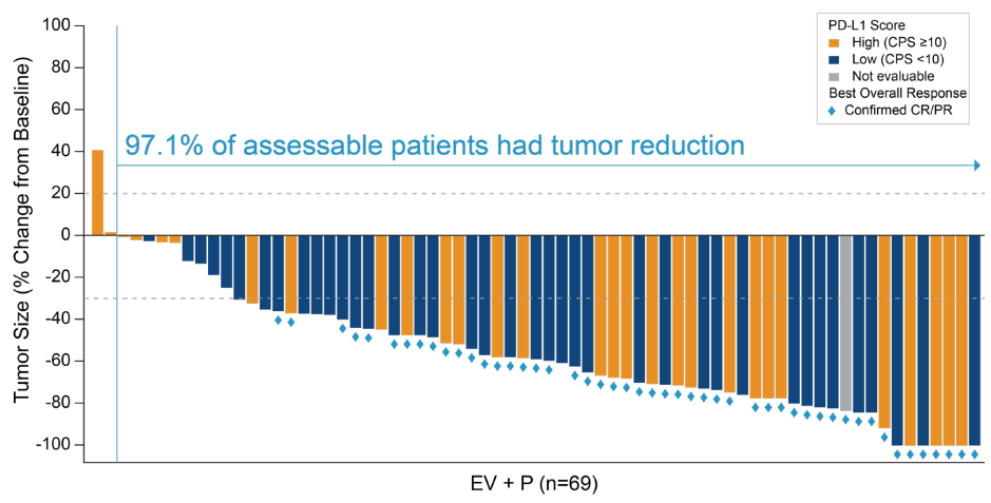
EV-103 Cohort K: Efficacy

	EV + Pembro[1] N=76	EV Mono[1] N=73
Confirmed ORR (95% CI)	49 (**64.5%**) (52.7-75.1)	33 (45.2%) (33.5-57.3)
Best overall response		
CR	8 (10.5%)	4 (5.5%)
PR	41 (53.9%)	29 (39.7%)
SD	17 (22.4%)	25 (34.2%)
PD	6 (7.9%)	7 (9.6%)
NE	3 (3.9%)	5 (6.8%)
No assessment	1 (1.3%)	3 (4.1%)
Median time to objective response, mo (range)	2.07 (1.1-6.6)	2.07 (1.9-15.4)
Median number of treatment cycles (range)	12.0 (1-34)	8.0 (1-33)

- EV + Pembro arm: 7/13 (53.8%) confirmed ORR observed in patients with liver metastases[1]

No formal statistical comparisons were conducted between the two treatment arms

EV + Pembro: Maximum Percent Reduction From Baseline of Target Lesion by BICR[2]



	EV + Pembro[1] N=76	EV Mono[1] N=73
mDOR, mo (95% CI)	**NR** (10.25-NR)	13.2 (6.14-NR)
mPFS, mo (95% CI)	**NR** (8.31-NR)	8.2 (6.05-15.28)
mOS, mo (95% CI)	**NR** (21.39-NR)	21.7 (15.47-NR)
Median follow-up, mo	17.6	18.2

1. Friedlander TW, et al. ASCO 2023. Abstract 4568. **2.** Rosenberg JE, et al. ESMO 2022. Abstract LBA73.

EV-302/KEYNOTE-A39 (NCT04223856)

Patient population

- Previously untreated la/mUC
- Eligible for platinum, EV, and P
- PD-(L)1 inhibitor naive
- GFR ≥30 mL/min[a]
- ECOG PS ≤2[b]

N=886

R 1:1

EV + Pembrolizumab
No maximum treatment cycles for EV, maximum 35 cycles for P

Chemotherapy[c]
(Cisplatin or carboplatin + gemcitabine)
Maximum 6 cycles

Treatment until disease progression per BICR, clinical progression, unacceptable toxicity, or completion of maximum cycles

Dual primary endpoints:

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

Select secondary endpoints:

- ORR per RECIST v1.1 by BICR and investigator assessment
- Safety

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

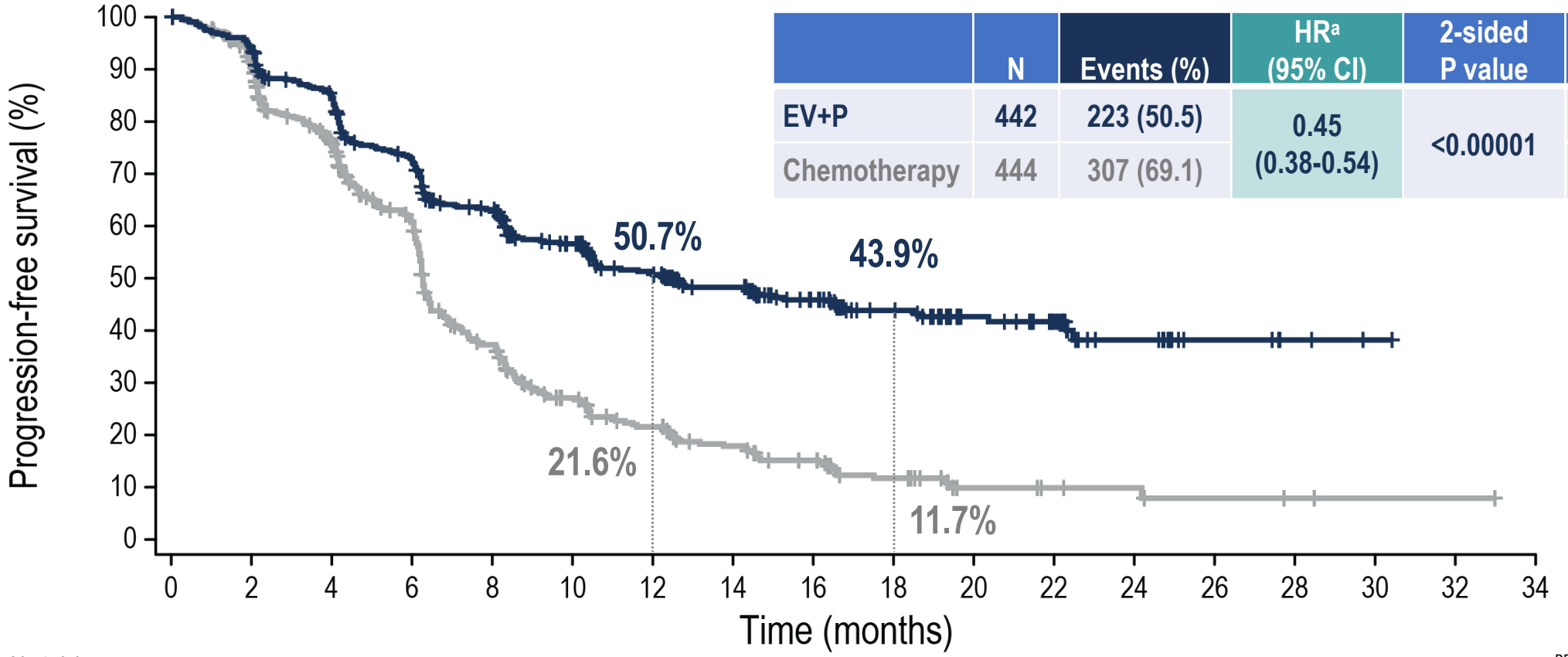
Powles T et al, ESMO 2023

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

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

Powles T et al, ESMO 2023

Data cutoff: 08 Aug 2023

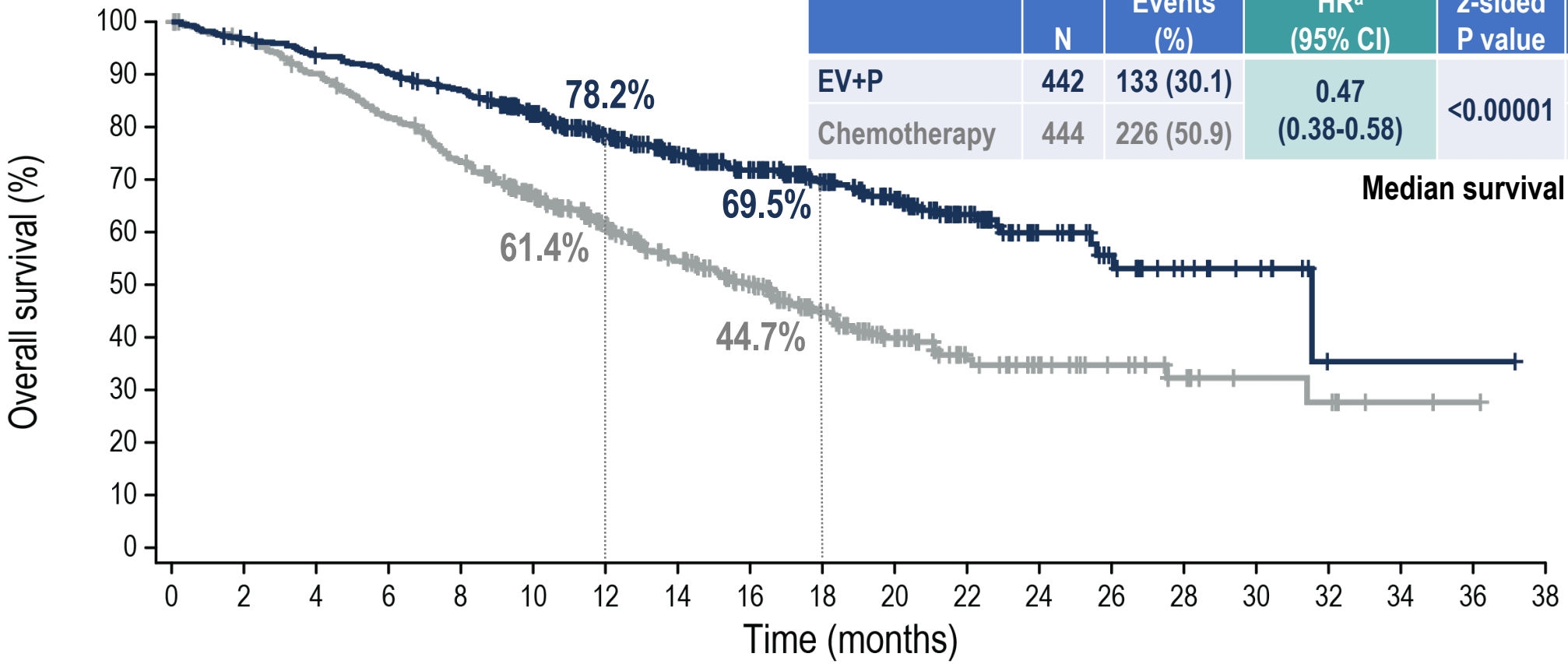
PFS at 12 and 18 months as estimated using Kaplan-Meier method
HR, hazard ratio; mPFS, median progression-free survival
[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm

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

Powles T et al, ESMO 2023

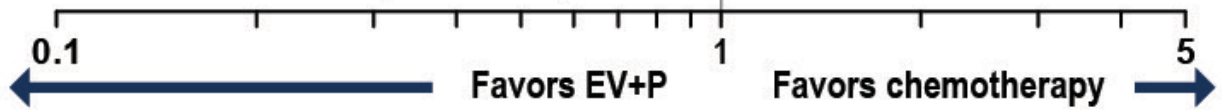
Data cutoff: 08 Aug 2023

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

Subgroup Analysis of OS

OS benefit in select pre-specified subgroups was consistent with results in overall population

Subgroup	Events/N EV+P	Events/N Chemotherapy	Hazard Ratio (95% CI)
Overall	133/442	226/444	0.47 (0.38-0.58)
Age			
<65 years	39/144	58/135	0.46 (0.30-0.71)
≥65 years	94/298	168/309	0.48 (0.38-0.63)
Sex			
Female	32/98	54/108	0.51 (0.32-0.80)
Male	101/344	172/336	0.47 (0.36-0.60)
ECOG PS			
0	44/223	94/215	0.36 (0.25-0.53)
1-2	89/219	131/227	0.54 (0.41-0.72)
Primary disease site of origin			
Upper tract	38/135	45/104	0.53 (0.34-0.83)
Lower tract	94/305	180/339	0.46 (0.36-0.59)
Liver metastases			
Present	43/100	67/99	0.47 (0.32-0.71)
Absent	90/342	159/345	0.47 (0.36-0.61)
PD-L1 expression			
Low (CPS <10)	53/184	99/185	0.44 (0.31-0.61)
High (CPS ≥10)	79/254	125/254	0.49 (0.37-0.66)
Cisplatin eligibility			
Eligible	69/244	106/234	0.53 (0.39-0.72)
Ineligible	64/198	120/210	0.43 (0.31-0.59)

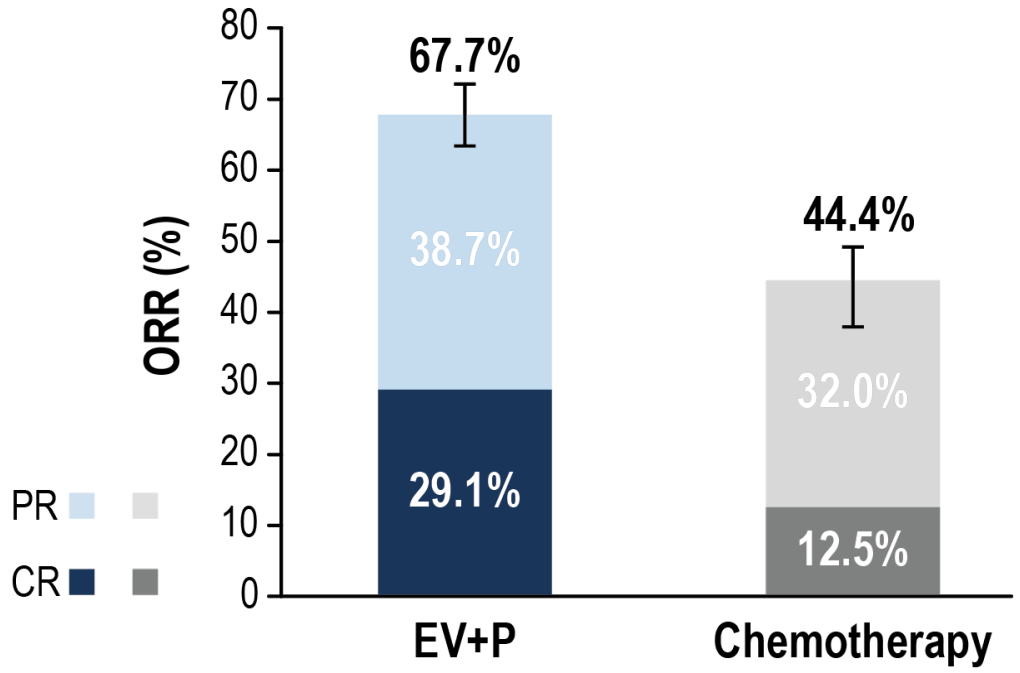


Powles T et al, ESMO 2023

Data cutoff: 08 Aug 2023

Confirmed Overall Response per BICR

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



	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[a], 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[b]	21 (4.8)	36 (8.2)
Median DOR (95% CI)	NR (20.2, NR)	7.0 (6.2, 10.2)

Powles T et al, ESMO 2023

Data cutoff: 08 Aug 2023

CR, complete response; DOR, duration of response; PR, partial response

[a]Best overall response according to RECIST v1.1 per BICR. CR or PR was confirmed with repeat scans ≥28 days after initial response

[b]Patients had either post-baseline assessment and the best overall response was determined to be not evaluable per RECIST v1.1 or no response assessment post-baseline

Summary & Conclusions

- EV-302/KEYNOTE-A39 is the first time that platinum-based chemotherapy has been surpassed in OS in patients with previously untreated la/mUC

- EV+P showed statistically significant and clinically meaningful improvement in efficacy over chemotherapy
  - PFS HR: 0.45; OS HR: 0.47
  - mPFS and mOS were nearly doubled in the EV+P arm compared with chemotherapy
  - Benefit in prespecified subgroups and stratification factors was consistent with the overall population

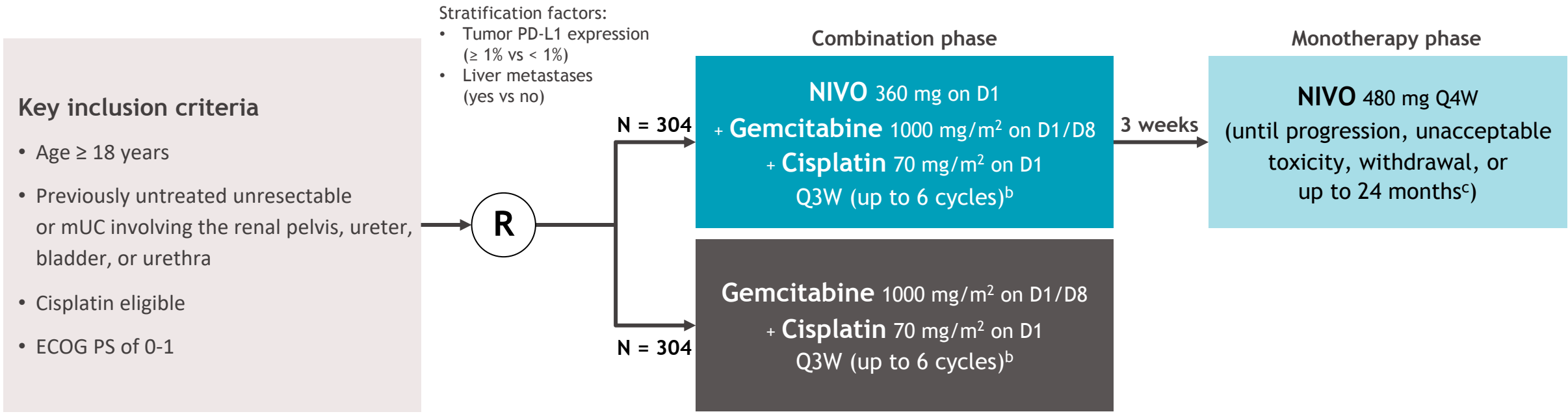
- The safety profile of EV+P was generally manageable, with no new safety signals observed

- These results support EV+P as a potential new standard of care for 1L la/mUC

Powles T et al, ESMO 2023

CheckMate 901 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

[a]Further CheckMate 901 trial design details are available at https://clinicaltrials.gov/ct2/show/NCT03036098. [b]Patients who discontinued cisplatin could be switched to gemcitabine-carboplatin for the remainder of the platinum doublet cycles (up to 6 in total). [c]A maximum of 24 months from first dose of NIVO administered as part of the NIVO + gemcitabine-cisplatin combination. [d]PD-L1 status was defined by the percentage of positive tumor cell membrane staining in a minimum of 100 tumor cells that could be evaluated with the use of the PD-L1 IHC 28-8 pharmDx immunohistochemical assay (Dako, Santa Clara, CA, USA).
BICR, blinded independent central review; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q×W, every × weeks; R, randomization.

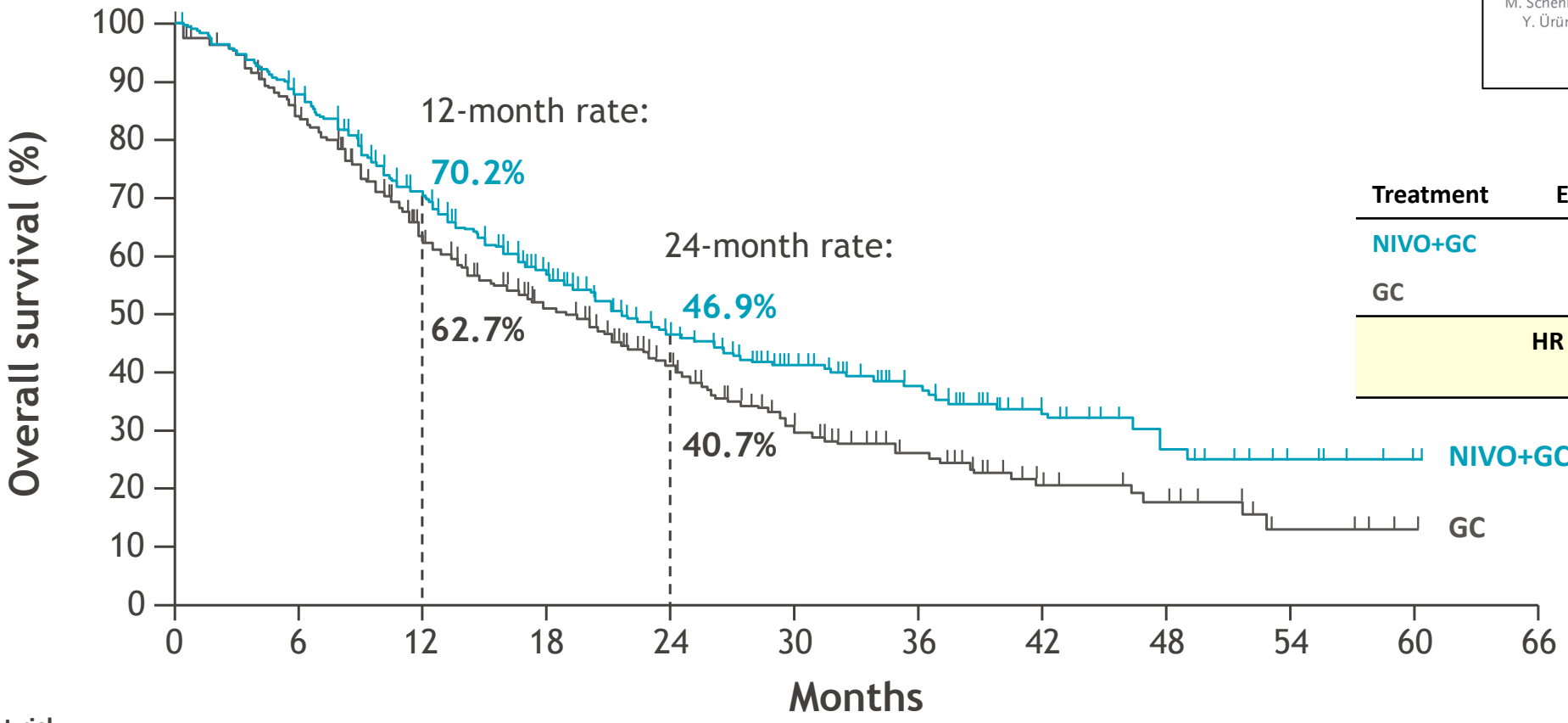
Van Der Heijden T et al, ESMO 2023

OS (primary endpoint)

ORIGINAL ARTICLE

Nivolumab plus Gemcitabine–Cisplatin in Advanced Urothelial Carcinoma

M.S. van der Heijden, G. Sonpavde, T. Powles, A. Necchi, M. Burotto, M. Schenker, J.P. Sade, A. Bamias, P. Beuzeboc, J. Bedke, J. Oldenburg, G. Chatta, Y. Ürün, D. Ye, Z. He, B.P. Valderrama, J.H. Ku, Y. Tomita, J. Filian, L. Wang, D. Purcea, M.Y. Patel, F. Nasroulah, and M.D. Galsky, for the CheckMate 901 Trial Investigators*



Treatment	Events/patients	Median OS (95% CI), months
NIVO+GC	172/304	21.7 (18.6-26.4)
GC	193/304	18.9 (14.7–22.4)
HR (95% CI), 0.78 (0.63–0.96) *P* = 0.0171		

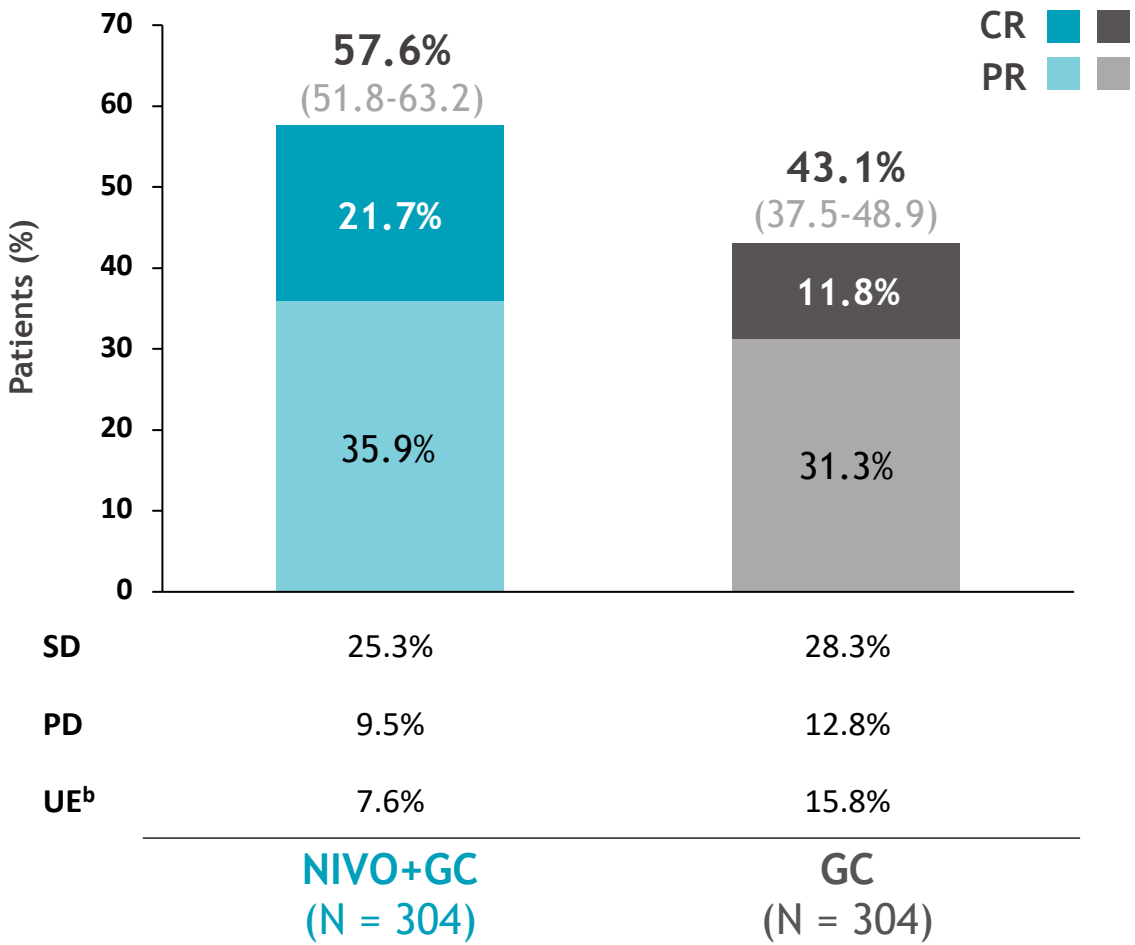
No. at risk												
NIVO+GC	304	264	196	142	97	69	48	25	15	7	2	0
GC	304	242	166	122	82	49	33	17	13	4	1	0

Van Der Heijden T et al, ESMO 2023

Median (range) study follow-up was 33.6 (7.4-62.4) months. OS was estimated in all randomized patients and defined as time from randomization to death from any cause. For patients without documented death, OS was censored on the last date the patient was known to be alive. For randomized patients with no follow-up, OS was censored at randomization.

Objective response outcomes (exploratory endpoints)

ORR (95% CI) and BOR per BICR[a]



Time to and duration of responses

Any objective response[c]	NIVO+GC (n = 175)	GC (n = 131)
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)

Complete response[d]	NIVO+GC (n = 66)	GC (n = 36)
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)

Van Der Heijden T et al, ESMO 2023

[a]In all randomized patients. [b]The most common reasons for UE response included death before first tumor assessment, withdrawal of consent, treatment stopped due to toxicity, patient never treated, and receipt of subsequent anticancer therapy before first tumor assessment. [c]Based on patients with an objective response per BICR (PR or CR as BOR). [d]Based on patients with a CR per BICR.
BOR, best overall response; CR, complete response; DoCR, duration of complete response; DoR, duration of objective response; NE, not estimable; PD, progressive disease; PR, partial response; Q, quartile; SD, stable disease; TTCR, time to complete response; TTR, time to objective response; UE, unevaluable.

Thank You!!

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