Neues aus der Uroonkologie
ASCO 2023

PD. Dr. med. Christoph Lutz

Praxis für Hämatologie und Onkologie Koblenz

05.07.2023

Übersicht

1. Prostatakarzinom
2. Nierenzellkarzinom
3. Urothelkarzinom

Presentation number 5004

2023 ASCO ANNUAL MEETING

TALAPRO-2: Phase 3 study of talazoparib plus enzalutamide versus placebo plus enzalutamide as first-line treatment for patients with metastatic castration-resistant prostate cancer harboring homologous recombination repair gene alterations (HRR-deficient population)

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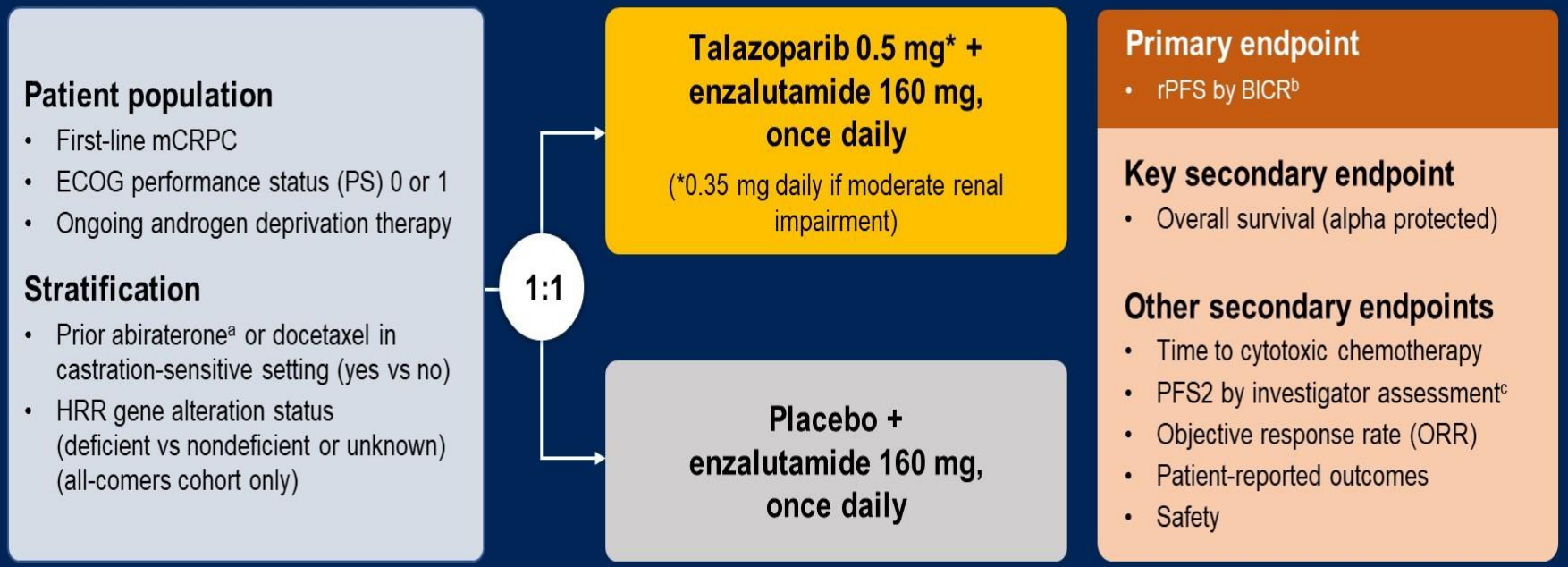
ClinicalTrials.gov identifier: NCT03395197.
This study was sponsored by Pfizer Inc. Astellas Pharma Inc. provided enzalutamide.

PRESENTED BY: Professor Karim Fizazi

TALAPRO-2: A Randomized, Double-blind, Placebo-Controlled Study

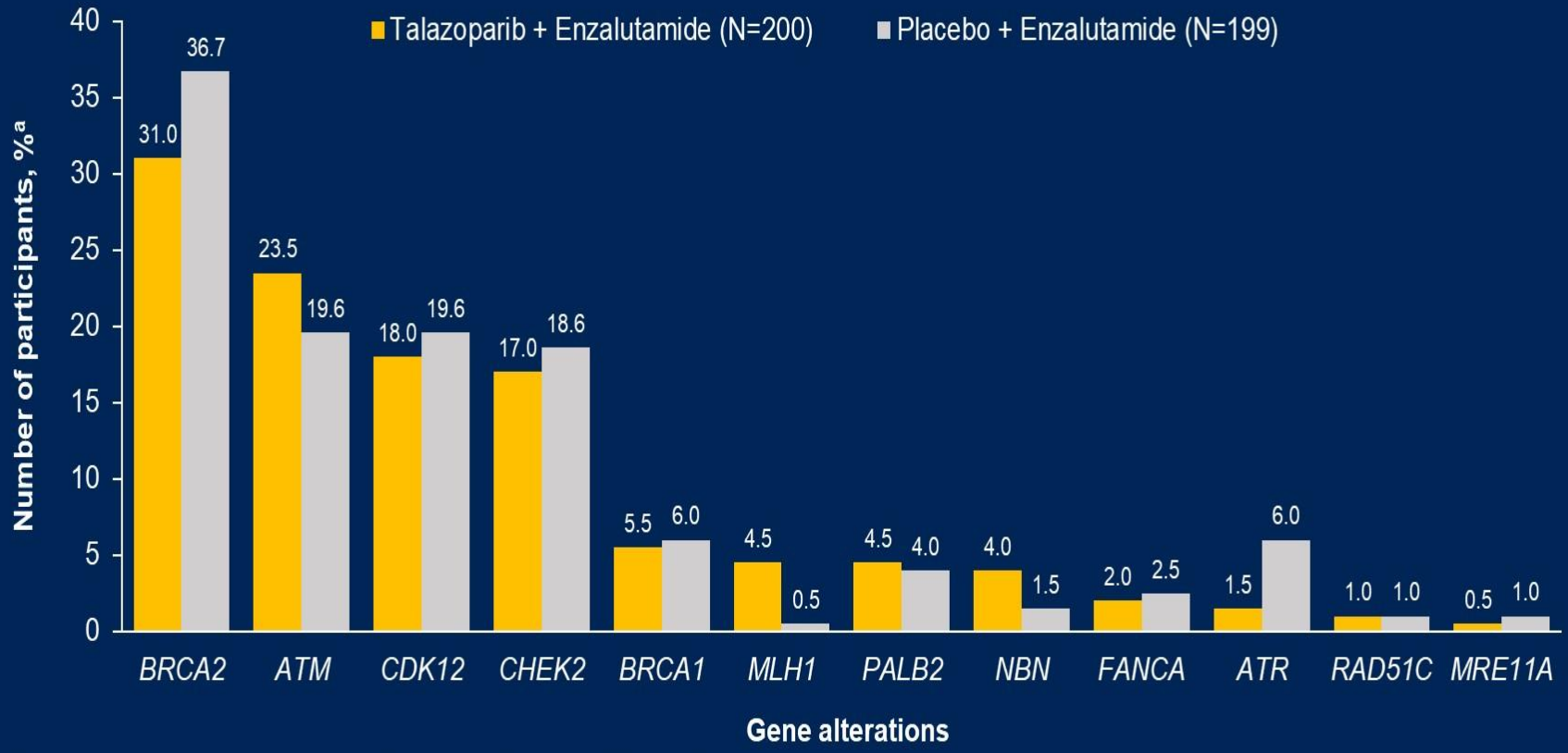


Samples prospectively assessed for HRR gene alterations *(BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12)* using FoundationOne®CDx and/or FoundationOne®Liquid CDx

BICR=blinded independent central review; rPFS=radiographic progression-free survival.
[a]One patient in each treatment arm received prior orteronel. [b]Per RECIST version 1.1 (soft tissue disease) and Prostate Cancer Clinical Trials Working Group 3 (bone disease). [c]Time from randomization to the date of documented progression on the first subsequent antineoplastic therapy or death from any cause, whichever occurred first.

TALAPRO-2 HRR-Deficient: Baseline HRR Gene Alterations

Representation of HRR gene alterations was consistent with previously published studies

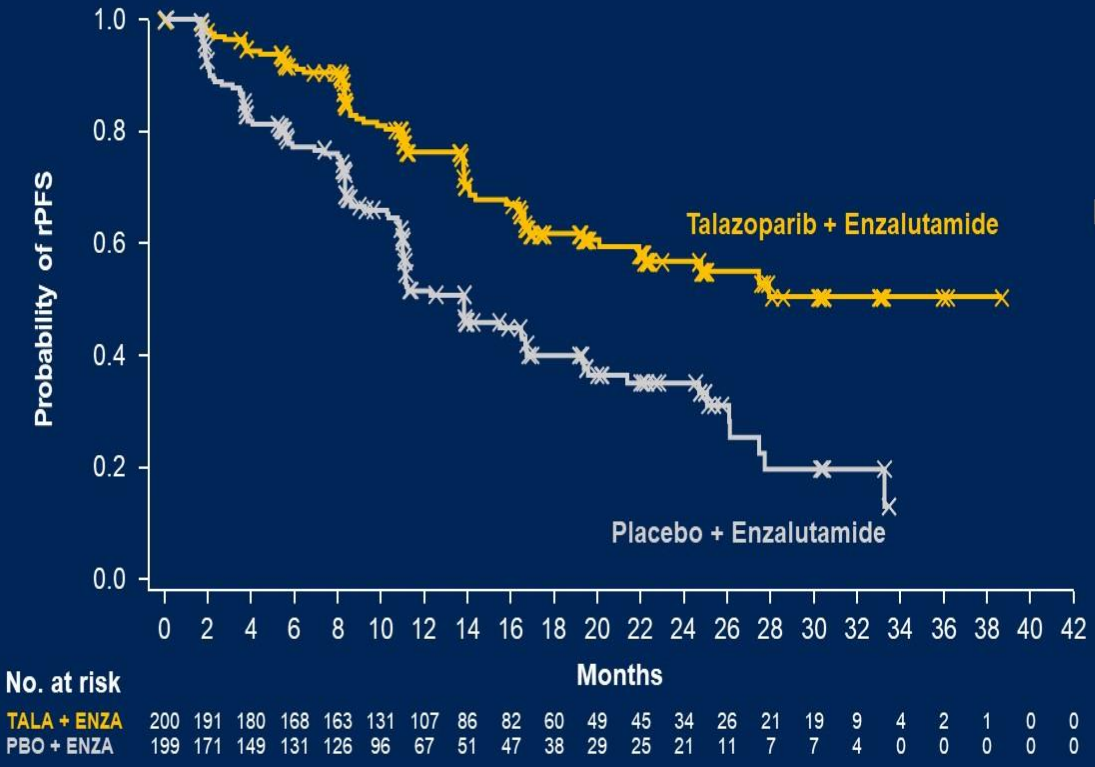


During the mid-point of the study (January-November 2021), recruitment of patients with *ATM* and/or *CDK12* alterations was paused to avoid over-representation.

[a]Number of participants with one or more alterations in corresponding gene. Three patients (1 in the talazoparib arm and 2 in the placebo arm) did not have HRR gene alterations, and 1 patient in the talazoparib arm was of unknown HRR gene alteration status.

TALAPRO-2 HRR-Deficient Primary Endpoint: rPFS by BICR

Treatment with talazoparib plus enzalutamide resulted in a 55% reduced risk of progression or death



	TALA + ENZA (N=200)	PBO + ENZA (N=199)
Events, n	66	104
Median (95% CI), months	Not reached (NR) (21.9–NR)	13.8 (11.0–16.7)
HR (95% CI)	0.45 (0.33–0.61); *P* < 0.0001	

Median follow-up for rPFS was 17.5 and 16.8 months, respectively

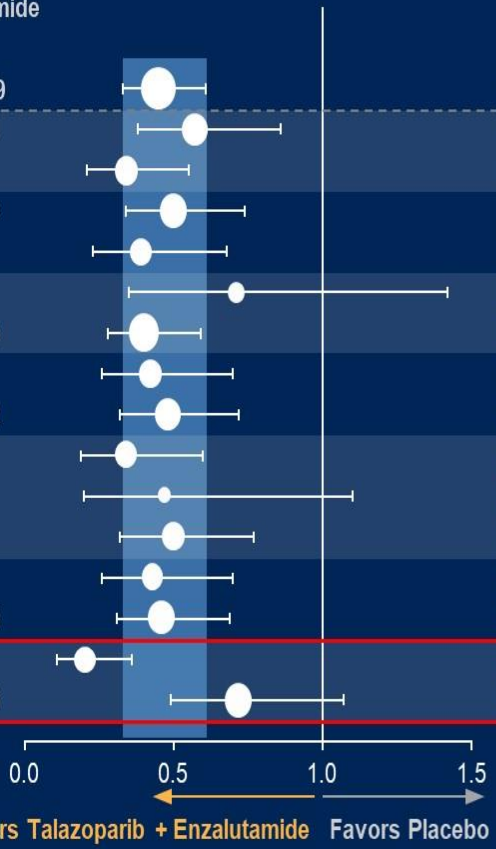
A consistent treatment effect was seen for investigator-assessed rPFS: HR 0.48 (95% CI, 0.33–0.67); *P* < 0.0001

Stratified hazard ratios (HRs) and 2-sided *P* values are reported throughout this presentation unless otherwise stated.

TALAPRO-2 HRR-Deficient: Subgroup Analysis of rPFS by BICR

A consistent treatment effect with talazoparib plus enzalutamide was seen in prespecified subgroups

Subgroup		Talazoparib + Enzalutamide Events/N	Placebo + Enzalutamide Events/N	HR (95% CI)	2-Sided *P* Value
Overall		66/200	104/199	0.45 (0.33–0.61)	< 0.0001
Age, years	≥70	41/105	56/111	0.57 (0.38–0.86)	0.006
	<70	25/95	48/88	0.34 (0.21–0.55)	< 0.0001
ECOG PS	0	47/128	63/118	0.50 (0.34–0.74)	0.0003
	1	19/72	41/81	0.39 (0.23–0.68)	0.0005
Gleason score	<8	13/42	20/52	0.71 (0.35–1.42)	0.33
	≥8	52/152	81/143	0.40 (0.28–0.57)	< 0.0001
Stage at diagnosis	M0	24/84	43/84	0.42 (0.26–0.70)	0.0005
	M1	42/115	59/112	0.48 (0.32–0.72)	0.0002
Site of metastasis	Bone only	17/79	36/78	0.34 (0.19–0.60)	0.0001
	Soft tissue only	7/20	25/40	0.47 (0.20–1.10)	0.075
	Bone and soft tissue	41/96	43/80	0.50 (0.32–0.77)	0.0014
Prior abiraterone[a] or docetaxel	Yes	26/75	39/74	0.43 (0.26–0.70)	0.0006
	No	40/125	65/125	0.46 (0.31–0.69)	< 0.0001
BRCA1/2	Yes	15/71	54/84	0.20 (0.11–0.36)	< 0.0001
	No	51/129	50/115	0.72 (0.49–1.07)	0.10

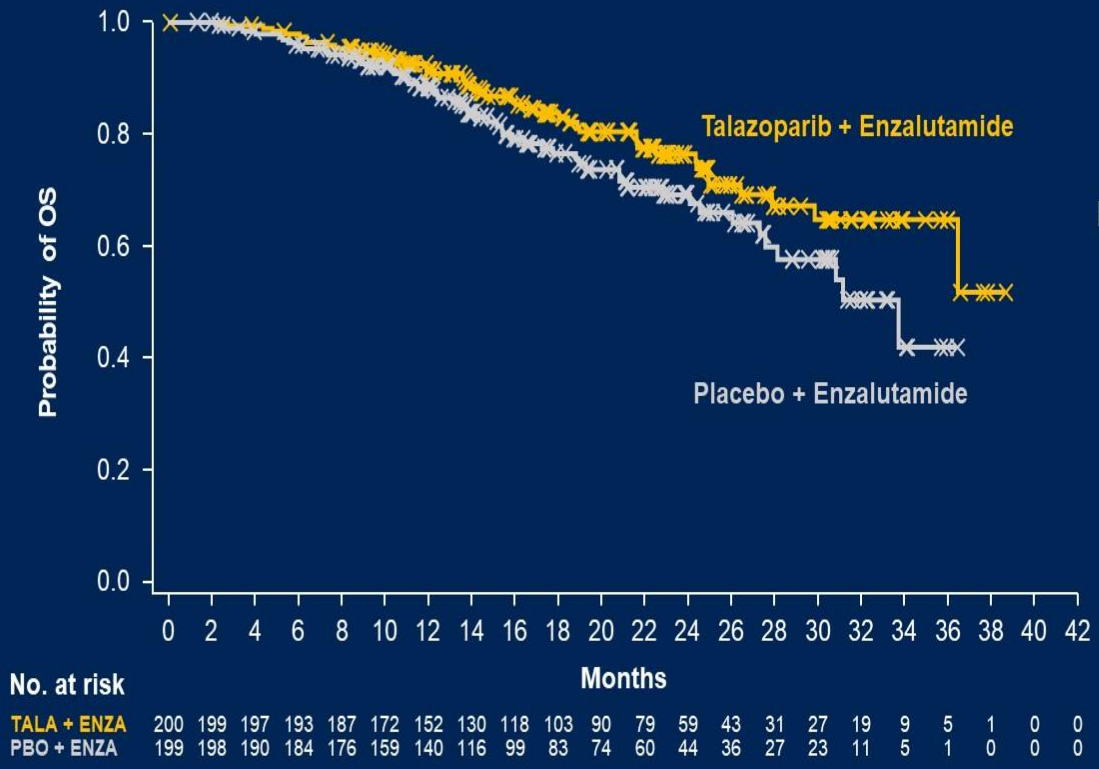


The HR for all patients, and by *BRCA1/2* status, was based on a Cox model stratified by the randomization stratification factors. For all other subgroups, the HR was based on an unstratified Cox model with treatment as the only covariate.

[a]Includes one patient in each treatment arm who received prior orteronel.

TALAPRO-2 HRR-Deficient: Overall Survival (Interim Analysis)

Overall survival data are immature (24% maturity overall)



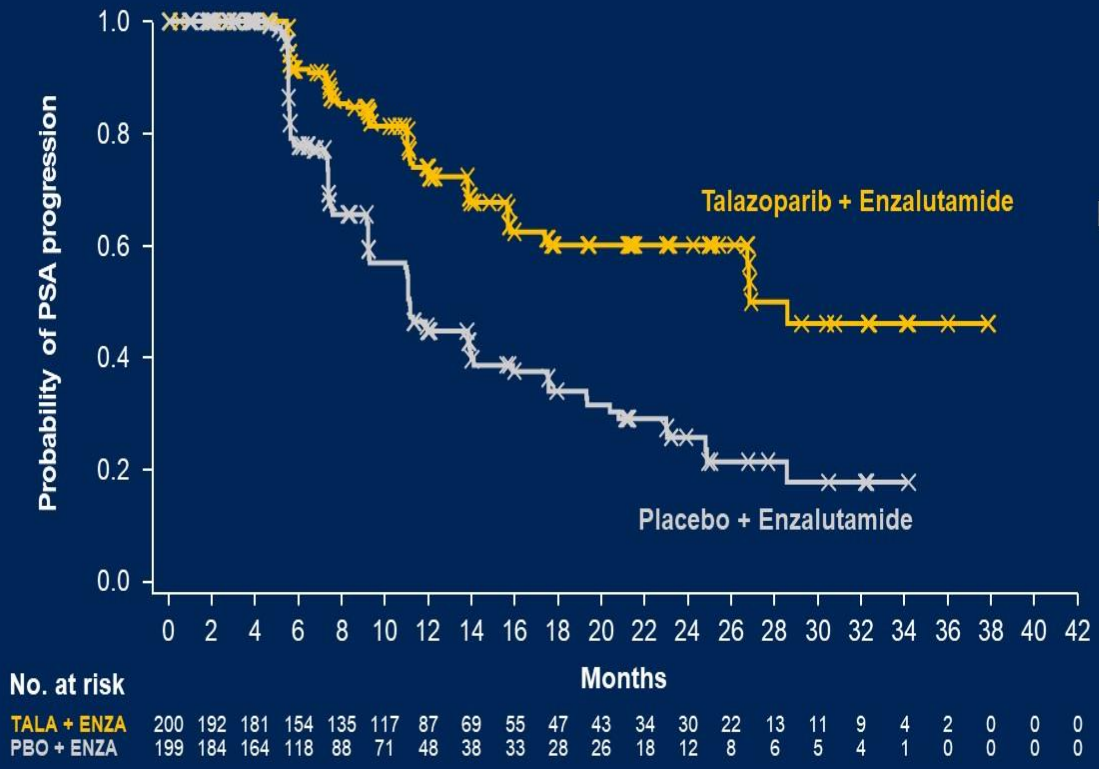
	TALA + ENZA (N=200)	PBO + ENZA (N=199)
Events, n	43	53
Median (95% CI), months	NR (36.4–NR)	33.7 (27.6–NR)
HR (95% CI)	HR 0.69 (95% CI, 0.46–1.03) *P* = 0.068	

***BRCA*m HR 0.61 (95% CI, 0.31–1.23; *P* = 0.16)**
non-*BRCA*m HR 0.71 (95% CI, 0.43–1.18; *P* = 0.18)

18 patients in the control arm and 3 patients in the talazoparib arm subsequently received olaparib

TALAPRO-2 HRR-Deficient: Time to PSA Progression

Treatment with talazoparib plus enzalutamide prolonged time to PSA progression

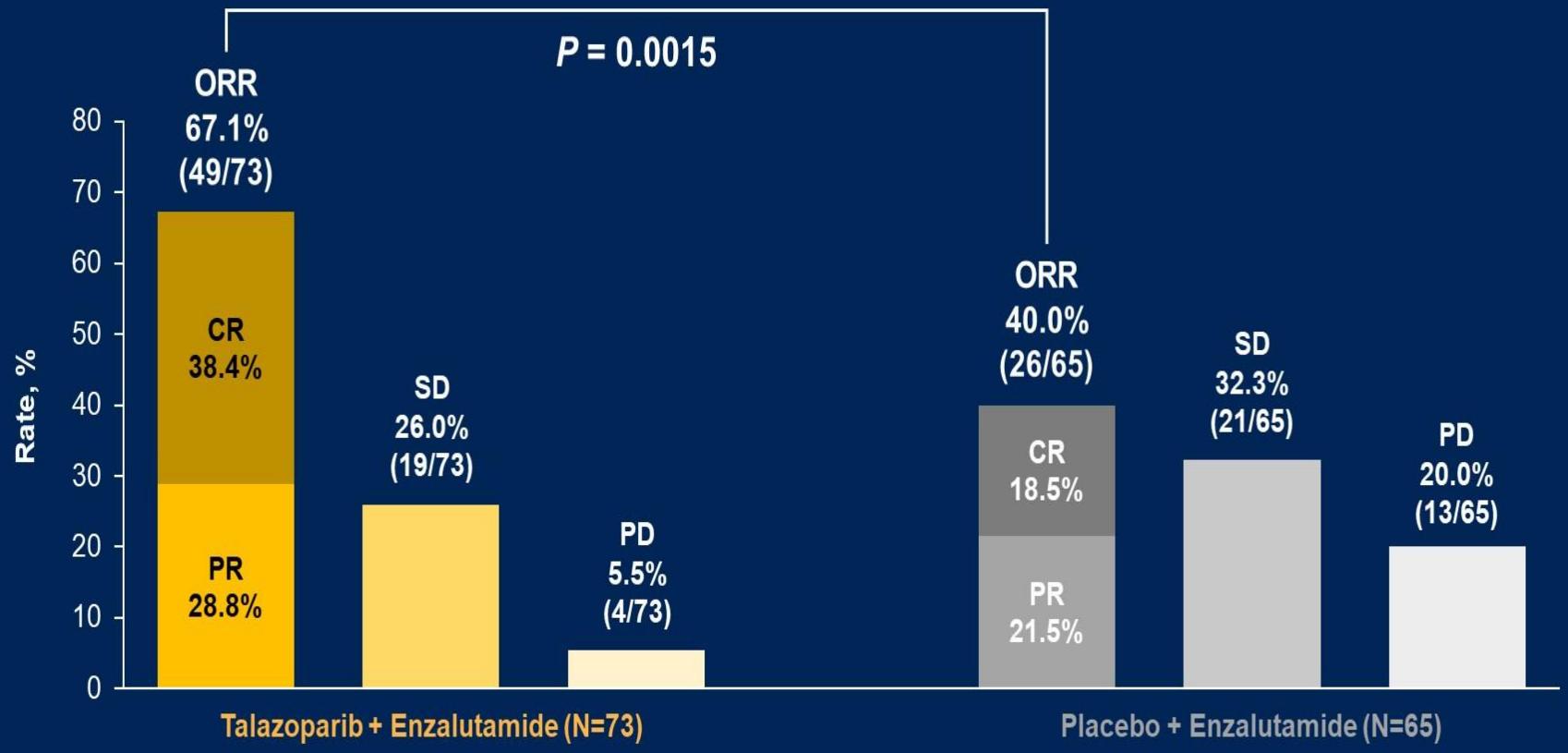


	TALA + ENZA (N=200)	PBO + ENZA (N=199)
Events, n	59	96
Median (95% CI), months	28.6 (26.7–NR)	11.1 (9.3–13.9)
HR (95% CI)	HR 0.41 (95% CI, 0.30–0.57) *P* < 0.0001	

PRESENTED BY: Professor Karim Fizazi

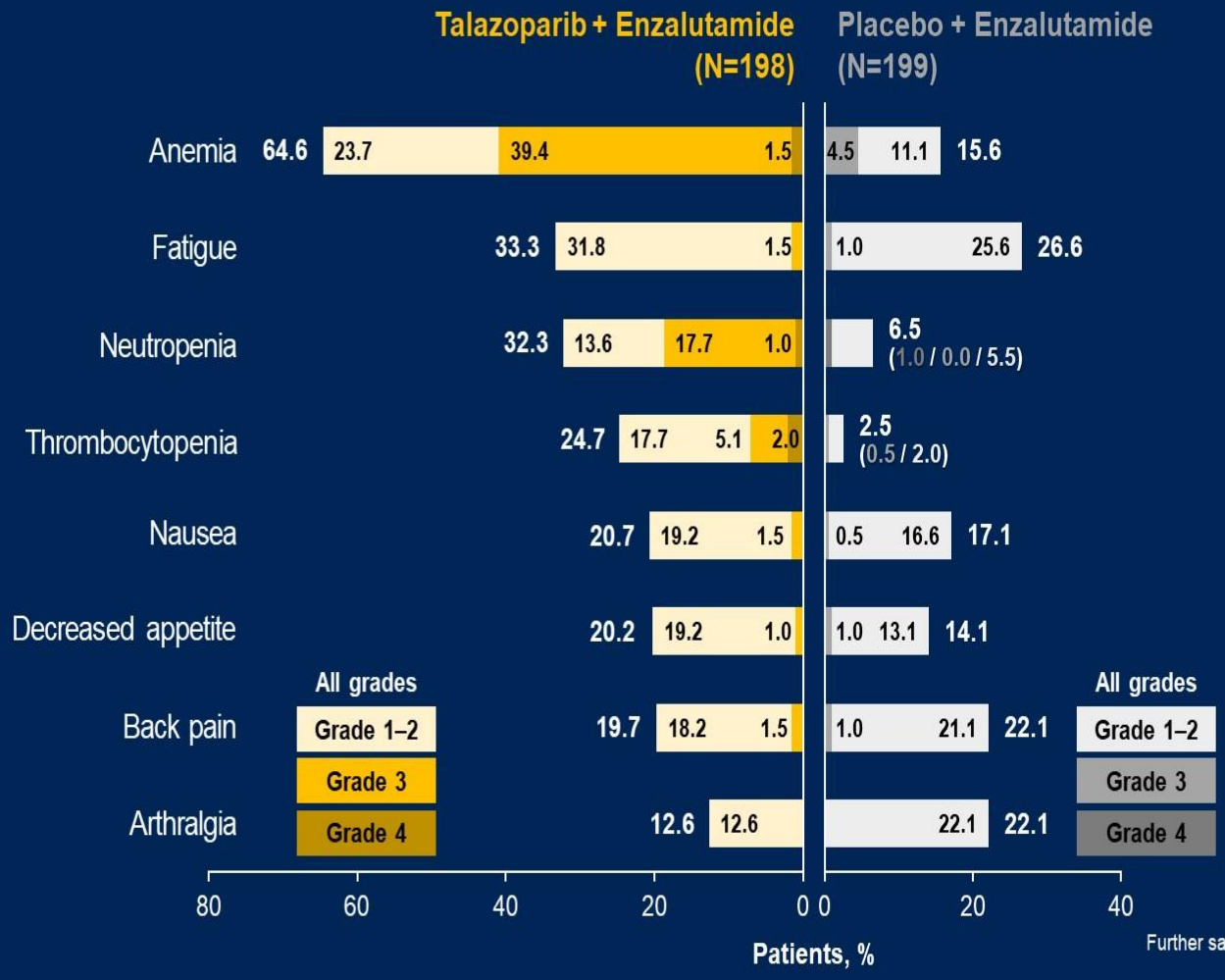
TALAPRO-2 HRR-Deficient: Objective Response by BICR

Higher rates of complete response (CR) suggest a cooperative effect of talazoparib plus enzalutamide treatment



PD=progressive disease; PR=partial response; SD=stable disease.

TALAPRO-2 HRR-Deficient: Most Common All-Cause TEAEs



In the talazoparib arm:

- Most common TEAEs leading to a dose reduction of talazoparib were:
  - Anemia (42.9%)
  - Neutropenia (15.2%)
  - Thrombocytopenia (5.6%)
- 55.6% had grade 1–2 anemia at baseline
- Grade 3–4 anemia
  - Median time to onset was 3.2 months
  - Reported in 40.9% of patients
- 4.0% discontinued talazoparib due to anemia
- The median relative dose intensity of talazoparib remained >80%

Further safety details can be found by accessing abstract No. 5053 (poster No. 147)

1. Prostatakarzinom
2. Nierenzellkarzinom
3. Urothelkarzinom

2023 ASCO ANNUAL MEETING

Efficacy and safety of atezolizumab plus cabozantinib vs cabozantinib alone after progression with prior immune checkpoint inhibitor treatment in metastatic renal cell carcinoma: Phase III CONTACT-03 study

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Phase III CONTACT-03 study

Key eligibility criteria

- Advanced/metastatic clear cell or non–clear cell[a] RCC with or without a sarcomatoid component
- Radiographic progression on or after prior ICI treatment
  - ICI as adjuvant, 1L or 2L (single agent or in combination with another permitted agent)
  - ICI in the immediately preceding line of therapy

R
1:1

N=522

Atezolizumab 1200 mg IV q3w + Cabozantinib 60 mg daily PO

Cabozantinib 60 mg daily PO

Stratification factors

- **IMDC risk group**
  0 vs 1-2 vs ≥3
- **Histology**
  Dominant clear cell without sarcomatoid vs dominant non-clear cell without sarcomatoid vs any sarcomatoid[b]
- **Most recent line of ICI**
  Adjuvant vs 1L vs 2L

Primary endpoints

- Independent centrally-assessed PFS[c]
- OS

Key secondary endpoints

- Investigator-assessed PFS[c]
- ORR (per central review and per investigator)[c]
- Duration of response (per central review and per investigator)[c]
- Safety

ClinicalTrials.gov ID, NCT04338269. IMDC, International Metastatic RCC Database Consortium. Patients were enrolled between July 28, 2020 and December 27, 2021.
[a] Papillary, chromophobe or unclassified (chromophobe requires sarcomatoid differentiation). [b] Clear cell or non-clear cell. [c] Assessed according to RECIST 1.1.

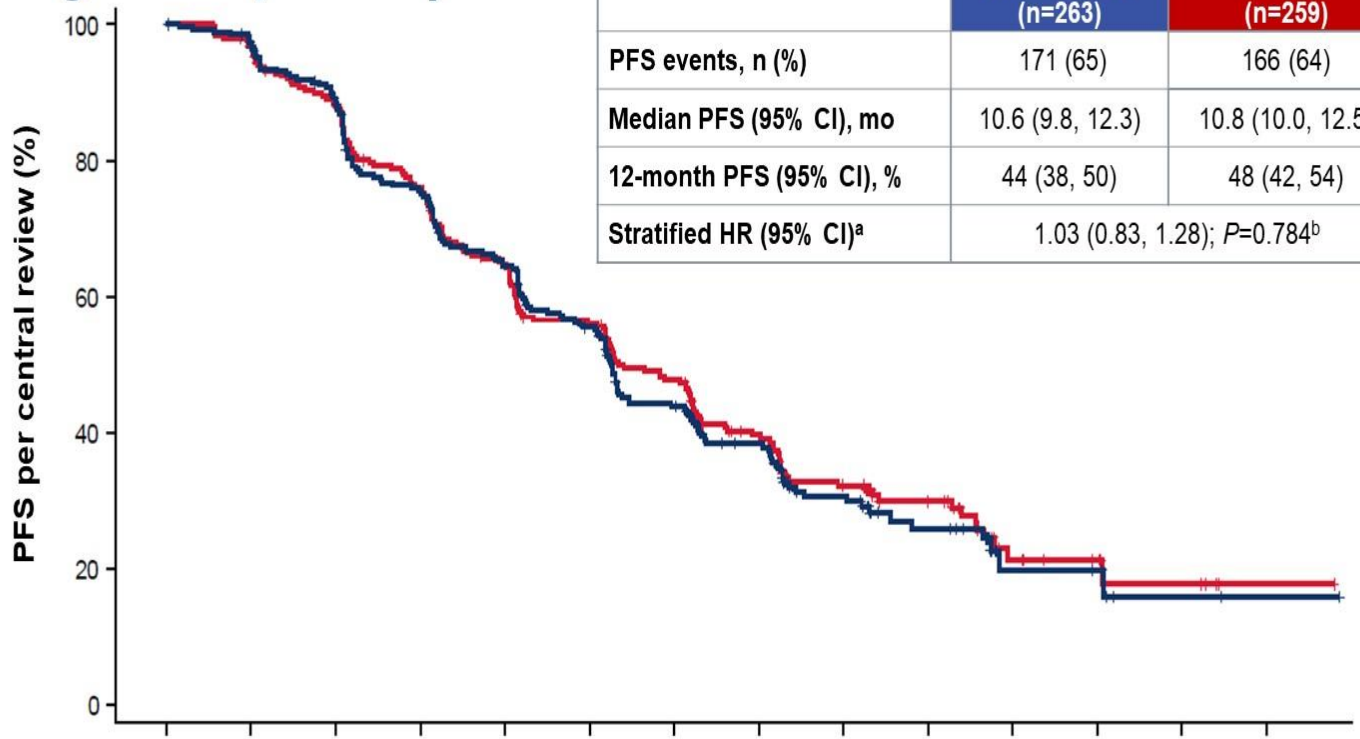
Most common prior systemic cancer treatment

	Atezo + Cabo (n=263)	Cabo (n=259)
First-line treatment, n (%)[a,b]	**262 (99.6)**	**258 (99.6)**
Ipilimumab + nivolumab	80 (30.5)	70 (27.1)
Sunitinib	77 (29.4)	72 (27.9)
Pazopanib	36 (13.7)	43 (16.6)
Axitinib + pembrolizumab	36 (13.7)	28 (10.9)
Nivolumab	6 (2.3)	10 (3.9)
Avelumab + axitinib	7 (2.7)	6 (2.3)
Bempegaldesleukin + nivolumab	3 (1.1)	9 (3.5)
Lenvatinib + pembrolizumab	6 (2.3)	3 (1.2)
Sorafenib	3 (1.1)	1 (0.4)
Second-line treatment, n (%)[a,b]	**119 (45.2)**	**125 (48.3)**
Nivolumab	104 (87.4)	116 (92.8)
Ipilimumab + nivolumab	4 (3.4)	3 (2.4)
Axitinib + pembrolizumab	2 (1.7)	3 (2.4)
Adjuvant treatment, n (%)[a,b]	**8 (3.0)**	**4 (1.5)**
Sunitinib	2 (25)	2 (50)

Percentages for each regimen were calculated based on the total number of patients receiving the corresponding line of therapy.
[a] Treatments were mutually exclusive within each line of therapy, and patients could have received agents for >1 line of treatment. [b] Only regimens received by ≥4 patients are shown.

Primary analysis of centrally reviewed PFS (primary endpoint)

	Atezo + Cabo (n=263)	Cabo (n=259)
PFS events, n (%)	171 (65)	166 (64)
Median PFS (95% CI), mo	10.6 (9.8, 12.3)	10.8 (10.0, 12.5)
12-month PFS (95% CI), %	44 (38, 50)	48 (42, 54)
Stratified HR (95% CI)[a]	1.03 (0.83, 1.28); *P*=0.784[b]	

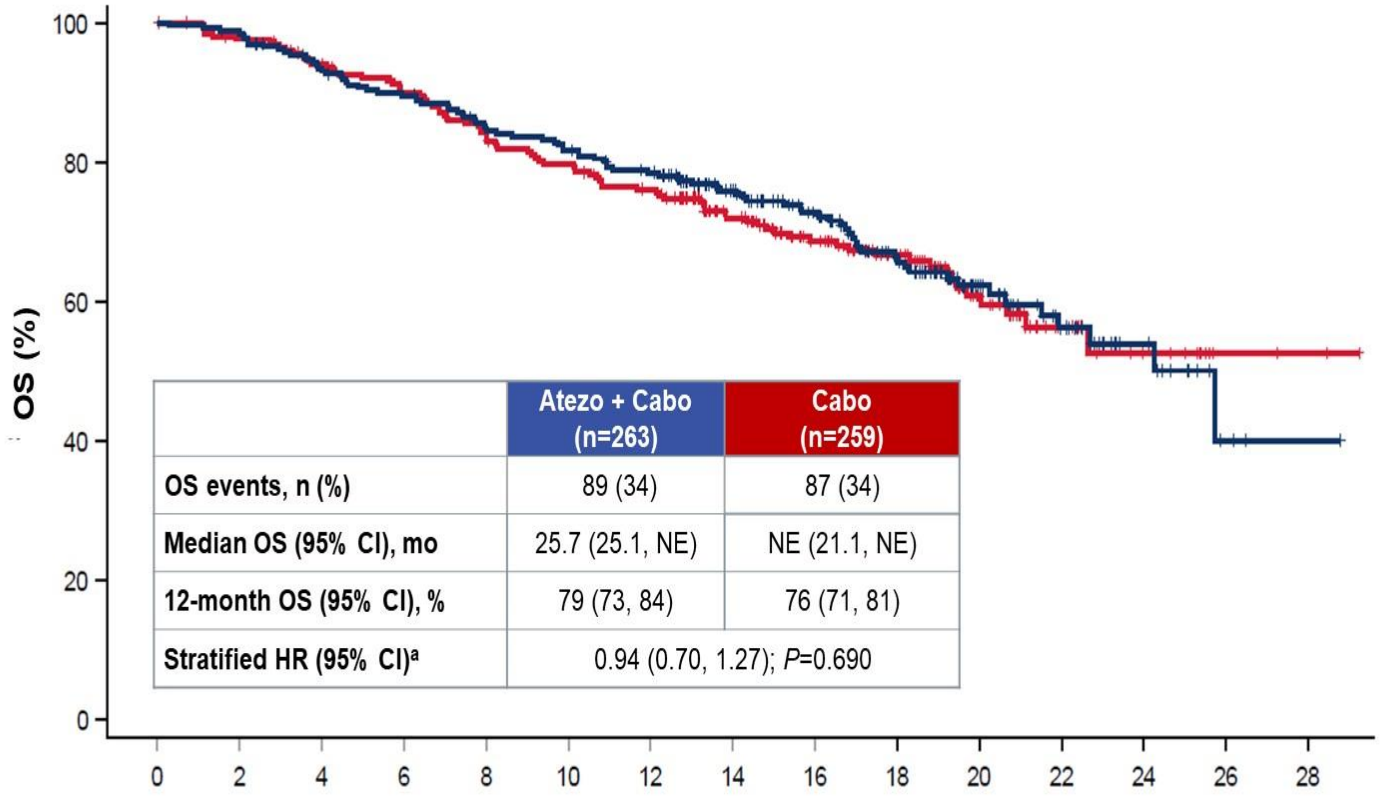


Number at risk

Atezo + Cabo	263	253	226	188	158	133	100	68	43	22	7	6	2	1
Cabo	259	242	216	183	153	130	109	71	52	34	12	8	5	1

[a] Stratified for IMDC risk group. [b] Not significant at α=0.02.

Interim analysis of OS (primary endpoint)



	Atezo + Cabo (n=263)	Cabo (n=259)
OS events, n (%)	89 (34)	87 (34)
Median OS (95% CI), mo	25.7 (25.1, NE)	NE (21.1, NE)
12-month OS (95% CI), %	79 (73, 84)	76 (71, 81)
Stratified HR (95% CI)[a]	0.94 (0.70, 1.27); *P*=0.690	

Number at risk

Atezo + Cabo	263	259	240	229	215	207	196	157	127	91	50	31	15	3	1
Cabo	259	247	235	221	207	195	182	145	113	88	50	22	11	3	2

[a] Stratified for IMDC risk group.

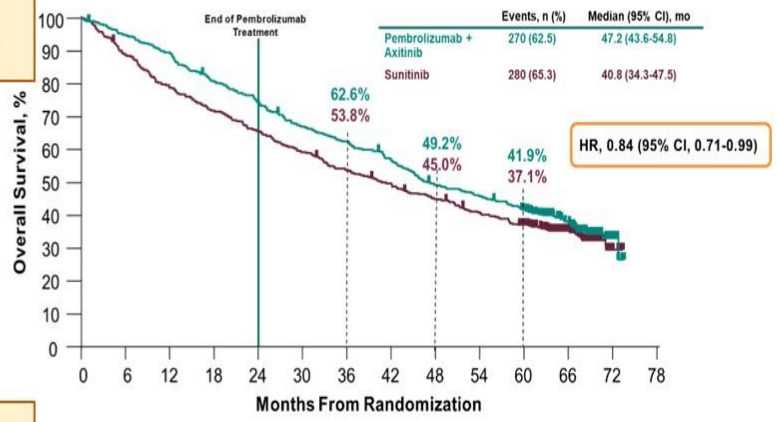
Safety summary

Adverse event, n (%)	Atezo + Cabo (n=262)	Cabo (n=256)
Any-cause AE	262 (100)	254 (99.2)
Any-cause treatment-related AE	252 (96.2)	249 (97.3)
Grade 3 or 4 AE	177 (67.6)	158 (61.7)
Grade 3 or 4 treatment-related AE	145 (55.3)	121 (47.3)
Death due to AE	17 (6.5)	9 (3.5)
Death due to treatment-related AE	3 (1.1)[a]	0
Serious AE	126 (48.1)	84 (32.8)
Serious treatment-related AE	63 (24.0)	30 (11.7)
AE leading to withdrawal from a trial drug	41 (15.6)	10 (3.9)
AE leading to withdrawal from atezo	29 (11.1)	–
AE leading to withdrawal from cabo	25 (9.5)	10 (3.9)
AE leading to interruption or reduction of a trial drug	240 (91.6)	223 (87.1)
AE leading to interruption of atezo[b]	159 (60.7)	–
AE leading to interruption or reduction of cabo	234 (89.3)	223 (87.1)

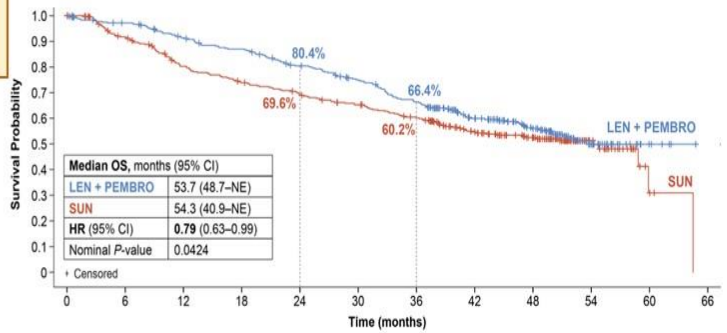
[a] Treatment-related AEs leading to death were immune-mediated enterocolitis and renal failure (both related to atezo) and intestinal perforation (related to cabo). [b] Dose reduction of atezo was not permitted.

Is IO+TKI superior to TKI alone for front-line ccRCC treatment? Yes (↑OS)

KN-426
(pembrolizumab+axitinib)



CLEAR
(pembrolizumab+lenvatinib)



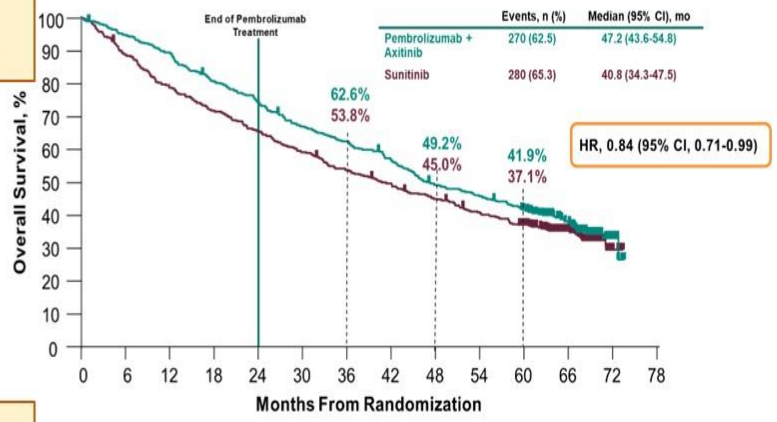
*Positive for OS, but questions around **durability****

Rini, ASCO 2023, LBA4501; Motzer & Hutson, ASCO 2023, 4501.

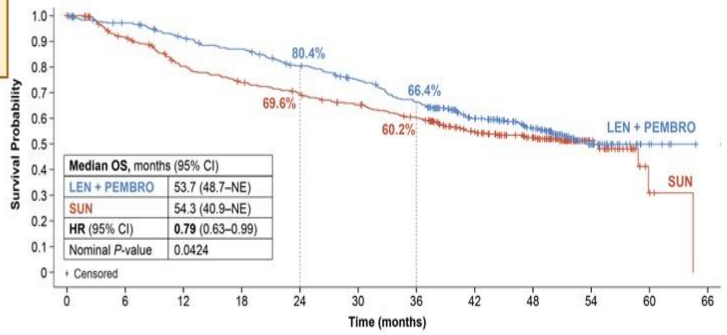
*Imbalance in subsequent therapies

Is IO+TKI superior to TKI alone for front-line ccRCC treatment? Yes (↑OS)

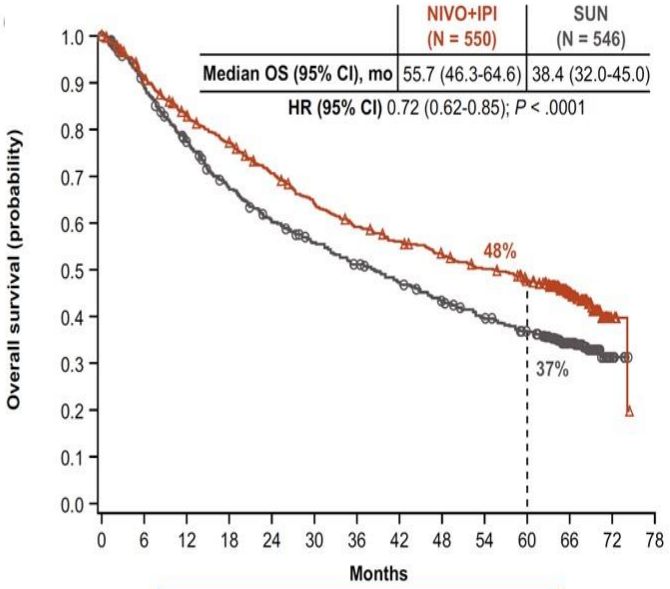
KN-426
(pembrolizumab+axitinib)



CLEAR
(pembrolizumab+lenvatinib)



CM-214
(nivolumab+ipilimumab)



IO+IO maintains OS benefit over time

Rini, ASCO 2023, LBA4501; Motzer & Hutson, ASCO 2023, 4501, Motzer, Cancer, 2022.

First-Line Lenvatinib Plus Pembrolizumab Treatment Across Non–Clear Cell Renal Cell Carcinomas: Results of the Phase 2 KEYNOTE-B61 Study

Chung-Han Lee[1]; Howard Gurney[2]; Vagif Atduev[3]; Cristina Suarez[4]; Miguel A. Climent[5]; David Pook[6]; Piotr Tomczak[7]; Philippe Barthelemy[8]; Jae Lyun Lee[9]; Taron Nalbandian[10]; Viktor Stus[11]; Thomas Ferguson[12]; Pawel Wiechno[13]; Erhan Gokmen[14]; Louis Lacombe[15]; Craig Gedye[16]; Joseph E. Burgents[17]; Manish Sharma[17]; Xiang Peng[17]; Laurence Albiges[18]

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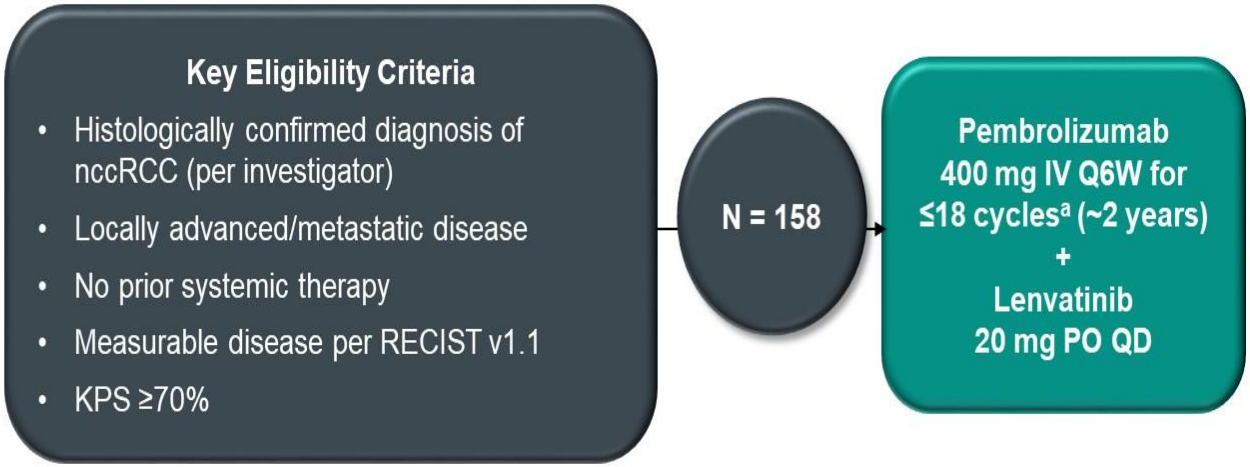
Background/Study Design of KEYNOTE-B61

- Immunotherapy-based combinations including pembrolizumab plus lenvatinib are standard of care for first-line clear cell RCC,[1] however these combinations are not well characterized in non–clear cell RCC
- Non–clear cell RCC is a heterogenous group of aggressive tumors with limited treatment options[2,3]
- Pembrolizumab plus lenvatinib showed antitumor activity in patients with advanced non–clear cell RCC who had opportunity for at least 24 weeks of follow-up (n = 82) in the initial analysis of the single-arm, phase 2 KEYNOTE-B61 (NCT04704219) study[4]

Tumor Assessments

- 12 weeks from allocation, then Q6W for 54 weeks, then Q12W thereafter



End Points

- Primary: ORR per RECIST v1.1 by BICR
- Secondary: CBR, DCR, DOR, and PFS per RECIST v1.1 by BICR; OS; safety and tolerability

BICR, blinded independent central review; CBR, clinical benefit rate; DCR, disease control rate; DOR, duration of response; IV, intravenously; KPS, Karnofsky Performance Status score; nccRCC, non–clear cell renal cell carcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q6W, every 6 weeks; Q12W, every 12 weeks; QD, every day; RCC, renal cell carcinoma.

1. Motzer R et al. *N Engl J Med*. 2021;384:1289-1300. 2. Escudier B et al. *Ann Oncol*. 2019;30:706-720. 3. Hsieh JJ et al. Nat Rev Dis Primers. 2017;3:17009. 4. Albiges L et al. *Ann Oncol*. 2022;suppl 7:S660-680.

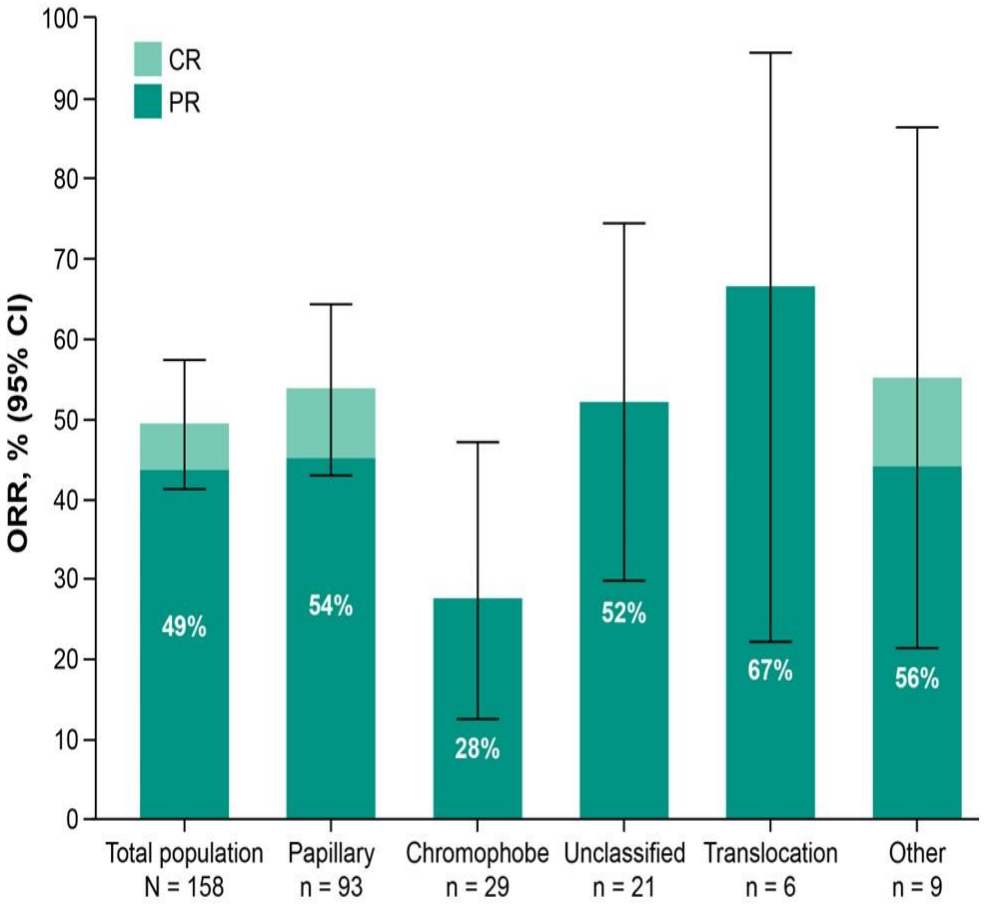
Baseline Characteristics

	Pembrolizumab + lenvatinib N = 158
Age, median (range)	60.0 (24-87)
Histology	
Papillary	93 (58.8)
Chromophobe	29 (18.4)
Unclassified	21 (13.3)
Translocation	6 (3.8)
Other	9 (5.7)
Presence of sarcomatoid features[a]	
Yes	19 (12.0)
No	96 (60.8)
Unknown	43 (27.2)
Site of metastases at screening	
Lymph node	102 (64.6)
Lung	54 (34.2)
Bone	49 (31.0)
Liver	31 (19.6)
Abdominal cavity	20 (12.7)
IMDC risk category	
Favorable	70 (44.3)
Intermediate/poor	88 (55.7)
PD-L1 status[b]	
CPS <1	50 (31.6)
CPS ≥1	93 (58.9)
Unknown	15 (9.5)

CPS, combined positive score; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium. Data are n (%) unless otherwise specified. [a]As determined by investigator review. [b]CPS was calculated as the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. Data cutoff date: November 7, 2022.

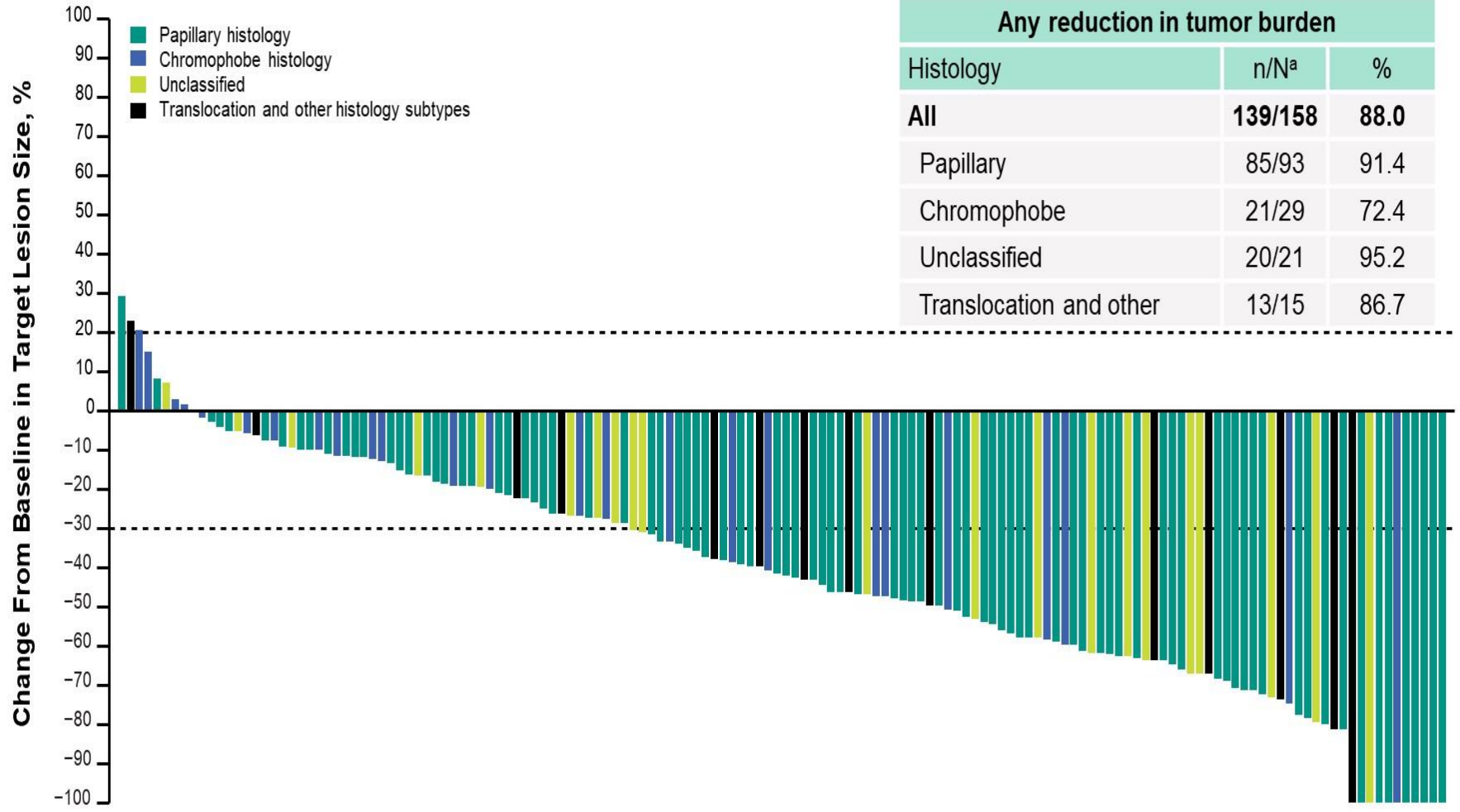
Best Confirmed Objective Response by Histology per RECIST v1.1 by Blinded Independent Central Review

	Pembrolizumab + lenvatinib N = 158
ORR (CR + PR), % (95% CI)	49 (41-57)
DCR (CR + PR + SD), % (95% CI)	82 (75-88)
CBR (CR, PR, or SD for ≥6 months), % (95% CI)	72 (64-78)
Best response, n (%)	
CR	9 (6)
PR	69 (44)
SD	52 (33)
PD	17 (11)
NE[a]	1 (0.6)
NA[b]	10 (6)



CR, complete response; NA, not applicable; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease. [a]Post-baseline assessment available but not evaluable. [b]No post-baseline assessment available. Data cutoff date: November 7, 2022.

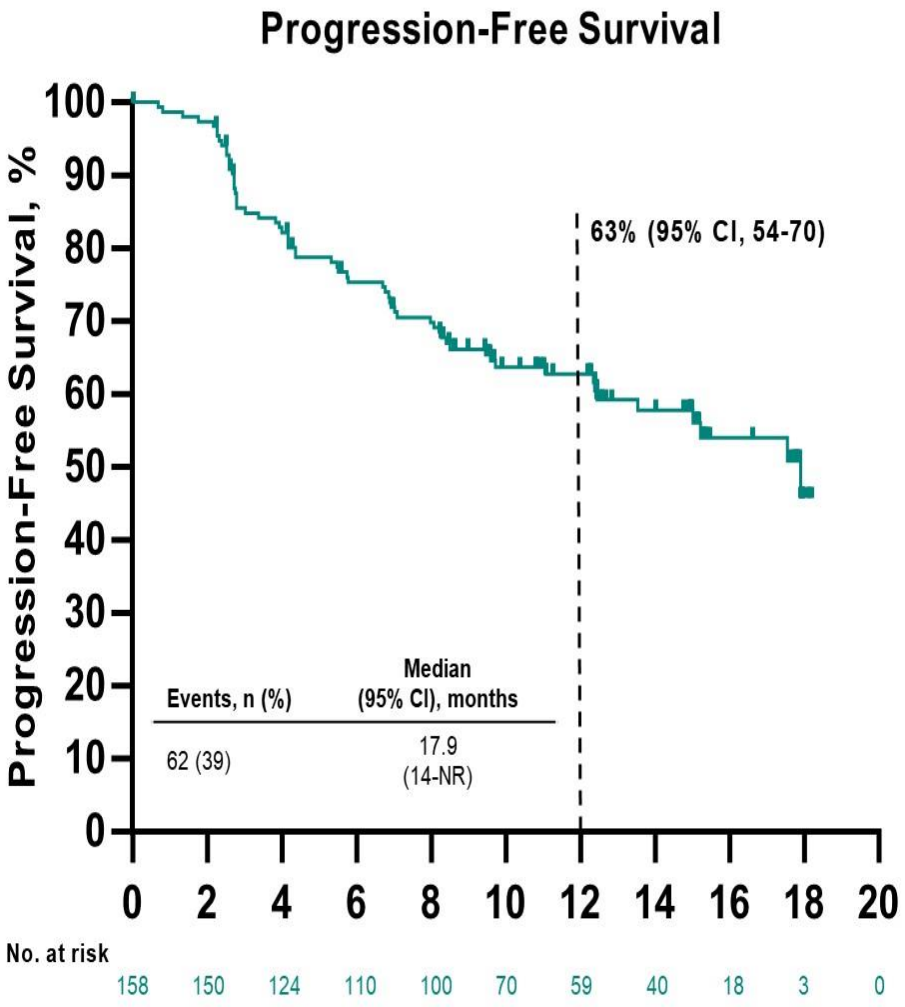
Best Percentage Change From Baseline in Target Lesion Size by Histology

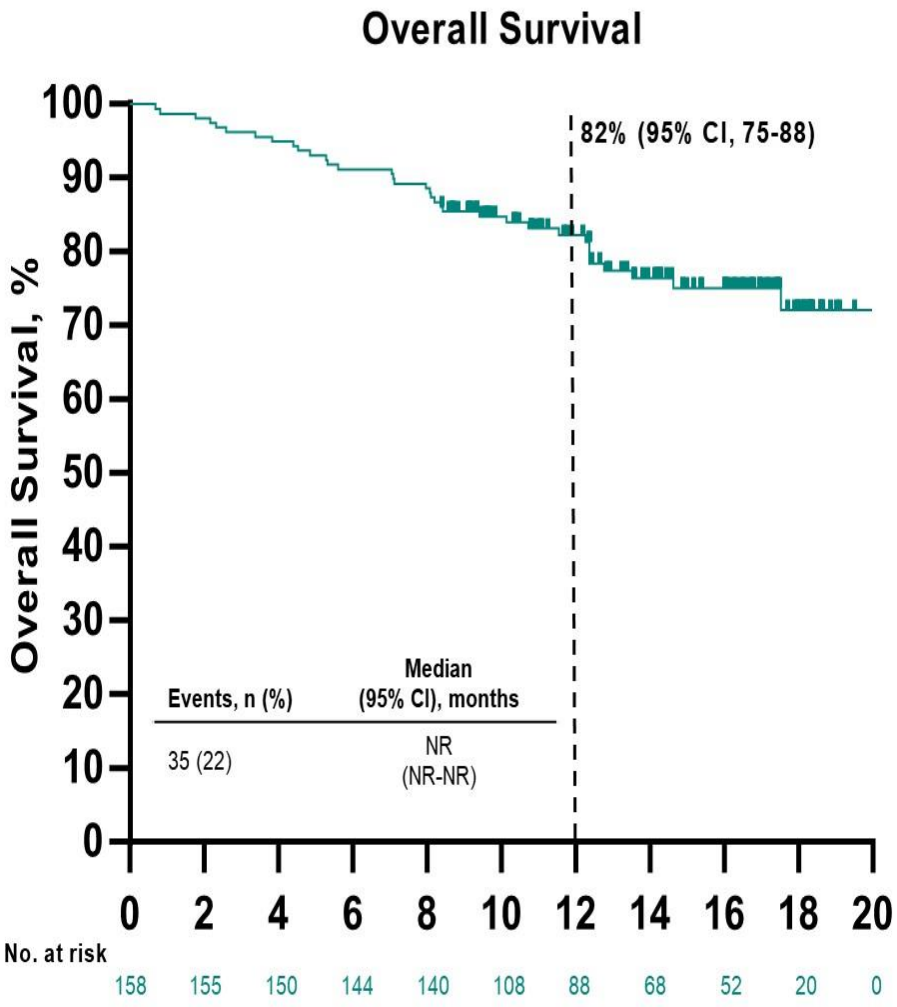


Any reduction in tumor burden		
Histology	n/N[a]	%
All	**139/158**	**88.0**
Papillary	85/93	91.4
Chromophobe	21/29	72.4
Unclassified	20/21	95.2
Translocation and other	13/15	86.7

[a]148 patients had a baseline and ≥1 postbaseline assessment. Data cutoff date: November 7, 2022.

Progression-Free Survival per RECIST v1.1 and Overall Survival





Data cutoff date: November 7, 2022.

1. Prostatakarzinom
2. Nierenzellkarzinom
3. Urothelkarzinom

Phase 3 THOR Study: Results of Erdafitinib Versus Chemotherapy in Patients With Advanced or Metastatic Urothelial Cancer With Select Fibroblast Growth Factor Receptor Alterations

Yohann Loriot[1], Nobuaki Matsubara[2], Se Hoon Park[3], Robert A. Huddart[4], Earle F. Burgess[5], Nadine Houede[6], Severine Banek[7], Brigitte Laguerre[8], Valentina Guadalupi[9], Ja Hyeon Ku[10], Spyros Triantos[11], Sydney Akapame[11], Kris Deprince[12], Sutapa Mukhopadhyay[13], Arlene O Siefker-Radtke[14]

[1]Department of Cancer Medicine, INSERM U981, Gustave Roussy, Université Paris-Saclay, Villejuif, France; [2]Department of Medical Oncology, National Cancer Center Hospital East, Chiba, Japan; [3]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [4]Section of Radiotherapy and Imaging, Institute of Cancer Research and Royal Marsden NHS Foundation Trust, Sutton, UK; [5]Medical Oncology Department, Levine Cancer Institute, Charlotte, NC; [6]Medical Oncology Department, Institut de Cancérologie du Gard - CHU Caremeau, Nîmes, France and Montpellier University, Montpellier, France; [7]Department of Urology, University Hospital Frankfurt, Goethe Universtity Frankfurt, Frankfurt am Main, Germany; [8]Department of Medical Oncology, Centre Eugene Marquis, Rennes, France; [9]Medical Oncology Department, Fondazione IRCCS Istituto Nazionale Dei Tumori, Milan, Italy; [10]Seoul National University Hospital, Seoul, South Korea; [11]Janssen Research & Development, Spring House, PA; [12]Janssen Research & Development, Beerse, Belgium; [13]Janssen Research & Development, Lexington, MA; [14]Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Presented at the 2023 ASCO Annual Meeting; June 2-6, 2023; Chicago, IL, USA.

Unmet Need for Post-Checkpoint Inhibitor Therapies in the Metastatic Urothelial Carcinoma Population

First-Line Systemic Therapy

Platinum-eligible population[1]

- Platinum-based chemotherapy +/- maintenance avelumab

Cisplatin-ineligible/platinum-ineligible population[1,2]

- Anti–PD-(L)1 *where approved*
- Pembrolizumab ± enfortumab vedotin *where approved*

Second-Line Systemic Therapy

Checkpoint inhibitor-naive population[1,2]

- Anti–PD-(L)1 *where approved*

Prior checkpoint inhibitor population[1,3]

- Single-agent chemotherapy (taxanes, vinflunine)
- Enfortumab vedotin, sacituzumab govitecan, and erdafitinib *where approved*

Post-Checkpoint Inhibitors

- Checkpoint inhibitors are used in both the first- and second-line settings[1,2]
- **~30% of patients with mUC respond** to immune checkpoint inhibitors[4]
- Treatment options after progression on PD-(L)1 inhibitors are limited[1,3]
- In the real-world setting, only **~30% of patients received subsequent anticancer treatment** after anti–PD-(L)1 discontinuation[5]
- No large, randomized studies have demonstrated survival benefit in biomarker-selected populations **after anti–PD-(L)1 treatment**

FGFR, fibroblast growth factor receptor; mUC, metastatic urothelial carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

1. National Comprehensive Cancer Network. Available at: https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed April 20, 2023. 2. Rhea LP, et al. *Clin Med Insights Oncol*. 2021;15:11795549211044963; 3. Bellmunt J, et al. *J Clin Oncol*. 2009;27:4454-4461; 4. Lopez-Beltran A, et al. *Cancers (Basel)*. 2021;13:131; 5. Morgans AK, et al. *Clin Genitourin Cancer*. 2022;20:543–552.

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

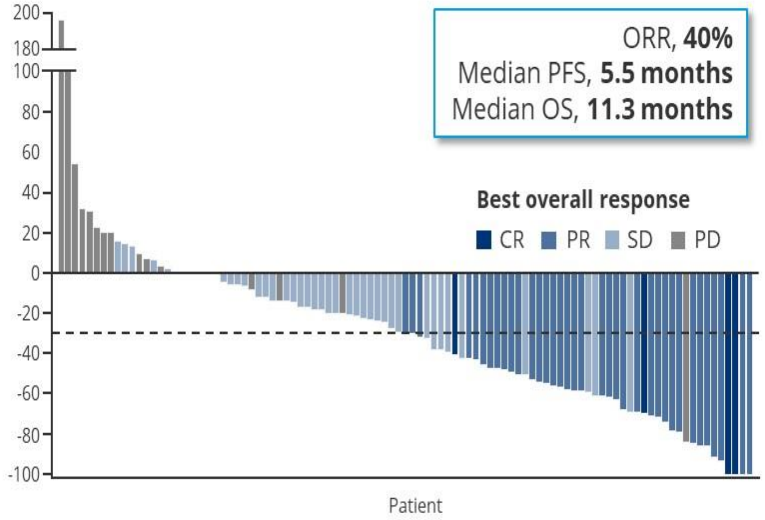
- ***FGFRalt*** are observed in **~20% of advanced or mUC** and may function as oncogenic drivers[1,2]

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.

Phase 3 THOR Study: Erdafitinib Versus Chemotherapy of Choice in Patients With Advanced Urothelial Cancer and Selected FGFR Aberrations

Cohort 1

Key eligibility criteria

- Age ≥18 years
- Metastatic or unresectable UC
- Confirmed disease progression
- Prior tx with anti–PD-(L)1
- 1-2 lines of systemic tx
- Select *FGFR3/2alt* (mutation/fusion)[a]
- ECOG PS 0-2

1:1
N=266[b]
R

Erdafitinib
(n=136)
Once-daily erdafitinib 8 mg with pharmacodynamically guided uptitration to 9 mg

Chemotherapy of Choice
(n=130)
docetaxel or vinflunine once every 3 weeks

Stratification factors: region (North America vs European Union vs rest of world), ECOG PS (0 or 1 vs 2), and disease distribution (presence vs absence of visceral [lung, liver, or bone] metastases)

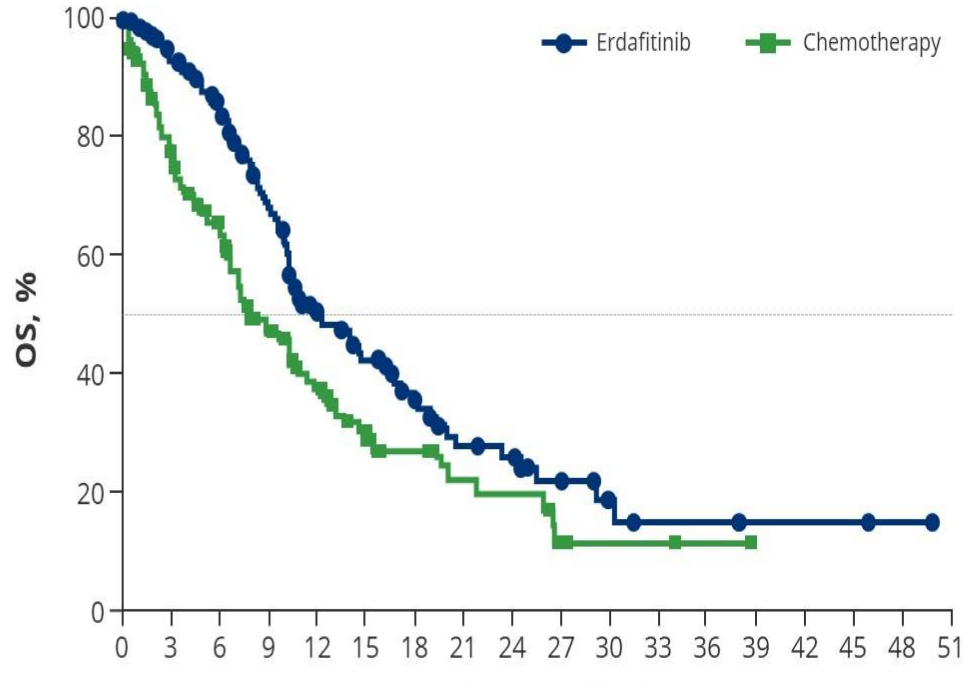
Primary end point:
- OS

Key secondary end points:
- PFS
- ORR
- Safety

NCT03390504

[a]Molecular eligibility can be confirmed using either central or local historical *FGFR* test results (Qiagen assay). If a patient was enrolled based on local historical testing, a tissue sample must still be submitted at the time of enrollment for retrospective confirmation (by central lab) of *FGFR* status. Tumors must have ≥1 of the following translocations: *FGFR2-BICC1*, *FGFR2-CASP7*, *FGFR3-TACC3_V1*, *FGFR3-TACC3_V3*, *FGFR3-BAIAP2L1*; or 1 of the following *FGFR3* gene mutations: R248C, S249C, G370C, Y373C.
[b]Number of patients randomized at the time of the interim analysis (data cutoff January 15, 2023).
ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; *FGFR3/2alt*, *FGFR3/2* alterations; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Q3W, every 3 weeks; tx, treatment; UC, urothelial cancer.

Overall Survival for Erdafitinib Was Superior to Investigator's Choice of Chemotherapy

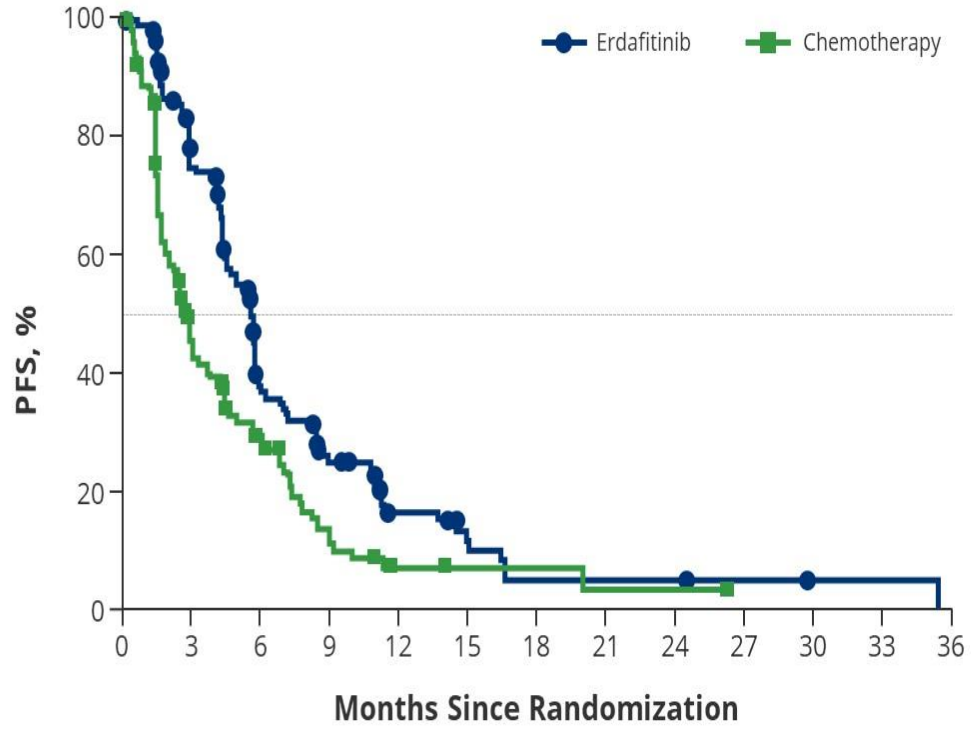


No. at risk																	
Erdafitinib	136	117	97	74	46	35	25	17	15	9	5	3	3	2	2	2	1	0
Chemotherapy	130	87	66	43	30	18	13	9	8	3	2	2	1	0	0	0	0	0

- Median follow-up was 15.9 months
- Median OS was 12.1 months for erdafitinib versus 7.8 months for chemotherapy
- Erdafitinib reduced the risk of death by 36% versus chemotherapy
  - HR, 0.64 (95% CI, 0.47-0.88; $P = 0.005$)[a]
- Based on these interim analysis results, the IDMC recommended to stop the study, unblind data, and cross over patients from chemotherapy to erdafitinib

CI, confidence interval; HR, hazard ratio; IDMC, independent data monitoring committee; OS, overall survival.
[a]The significance level for stopping for efficacy was p=0.019, corresponding to a HR of 0.69.

Erdafitinib Significantly Improved Progression-Free Survival Versus Chemotherapy

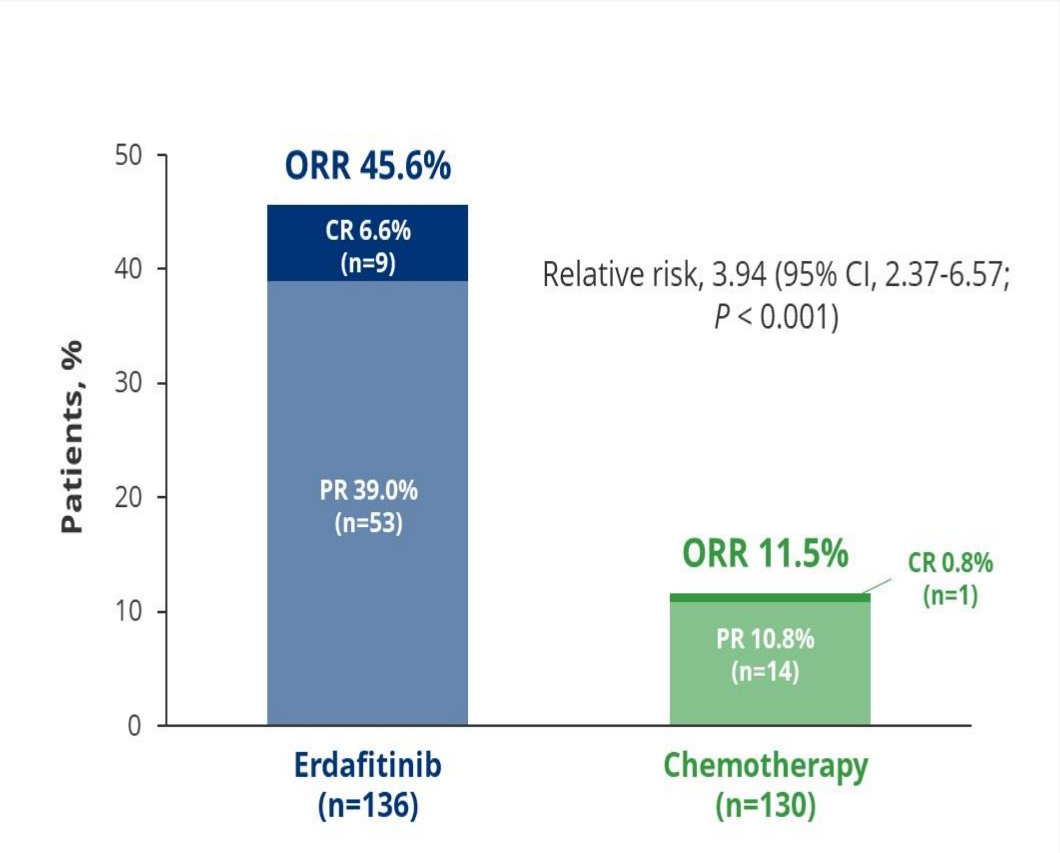


No. at risk													
Erdafitinib	136	90	39	24	12	7	3	3	3	2	1	1	0
Chemotherapy	130	43	23	9	4	2	2	1	1	0	0	0	0

- Median PFS was 5.6 versus 2.7 months for erdafitinib versus chemotherapy
- Erdafitinib reduced the risk of progression or death by 42% versus chemotherapy
  - HR, 0.58 (95% CI, 0.44-0.78; *P* = 0.0002)

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Objective Response Rate Was Significantly Higher for Erdafitinib Versus Chemotherapy[a]



CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response.
[a]Responses were best overall response per investigator assessment.

The Safety Profiles Were Consistent With the Known Profiles of Erdafitinib and Chemotherapy (1/2)

Patients with AEs, n (%)[a]	Erdafitinib (n=135)	
	Any grade	Grade 3-4
≥1 treatment-related AE	131 (97.0)	62 (45.9)
Hyperphosphatemia	106 (78.5)	7 (5.2)
Diarrhea	74 (54.8)	4 (3.0)
Stomatitis	62 (45.9)	11 (8.1)
Dry mouth	52 (38.5)	0
PPE syndrome	41 (30.4)	13 (9.6)
Onycholysis	31 (23.0)	8 (5.9)
Patients who discontinued study treatment, n (%)		
Discontinuation due to treatment-related AEs	11 (8.1%)[b]	

- **In the erdafitinib group:**
  - 18 patients (13.3%) had treatment-related serious AEs
  - 1 treatment-related death occurred[c]
  - AEs with erdafitinib were mostly manageable with dose modifications and supportive care
- **In the chemotherapy group:**
  - 27 patients (24.1%) had treatment-related serious AEs
  - 6 treatment-related deaths occurred[d]

Patients with AEs, n (%)[e]	Chemotherapy (n=112)	
	Any grade	Grade 3-4
≥1 treatment-related AE	97 (86.6)	52 (46.4)
Anemia	31 (27.7)	7 (6.3)
Alopecia	24 (21.4)	0
Nausea	22 (19.6)	2 (1.8)
Neutropenia	21 (18.8)	15 (13.4)
Leukopenia	13 (11.6)	9 (8.0)
Febrile neutropenia	9 (8.0)	10 (8.9)
Patients who discontinued study treatment, n (%)		
Discontinuation due to treatment-related AEs	15 (13.4)[f]	

[a]AEs by preferred term are listed if events of any grade occurred in ≥30% of patients in the erdafitinib group or if events of grade 3-4 occurred in ≥5% of patients.
[b]Most frequent treatment-related AEs leading to discontinuation of erdafitinib included eye disorders (3 patients) and skin and subcutaneous disorders (3 patients).
[c]Treatment-related AE leading to death was reported as sudden death.
[d]Treatment-related AEs leading to death in the chemotherapy arm included febrile bone marrow aplasia (2 patients), febrile neutropenia (1 patient), septic shock (2 patients), and atypical pneumonia (1 patient).
[e]AEs by preferred term are listed if events of any grade occurred in ≥20% of patients in the chemotherapy group or if events of grade 3-4 occurred in ≥5% of patients.
[f]Most frequent treatment-related AEs leading to discontinuation of chemotherapy included blood and lymphatic system disorders (5 patients) and infections and infestations (3 patients).
AE, adverse event; PPE, palmar-plantar erythrodysesthesia.

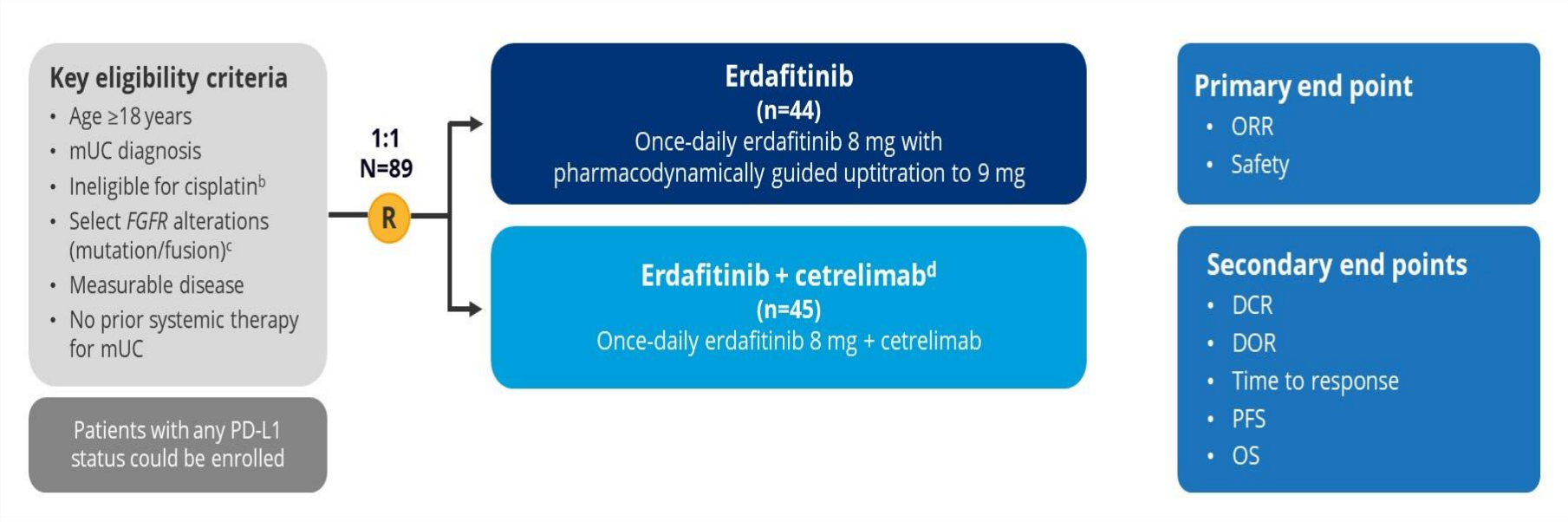
Erdafitinib Versus Erdafitinib Plus Cetrelimab for Patients With Metastatic Urothelial Carcinoma and Fibroblast Growth Factor Receptor Alterations: Final Results From the Phase 2 NORSE Study

Arlene Siefker-Radtke[1], Tom Powles[2], Victor Moreno[3], Taek Won Kang[4], Irfan Cicin[5], Angela Girvin[6], Sydney Akapame[6], Spyros Triantos[6], Anne O'Hagan[6], Wei Zhu[7], Meggan Tammaro[6], Yohann Loriot[8]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Barts Cancer Institute, Experimental Cancer Medicine Centre, Queen Mary University of London, St. Bartholomew's Hospital, London, UK; [3]START Madrid-FJD, Fundación Jiménez Díaz, University Hospital, Madrid, Spain; [4]Department of Urology, Chonnam National University Medical School, Gwangju, Republic of Korea; [5]Department of Medical Oncology, Trakya University Faculty of Medicine, Edirne, Turkey; [6]Janssen Research & Development, Spring House, PA; [7]Janssen Research & Development, Raritan, NJ; [8]Institut Gustave Roussy, Université Paris-Sud, Université Paris-Saclay, Villejuif, France

Presented at the 2023 ASCO Annual Meeting; June 2-6, 2023; Chicago, IL, USA.

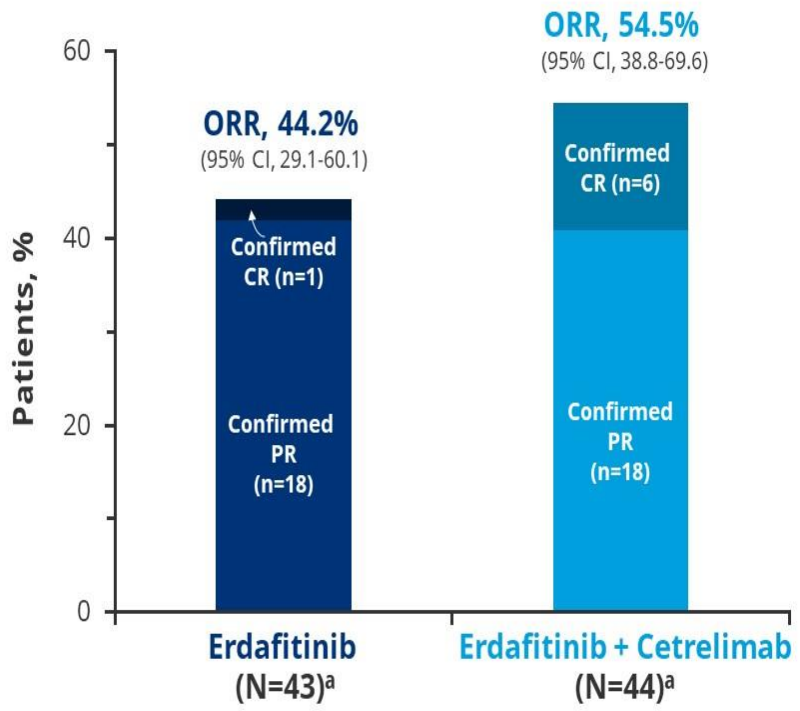
NORSE Phase 2 Study Design[a]



- Molecular eligibility was determined by central or local testing; a total of 1430 patients underwent central molecular screening[c]
- **No formal statistical comparisons** between arms were prespecified

[a]Data cutoff was December 19, 2022.
[b]Cisplatin-ineligible patients were defined as meeting ≥1 of the following criteria: (1) impaired renal function defined as calculated by Cockcroft-Gault (≥30 to <60 mL/min), (2) Grade ≥2 peripheral neuropathy, (3) Grade ≥2 hearing loss, or (4) ECOG Performance Status 2.
[c]Central or local *FGFR* testing. Local test reports were submitted for central verification, and archival tumor tissue and blood samples were submitted for retrospective confirmation of *FGFR* status (retrospective central confirmation did not affect the patient's study eligibility). Central testing was based on archival or fresh biopsy tumor tissue.
[d]6 patients in the erdafitinib plus cetrelimab group were uptitrated before uptitration was discontinued in the erdafitinib plus cetrelimab group following protocol amendment 3.
DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; FGFR, fibroblast growth factor receptor; mUC, locally advanced or metastatic urothelial carcinoma; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; R, randomization.

ORR of 44% and 55% Was Observed With Erdafitinib and Erdafitinib + Cetrelimab, Respectively



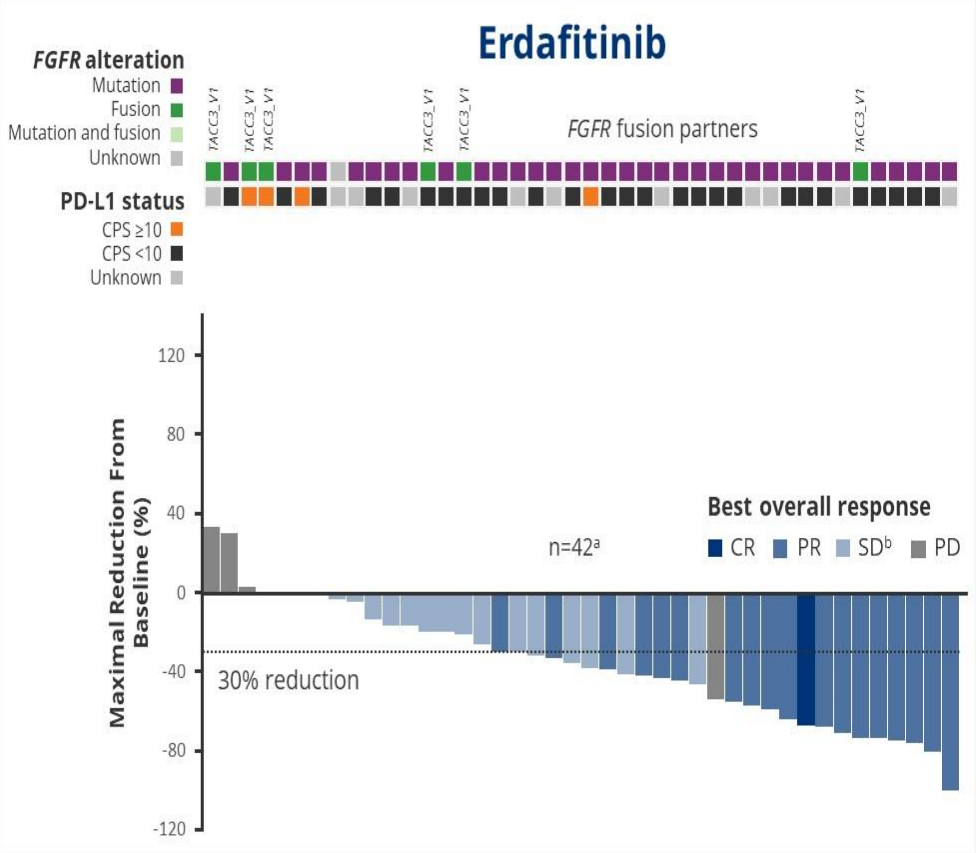
Responses are investigator assessed.

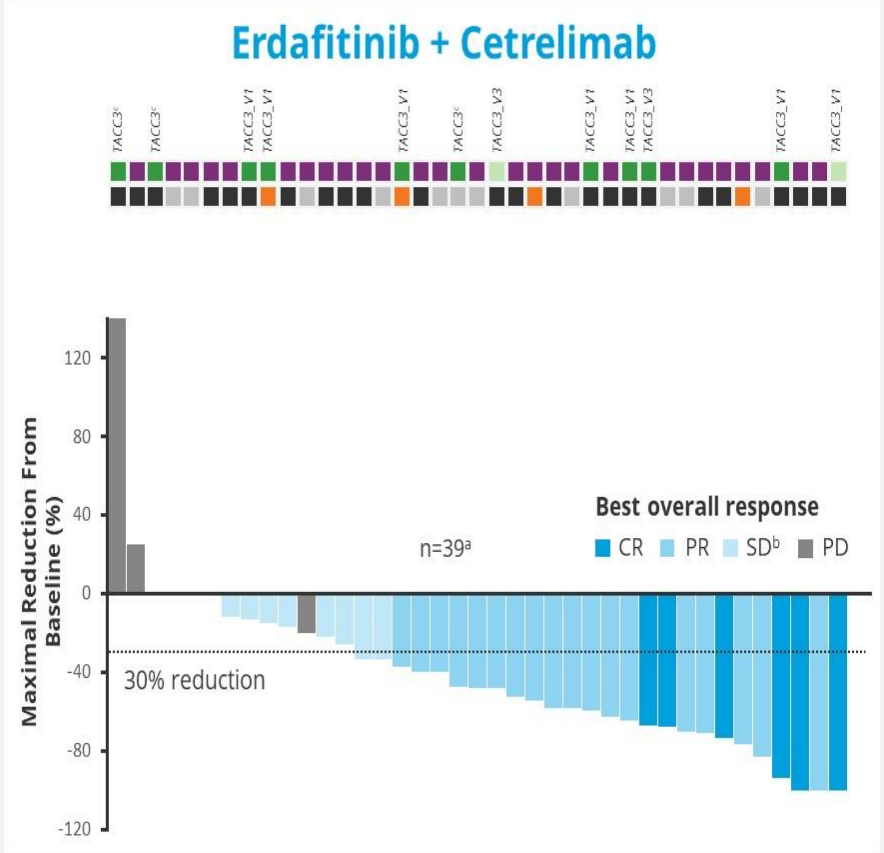
- ORR with erdafitinib monotherapy was consistent with previous results in *FGFR*-altered mUC, and responses were durable
- ORR >50% was observed with combination therapy, with a durable DOR
  - For patients with CR in the combination arm (n=6), median DOR has not been reached
- In patients with CPS <10, ORR was 46.4% in monotherapy and 50.0% in combination arm
  - Data are limited in patients with PD-L1 high status (CPS ≥10)

	Erdafitinib (N=43)	Erdafitinib + Cetrelimab (N=44)
DCR, median (95% CI), %	88.4 (74.9-96.1)	79.5 (64.7-90.2)
DOR, median (95% CI), months	9.72 (4.6-NE)	11.10 (8.8-NE)

[a]1 patient in the erdafitinib group and 5 patients in the erdafitinib plus cetrelimab group were inevaluable.
CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; mUC, locally advanced or metastatic urothelial carcinoma; NE, not evaluable; ORR, objective response rate; PR, partial response.

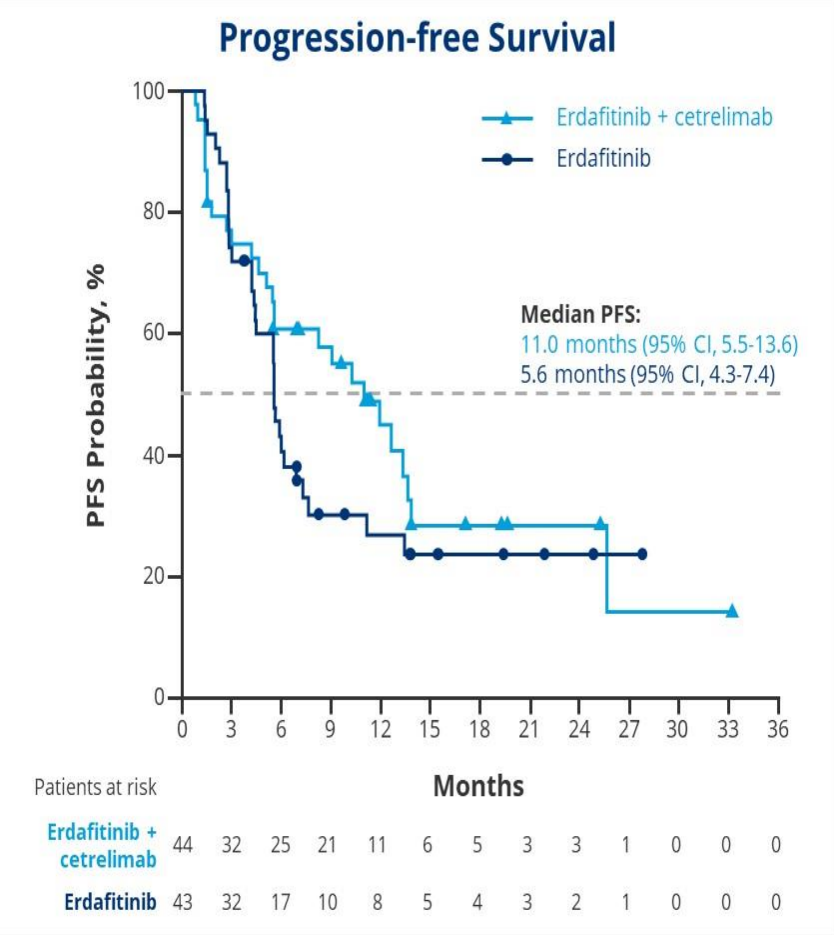
Erdafitinib Alone and in Combination With Cetrelimab Showed Responses in the Cisplatin-Ineligible Population

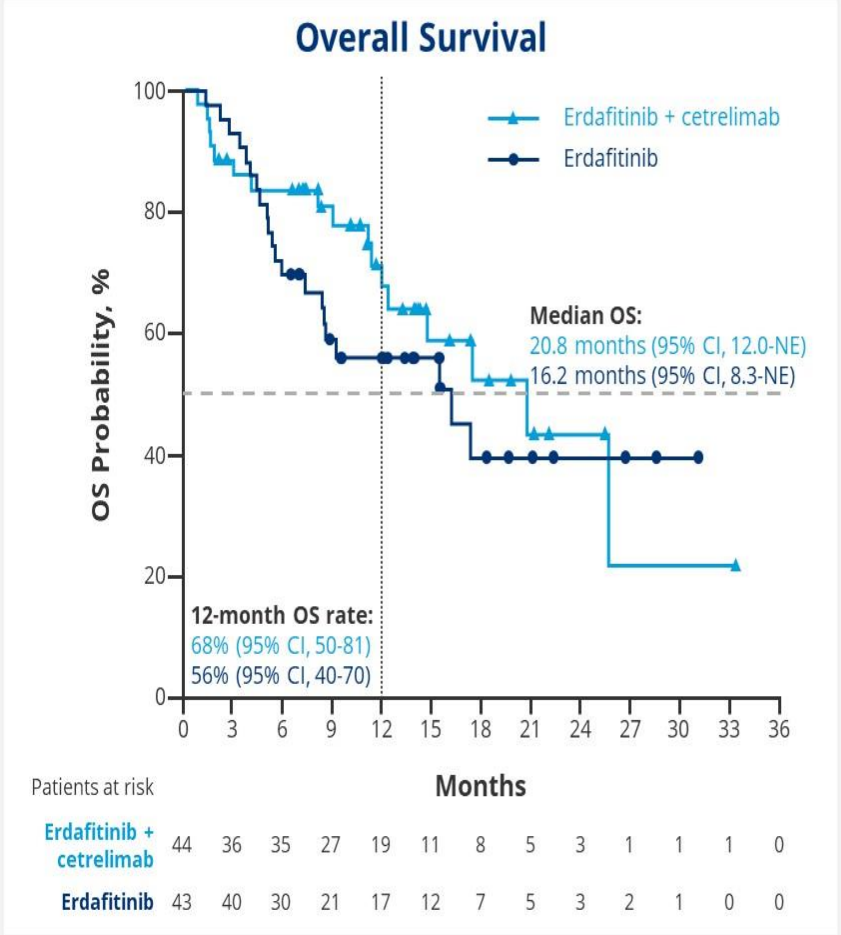




[a]1 patient in the erdafitinib group and 5 patients in the erdafitinib plus cetrelimab group were inevaluable.
[b]For a response to qualify as SD, follow-up measurements must have met the stable disease criteria at least once at a minimum interval ≤6 weeks after the first dose of study agent.
[c]*FGFR-TACC* fusion was detected by local testing or central blood sample, but not confirmed by central tissue testing.
CPS, combined positive score; CR, complete response; FGFR, fibroblast growth factor receptor; PD, disease progression; PR, partial response; SD, stable disease.

PFS and OS Underscore Durable Responses to the Erdafitinib + Cetrelimab Combination (Median Follow-up 14 Months)





CI, confidence interval; NE, not evaluable; OS, overall survival; PFS, progression-free survival.

2023 ASCO ANNUAL MEETING

MULTICENTER RANDOMIZED PHASE III OF DOSE DENSE MVAC OR GC AS PERIOPERATIVE CHEMOTHERAPY FOR MUSCLE INVASIVE BLADDER CANCER

Overall Survival at 5 years in the GETUG/AFU V05 VESPER trial

Ch Pfister, G Gravis, A Flechon, C Chevreau, H Mahammedi, B Laguerre, A Guillot,

F Joly, Y Allory, V Harter and S Culine for the Vesper trial investigators

Getug

Association Française d'Urologie
www.urofrance.org

Trial design (1)

Chemotherapy

- **4 cycles of GC** — Gemcitabine 1250 mg/m^2 d1 and d8; Cisplatin 70 mg/m^2 d1 — **every 3 weeks**
- **6 cycles of ddMVAC** — Methotrexate 30 mg/m^2 d1; Vinblastine 3 mg/m^2 d2; Doxorubicin 30 mg/m^2 d2; Cisplatin 70 mg/m^2 d2; ***+ G-CSF support from d3 to d9*** — **every 2 weeks**

Trial design (2)

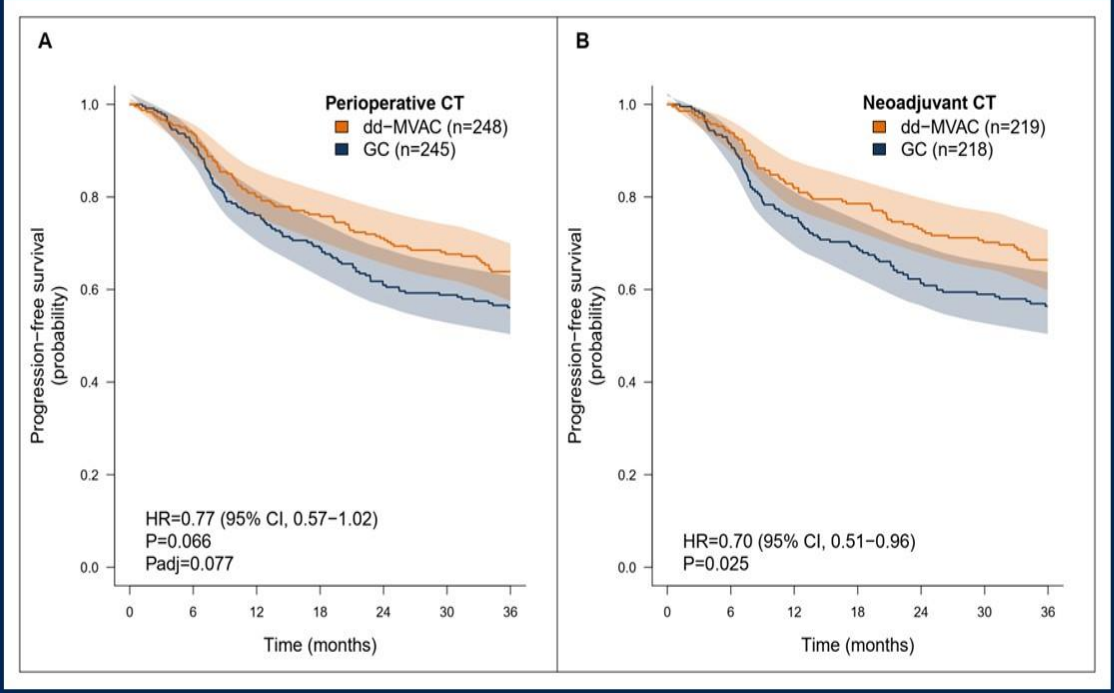
Inclusion criteria

- Pure or mixed urothelial bladder cancer *(neuroendocrine excluded)*
- ECOG PS < 2 and all criteria for cisplatin eligibility
- Written informed consent

AND

- ≥ T2, N0 *(LN ≤ 10 mm on CT scan)*, M0 (Neoadjuvant CT)
- > pT2 or pN+ and M0 (Adjuvant CT)

PFS at 3 years

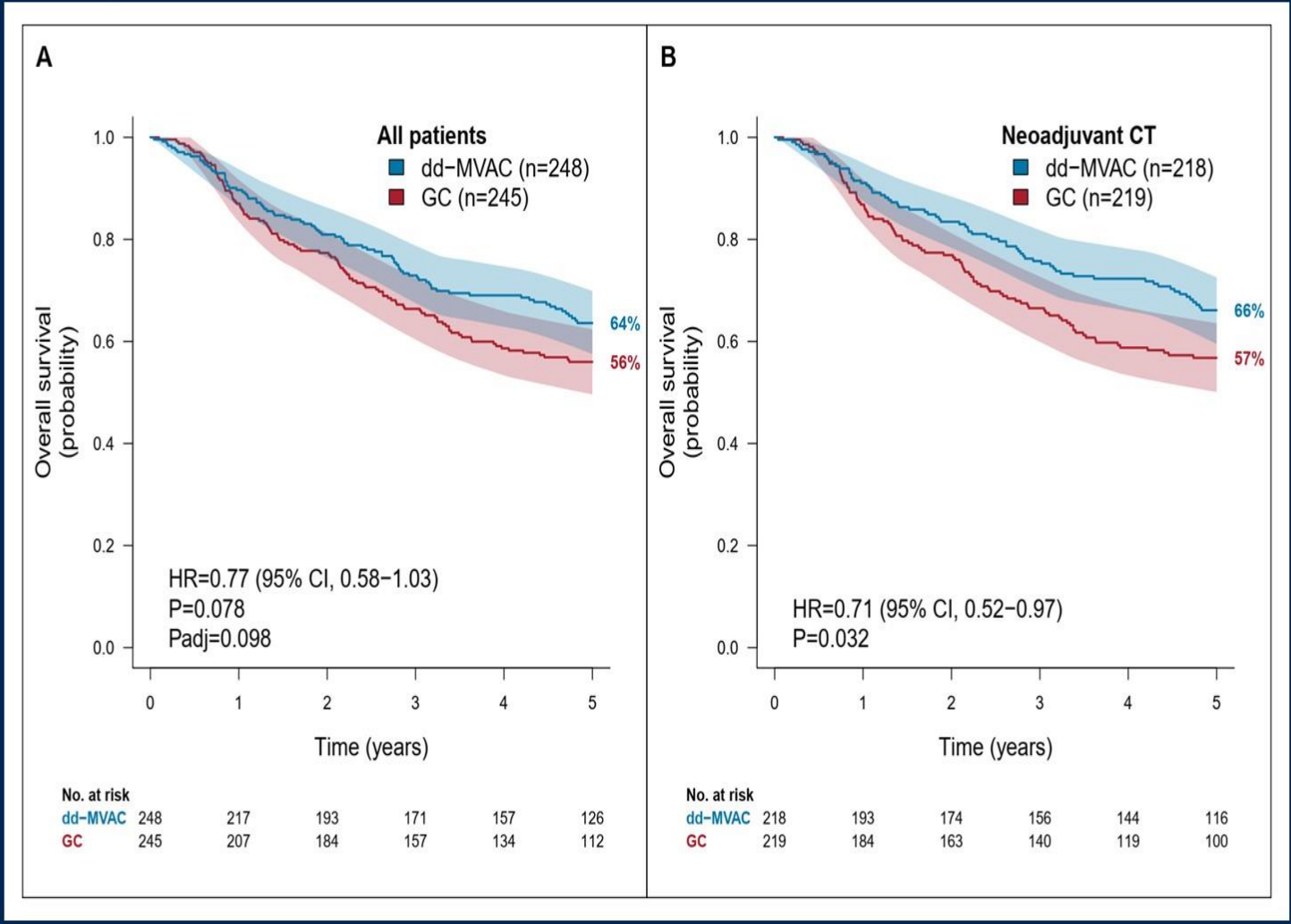


Perioperative dd-MVAC improve 3-y PFS over GC

In the neoadjuvant group, better bladder tumor local control with a significant improvement on 3-y PFS in the dd-MVAC arm

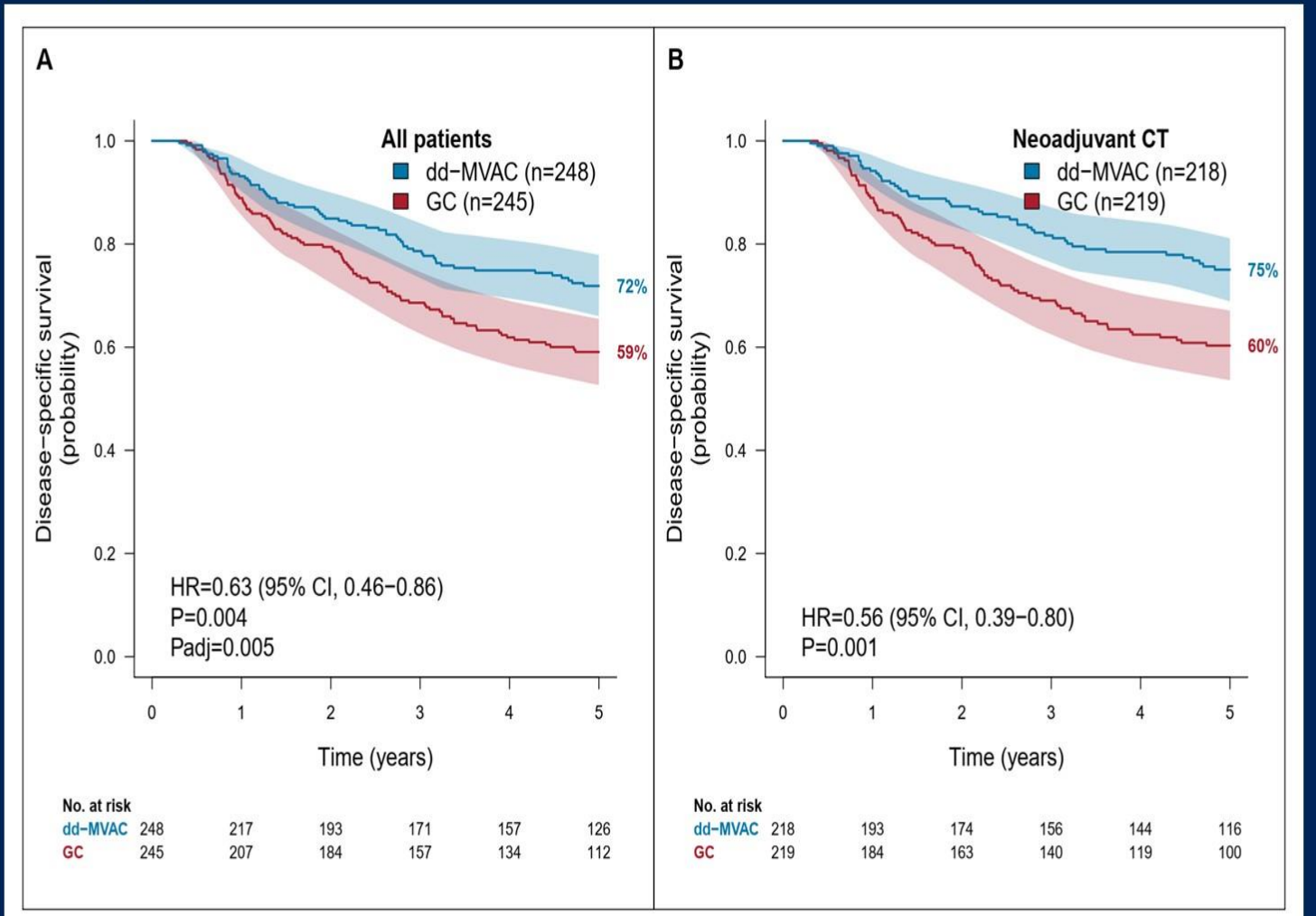
Pfister et al. J Clin Oncol 2022

Results (1) Overall Survival at 5 years



Results (2)

Disease-specific Survival



Results (3)

Causes of Death

	GC	dd-MVAC
Bladder cancer progression	94	63
Toxic death	1	3
Cardiovascular event	3	5
Second cancer	2	2
Intercurrent disease	2	7
Unknown cause of death without relapse	1	5
Other undocumented death	1	1

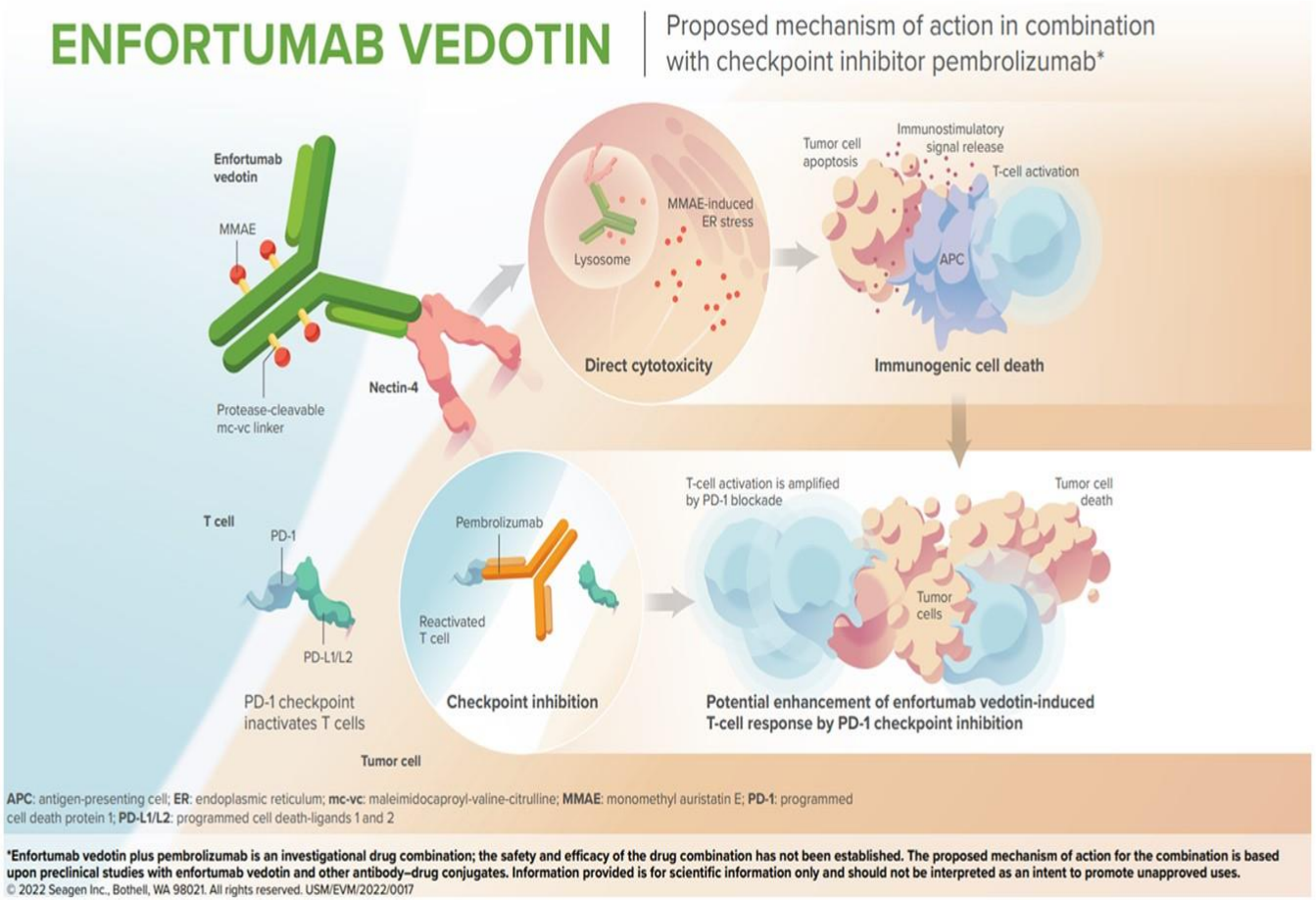
2023 ASCO ANNUAL MEETING

Study EV-103 Dose Escalation/Cohort A: Long-term Outcome of Enfortumab Vedotin + Pembrolizumab in First-line (1L) Cisplatin-ineligible Locally Advanced or Metastatic Urothelial Carcinoma (la/mUC) with Nearly 4 Years of Follow-up

Shilpa Gupta, MD[1]; Jonathan E. Rosenberg, MD[2]; Rana R. McKay, MD[3]; Thomas W. Flaig, MD[4]; Daniel Peter Petrylak, MD[5]; Christopher J. Hoimes, DO[6]; Terence W. Friedlander, MD[7]; Mehmet Asim Bilen, MD[8]; Sandy Srinivas, MD[9]; Earle Burgess, MD[10]; Jaime R. Merchan, MD[11]; Scott Tagawa, MD[12]; Jason Brown, MD[13]; Yao Yu, PhD[14]; Anne-Sophie Carret, MD[14]; Heidi S. Wirtz, PharmD, PhD[14]; Maria Guseva, MD, PharmD[15]; Blanca Homet Moreno, MD, PhD[16]; Matthew I. Milowsky, MD[17]

[1]Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH, USA; [2]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; [3]University of California San Diego, San Diego, CA, USA; [4]University of Colorado Comprehensive Cancer Center, Aurora, CO, USA; [5]Yale Cancer Center, New Haven, CT, USA; [6]Duke Cancer Institute, Duke University, Durham, NC, USA; [7]University of California San Francisco Medical Center, San Francisco, CA, USA; [8]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [9]Stanford University Medical Center, Stanford, CA, USA; [10]Atrium Health Levine Cancer Institute, Charlotte, NC, USA; [11]University of Miami, Miami, FL, USA; [12]Weill Cornell Medical Center, New York, NY, USA; [13]University Hospitals Cleveland Medical Center, Cleveland, OH, USA; [14]Seagen Inc, Bothell, WA, USA; [15]Astellas Pharma, Northbrook, IL, USA; [16]Merck & Co., Inc., Rahway, NJ, USA; [17]University of North Carolina, Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA

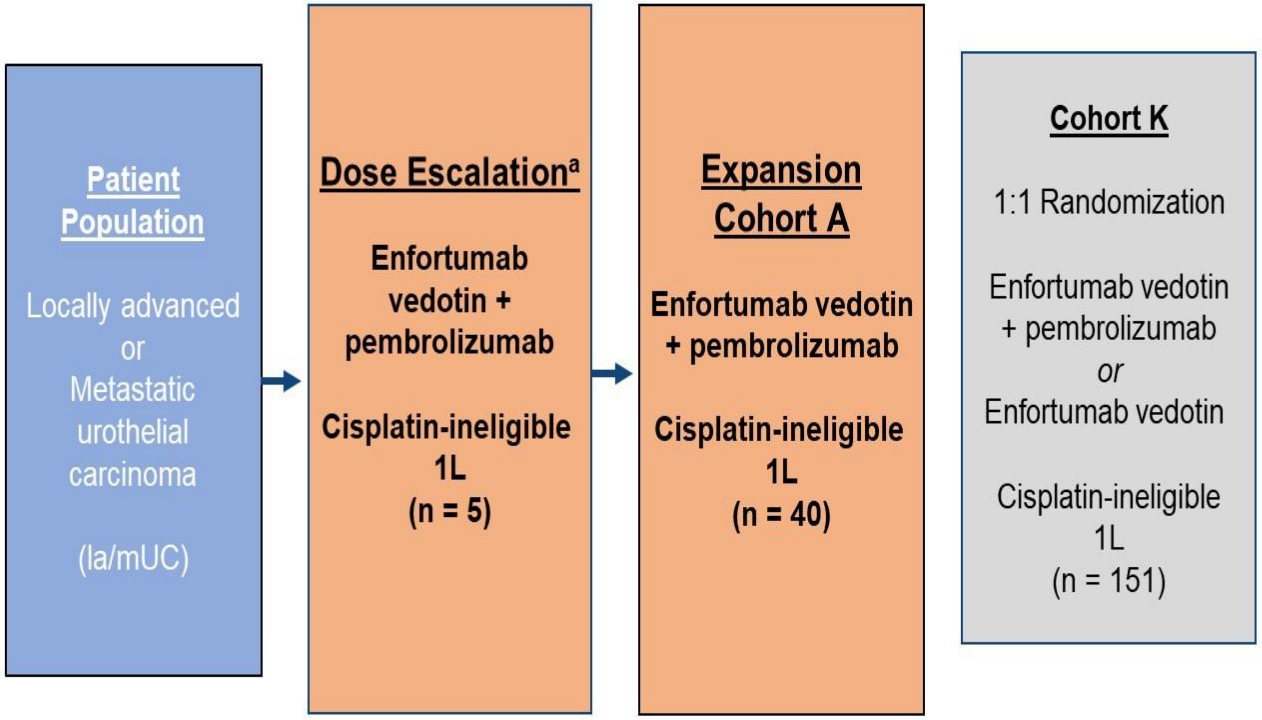
Rationale of Combining Enfortumab Vedotin and Pembrolizumab



*Enfortumab vedotin plus pembrolizumab is an investigational drug combination; the safety and efficacy of the drug combination has not been established. The proposed mechanism of action for the combination is based upon preclinical studies with enfortumab vedotin and other antibody–drug conjugates. Information provided is for scientific information only and should not be interpreted as an intent to promote unapproved uses.

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).

Overall Objective Response Rates by BICR

High confirmed ORR (73.3%) with high concordance rate between BICR and INV assessments

	Dose Escalation + Cohort A (N = 45)
Objective Response Rate, n (%)	33 (73.3)
95% CI[a] for ORR	58.1-85.4
Best Overall Response, n (%)	
Complete response	7 (15.6)
Partial response	26 (57.8)
Stable disease	5 (11.1)
Progressive disease	5 (11.1)
No assessment[b]	2 (4.4)
Disease Control Rate, n (%)	38 (84.4)
95% CI[a] for DCR	70.5-93.5
Concordance rate of BOR between BICR and INV[c] assessment	95.3%

BICR = blinded independent central review; BOR = best overall response; CI = confidence interval; DCR = disease control rate; INV = investigator; ORR = objective response rate

[a]CI was computed using the Clopper-Pearson method (Clopper 1934)

[b]Patients had no response assessment post-baseline

[c]ORR per INV assessment was 33/45 (73.3%)

Duration of Treatment and Summary of Disposition

40% of patients remain on study after ~4 years of follow-up

	Dose Escalation + Cohort A (N = 45)
Patients on treatment, n (%)	0
Patients off treatment, n (%)	45 (100%)
Reason for treatment discontinuation, n (%)	
Progressive disease per INV	19 (42.2)
Adverse event	15 (33.3)
Patient decision[a]	9 (20.0)
Physician decision[b]	1 (2.2)
Other[c]	1 (2.2)
Patients off study, n (%)	27 (60.0)
Reason for study discontinuation, n (%)	
Death	22 (48.9)
Patient withdrawal of consent	4 (8.9)
Lost to follow-up	1 (2.2)
Median follow-up (min, max)	47 months (0.66, 55.49)

INV = investigator assessment; UC = urothelial carcinoma

[a]2 patients no longer wanted treatment and/or chose hospice; 2 had no evidence of disease; 2 underwent surgery for UC (1 radical cystectomy, 1 nephroureterectomy), 1 wanted standard of care without protocol restriction, 1 had multiple adverse events, and 1 withdrew consent

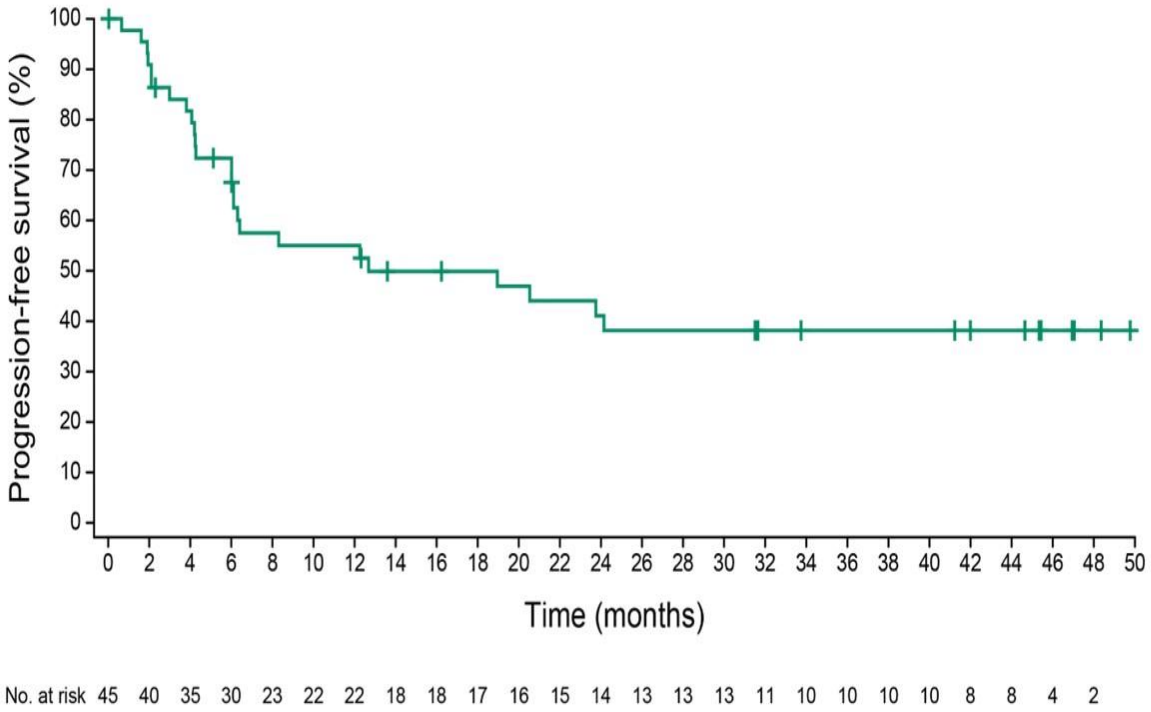
[b]Patient with sustainable partial response and treatment hold of > 1 year

[c]Patient completed 35 cycles of pembrolizumab and EV discontinued earlier due to grade 2 peripheral neuropathy

- Patients were treated for a median duration of 7 months (min, max: 0.7, 32.9)
- Patients received a median of 9 treatment cycles (min, max: 1, 36)

Progression-Free Survival by BICR

41.1% of patients were progression-free at 24 months

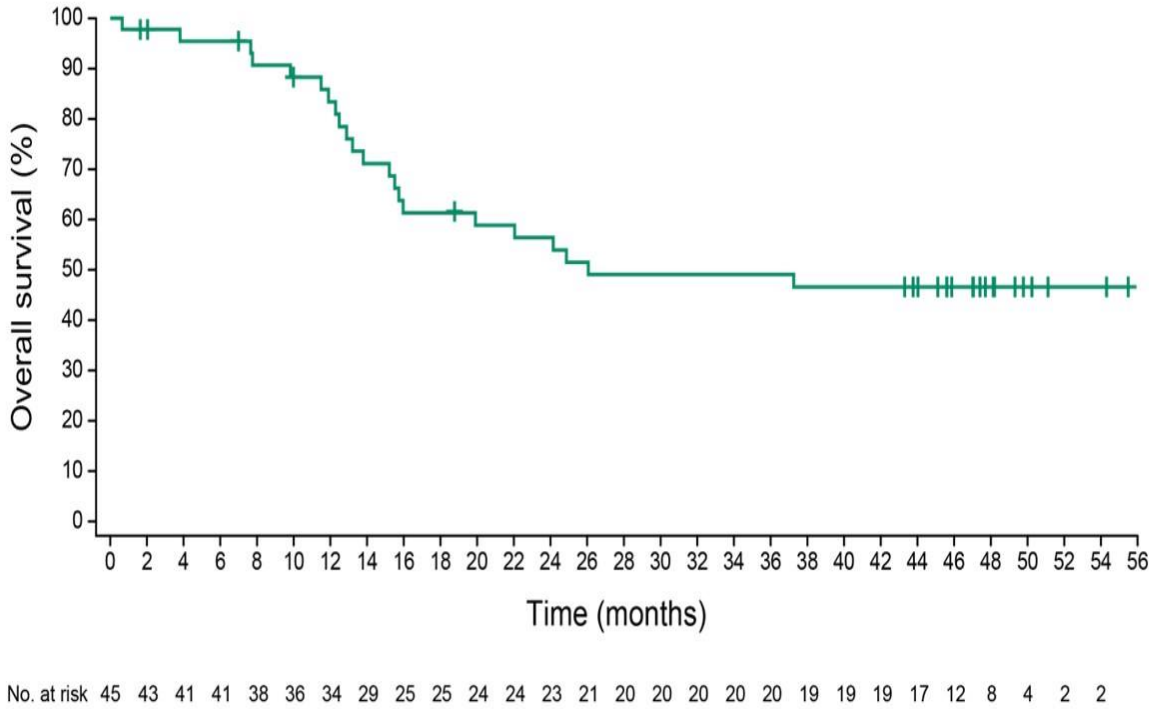


	Dose Escalation + Cohort A (N = 45)
PFS events, n	25
Median PFS (95% CI[a])	12.7 months (6.11-NE)
PFS rate[b] at:	
6 months, % (95% CI[a])	72.4 (56.47-83.26)
12 months, % (95% CI[a])	55.0 (38.84-68.58)
24 months, % (95% CI[a])	41.1 (25.69-55.88)

BICR = blinded independent central review; CI = confidence interval; NE = not estimable; PFS = progression-free survival
[a]CI was calculated using the complementary log-log transformation method (Collett, 1994)
[b]As estimated using Kaplan-Meier method

Overall Survival

Median survival exceeds 2 years



	Dose Escalation + Cohort A (N = 45)
OS events, n	22
Median OS (95% CI[a])	26.1 months (15.51-NE)
OS rate[b] at:	
6 months, % (95% CI[a])	95.4 (83.00-98.84)
12 months, % (95% CI[a])	83.4 (68.25-91.72)
24 months, % (95% CI[a])	56.4 (40.03-69.91)
Median follow-up time	47.0 months

CI = confidence interval; NE = not estimable; OS = overall survival
[a]CI was calculated using the complementary log-log transformation method (Collett, 1994)
[b]As estimated using Kaplan-Meier method

Treatment-Related Adverse Events of Special Interest for Enfortumab Vedotin

Skin reactions and PN were the most common treatment-related AESI for EV

	Dose Escalation + Cohort A (N = 45)	
	Any Grade n (%)	**Grade ≥3 n (%)**
Skin reactions	30 (66.7)	9 (20.0)
Rash maculo-papular	16 (35.6)	5 (11.1)
Rash macular	7 (15.6)	0
Peripheral neuropathy[a]	28 (62.2)	2 (4.4)
Ocular disorders	18 (40.0)	0
Dry eye	16 (35.6)	0
Blurred vision	5 (11.1)	0
Corneal disorders	1 (2.2)	0
Hyperglycemia	5 (11.1)	4 (8.9)
Infusion related reactions	3 (6.7)	1 (2.2)

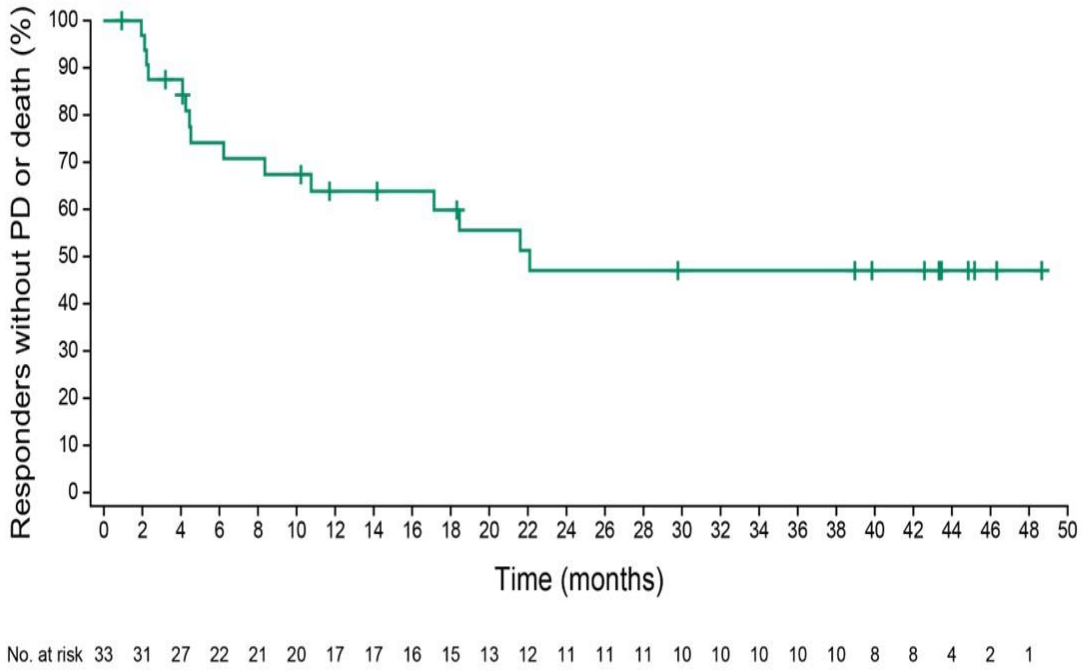
AESI = adverse events of special interest; EV = enfortumab vedotin; PN = peripheral neuropathy; TRAE = treatment-related adverse events

[a] Peripheral neuropathy Standardised MedDRA Queries (broad scope). n=8 patients had pre-existing peripheral neuropathy and n=37 did not have pre-existing peripheral neuropathy. Pre-existing condition includes medical history and conditions ongoing at baseline

- Most of the events were of low grade (1 or 2)
- The TRAEs for EV were consistent with previously observed results

Duration of Response by BICR

1L EV+P is associated with durable responses



	Dose Escalation + Cohort A (N = 45)
DOR events, n	15
Median DOR (95% CI[a])	22.1 months (8.38-NE)
Patients without PD or death at:	
6 months, % (95% CI[a])	74.1 (54.82-86.17)
12 months, % (95% CI[a])	63.9 (44.19-78.17)
24 months, % (95% CI[a])	47.0 (27.57-64.31)

BICR = blinded independent central review; CI = confidence interval; DOR = duration of response; EV = enfortumab vedotin; NE = not estimable; P = pembrolizumab, PD = progressive disease; 1L = first-line
[a]CI was calculated using the complementary log-log transformation method (Collett, 1994)

Subsequent Anticancer-Related Therapies

Patient may have received more than one subsequent anticancer therapy; systemic therapy was the most common

	Dose Escalation + Cohort A (N = 45)
Patients receiving subsequent cancer-related therapy/therapies, n (%)	27 (60.0)
Systemic therapy	22 (48.9)
Palliative radiotherapy	4 (8.9)
Surgical procedure[a]	4 (8.9)
Other[b]	1 (2.2)
First subsequent systemic therapy, n (%)	
Pembrolizumab[c]	8 (17.8)
Carboplatin-based therapy	5 (11.1)
Other[d]	4 (8.9)
Enfortumab vedotin[e]	3 (6.7)
Sacituzumab govitecan	2 (4.4)

AE = adverse event; EV = enfortumab vedotin; P = pembrolizumab; PN = peripheral neuropathy; TURBT = transurethral resection of bladder tumour; 1L = first-line

[a]Radical cystectomy (n=1), nephroureterectomy (n=1), craniotomy (n=1), TURBT (n=1)

[b]Intravesicular gemcitabine

[c]Reasons for study treatment discontinuation: AE (n=4; all PN), investigator-assessed clinical or radiographic progression (n=3), patient decision (n=1); number of cycles of study treatment received (range): 7-21

[d]Includes Cisplatin-based therapy (n=1), Gemcitabine (n=1), Erdafitinib (n=1), other (n=1)

[e]Reasons for study treatment discontinuation: investigator-assessed radiographic progression (n=2), patient decision (n=1); number of cycles of study treatment received (range): 13-36

- 3 of 8 patients who received subsequent pembrolizumab, did so following progression on EV+P
- 2 of 3 patients who received subsequent EV, did so following progression on EV+P

2023 ASCO® ANNUAL MEETING

Adjuvant nivolumab plus ipilimumab vs placebo for patients with localized renal cell carcinoma at high risk of relapse after nephrectomy: subgroup analyses from the phase 3 CheckMate 914 (Part A) trial

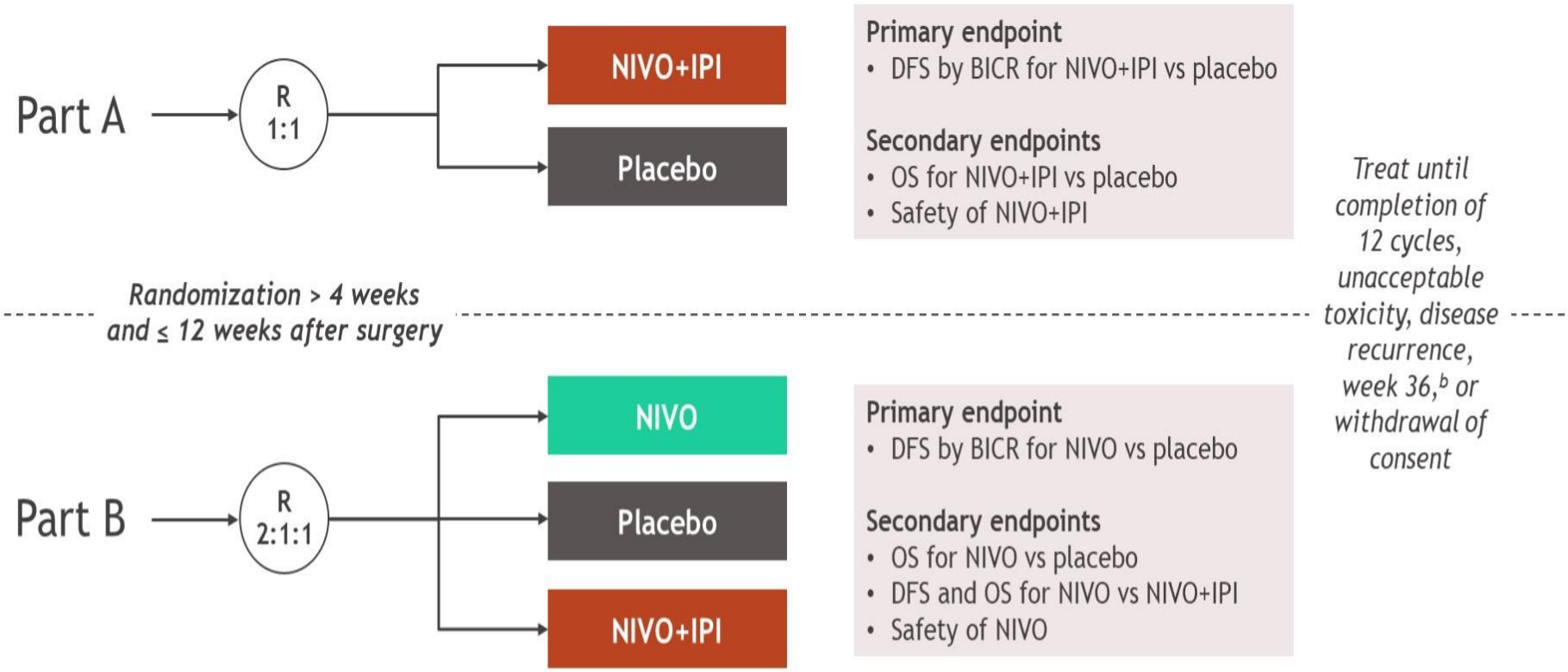
Robert J. Motzer,[1] Paul Russo,[1] Viktor Grünwald,[2] Yoshihiko Tomita,[3] Philippe Barthélémy,[4] Jeffrey C. Goh,[5] Hernan Javier Cutuli,[6] Steven Blum,[7] Sai Vikram Vemula,[7] Burcin Simsek,[7] Julia Spiridigliozzi,[7] Aleksander Chudnovsky,[7] Axel Bex[8,9]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Clinic for Internal Medicine (Tumor Research) and Clinic for Urology, West-German Cancer Center Essen, University Hospital Essen, Essen, Germany; [3]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [4]Institut de Cancérologie Strasbourg Europe, Strasbourg, France; [5]ICON Research, South Brisbane, QLD, Australia; [6]Hospital Sirio Libanes, Buenos Aires, Argentina; [7]Bristol Myers Squibb, Princeton, NJ; [8]Netherlands Cancer Institute, Amsterdam, the Netherlands; [9]University College London, London, UK

Abstract number 4506

CheckMate 914 study design (Part A and Part B)

Adult patients with localized clear cell RCC at high risk of relapse after radical or partial nephrectomy[a]



- Patient populations for Part A and Part B were mutually exclusive

[a]Stratification was based on type of nephrectomy and TNM staging. [b]Expected treatment duration of 24 weeks. Treatment could be extended up to 36 weeks to accommodate dose delays.
BICR, blinded independent central review; OS, overall survival; R, randomization; TNM, tumor, node, metastasis.

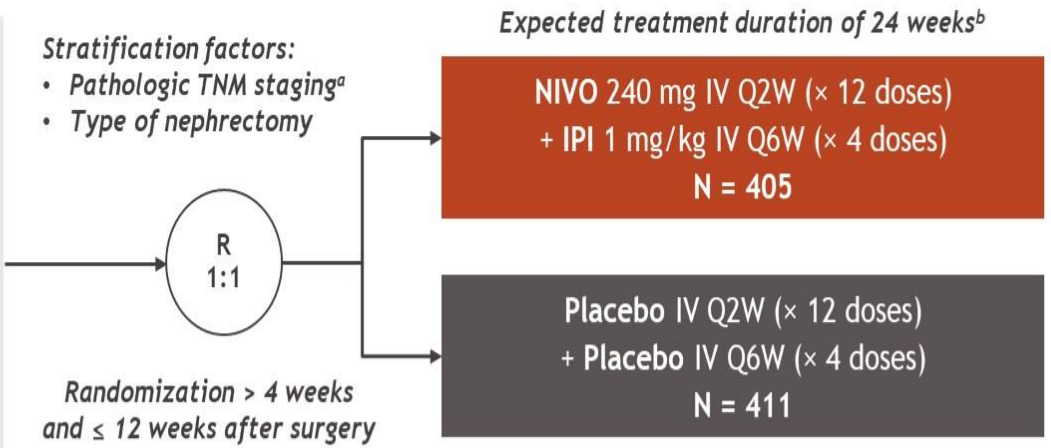
1. ClinicalTrials.gov. Accessed April 6, 2023. https://clinicaltrials.gov/ct2/show/NCT03138512.

Study design and treatment schedule (Part A)

N = 816

Key inclusion criteria[1,2]

- Radical or partial nephrectomy
- Predominant clear cell histology
- Pathologic TNM staging:
  - pT2a, G3 or G4, N0 M0/pT2b, G any, N0 M0
  - pT3, G any, N0 M0
  - pT4, G any, N0 M0/pT any, G any, N1 M0
- No evidence of residual disease or metastases after nephrectomy, confirmed by BICR

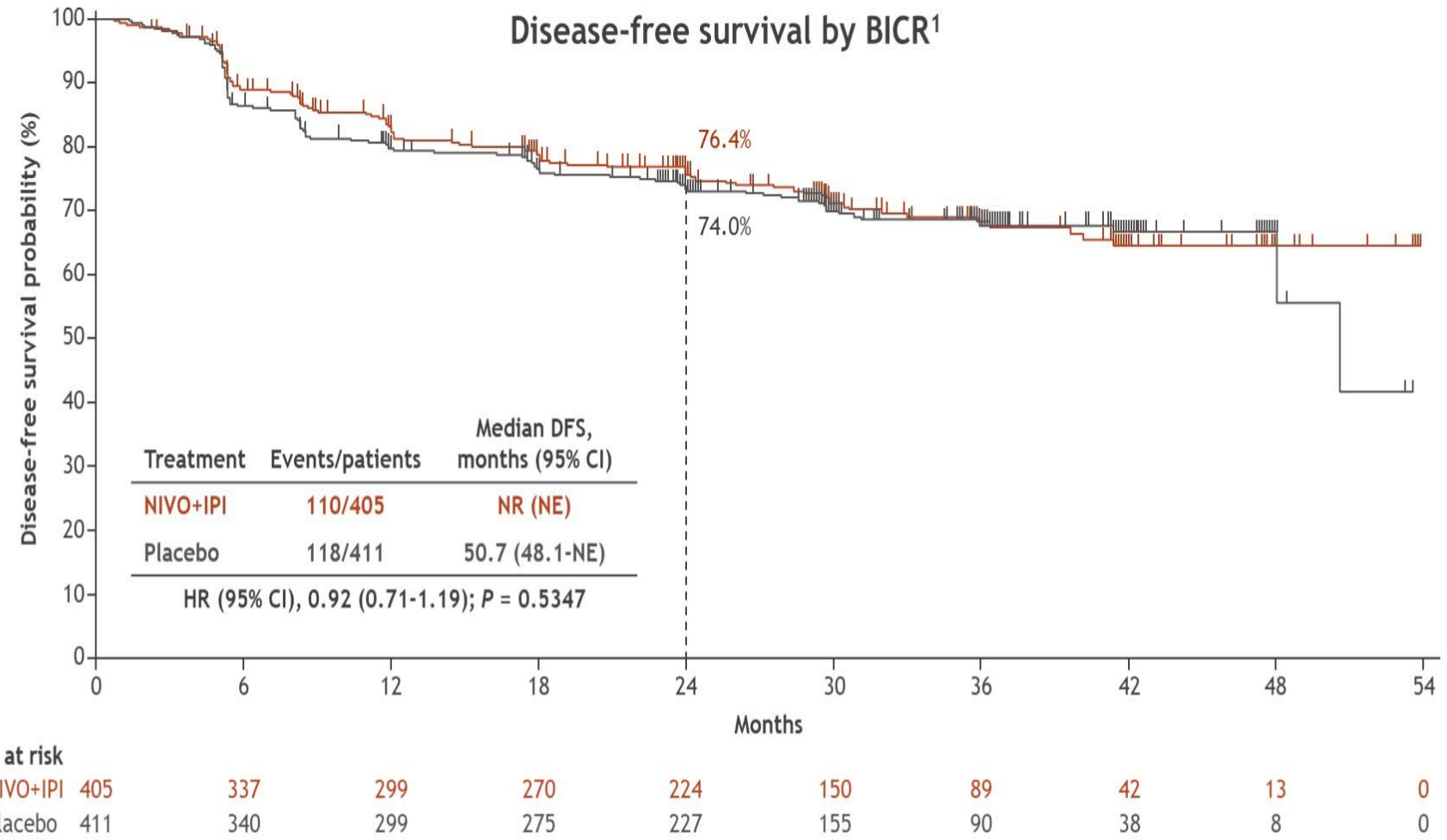


Primary endpoint: DFS by BICR for NIVO+IPI vs placebo
Secondary endpoints: OS for NIVO+IPI vs placebo, safety of NIVO+IPI

Schedule	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7		Cycle 8		Cycle 9		Cycle 10		Cycle 11		Cycle 12	
Study week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Dosing[c]	NIVO+IPI		NIVO		NIVO		NIVO+IPI		NIVO		NIVO		NIVO+IPI		NIVO		NIVO		NIVO+IPI		NIVO		NIVO	
	PBO+PBO		PBO		PBO		PBO+PBO		PBO		PBO		PBO+PBO		PBO		PBO		PBO+PBO		PBO		PBO	

Median follow-up, 37.0 months (minimum follow-up, 15.4 months).
[a]Stratification by TNM staging (pT2a, G3 or G4, N0 M0 or pT2b, G any, N0 M0 vs pT3, G any, N0 M0 vs pT4, G any, N0 M0 or pT any, G any, N1 M0). [b]Treatment could be extended up to 36 weeks to accommodate dose delays. [c]Dose given on day 1 of each cycle.
G, grade; IV, intravenously; PBO, placebo; Q×W, every × weeks.
1. ClinicalTrials.gov. Accessed April 28, 2023. https://clinicaltrials.gov/ct2/show/NCT03138512. 2. Motzer RJ, et al. *Lancet* 2023;401:821-832.

Adjuvant NIVO+IPI in CheckMate 914 (primary endpoint)



As the DFS endpoint was not met, no formal OS analysis was performed (in total, there were 33 deaths in the NIVO+IPI arm and 28 deaths in the placebo arm).

1. Motzer RJ, et al. *Lancet* 2023;401:821-832.

CI, confidence interval; HR, hazard ratio. NE, not estimable; NR, not reached.

Efficacy assessments in select subgroups

- *Pathological TNM stage*
- *RCC pathology grade*
- *Sarcomatoid features*
- *Tumor PD-L1 expression*

Key baseline characteristics *of ITT patients in select subgroups*

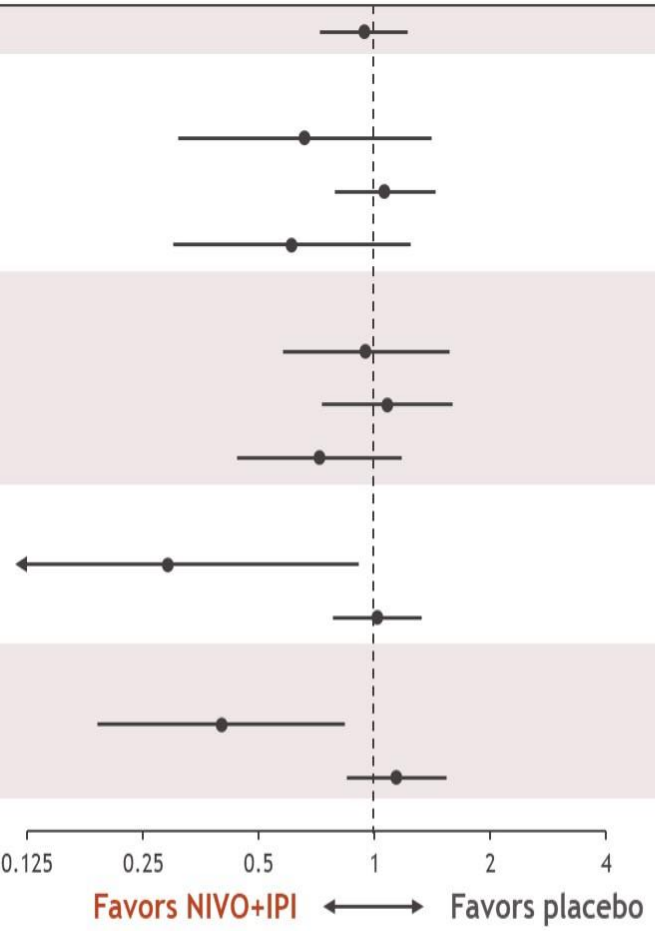
	NIVO+IPI (n = 405)	Placebo (n = 411)
Pathological TNM staging per CRF, %		
pT2a, G3 or G4, N0 M0 or pT2b, G any, N0 M0	15	14
pT3, G any, N0 M0	77	77
pT4, G any, N0 M0 or pT any, G any, N1 M0	8	9
RCC pathology grade per CRF, %[a,b]		
G1-2	34	36
G3	47	42
G4	20	22
Sarcomatoid features, %[a]	5	5
Baseline tumor PD-L1 status, %[c,d]		
≥ 1%	14	11
< 1% or indeterminate/not evaluable	75	78
Not reported	11	11

[a]RCC pathology grade and sarcomatoid status were determined by a local pathologist. [b]Data were reported using the Fuhrman grading system for the duration of enrollment. If assessment of RCC pathology grade was performed using the WHO/ISUP system, grade was correlated back to the Fuhrman system in order to assess eligibility. [c]PD-L1 testing was performed locally (Labcorp) using a validated TPS-based PD-L1 immunohistochemical assay (Dako PD-L1 IHC 28-8 pharmDx). [d]Data by tumor PD-L1 expression were analyzed from a March 2023 database lock as these data were not available from the July database lock used for all other data reported in this presentation.

CRF, case report form; ISUP, International Society of Urological Pathology; ITT, intent-to-treat (all randomized population); PD-L1, programmed death ligand 1; TPS, tumor proportion score; WHO, World Health Organization.

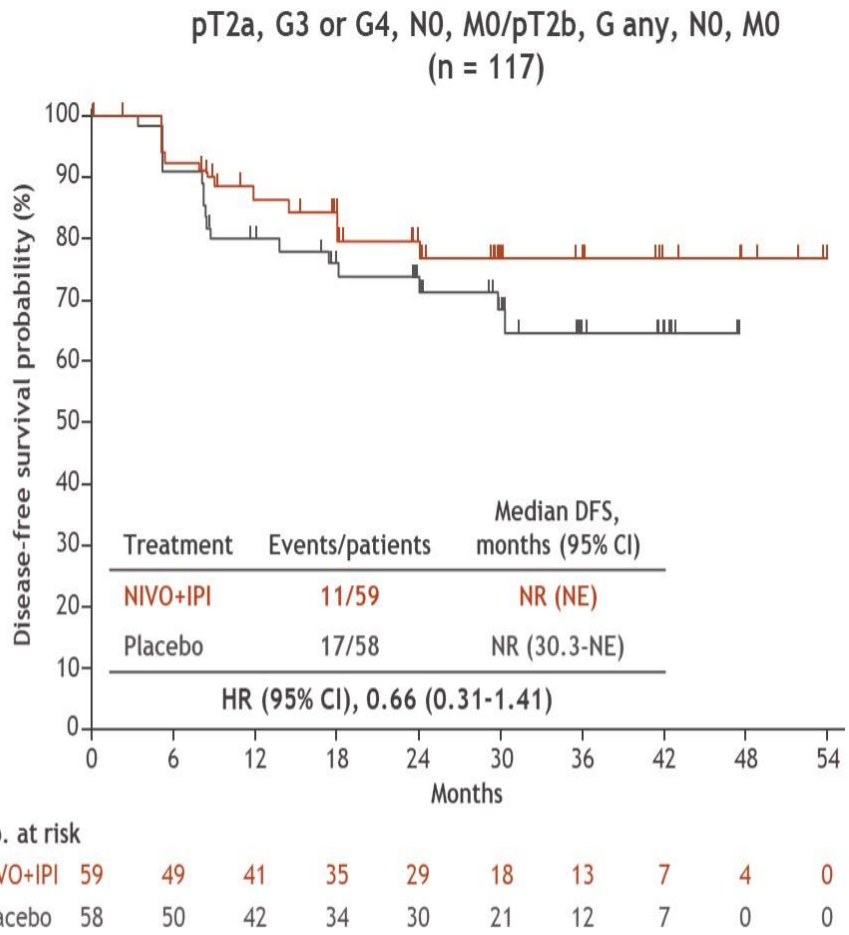
Disease-free survival per BICR *in select subgroups*

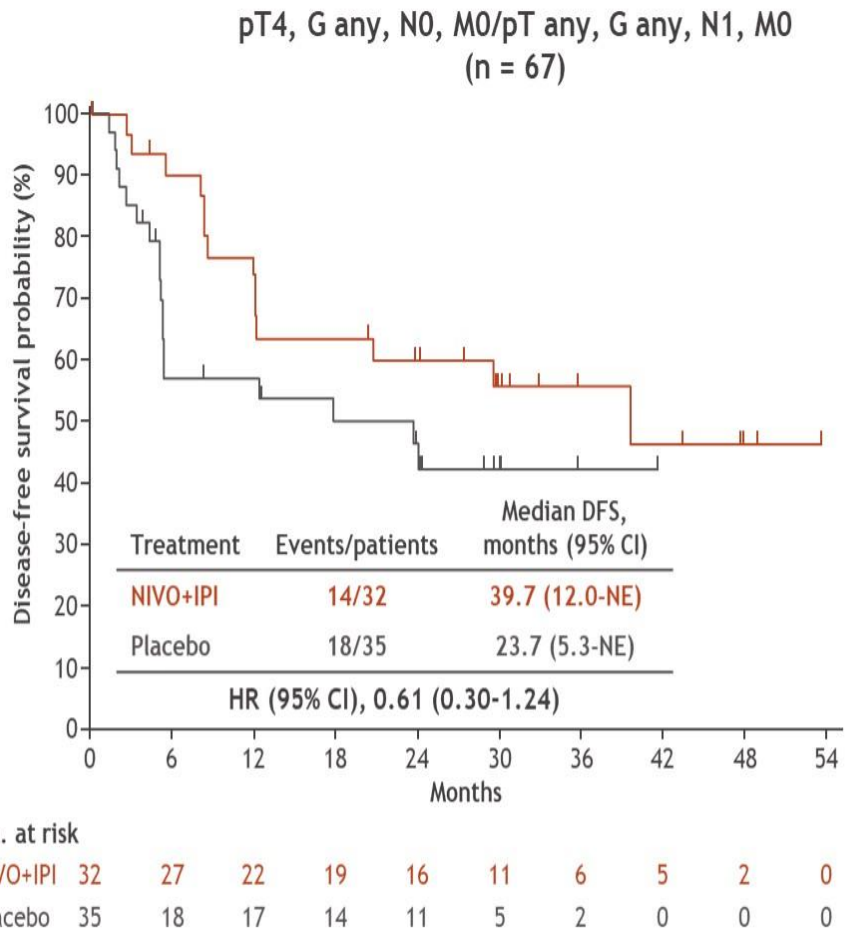
Subgroup	NIVO+IPI Events/no. of patients	Placebo Events/no. of patients	Unstratified HR for DFS (95% CI)
Overall	110/405	118/411	0.94 (0.72-1.22)
TNM staging per CRF			
pT2a, G3 or G4, N0 M0/pT2b, G any, N0 M0	11/59	17/58	0.66 (0.31-1.41)
pT3, G any, N0 M0	85/313	83/317	1.06 (0.79-1.44)
pT4, G any, N0 M0/pT any, G any, N1 M0	14/32	18/35	0.61 (0.30-1.24)
RCC pathology grade[a] per CRF			
G1-2	29/136	33/147	0.95 (0.58-1.57)
G3	54/189	47/173	1.08 (0.73-1.60)
G4	27/80	38/91	0.72 (0.44-1.18)
Sarcomatoid features			
Yes	4/19	12/21	0.29 (0.09-0.91)
No	106/386	106/390	1.02 (0.78-1.33)
Baseline tumor PD-L1 status[b]			
≥ 1%	11/56	20/46	0.40 (0.19-0.84)
< 1% or indeterminate/not evaluable	89/305	85/320	1.14 (0.85-1.54)



[a]Data were reported using the Fuhrman grading system for the duration of enrollment. If assessment of RCC pathology grade was performed using the WHO/ISUP system, grade was correlated back to the Fuhrman system in order to assess eligibility. [b]Data by tumor PD-L1 expression were analyzed from a March 2023 database lock as these data were not available from the July database lock used for all other data reported in this presentation.

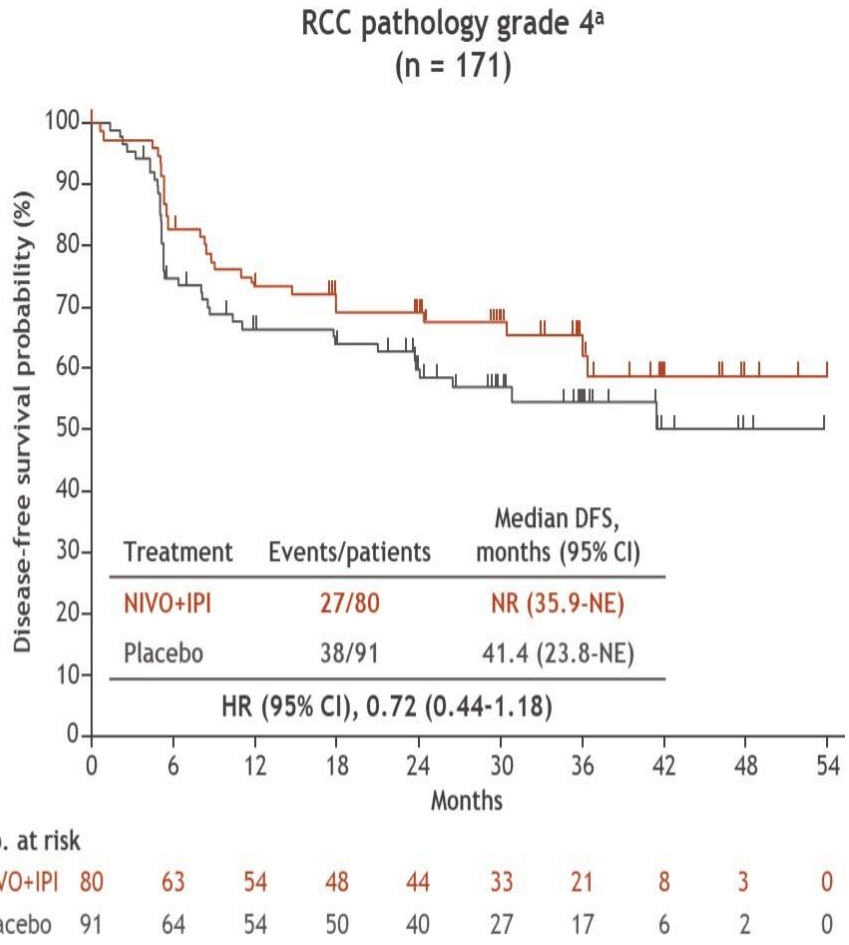
Disease-free survival per BICR *by pathological TNM stage*

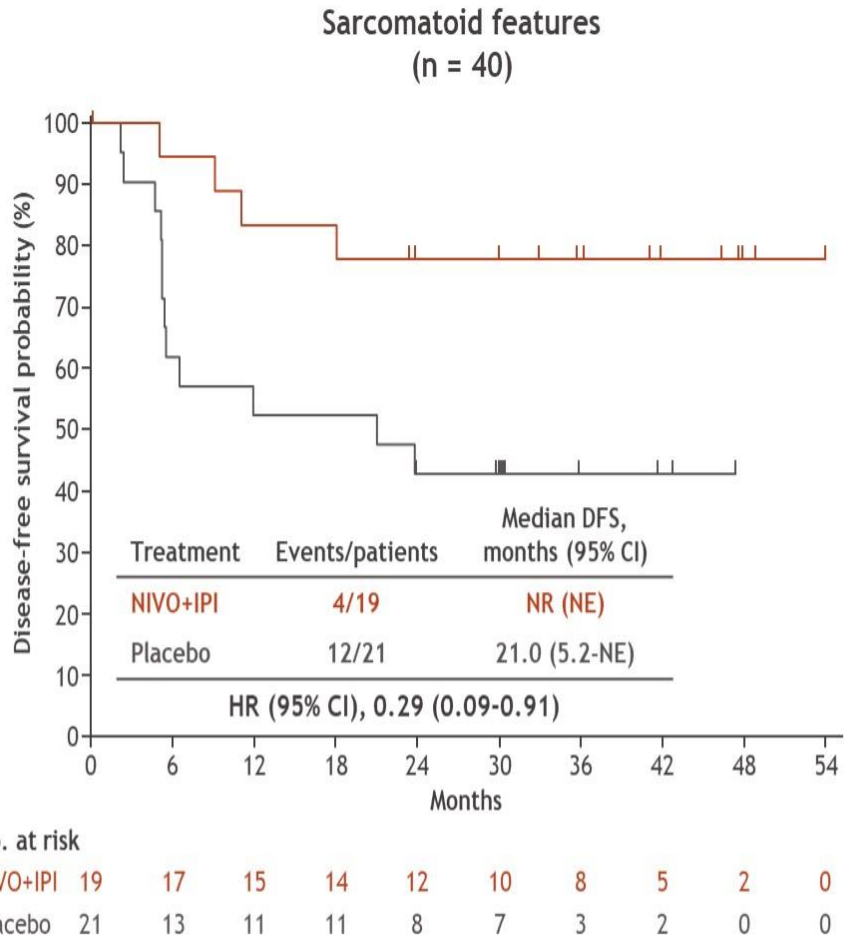




Pathological TNM stage was collected per CRF.

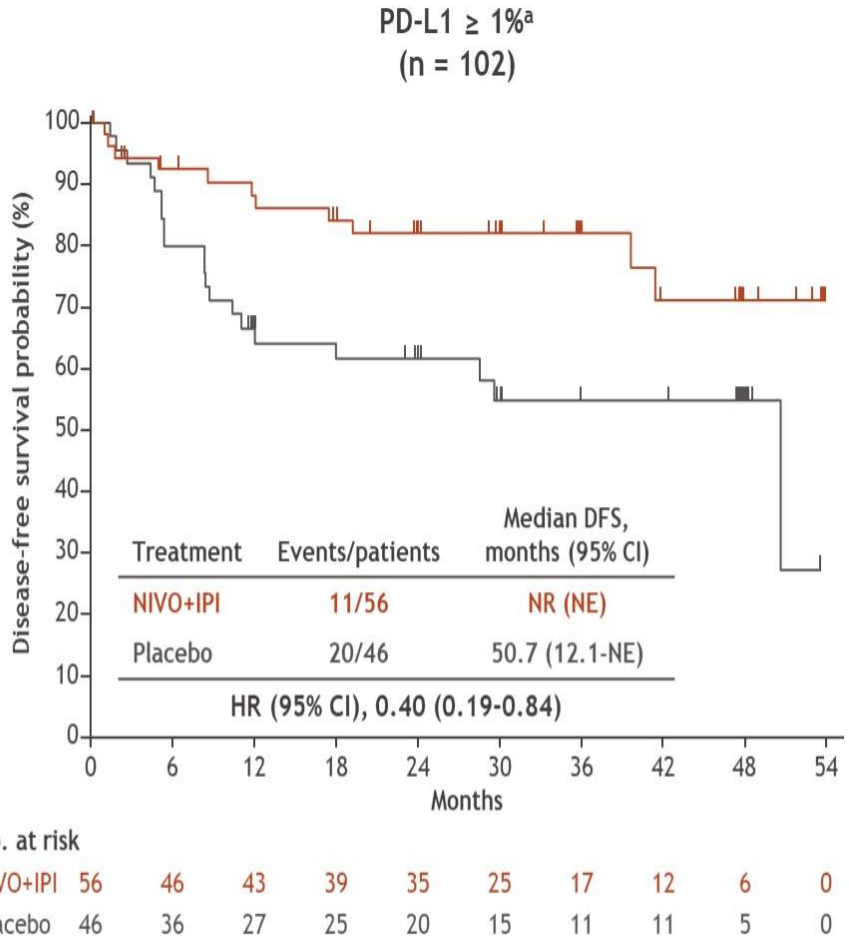
Disease-free survival per BICR *in patients with RCC pathology grade 4* or *sarcomatoid features*

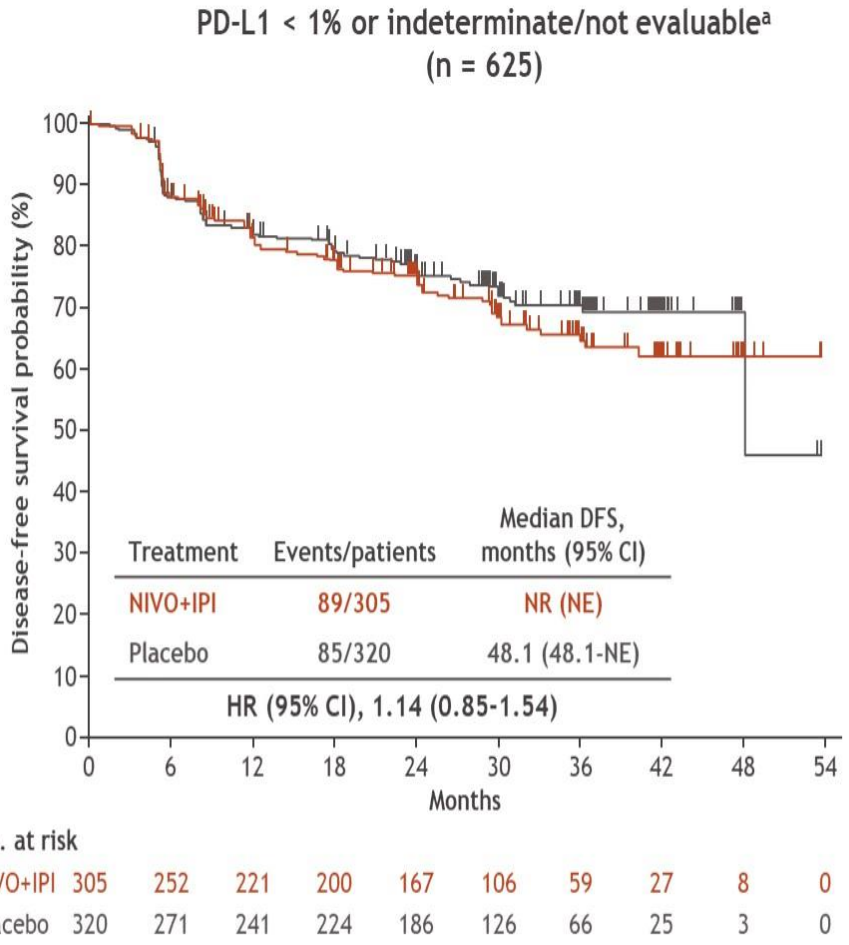




[a]Data were reported using the Fuhrman grading system for the duration of enrollment. If assessment of RCC pathology grade was performed using the WHO/ISUP system, grade was correlated back to the Fuhrman system in order to assess eligibility.

Disease-free survival per BICR *in patients by PD-L1 expression*





[a]Data by tumor PD-L1 expression were analyzed from a March 2023 database lock as these data were not available from the July database lock used for all other data reported in this presentation.

Characteristics and outcomes of patients with ≤ 6 treatment cycles

- We assessed the relationship between early treatment discontinuation and treatment outcomes
- The majority (77/132) of patients who discontinued treatment due to AEs received ≤ 6 treatment cycles (1-2 doses of the NIVO+IPI combination)
- 102 (25%) of 404 treated patients in the NIVO+IPI arm received ≤ 6 treatment cycles

Schedule	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7		Cycle 8		Cycle 9		Cycle 10		Cycle 11		Cycle 12	
Study week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Treatment	NIVO+IPI		NIVO		NIVO		NIVO+IPI		NIVO		NIVO		Treatment discontinued											
	PBO+PBO		PBO		PBO		PBO+PBO		PBO		PBO													

AE, adverse event.

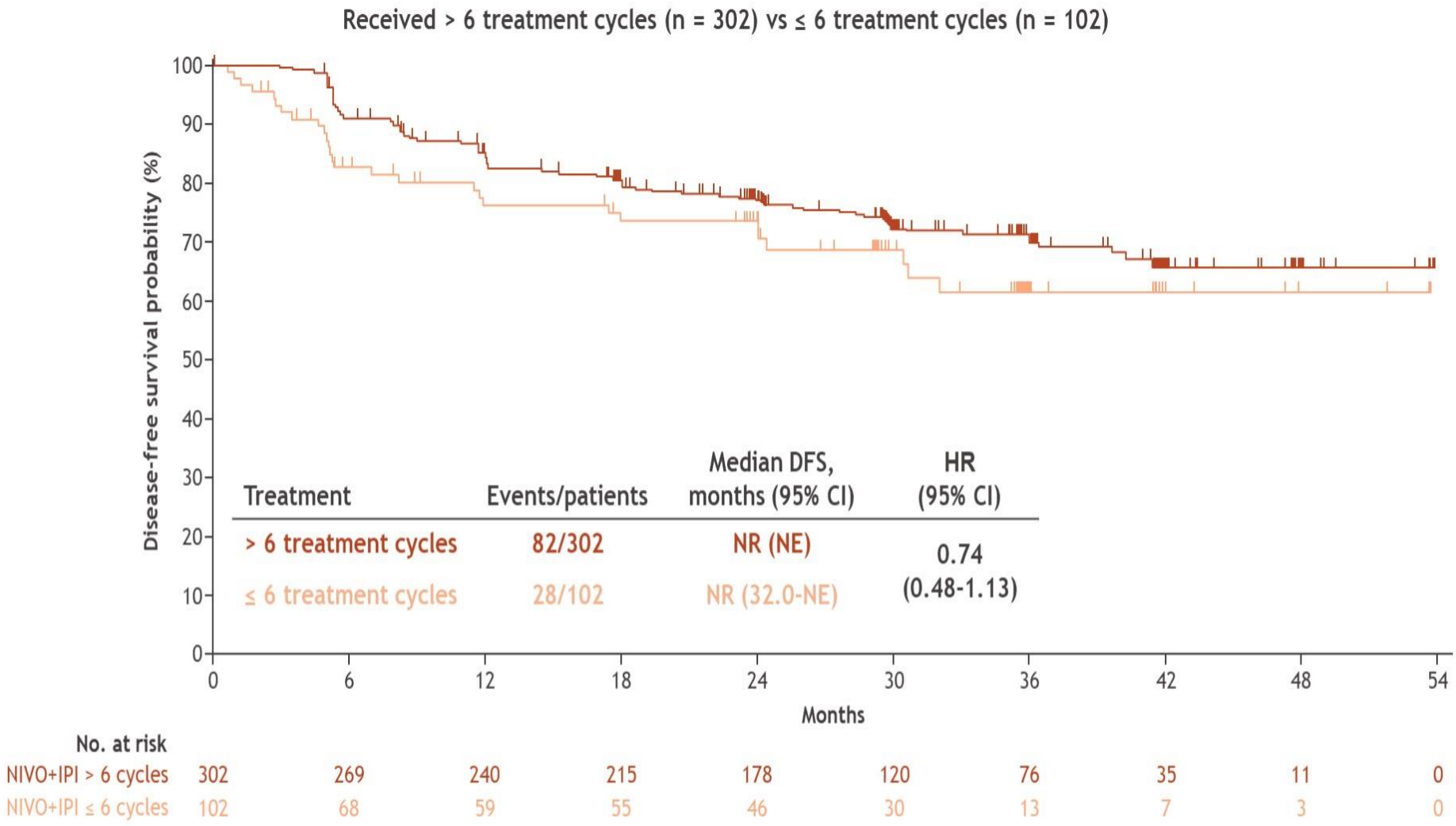
Drug exposure, topline safety, and patient disposition *in patients who received ≤ 6 treatment cycles*

	NIVO (n = 102)	IPI (n = 101)
Median no. of doses received (range)	3 (1-6)	1 (1-2)
	NIVO+IPI (n = 102)	
Median duration of therapy (range), months	1.1 (< 0.1-4.4)	
Any grade treatment-related AEs, n (%)[a]	93 (91)	
Grade 1-2	40/93 (43)	
Grade ≥ 3	53/93 (57)	
Any grade treatment-related AEs leading to treatment discontinuation, n (%)[a]	69 (68)	
Grade 1-2	29/69 (42)	
Grade ≥ 3	40/69 (58)	

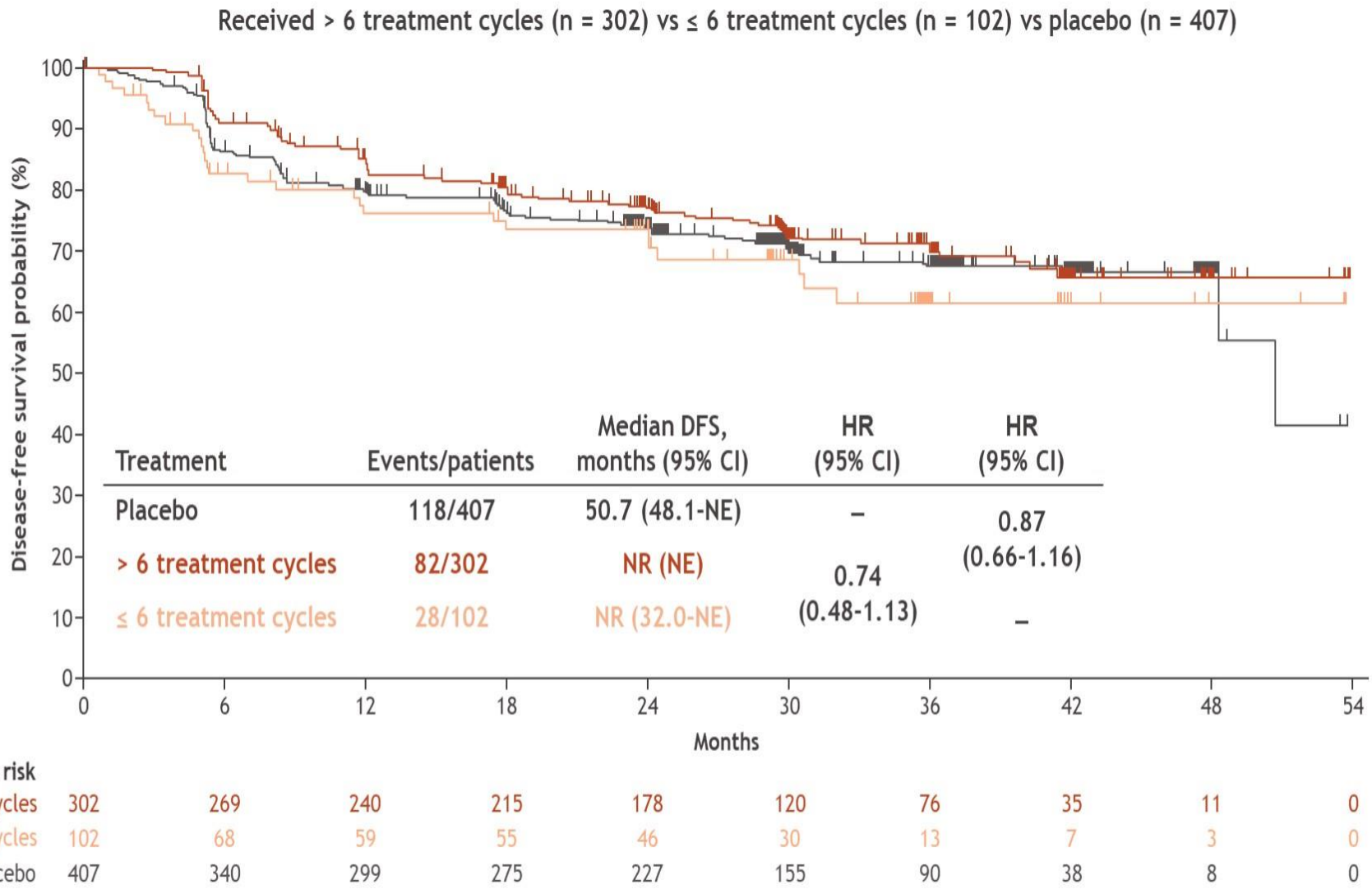
- The most common any-grade treatment-related AEs leading to discontinuation were diarrhea (6%), increased alanine aminotransferase (4%), and thyroiditis (4%)

[a]Includes events reported in all treated patients between first dose and 30 days after the last dose of study drug.

Disease-free survival per BICR *by treatment cycles received*



Disease-free survival per BICR *by treatment cycles received*



Patient-reported outcomes in all treated patients

- *EQ-5D-3L*
- *FKSI-19*

Patient-reported outcomes assessments

EQ-5D-3L[1,2] (global health status)

- Utility index: 5 items; range, 0 (death) - 1 (full health)
  - Meaningful change threshold: ≥ 0.08 points vs baseline[a]

FKSI-19[3,4] (kidney cancer symptom index)

- Total score: 19 items; range, 0-76
  - Meaningful change threshold: ≥ 5 points vs baseline[b]
- Disease-related symptoms: 9 items; range, 0-36
  - Meaningful change threshold: ≥ 3 points vs baseline[b]

Schedule		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7		Cycle 8		Cycle 9		Cycle 10		Cycle 11		Cycle 12	
Targeted week		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Collection		PRO				PRO						PRO						PRO						PRO	
Completion rate, %[c]																									
EQ-5D	NIVO+IPI	98		-		97		-		-		96		-		-		94		-		-		99	
	Placebo	97		-		97		-		-		96		-		-		97		-		-		99	
FKSI-19	NIVO+IPI	98		-		97		-		-		95		-		-		95		-		-		98	
	Placebo	96		-		98		-		-		97		-		-		97		-		-		99	

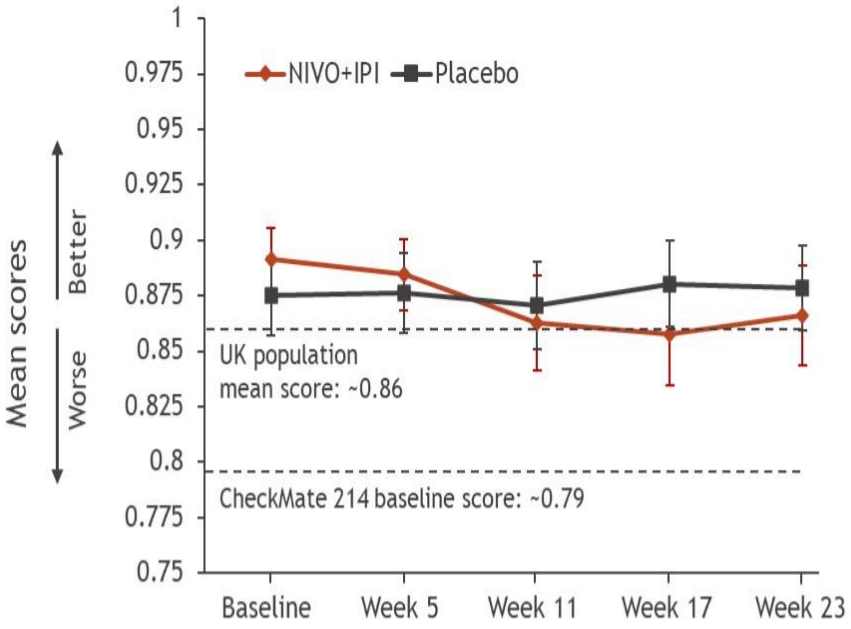
[a]EQ-5D-3L threshold is based on literature.[2] [b]As there are no established thresholds for the FKSI-19 scores, except for the DRS where 2-3 points was suggested in the literature,[4] the threshold used here was established using a distribution-based approach. Specifically, one-half the baseline standard deviation rounded to the next integer was used. [c]Completion rate is equal to the number of patients who filled the questionnaire divided by number of available patients.

1. EuroQol Group. *Health Policy* 1990;16:199-208. 2. Pickard AS, et al. *Health Qual Life Outcomes* 2007;5:70. 3. Rothrock NE, et al. *Value Health* 2013;16:789-796. 4. Cella D, et al. *Value Health* 2007;10:285-293.

EQ-5D-3L, EuroQoL Group's 3-level version of the EQ-5D; FKSI-19, Functional Assessment of Cancer Therapy-Kidney Symptom Index 19.

Mean scores and changes from baseline in EQ-5D-3L (utility index)

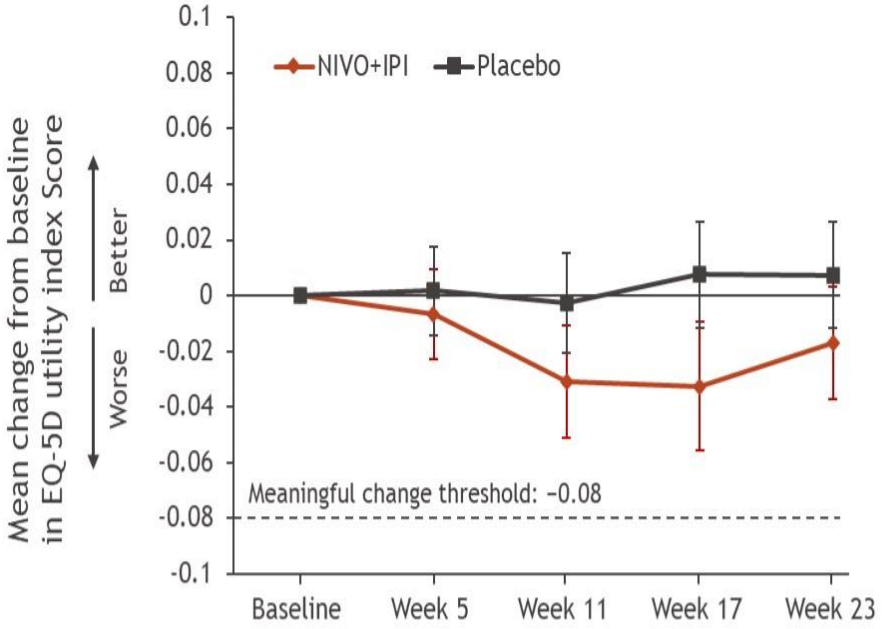
EQ-5D utility index score over time[1]



No. of patients with measurement at time point

NIVO+IPI	395	364	312	270	250
Placebo	395	388	378	367	361

- Mean scores over time with NIVO+IPI were comparable to or higher than the referenced general population (UK) score



No. of patients with measurement at time point

NIVO+IPI	395	358	306	265	245
Placebo	395	380	369	358	351

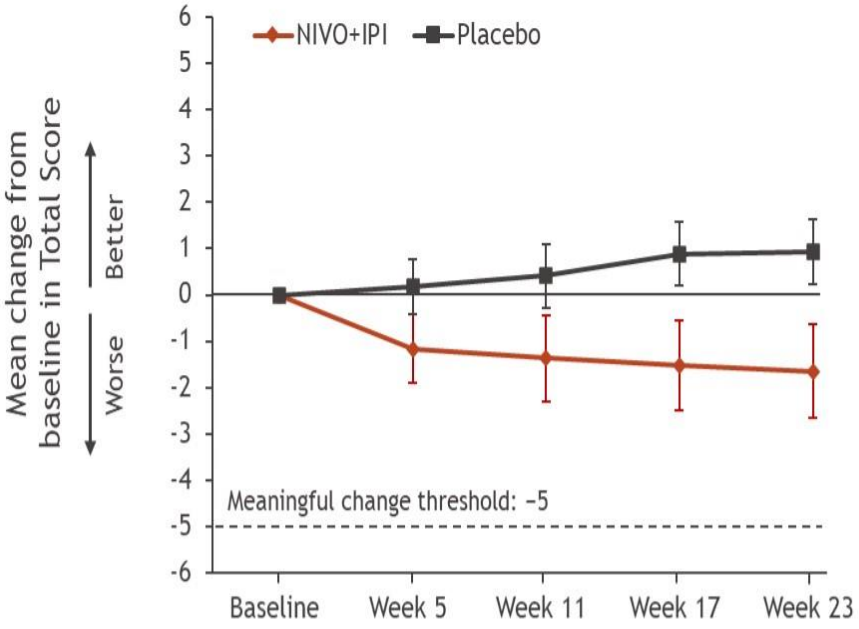
- Mean change from baseline with NIVO+IPI did not reach the threshold for meaningful change

Higher score indicates better health state. Bars show 95% CIs.

1. Pickard AS, et al. *Health Qual Life Outcomes* 2007;5:70.

Mean changes from baseline in FKSI-19 total and DRS scores

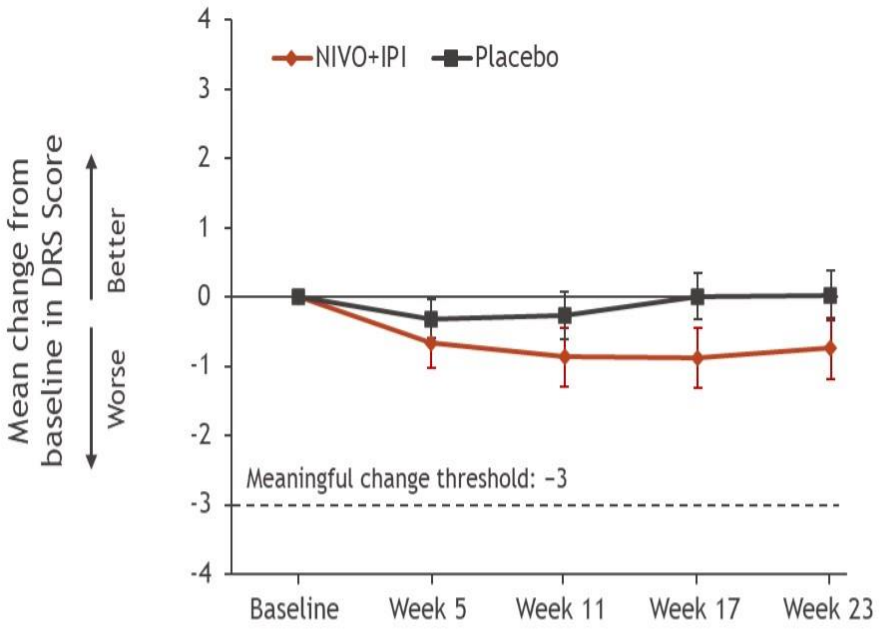
FKSI-19 total score over time[1a]



No. of patients with measurement at time point

	Baseline	Week 5	Week 11	Week 17	Week 23
NIVO+IPI	395	358	304	266	242
Placebo	391	379	369	353	348

FKSI-DRS score over time[2a]



No. of patients with measurement at time point

	Baseline	Week 5	Week 11	Week 17	Week 23
NIVO+IPI	395	358	304	266	242
Placebo	391	379	369	353	348

- Mean changes from baseline with NIVO+IPI in FKSI-19 total and DRS scores did not reach the threshold considered meaningful based on the literature[1,2]

Higher score indicates better health state. Bars show 95% CIs.

[a]As there are no established thresholds for the FKSI-19 scores, except for the DRS where 2-3 points was suggested in the literature,[2] the threshold used here was established using a distribution-based approach. Specifically, one-half the baseline standard deviation rounded to the next integer was used.

1. Rothrock NE, et al. *Value Health* 2013;16:789-796. 2. Cella D, et al. *Value Health* 2007;10:285-293.

Summary

- Exploratory analyses from CheckMate 914 Part A suggest that tumor-specific characteristics (eg, sarcomatoid features) influenced outcome of adjuvant NIVO+IPI treatment
- Early treatment discontinuation (≤ 6 cycles) was associated with shorter disease-free survival but did not appear to be a key factor in trial outcome
- Health-related quality of life scores were relatively stable in the NIVO+IPI group over the entire treatment period, with no meaningful differences compared with placebo
- CheckMate 914 Part B is ongoing to investigate the role of NIVO monotherapy