UPDATES IN KIDNEY AND UROTHELIAL CANCERS

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UPDATES IN KIDNEY AND UROTHELIAL CANCERS: OVERVIEW

- Urothelial Cancer
  - ASCO GU 2022: Abstract 440 (upper tract UC)
  - ASCO 2022: Abstract 4516 (third line mUC)
  - ESMO 2022: Abstract LBA73 (first line mUC)
- Renal Cell Carcinoma
  - ASCO GU 2022: Abstract 290 (KEYNOTE 564: 30 month follow up)
    - IMMOTION 010/PROSPER/CHECKMATE 914
  - ESMO 2022: Abstract 1449 (CLEAR: 33 month follow up)
  - ESMO 2022: Abstract LBA 8 (COSMIC 313)

ABSTRACT 440:

ASCO Genitourinary Cancers Symposium

Final Results of a Multicenter Prospective Phase II Clinical Trial of Gemcitabine and Cisplatin as Neoadjuvant Chemotherapy in Patients with High-Grade Upper Tract Urothelial Carcinoma

February 18, 2022

Wesley Yip, MD

Urologic Oncology Fellow
Memorial Sloan Kettering Cancer Center

Slides adapted from Nathan Wong, MD

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Study Design

- Multicenter Prospective Single-Arm Phase II Study
- 12 weeks of GC administered every 21 days x 4 cycles
- Radical nephroureterectomy or ureterectomy with templated LND
  - Within 12 weeks of chemotherapy
- Follow-up
  - Cytology and cystoscopy q3m x 18m, q6m x 18m then q1y
  - Imaging q6m x 18m then q1y

Key Eligibility
High-risk UTUC 1) High-grade biopsy and/or 2) Imaging (cT2-T4a) and positive selective cytology
No metastasis (imaging within 28 days)
eGFR ≥ 55 ml/min by CKD-EPI
Karnofsky Performance Status ≥ 70%

Chemotherapy
Gemcitabine 1000 mg/m^2 days 1 and 8
Cisplatin[1] 35 mg/m^2 days 1 and 8

[1]Instead of standard dose at 70mg/m^2 on day 1

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ABSTRACT 440: STUDY DESIGN

- Multicenter prospective single arm phase 2 study
- 12 weeks of GC chemotherapy every 21 days
- Radical nephroureterectomy or ureterectomy with templated LND within 12 weeks of chemotherapy
- Follow up: cytology/cystoscopy q 3 months x 18 months, q 6 months x 18 months, and then every year

Key Eligibility
High-risk UTUC 1) High-grade biopsy and/or 2) Imaging (cT2-T4a) and positive selective cytology
No metastasis (imaging within 28 days)
eGFR ≥ 55 ml/min by CKD-EPI
Karnofsky Performance Status ≥ 70%

Chemotherapy
Gemcitabine 1000 mg/m^2 days 1 and 8
Cisplatin[1] 35 mg/m^2 days 1 and 8

- Primary Endpoint:
  Pathologic response (< ypT2N0)
- Secondary Endpoints:
  Pathologic CR
  Time to disease progression
  Overall Survival
  Safety/tolerability

58 pts enrolled. 58 underwent NAC. 57 underwent surgery

Patient Characteristics

Characteristic	N = 57
Median age, years (IQR)	66 (58, 71)
Male	36 (63%)
Race	
White	54 (95%)
Black	2 (4%)
Asian	1 (2%)
Smoking status	
Current	11 (19%)
Former	25 (44%)
Never	21 (37%)
Karnofsky Performance Status (range)	90 (70-100)
eGFR (range)	67 (62,77)
Endoscopic Biopsy Grade	
High	53 (93%)
Low	0 (0%)
Not performed	4 (7%)

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ONCOLOGIC OUTCOMES

Pathologic Response		N = 57
Responders (<ypT2N0)		36 (63%)
	T0	11 (19%)
	Ta	10 (18%)
	Tis	7 (12%)
	T1	8 (14%)
Non-Responders (≥ypT2Nany)		21 (37%)
	T2	5 (9%)
	T3	9 (16%)
	TanyN+	7 (12%)
Progression prior to surgery		0 (0%)

Median follow up for survivors: 3.1 years

- 2-year PFS: 78%
- 5-year PFS: 65%

- 2-year OS: 93%
- 5-year OS: 79%

No safety signals

89% of Pts received at least 3 cycles

All patients were able to undergo surgery (within 7 weeks)

Yip et al. GU ASCO 2022

ABSTRACT 4516: LONG-TERM OUTCOMES IN EV-301: 24-MONTH FINDINGS FROM THE PHASE 3 TRIAL OF ENFORTUMAB VEDOTIN VS CHEMOTHERAPY IN PATIENTS WITH PREVIOUSLY TREATED ADVANCED UROTHELIAL CARCINOMA

Jonathan E. Rosenberg, MD[1]; Thomas Powles, MD[2]; Guru P. Sonpavde, MD[3]; Yohann Loriot, MD, PhD[4]; Ignacio Duran, MD, PhD[5]; Jae-Lyun Lee, MD, PhD[6]; Nobuaki Matsubara, MD[7]; Christof Vulsteke, MD, PhD[8]; Daniel Castellano, MD[9]; Ronac Mamtani, MD[10]; Chunzhang Wu, PhD[11]; Maria Matsangou, MD[11]; Mary Campbell, MD[12]; Daniel P. Petrylak, MD[13]

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Courtesy of Jonathan E. Rosenberg, MD

ENFORTUMAB VEDOTIN FOR PREVIOUSLY TREATED ADVANCED UROTHELIAL CARCINOMA

- The 5-year relative survival rate for metastatic bladder cancer is ≈8%[1]
- Enfortumab vedotin (EV), an antibody–drug conjugate directed against Nectin-4, demonstrated overall survival (OS) and progression-free survival (PFS) benefit in patients with locally advanced or metastatic (la/m) urothelial carcinoma (UC) in the open-label, confirmatory phase 3 EV-301 trial (NCT03474107) at the prespecified interim analysis[2]

Efficacy and safety are presented for EV vs chemotherapy over a median follow-up period of ≈2 years

Key eligibility criteria:
- Histologically/Cytologically confirmed UC
- Radiographic progression/ relapse during or after PD-1/L1 treatment for advanced UC
- Prior platinum-containing regimen for advanced UC
- ECOG PS 0–1

1:1 randomization with stratification

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

Preselected chemotherapy (N=307)
Docetaxel 75 mg/m^2 or paclitaxel 175 mg/m^2 or vinflunine 320 mg/m^2
on day 1 of each 21-d cycle

Primary end point: Overall survival

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

Investigator-assessed per RECIST v1.1

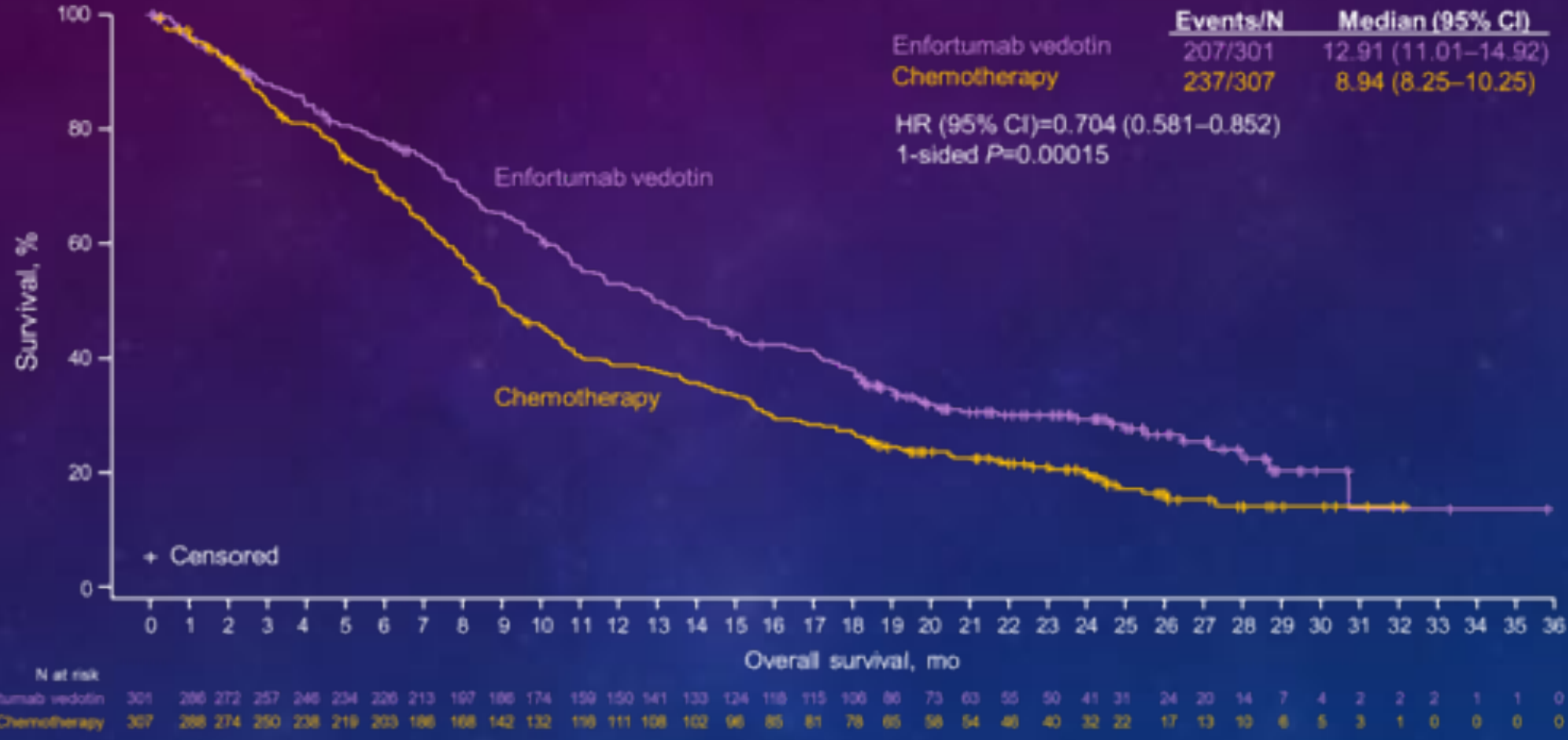
Findings from the prespecified, event-driven OS analysis when 439 deaths occurred are presented

ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; la/m, locally advanced or metastatic; OS, overall survival; PD-1/L1, programmed cell death protein-1/programmed death-ligand 1; RECIST, Response Evaluation Criteria In Solid Tumors; UC, urothelial carcinoma.

1. National Cancer Institute. https://seer.cancer.gov/statfacts/html/urinb.html. **2.** Powles T, et al. *N Engl J Med*. 2021;384:1125-1135.

Courtesy of Jonathan E. Rosenberg, MD

OVERALL SURVIVAL

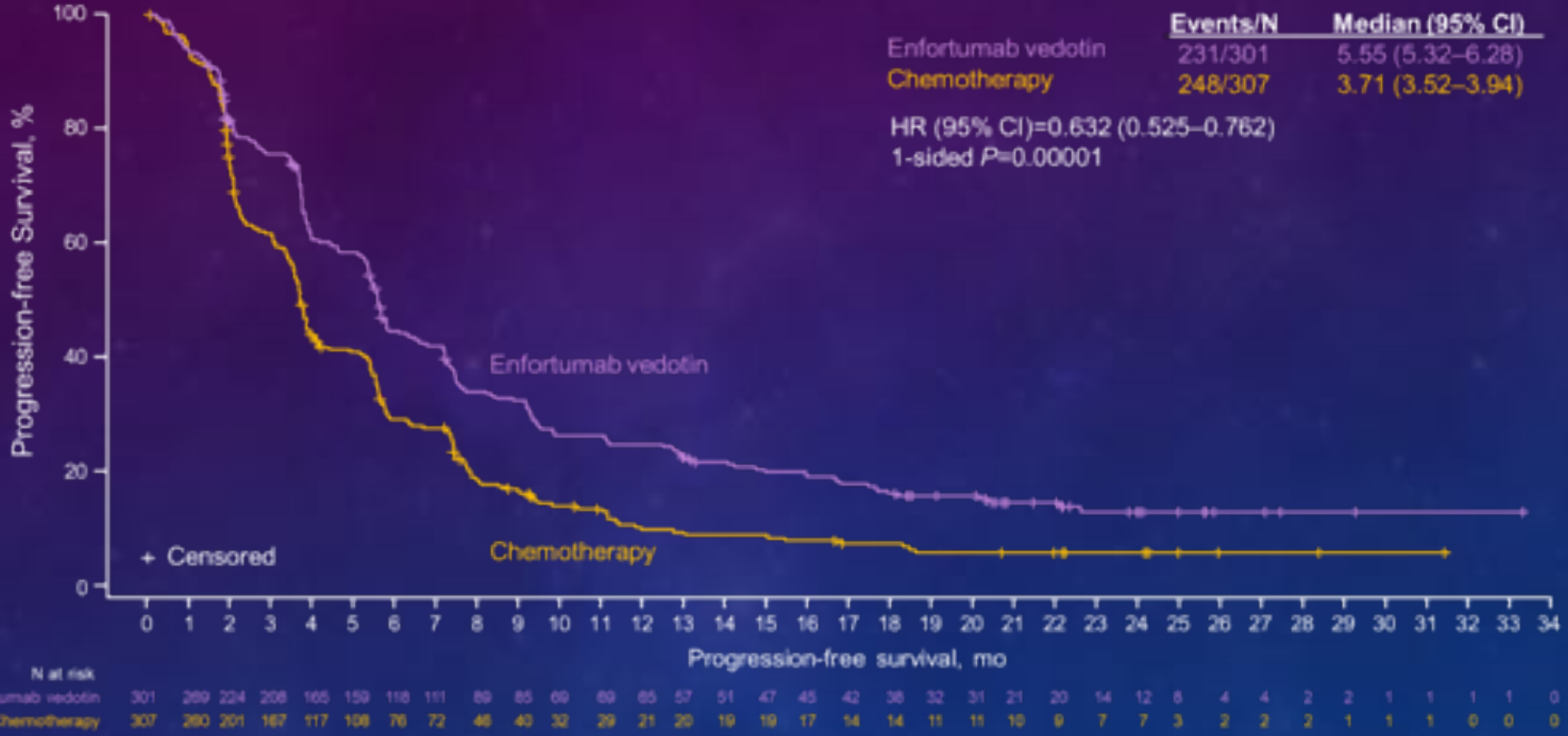


Data shown for intention-to-treat population.
HR, hazard ratio.

Data cutoff date: July 30, 2021

Courtesy of Jonathan E. Rosenberg, MD

PROGRESSION-FREE SURVIVAL

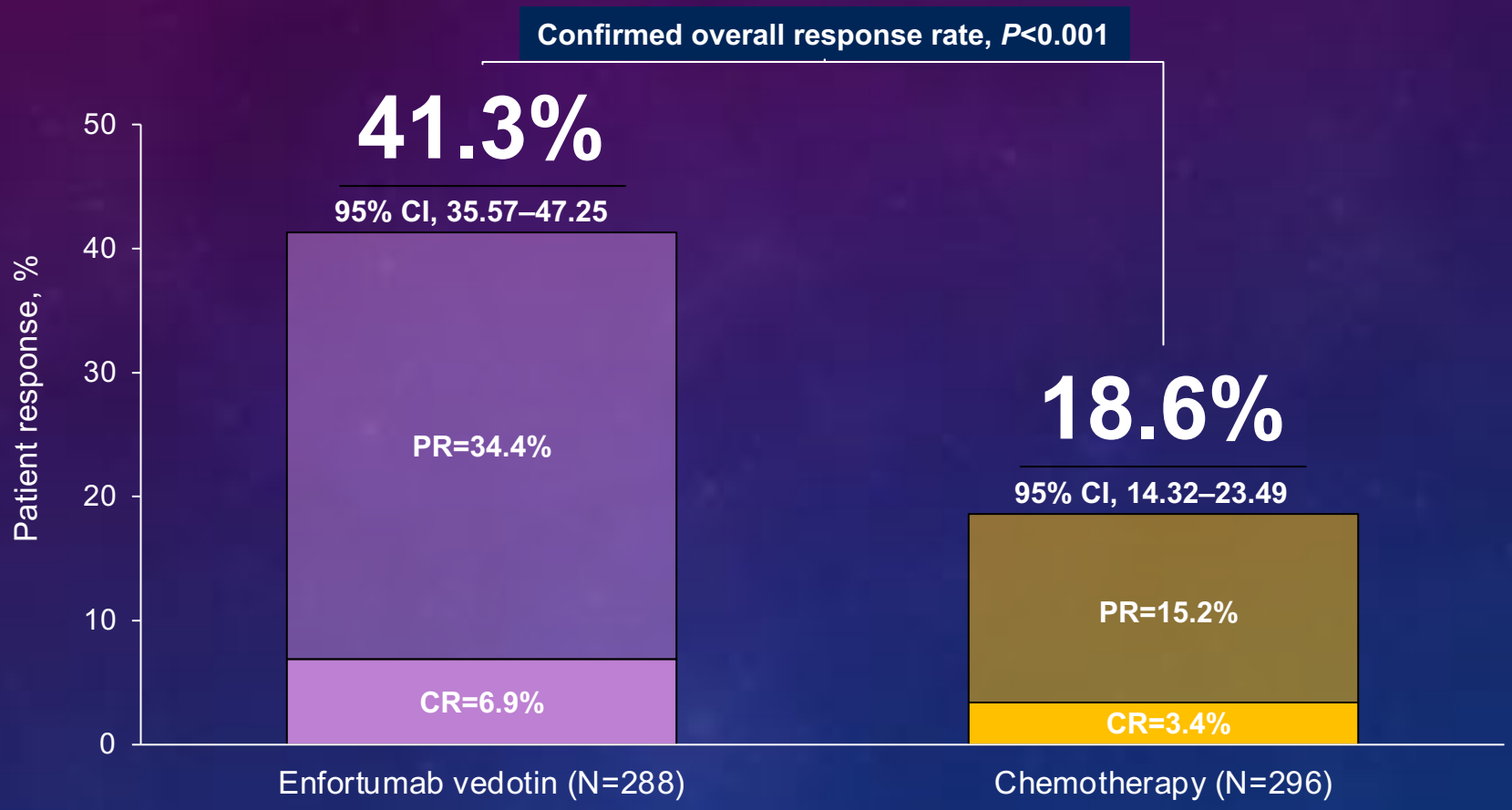


Data shown for intention-to-treat population.
HR, hazard ratio.

Data cutoff date: July 30, 2021

Courtesy of Jonathan E. Rosenberg, MD

EV 301: INVESTIGATOR-ASSESSED CLINICAL RESPONSE



Disease control rate (95% CI),[a] %	**71.9 (66.30–76.99)**	**53.4 (47.52–59.17)**	***P*<0.001**

Response as assessed by investigator per RECIST version 1.1. Assessed in the response evaluable population.
CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors.
[a]Proportion of patients with best overall response of confirmed CR, PR, or SD (≥7 wk); enfortumab vedotin vs chemotherapy.

Courtesy of Jonathan E. Rosenberg, MD

LBA 73: Study EV-103 Cohort K: Antitumor activity of enfortumab vedotin monotherapy or in combination with pembrolizumab in previously untreated cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer (la/mUC)

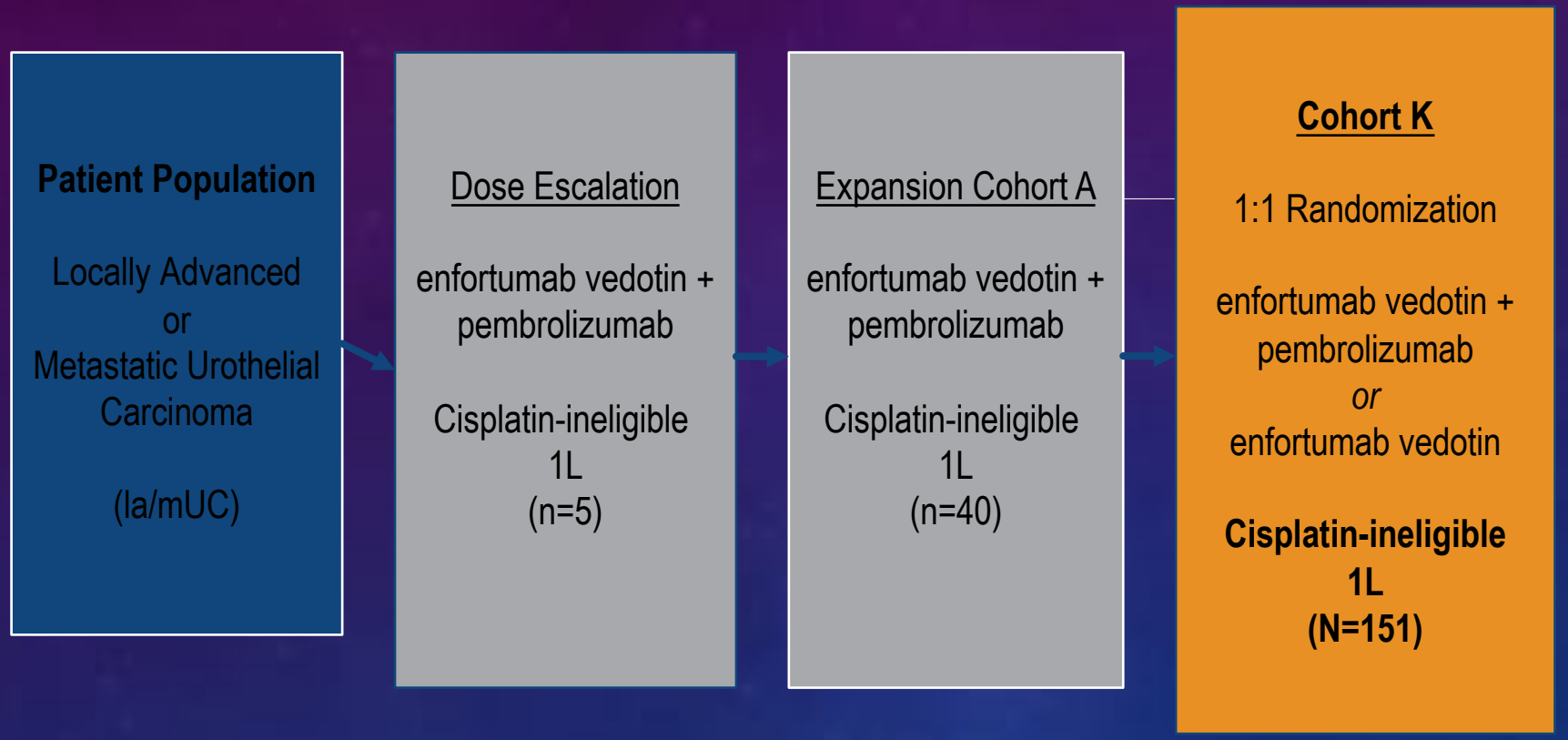
Jonathan E. Rosenberg, Matthew I. Milowsky, Chethan Ramamurthy, Nataliya Mar, Terence W. Friedlander, Rana R. McKay, Cristiano Ferrario, Sergio Bracarda, Saby George, Helen H. Moon, Daniel M. Geynisman, Daniel P. Petrylak, Delphine Borchiellini, Earle Burgess, Pablo Maroto, Anne-Sophie Carret, Yao Yu, Maria Guseva, Blanca Homet Moreno, Peter H. O'Donnell

ESMO 2022

Courtesy of Jonathan E. Rosenberg, MD

EV-103 Cohort K

Part of an open-label, multiple cohort, phase 1b/2 study in patients with urothelial carcinoma



- **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 endpoint:** confirmed ORR by RECIST v1.1 per BICR
- **Key secondary endpoints:** confirmed ORR per RECIST v1.1 by investigator, DOR, DCR, PFS, OS, safety/ tolerability, and lab abnormalities

Statistical considerations

- The sample size was based on precision of the estimate for ORR characterized by 95%CIs
- No formal statistical comparisons between the 2 treatment arms

Stratification factors: Liver metastases (present/absent) and ECOG PS (0 or 1/2); **Exploratory endpoints**: pharmacokinetics, antitherapeutic antibody, biomarkers of activity including baseline PD-L1 status and Nectin-4 expression, progression-free survival on subsequent therapy by investigator, patient reported outcomes; **Cohort K** completed enrollment on 11 Oct 2021; **Data cutoff was 10 Jun 2022**

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Key Demographic and Baseline Disease Characteristics

Representative of the 1L cisplatin-ineligible la/mUC population

	EV+P (N=76)	EV Mono (N=73)
Male sex, n (%)	54 (71.1)	56 (76.7)
Age (yrs), median (range)	71 (51, 91)	74 (56, 89)
White race, n (%)	61 (80.3)	55 (75.3)
ECOG PS, n (%)		
0	33 (43.4)	28 (38.4)
1	33 (43.4)	35 (47.9)
2	10 (13.2)	10 (13.7)
Primary tumor location, n (%)		
Lower tract	46 (60.5)	51 (69.9)
Upper tract	30 (39.5)	21 (28.8)

	EV+P (N=76)	EV Mono (N=73)
Metastasis disease sites, n (%)		
Bone	19 (25.0)	21 (28.8)
Liver	13 (17.1)	13 (17.8)
Lung	37 (48.7)	30 (41.1)
Metastasis category, n (%)		
Lymph node only	10 (13.2)	12 (16.4)
Visceral disease	64 (84.2)	60 (82.2)
Not applicable[1]	2 (2.6)	1 (1.4)
PD-L1 status by combined positive score,[2] n (%)		
CPS<10	44 (57.9)	38 (52.1)
CPS≥10	31 (40.8)	28 (38.4)
Not Evaluable	1 (1.3)	7 (9.6)

CPS: Combined Positive Score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; Mono: monotherapy; PD-L1: Programmed death-ligand 1

[1]Patients had locally advanced disease without metastasis to lymph nodes or distant organs.

[2]PD-L1 tested using the PD-L1 IHC 22C3 pharmDx assay from Agilent

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Overall Response Rate by BICR

EV+P: 64.5% confirmed ORR with rapid responses

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

EV+P

- 41/49 (85.7%) of responses observed at first assessment (week 9±1 wk)
- cORRs were consistent across all pre-specified subgroups
- 7/13 (53.8%) cORR observed in patients with liver metastases

EV monotherapy

- Activity is consistent with prior results in 2L+ la/mUC

Data cutoff: 10Jun2022

BICR: Blinded Independent Central Review; cORR: Confirmed Objective Response Rate; NR: Not Reached

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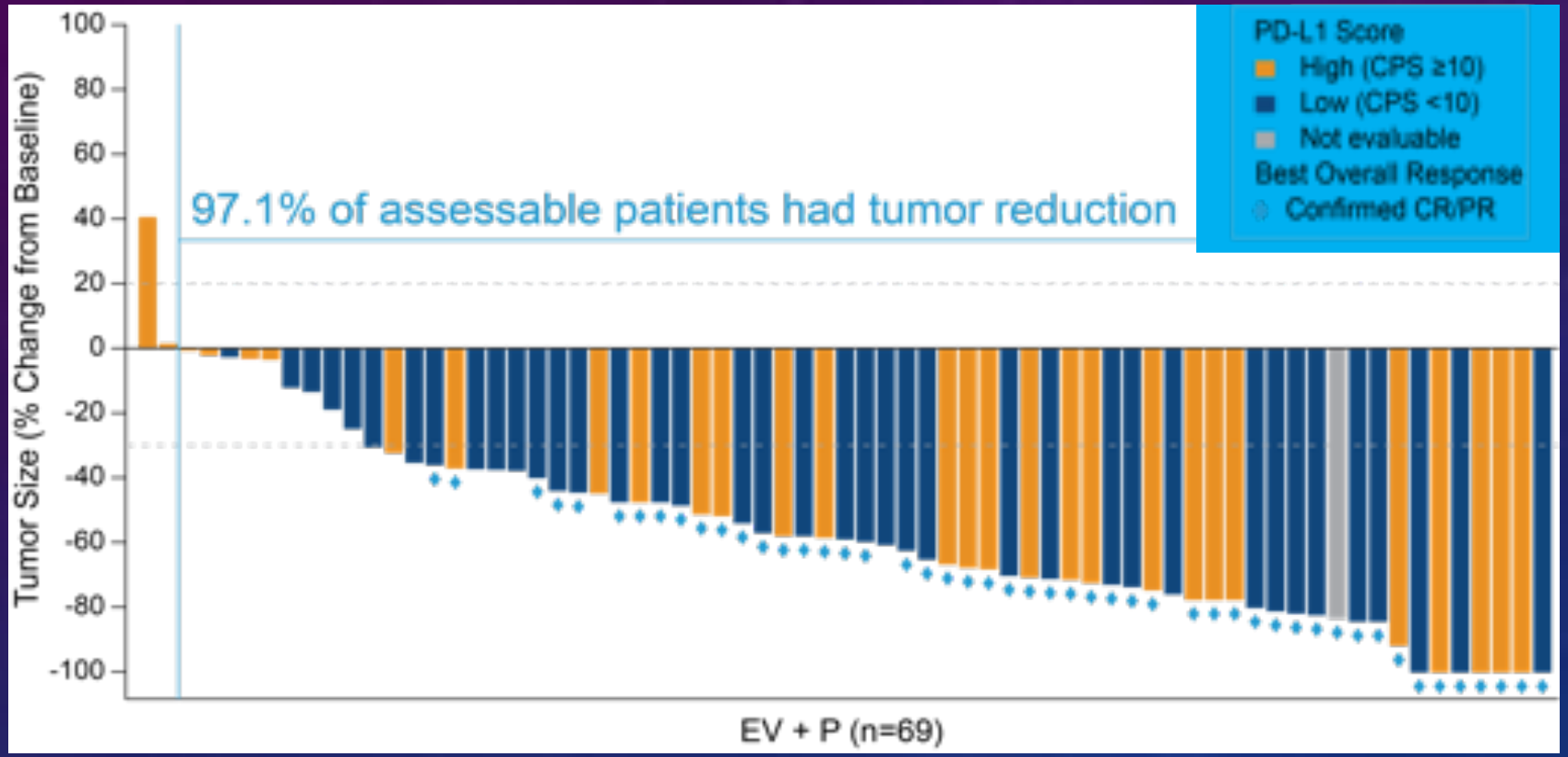
EV+P: Maximum Percent Reduction from Baseline of Target Lesion by BICR



- Activity seen regardless of PD-L1 status
  - 27/44 (61.4%) cORR in CPS<10
  - 21/31 (67.7%) cORR in CPS≥10

BICR: Blinded Independent Central Review; CPS: Combined Positive Score; CR: Complete Response; PD-L1: Programmed Death-Ligand 1 PR: Partial Response

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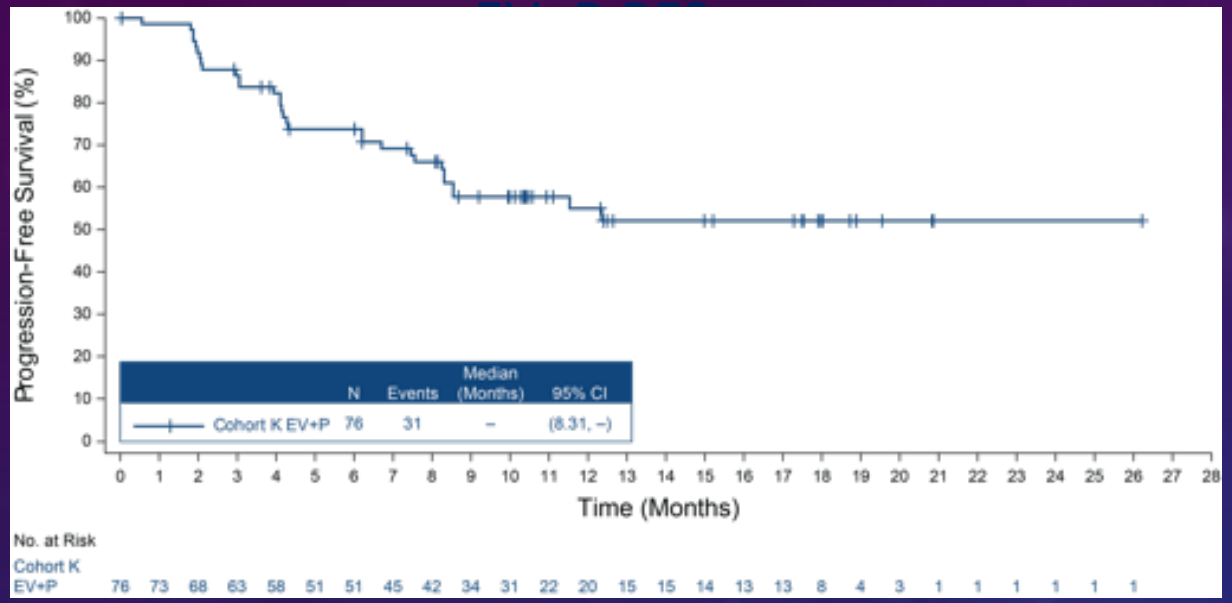
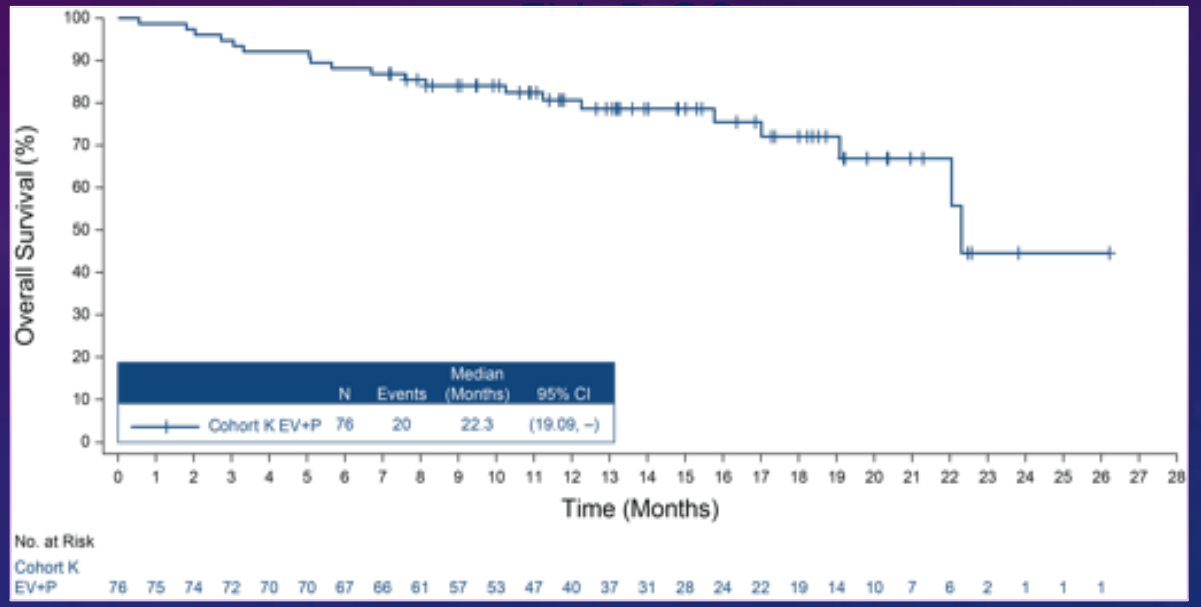
Progression-Free Survival per BICR and Overall Survival

Secondary Endpoints: PFS and OS for EV+P; data expected to evolve with follow-up





	EV+P (N=76)	EV Mono (N=73)
PFS events, n	31	38
mPFS (95% CI), mos	- (8.31, -)	8.0 (6.05, 10.35)
PFS at 12 mos, %	55.1%	35.8%

	EV+P (N=76)	EV Mono (N=73)
OS Events, n	20	26
mOS (95% CI), mos	22.3 (19.09, -)	21.7 (15.21, -)
OS at 12 mos, %	80.7%	70.7%
Median follow-up time, mos	14.8	15.0

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Treatment-Related Adverse Events (TRAEs)

Most common AEs with EV+P were fatigue, peripheral sensory neuropathy, alopecia, and maculo-papular rash

TRAEs **Any Grades** by Preferred Term **≥20% of Patients**	EV+P (N=76) n (%)		EV Mono (N=73) n (%)	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Overall	76 (100.0)	48 (63.2)	68 (93.2)	35 (47.9)
Fatigue	43 (56.6)	7 (9.2)	29 (39.7)	6 (8.2)
Peripheral sensory neuropathy	39 (51.3)	1 (1.3)	32 (43.8)	2 (2.7)
Alopecia	35 (46.1)	0	26 (35.6)	0
Rash maculo-papular	35 (46.1)	13 (17.1)	21 (28.8)	1 (1.4)
Pruritus	30 (39.5)	3 (3.9)	19 (26.0)	1 (1.4)
Dysgeusia	23 (30.3)	0	25 (34.2)	0
Weight decreased	23 (30.3)	3 (3.9)	21 (28.8)	1 (1.4)
Diarrhea	22 (28.9)	5 (6.6)	20 (27.4)	4 (5.5)
Decreased appetite	20 (26.3)	0	28 (38.4)	0
Nausea	19 (25.0)	0	25 (34.2)	1 (1.4)
Dry eye	15 (19.7)	0	8 (11.0)	0

Serious TRAEs
- 18 (23.7%) EV+P
- 11 (15.1%) EV Mono

TRAEs leading to death (per investigator)
- 3 (3.9%) EV+P (Pneumonitis, Respiratory failure, Sepsis)
- 2 (2.7%) EV Mono (Multiple organ dysfunction, Respiratory failure)

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UROTHELIAL CANCER ABSTRACTS: CONCLUSIONS

- Abstract 440 (NAC in upper tract UC): Favorable Path response rate (63%) and CR (19%) in high grade upper tract UC. Treatment feasible. Did not delay surgery.
  - Contemporary prospective study showing benefit of NAC in a rare disease
- Abstract 4516 (EV in third line): After a median follow-up period of approximately 2 years, EV maintained a clinically meaningful and significant OS benefit versus chemotherapy consistent with findings from the primary efficacy results (which had occurred at the interim analysis)
- Abstract LBA73 (First line mUC): In this patient population with a high unmet need, EV+P showed encouraging activity in 1L cisplatin-ineligible patients with la/mUC in EV-103
  - High ORR by BICR (64.5%) and rapid responses; median DOR not reached
  - promising PFS and OS expected to continue to evolve
  - Still experimental

RENAL CELL CARCINOMA

ABSTRACT 290: PEMBROLIZUMAB AS POST NEPHRECTOMY ADJUVANT THERAPY FOR PATIENTS WITH RENAL CELL CARCINOMA: RESULTS FROM 30-MONTH FOLLOW-UP OF KEYNOTE-564.

- **Toni K. Choueiri, Piotr Tomczak, Se Hoon Park, Balaji Venugopal, Tom Ferguson, Stefan N. Symeonides, Jaroslav Hajek, Yen-Hwa Chang, Jae-Lyun Lee, Naveed Sarwar, Antoine Thiery-Vuillemin, Marine Gross-Goupil, Mauricio Mahave, Naomi B. Haas, Piotr Sawrycki, Lei Xu, Kentaro Imai, Jacqueline Willemann-Rogerio, David I. Quinn, Thomas Powles**

GU ASCO 2022

KEYNOTE-564 Study Design

Key Eligibility Criteria

- Histologically confirmed clear cell renal cell carcinoma
- Nephrectomy ≤12 weeks prior to randomization
- No prior systemic therapy
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment

Stratification Factors

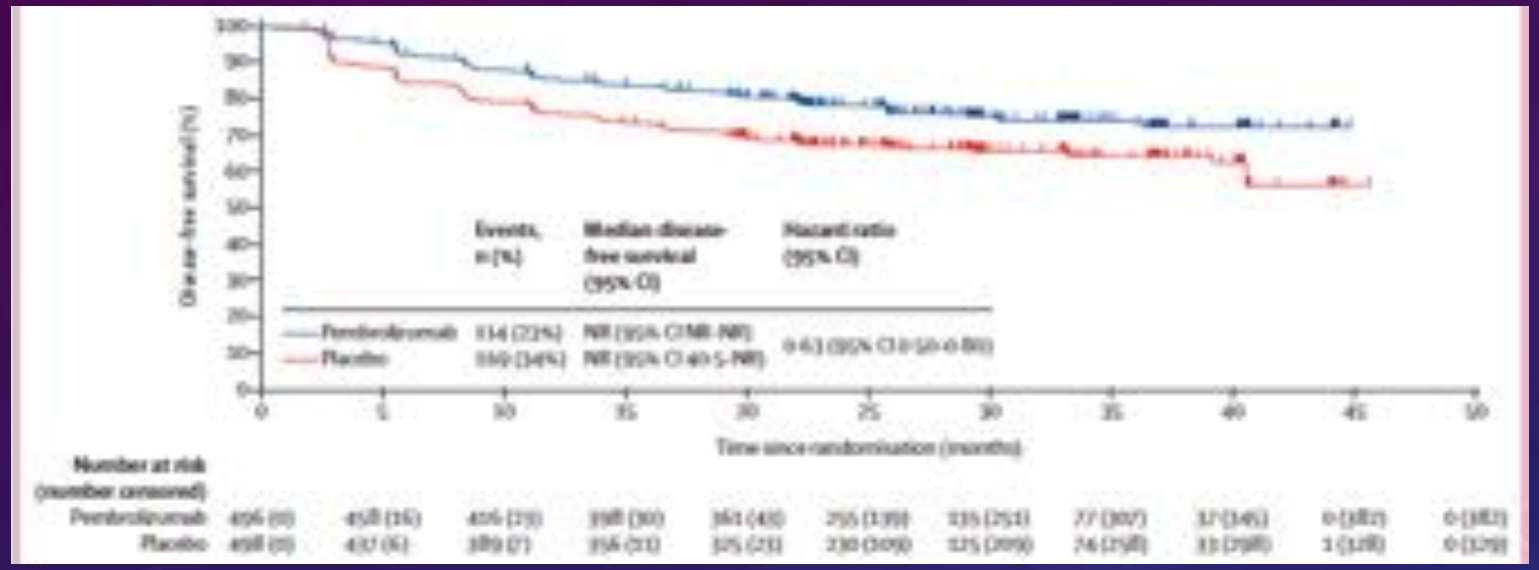
- M0 vs M1 NED
- M0 group further stratified:
  - ECOG PS 0 vs 1
  - US vs non-US

R (1:1)

- Pembrolizumab 200 mg Q3W for ~1 year[a]
- Placebo Q3W for ~1 year[a]

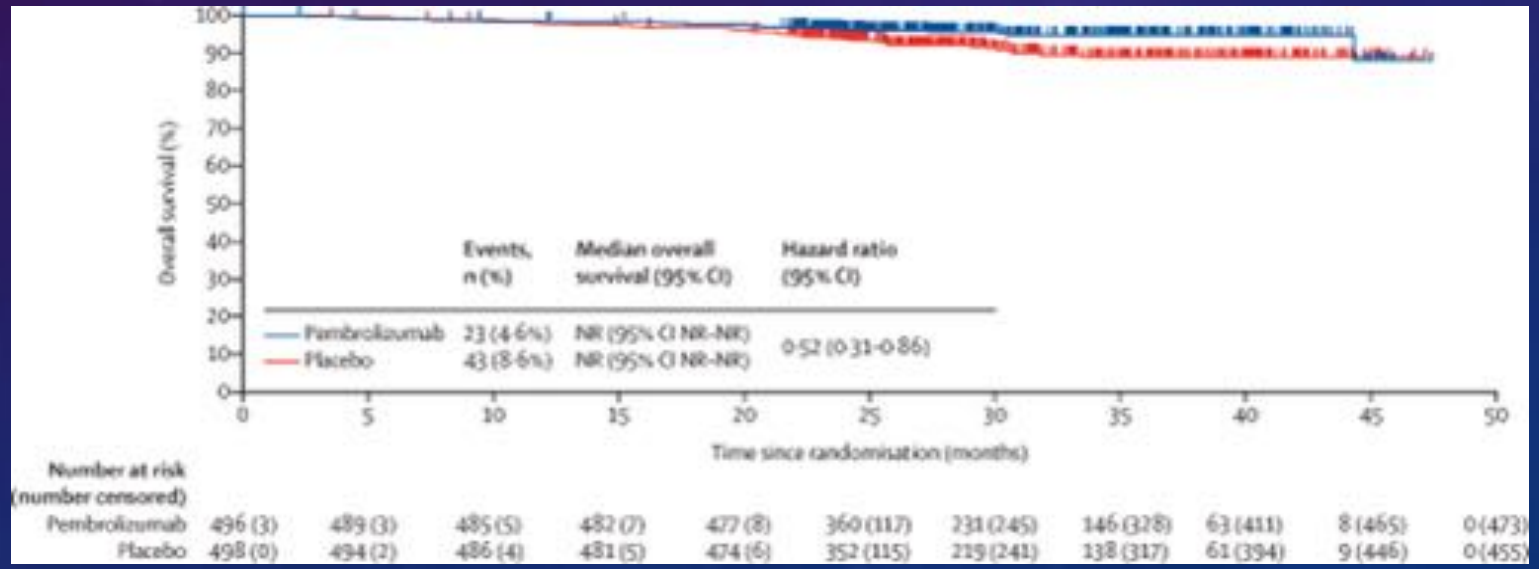
- Primary end point: DFS per investigator
- Key secondary end point: OS
- Other secondary end points: Safety

KEYNOTE 564: DISEASE FREE AND AND OVERALL SURVIVAL



DISEASE FREE SURVIVAL (NR)

- 24-month f/u
  HR: 0.68 (95% CI 0.53-0.87)
- <u>30-month f/u:</u>
  HR 0.63 (95% CI 0.50-0.80)

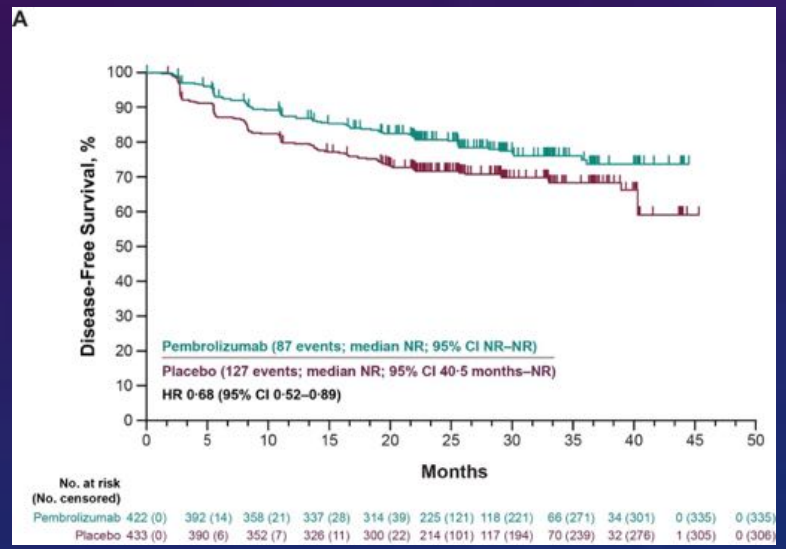


OVERALL SURVIVAL (NR)

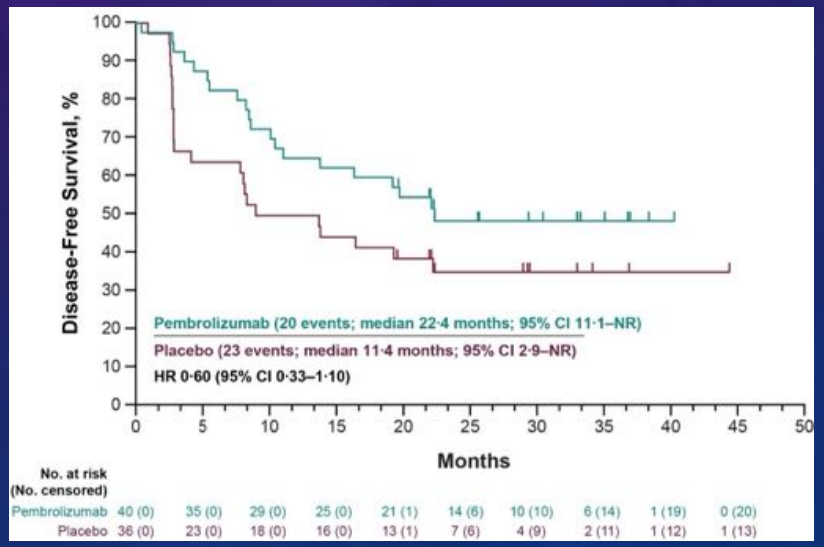
- 24-month f/u:
  HR:0.54 (95% CI 0.30-0.96)
- <u>30-month f/u:</u>
  HR: 0.52 (95% CI 0.31-0.86)

KEYNOTE 564: DISEASE FREE SURVIVAL BY RISK CATEGORIES

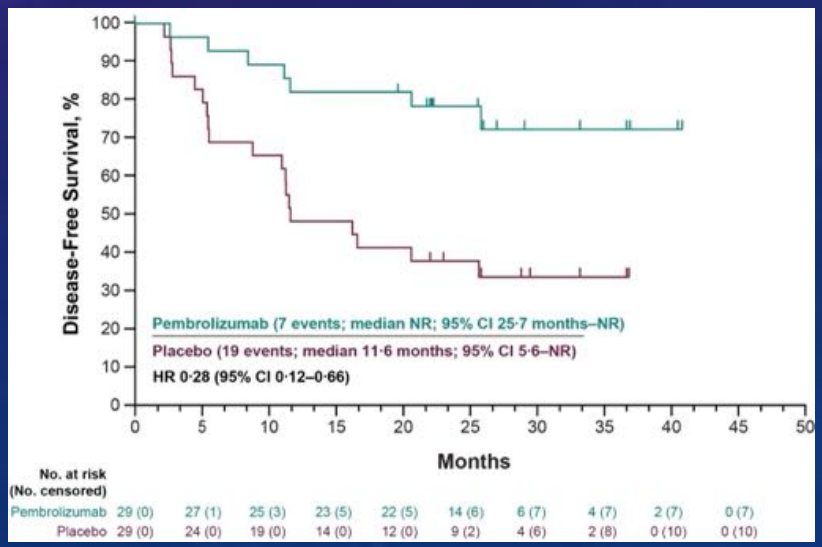
Intermediate-High Risk		High Risk		M1 NED
pT2	pT3	pT4	Any pT	NED after resection of oligometastatic sites ≤1 year from nephrectomy
Grade 4 or sarcomatoid	Any grade	Any grade	Any grade	
N0	N0	N0	N+	
M0	M0	M0	M0	



HR: 0.68 (95% CI 0.52-0.89)



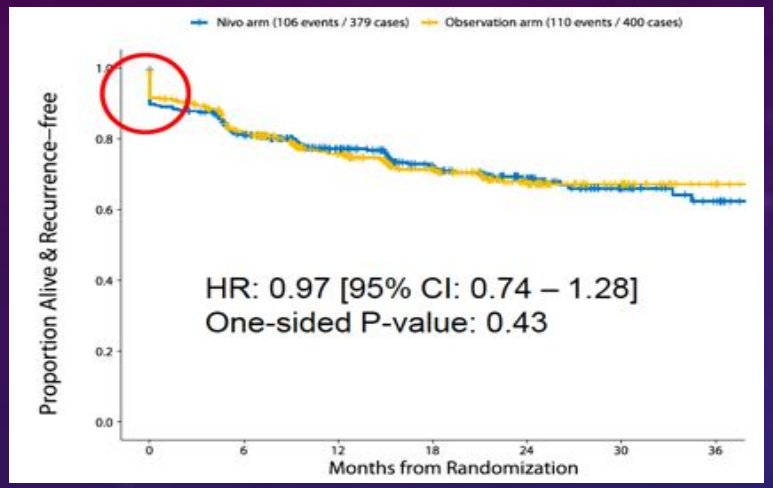
HR: 0.60 (95% CI 0.33-1.10)



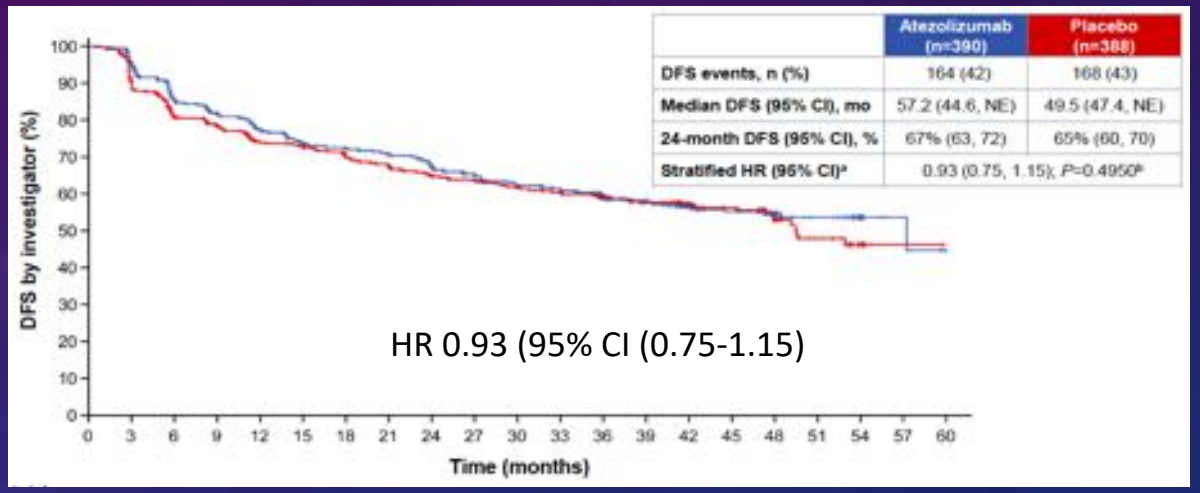
HR: 0.28 (95% CI 0.12-0.66)

OTHER ADJUVANT RCC TRIALS PRESENTED AT ASCO/ESMO 2022

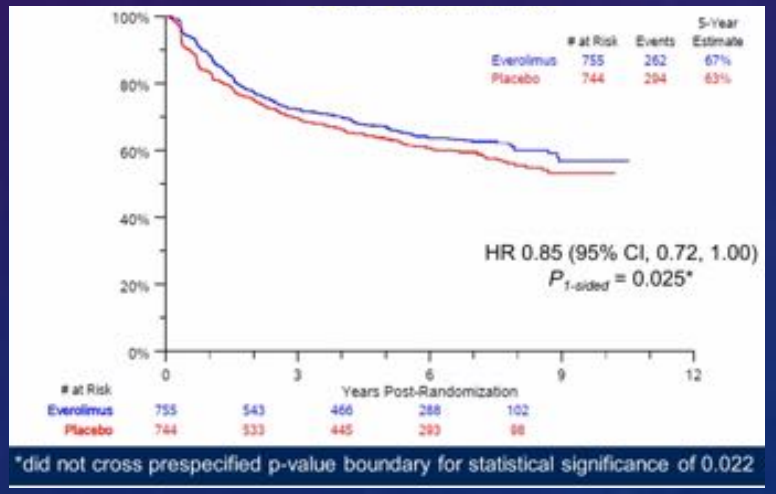
PROSPER RCC: LBA 67
Periop Nivolumab vs observation



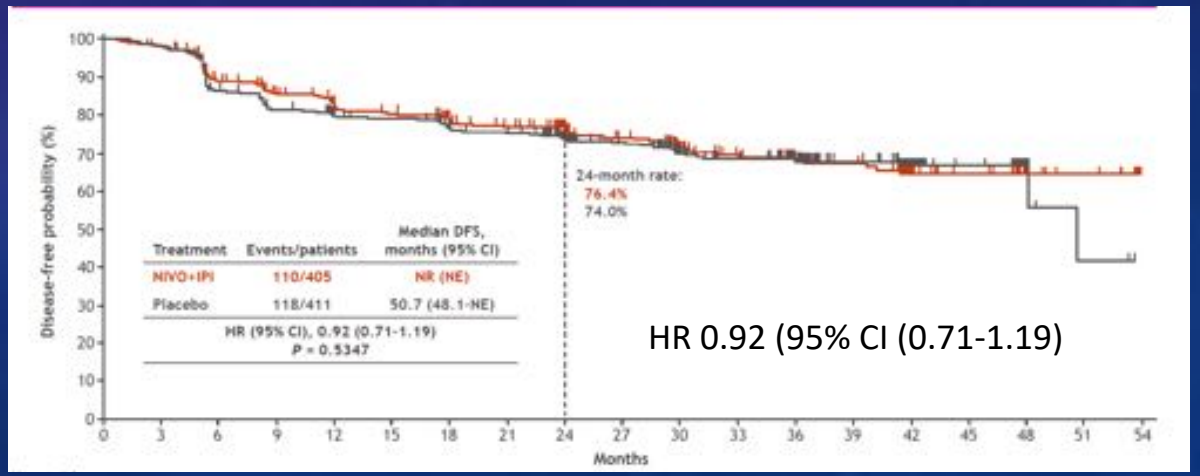
IMMOTION 010 (Abstract 4634): Atezolizumab vs. Placebo)



EVEREST: Everolimus vs Placebo



Checkmate 914 (LBA 4): IPI/NIVO vs. Placebo)



Abstract 1449: Updated efficacy of lenvatinib plus pembrolizumab versus sunitinib in patients with advanced renal cell carcinoma in the CLEAR study

Camillo G. Porta[1], Masatoshi Eto[2], Robert J. Motzer[3], Ugo De Giorgi[4], Tomas Buchler[5], Naveen S. Basappa[6], Maria Jose Mendez Vidal[7], Sergei Tjulandin[8], Se Hoon Park[9], Bohuslav Melichar[10], Thomas Hutson[11], Carlos Alemany[12], Bradley McGregor[13], Cixin Steven He[14], Rodolfo Perini[15], Kalgi Mody[16], Jodi McKenzie[16], Toni Choueiri[13]

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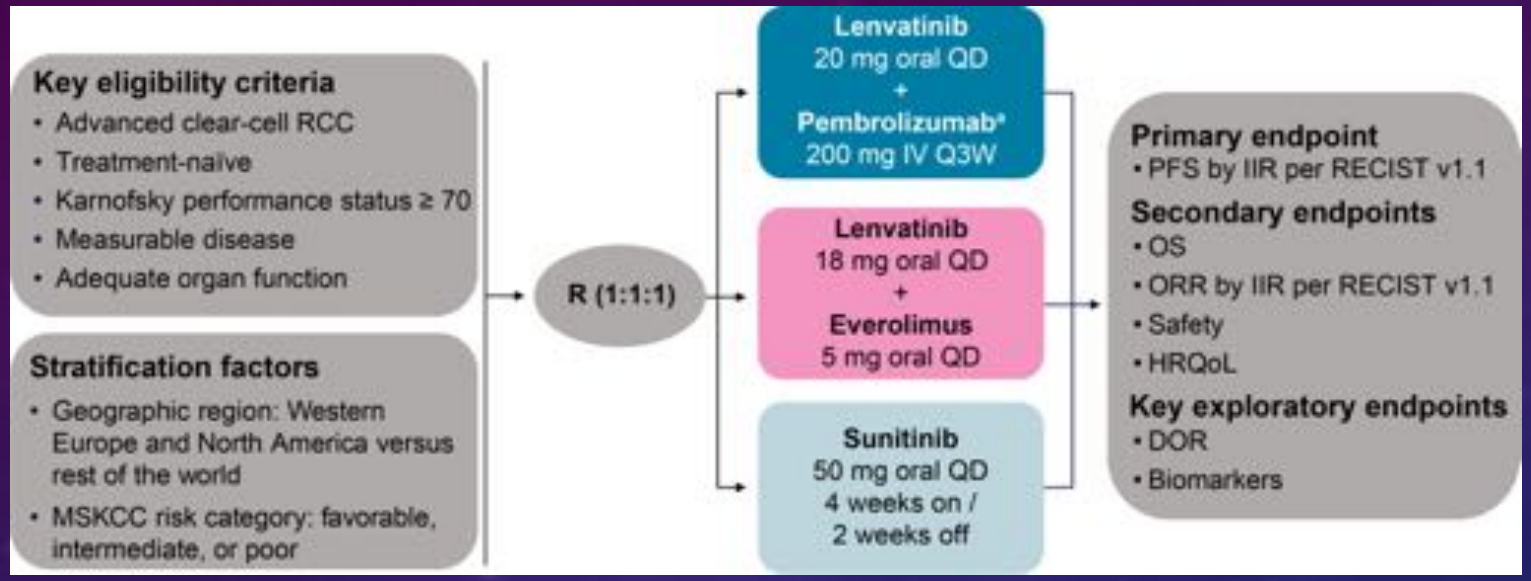
Presented by Camillo G. Porta, MD

Introduction and methods



[a]Patients could receive a maximum of 35 pembrolizumab treatments.

- The primary analysis of the phase 3 CLEAR study showed statistically significant and clinically meaningful improvements in PFS, OS, and ORR with LEN + PEMBRO vs SUN in pts with aRCC in the 1L setting (Motzer 2021, *NEJM*).
- We report updated PFS, ORR and DOR (by IIR per RECIST v1.1), and OS* (data cutoff date: 31 March 2021; 7 additional months of follow-up) for LEN + PEMBRO (median follow-up: 33.7 months) and SUN arms (median follow-up: 33.4 months).
- We also describe pts who completed 2 years of PEMBRO and continued on LEN monotherapy.

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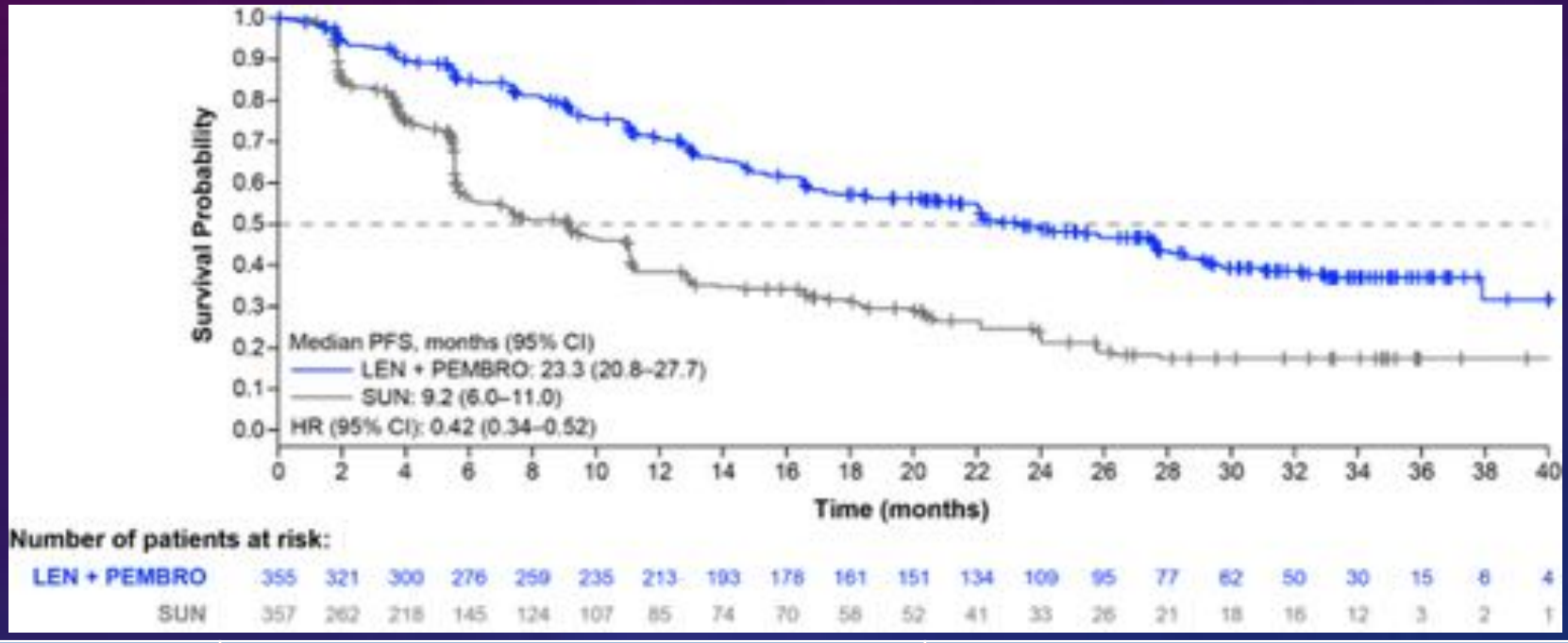
Continued improvement in PFS (by IIR per RECIST v1.1) with LEN + PEMBRO vs SUN



	MSKCC			IMDC		
	Poor risk	Intermediate risk	Favorable risk	Poor risk	Intermediate risk	Favorable risk
LEN +PEMBRO vs SUN HR (95% CI)	0.18 (0.08–0.42)	0.46 (0.35–0.60)	0.43 (0.29–0.64)	0.30 (0.14–0.62)	0.41 (0.30–0.54)	0.47 (0.32–0.69)

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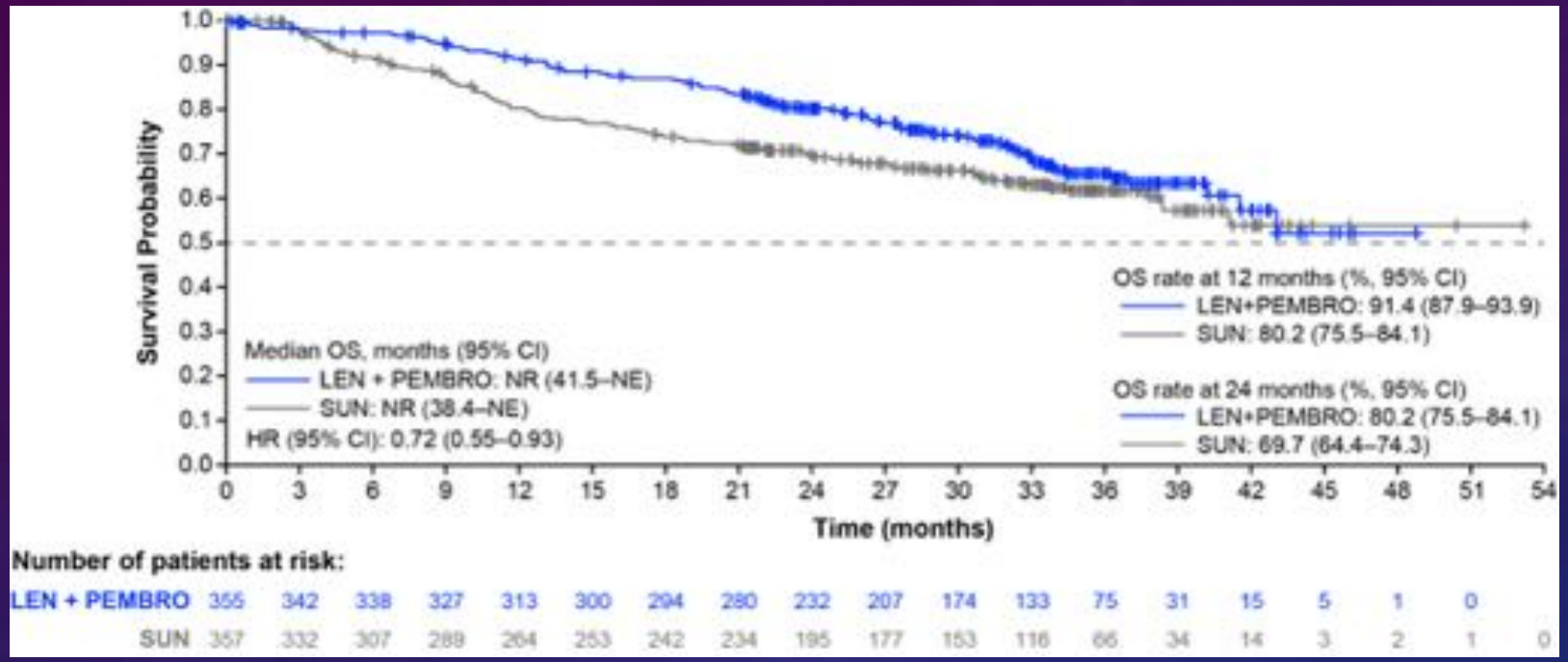
Continued improvement in OS with LEN + PEMBRO vs SUN



- Beyond the median duration of follow-up, there was a high rate of censoring.

	MSKCC			IMDC		
	Poor risk	Intermediate risk	Favorable risk*	Poor risk	Intermediate risk	Favorable risk*
LEN +PEMBRO vs SUN HR (95% CI)	0.50 (0.25–1.02)	0.71 (0.52–0.97)	1.00 (0.51–1.96)	0.39 (0.20–0.77)	0.72 (0.52–1.00)	1.22 (0.66–2.26)*

*Median OS was not reached for either arm, and few events were observed for patients in these risk groups.

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Tumor response by IIR per RECIST v1.1

	Lenvatinib + Pembrolizumab (N = 355)	Sunitinib (N = 357)
Objective response rate, n (%)	252 (71.0)	129 (36.1)
95% CI[a]	(66.3, 75.7)	(31.2, 41.1)
Difference (%) (95% CI)[a]	34.9 (28.0, 41.7)	
Relative risk[b]	1.97 (1.69, 2.29)	
Best overall response, n (%)		
Complete response	61 (17.2)	15 (4.2)
Partial response	191 (53.8)	114 (31.9)
Stable disease[c]	68 (19.2)	136 (38.1)
Progressive disease	19 (5.4)	50 (14.0)
Unknown/Not evaluable	16 (4.5)	42 (11.8)
Median duration of objective response, mo (95% CI)	26.0 (22.2, 41.4)	14.7 (9.4, 16.8)

[a]95% CI is constructed using the method of normal approximation; [b]relative risk is calculated using the Cochran-Mantel-Haenszel method, stratified by IxRS stratification factors; [c]must be ≥ 7 weeks after randomization.

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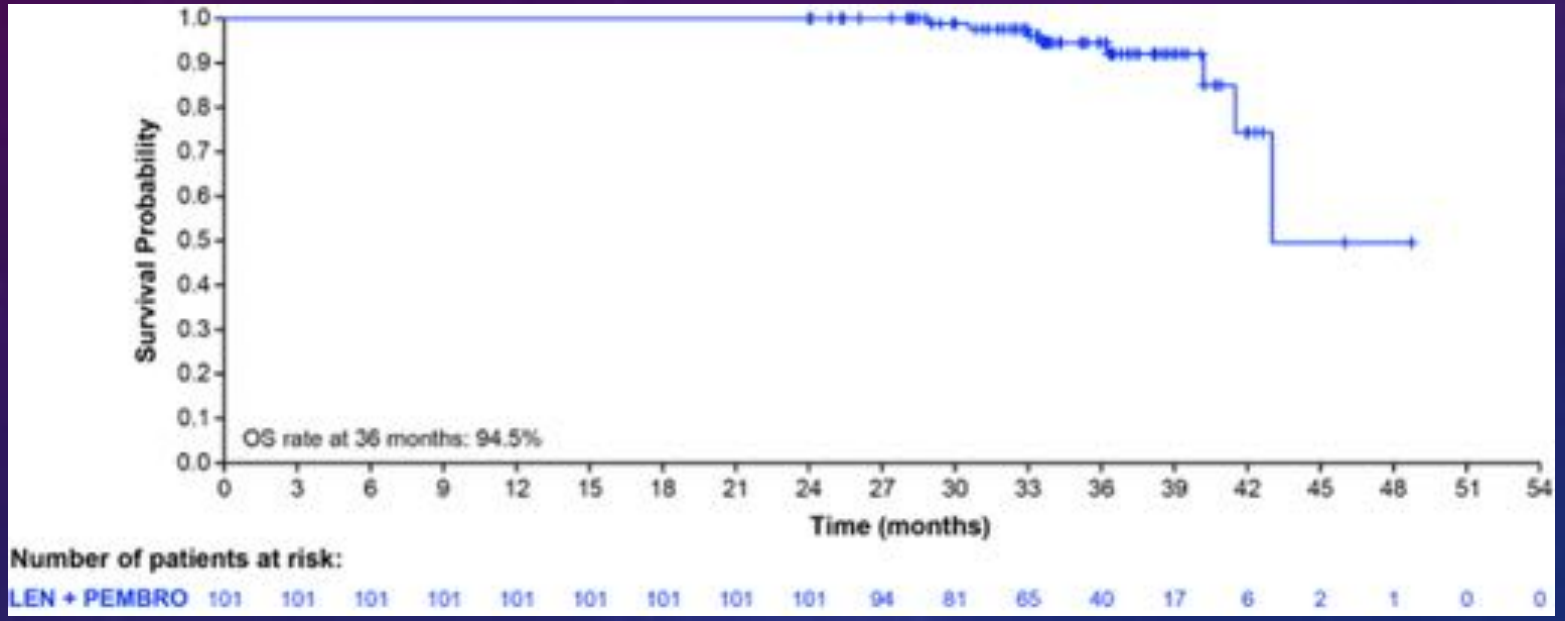
Overall survival in patients who completed 2 years of PEMBRO and continued on LEN monotherapy



- Of pts who completed 2 yrs of PEMBRO (n = 101 of 355 pts), most (n = 65) had IMDC intermediate/ poor risk disease and fewer (n = 36) had favorable risk disease, consistent with the ITT population.

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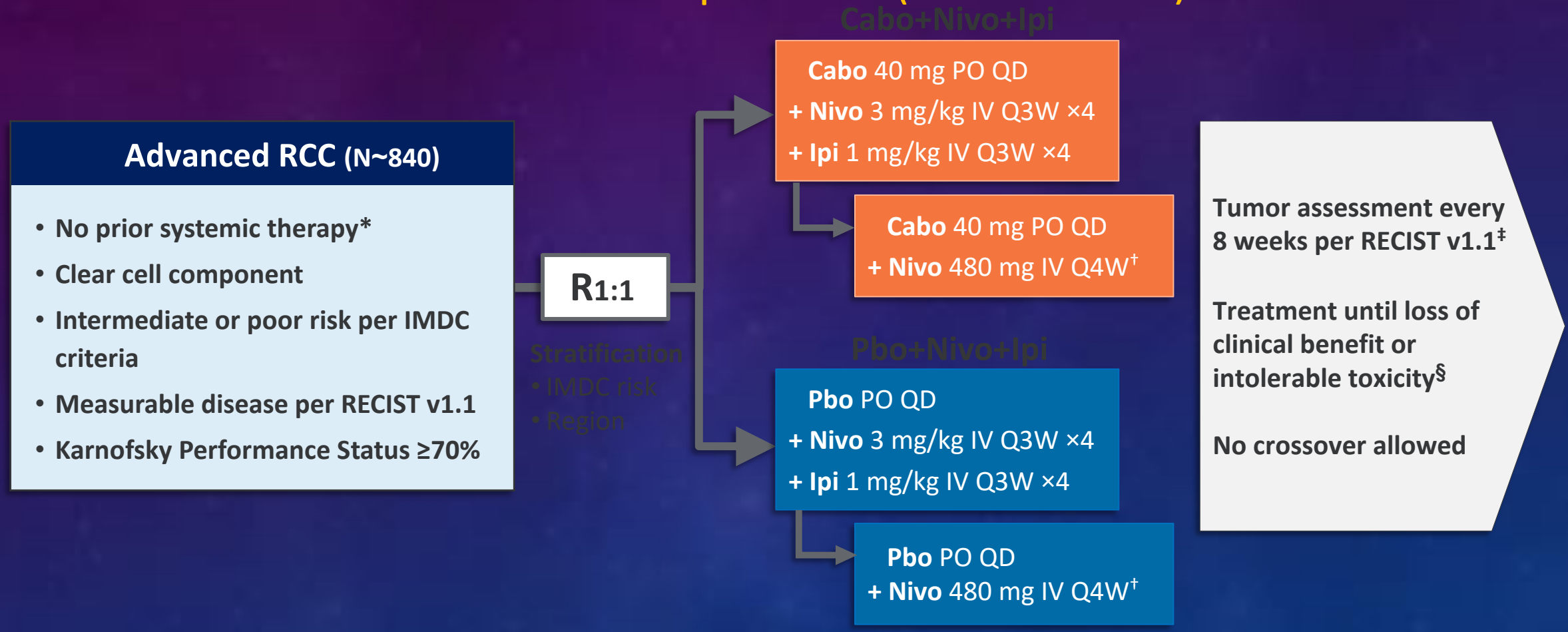
LB8: Phase 3 study of cabozantinib in combination with nivolumab and ipilimumab in previously untreated advanced renal cell carcinoma of IMDC intermediate or poor risk (COSMIC-313)



*One prior systemic adjuvant therapy allowed for completely resected RCC and if recurrence occurred ≥6 months after the last dose of adjuvant therapy; adjuvant PD-1 or PD-L1 inhibitor in combination with a CTLA-4 inhibitor not permitted. †Nivolumab given for a maximum of 2 years. ‡Tumor assessment (RECIST v1.1) at week 10, then every 8 weeks through week 50, then every 12 weeks thereafter. §Discontinuation of one agent did not mandate discontinuation of all agents.

Slides Courtesy of Dr. Toni K. Choueiri

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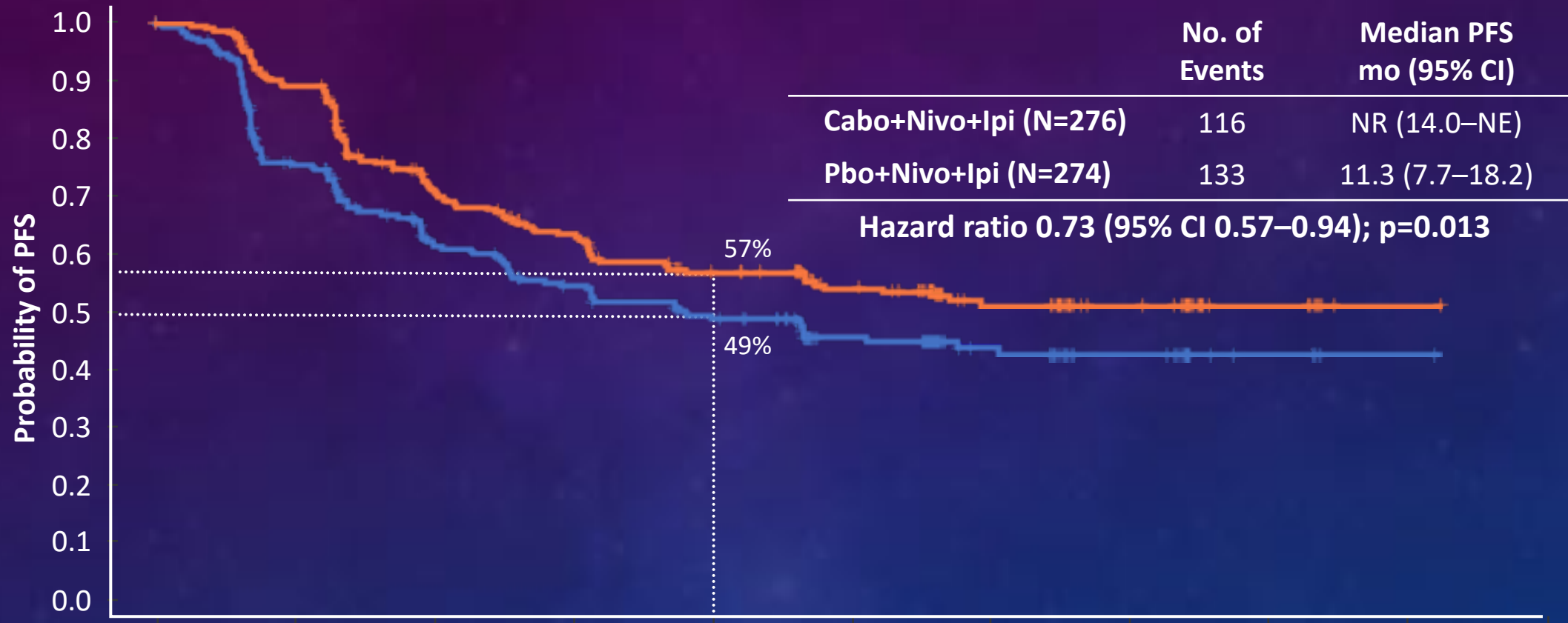
Progression-Free Survival: Final Analysis (PITT Population)



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=276)	116	NR (14.0–NE)
Pbo+Nivo+Ipi (N=274)	133	11.3 (7.7–18.2)

Hazard ratio 0.73 (95% CI 0.57–0.94); p=0.013

Number at Risk											
Cabo+Nivo+Ipi	276	234	170	145	119	97	56	33	10	1	0
Pbo+Nivo+Ipi	274	185	136	115	98	69	37	19	5	1	0

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PFS per RECIST v1.1 by BIRC.

Date of the 249th event: Aug 23, 2021

Courtesy of Dr. Toni K. Choueiri

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Tumor Response (PITT Population)

	Cabo+Nivo+Ipi (N=276)	Pbo+Nivo+Ipi (N=274)
Objective response rate (95% CI), %	43 (37.2–49.2)	36 (30.1–41.8)
Best overall response, n (%)		
Complete response	7 (3)	9 (3)
Partial response	112 (41)	89 (32)
Stable disease	119 (43)	100 (36)
Progressive disease	23 (8)	55 (20)
Not evaluable	15 (5)	21 (8)
Disease control rate, %	86	72
Median time to objective response (range), mo	2.4 (1.5–17.1)	2.3 (1.9–16.8)
Median duration of response (95% CI), mo	NR (20.2–NE)	NR (NE–NE)

Tumor response per RECIST v1.1 by BIRC
Disease control rate = complete response + partial response + stable disease

Data cut-off: Jan 31, 2022

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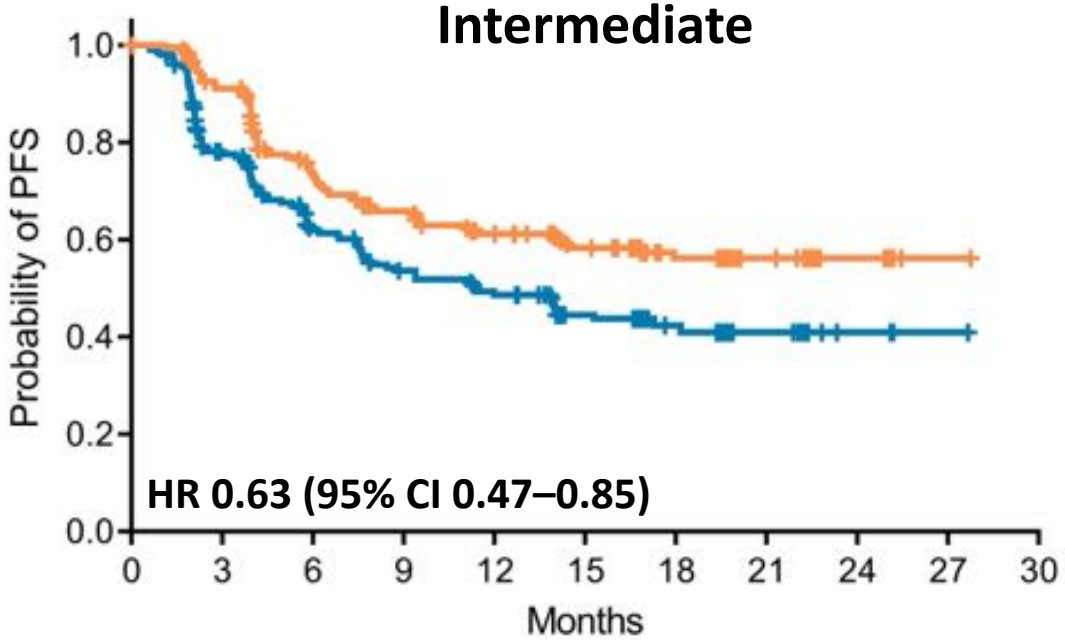
PFS and ORR by IMDC Risk Group (PITT Population)

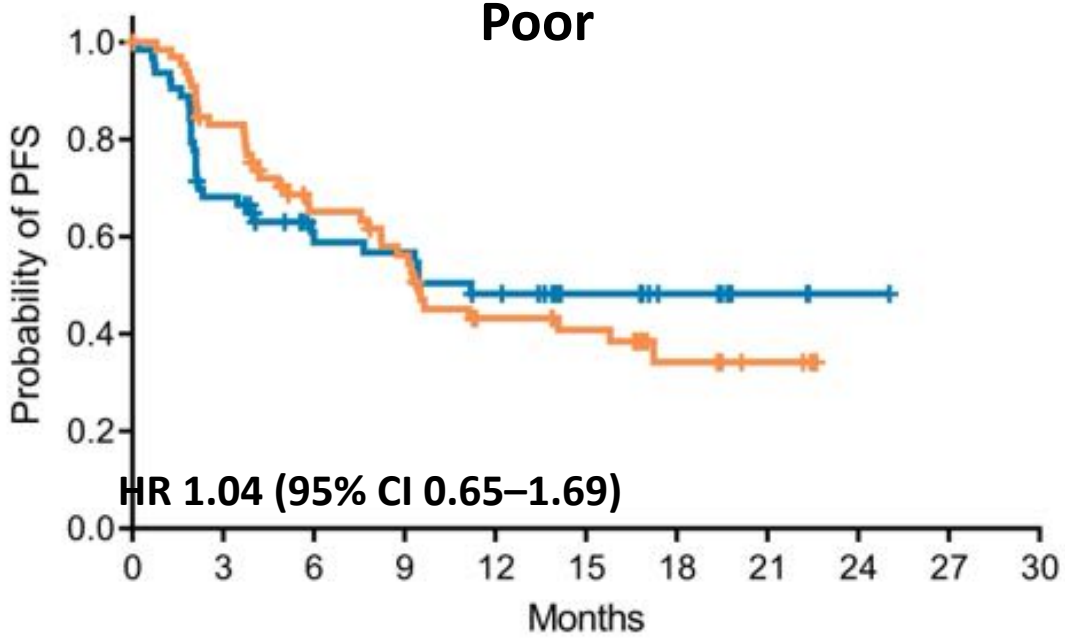
Intermediate



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=209)	79	NR (16.9–NE)
Pbo+Nivo+Ipi (N=208)	103	11.4 (7.6–17.3)

ORR: 45% (95% CI, 38.1–52.0) for Cabo+Nivo+Ipi vs
35% (95% CI, 28.6–42.0) for Pbo+Nivo+Ipi

Poor



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=67)	37	9.5 (7.8–17.3)
Pbo+Nivo+Ipi (N=66)	30	11.2 (4.0–NE)

ORR: 37% (95% CI, 25.8–50.0) for Cabo+Nivo+Ipi vs
38% (95% CI, 26.2–50.7) for Pbo+Nivo+Ipi

PFS and ORR per RECIST v1.1 by BIRC. IMDC risk group is per IxRS.

Date of the 249th PFS event: Aug 23, 2021
Data cut-off for ORR: Jan 31, 2022

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Summary of Adverse Events (Safety Population)

	Cabo+Nivo+Ipi (N=426)		Pbo+Nivo+Ipi (N=424)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse events				
Any event,* %	99	73	91	41
Alanine aminotransferase increased	46	26	17	6
Aspartate aminotransferase increased	44	20	16	5
Diarrhea	41	4	18	3
Palmar-plantar erythrodysesthesia	28	3	4	0
Hypothyroidism	24	<1	15	0
Hypertension	23	8	5	2
Fatigue	22	2	21	1
Lipase increased	22	9	13	6
Amylase increased	20	5	12	2
Rash	20	2	20	1
Pruritus	20	0	26	<1

- Grade 5 TRAEs occurred in 3 patients (1%) with Cabo+Nivo+Ipi (gastrointestinal hemorrhage, hepatic failure, and respiratory failure) and 3 patients (1%) with Pbo+Nivo+Ipi (renal failure, myocarditis, and sudden death) ≤30 days after last dose; through 100 days after last dose, two additional patients had grade 5 TRAEs with Cabo+Nivo+Ipi (immune-mediated hepatitis and acute hepatic failure) and one additional patient with Pbo+Nivo+Ipi (perforated ulcer)
- Use of high-dose corticosteroids (≥40 mg of prednisone or equivalent) for AEs was 58% with Cabo+Nivo+Ipi and 35% with Pbo+Nivo+Ipi

*Occurring in ≥20% of either treatment group.

Data cut-off: Jan 31, 2022

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RENAL CELL CARCINOMA ABSTRACTS: CONCLUSIONS

- ASCO/ESMO 2022: Important contributions in the adjuvant setting (5 large randomized perioperative or adjuvant trials), and some advances in the first line setting (confirmation of IO-TKI doublets and early evidence of benefit from triplets
- Abstract 290 (Keynote 564): After a median follow-up period of 30 months adjuvant pembrolizumab maintained a clinically meaningful and significant PFS benefit versus placebo in the adjuvant setting.
  - Checkmate 914, IMMOTION 010, PROSPER RCC, EVEREST: Negative
- Abstract 1449 (CLEAR): LEN + PEMBRO continued to show a clinically meaningful benefit in PFS, OS, and ORR vs SUN, consistent with primary analysis results of the CLEAR study (Motzer 2021, *NEJM*).
- Abstract LBA 8 (COSMIC 313): COSMIC-313 study demonstrated a significant benefit in PFS with Cabo+Nivo+Ipi vs Pbo+Nivo+Ipi in previously untreated patients with advanced RCC of IMDC intermediate or poor risk
  - This was the first study to use an immuno-oncology doublet standard of care as the control
  - OS data not mature
  - Hepatic toxicity higher in triplet than doublet

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