The Clinical Implications of Key Recent Data Sets in Oncology: A Daylong Multitumor Educational Symposium in Partnership with Florida Cancer Specialists

A CME/MOC- and NCPD-Accredited Event

Saturday, October 22, 2022
7:30 AM – 5:30 PM ET

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1 — Lung Cancer: *Drs Langer and Lovly*

Module 2 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs LaCasce and Smith*

Module 3 — Prostate and Bladder Cancers: *Drs Morgans and Yu*

Module 4 — Renal Cell Carcinoma: *Prof Powles*

Module 5 — Multiple Myeloma: *Dr Usmani*

Module 6 — Hepatobiliary Cancers: *Prof Abou-Alfa*

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Agenda

Module 7 — Breast Cancer: *Drs Goetz and Krop*

Module 8 — Endometrial Cancer: *Dr Westin*

Module 9 — Ovarian Cancer and PARP Inhibitors: *Dr O'Malley*

Module 10 — Gastrointestinal Cancers: *Drs Messersmith and Strickler*

Module 11 — Melanoma: *Prof Long*

Renal Cell Carcinoma Faculty

Thomas Powles, MBBS, MRCP, MD
Professor of Genitourinary Oncology
Barts Cancer Institute
Director of Barts Cancer Centre
Queen Mary University of London
London, United Kingdom

Renal Cell Carcinoma Agenda

MODULE 1: Management of High-Risk Renal Cell Carcinoma (RCC) in the Adjuvant Setting

MODULE 2: Optimal First-Line Therapy for Patients with Metastatic RCC

MODULE 3: Treatment Approaches for Relapsed/Refractory Metastatic RCC

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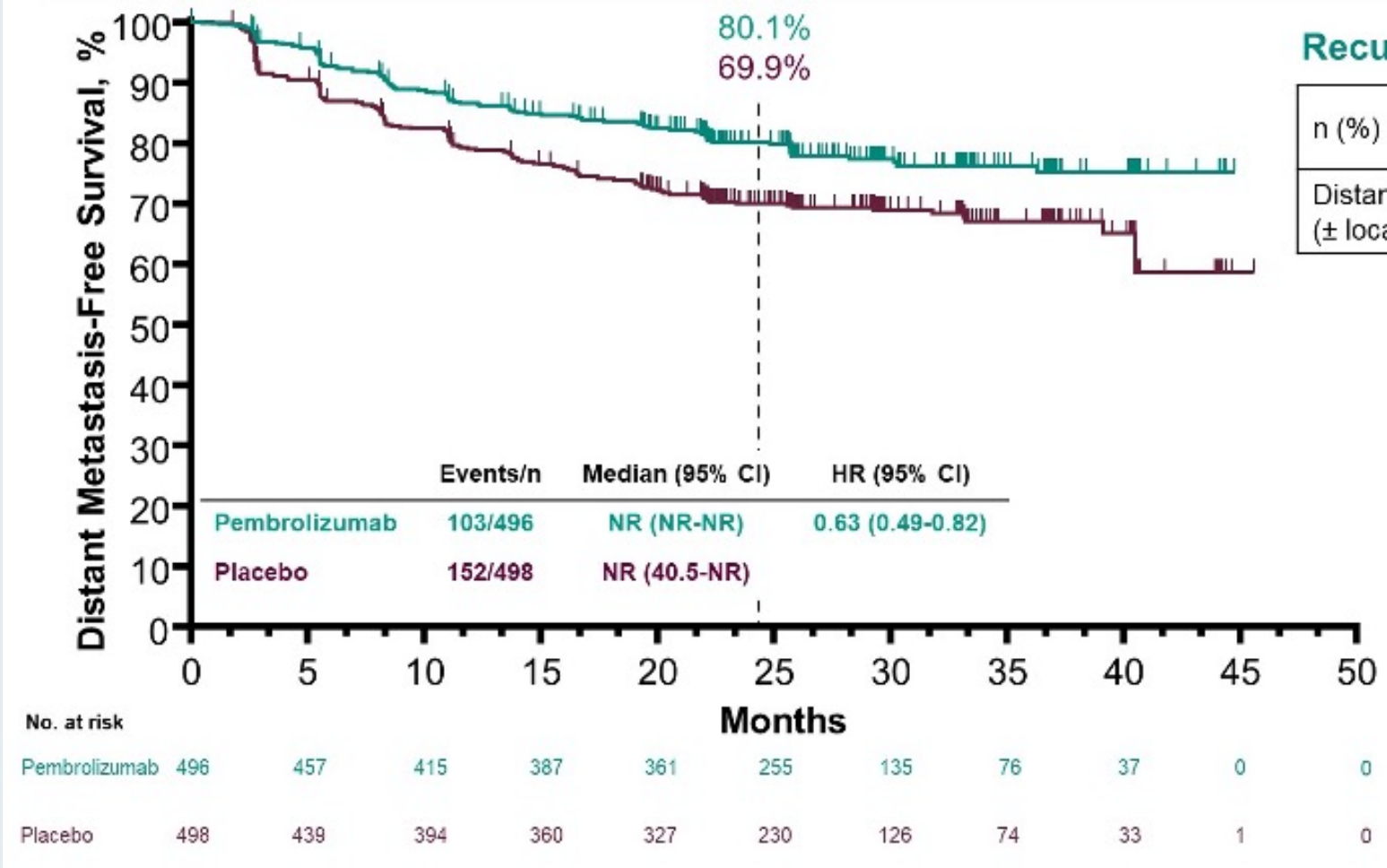
Adjuvant pembrolizumab for postnephrectomy renal cell carcinoma: Expanded efficacy analyses from KEYNOTE-564

T. K. Choueiri[1]; P. Tomczak[2]; S. H. Park[3]; B. Venugopal[4]; T. Ferguson[5]; S. N. Symeonides[6]; J. Hajek[7]; Y.-H. Chang[8]; J.-L. Lee[9]; N. Sarwar[10]; A. Thiery-Vuillemin[11]; M. Gross-Goupil[12]; M. Mahave[13]; N. B. Haas[14]; P. Sawrycki[15]; H. Gurney[16]; L. Xu[17]; K. Imai[17]; J. Burgents[17]; T. Powles[18]

[1]Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA; [2]Poznan University of Medical Sciences, Poznan, Poland; [3]Sungkyunkwan University, Samsung Medical Center, Seoul, South Korea; [4]Beatson West of Scotland Cancer Centre and University of Glasgow, Glasgow, United Kingdom; [5]Fiona Stanley Hospital, Perth, WA, Australia; [6]Edinburgh Cancer Centre and University of Edinburgh, Edinburgh, United Kingdom; [7]Fakultni Nemocnice Ostrava, Ostrava, Czech Republic; [8]Taipei Veterans General Hospital, Taipei, Taiwan; [9]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [10]Imperial College Healthcare NHS Trust, London, United Kingdom; [11]University Hospital Jean Minjoz, Besançon, France; [12]University Hospital of Bordeaux, Bordeaux, France; [13]Fundacion Arturo Lopez Perez FALP, Santiago, Chile; [14]Abramson Cancer Center, Penn Medicine, Philadelphia, PA, USA; [15]Provincial Hospital in Torun, Torun, Poland; [16]Macquarie University, Sydney, NSW, Australia; [17]Merck & Co., Inc., Rahway, NJ, USA; [18]Barts Health NHS Trust and the Royal Free NHS Foundation Trust, Barts Cancer Institute, and Queen Mary University of London, London, United Kingdom

ASCO 2022;Abstract 4512

KEYNOTE-564: Pembrolizumab as Adjuvant Therapy for Patients with Renal Cell Carcinoma – Disease-Free Survival



Recurrence events

n (%)	Pembrolizumab n = 496	Placebo n = 498
Distant (± local)	95 (19.2)	140 (28.1)

Choueiri TK et al. ASCO 2022;Abstract 4512.

RTP RESEARCH TO PRACTICE

Pembrolizumab as Post Nephrectomy Adjuvant Therapy for Patients with Renal Cell Carcinoma: Results from 30-month Follow-up of KEYNOTE-564

Toni K. Choueiri[1]; Piotr Tomczak[2]; Se Hoon Park[3]; Balaji Venugopal[4]; Thomas Ferguson[5]; Stefan Symeonides[6]; Jaroslav Hajek[7]; Yen-Hwa Chang[8]; Jae Lyun Lee[9]; Naveed Sarwar[10]; Antoine Thiery-Vuillemin[11]; Marine Gross-Goupil[12]; Mauricio Mahave[13]; Naomi Haas[14]; Piotr Sawrycki[15]; Lei Xu[16];Joseph E. Burgents[16]; Kentaro Imai[16]; Jaqueline Willemann-Rogerio[16]; David I. Quinn[17]; Thomas Powles[18], on behalf of the KEYNOTE-564 Investigators

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Poznań University of Medical Sciences, Poznań, Poland; [3]Sungkyunkwan University, Samsung Medical Center, Seoul, South Korea; [4]Beatson West of Scotland Cancer Centre, Glasgow, U.K. and University of Glasgow, Glasgow, UK; [5]Fiona Stanley Hospital, Perth, Australia; [6]Edinburgh Cancer Centre and University of Edinburgh, UK; [7]Fakultni Nemocnice Ostrava, Ostrava, Czech Republic; [8]Taipei Veterans General Hospital, Taipei, Taiwan; [9]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [10]Imperial College Healthcare NHS Trust, London, UK; [11]University Hospital Jean Minjoz, Besançon, France; [12]University Hospital Bordeaux-Hôpital Saint-André, Bordeaux, France; [13]Fundacion Arturo Lopez Perez FALP, Santiago, Chile; [14]Abramson Cancer Center, Philadelphia, PA, USA; [15]Wojewodzki Szpital Zespolony im. L. Rydygiera w Toruniu, Torun, Poland; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [18]Royal Free Hospital NHS Trust, University College London, London, UK.

Genitourinary Cancers Symposium 2022;Abstract 290.

KEYNOTE-564: Pembrolizumab as Adjuvant Therapy for Patients with RCC – Safety Summary

Participants with ≥1 AE, n (%)	Primary Analysis (24.1 mo)		Updated Analysis (30.1 mo)	
	Pembro Arm (N = 488)	Placebo Arm (N = 496)	Pembro Arm (N = 488)	Placebo Arm (N = 496)
All-cause AEs	470 (96.3%)	452 (91.1%)	470 (96.3%)	453 (91.3%)
Grade 3–5	158 (32.4%)	88 (17.7%)	157 (32.2%)	88 (17.7%)
Led to treatment discontinuation	101 (20.7%)	10 (2.0%)	103 (21.1%)	11 (2.2%)
Led to death	2 (0.4%)	1 (0.2%)	2 (0.4%)	1 (0.2%)
Serious all-cause AEs[a]	100 (20.5%)	56 (11.3%)	101 (20.7%)	57 (11.5%)
Led to treatment discontinuation	49 (10.0%)	5 (1.0%)	49 (10.0%)	5 (1.0%)
Treatment-related AEs	386 (79.1%)	265 (53.4%)	386 (79.1%)	265 (53.4%)
Grade 3–4	92 (18.9%)	6 (1.2%)	91 (18.6%)	6 (1.2%)
Led to treatment discontinuation	86 (17.6%)	3 (0.6%)	89 (18.2%)	4 (0.8%)
Led to death	0	0	0	0
Immune-mediated AEs[b]	169 (34.6%)	29 (5.8%)	170 (34.8%)	29 (5.8%)
Grade 3–4	42 (8.6%)	3 (0.6%)	43 (8.8%)	3 (0.6%)
High-dose (≥40 mg/day) systemic corticosteroid treatment for AEs prespecified to be immune-mediated, n (%)	36 (7.4%)	3 (0.6%)	37 (7.6%)	3 (0.6%)

[a]Serious AEs were AEs that were life-threatening, required hospitalization, resulted in death or persistent/significant disability/incapacity, or were judged as serious per investigator. [b]Based on a prespecified list of terms included regardless of attribution to study treatment by investigator. No deaths due to immune-mediated AEs occurred.
As-treated population included all participants who received ≥1 dose of study treatment. Median duration (range) of treatment was 11.1 (0.0–14.3) months with pembro and 11.1 (0.0–15.4) months with placebo.
Primary analysis data cutoff date: December 14, 2020. Updated analysis data cutoff date: June 14, 2021.

AE = adverse event

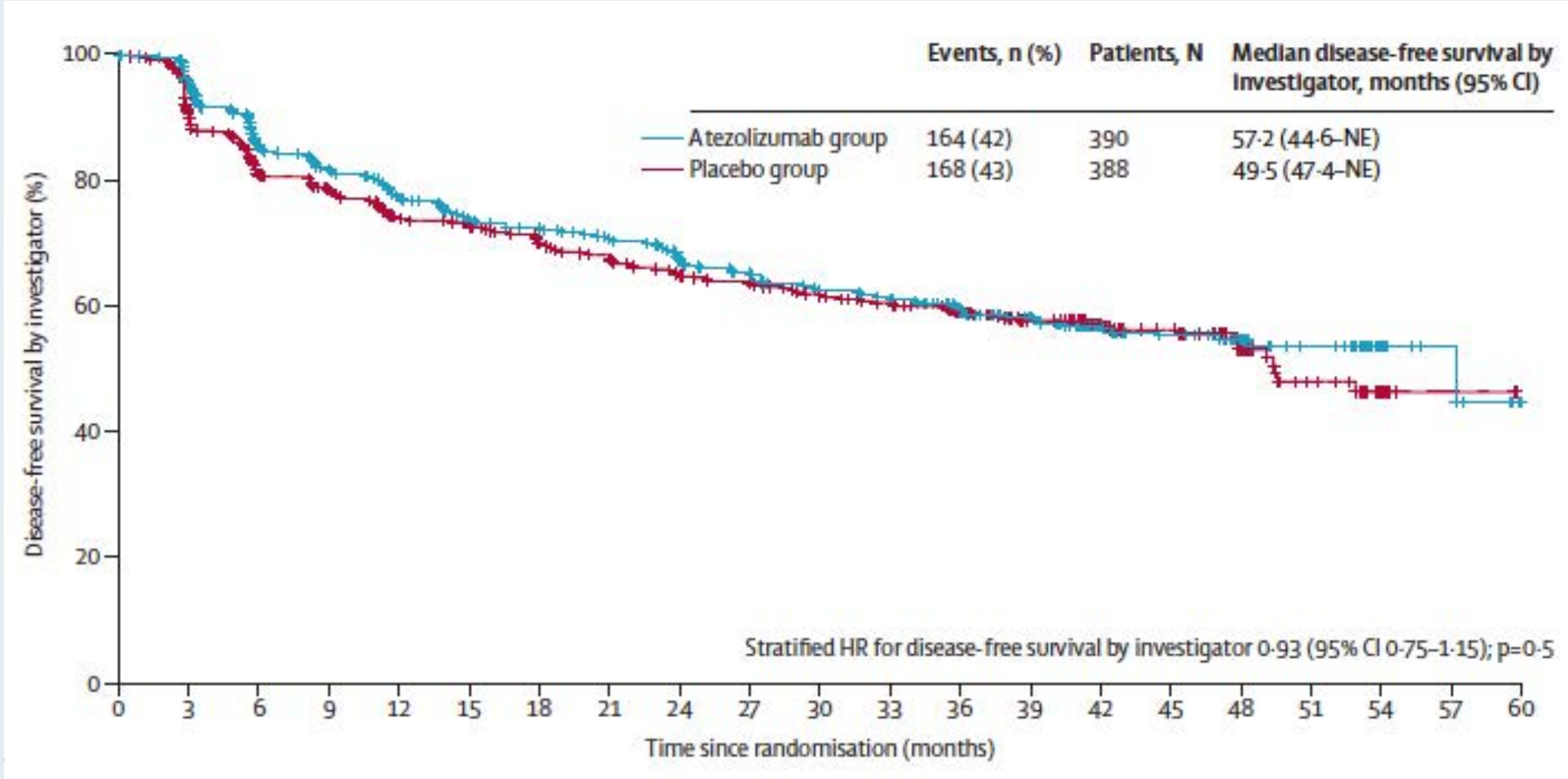
Choueiri TK et al. Genitourinary Cancers Symposium 2022;Abstract 290.

Lancet 2022 September 9;[Online ahead of print].

Adjuvant atezolizumab versus placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): a multicentre, randomised, double-blind, phase 3 trial

Sumanta Kumar Pal, Robert Uzzo*, Jose Antonio Karam, Viraj A Master, Frede Donskov, Cristina Suarez, Laurence Albiges, Brian Rini, Yoshihiko Tomita, Ariel Galapo Kann, Giuseppe Procopio, Francesco Massari, Matthew Zibelman, Igor Antonyan, Mahrukh Huseni, Debasmita Basu, Bo Ci, William Leung, Omara Khan, Sarita Dubey, Axel Bex*

IMmotion010 Primary Endpoint: Disease-Free Survival with Atezolizumab as Adjuvant Therapy for RCC



Pal SK et al. *Lancet* 2022 September 9;[Online ahead of print].

RTP RESEARCH TO PRACTICE

Select Ongoing Phase III Clinical Trials of Immune Checkpoint Inhibitors as Neoadjuvant or Adjuvant Therapy for High-Risk RCC

Trial identifier	N	Study arms	Estimated primary completion date
PROSPER (NCT03055013)	766	• Nivolumab → nephrectomy → nivolumab • Nephrectomy	November 2023
RAMPART (NCT03288532)	1,750	• Active monitoring • Durvalumab • Durvalumab + tremelimumab	July 2024
MK-6482-022 (NCT05239728)	1,600	• Pembrolizumab + belzutifan • Pembrolizumab + placebo	October 2027

www.clinicaltrials.gov. Accessed September 2022.

Renal Cell Carcinoma Agenda

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1ST LINE RENAL CANCER AND COSMIC-313.

Thomas Powles

Director of Barts Cancer Centre.

The story so far: PD-1 based therapy with VEGF TKI or CTLA-4 depending on IMDC risk group.

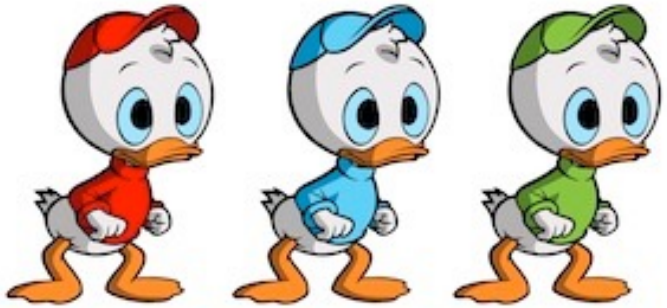
Good risk disease	Intermediate and poor risk disease
VEGF TKI and PD1 inhibition	VEGF TKI and PD1 inhibition
Sunitinib or pazopanib	CTLA4 and PD1 inhibition

ITT data

Subset data

VEGF TKI & PD1 combinations

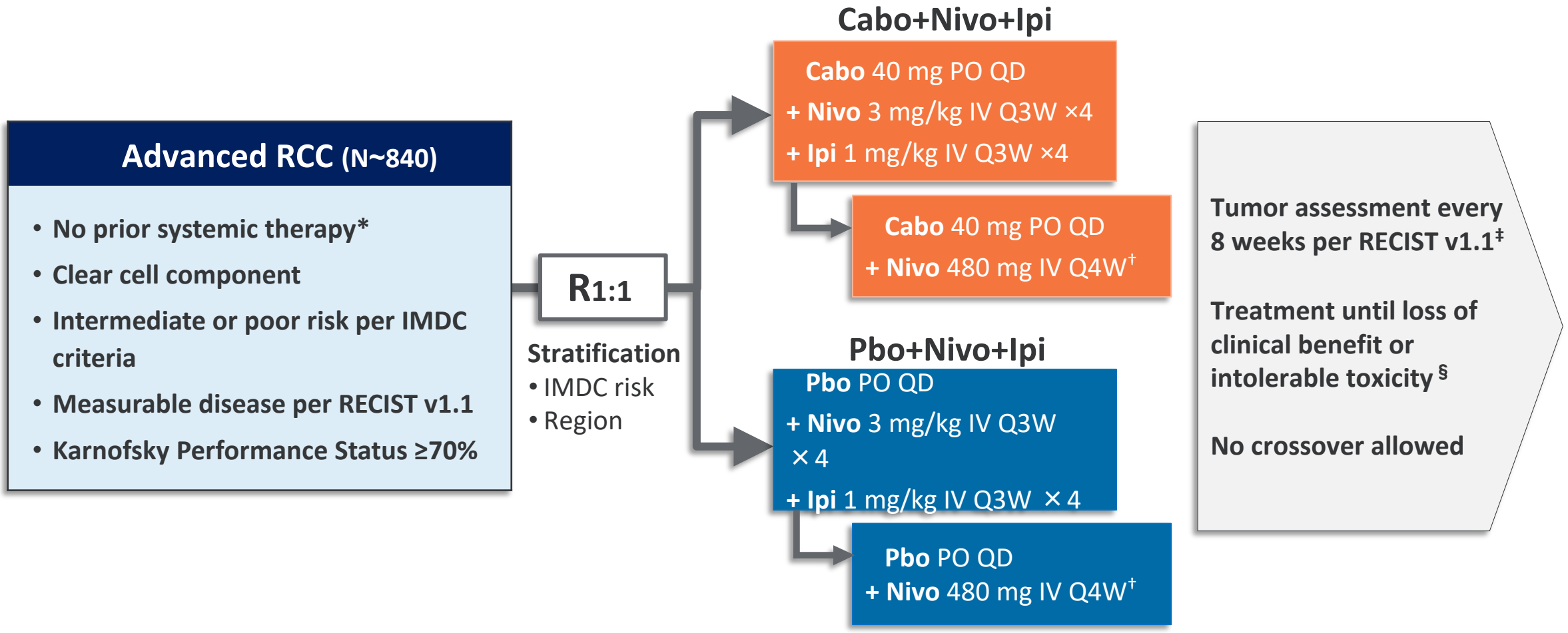
More similarities than differences



CTLA4 & PD1 combination

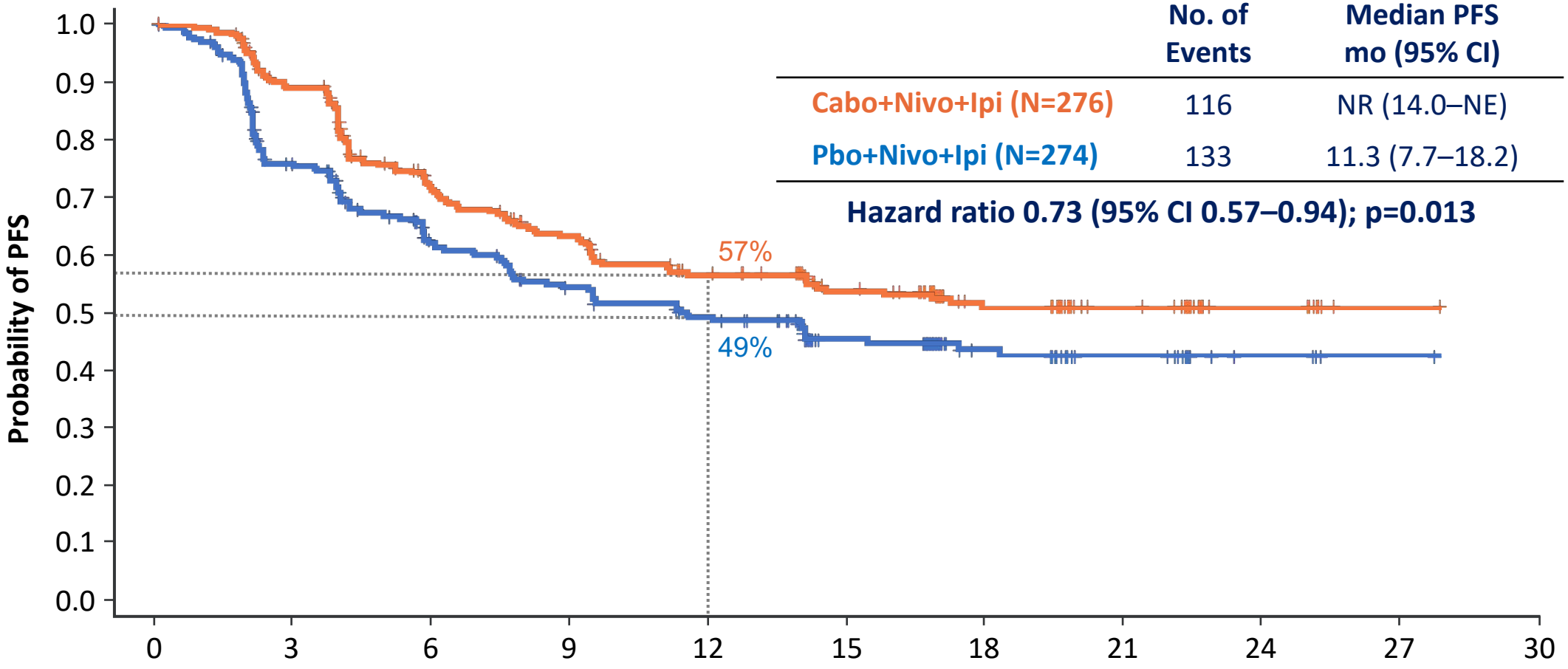
- Less good than VEGF/PD1 at getting initial control of disease
- Thought to be associated with more durable remissions
- Randomised data awaited

COSMIC-313 Study Design



*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.

COSMIC-313: PFS 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

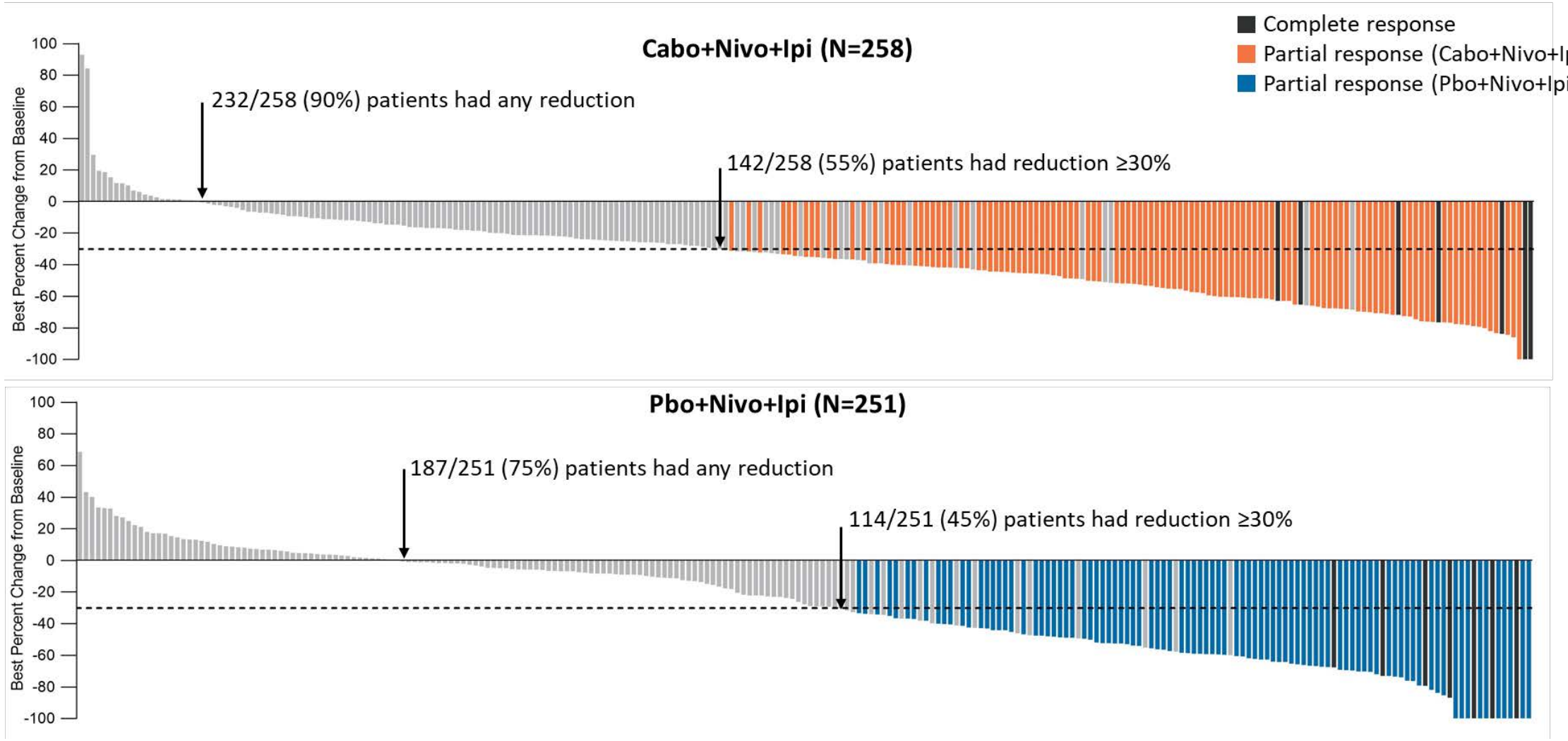
Number at Risk

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

PFS per RECIST v1.1 by BIRC.

Data cut-off: Aug 23, 2021

More shrinkage with triplet but less deep responses



Sumanta K. Pal, MD, FASCO

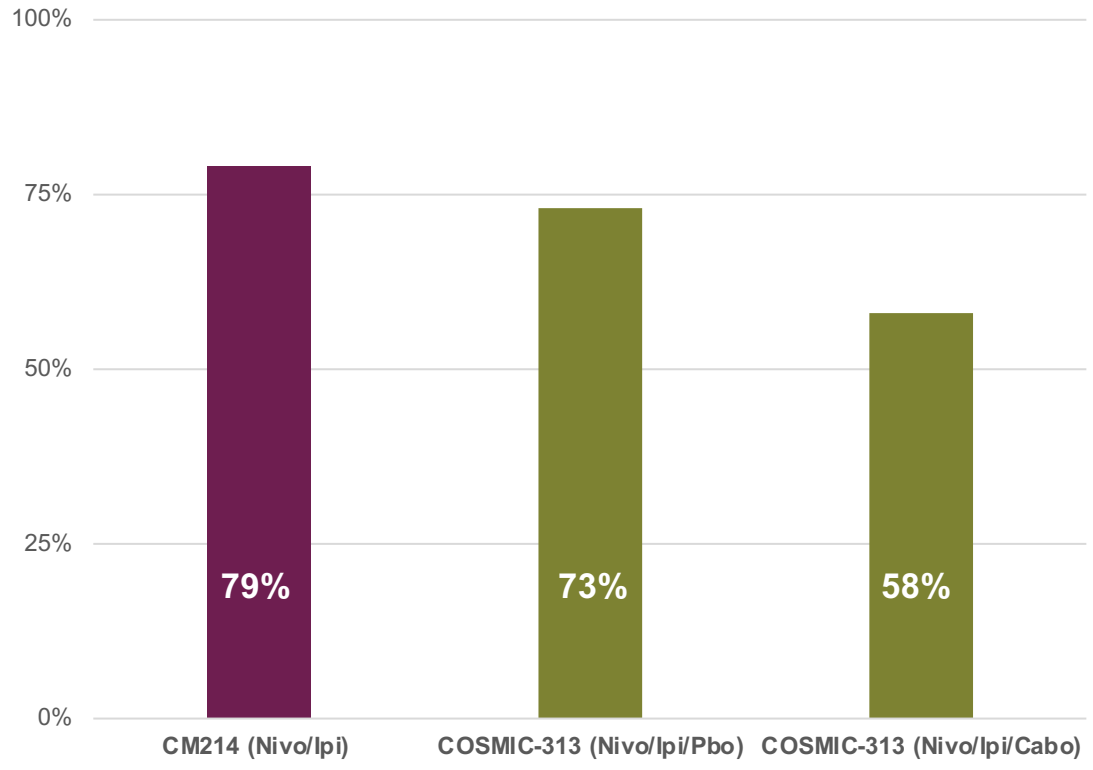
Treatment Exposure and Discontinuation (Safety Population)

	Cabo+Nivo+Ipi (N=426)	Pbo+Nivo+Ipi (N=424)
Median duration of exposure of study treatment (range), mo	10.9 (0.2–28.5)	10.3 (0.1–28.1)
Median average daily dose (range) of Cabo or Pbo, mg	23.2 (3.6–40.0)	36.1 (0.8–40.0)
Median Nivo infusions (range) received, no	10 (1–27)	9 (1–27)
Doses of Ipi received, %		
4	58	73
3	13	14
2	22	7
1	7	6
Any dose hold due to an AE, %	90	70
Any dose reduction of Cabo or Pbo due to an AE, %	54	20
Treatment-related AE leading to discontinuation, %		
Any study treatment	45	24
Cabo or Pbo	28	14
Nivo	26	18
Ipi	30	12
All treatment components (due to the same AE)	12	5

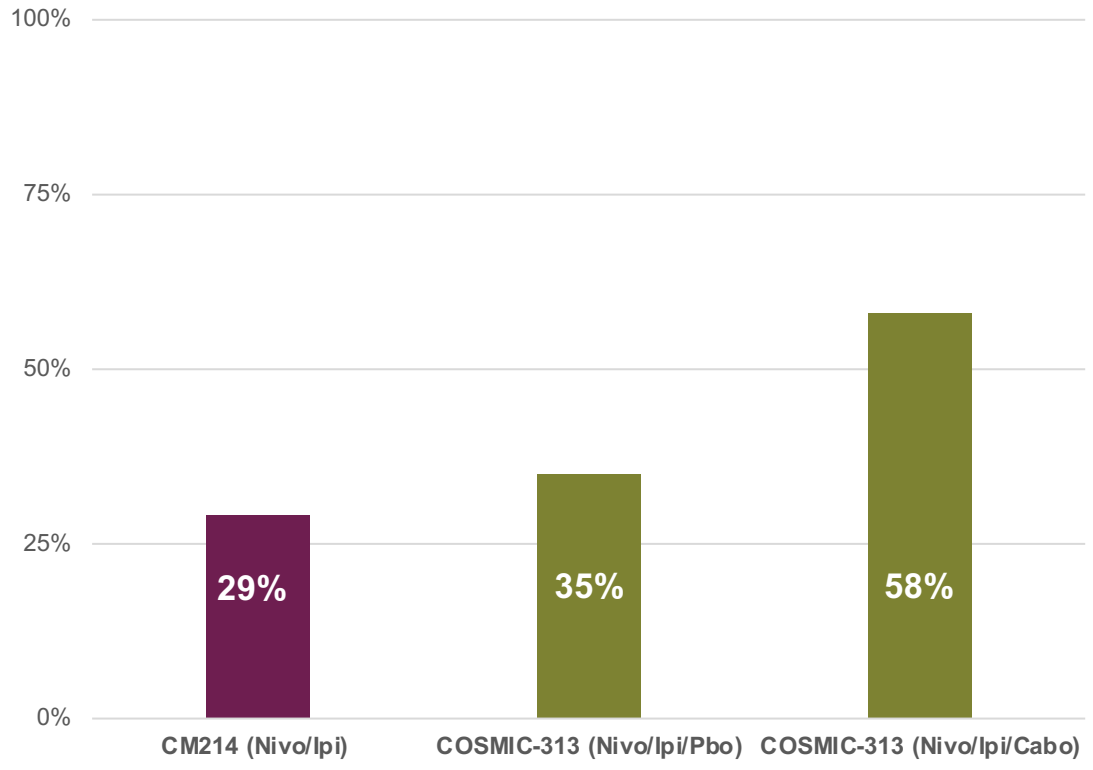
Data cut-off: Jan 31, 2022

Toxicity limited drug delivery

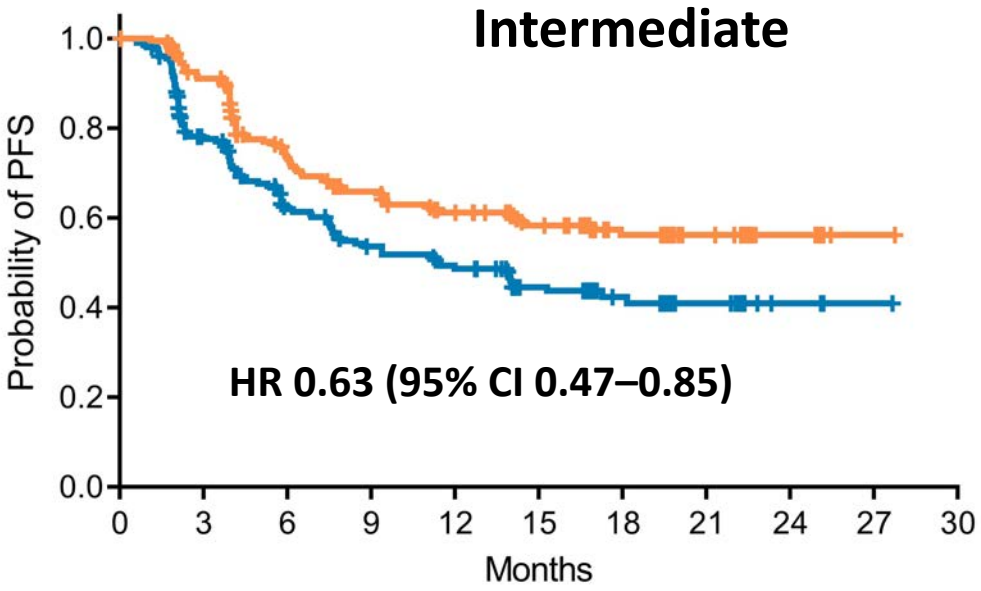
Proportion of patients receiving 4 doses of ipilimumab

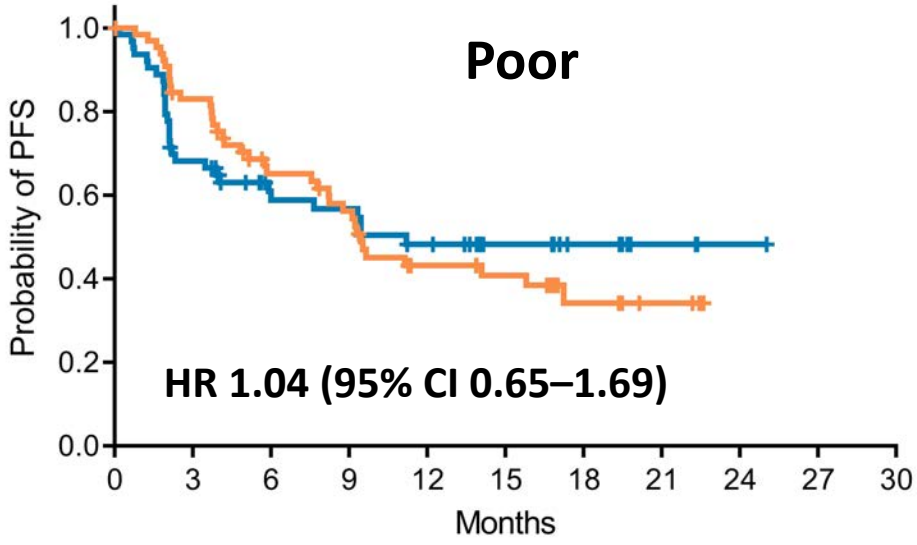


Proportion of patients receiving >40 mg of prednisone or equivalent



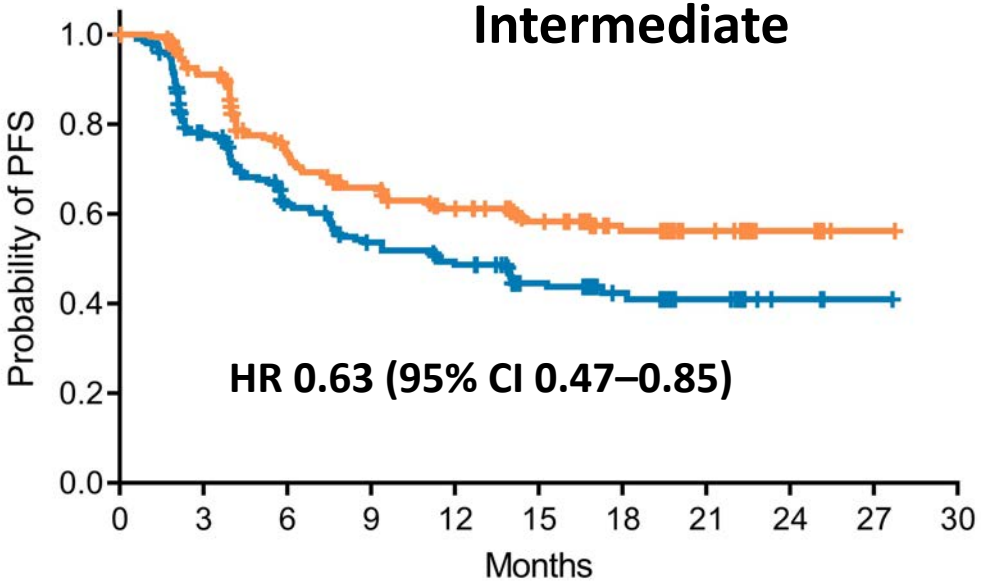
COSMIC-313: PFS by IMDC Risk Group (PITT Population)

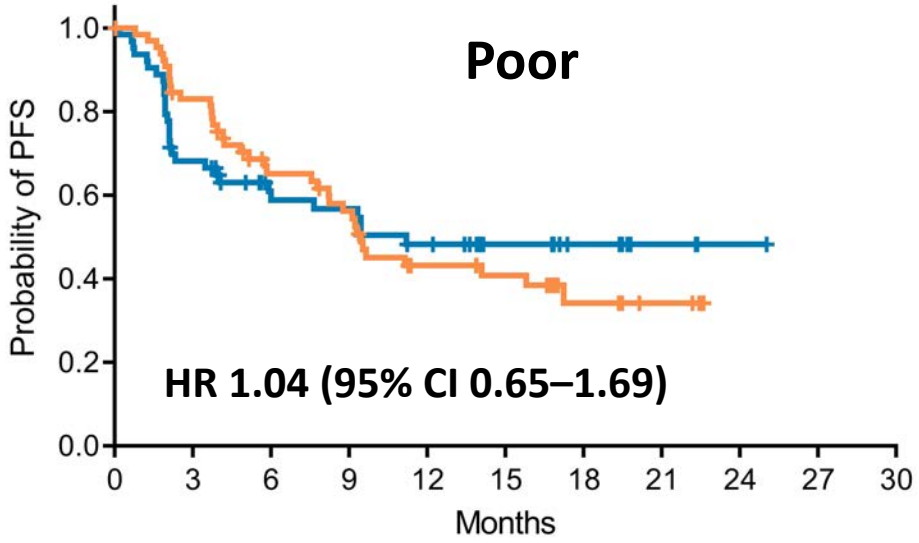


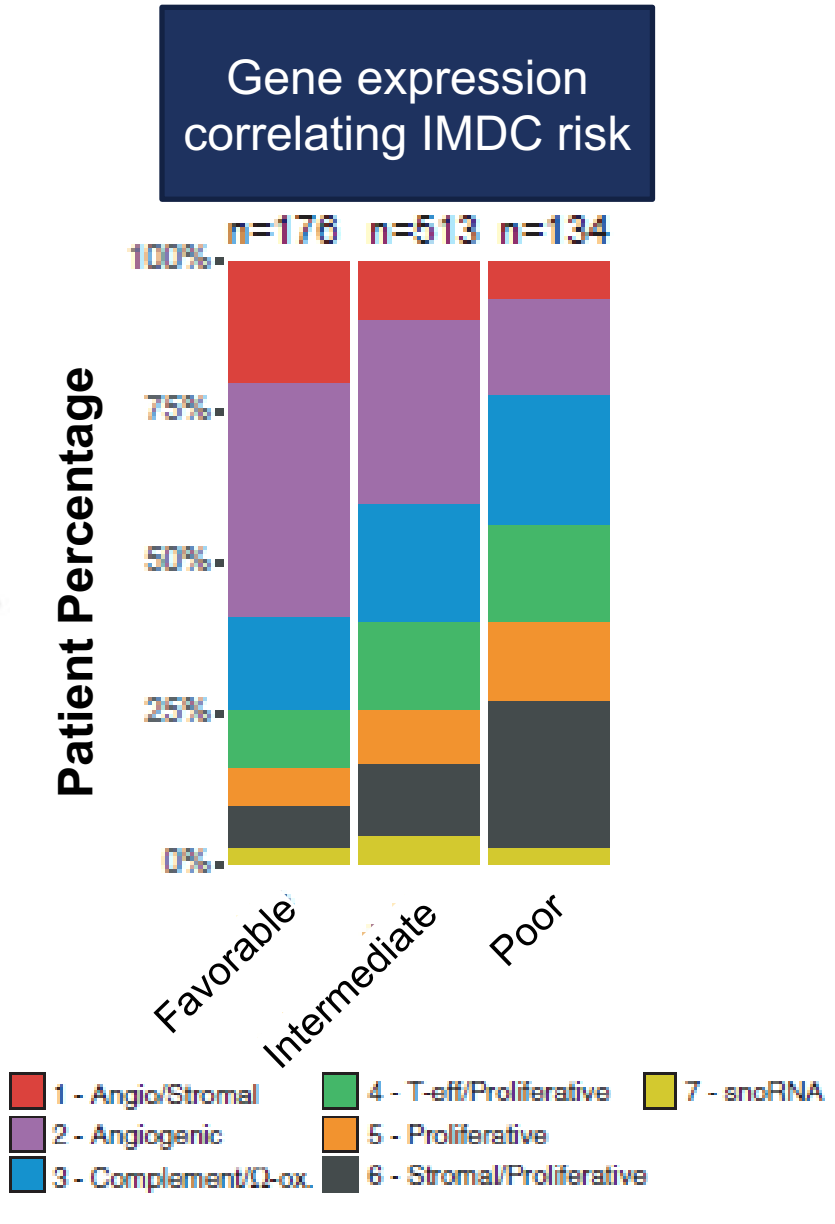


Data cut-off: Aug 23, 2021

COSMIC-313: PFS by IMDC Risk Group (PITT Population)

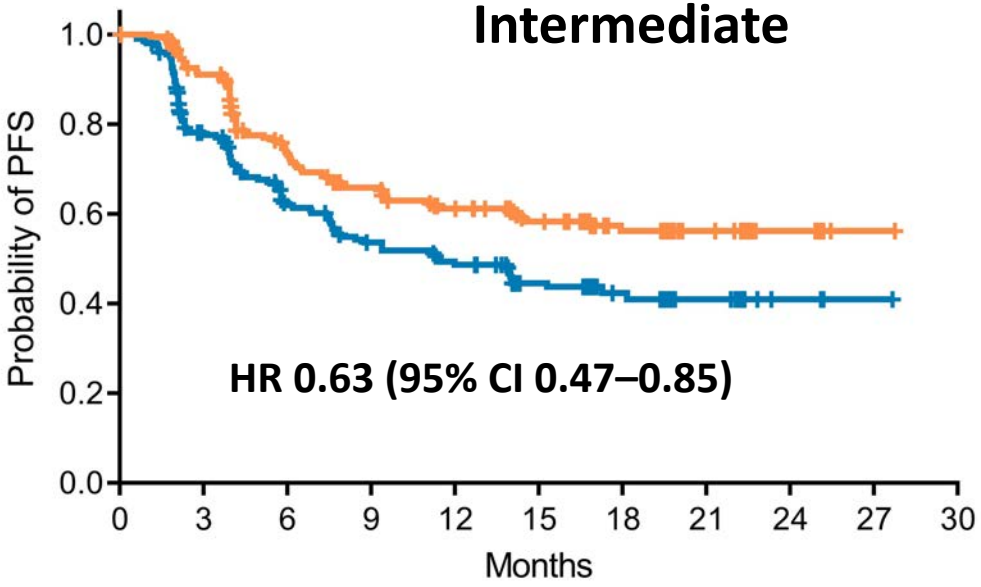


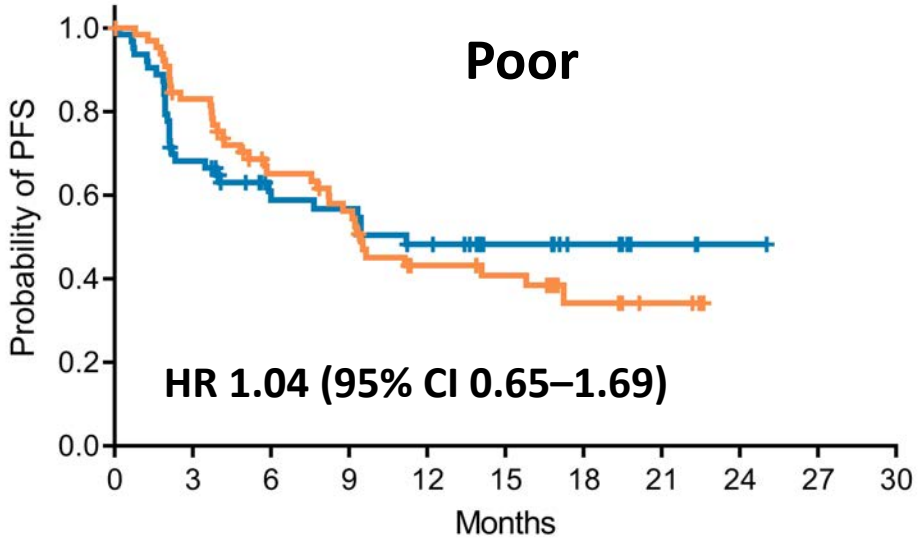




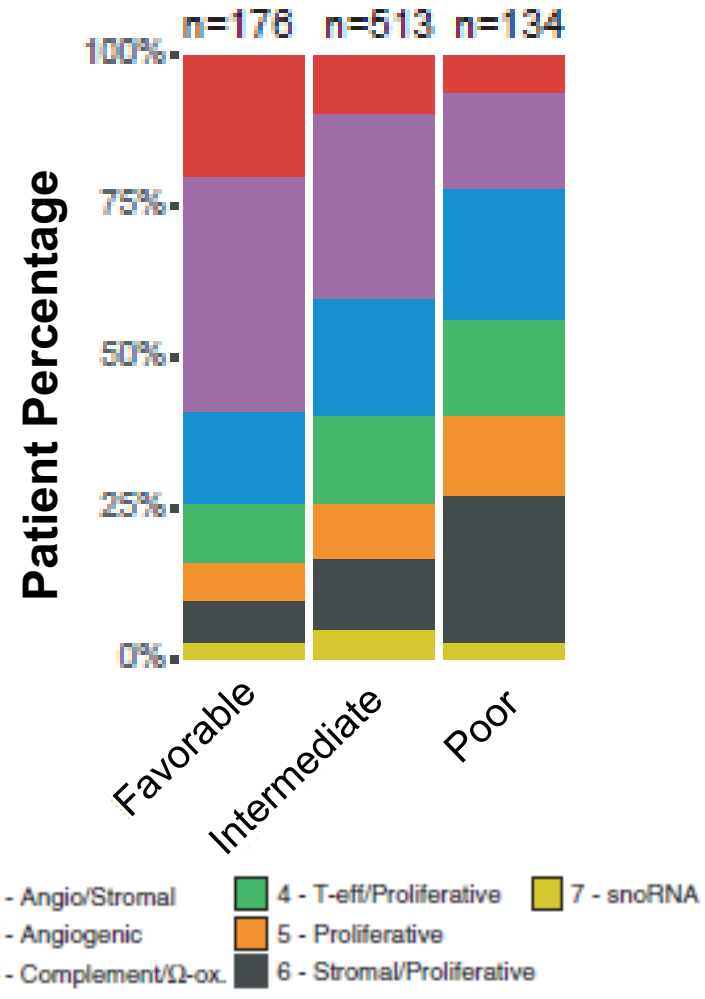
Data cut-off: Aug 23, 2021

COSMIC-313: PFS by IMDC Risk Group (PITT Population)

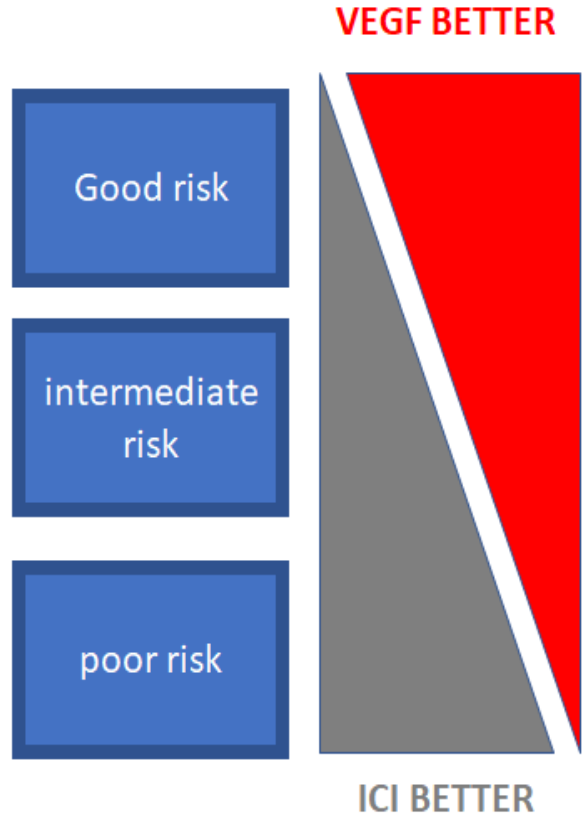




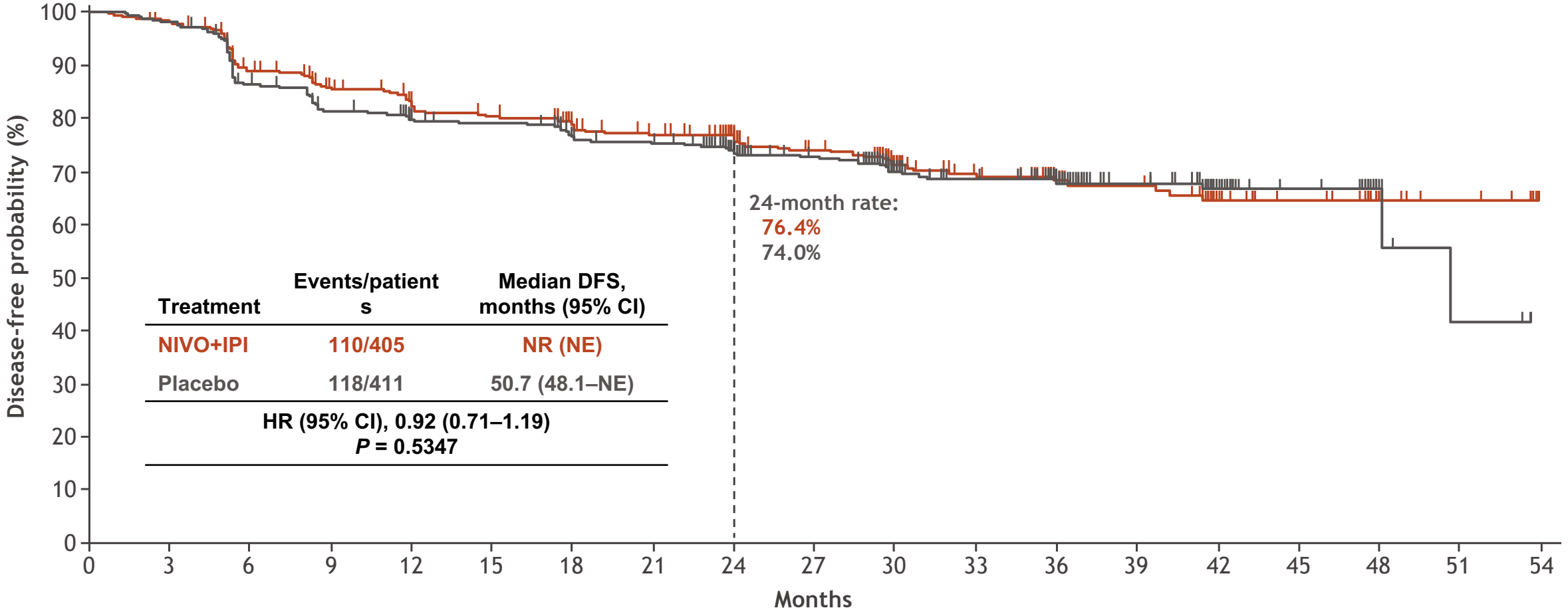
Gene expression correlating IMDC risk



A summary of efficacy and IMDC risk



Does a negative adjuvant trial for ipilimumab and nivolumab have any impact on how we think about 1st line?



Median (range) follow-up, 37.0 (15.4–58.0) months.
As the DFS endpoint was not met, no formal analysis of OS was performed (in total, there were 33 deaths in the NIVO+IPI arm and 28 deaths in the placebo arm).

What does all this mean?

- It's unlikely the triple of cabo/ipi/nivo will have a big impact on 1st line treatment without an OS advantage.
- It’s hard to identify a patient population to treat, we thought the IMDC poor risk to get control, but the data doesn’t support that.
- Triplet therapy looked difficult to give.
- Other triplet trials may be different and these results are awaited.

Checkpoint Inhibitor Combinations Approved as First-Line Treatment for RCC Before 2021

	CheckMate 214[a]	KEYNOTE-426[b]	JAVELIN Renal 101[c]
Randomization	Nivolumab/ipilimumab vs sunitinib	Pembrolizumab/axitinib vs sunitinib	Avelumab/axitinib vs sunitinib
N	550 vs 546	432 vs 429	442 vs 444
Median overall survival	55.7 mo vs 38.4 mo (HR 0.72)	Not reached vs 35.7 mo (HR 0.68)	Not estimable vs not estimable (HR 0.80)
Median progression-free survival	12.3 mo vs 12.3 mo (HR 0.86)	15.4 mo vs 11.1 mo (HR 0.71)	13.3 mo vs 8.0 mo (HR 0.69)

[a] Motzer RJ et al. *Cancer* 2022;128(11):2085-97. [b] Powles T et al. *Lancet Oncol* 2020;21:1563-73.
[c] Choueiri TK et al. *Ann Oncol* 2020;31(8):1030-9.

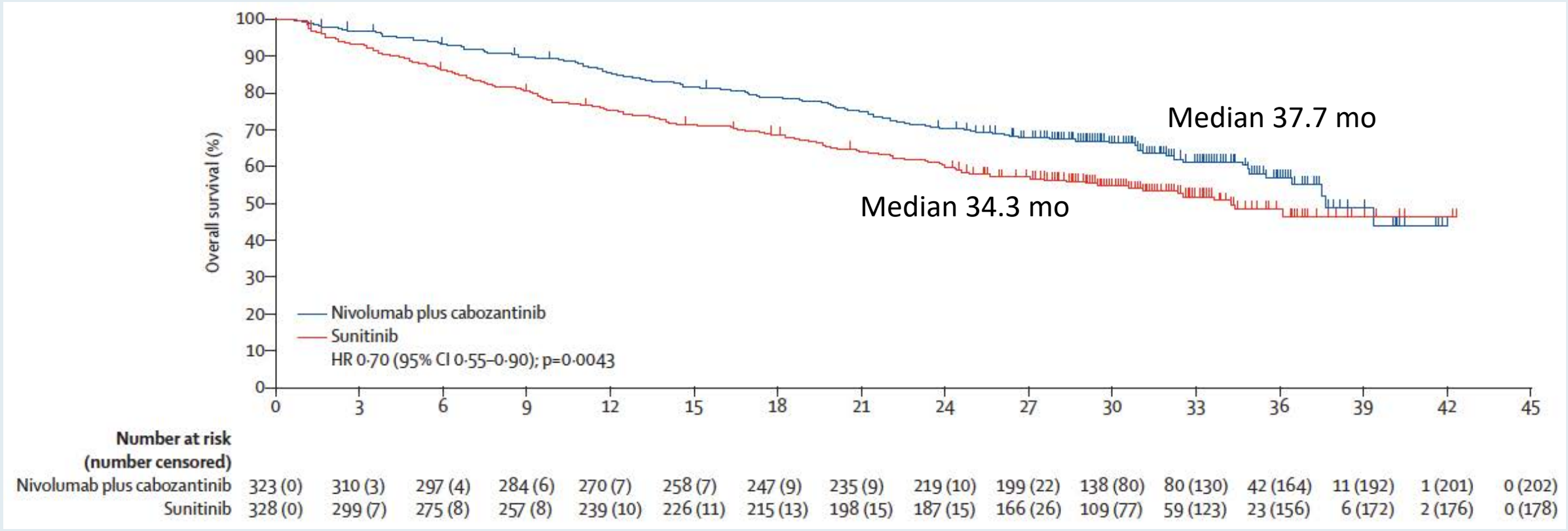
Lancet Oncol 2022;23(7):888-98.

Articles

Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomised, phase 3 trial

Robert J Motzer, Thomas Powles, Mauricio Burotto, Bernard Escudier, Maria T Bourlon, Amishi Y Shah, Cristina Suárez, Alketa Hamzaj, Camillo Porta, Christopher M Hocking, Elizabeth R Kessler, Howard Gurney, Yoshihiko Tomita, Jens Bedke, Joshua Zhang, Burcin Simsek, Christian Scheffold, Andrea B Apolo, Toni K Choueiri

CheckMate 9ER: Overall Survival (Median Follow-Up 32.9 Months)

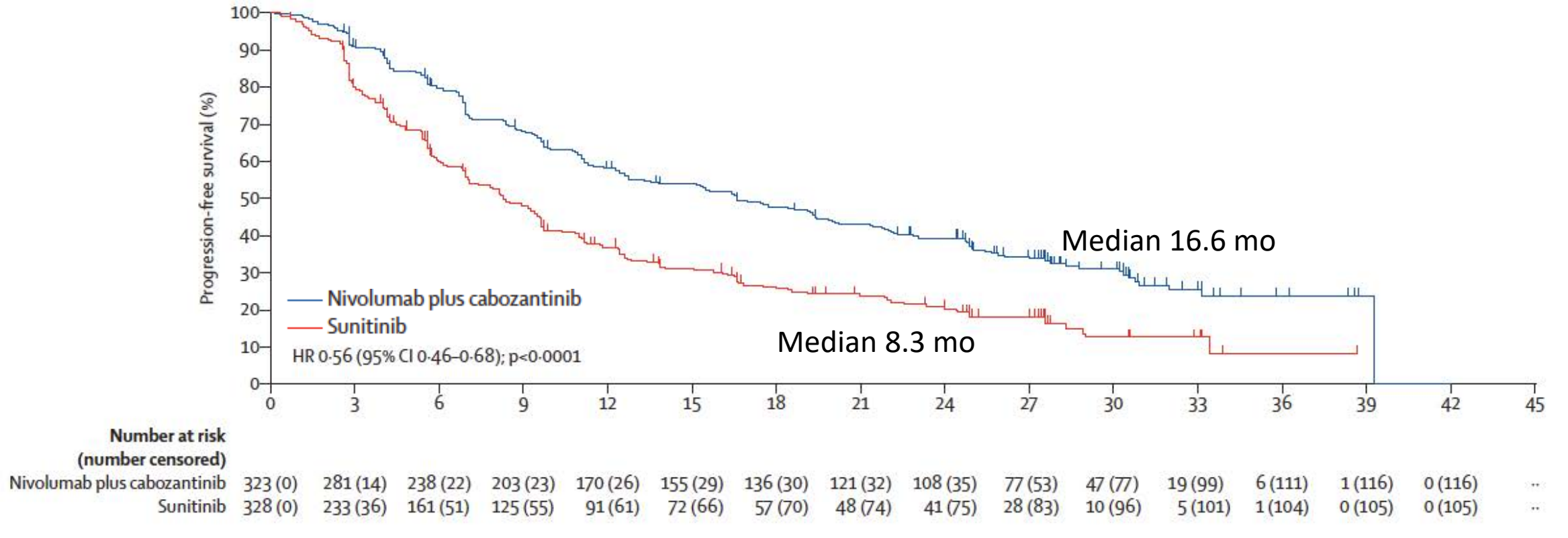


Number at risk (number censored)															
Nivolumab plus cabozantinib	323 (0)	310 (3)	297 (4)	284 (6)	270 (7)	258 (7)	247 (9)	235 (9)	219 (10)	199 (22)	138 (80)	80 (130)	42 (164)	11 (192)	1 (201)	0 (202)
Sunitinib	328 (0)	299 (7)	275 (8)	257 (8)	239 (10)	226 (11)	215 (13)	198 (15)	187 (15)	166 (26)	109 (77)	59 (123)	23 (156)	6 (172)	2 (176)	0 (178)

Motzer RJ et al. *Lancet Oncol* 2022;23(7):888-98.

RTP RESEARCH TO PRACTICE

CheckMate 9ER: Progression-Free Survival (Median Follow-Up 32.9 Months)



Number at risk (number censored)															
Nivolumab plus cabozantinib	323 (0)	281 (14)	238 (22)	203 (23)	170 (26)	155 (29)	136 (30)	121 (32)	108 (35)	77 (53)	47 (77)	19 (99)	6 (111)	1 (116)	0 (116)	..
Sunitinib	328 (0)	233 (36)	161 (51)	125 (55)	91 (61)	72 (66)	57 (70)	48 (74)	41 (75)	28 (83)	10 (96)	5 (101)	1 (104)	0 (105)	0 (105)	..

Motzer RJ et al. *Lancet Oncol* 2022;23(7):888-98.

CheckMate 9ER: Response Summary (Median Follow-Up 32.9 Months)

	Nivolumab plus cabozantinib group (n=323)	Sunitinib group (n=328)
Confirmed objective response (n [%; 95% CI])	180 (56%; 50–61)	93 (28%; 24–34)
Confirmed best overall response		
Complete response	40 (12%)	17 (5%)
Partial response	140 (43%)	76 (23%)
Stable disease	105 (33%)	134 (41%)
Progressive disease	20 (6%)	45 (14%)
Unable to determine	18 (6%)	55 (17%)
Not reported	0	1 (<1%)
Median time to response (IQR), months	2·8 (2·8–4·2)	4·2 (2·8–7·1)
Median duration of response (95% CI), months	23·1 (20·2–27·9)	15·1 (9·9–20·5)

Motzer RJ et al. *Lancet Oncol* 2022;23(7):888-98.

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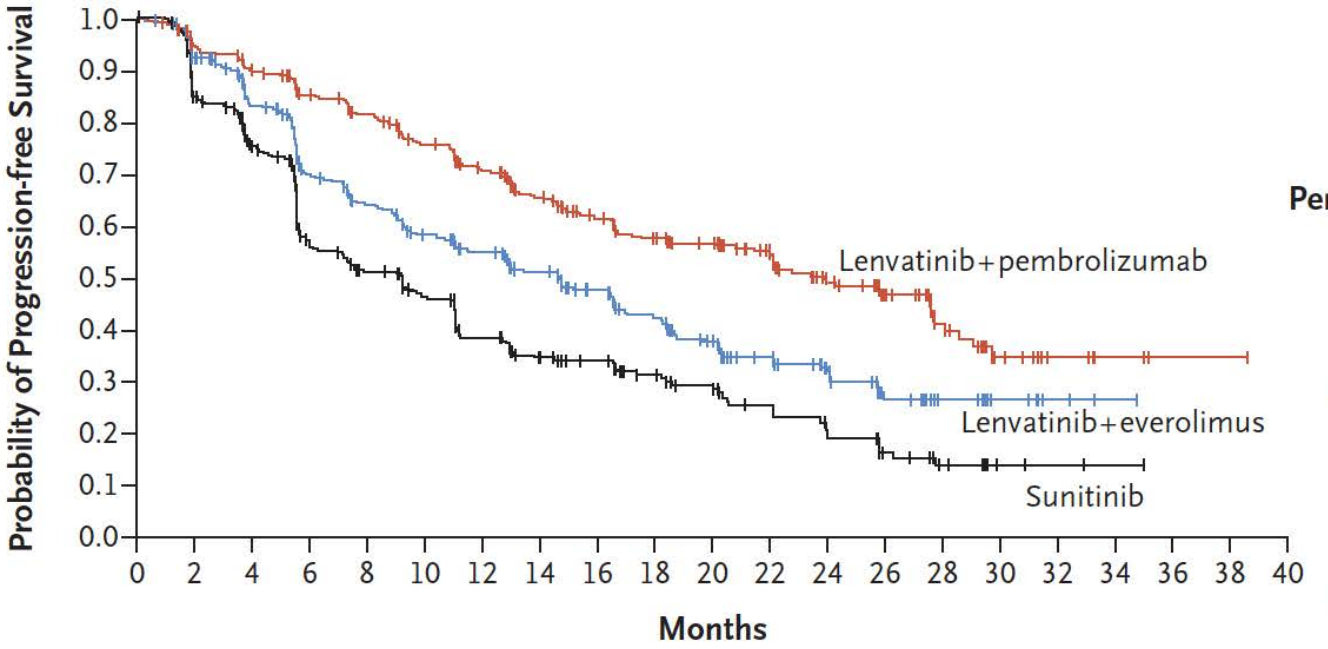
Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma

R. Motzer, B. Alekseev, S.-Y. Rha, C. Porta, M. Eto, T. Powles, V. Grünwald, T.E. Hutson, E. Kopyltsov, M.J. Méndez-Vidal, V. Kozlov, A. Alyasova, S.-H. Hong, A. Kapoor, T. Alonso Gordoa, J.R. Merchan, E. Winquist, P. Maroto, J.C. Goh, M. Kim, H. Gurney, V. Patel, A. Peer, G. Procopio, T. Takagi, B. Melichar, F. Rolland, U. De Giorgi, S. Wong, J. Bedke, M. Schmidinger, C.E. Dutcus, A.D. Smith, L. Dutta, K. Mody, R.F. Perini, D. Xing, and T.K. Choueiri, for the CLEAR Trial Investigators*

CLEAR: Progression-Free Survival Analyses

Progression-free survival



No. at Risk

Lenvatinib+pembrolizumab	355	321	300	276	259	235	213	186	160	136	126	106	80	56	30	14	6	3	1	1	0
Lenvatinib+everolimus	357	305	259	207	185	163	149	125	105	85	70	53	37	20	13	7	3	1	0		
Sunitinib	357	262	218	145	124	107	85	69	62	49	42	32	25	16	9	3	2	1	0		

Median Progression-free Survival (95% CI)

	mo
Lenvatinib+ Pembrolizumab	23.9 (20.8–27.7)
Lenvatinib+ Everolimus	14.7 (11.1–16.7)
Sunitinib	9.2 (6.0–11.0)

Hazard ratio for disease progression or death (lenvatinib+ pembrolizumab vs. sunitinib), 0.39 (95% CI, 0.32–0.49); P<0.001

Hazard ratio for disease progression or death (lenvatinib+ everolimus vs. sunitinib), 0.65 (95% CI, 0.53–0.80); P<0.001

Overall survival was longer with lenvatinib and pembrolizumab than with sunitinib (HR 0.66; $p = 0.005$) but was not longer with lenvatinib and everolimus than with sunitinib (HR 1.15; $p = 0.30$).

Motzer R et al. *N Engl J Med* 2021;384(14):1289-300.

CLEAR: Updated OS by Risk Group and Treatment Arm

	MEDIAN OS, MONTHS		
Subgroup	Lenvatinib/pembrolizumab	Sunitinib	HR (95% CI)
All patients	NE	NE	0.72 (0.55-0.93)
MSKCC favorable risk	NE	NE	1.00 (0.51-1.96)
MSKCC intermediate risk	43.0	41.1	0.71 (0.52-0.97)
MSKCC poor risk	33.0	17.1	0.50 (0.25-1.02)
IMDC favorable risk	NE	NE	1.22 (0.66-2.26)
IMDC intermediate risk	43.0	41.1	0.72 (0.52-1.00)
IMDC poor risk	36.9	10.4	0.39 (0.20-0.77)

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium criteria; MSKCC, Memorial Sloan Kettering Cancer Center criteria; OS, overall survival.

Choueiri TK et al. International Kidney Cancer Symposium 2021;Abstract E41.

PARIS 2022 ESMO congress

Abstract LBA8

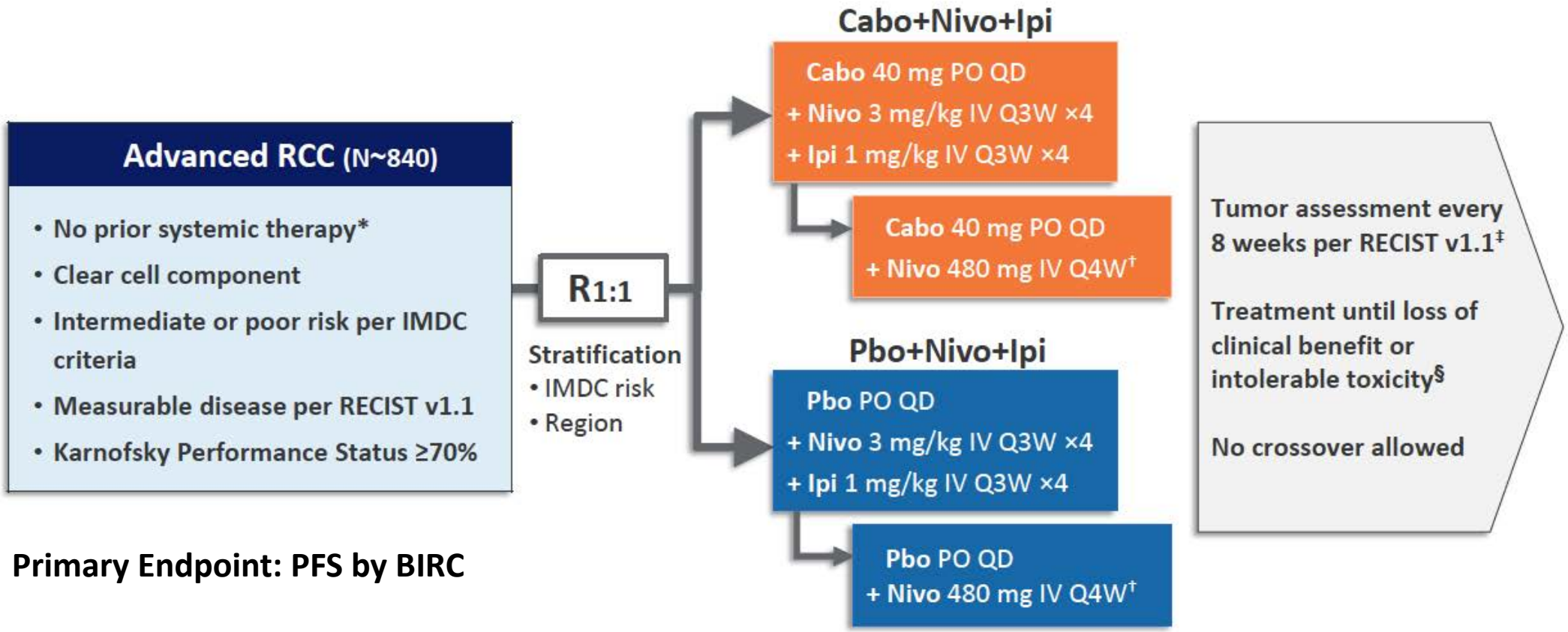
Phase 3 study of cabozantinib in combination with nivolumab and ipilimumab in previously untreated advanced renal cell carcinoma of IMDC intermediate or poor risk (COSMIC-313)

Toni K. Choueiri,[1] Thomas Powles,[2] Laurence Albiges,[3] Mauricio Burotto,[4] Cezary Szczylik,[5] Bogdan Zurawski,[6] Eduardo Yanez Ruiz,[7] Marco Maruzzo,[8] Alberto Suarez Zaizar,[9] Luis Enrique Fein,[10] Fabio A. Schutz,[11] Daniel Y.C. Heng,[12] Fong Wang,[13] Fabio Mataveli,[13] Yu-Lin Chang,[13] Maximiliano van Kooten Losio,[14] Cristina Suarez,[15] Robert J. Motzer[16]

[1]Dana–Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA; [2]Barts Cancer Institute, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, Royal Free National Health Service Trust, London, UK; [3]Institut Gustave Roussy, Université Paris Saclay, Villejuif, France; [4]Bradford Hill Clinical Research Center, Santiago, Chile; [5]European Health Centre, Otwock, Warsaw, Poland; [6]Professor Franciszek Lukaszczyk Oncology Center, Bydgoszcz, Poland; [7]James Lind Centro de Investigacion del Cancer, Temuco, Chile; [8]Oncology Unit 1, Department of Oncology, Istituto Oncologico Veneto IOV - IRCCS, Padua, Italy; [9]Consultorio de Medicina Especializada Dentro de Condominio San Francisco, Benito Juarez, Mexico City, Mexico; [10]Instituto de Oncologia de Rosario, Rosario, Argentina; [11]Beneficência Portuguesa de Sao Paulo, Sao Paulo, Brazil; [12]Tom Baker Cancer Center, University of Calgary, Calgary, Alberta, Canada; [13]Exelixis, Inc., Alameda, CA, USA; [14]Bristol Myers Squibb, Boudry, Neuchâtel, Switzerland; [15]Vall d'Hebron Institute of Oncology, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [16]Memorial Sloan Kettering Cancer Center, New York, NY, USA

RTP RESEARCH TO PRACTICE

COSMIC-313: Phase III Trial Schema



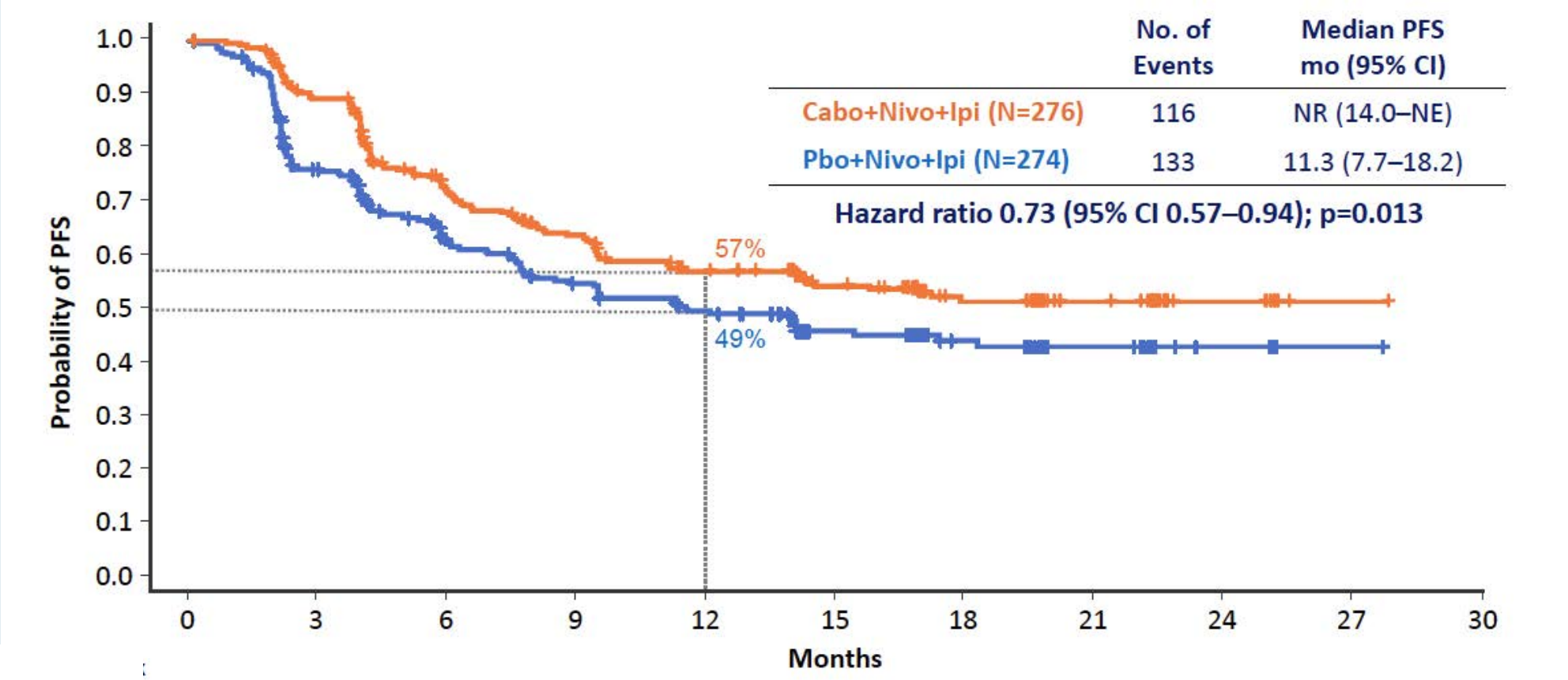
Primary Endpoint: PFS by BIRC

*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.

PFS = progression-free survival; BIRC = blinded independent review committee

Choueiri TK et al. ESMO 2022;Abstract LBA8.

COSMIC-313 Primary Endpoint: Final Analysis of PFS in PITT Population*

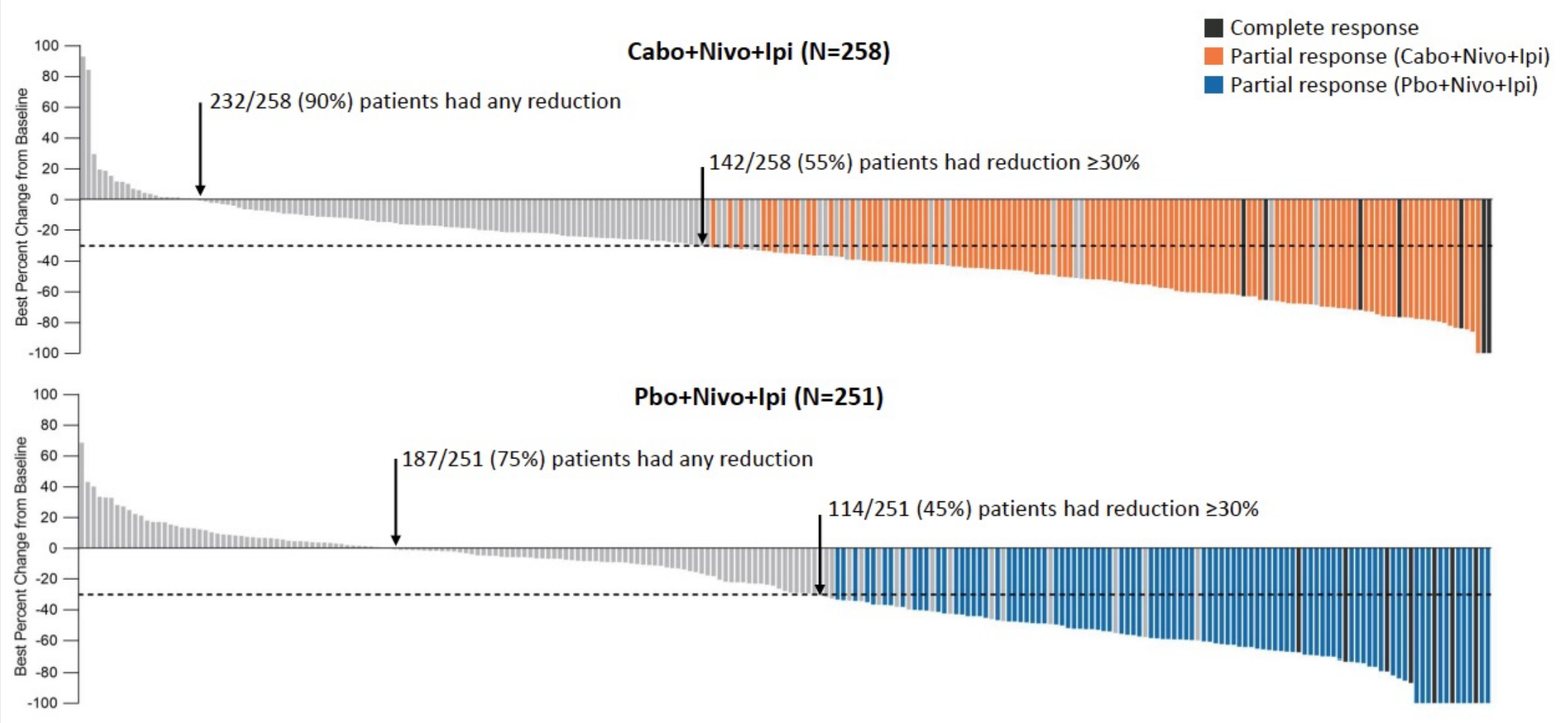


* PITT population is the first 550 randomly assigned patients

Subgroup analyses of PFS were generally consistent with results for the primary endpoint; analysis suggested greater benefit with Cabo + Nivo + Ipi for patients with IMDC intermediate risk compared to poor risk

Choueiri TK et al. ESMO 2022;Abstract LBA8.

COSMIC-313: Best Change from Baseline in Sum of Diameters of Target Lesions in PITT Population



Choueiri TK et al. ESMO 2022;Abstract LBA8.

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COSMIC-313: Summary of Adverse Events

	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.

Choueiri TK et al. ESMO 2022;Abstract LBA8.

Renal Cell Carcinoma Agenda

MODULE 1: Management of High-Risk Renal Cell Carcinoma (RCC) in the Adjuvant Setting

MODULE 2: Optimal First-Line Therapy for Patients with Metastatic RCC

MODULE 3: Treatment Approaches for Relapsed/Refractory Metastatic RCC

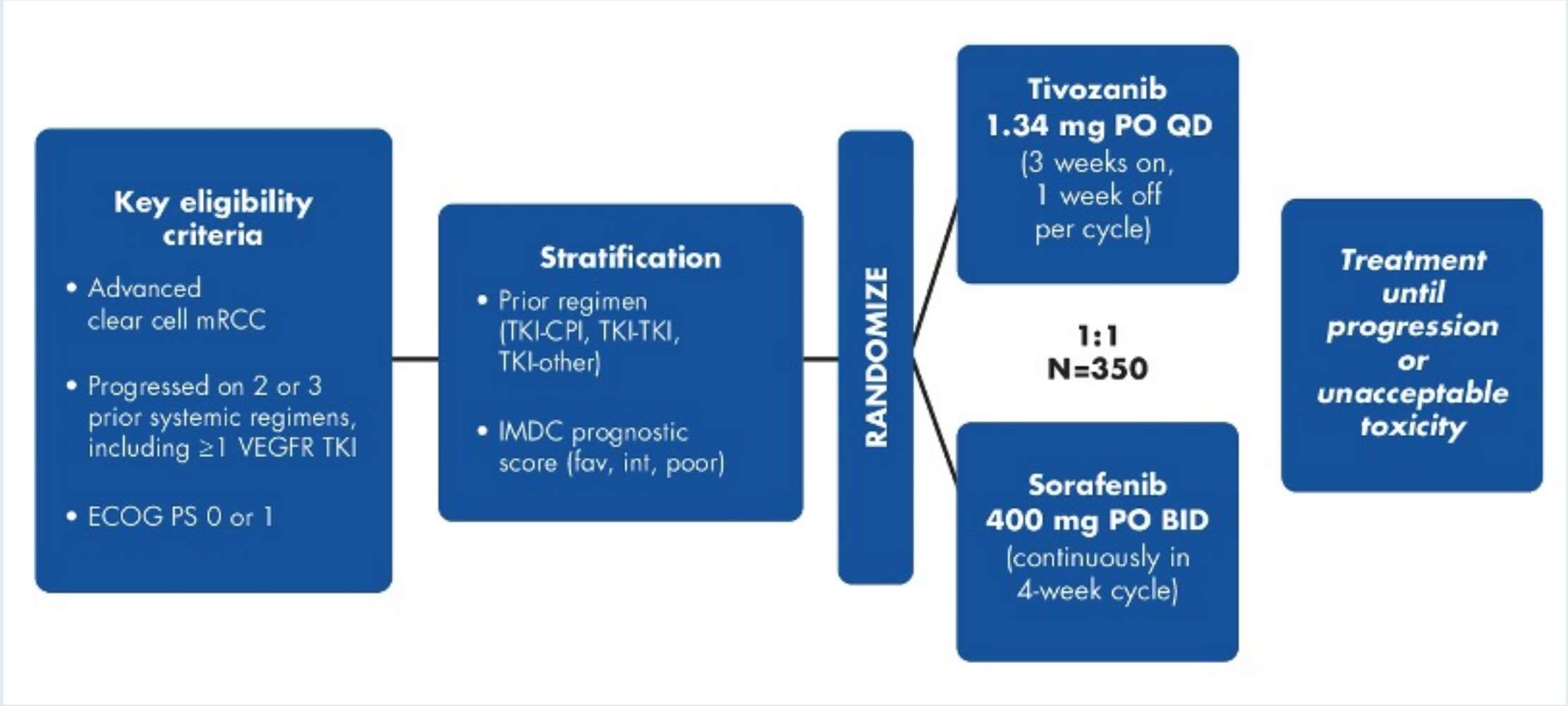
RTP RESEARCH TO PRACTICE

Long-Term PFS from TIVO-3: Tivozanib (TIVO) versus Sorafenib (SOR) in Relapsed/Refractory (R/R) Advanced RCC

Atkins MB et al.

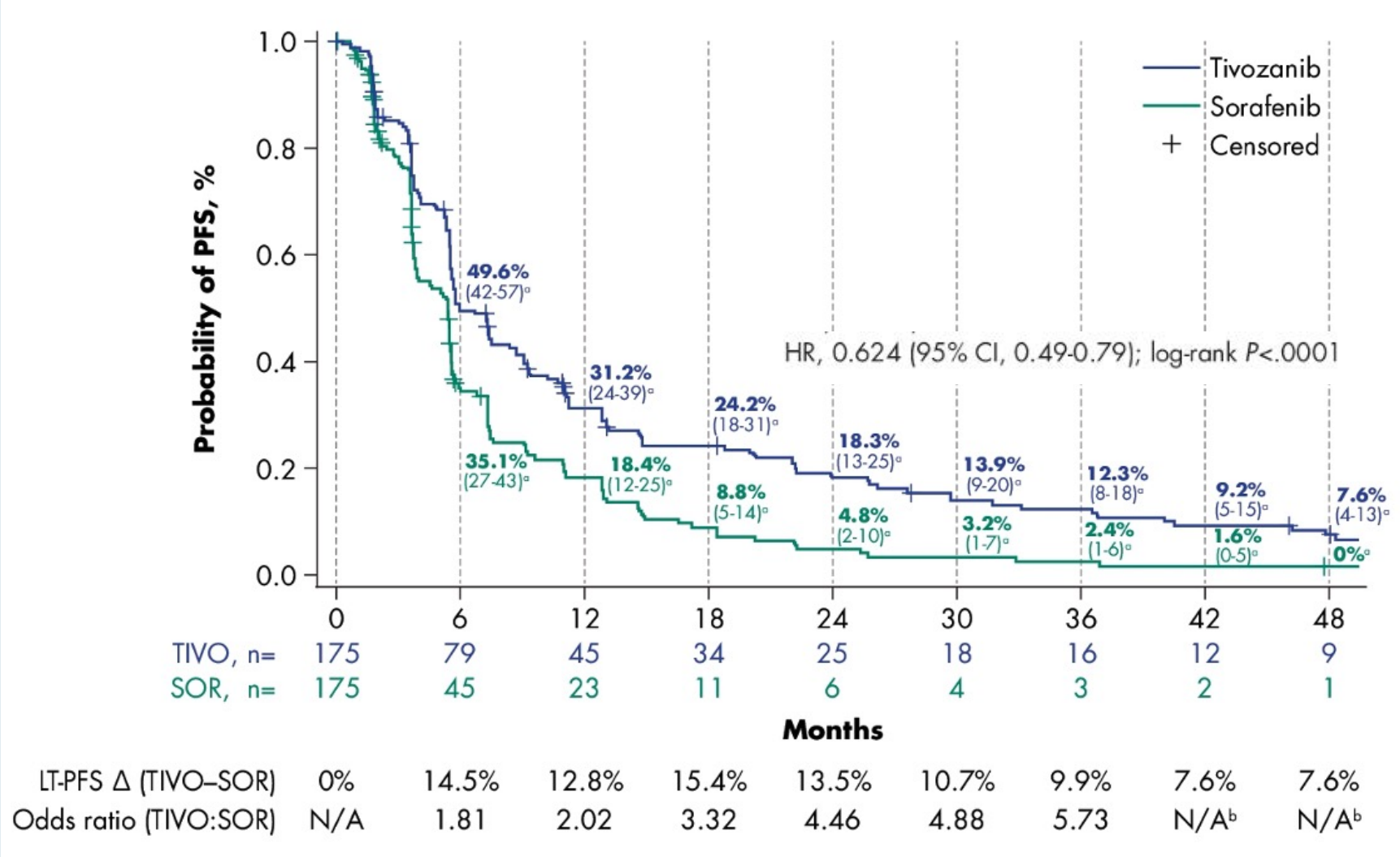
Genitourinary Cancers Symposium 2022;Abstract 362.

TIVO-3: Phase III Trial Design



Atkins MB et al. Genitourinary Cancers Symposium 2022;Abstract 362.

TIVO-3: Landmark Analysis Long-Term PFS (LT-PFS)



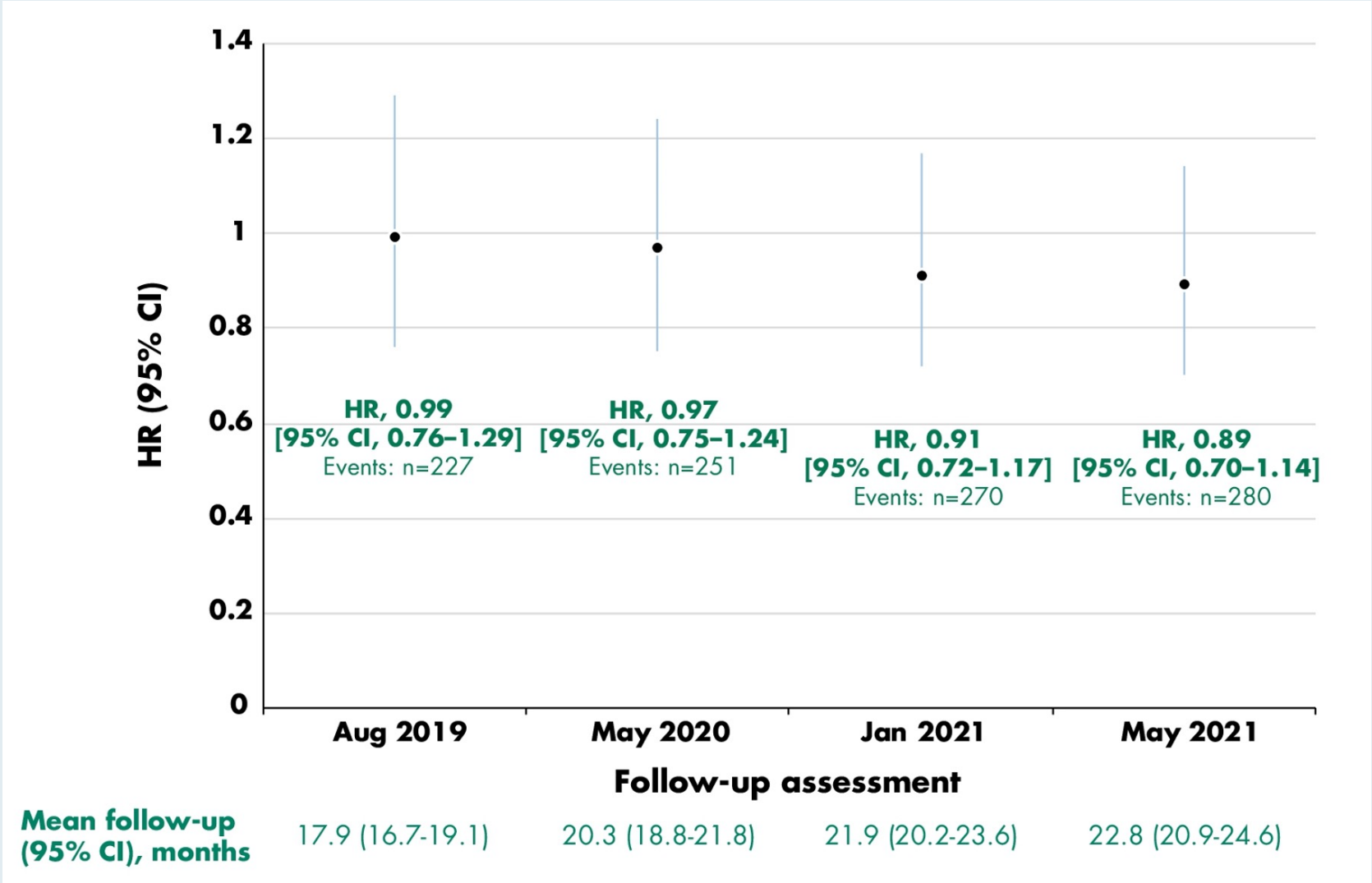
Atkins MB et al. Genitourinary Cancers Symposium 2022;Abstract 362.

Maturation of Overall Survival (OS) in TIVO-3 with Long-Term Follow-Up

Rini BI et al.

ASCO 2022;Abstract 4557.

TIVO-3: Serial Overall Survival with Extended Follow-Up (22.8 Months)



Rini BI et al. ASCO 2022;Abstract 4557.

TIVO-3: Unconditioned (ITT Population) and Landmark PFS-Conditioned Overall Survival with Extended Follow-Up

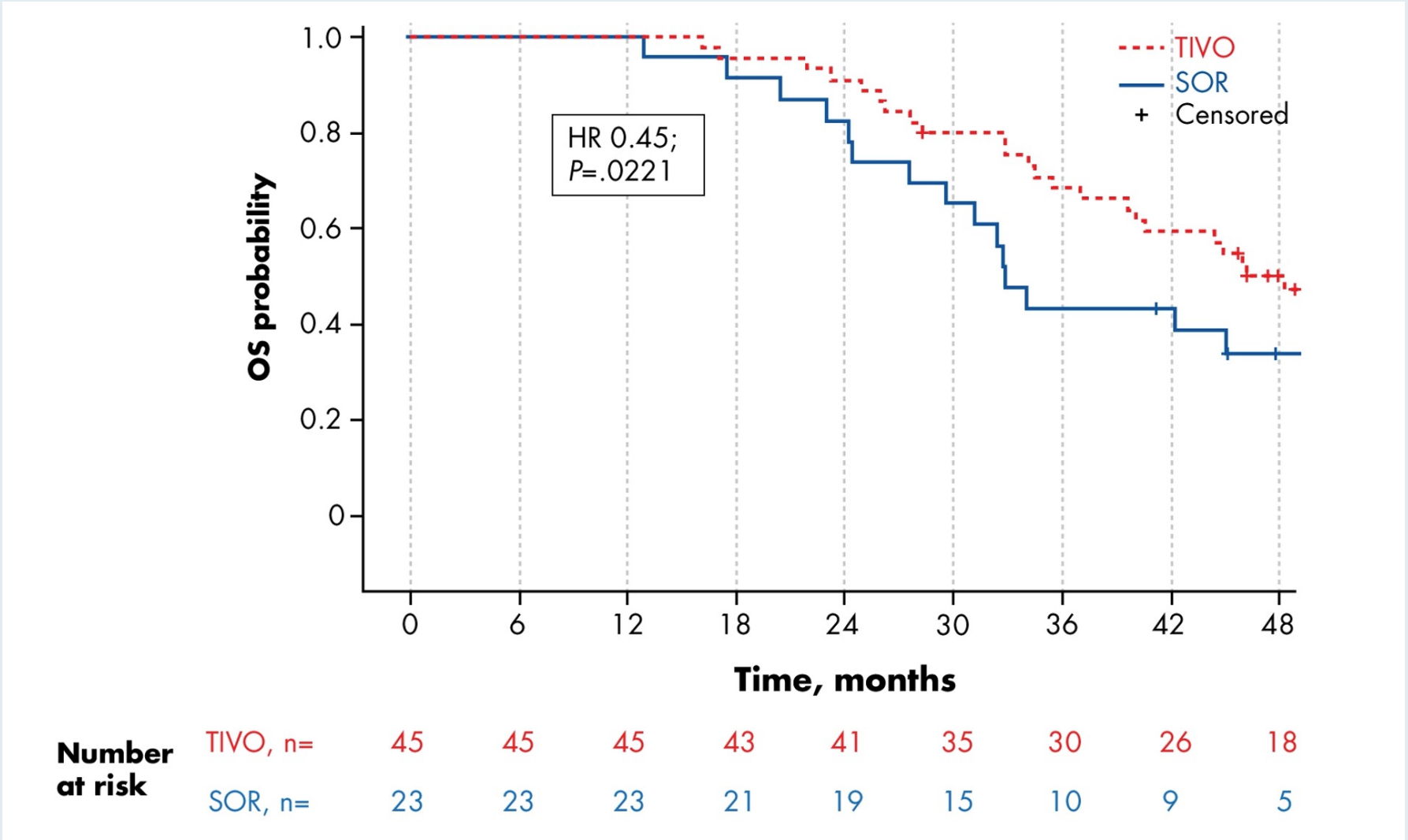
Population	Group	At risk, n	Events	Median OS (95% CI), months	HR (95% CI)	Stratified log-rank *P* value
Unconditioned (ITT population)	TIVO	175	138	16.4 (13.4-21.9)	0.89 (0.70-1.14)	0.3533
	SOR	175	142	19.1 (14.9-24.2)		
Conditioned on PFS ≥12 months	TIVO	45	25	48.3 (32.8-NR)	**0.45 (0.22-0.91)**	**0.0221**
	SOR	23	17	32.8 (27.6-50.0)		
Conditioned on PFS ≥18 months	TIVO	34	8	54.3 (44.9-NR)	0.46 (0.15-1.39)	0.1617
	SOR	11	5	50.0 (32.4-NR)		

NR, not reached.

PFS = progression-free survival

Rini BI et al. ASCO 2022;Abstract 4557.

TIVO-3: Conditional Overall Survival (OS) for Patients with 12-Month Progression-Free Survival



Rini BI et al. ASCO 2022;Abstract 4557.

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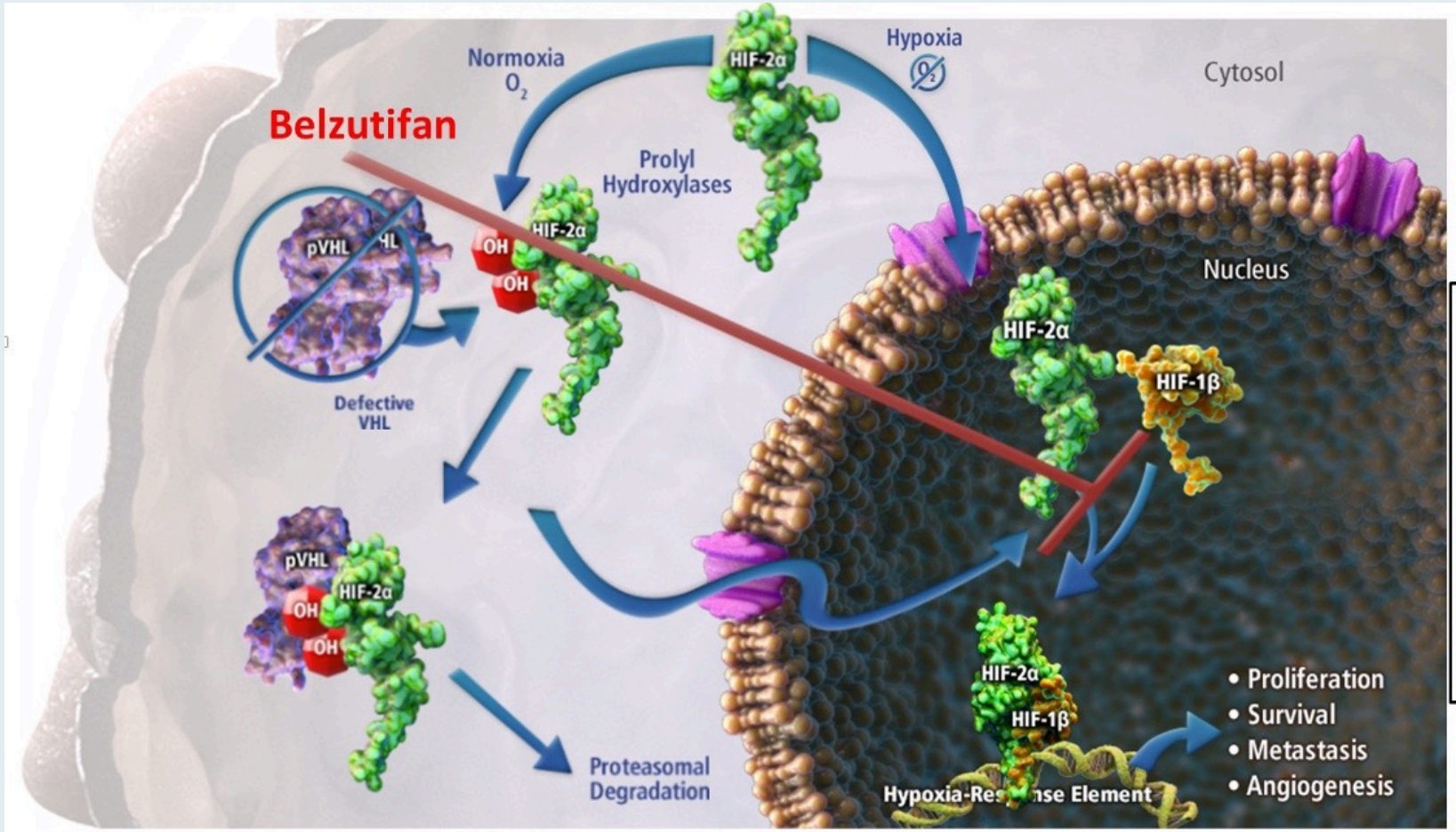
Belzutifan Is a Selective Small Molecule Inhibitor of HIF-2-alpha



- 90% of patients with sporadic ccRCC have defective pVHL function[1]
- Loss of pVHL function results in constitutive activation of HIF-2α[2]
- Belzutifan is a potent, selective, small molecule HIF-2α inhibitor

1. Linehan WM, Rickets CJ. *Nat Rev Urol.* 2019;16:539-552. 2. Couvé S et al. *Cancer Res.* 2014;74:6554-6564.

ccRCC = clear cell RCC

Bauer TD et al. Genitourinary Cancers Symposium 2021;Abstract 273.

The NEW ENGLAND JOURNAL of MEDICINE

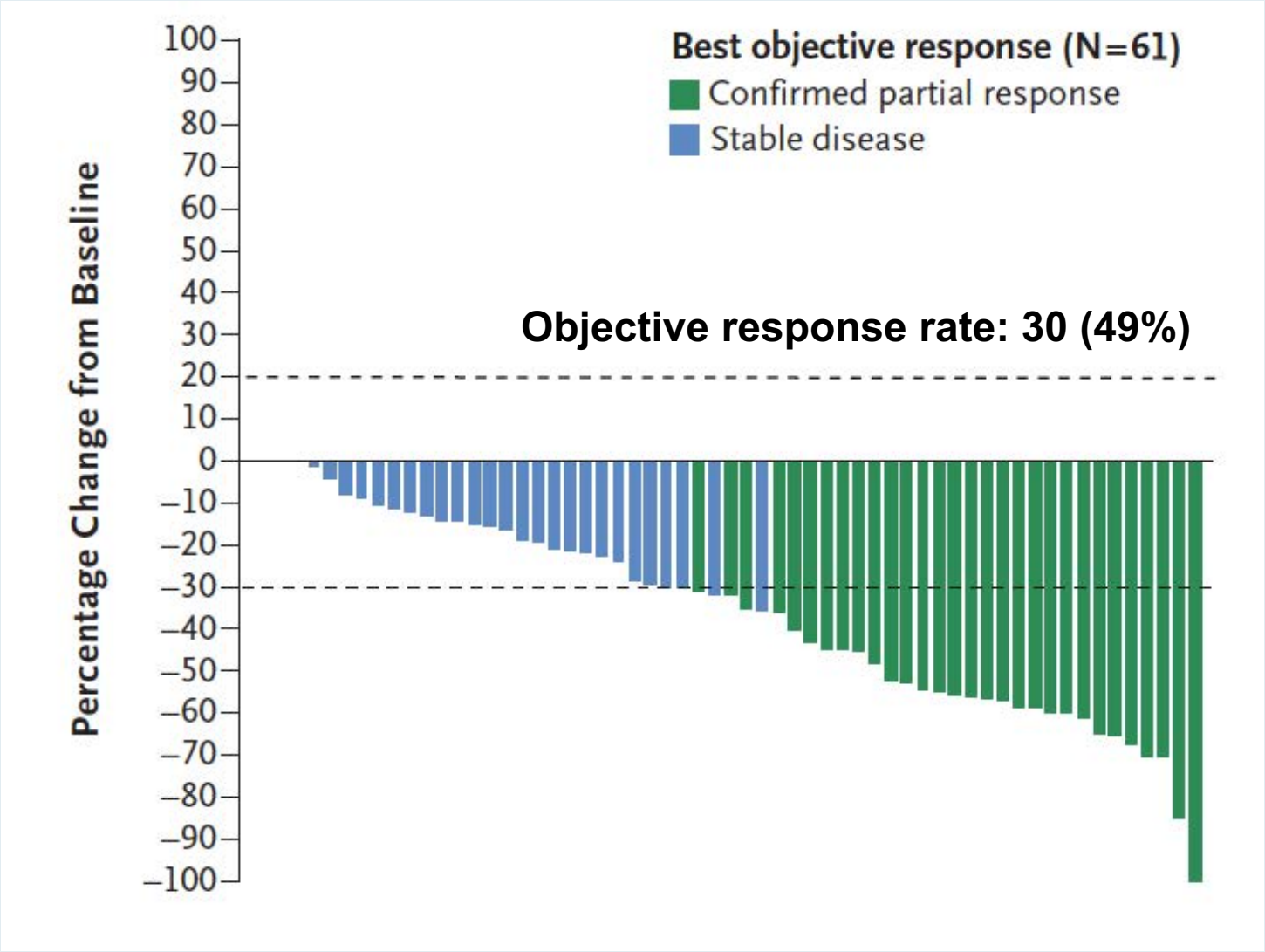
ORIGINAL ARTICLE

Belzutifan for Renal Cell Carcinoma in von Hippel–Lindau Disease

Eric Jonasch, M.D., Frede Donskov, M.D., Ph.D., Othon Iliopoulos, M.D., W. Kimryn Rathmell, M.D., Ph.D., Vivek K. Narayan, M.D., Benjamin L. Maughan, M.D., Stephane Oudard, M.D., Tobias Else, M.D., Jodi K. Maranchie, M.D., Sarah J. Welsh, M.D., Sanjay Thamake, Ph.D., Eric K. Park, M.D., Rodolfo F. Perini, M.D., W. Marston Linehan, M.D., and Ramaprasad Srinivasan, M.D., Ph.D., for the MK-6482-004 Investigators*

N Engl J Med 2021;385:2036-46.

Phase II Trial of Belzutifan: Maximum Change in Target Renal Tumors



Jonasch E et al. *N Engl J Med* 2021;385:2036-46.

Phase II Trial of Belzutifan: Select Adverse Events

Adverse event (n = 61)	Any grade	Grade 3
Anemia	55 (90%)	5 (8%)
Fatigue	40 (66%)	3 (5%)
Dyspnea	14 (23%)	1 (2%)
Myalgia	12 (20%)	1 (2%)
Hypertension	10 (16%)	5 (8%)
Diarrhea	8 (13%)	1 (2%)

Jonasch E et al. *N Engl J Med* 2021;385:2036-46.

Select Ongoing Phase III Clinical Trials of Belzutifan for Advanced RCC

Trial identifier	N	Study arms	Estimated primary completion date
MK-6482-012 (NCT04195750)	736	• Belzutifan • Everolimus	September 2025
MK-6482-012 (NCT04736706)	1,653	• Belzutifan + pembrolizumab + lenvatinib • Pembrolizumab/quavonlimab + lenvatinib • Pembrolizumab + lenvatinib	October 2026
NCT04586231	708	• Belzutifan + lenvatinib • Cabozantinib	December 2024

www.clinicaltrials.gov. Accessed September 2022.

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Thank you for joining us!

CME, MOC and NCPD credit information will be emailed to each participant within 5 business days.

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