Updates in RCC and Urothelial Cancer

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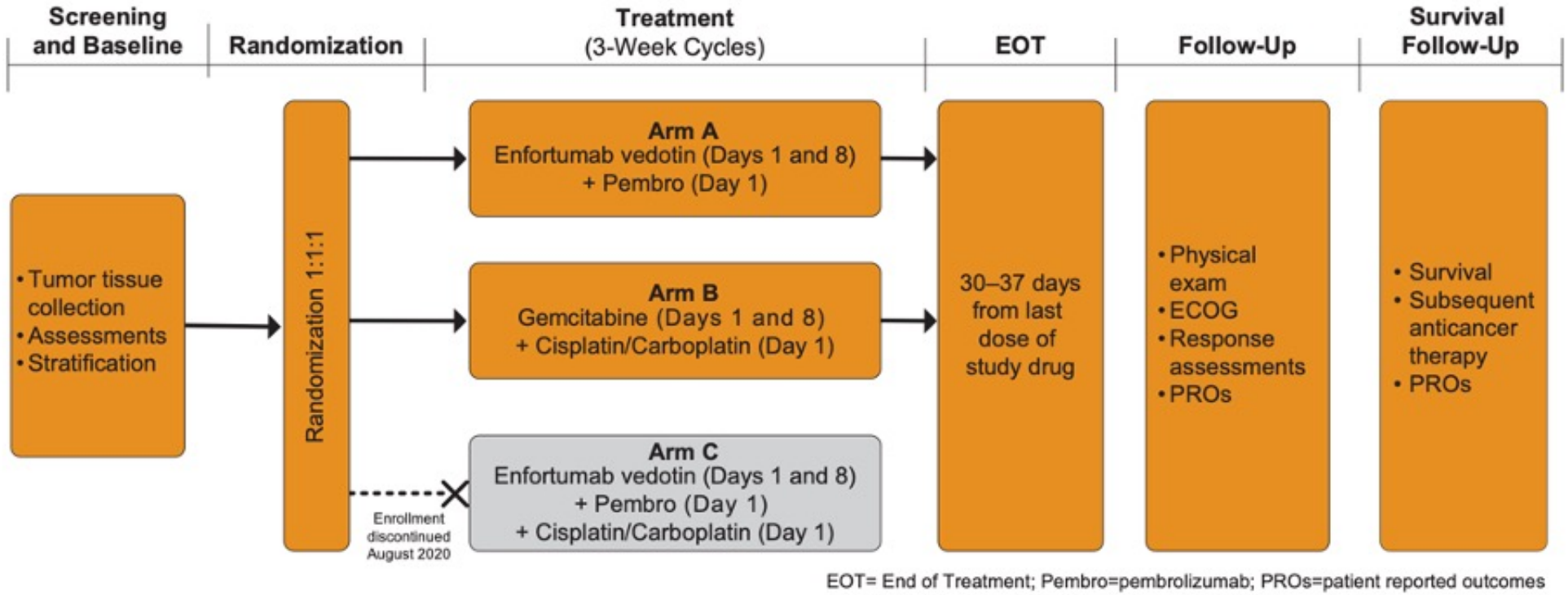
Urothelial Cancer: Remarkable Advances

Enfortumab + pembro shows remarkable OS benefit

Checkmate 901: Cis + gem +/- nivo shows OS benefit

EV-302 Enfortumab vs Platinum Based Chemo



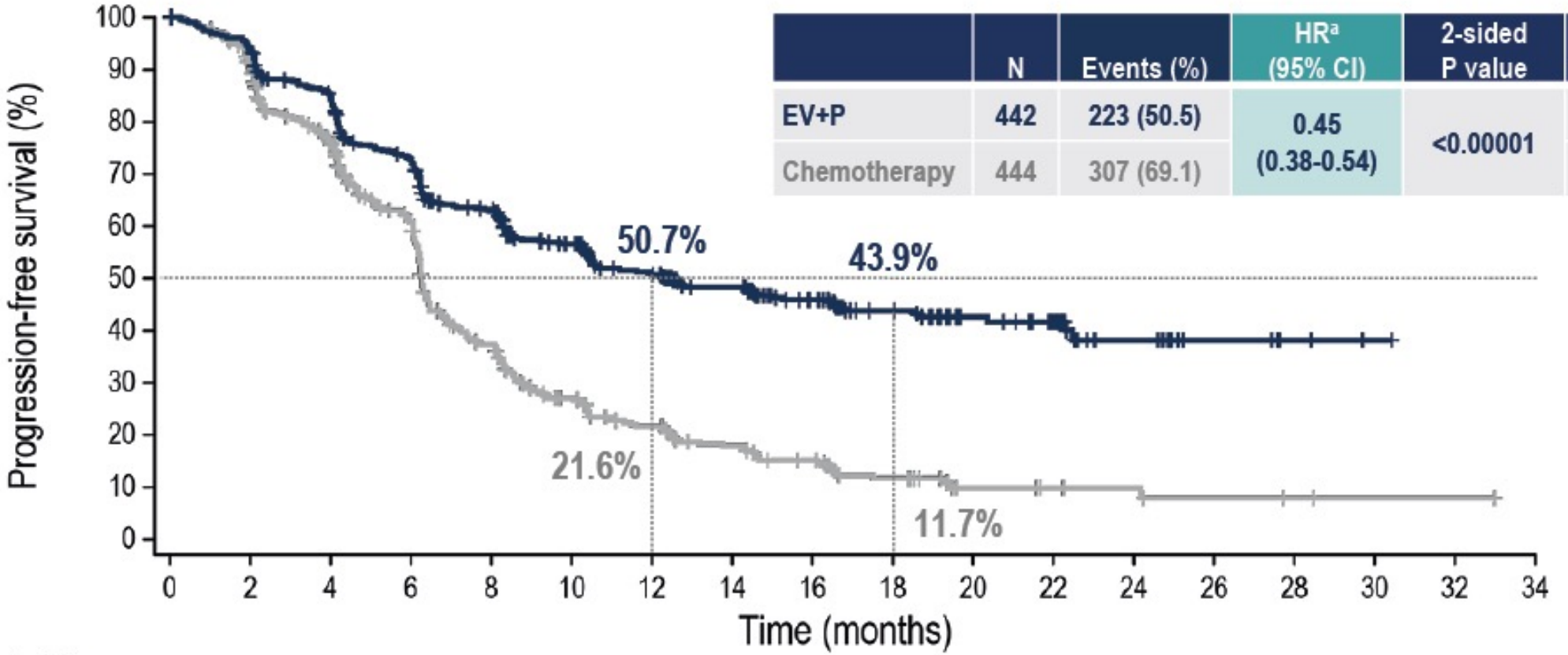
EOT= End of Treatment; Pembro=pembrolizumab; PROs=patient reported outcomes

- Stratification Factors for Randomization: cisplatin eligibility (eligible/ineligible), liver metastases (present/absent), PD-L1 expression (high/low)
- Follow-up until disease progression, death, consent withdrawal, or study closure

Progression-Free Survival per BICR

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

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



N at risk

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

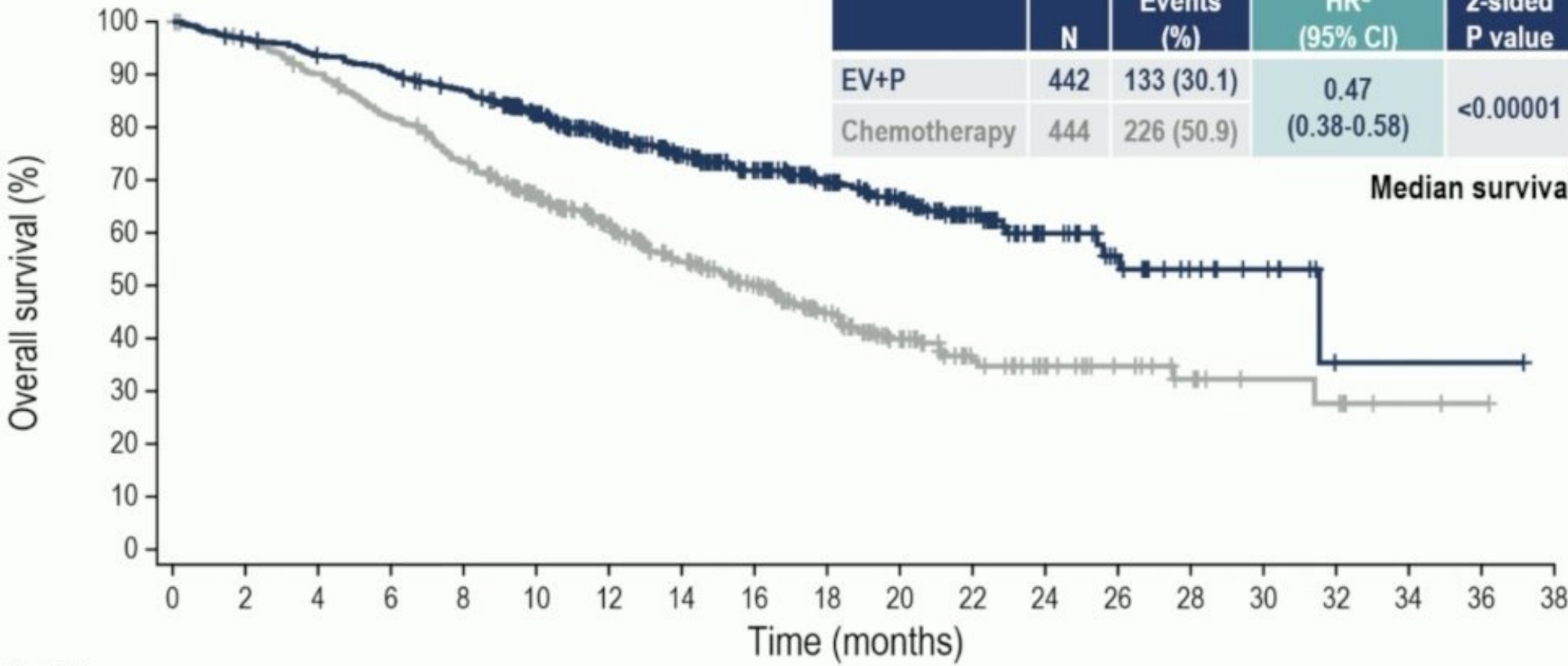
mPFS at 12 and 18 months as estimated using Kaplan-Meier method
HR, hazard ratio; mPFS, median progression-free survival
[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm

Overall Survival

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

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

Median survival follow-up: 17.2 months

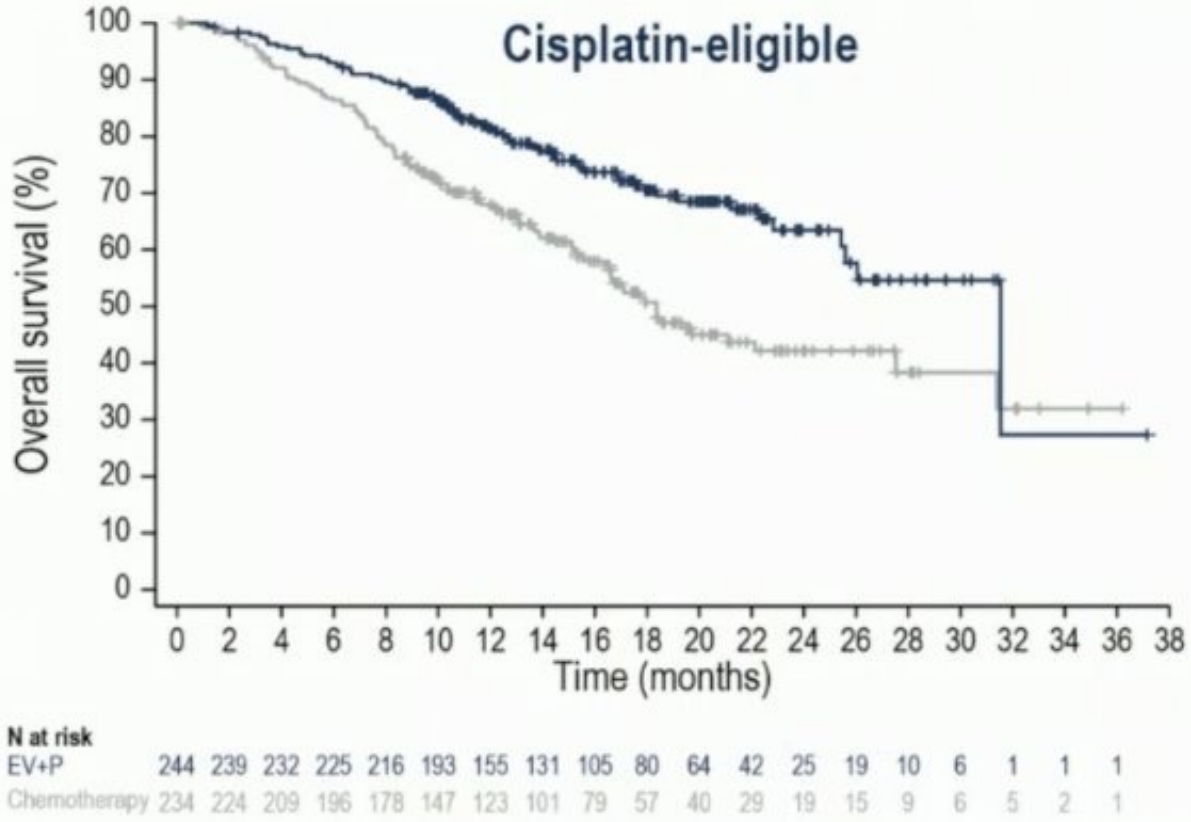


N at risk

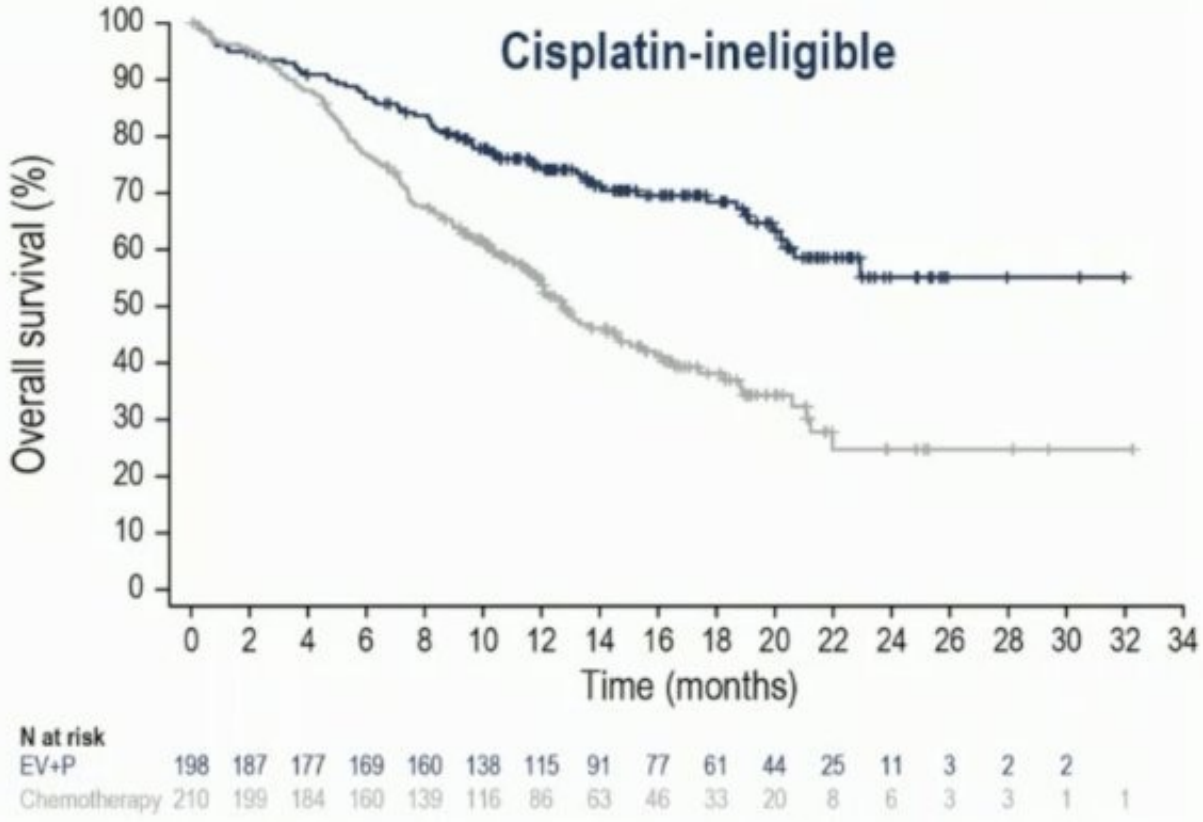
EV+P	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

OS Subgroup Analysis: Cisplatin Eligibility

OS benefit was consistent with overall population regardless of cisplatin eligibility



	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	69	0.53 (0.39-0.72)	31.5 (25.4-NR)
Chemotherapy	106		18.4 (16.4-27.5)



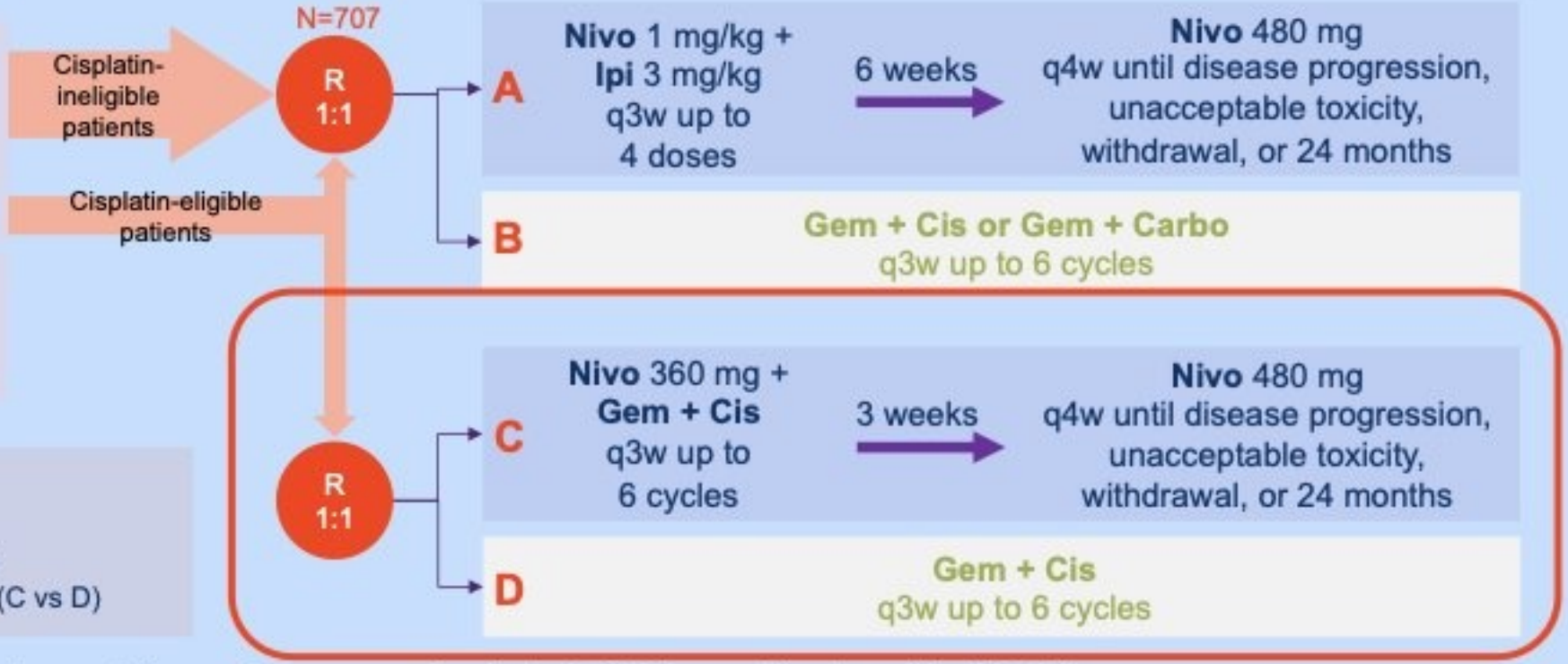
	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	64	0.43 (0.31-0.59)	NR (20.7-NR)
Chemotherapy	120		12.7 (11.4-15.5)

CheckMate 901: Phase 3 Trial of Nivolumab in Combination

N=1307
- Previously untreated unresectable or metastatic UC (1L)
- Cisplatin eligible or ineligible
- ECOG PS 0-1

Stratification Factors
- PD-L1 expression <1%
- Cisplatin eligibility
- Presence of liver metastases

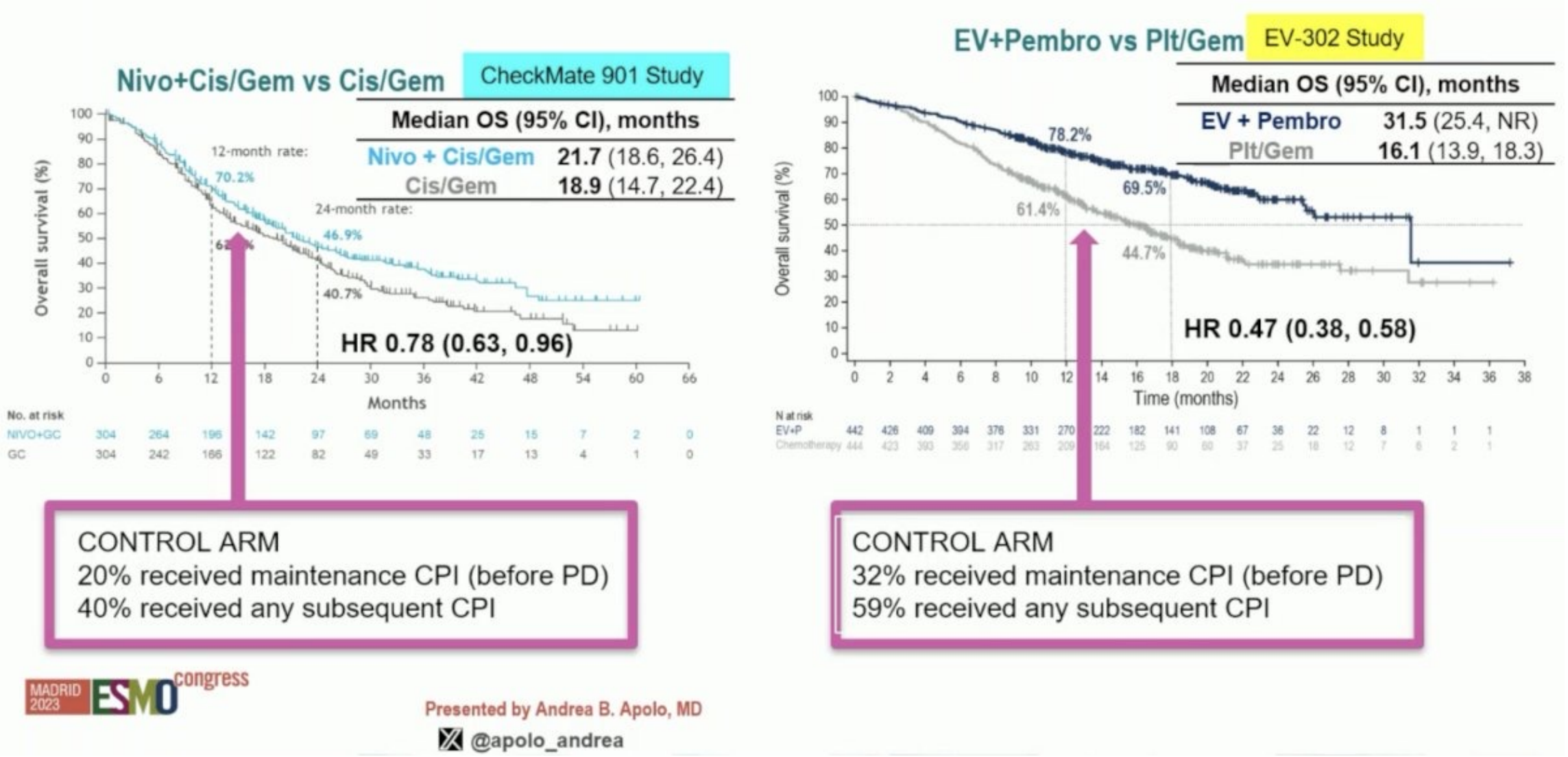
Primary endpoints
- OS in patients with PD-L1 ≥1% (A vs B)
- OS in cisplatin-ineligible patients (A vs B)
- OS and PFS in cisplatin-eligible patients (C vs D)



- Nivo + Ipi vs Chemo did not meet the primary endpoint of OS in patients with PD-L1 ≥1%
- Ongoing assessment of Nivo + Ipi vs Carbo + Gem in cisplatin-ineligible patients
- Ongoing substudy of Nivo + Cis + Gem vs Cis + Gem

Galsky MD. ASCO 2018. Abstract TPS4588.

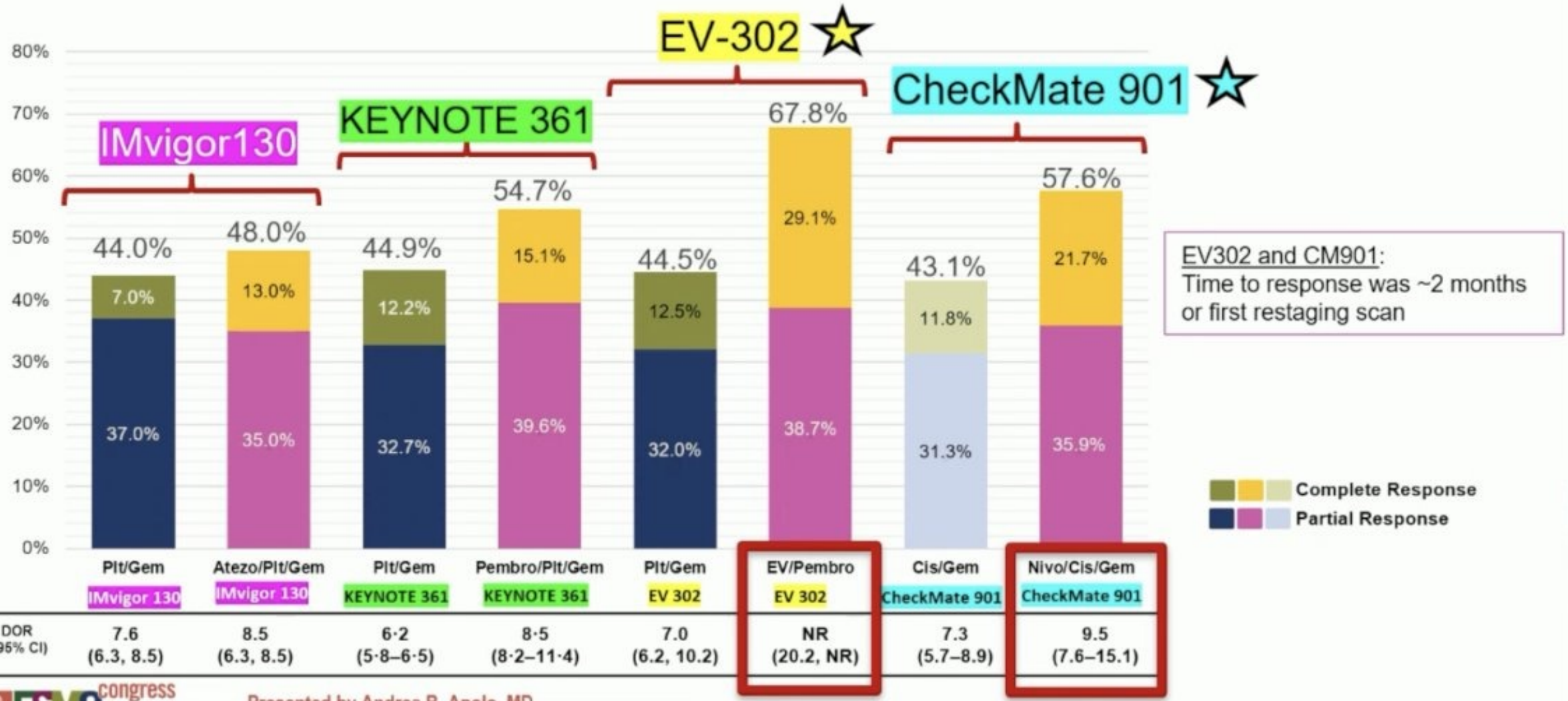
EV302 and Checkmate 901



Cross-trial comparison on display

WARNING

EV + Pembro's Duration of Response is longer



EV302 and CM901:
Time to response was ~2 months or first restaging scan

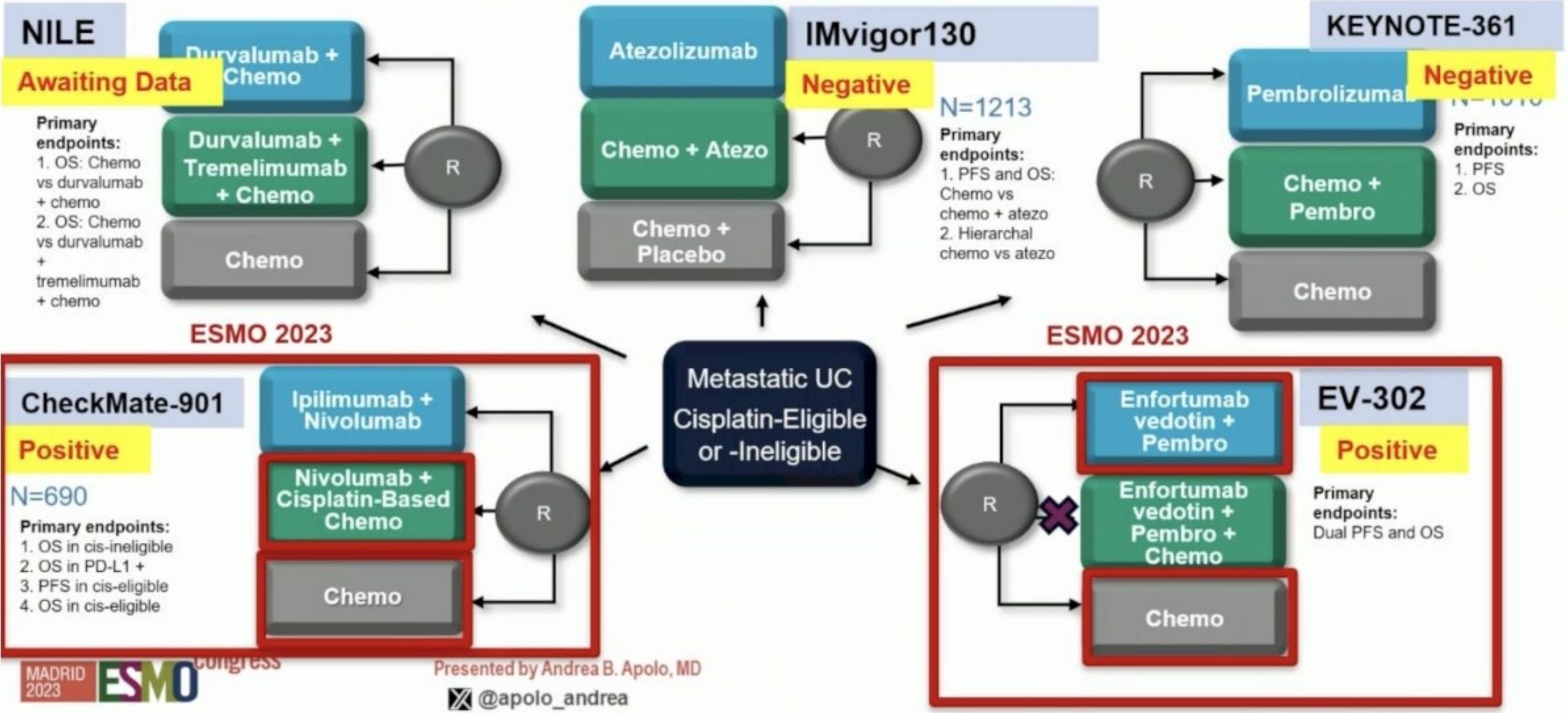
	Plt/Gem IMvigor 130	Atezo/Plt/Gem IMvigor 130	Plt/Gem KEYNOTE 361	Pembro/Plt/Gem KEYNOTE 361	Plt/Gem EV 302	EV/Pembro EV 302	Cis/Gem CheckMate 901	Nivo/Cis/Gem CheckMate 901
Median DOR Months, (95% CI)	7.6 (6.3, 8.5)	8.5 (6.3, 8.5)	6·2 (5·8–6·5)	8·5 (8·2–11·4)	7.0 (6.2, 10.2)	NR (20.2, NR)	7.3 (5.7–8.9)	9.5 (7.6–15.1)

MADRID 2023 ESMO congress

Presented by Andrea B. Apolo, MD

@apolo_andrea

First-line Phase 3 Trials with Checkpoint-Inhibitor Combinations vs Platinum-based Chemo for Metastatic Urothelial Carcinoma



MADRID 2023 ESMO Congress

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@apolo_andrea

New Paradigm of Bladder Cancer Therapy

Front Line Therapy Options:
Enfortumab + Pembro
OR
Cisplatin + Gemcitabine + Nivolumab

Second Line:
Enfortumab
Sacituzumab?
Platinum + Gem?

Clinical trial: S1937 Eribulin + gem vs physicians choice

FGFR3 mutation:
Erdafitinib

Third Line:

Clinical Trial

Her-2 ADC?

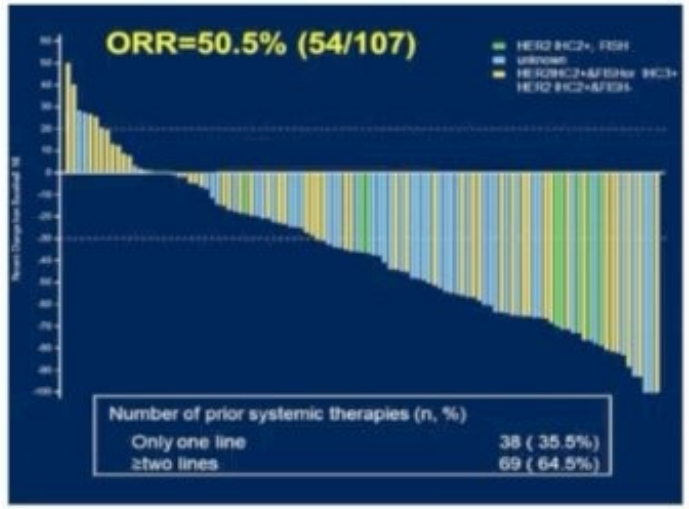
Sacituzumab

Does CPI combine best with ADCs with MMAE payloads?

Disitamab vedotin in HER2 2/3+ Metastatic Urothelial Carcinoma

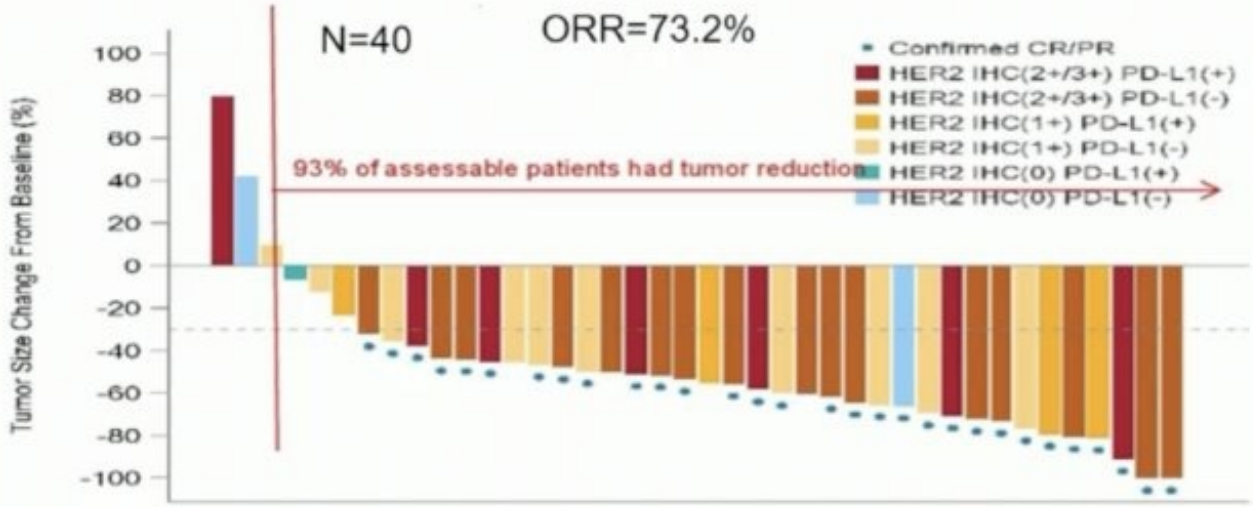
Disitamab vedotin

N=107 In the Second or Third-line setting



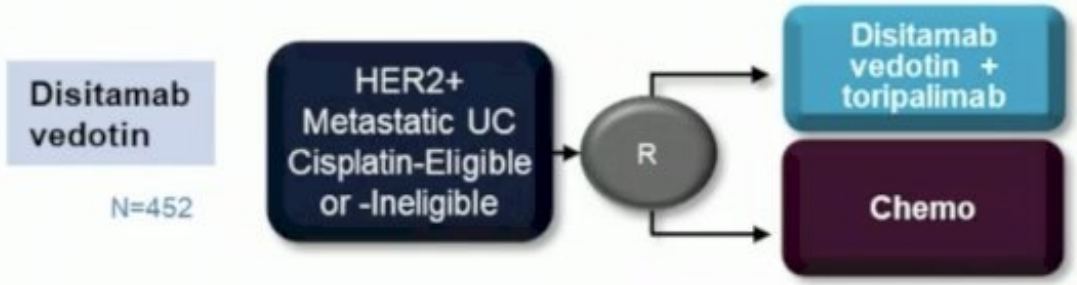
Sheng, et al. ASCO 2022 abstract 4518

Disitamab vedotin + toripalimab

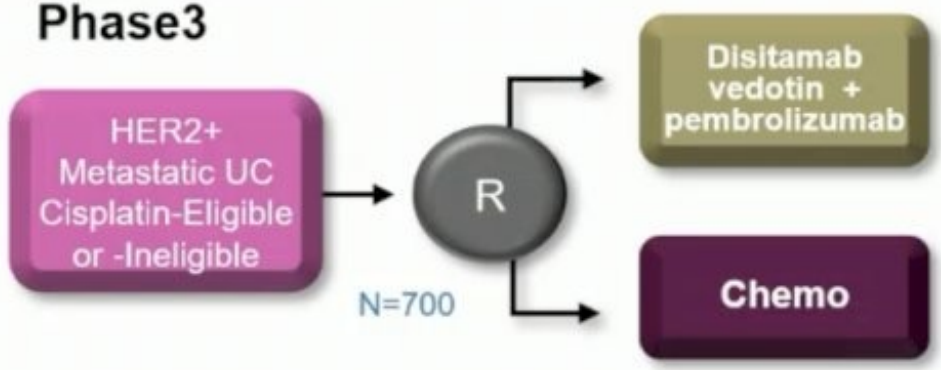


Sheng, X., et al. ASCO 2023

Phase 3



Phase3



Presented by Andrea B. Apolo, MD

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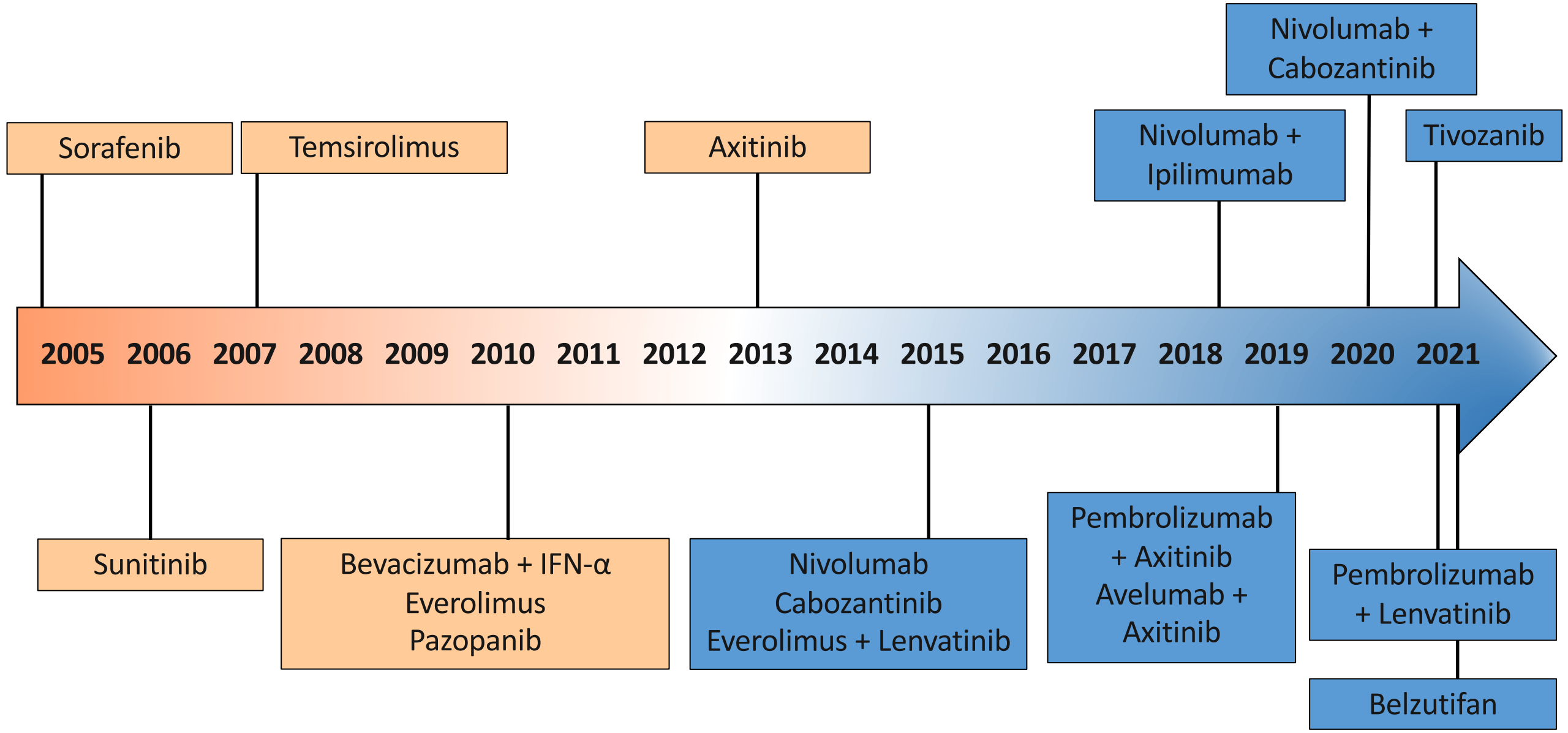
Therapy in RCC

- Updates on nivo + ipi in met RCC
- Updates on Checkmate 9ER
- RFS and OS benefit with adjuvant pembrolizumab

Treatment Landscape of Metastatic RCC



Key Studies in Front Line Metastatic RCC

Motzer et al. NEJM 2021 Lenvatinib + Pembro vs Sunitinib: (CLEAR)

Choueiri T, et al. NEJM 2021 Cabo + Nivo vs Sunitinib: (Checkmate 9ER)

Motzer et al. NEJM 2019 Nivolumab/Ipilimumab vs Sunitinib (CheckMate 214)

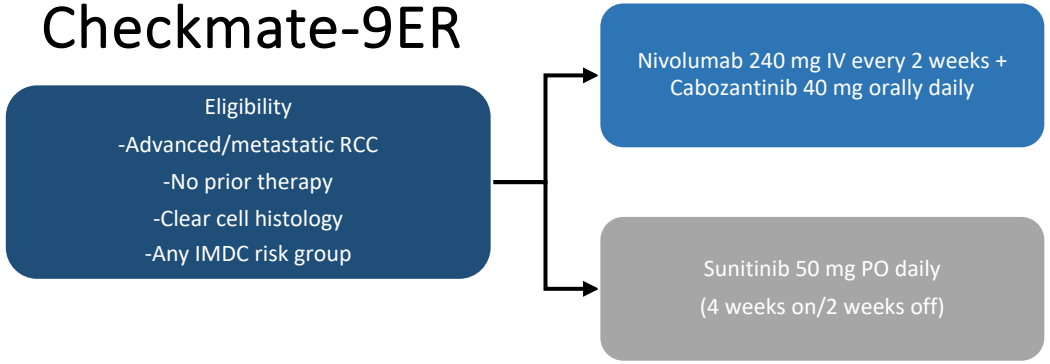
Choueiri et al. NEJM 2019 Axitinib/Avelumab vs Sunitinib (JAVELIN 101)

Rini B et al. NEJM 2019 Axitinib/Pembrolizumab vs Sunitinib (KEYNOTE 426)

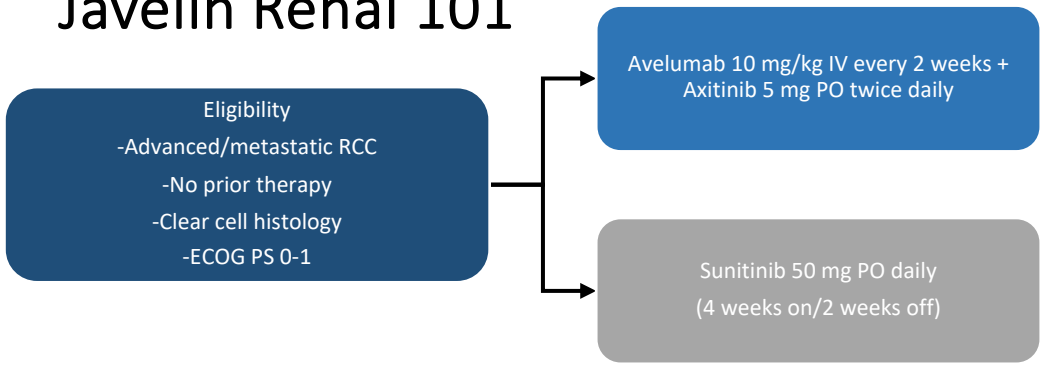
Choueiri T, et al. J Clin Oncol 2017 CABOSUN trial: Cabozantinib vs Sunitinib

Bird's-eye view of practice-changing trials

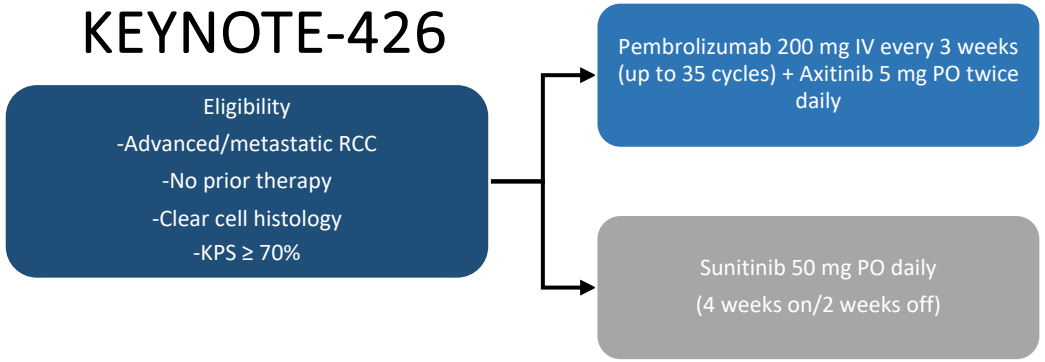
Checkmate-9ER



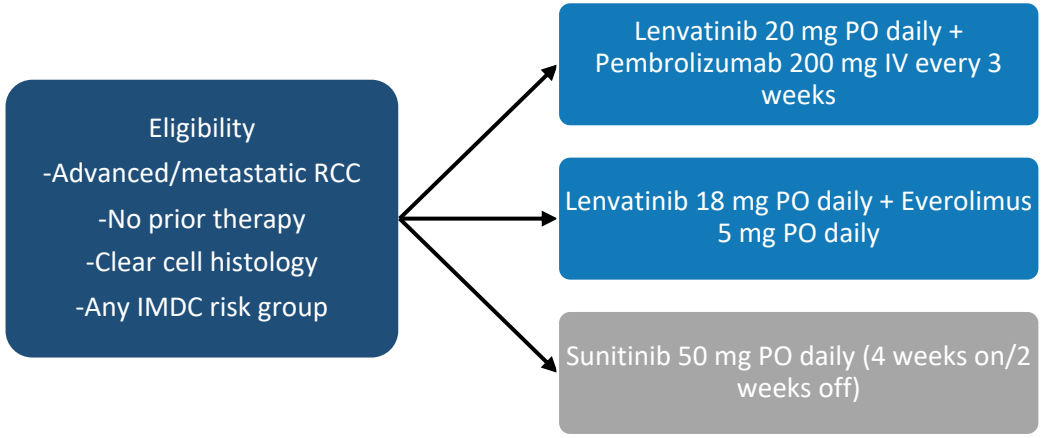
Javelin Renal 101



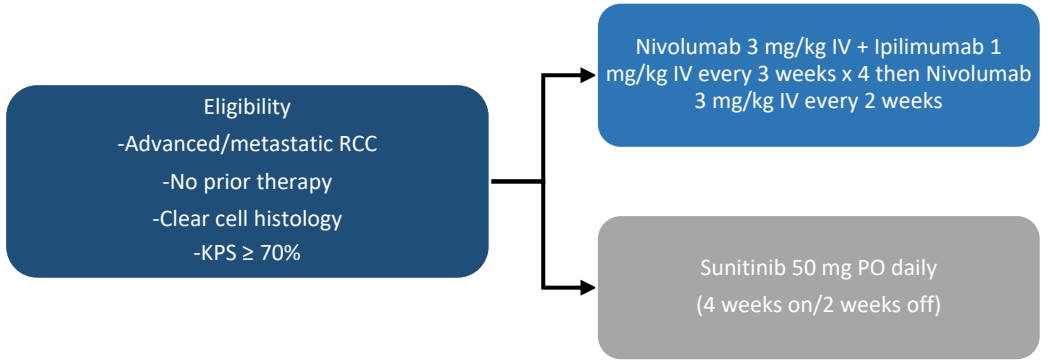
KEYNOTE-426



Phase 3 Clear Trial



CheckMate - 214



Frontline Immunotherapy Combination Studies

Baseline Characteristics

Variable		Nivolumab + Ipilimumab CheckMate-214 n=1096	Pembrolizumab + Axitinib Keynote 426 n=861	Avelumab + Axitinib Javelin 101 n=886	Nivolumab + Cabozantinib CheckMate-9ER n=651	Pembrolizumab + Lenvatinib Clear n=1096
IMDC Risk Group	Favorable	23%	33%	21%	23%	32%
	Intermediate	61%	56%	62%	58%	54%
	Poor	17%	13%	16%	19%	10%
Previous Nephrectomy		81%	83%	80%	69%	73%
PD-L1 Expression ≥1%		24% (Dako PD-L1 28-8; Tumor)	60% (Agilent Tech PD-L1 22C3; CPS)	63% (Ventana PD-L1 SP263; Immune)	25% (Dako PD-L1 28-8; Tumor)	31% (Agilent Tech PD-L1 22C3; CPS)
Primary Endpoint		ORR, PFS, OS in Int/Poor (IRC)	OS, PFS (IRC)	OS, PFS in PD-L1+ (IRC)	PFS (IRC)	PFS (IRC)

IMDC=International Metastatic RCC Database Consortium; PD-L1=Programmed Death Ligand 1; CPS=Combined positive score (TC+IC positive/TC all); ORR=Objective response rate; PFS=Progression-free survival; OS=Overall survival; Int=Intermediate; IRC=Independent review committee.

Motzer et al, NEJM, 2018; Rini et al, NEJM, 2019; Motzer et al, NEJM, 2019; Choueiri et al, NEJM, 2021; Motzer et al, NEJM, 2021.

First-line IO Combination Trials in mRCC

	CheckMate 214[1] Ipi/Nivo vs Sun (n = 550 vs n = 546)	KEYNOTE-426[2] Axi/Pembro vs Sun (n = 432 vs n = 429)	CheckMate 9ER[3] Cabo/Nivo vs Sun (n = 323 vs n = 328)	CLEAR[4] Len/Pembro vs Sun (n = 355 vs n = 357)
mOS, mo HR (CI)	55.7 vs 38.4 **0.72** (0.62-0.85)	45.7 vs 40.1 **0.73** (0.60-0.88)	NR vs 29.5 **0.66** (0.50-0.87)	NR vs NR **0.72** (0.55-0.93)
Landmark OS 12 mo Landmark OS 24 mo	**83%** vs 78% **71%** vs 61%	**90%** vs 79% **74%** vs 66%	**86%** vs 76% **72%** vs 60% (est)	**90%** vs 79% (est.) **79%** vs 70%
mPFS, mo HR (CI)	**12.2** vs 12.3 0.86 (0.73-1.01)	**15.7** vs 11.1 0.68 (0.58-0.80)	**17.0** vs 8.3 0.52 (0.43-0.64)	**23.9** vs 9.2 0.39 (0.32-0.49)
ORR, %	**39** vs 32	**60** vs 40	**55** vs 27	**71** vs 36
CR, %	**12** vs 3	**10** vs 4	**9** vs 4	**16** vs 4
Median f/u, mo	**67.7**	**42.8**	**23.5**	**33.7**
Primary PD, %	**18**	**11**	**6**	**5**
Prognostic risk, % ▪ Favorable ▪ Intermediate ▪ Poor	 23 61 17	 32 55 13	 23 58 19	 31 59 9
Prior nephrectomy	82%	83%	69%	74%
Subsequent systemic Tx for Sun arm, %	Overall (68%) IO (42%)	Overall (69%) IO (48%)	Overall (40%) IO (29%)	Overall (71%) IO (53%)

1. Motzer. ESMO 2021. Abstr 661P. 2. Rini. ASCO 2021. Abstr 4500.
3. Motzer. ASCO GU 2021. Abstr 308. 4. Motzer. ASCO GU 2021. Abstr 269.

Subgroups: Synchronous Mets had 50% the Median OS as compared to entire group!

McDermott D, et al. IKCS 2018, Albiges L et al ESMO 2020 abstr 711P

Patient population	Ipi + Nivo	Sunitinib
Intermediate/Poor Risk	ORR 41.9%/ CR 10.2% Median OS 48 months	ORR 29.4%/ CR 1.3% Median OS 26 months
Sarcomatoid RCC	ORR 56.7%/ CR 18.3 % Median OS 31.2 months 30 month OS 53%	ORR 19.2%/ CR 0% Median OS 13.6 months 30 month OS 29%
Synchronous mRCC with primary	**Primary ORR 34%** **DOR 20.5 months** **Med OS 26 months**	**Primary ORR 14.5%** **DOR 14.5 months** **Med OS 14 months**
Treatment Free Survival	31% free of therapy Median TFS 7.8 months	12% free of therapy Median TFS 3.3 months

Synchronous Primary Tumor and Metastases

- Contemporary randomized cytoreductive nephrectomy trials reveal that resection of primary tumor did not improve survival outcomes {CARMENA and SURTIME}
- Sequential trial shows that initial systemic therapy followed by nephrectomy has better survival outcomes than upfront nephrectomy
- In setting of I-O based regimens the role of nephrectomy has not been evaluated
- SWOG 1931 (PROBE) trial is addressing this question.

Phase III Trial of Immunotherapy-based Combination Therapy with or without Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma (SWOG 1931/PROBE Trial)

Lead investigators:

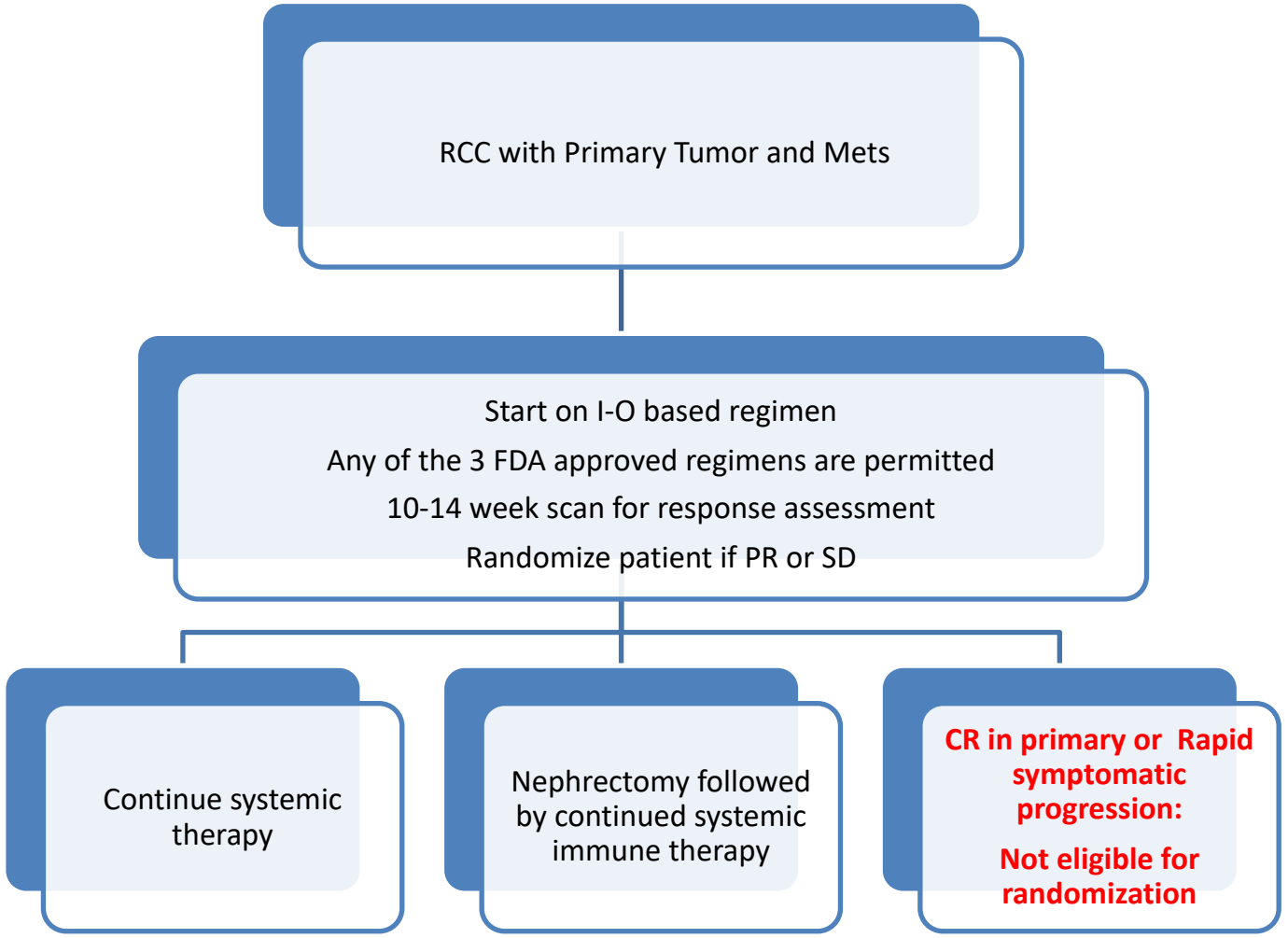
Hyung Kim MD

Ulka Vaishampayan MD

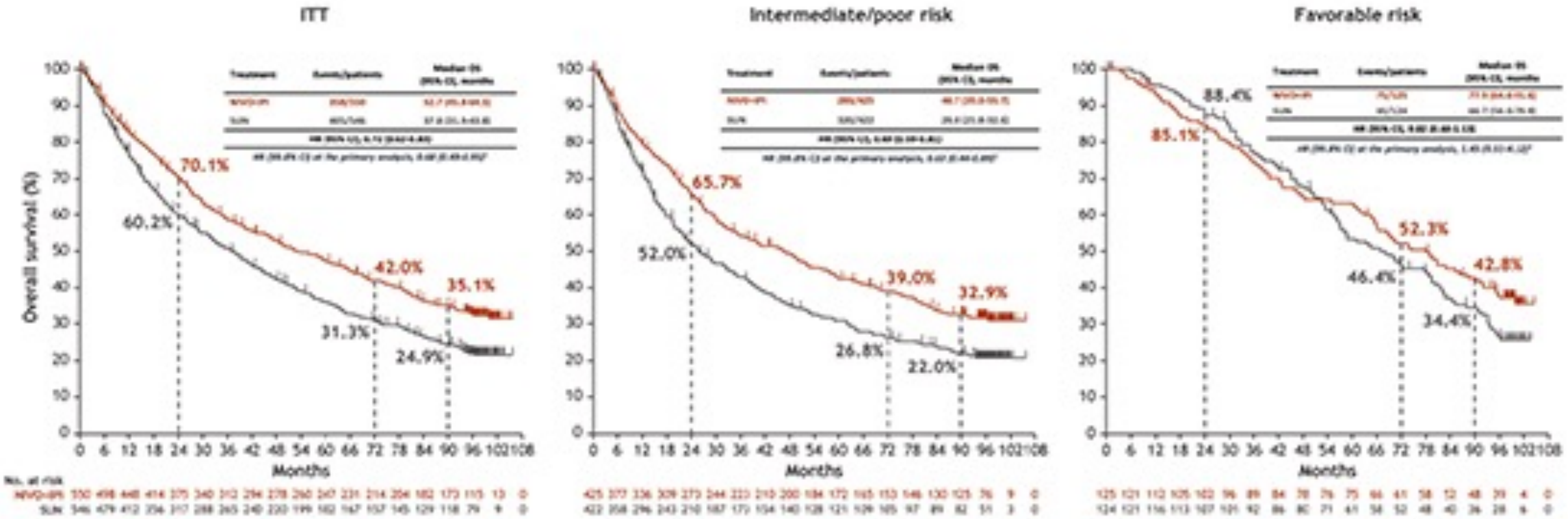
Biostatisticians: Cathy Tangen and Eddie Mayerson

Patient Advocate: Peggy Zuckerman

SWOG 1931/PROBE Trial
Primary Endpoint: Overall Survival



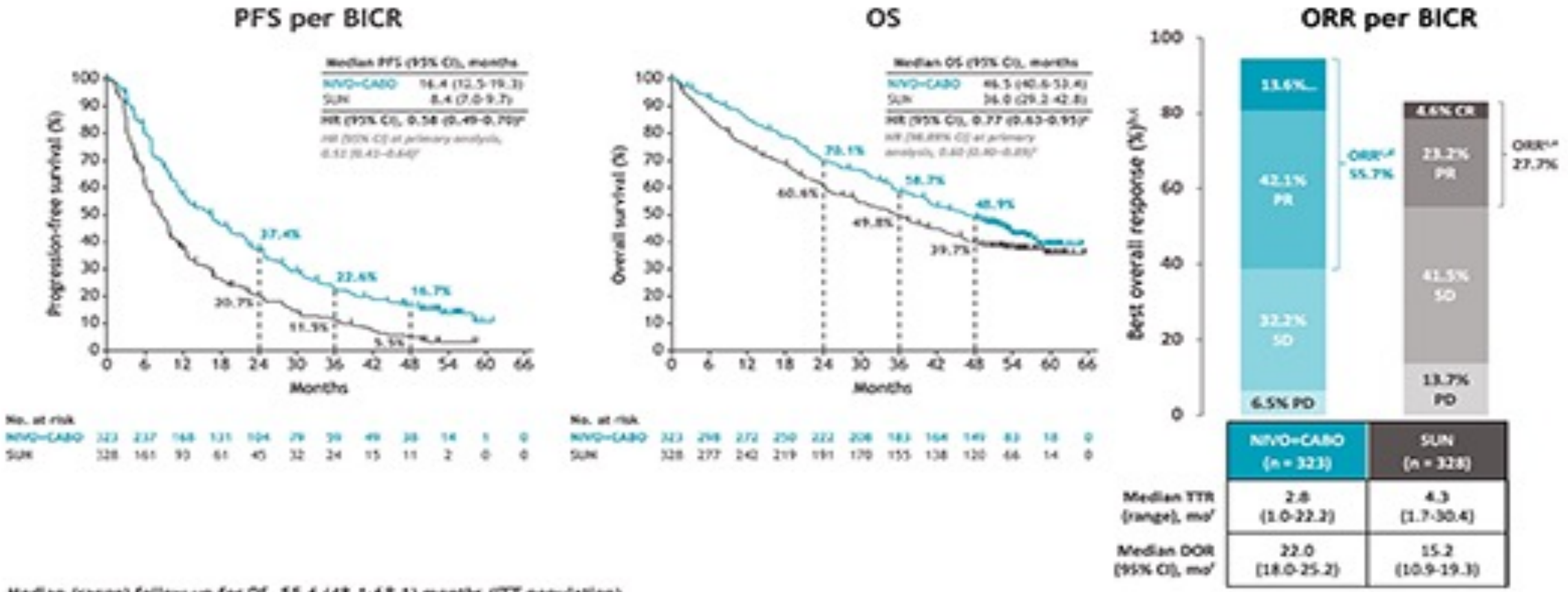
Long term OS with Ipi +Nivo CM-214



Stratified Cox proportional hazards model.

1. Motzer RJ, et al. *N Engl J Med* 2018;378:1277–1290.

Checkmate 9ER Update



Median (range) follow-up for OS, 55.6 (48.1-68.1) months (ITT population).
[a]Stratified Cox proportional hazards model used for HR. [b]Unable to determine/not reported: 5.6% for NIVO+CABO; 17.1% for SUN. [c]No. of patients with ORR and BOR in NIVO+CABO arm: ORR, n = 180; CR, n = 44; PR, n = 136; SD, n = 104; PD, n = 21. No. of patients with ORR and BOR in SUN arm: ORR, n = 91; CR, n = 15; PR, n = 76; SD, n = 136; PD, n = 45. [d]95% CI, 50.1-61.2. [e]95% CI, 23.0-32.9. [f]TTR and DOR were calculated only for patients who had a CR or PR.

1. Choueiri TK, et al. *N Engl J Med* 2021;384:829-841.

Systemic Therapy of RCC: Second line and Beyond

Cabozantinib

Nivolumab

Lenvatinib + Everolimus

Tivozanib

Belzutifan

Type of Progression: Oligoprogression/ Diffuse Progression

- Oligo progression
- Consider size/location
- Symptomatic vs asymptomatic
- Amenable to local therapy
- Consider SBRT/ resection and continue systemic therapy
- Consider time to progression on current therapy
- Tolerability of current therapy

- Diffuse Progression
- Prior therapy MOA
- Location: symptomatic vs asymptomatic
- Location of metastases: adrenal/pancreas mets consider local therapy
- Bone mets: consider systemic and local therapy
- Prior therapy depth and duration of response

Key Studies in Pretreated Metastatic RCC

Chouieri T. et al. NEJM 2015 Cabozantinib vs Everolimus: (METEOR)

Motzer R, et al. NEJM 2015 Nivo vs Everolimus: (Checkmate 025)

Rini B, et al. Lancet 2011 Axitinib vs Sorafenib (AXIS)

Rini B. et al. Lancet Oncol 2020 TIVO-3 Tivozanib vs Sorafenib (TIVO-3)

Motzer R, et al. Lancet Oncol 2015 Lenvatinib + Everolimus vs Everolimus

HCRN GU-16-260 trial, Fraction trial and Omnivore trial,McKay R, et al.

Therapies for Relapsed or Refractory Stage IV RCC

- Second-line treatments for advanced or metastatic RCC may include targeted therapies and immunotherapy combinations

Immunotherapy-Based Regimens

- **Nivolumab**
- **Nivolumab + ipilimumab**
- Axitinib + pembrolizumab
- Axitinib + avelumab
- Cabozantinib + nivolumab
- Lenvatinib + pembrolizumab

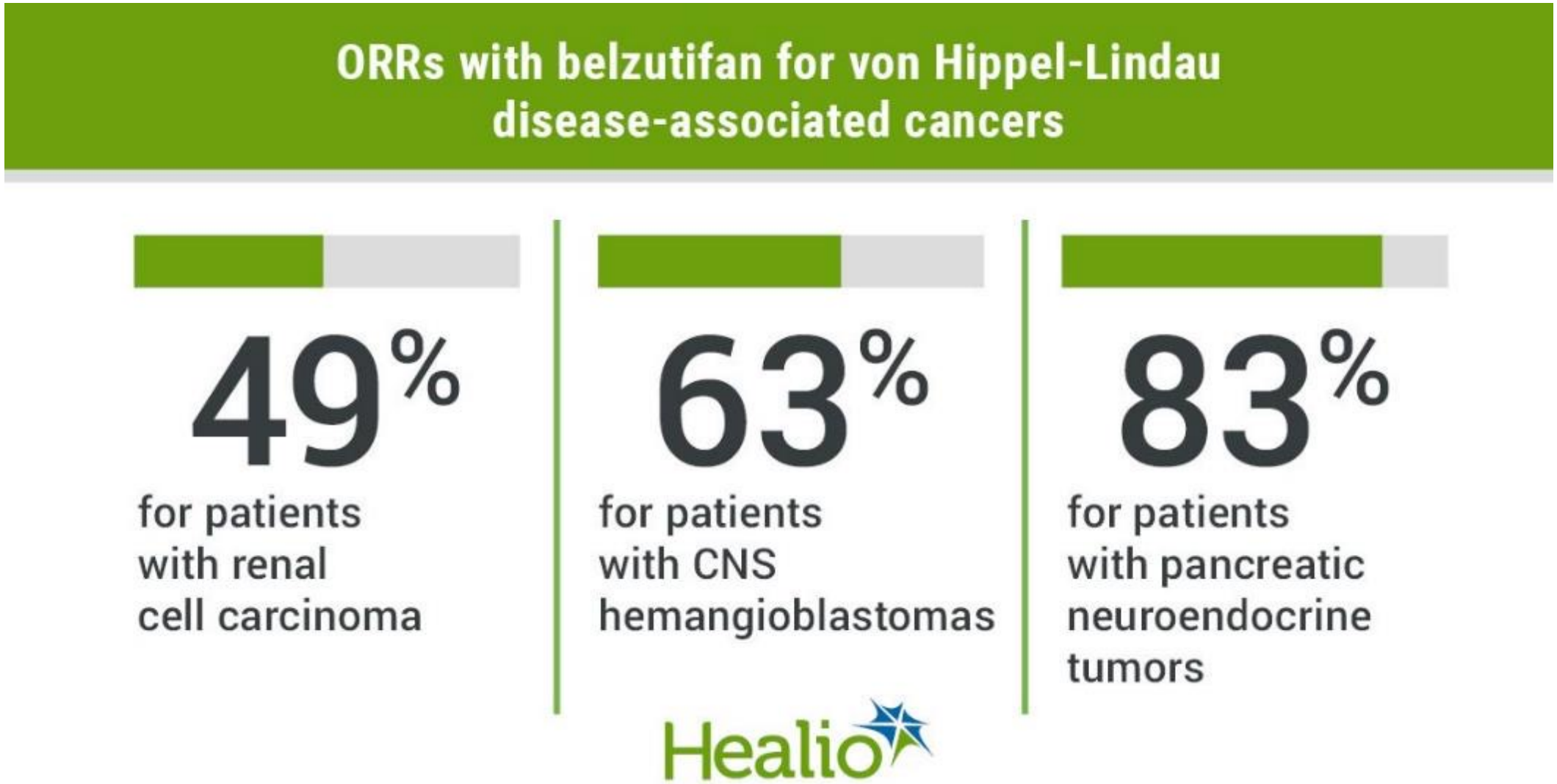
Targeted Therapies

- **Cabozantinib**
- **Lenvatinib + everolimus**
- Axitinib
- Everolimus
- Pazopanib
- Sunitinib
- Tivozanib
- Belzutifan

Other Targeted Treatments for Select Circumstances

- Belzutifan (for VHL-associated RCC)
- Bevacizumab
- Sorafenib
- High-dose IL-2
- Temsirolimus

HIF 2 alpha inhibitor belzutifan



Belzutifan Versus Everolimus in Patients With Previously Treated Advanced Clear Cell Renal Cell Carcinoma: Randomized Open-Label Phase 3 LITESPARK-005 Study

Laurence Albiges[1], Brian Rini[2], Katriina Peltola[3], Guillermo de Velasco[4], Mauricio Burotto[5], Cristina Suarez Rodriguez[6], Pooja Ghatalia[7], Roberto Iacovelli[8], Elaine T. Lam[9], Elena Verzoni[10], Mahmut Gumus[11], Walter M. Stadler[12]; Christian Kollmannsberger[13], Bohuslav Melichar[14], Balaji Venugopal[15], Aobo Wang[16], Rodolfo F. Perini[16], Donna Vickery[16], Thomas Powles[17], Toni K. Choueiri[18]

[1]Département de Médecine Oncologique, Gustave Roussy, Université Paris Saclay, Villejuif, France; [2]Vanderbilt Ingram Cancer Center, Nashville, TN, USA; [3]HUS Helsinki University Hospital, Comprehensive Cancer Center, Helsinki, Finland; [4]University Hospital 12 de Octubre, Madrid, Spain; [5]Bradford Hill Clinical Research Center, Santiago, Chile; [6]Medical Oncology, Vall d´Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d´Hebron, Vall d´Hebron Barcelona Hospital Campus, Barcelona, Spain; [7]Fox Chase Cancer Center, Philadelphia, PA, USA; [8]Fondazione Policlinico Universitario A. Gemelli IRCC, Rome, Italy; [9]University of Colorado Cancer Center, Aurora, CO, USA; [10]Istituto Nazionale dei Tumori, Milano, Italy; [11]Göztepe Prof. Dr. Süleyman Yalçın Şehir Hastanesi-oncology, Istanbul, Türkiye; [12]The University of Chicago Medical Center, Chicago, IL, USA; [13]BC Cancer–Vancouver Center, Vancouver, BC, Canada; [14] Department of Oncology, Palacký University Hospital, Olomouc, Czech Republic; [15]The Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, UK; [16]Merck & Co., Inc., Rahway, NJ, USA; [17]St Bartholomew's Hospital–Barts Health NHS Trust, London, UK; [18]Dana-Farber Cancer Institute, Boston, MA, USA

LITESPARK-005 Study (NCT04195750)

Key Eligibility Criteria

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

R 1:1

N = 374 → **Belzutifan** 120 mg orally daily

N = 372 → **Everolimus** 10 mg orally daily

Stratification Factors

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

Dual Primary Endpoints:

- PFS per RECIST 1.1 by BICR
- OS

Key Secondary Endpoint:

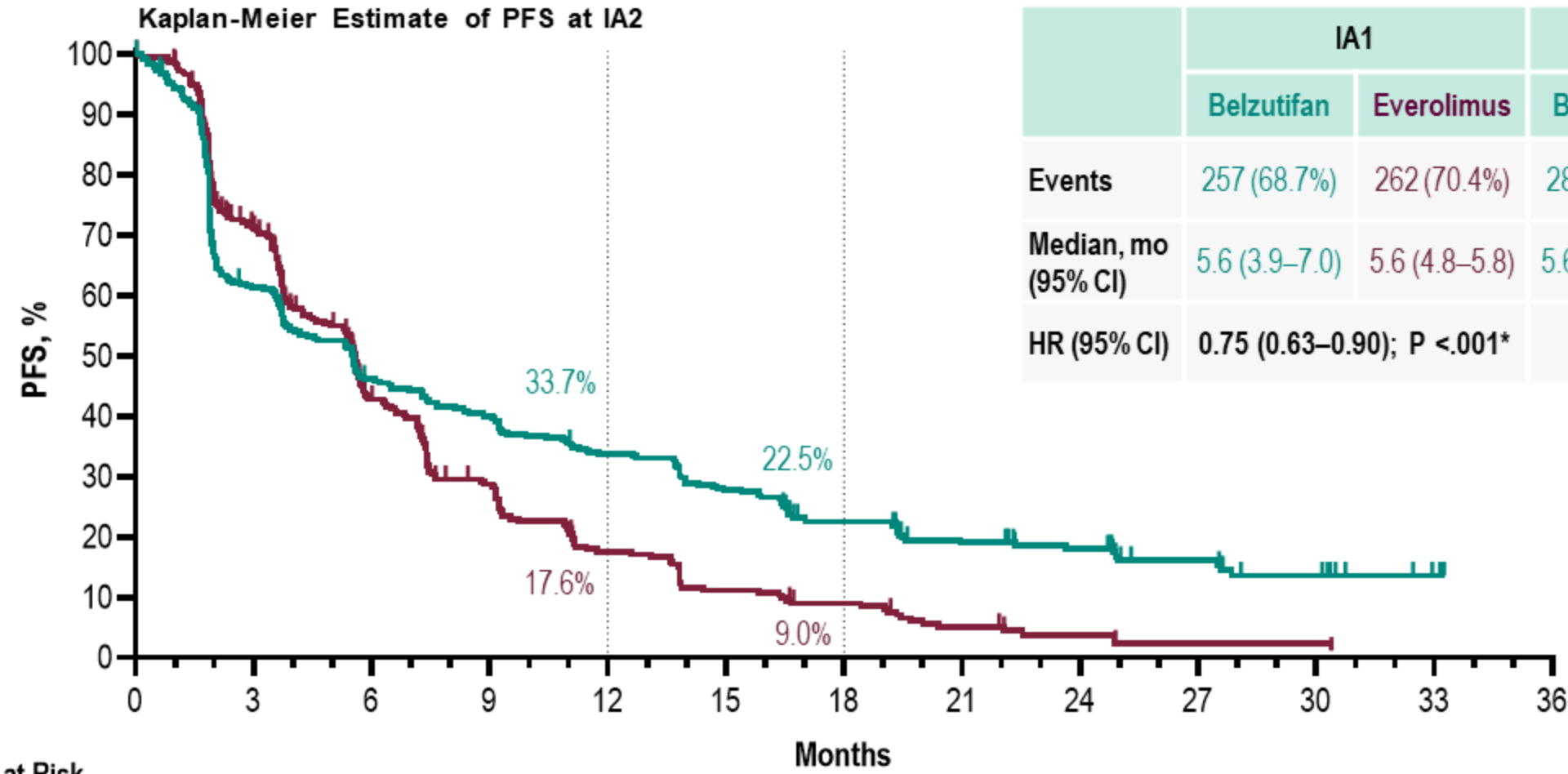
- ORR per RECIST 1.1 by BICR

Other Secondary Endpoints Include:

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

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

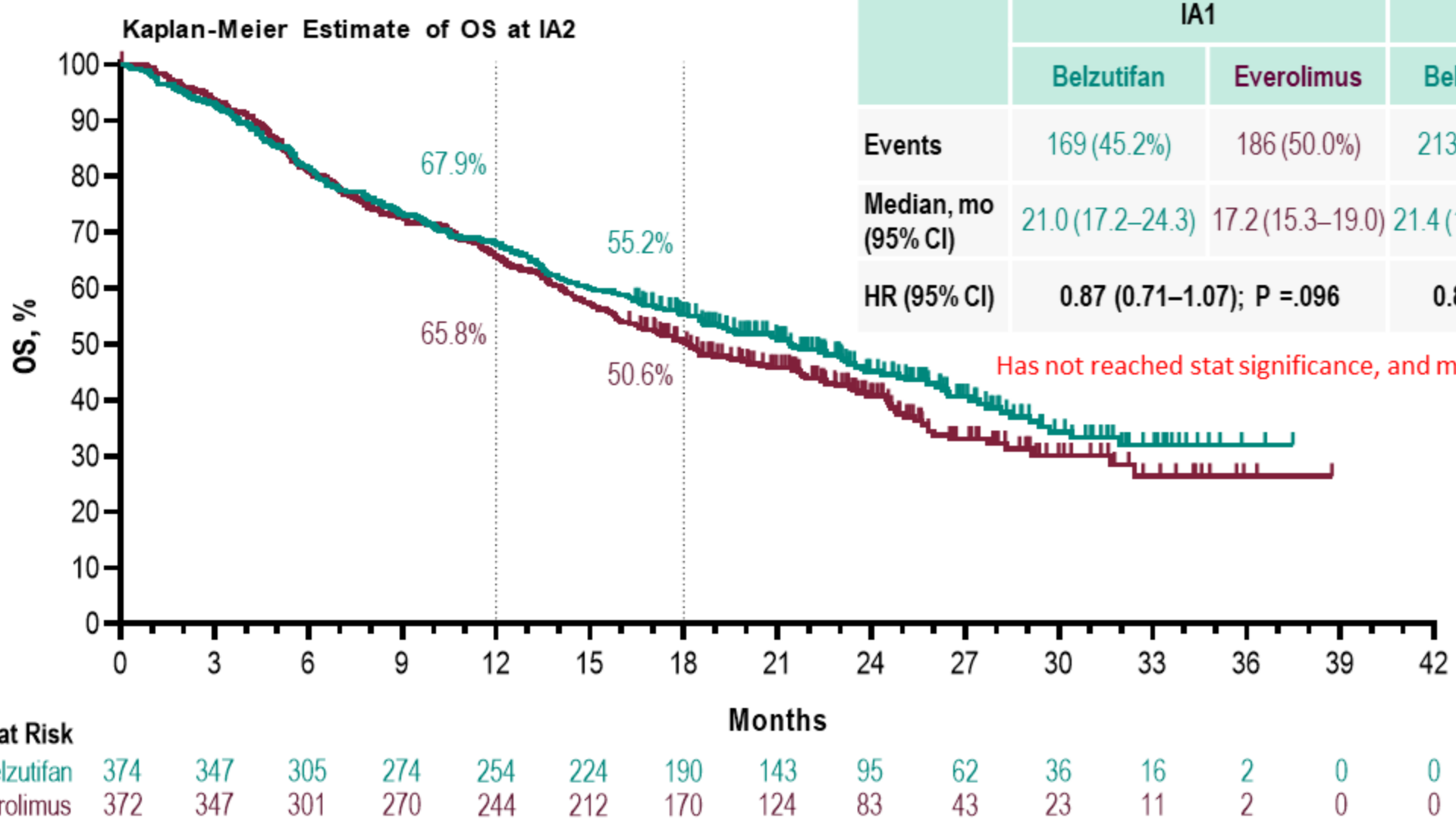
Primary Endpoint: PFS per RECIST 1.1 by BICR



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

* denotes statistical significance. Primary PFS endpoint was met at IA1 and was not formally statistically tested at IA2. Data cutoff date for IA1: November 1, 2022. Data cutoff date for IA2: June 13, 2023.

Primary Endpoint: OS



	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	169 (45.2%)	186 (50.0%)	213 (57.0%)	228 (61.3%)
Median, mo (95% CI)	21.0 (17.2–24.3)	17.2 (15.3–19.0)	21.4 (18.2–24.3)	18.1 (15.8–21.8)
HR (95% CI)	0.87 (0.71–1.07); P =.096		0.88 (0.73–1.07); *P* =.099	

Has not reached stat significance, and may not at final OS analysis

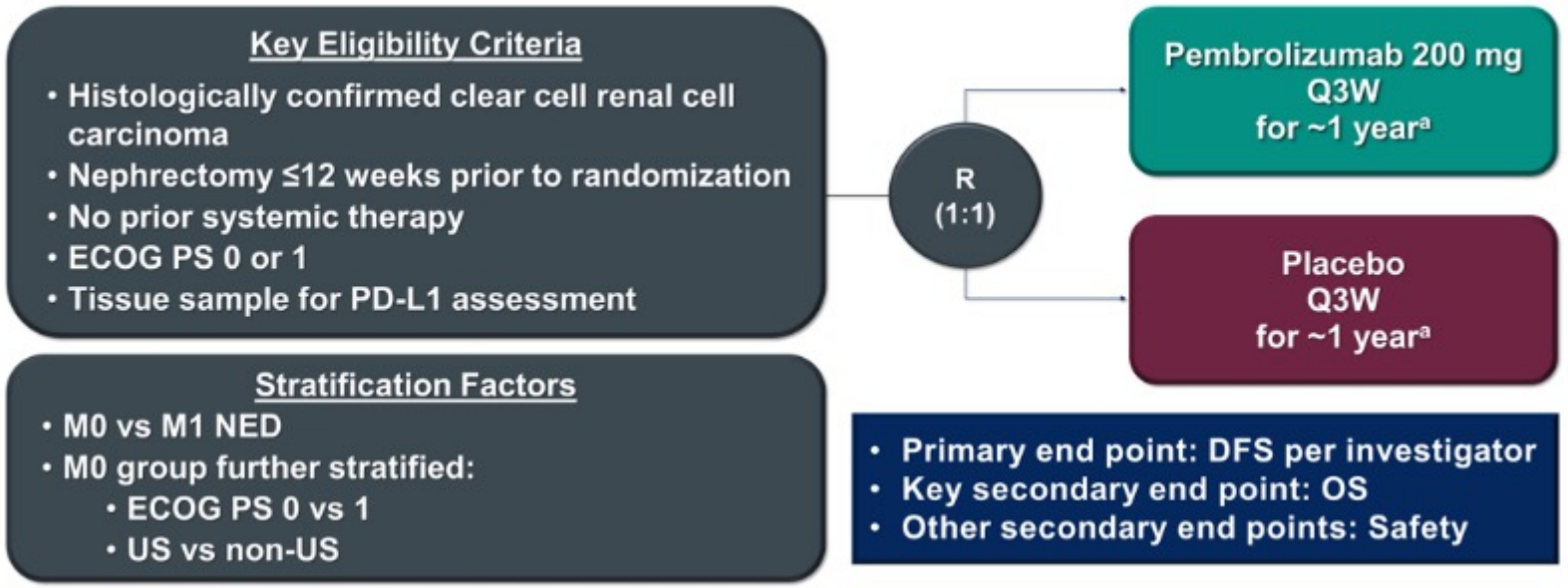
Data cutoff date for IA1: November 1, 2022. Data cutoff date for IA2: June 13, 2023.

Adjuvant Therapy in RCC

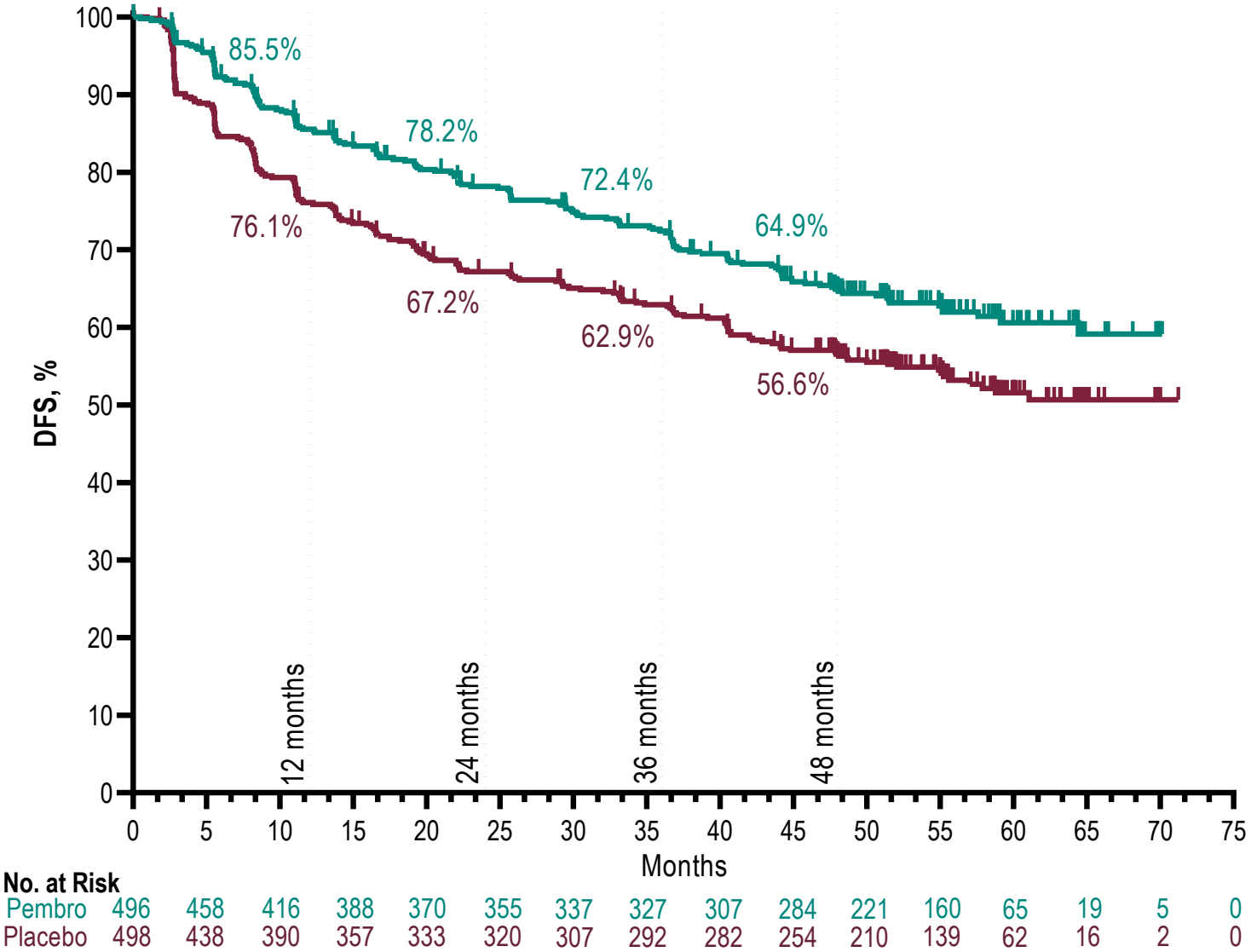
ROGEL CANCER CENTER
MICHIGAN MEDICINE

RFS and OS benefit with pembrolizumab

Adjuvant Pembro trial:Keynote 564 Pembro Vs Placebo Trial: Choueiri T, et al ASCO 2021



Updated Disease-Free Survival by Investigator, Intention-to-Treat Population



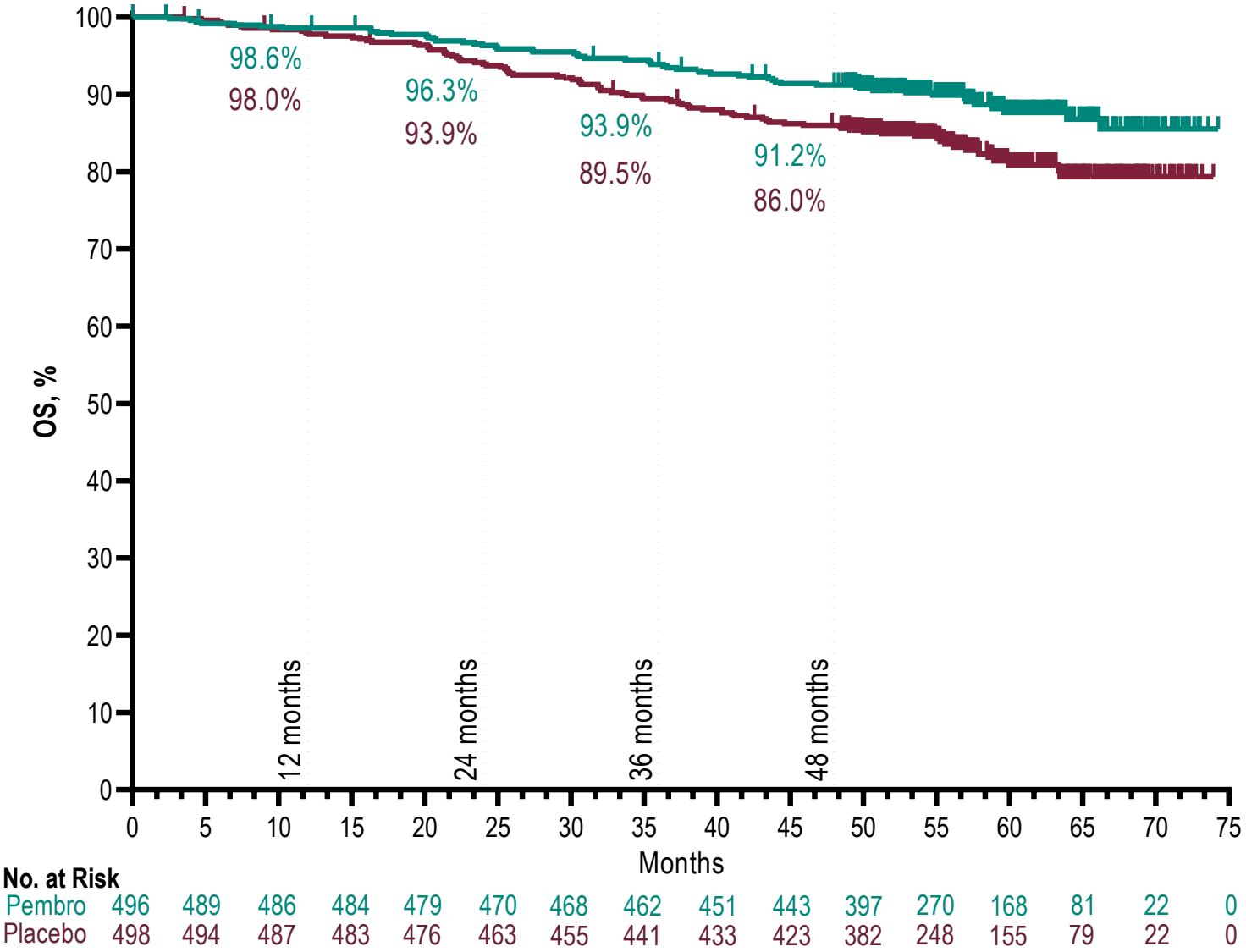
	Pembro (N = 496)	Placebo (N = 498)
Events, n	174	224
Median, mo (95% CI)	NR (NR–NR)	NR (54.9–NR)
Median follow-up was 57.2 months (range, 47.9–74.5)		

HR 0.72 (95% CI 0.59–0.87)

Primary DFS endpoint was met at IA1 and was not formally statistically tested thereafter.

Data cutoff date: September 15, 2023.

Overall Survival, Intention-to-Treat Population



	Pembro (N = 496)	Placebo (N = 498)
Events, n	55	86
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)
Median follow-up was 57.2 months (range, 47.9–74.5)		

HR 0.62 (95% CI 0.44–0.87); *P* =.002*

*** denotes statistical significance**. P-value boundary for OS at IA3 was 0.0072 (1-sided) per Lan-DeMets O'Brien-Fleming spending approximation α-spending function. As this key secondary endpoint was formally met, any future OS analyses will be descriptive only.

Data cutoff date: September 15, 2023.

ADJUVANT THERAPY in RCC

- Sunitinib showed benefit in one trial (S-TRAC) and no benefit in the ASSURE trial
- Pazopanib, Axitinib and Sorafenib- no benefit in adjuvant setting
- **Pembro: 11% DFS benefit, and OS benefit noted in one trial**
- Adjuvant atezolizumab: no benefit
- Adjuvant nivolumab : No benefit
- Nivo + ipi adjuvant 6 months : no benefit
- **S0931 Everolimus: benefit only in very high risk subset, Overall no benefit.**
- Majority of adjuvant trials in RCC are negative

CONCLUSIONS/TAKE AWAY: RCC

- PD-1 inhibition is now considered the backbone of frontline combination regimens in RCC. About 30% of met RCC patients are in long term remission CM-214 trial 99 months update.
- The subset of patients presenting with primary tumor and metastases are still showing attenuated survival [median OS 27 mths vs 46 mths with ipi+nivo]
- S1931/PROBE trial is evaluating the impact of adding nephrectomy after 10-14 weeks of I-O based combination systemic therapy.
- VEGF-TKI is the backbone of second line therapy.
- Addition of ipilimumab in later lines gives minimal benefit
- Hif-2 alpha inhibitor is a new target, Belzutifan was FDA approved in RCC third line setting

How do you decide on Therapy Choice?

- Toxicity/efficacy balance
- Histology
- Sites of mets
- IMDC risk
- Oligometastatic disease
- QOL
- Cost/access

New Directions

- Live biotherapeutics to enhance IO in RCC
- Novel HIF-2 alpha inhibitors
- CD70 Antibody Drug Conjugates
- Immune therapy in combination with TGF beta inhibitors
- Novel cytokines

RCC and Urothelial Cancer Therapy is now a MARATHON!