Society for Immunotherapy of Cancer

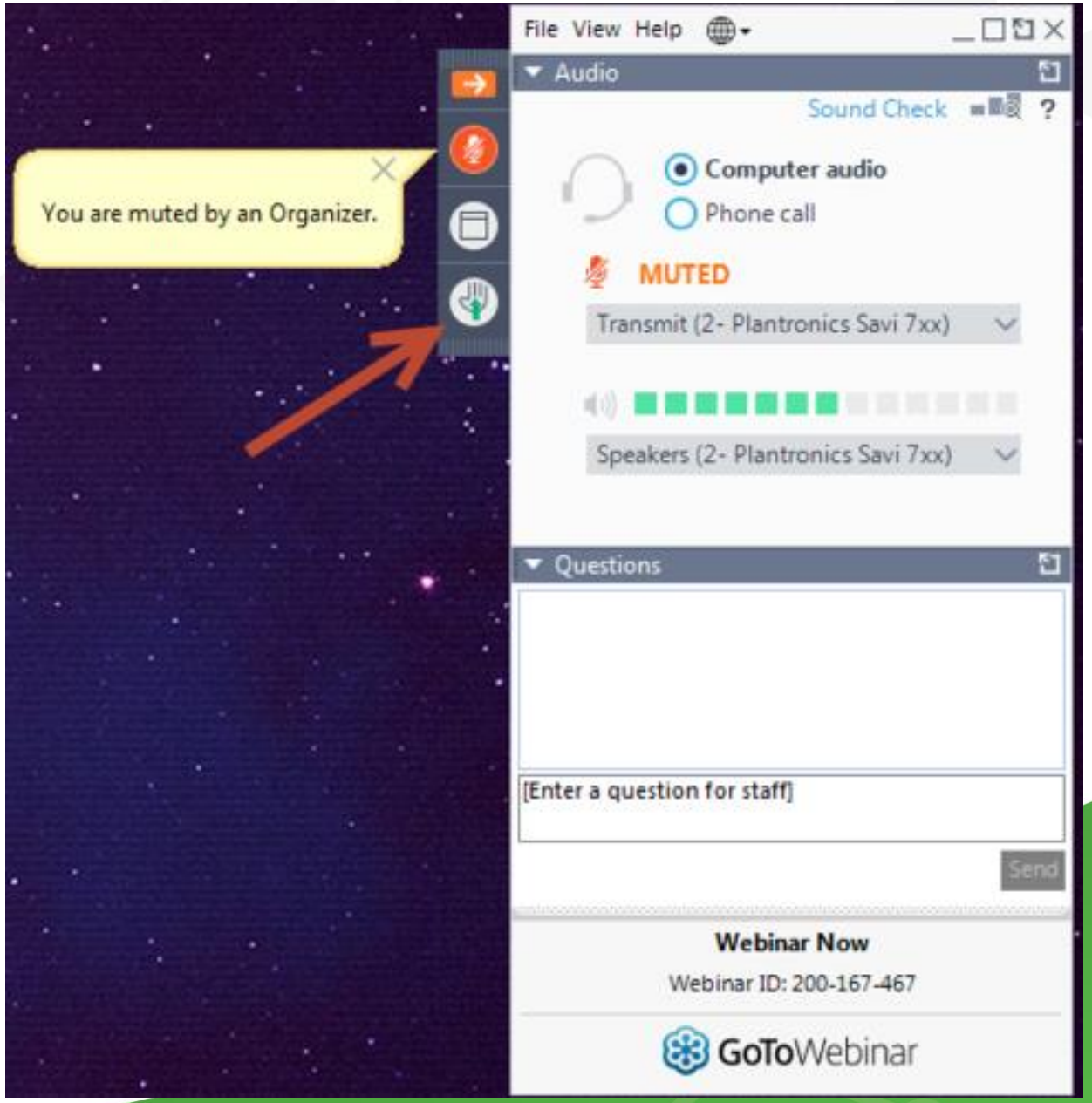
Welcome to the Advances in Cancer Immunotherapy™ Webinar Series – Updates from the Field: ESMO Congress 2018 Clinical Trials

Thursday, November 15, 2018

1-2 p.m. CST

Welcome to the Advances in Cancer Immunotherapy™ Post-Program Webinar

Raise your hand if…



Society for Immunotherapy of Cancer

Webinar Agenda

1:00-1:05 p.m. CST	Welcome and Introductions
1:05-1:40 p.m. CST	ESMO 2018 Clinical Trials overview
1:40-1:55 p.m. CST	Question and Answer Session
1:55-2:00 p.m. CST	Closing Remarks

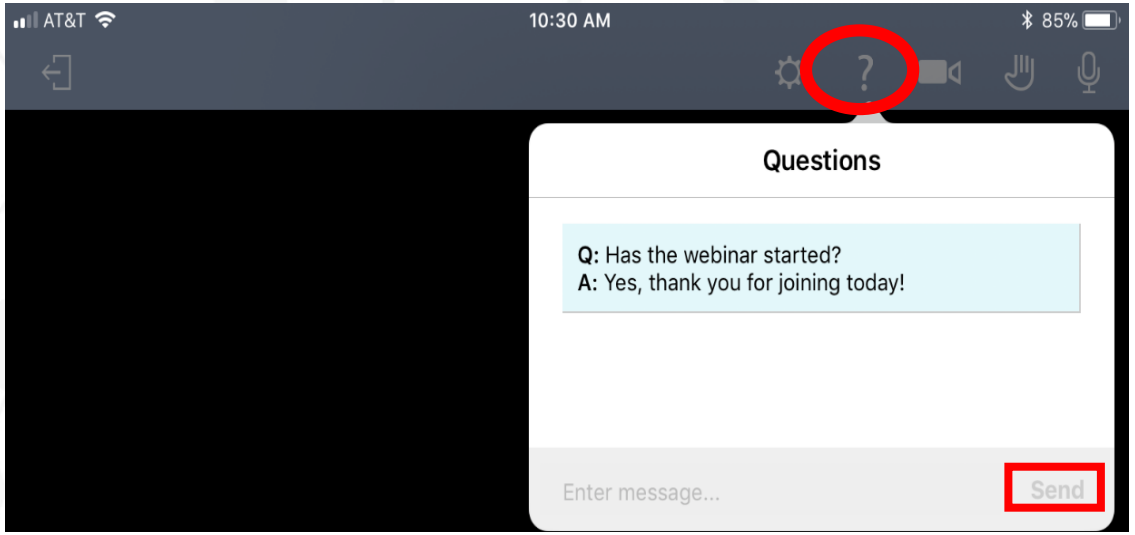
sitc
Society for Immunotherapy of Cancer

Question and Answer

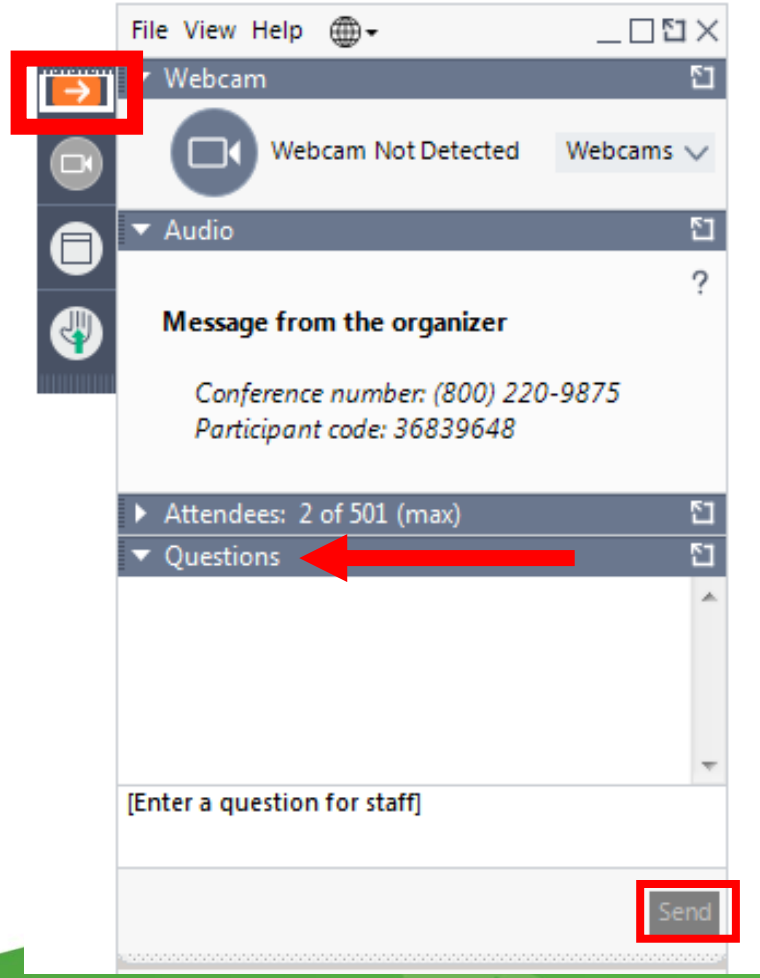
To submit a question:

Type your question in the Questions box of your webinar panel.

Mobile View



Desktop View



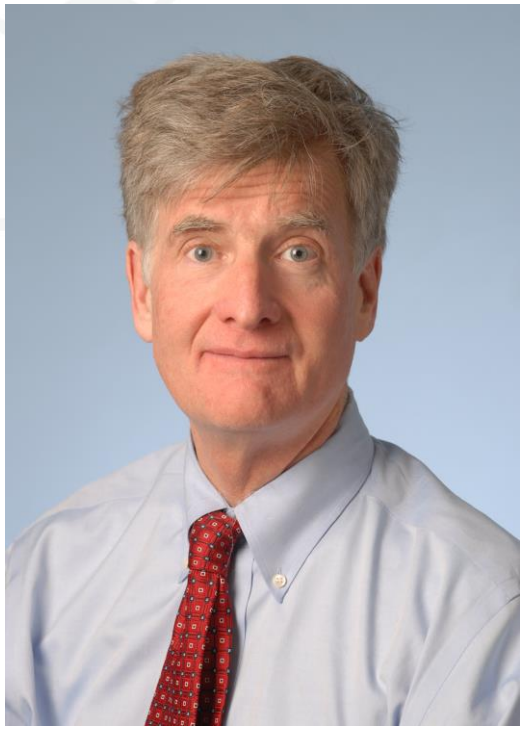
Society for Immunotherapy of Cancer

Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this webinar is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this webinar should not be used by clinicians without evaluation of their patient's conditions and possible contraindications and/or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

sitc
Society for Immunotherapy of Cancer

Webinar Faculty



Theodore F. Logan, MD
Indiana University Simon Cancer Center

David F. McDermott, MD
Beth Israel Deaconess Medical Center

sitc
Society for Immunotherapy of Cancer

Society for Immunotherapy of Cancer

Updates from the Field: ESMO Congress 2018 Clinical Trials

David McDermott, MD
Beth Israel Deaconess Medical Center
Dana Farber/Harvard Cancer Center
Harvard Medical School

Disclosures

- Consultant
  - Array Biopharma
  - Bristol-Myers Squibb
  - Calithera Biosciences
  - Exelixis
  - Genentech
  - Merck
  - Novartis
  - Pfizer
  - Jounce
- Research funding
  - Prometheus Labs
  - Bristol-Myers Squibb

Society for Immunotherapy of Cancer

Rational Application of Combination IO Therapy: Lessons Learned from IMmotion 150

- Trial Design
- Patient Selection
- **Novel Endpoints**
  - **Will Next Gen Biomarkers advance the field?**

Society for Immunotherapy of Cancer

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

David F. McDermott[1*], Mahrukh A. Huseni[2], Michael B. Atkins[3], Robert J. Motzer[4], Brian I. Rini[5], Bernard Escudier[6], Lawrence Fong[7], Richard W. Joseph[8], Sumanta K. Pal[9], James A. Reeves[10], Mario Sznol[11], John Hainsworth[12], W. Kimryn Rathmell[13], Walter M. Stadler[14], Thomas Hutson[15], Martin E. Gore[16], Alain Ravaud[17], Sergio Bracarda[18], Cristina Suárez[19], Riccardo Danielli[20], Viktor Gruenwald[21], Toni K. Choueiri[22], Dorothee Nickles[2], Suchit Jhunjhunwala[2], Elisabeth Piault-Louis[2], Alpa Thobhani[23], Jiaheng Qiu[2], Daniel S. Chen[2], Priti S. Hegde[2], Christina Schiff[2], Gregg D. Fine[2] and Thomas Powles[24]

Molecular correlates differentiate response to atezolizumab + bevacizumab vs sunitinib: results from a Phase III study (IMmotion151) in untreated metastatic renal cell carcinoma

Brian I. Rini,[1] Mahrukh Huseni,[2] Michael B. Atkins,[3] David F. McDermott,[4] Thomas Powles,[5] Bernard Escudier,[6] Romain Banchereau,[2] Li-Fen Liu,[2] Ning Leng,[2] Jinzhen Fan,[2] Jennifer Doss,[2] Stefani Nalle,[2] Susheela Carroll,[2] Shi Li,[2] Christina Schiff,[2] Marjorie Green,[2] Robert J. Motzer[7]

[1]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [2]Genentech, Inc., South San Francisco, CA, USA; [3]Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA; [4]Beth Israel Deaconess Medical Center, Boston, MA, USA; [5]Barts Cancer Institute and the Royal Free Hospital, Queen Mary University of London, London, UK; [6]Gustave Roussy, Villejuif, France; [7]Memorial Sloan Kettering Cancer Center, New York, NY, USA

sitc
Society for Immunotherapy of Cancer

Rini B, et al. IMmotion151 Biomarkers.
ESMO 2018 [abstract LBA31].
http://bit.ly/2yaVgyI

IMmotion151: Study Design

Key eligibility

- Treatment-naive advanced or metastatic RCC
- Clear cell and/or sarcomatoid histology
- KPS ≥ 70
- Tumour 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 q3w[b] + Bevacizumab 15 mg/kg IV q3w[b]

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

Co-primary endpoints

- PFS[c] in PD-L1+
- OS in ITT

Exploratory endpoints include:

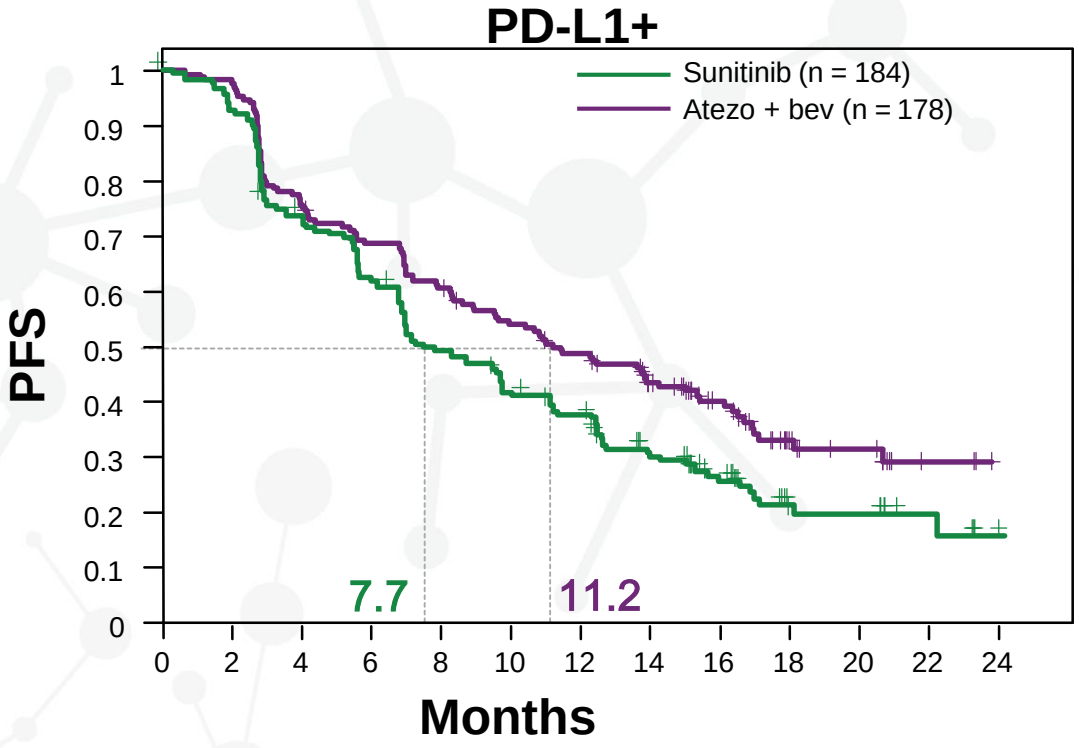
- Validation of gene signatures from IMmotion150 and their association with PFS
- Biomarker characterisation in MSKCC risk subgroups and sarcomatoid tumours

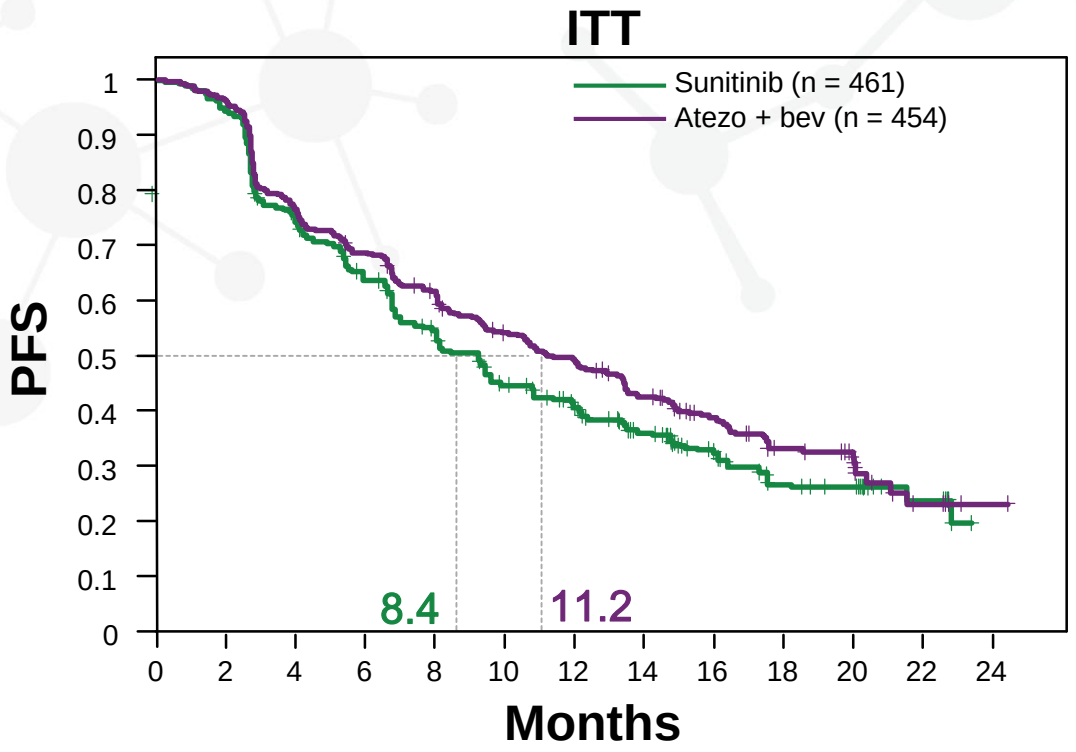
sitc
Society for Immunotherapy of Cancer

IC, tumour-infiltrating immune cell; IHC, immunohistochemistry; ITT, intent-to-treat; IV, intravenous; KPS, Karnofsky performance status; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PO, by mouth; q3w, every 3 weeks; QD, once a day; R, randomised; RCC, renal cell carcinoma; TME, tumour microenvironment.
[a] ≥ 1% IC: 40% prevalence using SP142 IHC assay. [b] No dose reduction for atezolizumab or bevacizumab. [c] Investigator assessed PFS per RECIST v1.1.

Rini B, et al. IMmotion151 Biomarkers. ESMO 2018 [abstract LBA31]. http://bit.ly/2yaVgyl

IMmotion151: PFS Summary





HR (95% CI)		
	PD-L1+	**ITT**
Atezo + bev vs sunitinib	**0.74 (0.57, 0.96); *P* = 0.02[a]**	**0.83 (0.70, 0.97)**

sitc
Society for Immunotherapy of Cancer

PFS-assessed by investigators. Minimum follow-up, 12 months. Median follow-up, 16 months (PD-L1+) and 15 months (ITT).
[a] The PFS analysis passed the pre-specified *P* value boundary of α = 0.04.
Motzer RJ, et al. ASCO GU 2018 [abstract 578].

Rini B, et al. IMmotion151 Biomarkers. ESMO 2018 [abstract LBA31]. http://bit.ly/2yaVgyl

IMmotion151: Gene Signature Analysis Scheme

IMmotion150 (n = 263)

Identification of gene signatures based on association with clinical outcome

- T_{eff}: *CD8a*, *IFNG*, *PRF1*, *EOMES*, *CD274*
- Angio: *VEGFA*, *KDR*, *ESM1*, *PECAM1*, *CD34*, *ANGPTL4*

↓

Absolute cutoff selection based on PFS HR

- T_{eff} cutoffs: 2.93 (40% prevalence)
- Angio cutoff: 5.82 (50% prevalence)

↓

IMmotion151 (n = 823)

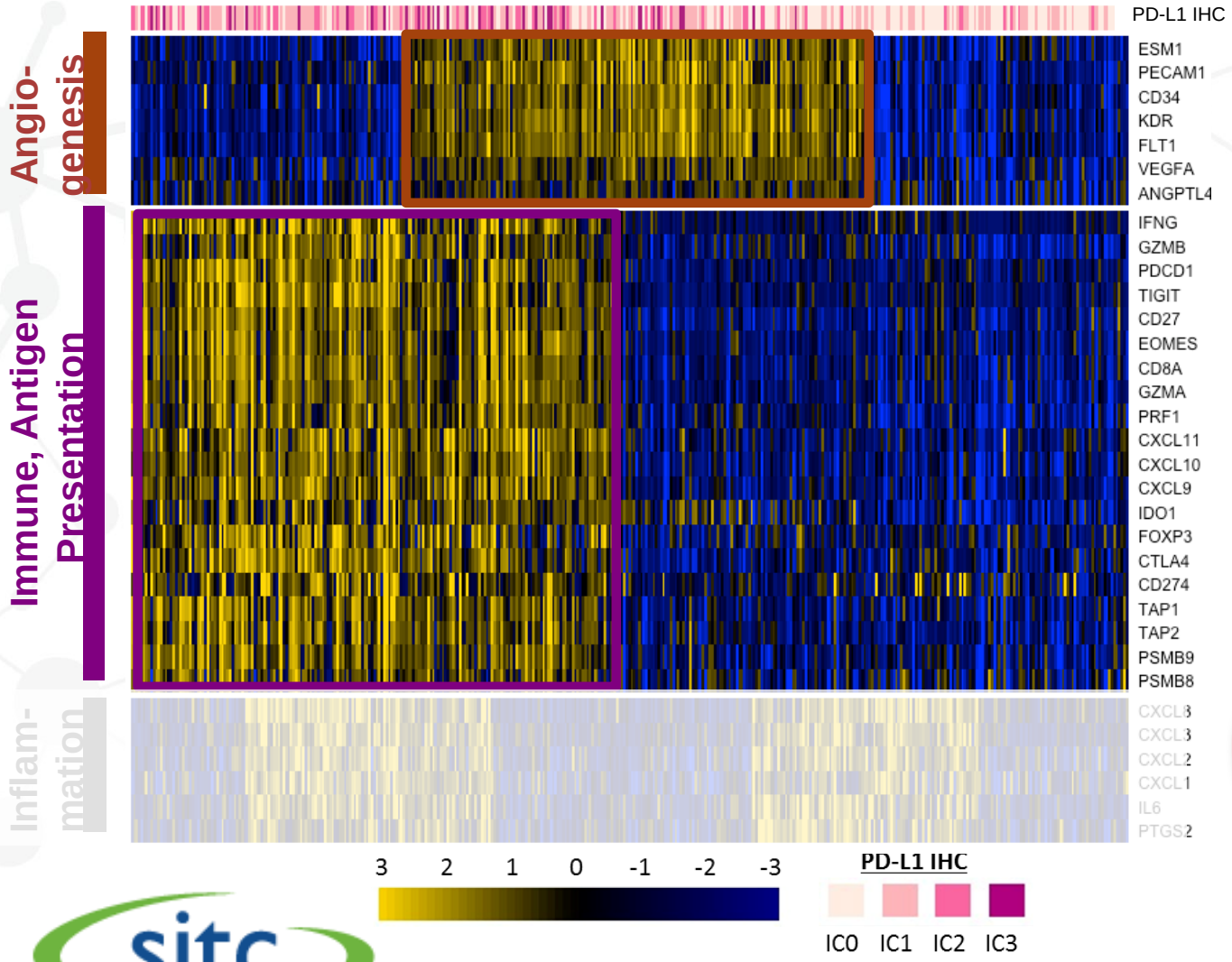
Pre-specified analysis of association with PFS

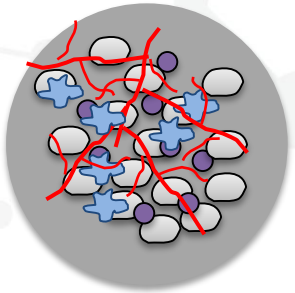
- Unstratified HR and log-rank tests were used for PFS analyses in biomarker-evaluable patients

sitc
Society for Immunotherapy of Cancer

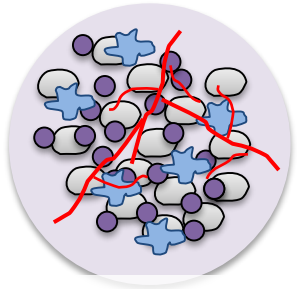
Rini B, et al. IMmotion151 Biomarkers. ESMO 2018 [abstract LBA31]. http://bit.ly/2yaVgyl

IMmotion151: Transcriptome Map Confirms Biological Subgroups Identification in IMmotion150





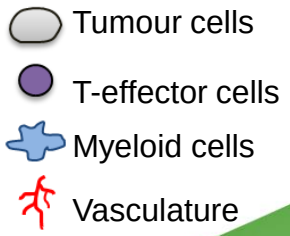
Angiogenesis^{High}



T-effector^{High}

T-effector^{High} Myeloid^{High}

T-effector^{High} Myeloid^{Low}

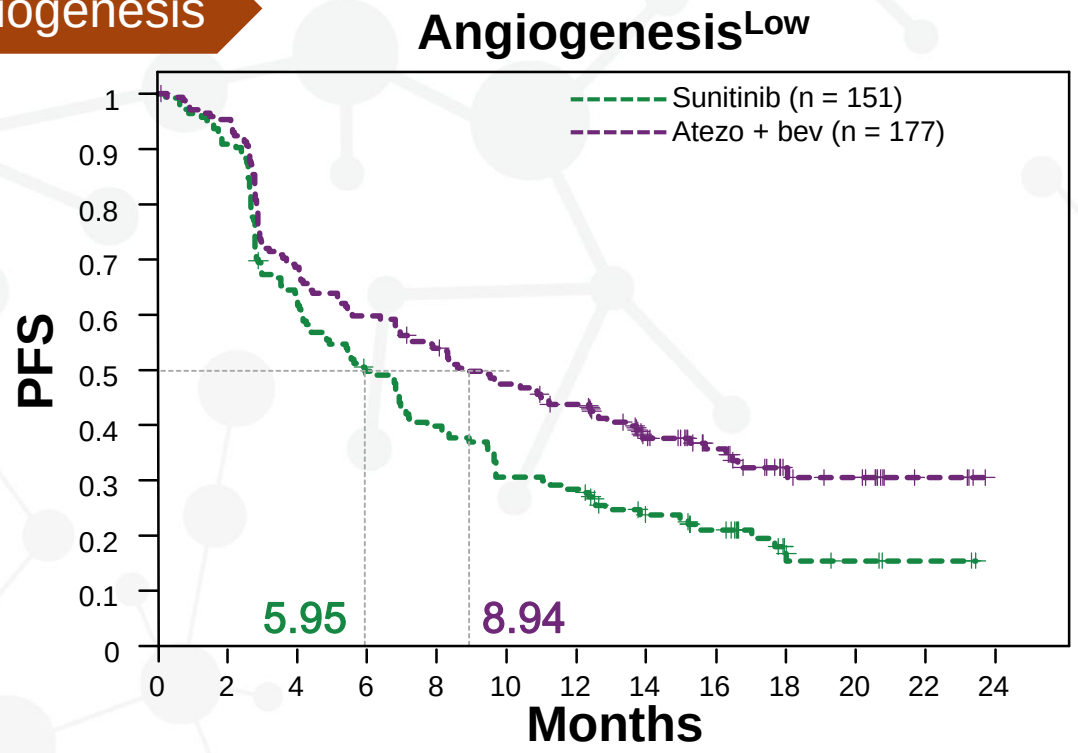


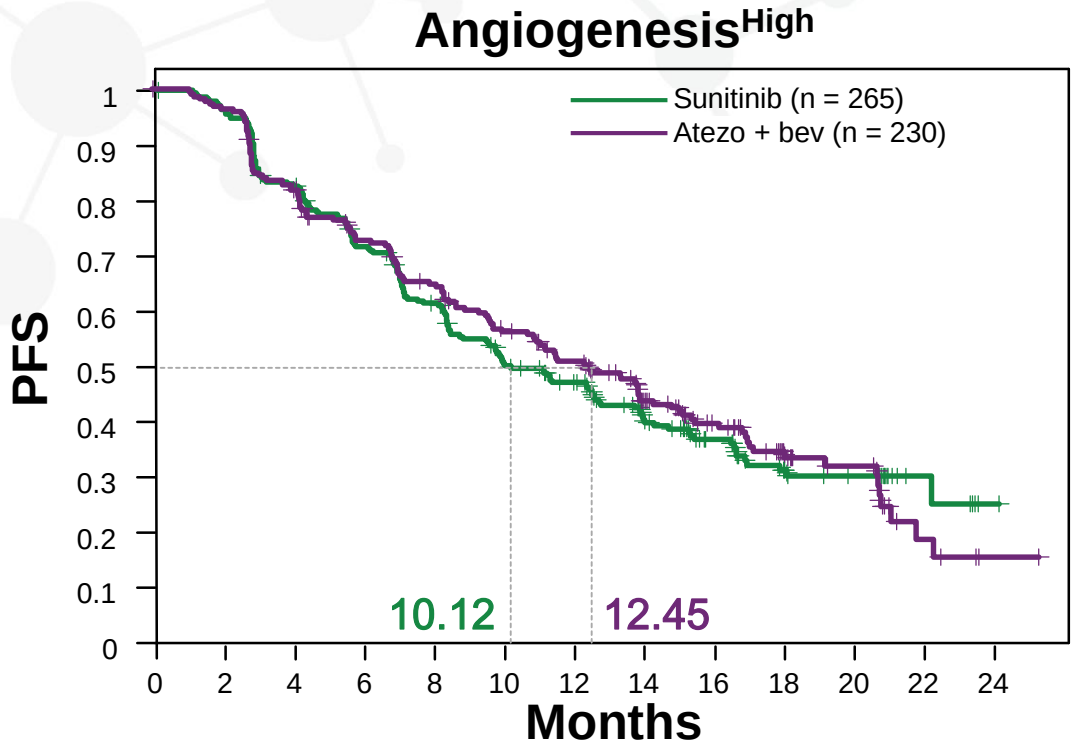
sitc
Society for Immunotherapy of Cancer

Rini B, et al. IMmotion151 Biomarkers. ESMO 2018 [abstract LBA31]. http://bit.ly/2yaVgyI

Atezolizumab + Bevacizumab Improved PFS vs Sunitinib in the Angiogenesis^{Low} Subset

Angiogenesis





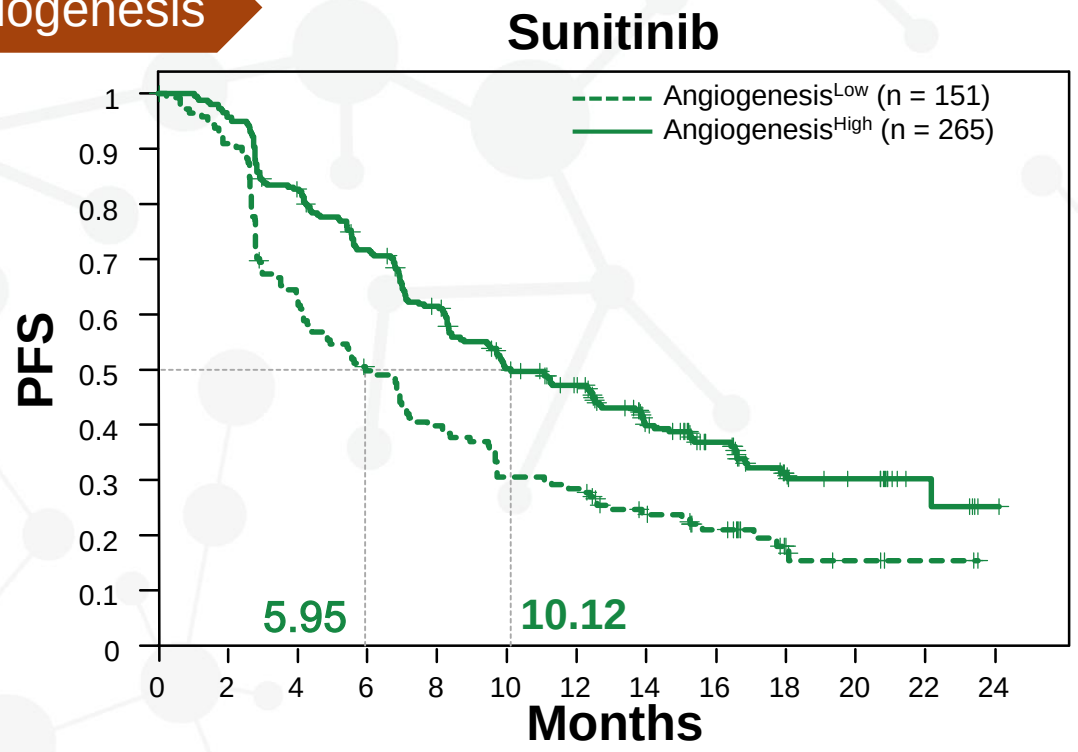
HR (95% CI)		
	Angiogenesis^{Low}	Angiogenesis^{High}
Atezo + bev vs sunitinib	0.68 (0.52, 0.88)	0.95 (0.76, 1.19)

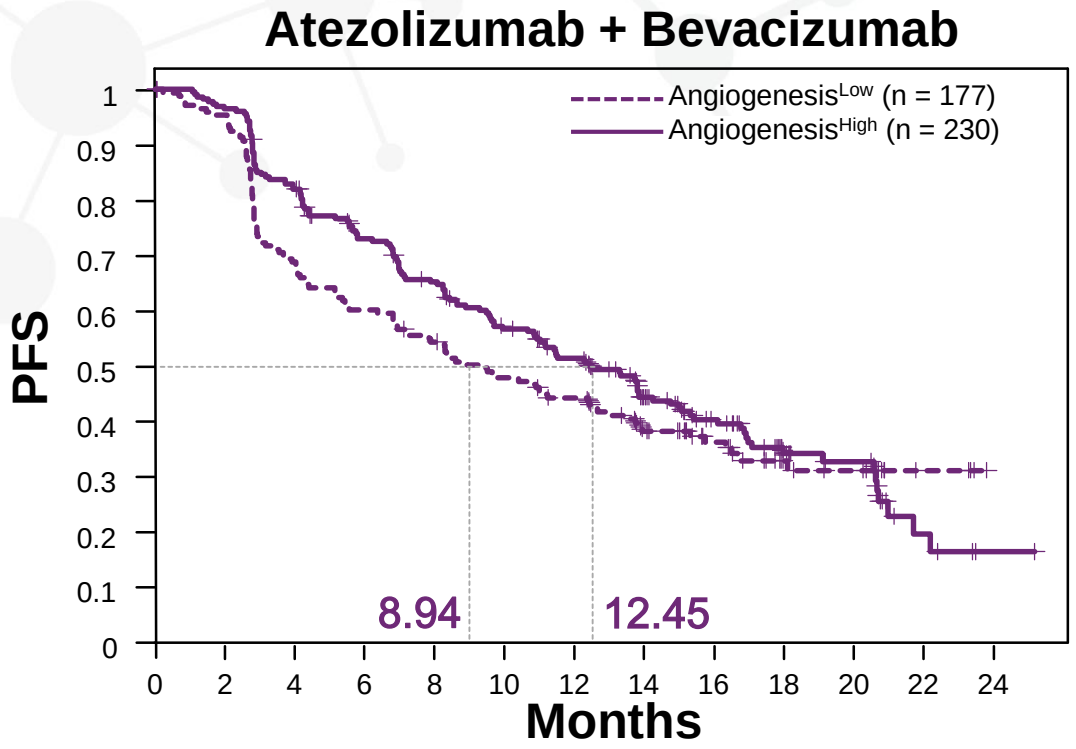
Society for Immunotherapy of Cancer

Rini B, et al. IMmotion151 Biomarkers. ESMO 2018 [abstract LBA31]. http://bit.ly/2yaVgyI

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

Angiogenesis





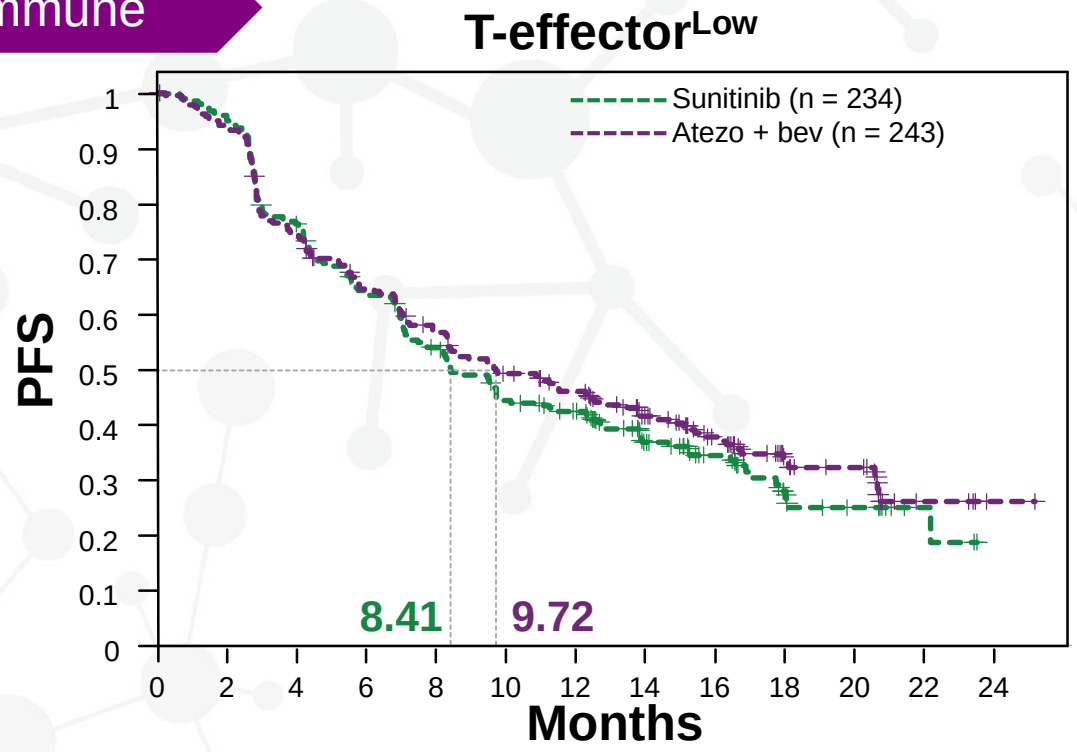
HR (95% CI)		
	Sunitinib	**Atezo + Bev**
Angiogenesis (High vs Low)	**0.59 (0.47, 0.75)**	**0.86 (0.67, 1.1)**

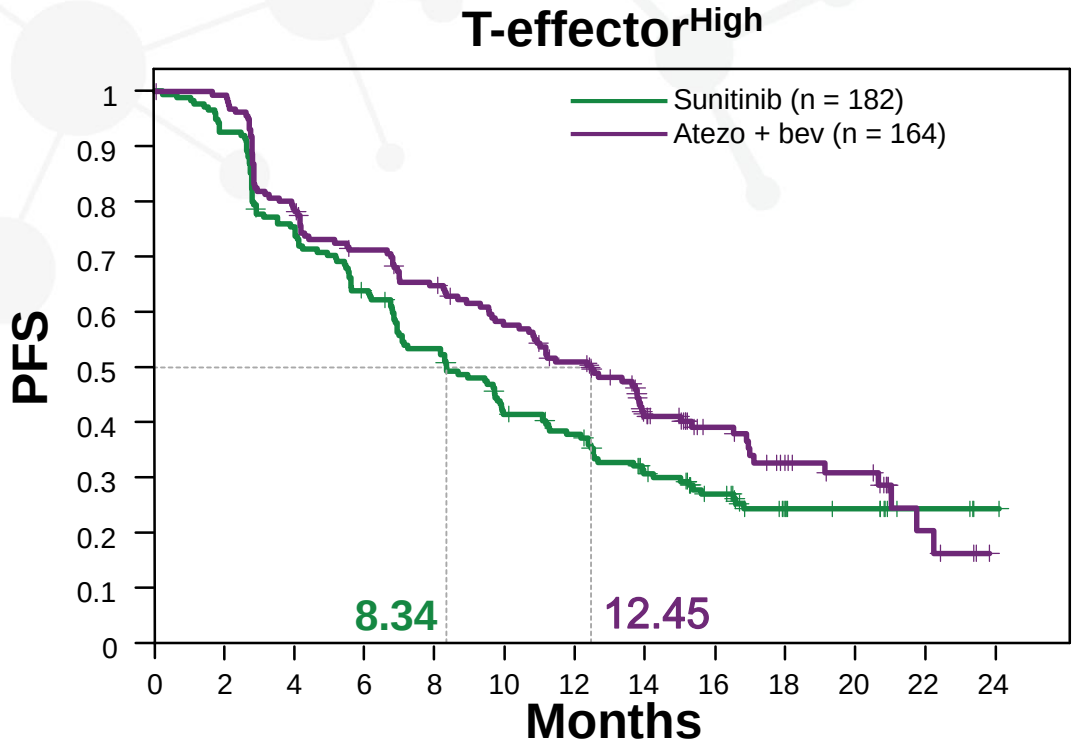
Society for Immunotherapy of Cancer

Rini B, et al. IMmotion151 Biomarkers. ESMO 2018 [abstract LBA31]. http://bit.ly/2yaVgyl

Atezolizumab + Bevacizumab Demonstrated Improved PFS vs Sunitinib in T_{eff}^{High} Subset

Immune





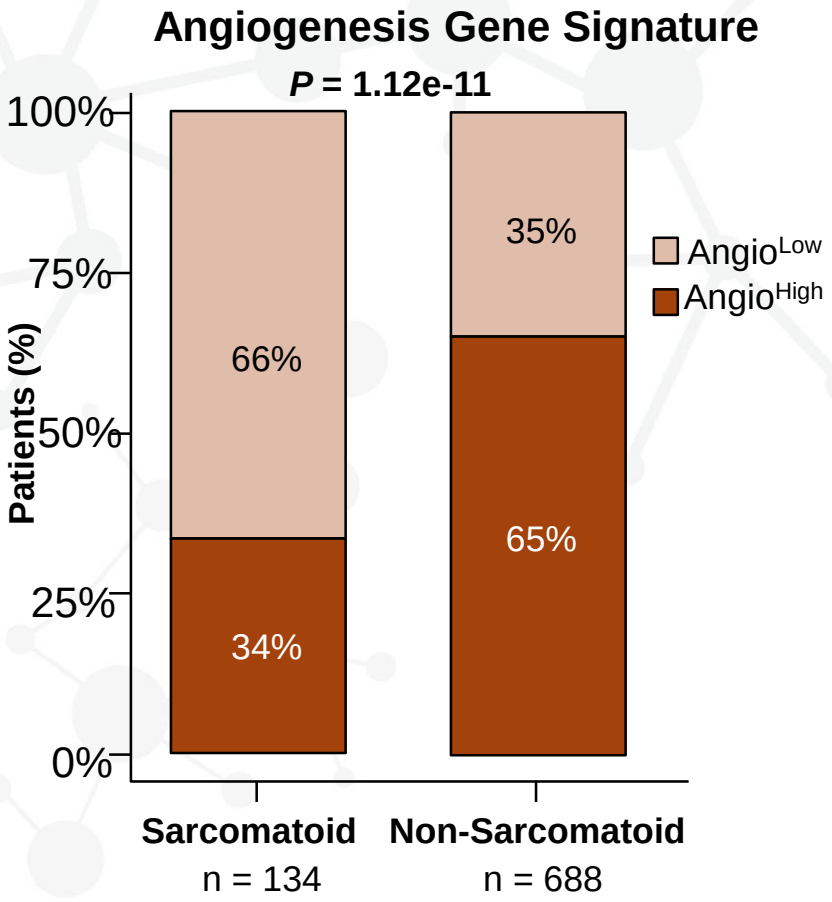
HR (95% CI)		
	T-effector^{Low}	T-effector^{High}
Atezo + bev vs sunitinib	0.91 (0.73, 1.14)	0.76 (0.59, 0.99)

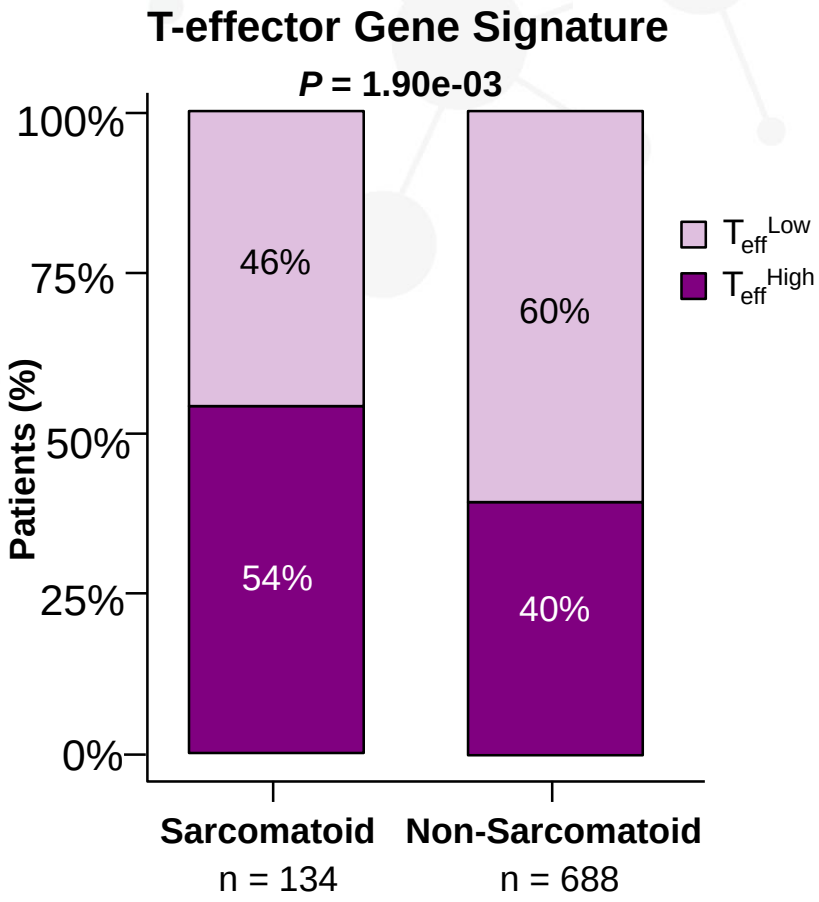
T-effector gene signature did not differentiate PFS within the sunitinib or atezolizumab + bevacizumab treatment arms

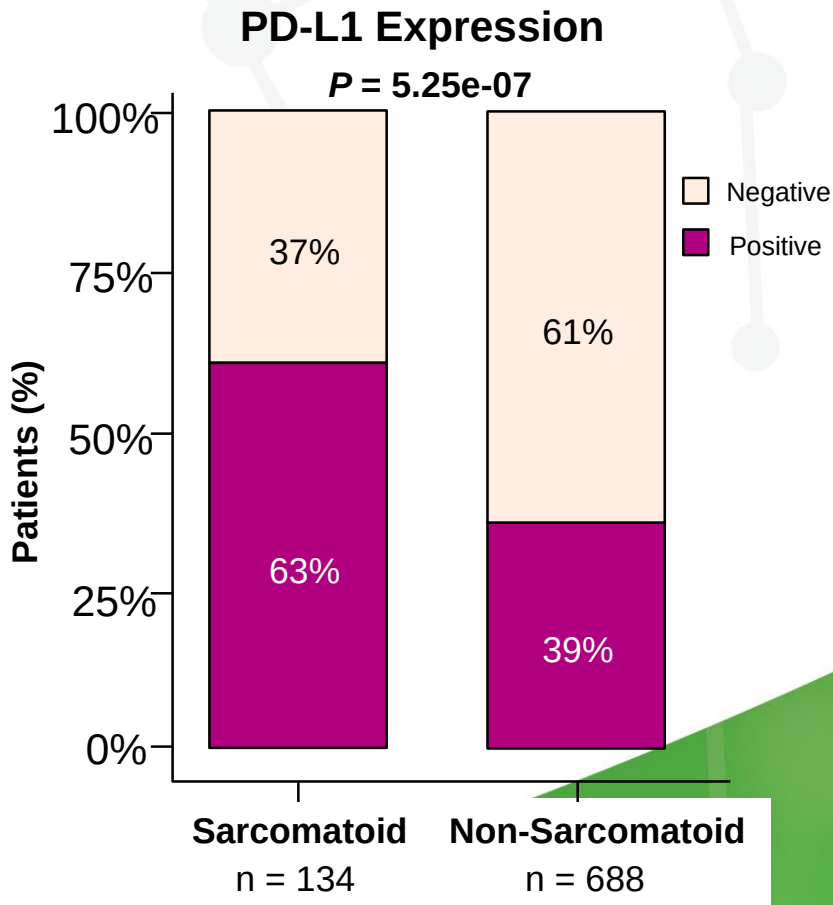
Rini B, et al. IMmotion151 Biomarkers. ESMO 2018 [abstract LBA31]. http://bit.ly/2yaVgyl

sitc
Society for Immunotherapy of Cancer

Angiogenesis Gene Expression Is Lower and PD-L1 Expression Is Higher in Sarcomatoid Tumours







Society for Immunotherapy of Cancer

Rini B, et al. IMmotion151 Biomarkers. ESMO 2018 [abstract LBA31]. http://bit.ly/2yaVgyl

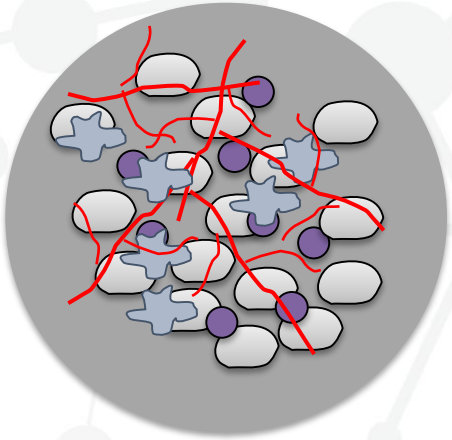
Summary

- Pre-specified analyses in IMmotion151 validated Angiogenesis and T-effector gene signatures identified in IMmotion150
  - Atezolizumab + bevacizumab improved PFS vs sunitinib in T-effector^{High} and Angiogenesis^{Low} tumours
  - Within the sunitinib arm, patients with an Angiogenesis^{High} gene signature showed improved PFS vs the Angiogenesis^{Low} subgroup
- MSKCC favourable-risk patients are characterised by a predominant Angiogenesis^{High} gene signature
- Sarcomatoid RCC is characterised by an Angiogenesis^{Low} gene signature and T-effector^{High} gene signature / higher PD-L1 expression vs non-sarcomatoid tumours
- Findings from this study further understanding of the biology of mRCC and inform future strategies to enable personalised therapy

sitc
Society for Immunotherapy of Cancer

Rini B, et al. IMmotion151 Biomarkers. ESMO 2018 [abstract LBA31]. http://bit.ly/2yaVgyI

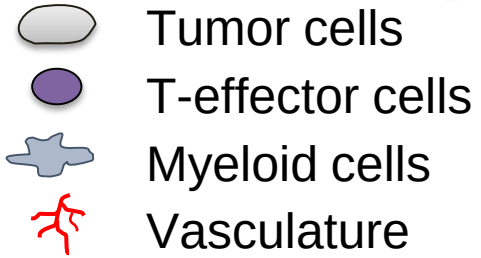
Molecular Correlates of Differential Response to Atezolizumab ± Bevacizumab vs Sunitinib in mRCC



Angiogenic

Clinical Activity

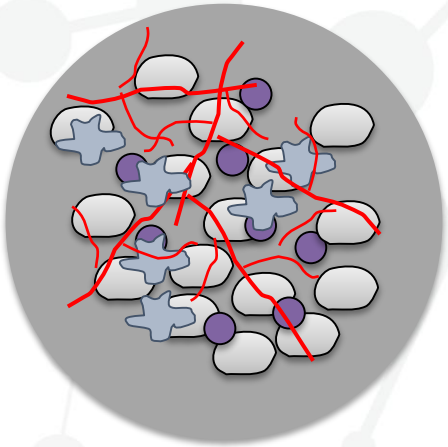
Sunitinib



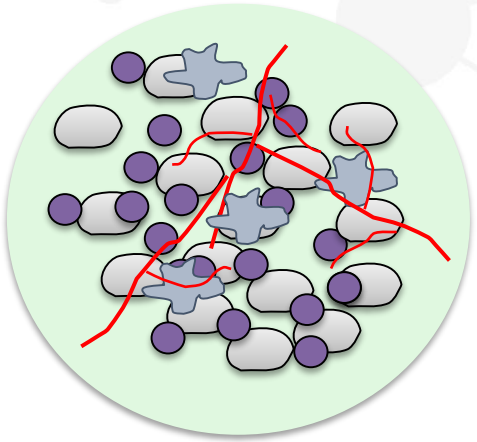
Society for Immunotherapy of Cancer

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

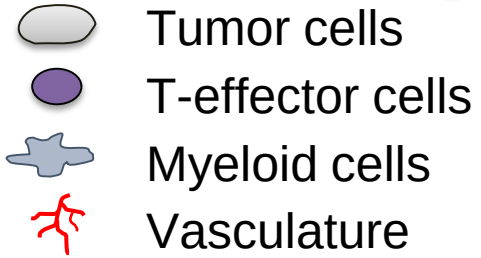
Molecular Correlates of Differential Response to Atezolizumab ± Bevacizumab vs Sunitinib in mRCC



Angiogenic



T-effector^{High}
Myeloid Inflammation^{Low}



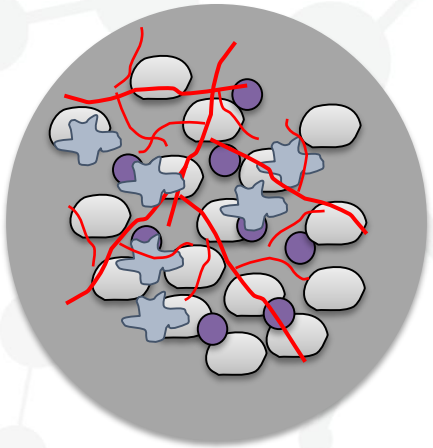
Clinical Activity

Sunitinib

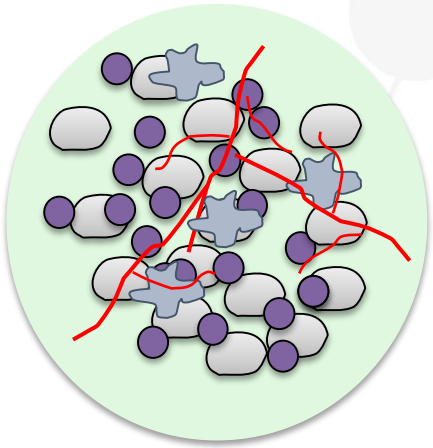
Atezolizumab

Society for Immunotherapy of Cancer

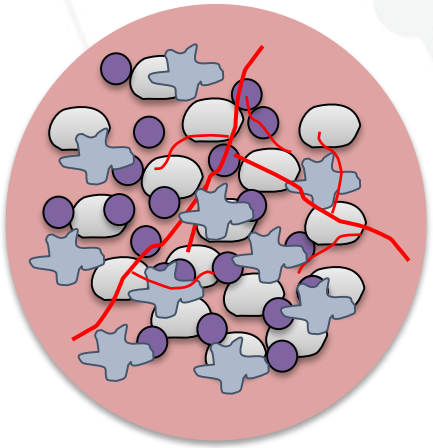
Molecular Correlates of Differential Response to Atezolizumab ± Bevacizumab vs Sunitinib in mRCC



Angiogenic



T-effector^{High} Myeloid Inflammation^{Low}



T-effector^{High} Myeloid Inflammation^{High} *Immune Suppressed*

Tumor cells
T-effector cells
Myeloid cells
Vasculature

Clinical Activity

Sunitinib

Atezolizumab

Atezolizumab + Bevacizumab

sitc
Society for Immunotherapy of Cancer

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

First-Line Phase 3 Trials in Advanced RCC

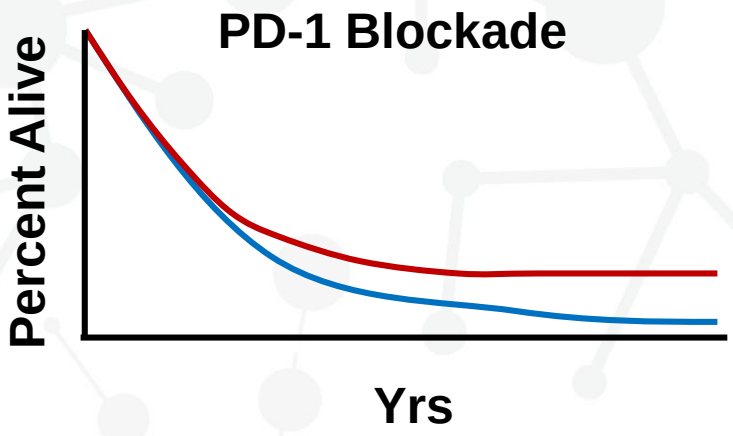
Control	Experimental Arm
Sunitinib	**Axitinib + avelumab**
Sunitinib	**Bevacizumab + atezolizumab**
Sunitinib	Nivolumab + cabozantinib
Sunitinib	Lenvatinib + everolimus or lenvatinib + pembrolizumab
Sunitinib	**Axitinib + pembrolizumab**
Sunitinib	**Nivolumab + ipilimumab** ✓

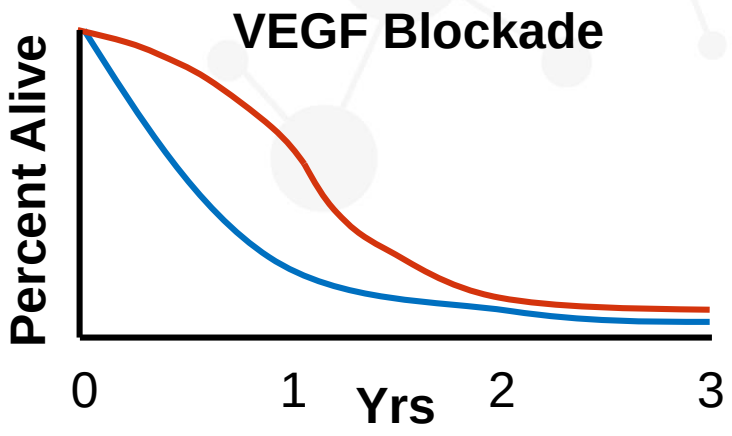
Are these approaches additive or synergistic?

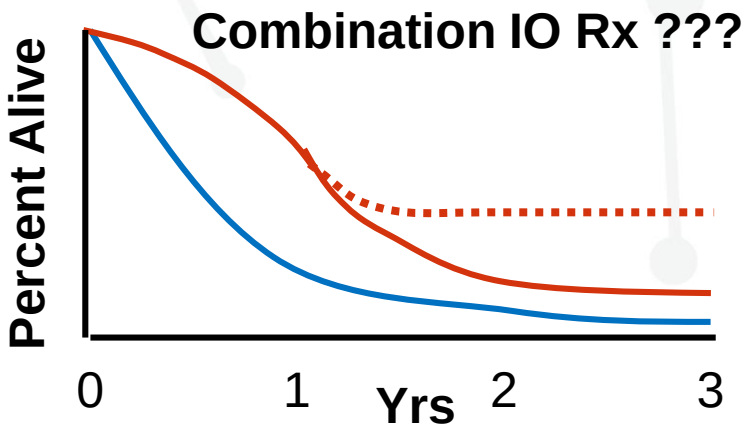
Bold = met primary endpoint

sitc
Society for Immunotherapy of Cancer

PD-1 Blockade Based Combinations in mRCC: Are they Additive or Synergistic?







- PD-1 + VEGF certainly **additive**
  - Improvements in the targeted therapy endpoints of ORR and mPFS are encouraging
    - OS may be prolonged, FDA approvals seem likely
- But are these combination **synergistic?**
- Do they generate improvements in **IO* endpoints?**
  - CR or near-CR, Landmark PFS, Long Term OS
  - Treatment-free Intervals - Remissions

sitc
Society for Immunotherapy of Cancer

IO – Immuno-oncology,

Side courtesy of T RIbas.

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

PD-L1 Ab (Avelumab) + VEGF TKI (Axitinib)

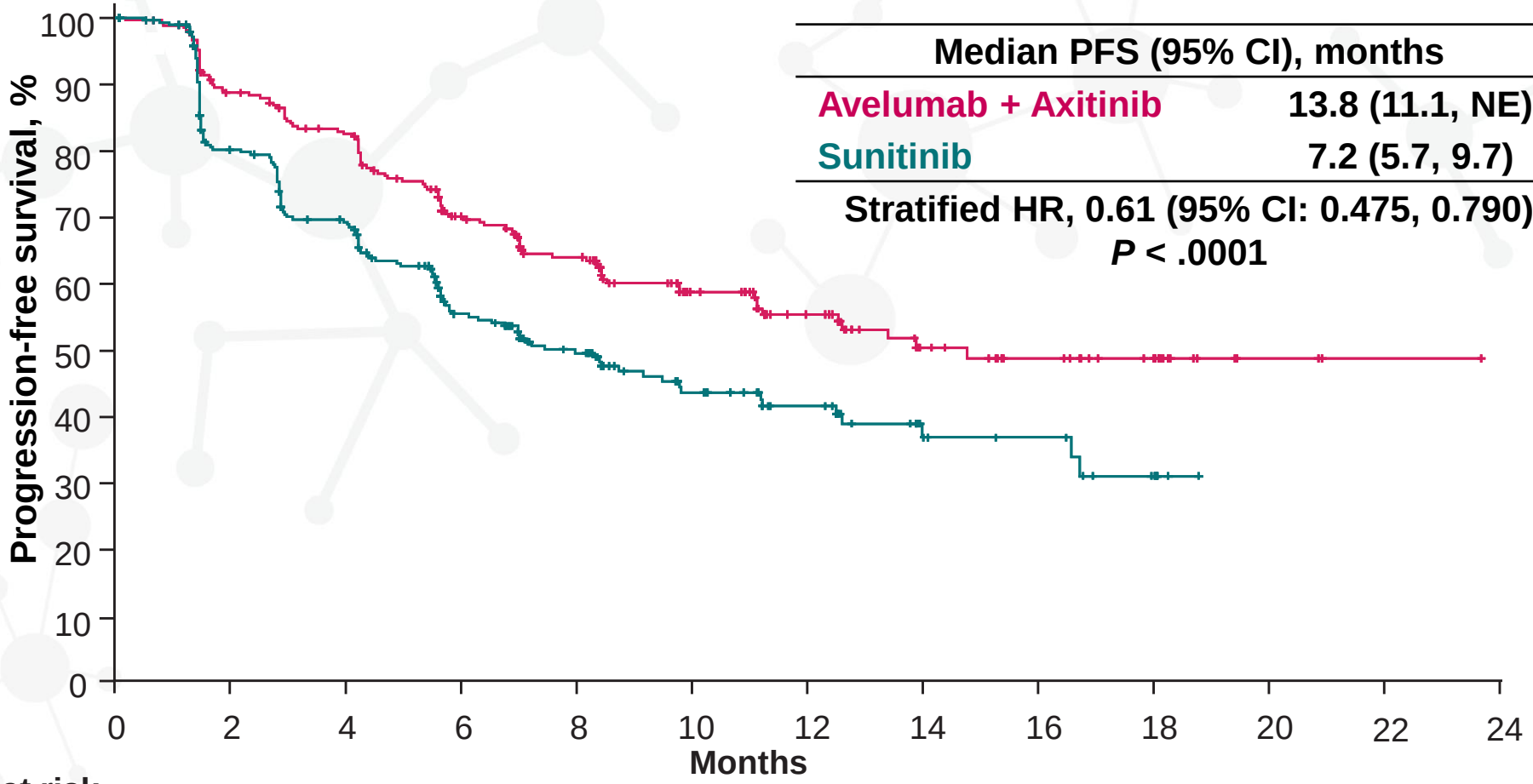
VEGF TKI (Sunitinib)

sitc
Society for Immunotherapy of Cancer

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		

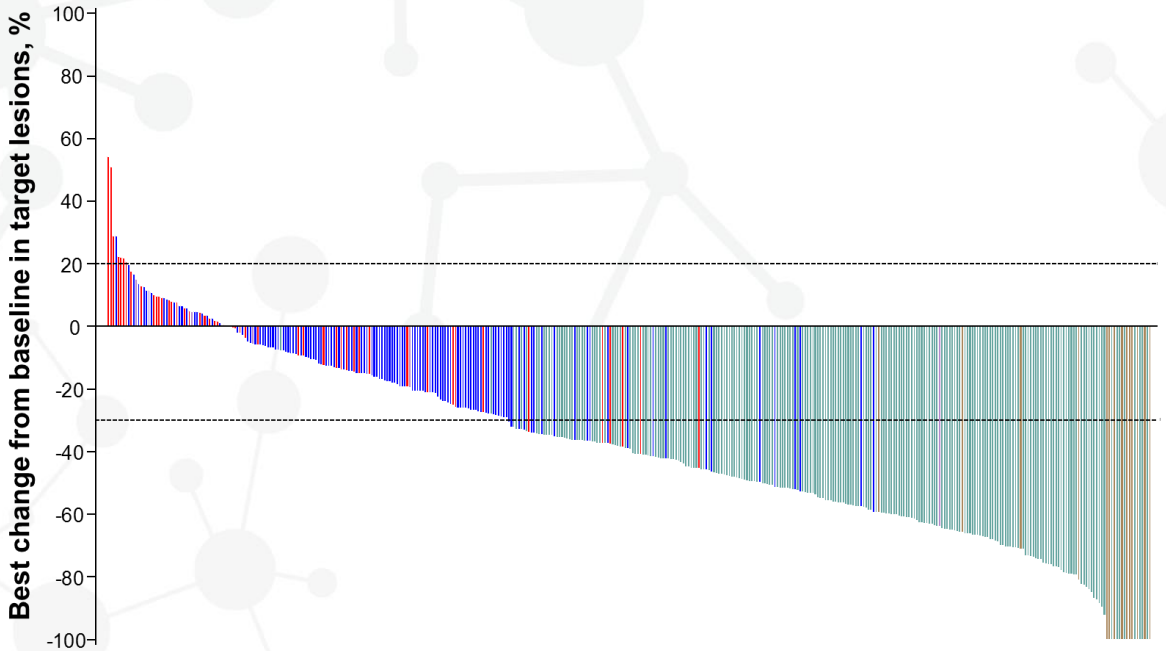
Minimum follow-up, 6 months. Median follow-up, 9.9 months (avelumab + axitinib) and 8.4 months (sunitinib).
The PFS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (*P* = .001).

Motzer et al ESMO 2018
NE, not estimable.

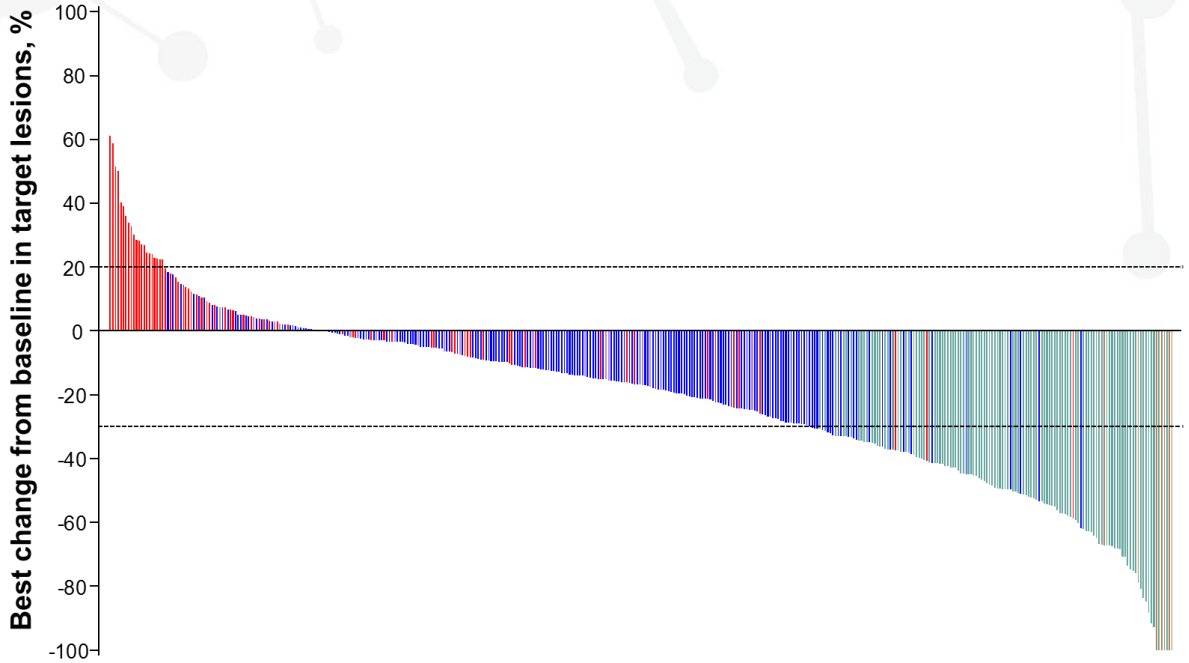
Society for Immunotherapy of Cancer

Percent change in target lesions in the overall population

Avelumab + Axitinib (N = 412)



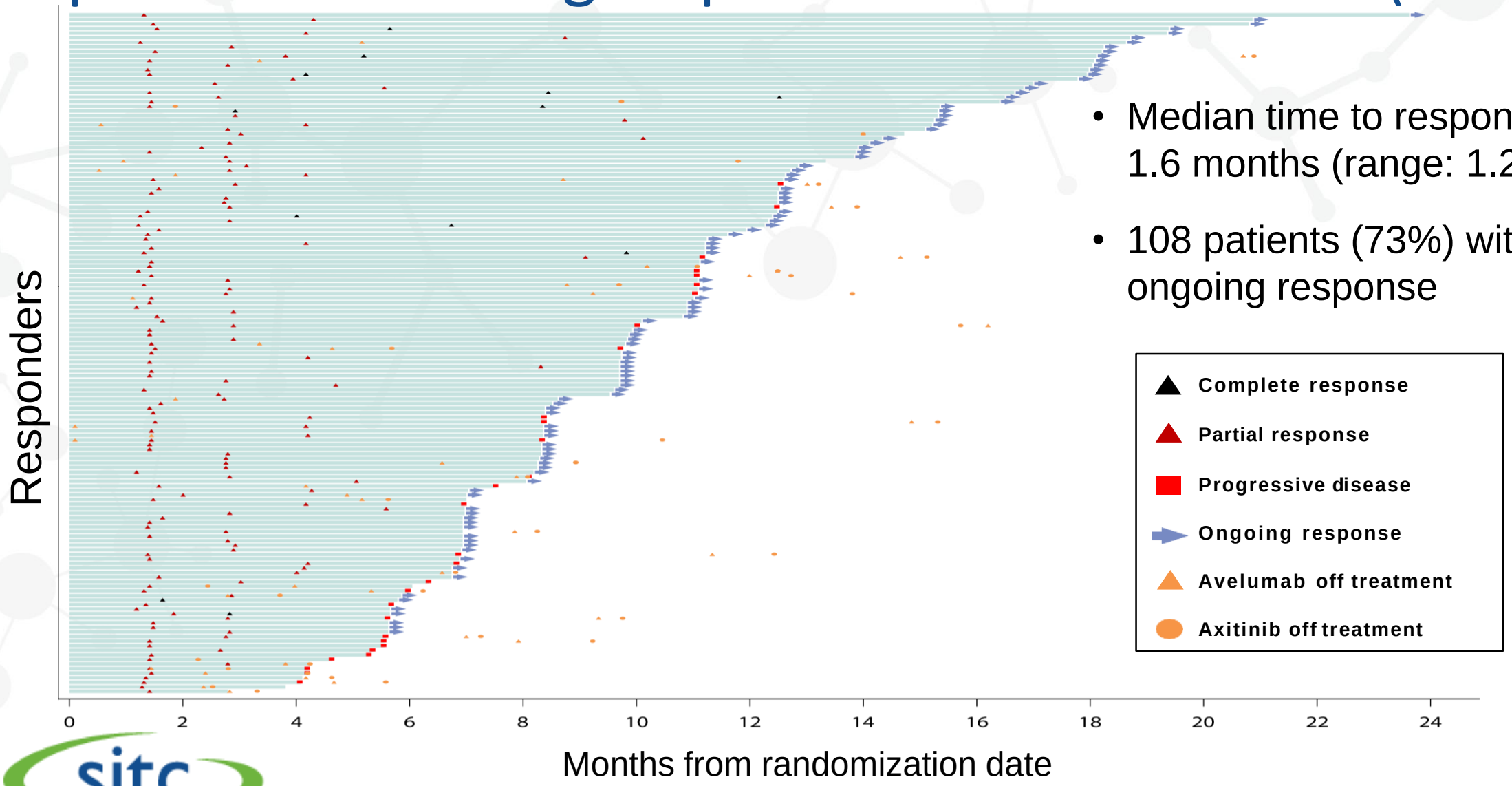
Sunitinib (N = 408)



Progressive disease Stable disease Partial response Complete response Not evaluable

Society for Immunotherapy of Cancer

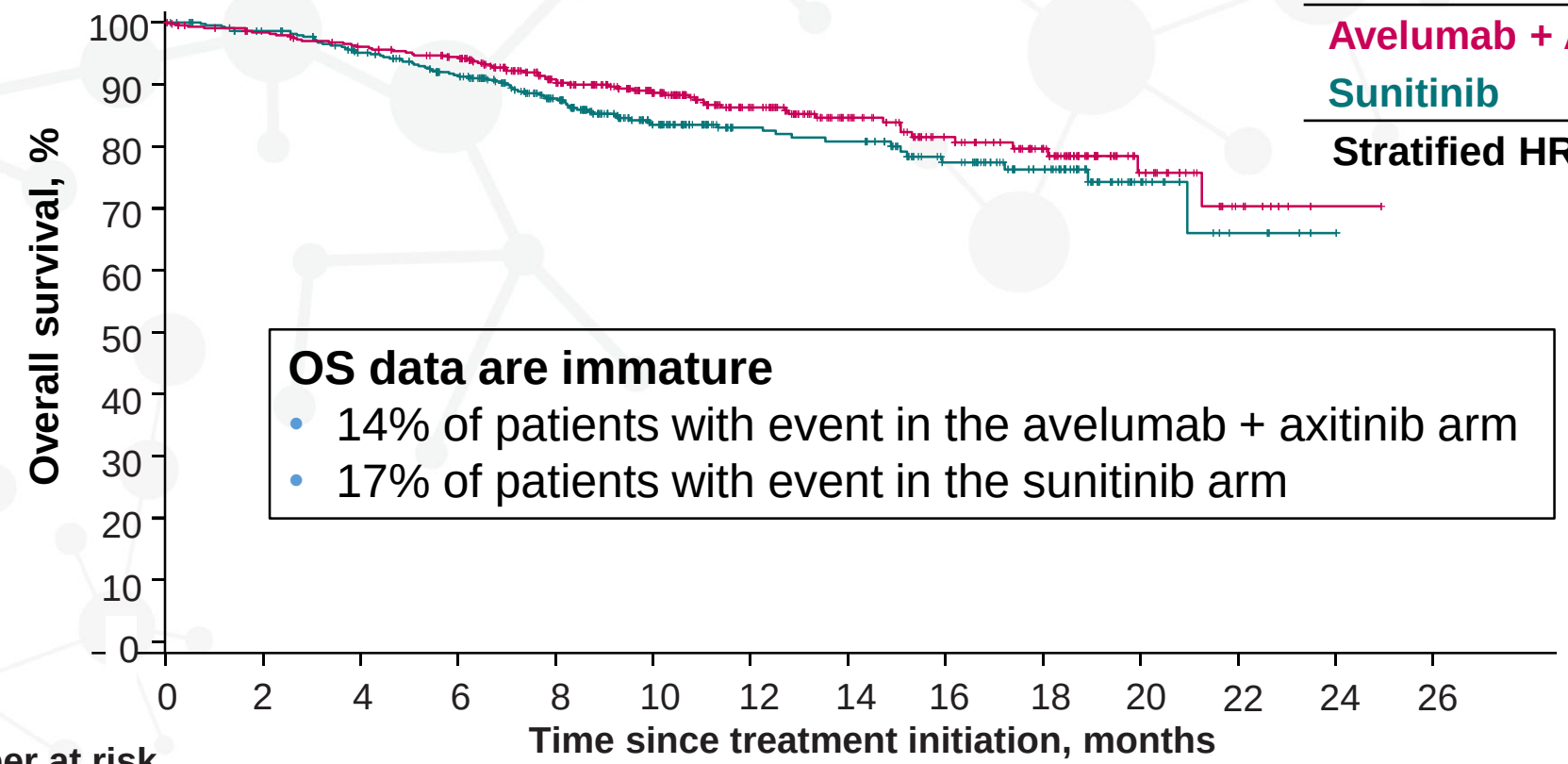
Response in PD-L1+ group: Avelumab + Axitinib (N = 149)



- Median time to response: 1.6 months (range: 1.2-10.1)
- 108 patients (73%) with ongoing response

sitc
Society for Immunotherapy of Cancer

OS in the overall population



Median OS (95% CI), months	
Avelumab + Axitinib	Not reached
Sunitinib	Not reached

Stratified HR, 0.78 (95% CI: 0.554, 1.084)
***P* = .0679**

OS data are immature

- 14% of patients with event in the avelumab + axitinib arm
- 17% of patients with event in the sunitinib arm

Number at risk

Avel + Axit:	442	426	412	396	319	252	187	121	93	70	27	8	1	0
Sunitinib:	444	426	401	373	295	224	175	113	84	59	17	5	1	0

Median follow-up, 12.0 months (avelumab + axitinib) and 11.5 months (sunitinib).

sitc
Society for Immunotherapy of Cancer

TRAEs in all treated patients (N = 873)

Secondary endpoint

	Avelumab + Axitinib (N = 434)		Sunitinib (N = 439)	
	All grades	Grade 3 (4)	All grades	Grade 3 (4)
All TRAEs, %	**95**	**51 (4)**	**96**	**48 (7)**
Diarrhea	54	5 (0)	45	3 (0)
Hypertension	48	24 (0)	32	15 (0)
Fatigue	36	3 (0)	36	4 (0)
Hand-foot syndrome	33	6 (0)	34	4 (0)
Dysphonia	27	1 (0)	3	0 (0)
Nausea	25	1 (0)	34	1 (0)
Hypothyroidism	24	< 1 (0)	13	< 1 (0)
Stomatitis	22	2 (0)	23	1 (0)
Decreased appetite	20	2 (0)	26	1 (0)
Dysgeusia	13	0 (0)	32	0 (0)
Increased alanine aminotransferase	13	4 (1)	10	2 (0)
Thrombocytopenia	3	< 1 (0)	18	5 (1)
Anemia	2	< 1 (0)	17	5 (< 1)
Neutropenia	1	< 1 (0)	18	7 (1)
TRAEs leading to discontinuation of all study drugs, %*	**4**		**8**	
TRAEs leading to death, %†	**1**		**< 1**	

sitc
Society for Immunotherapy of Cancer

Treatment-related adverse events (**TRAEs**) of any grade occurring in ≥ 20% of patients or grade 3-4 in ≥ 3% of patients are shown. * No events occurred in ≥ 1% of patients. † Grade 5 events occurred in 3 patients in the avelumab + axitinib arm (myocarditis, necrotizing pancreatitis, sudden death; n = 1 each); in 1 patient in the sunitinib arm (intestinal perforation).

AEs of special interest in all treated patients

Secondary endpoint

	Avelumab + Axitinib (N = 434)	
	All grades	**Grade 3 (4)**
All immune-related AEs, %	**38**	**8 (1)**
Hypothyroidism	21	< 1 (0)
Liver function test abnormalities	5	4 (< 1)
Adrenal insufficiency	2	1 (0)
Diarrhea	2	1 (0)
Acute kidney injury	1	1 (0)
Colitis	1	1 (0)
Hepatotoxicity	1	1 (0)
Infusion-related reaction, %	**12**	**1 (0)**

High-dose corticosteroids* were administered to 11% of patients who experienced an immune-related AE.

Immune-related AEs of any grade occurring in ≥ 5% of patients or grade 3 in ≥ 1% of patients are shown. * ≥40 mg total daily prednisone or equivalent.

sitc
Society for Immunotherapy of Cancer

JAVELIN Renal 101: efficacy summary

	PD-L1+ group (N = 560)		Overall population (N = 886)	
	Avelumab + Axitinib (N = 270)	Sunitinib (N = 290)	Avelumab + Axitinib (N = 442)	Sunitinib (N = 444)
PFS per IRC*				
Median, months	13.8	7.2	13.8	8.4
95% CI	11.1, NE	5.7, 9.7	11.1, NE	6.9, 11.1
Benefit vs sunitinib (HR; *P* value)	0.61; *P* < .0001	-	0.69; *P* = .0001	-
Objective response rate per IRC, %	55	26	51	26
95% CI	49.0, 61.2	20.6, 30.9	46.6, 56.1	21.7, 30.0
PFS per investigator assessment				
Median, months	13.3	8.2	12.5	8.4
95% CI	9.8, NE	6.9, 8.5	11.1, 15.2	8.2, 9.7
Benefit vs sunitinib (HR; *P* value)	0.51; *P* < .0001	-	0.64; *P* < .0001	-
Objective response rate per investigator assessment, %	62	30	56	30
95% CI	55.8, 67.7	24.5, 35.3	51.1, 60.6	25.9, 34.7

Society for Immunotherapy of Cancer

* PFS benefit per IRC was observed in patients regardless of PD-L1 status and in all prognostic risk groups.

Conclusions

- JAVELIN Renal 101 demonstrated longer progression-free survival and higher objective response rate for avelumab + axitinib compared with sunitinib for treatment-naive patients with advanced RCC
- Progression-free survival benefit was observed in patients regardless of PD-L1 status and in all prognostic risk groups
- The study continues to follow-up for overall survival
- Avelumab + axitinib demonstrated a favorable safety profile
- These results support avelumab + axitinib as a new first-line standard of care for patients with advanced RCC

sitc
Society for Immunotherapy of Cancer

Poll question

In the JAVELIN 101 study, avelumab and axitinib proved superior to sunitinib on all of the following endpoints except:

a. Overall response rate

b. PFS in the ITT population

c. Overall survival

d. PFS in the PD-L1 + population

Society for Immunotherapy of Cancer

mRCC PD-1 Based Combination Trial Comparison

	Ave + Axi[1] Javelin 101	Nivo + Ipi[2] CheckMate 214
	ITT	ITT
Phase	3	3
Comparator	Sunitinib	Sunitinib
N	442	550
Median follow-up, months	9.9	25.2
mPFS, months	13.2[†]	12.4[†]
HR (95% CI)	0.61 (0.48, 0.79)	0.68 (0.49, 0.95)[§]
ORR, %	55[†]	39[†]
CR, %	**3**	**9**
TRAEs, % All grades/Grade 3 or 4	95/51	93/46[¶]
Discontinuations due to AEs/TRAEs, %	NA/4	NA/22

*Data represent a summary of reported data and are not intended for cross-trial comparisons. [†]IRRC-assessed.

1. Motzer et al Presented at: ESMO 2018. 2. Motzer, et al. NEJM 2017.

sitc
Society for Immunotherapy of Cancer

Standard Therapy for mRCC: 2028

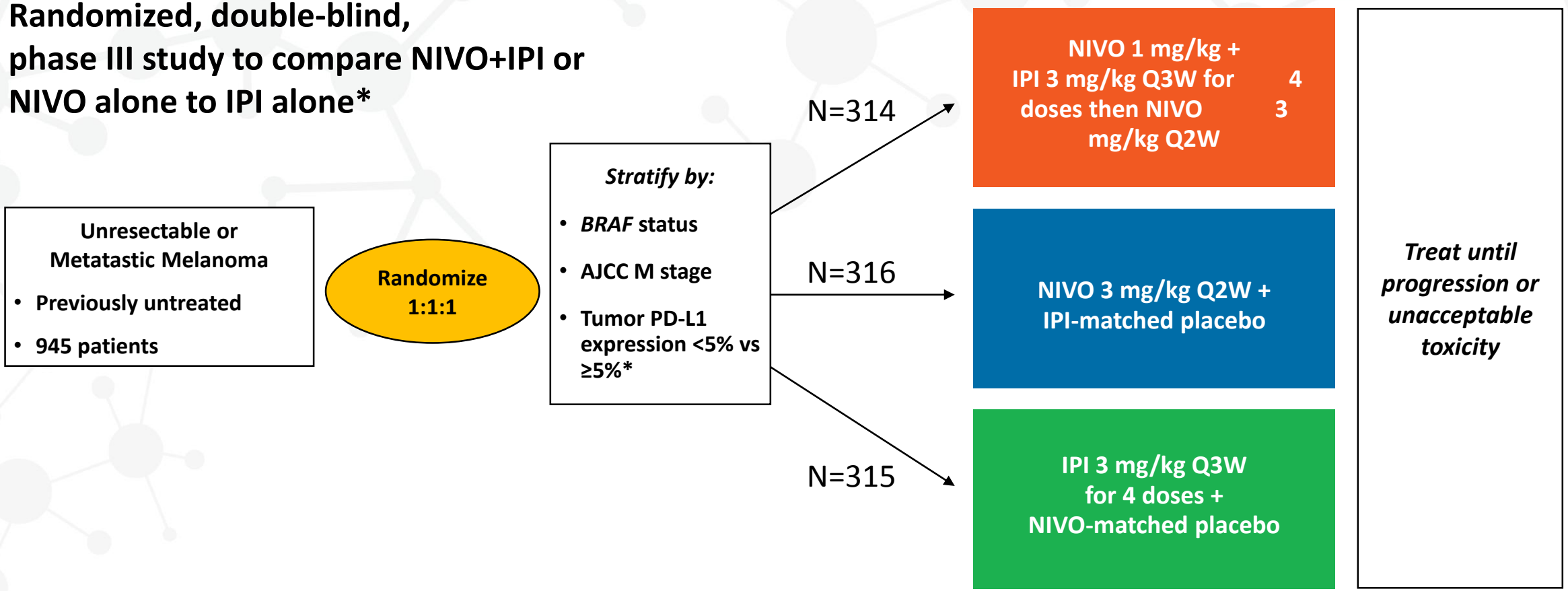
Setting	NCCN	Alternative
1st-Line Therapy	**Treatment based on TME* Profile**	
2nd-Line Therapy	**Not Necessary**	

Society for Immunotherapy of Cancer

*TME – Tumor Microenvironment, Smyth et al, Nat Rev Clin Oncol 2016

CheckMate 067: Study Design

Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone*



Database lock: Sept 13, 2016 (median follow-up ~30 months in both NIVO-containing arms)

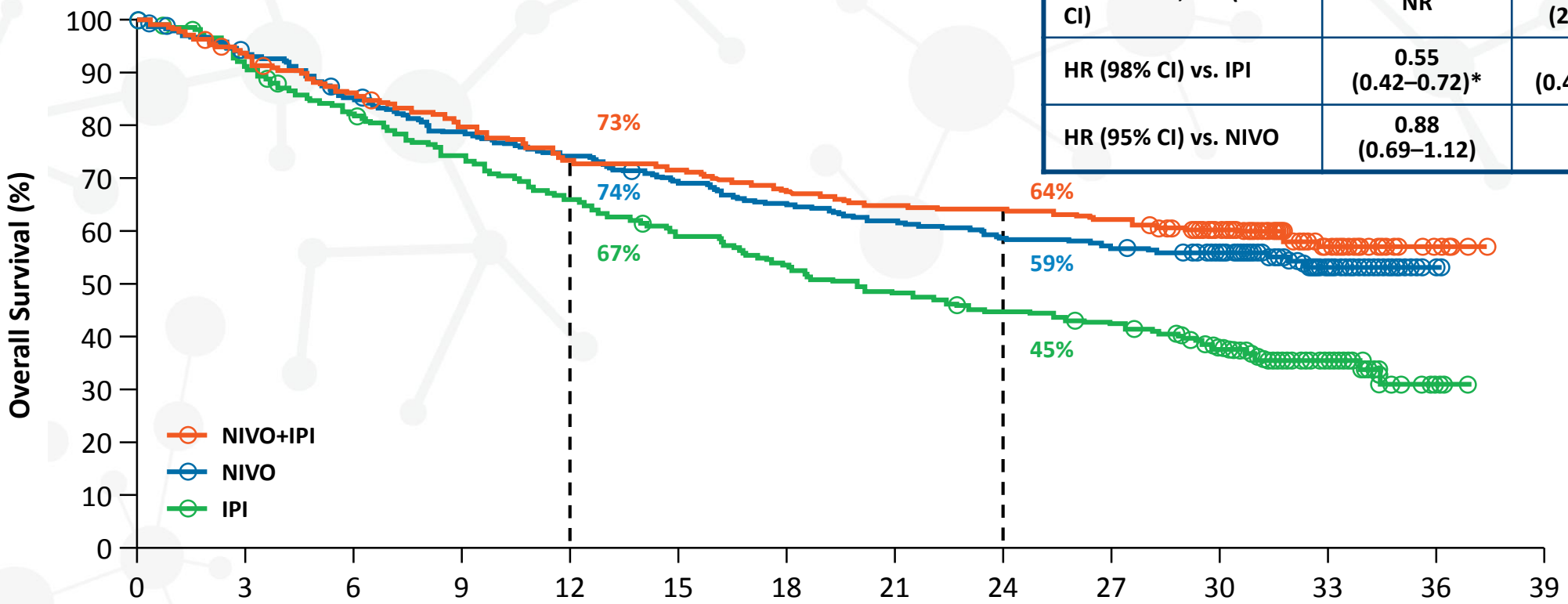
**The study was not powered for a comparison between NIVO and NIVO+IPI*

sitc
Society for Immunotherapy of Cancer

Overall Survival: CM 067

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median OS, mo (95% CI)	NR	NR (29.1–NR)	20.0 (17.1–24.6)
HR (98% CI) vs. IPI	0.55 (0.42–0.72)*	0.63 (0.48–0.81)*	--
HR (95% CI) vs. NIVO	0.88 (0.69–1.12)	--	--

*$P<0.0001$



Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	170	49	7	0
NIVO	316	292	265	244	230	213	201	191	181	175	157	55	3	0
IPI	315	285	254	228	205	182	164	149	136	129	104	34	4	0

sitc
Society for Immunotherapy of Cancer

Database lock: Sept 13, 2016, minimum f/u of 28 months

Patients who discontinued NIVO+IPI for AEs

- Pooled analysis of CM067/CM069 showed a subset of patients who discontinued NIVO+IPI early because of AEs achieved a meaningful treatment-free interval
- 176/407 (43%) discontinued for AEs; **96 (24%) in induction phase**
- ~1/3 who discontinued started subsequent systemic anti-cancer therapy
- Median time to subsequent therapy 25mo among the 96 pts who d/c during induction phase

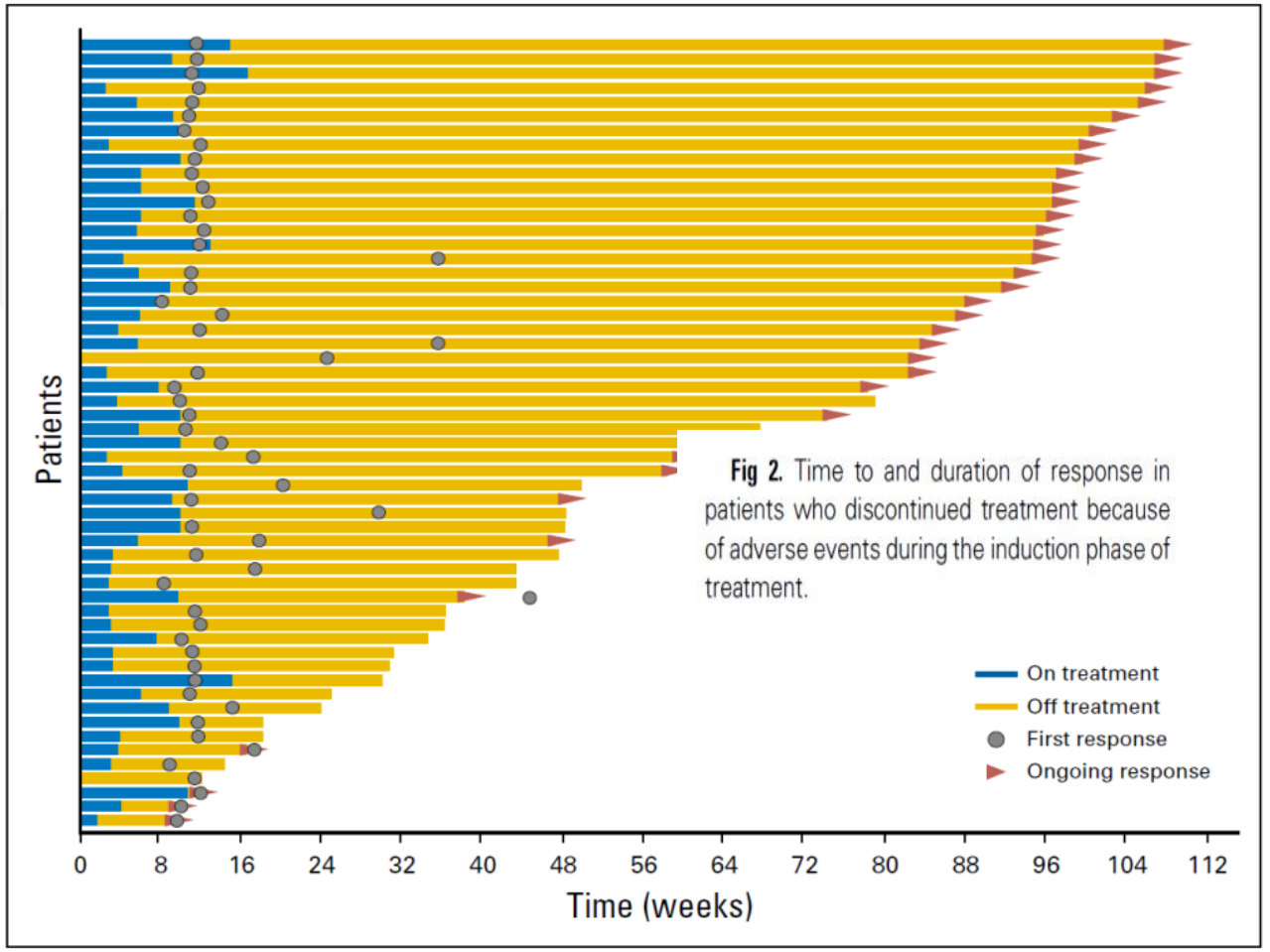


Fig 2. Time to and duration of response in patients who discontinued treatment because of adverse events during the induction phase of treatment.

Schadendorf et al. JCO 2017;35(34):3807

Society for Immunotherapy of Cancer

Overall Survival at 4 years of Follow-up in a Phase 3 Trial of Nivolumab Plus Ipilimumab Combination Therapy in Advanced Melanoma (CheckMate 067)

F. Stephen Hodi,[1] Vanna Chiarion-Sileni,[2] Rene Gonzalez,[3] Jean-Jacques Grob,[4] Piotr Rutkowski,[5] C. Lance Cowey,[6] Christopher D. Lao,[7] Dirk Schadendorf,[8] John Wagstaff,[9] Reinhard Dummer,[10] Pier Francesco Ferrucci,[11] Michael Smylie,[12] Andrew G. Hill,[13] David Hogg,[14] Ivan Marquez-Rodas,[15] Joel Jiang,[16] Jasmine Rizzo,[16] James Larkin,[17*] Jedd D. Wolchok[18*]

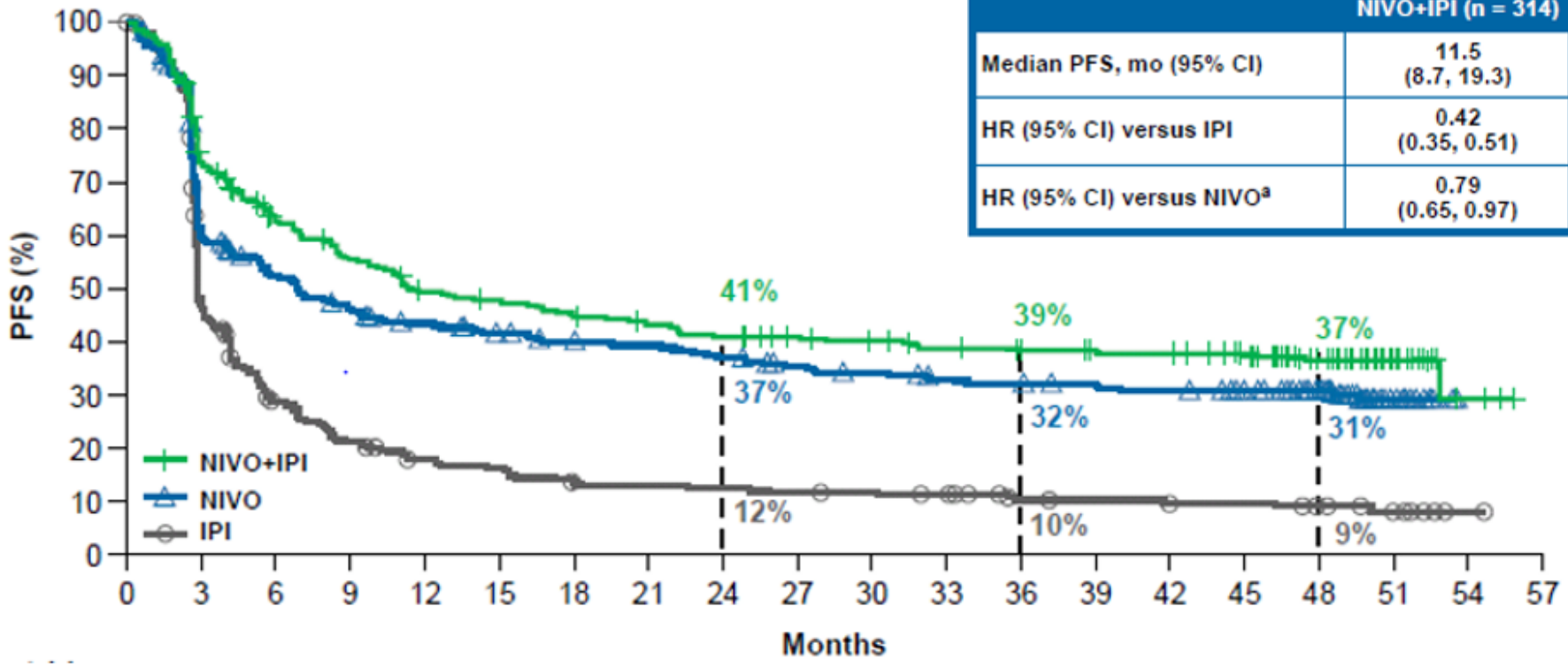
[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; [3]University of Colorado Cancer Center, Denver, CO, USA; [4]Aix-Marseille University, APHM Hospital CHU Timone, Marseille, France; [5]Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland; [6]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [7]University of Michigan, Ann Arbor, MI, USA; [8]University of Essen, Essen, and German Cancer Consortium, Heidelberg, Germany; [9]The College of Medicine, Swansea University, Swansea, UK; [10]Universitäts Spital, Zurich, Switzerland; [11]European Institute of Oncology, Milan, Italy; [12]Cross Cancer Institute, Edmonton, AB, Canada; [13]Tasman Oncology Research, Southport, QLD, Australia; [14]Princess Margaret Cancer Centre, Toronto, ON, Canada; [15]General University Hospital Gregorio Marañón, Madrid, Spain; [16]Bristol-Myers Squibb, Princeton, NJ, USA; [17]The Royal Marsden Hospital NHS Foundation Trust, London, UK; [18]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA;
*Contributed equally to this study.

sitc
Society for Immunotherapy of Cancer

ESMO Abstract Number LBA44

Progression-Free Survival

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median PFS, mo (95% CI)	11.5 (8.7, 19.3)	6.9 (5.1, 10.2)	2.9 (2.8, 3.2)
HR (95% CI) versus IPI	0.42 (0.35, 0.51)	0.53 (0.44, 0.64)	–
HR (95% CI) versus NIVO[a]	0.79 (0.65, 0.97)	–	–



Patients at risk:

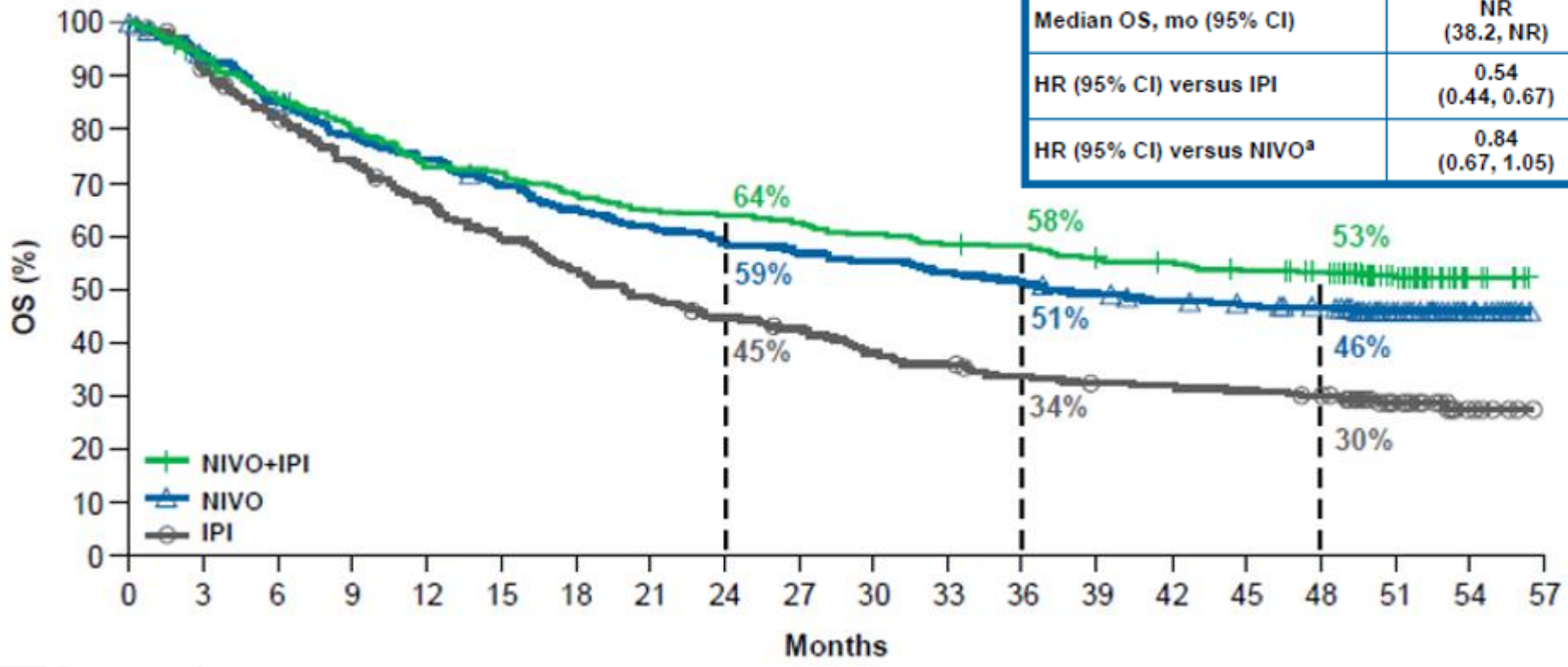
NIVO+IPI	314	218	175	155	136	131	124	117	110	104	101	95	93	89	88	81	53	19	3	0
NIVO	316	177	151	132	120	112	106	103	97	88	84	79	77	75	72	66	50	18	0	0
IPI	315	136	78	58	46	42	34	32	31	29	28	26	19	18	16	16	11	7	1	0

[a]Descriptive analysis

sitc
Society for Immunotherapy of Cancer

Overall Survival

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2, NR)	36.9 (28.3, NR)	19.9 (16.9, 24.6)
HR (95% CI) versus IPI	0.54 (0.44, 0.67)	0.65 (0.53, 0.79)	–
HR (95% CI) versus NIVO[a]	0.84 (0.67, 1.05)	–	–



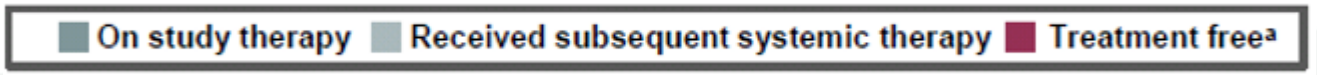
Patients at risk:

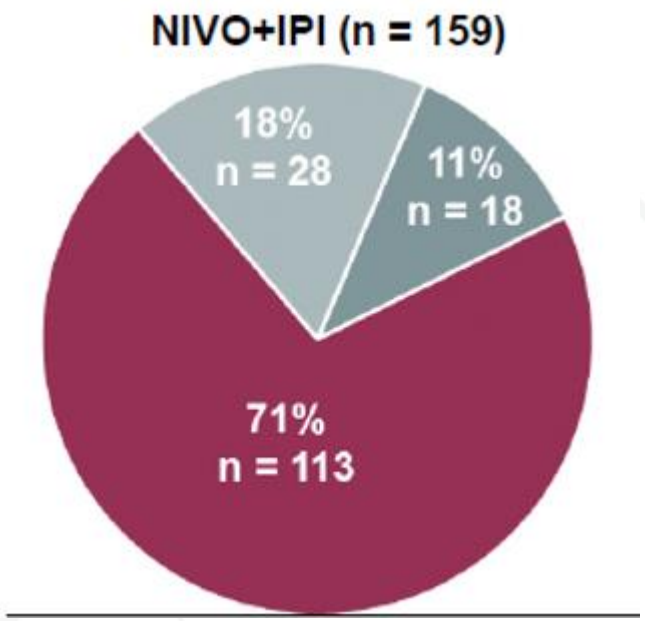
NIVO+IPI	314	292	265	247	226	221	209	200	198	192	186	180	178	171	166	160	154	96	13	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	144	140	135	85	18	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	99	94	93	90	86	50	11	0

[a]Descriptive analysis

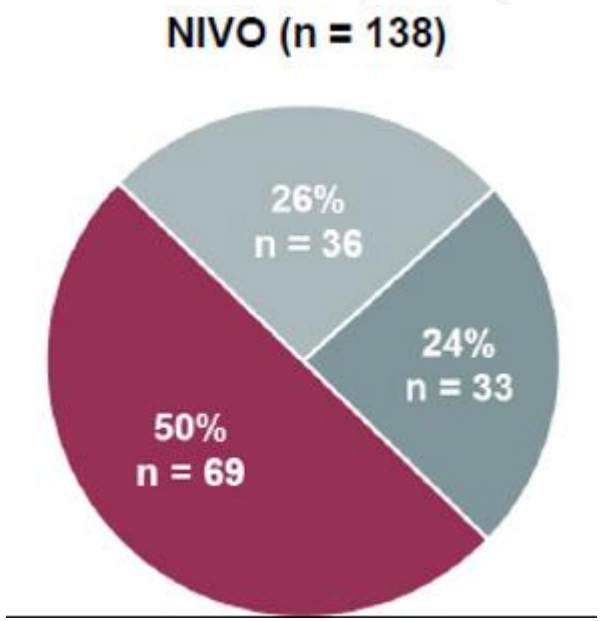
sitc
Society for Immunotherapy of Cancer

Patients Alive at 4 Years

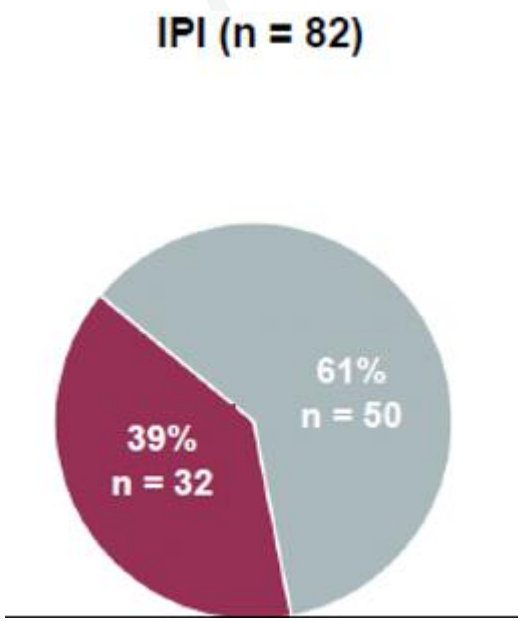




Median follow-up 51.6 mo (IQR 50.4-52.8)



Median follow-up 51.7 mo (IQR 50.4-52.9)



Median follow-up 51.4 mo (IQR 50.4-52.7)

At the time of the 4-year follow-up, 71% of patients in the NIVO+IPI group were treatment free, which is increased from that observed at the 3-year follow-up (67%; 114/170)

[a]Off study treatment for any reason and never received subsequent systemic therapy

sitc
Society for Immunotherapy of Cancer

Safety Summary

Patients reporting event	NIVO+IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AE, %	95.8	59.1	86.3	22.4	86.2	27.7
Treatment-related AE leading to discontinuation, %	40.3	30.4	12.5	8.0	15.1	13.5
Treatment-related death, n (%)	2 (0.6)		1 (0.3)		1 (0.3)	

- No new safety signals were observed with the additional follow-up
- No additional deaths due to study drug toxicity were reported since the prior analysis
  - Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO+IPI (n=1 each and both occurred >100 days after last treatment), neutropenia for NIVO (n=1), and colonic perforation for IPI (n=1)
- Patients who discontinued NIVO+IPI during induction due to a treatment-related AE had similar 4-year PFS (35%) and OS (54%) to patients in the overall population (37% and 53%, respectively)

sitc
Society for Immunotherapy of Cancer

Summary

- A durable, sustained clinical benefit can be achieved with first-line NIVO-IPI or NIVO alone in patients with advanced melanoma
  - Benefit was observed across clinically relevant subgroups, including *BRAF* mutation status
  - NIVO+IPI and NIVO showed improved efficacy over IPI regardless of tumor PD_L1 expression as stratified on study
- Continued separation of the survival curves indicated sustained improvement for NIVO+IPI vs. NIVO
  - Median OS has been reached for IPI and NIVO but not NIVO+IPI
  - NIVO+IPI patients who discontinued treatment early due to an AE had survival benefits similar to the overall population
- First-line NIVO+IPI may reduce the need for subsequent therapy or delay its use
- The safety profile was similar to the prior analysis, with no new safety signals and no additional treatment-related deaths

sitc
Society for Immunotherapy of Cancer

IMpassion130: Results from a global, randomised, double-blind, Phase III study of atezolizumab + *nab*-paclitaxel vs placebo + *nab*-paclitaxel in treatment-naive locally advanced or metastatic triple-negative breast cancer

Peter Schmid,[1] Sylvia Adams,[2] Hope S. Rugo,[3] Andreas Schneeweiss,[4] Carlos H. Barrios,[5] Hiroji Iwata,[6] Véronique Diéras,[7] Roberto Hegg,[8] Seock-Ah Im,[9] Gail Shaw Wright,[10] Volkmar Henschel,[11] Luciana Molinero,[12] Stephen Y. Chui,[12] Roel Funke,[12] Amreen Husain,[11] Eric P. Winer,[13] Sherene Loi,[14] Leisha A. Emens[15]

[1]Barts Cancer Institute, Queen Mary University of London, London, UK; [2]New York University Langone Medical Center, New York, NY, USA; [3]University of California San Francisco Comprehensive Care Center, San Francisco, CA, USA; [4]University Hospital Heidelberg, Heidelberg, Germany; [5]Centro de Pesquina Clínica, HSL, PUCRS, Porto Alegre, Brazil; [6]Aichi Cancer Center Hospital, Aichi, Japan; [7]Department of Medical Oncology, Institut Curie, Paris, France; [8]University of São Paulo, São Paulo, Brazil; [9]Seoul National University Hospital, Seoul, Korea; [10]Florida Cancer Specialists & Research Institute, New Port Richey, FL, USA; [11]Roche, Basel, Switzerland; [12]Genentech, Inc., South San Francisco, CA, USA; [13]Dana-Farber Cancer Institute, Boston, MA, USA; [14]Peter MacCallum Cancer Centre, Melbourne, Australia; [15]Bloomberg~Kimmel Institute for Cancer Immunotherapy at Johns Hopkins, Baltimore, MD, USA, now with UPMC Hillman Cancer Center, Pittsburgh, PA USA

sitc
Society for Immunotherapy of Cancer

Schmid P, et al. IMpassion130
ESMO 2018 (LBA1_PR)
http://bit.ly/2DMhayg

Triple-negative breast cancer (TNCB)

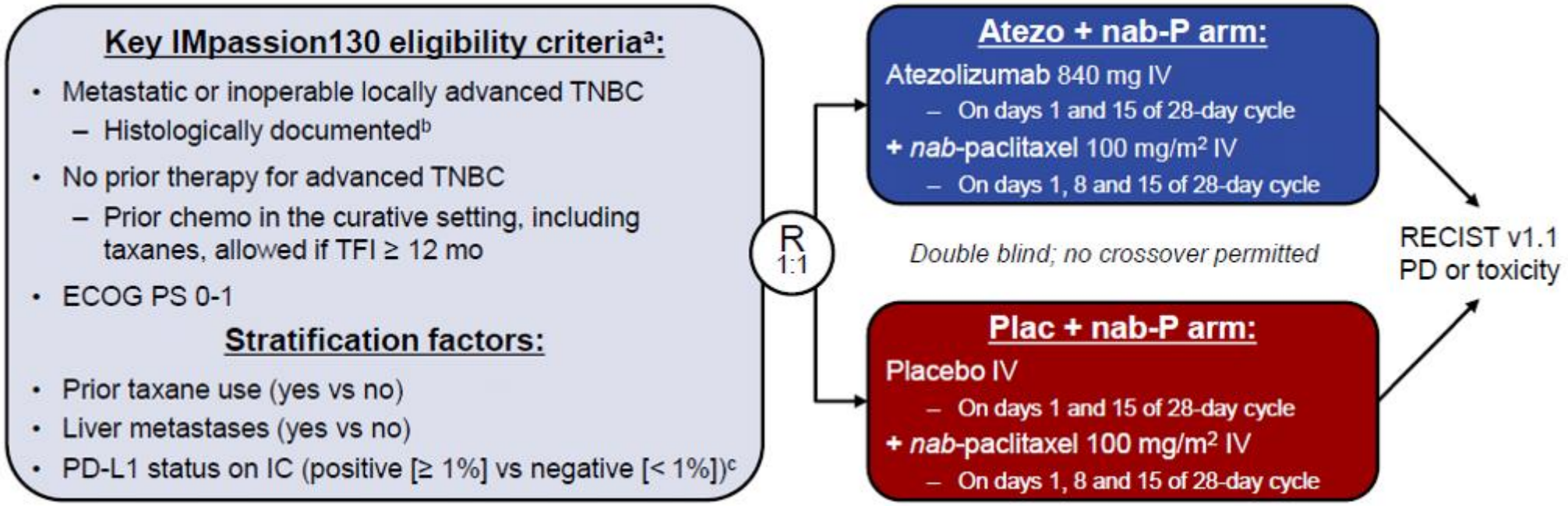
- Patients with advanced or metastatic TNBC experience poor outcomes relative to patients with other breast cancer subtypes,[1] with median OS of ~ 18 months or less[2-4]
- First-line treatment typically includes single-agent taxane or anthracycline chemotherapy[5,6]
- No targeted therapies have improved OS to date
- Checkpoint inhibition may be a useful approach in the treatment of TNBC
  - PD-L1 can inhibit anti-cancer immune responses[7]
  - PD-L1 in TNBC is expressed mainly on tumour-infiltrating immune cells (IC)[8,9]

1. den Brok *BCRT* 2017. 2. Gobbini *EJC* 2018. 3. Yardley *Ann Oncol* 2018. 4. Miles *Ann Oncol* 2013. 5. NCCN 2018. 6. Cardoso *Ann Oncol* 2018. 7. Chen *Immunity* 2013. 8. Sabatier *Oncotarget* 2015. 9. Mittendorf *CIR* 2014.

Schmid P, et al. IMpassion130
ESMO 2018 (LBA1_PR)
http://bit.ly/2DMhayg

sitc
Society for Immunotherapy of Cancer

IMpassion130 study design



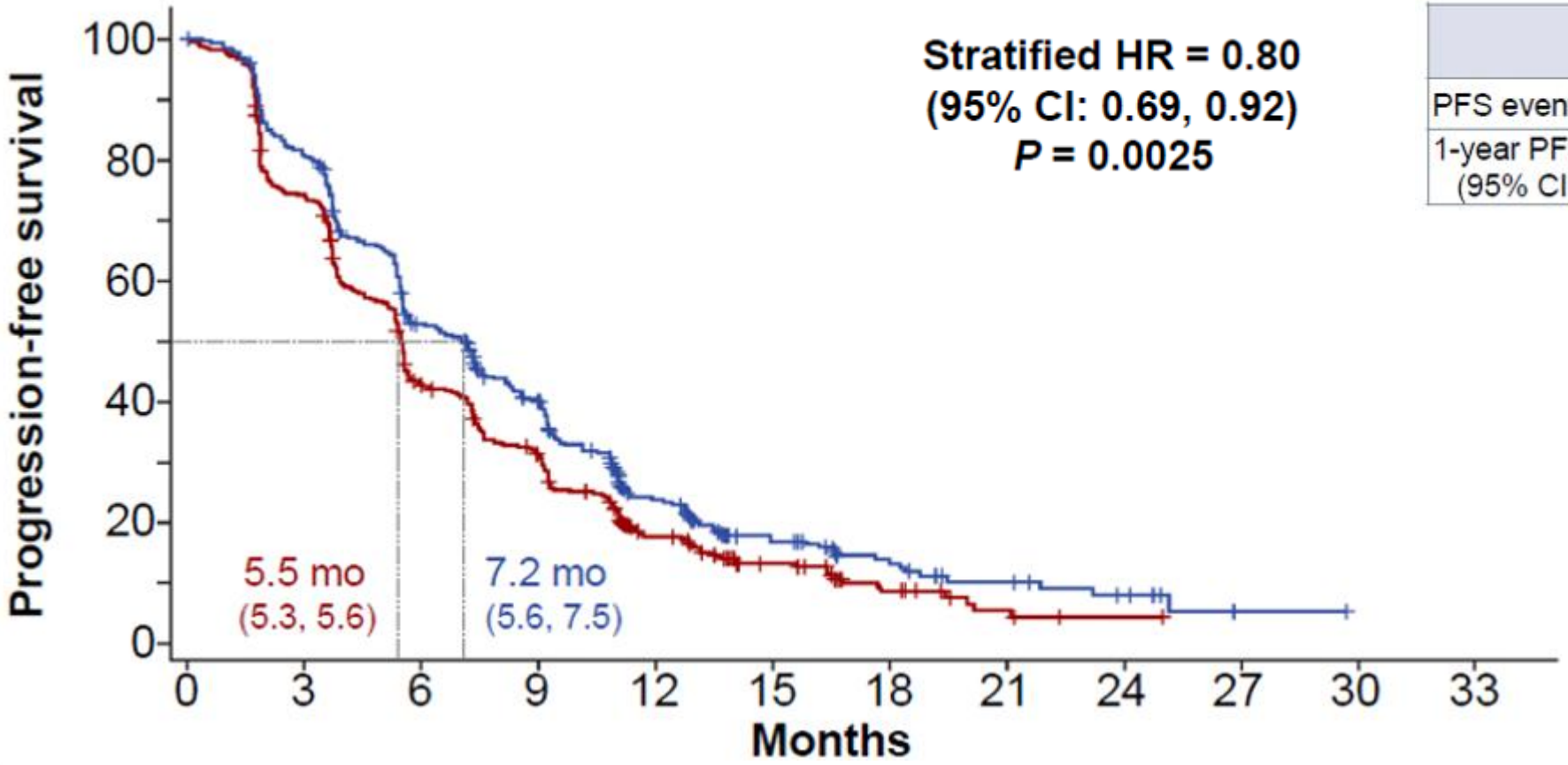
- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations[d]
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

IC, tumour-infiltrating immune cell; TFI, treatment-free interval. [a] ClinicalTrials.gov: NCT02425891. [b] Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines. [c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). [d] Radiological endpoints were investigator assessed (per RECIST v1.1).

Schmid P, et al. IMpassion130
ESMO 2018 (LBA1_PR)
http://bit.ly/2DMhayg

sitc
Society for Immunotherapy of Cancer

Primary PFS analysis: ITT population



Stratified HR = 0.80
(95% CI: 0.69, 0.92)
***P* = 0.0025**

	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
PFS events, n	358	378
1-year PFS (95% CI), %	24% (20, 28)	18% (14, 21)

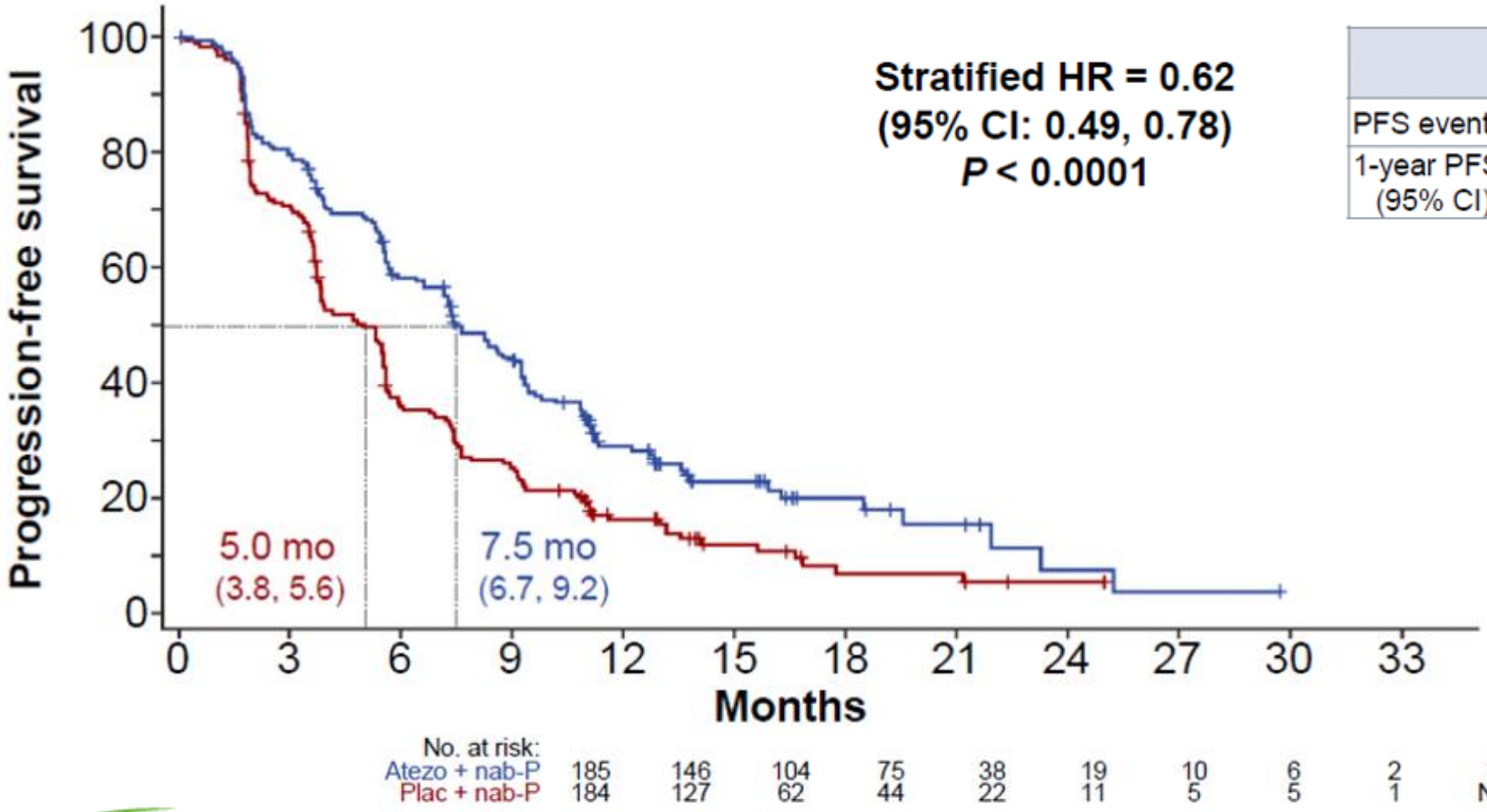
No. at risk:												
Atezo + nab-P	451	360	226	164	77	34	20	11	6	1	NE	NE
Plac + nab-P	451	327	183	130	57	29	13	5	1	NE	NE	NE

NE, not estimable. Data cutoff: 17 April 2018. Median PFS durations (and 95% CI) are indicated on the plot. Median follow-up (ITT): 12.9 months.

Schmid P, et al. IMpassion130
ESMO 2018 (LBA1_PR)
http://bit.ly/2DMnayg

sitc
Society for Immunotherapy of Cancer

Primary PFS analysis: PD-L1+ population



Stratified HR = 0.62
(95% CI: 0.49, 0.78)
***P* < 0.0001**

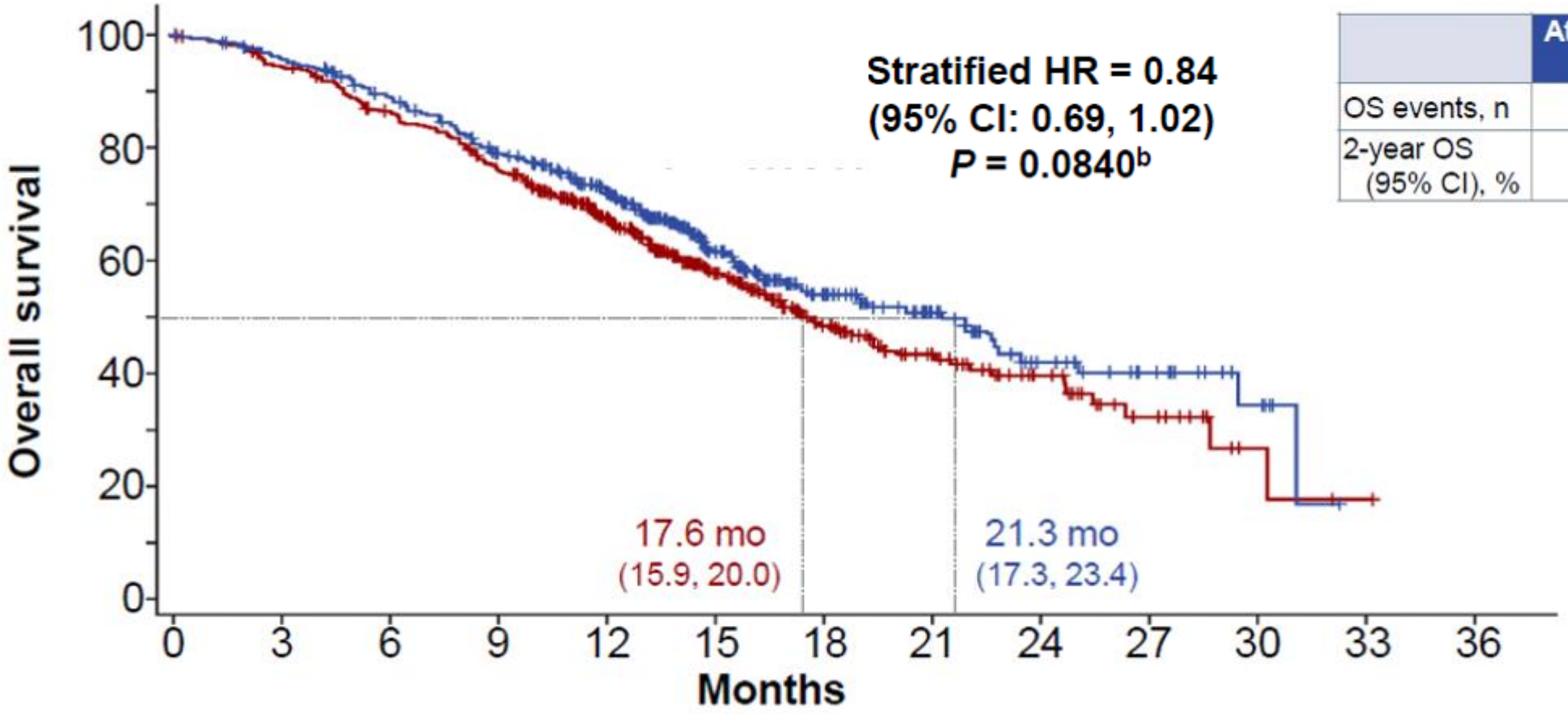
	Atezo + nab-P (n = 185)	Plac + nab-P (n = 184)
PFS events, n	138	157
1-year PFS (95% CI), %	29% (22, 36)	16% (11, 22)

Data cutoff: 17 April 2018.

sitc
Society for Immunotherapy of Cancer

Schmid P, et al. IMpassion130
ESMO 2018 (LBA1_PR)
http://bit.ly/2DMhayg

Interim OS analysis: ITT population[a]



	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
OS events, n	181	208
2-year OS (95% CI), %	42% (34, 50)	40% (33, 46)

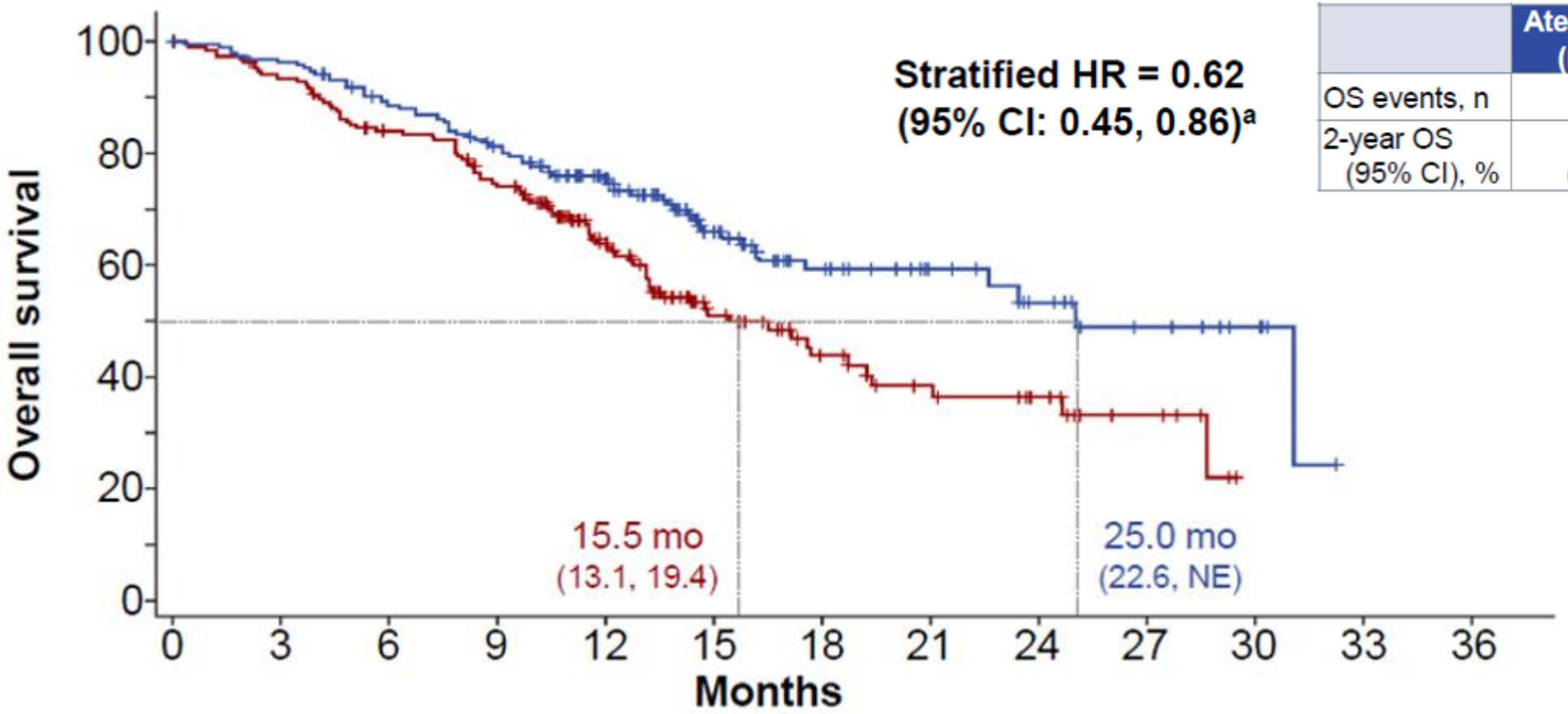
No. at risk:													
Atezo + nab-P	451	426	389	337	271	146	82	48	26	15	6	NE	NE
Plac + nab-P	451	419	375	328	246	145	89	52	27	12	3	1	NE

Data cutoff: 17 April 2018. Median OS durations (and 95% CI) are indicated on the plot. Median follow-up (ITT): 12.9 months.
[a] For the interim OS analysis, 59% of death events had occurred. [b] Significance boundary was not crossed.

sitc
Society for Immunotherapy of Cancer

Schmid P, et al. IMpassion130
ESMO 2018 (LBA1_PR)
http://bit.ly/2DMhayg

Interim OS analysis: PD-L1+ population



	Atezo + nab-P (n = 185)	Plac + nab-P (n = 184)
OS events, n	64	88
2-year OS (95% CI), %	54% (42, 65)	37% (26, 47)

sitc
Society for Immunotherapy of Cancer

Schmid P, et al. IMpassion130
ESMO 2018 (LBA1_PR)
http://bit.ly/2DMhayg

IMpassion130 conclusions

- IMpassion130 is the first Phase III study to demonstrate a benefit with first-line immunotherapy in mTNBC
  - Atezolizumab + *nab*-paclitaxel resulted in statistically significant PFS benefit in the ITT and PD-L1+ populations (ITT HR = 0.80 [95% CI: 0.69, 0.92] and PD-L1+ HR = 0.62 [95% CIL 0.49, 0.78]), which was clinically meaningful in the PD-L1+ population
  - At this first interim OS analysis, clinically meaningful improvement in OS with atezolizumab + *nab*-paclitaxel (v placebo + *nab*-paclitaxel) was observed in the PD-L1+ population, with a HR of 0.62 and a median OS improvement from 15.5 months to 25.0 months (formal OS testing in PD-L1+ patients not performed per hierarchical study design)
  - No detriment observed for the PD-L1 - subgroup
- Atezolizumab + *nab*-paclitaxel was well tolerated, with a safety profile consistent with each agent
- For patients with PD-L1+ tumours,[a] these data establish atezolizumab + *nab*-paclitaxel as a new standard of care

sitc
Society for Immunotherapy of Cancer

Schmid P, et al. IMpassion130
ESMO 2018 (LBA1_PR)
http://bit.ly/2DMhayg

[a] PD-L1 expression on ≥1% of tumour-infiltrating immune cells.

Conclusions

- To foster the rational application of IO Rx
- FDA/Industry Support for:
  - Innovative Trial Design
  - Next Gen Biomarkers
  - IO Endpoints
- Focus on the Patient's Goal:
  - Increasing Treatment-free Survival

sitc
Society for Immunotherapy of Cancer

Poll Question

Immunotherapy clinical trial endpoints/outcomes include all of the following except:

a. Complete response
b. Durable overall survival
c. Median progression-free survival
d. Treatment-free interval

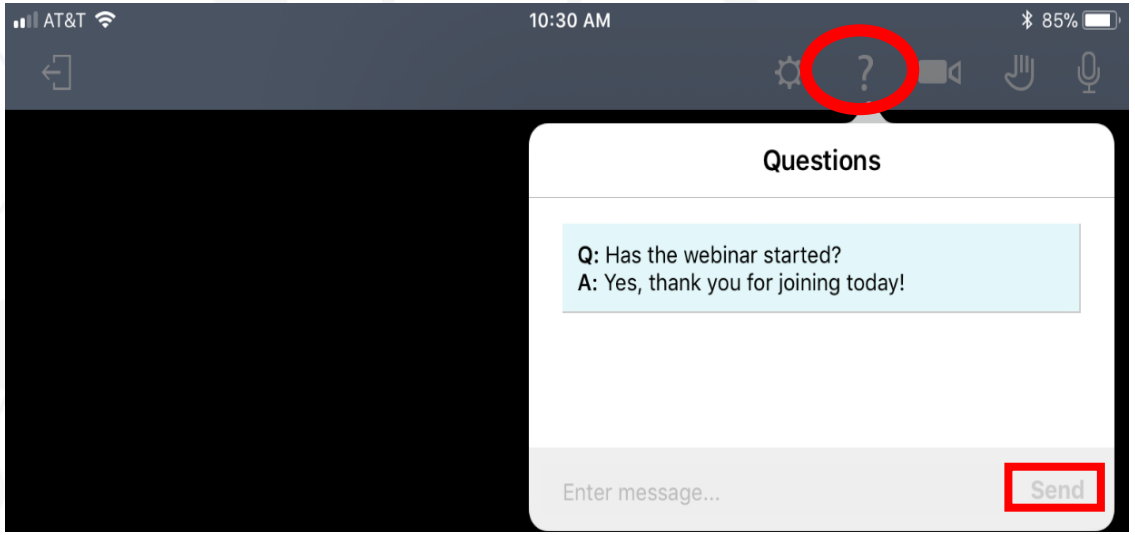
Society for Immunotherapy of Cancer

Question and Answer

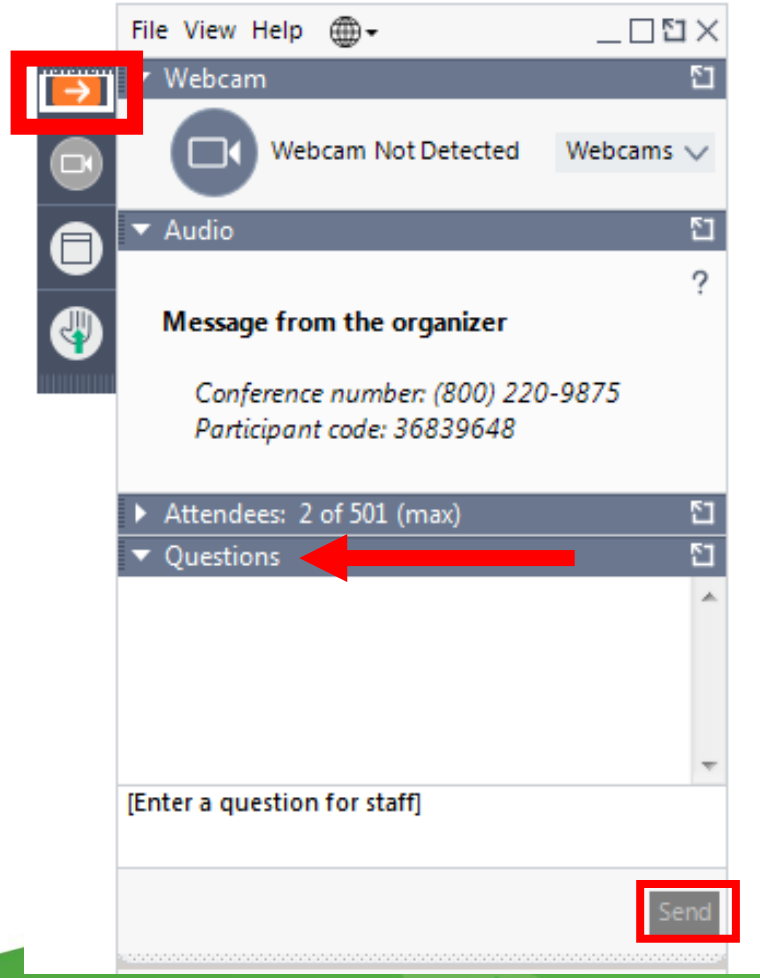
To submit a question:

Type your question in the Questions box of your webinar panel.

Mobile View



Desktop View



Society for Immunotherapy of Cancer

ACI Webinar Series

SAVE THE DATE!

Monday, December 10, 2018

1:00-2:00 p.m. CST

Faculty Experts:

Christian M. Capitini, MD – *University of Wisconsin Carbone Cancer Center*

Zachary S. Morris, MD – *University of Wisconsin School of Medicine and Public Health*

To register, please visit: sitcancer.org/education/aci/online

sitc

Society for Immunotherapy of Cancer