Renal Hücreli Karsinom Tedavisinde Güncel Yaklaşım

Dr.Erdinç Nayır

VM Medicalpark Mersin Hastanesi

Sunum Planı

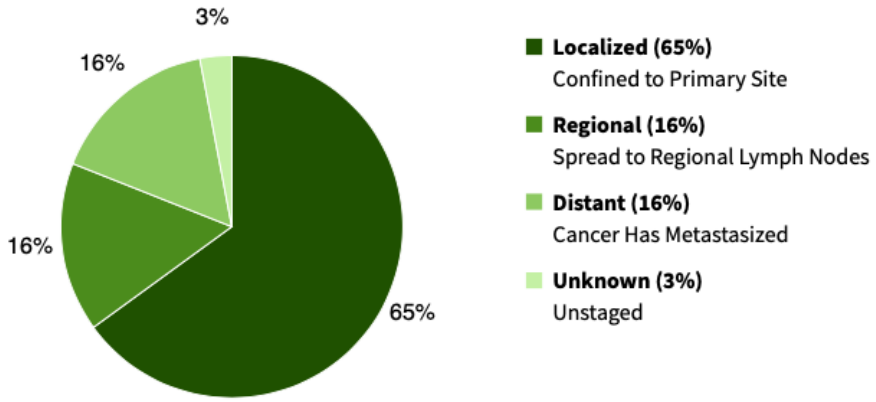
- **Giriş**
- **ASCO 2020, ASCO GU 2020 ve ESMO 2020’den önemli çalışmalar**
- **Güncel durum ve kılavuzlar**

RCC

Estimated New Cases

	Males			Females	
Prostate	174,650	20%		Breast	268,600	30%
Lung & bronchus	116,440	13%		Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%		Colon & rectum	67,100	8%
Urinary bladder	61,700	7%		Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%		Melanoma of the skin	39,260	4%
Kidney & renal pelvis	44,120	5%		Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%		Non-Hodgkin lymphoma	33,110	4%
Oral cavity & pharynx	38,140	4%		Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%		Pancreas	26,830	3%
Pancreas	29,940	3%		Leukemia	25,860	3%
All Sites	**870,970**	**100%**		**All Sites**	**891,480**	**100%**

Percent of Cases by Stage



Estimated New Cases in 2020	73,750
% of All New Cancer Cases	4.1%

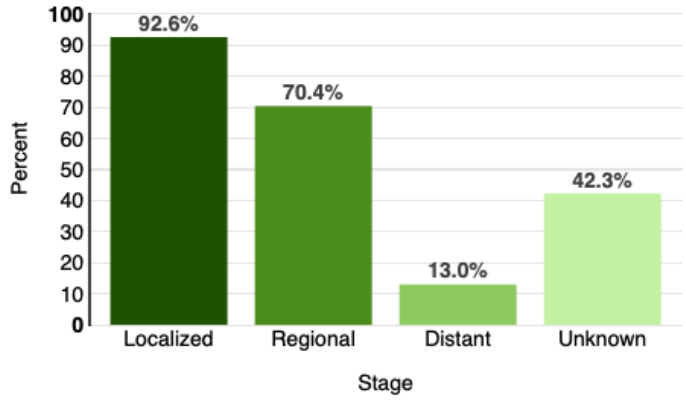
Estimated Deaths in 2020	14,830
% of All Cancer Deaths	2.4%

5-Year Relative Survival

75.2%

2010–2016

5-Year Relative Survival

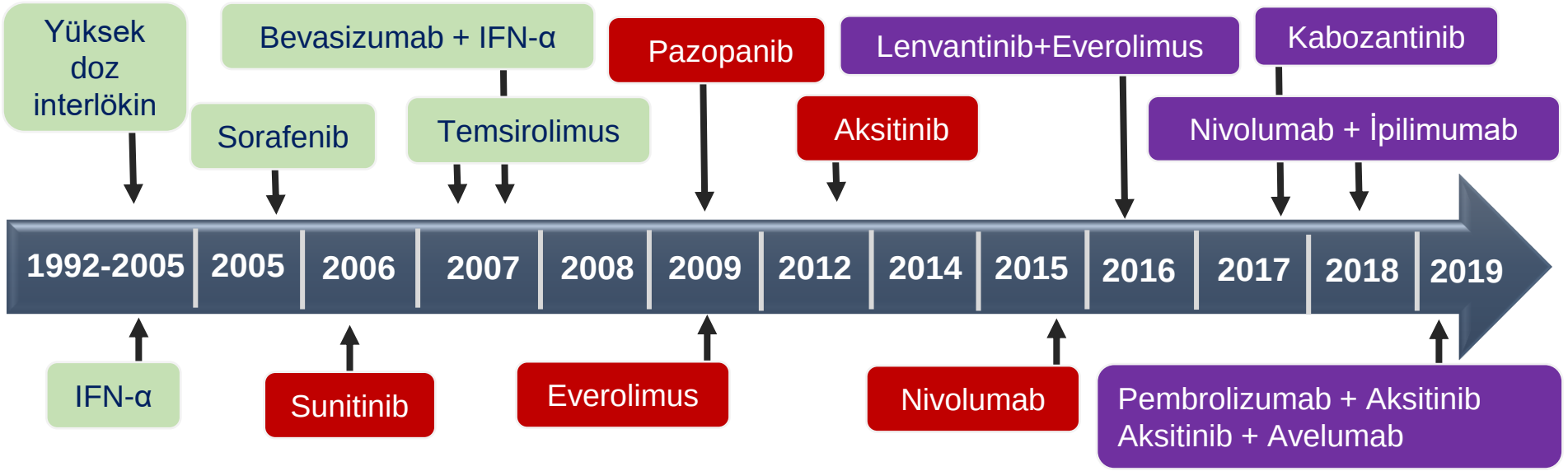


https://seer.cancer.gov/statfacts/html/kidrp.html, 10.11.2020, CA CANCER J CLIN 2019;69:7–34

Tedavi Seçenekleri

- İnterferon, IL-2
- Anti-VEGF yolağı (Sunitinib, pazopanib, axitinib, tivozanib, bevasizumab)
- mTOR yolağı (Everolimus, temsirolimus)
- RET yolağı (Kabozantinib)
- İmmünoterapi (Nivolumab, ipilimumab, avelumab, pembrolizumab)

mRHK tedavisinde kullanılan ilaçlar

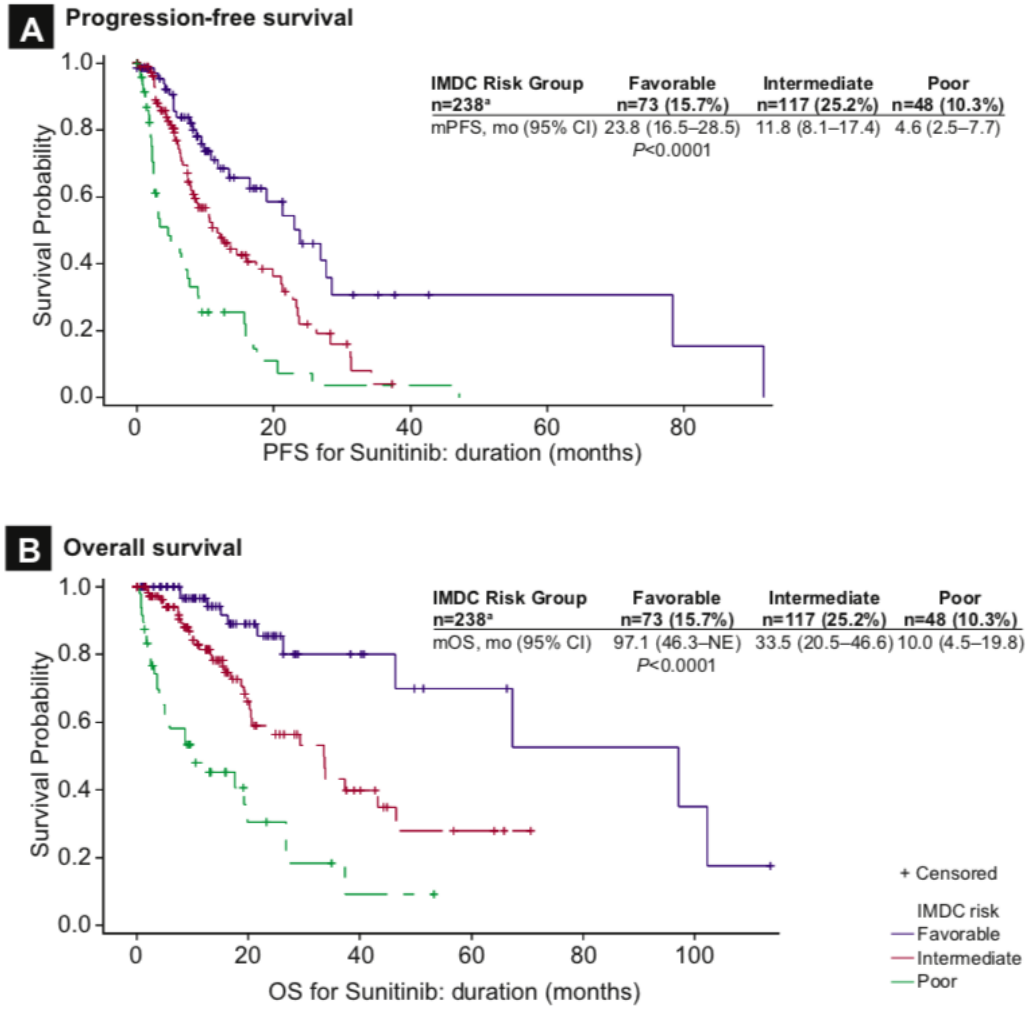


MSKCC ve IMDC kriterleri

MSKCC	
Tanı ve tedavi arasında geçen süre	<1 yıl
Karnofsky performans statüsü	<%80
Serum LDH düzeyi	>1,5 x NÜS
Düzeltilmiş serum kalsiyumu	>NÜS
Hemoglobin düzeyi	<NAS
İyi risk grubu: Risk faktörü yok Orta risk grubu: 1-2 risk faktörü var Kötü risk grubu: 3 veya daha fazla risk faktörü var	

IMDC	
Tanı ve sistemik tedavi arasında geçen süre	<1 yıl
Karnofsky performans statüsü	<%80
Hemoglobin düzeyi	<NAS
Kalsiyum	>NÜS
Nötrofil	>NÜS
Platelet	>NÜS
İyi risk grubu: Risk faktörü yok Orta risk grubu: 1-2 risk faktörü var Kötü risk grubu: 3-6 risk faktörü var	

ADONIS Çalışması



Real-world Experience With Sunitinib Treatment in Patients With Metastatic Renal Cell Carcinoma: Clinical Outcome According to Risk Score

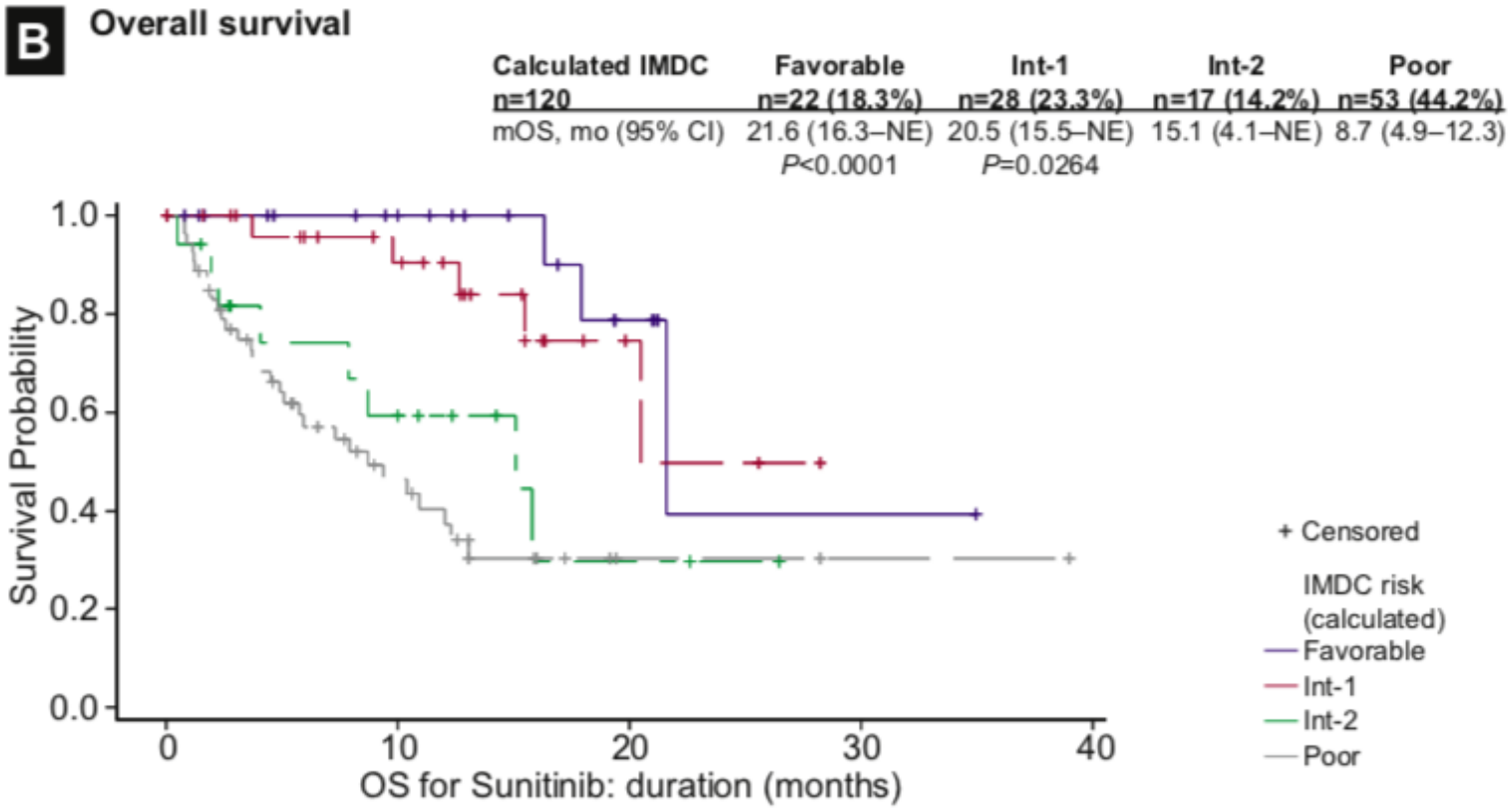
Manuela Schmidinger,[1] Camillo Porta,[2] Stephane Oudard,[3] Gwenael Denechere,[4] Yves Brault,[5] Lucile Serfass,[4] Nuno Costa,[6] James Larkin[7]

Table 2 PFS and OS for First-line Sunitinib-treated Patients, by IMDC Risk Group

IMDC Risk Group n = 238[a]	Favorable n = 73 (15.7%)	Intermediate n = 117 (25.2%)	Poor n = 48 (10.3%)
Median PFS, mos (95% CI)	23.8 (16.5-28.5)	11.8 (8.1-17.4)	4.6 (2.5-7.7)
Median OS, mos (95% CI)	97.1 (46.3-NE)[b]	33.5 (20.5-46.6)	10.0 (4.5-19.8)

Clin Genitourin Cancer 2020 Oct;18(5):e588-e597

ADONIS Çalışması



Sunitinib ile IMDC iyi risk grubundaki hastalar ile, orta risk grubundaki 1 riske sahip hastalarda mOS benzerdir ve diğer risk gruplarına göre anlamlı olarak daha uzundur.

KEYNOTE – 426

Pembrolizumab Plus Axitinib Versus Sunitinib as First-Line Therapy for Advanced Renal Cell Carcinoma: Updated Analysis of KEYNOTE-426

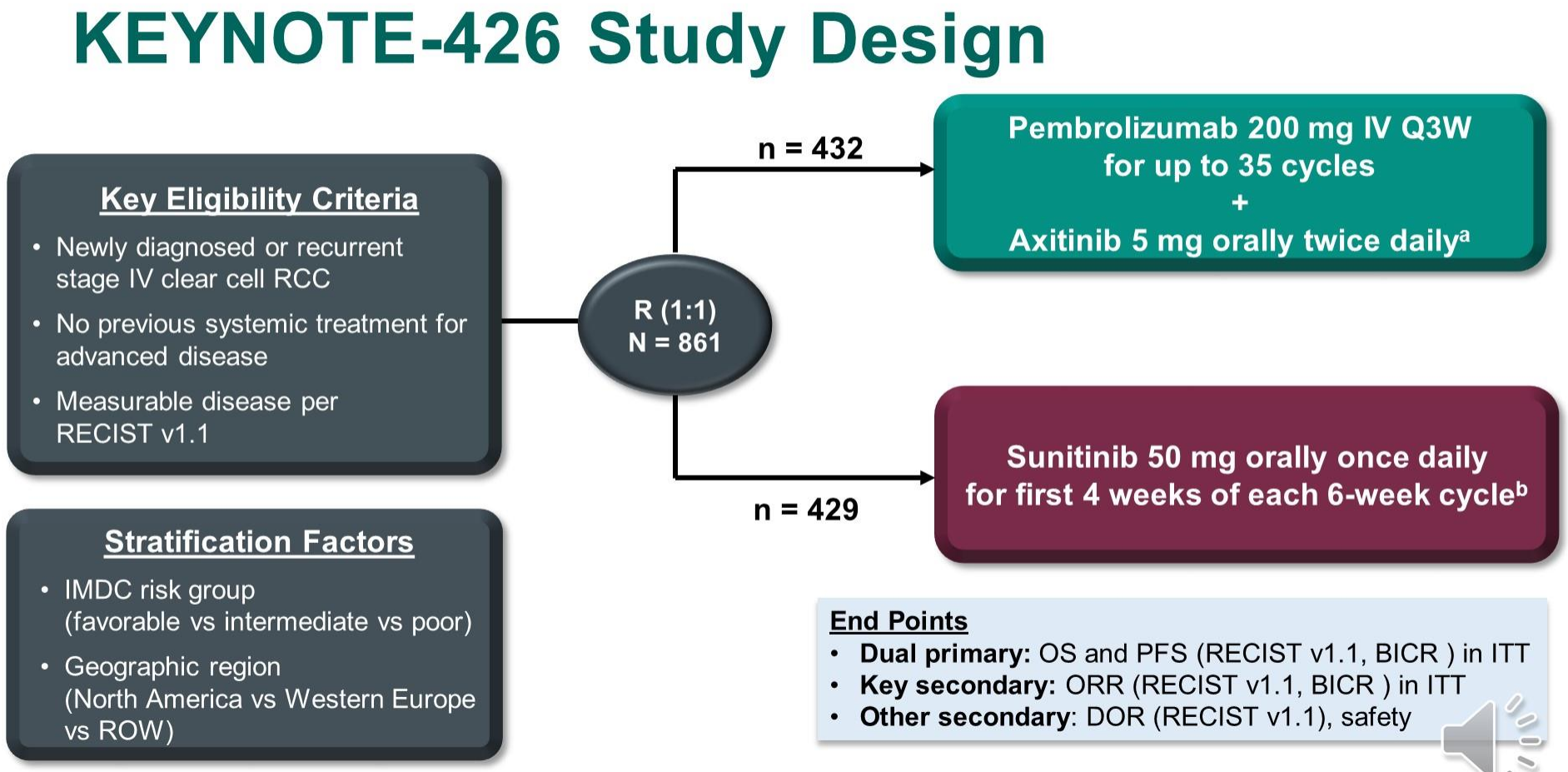
E. R. Plimack[1]; B. I. Rini[2]; V. Stus[3]; R. Gafanov[4]; T. Waddell[5]; D. Nosov[6]; F. Pouliot[7]; D. Soulières[8]; B. Melichar[9]; I. Vynnychenko[10]; S. J. Azevedo[11]; D. Borchiellini[12]; R. S. McDermott[13]; J. Bedke[14]; S. Tamada[15]; L. Yin[16]; M. Chen[16]; L. R. Molife[17]; M. B. Atkins[18]; T. Powles[19]

[1]Fox Chase Cancer Center, Philadelphia, PA, USA; [2]Clevland Clinic Taussig Cancer Institute, Cleveland, OH, USA (currently at Vanderbilt-Ingram Cancer Center, Nashville, TN, USA); [3]Dnipropetrovsk Medical Academy of Ministry of Health of Ukraine, Dnipro, Ukraine; [4]Russian Scientific Center of Roentgenoradiology, Moscow, Russia; [5]The Christie NHS Foundation Trust, Manchester, United Kingdom; [6]Central Clinical Hospital With Outpatient Clinic, Moscow, Russia; [7]CHU of Quebec and Laval University, Quebec City, QC, Canada; [8]Centre Hospitalier de l'Universitaire de Montréal, Montréal, QC, Canada; [9]Palacky University Medical School and Teaching Hospital, Olomouc, Czech Republic; [10]Sumy State University, Sumy Regional Oncology Center, Sumy, Ukraine; [11]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; [12]Centre Antoine Lacassagne, Université Côte d'Azur, Nice, France; [13]Adelaide and Meath Hospital and University College Dublin, Dublin, Ireland; [14]Eberhard-Karls University Tübingen, Tübingen, Germany; [15]Osaka City University Hospital, Osaka, Japan; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]MSD UK, London, United Kingdom; [18]Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA; [19]Barts Health NHS Trust and the Royal Free NHS Foundation Trust, Barts Cancer Institute, and Queen Mary University of London, London, United Kingdom

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

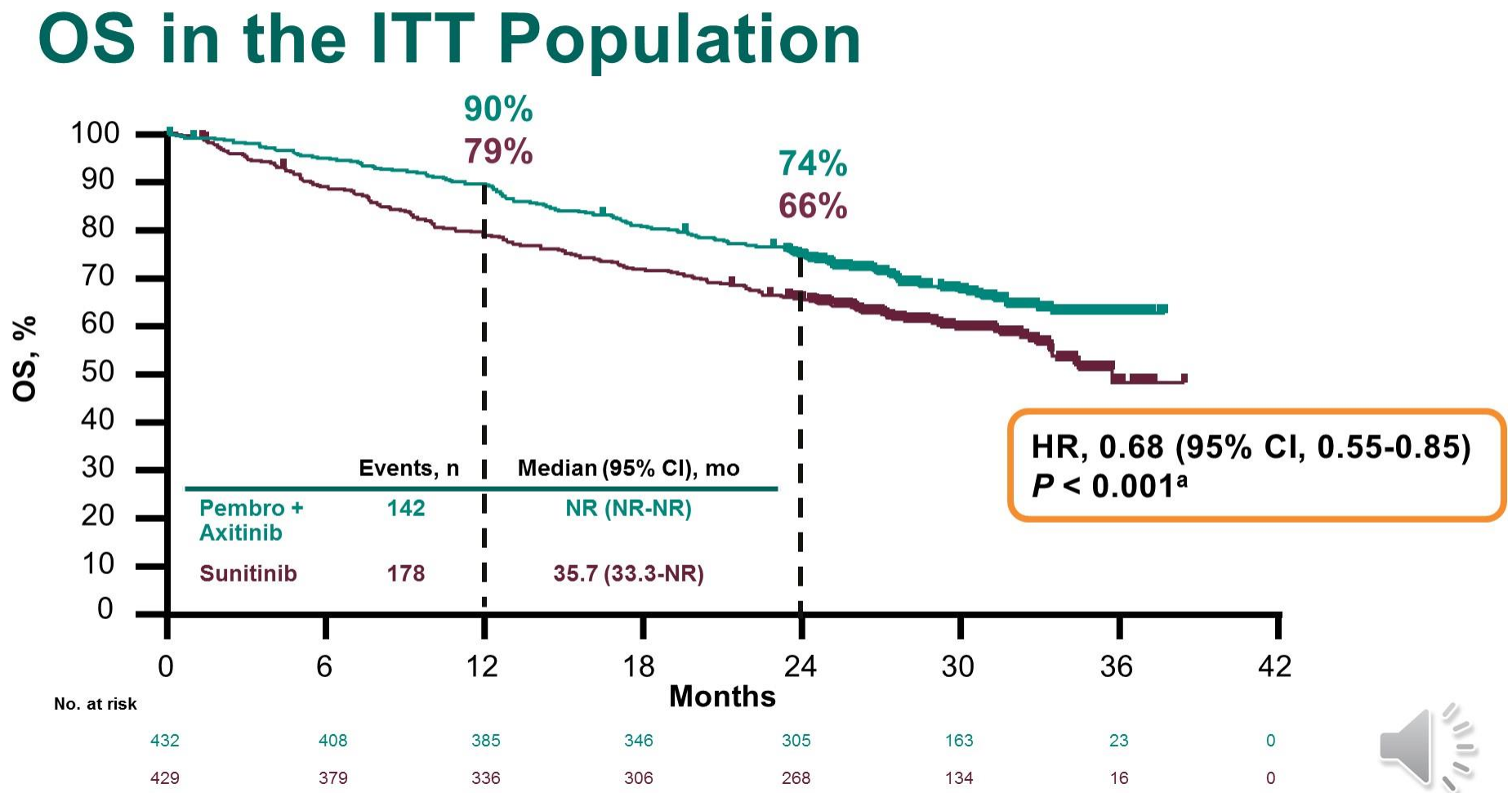
PRESENTED BY: Elizabeth R. Plimack, MD

KEYNOTE – 426



[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity. [b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 weeks of each 6-week cycle to manage toxicity. Data cutoff: January 6, 2020.

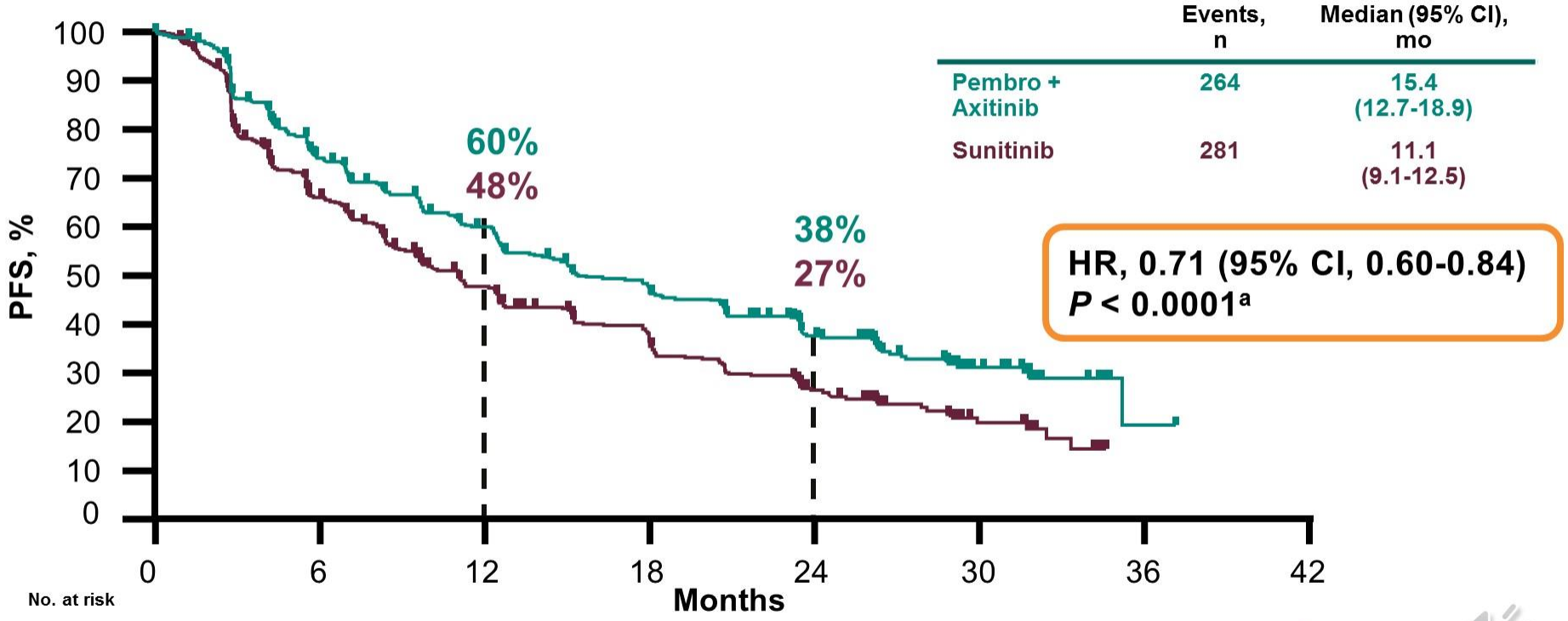
KEYNOTE – 426



[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to OS; only nominal *P* values are reported. Data cutoff: January 6, 2020.

KEYNOTE – 426

PFS in the ITT Population



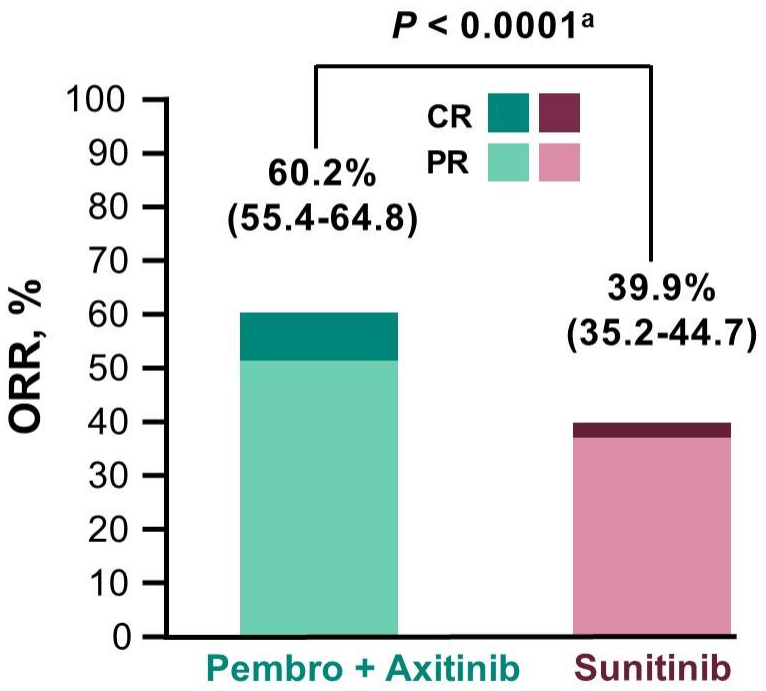
	Events, n	Median (95% CI), mo
Pembro + Axitinib	264	15.4 (12.7-18.9)
Sunitinib	281	11.1 (9.1-12.5)

HR, 0.71 (95% CI, 0.60-0.84)
P < 0.0001[a]

[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to PFS; only nominal *P* values are reported. Data cutoff: January 6, 2020.

KEYNOTE – 426

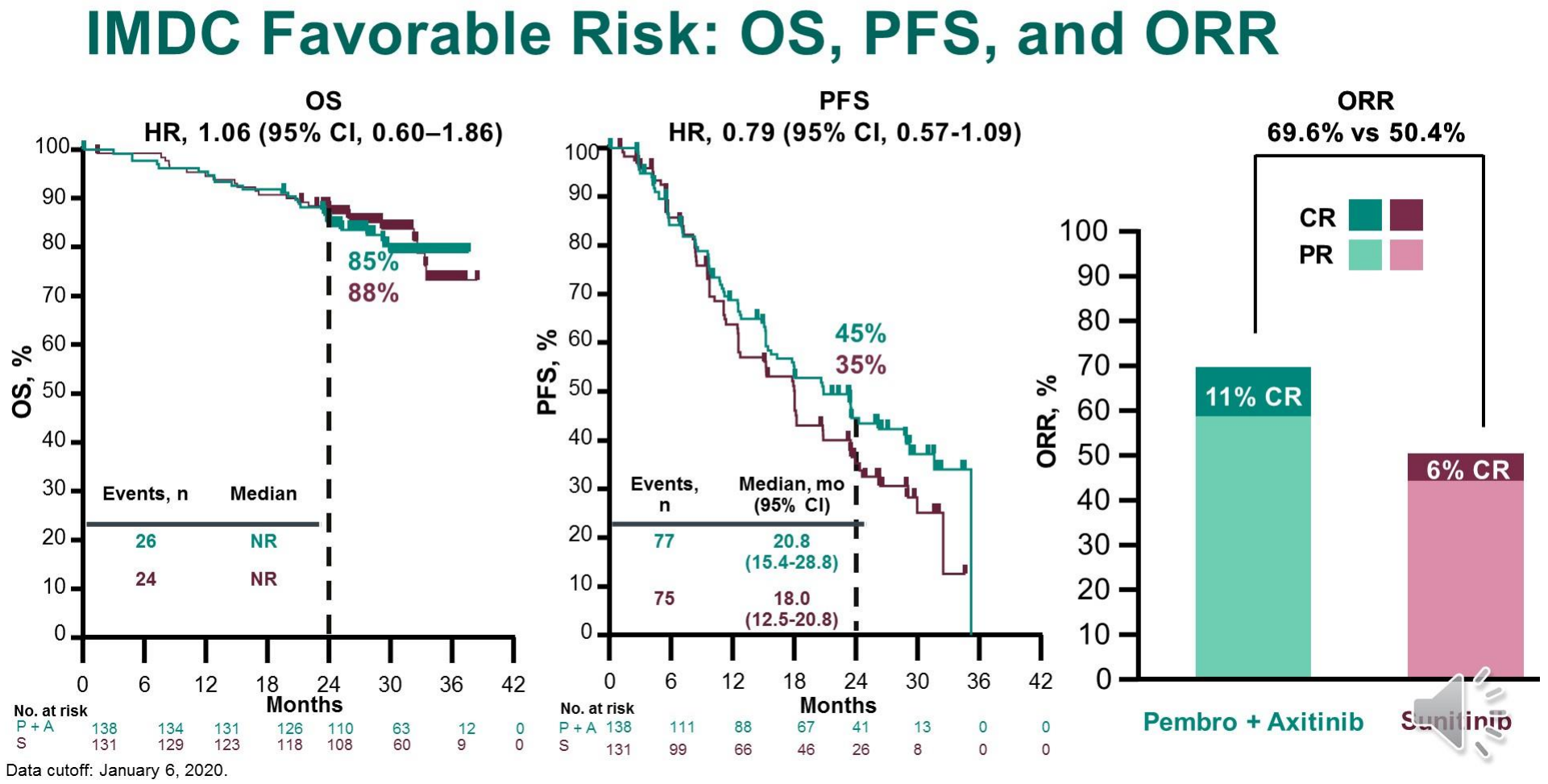
Confirmed Objective Response Rate
ITT Population



	Pembro + Axitinib n = 432	Sunitinib n = 429
Best response, n (%)		
CR	38 (8.8)	13 (3.0)
PR	222 (51.4)	158 (36.8)
SD	100 (23.1)	150 (35.0)
PD	49 (11.3)	74 (17.2)
NE[b]	16 (3.7)	28 (6.5)
NA[c]	7 (1.6)	6 (1.4)
Duration of response, median (range), mo	23.5 (1.4+ to 34.5+)	15.9 (2.3 to 31.8+)

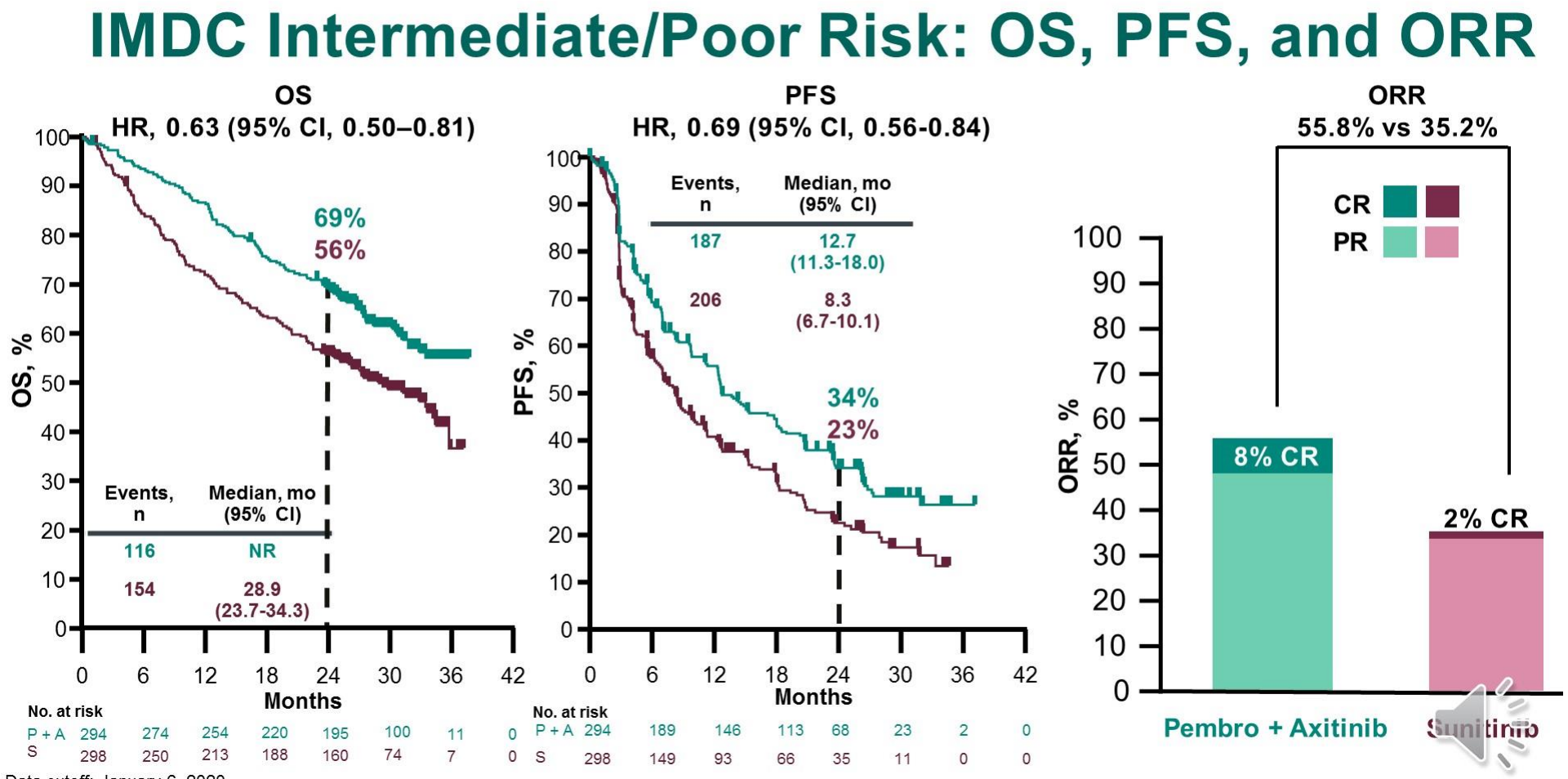
[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to confirmed objective response; only nominal *P* values are reported. [b]Postbaseline assessment available but not evaluable (ie, all postbaseline assessments with insufficient data for assessment of response per RECIST v1.1 or CR/PR/SD <6 weeks from randomization). [c]No postbaseline assessment available for response evaluation; + indicates an ongoing response at time of last disease assessment. Data cutoff: January 6, 2020.

KEYNOTE – 426



Data cutoff: January 6, 2020.

KEYNOTE – 426



Data cutoff: January 6, 2020.

KEYNOTE – 426

- KEYNOTE 426 mRCC 1. basamak uzun dönem sonuçları **Pembro+axitinib > Sunitinib**
- **Orta ve Kötü risk faktörlü** hastalarda **OS, PFS, ORR ve CR (%9 vs %3) üstünlük devam ediyor**
- Pembro kolunda ilk 6 ayda tümör yükünde **>%80 olanlarda CR benzer sağ kalım** sonuçları saptandı.
- **1.basamak tedavide Pembrolizumab +Axitinib** kombinasyonun standart olarak devam ettirmektedir

mRCC ve Nivolumab

- CheckMate 025 **TKİ dirençli hastalarda 2. basamakta standart**
- CheckMate 214 **Nivo+İpi kombinasyonu 1. basamakta standart**
- **Nivolumab:**
  - 1.basamakta tüm gruplarda etkin mi?
  - Monoterapi sonrası ipilimumab ile kombine kullanılırsa?

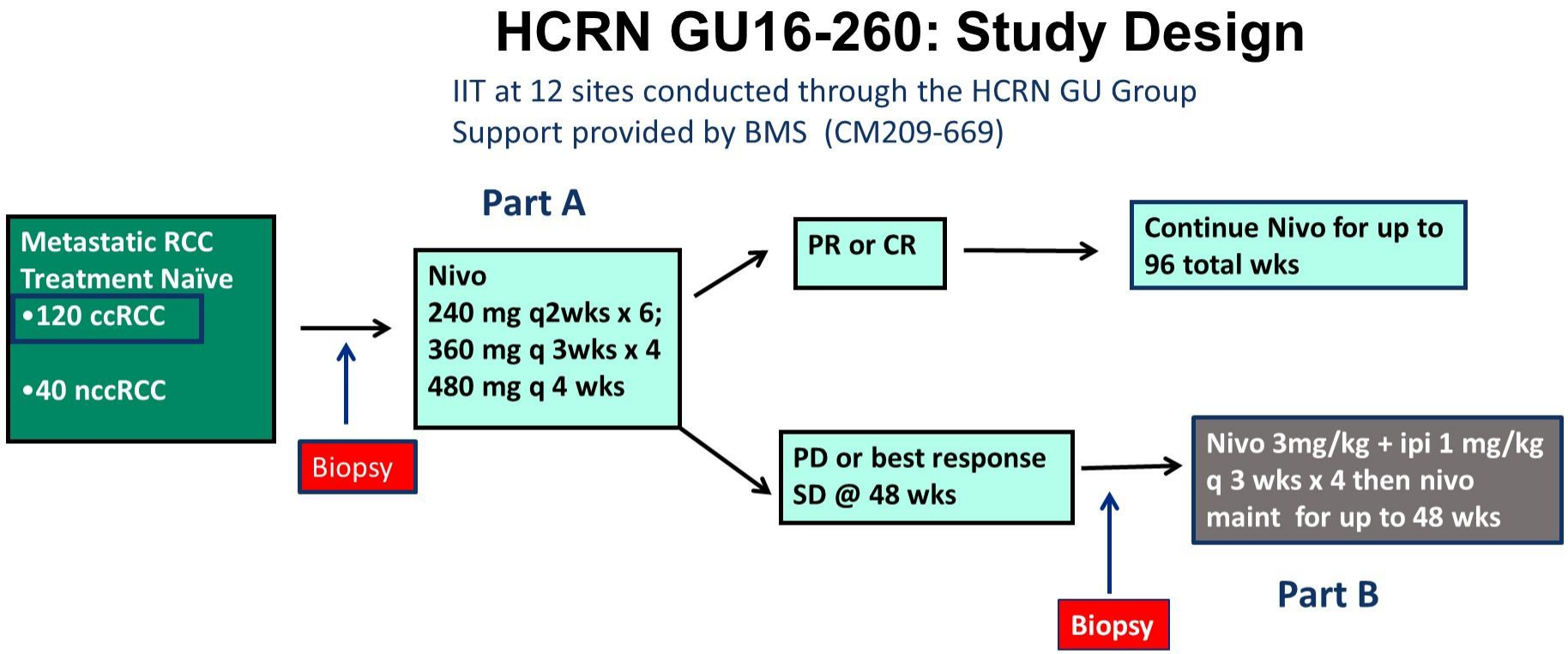
GU16-260 Çalışması

Phase II Study of Nivolumab and Salvage Nivolumab + Ipilimumab in Treatment-Naïve Patients with Advanced Renal Cell Carcinoma (HCRN GU16-260)

Michael B. Atkins[1], Opeyemi A. Jegede[2], Naomi B. Haas[3], David F. McDermott[4], Mehmet A. Bilen[5], Charles G. Drake[6], Jeffrey A. Sosman[7], Robert Alter[8], Elizabeth R. Plimack[9], Brian Rini[10], Michael Hurwitz[11], David Peace[12], Sabina Signoretti[13], Catherine J. Wu[2], Paul J. Catalano[2], Hans Hammers[14]

[1]Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC; [2]Dana Farber Cancer Institute, Boston, MA; [3]University of Pennsylvania Abramson Cancer Center, Philadelphia, PA; [4]Beth Israel Deaconess Medical Center, Boston, MA; [5]Winship Cancer Institute of Emory University, Atlanta GA; [6]Columbia Herbert Irving Comprehensive Cancer Center, New York, NY; [7]Northwestern Lurie Comprehensive Cancer Center, Chicago, IL; [8]John Theurer Cancer Center, Hackensack, NJ; [9]Fox Chase Cancer Center, Philadelphia, PA; [10]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH (currently at Vanderbilt-Ingram Cancer Center, Nashville, TN); [11]Yale-Smilow Comprehensive Cancer Center, New Haven, CT; [12]University of Illinois Chicago, Chicago, IL; [13]Brigham and Women's Hospital Boston, MA, [14]University of Texas Southwestern Sammons Cancer Center, Dallas, TX.

GU16-260 Çalışması



GU16-260 Çalışması

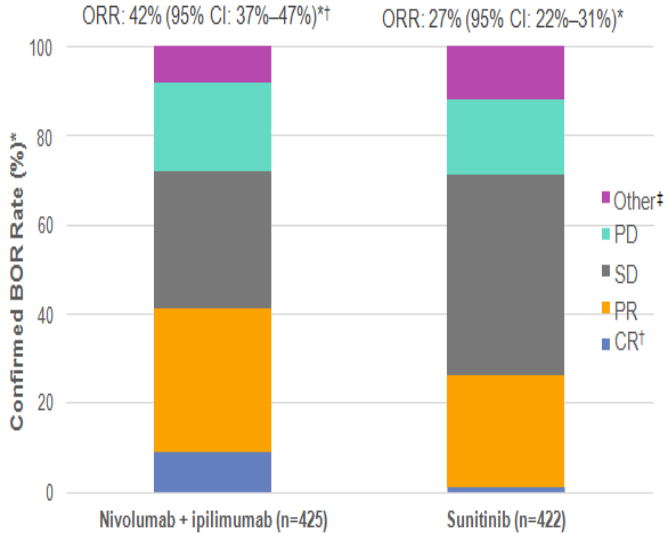
Objective Response Rates: Nivo Monotherapy: Part A

Best Response N (%)	IMDC Risk Category (N)			Total (N= 123) N (%)
	Favor (30) N (%)	Interm (80) N (%)	Poor (12) N (%)	
CR	4 (13.3)	3 (3.8)	0	7 (5.7)
PR*	11 (36.7)	17 (21.2)	3 (25)	32 (26.0)
SD	15 (50.0)	26 (32.5)	5 (42)	46 (37.4)
PD	0	34 (42.5)	4 (33)	38 (30.9)
ORR	15/30 (50)	20/80 (25)	3/12 (25)	39/123 (31.7)
(95% CI) %	(31.3,68.7)	(16.6, 35.1)		(23.6, 40.7)

*** 1 PR with missing IMDC Risk Category**

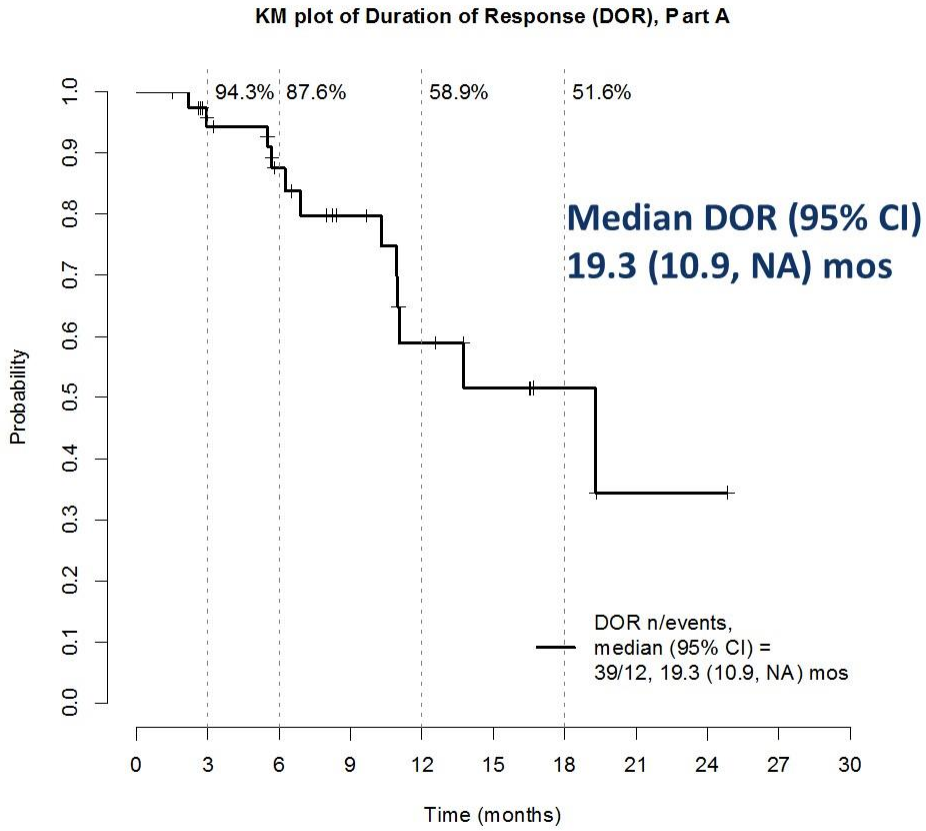
ORR: 39/123 = 31.7%
95% CI (23.6, 40.7%)

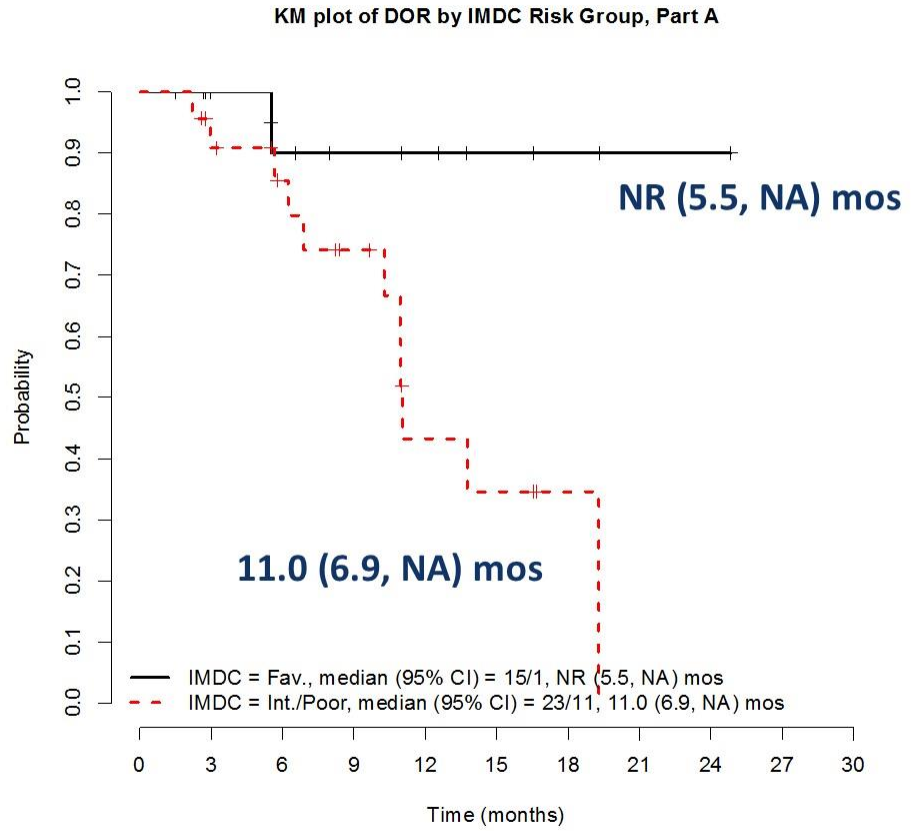
Sarcomatoid RCC ORR
7/22 = 31.8% (all PRs)
95% CI (13.9, 54.9%)



GU16-260 Çalışması

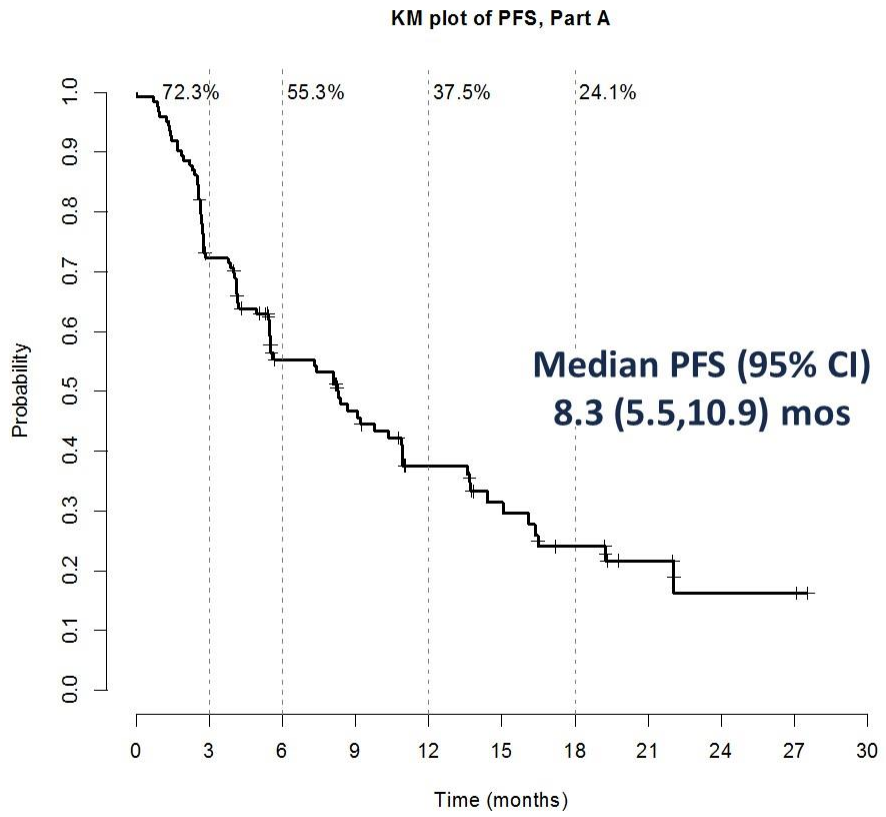
Duration of Response: Nivo Monotherapy (Part A)

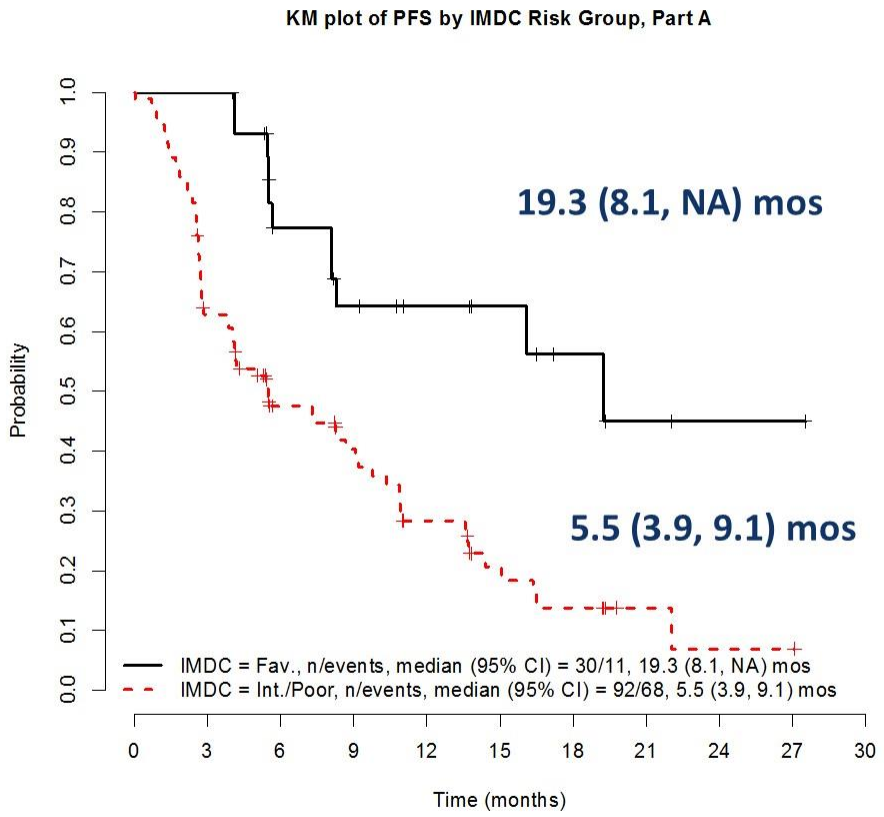




GU16-260 Çalışması

Progression Free Survival: Nivo Monotherapy (Part A)





GU16-260 Çalışması

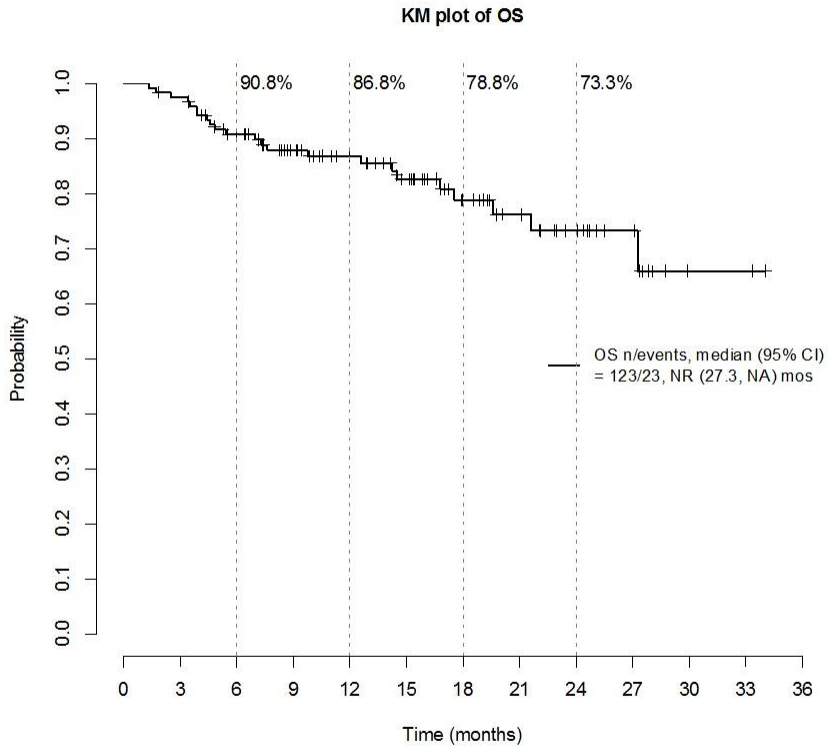
Objective Response Rates: Nivo/Ipi Salvage (Part B)

Best Response N (%)	IMDC Risk Category (N=30)			Total N (%)
	Favor (4)	Interm (24)	Poor (2)	
CR	0	0	0	0
PR	2 (50)	2 (8.3)	0	4 (13.3)
SD	1 (25)	6 (25)	0	7 (23.3)
PD	1 (25)	16 (66.7)	2 (100)	19 (63.3)

ORR: 4/30 = 13.3%
95% CI (3.8, 30.7)

GU16-260 Çalışması

Overall Survival: ccRCC



100/123 = 81% of patients remain alive

GU16-260 Çalışması

- **Nivo monoterapisi etkin bir tedavi**

- Özellike iyi risk grupları başta olmak üzere 1. basamak tedavide Nivolumab monoterapisi seçenek olabilir. Ancak **salvage IO+IO vs IO+TKI ??**

Pembro + Lenvatinib 2L

Phase 2 trial of lenvatinib plus pembrolizumab for disease progression after PD-1/PD-L1 immune checkpoint inhibitor (ICI) in metastatic clear cell renal cell carcinoma

Chung-Han Lee[1], Amishi Y. Shah[2], James J. Hsieh[3], Arpit Rao[4], Alvaro Pinto[5], Mehmet Asim Bilen[6], Allen Lee Cohn[7], Christopher Di Simone[8], David R. Shaffer[9], Regina Girones Sarrio[10], Sara Gunnestad Ribe[11], Jane Wu[12], Emmett V. Schmidt[13], Rodolfo Perini[13], Peter Kubiak[12], Alan D. Smith[14], Robert J. Motzer[1]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]MD Anderson Cancer Center, University of Texas, Houston, TX, USA; [3]Washington University School of Medicine, St. Louis, MO, USA; [4]Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA; [5]Hospital Universitario La Paz, Madrid, Spain; [6]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [7]Rocky Mountain Cancer Center, Denver, CO, USA; [8]Arizona Oncology Associates, Tucson, AZ, USA; [9]New York Oncology Hematology, Albany, NY, USA; [10]Medical Oncology Service, Hospital Universitari i Politècnic La FE, Valencia, Spain; [11]Sorlandet Hospital Kristiansand, Kristiansand, Norway; [12]Eisai Inc., Woodcliff Lake, NJ, USA; [13]Merck & Co. Inc., Kenilworth, NJ, USA; [14]Eisai Ltd., Hatfield, UK.

Pembro + Lenvatinib

- **1. basamak tedavide TKİ+ICI standart, peki sonrası?**

- **Lenvatinib** preklinik modellerde **pembrolizumabın etkinliğini artırdığı** gösterildi

Pembro + Lenvatinib

Phase IB/II Trial of Lenvatinib Plus Pembrolizumab in Patients With Advanced Renal Cell Carcinoma, Endometrial Cancer, and Other Selected Advanced Solid Tumors

Matthew H. Taylor, MD[1]; Chung-Han Lee, MD, PhD[2]; Vicky Makker, MD[2]; Drew Rasco, MD[3]; Corina E. Dutcus, MD[4]; Jane Wu, PhD[4]; Daniel E. Stepan, MD[5]; Robert C. Shumaker, PhD[4]; and Robert J. Motzer, MD[2]

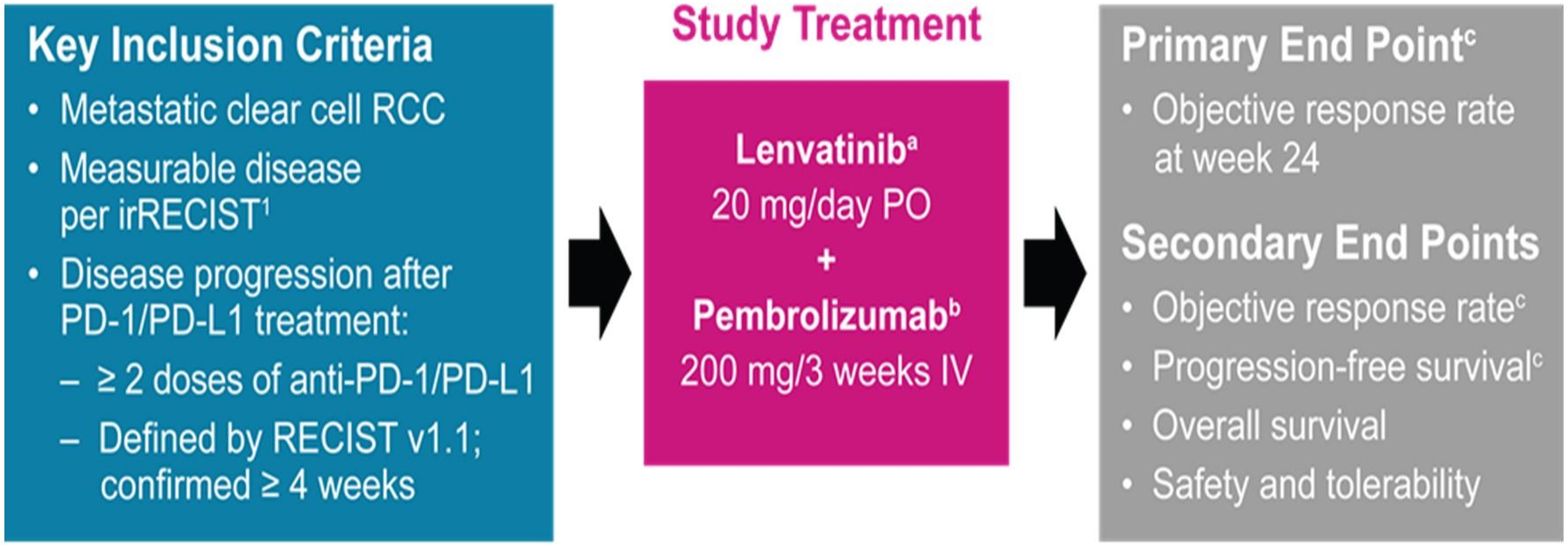
TABLE 4. Efficacy Outcomes (investigator review, immune-related RECIST)

Parameter	RCC (n = 30)	Endometrial (n = 23)	SCCHN (n = 22)	Melanoma (n = 21)	NSCLC (n = 21)	Urothelial (n = 20)
Best overall response						
Complete response	0 (0)	2 (9)	1 (5)	1 (5)	1 (5)	1 (5)
Partial response	21 (70)	10 (44)	9 (41)	9 (43)	6 (29)	4 (20)
Stable disease	8 (27)	10 (44)	10 (46)	7 (33)	10 (48)	9 (45)
Progressive disease	1 (3)	1 (4)	0 (0)	3 (14)	2 (10)	2 (10)
Unknown	0 (0)	0 (0)	2 (9)	1 (5)	2 (10)	4 (20)
ORR[a]	21 (70)	12 (52)	10 (46)	10 (48)	7 (33)[b]	5 (25)
(95% CI)	(50.6 to 85.3)	(30.6 to 73.2)	(24.4 to 67.8)	(25.7 to 70.2)	(14.6 to 57.0)	(8.7 to 49.1)
ORR_{Week24}	19 (63)	12 (52)	8 (36)	10 (48)	7 (33)	5 (25)
(95% CI)	(43.9 to 80.1)	(30.6 to 73.2)	(17.2 to 59.3)	(25.7 to 70.2)	(14.6 to 57.0)	(8.7 to 49.1)
Median DOR, months (95% CI)	20.0 (9.0 to 22.9)	NE (2.6 to NE)	8.2 (2.2 to 12.6)	12.5 (2.7 to NE)	10.9 (2.4 to NE)	NE (6.5 to NE)
Median PFS, months (95% CI)	19.8 (9.9 to 24.1)	9.7 (4.2 to NE)	4.7 (4.0 to 9.8)	5.5 (2.6 to 15.8)	5.9 (2.3 to 13.8)	5.4 (1.3 to NE)

JCO 2020;38:1154-1163

Pembro + Lenvatinib 2L

Study Design for the Phase 2 RCC Cohort



[a] Dose reductions to lenvatinib 14 mg/day, 10 mg/day, 8 mg/day and 4 mg/day were allowed to manage toxicities; dose reductions below 4 mg/day were discussed with the sponsor; [b] maximum of 35 treatments (approximately 2 years); [c] per irRECIST, by investigator assessment.

1. Perrone A. Immuno-Oncology 360° conference. New York, NY. 2016.
IV, intravenously; PO, by mouth; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1.

Pembro + Lenvatinib 2L

Previous Systemic Cancer Therapy

Characteristics	(N = 104)
Number of prior anticancer regimens[a], %	
1	39
≥ 2	62
Prior regimens[b], %	
Anti-PD-1/PD-L1[c]	100
Anti-PD-1/PD-L1 and Anti-VEGF[d]	65
Nivolumab + ipilimumab	37
Duration of prior ICI regimen, months	
Median (interquartile range)	7 (3–13)

[a] Percentages may not add up to 100% because of rounding; [b] patients can belong to > 1 category; [c] in combination or as monotherapy; [d] in combination or sequentially.

Pembro + Lenvatinib 2L

Tumor Response by Investigator Assessment

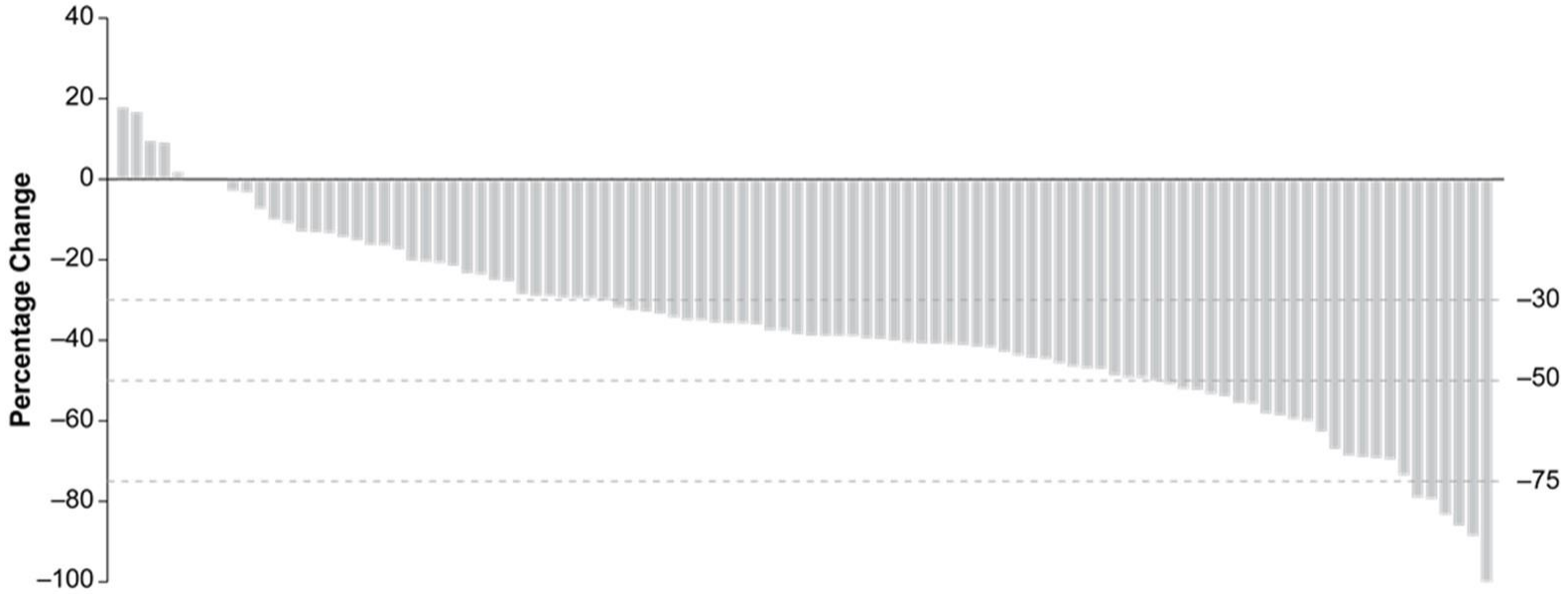
Parameter	irRECIST N = 104	RECIST v1.1[a] N = 104
ORR at week 24, % (95% CI)	51 (41–61)	–
ORR, % (95% CI)	55 (45–65)	52 (42–62)
Best objective response, %		
Partial response	55	52
Stable disease	36	38
Progressive disease	5	6
Not evaluable	5	5
Median DOR, months (95% CI)	12 (9–18)	12 (9–18)

[a] Up to 10 target lesions could be selected (up to 5 per organ).

DOR, duration of response.

Pembro + Lenvatinib 2L

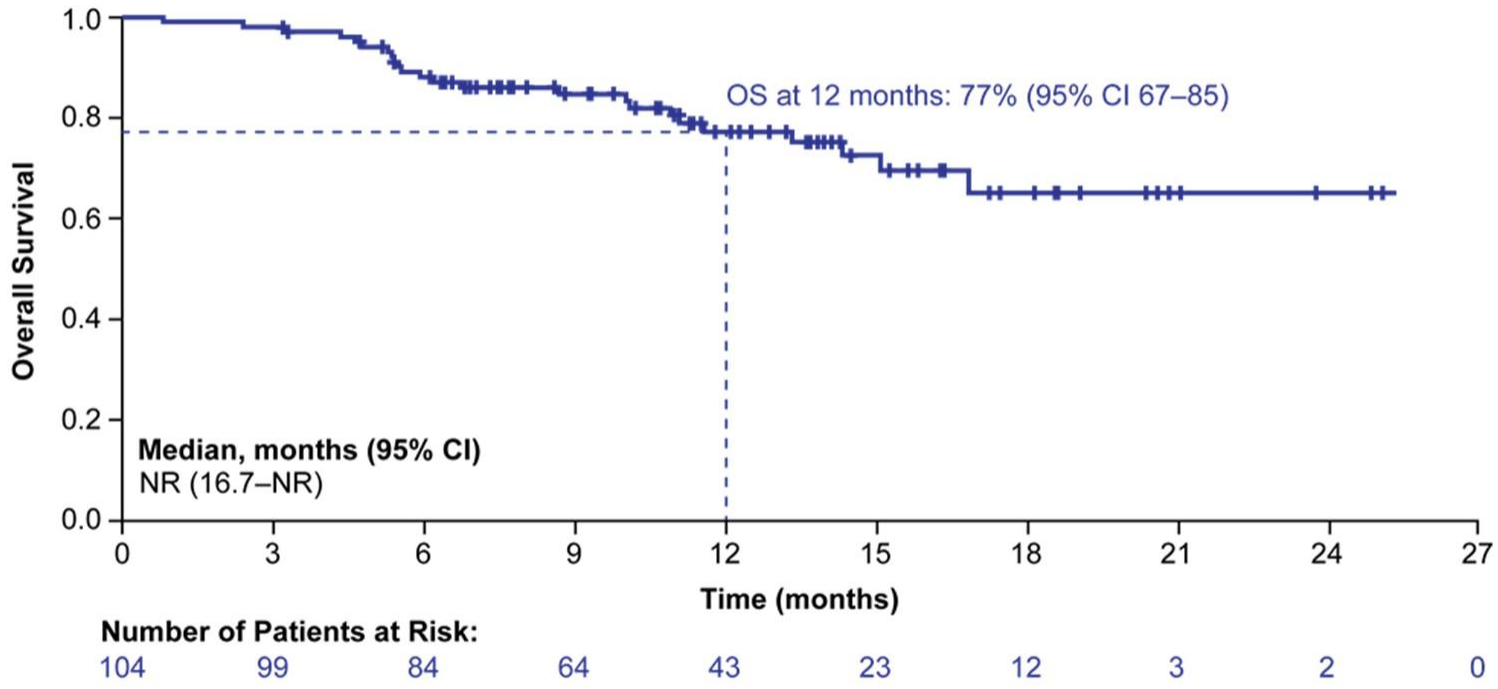
Percentage Change in Sum of Diameters of Target Lesions From Baseline to Nadir[a]



Note: Each bar represents 1 patient.
[a] By irRECIST per investigator assessment.

Pembro + Lenvatinib 2L

OS Kaplan–Meier Curve



NR, not reached.

Pembro + Lenvatinib 2L

Efficacy Results by Prior Anticancer Therapy Subgroup[a]

Parameter	Anti-PD-1/ PD-L1[b] (N = 104)	Anti-PD-1/PD-L1 and Anti-VEGF[c] (n = 68)	Nivolumab + Ipilimumab (n = 38)
ORR, % (95% CI)	55 (45–65)	59 (46–71)	47 (31–64)
Best objective response, %			
Partial response	55	59	47
Stable disease	36	31	42
Progressive disease	5	6	8
Not evaluable	5	4	3
Median duration of response, months (95% CI)	12 (9–18)	9 (7–17)	NR (7–NR)

[a] By irRECIST per investigator assessment. Patients can belong to > 1 category; [b] in combination or as monotherapy; [c] in combination or sequentially.

Pembro + Lenvatinib 2L

- **Pembro + Lenvatinib kombinasyonu daha önce tekli veya kombine ICI almış bir hastada ümit verici sonuçlara sahiptir.**

- irRECIST vs RECIST fark yoktur.

- Standart olmadan önce faz III datası beklenmelidir.

Update of First-line Nivolumab + Ipilimumab vs Sunitinib in Patients With Adv RCC (CheckMate 214)

- **CheckMate 214 ilk analizinde orta/kötü riskli hastalarda OS ve ORR Nivo + Ipi > Sunitinib**[1]
  - Median OS: NR (95% CI: 35.6-NE) for Nivo + Ipi vs 26.0 mos for sunitinib (HR: 0.63; *P* < .001)
  - ORR: %42 Nivo + Ipi vs %27 with sunitinib (*P* < .001)
  - Median PFS per IRRC: 11.6 mos with Nivo + Ipi vs 8.4 mos with sunitinib (*P* = .03)

- FDA 2018'de **Nivo + İpi kombinasyonunu orta / kötü riskli ileri/met RCC** hastalarında 1.basamakta kullanımını onaylandı.

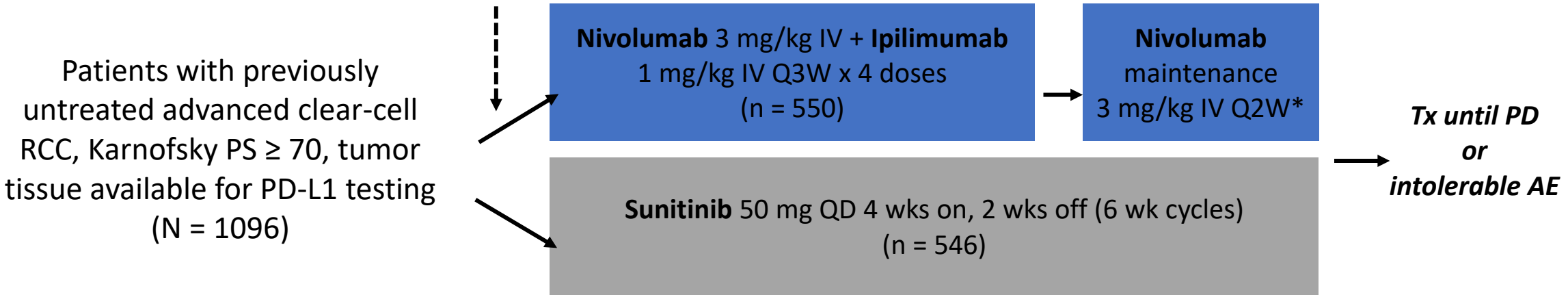
- ASCO GU 2020'de **42.aydaki etkinlik ve güvenlik** datası açıklandı.[2]

1. Motzer. NEJM. 2018;378:1277. 2. Tannir. ASCO GU 2020. Abstr 609.

CheckMate 214

- Randomized, open-label phase III trial, response assessed using RECIST v1.1

Stratified by IMDC prognostic score (0 vs 1-2 vs 3-6), region (US vs Canada/W Europe/N Europe vs rest of world)



*Protocol amended November 2017 to allow cohort A patients to d/c after 2 yrs of study tx.

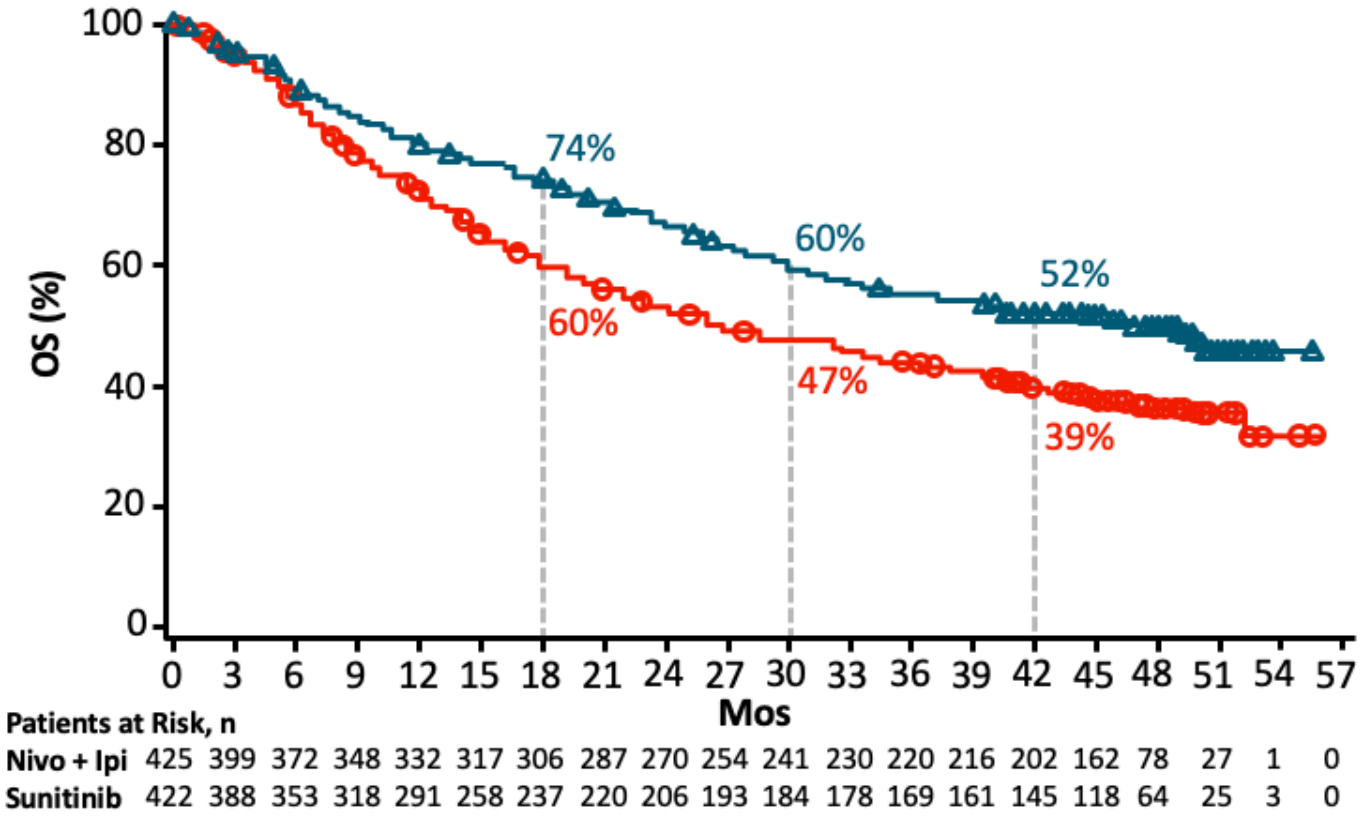
- Primary endpoints: ORR, PFS (both per IRRC), and OS in IMDC stratified intermediate- and poor-risk patients
- Secondary endpoints: ORR, PFS (both per IRRC), OS in ITT patients, and safety in all patients
- Exploratory endpoints: ORR, PFS (both per IRRC), and OS in IMDC favorable-risk patients

Tannir. ASCO GU 2020. Abstr 609. Motzer. Lancet Oncol. 2019;20:1370.

CheckMate 214

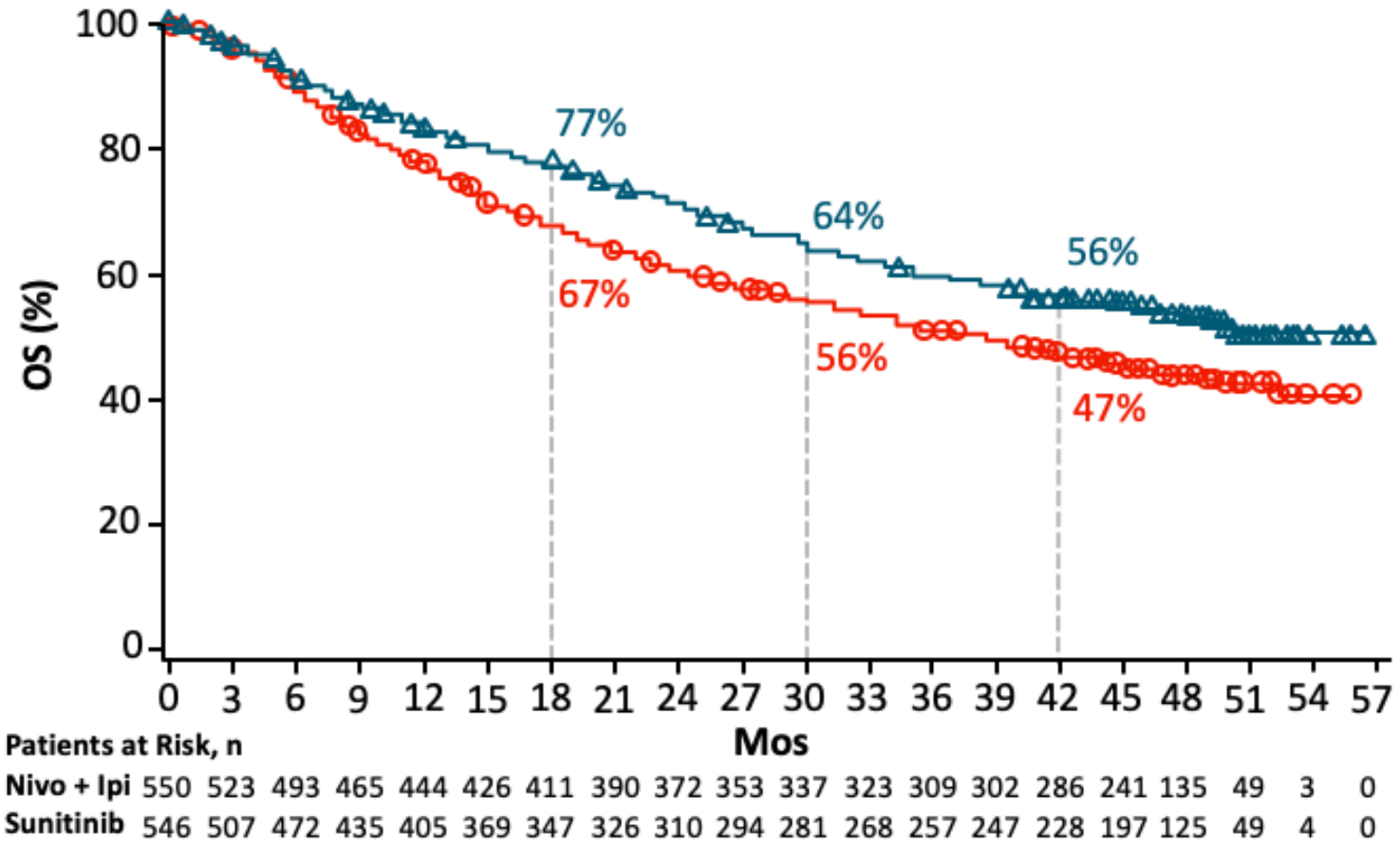
	Primary: Intermediate-/ Poor-Risk Patients		Secondary: ITT Patients		Exploratory: Favorable-Risk Patients	
	Nivo + Ipi (n = 425)	Sunitinib (n = 422)	Nivo + Ipi (n = 550)	Sunitinib (n = 546)	Nivo + Ipi (n = 125)	Sunitinib (n = 124)
IMDC prognostic score, %						
▪ Favorable (0)	0	0	23	23	100	100
▪ Intermediate (1/2)	79	79	61	61	0	0
▪ Poor (3-6)	21	21	17	16	0	0
Region, %						
▪ US	26	26	28	28	34	34
▪ Canada/Europe	35	35	37	36	42	43
▪ Rest of the world	39	39	35	36	24	23

CheckMate 214: Updated OS in Intermediate-/ Poor-Risk Population



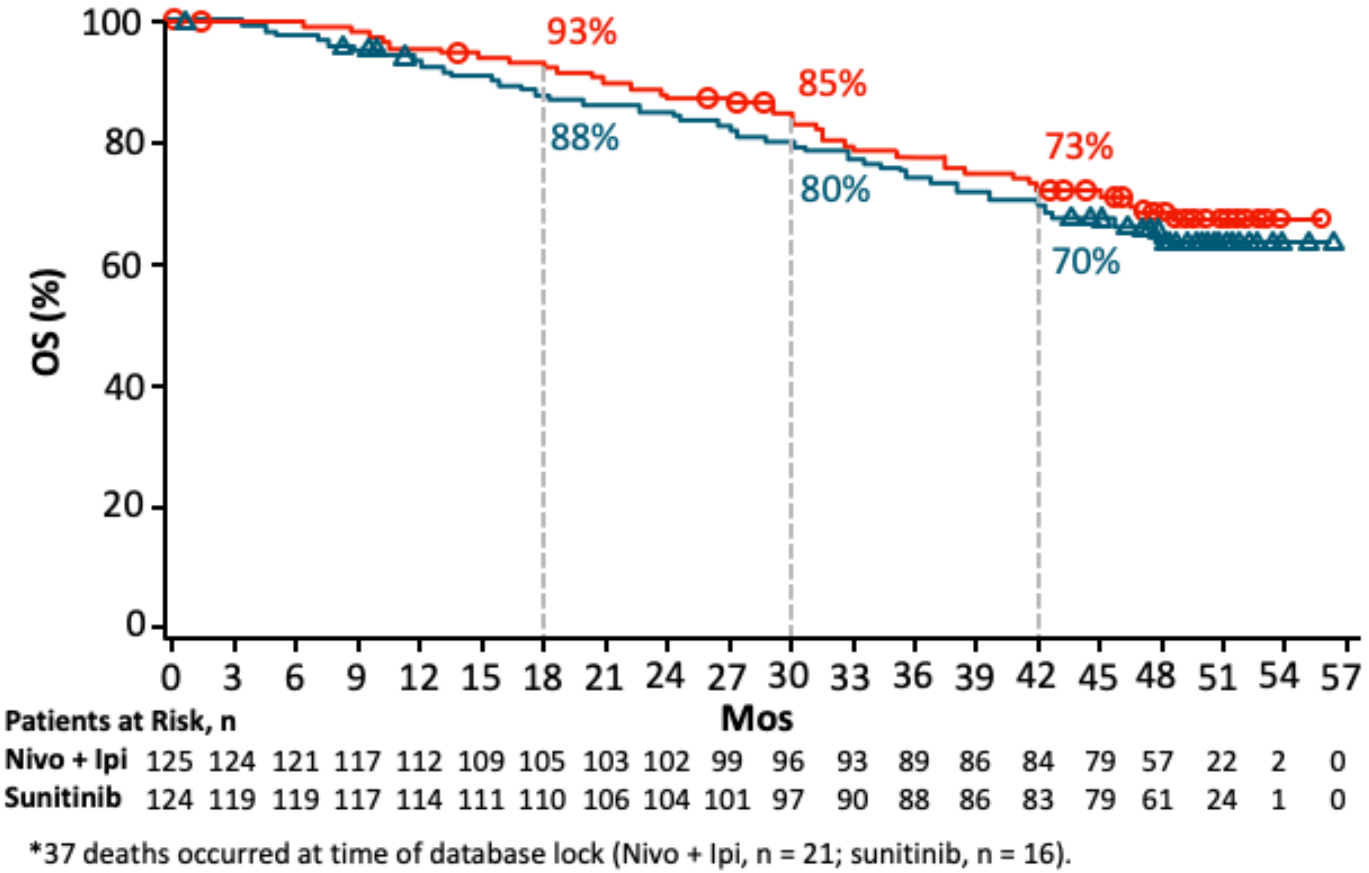
Minimum Follow-up, Mos	OS	Nivo + Ipi (n = 425)	Sunitinib (n = 422)
17.5	Median, mos (95% CI)	NR (28.2-NE)	NR (22.1-NE)
	HR (99.8% CI)	0.63 (0.44-0.89) *P* < .001	
30	Median, mos (95% CI)	NR (35.6-NE)	26.6 (22.1-33.4)
	HR (95% CI)	0.66 (0.54-0.80) *P* < .0001	
42	Median, mos (95% CI)	47.0* (35.6-NE)	26.6 (22.1-33.5)
	HR (95% CI)	0.66 (0.55-0.80) *P* < .0001	

CheckMate 214: Updated OS in ITT Population



Minimum Follow-up, Mos	OS	Nivo + Ipi (n = 550)	Sunitinib (n = 546)
17.5	Median, mos (95% CI)	NR (NE)	32.9 (NE)
	HR (99.8% CI)	0.68 (0.49-0.95) *P* < .001	
30	Median, mos (95% CI)	NR (NE)	37.9 (32.2-NE)
	HR (95% CI)	0.71 (0.59-0.86) *P* = .0003	
42	Median, mos (95% CI)	NR (46.3-NE)	38.4 (32.0-44.7)
	HR (95% CI)	0.72 (0.61-0.86) *P* = .0002	

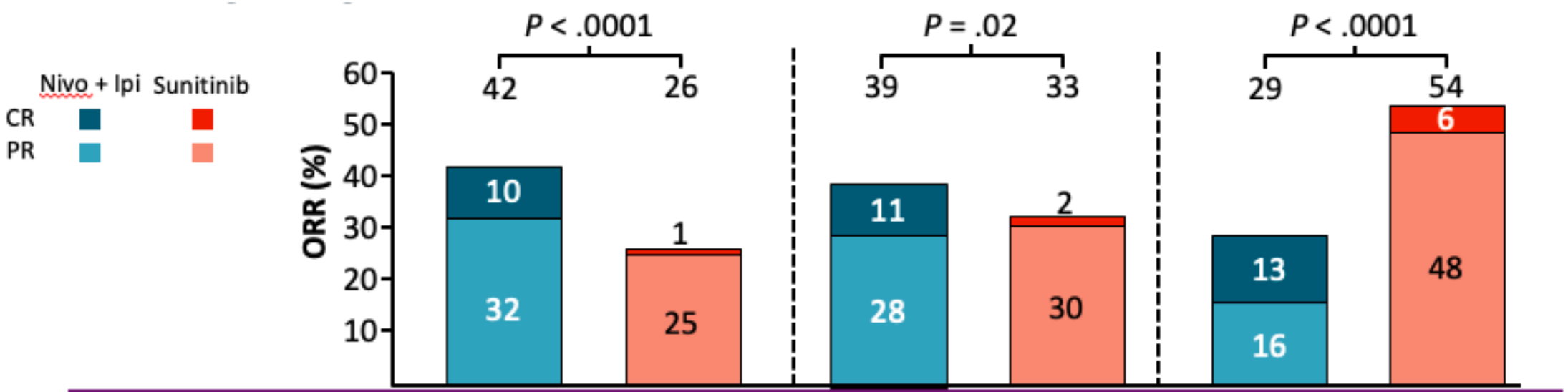
CheckMate 214: Updated OS in Favorable-Risk Population



*37 deaths occurred at time of database lock (Nivo + Ipi, n = 21; sunitinib, n = 16).

Minimum Follow-up, Mos	OS	Nivo + Ipi (n = 125)	Sunitinib (n = 124)
17.5*	Median, mos (95% CI)	NR (NE)	NR (NE)
	HR (99.8% CI)	1.45 (0.51-4.12) *P* = .27	
30	Median, mos (95% CI)	NR (NE)	NR (NE)
	HR (95% CI)	1.22 (0.73-2.04) *P* = .44	
42	Median, mos (95% CI)	NR (NE)	NR (NE)
	HR (95% CI)	1.19 (0.77-1.85) *P* = .44	

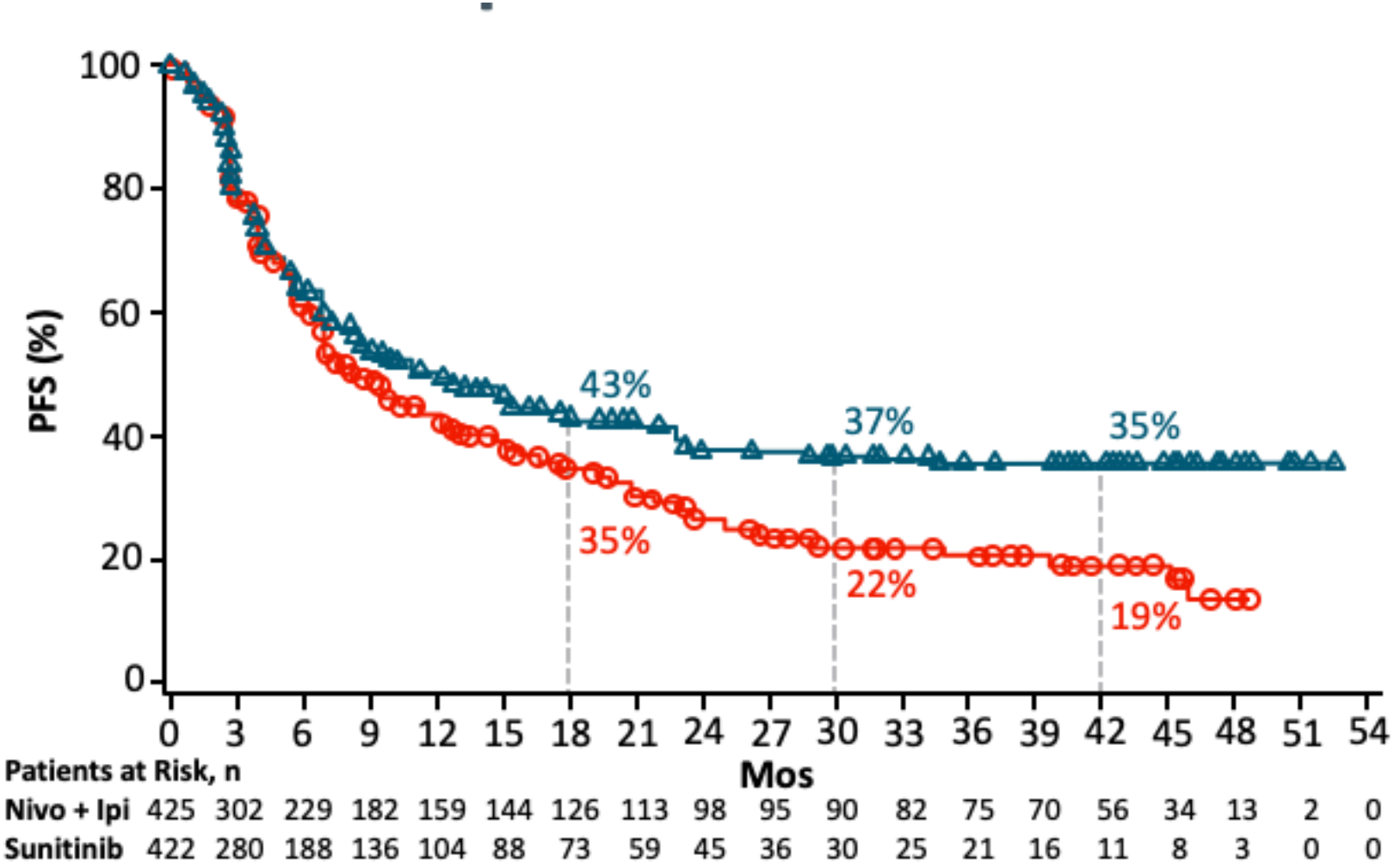
CheckMate 214: Confirmed Response per IRRC in Efficacy Populations



	Primary: Intermediate/Poor Risk		Secondary: ITT Population		Exploratory: Favorable Risk	
	Nivo + Ipi (n = 425)	Sunitinib (n = 422)	Nivo + Ipi (n = 550)	Sunitinib (n = 546)	Nivo + Ipi (n = 125)	Sunitinib (n = 124)
Median DoR, mos (95% CI)	NR (NE)	19.7 (16.4-26.4)	NR (NE)	24.8 (19.4-27.3)	NR (40.1-NE)	27.4 (23.5-40.3)
Ongoing response, n/N (%)	121/179 (68)	58/111 (52)	146/215 (68)	94/178 (53)	25/36 (69)	36/67 (54)
Stable disease, %	31	44	36	42	54	32

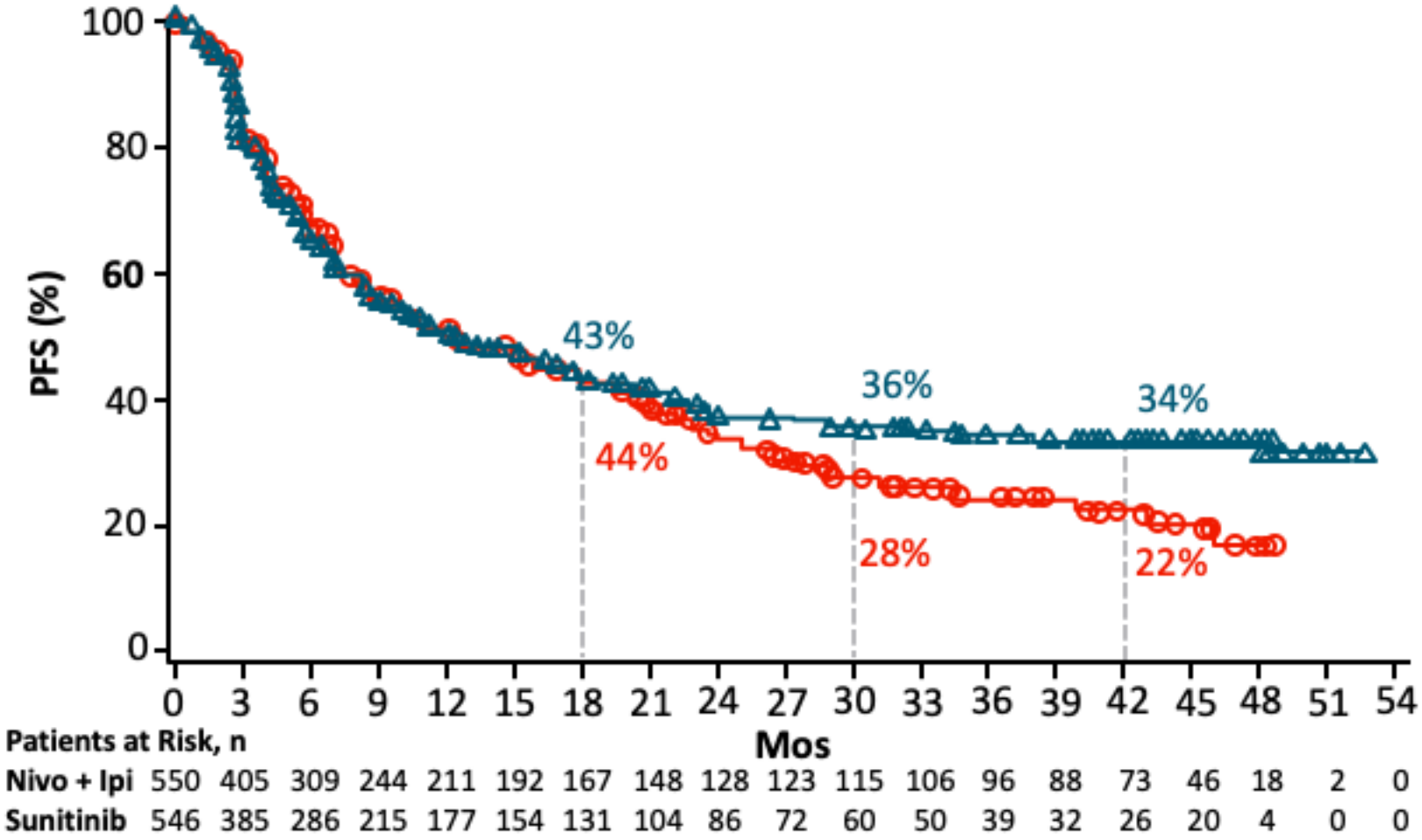
42% (203/489) of evaluable* ITT patients receiving Nivo + Ipi attained ≥ 50% best tumor burden reduction vs 27% (122/458) with sunitinib

CheckMate 214: Updated PFS in Intermediate-/ Poor-Risk Population



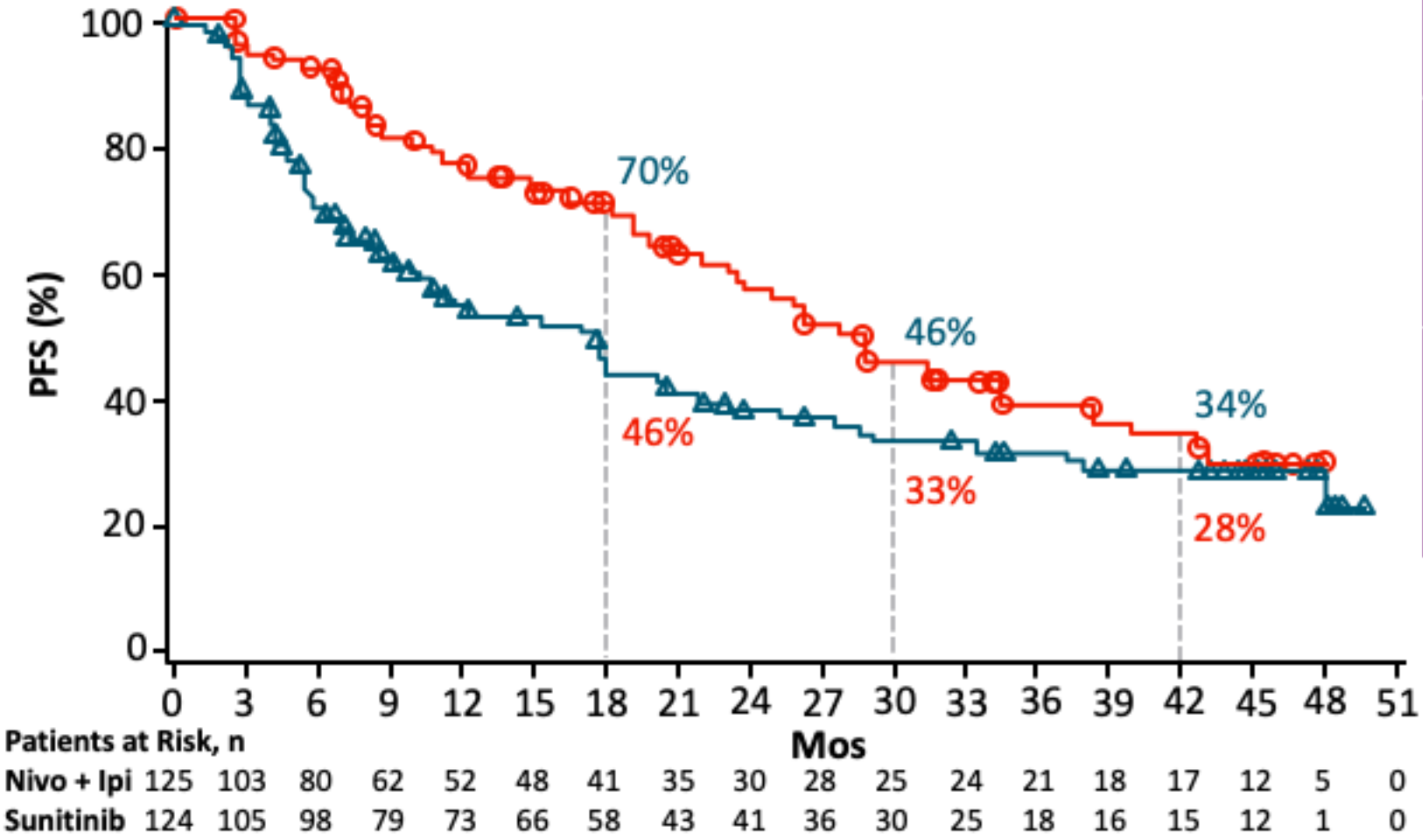
Minimum Follow-up, Mos	PFS	Nivo + Ipi (n = 425)	Sunitinib (n = 422)
17.5	Median, mos (95% CI)	11.6 (8.7-15.5)	8.4 (7.0-10.8)
	HR (99.1% CI)	0.82 (0.64-1.05) *P* = .03	
42	Median, mos (95% CI)	12.0 (8.7-15.5)	8.3 (7.0-11.1)
	HR (95% CI)	0.76 (0.63-0.91) *P* < .01	

CheckMate 214: Updated PFS in ITT Population



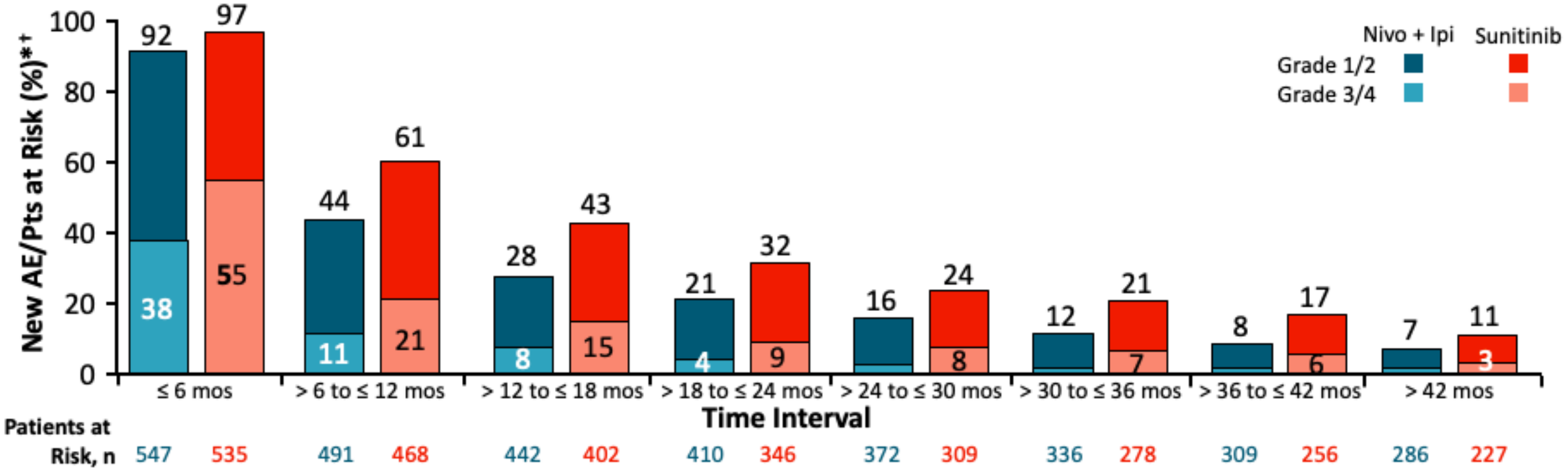
Minimum Follow-up, Mos	PFS	Nivo + Ipi (n = 550)	Sunitinib (n = 546)
17.5	Median, mos (95% CI)	12.4 (9.9-16.5)	12.3 (9.8-15.2)
	HR (99.1% CI)	0.98 (0.79-1.23) *P* = .85	
42	Median, mos (95% CI)	12.5 (9.8-17.0)	12.3 (9.8-16.6)
	HR (95% CI)	0.89 (0.76-1.05) *P* = .16	

CheckMate 214: Updated PFS in Favorable-Risk Population



Minimum Follow-up, Mos	PFS	Nivo + Ipi (n = 125)	Sunitinib (n = 124)
17.5	Median, mos (95% CI)	15.3 (9.7-20.3)	25.1 (20.9-NE)
	HR (99.1% CI)	2.18 (1.29-3.68) *P* < .0001	
42	Median, mos (95% CI)	17.8 (10.3-20.7)	27.7 (23.2-34.5)
	HR (95% CI)	1.62 (1.14-2.32) *P* < .01	

CheckMate 214: Post Hoc Analysis of Treatment-Related Adverse Events



- Treatment-related select AE frequency and corticosteroid use showed similar patterns over time in the Nivo + Ipi cohort
  - Treatment-related AEs of any grade: 94% with Nivo + Ipi vs 97% with sunitinib; grade 3/4 AEs: 47% with Nivo + Ipi vs 64% with sunitinib
- 42-mo OS: 66% for patients discontinuing due to treatment-related AEs vs 56% for ITT population

CheckMate 214: Conclusions

- Long-term follow-up of Checkmate 214 confirmed improved OS and ORR with Nivo + Ipi vs sunitinib in intermediate/poor-risk and ITT patients
  - Both intermediate-/poor-risk and ITT patient populations experienced PFS curve plateaus at ~ 35% after 30 mos with Nivo + Ipi
  - For patients with favorable-risk disease (exploratory subgroup), efficacy data (ORR and PFS) favored use of sunitinib vs Nivo + Ipi
- Incidence of treatment-related AEs, treatment-related select AEs, and corticosteroid use decreased over time and no new safety signals observed with Nivo + Ipi
  - Discontinuation of Nivo + Ipi due to treatment-related AEs did not affect OS

Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase 3 CheckMate 9ER trial

Toni K. Choueiri,[1] Thomas Powles,[2] Mauricio Burotto,[3] Maria T. Bourlon,[4] Bogdan Zurawski,[5] Víctor Manuel Oyervides Juárez,[6] James J. Hsieh,[7] Umberto Basso,[8] Amishi Y. Shah,[9] Cristina Suarez,[10] Alketa Hamzaj,[11] Carlos Barrios,[12] Martin Richardet,[13] David Pook,[14] Yoshihiko Tomita,[15] Bernard Escudier,[16] Joshua Zhang,[17] Burcin Simsek,[17] Andrea B. Apolo,[18] Robert J. Motzer[19]

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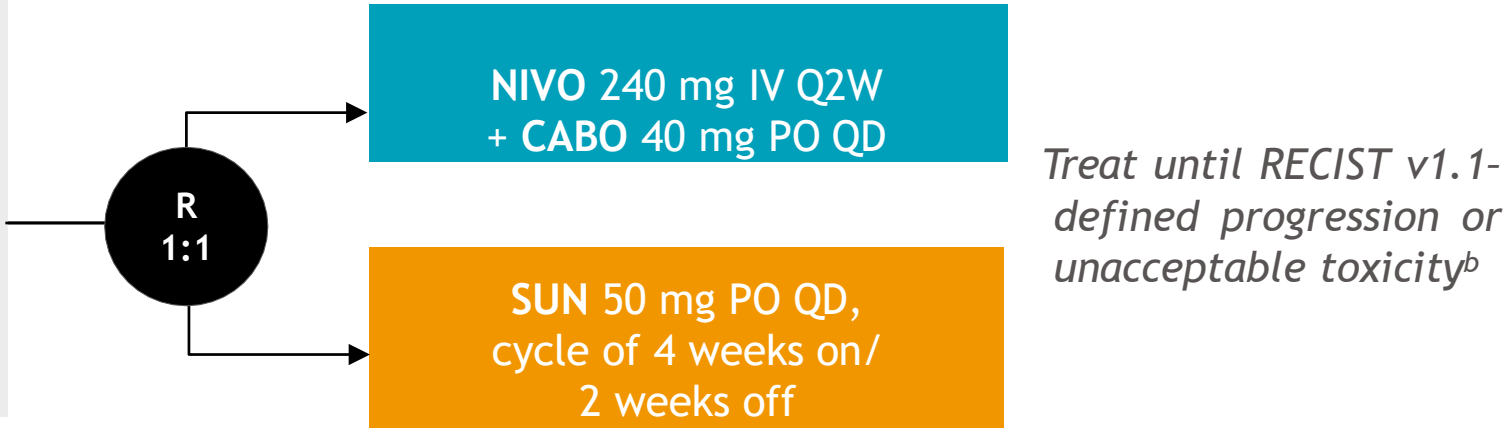
N = 651

Key inclusion criteria[1,2]

- Previously untreated advanced or metastatic RCC
- Clear cell component
- Any IMDC risk group

Stratification factors:

- IMDC risk score
- Tumor PD-L1 expression[a]
- Geographic region



Treat until RECIST v1.1–defined progression or unacceptable toxicity[b]

Median study follow-up, 18.1 months (range, 10.6–30.6 months)

Primary endpoint: PFS

Secondary endpoints: OS, ORR, and safety

[a]Defined as the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry 28-8 pharmDx assay.
[b]NIVO dosing may not exceed a total of 2 years (from cycle 1); CABO and SUN treatment may continue beyond 2 years in the absence of progression or unacceptable toxicity. Patients may be treated beyond progression.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IV, intravenously; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; PO, orally; Q2W, every 2 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.
1. Clinicaltrials.gov/ct2/show/NCT03141177. Accessed June 8, 2020; 2. Choueiri TK et al. Poster presented at the American Society of Clinical Oncology Annual Meeting 2018. TPS4598.

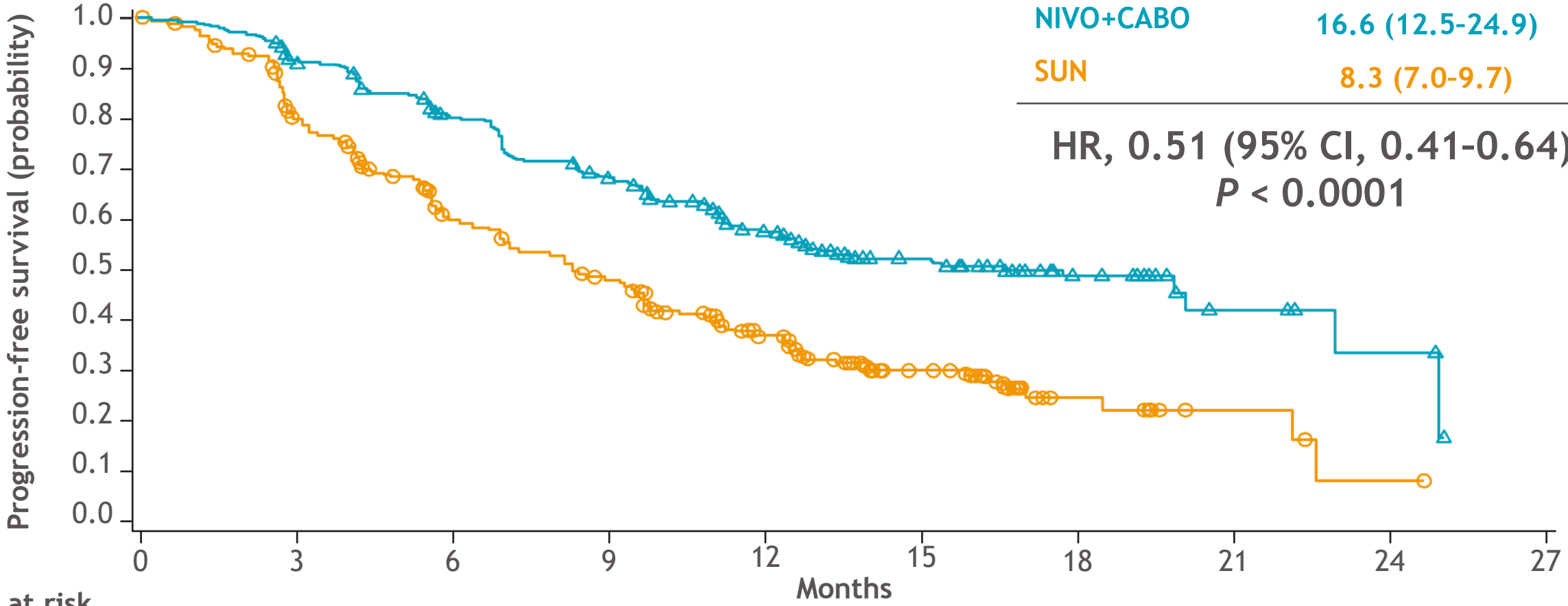
CheckMate 9ER trial

	NIVO+CABO (n = 323)	SUN (n = 328)
Median age (range), year	62 (29-90)	61 (28-86)
Male, %	77	71
IMDC prognostic score, %		
Favorable (0)	23	22
Intermediate (1-2)	58	57
Poor (3-6)	19	21
Tumor PD-L1 expression, %		
≥1%	26	25
<1% or indeterminate	74	75
Region, %		
US/Europe	49	49
Rest of the world	51	51
No. of sites with target/non-target lesions, %		
1	20	21
≥ 2	80	78
Most common sites of metastasis, %		
Lung	74	76
Lymph node	40	40
Bone	24	22
Liver	23	16

CheckMate 9ER trial

Median PFS, months (95% CI)	
NIVO+CABO	16.6 (12.5-24.9)
SUN	8.3 (7.0-9.7)

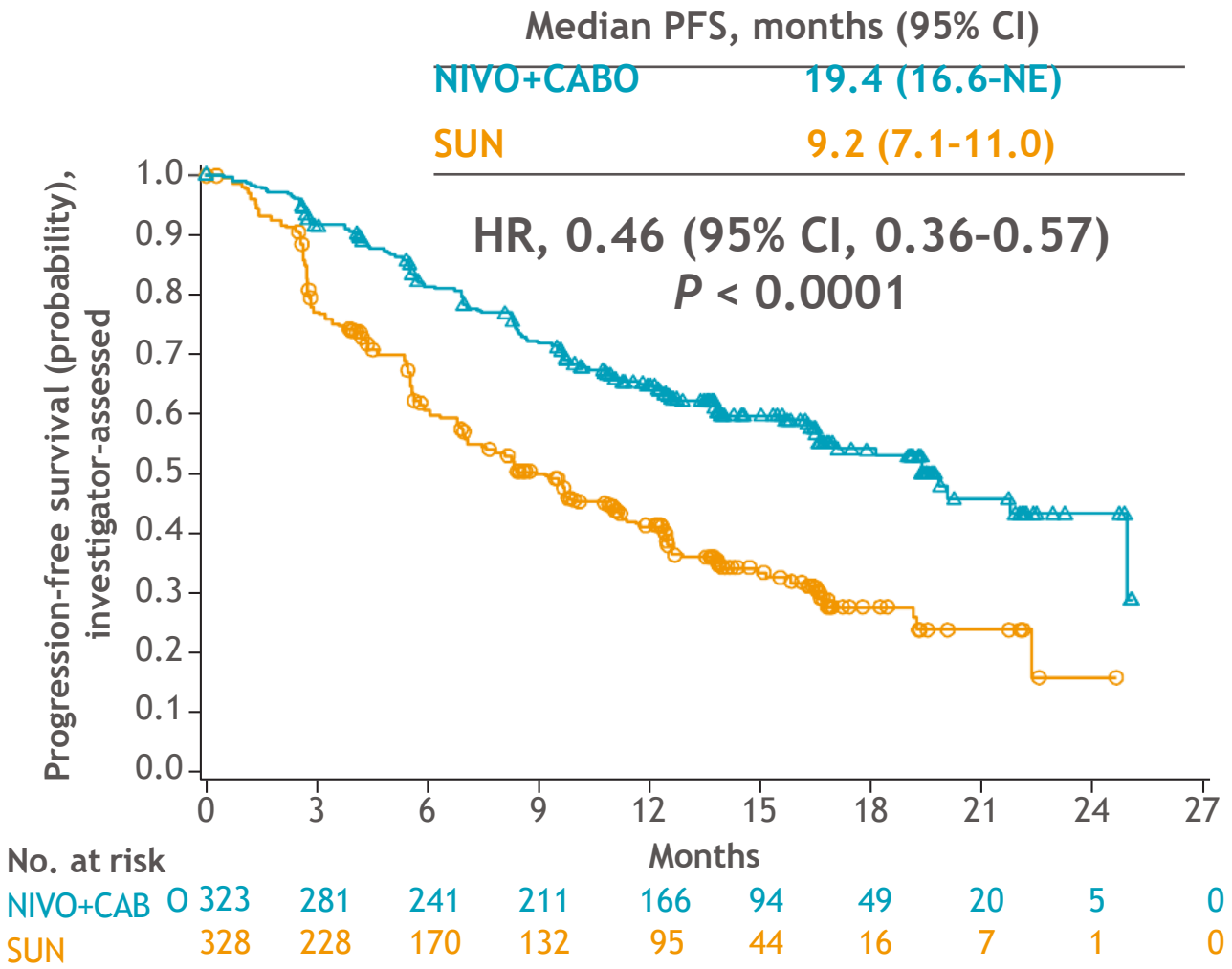
HR, 0.51 (95% CI, 0.41-0.64)
P < 0.0001



No. at risk									
NIVO+CABO	323	279	234	196	144	77	35	11	4	0
SUN	328	228	159	122	79	31	10	4	1	0

Minimum study follow-up, 10.6 months.

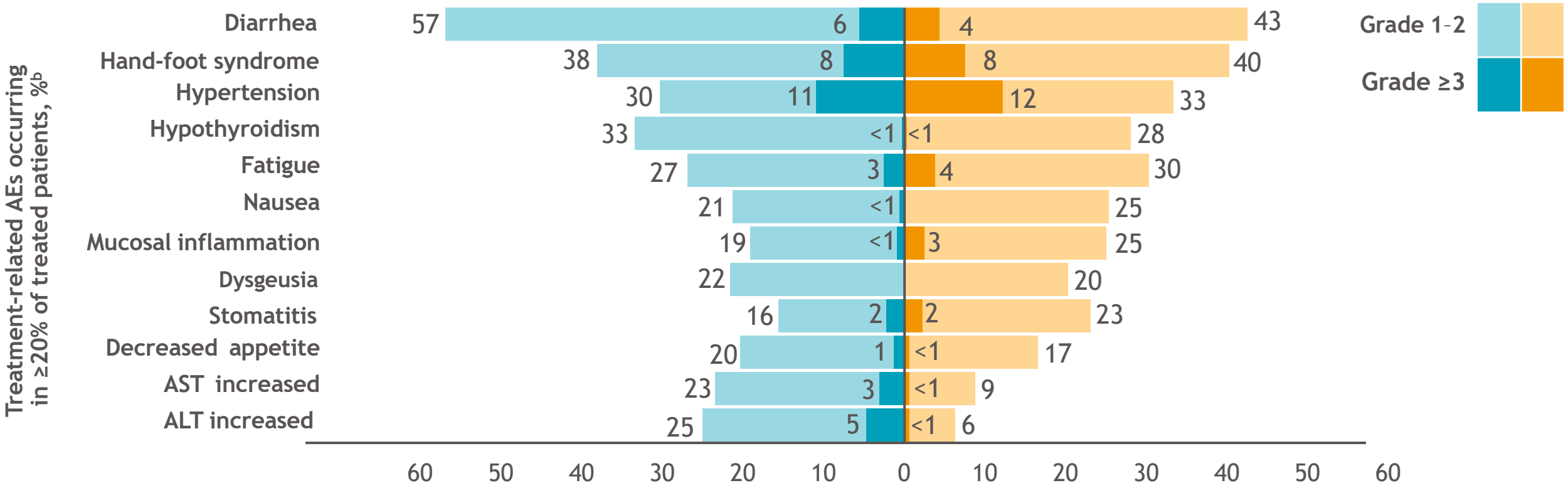
CheckMate 9ER trial



Outcome, %	NIVO+CABO (n = 323)	SUN (n = 328)
ORR, % (95% CI)	59.4 (53.9-64.8)	32.0 (27.0-37.4)
	P < 0.0001	
Best overall response, %		
Complete response	3.4	1.8
Partial response	56.0	30.2
Stable disease	30.0	35.4
Progressive disease	5.3	21.0
Not evaluable/not assessed[a]	5.3	11.6

CheckMate 9ER trial

Events, %[a]	NIVO+CABO, n = 320		SUN, n = 320	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
All-cause AEs	100	75	99	71
Treatment-related AEs	97	61	93	51



CheckMate 9ER trial

- Faz 3 CheckMate 9ER trial bütün etkinlik sonlanım noktalarını karşıladı, **1.basamakta NIVO+CABO sunitinibe karşı üstün:**
  - **PFS: Hastalık progresyonunda %49 azalma**
  - **OS: Ölüm riskinde %40 azalma**
  - **ORR: %29 artma**
- NIVO + CABO, yan etkiye bağlı tedavi kesme oranları düşük ve genellikle iyi tolere edilmiştir.
- Hastalar, sunitinibe kıyasla NIVO + CABO ile anlamlı daha iyi yaşam kalitesine sahipti
- Bu sonuçlar, ileri evre RCC'li hastalar için **potansiyel bir ilk seçenek olarak NIVO + CABO'yu** desteklemektedir.

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Cabozantinib in combination with atezolizumab as first-line therapy for advanced clear-cell renal cell carcinoma: results from the COSMIC-021 study

Sumanta Pal,[1] Che-Kai Tsao,[2] Cristina Suarez,[3] William Kelly,[4] Lance Pagliaro,[5] Ulka Vaishampayan,[6] Yohann Loriot,[7] Sandy Srinivas,[8] Bradley McGregor,[9] Ashok Panneerselvam,[10] Dominic Curran,[10] Toni K. Choueiri,[9] and Neeraj Agarwal[11]

[1]Department of Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [2]Tisch Cancer Institute, Mount Sinai Hospital, New York, NY, USA; [3]Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; [4]Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA; [5]Department of Oncology, Mayo Clinic, Rochester, MN, USA; [6]Karmanos Cancer Center, Wayne State University, Detroit, MI, USA; [7]Department of Cancer Medicine, Gustave Roussy Institute, University Paris-Saclay, Villejuif, France; [8]Division of Medical Oncology, Stanford University Medical Center, Stanford, CA, USA; [9]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [10]Exelixis, Inc., Alameda, CA, USA; [11]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA.

The COSMIC-021 study is sponsored by Exelixis

Study Design for Patients with ccRCC

Advanced or metastatic ccRCC
- No prior systemic therapy for RCC
- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1

Expansion Cohorts

April 2018*	January 2019*
Cabozantinib 40 mg QD PO + Atezolizumab 1200 mg Q3W IV (N=30)	Cabozantinib 60 mg QD PO + Atezolizumab 1200 mg Q3W IV (N=30)

Tumor assessments per RECIST v1.1 by the investigator every 6 weeks for the first year and every 12 weeks thereafter; treatment until loss of clinical benefit or intolerable toxicity.

- 10 patients with previously untreated ccRCC were enrolled in the dose-escalation phase (4 at a dose level of 40 mg and 6 at a dose level of 60 mg)
- Data are presented for all 70 ccRCC patients with a data cutoff of July 21, 2020 and a median follow-up of 25.8 months (range, 20-33) for the 40 mg dose group and 15.3 months (range, 10-32) for the 60 mg dose group

Primary Endpoint: ORR by the investigator per RECIST v1.1
Secondary Endpoint: Safety
Exploratory endpoints include PFS and correlations of biomarkers with outcomes

*Date of the first patient enrolled.

Demographics and Baseline Characteristics

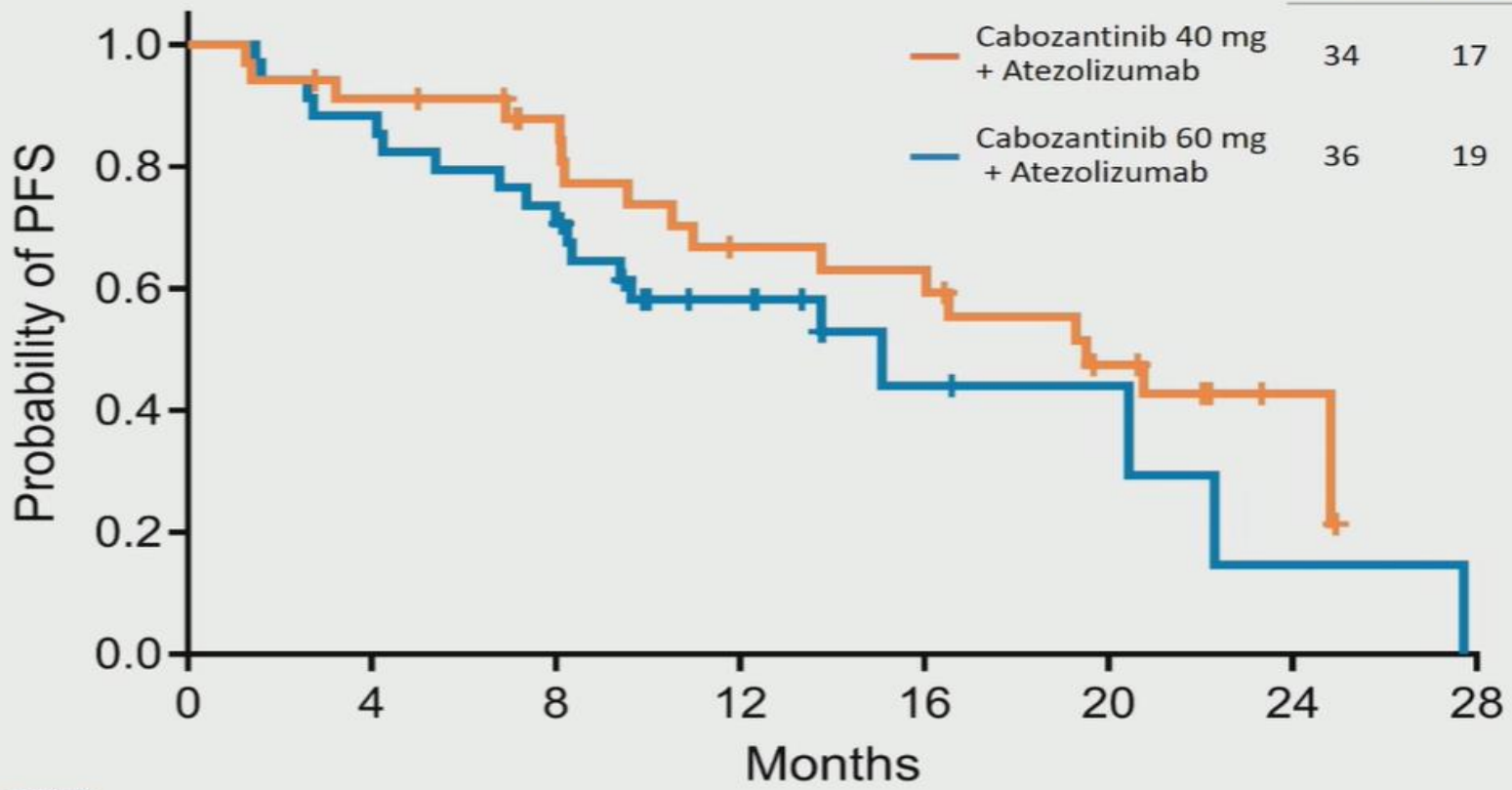
	Cabozantinib 40 mg + Atezolizumab 1200 mg (N=34)	Cabozantinib 60 mg + Atezolizumab 1200 mg (N=36)
Median age, years (range)	68 (39–87)	60 (42–82)
Male, n (%)	27 (79)	26 (72)
ECOG performance status, n (%)		
0	27 (79)	25 (69)
1	7 (21)	11 (31)
IMDC risk group, n (%)		
Favorable	7 (21)	14 (39)
Intermediate	26 (76)	21 (58)
Poor	1 (3)	1 (3)
Sarcomatoid component, n (%)	9 (26)	2 (6)
Prior nephrectomy, n (%)	29 (85)	32 (89)
≥3 sites of disease, n (%)	18 (53)	14 (39)
Metastatic sites, n (%)		
Lung	27 (79)	27 (75)
Lymph node	16 (47)	15 (42)
Liver	5 (15)	3 (8)
Bone	4 (12)	4 (11)

Tumor Response per Investigator by RECIST 1.1

	Cabozantinib 40 mg + Atezolizumab 1200 mg (N=34)	Cabozantinib 60 mg + Atezolizumab 1200 mg (N=36)
Objective response rate (80% CI), %	53 (41–65)	58 (46–70)
Best overall response, n (%)		
Complete response	1 (3)	4 (11)
Partial response	17 (50)	17 (47)
Stable disease	14 (41)	12 (33)
Progressive disease	2 (6)	2 (6)
Missing	0	1 (3)
Disease control rate,* %	94	92
Duration of response, median (range), mo	NE (12.4–NE)	15.4 (8.1–NE)
Time to objective response, median (range), mo	1.4 (1–19)	1.5 (1–7)

*Disease control rate = complete response + partial response + stable disease

Progression-Free Survival



	N	No. of Events	Median (95% CI), months
Cabozantinib 40 mg + Atezolizumab	34	17	19.5 (11.0–NR)
Cabozantinib 60 mg + Atezolizumab	36	19	15.1 (8.2–22.3)

COSMİC – 021 çalışması sonucu

- Kabozantinib ve atezolizumab kombinasyonu tedavi edilmemiş ileri evre ccRCC'de klinik aktivite gösterdi
  - **40 mg QD kabozantinib doz grubunda ORR %53; mPFS 19,5 ay**
  - **60 mg QD kabozantinib doz grubunda ORR %58; mPFS 15,1 ay**

- Bazal PDL1 pozitifliği ve yüksek CD8; daha iyi toplam cevap ve daha fazla tümör boyutunda azalma ile ilişkili
- Kombinasyonun Güvenlik profili her iki doz grubunda da kabul edilebilir
- Faz 3 CONTACT 03 çalışması (daha önce check point inh. ile tedavi edilmiş RCC'de kabozantinib atezolu ve atezosuz) devam etmektedir.

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COSMIC-021-in the context of L1 mRCC

	COSMIC-021 CABO 40 mg + ATEZO (N=34)	COSMIC-021 CABO 60mg + ATEZO (N=36)	9-ER CABO 40mg + NIVO (N=323)	KEYNOTE426 AXITINIB + PEMBRO (n=432)	JAVELIN AXITINIB + AVELUM (n=442)	LENVATINIB + PEMBRO (n=104)	TINIVO TIVOZANIB + NIVO (n=25)
Median Follow up , mo	25.8	15.3	18.1	12.8	11.6	-	19.0
ORR - BICR ORR - Investigator	- 53	- 58	55.7 59.4	59.3	51.4	52 (pretreated population)	56%
Progressive disease, n(%) - BICR	2 (6%)	2 (6%)	5.6%	11%	11.5%	6%	4%
Disease control rate, % - BICR	94%	92%	88%	83.3%	81%	93%	96%
PFS, Median (95% CI), months	19.5 (11.0–NR)	15.1 (8.2–22.3)	16.6 (12.5–24.9)	15.4 (12.7-18.9)	13.8	11.3	18.9
OS, Median(95% CI), months	-	-					
TRAE, G3/4: n (%) IRAE, G3/4: n (%) Pts requiring high-dose steroids for Aes Any grade TRAE leading to any discont.	24 (71%) 6 (18%) 3 (9%) NR	24 (67%) 7 (19%) 6 (25%) NR	61% NR 19% 15.3%	70% NR NE	51%	15%	80% 56% 32%

ORR & PFS are similar to other VEGFR-TKI

Choueiri et al. ESMO 2020 presidential session; Rini et al. NEJM 2019; Motzer et al. 2019; Lee et al. ASCO 2020. Albiges et al. *in press* 2020

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Results from the phase 2 BIOmarker driven trial with Nivolumab (N) and Ipilimumab or VEGFR tyrosine Kinase inhibitor (TKI) in naïve metastatic Kidney cancer (m-ccRCC) patients (pts): the BIONIKK trial (NCT02960906)

Abstract #2182, LBA25

Monday, 21st Septembre 2020

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On behalf of the BIONIKK co-investigators:

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BACKGROUND: BIONIKK trial

Analysis of transcriptomic data from frozen ccRCC, revealed 4 groups of patients (ccrcc1 to 4) with distinct TME composition and distinct outcomes with sunitinib (S) [1, 2]:

- ccrcc1 “immune-low” and ccrcc4 “immune-high” tumors were associated with poorest outcomes
- ccrcc2 “angio-high” and ccrcc3 “normal-like” tumors were associated with best outcomes

A 35-gene signature (frozen samples, RT-qPCR) was constructed to classify pts by pts in the 4 groups[1]

Hypotheses:

- **N alone should provide good outcomes in ccrcc4**
- **NI combination should be necessary to improve outcomes in ccrcc1**
- **TKI (S or Pazopanib (P)) should provide good outcomes in ccrcc2 and 3**

1. Beuselinck B. et al, Clin Can Research 2015
2. Becht E. et al, Oncoimmunology 2015

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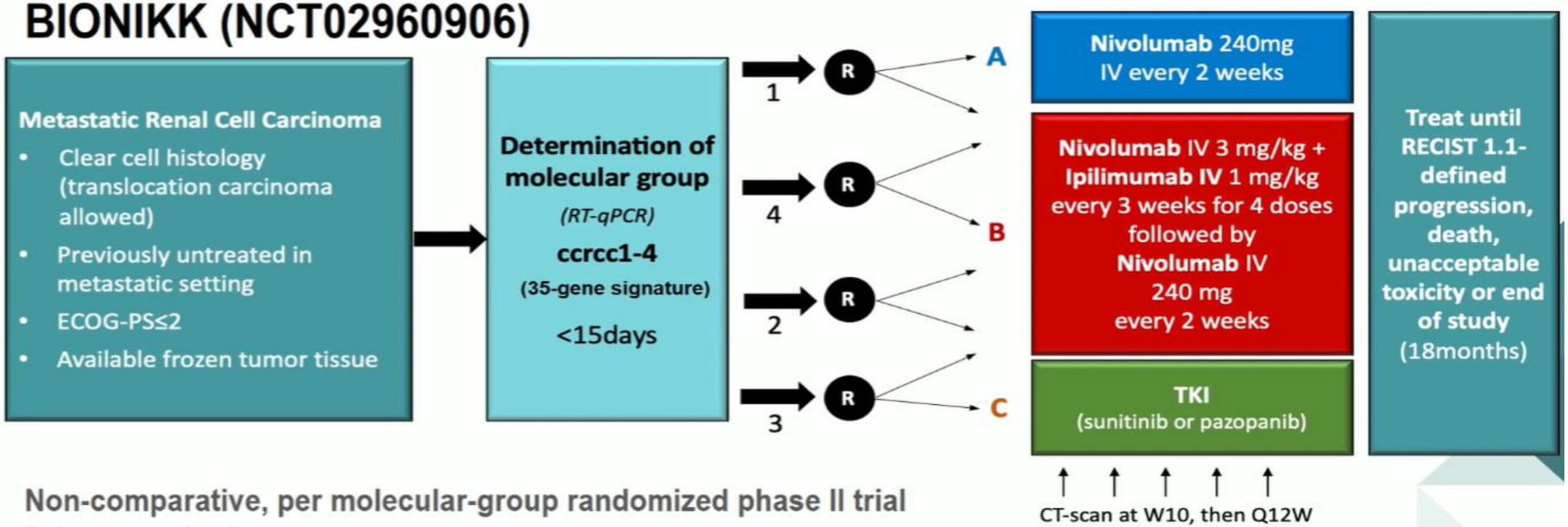
METHODS: study design

BIONIKK (NCT02960906)



Non-comparative, per molecular-group randomized phase II trial

Primary endpoint:

Overall response rate (ORR: CR+PR) using RECIST 1.1 per investigator

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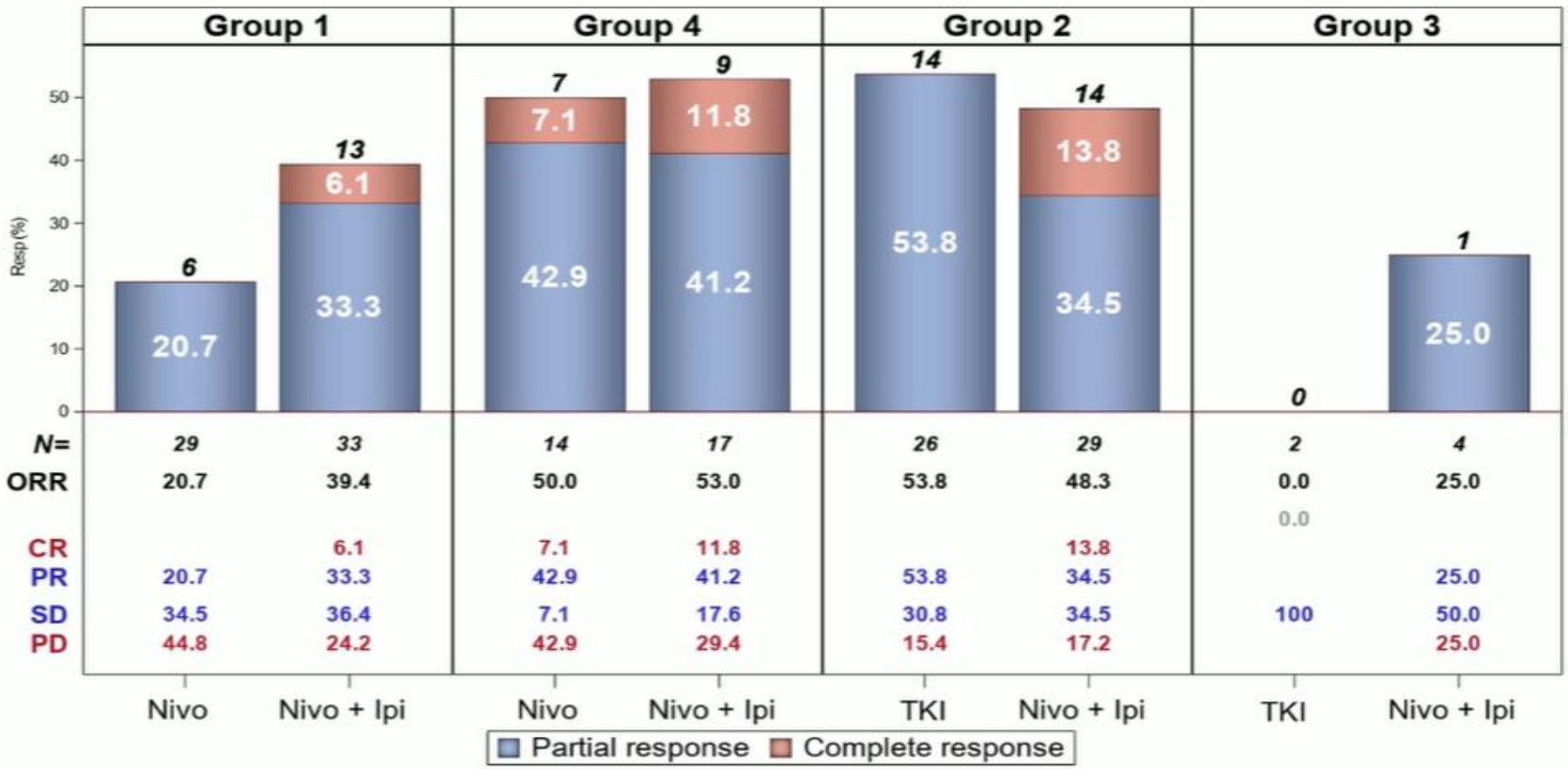
RESULTS: Primary Endpoint: Objective Response Rate (2)

Evaluable patients in Target Cohort (TCE, n=154), RECIST 1.1 (investigator)



[1]TCE: evaluable pts in target cohort
[2]ACE: evaluable pts in additionnal cohort

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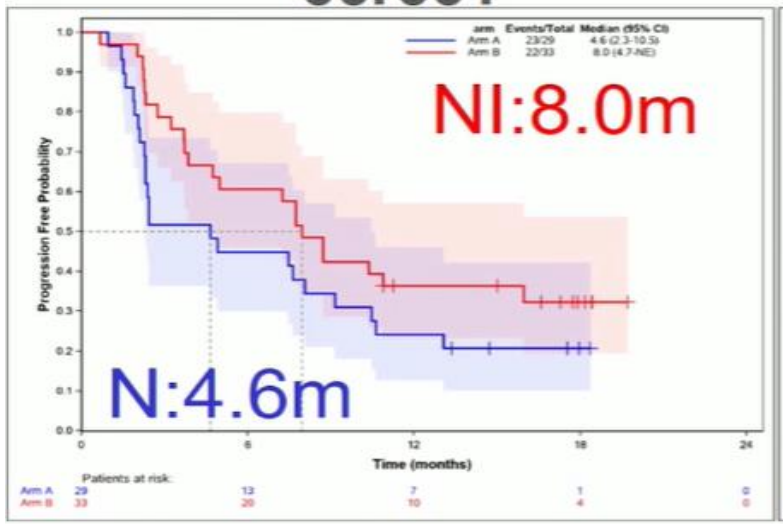
RESULTS: Progression Free Survival (PFS)

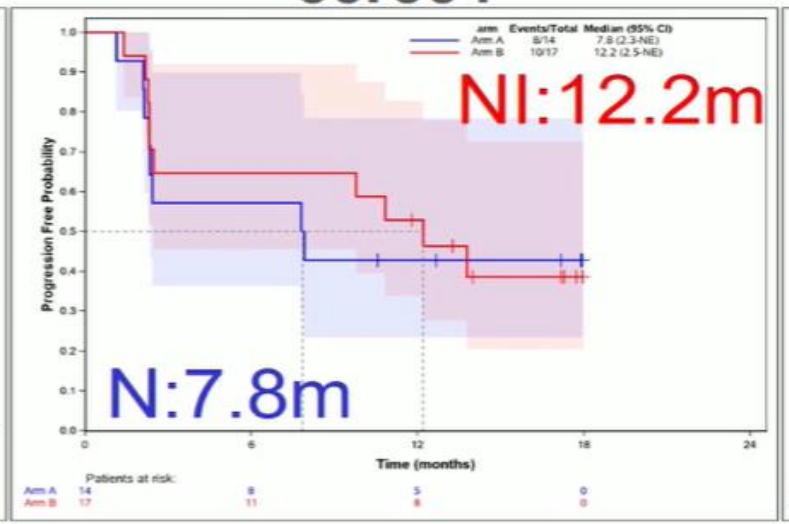
Target cohort (TCE, n=154)

Median follow-up: 16 months

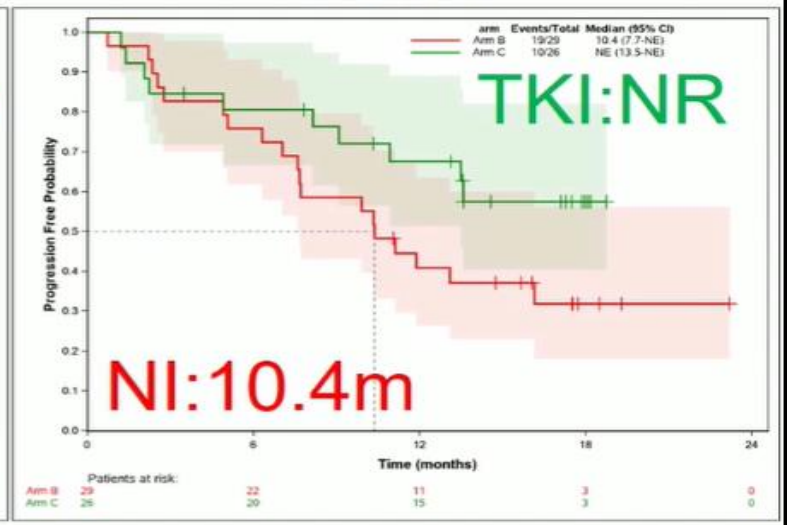
ccrcc1



ccrcc4



ccrcc2



ccrcc3

No KM curve showed here because of the limited number of pts (n=6)

**No statistical test perfomed due to the non-comparative design of the study.*

Sonuç

- Metastatik ccRCC'deki real-time moleküler grup değerlendirmesi baz alınarak tedavinin planlandığı prospektif ilk randomize klinik çalışmadır.
- **ccrcc grupları yanıt oranlarını artırmaya fayda sağlayabilir**
- En yüksek yanıt oranı nivolumab monoterapisi ile ccrcc4 tümörlü hastalarda görüldü (ccrcc1 grubunun iki katı)
- ccrcc1 grubunda **nivolumab+ipilimumab kombinasyonu gerekli**
- ccrcc2 tümörlerde **TKI çok yüksek yanıt** oranlarına sahip
- BIONIKK çalışması TKI, tekli nivolumab ve nivolumab+ipilimumab için en uygun adayların seçilmesi için kanıtlar sağlamaktadır.
- Transkriptomik analizleri, in situ protein expresyonunu ve circulating immune hücrelerin analizini içeren biomarker programı şu anda devam etmektedir

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY

Risk	Preferred regimens	Other recommended regimens	Useful in certain circumstances
Favorable[a]	• Axitinib + pembrolizumab[b] • Pazopanib • Sunitinib	• Ipilimumab + nivolumab[b] • Axitinib + avelumab[b] • Cabozantinib (category 2B)	• Active surveillance[c] • Axitinib (category 2B) • High-dose IL-2[d]
Poor/ intermediate[a]	• Ipilimumab + nivolumab[b] (category 1) • Axitinib + pembrolizumab[b] (category 1) • Cabozantinib	• Pazopanib • Sunitinib • Axitinib + avelumab[b]	• Axitinib (category 2B) • High-dose IL-2[d] • Temsirolimus[e]

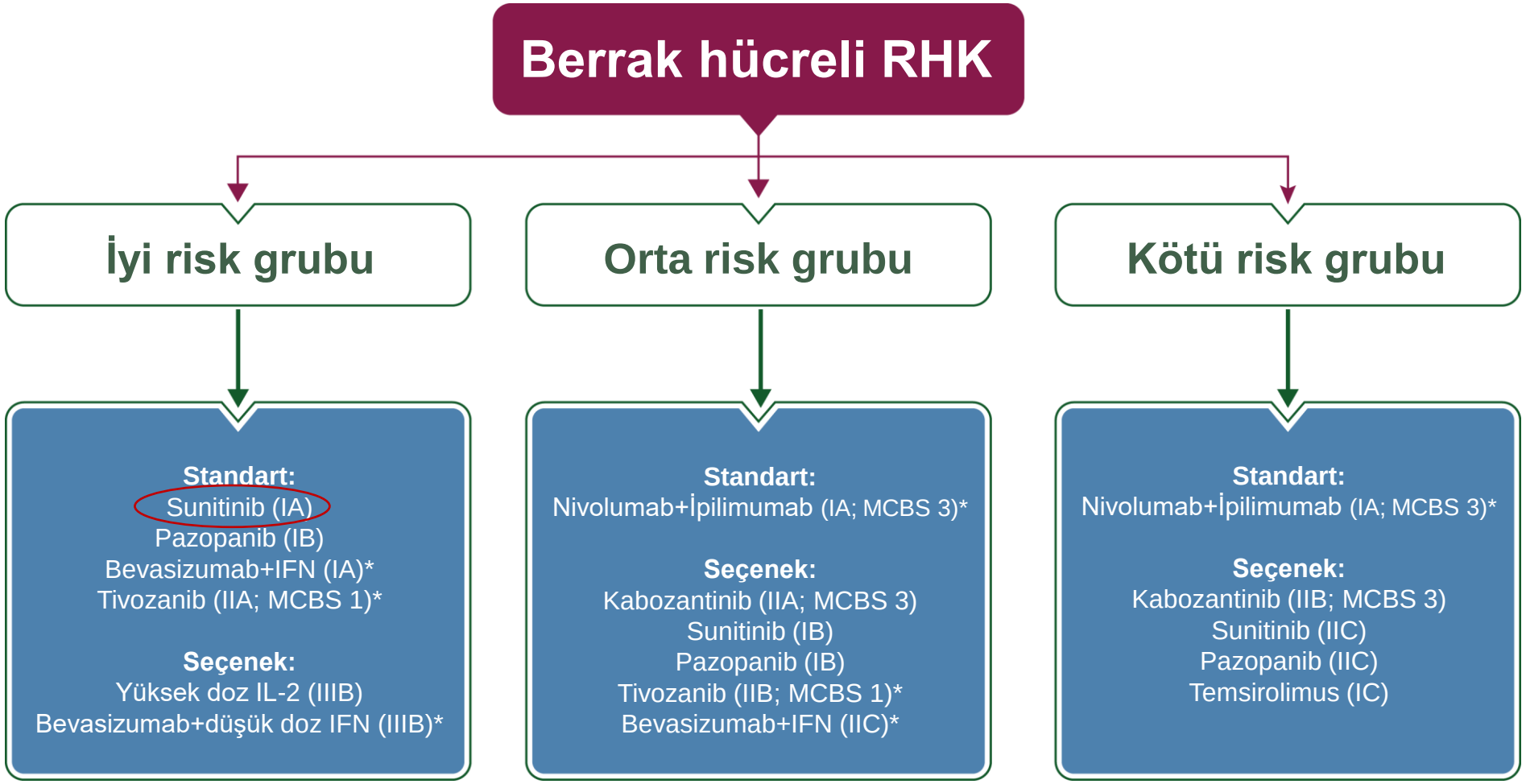
SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY

Preferred regimens	Other recommended regimens	Useful in certain circumstances
• Cabozantinib (category 1) • Nivolumab[b] (category 1) • Ipilimumab + nivolumab[b]	• Axitinib (category 1) • Lenvatinib + everolimus (category 1) • Axitinib + pembrolizumab[b] • Everolimus • Pazopanib • Sunitinib • Axitinib + avelumab[b] (category 3)	• Bevacizumab[f] (category 2B) • Sorafenib (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B)

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY[g]		
Preferred regimens	**Other recommended regimens**	**Useful in certain circumstances**
• Clinical trial • Sunitinib	• Cabozantinib • Everolimus • Lenvatinib + everolimus	• Axitinib • Bevacizumab[f] • Erlotinib • Nivolumab[b] • Pazopanib • Bevacizumab[f] + erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC) • Bevacizumab[f] + everolimus • Temsirolimus[e] (category 1 for poor-prognosis risk group; category 2A for other risk groups)

ESMO 2019


Berrak hücreli RHK
İyi risk grubu
Orta risk grubu
Kötü risk grubu
Standart:
Sunitinib (IA)
Pazopanib (IB)
Bevasizumab+IFN (IA)*
Tivozanib (IIA; MCBS 1)*
Seçenek:
Yüksek doz IL-2 (IIIB)
Bevasizumab+düşük doz IFN (IIIB)*
Standart:
Nivolumab+İpilimumab (IA; MCBS 3)*
Seçenek:
Kabozantinib (IIA; MCBS 3)
Sunitinib (IB)
Pazopanib (IB)
Tivozanib (IIB; MCBS 1)*
Bevasizumab+IFN (IIC)*
Standart:
Nivolumab+İpilimumab (IA; MCBS 3)*
Seçenek:
Kabozantinib (IIB; MCBS 3)
Sunitinib (IIC)
Pazopanib (IIC)
Temsirolimus (IC)

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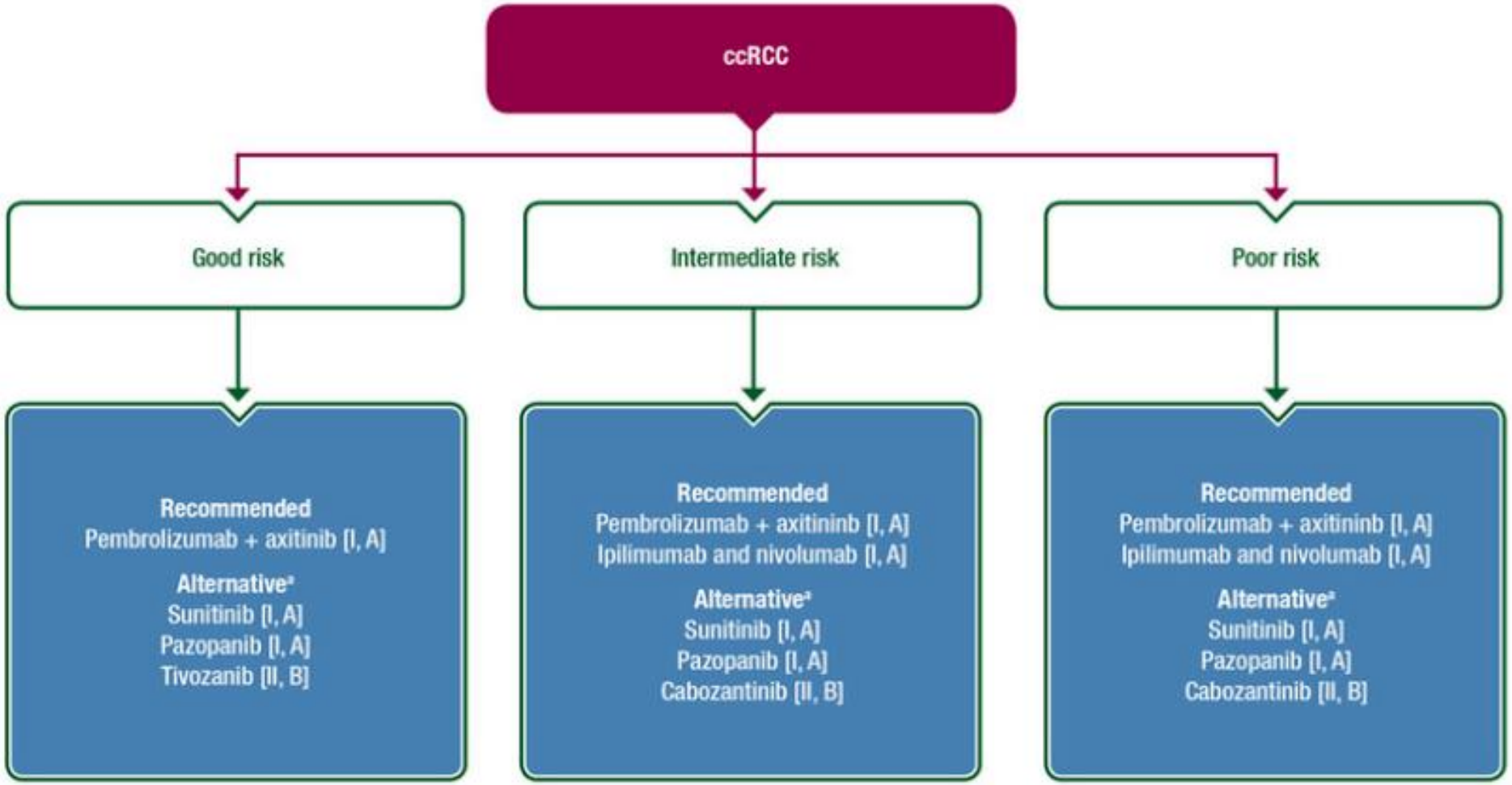

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