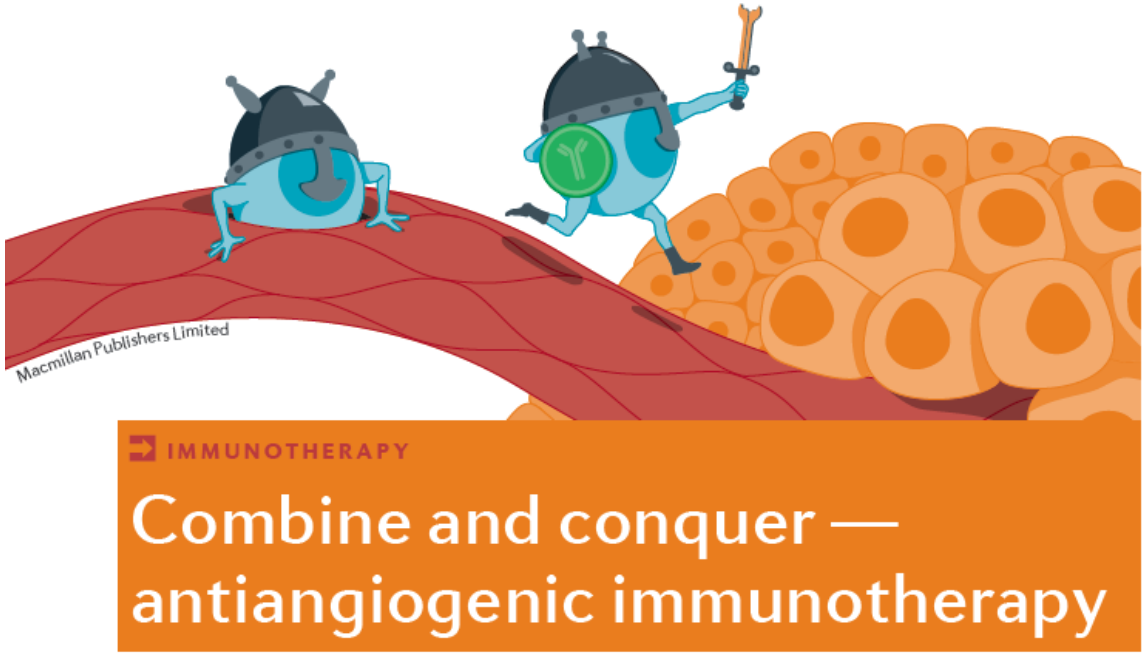
Nature Reviews Clinical Oncology | Published online 3 May 2017; doi:10.1038/nrclinonc.2017.65



Anti-angiogenesis combined with immunotherapeutics

Solange Peters MD-PhD
Head Medical Oncology and Thoracic Clinic
Oncology Department & Ludwig Institute
Lausanne University Hospital
Switzerland

Disclosure information – Solange Peters

I have received education grants, provided consultation, attended advisory boards and/or provided lectures for the following organizations, from whom I have received honoraria:

- Consultation / Advisory role: Abbvie, Amgen, AstraZeneca, Bayer, Biocartis, Bioinvent, Blueprint Medicines, Boehringer-Ingelheim, Bristol-Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, Eli Lilly, F. Hoffmann-La Roche, Foundation Medicine, Illumina, Janssen, Merck Sharp and Dohme, Merck Serono, Merrimack, Novartis, Pharma Mar, Pfizer, Regeneron, Sanofi, Seattle Genetics and Takeda

- Talk in a company's organized public event: AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, F. Hoffmann-La Roche, Illumina, Merck Sharp and Dohme, Novartis, Pfizer, Sanofi, Takeda

- Receipt of grants/research supports: (Sub)investigator in trials (institutional financial support for clinical trials) sponsored by Amgen, AstraZeneca, Biodesix, Boehringer-Ingelheim, Bristol-Myers Squibb, Clovis, F. Hoffmann-La Roche, Illumina, Merck Sharp and Dohme, Merck Serono, Novartis, and Pfizer

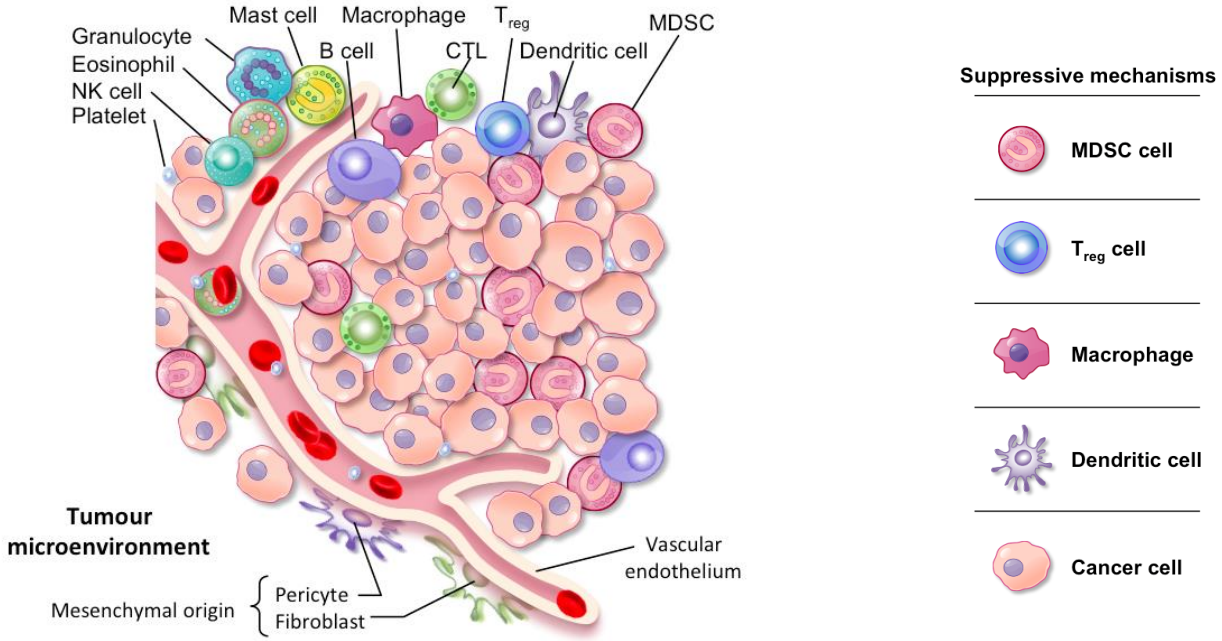
AGENDA

- Rational for anti-angiogenesis and IO combinations
- Lung cancer paradigm: from phase 1 to phase 3 trials
- Combinatorial advances in RCC
- Ongoing efforts in early clinical trials across diseases

AGENDA

- Rational for anti-angiogenesis and IO combinations
- Lung cancer paradigm: from phase 1 to phase 3 trials
- Combinatorial advances in RCC
- Ongoing efforts in early clinical trials across diseases

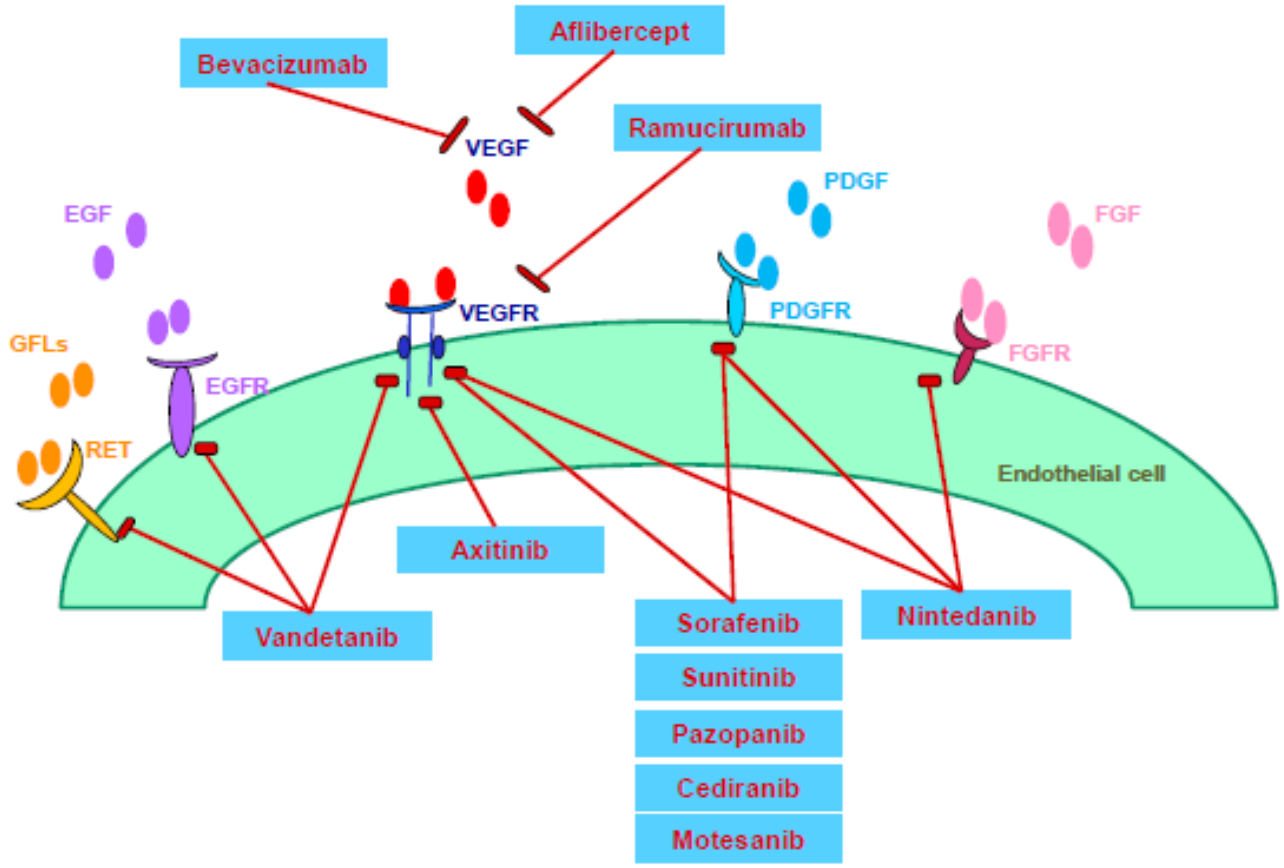
Cellular constituents of immune escape within the tumour microenvironment



- Tumor masses contain regulatory lymphocytes, myeloid derived suppressor cells, alternatively activated macrophages, and dendritic cells
- Immune cells in tumors are dysregulated and functionally impaired
- Ablation or reprogramming of this aberrant microenvironment might dramatically augment cancer therapies

Kerkar & Restifo. Cancer Res 2012

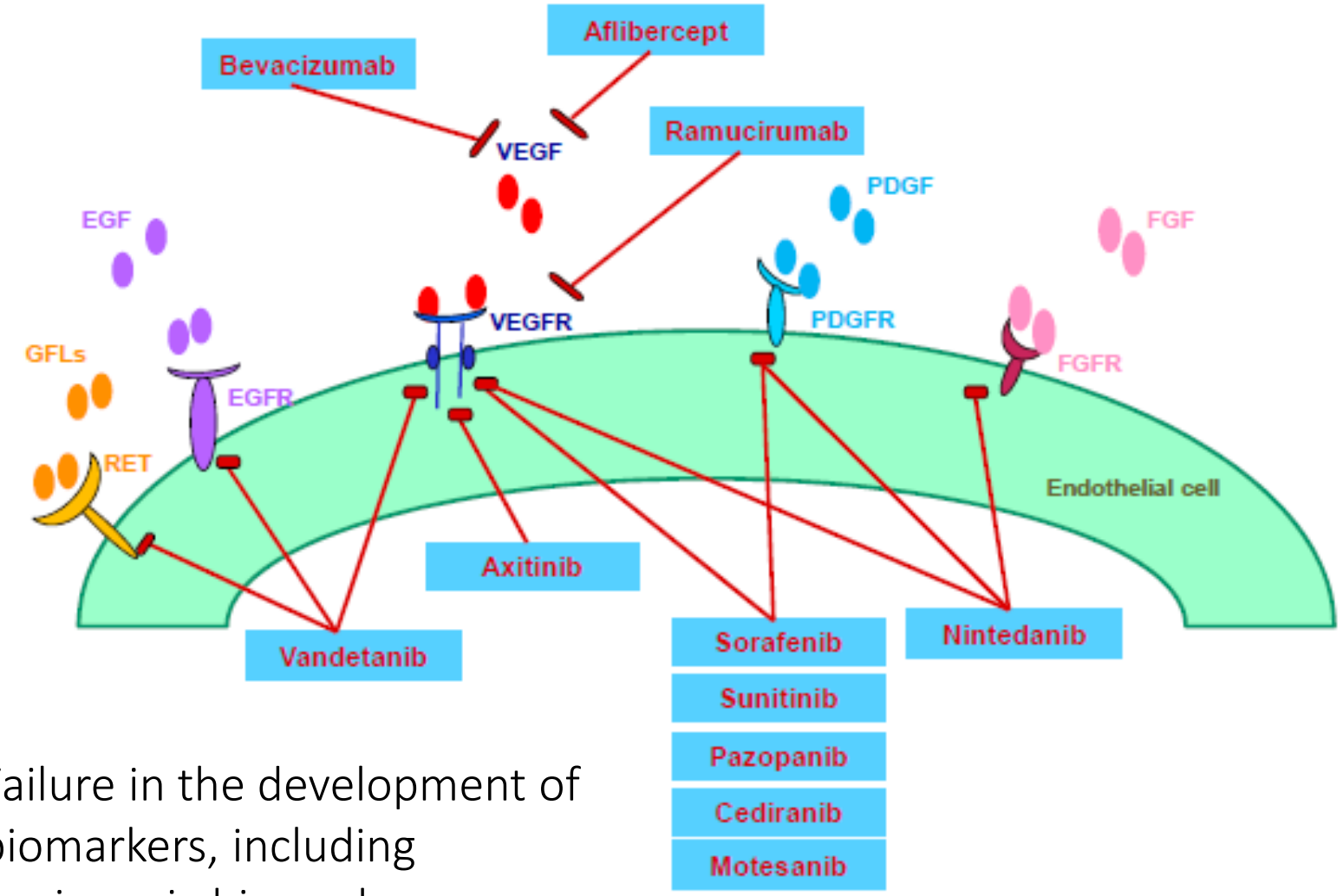
VEGF targeted therapies



VEGF expression is driven by the tumour and is also an HIF-dependent pro-angiogenic factor, in the context of cancer hypoxic niches

Manzo A et al JMC 2017

Mechanisms of action of anti-angiogenic therapies



Failure in the development of biomarkers, including angiogenic biomarkers

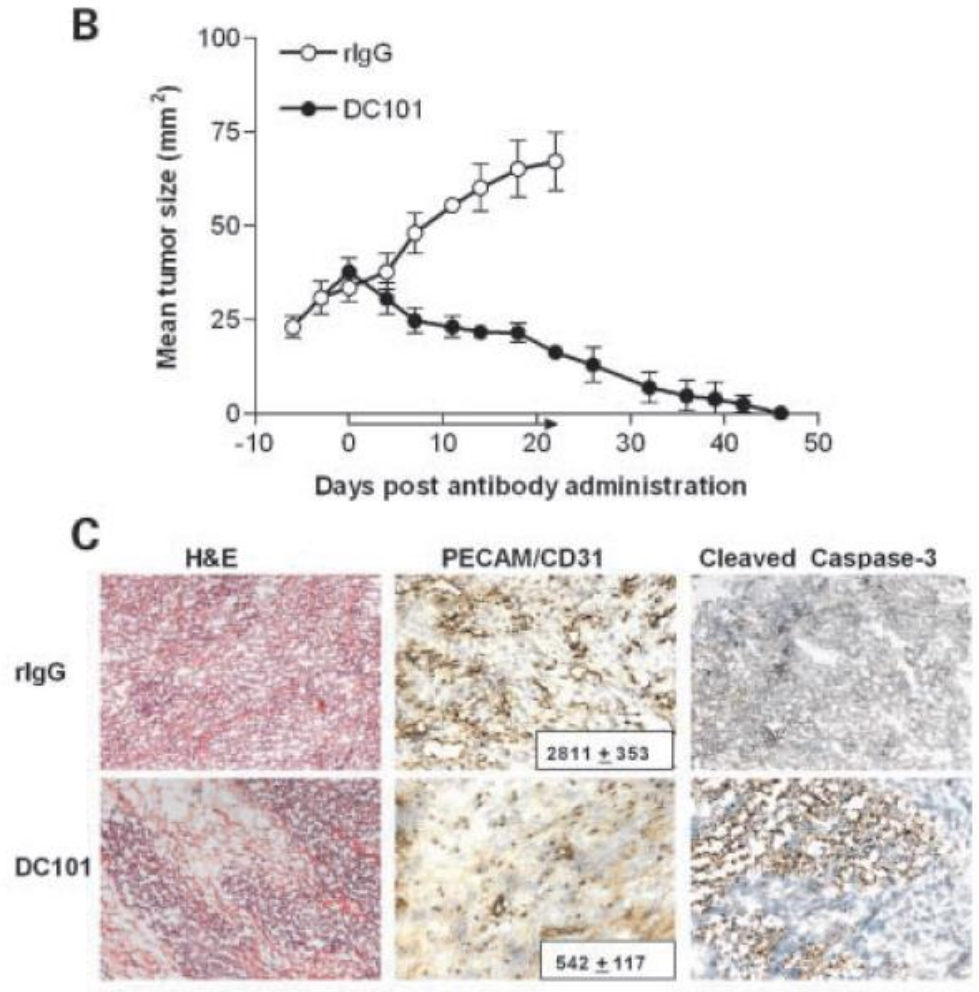
Effects on cancer cell

Hypoxia and effects on vasculature

Effects on the stroma

Manzo A et al JMC 2017

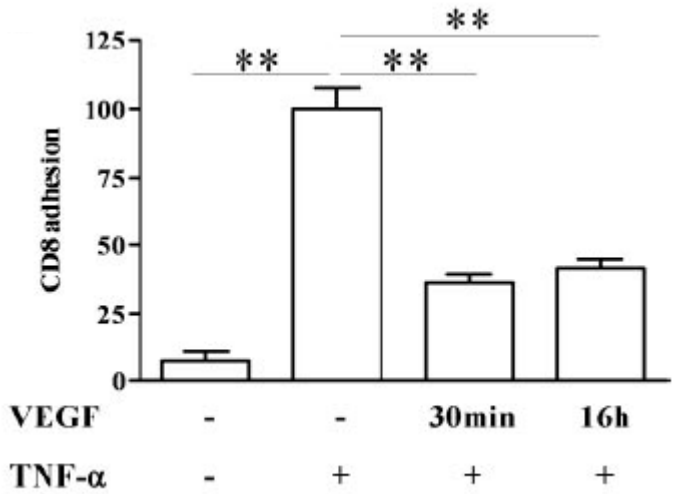
VEGF blockade induces antitumor immune response, increases T cell homing and improves vaccine therapy

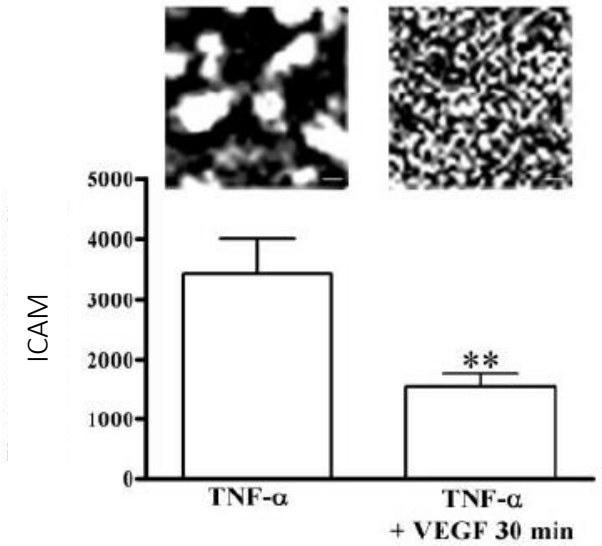


- DC101: monoclonal antibody for VEGFR2
- DC101 inhibits tumor growth, decreases angiogenesis, and increases apoptosis within tumors of mice
- Combining DC101 with neu-specific vaccination accelerated tumor regression

Manning et al, Clin Ca Res, 2007

VEGF blocks T cell adhesion on endothelium





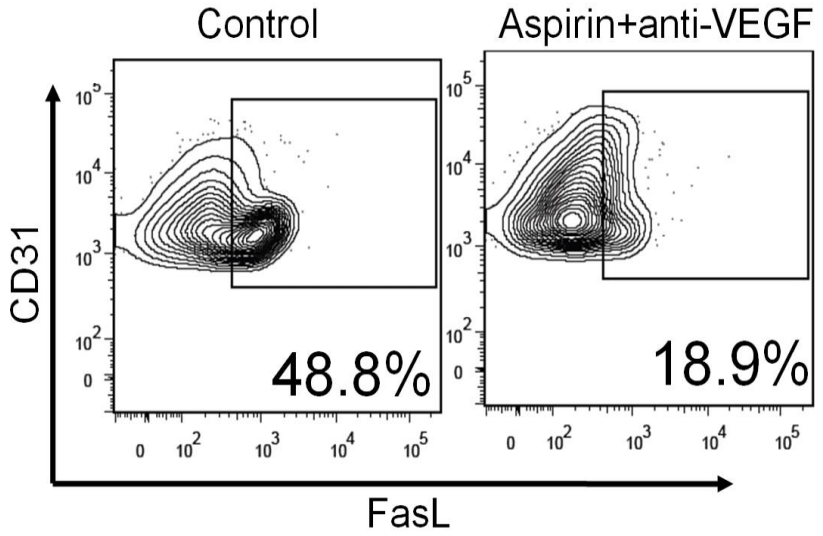
Dramatic inhibition of lymphocyte adhesion on activated endothelial cells following either short or long VEGF pretreatments.

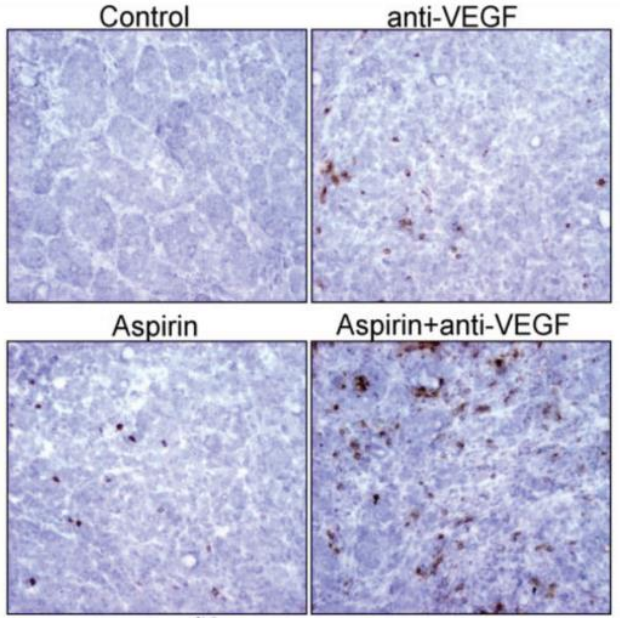
Bouzin et al, J Immunol 2007

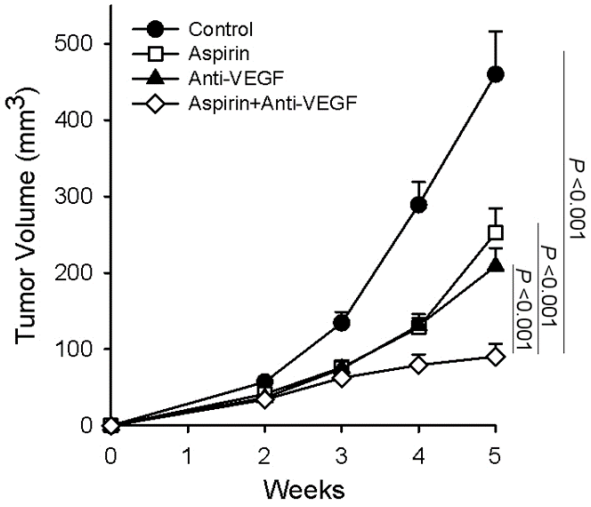
Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors

nature medicine

Gregory T Motz[1], Stephen P Santoro[1], Li-Ping Wang[2], Tom Garrabrant[1], Ricardo R Lastra[2], Ian S Hagemann[2], Priti Lal[2], Michael D Feldman[2], Fabian Benencia[1] & George Coukos[1,3]







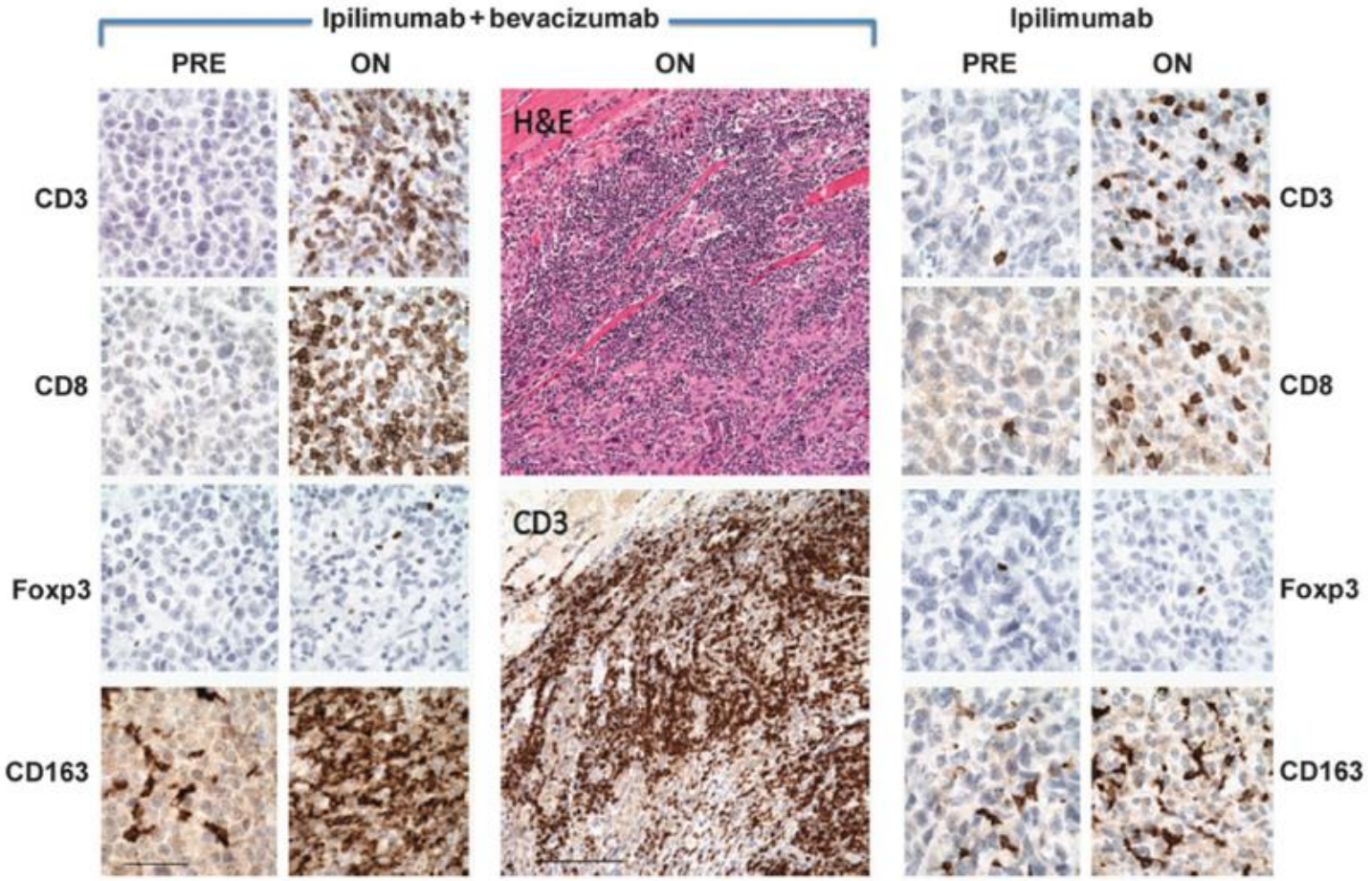
- VEGF-A induced FasL expression on endothelial cells, which acquired the ability to kill CD8+ T cells, but not Tregs
  -> VEGF and PGE2 blockade reduce endothelial FasL and increase in the influx of tumor-rejecting CD8+ over FoxP3+ T cells.

Research Article

Cancer Immunology Research

Bevacizumab plus Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi[1], Donald Lawrence[4], Cecilia Lezcano[10], Xinqi Wu[1], Jun Zhou[1], Tetsuro Sasada[1], Wanyong Zeng[1], Anita Giobbie-Hurder[2], Michael B. Atkins[11], Nageatte Ibrahim[1], Philip Friedlander[12], Keith T. Flaherty[4], George F. Murphy[5], Scott Rodig[5], Elsa F. Velazquez[7,9], Martin C. Mihm Jr[5], Sara Russell[6], Pamela J. DiPiro[3], Jeffrey T. Yap[3], Nikhil Ramaiya[3], Annick D. Van den Abbeele[3], Maria Gargano[1], and David McDermott[8]

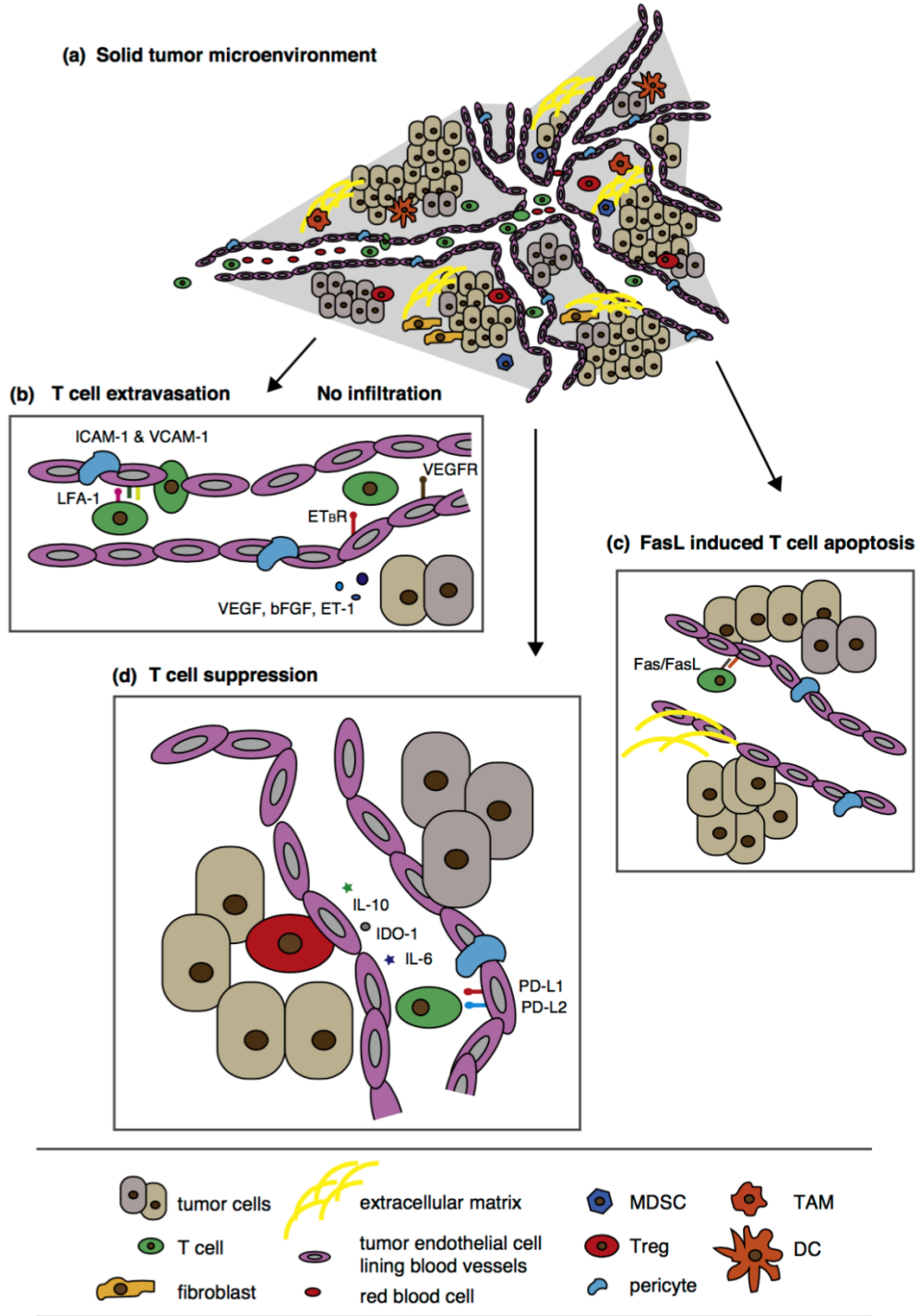


- Endothelial activation with increased lymphocyte and myeloid/monocyte cell trafficking into tumor deposits
- Peripheral blood circulating memory T cells count was increased resulting from the addition of bevacizumab

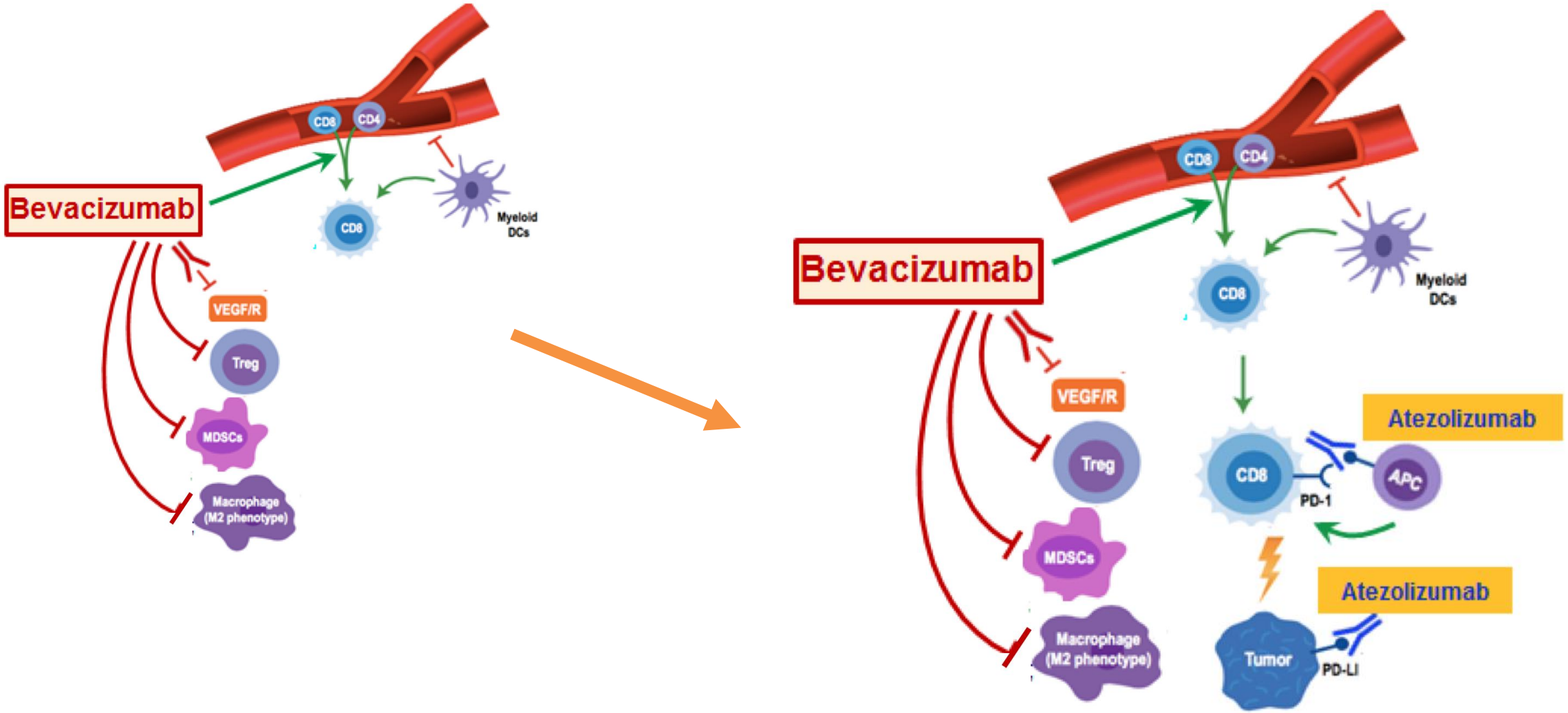
In Summary
Angiogenic factors and immune response

- Angiogenic factors impair lymphocyte trafficking across endothelia

- VEGF has profound effects on cancer immunity
  - By inhibiting dendritic cell maturation and antigen presentation
  - By inhibiting T-cell responses (upregulation PD-L1, PD-L2, IDO-1, IL-6, IL-10…)
  - By inducing proliferation of regulatory T cells
  - By favoring accumulation of myeloid-derived suppressor cells


(a) Solid tumor microenvironment
(b) T cell extravasation
No infiltration
ICAM-1 & VCAM-1
VEGFR
LFA-1
ETBR
VEGF, bFGF, ET-1
(c) FasL induced T cell apoptosis
Fas/FasL
(d) T cell suppression
IL-10
IDO-1
IL-6
PD-L1
PD-L2
tumor cells
T cell
fibroblast
extracellular matrix
tumor endothelial cell lining blood vessels
red blood cell
MDSC
Treg
pericyte
TAM
DC

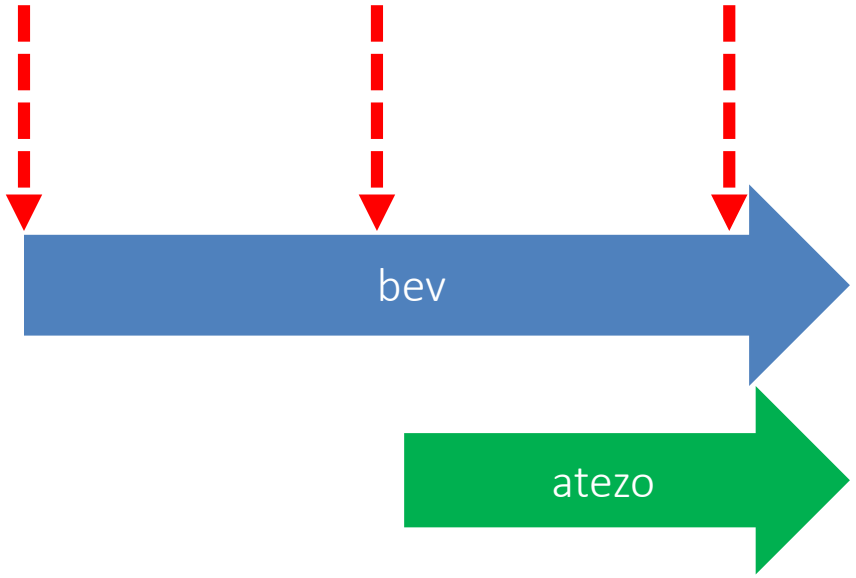
Pharmas’ schemes



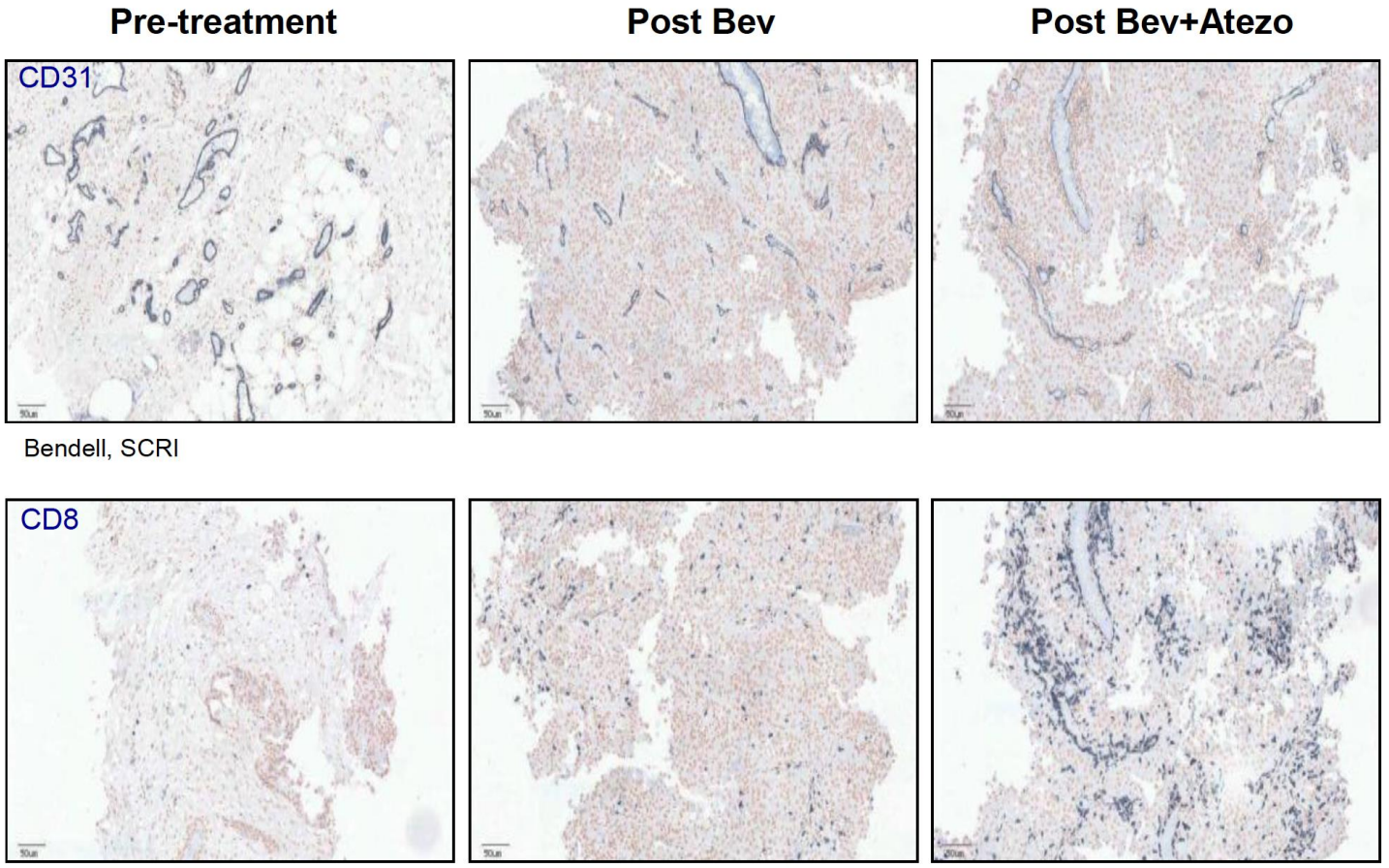
Effects of bevacizumab and atezolizumab on key VEGF and immune parameters

10 patients with metastatic RCC

Biopsy at 3 time points



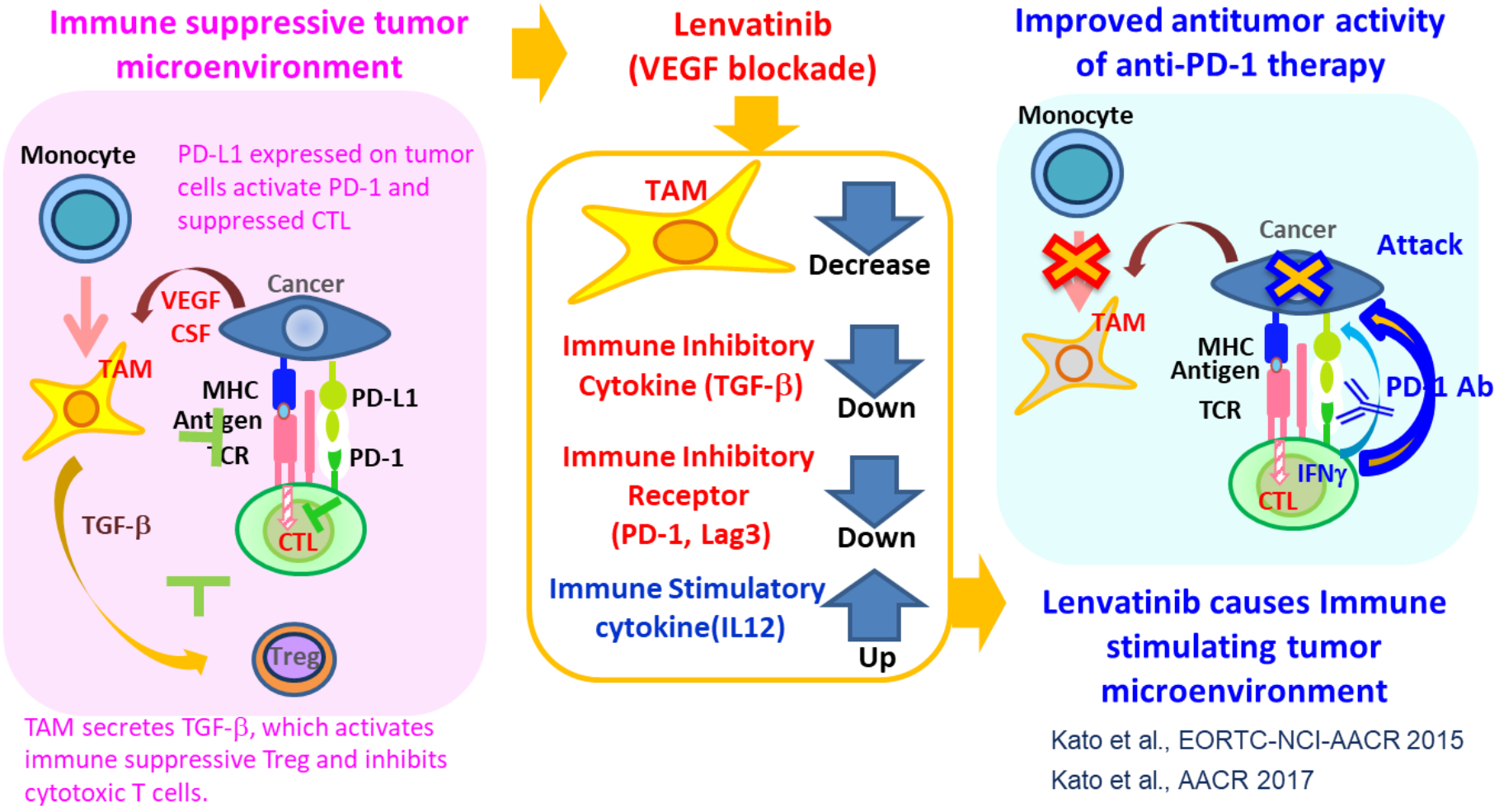
Patient 3, Female, 62 years old



Bendell, SCRI

Wallin et al Nat Comm 2016

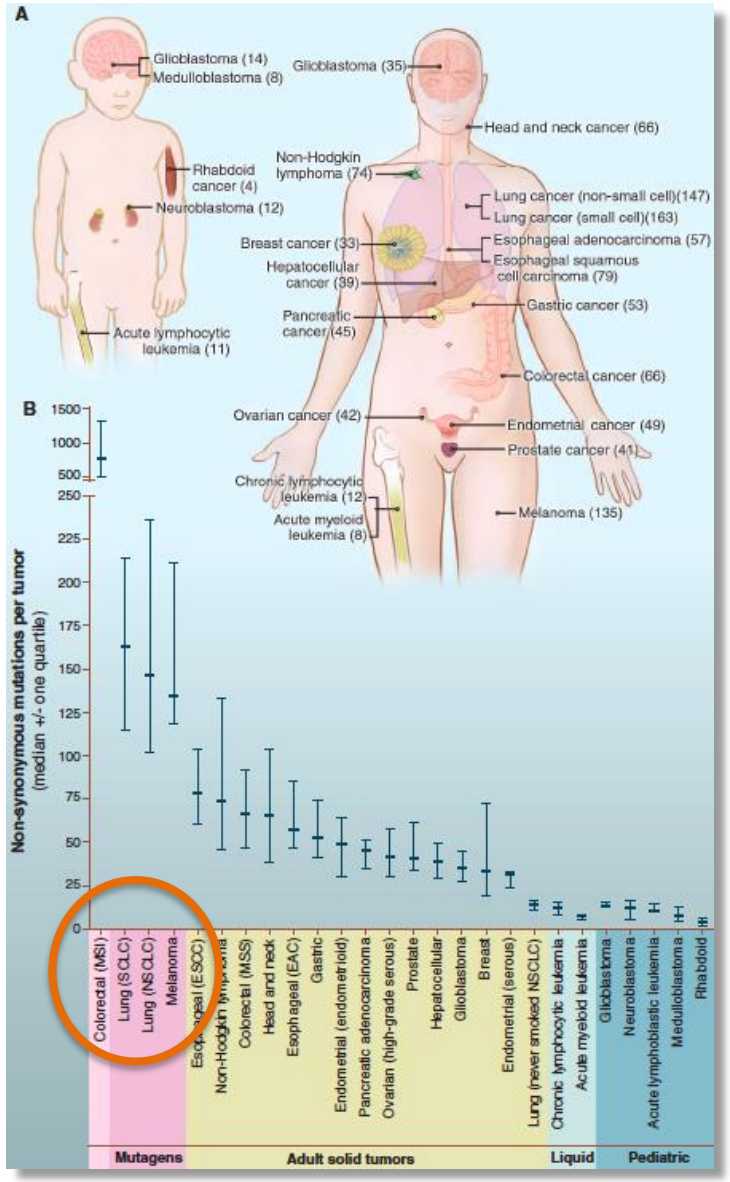
Pharmas' schemes (2)



AGENDA

- Rational for anti-angiogenesis and IO combinations
- Lung cancer paradigm: from phase 1 to phase 3 trials
- Combinatorial advances in RCC
- Ongoing efforts in early clinical trials across diseases

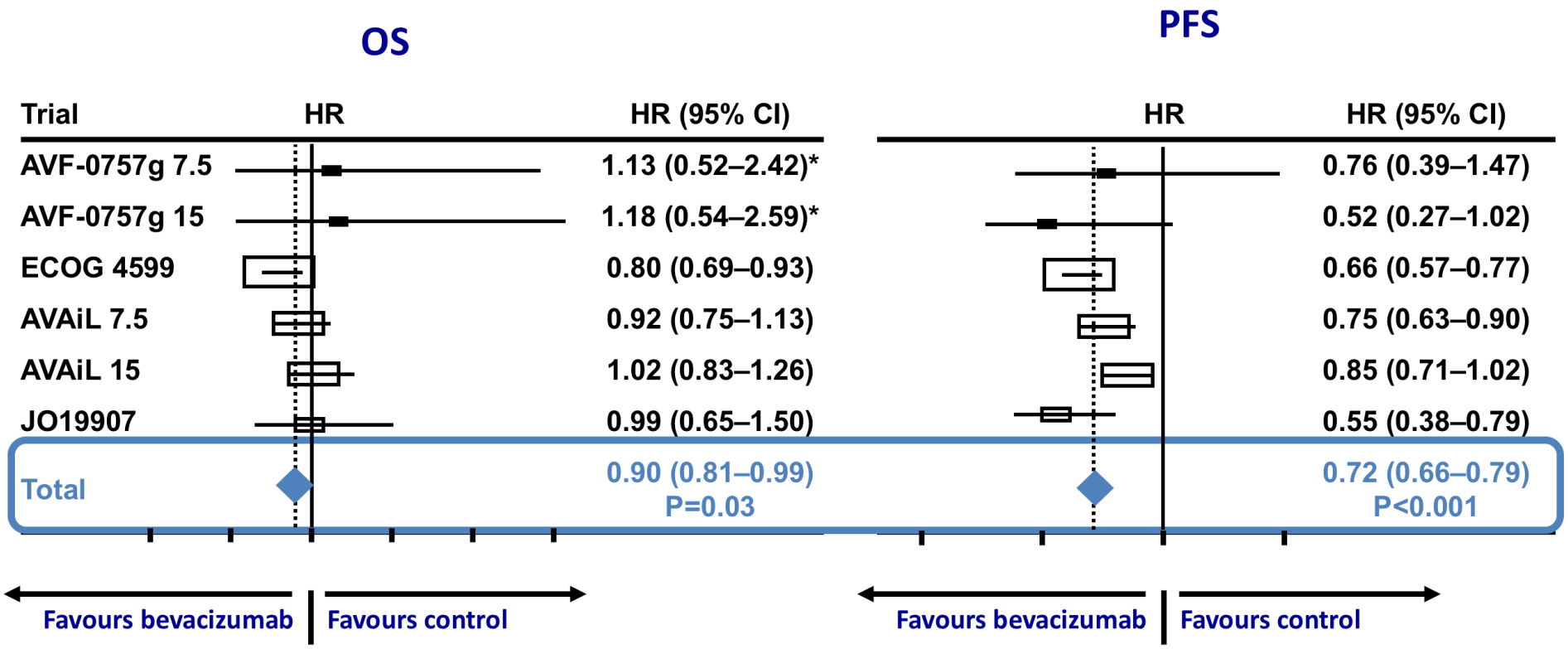
Lung cancer facts



- Lung cancer is characterized by a strongly immunosuppressive environment
- We have been enrolling thousands of patients in strictly negative vaccine trials
- Lung tumors display ~200 nonsynonymous mutations per tumor. Lung cancers from smokers have 10 times more mutations
- Checkpoint blockade is active in selected NSCLC patients only – and resistance is our ceiling

Vogelstein, Science 2013
Lawrence, Nature 2013

Bevacizumab with platinum-based chemotherapy Pooled Analysis in NSCLC

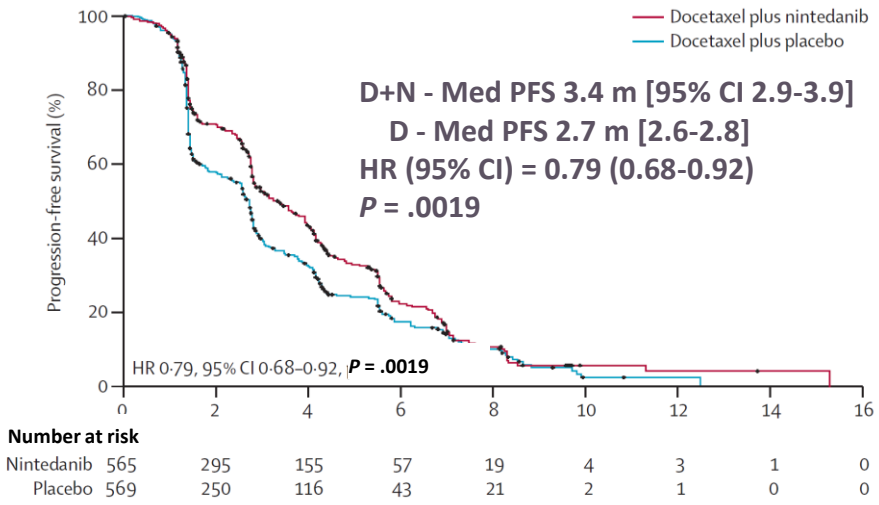


Soria JC, et al. Ann Oncol. 2013;24(1):20-30.

Antiangiogenic Agents in 2nd Line?

LUME-LUNG 1 Trial[1]: Docetaxel +/- nindetanib (VEGFR TKI)

- PFS (primary endpoint)

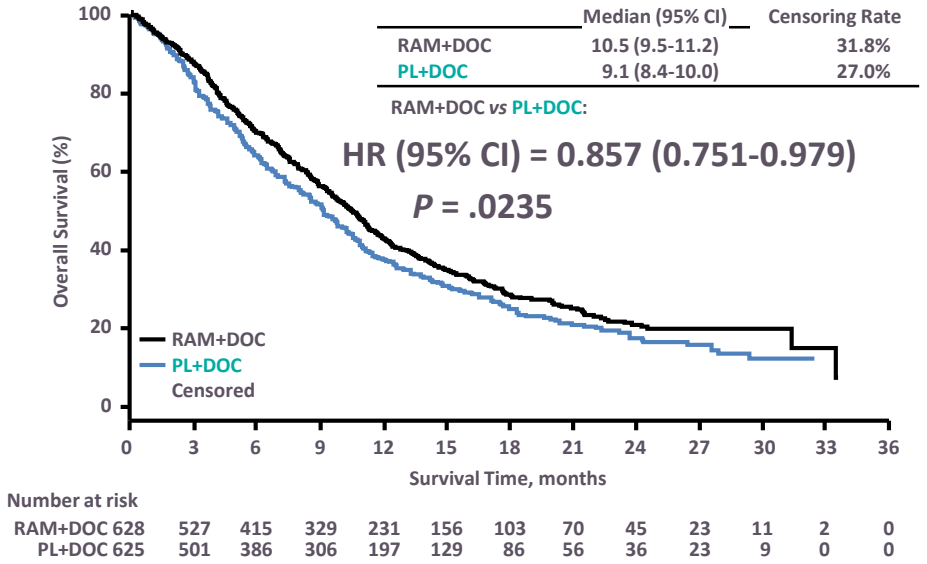


OS benefit in adenocarcinoma

PFS benefit in first-line refractory patients (HR= 0.67 [0.43-1.04], P = .0725)

REVEL Trial[2]: Docetaxel +/- ramucirumab (VEGFR2 Ab)

- OS (primary endpoint)

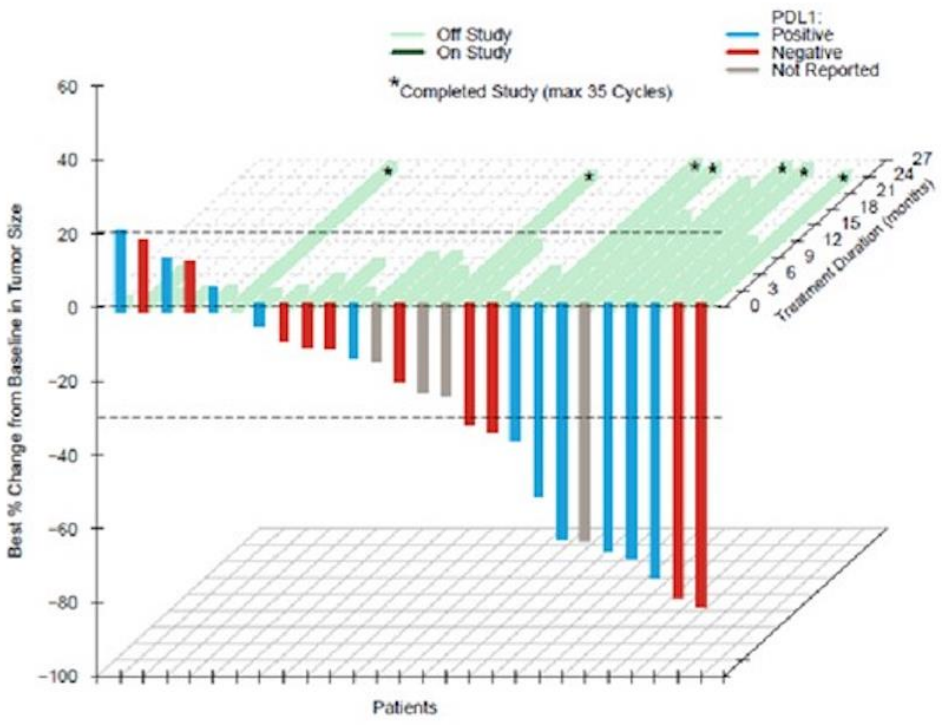


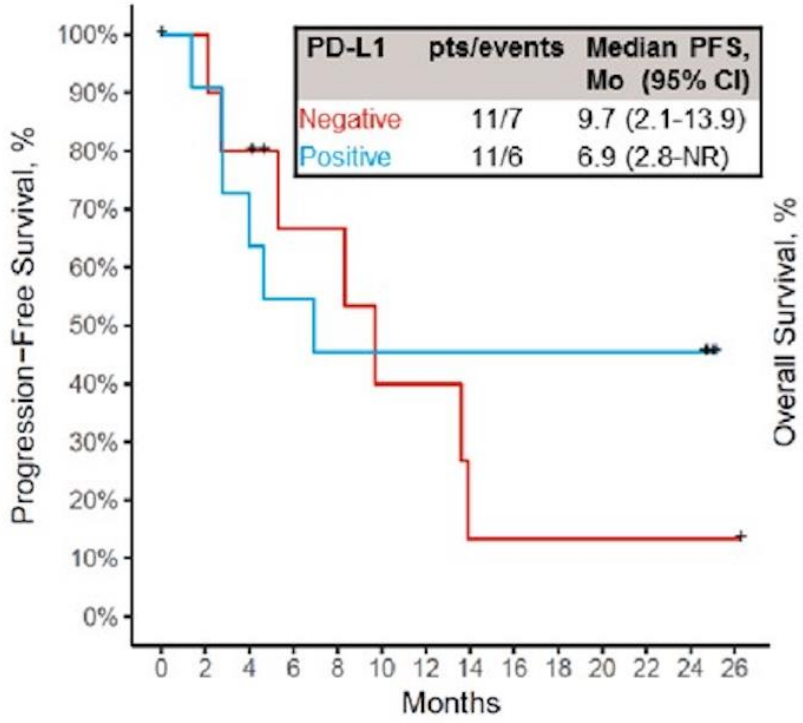
OS benefit in SCC and non SCC

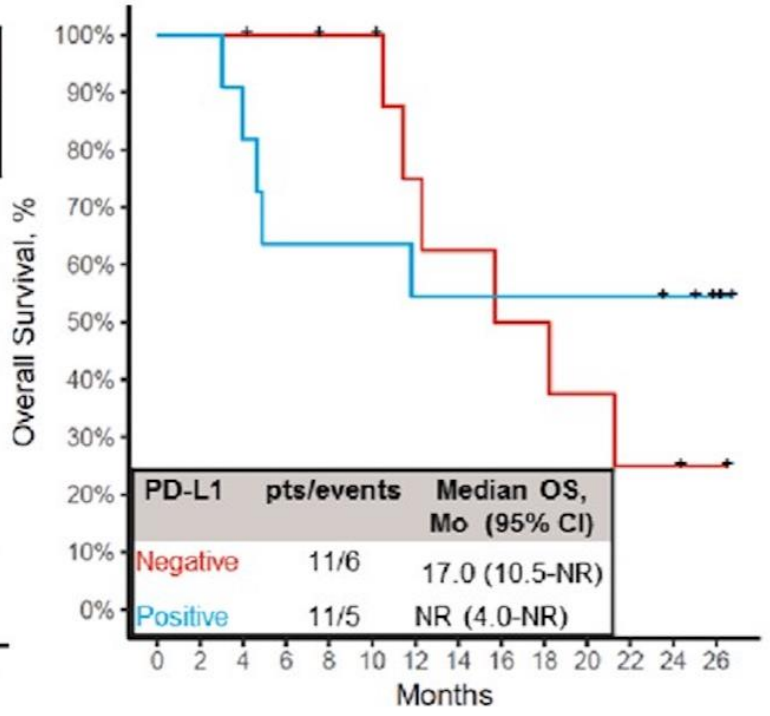
VEGFR, vascular endothelial growth factor receptors

Reck M, et al. *Lancet Oncol.* 2014;15(2):143-155. Perol M, et al. *J Clin Oncol.* 2014;32(5S): Abstract LBA8006.

Pembrolizumab + ramucirumab in NSCLC



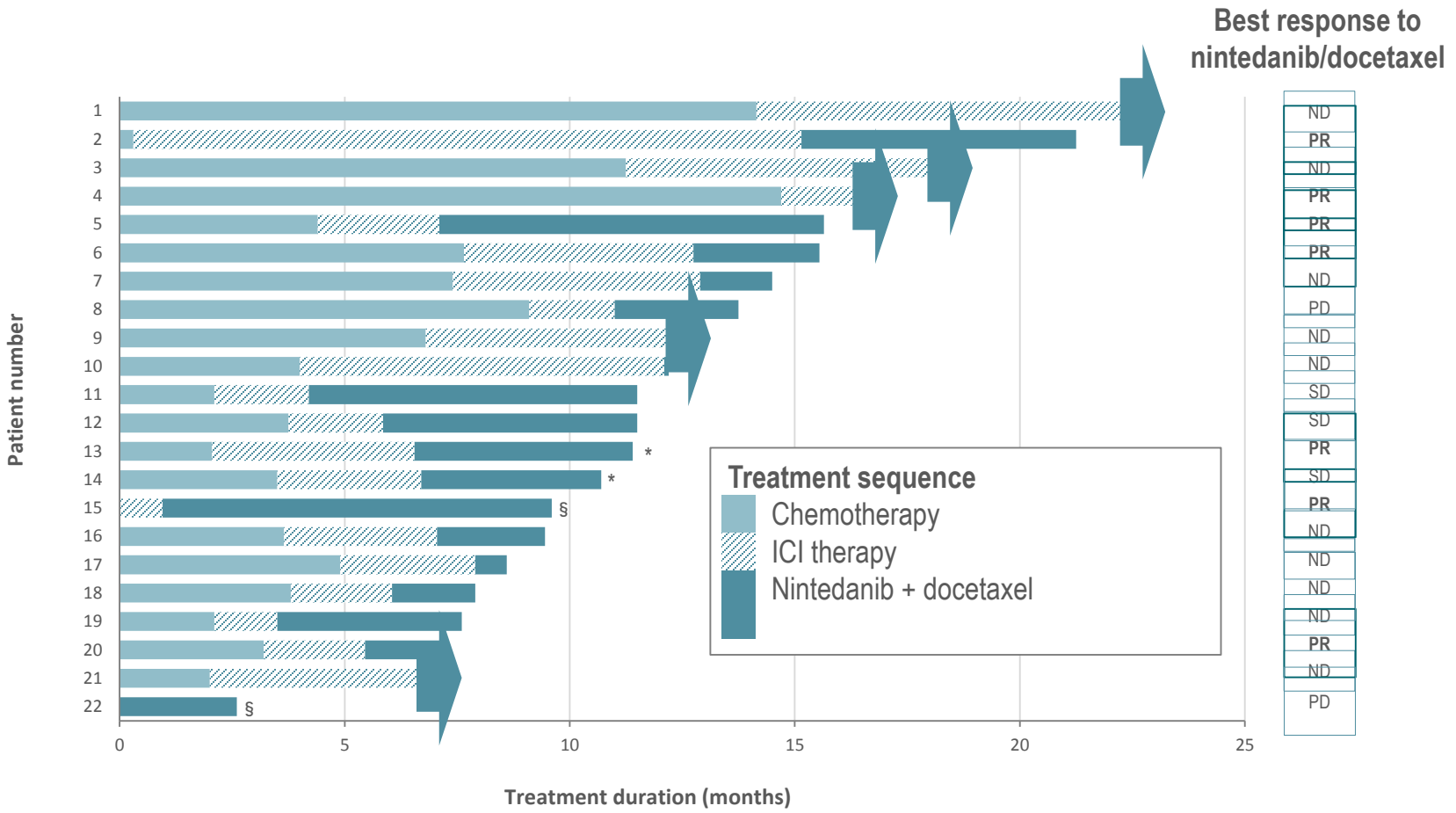




Lung-MAP ongoing phase 2 trial in IO-resistance

	NSCLC (2nd-4th line)	
PD-L1 Status	**TPS <1% n=11**	**TPS ≥1% n=11**
ORR, % (95% CI)	18 (2.3-51.8)	45 (16.7-76.6)
Time to response	2.8 (2.8-2.8)	1.4 (1.3-5.3)
Duration of response	NR (11.1-NR)	NR (NR-NR)
Disease control, % (95% CI)	82 (48.2-97.7)	91 (58.7-99.8)
Duration of stable disease	8.3 (2.7-13.6)	4.0 (2.8-6.9)

Nintedanib + docetaxel after anti PD(L)-1 in NSCLC

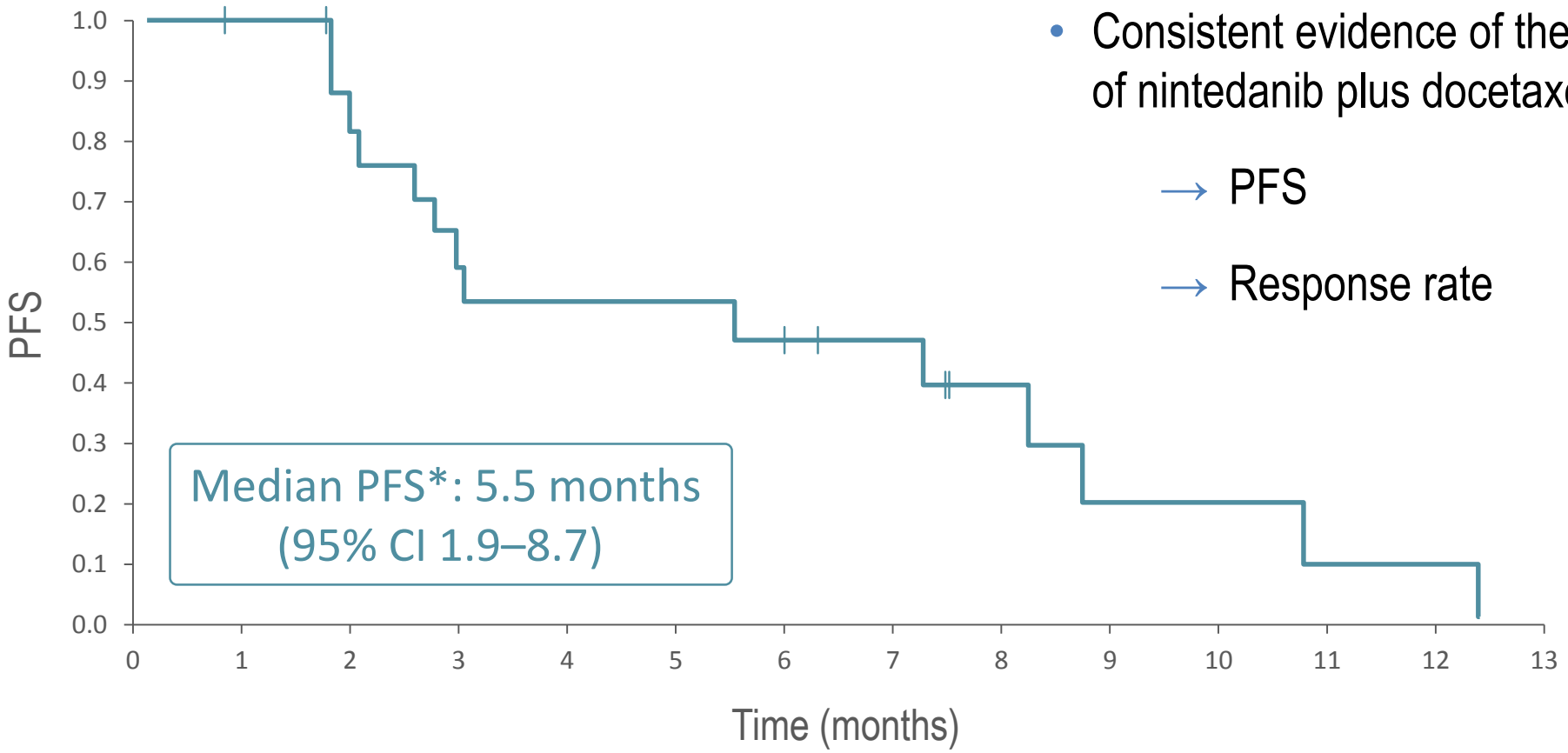


Best response	n (%) N=12
Partial response	**7 (58)**
Stable disease	3 (25)
Disease control rate	**10 (83)**

ICI, immune checkpoint inhibitor; ND, not documented; PD, progressive disease; PR, partial response; SD, stable disease.
*Single-agent nintedanib treatment ongoing; § Previous therapies not documented.

Grohé, ELCC 2019

Nintedanib + docetaxel after anti PD(L)-1 in NSCLC



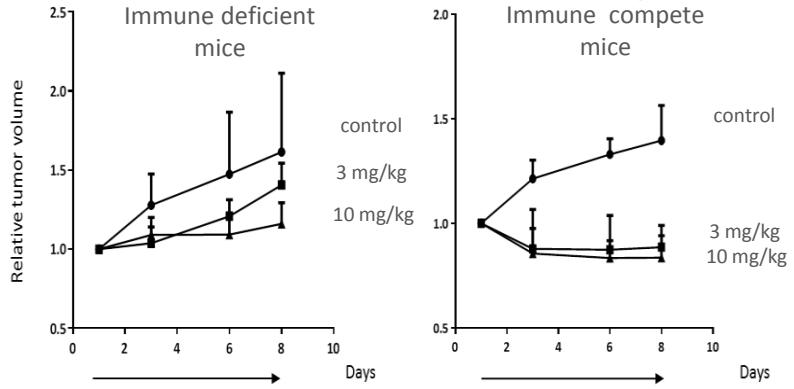
- Consistent evidence of the clinical benefit of nintedanib plus docetaxel, in terms of:
  - → PFS
  - → Response rate

CI, confidence interval; PFS, progression-free survival.
*n=21: 10 patients had disease progression, four patients had died, and seven patients had been censored. Data not yet available for one patient.

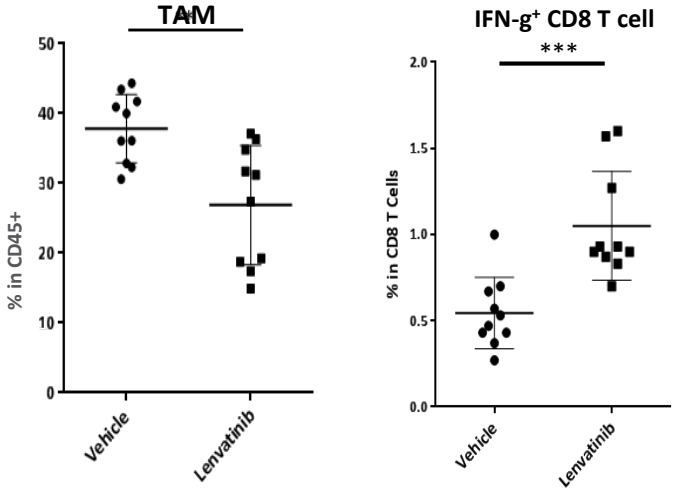
Grohé, ELCC 2019

Lenvatinib and pembrolizumab in IO naive (KEYNOTE-146)

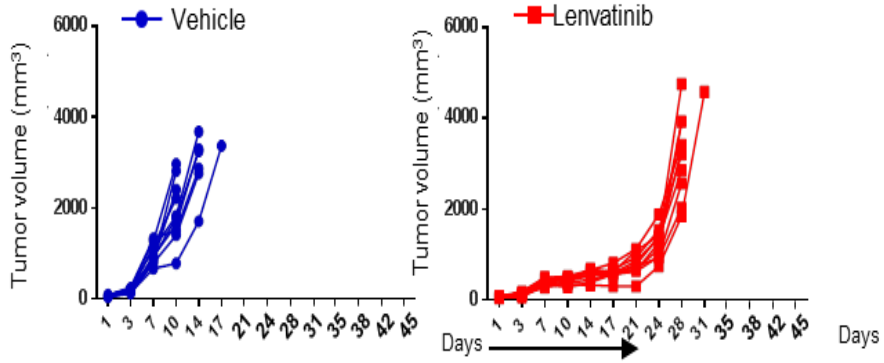
Lenvatinib is more effective in immune competent mice in HCC model

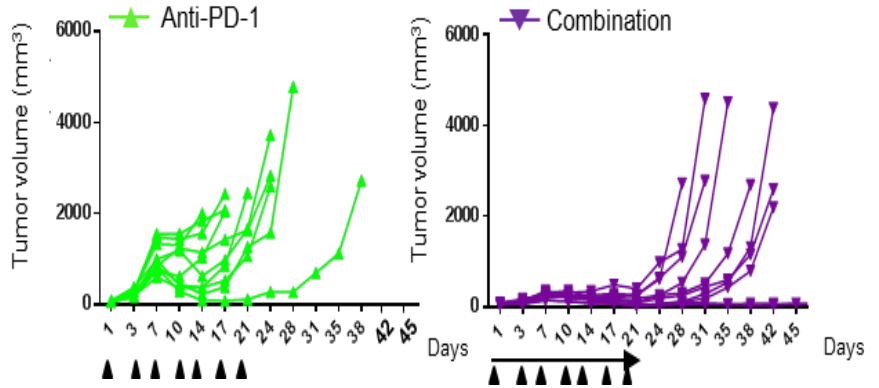


Immune cell profiling



Combination antitumor activity in combination with lenvatinib and mice anti-PD-1 Ab in CT26 mice model

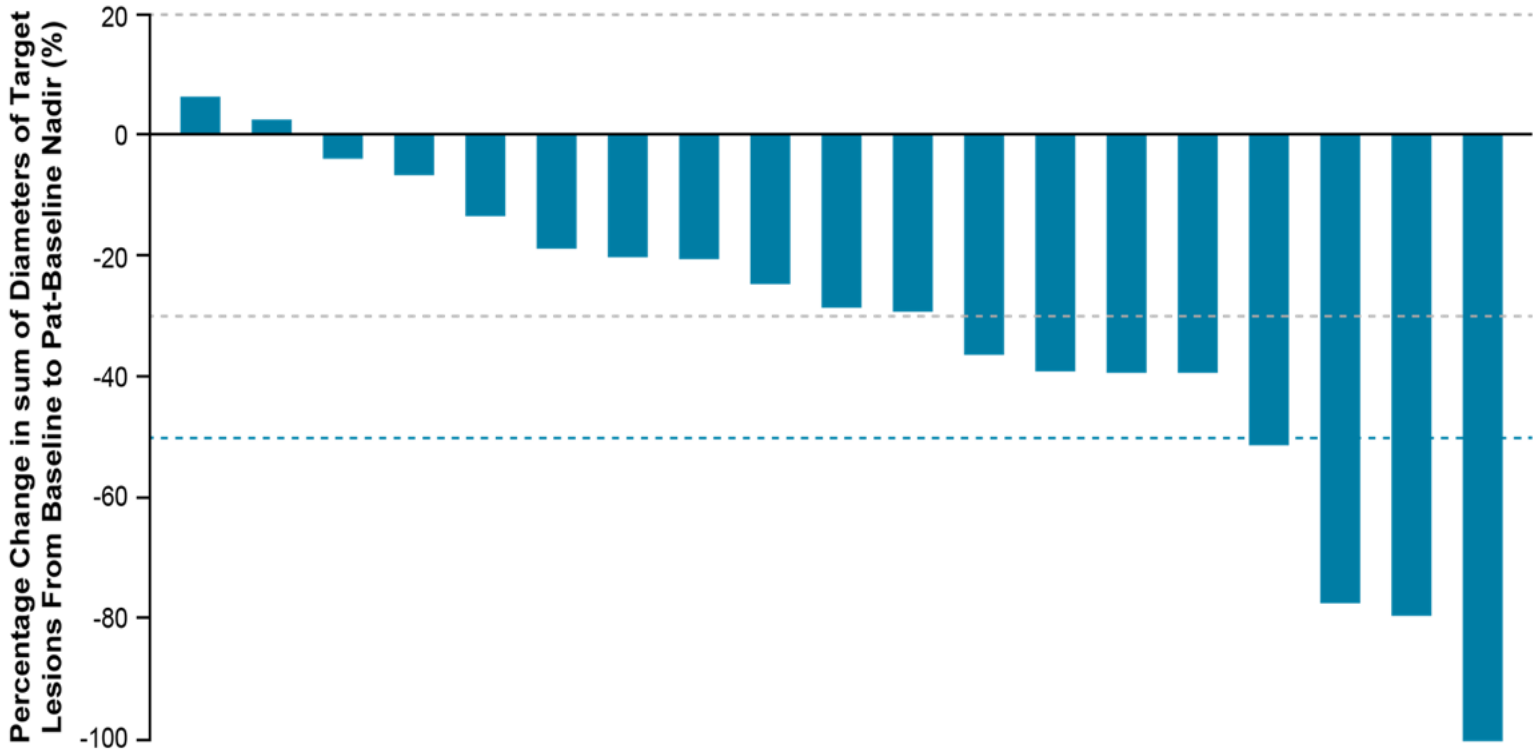




Kato et al., EORTC-NCI-AACR 2015

Kato et al., AACR 2017

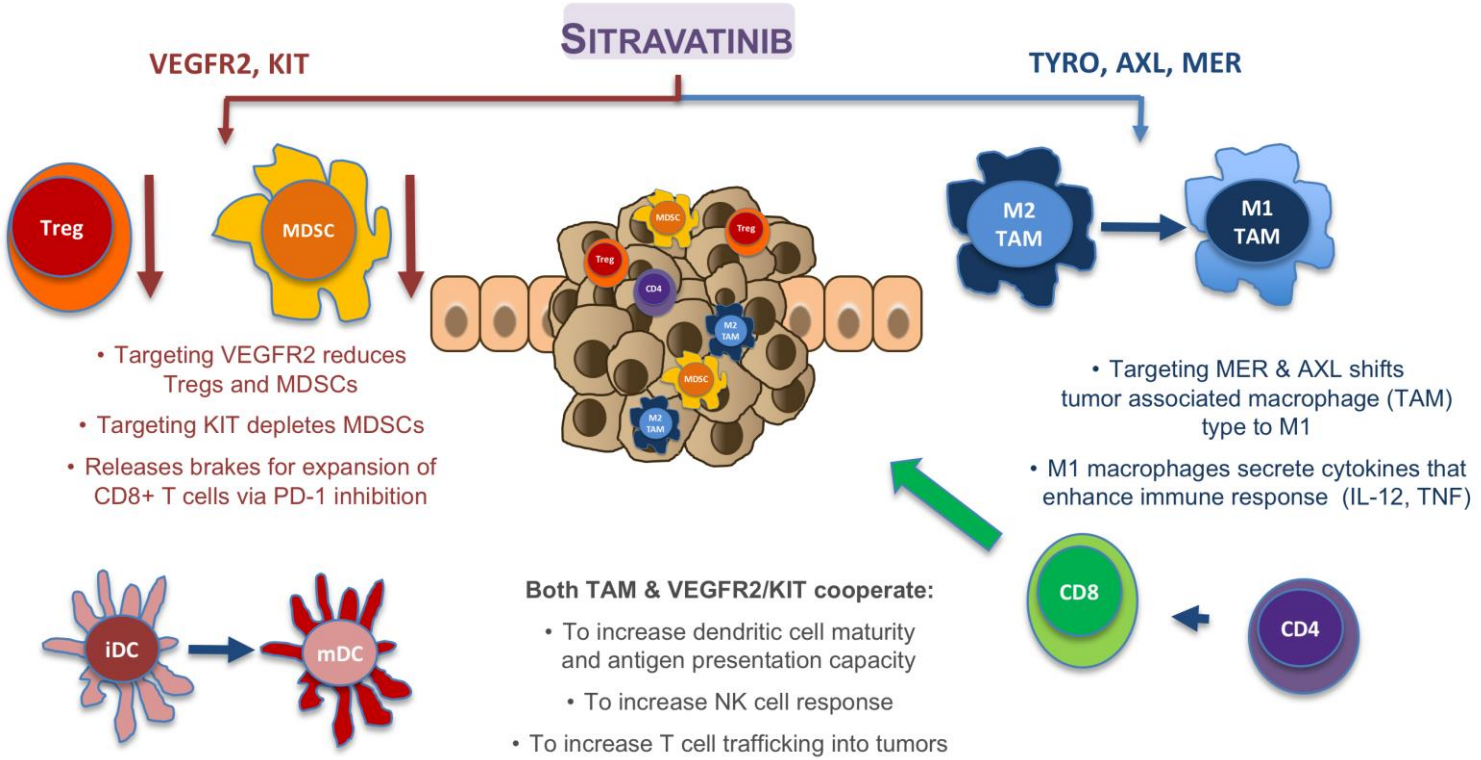
Lenvatinib and pembrolizumab in IO naive (KEYNOTE-146)



Primary end point: $ORR_{Week24:}$ 33% (95% CI: 14.6–57.0)

Rudin, SITC 2018

Multi-steps immune simulation
Sitravatinib/nivolumab in IO resistant NSCLC



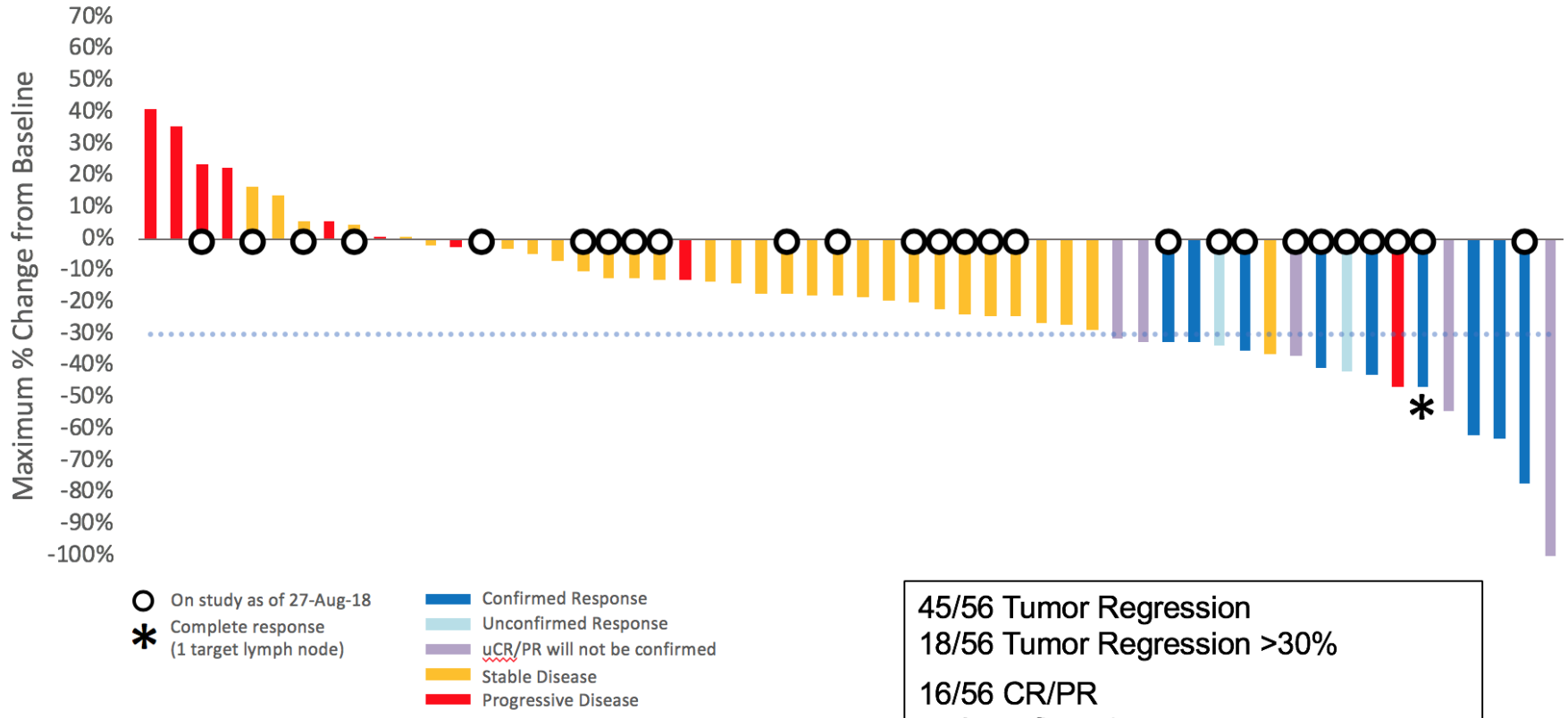
Sitravatinib (MGCD516) TKI

- TAM family (AXL and MER)
  - Target cellular IC50: 1nM.
- Split family RTKs (**VEGFR2**,PDGFRα and KIT)
  - Target cellular IC50: 5-10 nM.
- RET, MET, DDR2, TrkA
  - Target cellular IC50: 10-25 nM.

MRTX-500 Clinical Activity

Preliminary Maximum Response in NSCLC Patients Who Failed Prior Checkpoint Therapy by Best Response

(CIT-Experienced Cohorts – Clinical Activity Evaluable Patients, N=56)



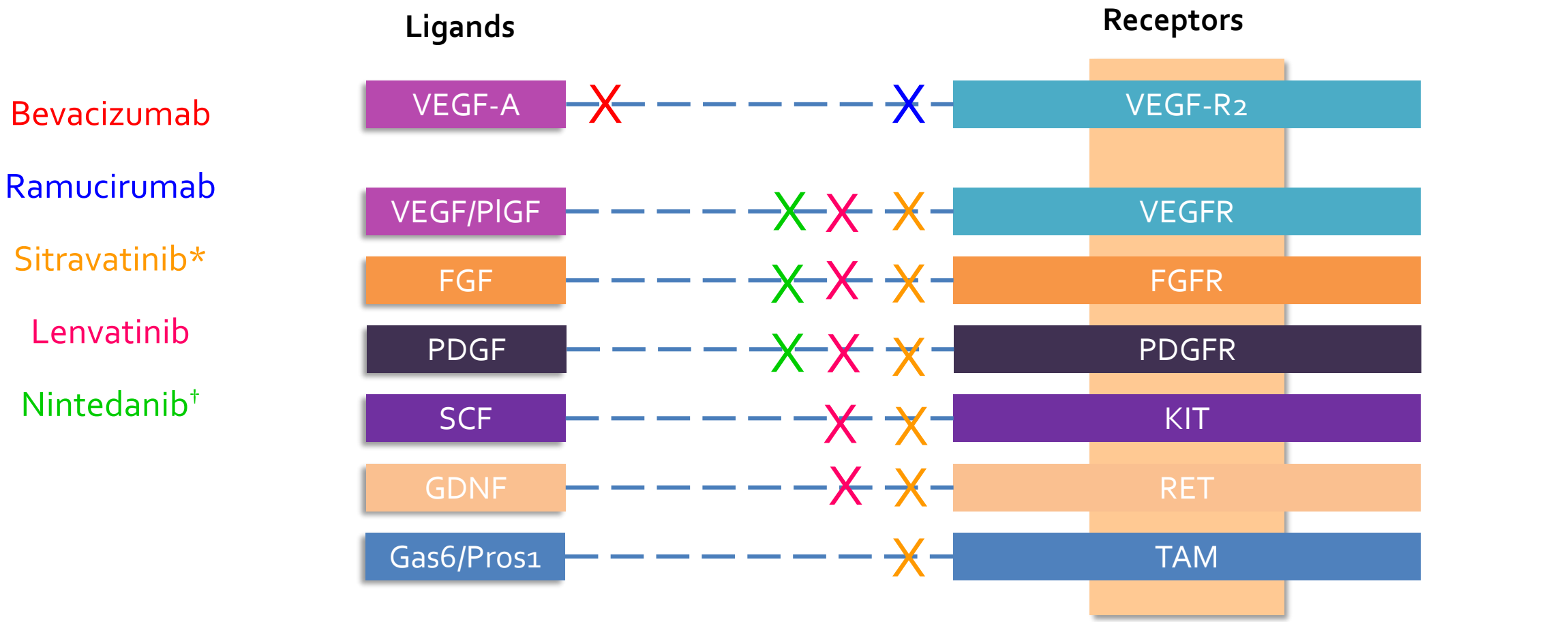
45/56 Tumor Regression
18/56 Tumor Regression >30%

16/56 CR/PR
- 9 confirmed
- 2 yet to be confirmed and on study
- 5 will not be confirmed

Study cycles of 28 days, with disease assessment scans every 2 cycles
Data as of 27-Aug-2018

MUNICH 2018 ESMO congress

Diversity of inhibitors in multiple tyrosine kinase pathways researched in I-O–experienced NSCLC

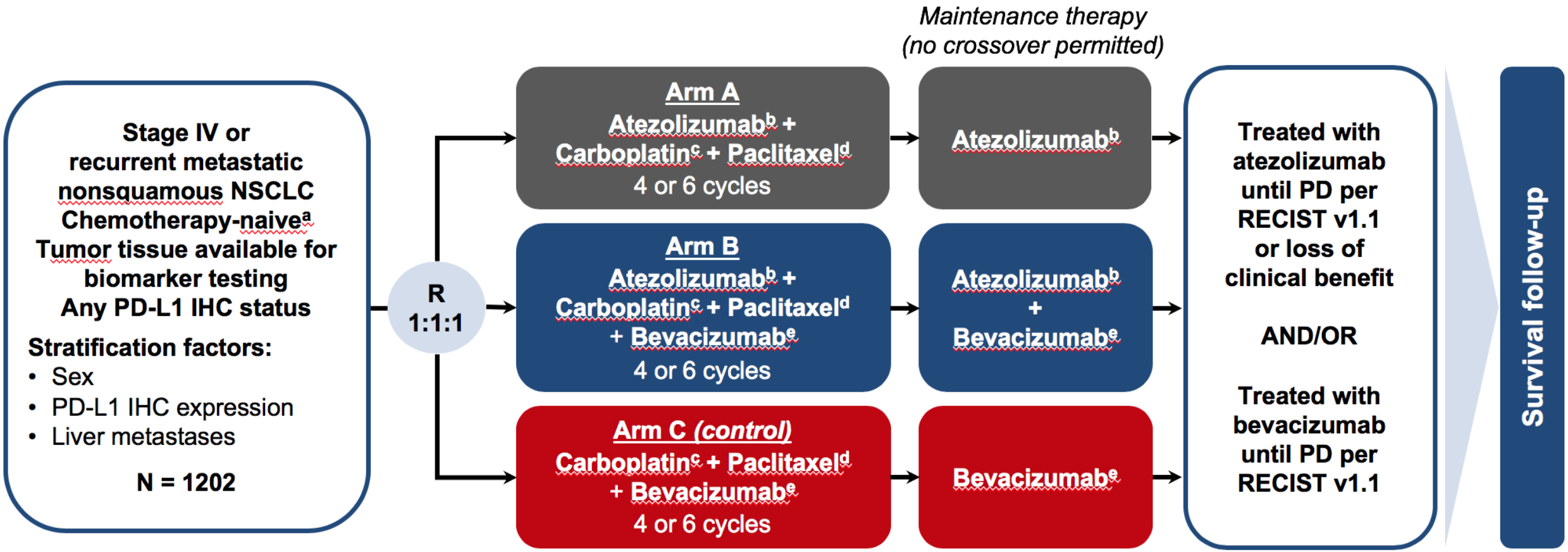


X = binding leading to inhibition of signal transduction

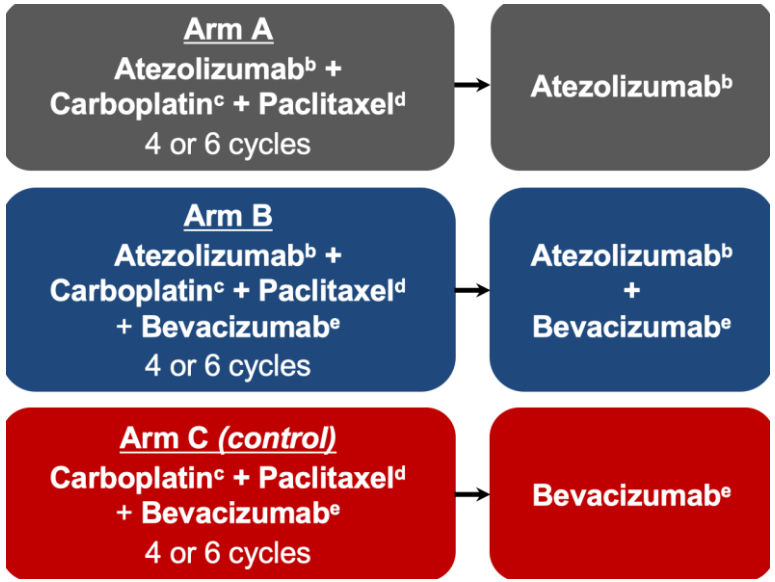
* Additional targets of sitravatinib include DDR2, Ephs, MET, and TRK; †Additional targets of nintedanib include Src, Lck, Lyn, and FLT-3

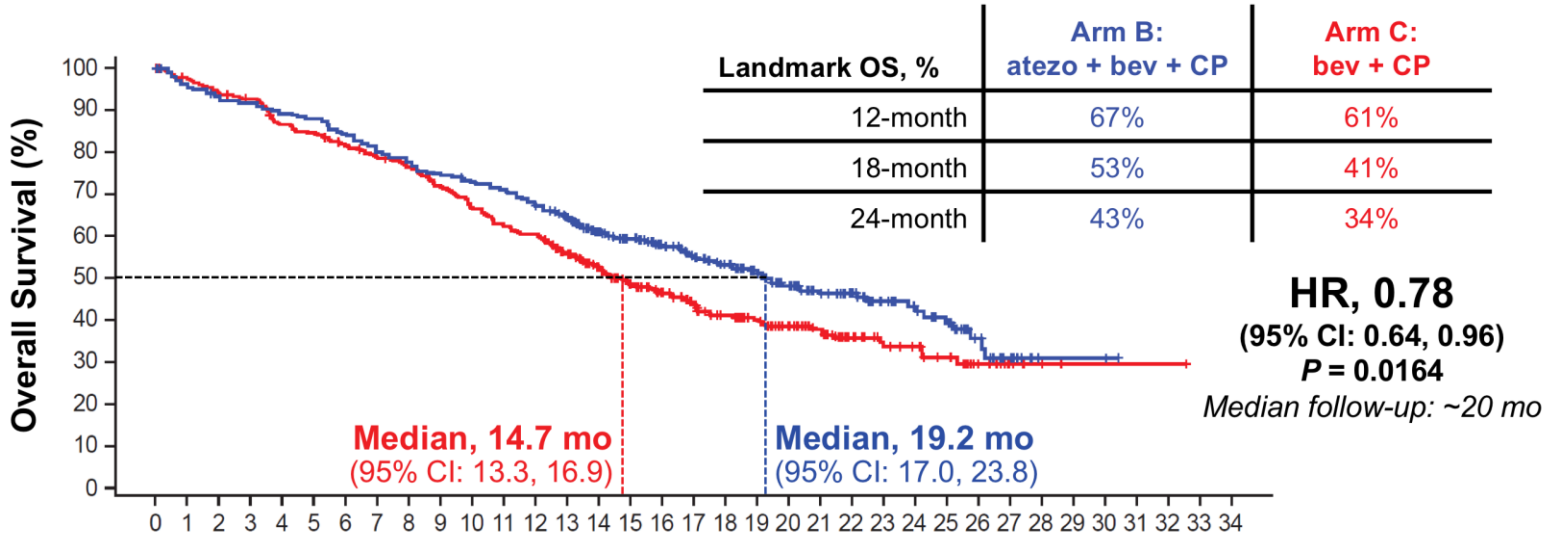
Borghaei, ELCC 2019

Impower 150 trial design

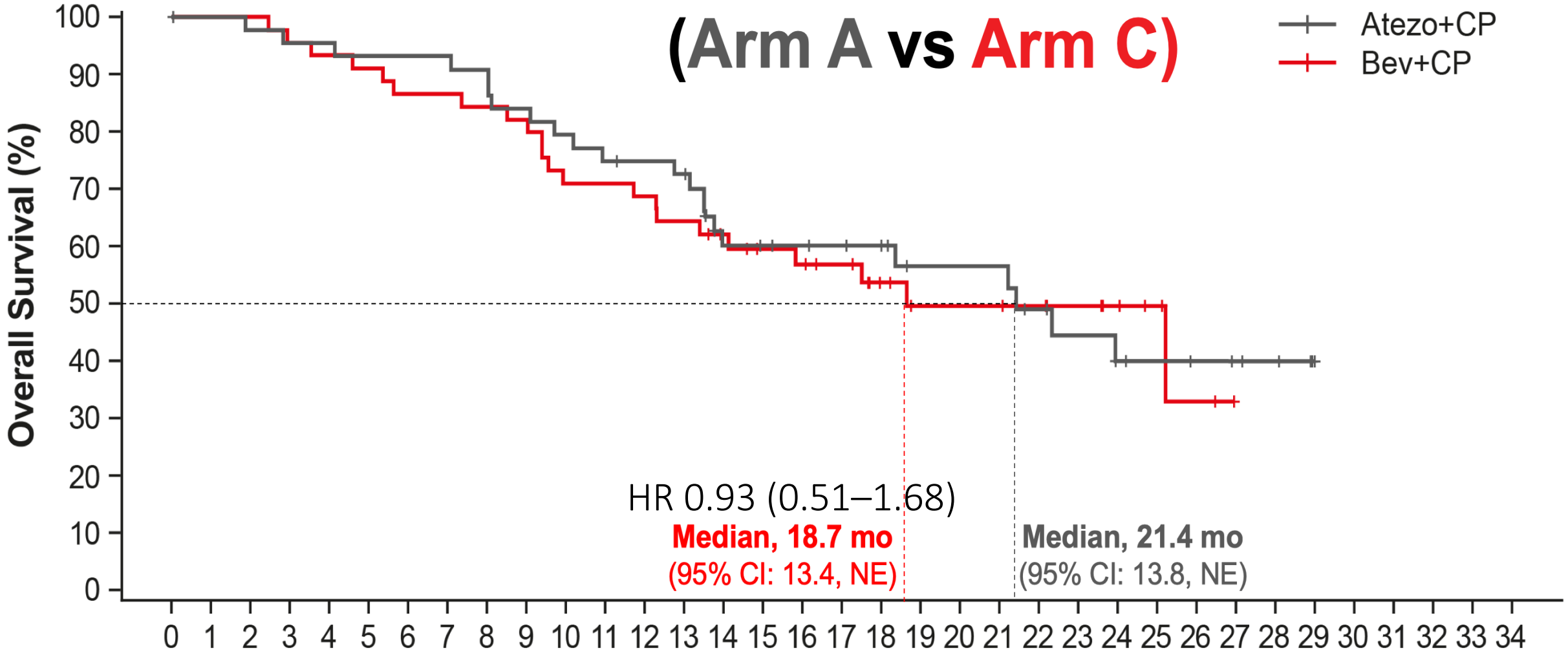


Carboplatin/paclitaxel/atezolizumab/bevacizumab is superior to carbo/pacli/bev irrespective of PD-L1 IMpower150



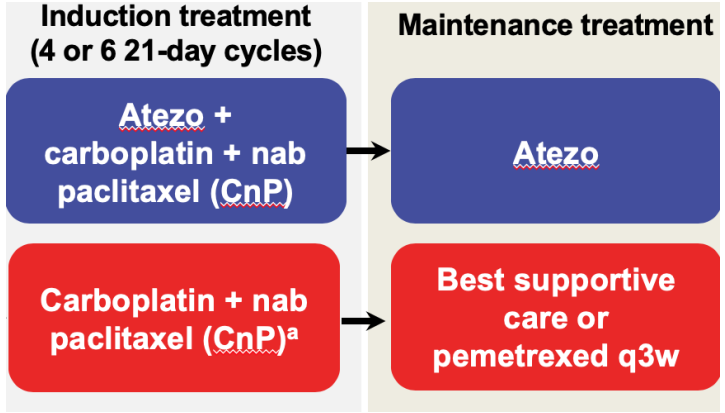


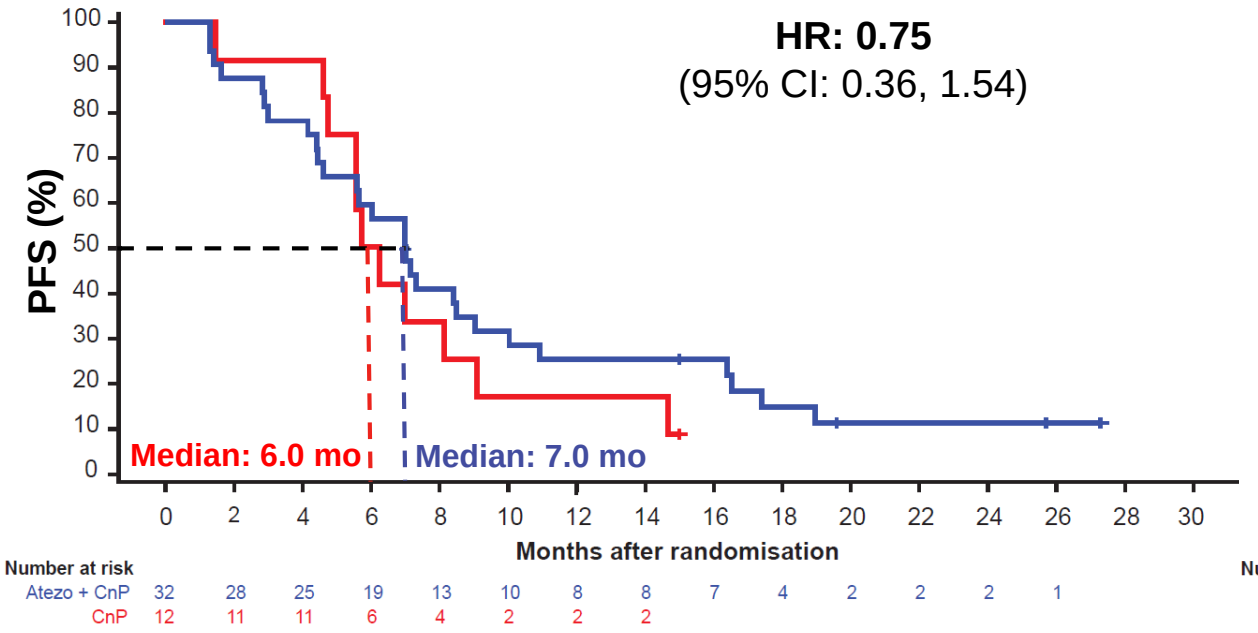
OS in EGFR-mt patients (Arm B vs Arm C)

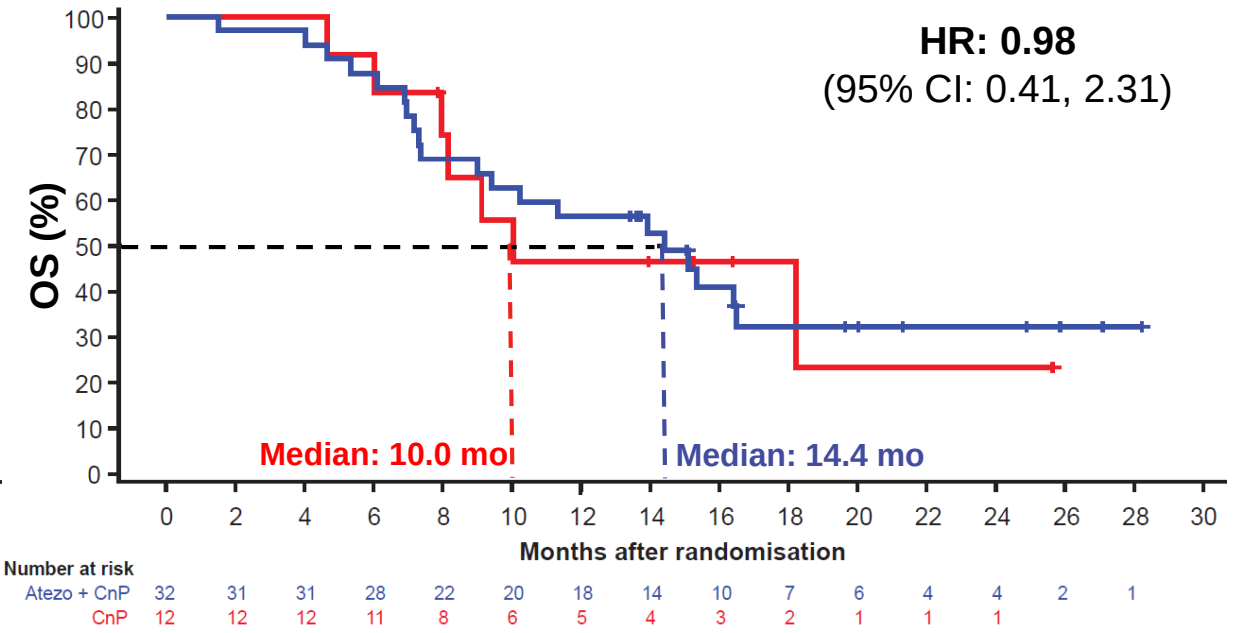


Reck, ELCC 2019

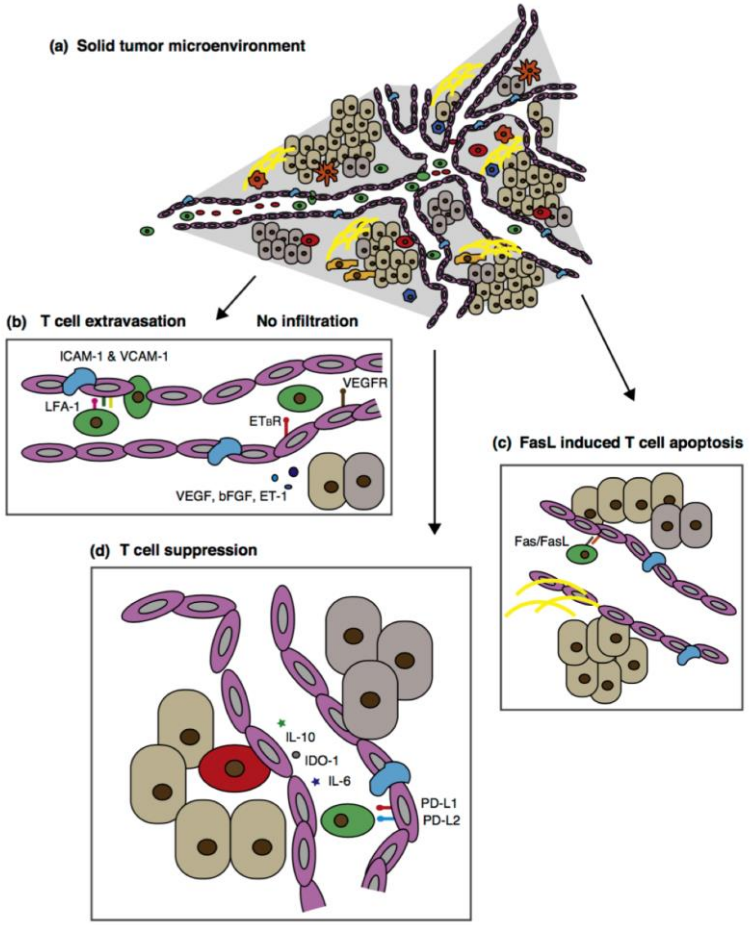
IMPower 130: Investigator-assessed PFS and OS in EGFR/ALK+

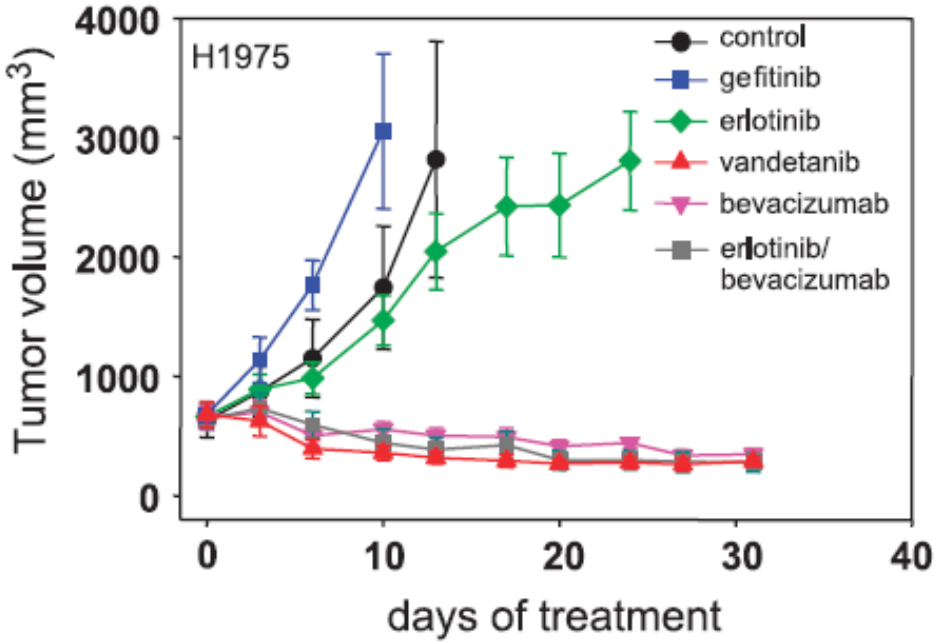






Is bevacizumab the game changer?

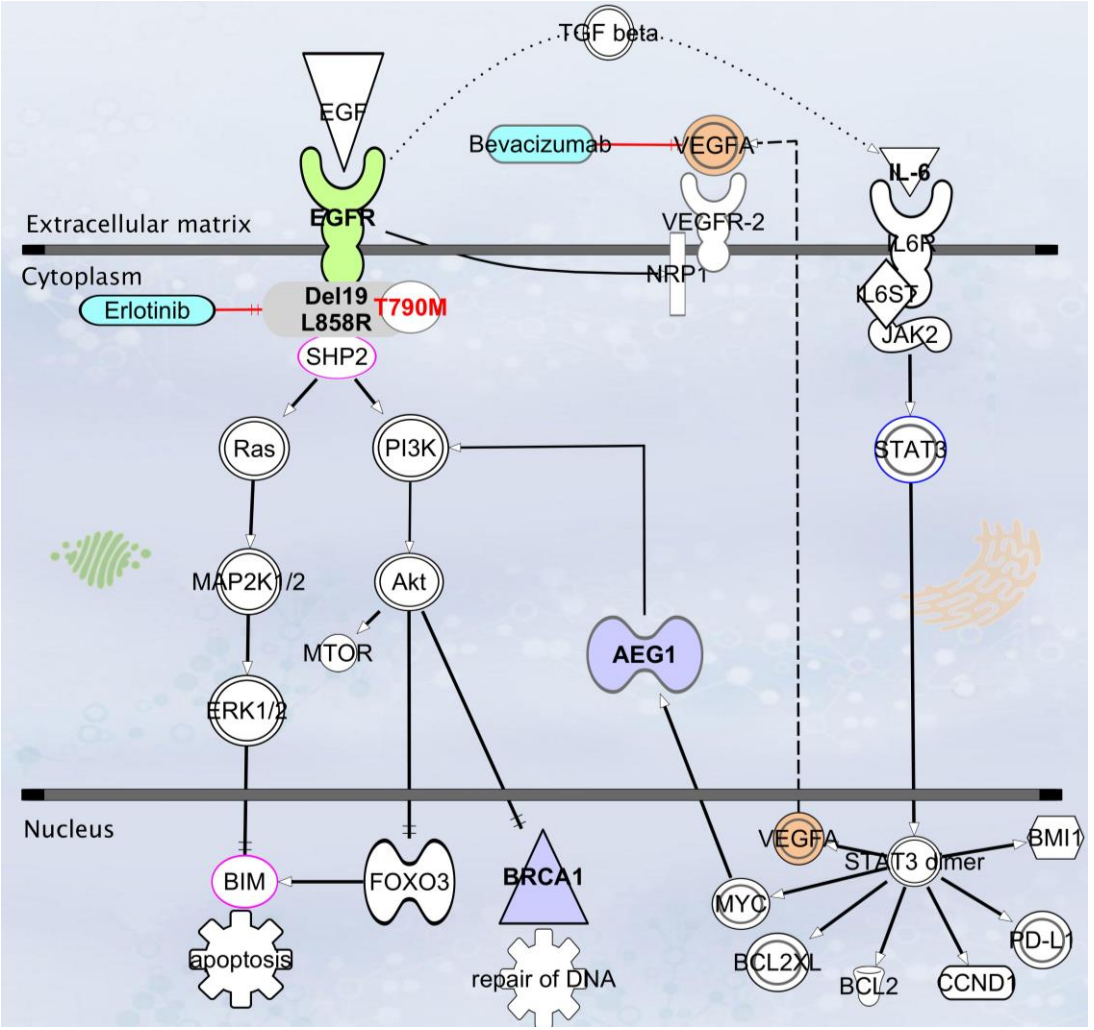




Combined VEGFR/EGFR pathway blockade may be beneficial in the presence EGFR mutation

Immune modulation in poorly immunogenic tumour?

Naumov et al, CCR 2009 (Heymach Group)



Anti-VEGF antibody inhibits IL-6/IL-6R regulation of VEGF.
Neither inhibition of PI3K or MAPK inhibits IL-6 mediated transcriptional up-regulation of VEGF.

Wei et al Oncogene 2003

AGENDA

- Rational for anti-angiogenesis and IO combinations
- Lung cancer paradigm: from phase 1 to phase 3 trials
- Combinatorial advances in RCC
- Ongoing efforts in early clinical trials across diseases

Anti-angiogenesis and IO in RCC : early trials

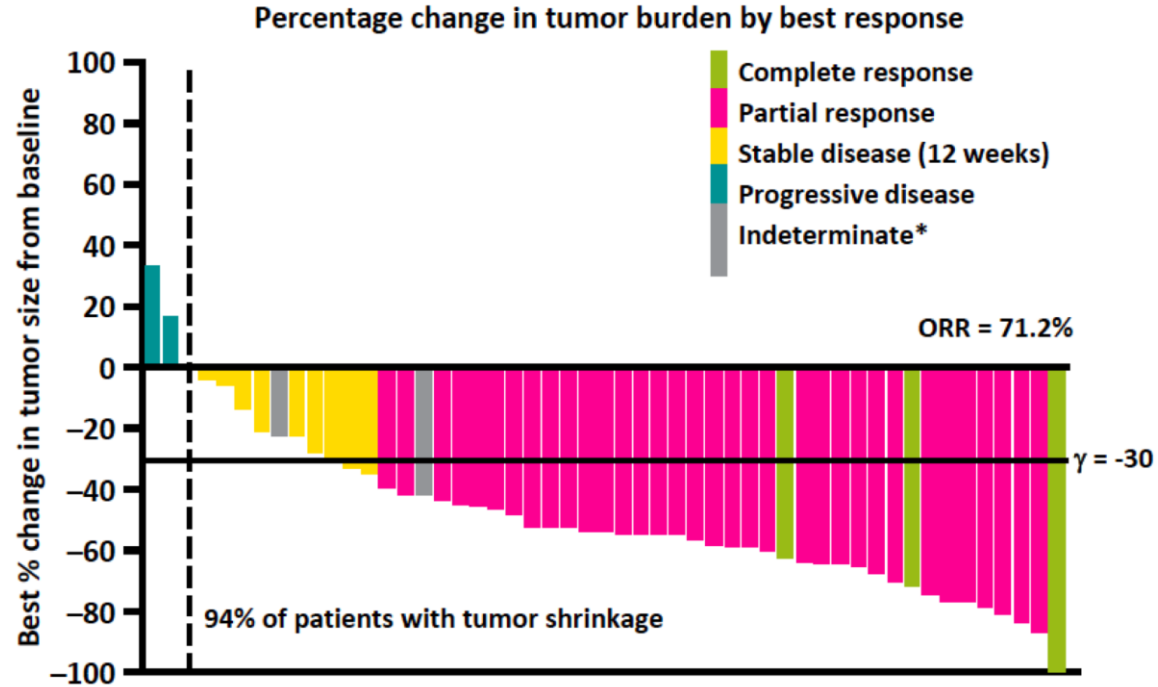
Combination	Line of therapy	# patients	ORR (% CR/% PR)	DCR (CR/PR/SD)	mPFS
Axitinib Avelumab	1st line	55	58% (6/52)	78%	N/A
Axitinib Pembrolizumab	1st line	52	67% (4/63)	88%	N/A
Pazopanib Pembrolizumab	1st line	10	60% (20/40)	100%	N/A
Lenvatinib Pembrolizumab	Post-VEGF	30	63% (0/63)	96%	N/A
Lenvatinib Pembrolizumab	1st line	12	83% (0/83)	100%	N/A
Bevacizumab Atezolizumab	1st line	101	32% (7/25)	N/A	11.7 mo
Cabozantinib Ipilimumab Nivolumab	Post-SOC	42 (GU: UC, RCC, others)	33% (8/25)	83%	5.8 mo

N/A: Not available
SOC: Standard of Care

Atkins M et al, ESMO 2016
McDermott D et al, GU ASCO 2017
Choueiri TK et al, ASCO 2017
Chowdhury S et al, ASCO 2017
Lee C et al, ESMO 2017
Nadal R et al, ESMO 2017

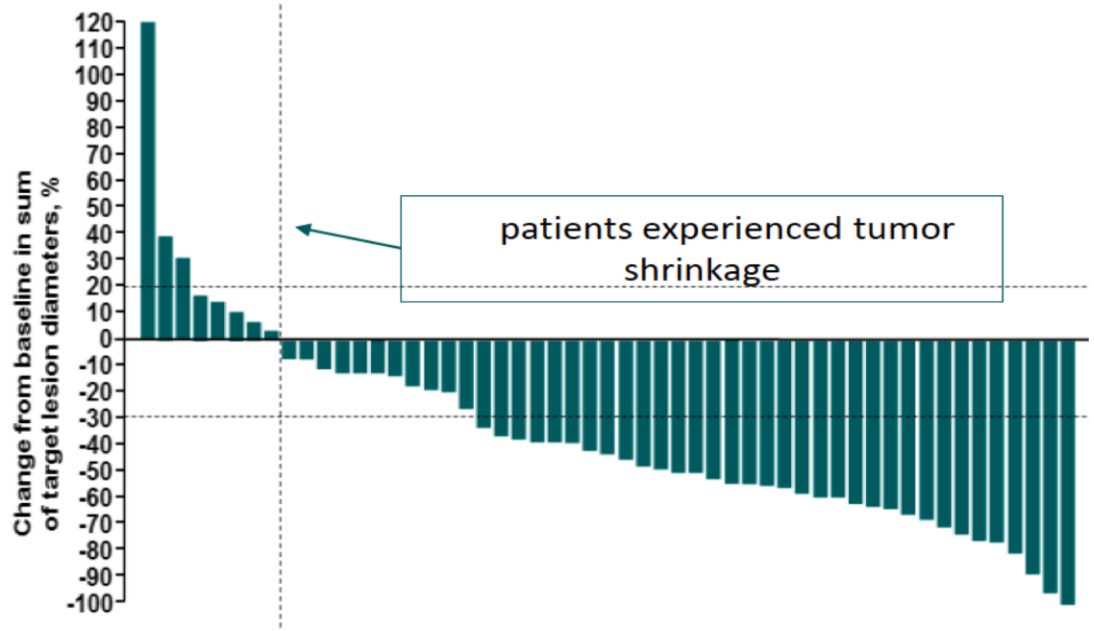
Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial

Michael B Atkins, Elizabeth R Plimack, Igor Puzanov, Mayer N Fishman, David F McDermott, Daniel C Cho, Ulka Vaishampayan, Saby George, Thomas E Olencki, Jamal C Tarazi, Brad Rosbrook, Kathrine C Fernandez, Mariajose Lechuga, Toni K Choueiri



Preliminary results for avelumab plus axitinib as first-line therapy in patients with advanced clear-cell renal-cell carcinoma (JAVELIN Renal 100): an open-label, dose-finding and dose-expansion, phase 1b trial

Toni K Choueiri, James Larkin, Mototsugu Oya, Fiona Thistlethwaite, Marcella Martignoni, Paul Nathan, Thomas Powles, David McDermott, Paul B Robbins, David D Chism, Daniel Cho, Michael B Atkins, Michael S Gordon, Sumati Gupta, Hirotsugu Uemura, Yoshihiko Tomita, Anna Compagnoni, Camilla Fowst, Alessandra di Pietro, Brian I Rini

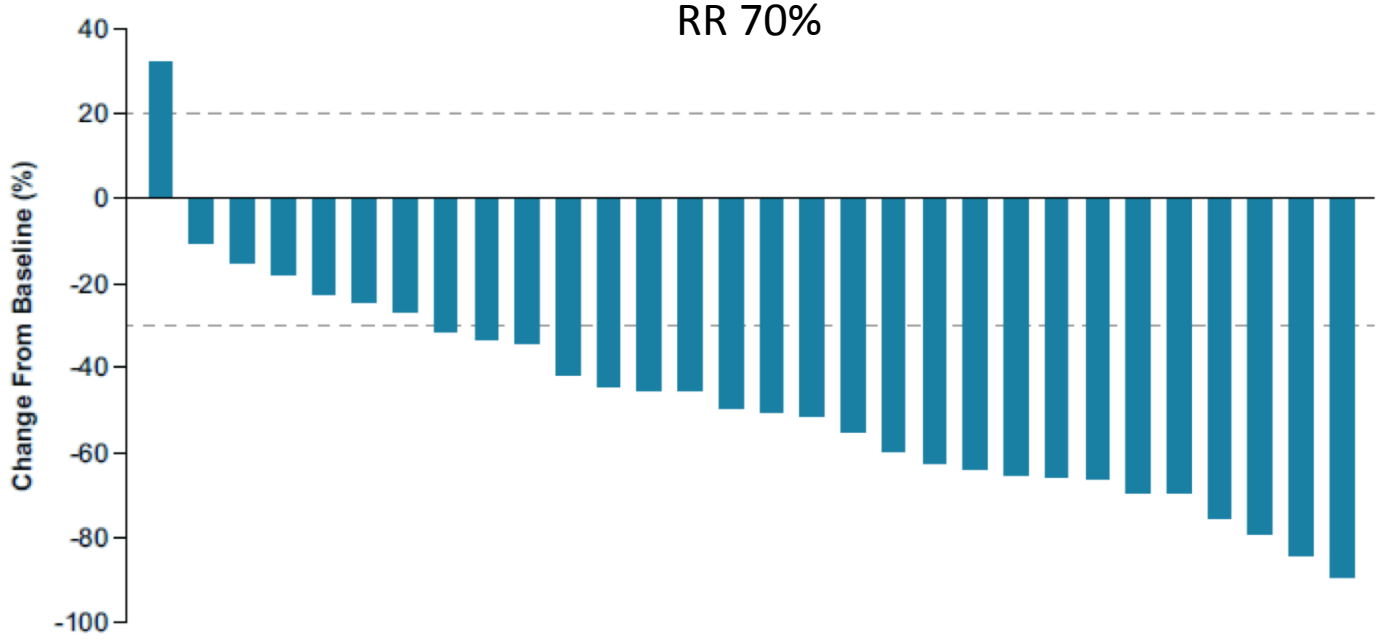


Lenvatinib and pembrolizumab in RCC

KEYNOTE-146

LENVIMA + KEYTRUDA FOR TREATMENT OF PATIENTS WITH aRCC

RR 70%



ALMOST ALL PATIENTS (N=29) EXPERIENCED TUMOR REDUCTION FROM BASELINE

Makker, ASCO 2018

JAVELIN RENAL 101: STUDY DESIGN

Key eligibility criteria:

- Treatment-naive aRCC with a clear cell component
- ≥ 1 measurable lesion as defined by RECIST v1.1
- Tumor tissue available for PD-L1 staining
- ECOG PS 0 or 1

Stratification:

- ECOG PS (0 vs 1)
- Geographic region (USA vs Canada/Western Europe vs ROW)

N = 886

R 1:1

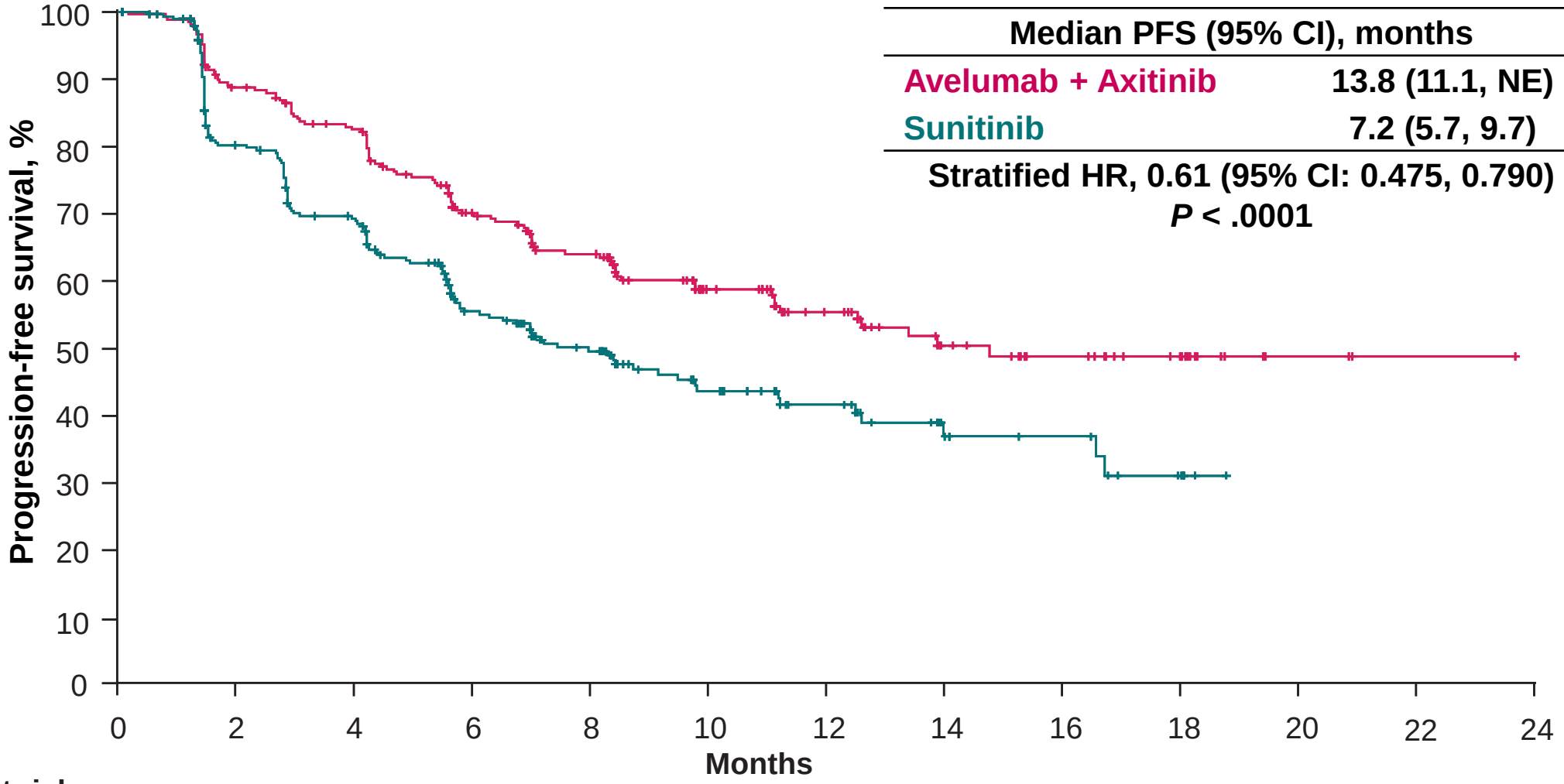
Avelumab 10 mg/kg IV Q2W + Axitinib 5 mg PO BID (6-week cycle)

Sunitinib 50 mg PO QD (4 weeks on, 2 weeks off)

BID, twice per day; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **IV**, intravenous; **PO**, orally; **Q2W**, every 2 weeks; **QD**, once per day; **ROW**, rest of the world.

PFS PER IRC IN THE PD-L1+ GROUP

Primary endpoint



Median PFS (95% CI), months	
Avelumab + Axitinib	13.8 (11.1, NE)
Sunitinib	7.2 (5.7, 9.7)

Stratified HR, 0.61 (95% CI: 0.475, 0.790)
P < .0001

Number at risk

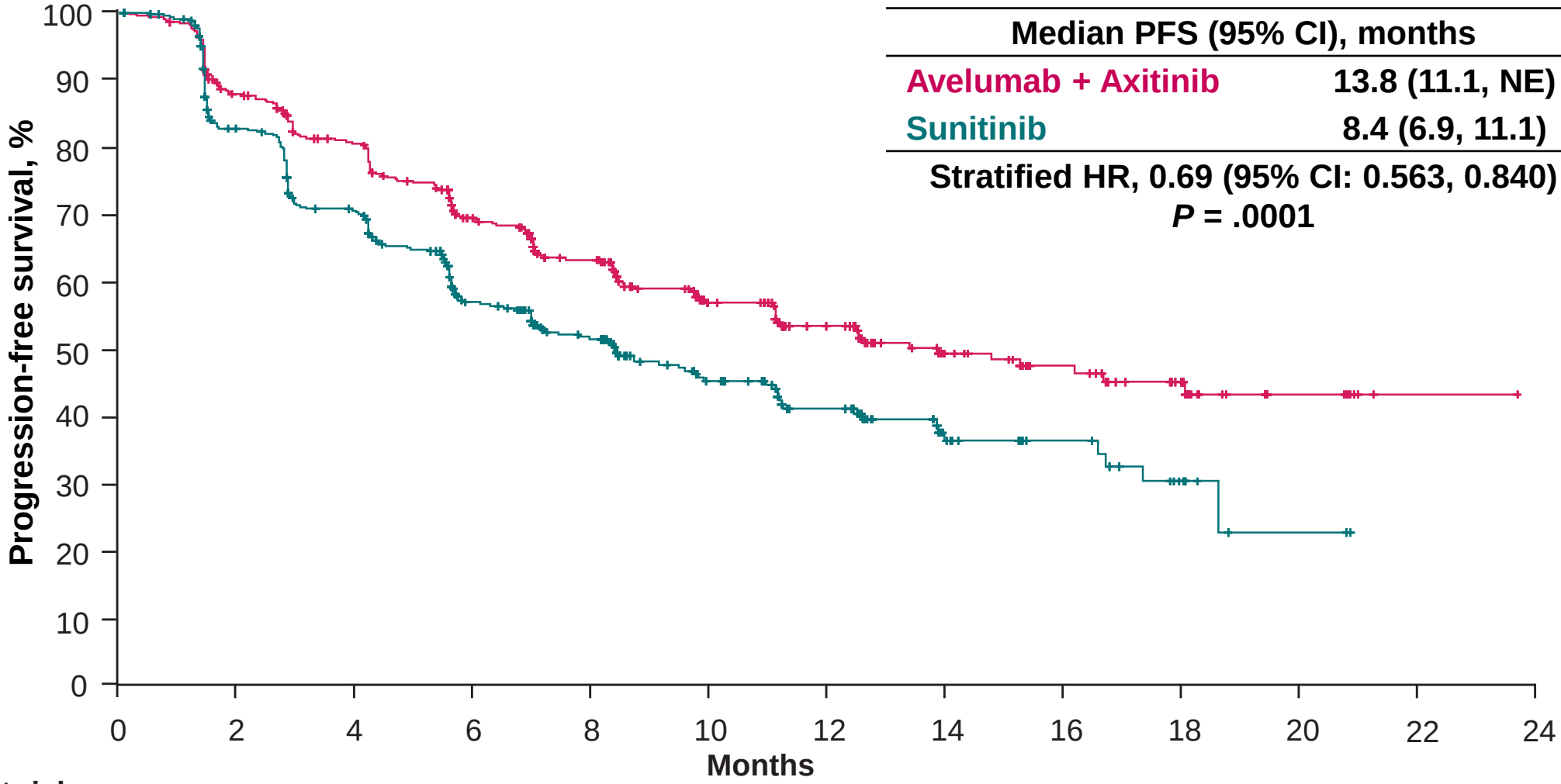
Avel + Axit:	270	227	205	154	120	76	53	32	23	13	3	1	0
Sunitinib:	290	210	174	119	85	49	35	16	13	5	0		

Minimum follow-up, 6 months. Median follow-up, 9.9 months (avelumab + axitinib) and 8.4 months (sunitinib).
The PFS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (*P* = .001).

NE, not estimable.

PFS PER IRC IN THE OVERALL POPULATION

Key secondary endpoint



Median PFS (95% CI), months	
Avelumab + Axitinib	13.8 (11.1, NE)
Sunitinib	8.4 (6.9, 11.1)

Stratified HR, 0.69 (95% CI: 0.563, 0.840)
***P* = .0001**

Number at risk

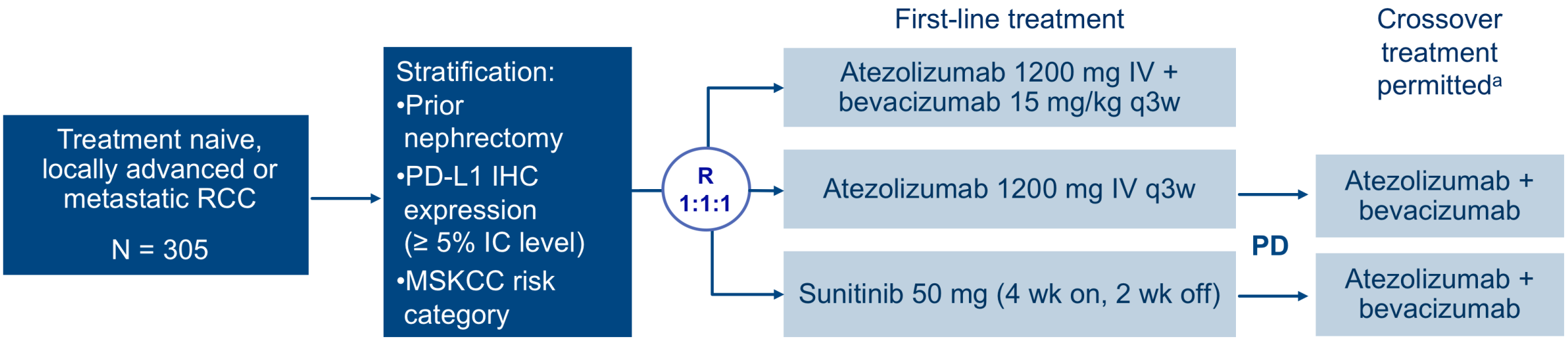
Avel + Axit:	442	364	321	250	193	127	94	57	42	24	8	1	0
Sunitinib:	444	329	271	192	144	90	64	29	20	8	2	0	

Minimum follow-up, 6 months. Median follow-up, 10.8 months (avelumab + axitinib) and 8.6 months (sunitinib).
The PFS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (*P* = .001).

IMmotion150 (Phase II) Trial Design

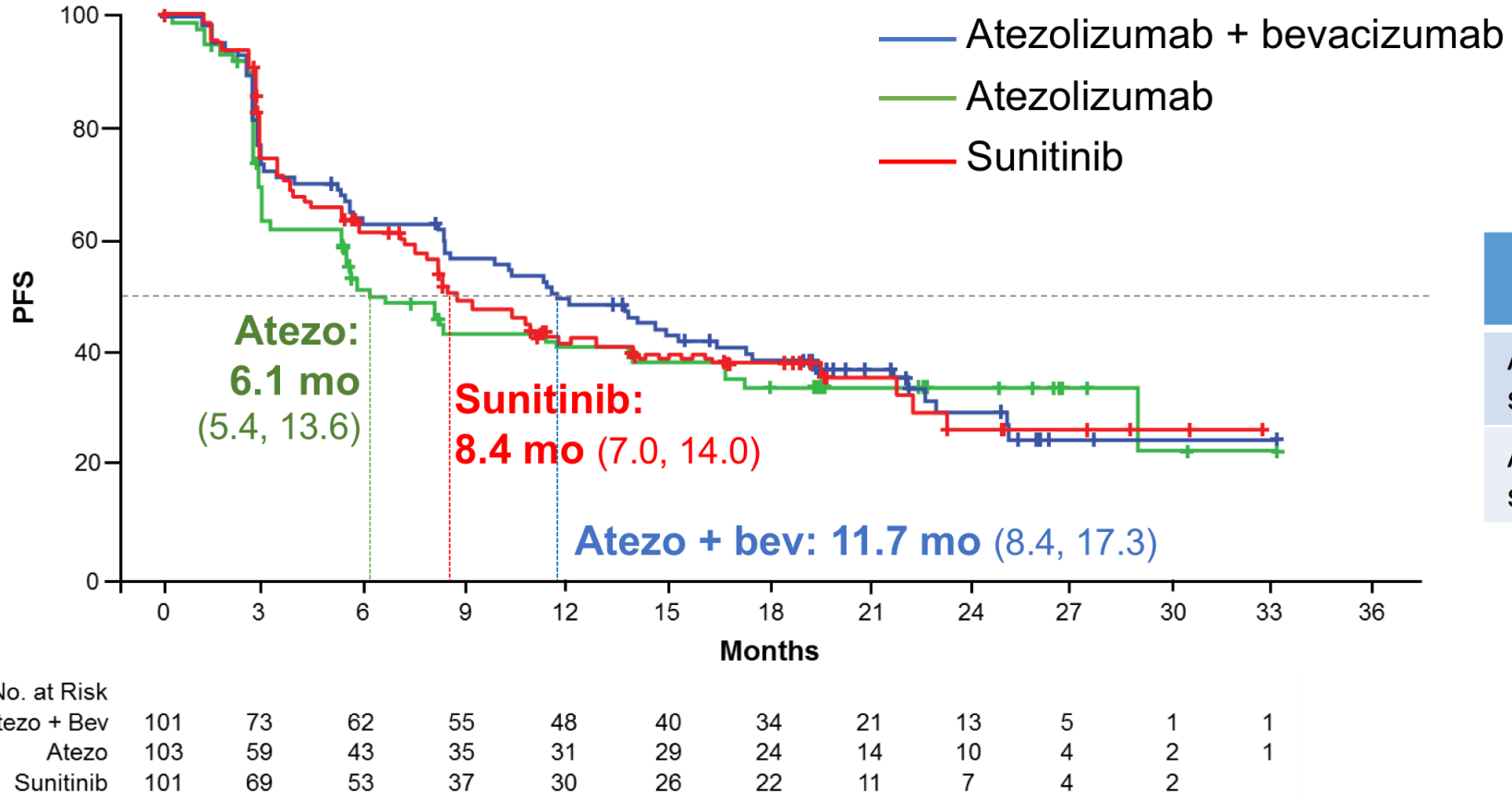
nature medicine
ARTICLES
https://doi.org/10.1038/s41591-018-0053-3

Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma



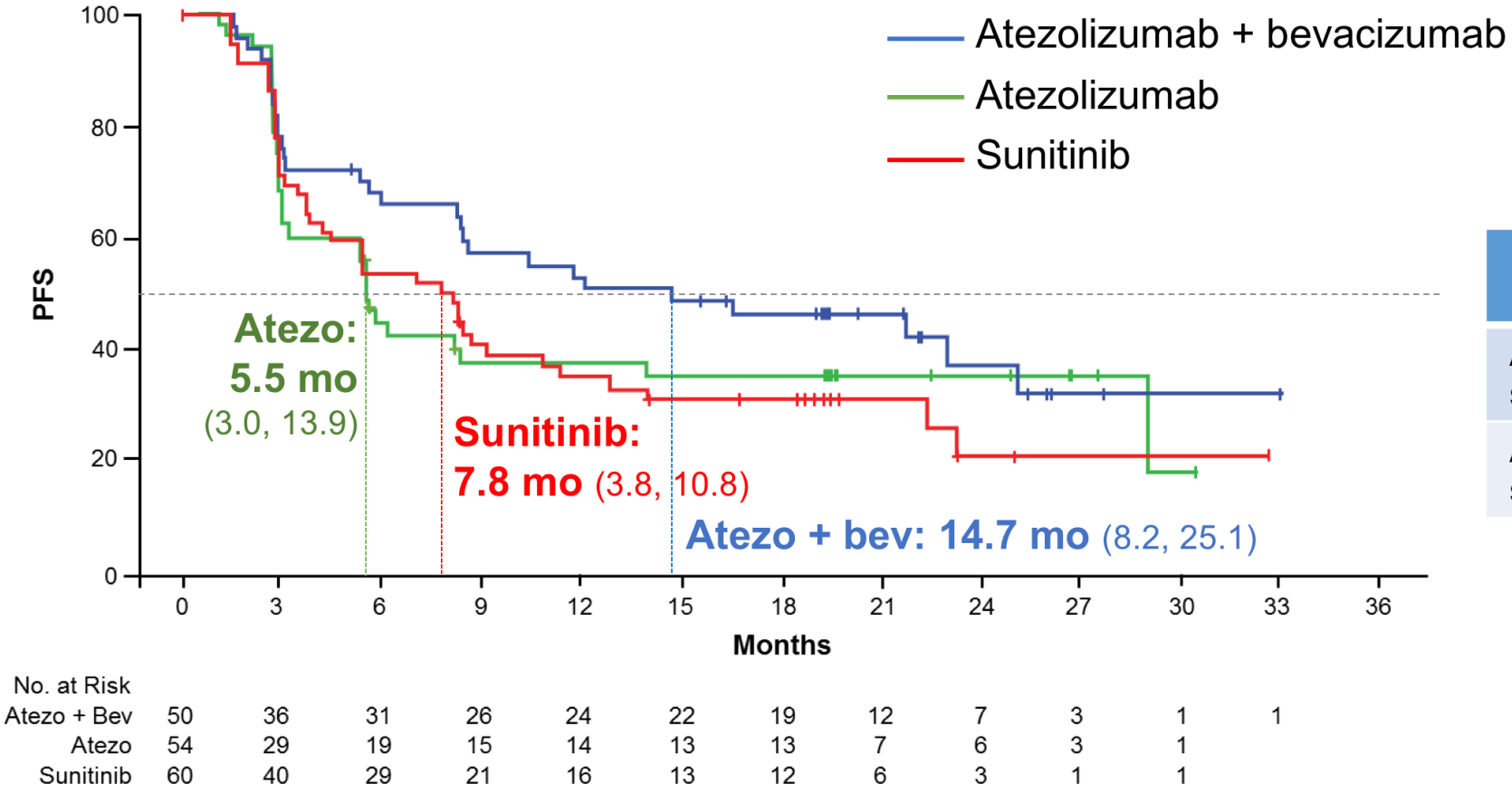
- The coprimary endpoints are PFS (RECIST v1.1 by IRF) in ITT and PD-L1+ patients

IMmotion150: IRF-Assessed PFS



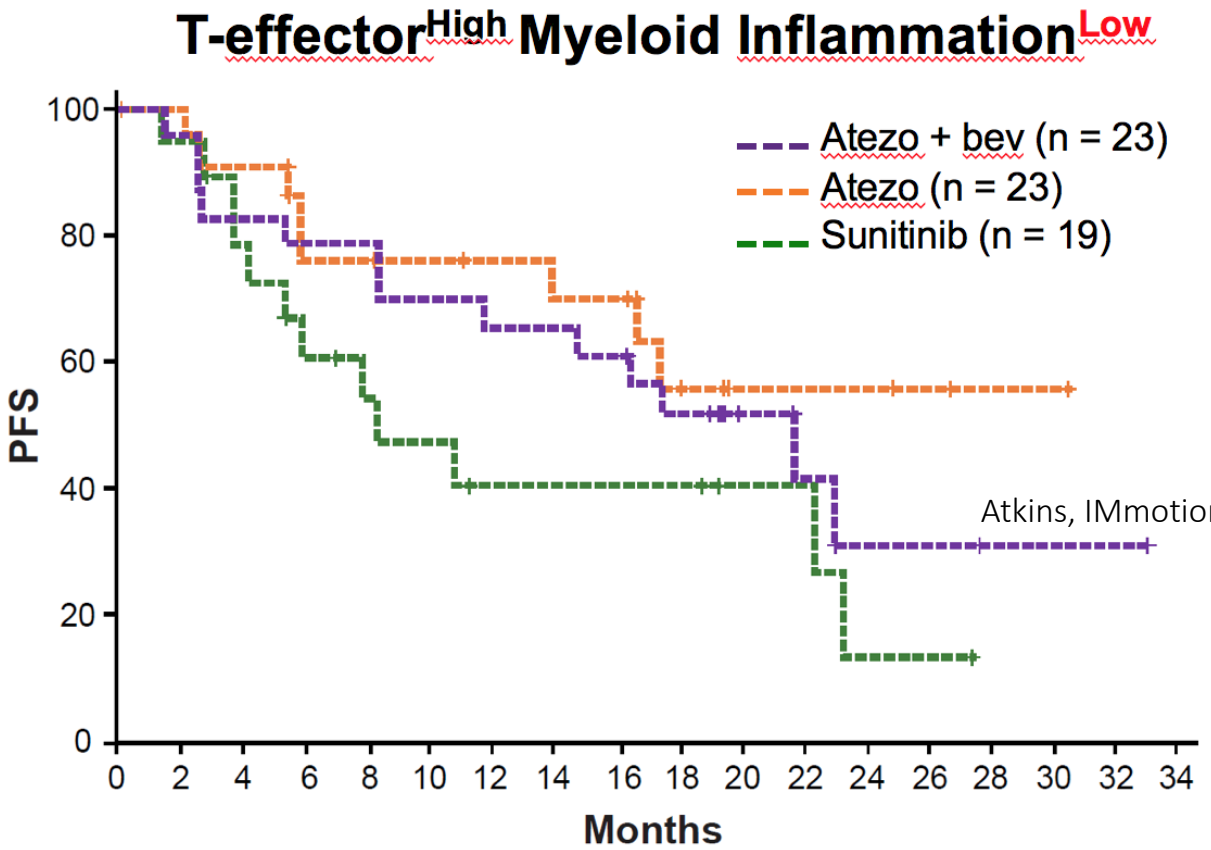
	Stratified HR (95% CI)	*P* Value[a]
Atezo + bev vs sunitinib	**1.00 (0.69, 1.45)**	0.982
Atezo vs sunitinib	**1.19 (0.82, 1.71)**	0.358

IMmotion150: IRF-Assessed PFS: PD-L1 positive (IC)

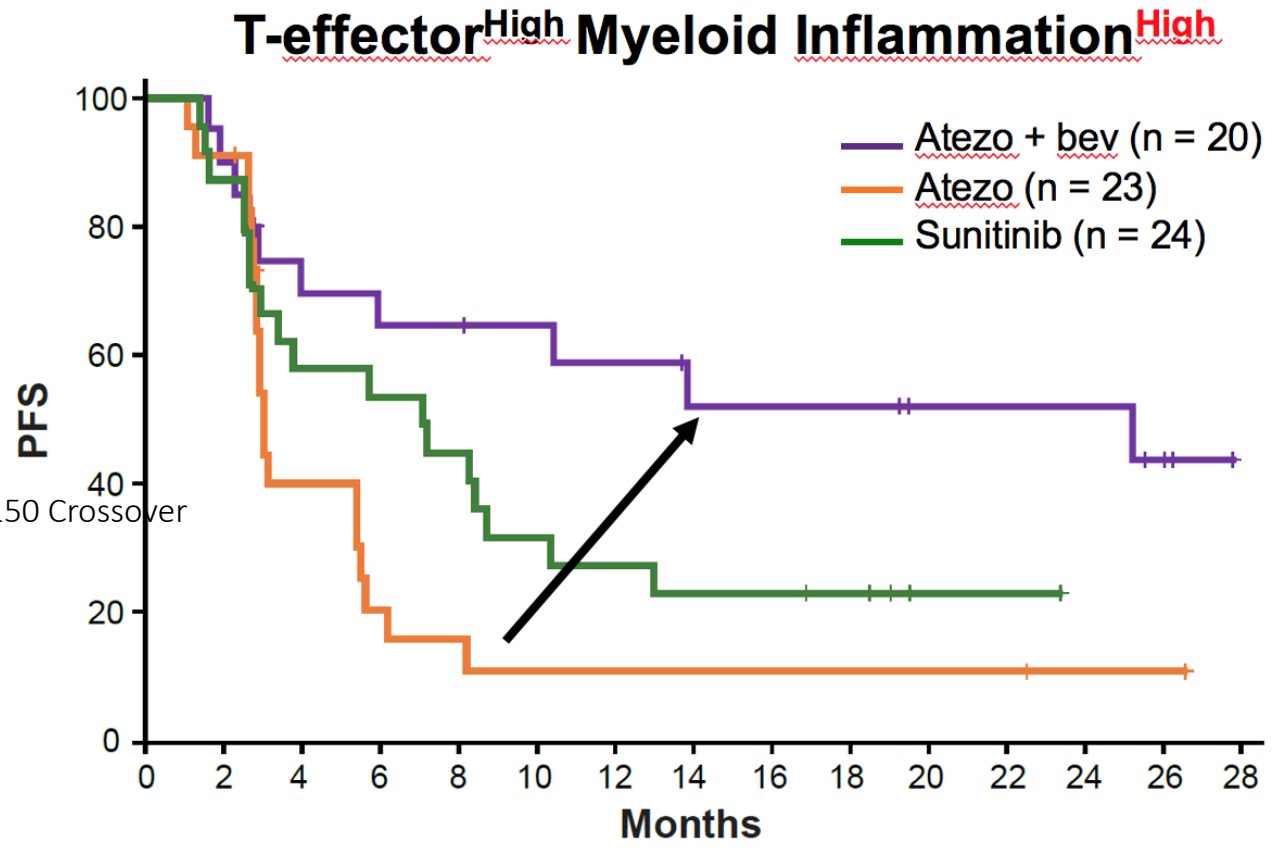


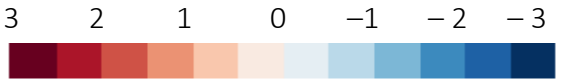
	Stratified HR (95% CI)	*P* Value[a]
Atezo + bev vs sunitinib	**0.64 (0.38, 1.08)**	0.095
Atezo vs sunitinib	**1.03 (0.63, 1.67)**	0.917

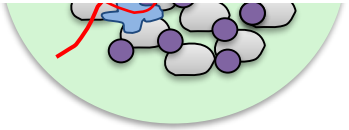
Transcriptome Map of Angiogenesis and Immune-Associated Genes Renal Cell Carcinoma



Atkins, IMmotion150 Crossover

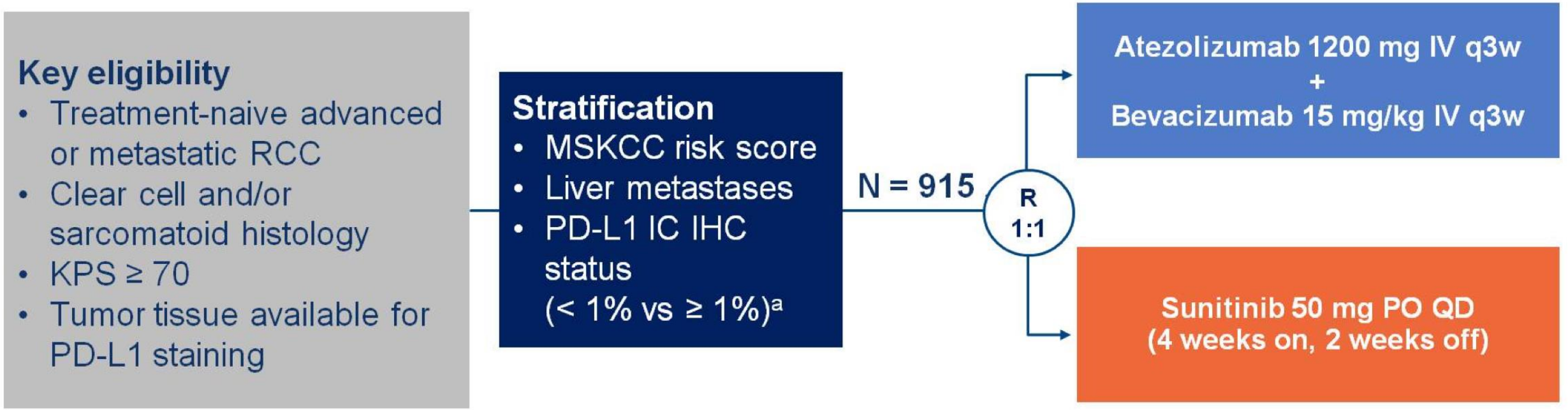






1. Brauer, Clin Cancer Res. 2012; 2. Herbst, Nature 2014; 3. Powles, SITC 2015; 4. Fehrenbacher, Lancet 2016. McDermott, AACR 2017.

IMmotion151: Trial design

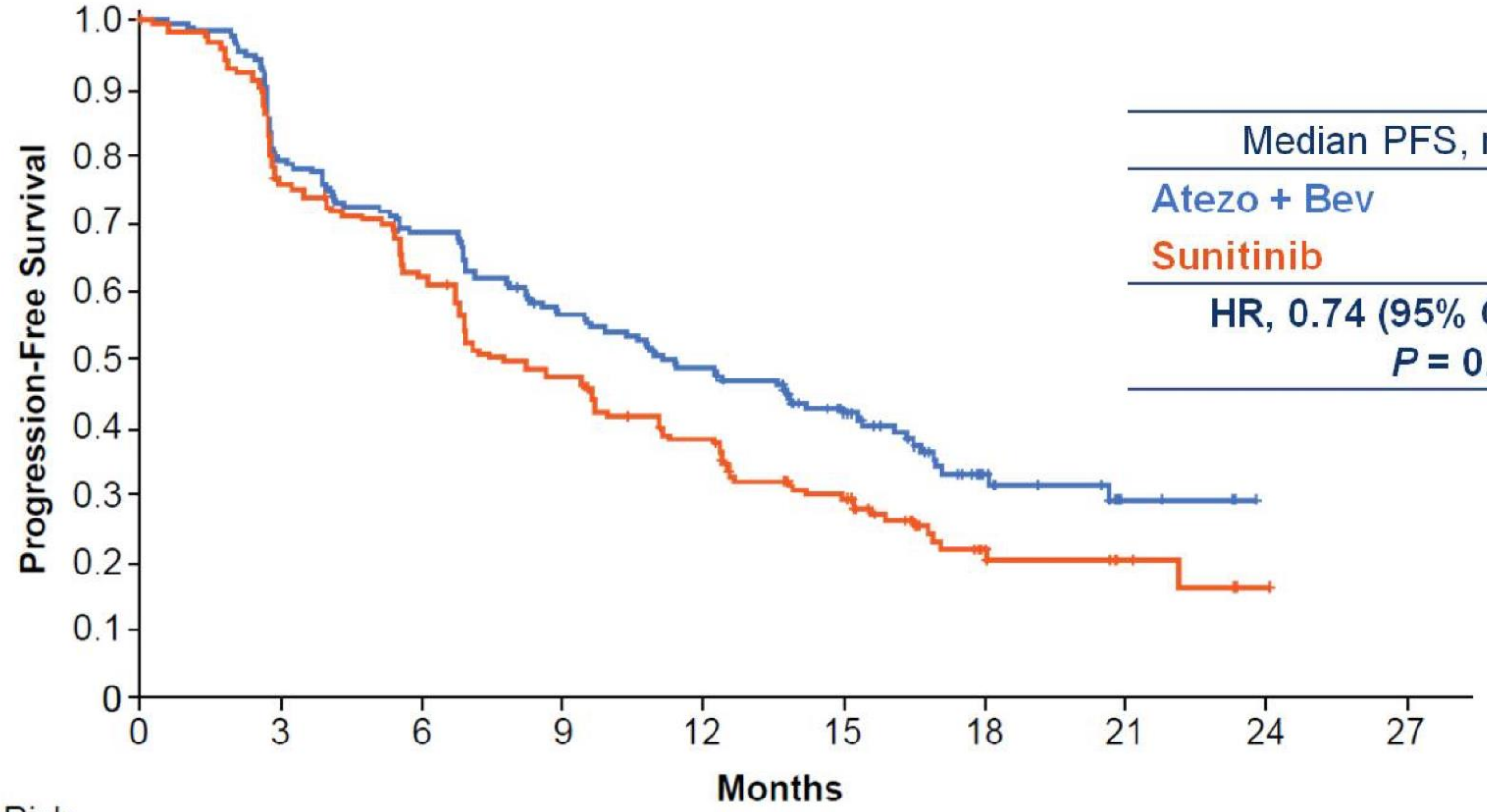


Co-primary endpoints
- PFS by INV assessment in PD-L1+
- OS in ITT

Other key endpoints
- PFS in ITT
- OS in PD-L1+
- ORR
- Patient-reported outcomes
- Safety

Motzer, ASCO GU 2018

IMmotion151: PFS in PD-L1 positive



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[a]	

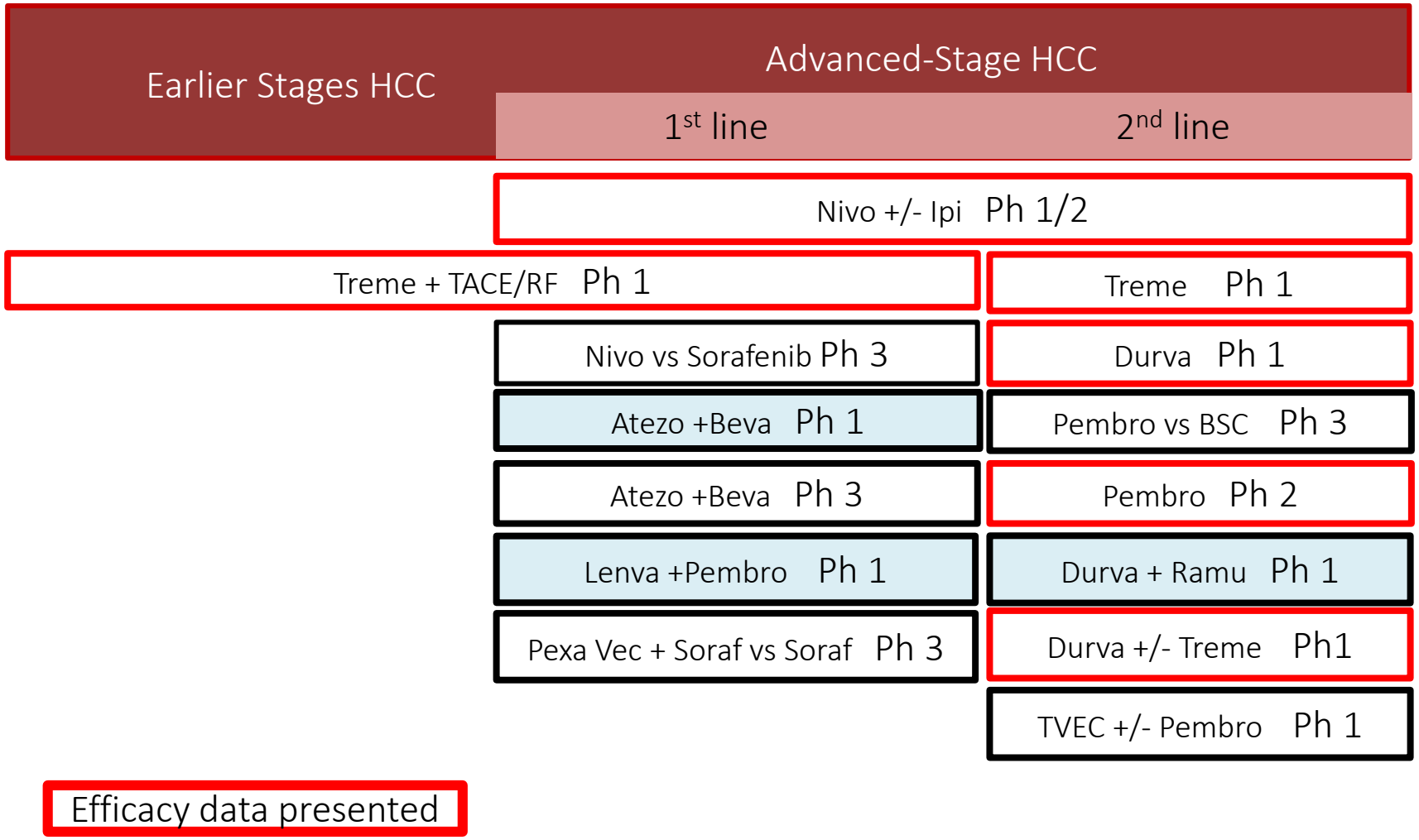
PD-L1–[a]	
Atezo + Bev n = 276	Sunitinib n = 277[b]
11.0 (8.3, 13.3)	8.4 (7.4, 10.1)
0.84 (0.67, 1.04)	

Motzer, ASCO GU 2018

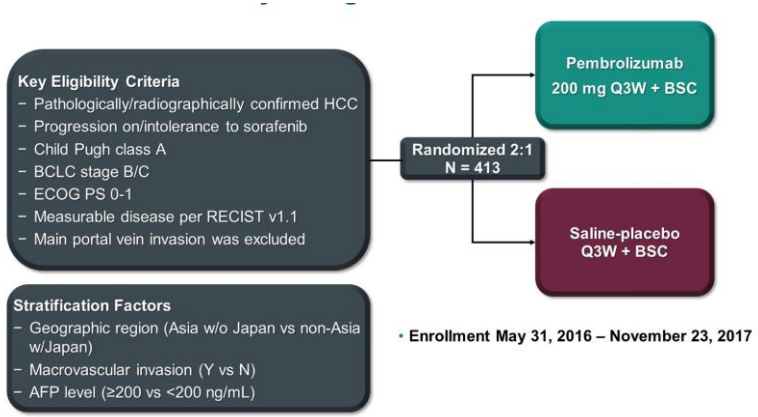
AGENDA

- Rational for anti-angiogenesis and IO combinations
- Lung cancer paradigm: from phase 1 to phase 3 trials
- Combinatorial advances in RCC
- Ongoing efforts in early clinical trials across diseases

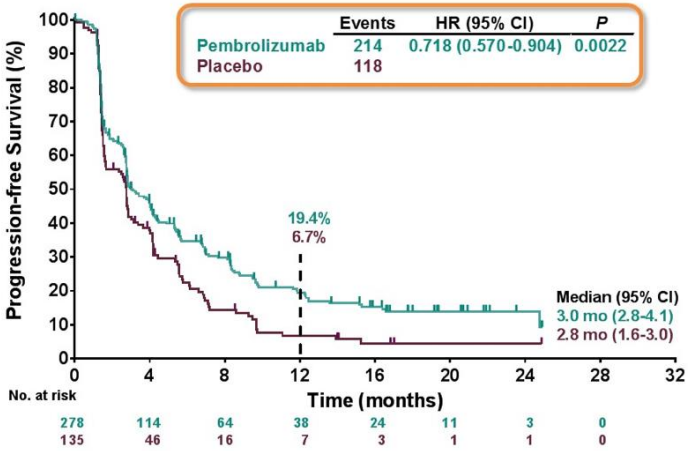
Anti-angiogenesis and IO trials for advanced HCC

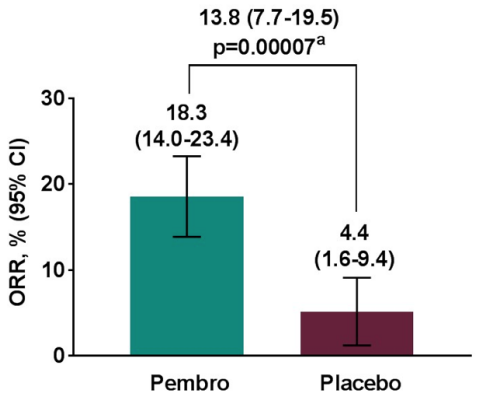


Reminder KEYNOTE-240

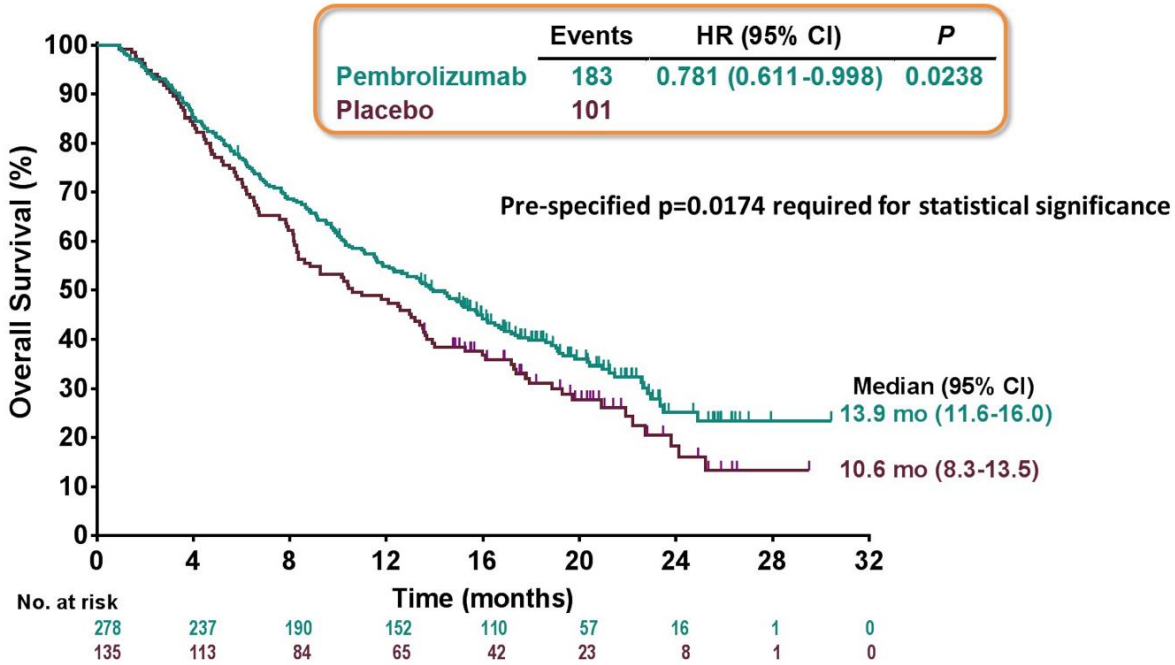


Final Analysis



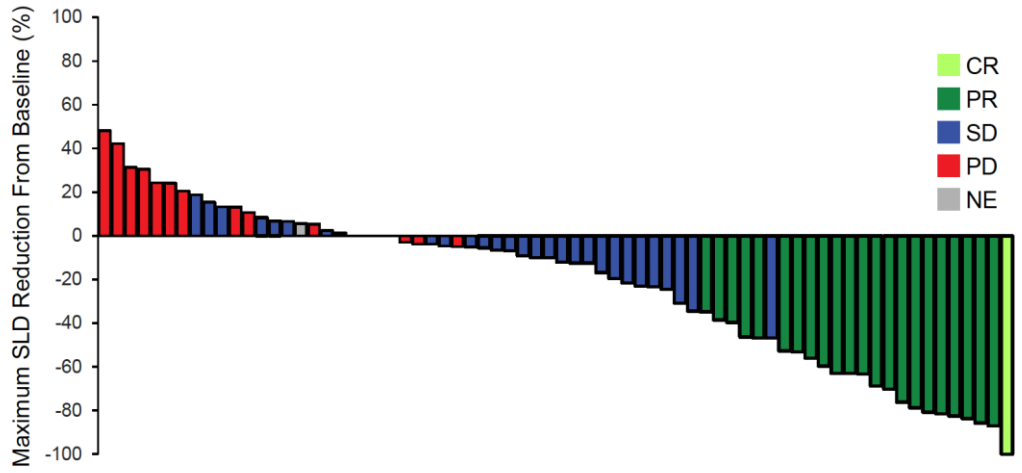


Overall Survival



PFS and OS: Not statistically significant

Expanding the atezolizumab-bevacizumab opportunity HCC cohort



anti–PD-1 or anti–PD-L1 therapeutic antibodies

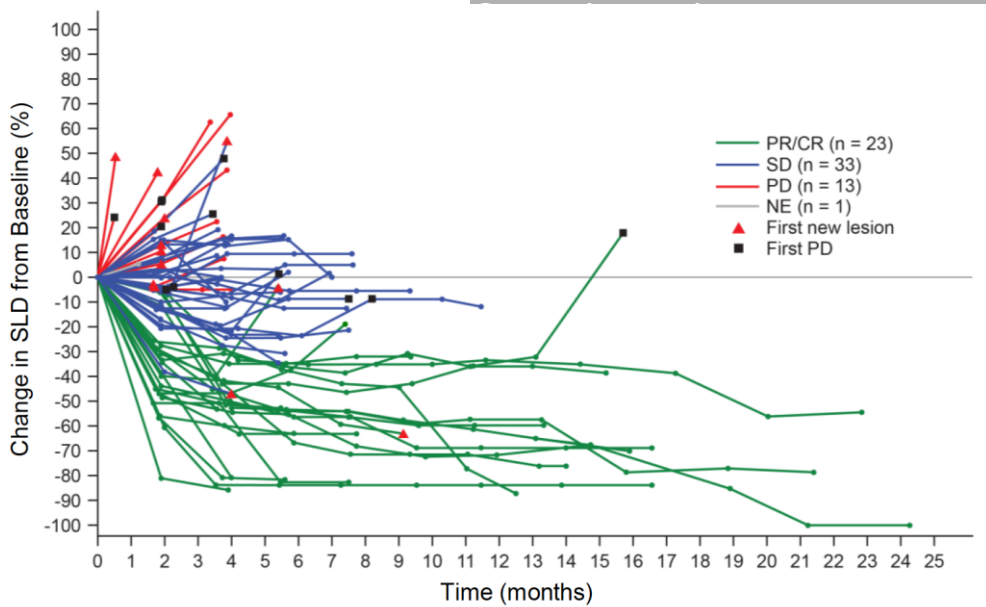
Primary endpoints

	n = 73
Median PFS (range), mo	14.9 (0.5 to 23.9+)
PFS events, n (%)	29 (40)
6-month PFS, %	65
Median follow-up, mo	7.2

Gastric cancer
Pancreatic cancer

olizumab)

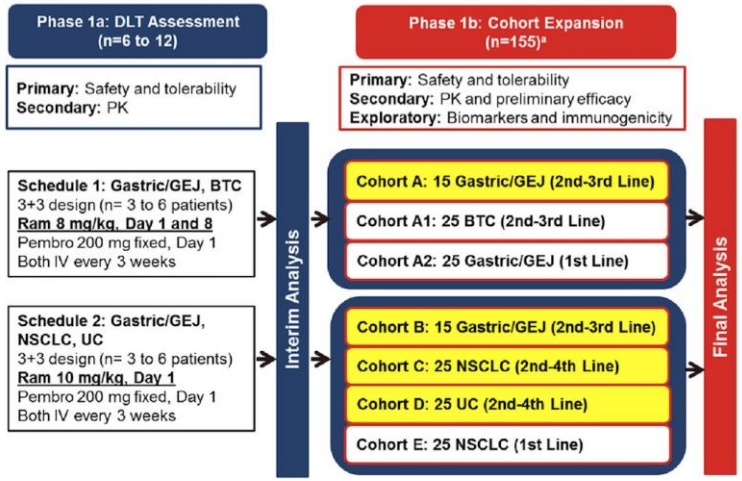
sessed OF

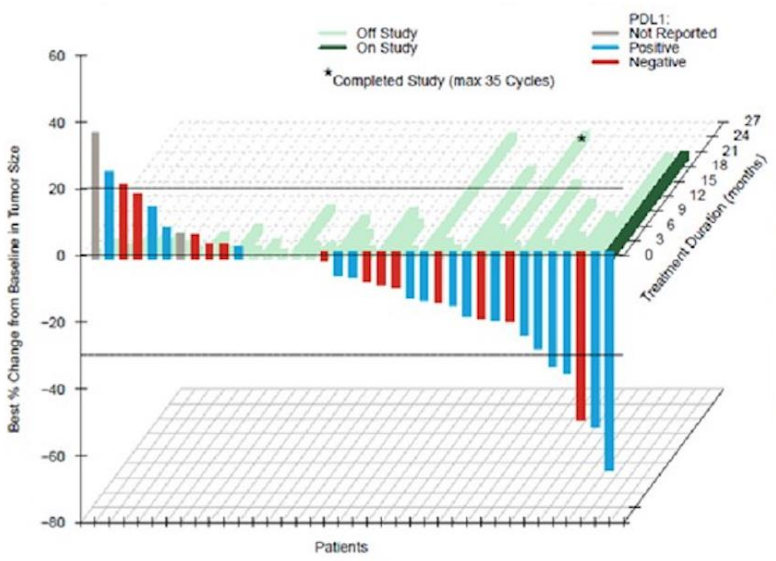


ORR	
Overall, n (%)[a]	**23/73 (32)**
CR	1/73 (1)
PR	22/73 (30)
SD	33/73 (45)
PD	13/73 (18)
By region, n/n (%)[b]	
Asia excluding Japan	12/41 (29)
Japan/USA	10/31 (32)
By aetiology, n/n (%)	
HBV	11/36 (31)
HCV	10/23 (43)
Non-viral	2/14 (14)
By baseline AFP, n/n (%)[c]	
< 400 ng/mL	12/41 (29)
≥ 400 ng/mL	11/27 (41)
By EHS/MVI, n/n (%)[d]	
EHS and/or MVI	18/64 (28)
MVI negative	13/32 (41)
EHS negative	9/22 (41)
Neither EHS nor MVI	5/8 (63)

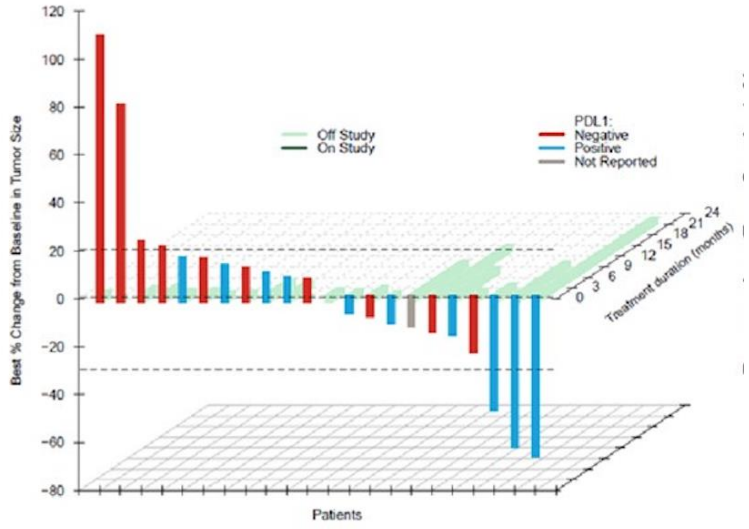
Stein, ASCO 2018; Lee ESMO Asia 2018

Basket with pembrolizumab-ramucirumab





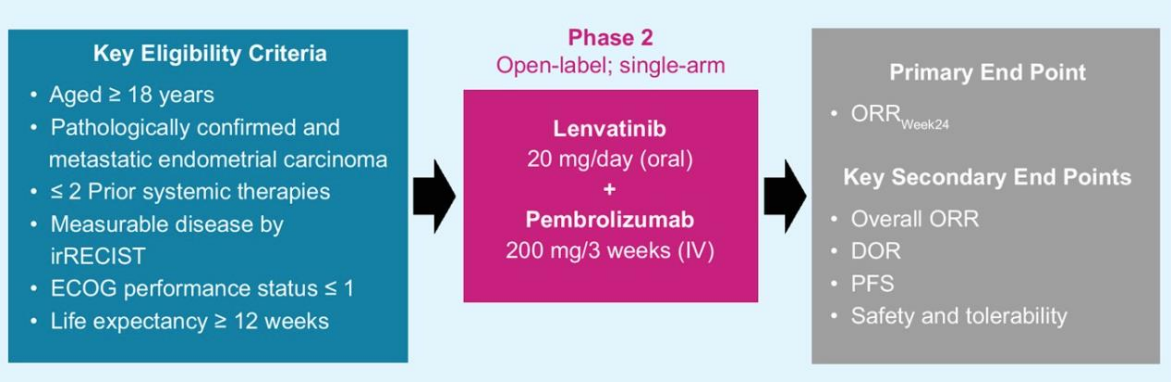
GEJ

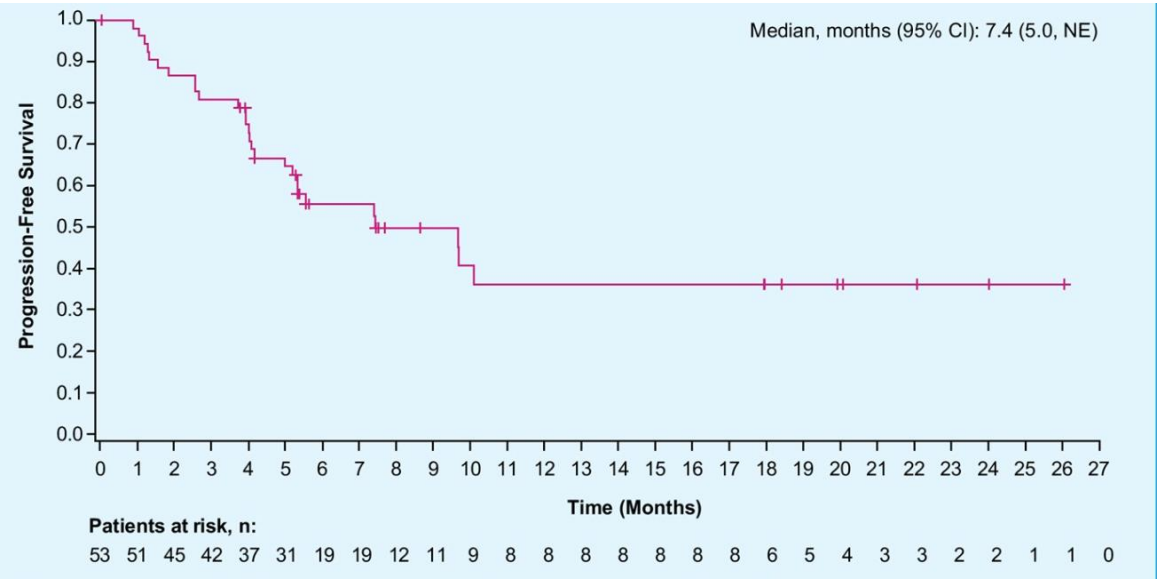


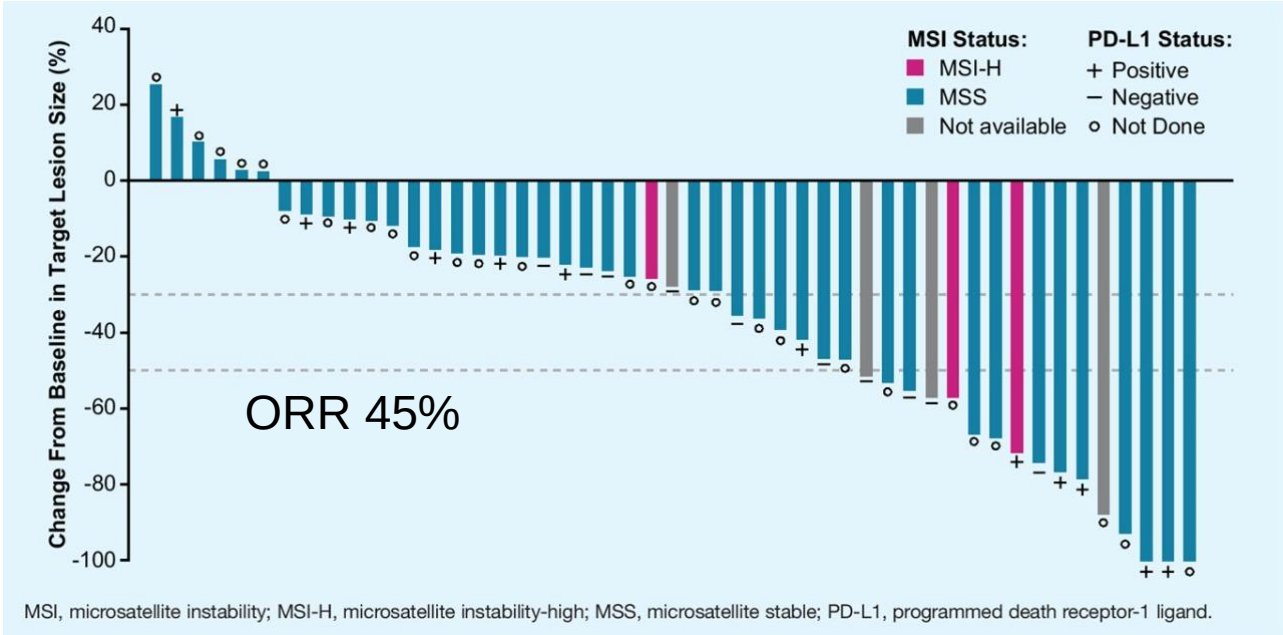
UC

PD-L1 Status	G/GEJ (2nd-3rd line) CPS <1% n=17	G/GEJ (2nd-3rd line) CPS ≥1% n=22	NSCLC (2nd-4th line) TPS <1% n=11	NSCLC (2nd-4th line) TPS ≥1% n=11	UC (2nd-4th line) CPS <1% n=11	UC (2nd-4th line) CPS ≥1% n=12
ORR, % (95% CI)	6 (0.1-28.7)	9 (1.1-29.2)	18 (2.3-51.8)	45 (16.7-76.6)	0	25 (5.5-57.2)

Lenvatinib and pembrolizumab in endometrial cancer



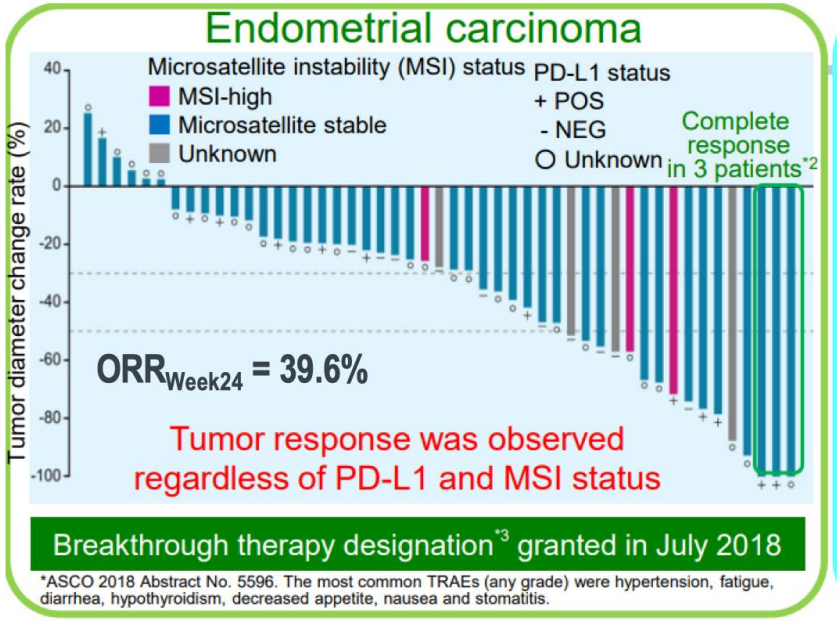


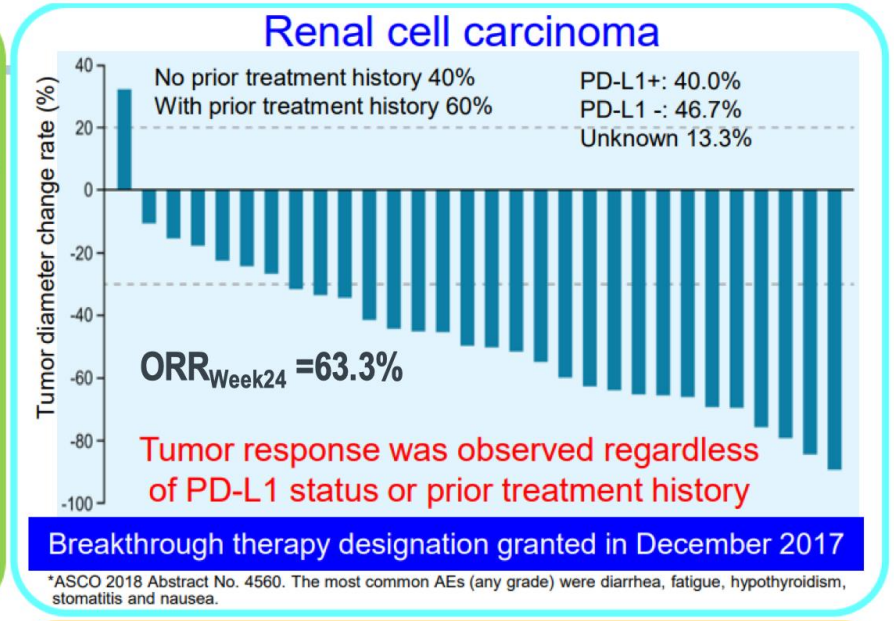


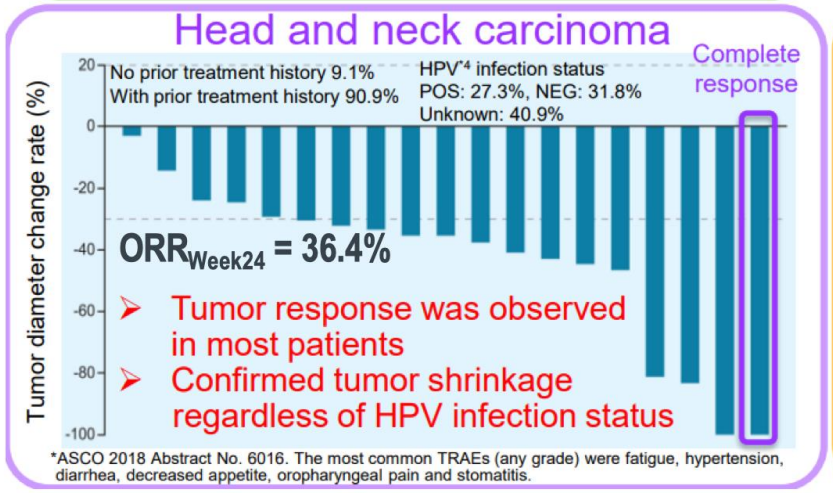
- FDA breakthrough designation August 2018
- Ongoing cohorts across diseases (3 randomized phase 2 trials in lung)

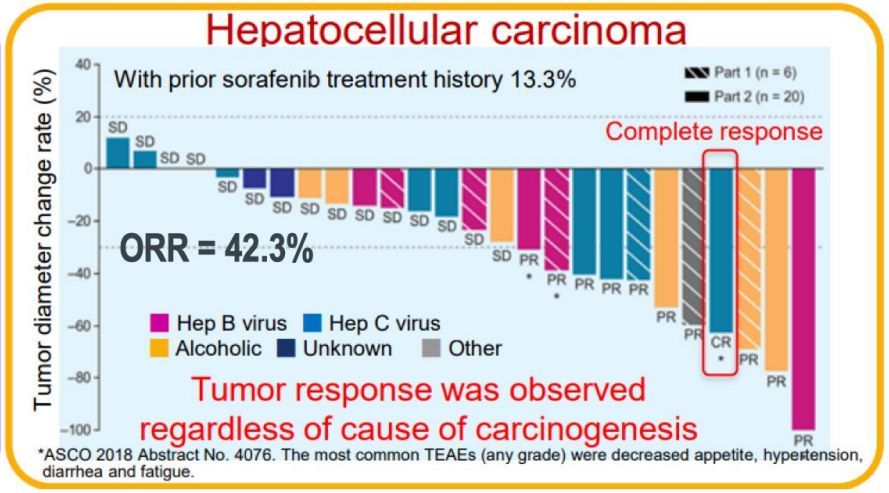
Makker, ASCO 2018

Lenvatinib and pembrolizumab across malignancies









Makker, ASCO 2018

Conclusions

Immunologic Research 2001;23–2/3:263–272

VEGF as a Mediator of Tumor-Associated Immunodeficiency

Joyce E. Ohm
David P. Carbone

Department of Medicine and Vanderbilt-Ingram Cancer Center Vanderbilt University Medical Center, Nashville, TN

- Rational for anti-angiogenic combination with immunotherapy is very solid and known since 20 years
- This strategy is extensively being explored in RCC, NSCLC, endometrial cancer and HCC, where it will define new standards of care
- Both anti-angiogenic TKIs and anti-VEGF therapies transversally demonstrate interesting signals of activity
- Integration of PD1, PD-L1 and possibly CTLA-4 inhibition have all shown some synergistic activity with anti-angiogenic drugs


Thank you for your attention