ESCOLA DE MEDICINA

PUCRS

Combination Therapy: A Historical Perspective

Checkmate 214 – Ipilimumab + Nivolumab for Advanced RCC

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March, 1st, 2018

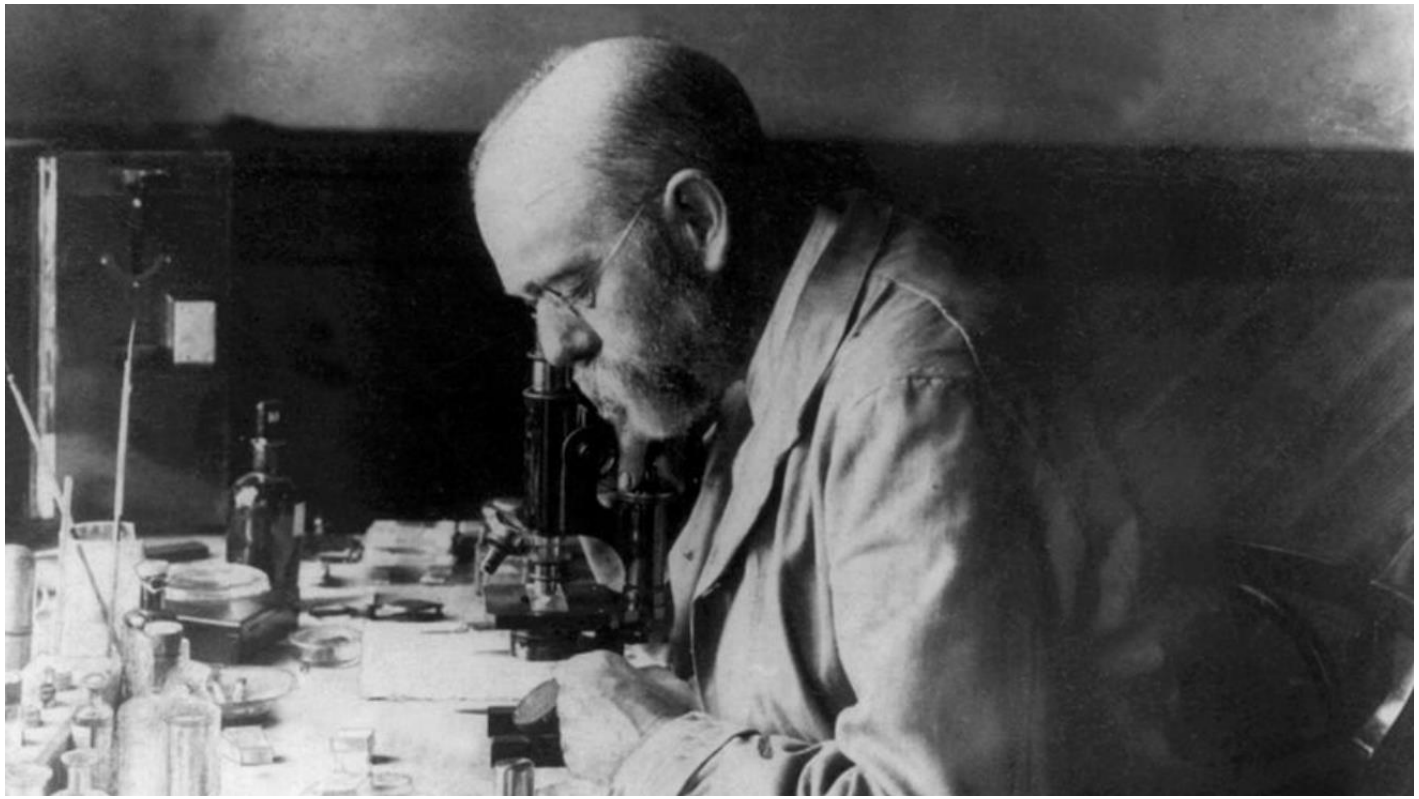
Disclosure

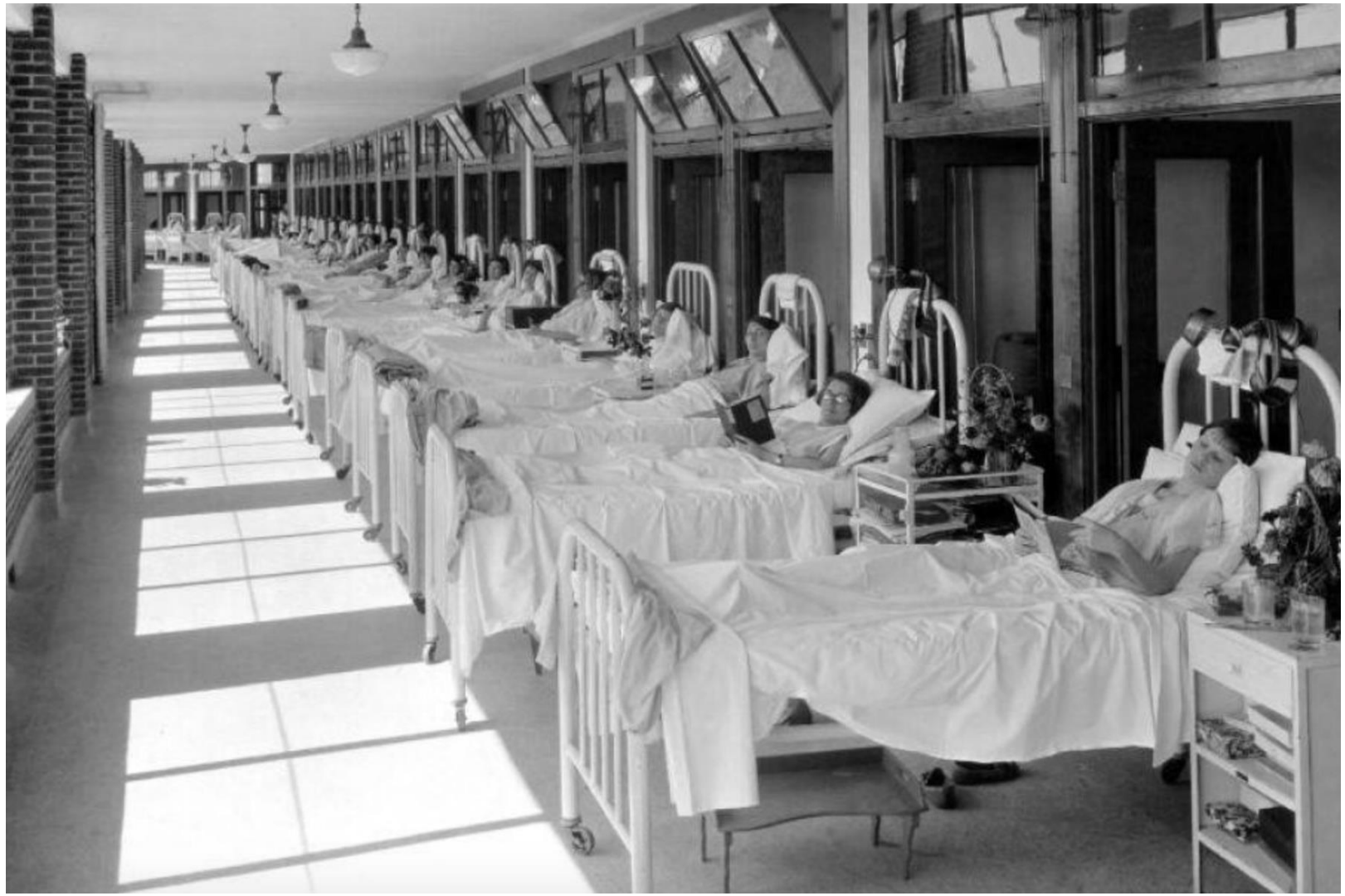
- Honoraria: Pfizer, BMS, Novartis, Roche, AstraZeneca, MSD
- Scientific Advisory Board: Janssen, Novartis, Roche, Pfizer
- Research Grant: CAPES – CNPq, BMS, AstraZeneca, MSD, Roche, Pfizer

Why to combine therapies?

- To enhance efficacy
- To target key pathways in a characteristically synergistic or an additive manner
- To reduce drug resistance
- Combination Chemotherapy – Medicine’s Attempt to Beat Darwin

Tuberculosis: a classic example





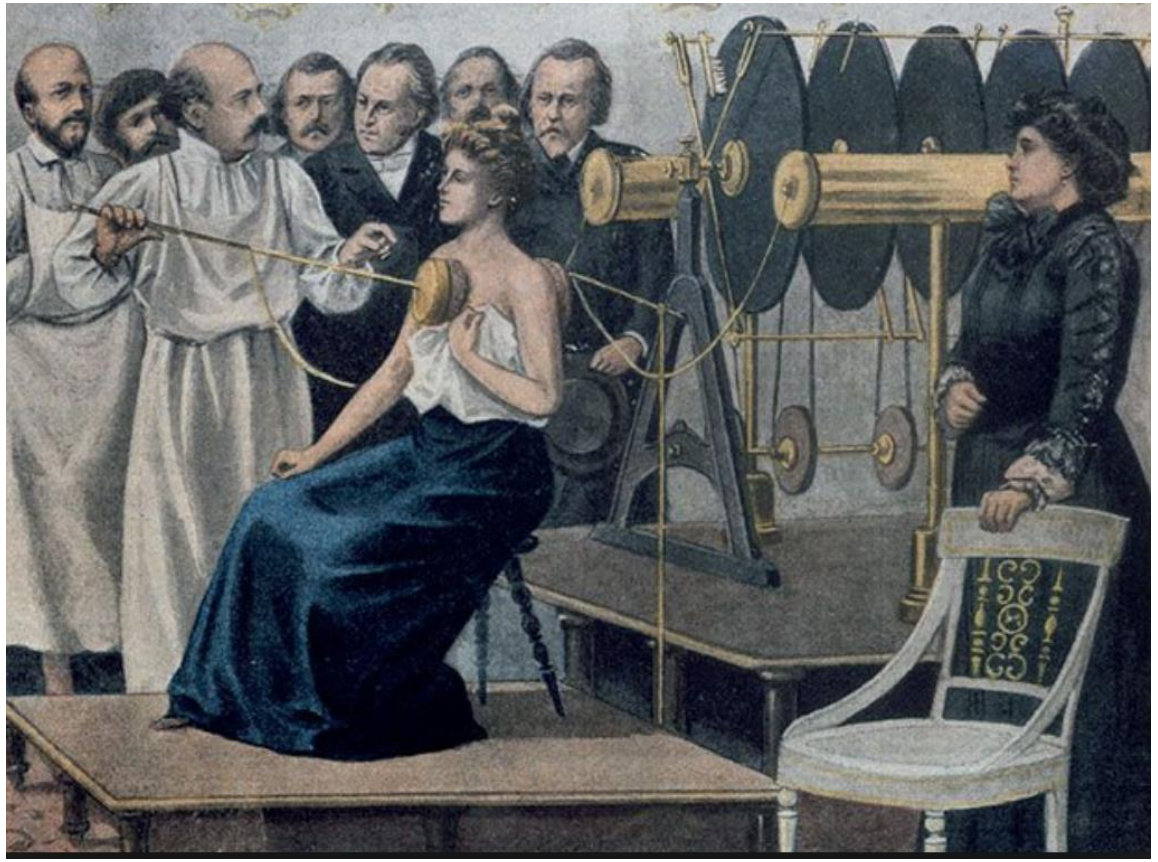
Luz

Repouso

Alimentação

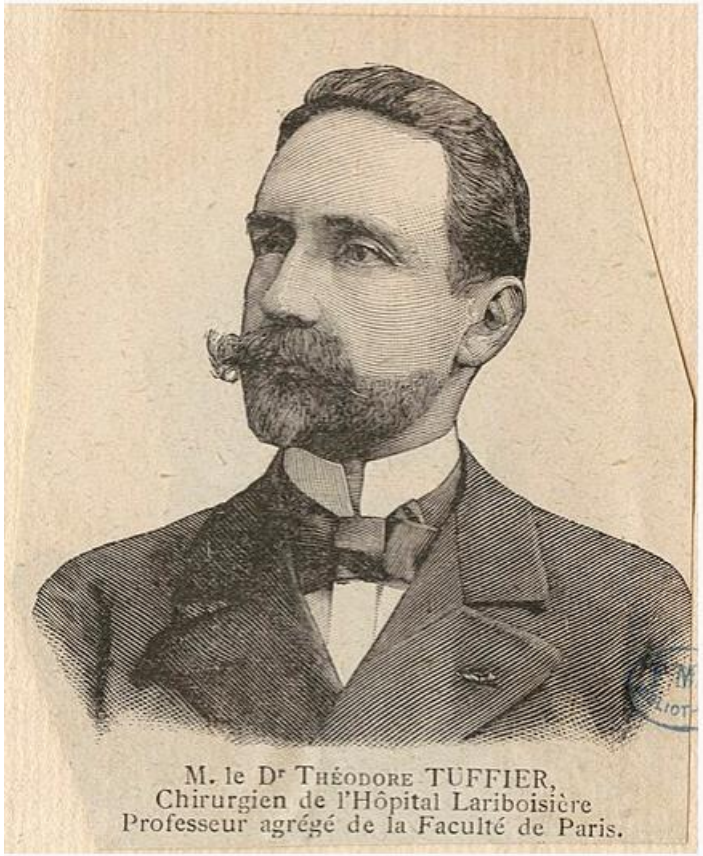
Ar seco dos climas altos

Francisque Crotte treating a patient with TB using electricity



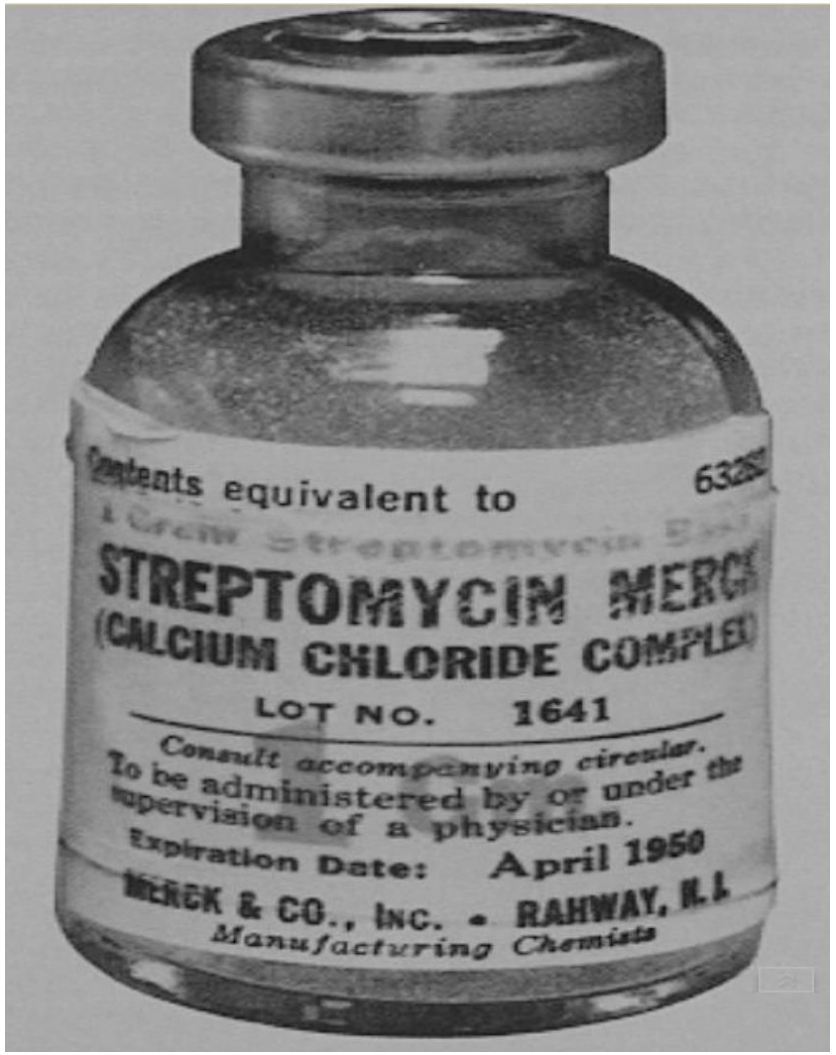
"Le Petit Journal", Paris, 1901

Theodore Tuffier: Surgical treatment for TB



M. le Dr Théodore TUFFIER,
Chirurgien de l'Hôpital Lariboisière
Professeur agrégé de la Faculté de Paris.

1944


Contents equivalent to
STREPTOMYCIN MERCK
(CALCIUM CHLORIDE COMPLEX)
LOT NO. 1641
Consult accompanying circular.
To be administered by or under the supervision of a physician.
Expiration Date: April 1950
MERCK & CO., INC. • RAHWAY, N.J.
Manufacturing Chemists

Improving the effectiveness of the treatment of tuberculosis

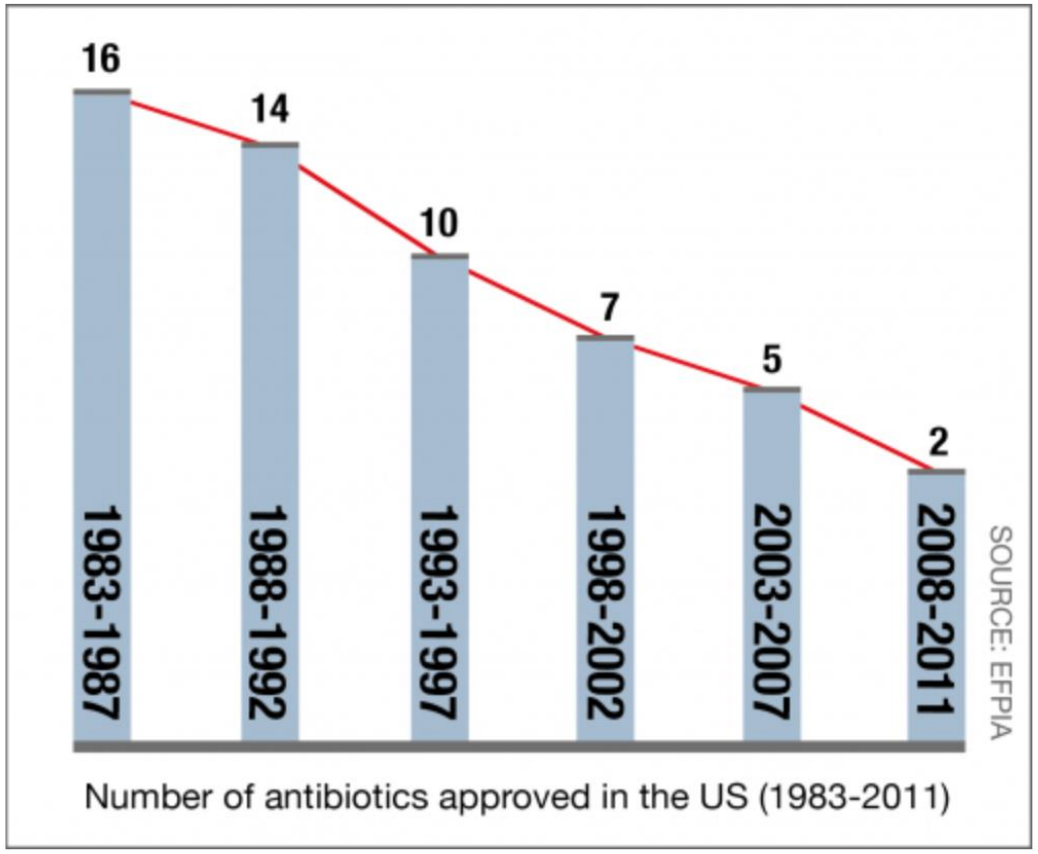
- 1952: Isoniazid, Pyrazinamide
- 1970: Rifampicin
- 2010: Ethambutol

The main reason for the improved effectiveness of combination therapy is prevention of the emergence of resistance to individual drugs

Slide do autor

Illustration: Don Smith

The emergence of resistance to multiple antimicrobial agents in pathogenic bacteria has become a significant global public health threat



Clinical Review & Education

Special Communication

Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults

2016 Recommendations of the International Antiviral Society–USA Panel

Huldrych F. Günthard, MD; Michael S. Saag, MD; Constance A. Benson, MD; Carlos del Rio, MD; Joseph J. Eron, MD; Joel E. Gallant, MD, MPH; Jennifer F. Hoy, MBBS, FRACP; Michael J. Mugavero, MD, MHSc; Paul E. Sax, MD; Melanie A. Thompson, MD; Rajesh T. Gandhi, MD; Raphael J. Landovitz, MD; Davey M. Smith, MD; Donna M. Jacobsen, BS; Paul A. Volberding, MD

Table 3. Recommended Initial Antiretroviral Therapy Regimens[a]

Regimen	Rating
Dolutegravir/abacavir/lamivudine	AIa
Dolutegravir plus tenofovir alafenamide/emtricitabine[b]	AIa
Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine[b]	AIa
Raltegravir plus tenofovir alafenamide/emtricitabine[b]	AIII

The life cycle of HIV (6 steps):

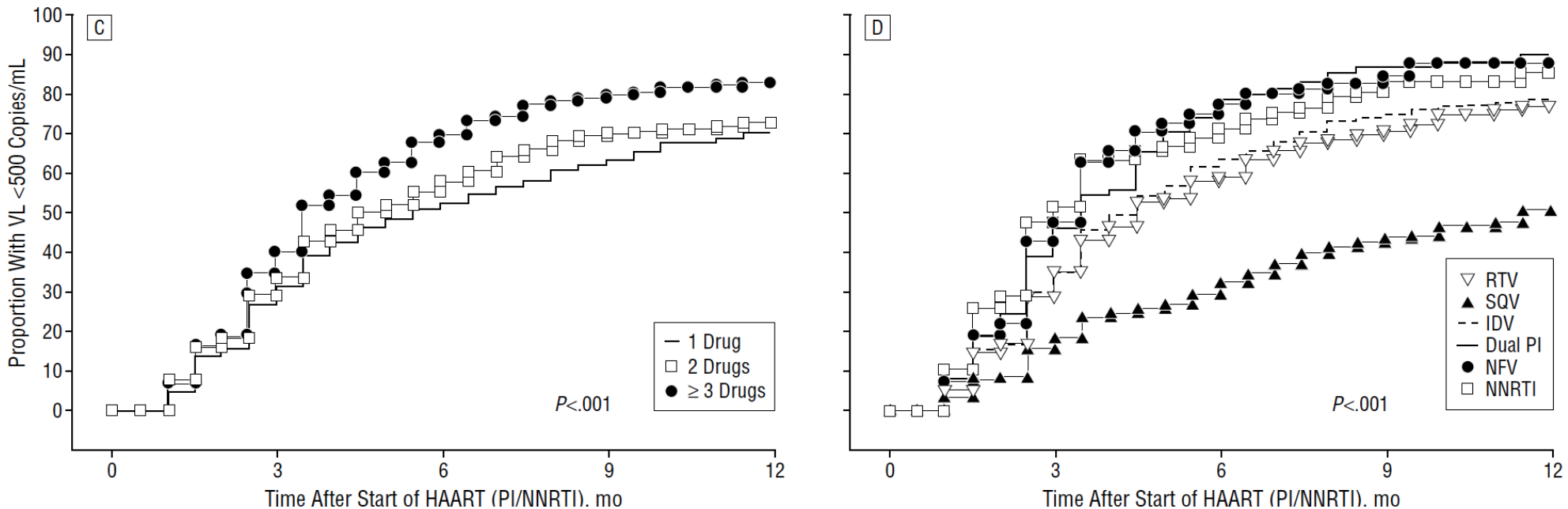
(1) entry (binding and fusion)
(2) reverse transcription
(3) Integration
(4) replication (transcription and translation)
(5) Assembly
(6) budding and maturation.

ORIGINAL INVESTIGATION

Predictors of Virological Success and Ensuing Failure in HIV-Positive Patients Starting Highly Active Antiretroviral Therapy in Europe

Results From the EuroSIDA Study

Roger Paredes, MD; Amanda Mocroft, PhD; Ole Kirk, MD; Adriano Lazzarin, MD; Simon E. Barton, MD; Jan van Lunzen, MD; Terese L. Katzenstein, PhD; Francisco Antunes, PhD; Jens D. Lundgren, MD, DMSc; Bonaventura Clotet, PhD; for the EuroSIDA Study Group



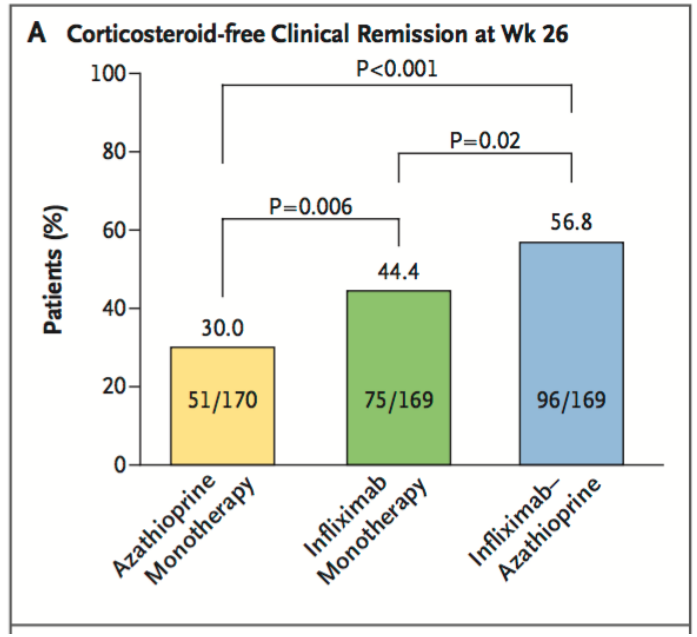
Arch Intern Med. 2000;160(8):1123-1132

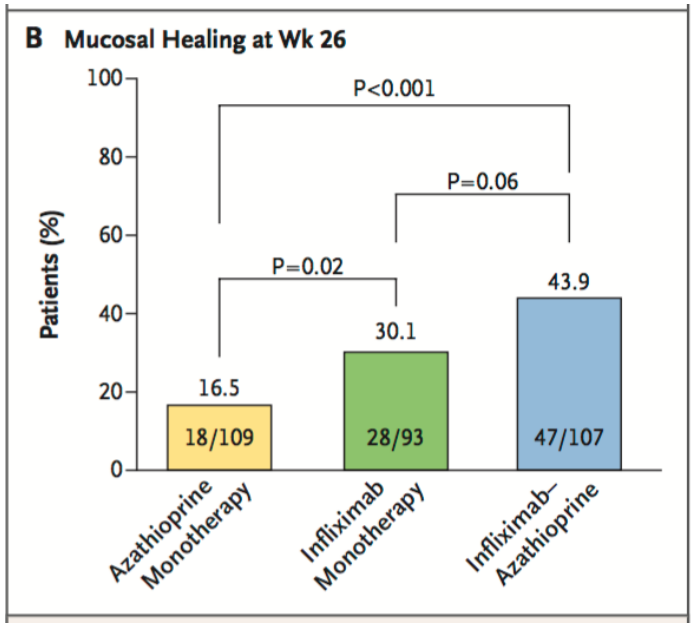
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease

Jean Frédéric Colombel, M.D., William J. Sandborn, M.D., Walter Reinisch, M.D., Gerassimos J. Mantzaris, M.D., Ph.D., Asher Kornbluth, M.D., Daniel Rachmilewitz, M.D., Simon Lichtiger, M.D., Geert D'Haens, M.D., Ph.D., Robert H. Diamond, M.D., Delma L. Broussard, M.D., Kezhen L. Tang, Ph.D., C. Janneke van der Woude, M.D., Ph.D., and Paul Rutgeerts, M.D., Ph.D., for the SONIC Study Group*





CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Combination Therapy Versus Monotherapy in Reducing Blood Pressure: Meta-analysis on 11,000 Participants from 42 Trials

David S. Wald, MD, Malcolm Law, FRCP, Joan K. Morris, PhD, Jonathan P. Bestwick, MSc, Nicholas J. Wald, FRS

Wolfson Institute of Preventive Medicine at Barts and The London Queen Mary's School of Medicine and Dentistry, Charterhouse Square, London, United Kingdom.

CLINICAL SIGNIFICANCE

- Monotherapy is the standard initial treatment for reducing blood pressure, with stepwise increases in dose if the desired decrease in blood pressure is not achieved.
- Combining drugs from different classes is approximately 5 times more effective in lowering blood pressure than increasing the dose of 1 drug.
- Combination therapy is the preferred initial strategy in the treatment of high blood pressure.

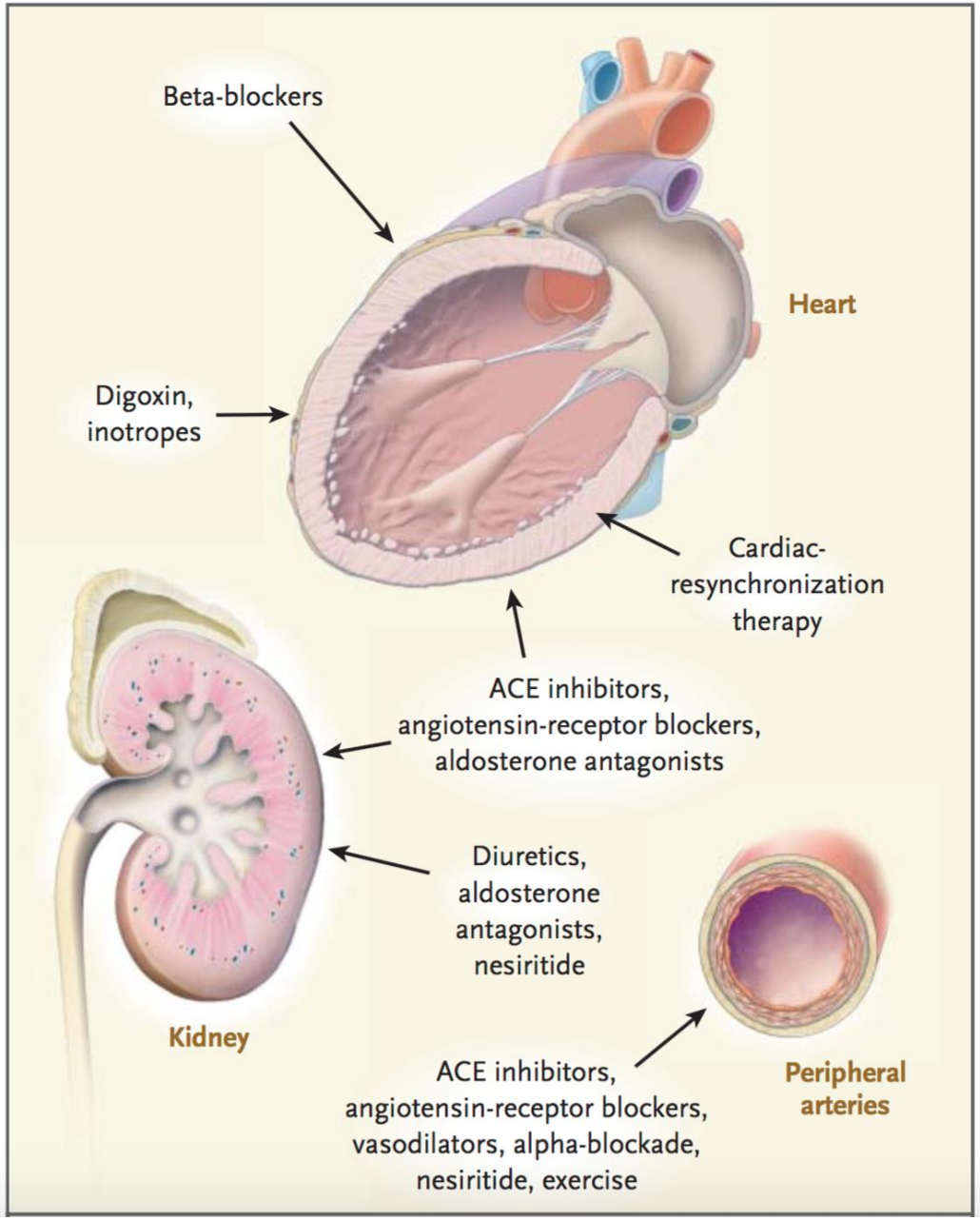
The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

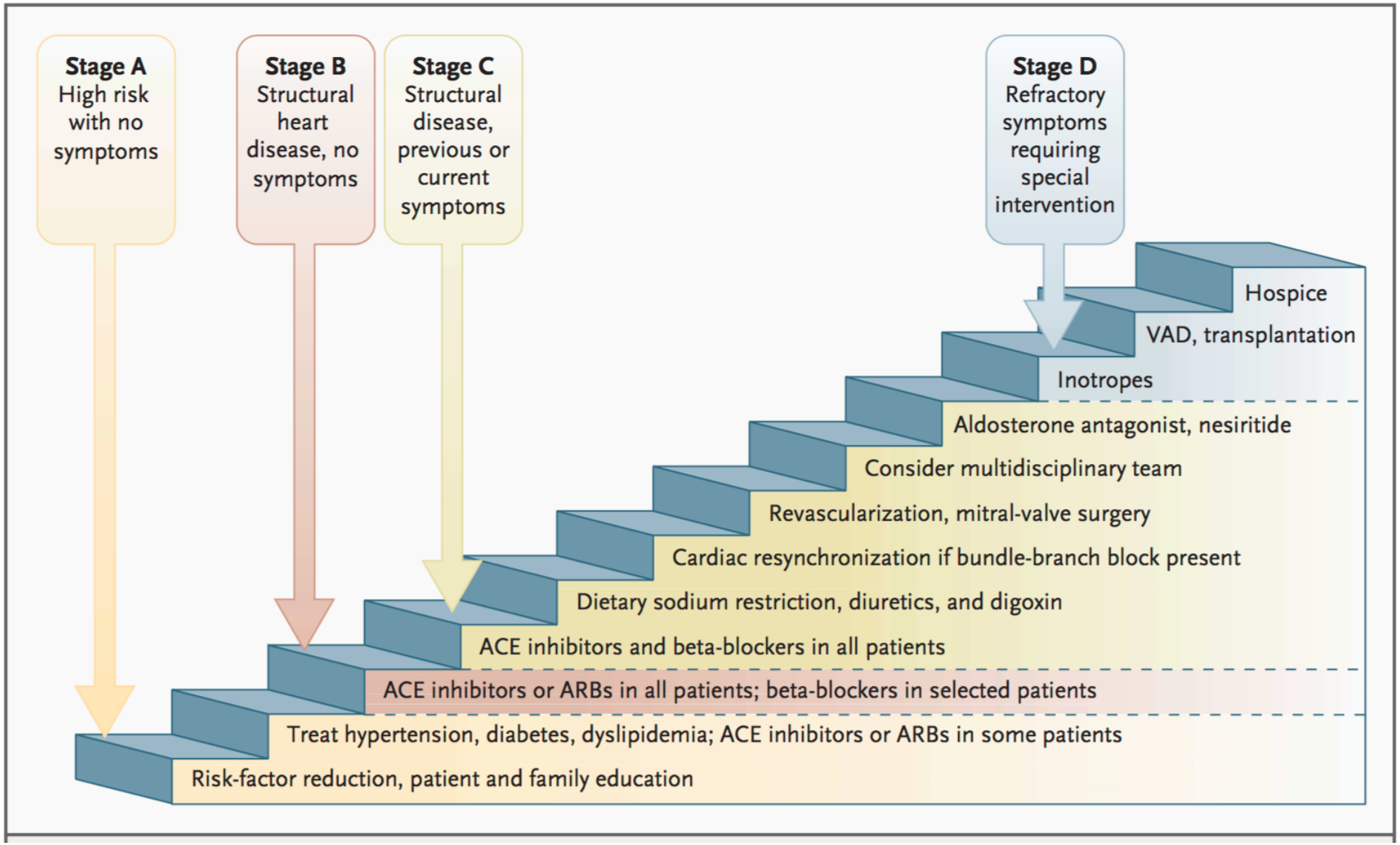
MEDICAL PROGRESS

Heart Failure

Mariell Jessup, M.D., and Susan Brozena, M.D.



N Engl J Med 2003;348:2007-18



N Engl J Med 2003;348:2007-18

But this is only the beginning!

Treatment of cancer may represent the field where combination strategies surely play a crucial role

The Effectiveness of Combinations of Antileukemic Agents in Inducing and Maintaining Remission in Children with Acute Leukemia

By Emil Frei, III,[1a] Myron Karon,[1] Robert H. Levin,[10] Emil J. Freireich,[1a] Robert J. Taylor,[1] Juliet Hananian,[2] Oleg Selawry,[2] James F. Holland,[2] Barth Hoogstraten,[3] Irving J. Wolman,[4] Esshagh Abir,[4] Arthur Sawitsky,[5] Stanley Lee,[5] Stephan D. Mills,[6] E. Omer Burgert, Jr.,[6] Charles L. Spurr,[7] Richard B. Patterson,[7] Franklin G. Ebaugh,[8] G. Watson James, III, and John H. Moon[9]

THE BROAD objective of the present study was to determine whether combinations of chemotherapeutic agents could improve the frequency and duration of complette remission in children with acute lymphocytic leukemia. The complete remission induction rate for the more effective remis-

VOLUME 32 · NUMBER 28 · OCTOBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ASCO 50TH ANNIVERSARY

Testicular Cancer: A Reflection on 50 Years of Discovery

Nasser Hanna and Lawrence H. Einhorn, *Indiana University School of Medicine, Indianapolis, IN*

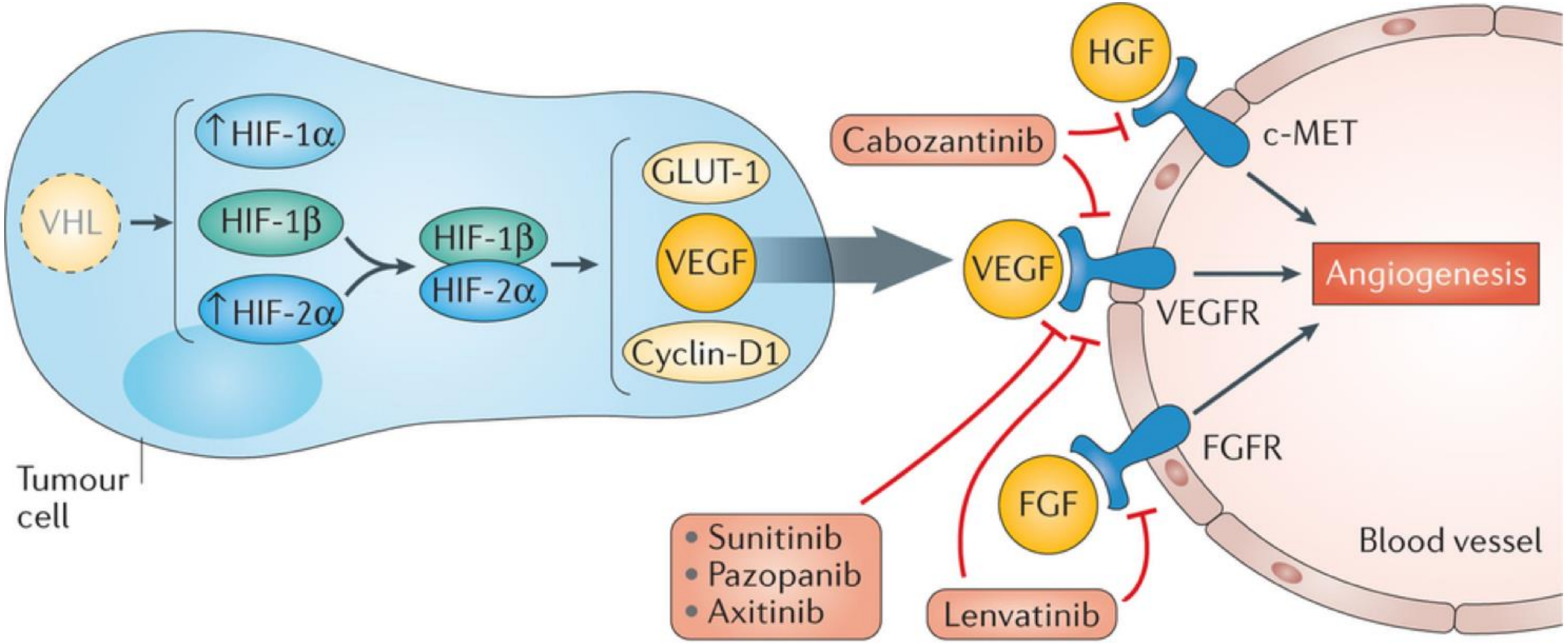
Testicular Cancer: cure in ~ 95% of all patients

Table 3. Landmark Achievements in Testicular Cancer

Year	Event	Significance	Ref
1937	hCG first reported in the urine of patients with testicular cancer	Improved ability to diagnose, stage, assess response, detect relapse, estimate prognosis	3
1940s	Seminomas are radiation-sensitive	95% cure rate for stage I or II seminoma prior to era of cisplatin-based chemotherapy	6
1960	Actinomycin-D based chemotherapy tested in advanced testicular cancer	Durable complete responses and some cures reported for the first time in patients with metastatic testicular cancer	40
1965	Discovery of cisplatin	Revolutionized the treatment of testicular cancer, achieving cures in > 80% of patients with metastatic disease	47
1974	PVB regimen first tested	Increased cure rate by 1 log compared with contemporaneous chemotherapy	50
1980s	Nerve-sparing RPLND	Preserves ejaculatory function in > 90% of patients undergoing this procedure	18-24
1981	PVB with or without maintenance vinblastine	Eliminated need for maintenance therapy	53
1985	EP regimen	Cures possible in the second-line setting	57
1987	PVB versus BEP	BEP supplants PVB as standard therapy	61
1989	BEP × 3 versus 4 cycles in good risk	Eliminates fourth cycle of BEP in good risk patients	63
1997	IGCCC prognostic groups	Allows for more accurate study of treatment outcomes by risk groups	66
2007	Largest series to date reported on HDCT in relapsed disease	Cures achieved in > third-line, poor-risk groups, including platinum-refractory patients	89

Abbreviations: BEP, bleomycin, etoposide, and cisplatin; EP, etoposide and cisplatin; hCG, human chorionic gonadotropin ; HDCT, high-dose chemotherapy; IGCCC, International Germ Cell Cancer Collaborative Group; PVB, cisplatin, vinblastine, and bleomycin; RPLND, retroperitoneal lymph-node dissection.

Clear Cell RCC: VHL Gene Mutation



Nature Reviews | Nephrology

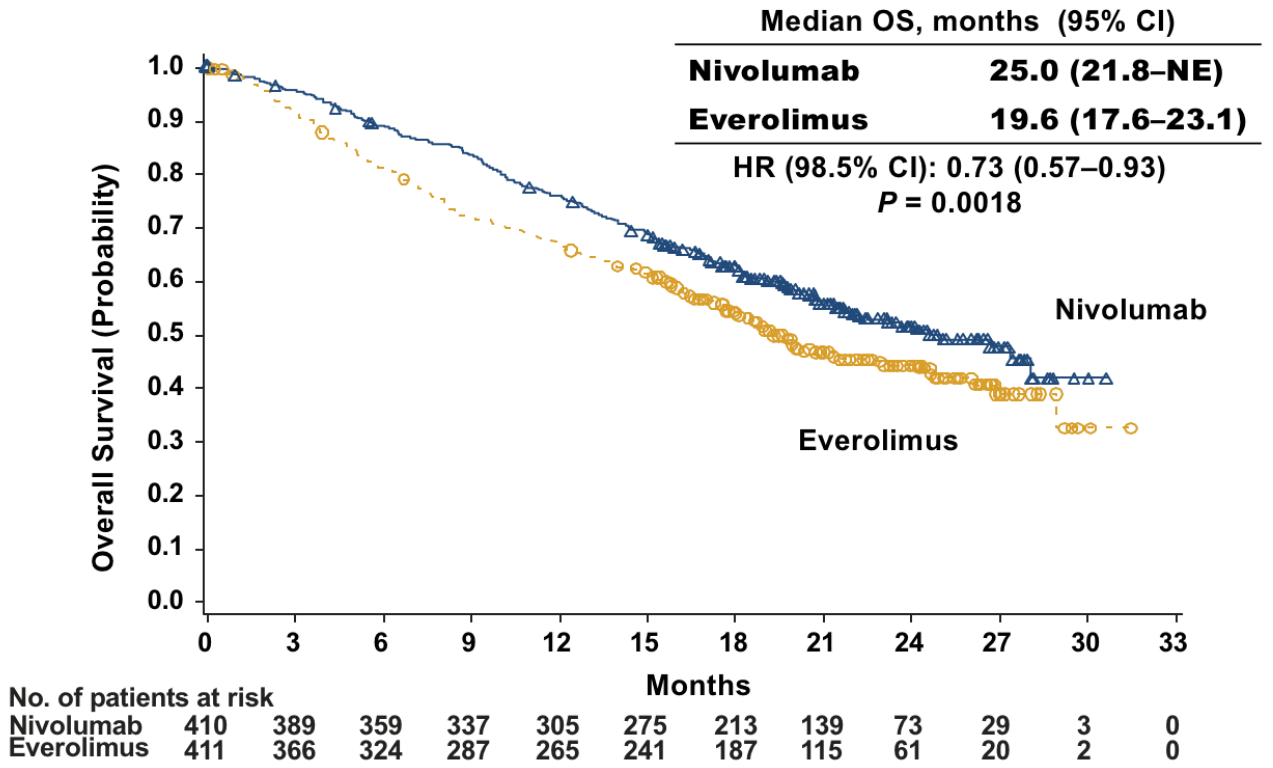
The NEW ENGLAND JOURNAL of MEDICINE

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*

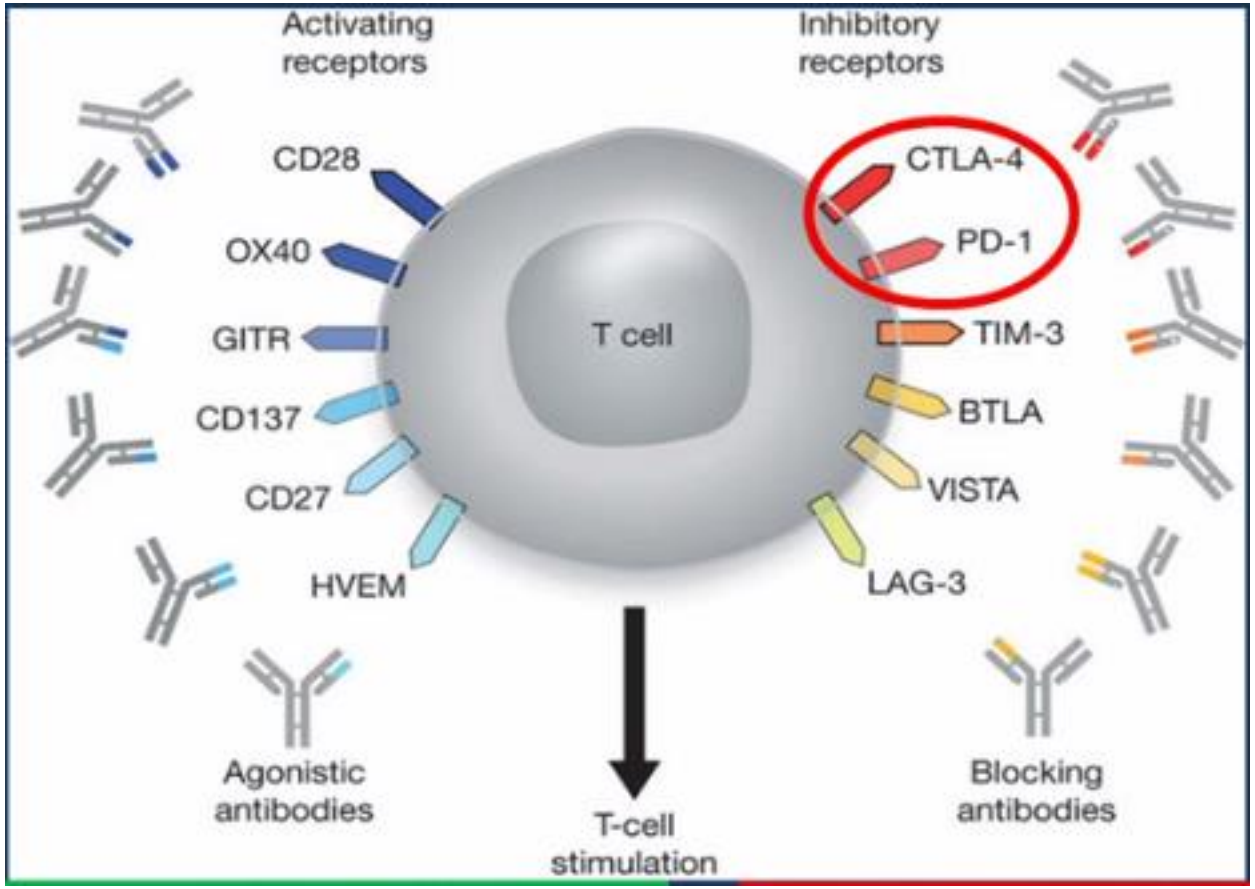
Overall survival



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

N. Engl J Med, Sep 2015

Ways to keeping the T-Cells “Active”

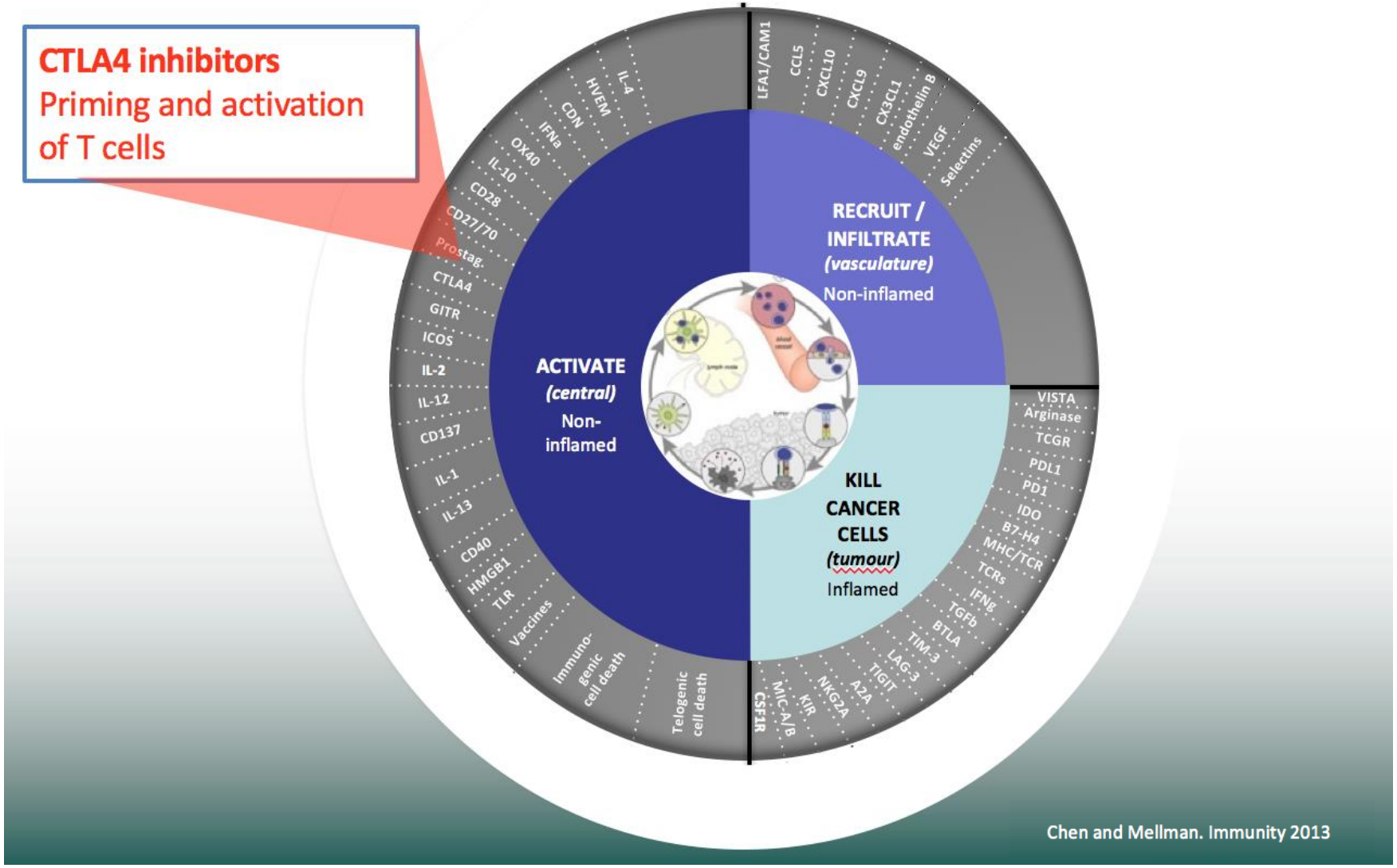


Turning up The Activating

Blocking the Inhibiting

Mellmann et al. Nature, 2011

How can we further enhance responses?



Nivolumab + Ipilimumab phase I (Checkmate 16)

Response	N3I1 (n=47)		N1I3 (n=47)	
			y	Treatment-Naïve (n=21)
Confirmed ORR, % 95% CI			4	42.9 21.8–66.0
BOR, %				
Complete respo				0
Partial response				42.9
Stable disease				28.6
Disease progression	27.3	8.0	11.5	23.8
Unable to determine	0	4.0	7.7	4.8

- ORR: 40%
- Ongoing responses: 42%
- Median PFS: 7.7 months
- 2-year OS rate: 67%

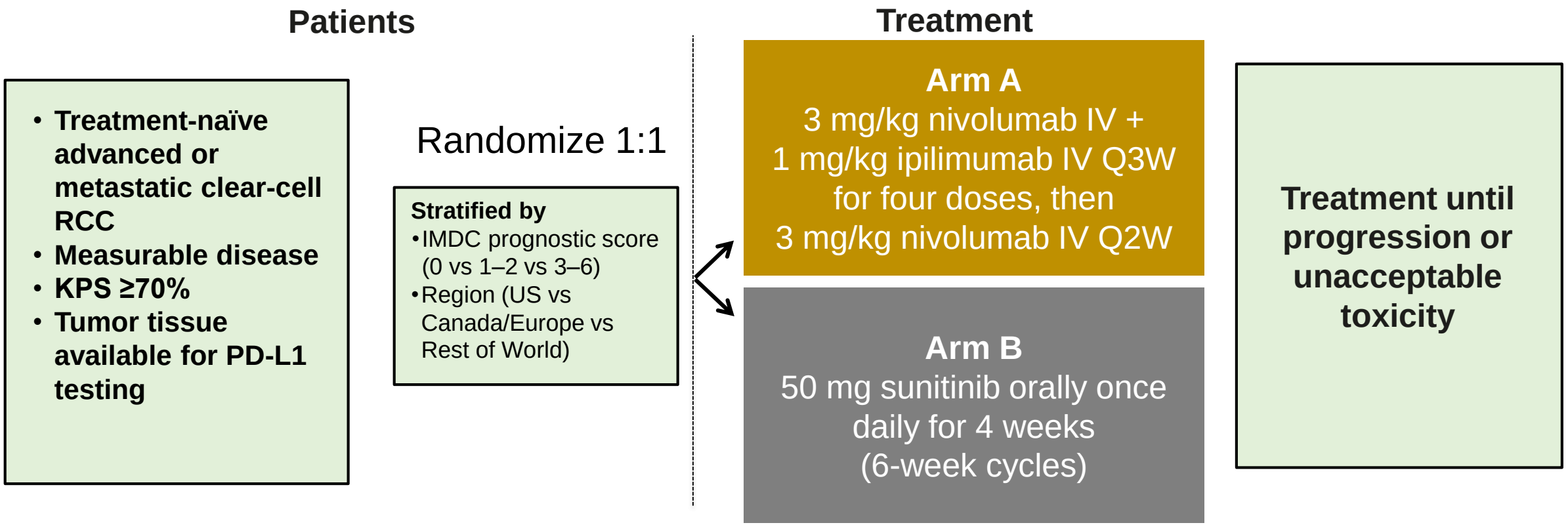
Hammers HJ et al. *J Clin Oncol* 2017.

CheckMate 214: Efficacy and Safety of Nivolumab Plus Ipilimumab vs Sunitinib for Treatment-Naïve Advanced or Metastatic Renal Cell Carcinoma, Including IMDC Risk and PD-L1 Expression Subgroups

Bernard Escudier,[1] Nizar M. Tannir,[2] David F. McDermott,[3] Osvaldo Arén Frontera,[4] Bohuslav Melichar,[5] Elizabeth R. Plimack,[6] Philippe Barthelemy,[7] Saby George,[8] Victoria Neiman,[9] Camillo Porta,[10] Toni K. Choueiri,[11] Thomas Powles,[12] Frede Donskov,[13] Pamela Salman,[14] Christian K. Kollmannsberger,[15] Brian Rini,[16] Sabeen Mekan,[17] M. Brent McHenry,[17] Hans J. Hammers,[18] Robert J. Motzer[19]

MADRID 2017 ESMO congress

CheckMate 214: Study design



IMDC, International Metastatic RCC Database Consortium; KPS, Karnofsky performance status; Q2W, every 2 weeks; Q3W, every 3 weeks

Co-primary endpoints

- **In IMDC intermediate- and poor-risk patients**
  - ORR (per independent radiology review committee, IRRC)
  - PFS (per IRRC)
  - OS
- **Statistical analyses**
  - Overall alpha is 0.05, split among the three co-primary endpoints
  - 0.001 for ORR, 0.009 for PFS, and 0.04 for OS
  - PFS analysis had 80% power and OS analysis had 90% power to detect a statistically significant difference between treatment arms

Secondary and exploratory endpoints

- **Secondary endpoints (in intention-to-treat [ITT] patients)**
  - ORR
  - PFS
  - OS
  - Adverse event incidence rate (in all treated patients)
- **Secondary efficacy endpoints** were subject to hierarchical testing, first testing in intermediate/poor-risk patients followed by testing in ITT patients, if significant
- **Exploratory endpoints**
  - ORR, PFS, and OS in favorable-risk patients
  - Outcomes by tumor PD-L1 expression level
  - Health-related quality of life based on NCCN Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19)

Escudier B. ESMO 2017

Baseline characteristics

Characteristic	IMDC intermediate/poor risk		Intention to treat	
	NIVO + IPI N = 425	SUN N = 422	NIVO + IPI N = 550	SUN N = 546
Median age, years	62	61	61	61
Male, %	74	71	75	72
IMDC prognostic score (IVRS), %				
Favorable (0)	0	0	22	20
Intermediate (1–2)	79	79	59	62
Poor (3–6)	21	21	19	18
Region (IVRS), %				
USA	26	26	28	28
Canada/Europe	35	35	37	36
Rest of the world	39	39	35	36
Quantifiable tumor PD-L1 expression, %	n = 384	n = 392	n = 499	n = 503
<1%	74	71	77	75
≥1%	26	29	23	25

Escudier B. ESMO 2017

MADRID 2017 ESMO congress

Baseline characteristics in favorable-risk patients were similar, except tumor PD-L1 expression was lower than the intermediate/poor-risk patients and ITT population

Baseline disease characteristics

Characteristic	IMDC intermediate/poor risk		Intention to treat	
	NIVO + IPI N = 425	SUN N = 422	NIVO + IPI N = 550	SUN N = 546
No. of sites with ≥1 target/non-target lesion				
1	21	20	22	22
≥2	79	80	78	78
Site of metastasis, %				
Lung	69	70	69	68
Lymph node	45	51	45	49
Liver	31	21	18	20
Bone	20	21	18	19

Escudier B. ESMO 2017

Co-primary endpoint
ORR: IMDC intermediate/poor risk

Outcome	N = 847	
	NIVO + IPI N = 425	SUN N = 422
Confirmed ORR,[a] % (95% CI)	**42 (37–47)**	**27 (22–31)**
	P < 0.0001	
Confirmed BOR,[a] %		
Complete response	9[b]	1[b]
Partial response	32	25
Stable disease	31	45
Progressive disease	20	17
Unable to determine/not reported	8	12
Duration of response, median (95% CI), months	Not reached (21.8–NE)	18.2 (14.8–NE)
Patients with ongoing response, %	72	63

- Median follow-up was 25.2 months

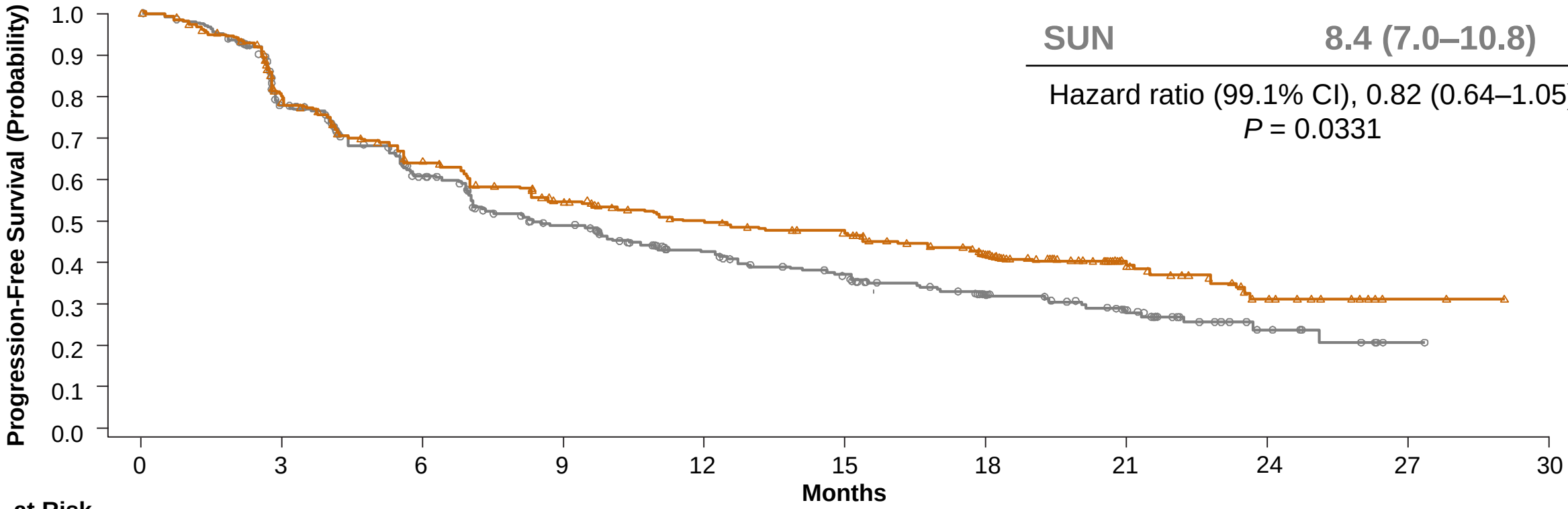
[a]IRRC-assessed ORR and BOR by RECIST v1.1; [b]*P* < 0.0001

Escudier B. ESMO 2017

Co-primary endpoint
PFS per IRRC: IMDC intermediate/poor risk

Median PFS, months (95% CI)	
NIVO + IPI	11.6 (8.7–15.5)
SUN	8.4 (7.0–10.8)

Hazard ratio (99.1% CI), 0.82 (0.64–1.05)
P = 0.0331



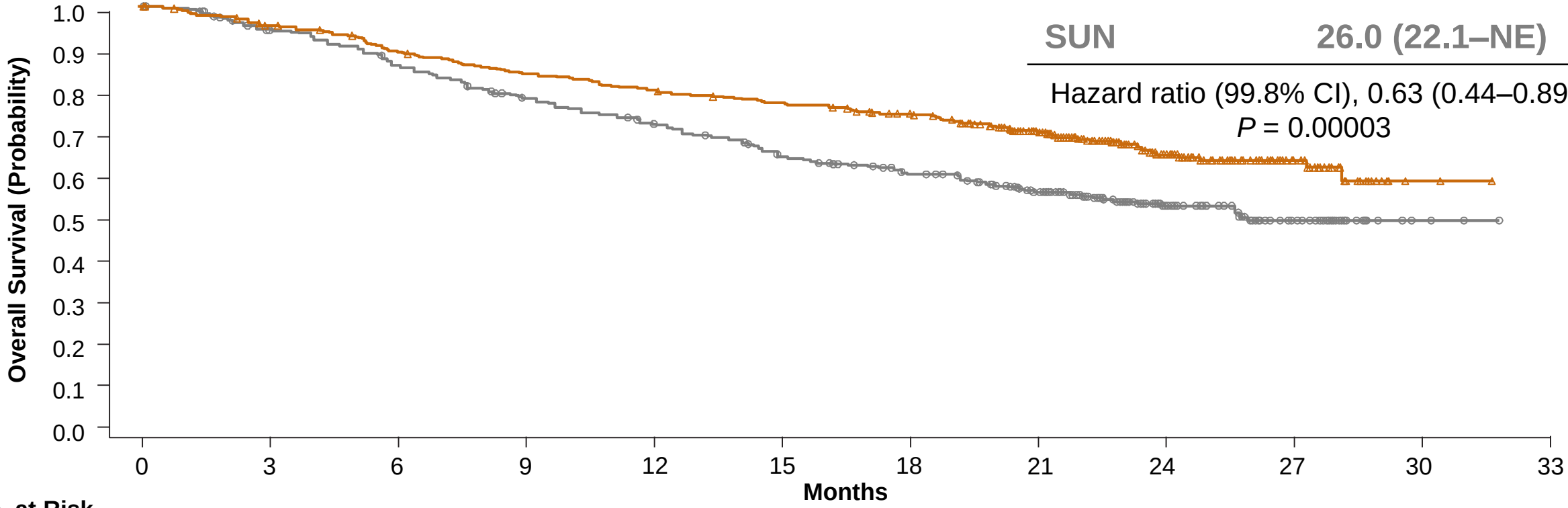
No. at Risk											
NIVO + IPI	425	304	233	187	163	149	118	46	17	3	0
SUN	422	282	191	139	107	86	57	33	11	1	0

Escudier B. ESMO 2017

Co-primary endpoint
OS: IMDC intermediate/poor risk

Median OS, months (95% CI)	
NIVO + IPI	NR (28.2–NE)
SUN	26.0 (22.1–NE)

Hazard ratio (99.8% CI), 0.63 (0.44–0.89)
P = 0.00003



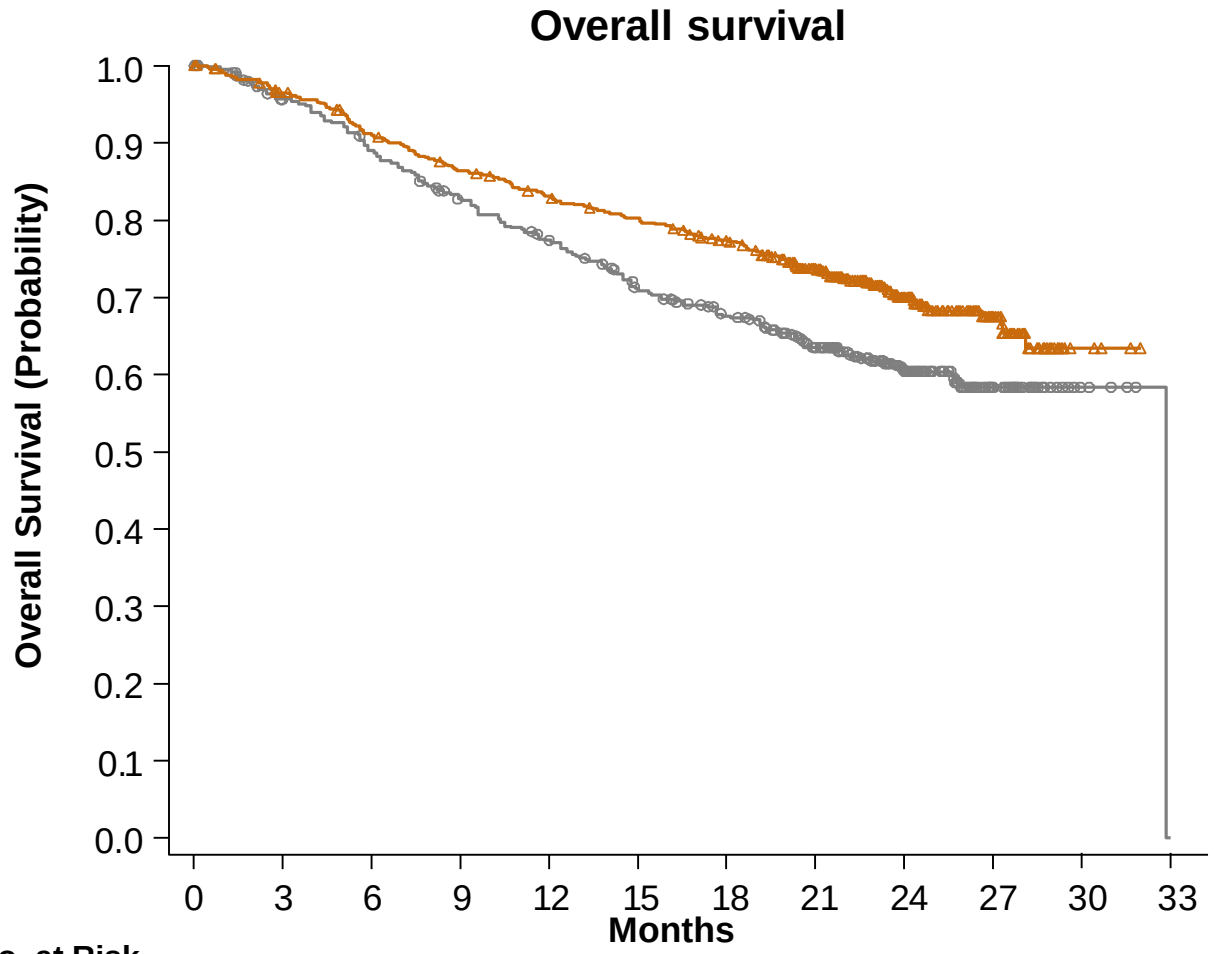
No. at Risk												
NIVO + IPI	425	399	372	348	332	318	300	241	119	44	2	0
SUN	422	387	352	315	288	253	225	179	89	34	3	0

Escudier B. ESMO 2017

Secondary endpoint
ORR, PFS, and OS: Intention to treat

Outcome	N = 1,096[a]	
	NIVO + IPI N = 550	**SUN N = 546**
Confirmed ORR,[b] % (95% CI)	**39 (35–43)**	**32 (28–36)**
	P = 0.0191	
PFS,[c] median (95% CI), months	12.4 (9.9–16.5)	12.3 (9.8–15.2)
	HR (99.1% CI) 0.98 (0.79–1.23) *P* = 0.8498	
OS, median (95% CI), months	NR (NE–NE)	32.9 (NE–NE)
	HR (99.8% CI) 0.68 (0.49–0.95) *P* = 0.00028	

[a]23% of patients in the NIVO + IPI arm and 25% of patients in the SUN arm had tumor PD-L1 expression ≥1%
[b]IRRC-assessed by RECIST v1.1
[c]IRRC-assessed



Exploratory endpoint
ORR and PFS: IMDC favorable risk

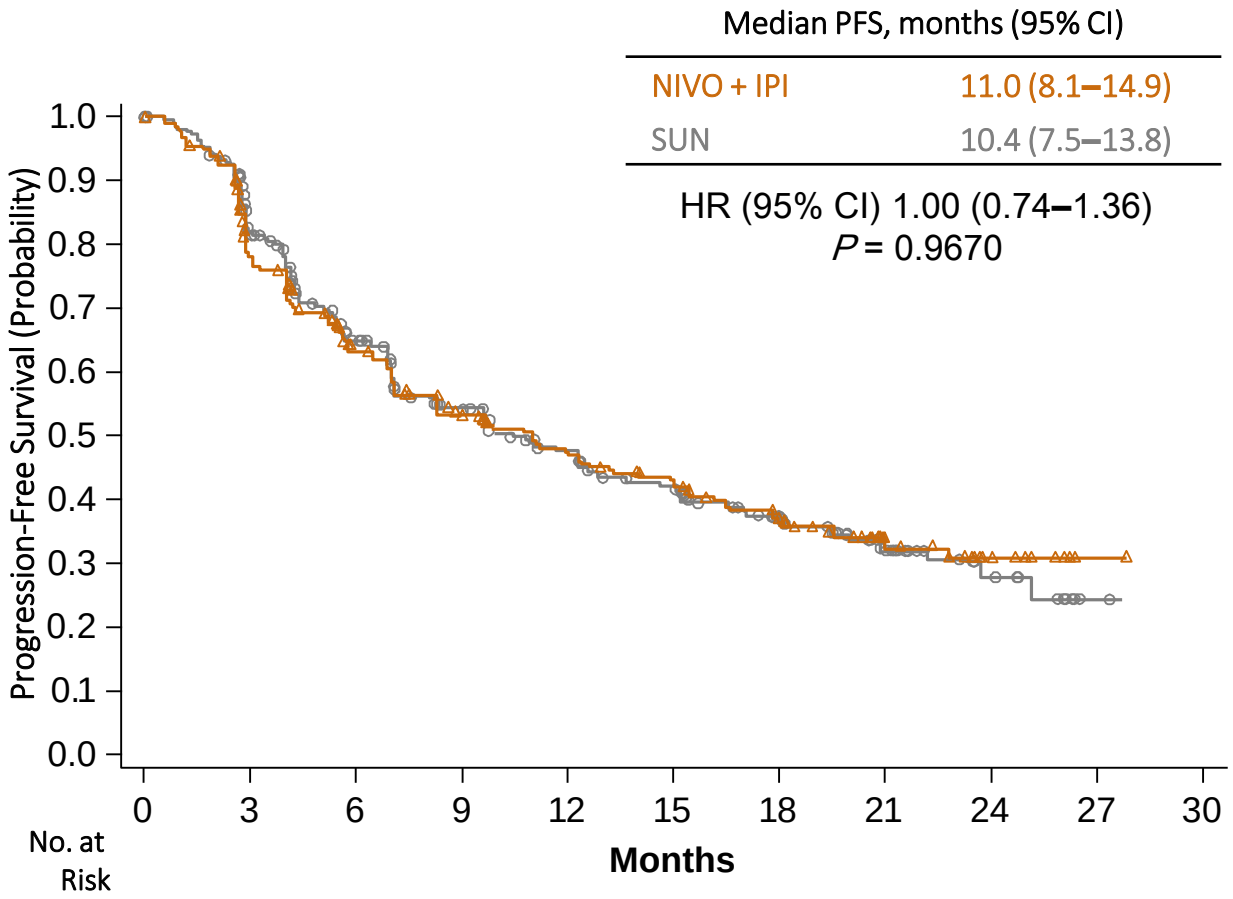
Outcome	N = 249[a]	
	NIVO + IPI N = 125	SUN N = 124
Confirmed ORR,[b] % (95% CI)	**29 (21–38)**	**52 (43–61)**
	P = 0.0002	
PFS,[c] median (95% CI), months	15.3 (9.7–20.3)	25.1 (20.9–NE)
	HR (99.1% CI) 2.18 (1.29–3.68) *P* < 0.0001	

[a]11% of patients in both arms had tumor PD-L1 expression ≥1%
[b]IRRC-assessed by RECIST v1.1
[c]IRRC-assessed

Exploratory endpoint

PFS by PD-L1 expression: IMDC intermediate/poor risk

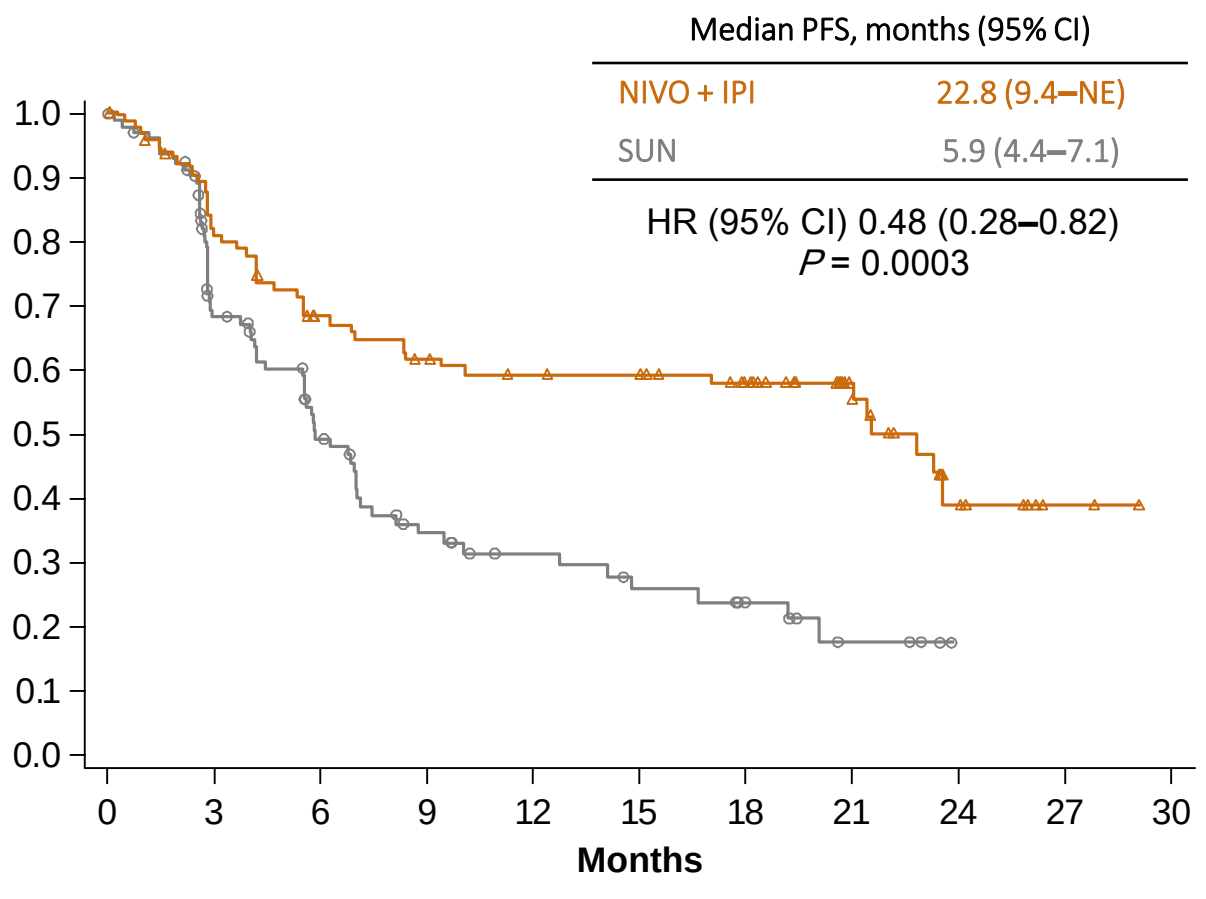
PD-L1 <1% (n = 562)



No. at Risk

NIVO	284	202	155	119	102	90	70	23	9	1	0
SUN	278	200	138	105	83	67	43	25	11	1	

PD-L1 ≥1% (n = 214)

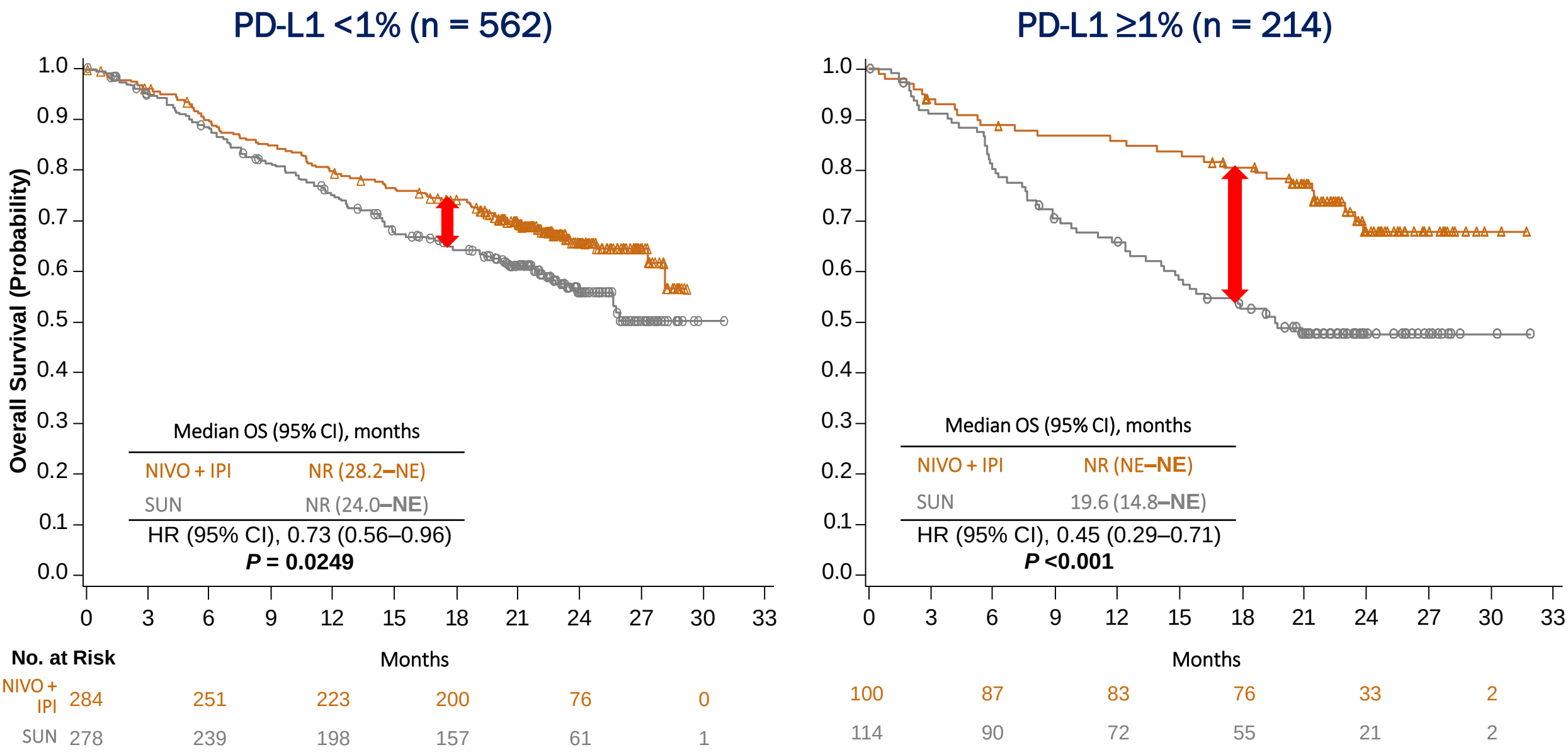


NIVO	100	77	61	54	50	48	41	21	8	2	0
SUN	114	63	40	24	17	13	9	4	0	0	3

OS by tumor PD-L1 expression:

IMDC intermediate/poor risk

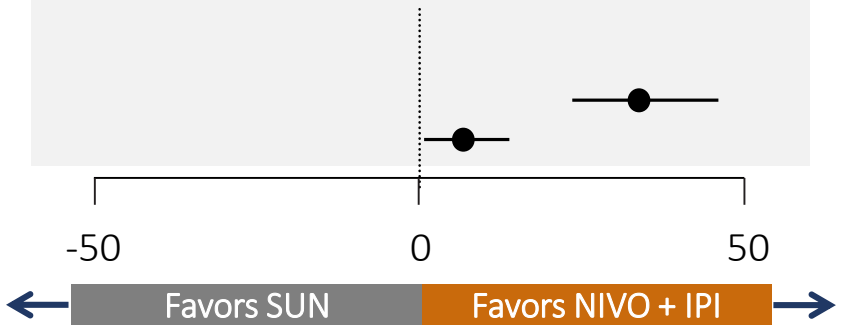
Motzer et al SITC 2017



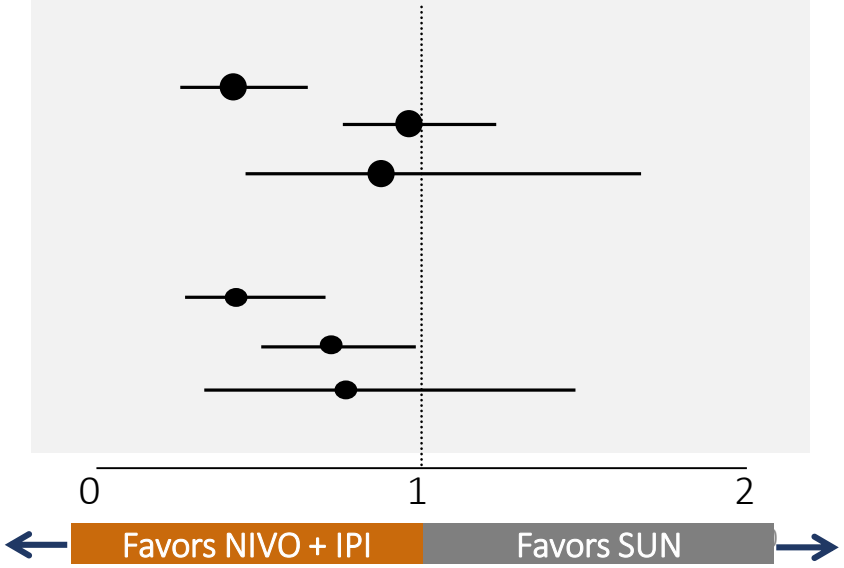
Efficacy by baseline PD-L1 expression: IMDC intermediate/poor risk

Motzer et al SITC 2017

Subgroup	NIVO + IPI No. of patients	SUN No. of patients	ORR difference (95% CI)	*P* value
ORR				
Baseline PD-L1 expression				
≥1%	100	114		< 0.0001
<1%	284	278		0.0252



Subgroup	NIVO + IPI No. of patients	SUN No. of patients	Hazard ratio (95% CI)	*P* value
PFS				
Baseline PD-L1 expression				
≥1%	100	114		0.0003
<1%	284	278		0.9670
Not reported	41	30		NA
OS				
Baseline PD-L1 expression				
≥1%	100	114		<0.001
<1%	284	278		0.0249
Not reported	41	30		NA



Treatment-related adverse events: All treated patients

	NIVO + IPI N = 547		SUN N = 535	
Event, %	Any grade	Grade 3–5	Any grade	Grade 3–5[a]
Treatment-related adverse events in ≥25% of patients	**93**	**46**	**97**	**63**
Fatigue	**37**	**4**	**49**	**9**
Pruritus	**28**	**<1**	**9**	**0**
Diarrhea	**27**	**4**	**52**	**5**
Nausea	**20**	**2**	**38**	**1**
Hypothyroidism	**16**	**<1**	**25**	**<1**
Decreased appetite	**14**	**1**	**25**	**1**
Dysgeusia	**6**	**0**	**33**	**<1**
Stomatitis	**4**	**0**	**28**	**3**
Hypertension	**2**	**<1**	**40**	**16**
Mucosal inflammation	**2**	**0**	**28**	**3**
Palmar-plantar erythrodysesthesia syndrome	**1**	**0**	**43**	**9**
Treatment-related AEs leading to discontinuation, %	**22**	**15**	**12**	**7**
Treatment-related deaths	**n = 7[b]**		**n = 4[c]**	

[a]Two patients had grade 5 cardiac arrest. [b]Pneumonitis, immune mediated bronchitis, lower GI hemorrhage, hemophagocytic syndrome, sudden death, liver toxicity, lung infection. [c]Cardiac arrest (n = 2), heart failure, multiple organ failure

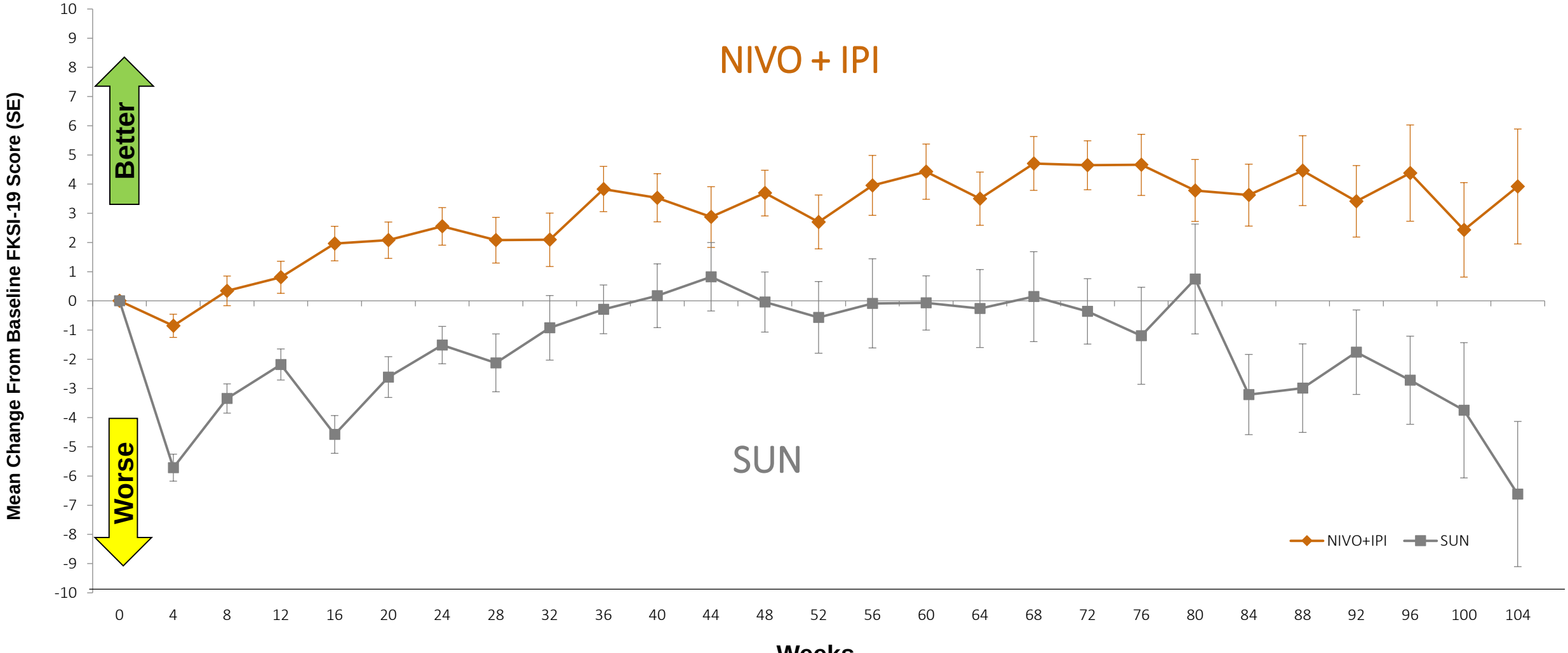
Immune-mediated adverse events: All treated patients

	NIVO + IPI N = 547	
Category, %	Any grade	Grade 3–4
Rash	**17**	**3**
Diarrhea/colitis	**10**	**5**
Hepatitis	**7**	**6**
Nephritis and renal dysfunction	**5**	**2**
Pneumonitis	**4**	**2**
Hypersensitivity/infusion reaction	**1**	**0**
Hypothyroidism	**19**	**<1**
Hyperthyroidism	**12**	**<1**
Adrenal insufficiency	**8**	**3**
Hypophysitis	**5**	**3**
Thyroiditis	**3**	**<1**
Diabetes mellitus	**3**	**1**

- 60% of patients treated with NIVO + IPI required systemic corticosteroids for an adverse event
- Secondary immunosuppression with infliximab (3%) and mycophenolic acid (1%) was reported

Escudier B. ESMO 2017

Patient-reported kidney cancer symptom index: IMDC intermediate/poor risk



No. at Risk

NIVO + IPI	425	347	281	239	212	180	166	152	143	139	125	108	76	44
SUN	422	371	284	221	184	147	127	113	104	93	80	64	43	26

Summary and conclusions

- In **IMDC intermediate/poor risk treatment-naïve aRCC**, CheckMate 214 demonstrated
  - Significantly improved ORR with NIVO + IPI versus SUN
    - 9.4% complete response rate
    - Durable responses, with median duration of response not reached
  - Median PFS improvement of >3 months with NIVO + IPI versus SUN
  - Significant OS benefit with NIVO + IPI versus SUN
    - Median OS: not reached (NIVO + IPI) and 26.0 months (SUN); HR 0.63; *P* = 0.00003
- Exploratory analysis of patients with tumor PD-L1 ≥1% demonstrated a higher ORR and improved PFS with NIVO + IPI versus SUN

Summary and conclusions

- **The safety profile of NIVO + IPI was manageable** and consistent with previous studies
  - More high-grade treatment-related adverse events were observed with SUN, although more patients had treatment-related adverse events leading to treatment discontinuation with NIVO + IPI
  - Patients in the NIVO + IPI arm experienced greater symptomatic improvement versus SUN
  - Throughout the course of the study, patients in the NIVO +IPI arm reported better symptom control relative to those in the SUN arm
- These results suggest that NIVO + IPI is a potential first-line treatment option for patients with aRCC, **with intermediate or poor IMDC risk, especially in those with PD-L1 expression ≥1%**

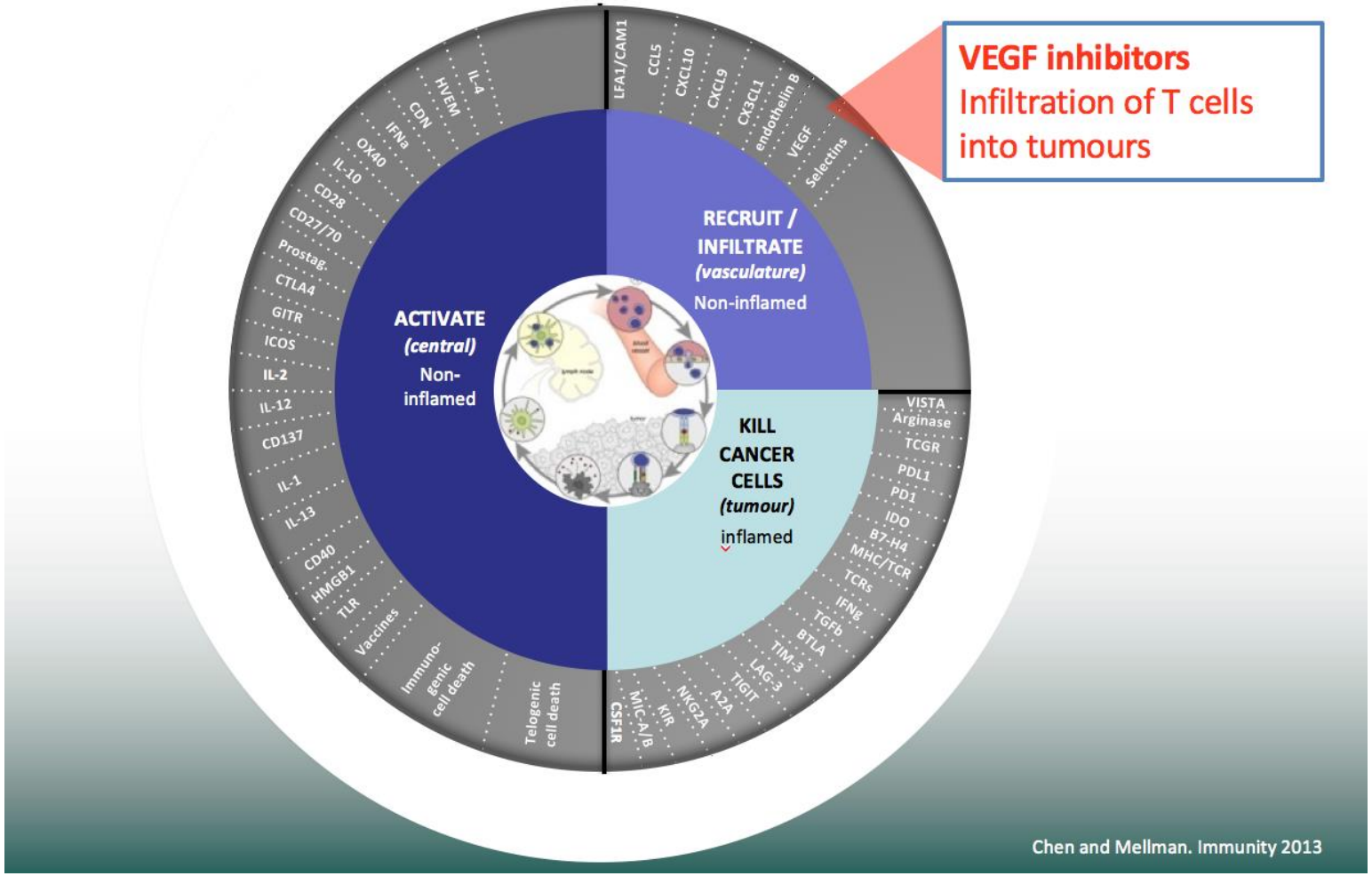
Toxicity may represent one limitation…

Fulminant type 1 diabetes caused by dual immune checkpoint blockade in metastatic renal cell carcinoma FREE

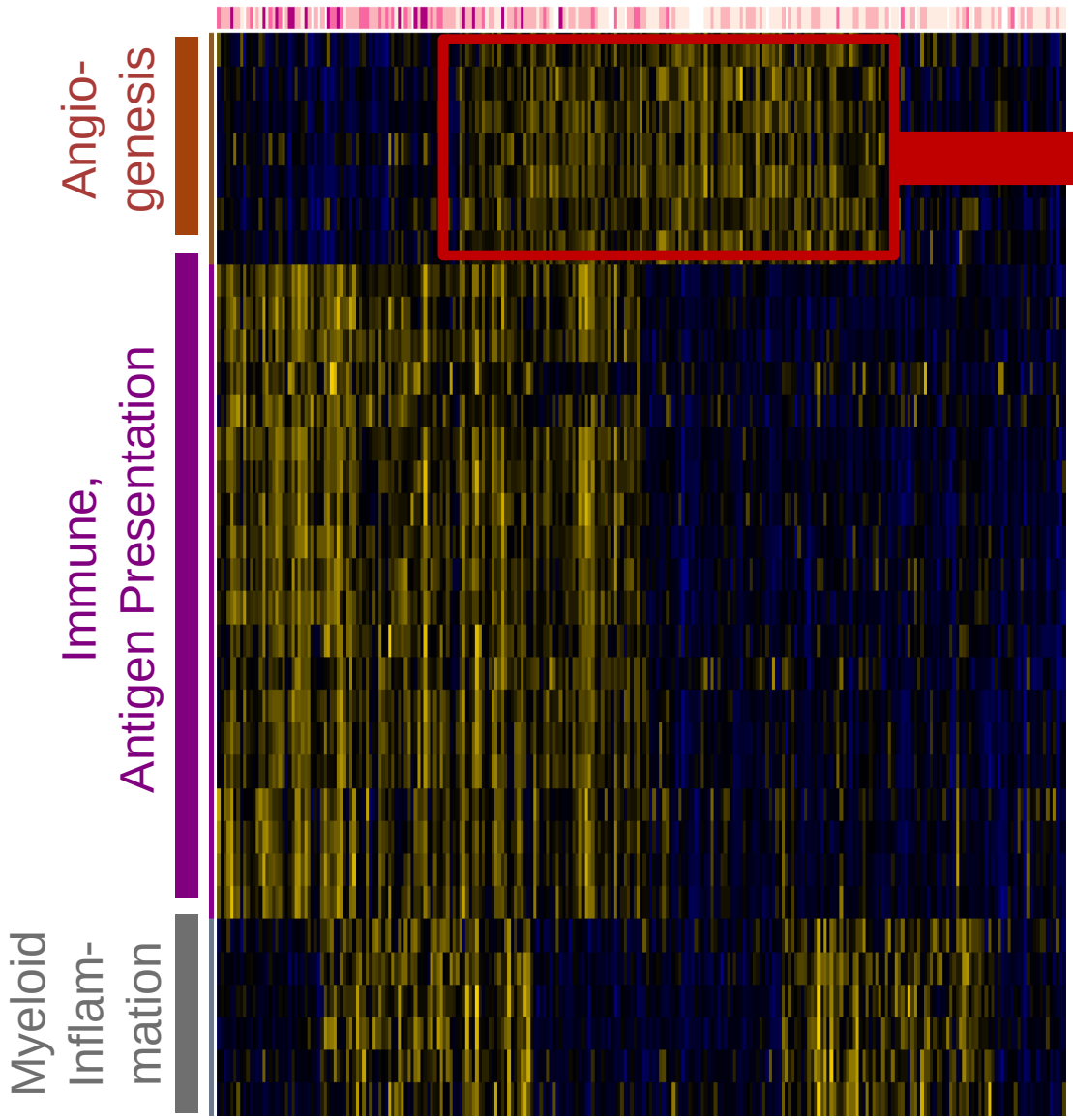
G. H. Teló, G. F. Carvalhal, C. G. S. Cauduro, V. S. Webber, C. H. Barrios, A. P. Fay ✉

Annals of Oncology, Volume 28, Issue 1, 1 January 2017, Pages 191–192,
https://doi.org/10.1093/annonc/mdw447
Published: 18 October 2016

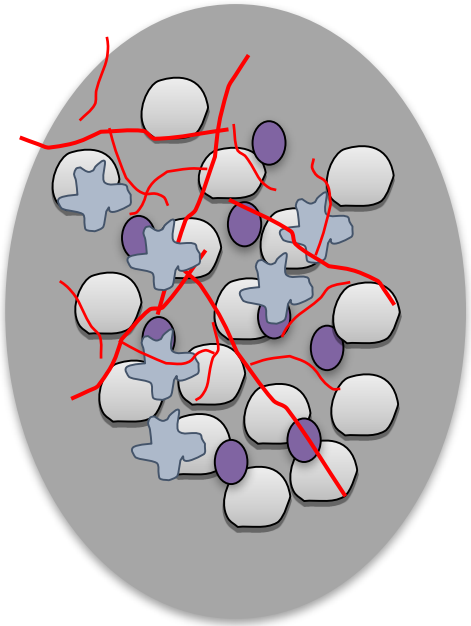
How can we further enhance responses?

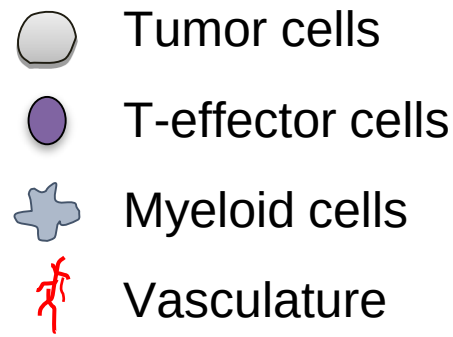


Transcriptome Map of Angiogenesis and Immune-Associated Genes in RCC Tumors



Angiogenesis^High





PD-L1 IHC

IC0IC1IC2IC3

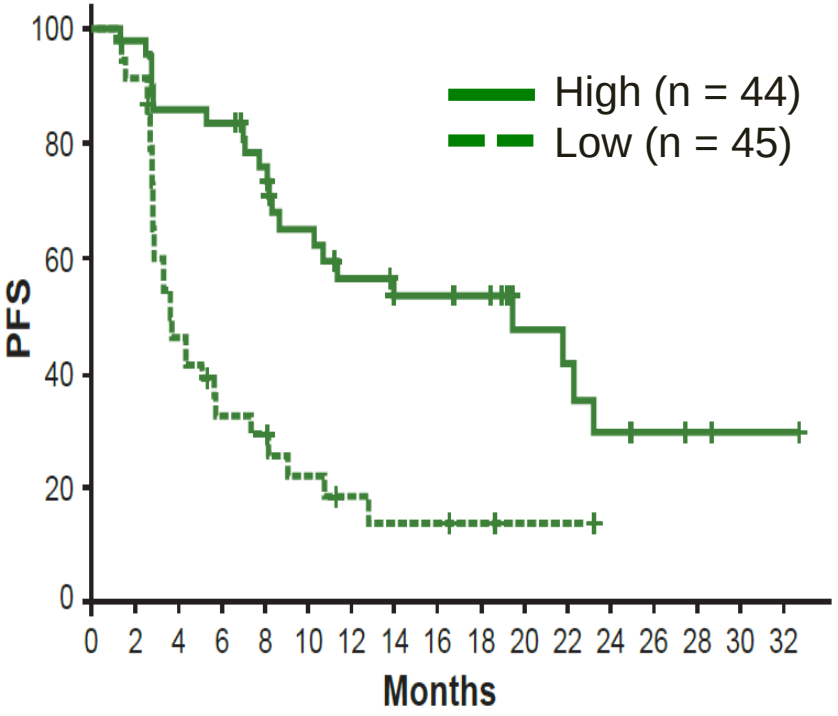
3 2 1 0 -1 -2 -3

Brauer, *Clin Cancer Res.* 2012; Herbst, *Nature* 2014; Powles, *SITC* 2015; Fehrenbacher, *Lancet* 2016.

AACR 2017

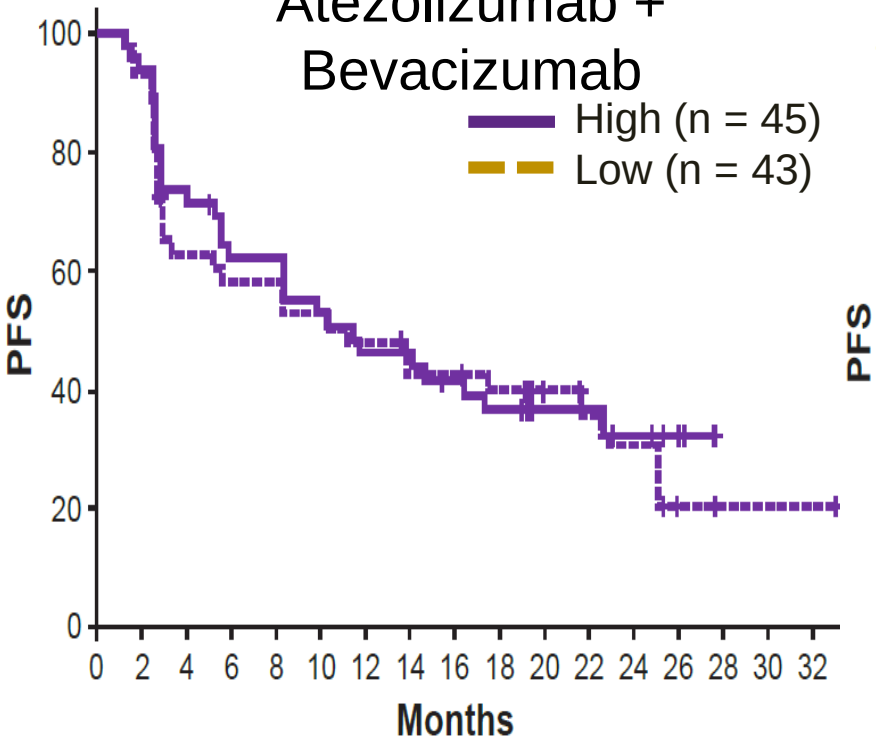
Sunitinib Demonstrated Improved PFS in Angiogenesis^{High} Subset vs Angiogenesis^{Low} Subset

Sunitinib



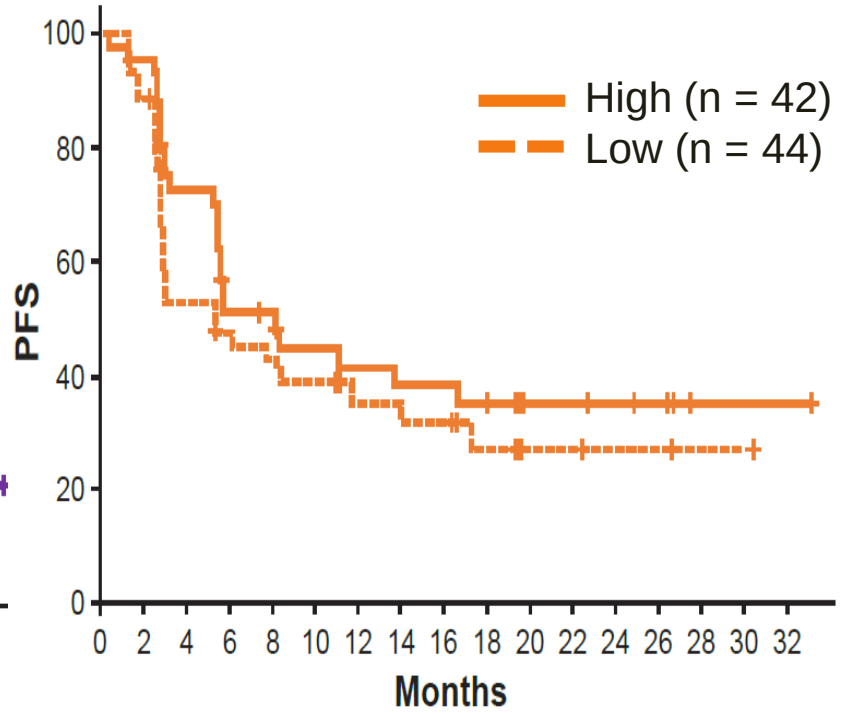
Sunitinib		
	HR	95% CI
Angiogenesis (High vs Low)	0.31	(0.18, 0.55)

Atezolizumab + Bevacizumab



Atezolizumab + Bevacizumab		
	HR	95% CI
Angiogenesis (High vs Low)	0.90	(0.54, 1.51)

Atezolizumab



Atezolizumab		
	HR	95% CI
Angiogenesis (High vs Low)	0.74	(0.42, 1.28)

- Angiogenesis gene signature: *VEGFA, KDR, ESM1, PECAM1, ANGPTL4, CD34*.
- Angiogenesis High: ≥ median expression, Angiogenesis Low: < median expression.

AACR 2017

Study Design

Key Eligibility:

- Treatment-naive advanced or metastatic RCC
- Clear cell and/or sarcomatoid histology
- KPS ≥ 70
- Tumor tissue available for PD-L1 staining

Stratification:

- •MSKCC risk score
- •Liver metastases
- •PD-L1 IC IHC status (< 1% vs ≥ 1%)a

N = 915

R 1:1

Atezolizumab 1200 mg IV q3wb + Bevacizumab 15 mg/kg IV q3wb

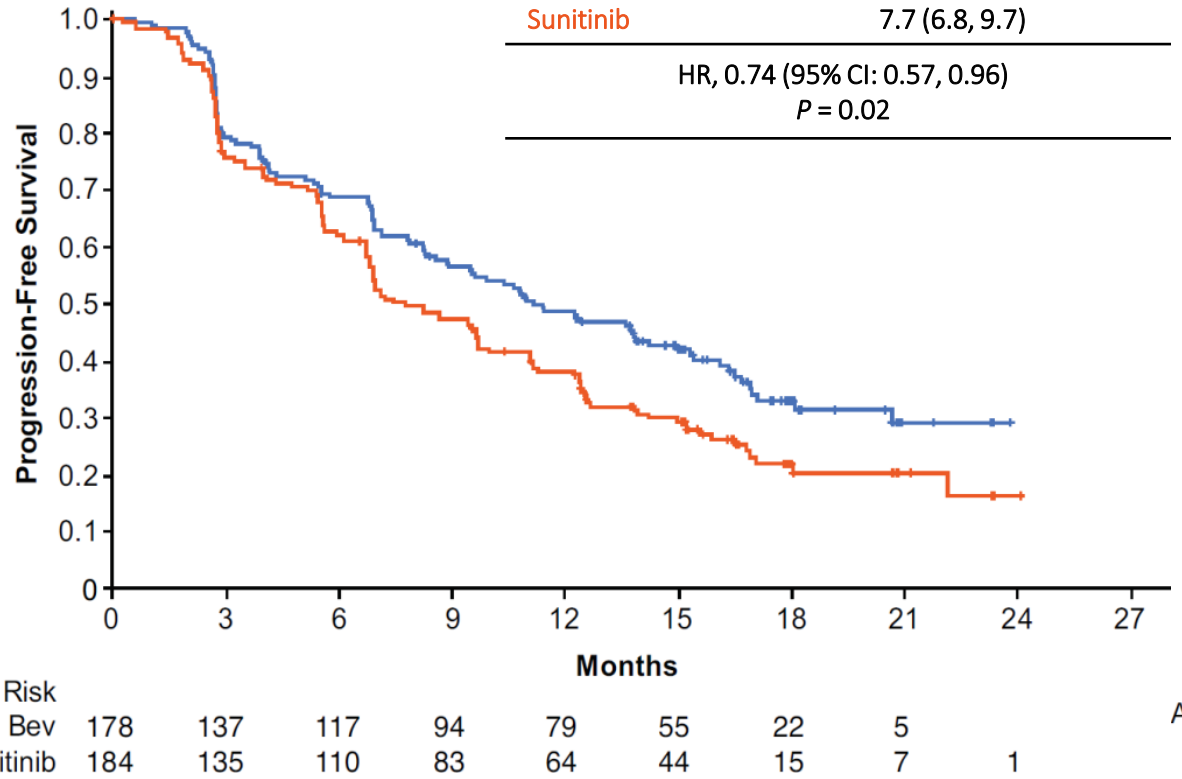
Sunitinib 50 mg/day orally (4 wk on, 2 wk off)

[a] ≥ 1% IC: 40% prevalence using SP142 IHC assay; [b] No dose reduction for atezolizumab or bevacizumab.

Co-Primary Endpoint

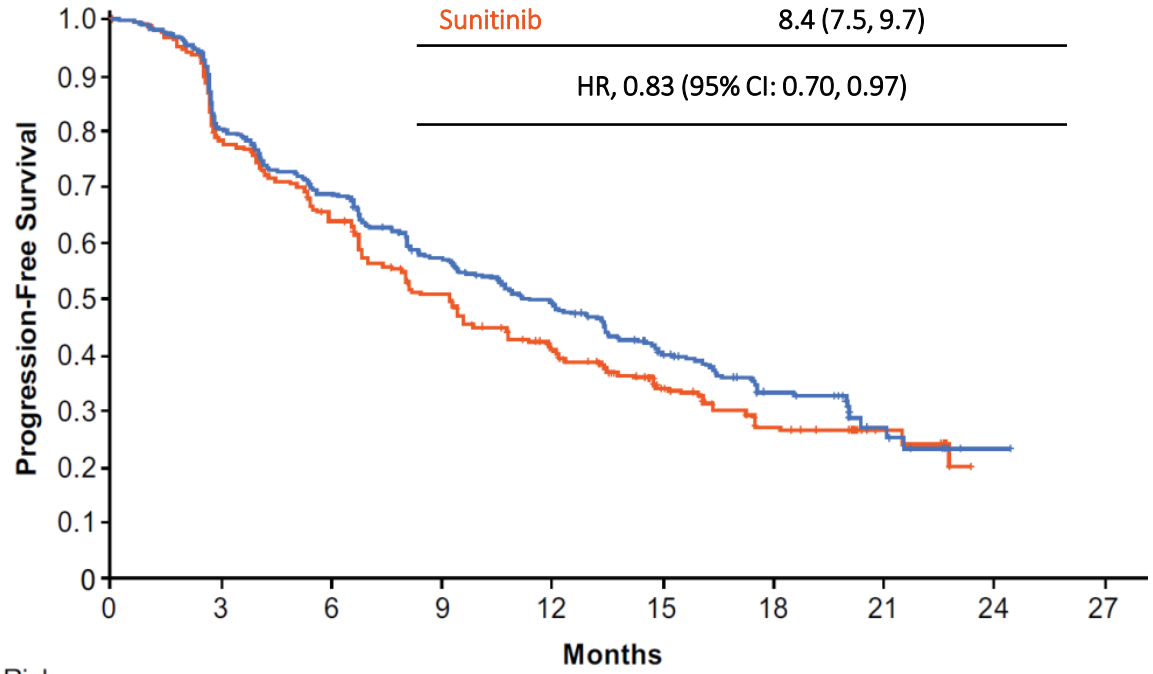
PFS (PD-L1+ & ITT)

	Median PFS, mo (95% CI)
Atezo + Bev	11.2 (8.9, 15.0)
Sunitinib	7.7 (6.8, 9.7)
HR, 0.74 (95% CI: 0.57, 0.96) *P* = 0.02	



No. at Risk									
Atezo + Bev	178	137	117	94	79	55	22	5	
Sunitinib	184	135	110	83	64	44	15	7	1

	Median PFS, mo (95% CI)
Atezo + Bev	11.2 (9.6, 13.3)
Sunitinib	8.4 (7.5, 9.7)
HR, 0.83 (95% CI: 0.70, 0.97)	



No. at Risk									
Atezo + Bev	454	355	294	236	196	126	57	15	1
Sunitinib	461	346	281	211	166	105	42	14	1

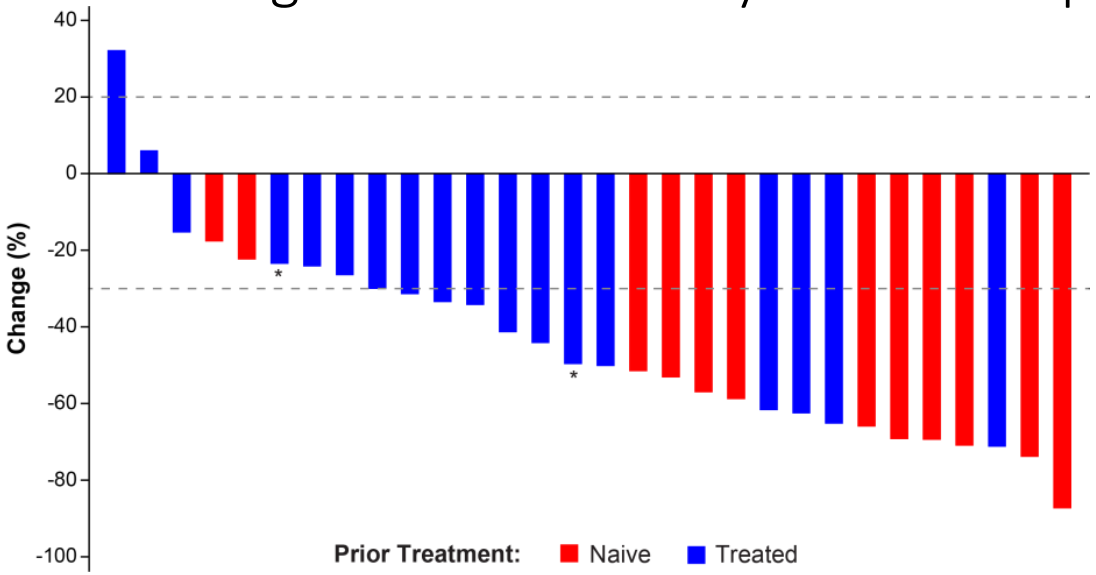
PFS assessed by investigators. Minimum follow-up, 12 mo. Median follow-up, 15 mo.

TKI/IO Combinations: Lenvatinib + Pembrolizumab

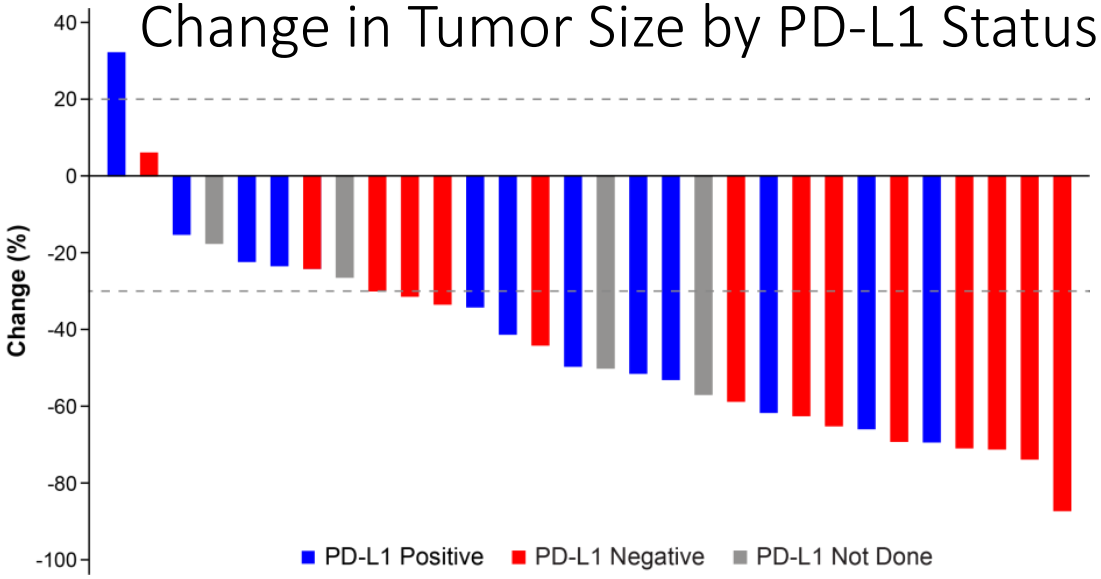
Parameter	Total (n = 30)	Treatment Naïve (n = 12)	Previous Treatments (n=18)
$ORR_{(Week\ 24)}$, n (%)	19 (63)	10 (83)	9 (50)
95% CI	44–80	52–98	26–74
ORR, n (%)	19 (63)	10 (83)	9 (50)
95% CI	44–80	52–98	26–74
BOR, n (%)			
Partial response	19 (63)	10 (83)	9 (50)
Stable disease	10 (33)	2 (17)	8 (44)
Progression	1 (3)	0	1 (6)

ESMO 2017.

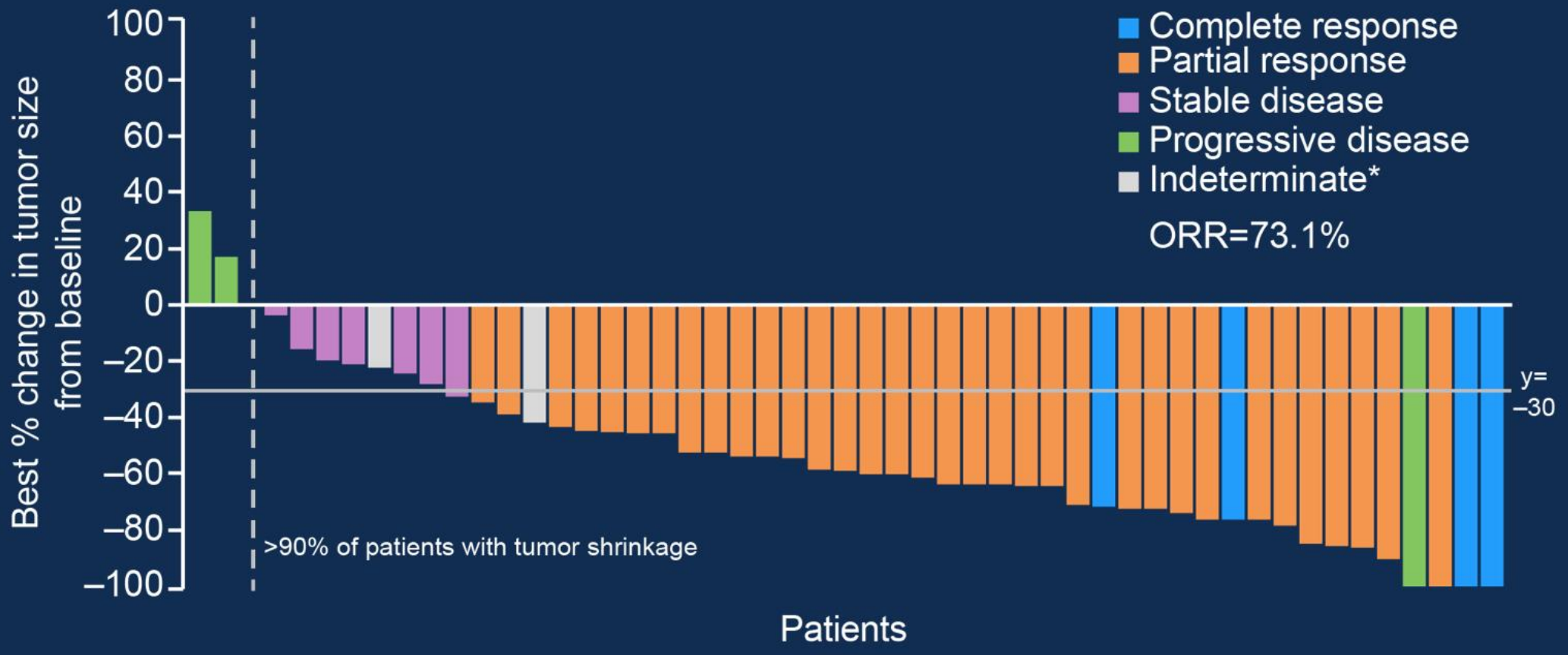
Change in Tumor Size by Prior Therapy



Change in Tumor Size by PD-L1 Status



Axitinib + Pembrolizumab



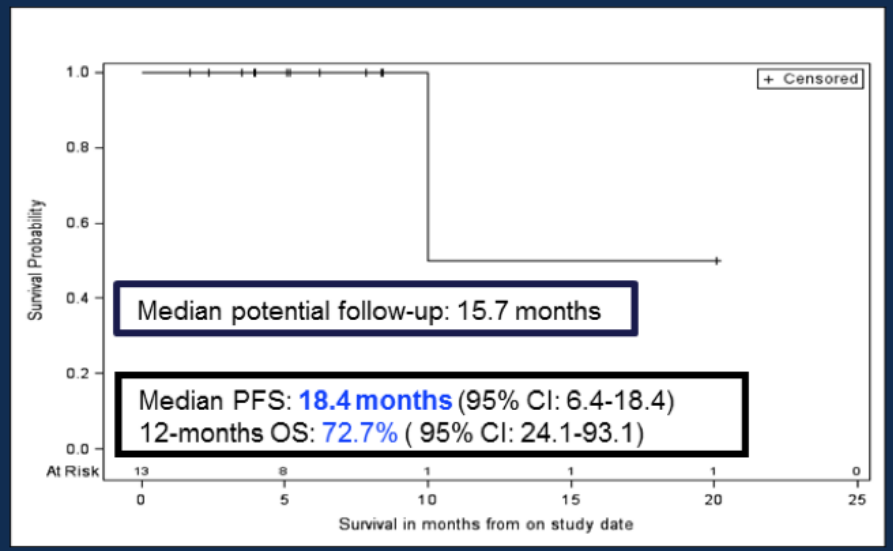
* Stable disease or partial response not confirmed, or no follow-up scans available.
ORR=objective response rate

Cabozantinib/Nivolumab +/- Ipilimumab

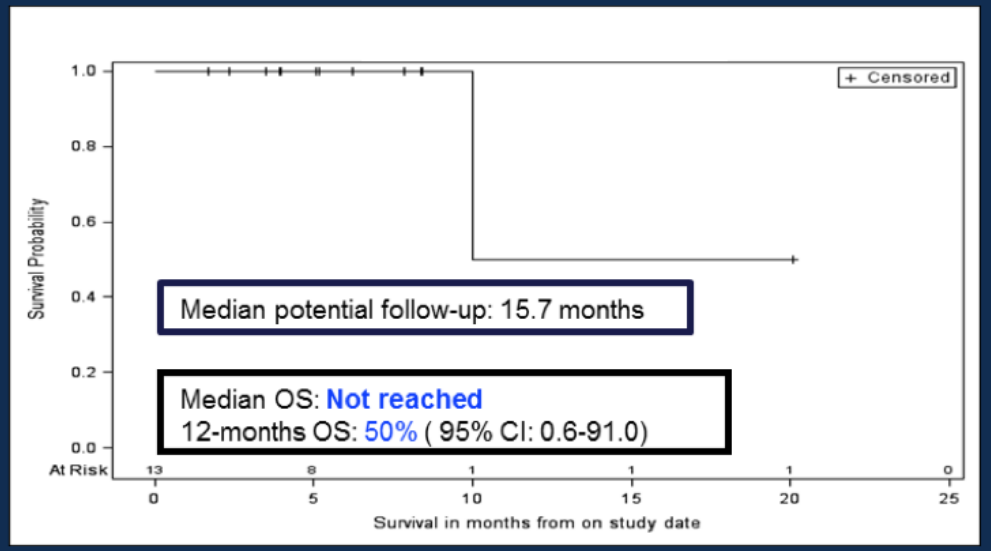
n (%)	Median F/U months	ORR	PR	CR	SD	PR+CR+SD
RCC N=13	5.2	**53.9%** (7/13) (95% CI: 25.1-80.8%)	**53.9%** (7/13) (95% CI: 25.1-80.8%)	0	**46.1%** (6/13) (95% CI: 19.2-74.9%)	**100%** (13/13) (95% CI: 75.3-100.0%)

RCC: Median Duration of Response: 18.4 months (95% CI: 6.4-18.4)

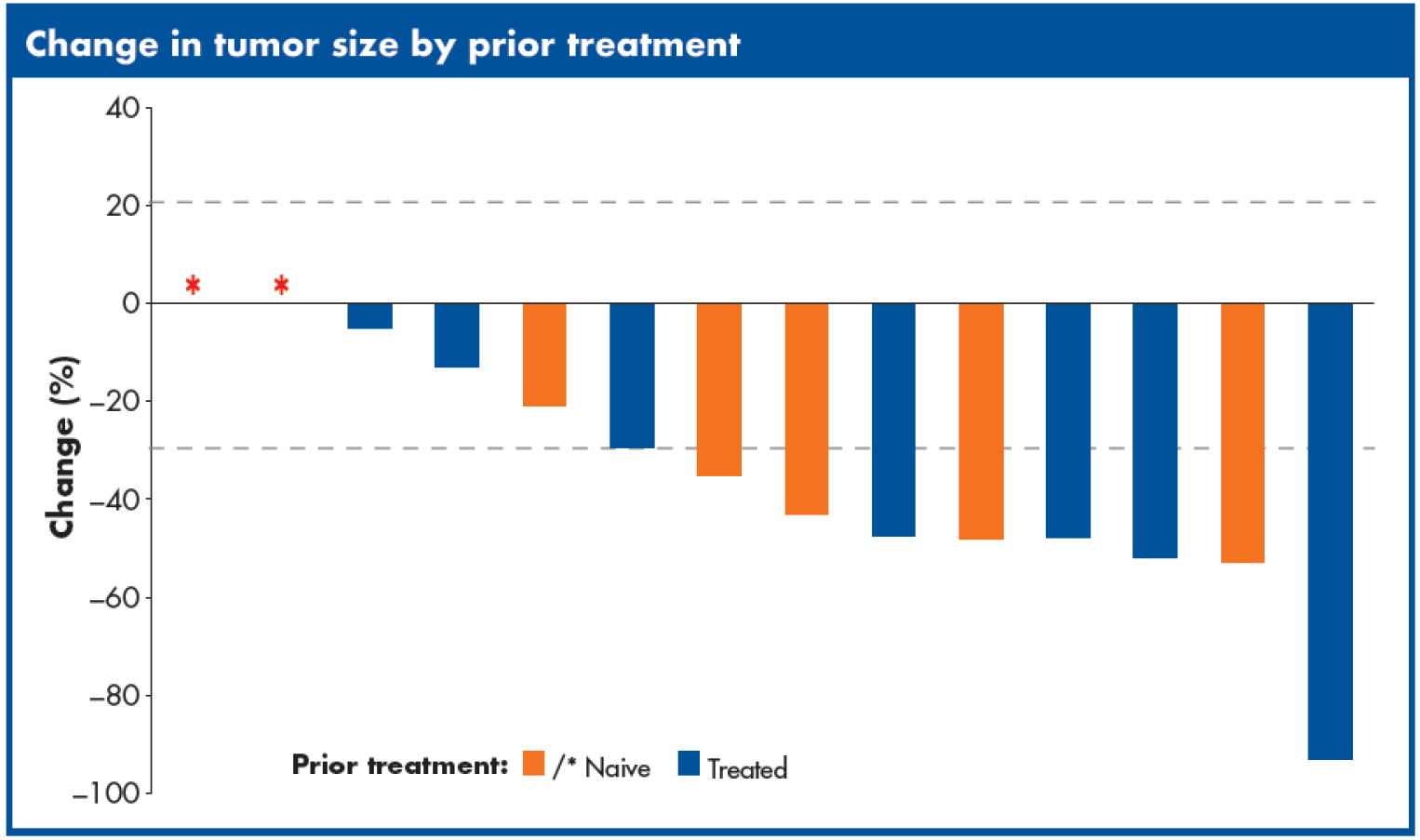
RCC: PFS



RCC: OS

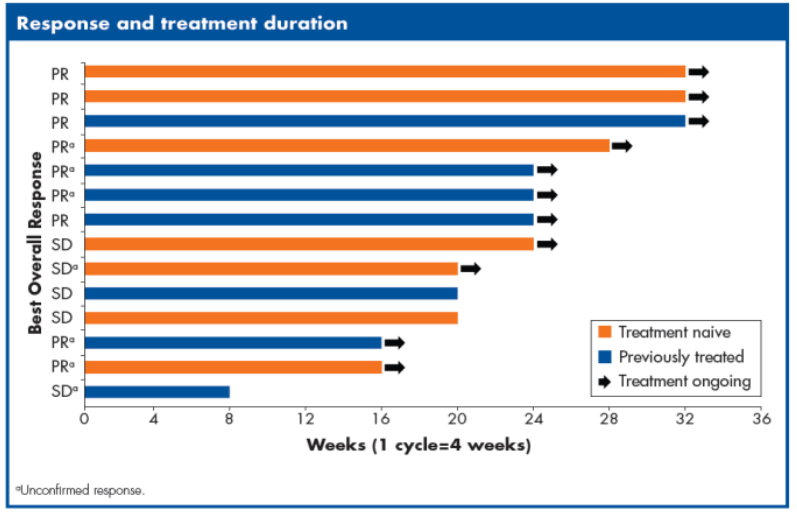


Tivozanib + Nivolumab



Response to treatment in patients receiving the full treatment dose with ≥2 treatment scans	
Best overall response, n (%)	**Patients (n=14)**
CR	0
PR	9 (64.3)[a]
SD	5 (35.7)[b]
Progressive disease	0
Objective response rate (CR + PR)	9/14 (64.3)
Disease control rate (CR + PR + SD)	14/14 (100)

CR, complete response; SD, stable disease.
[a]Includes 5 patients with an unconfirmed response.
[b]Includes 2 patients with an unconfirmed response.



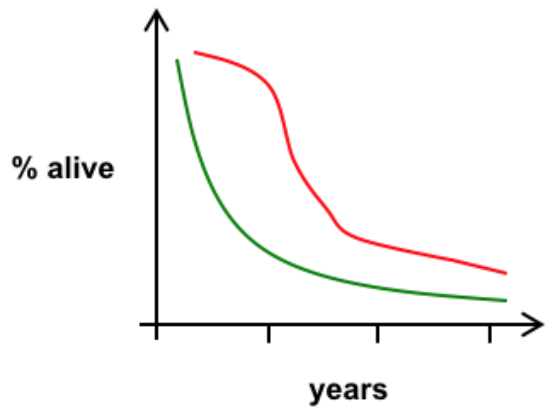
Presented by: Dr. Bernard Escudier - GUCS 2018

Future: Combination of therapies

Immunotherapy

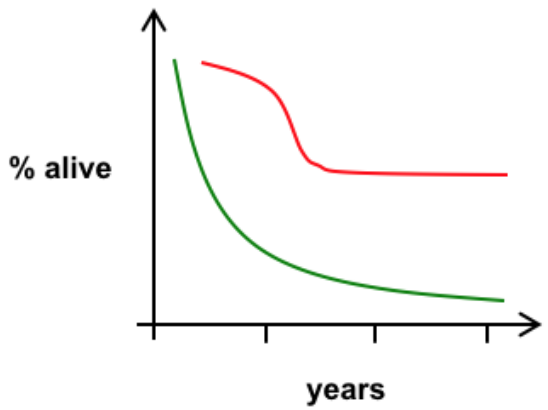
Moderate Responses
Long-term duration

Targeted Therapy



High Responses
Short-term duration

Combination



High Responses
Long-term duration

?

ESCOLA DE MEDICINA

PUCRS

Combination Therapy: A Historical Perspective

Checkmate 214 – Ipilimumab + Nivolumab for Advanced RCC

André P. Fay, MD, PhD

andre.fay@pucrs.br

March, 1st, 2018