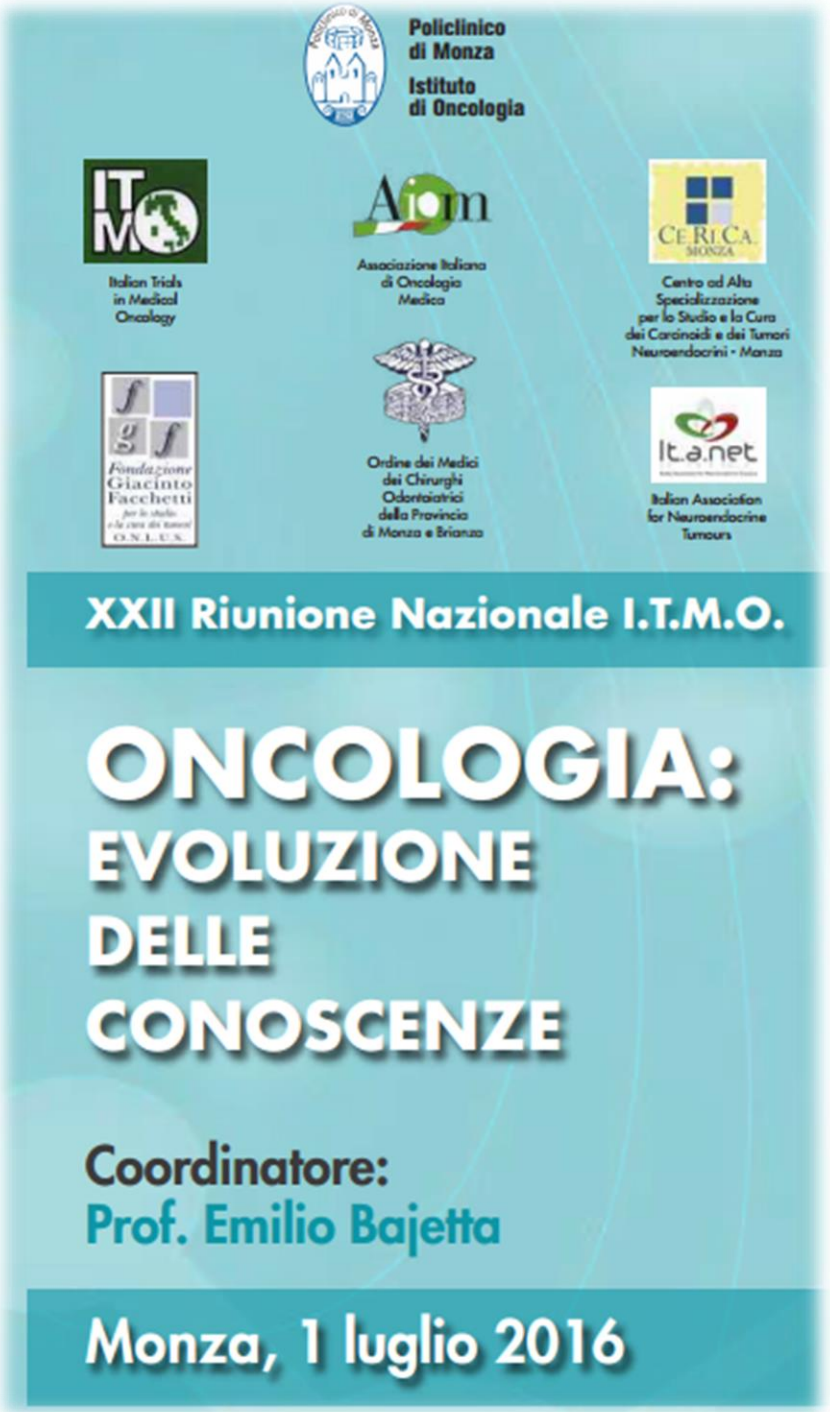


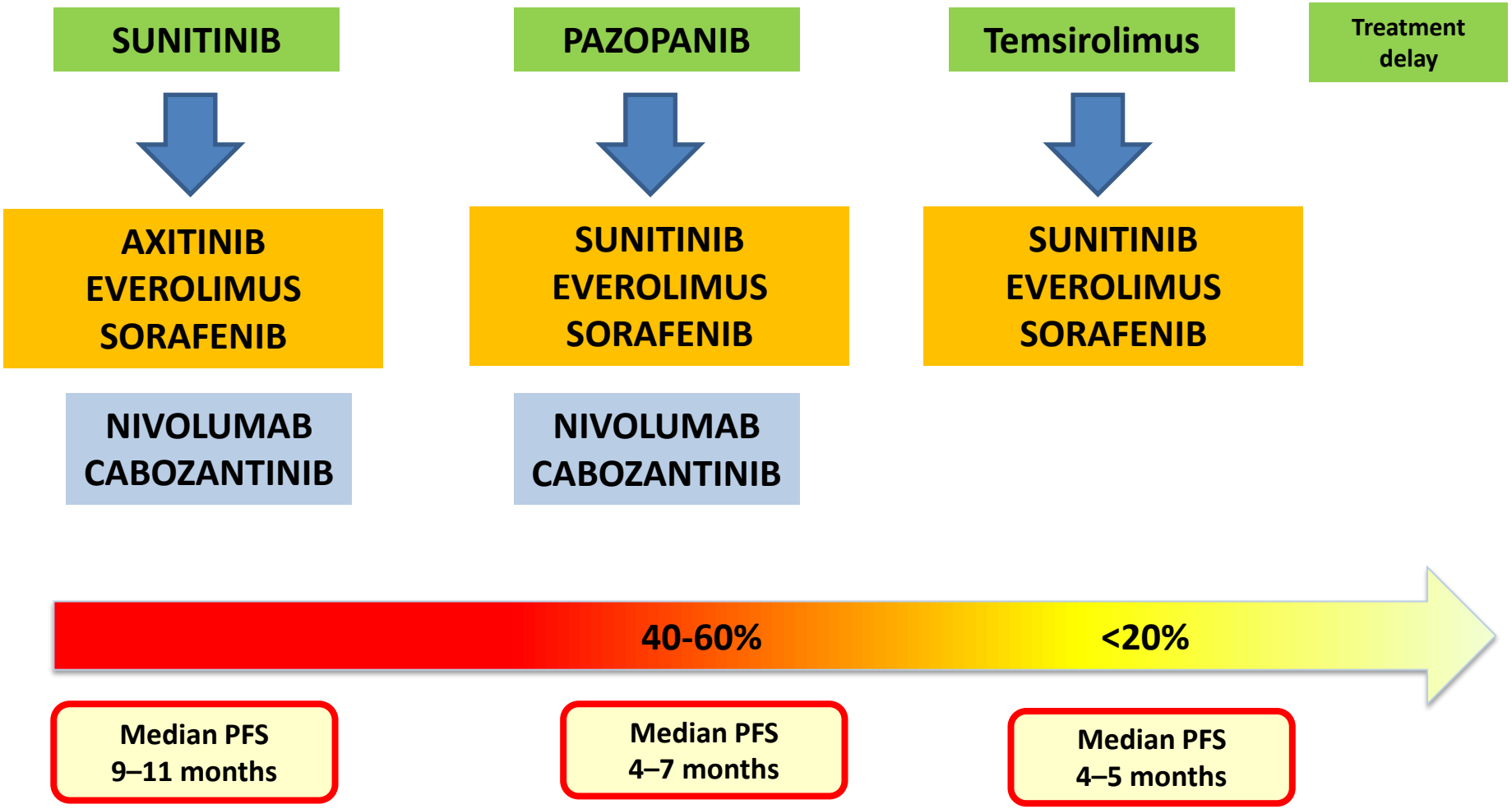
Terapie “avanzate” per le neoplasie renali e prostatiche

Giuseppe Procopio

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

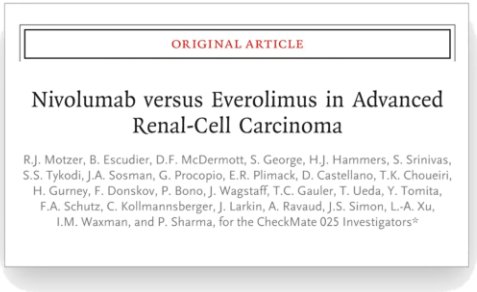
Renal Cell Carcinoma

Treatment options



1. Levy *et al. Eur J Cancer* 2013; 2. Sonpavde *et al. Eur Urol* 2012; 3. Iacovelli *et al. Eur J Cancer* 2013; 4. Pal *et al.* ASCO GU 2013; 5. Heng *et al.* ASCO 2013.

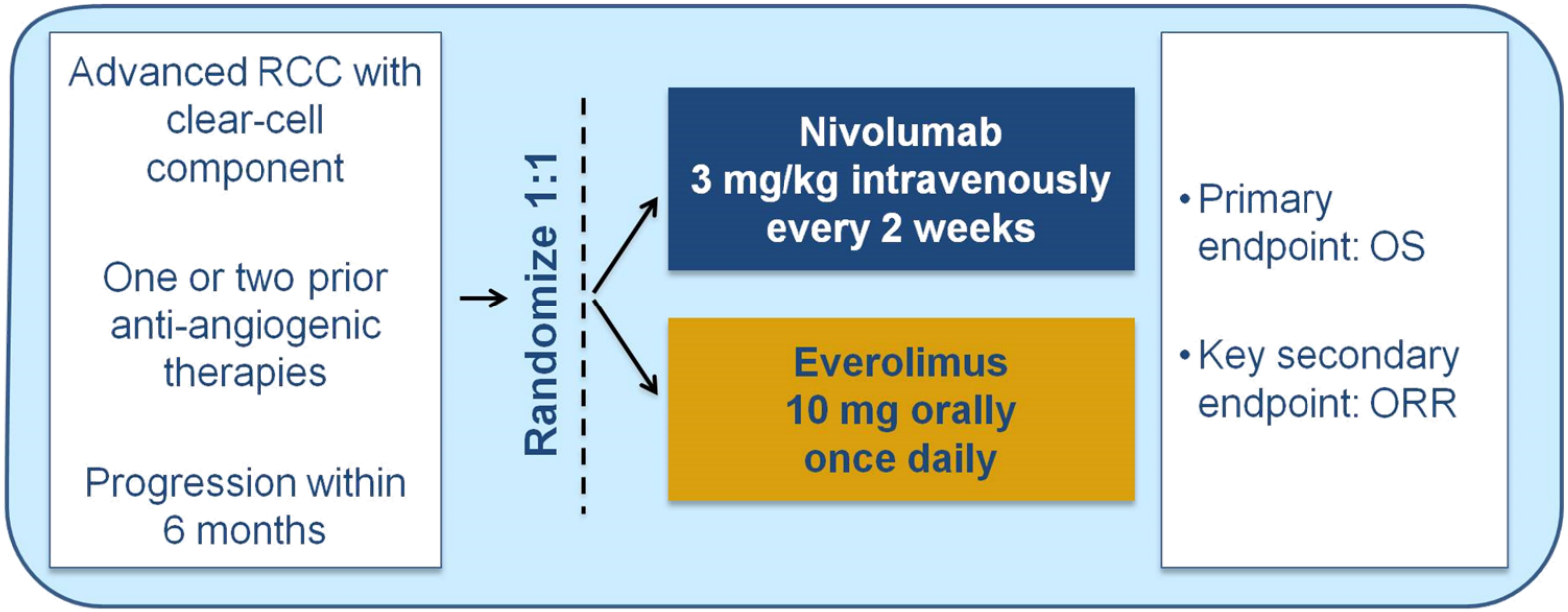
The NEW ENGLAND JOURNAL of MEDICINE


ORIGINAL ARTICLE

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, T.K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gauler, T. Ueda, Y. Tomita, F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J.S. Simon, L.-A. Xu, I.M. Waxman, and P. Sharma, for the CheckMate 025 Investigators*

Study conduct



- 821 patients randomized from October 2012 through March 2014
- Study halted July 2015 at preplanned interim analysis of OS

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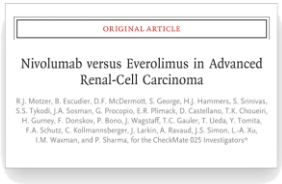
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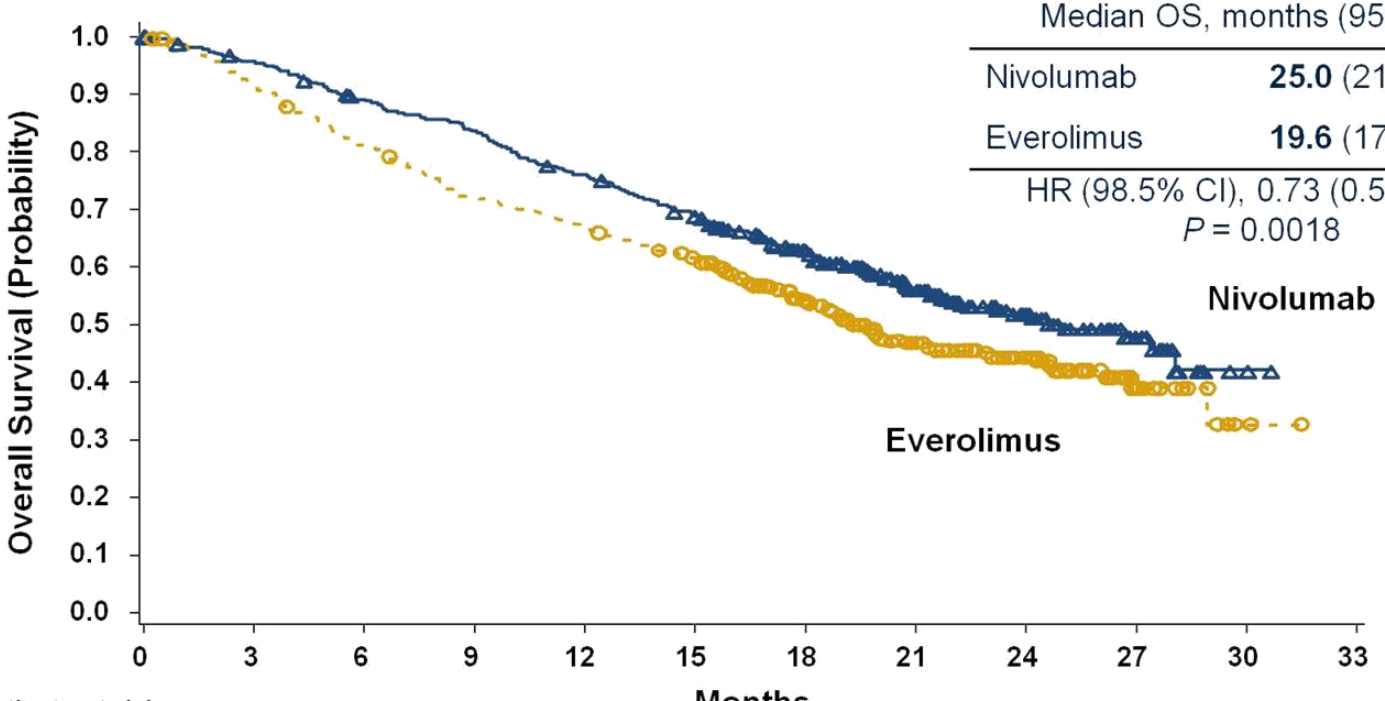
Overall survival



Median OS, months (95% CI)	
Nivolumab	**25.0** (21.8–NE)
Everolimus	**19.6** (17.6–23.1)

HR (98.5% CI), 0.73 (0.57–0.93)
P = 0.0018

No. of patients at risk

Nivolumab	410	359	305	213	73	3
Everolimus	411	324	265	187	61	2

Minimum follow-up was 14 months. NE, not estimable.

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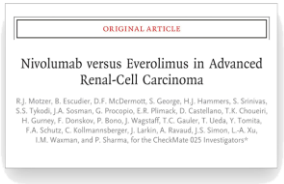
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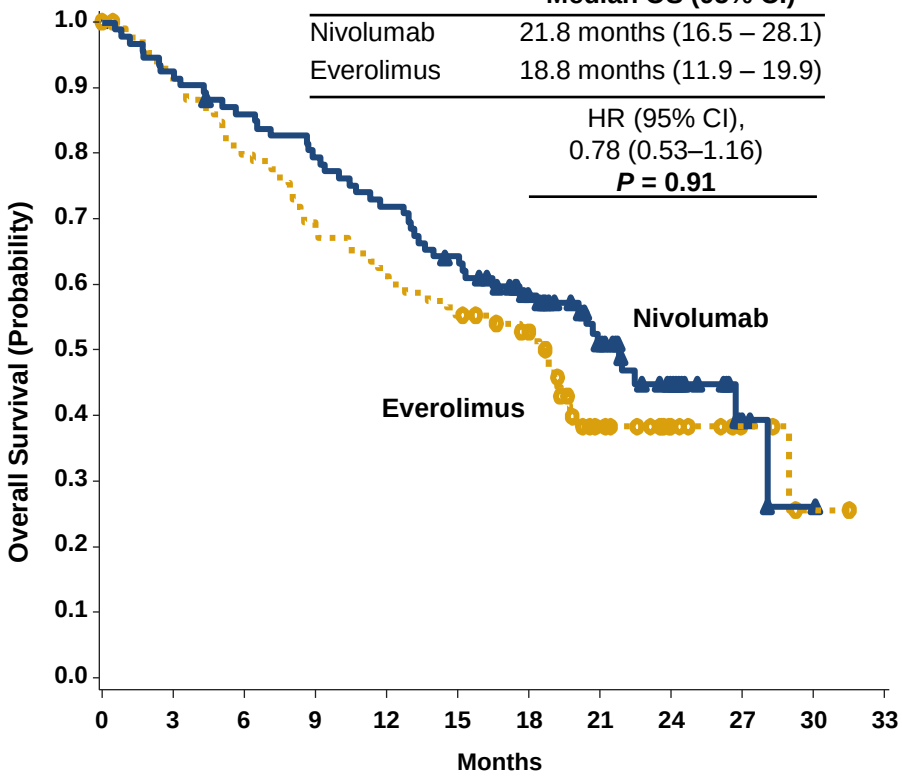
PD-L1 ≥1%

	Median OS (95% CI)
Nivolumab	21.8 months (16.5 – 28.1)
Everolimus	18.8 months (11.9 – 19.9)

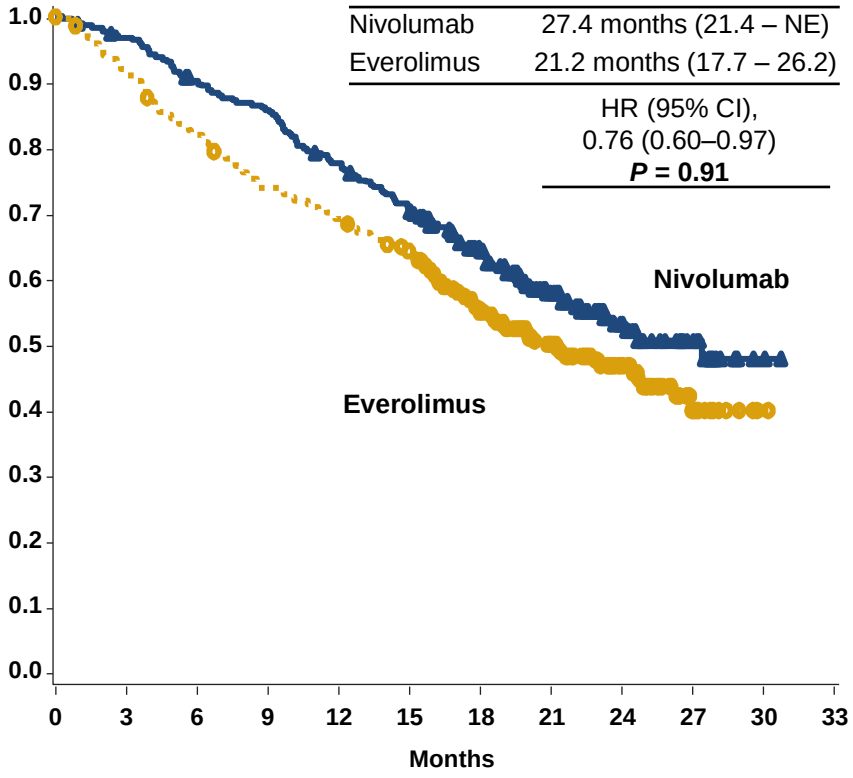
HR (95% CI), 0.78 (0.53–1.16)
***P* = 0.91**



PD-L1 <1%

	Median OS (95% CI)
Nivolumab	27.4 months (21.4 – NE)
Everolimus	21.2 months (17.7 – 26.2)

HR (95% CI), 0.76 (0.60–0.97)
***P* = 0.91**



No. of patients at risk

Nivolumab	94	86	79	73	66	58	45	31	18	4	1	0
Everolimus	87	77	68	59	52	47	40	19	9	4	1	0

Nivolumab	276	265	245	233	210	189	145	94	48	22	2	0
Everolimus	299	267	238	214	200	182	137	92	51	16	1	0

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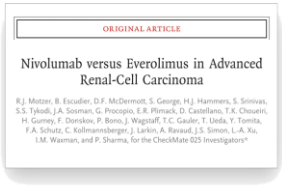
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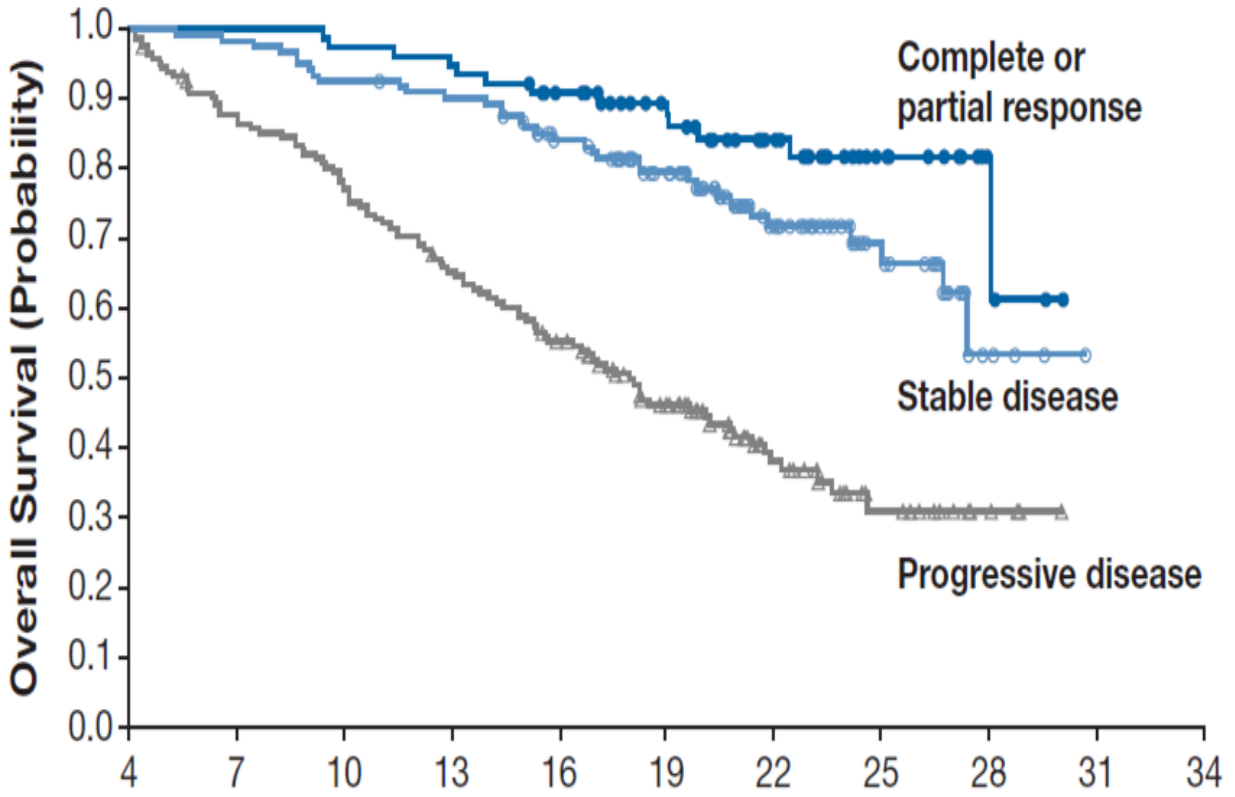
Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, T.K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gauler, T. Ueda, Y. Tomita, F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J.S. Simon, L.-A. Xu, I.M. Waxman, and P. Sharma, for the CheckMate 025 Investigators*

Parameter	Nivolumab N = 410	Everolimus N = 411
Objective response rate, %	25	5
Odds ratio (95% CI)	5.98 (3.68–9.72)	
***P* value**	<0.0001	
Best overall response, %		
Complete response	1	1
Partial response	24	5
Stable disease	34	55
Progressive disease	35	28
Not evaluated	6	12

Overall Survival With Nivolumab Based on BOR by Month 4

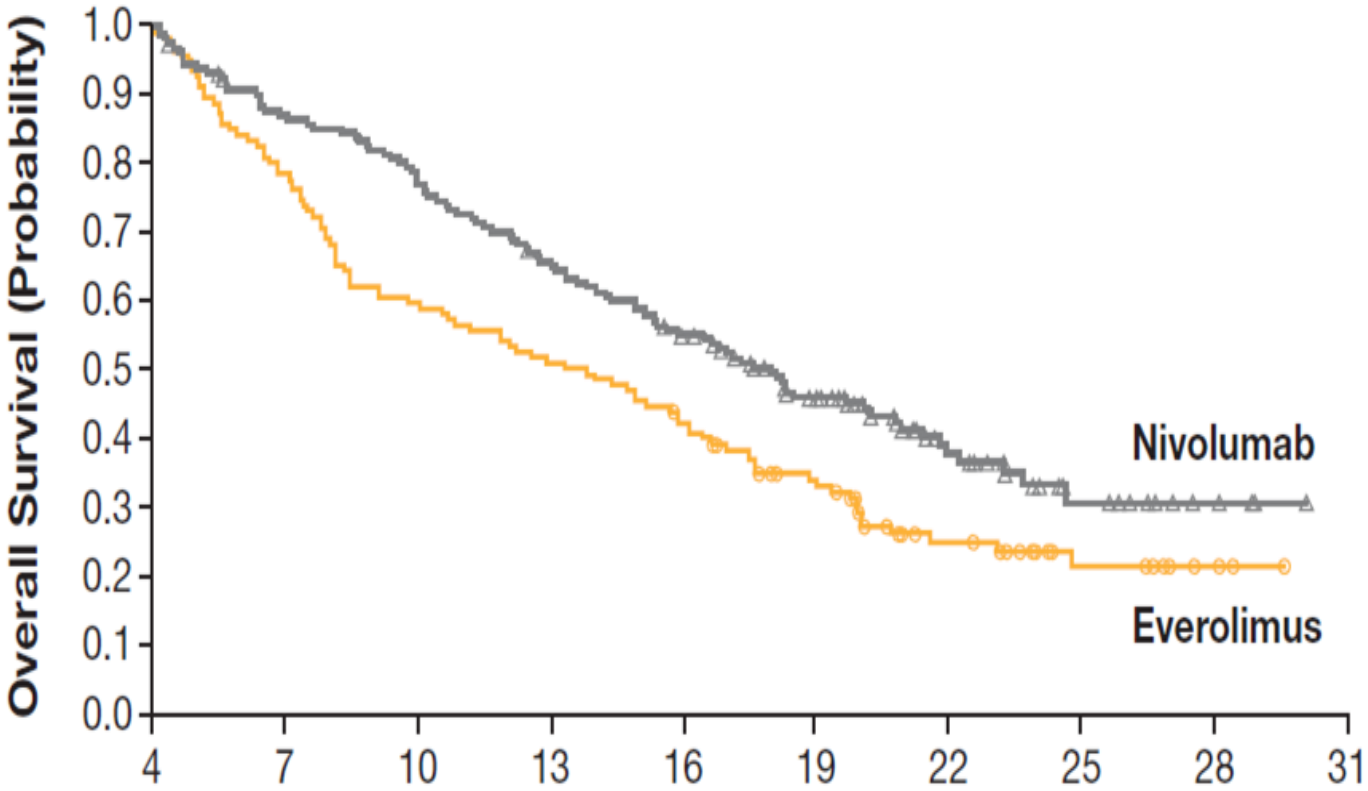


No. of patients at risk

Complete/partial response	77	77	75	73	66	53	37	17	4	0	0
Stable disease	121	119	112	108	94	76	48	23	4	0	0
Progressive disease	164	140	124	105	86	60	31	12	4	0	0

Motzer et al. ASCO 2016

Overall Survival With Nivolumab Versus Everolimus Based on BOR of Progressive Disease by Month 4



No. of patients at risk										
Nivolumab	164	140	124	105	86	60	31	12	4	0
Everolimus	127	100	76	65	54	37	20	10	4	0

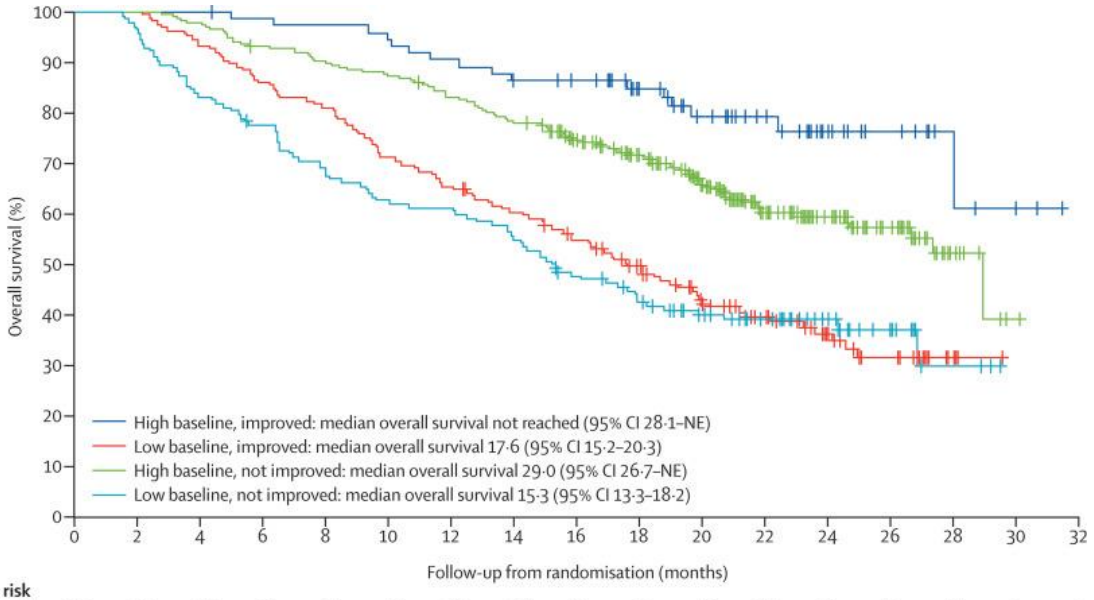
Motzer et al. ASCO 2016

QoL in CheckMate 025

THE LANCET Oncology

Quality of life in patients with advanced renal cell carcinoma given nivolumab versus everolimus in CheckMate 025: a randomised, open-label, phase 3 trial

David Cella, Viktor Grünwald, Paul Nathan, Justin Doan, Homa Dastani, Fiona Taylor, Bryan Bennett, Michael DeRosa, Scott Berry, Kristine Broglio, Elmer Berghorn, Robert J Motzer

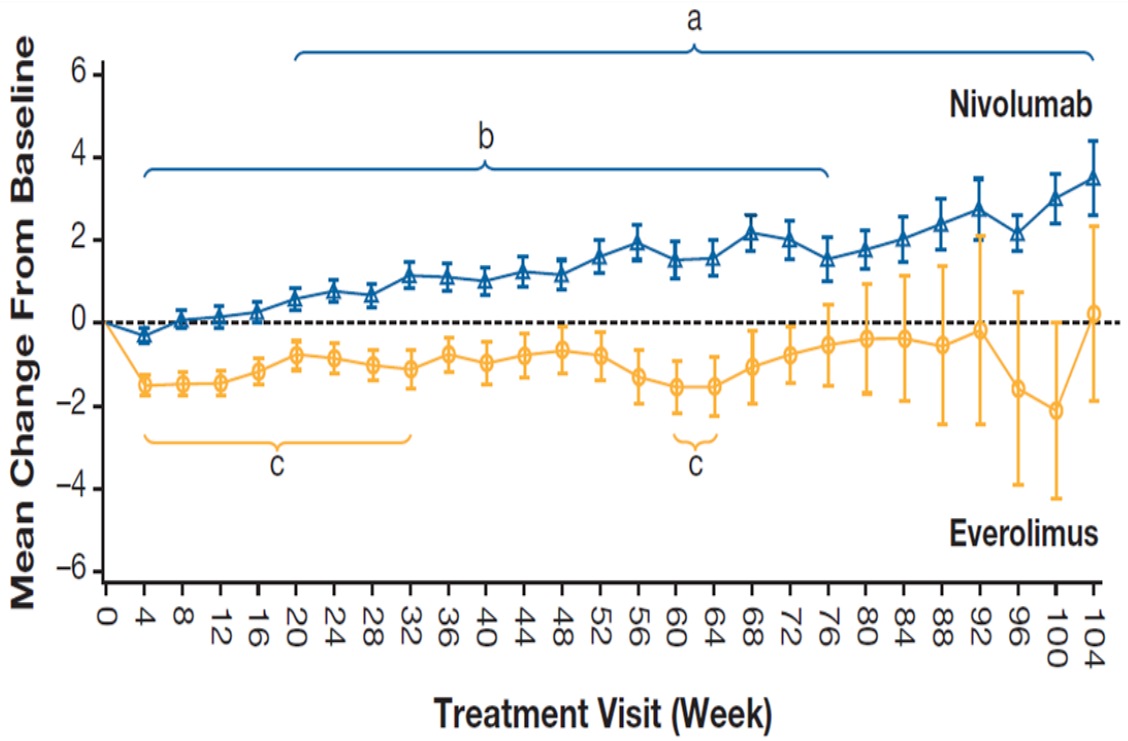


Number at risk

High baseline, improved	75	75	75	73	72	70	67	64	61	50	39	28	16	10	5	3	0
Low baseline, improved	165	165	154	142	134	118	108	98	87	73	57	41	26	17	4	0	0
High baseline, not improved	304	304	297	282	273	265	251	237	214	185	142	90	60	37	10	1	0
Low baseline, not improved	143	139	119	110	98	89	87	78	66	56	45	35	22	12	3	0	0

Improvement up to 12 weeks as a 2-point change in FKSI-DRS score from baseline (time 0)

Mean Change From Baseline in HRQoL Scores by FKSI-DRS: Descriptive Analysis



No. of patients at risk

Nivolumab	361	334	302	267	236	208	186	164	159	144	132	119	112	97	90	89	81	72	63	59	53	44	43	31	30	26	20
Everolimus	343	316	270	219	191	157	143	122	102	97	87	74	73	63	58	49	44	35	30	28	24	21	15	12	12	9	9

Note: Only time points where data were available for ≥5 patients are plotted

[a]Significant improvement ($P < 0.05$) from baseline in FKSI-DRS for nivolumab

[b]Significant difference ($P < 0.05$) in FKSI-DRS mean change from baseline scores between nivolumab and everolimus arms

[c]Significant deterioration ($P < 0.05$) from baseline in FKSI-DRS for everolimus

QoL in CheckMate 025

Jun 2016
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e220-e262

Improved quality of life is the way to longer life

*Giuseppe Procopio, Raffaele Ratta, Filippo de Braud
Medical Oncology 1, Fondazione IRCSS Istituto Nazionale dei Tumori, Milan 20133, Italy
giuseppe.procopio@istitutotumori.mi.it

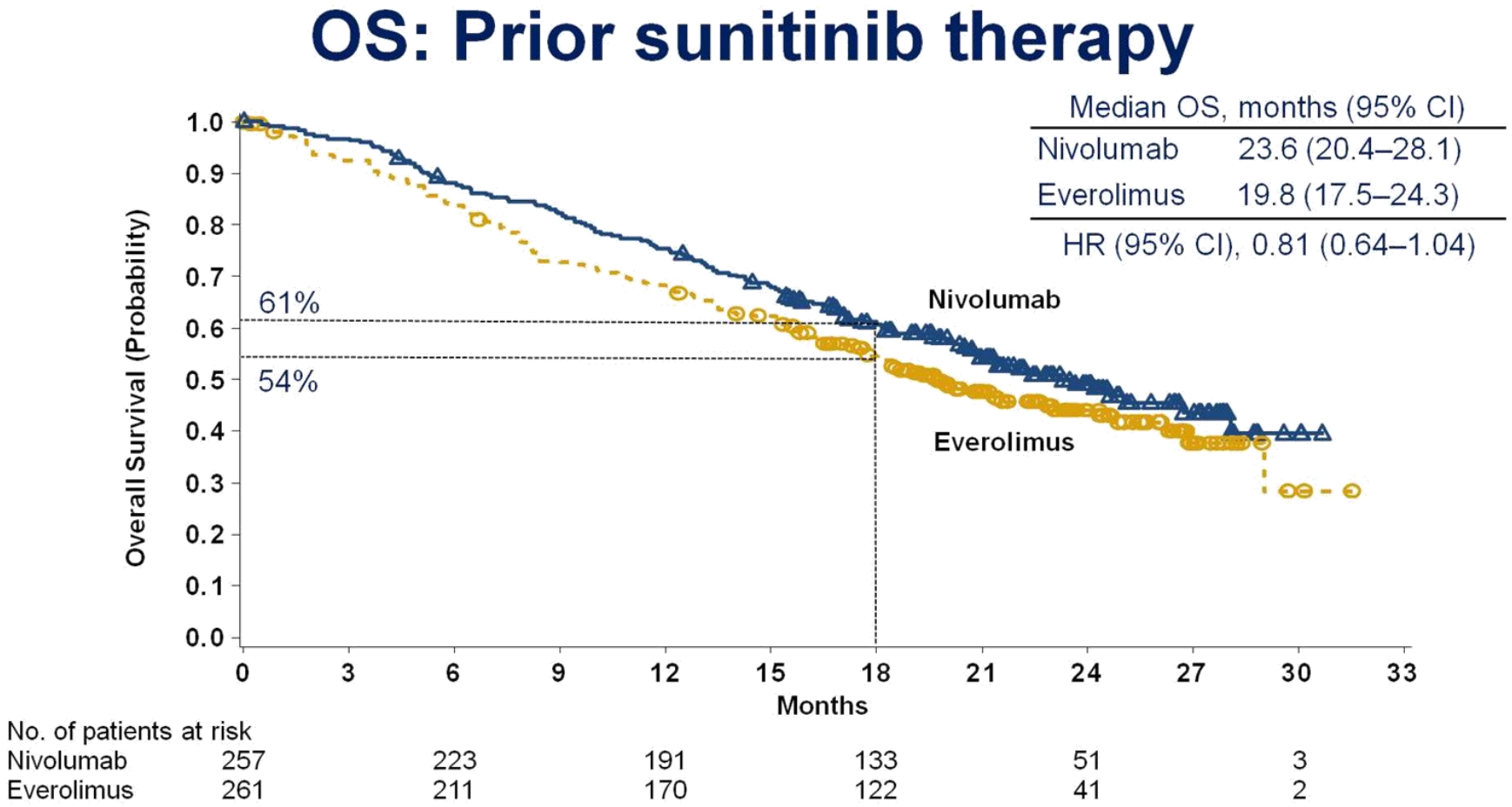
- Nivolumab improves OS and QoL, with clinical and statistical significance

- Patients' quality of life mainly depends on the toxicity of the treatment, whereas the correlation between quality of life and the desired cytoreductive effect and delay to progression is not well defined

- The physician's and patient's perceptions of toxicity often differ

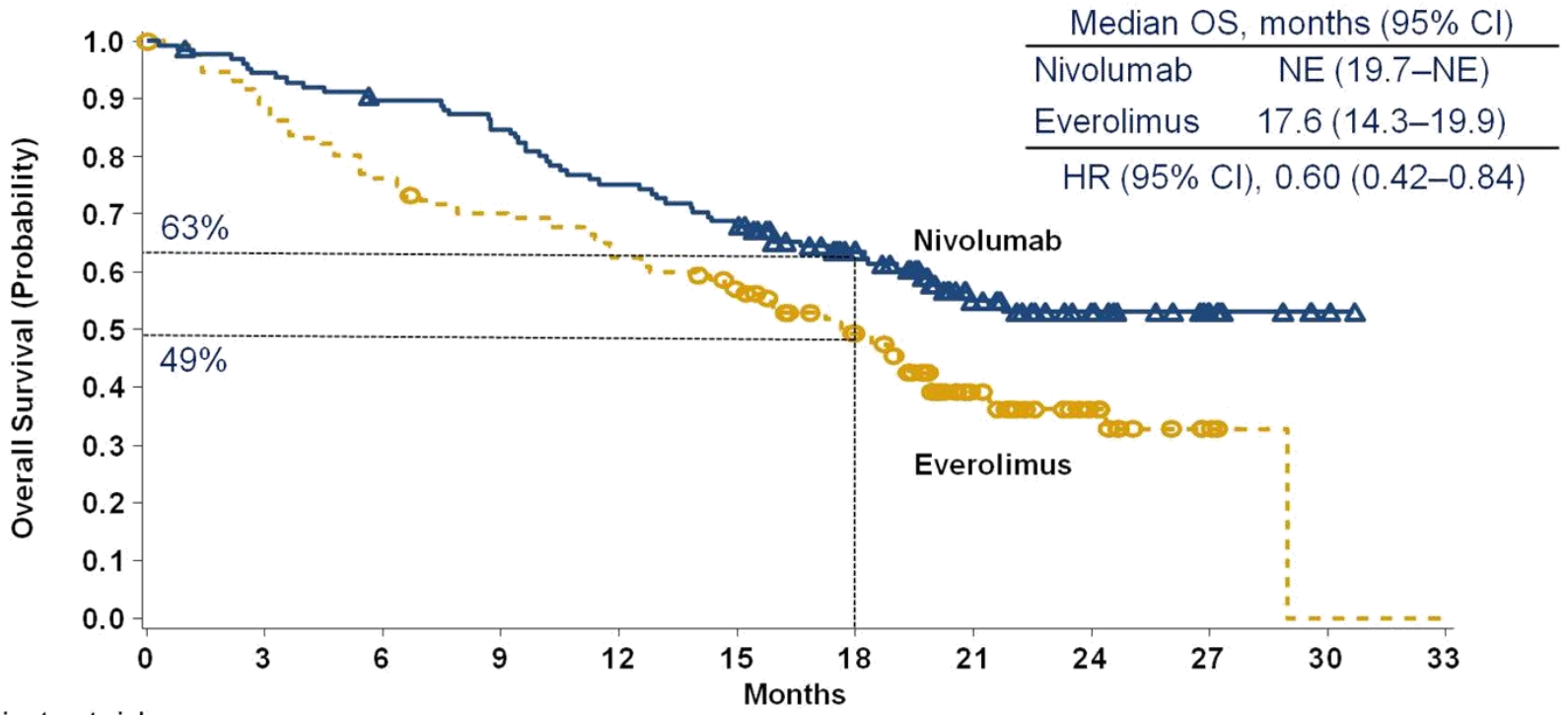
- The definition of the correct endpoint in clinical trials remains essential; progression-free survival is often chosen as a surrogate for overall survival but the two are not always correlated

CheckMate 025 phase III trial of nivolumab versus everolimus in advanced renal cell carcinoma: Outcomes by key baseline factors and prior therapies



Motzer et al. ASCO 2016

OS: Prior pazopanib therapy



No. of patients at risk

Nivolumab	126	111	93	62	19	2
Everolimus	136	100	81	52	13	0

Motzer et al. ASCO 2016

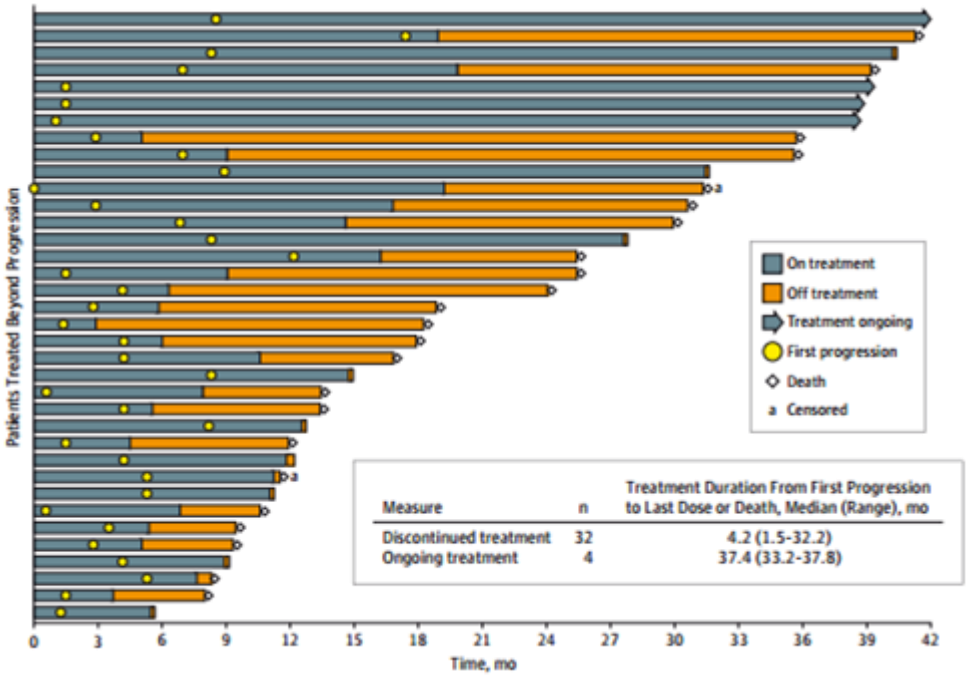
Safety and Efficacy of Nivolumab in Patients With Metastatic Renal Cell Carcinoma Treated Beyond Progression

JAMA Oncology

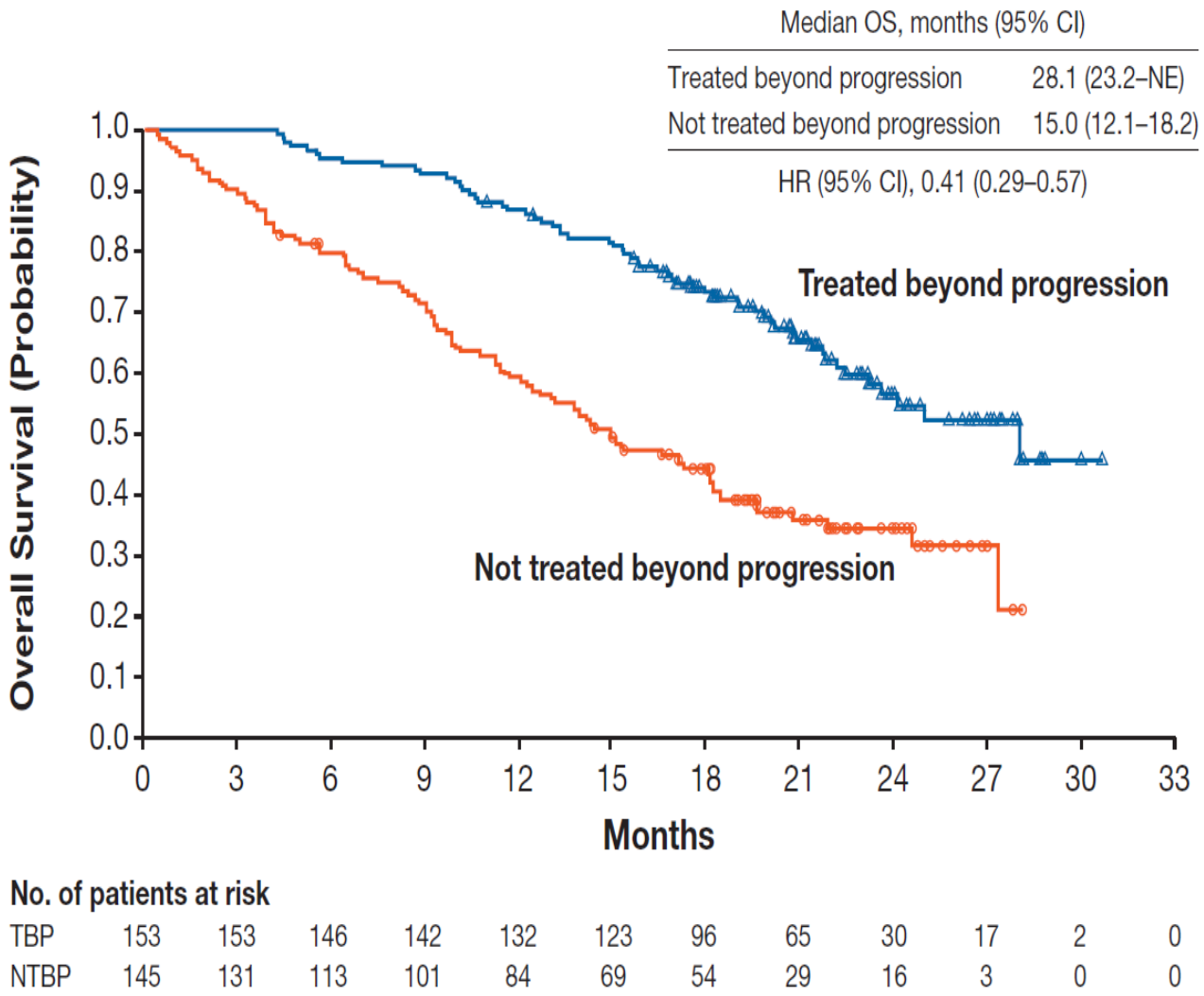
Saby George, MD; Robert J. Motzer, MD; Hans J. Hammers, MD, PhD; Bruce G. Redman, DO; Timothy M. Kuzel, MD; Scott S. Tykodi, MD, PhD; Elizabeth R. Plimack, MD, MS; Joel Jiang, PhD; Ian M. Waxman, MD; Brian I. Rini, MD

May 2016

A proportion of patients who continued treatment beyond RECIST-defined first progression demonstrated sustained reductions in tumor burden or stabilization in the size of target lesions, with an acceptable safety profile.



Overall Survival With Nivolumab



NTBP = not treated beyond progression; TBP = treated beyond progression

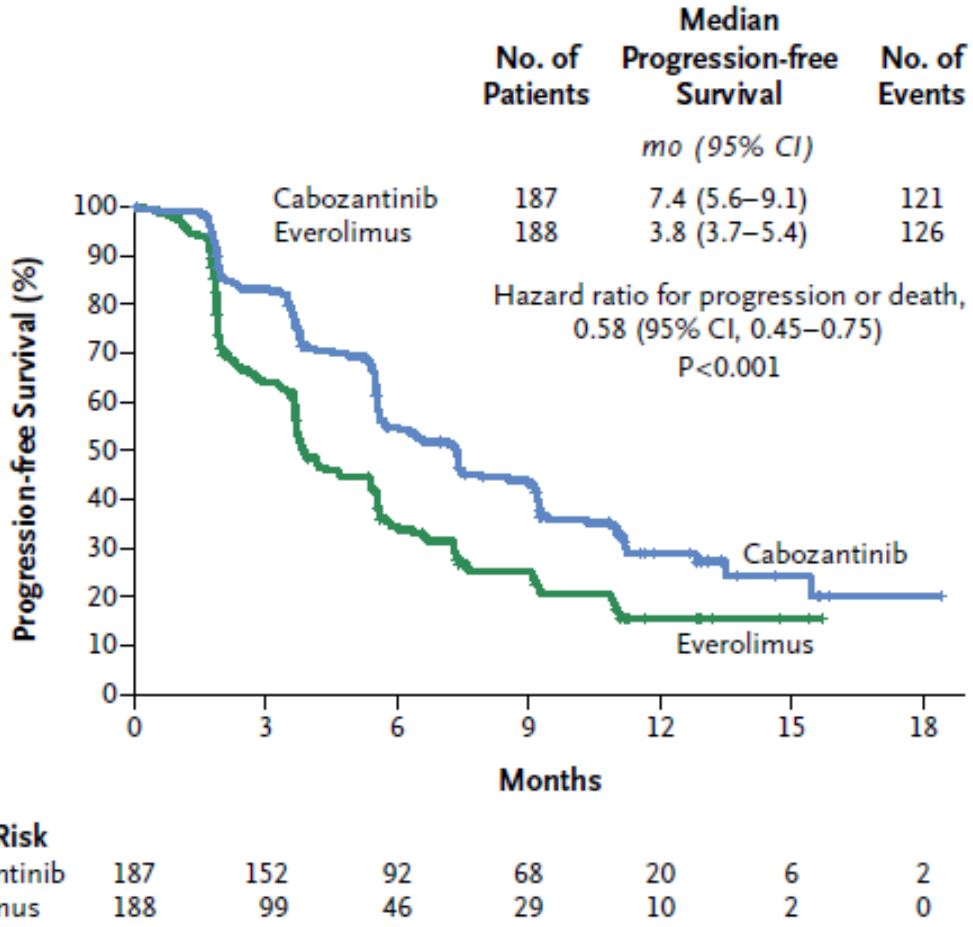
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

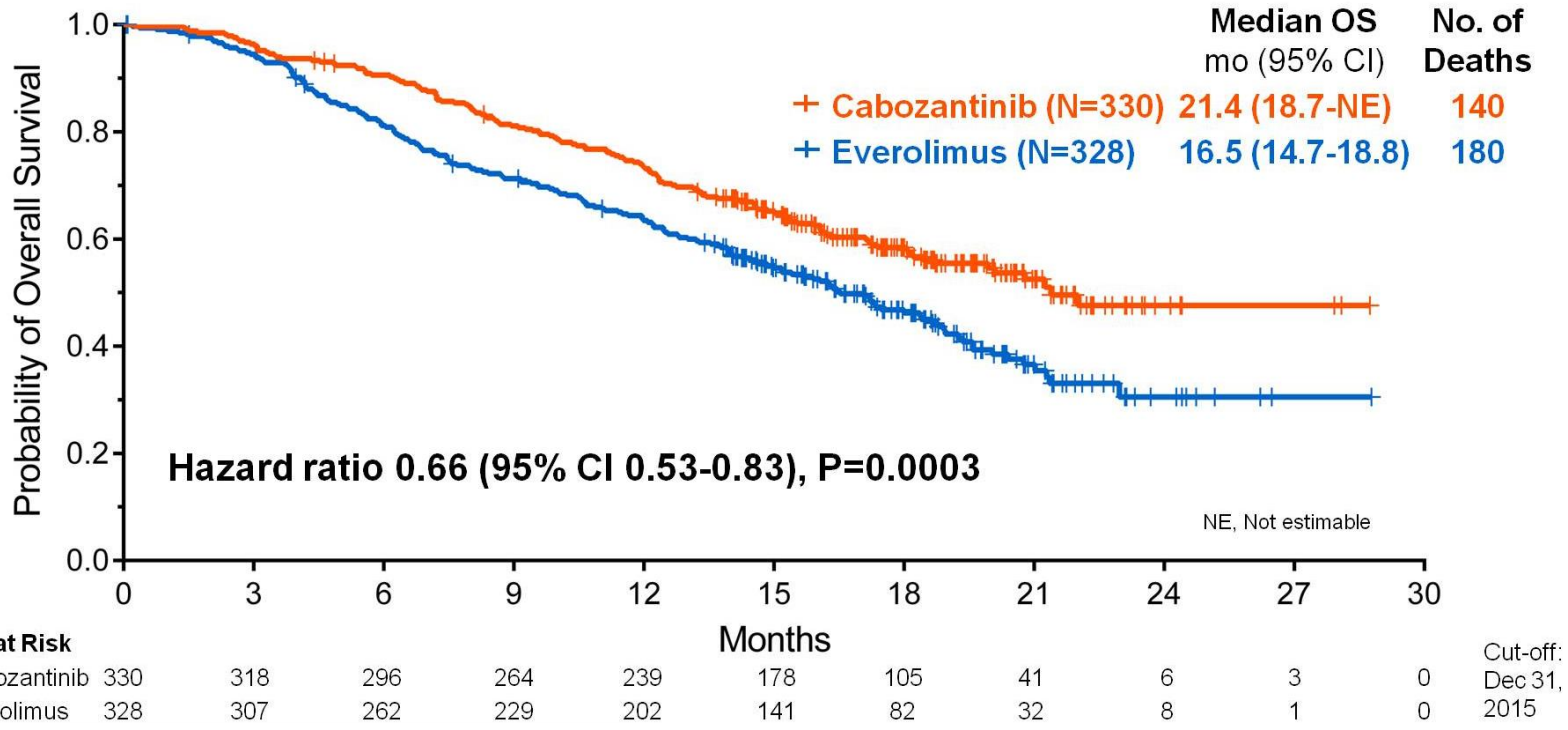
Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma

T.K. Choueiri, B. Escudier, T. Powles, P.N. Mainwaring, B.I. Rini, F. Donskov, H. Hammers, T.E. Hutson, J.-L. Lee, K. Peltola, B.J. Roth, G.A. Bjarnason, L. Géczi, B. Keam, P. Maroto, D.Y.C. Heng, M. Schmidinger, P.W. Kantoff, A. Borgman-Hagey, C. Hessel, C. Scheffold, G.M. Schwab, N.M. Tannir, and R.J. Motzer, for the METEOR Investigators*

Primary endpoint: PFS

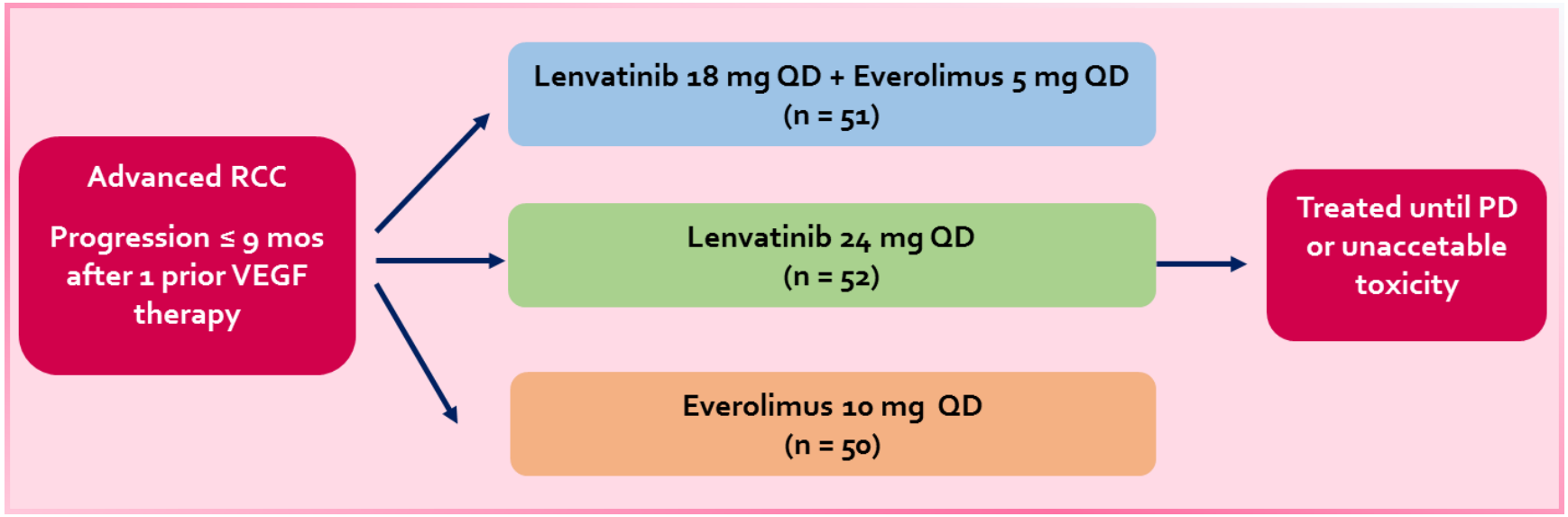


Secondary endpoint: OS



Lenvatinib vs Everolimus vs L+E

Randomized phase II, three-arm trial of lenvatinib (LEN), everolimus (EVE), and LEN+EVE in patients (pts) with metastatic renal cell carcinoma (mRCC)

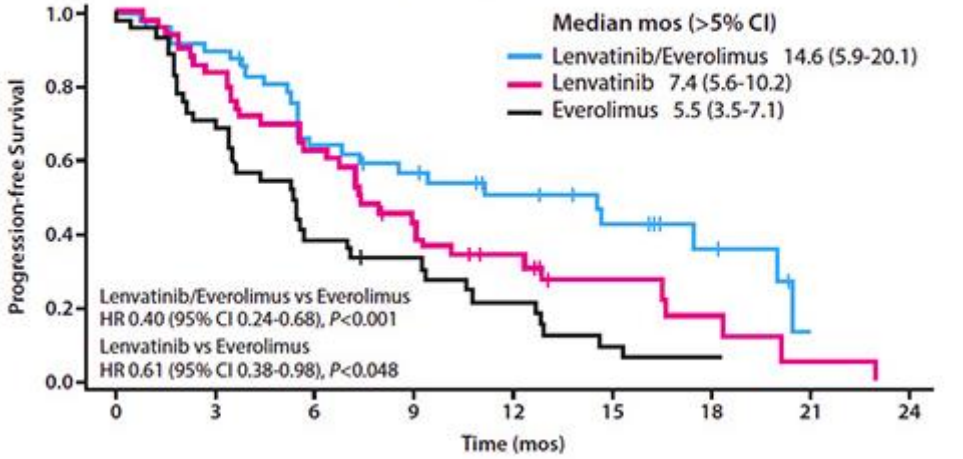


Primary endpoint: PFS with levantinib ± everolimus versus everolimus alone

Secondary endpoints: PFS with levantinib ± everolimus versus levantinib alone, ORR, OS, safety

Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial

Robert J Motzer, Thomas E Hutson, Hilary Glen, M Dror Michaelson, Ana Molina, Timothy Eisen, Jacek Jassem, Jakub Zolnierek, Jose Pablo Maroto, Begoña Mellado, Bohuslav Melichar, Jiri Tomasek, Alton Kremer, Han-Joo Kim, Karen Wood, Corina Dutcus, James Larkin

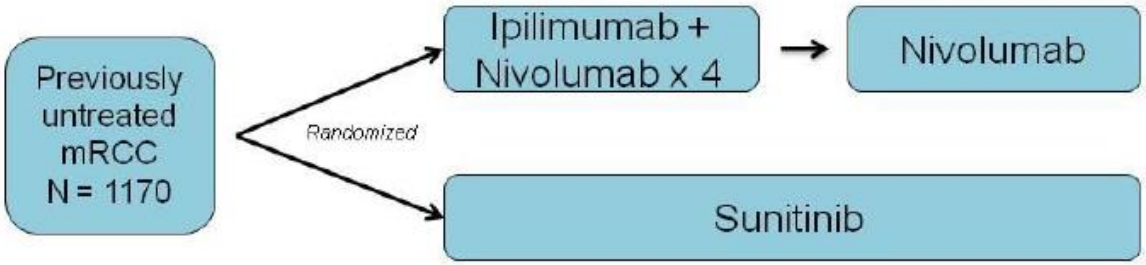


AE, %	Lenvatinib/Everolimus (n = 51)		Lenvatinib (n = 52)		Everolimus (n = 50)	
Discontinuation due to AE	18		21		10	
Dose reduction	71 (Len) 2 (Eve)		62		26	
	All	Gr 3/4	All	Gr 3/4	All	Gr 3/4
Treatment-emergent AE	100	71/14	100	83/10	100	52/12
Diarrhea	84	20	71	12	34	2
Fatigue/asthenia	59	14	50	8	38	0/2
Vomiting	45	8	39	4	10	0
Nausea	41	6	62	8	16	0
Hypertension	41	14	48	17	10	2
Decreased weight	31	2	48	6	8	0
Stomatitis	29	0	25	2	42	2
Dyspnea	24	0/2	21	2	22	8
Dysphonia	20	0	37	0	4	0
Rash	18	0	17	0	22	0

	Lenvatinib +Everolimus (n = 51)	Lenvatinib (n = 52)	Everolimus (n= 50)
Median PFS, mos	14,6 (*P* < ,001)	7,4 (*P* = ,0481)	5,5
Median OS, mos	25,5 (*P* <=,024)	19,1 (*P* <=,68)	15,4
ORR, %	43	27	6

Ongoing trials

Randomized Phase III (NCT02231749)



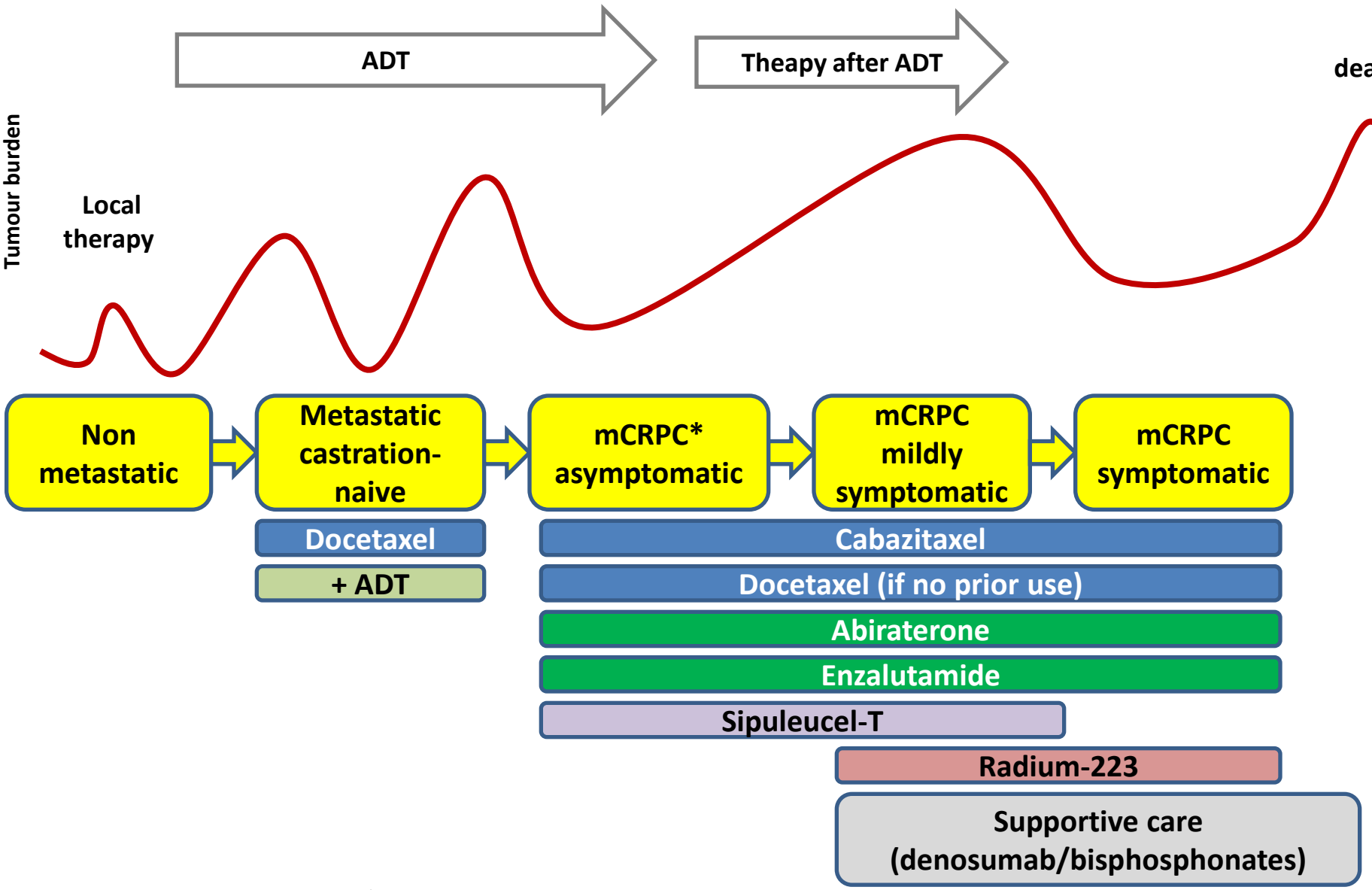
- Treatment-naïve patients
- 1:1 randomization
- Co-Primary endpoints: PFS per RECIST v1.1; OS
- Induction: Ipilimumab 1mg/m2 + nivolumab 3mg/m2 q21d x 4
- Must complete 4 induction doses to remain on trial
- No crossover

Cytoreductive Nephrectomy: Selection criteria

- Multidisciplinary team work
- In 2016, we should continue performing cytoreductive nephrectomy in
  - Younger patients
  - Clear-cell histology
  - Good performance status
  - Limited metastatic burden
  - 3 or less MDACC or IMDC risk factors
  - Preferably in high-volume centers
- **BUT**, patients who fall in other categories should not be automatically denied nephrectomy

Prostate Cancer

Treatment paradigm for CRPC is evolving: 2016



*castration testosterone treshold ≤50 ng/dl

Malattia ormonosensibile

How similar are the men participating in these studies?

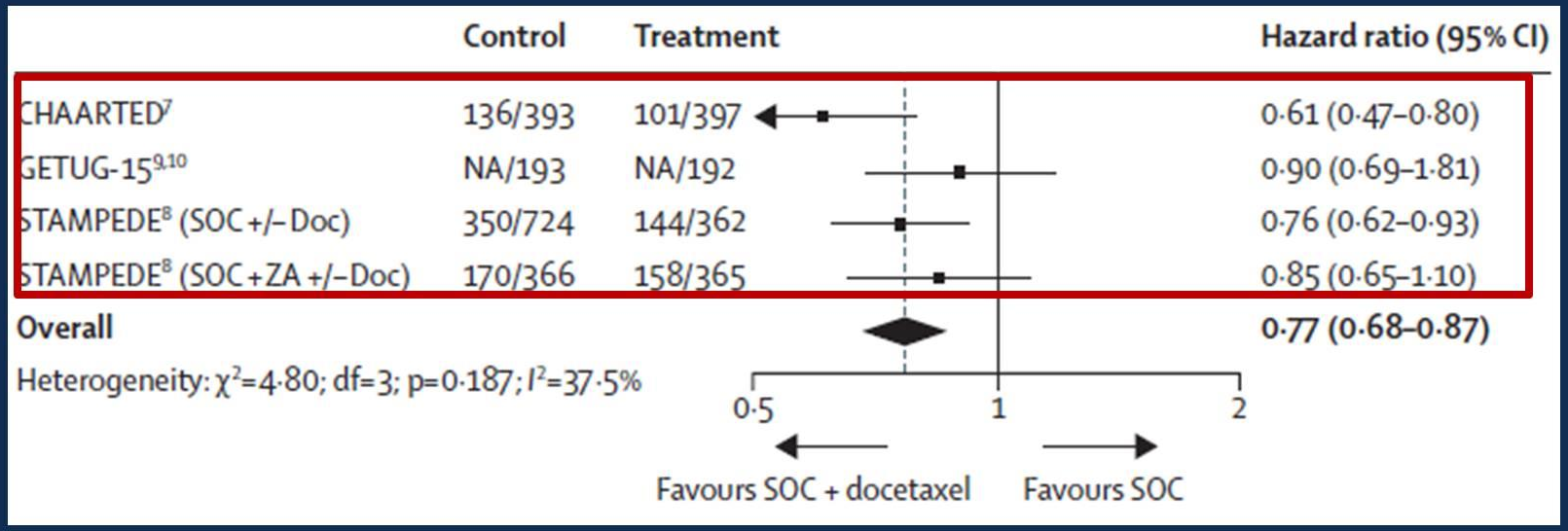
	Median age	% with mets at presentation	% high risk*
GETUG-15	64	71%	52%
CHAARTED	63	75%	65%
STAMPEDE	65	Most of them	Unknown

*high-volume" disease was defined as visceral metastases and/or ≥4 bone metastases with at least one metastasis beyond the pelvis or vertebral column.

These trials do NOT represent men with slowly progressive disease who develop metastases several years after diagnosis (+/- local treatment)

Overall Survival in M1 Patients

Addition of Docetaxel to Standard of Care: Systematic Review and Meta-Analyses



Conclusion of the authors

docetaxel + SOC should be considered standard care for M1 hormone-sensitive prostate cancer men who are starting treatment for the first time (and are fit for chemotherapy)

Vale CL et al, Lancet Oncol 2015

RECOMMENDATION #1

Men with high-risk metastatic prostate cancer, especially those presenting with metastases at or soon after diagnosis, who are judged fit to receive chemotherapy, should be offered 6 cycles of docetaxel in addition to ADT

Quality of life (QOL) analysis from CHAARTED: Chemohormonal Androgen Ablation Randomized Trial in Prostate Cancer (E3805)

Linda J. Patrick-Miller, Yu-Hui Chen, Michael Carducci, David Cella, Robert S. DiPaola, Benjamin Gartrell, Glenn Liu, David Jarrard, Alicia Morgans, Yu-Ning Wong, Jorge Garcia, Maha Hussain, Christopher Sweeney

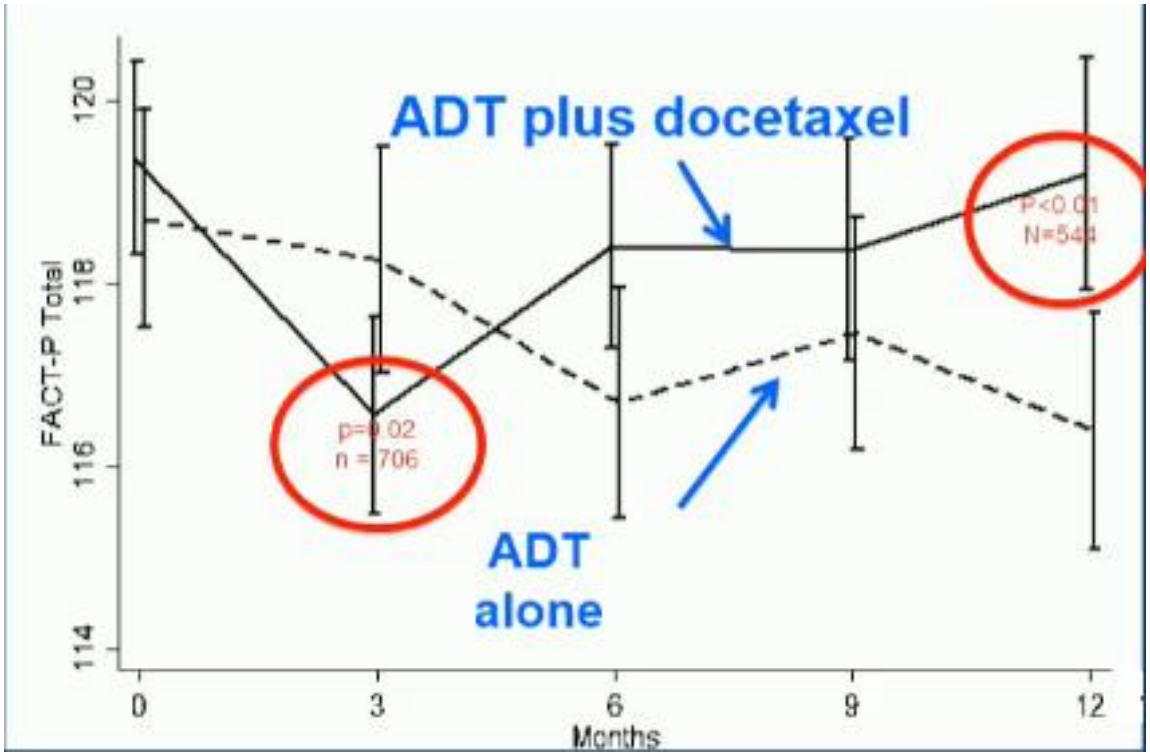
ECOG-ACRIN
cancer research group
Reshaping the future of patient care

PRESENTED AT: ASCO ANNUAL MEETING '16

Federally Funded Research

Presented By Linda J. Patrick-Miller at 2016 ASCO Annual Meeting

Primary Endpoint: Overall QOL



QOL with early docetaxel compared to ADT:

- Poorer at 3 months (90% RR)
- Not different at 6 months
- Superior at 12 months (69% RR)

Chemotherapy in hormonosensitive disease: EARLY!

- Mets at diagnosis

(Synchronous disease or < 6 months)

- High volume

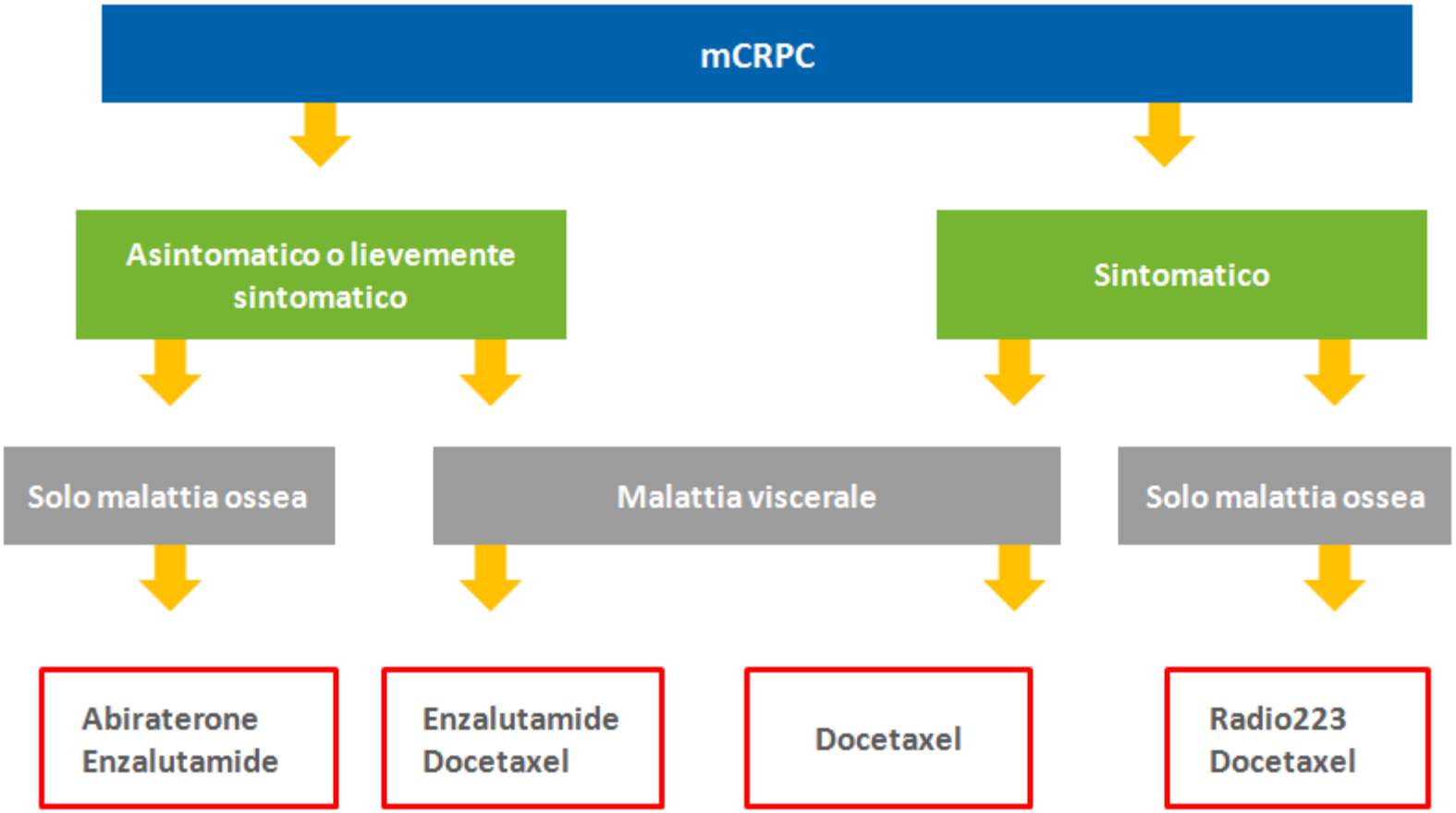
(Visceral mets liver or high volume disease [Charteed criteria?])

- Patient fit

(Younger, longer life expectancy, no comorbidities)

La progressione di malattia, radiologica, sintomatica o biochimica, in presenza di livelli di testosterone < 50 ng/mL identifica la fase di resistenza alla castrazione

Algoritmo decisionale nel mCRPC



GU Team INT

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