Clinical Trial Design Considerations for Evaluating Efficacy in Immuno-oncology Clinical Trials

David McDermott, MD

Beth Israel Deaconess Medical Center

Dana Farber/Harvard Cancer Center

Harvard Medical School

Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

NCI Designated Comprehensive Cancer Center

A founding member of Dana-Farber/Harvard Cancer Center

Disclosures

Consultant

- Array Biopharma
- Bristol-Myers Squibb
- Calithera Biosciences
- Exelixis
- Genentech
- Merck
- Novartis
- Pfizer
- Jounce

Research funding

- Prometheus Labs
- Bristol-Myers Squibb

mRCC: Most Applied Sequence 2017*

Setting	NCCN	Alternative
1st-Line Therapy	VEGF Blockade	
2nd-Line Therapy	PD-1 Blockade	

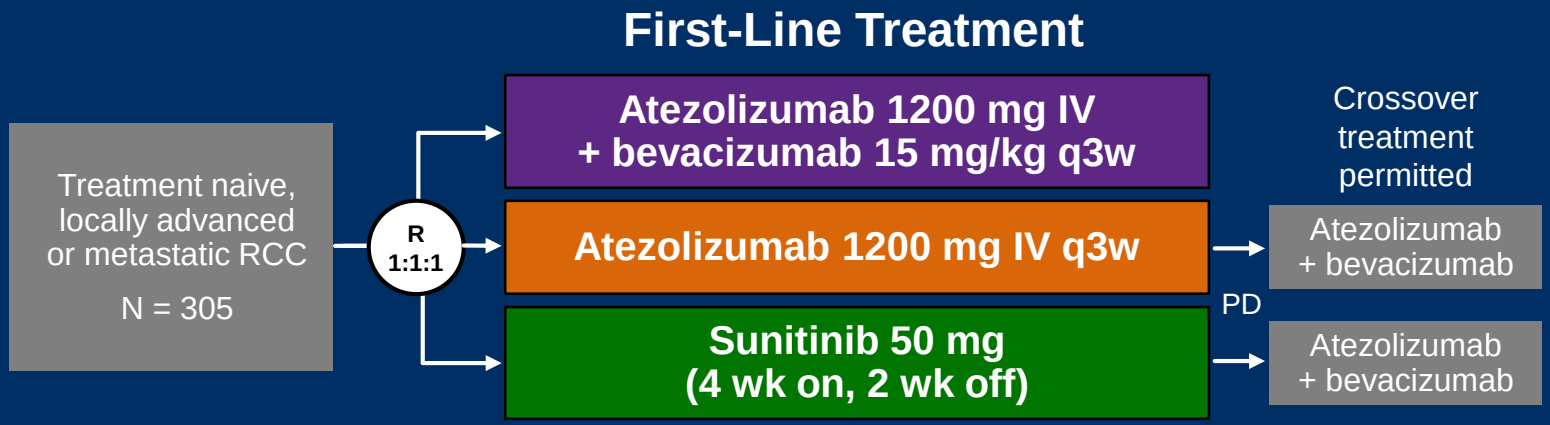
*Motzer RJ et al. NEJM 2015.

mRCC: Fusion of First and Second-line Therapy

Setting	NCCN[a]	Alternative
Treatment Naive	**PD-1 + VEGF Blockade[d]**	
3rd-Line Therapy		

[c]Pending FDA review. Motzer RJ et al. SITC 2016. Abstract O38. [d]Motxer et al, GU ASCO Abstract.

IMmotion150 Trial: Randomized Phase 2, Three Arm Design

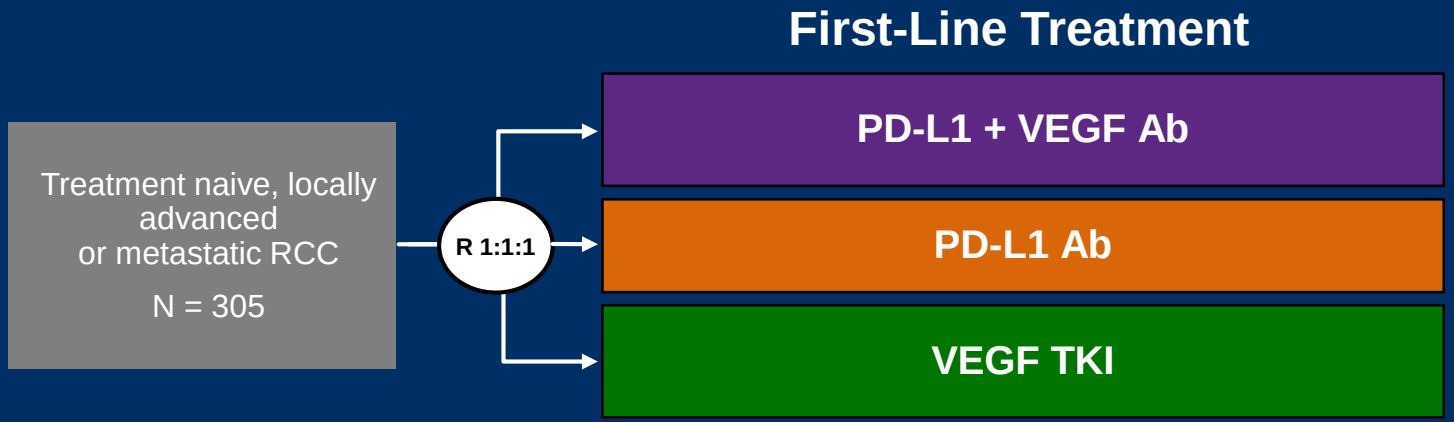


McDermott D, et al. IMmotion150 biomarkers: Nature Med 2018

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

- **Trial Design**
- Patient Selection
- Novel Endpoints

IMmotion150 Trial Design: Randomized P2

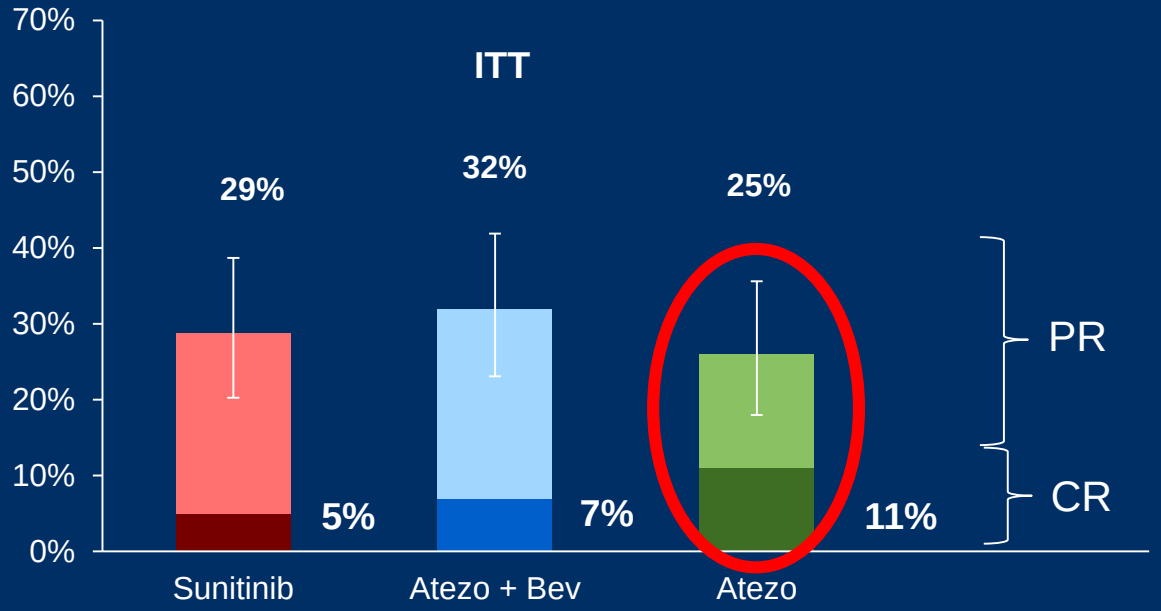


- IMmotion150 was designed to be **hypothesis generating** and inform the Phase III study IMmotion151
- First Randomized Trial to:
  - Explore ICB (atezo) + Targeted Therapy (bev)
  - **Explore the association between outcome and TME gene signatures**
- **First RCC Trial to:**
  - **Explore single agent ICB in 1st Line**

TME, tumor microenvironment; ICB, immune checkpoint blockade

McDermott D, et al. Nature Med 2018

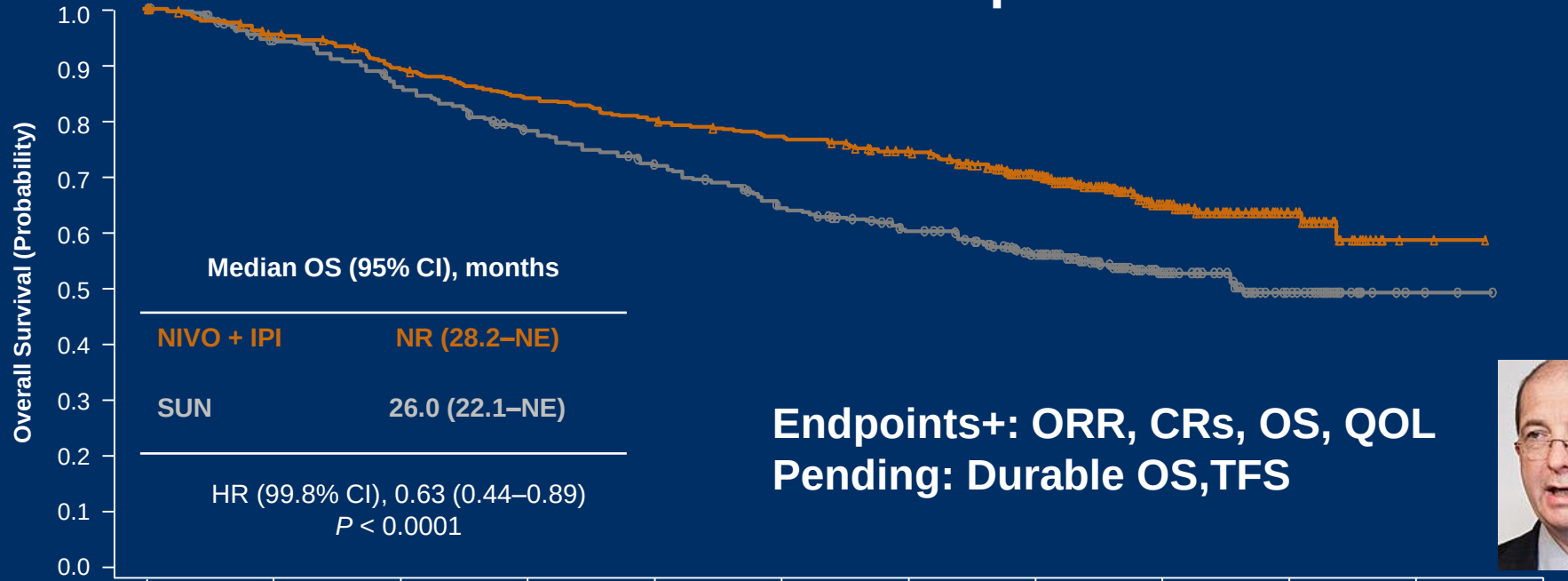
IMmotion 150: 1L Single Agent PD-L1 Blockade Activity



- 75% of responses are ongoing across treatment arms, and the median duration of response is not estimable due to an insufficient number of PFS events in responders

Confirmed responses measured by independent review facility.
CR, complete response; PR, partial response.
Clinical cutoff, Oct 17, 2016. Median duration of follow-up, 20.7 mo. McDermott, ASCO GU 2017.

PD-1 + CTLA-4 Blockade (CM214)
OS: IMDC intermediate/poor risk



Endpoints+: ORR, CRs, OS, QOL
Pending: Durable OS,TFS

Motzer RJ et al. NEJM 2017

mRCC: Era of Front-Line Combination Therapy

Setting	NCCN	Alternative
1st-Line Therapy	PD-1 + CTLA-4 Blockade*	
2nd-Line Therapy		

*Intermediate/Poor Risk Motzer RJ et al. NEJM 2017. FDA but not yet EMA approved.

YAHOO! FINANCE

Bristol-Myers to get negative CHMP opinion on renal cancer drugs

REUTERS **Reuters** July 26, 2018, 3:59 PM GMT+1

NEW YORK, July 26 (Reuters) - Bristol-Myers Squibb Co said on Thursday it was told by European regulators that they will recommend against approving the company's drugs Opdivo and Yervoy to treat first-line renal cancer.

CHMP discussed whether the **contribution of ipilimumab** to the efficacy of the combination therapy in the proposed dosage has been sufficiently demonstrated and some concern was expressed.

CHMP – Committee on Human Medicinal Products

PD-1 then CTLA-4 Blockade

Trial Diagram – HCRN GU 260 (BMS 209-669)

Metastatic Kidney Cancer Treatment Naïve
- **120 ccRCC**
- **40 nccRCC**

→ **Nivolumab 240 mg/kg IV Q2wks**

→ **PR or CR: Continue Nivolumab 360 mg/kg IV Q3wks x up to 84 wks**

→ **PD or best response SD @ 1 year: Re-induce with N3/I1 q3 weeks x 4 , up to 4 combination doses**

→ **PR or CR: Continue Nivolumab 360 mg/kg IV Q3wks x 48 wks**

Extensive Biomarker studies to be done in collaboration with the DFHCC Kidney Cancer UTSW SPORE Investigators

Opened 4/17/17

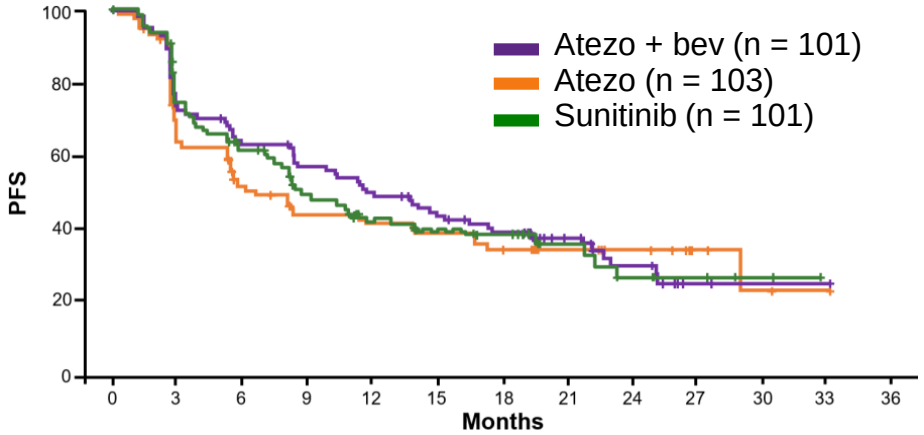
Atkins, Hammers, Signoretti
NCT03117309

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

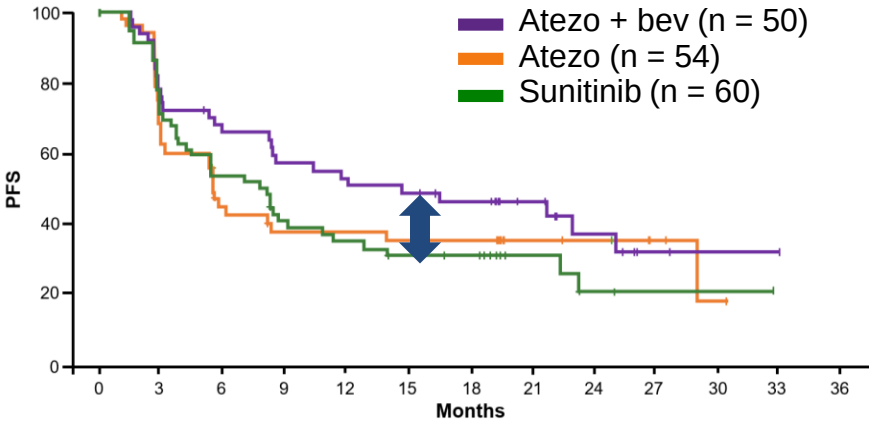
- Trial Design
- **Patient Selection**
  - **Which patients benefits from Combination Rx?**
- Novel Endpoints

Encouraging Efficacy by PFS of Atezolizumab + Bevacizumab vs Sunitinib in Patients With IC PD-L1 Expression

PFS in ITT



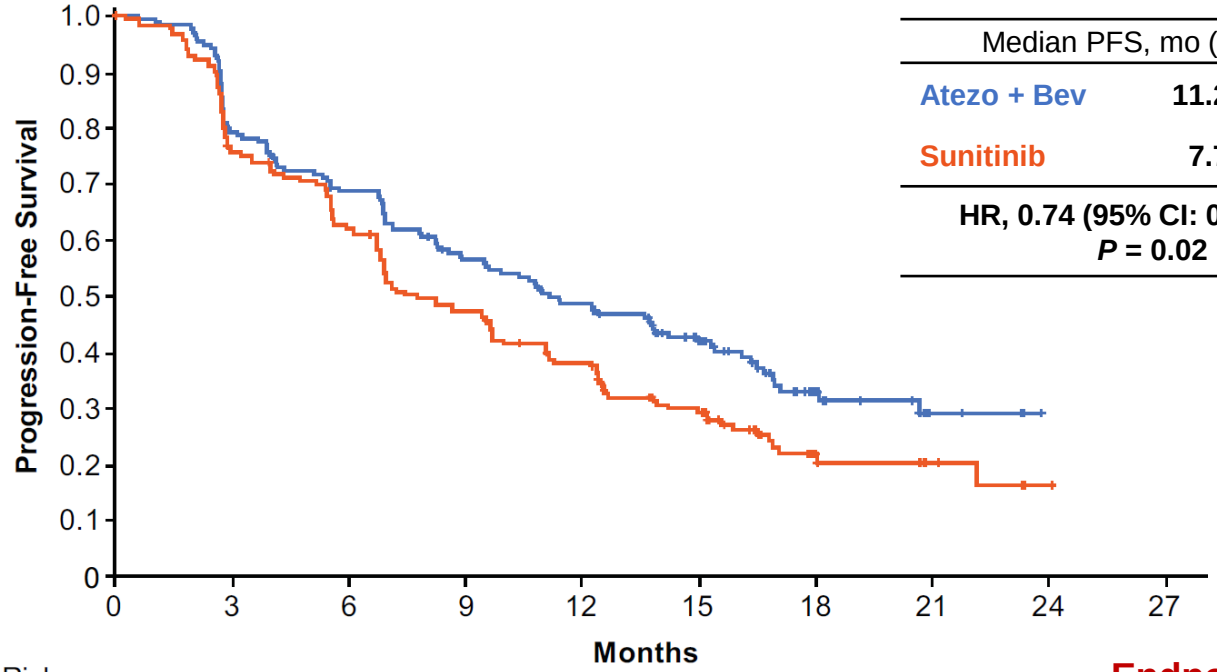
PFS in ≥ 1% PD-L1 IC



Atezo, atezolizumab; bev, bevacizumab. IRF-assessed PFS.
McDermott et al, Nat Med 2018.

Anti-PD-L1/VEGF Antibodies (IM151)
Progression-Free Survival in PD-L1+

Co-Primary Endpoint



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

Endpoints+: PFS
Pending: OS, TFS

PFS assessed by investigators. Minimum follow-up, 12 mo. Median follow-up, 15 mo. The PFS analysis passed the pre-specified *P* value boundary of alpha = 0.04.

OncLive®
Bringing the Global Oncology Community Together

Pembrolizumab Combo Fails in Melanoma

Jason M. Broderick @jasoncology
Published: Friday, Apr 06, 2018

The combination of the PD-1 inhibitor pembrolizumab (Keytruda) and the IDO1 inhibitor epacadostat failed to improve progression-free survival (PFS) versus single-agent pembrolizumab in patients with unresectable or metastatic melanoma, according to findings from the phase III ECHO-301/KEYNOTE-252 trial.

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

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

nature medicine

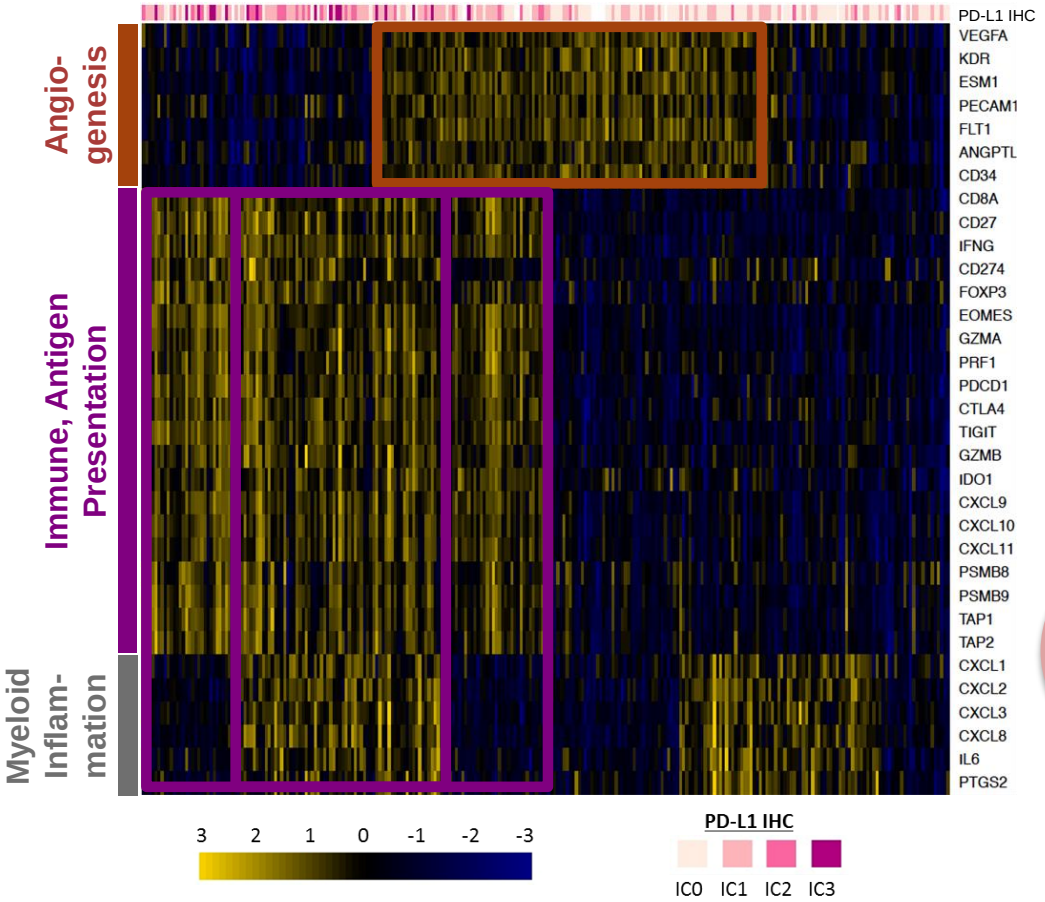
ARTICLES

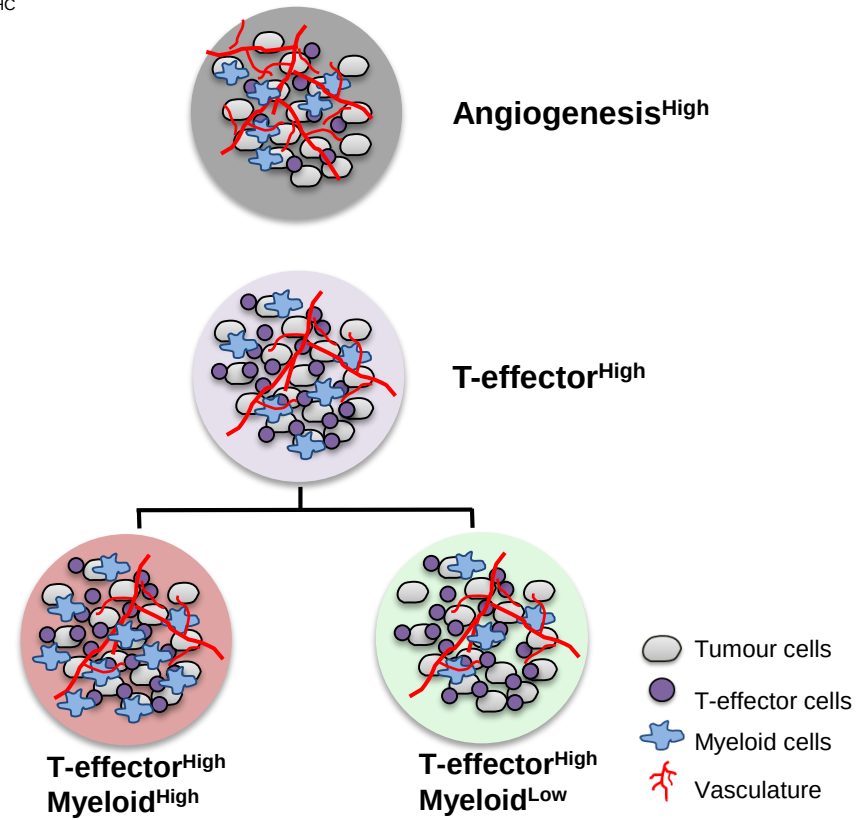
https://doi.org/10.1038/s41591-018-0053-3

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]

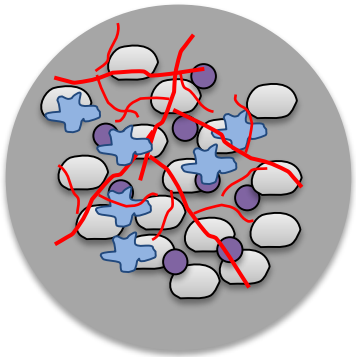
IMmotion150: Transcriptome Map of Angiogenesis and Immune-Associated Genes in RCC Tumours





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

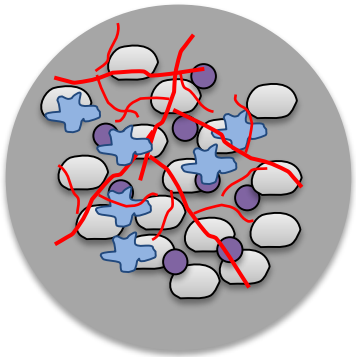
Clinical Activity

Sunitinib

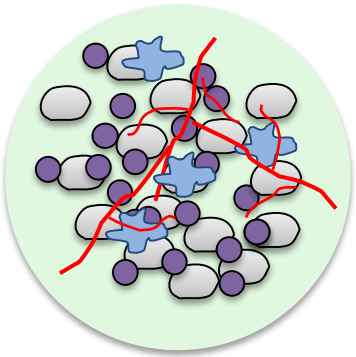
Tumor cells
T-effector cells
Myeloid cells
Vasculature

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}

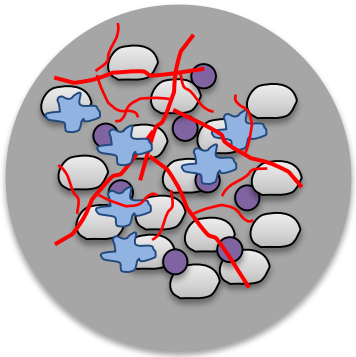
Clinical Activity

Sunitinib

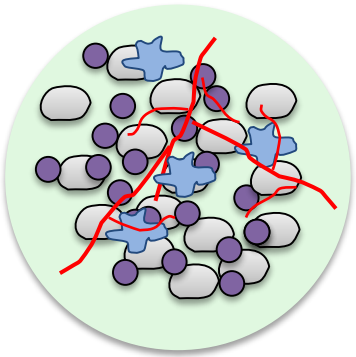
Atezolizumab

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

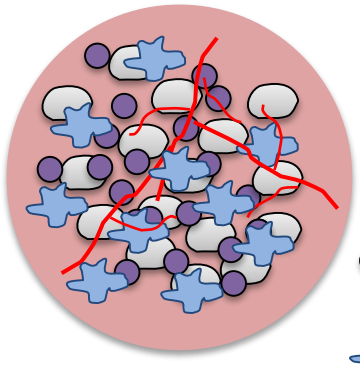
Molecular Correlates of Differential Response to Atezolizumab ± Bevacizumab vs Sunitinib in mRCC



Angiogenic



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



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

Immune Suppressed

Tumor cells
T-effector cells
Myeloid cells
Vasculature

Clinical Activity

Sunitinib

Atezolizumab

Atezolizumab + Bevacizumab

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

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

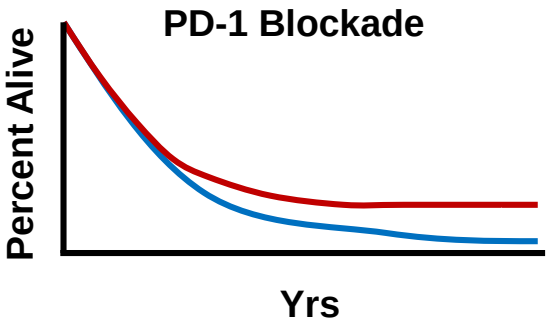
First-Line Phase 3 Trials in Advanced RCC

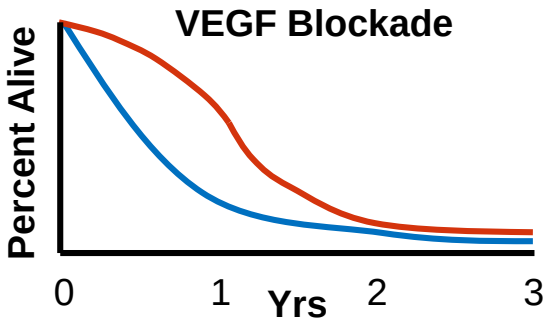
Control	Experimental Arm
Sunitinib	**Axitinib + avelumab**
Sunitinib	**Bevacizumab + atezolizumab**
Sunitinib	Nivolumab + cabozantinib
Sunitinib	Lenvatinib + everolimus or lenvatinib + pembrolizumab
Sunitinib	**Axitinib + pembrolizumab**
Sunitinib	**Nivolumab + ipilimumab** ✓

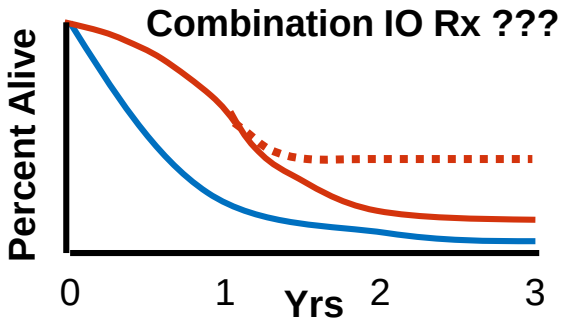
Are these approaches additive or synergistic?

Bold = met primary endpoint

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





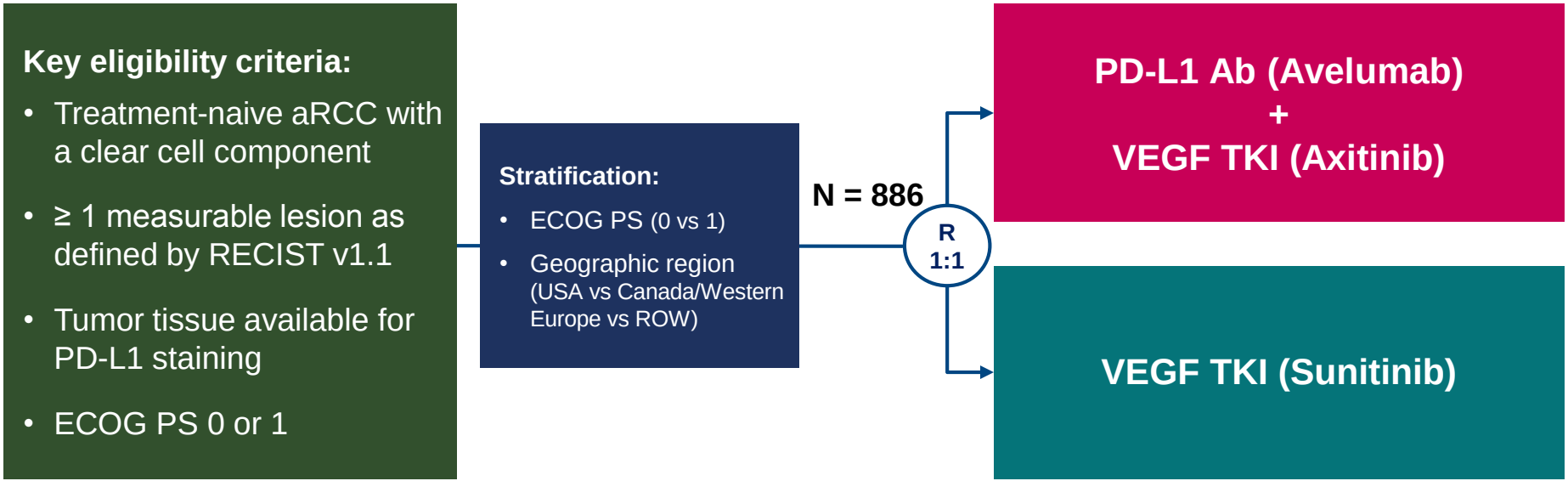


- PD-1 + VEGF certainly **additive**
  - Improvements in the targeted therapy endpoints of ORR and mPFS are encouraging
    - OS may be prolonged, FDA approvals seem likely
- But are these combination **synergistic?**
- Do they generate improvements in **IO* endpoints?**
  - CR or near-CR, Landmark PFS,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

IO – Immuno-oncology,

Side courtesy of T RIbas.

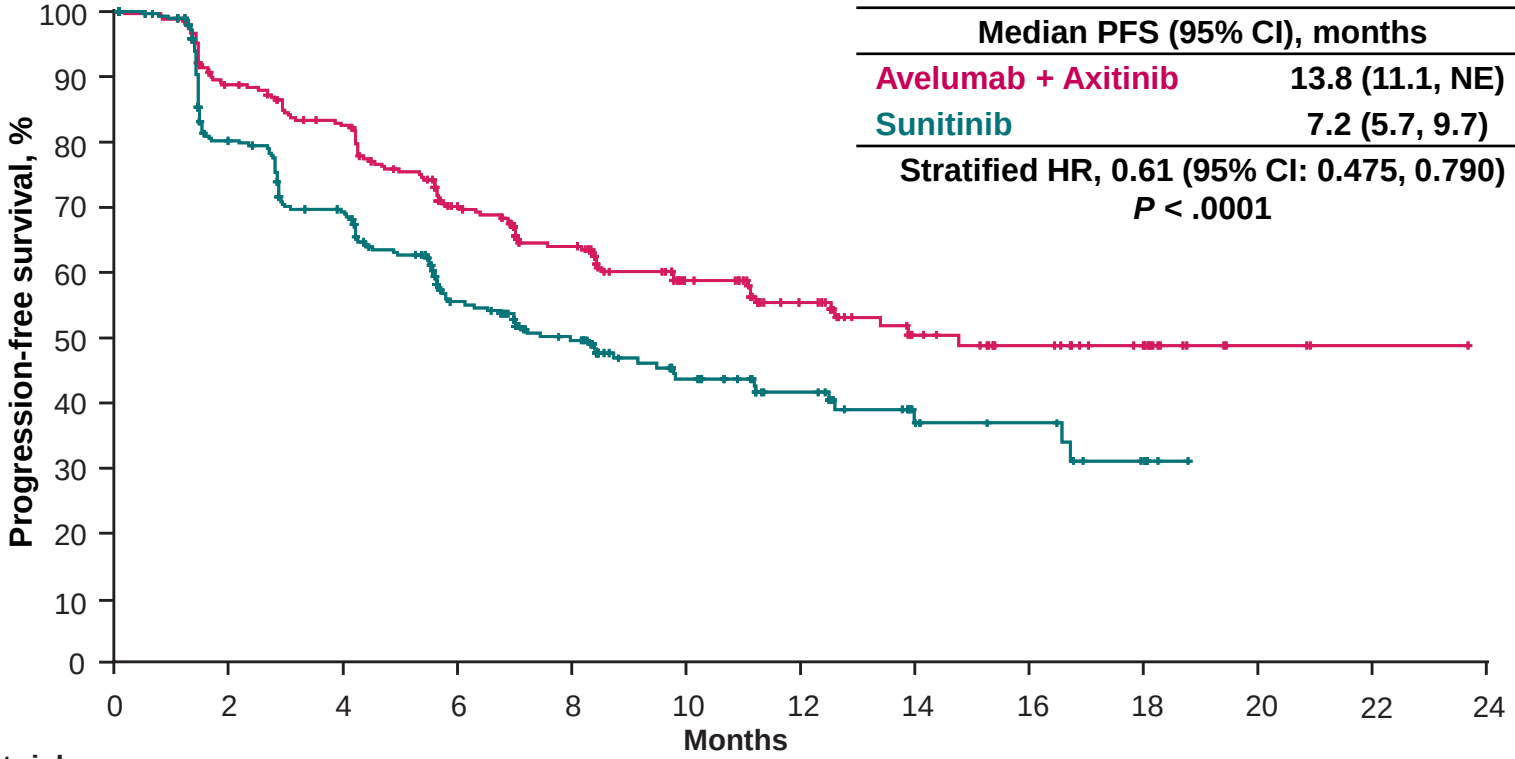
JAVELIN Renal 101: study design



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.

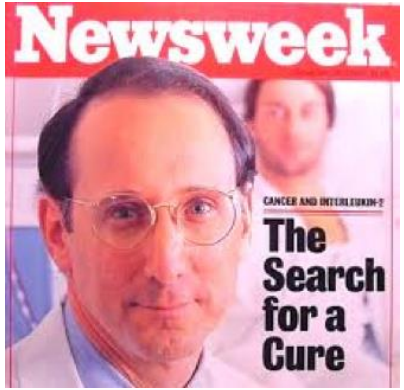
mRCC PD-1 Based Combination Trial Comparison

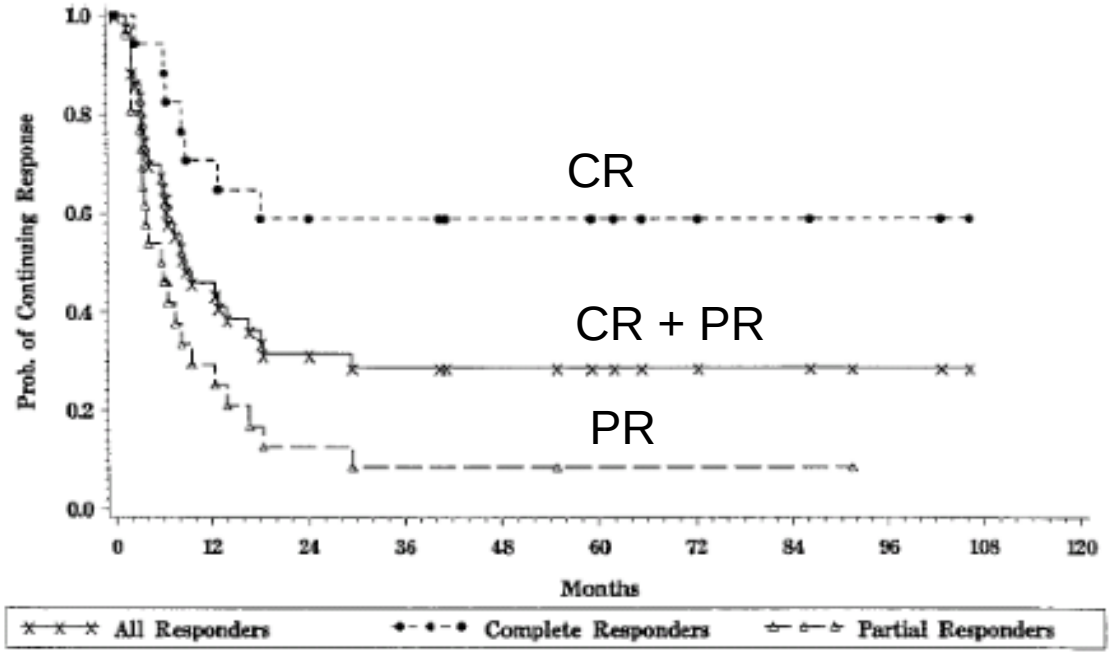
	Ave + Axi[1] Javelin 101	Nivo + Ipi[2] CheckMate 214
	ITT	ITT
Phase	3	3
Comparator	Sunitinib	Sunitinib
N	442	550
Median follow-up, months	9.9	25.2
mPFS, months	13.2†	12.4†
HR (95% CI)	0.61 (0.48, 0.79)	0.68 (0.49, 0.95) §
ORR, %	55†	39†
CR, %	**3**	**9**
TRAEs, % All grades/Grade 3 or 4	95/51	93/46¶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

Proof of Principle:
Deep HD IL-2 responses produce remissions



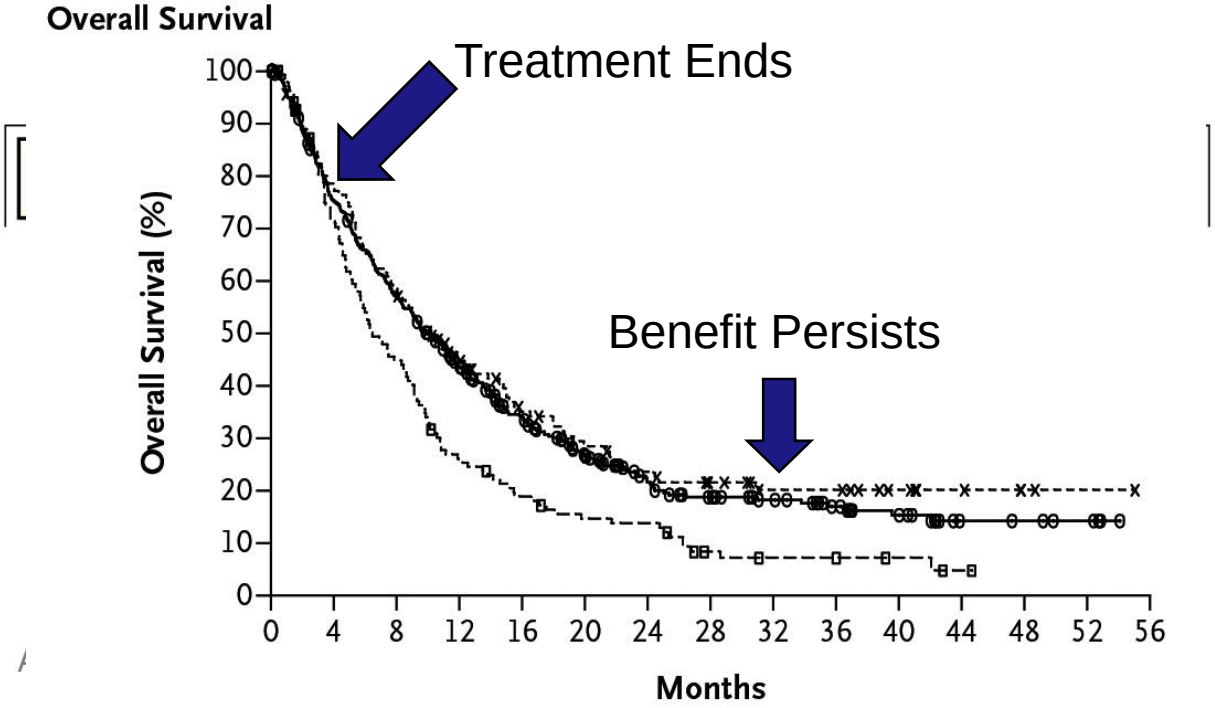


Atkins et al. J Clin Oncol. 1999

Deep Responses = Durable Survival
Target Tumor reduction and length of survival with PD-1 blockade (CM-003)

[a]Includes all patients with target lesion at baseline and ≥1 on-treatment tumor assessment. Asterisks in waterfall plot represent responders (ie, achieved a partial response or complete response).
Denotes changes truncated at 100%.
CR = complete response; ORR = objective response rate; PR = partial response; ST = stable disease.

Topalian et al, # P216 SITC 2017



No. at Risk

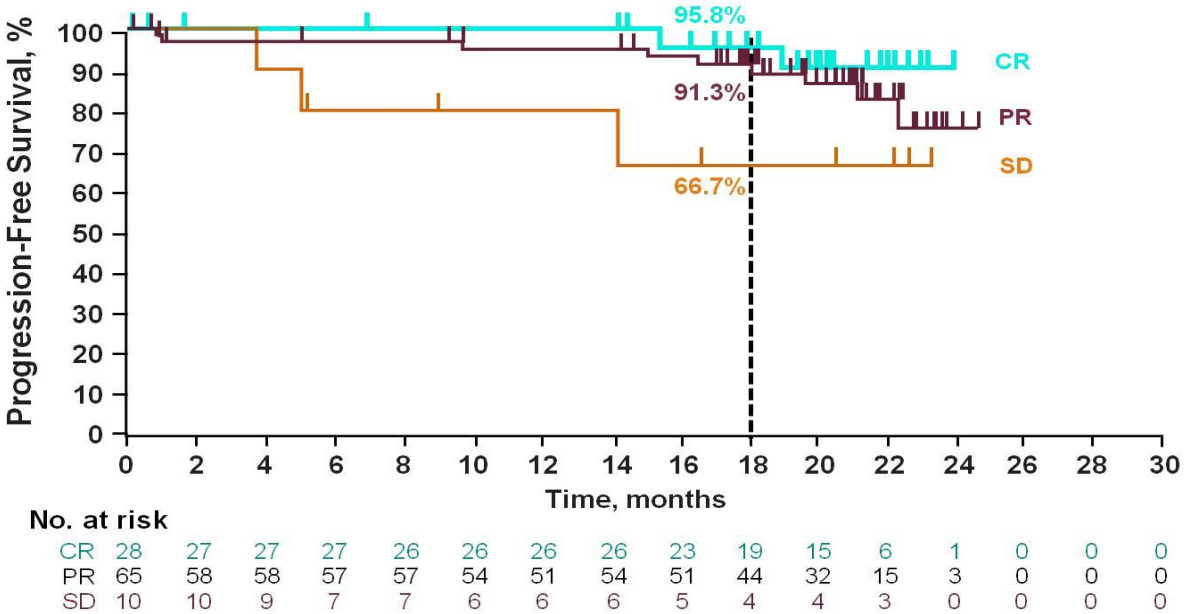
Ipi plus gp100	403	297	223	163	115	81	54	42	33	24	17	7	6	4	0
Ipi	137	106	79	56	38	30	24	18	13	13	8	5	2	1	0
gp100	136	93	58	32	23	17	16	7	5	5	3	1	0	0	0

Ipi plus gp100 Censored | Ipi Censored | gp100 Censored

Hodi FS et al. N Engl J Med 2010

Can we stop PD-1 Blockade in Metastatic Melanoma?

PFS[a] in Patients Who Completed Protocol-Specified Time on Pembrolizumab (n = 103)



[a]Per immune-related response criteria by investigator review; time is measured from last dose of pembrolizumab. Data cutoff: Dec 4, 2017.

Presented By Georgina Long at 2018 ASCO Annual Meeting

ONGOING CLINICAL TRIALS FOR TREATMENT OPTIMIZATION

Estimated primary completion date:
November 30, 2020

OMNIVORE[1]: Response-based approach to treatment with nivolumab in advanced/metastatic RCC

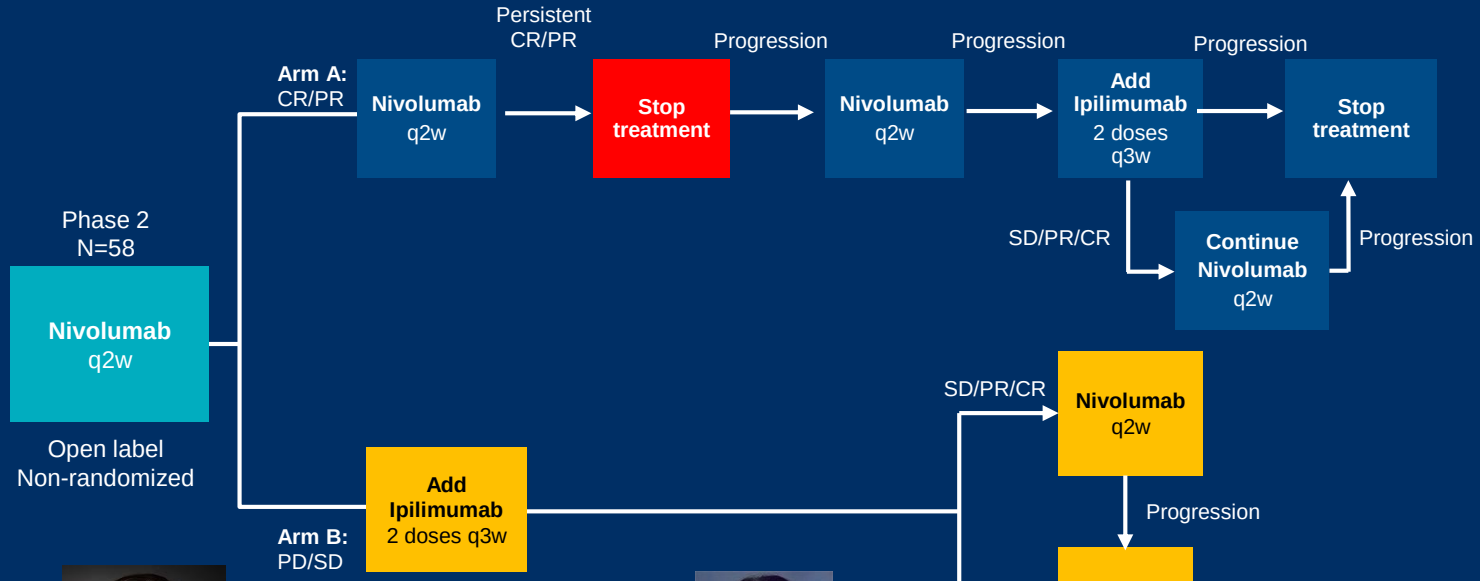
Eligibility:

- Advanced /mRCC: clear cell or non-clear cell
- Biopsy tissue available
- Pretreated or treatment-naïve
- No prior ICI therapy for metastatic RCC
- No active CNS metastases
- ECOG PS 0–2
- Adequate organ function

Primary endpoints:

- ***Arm A:*** Persistent PR/CR at 1 year after nivolumab D/C
- ***Arm B:*** Number of patients converted from PD/SD to PR/CR upon addition of Ipilimumab (evaluated 1 year after Nivolumab D/C)

Secondary endpoints: PFS, OS, salvage therapy-free interval (arm A), irORR, safety



PI: Harshman, McKay, Choueiri.
Location: United States
Sponsor: Dana-Farber Cancer Institute

1. NCT03203473

Rational Application of Combination IO Therapy:

- **Novel Endpoints**
  - Make IO Endpoints Primary
    - More remissions = Achieving patient's goal
    - Near CR endpoint = shorter timelines for R&D
    - Stopping Rx = Reduced Toxicity/Cost
  - Conventional Endpoints (e.g. PFS and OS)
    - May not be comprehensive

Why should we aim to stop therapy?

Regimen cost for "typical" patient (80 kg) with Melanoma in Phase 3 (Checkmate 067)[a]

Drug	Median Doses	Cost
Nivolumab	15	$89,000
Nivolumab + ipilimumab	4	$150,000
Remission	0	0

- Nivolumab: $24.70/mg[b]
- Ipilimumab: $135.18/mg[b]

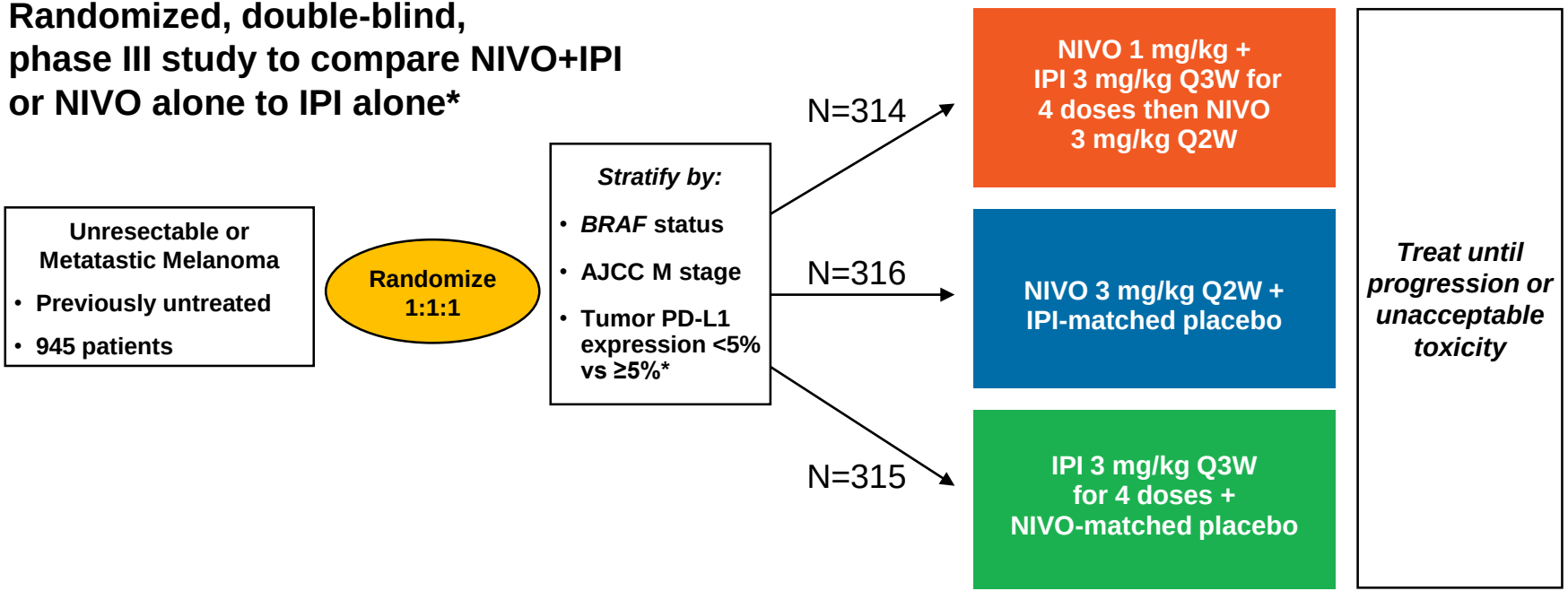
[a]Larkin J et al. *N Engl J Med.* 2015; 373:23-34.
[b]First quarter 2016, in US dollars.

Rational Application of Combination IO Therapy:

- **Novel Endpoints**
  - Make IO Endpoints Primary
    - Near CR endpoint = shorter timelines for R&D
    - More remissions = Achieving patient's goal
    - Stopping Rx = Reduced Toxicity/Cost
  - **Conventional Endpoints (e.g. PFS and OS)**
    - May not be comprehensive

CheckMate 067: Study Design

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



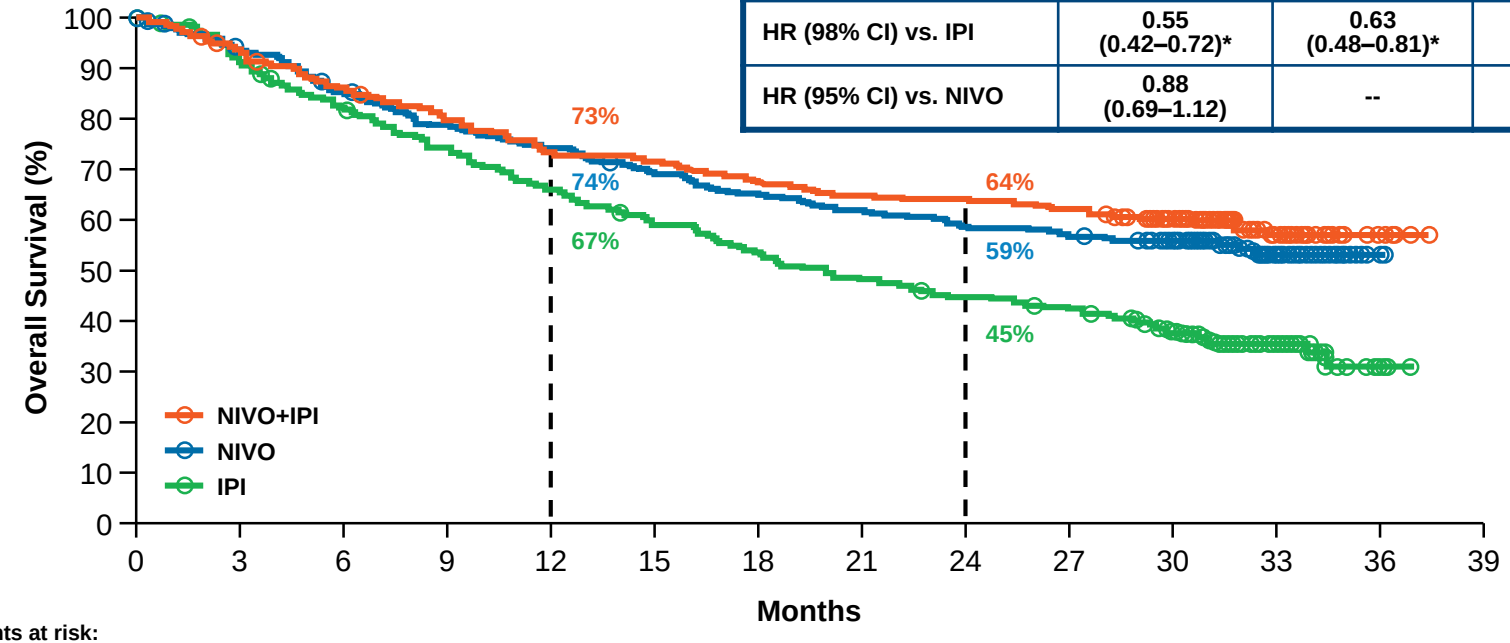
Database lock: Sept 13, 2016 (median follow-up ~30 months in both NIVO-containing arms)

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

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

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

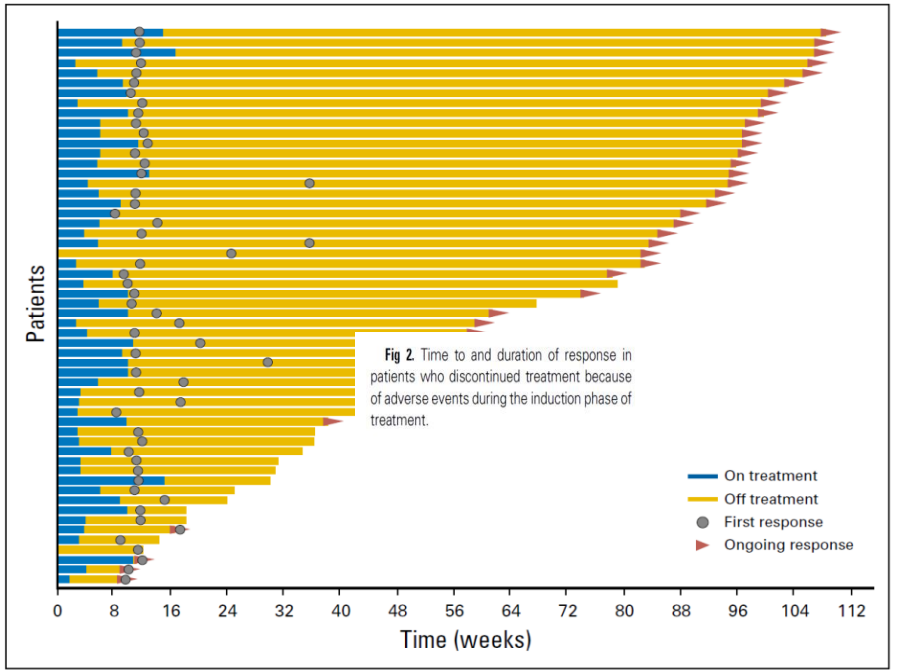


Fig 2. Time to and duration of response in patients who discontinued treatment because of adverse events during the induction phase of treatment.

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

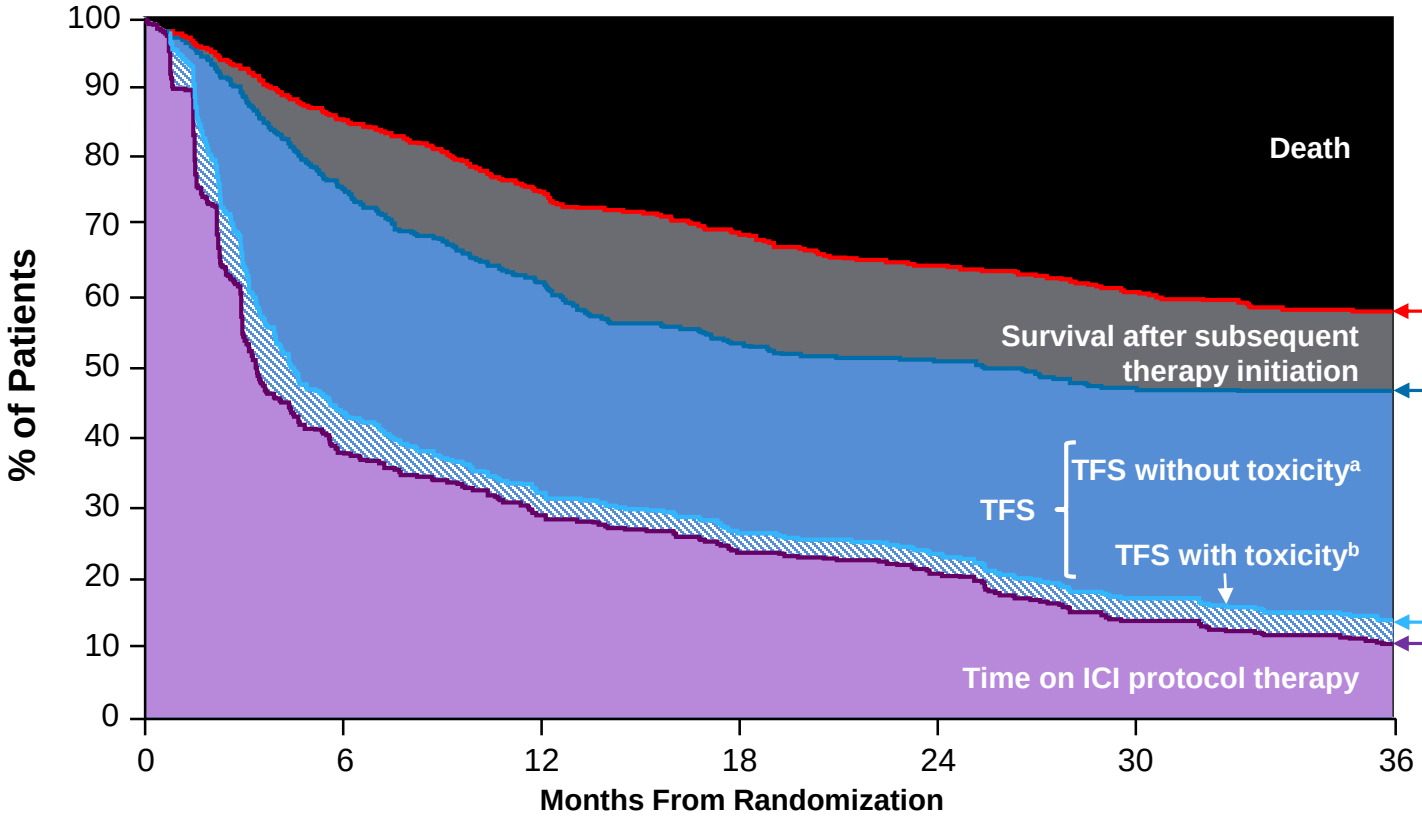
Treatment-Free Survival, a Novel Outcome Applied to Immuno-oncology Agents in Advanced Melanoma

Meredith M. Regan[1], Lillian Werner[1], Ahmad A. Tarhini[2], Sumati Rao[3], Komal Gupte-Singh[3], Corey Ritchings[3], Michael B. Atkins[4], David F. McDermott[5]

[1]Dana-Farber Cancer Institute; [2]Cleveland Clinic Taussig Cancer Institute; [3]Bristol-Myers Squibb; [4]Georgetown-Lombardi Comprehensive Cancer Center; [5]Beth Israel Deaconess Medical Center

Please visit SITC Poster #380 for more details

Health States Based on Time-to-Event Endpoints: Definitions



Time-to-Event Endpoints

Overall survival: From randomization until death, or censored at date last known alive

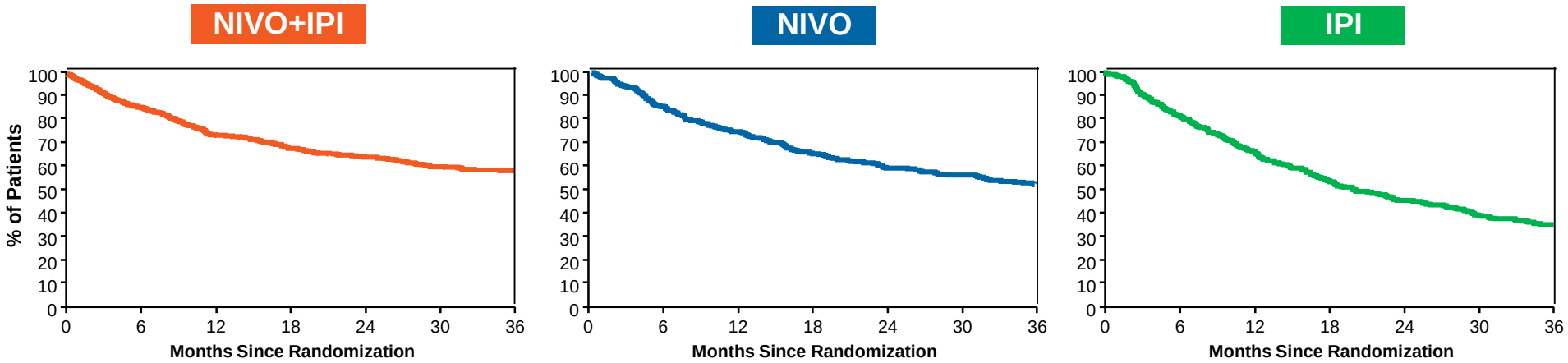
Time to subsequent therapy initiation or death: From randomization until subsequent systemic anticancer therapy initiation or death, whichever occurred first, or censored at date last known alive and free of subsequent therapy

Time to cessation of both ICI protocol therapy and toxicity[c]: From randomization until cessation of ICI protocol therapy plus duration of time with toxicity[c] (or censored if alive on protocol therapy or treatment-free with toxicity)

Time to ICI protocol therapy cessation: From randomization until cessation of ICI protocol therapy (or censored at date last known alive on ICI protocol therapy)

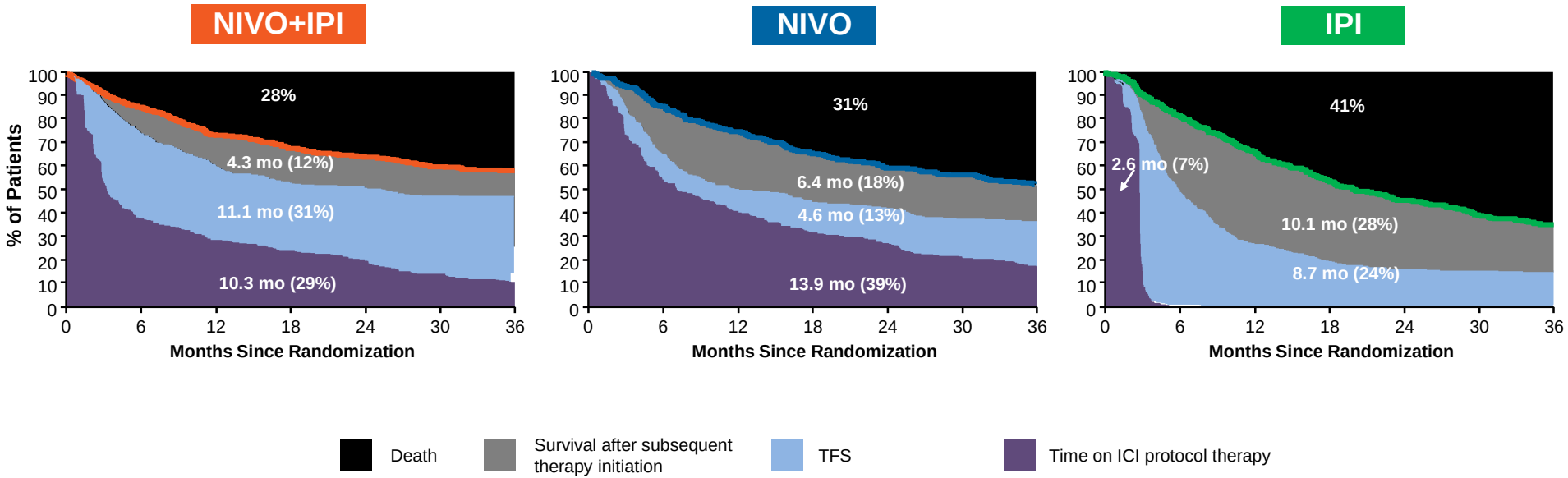
[a]Time after cessation of ICI protocol therapy without toxicity, before initiation of subsequent systemic anticancer therapy or death
[b]Time after cessation of ICI protocol therapy with toxicity while treatment-free
[c]Includes toxicity persisting since protocol therapy and toxicity newly presenting after protocol therapy cessation

Health States Over a 36-Month Period



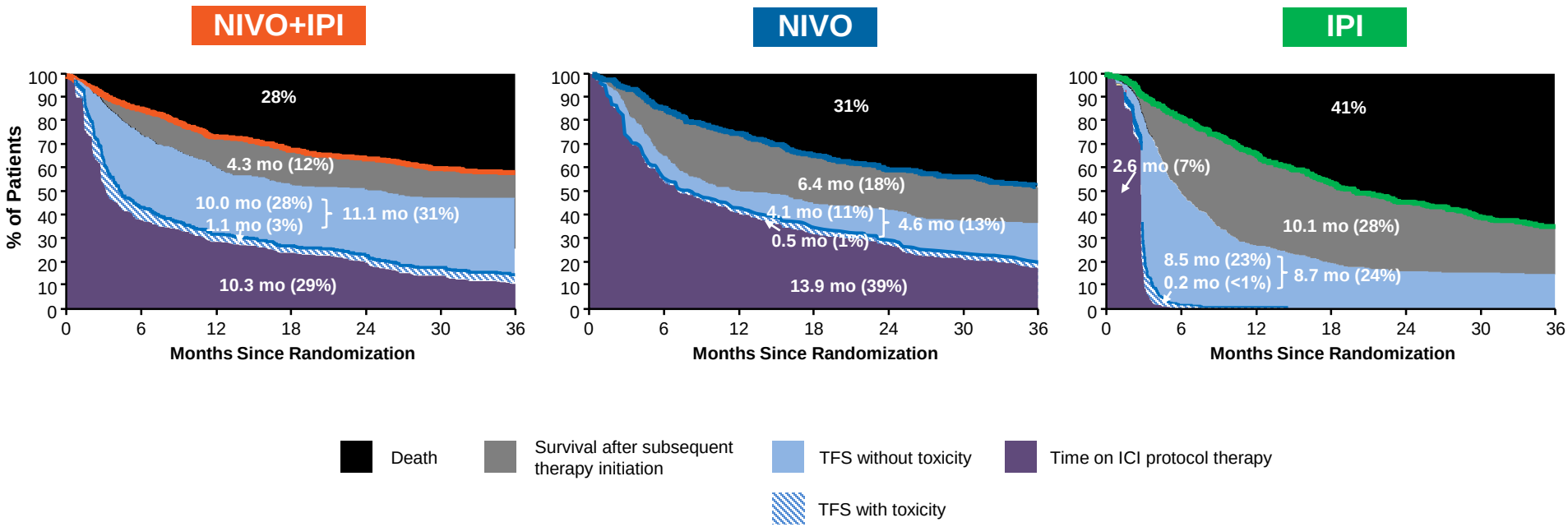
Data labels represent the mean number of months at any health state and the percentage of time in the 36-month period.
mo=months.

Health States Over a 36-Month Period



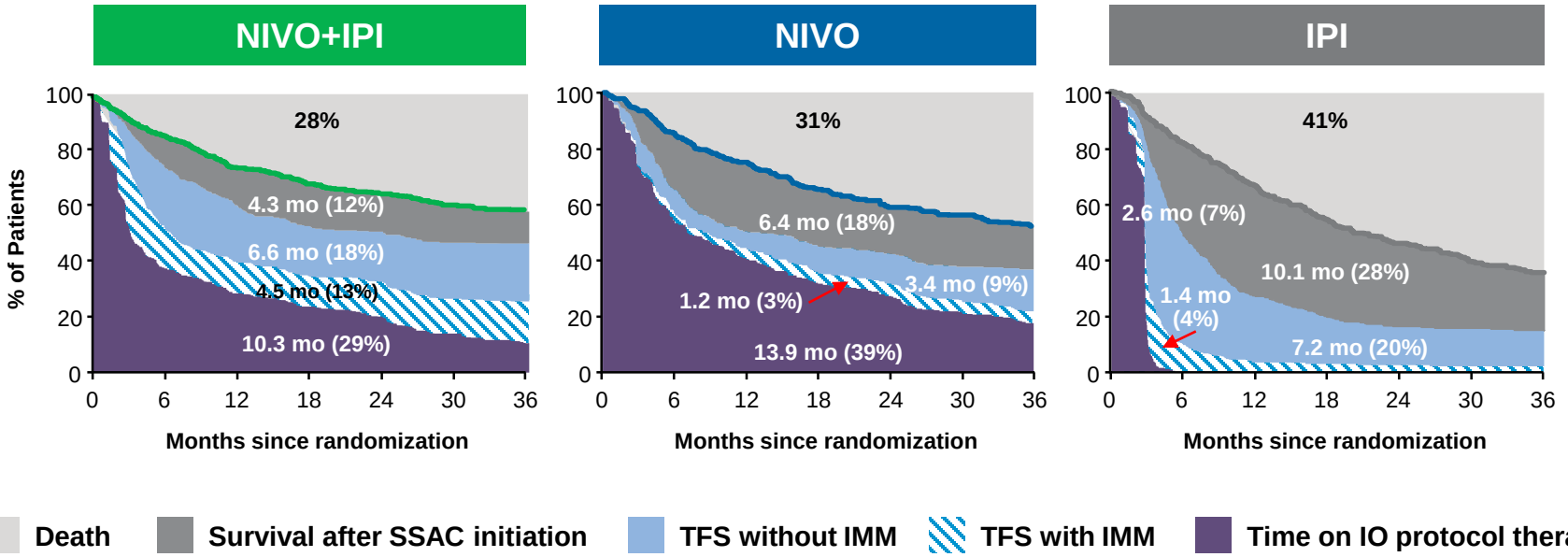
Data labels represent the mean number of months at any health state and the percentage of time in the 36-month period.
mo=months.

Health States: TFS Without / With Toxicity
Defined by Grade 3-4 trAEs



Data labels represent the mean number of months at any health state and the percentage of time in the 36-month period.
mo=months.

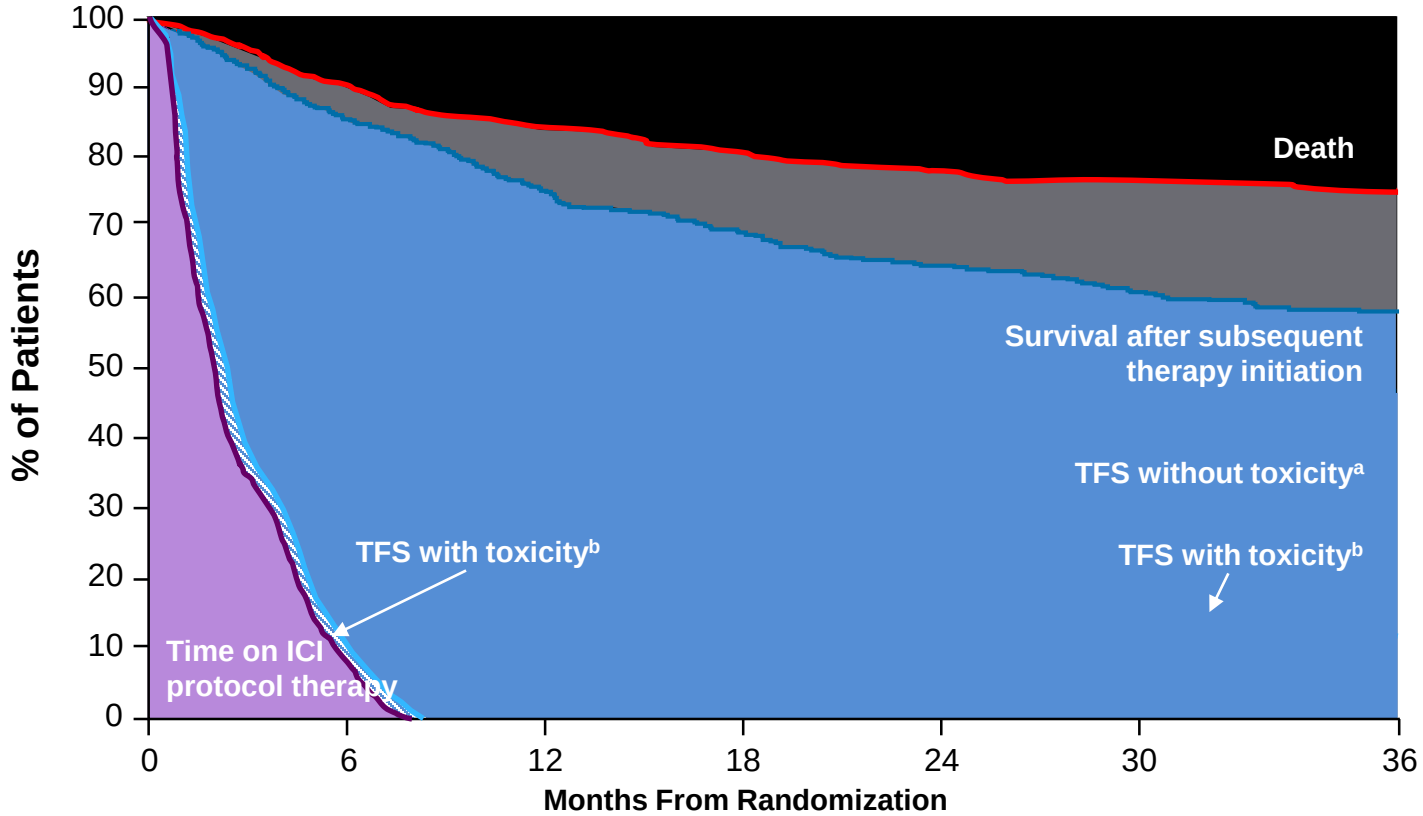
Health States:
TFS With and Without IMM Use



Data labels represent the mean number of months in any health state and the percentage of time in the 36-month period. mo, months

Regan et al SITC 2018 Abstract #380

Health States Based on Time-to-Event Endpoints: Desired State



[a]Time after cessation of ICI protocol therapy without toxicity, before initiation of subsequent systemic anticancer therapy or death
[b]Time after cessation of ICI protocol therapy with toxicity while treatment-free
[c]Includes toxicity persisting since protocol therapy and toxicity newly presenting after protocol therapy cessation

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

Standard Therapy for mRCC: 2028

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

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

Acknowledgements

- DFHCC Collaborators
  - Kidney Cancer
    - Toni Choueiri
    - Sabina Signoretti
    - Bill Kaelin (SPORE co-PI)
    - Gordon Freeman
    - Dror Michaelson
    - Cathy Wu
  - Melanoma
    - Steve Hodi
    - Ryan Sullivan
    - Beth Buchbinder
    - Keith Flaherty
- GLCCC – Mike Atkins, Dick Schegel
- MIT – David Sabatini
- HMS – Arlene Sharpe

- Funding
  - Kidney Cancer SPORE - P50-CA101942
  - DFHCC Kidney Cancer Program - P30-CA006516
  - Department of Defense - KC170036
  - BIDMC Development Office

- Research Administration
  - Tara Johnston
  - Mary Mahoney, Ramesh Gunawardena
  - Stephanie Wasserman, Denise Graham, Vikas Sukhatme

Our BIDMC Team

- Medical Onc
  - Jim Mier, Rupal Bhatt, Anu Desai, Kathleen Mahoney, Virginia Seery, Reed Drews, Xin Gao, Ben Izar, David Miller, Lowell Schnipper
- Surgical Onc/Dermatology
  - Nick Tawa, Leah Abbott, Caroline Kim, Peggy Wu, Drew Wagner, Jodi Mechaber, Sharukh Jalisi
- RN Coordinators
  - Michelle Perkins, Paddy Connelly
- Clinical Research Team
  - Rose Marujo, Chrissy D'Alessandro, Sue Gotthardt, Nordine Benhaga, Connor Gray, Kristin Curreri, Angelina McKenna, Frank Riley, Sarah Kim, Chrissy Byrnes, Steve Buchholz, Eva Glieberman, Janine Morrissey
- Administrative Support
  - Ali Levy, Myrna Campbell

Our BIDMC Team

- Inpatient Nursing Leadership
  - Brid Walsh
- Nursing
  - Reisman 11, Shapiro 9, Gryzmish 7
- Social Work
  - Frank Mahoney
- Palliative Care
  - Mary Buss, Katie Rimer
- Psychiatry
  - Lisa Carbone
- Radiation Oncology
  - Matthew Abrams, Irving Kaplan
- Neuro Onc
  - Eric Wong, Eric Uhlmann

- Radiology
  Kevin Donohoe
- Pathology

  Derm - Steve Tahan, Beverly Faulkner-Jones, Ashley Ward, MJ Zimarowski
  GU - Seymour Rosen, Huihui Ye, Mamta Gupta