Case Studies in Immunotherapy for the Treatment of Renal Cell Carcinoma

January 20, 2022

11:00 a.m. – 12:00 p.m. ET

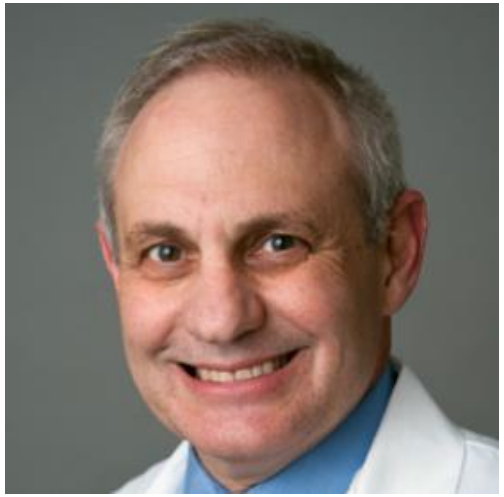
sitc Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

AMGEN MERCK

The Practical Management Pearls and Case Studies Webinars are part of the Cancer Immunotherapy Clinical Practice Guidelines Advanced Webinar Series supported, in part, by grants from Amgen and Merck & Co., Inc. (as of 9/15/2021)

Webinar faculty



Michael B. Atkins, MD – *Georgetown Lombardi Comprehensive Cancer Center*

Expert Panel Chair

Martin H. Voss, MD – *Memorial Sloan Kettering Cancer Center*

Virginia Seery, MSN, RN, ANP-BC, AOCNP – *Beth Israel Deaconess Medical Center*

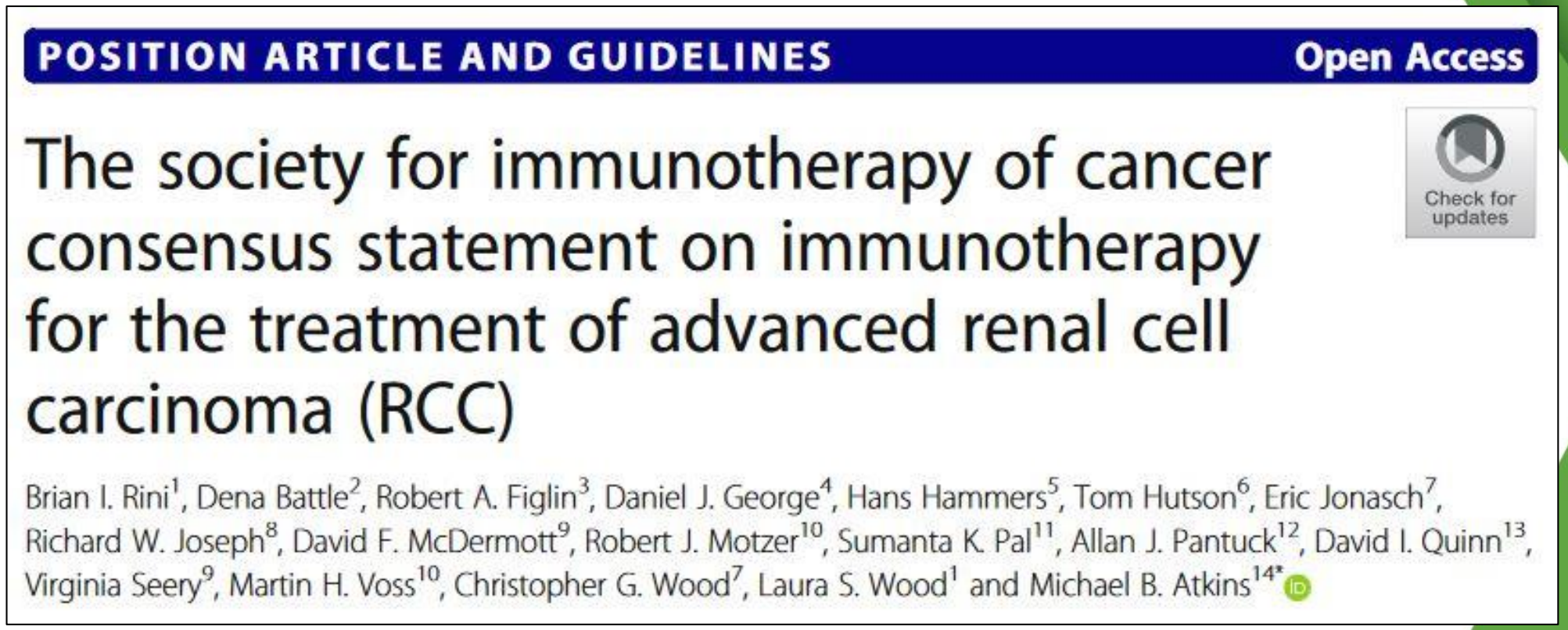
Learning objectives

- Plan immunotherapy treatment regimens for challenging patient populations
- Identify management strategies for uncommon and/or atypically responsive toxicities
- Select appropriate treatment strategies for patients with relapsed and/or unresponsive disease
- Articulate the potential risks and benefits for proceeding with any other possible interventions specific to RCC in the context of an immunotherapy treatment plan

Webinar outline

- Development of the guideline
- Case 1: Clear cell RCC + sarcomatoid features with cord compression
- Case 2: Clear cell RCC with large metastatic burden including symptomatic endobronchial disease
- Toxicity Management issues
- Case 3: Metastatic RCC and Crohn’s Disease

Development of the guideline



POSITION ARTICLE AND GUIDELINES Open Access

The society for immunotherapy of cancer consensus statement on immunotherapy for the treatment of advanced renal cell carcinoma (RCC)

Brian I. Rini[1], Dena Battle[2], Robert A. Figlin[3], Daniel J. George[4], Hans Hammers[5], Tom Hutson[6], Eric Jonasch[7], Richard W. Joseph[8], David F. McDermott[9], Robert J. Motzer[10], Sumanta K. Pal[11], Allan J. Pantuck[12], David I. Quinn[13], Virginia Seery[9], Martin H. Voss[10], Christopher G. Wood[7], Laura S. Wood[1] and Michael B. Atkins[14*]

Development of the guideline

- Developed according to the Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines
- Panel consisted of 18 experts in the field
- Recommendations are based upon published literature evidence, or clinical evidence where appropriate
- Consensus was defined at 75% approval among voting members

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Case discussions: First-line treatment of IMDC Intermediate/Poor risk clear cell RCC

Martin H. Voss, MD

Clinical Director, Genitourinary Oncology Service

Associate Member, **Memorial Sloan Kettering Cancer Center**

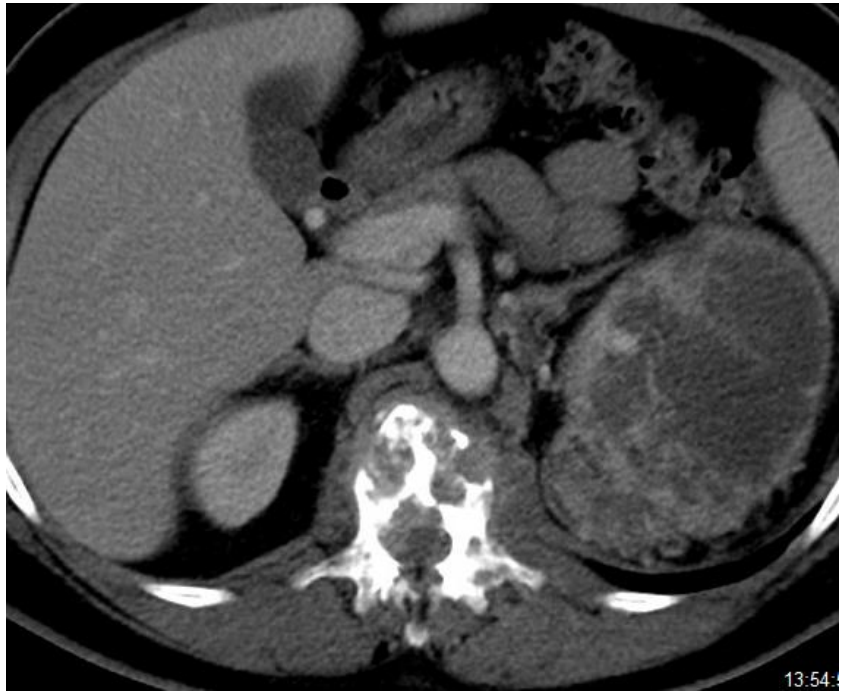
Disclosures

- Consulting: Aveo, Calithera, Corvus, Eisai, Exelixis, Genentech, GSK, Merck, Novartis, Onquality, Pfizer
- Research funding: BMS, Genentech, Pfizer, Novartis
- Travel: Medimmune, Novartis, Takeda
- Research payments to my institution: Aravive, Astra Zeneca, Aveo, BMS, Calithera, Corvus, Exelixis, Genentech, Merck, Novartis, Pfizer, Takeda

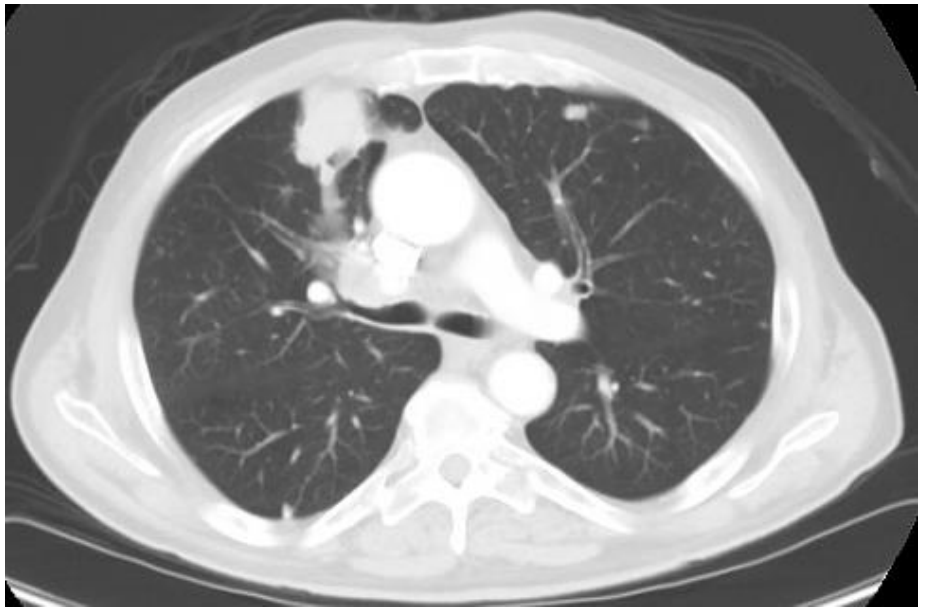
Case 1: 58y old man with back pain and night sweats

58M with 6wks worsening back pain and night sweats. Sensory loss b/l thighs.

- ECOG: 1
- CBC: Hgb 10.0g/dL, WBC 11K/mcL, pltls 400K/mcL, Ca wnl,
- PMH: HTN (controlled), HL

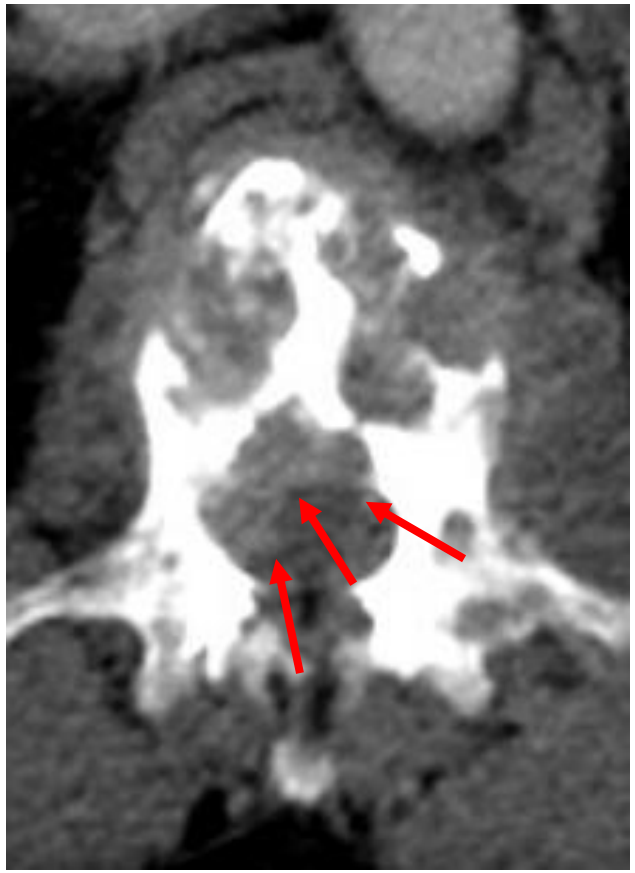


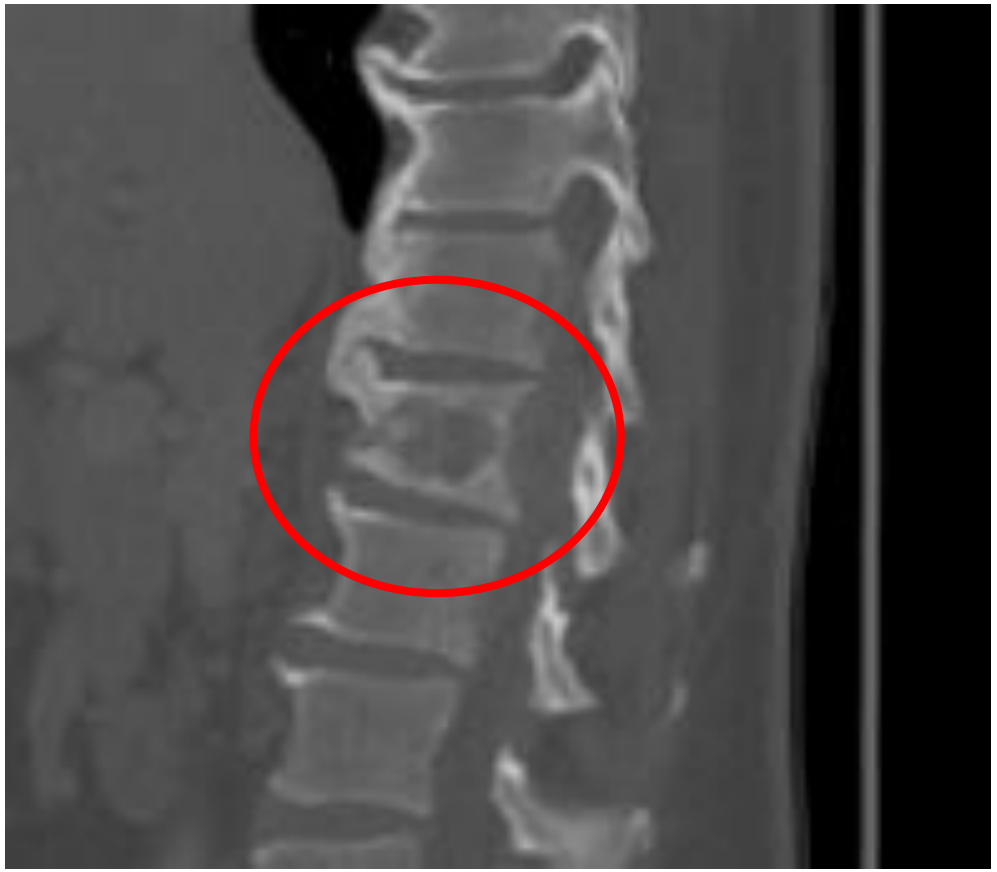
CT Abd/Pelvis: large L renal mass; T12 paraspinal/spinal mets; RP LAN

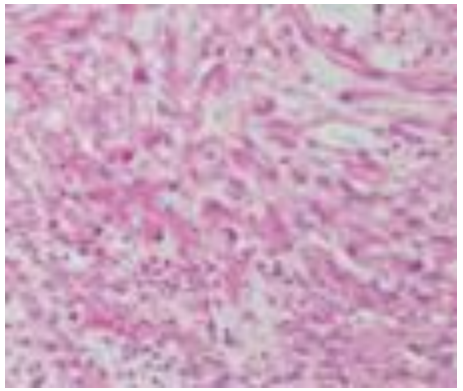


CT chest: b/l pulmonary mets up to 2.6cm longest diameter; hilar and subcarinal LAN

Spinal metastases with compression fracture, epidural disease and canal + cord compromise



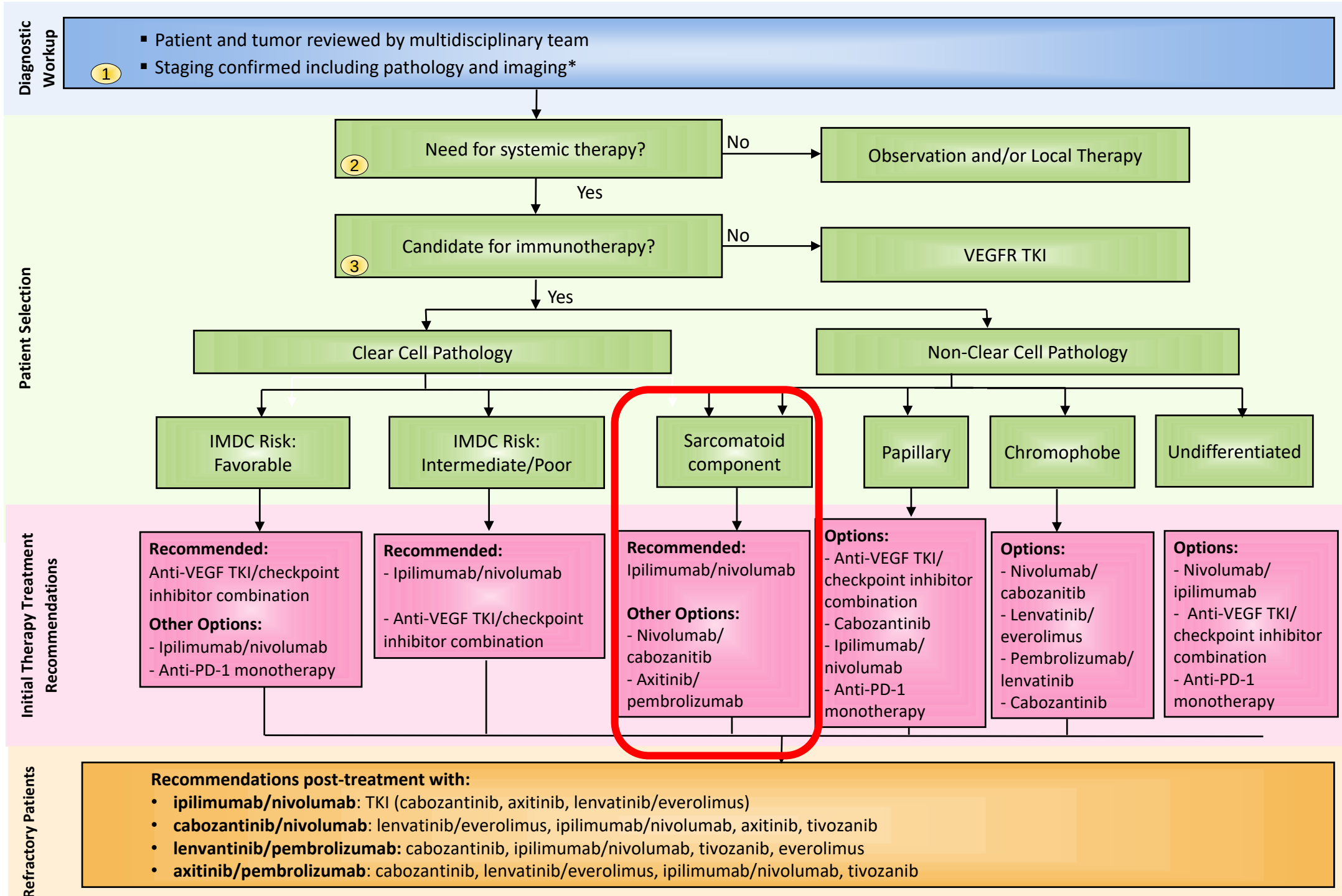




Core biopsy renal mass: clear cell RCC with extensive sarcomatoid features

Clear cell RCC + sarcomatoid features with cord compression – how would you treat ?

1. Spinal surgery, then axitinib + pembrolizumab after recovery
2. Spinal surgery, then XRT, then single agent nivolumab
3. Cabozantinib + nivolumab, then surgery +/- radiation
4. Ipilimumab + nivolumab, then surgery +/- radiation
5. Radiation, then temsirolimus, then consider surgery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Patient and tumor reviewed by multidisciplinary team
Staging confirmed including pathology and imaging*
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Need for systemic therapy?
No
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Yes
3
Candidate for immunotherapy?
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VEGFR TKI
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Clear Cell Pathology
Non-Clear Cell Pathology
IMDC Risk: Favorable
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Sarcomatoid component
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Undifferentiated
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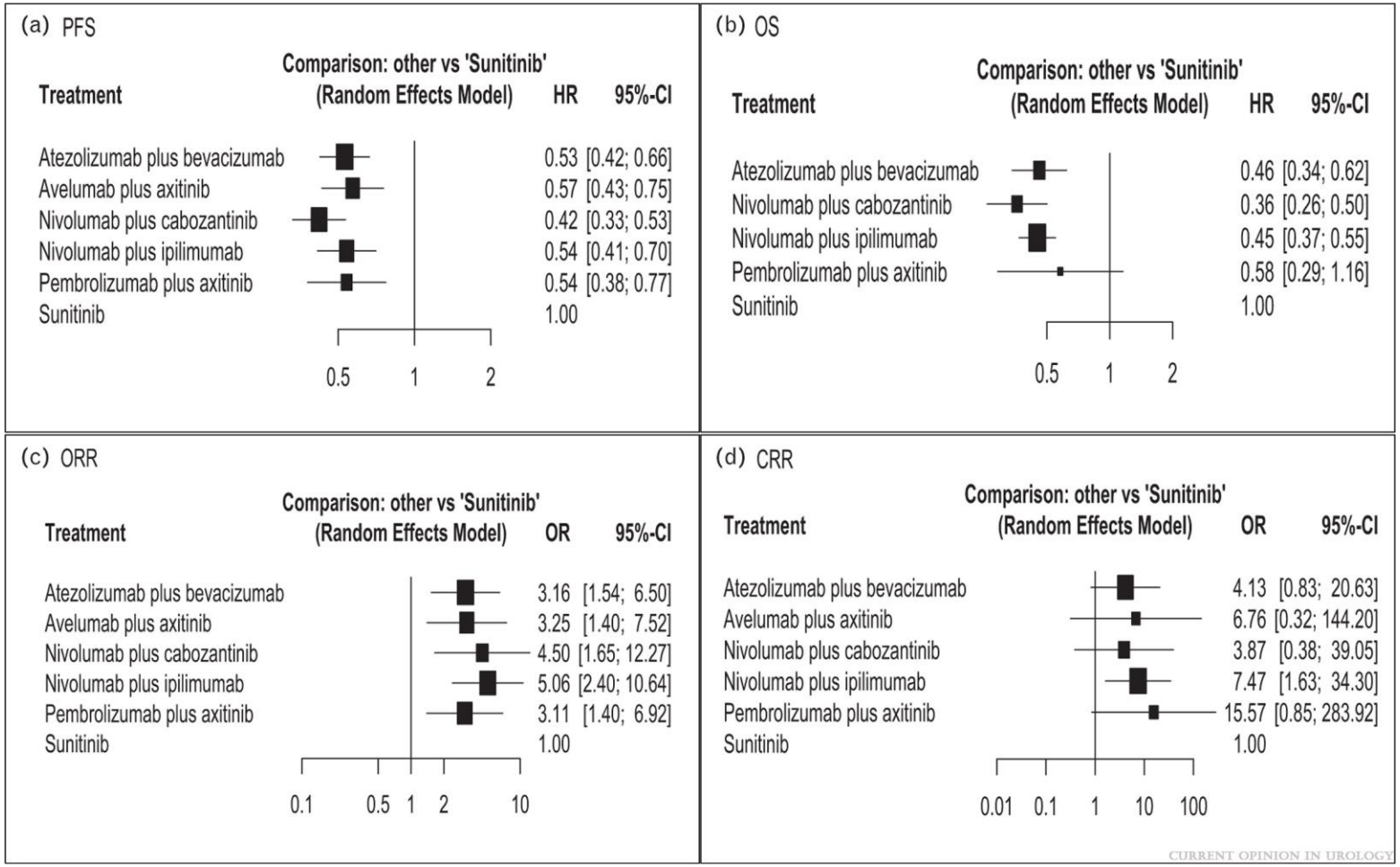
lenvantinib/pembrolizumab: cabozantinib, ipilimumab/nivolumab, tivozanib, everolimus
axitinib/pembrolizumab: cabozantinib, lenvatinib/everolimus, ipilimumab/nivolumab, tivozanib

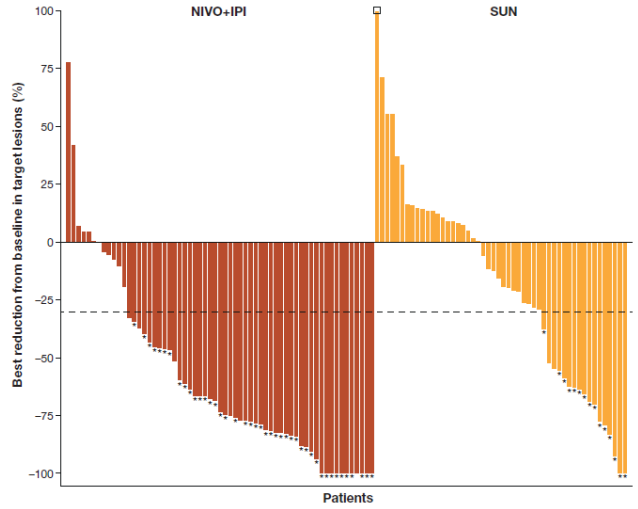
Sarcomatoid features: benefits of combination therapy over TKI alone



- Forest plots showing the association of systemic therapy in metastatic renal cell carcinoma with (a) progression-free survival (PFS), (b) overall survival (OS), (c) objective response rate (ORR), (d) complete response rate (CRR).

Quhal, et al.; Curr Op Uro 32(1):61-68, January 2022

Ipilimumab/Nivolumab vs. Sunitinib



	Patients with sRCC and I/P-risk disease	
	NIVO+IPI (*N* = 74)	SUN (*N* = 65)
Confirmed ORR (95% CI), %	61 (49–72)	23 (14–35)
P	<0.0001	
Best overall response, *n* (%)		
Complete response	14 (19)	2 (3)
Partial response	31 (42)	13 (20)
Stable disease	8 (11)	26 (40)
Progressive disease	15 (20)	15 (23)
Unable to determine/not reported	6 (8)	9 (14)

Tannir et al., CCR 2021 Jan 1;27(1):78-86

Cabozantinib/Nivolumab vs. Sunitinib

	With sRCC		Without sRCC[a]	
	NIVO+CABO n = 34	SUN n = 41	NIVO+CABO n = 279	SUN n = 278
PFS HR (95% CI)	0.39 (0.22–0.70)		0.54 (0.43–0.69)	
Median PFS, months	10.9	4.2	17.7	9.4
OS HR (95% CI)	0.36 (0.16–0.82)		0.68 (0.48–0.95)	
Median OS, months	NR	19.7	NR	NR
ORR, % (95% CI)	55.9 (37.9–72.8)	22.0 (10.6–37.6)	56.6 (50.6–62.5)	28.4 (23.2–34.1)

Motzer et al. ASCO GU 2021, Abstract

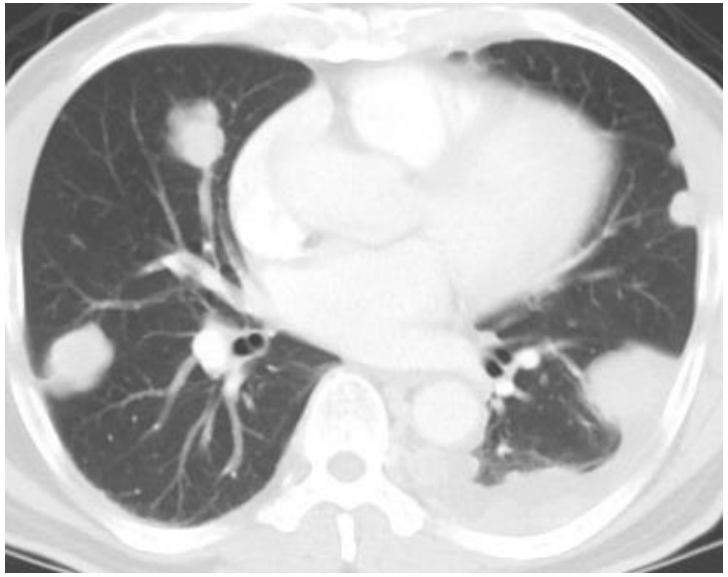
Patient course

- Oct 1st: start first-line ipilimumab/nivolumab
- Oct 7th: Laminectomy with radical excision of spinal / paraspinal tumor and spinal fixation
- Oct 22nd : ipilimumab/nivolumab #2
- Grade 1 pruritus
- Oct 25th: IGRT T10-L2
- Grade 2 rash
- Nov 15th: ipilimumab/nivolumab #3
- Dec 5th : ipilimumab/nivolumab #4
- Dec 27th : CT CAP regression renal mass max diameter 12cm->9cm; reduction size thoracic LAN; resolution several pulmonary nodules

Case 1: 67 yo man with cough & weight loss

67M with involuntary weight loss, new DOE and worsening cough

- ECOG: 2
- CBC: Hgb 14.2g/dL, WBC 12.5 K/mcL, pltls 490K/mcL, corr Ca 11.2,
- PMH: DM2, OSA



CT chest: b/l pulmonary mets; moderate L pleural effusion; RLL bronchus ? obstructed

67M with involuntary weight loss, new DOE and worsening cough

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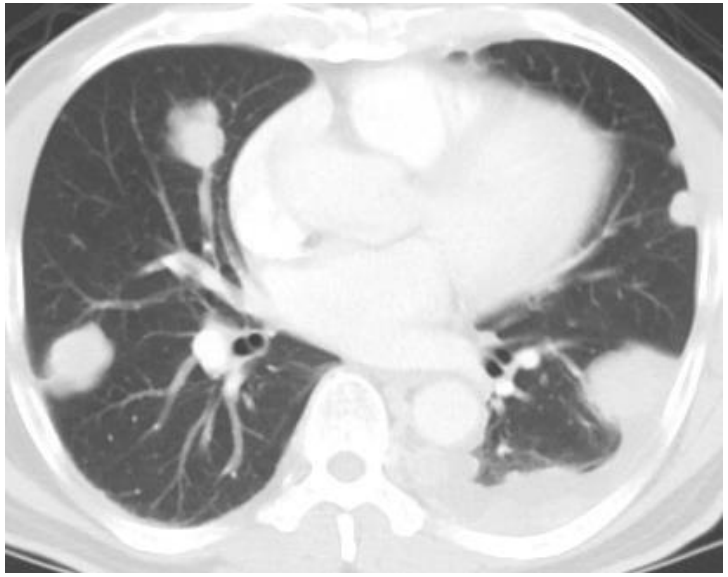

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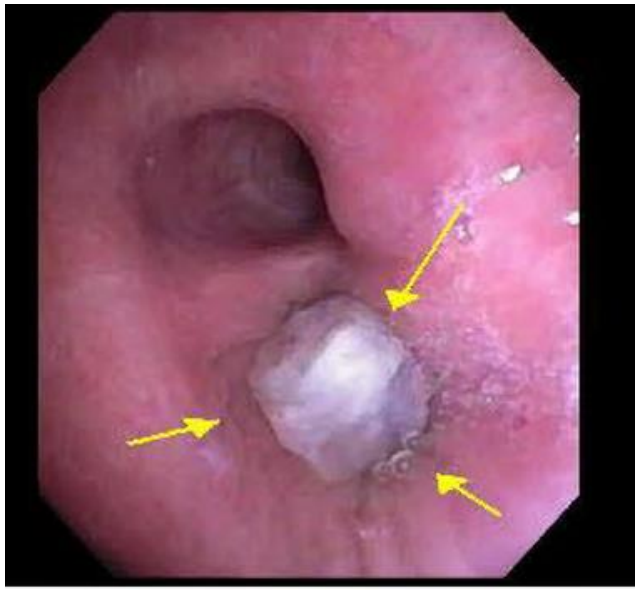

Bronchoscopy: RLL obstructed by endobronchial mass, partly excised; path: clear cell RCC

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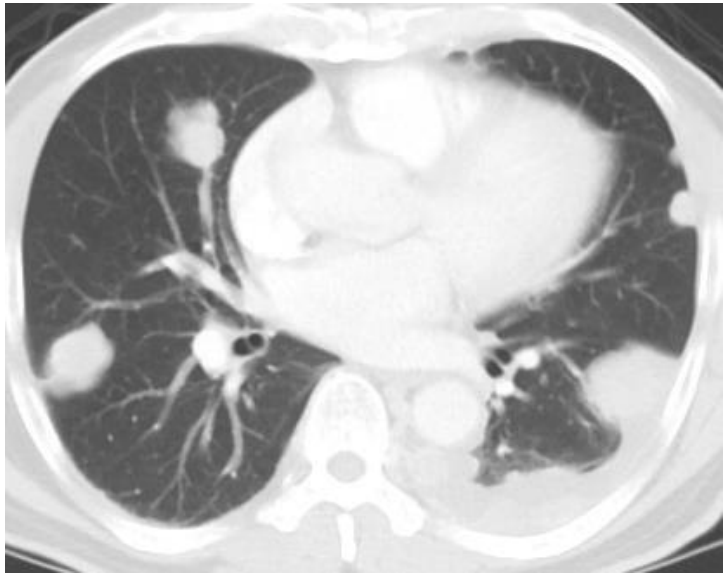

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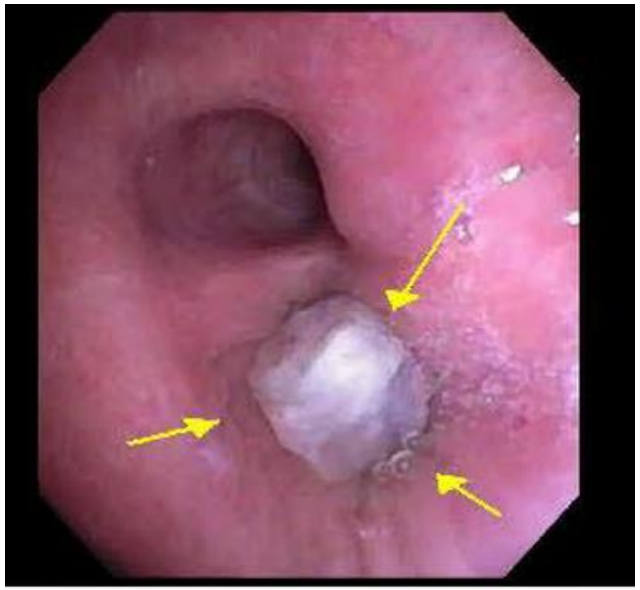

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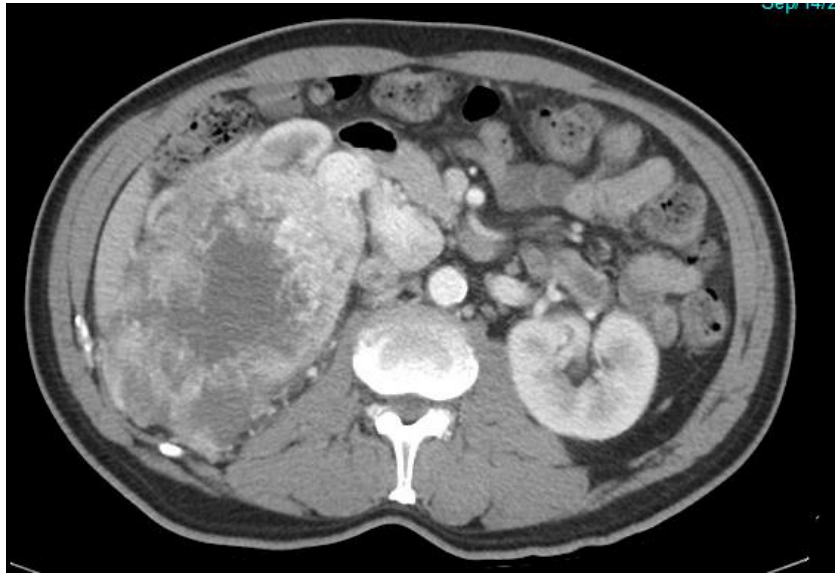
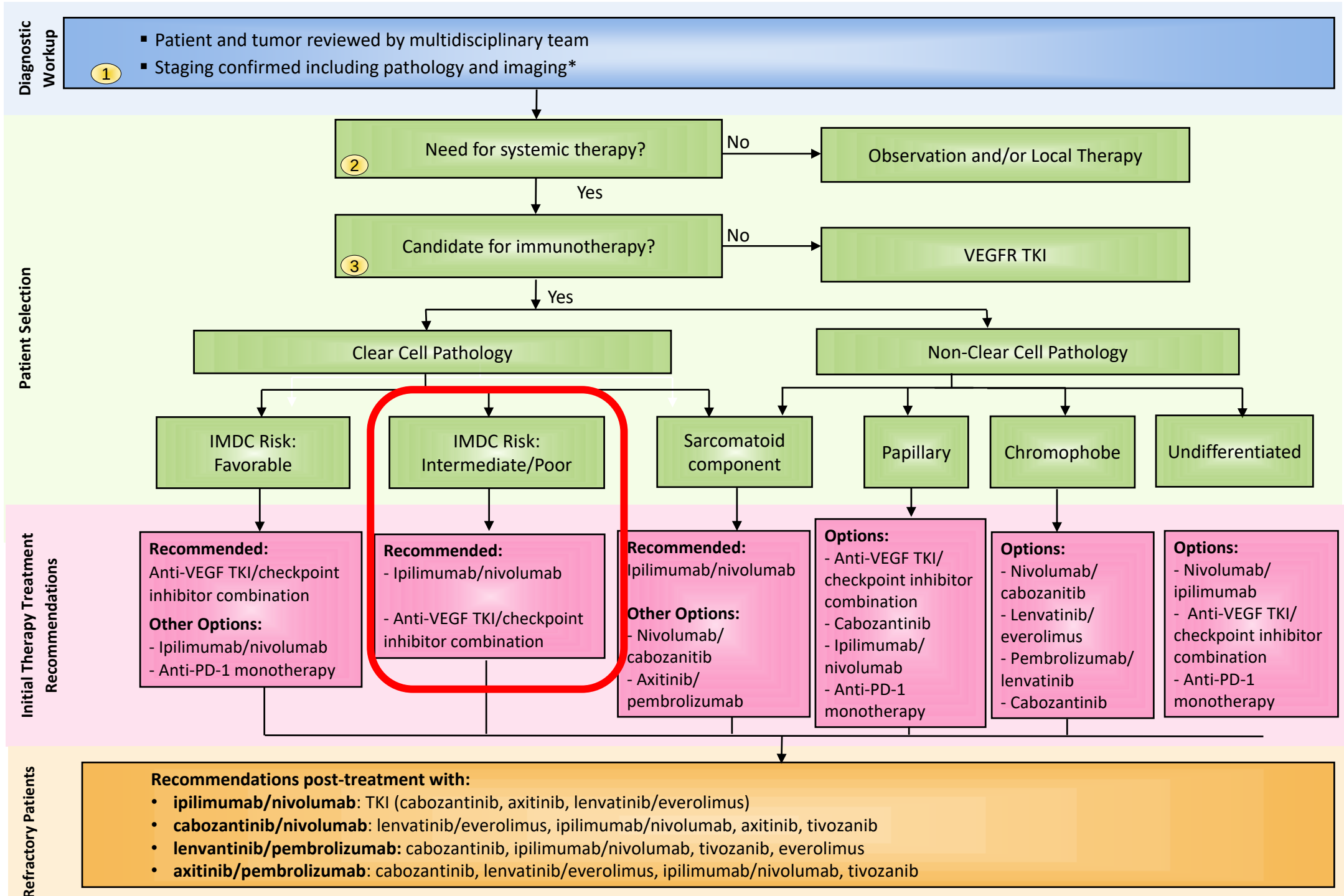


CT AP: large renal primary tumor with infra-hepatic IVC thrombus; bi-lobar hepatic metastases

Clear cell RCC with large metastatic burden including symptomatic endobronchial disease – what would you do next?

1. Start ipilimumab + nivolumab
2. Start Cabozantinib monotherapy
3. Start lenvatinib + pembrolizumab
4. Start lenvatinib + everolimus
5. Refer for upfront cytoreductive nephrectomy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axitinib/pembrolizumab: cabozantinib, lenvatinib/everolimus, ipilimumab/nivolumab, tivozanib

PD rate – relevant in patients with symptomatic, high-pace disease

	CheckMate-214*		KEYNOTE-426*	CheckMate 9ER	CLEAR
	Ipilimumab + Nivolumab		**Axitinib + Pembrolizumab**	**Cabozantinib + Nivolumab**	**Lenvatinib + Pembrolizumab**
Median Follow-Up	55 months		30.6 months	18.1 months	26.6 months
Total Patients	1096		861	651	1069
IMDC Fav/Int/Poor	23/61/17		31.9/55.1/13	22.6/57.6/19.7	31/59.2/9.3
Sarcomatoid Features (%)	13.2		17.9	11.5	7.9
Nephrectomy status (%)	82		82.6	68.7	73.8
	Int/Poor	ITT			
ORR (%)	**41.9**	**39.1**	**60**	**55.7**	**71**
CR (%)	**10.4**	**10.7**	**9**	**8**	**16.1**
PD (%)	19.3	17.6	11	5.6	5.4
Median PFS (months)	**11.2**	**12.2**	**15.4**	**16.6**	**23.9**
PFS HR (CI)	0.74 (0.62-0.88)	0.89 (0.76-1.05)	0.71 (0.6-0.84)	0.51 (0.41-0.64)	0.39 (0.32-0.49)
OS HR (CI)	0.65 (0.54-0.78)	0.69 (0.59-0.81)	0.68 (0.55-0.85)	0.6 (0.4-0.89)	0.66 (0.49-0.88)

*Data summarized for review and discussion only; not valid for cross-trial comparisons.

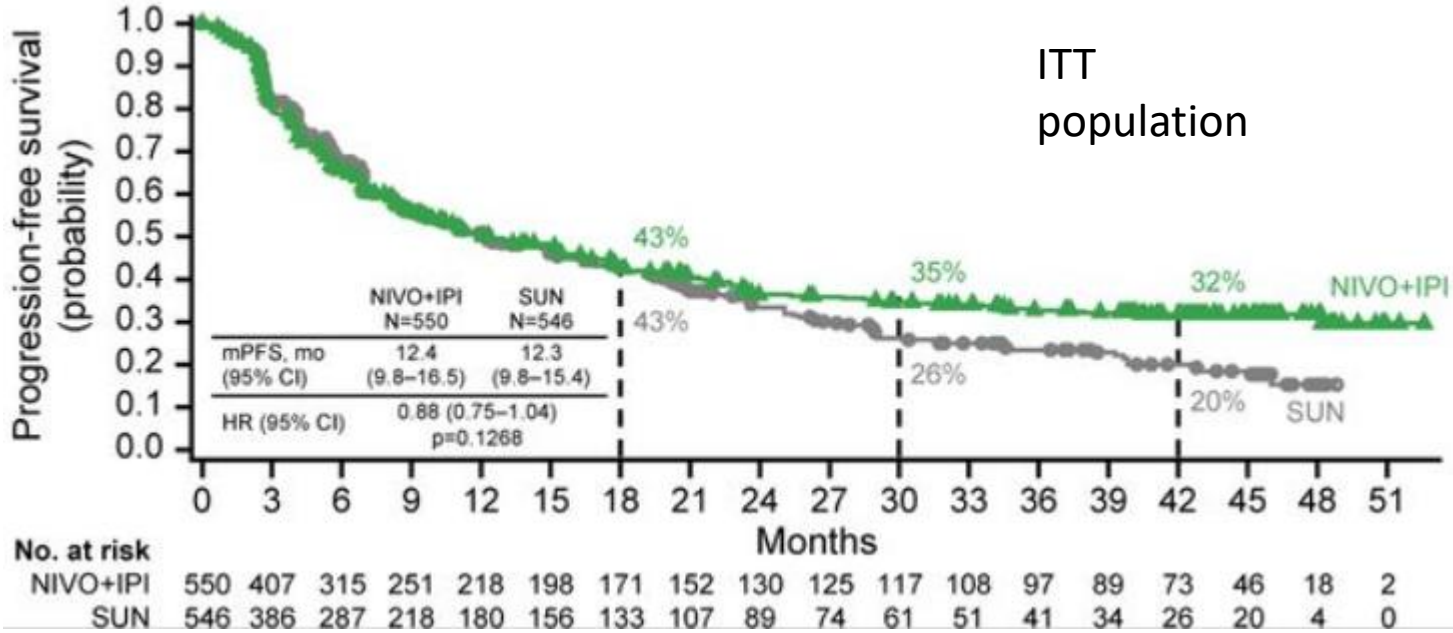
Motzer et al., NEJM 2018 ; Rini et al., NEJM 2019 ; Motzer et al., NEJM 2019 ;
Choueiri et al., NEJM 2021 ; Motzer et al., NEJM 2021

Courtesy of R. Kotecha

CheckMate214

Ipilimumab + Nivolumab

Motzer et al. JITC. 2020 Jul;8(2):e000891

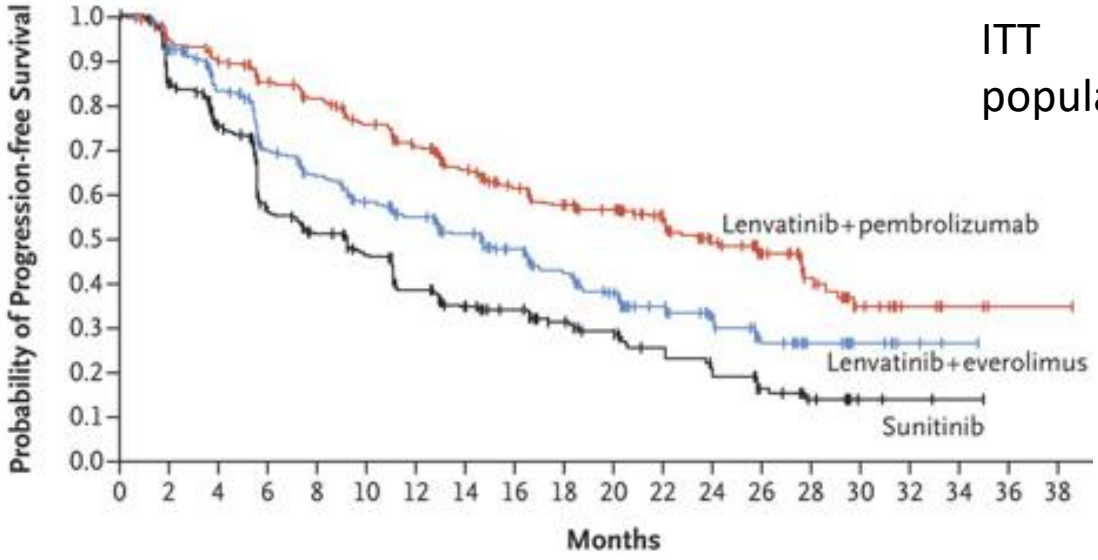


ITT population

CLEAR

Lenvatinib + Pembrolizumab

Motzer et al. NEJM. 2021 Apr 8;384(14)



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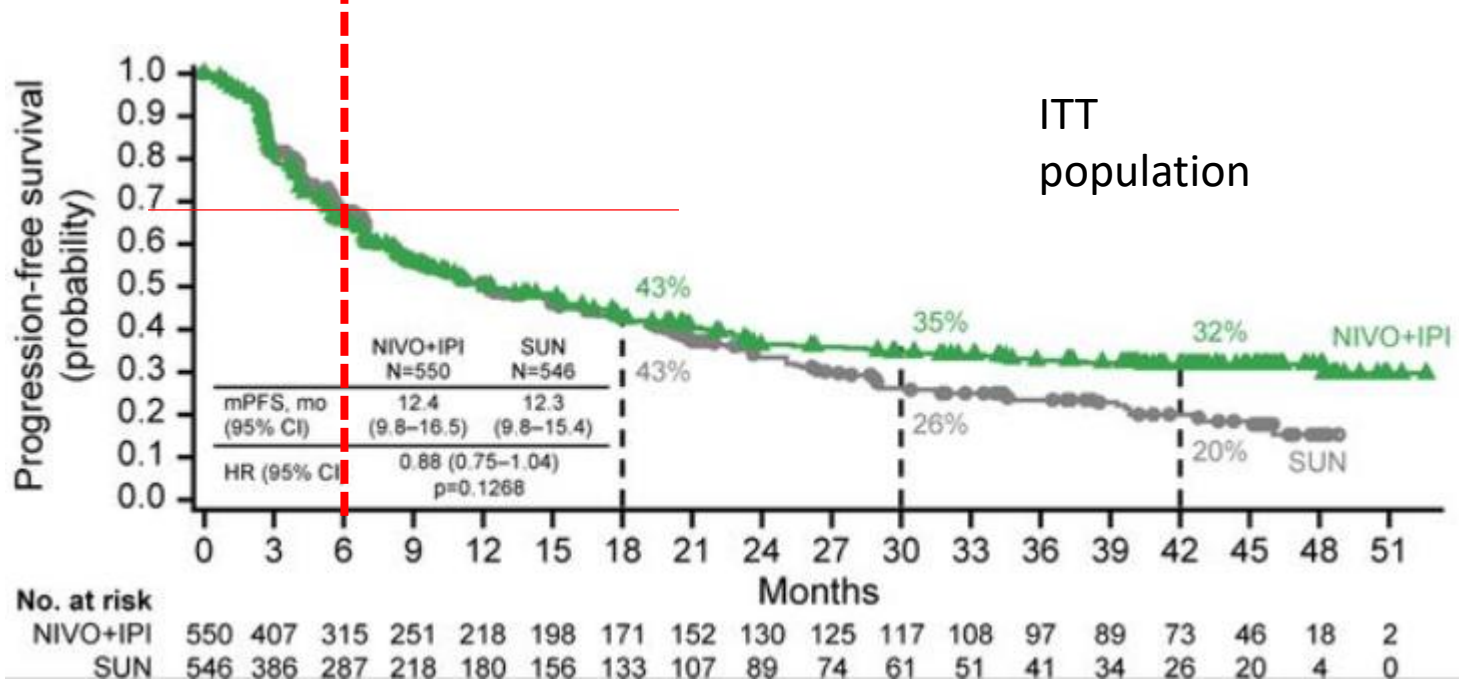

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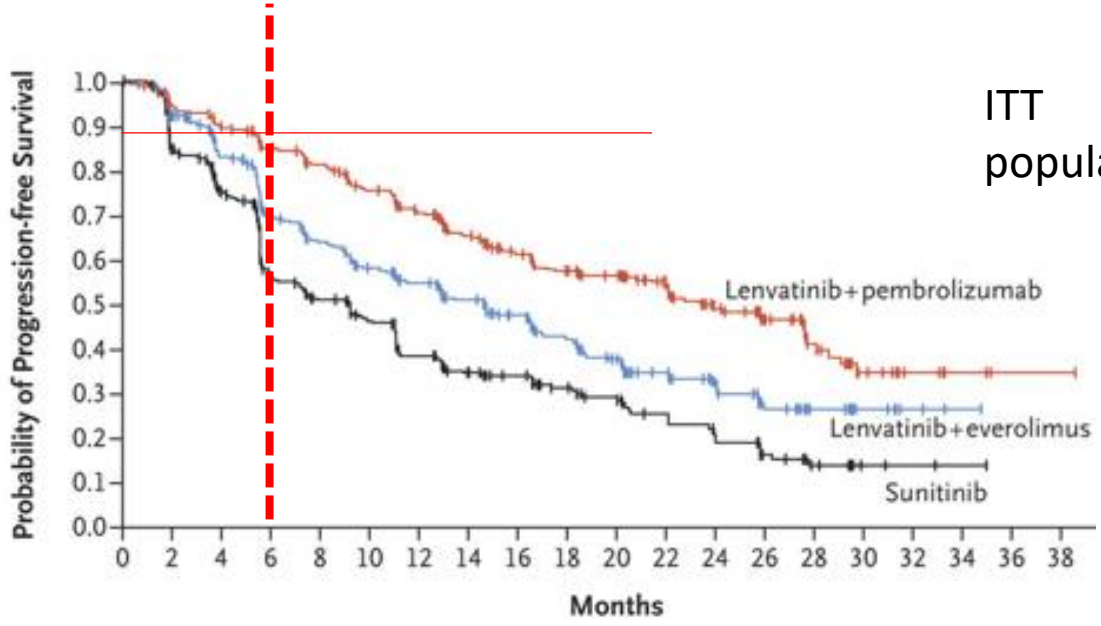

ITT population

Patient course

- Sept 15: start first-line Lenvatinib/pembrolizumab
- Oct 6: cough notably improved; 2wks later resolved
- Oct 27: new transaminitis
- Nov: rechallenge
- Dec: CT with very good response
- Dec: Lenvatinib dose reduced (HFS, fatigue)

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Toxicity Management

Virginia Seery, MSN, RN, ANP-BC, AOCNP®
Nurse Practitioner
Beth Israel Deaconess Medical Center

Disclosures

- Advisory Board or Panel: Exelixis, Aveo
- Speaker’s Bureau: Clinigen
- Consultant: Apricity Health

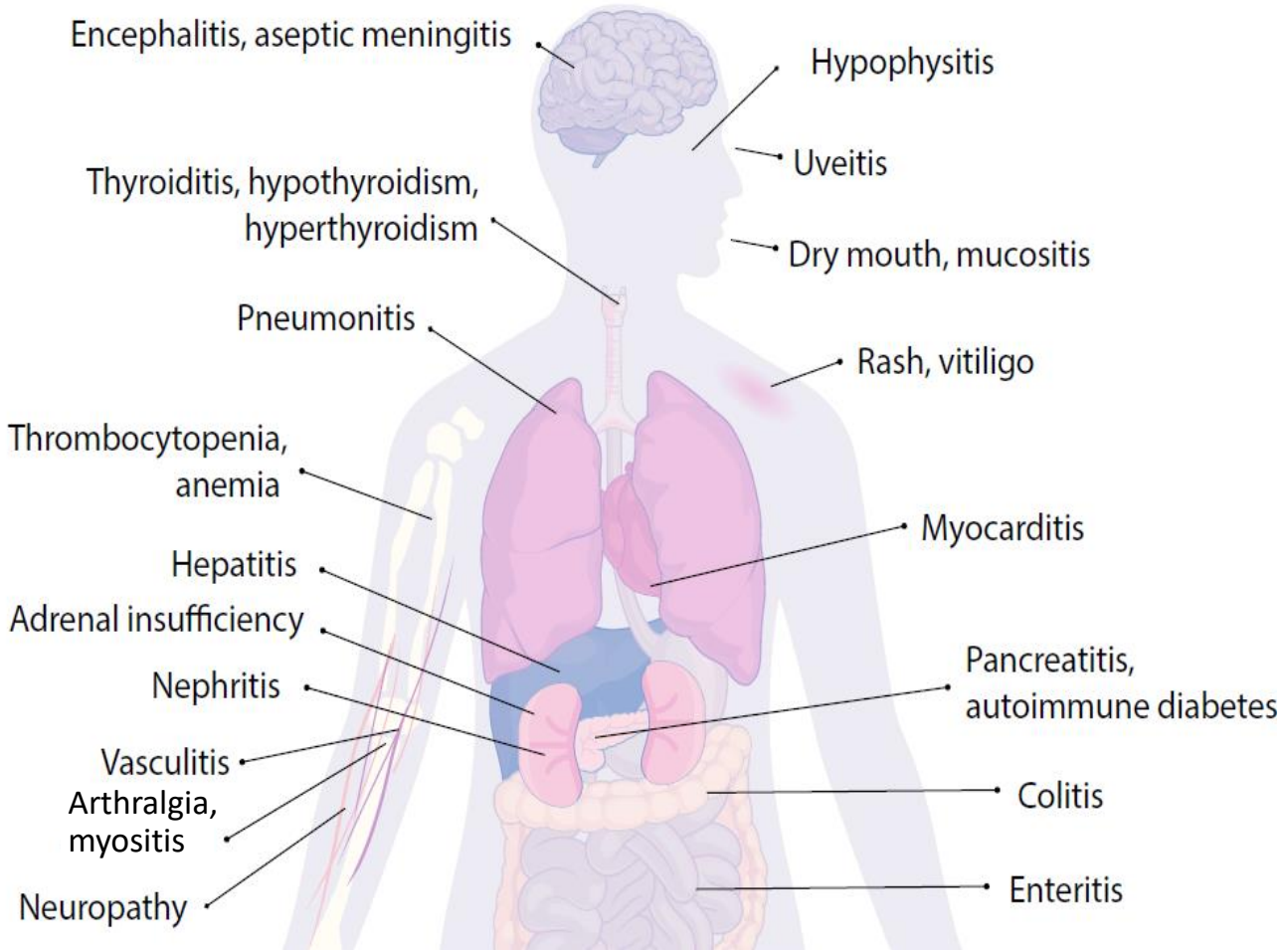
RCC Treatment-Related Adverse Events

- VEGF or mTOR inhibitor monotherapy
- Nivolumab monotherapy
- Checkpoint inhibitor combination strategies
  - Combined immunotherapy
  - Immunotherapy + VEGF therapy or mTOR inhibitor
- Focus on side effects of drug class

The Spectrum of irAEs

1. Taking the brakes off the immune system can help the body fight cancer, but can also lead to toxicity from an activated immune system

2. Any organ system can be affected



1. Postow MA et al. *N Engl J Med*. 2018;378:158-168. 2. Brahmer JR et al. *J Clin Oncol*. 2018;36:1714-1768.

VEGF Targeted Therapy AEs

- Fatigue
- HTN
- Hand-foot syndrome
- Arthralgias/myalgias
- Rash
- QTc prolongation
- Dysphonia
- Hair/skin hypopigmentation

- GI
  - Mucositis
  - Nausea
  - Diarrhea
  - Weight loss
  - Taste changes
  - Anorexia
  - Dyspepsia

Cabometyx® prescribing information, 2020;
Sutent® prescribing information, 2020 Votrient® prescribing information, 2020.

Combination therapy challenges

- May have overlapping/additive toxicities
- Determine which drug is likely etiology
- When/how to restart treatment

Skin toxicity

- Be proactive – moisturize skin daily
- Happens soon after therapy starts
- Pruritus without rash seen
- Topical steroids/oral antihistamines are often used
- Decision to continue or hold IO therapy depends on grade of skin toxicity/rash (i.e. % BSA involved or mucosal involvement)
- Possible hold of IO for grade 2
- Hold IO for grade 3/4 toxicity
- Oral or IV steroids to treat grade 3/4 toxicity or persistent grade 2

Liver toxicity

- Higher incidence with IO and VEGF TKI combinations
- Tends to occur around week 6-7
- Hold for grade 2 or higher LFTs
- Frequent recheck of LFTs
- Steroid use for symptomatic grade 2 or grade 3/4
- Taper steroids slowly
- If secondary immunosuppression needed, avoid infliximab due to potential for liver toxicity

Hand foot syndrome

- Proactive: Moisturizers, urea based creams
- Gel insoles
- Avoid extreme temperatures of hands/feet
- Avoid overuse
- Treatment:
  - Hold therapy early
  - Topical steroid cream
  - Consider dose reduction

Fatigue

- Common issue for RCC patients (anemia, stress, therapy AEs)
- Check thyroid, adrenal and pituitary function
- Balance rest with activity
- Ensure adequate sleep (symptom control)
- Stimulants may help

Toxicity management

Multidisciplinary approach is key

Goals:

- Allow restart of effective therapy
- Minimize new issues
- Maintain good quality of life

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Case: 62 yo man with metastatic RCC and Crohn's Disease

Michael B. Atkins, M.D.
Deputy Director
Georgetown-Lombardi Comprehensive Cancer Center
William M. Scholl Professor and Vice-Chair
Department of Oncology
Georgetown University Medical Center

Disclosures/ Potential Conflicts

Consultant:

BMS, Merck, Novartis, Genentech/Roche, Pfizer, Exelixis, Eisai, Aveo, Arrowhead, Agenus, Iovance, ImmunoCore, Neoleukin, SeaGen, AstraZeneca, Calithera, Sanofi

Advisory Boards:

Novartis, Pfizer, Merck, BMS, Pyxis Oncology, Werewolf, Genentech/Roche Adagene, Elpis, Asher Bio, Idera

Research Support (to institution):

BMS, Merck, Pfizer, Genentech/Roche, Moderna, Calithera

Stock Options: Werewolf and Pyxis Oncology

Other: UpToDate: Melanoma, RCC and Immunotherapy Sections Editor

Last 36 Mos

RCC Case (History 1)

- 62 yo man with 7 year h/o Crohn's Disease Rx'ed with intermittent azathioprine and steroids with response, presented with abd pain, weight loss and fatigue
- Abd MRI: 12 cm R upper pole renal mass with paracaval adenopathy
- R radical nephrectomy revealed a 12 cm ccRCC with 90% sarcomatoid features; 2/6 LNs + (T3a N1a M0); declined adjuvant Rx
- 2 mos post-op: he has night sweats, anorexia; CT CAP showed 4.4 cm mass in R Nx bed, sub-cm pulm nodules and abd LNs

- How would you treat?

How would you treat?

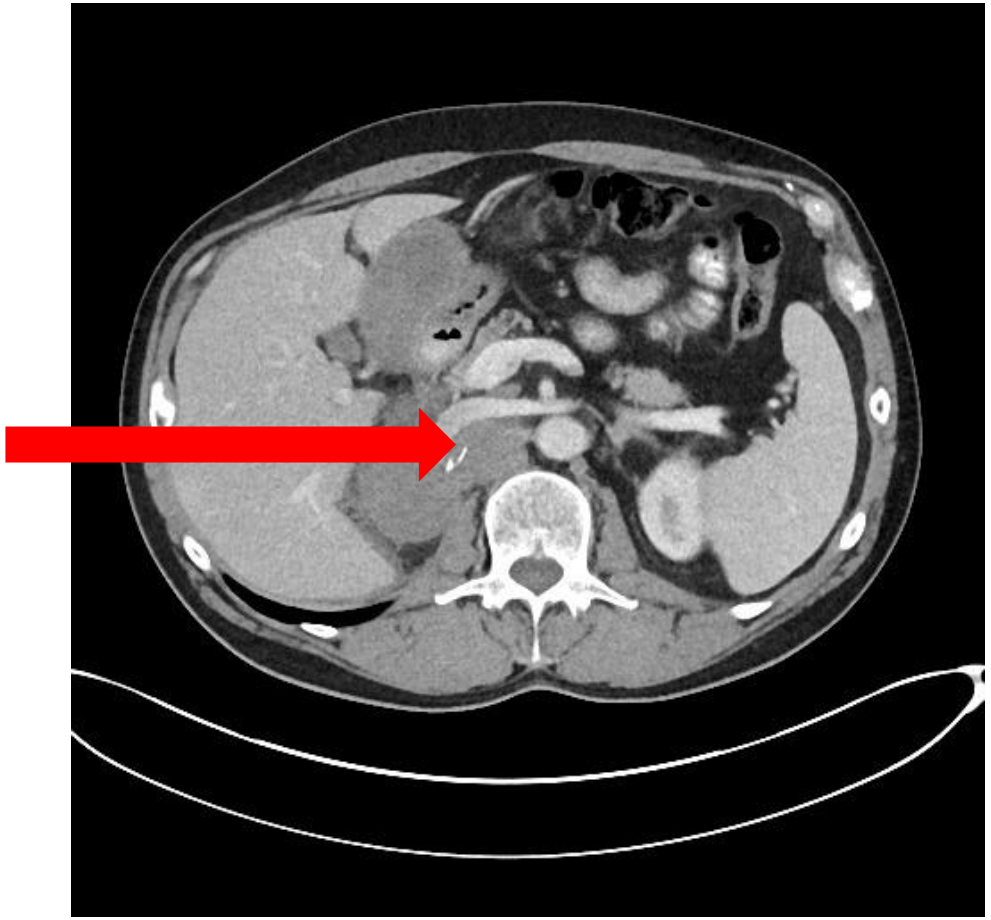
- Sunitinib/Pazopanib
- Cabozantinib
- Ipilimumab/Nivolumab
- Axitinib/Pembrolizumab
- Other

RCC Case History (2)

- Patient started on cabozantinib 60 mg daily by outside oncologist
- Symptoms persisted and CT scan 12 weeks into treatment showed significant interval progression

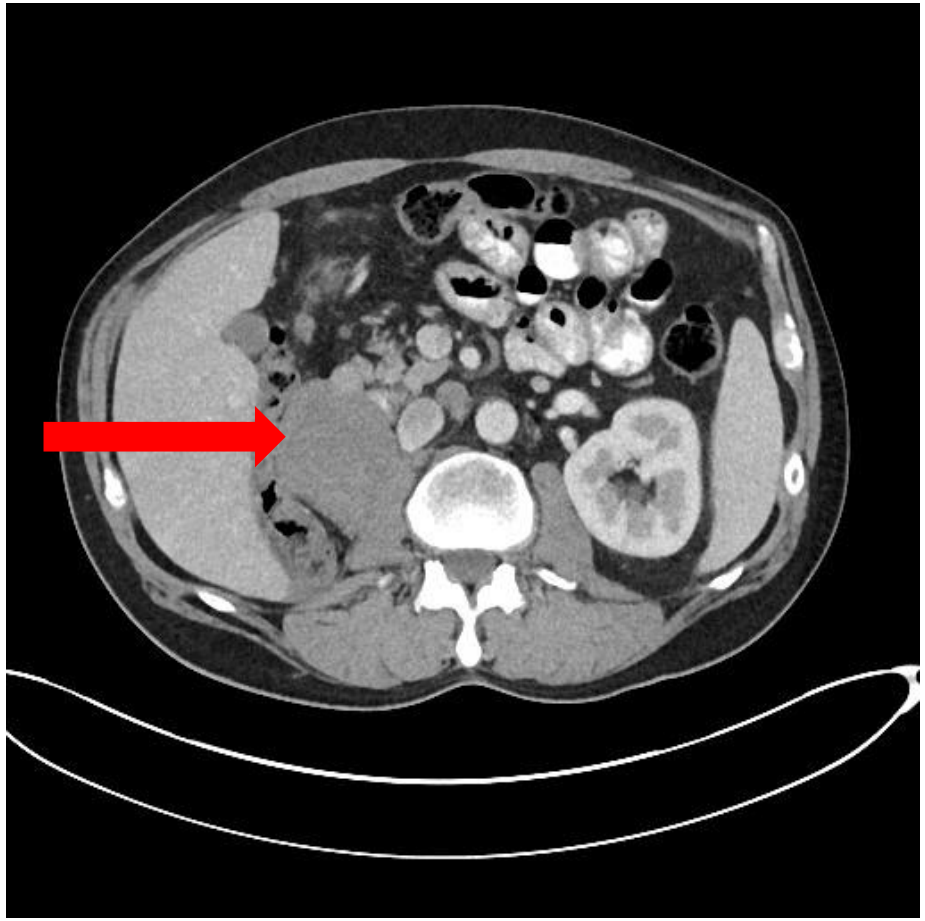
Abdominal Nodes

4/2018



R Nx Bed Lesion

4/2018



How would you treat?

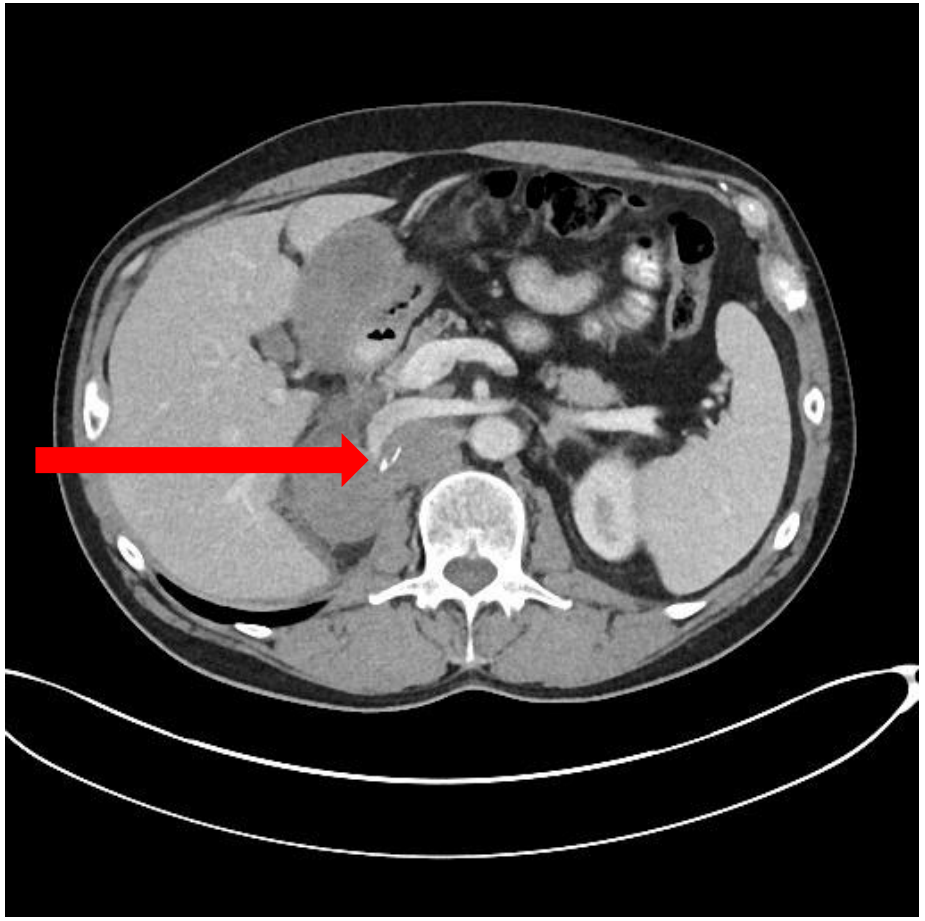
- Lenvatinib + everolimus
- Lenvatinib + Pembro
- Ipilimumab/Nivolumab
- Nivo monotherapy
- Other

RCC Case History (3)

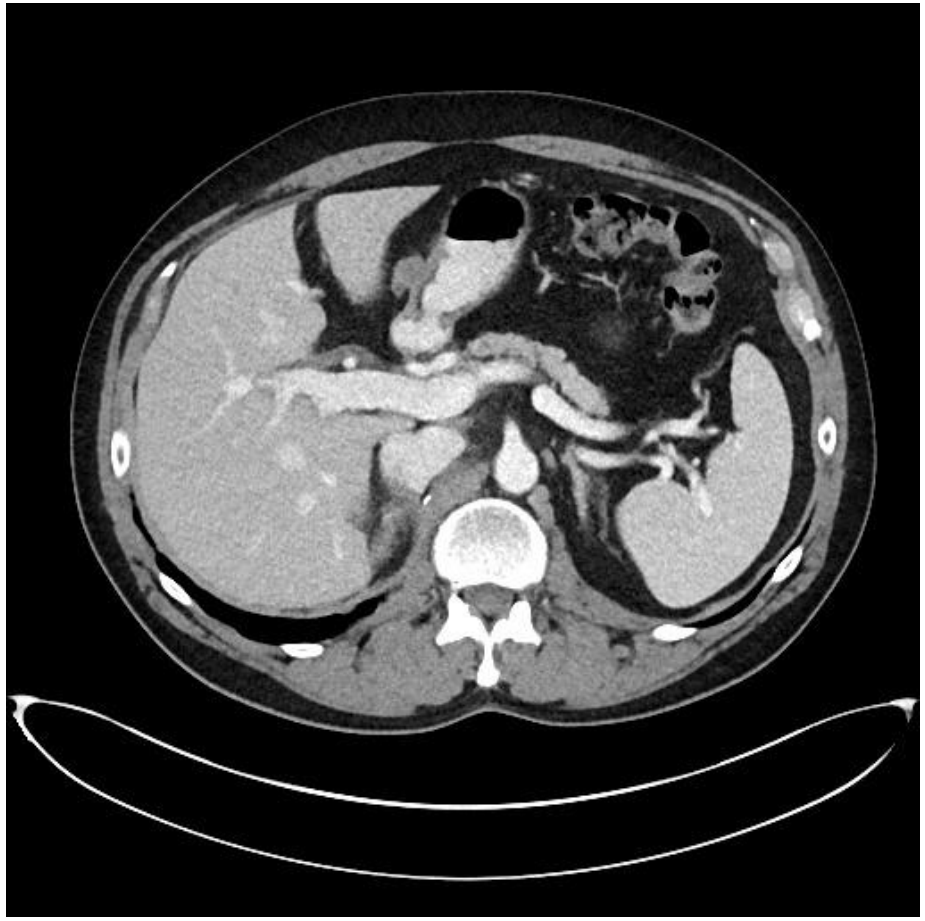
- He was begun on nivo monotherapy
- Underwent colonoscopy at baseline and q3months
- Symptoms rapidly improved, he regained energy and the previously lost weight
- Scans showed major response
- He experienced rash, joint pains, feet parasthesias, but no Crohn’s flare

Abdominal Nodes

4/2018

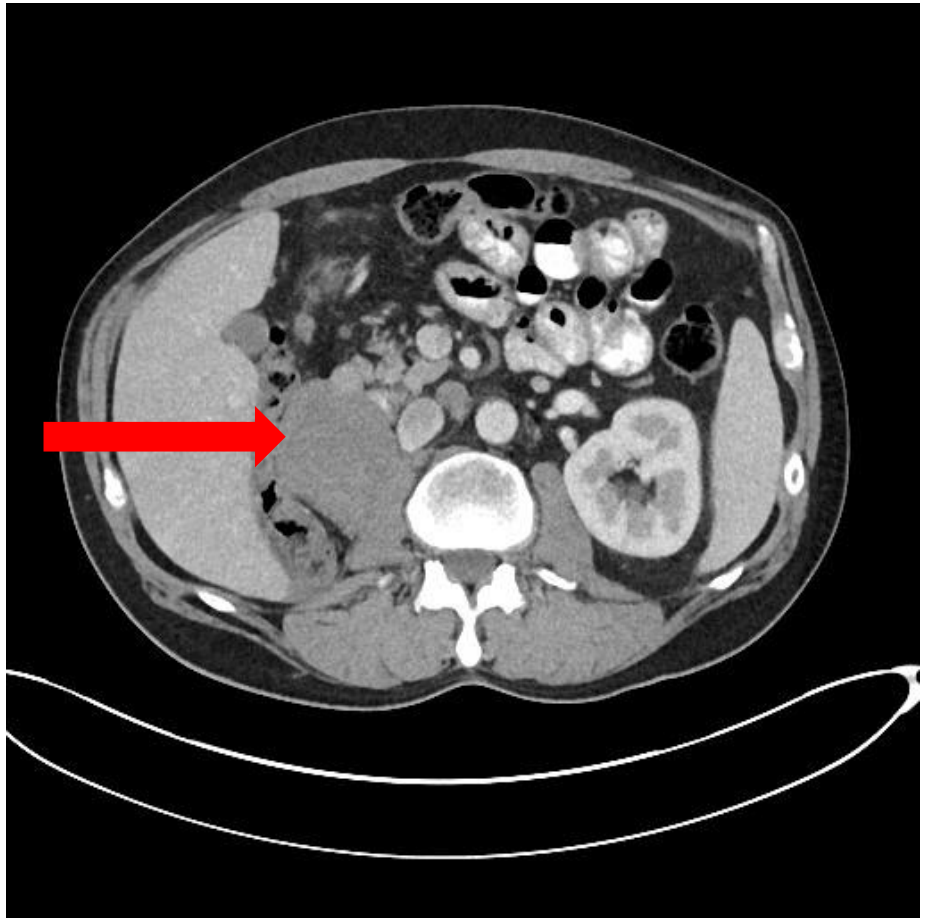


4/2020

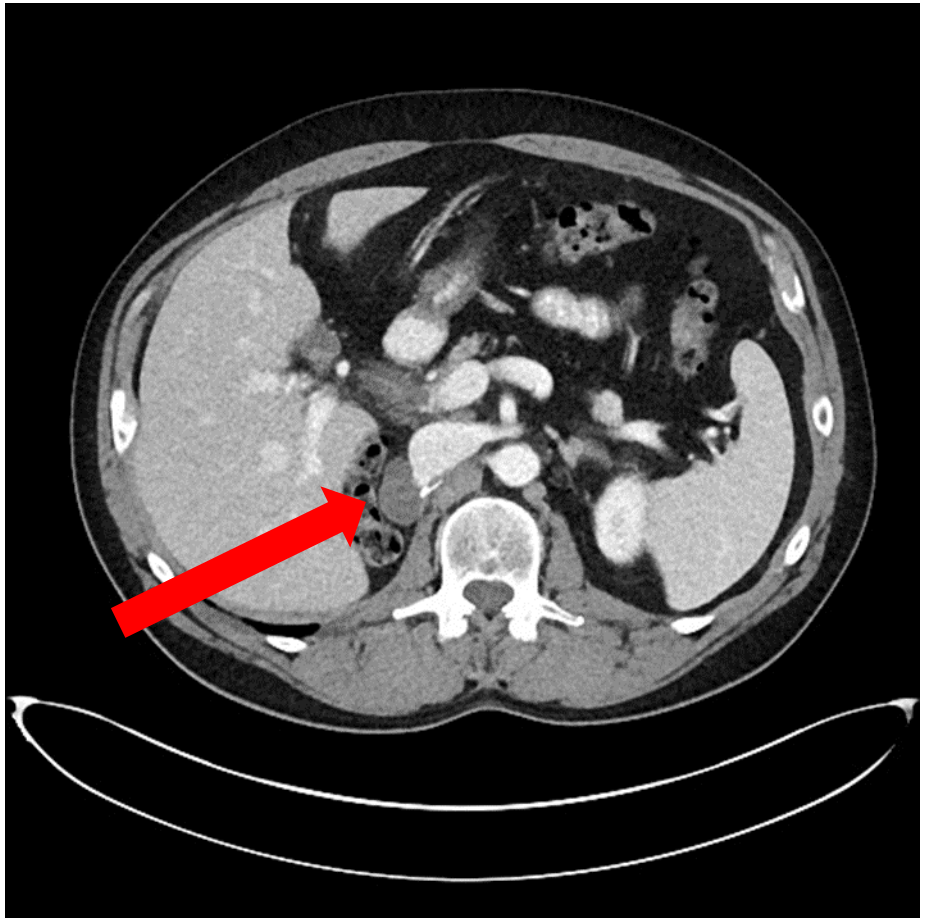


R Nx Bed Lesion

4/2018



4/2020



How would you manage?

- Continue nivolumab with support meds for irAEs
- Switch to Lenvatinib +everolimus
- Evaluate for residual disease to potentially stop nivo
- Stop nivo and observe
- Other

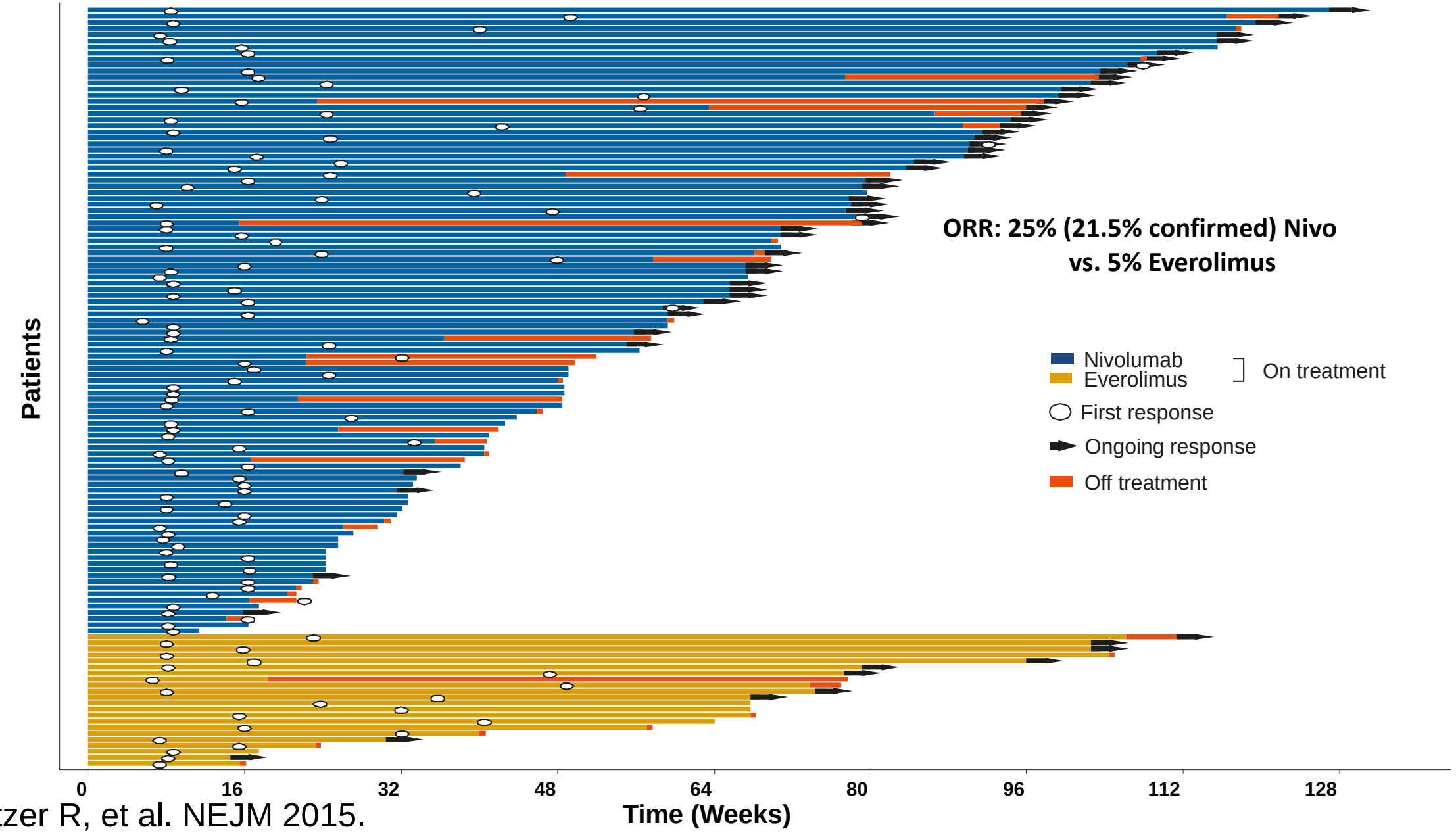
RCC Case History (4)

- PET-CT showed residual uptake in nephrectomy bed lesion
- Biopsy of residual Nx bed lesion after 2 years of Rx showed no cancer.
- Treatment stopped; patient observed q 3 months
- No disease progression observed, now > 20 months later.

Topics to Discuss

- Anti-PD1 monotherapy in the front-line
- Stopping Treatment Decisions

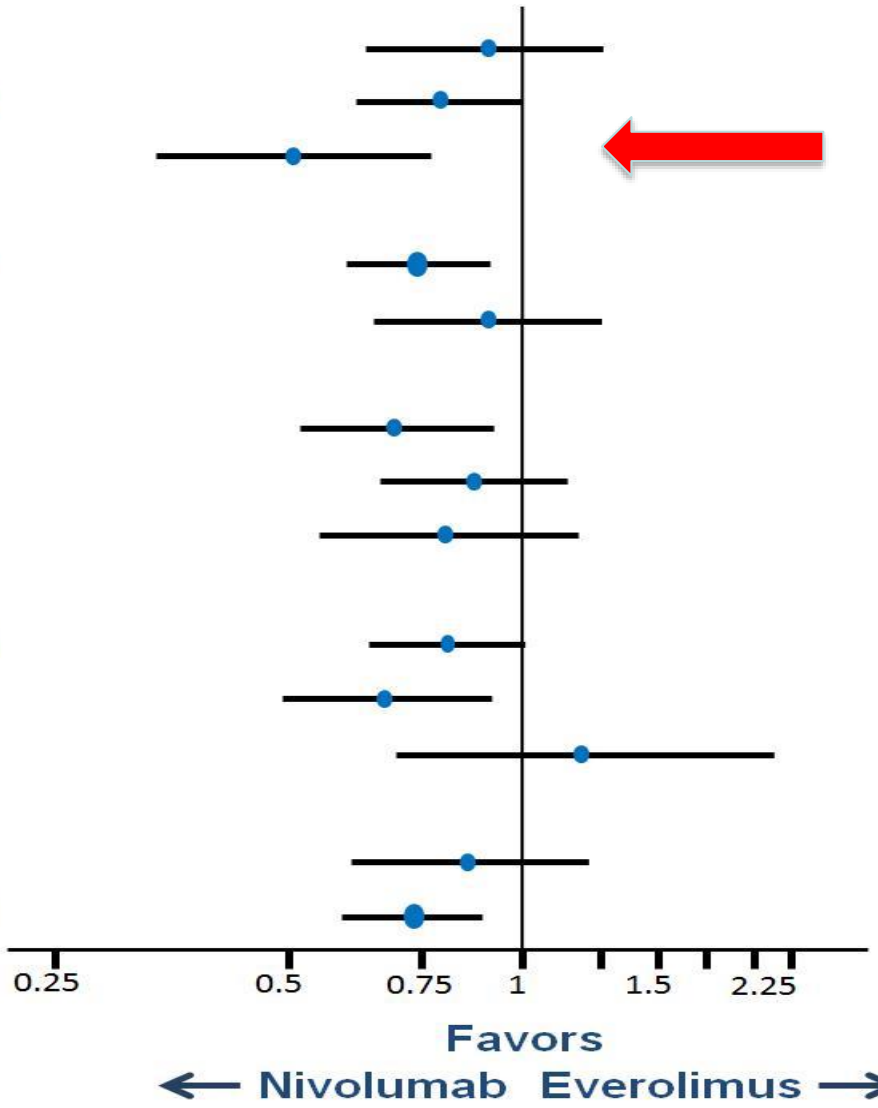
CM-025: Response Characteristics



Motzer R, et al. NEJM 2015.

Overall survival by subgroup analyses

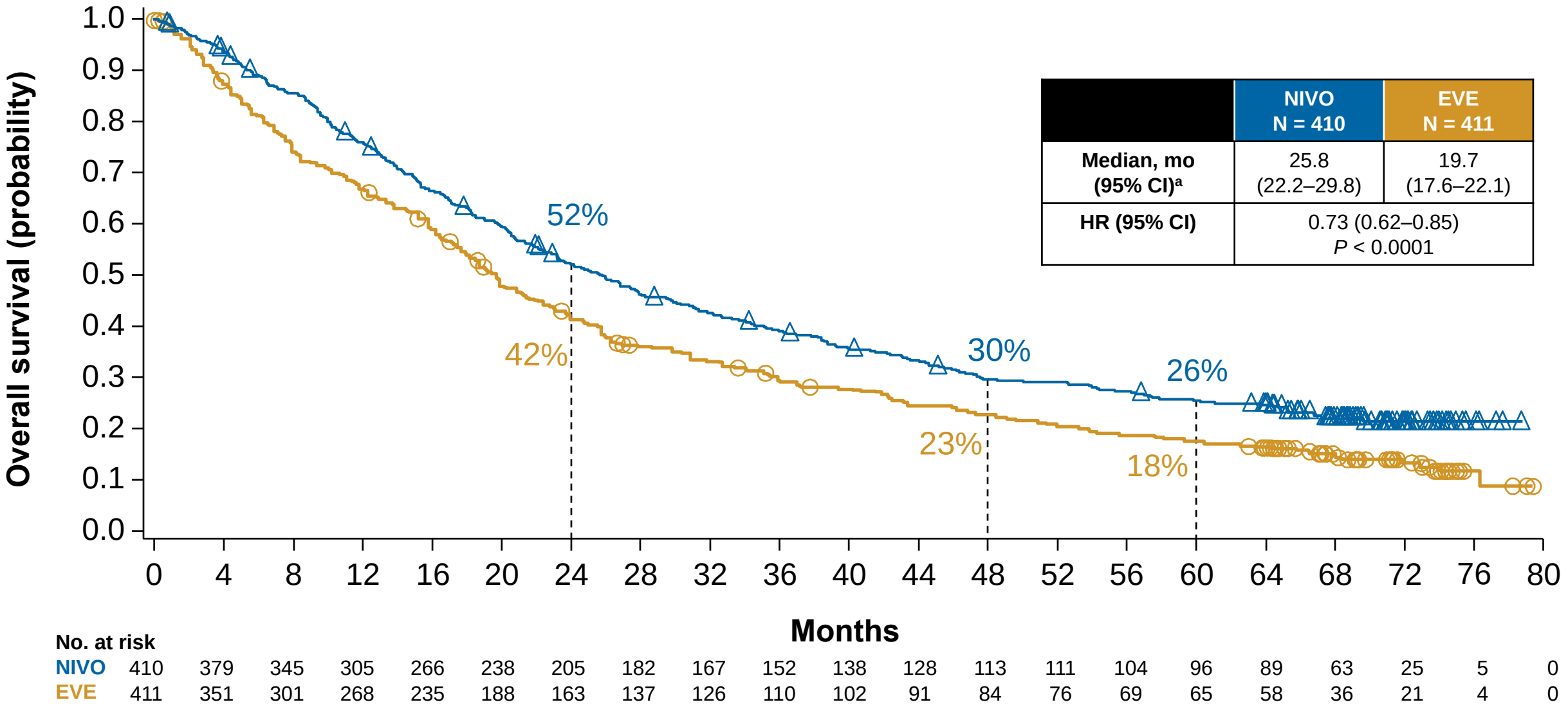
Subgroup	Nivolumab n/N	Everolimus n/N
MSKCC risk group		
Favorable	45/145	52/148
Intermediate	101/201	116/203
Poor	37/64	47/60
Prior anti-angiogenic regimens		
1	128/294	158/297
2	55/116	57/114
Region		
US/Canada	66/174	87/172
Western Europe	78/140	84/141
Rest of the world	39/96	44/98
Age, years		
<65	111/257	118/240
≥65 to <75	53/119	77/131
≥75	19/34	20/40
Sex		
Female	48/95	56/107
Male	135/315	159/304



Motzer R, et al. NEJM 2015.

Analyses based on interactive voice response system data.

Overall Survival



	NIVO N = 410	EVE N = 411
Median, mo (95% CI)[a]	25.8 (22.2–29.8)	19.7 (17.6–22.1)
HR (95% CI)	0.73 (0.62–0.85) *P* < 0.0001	

No. at risk

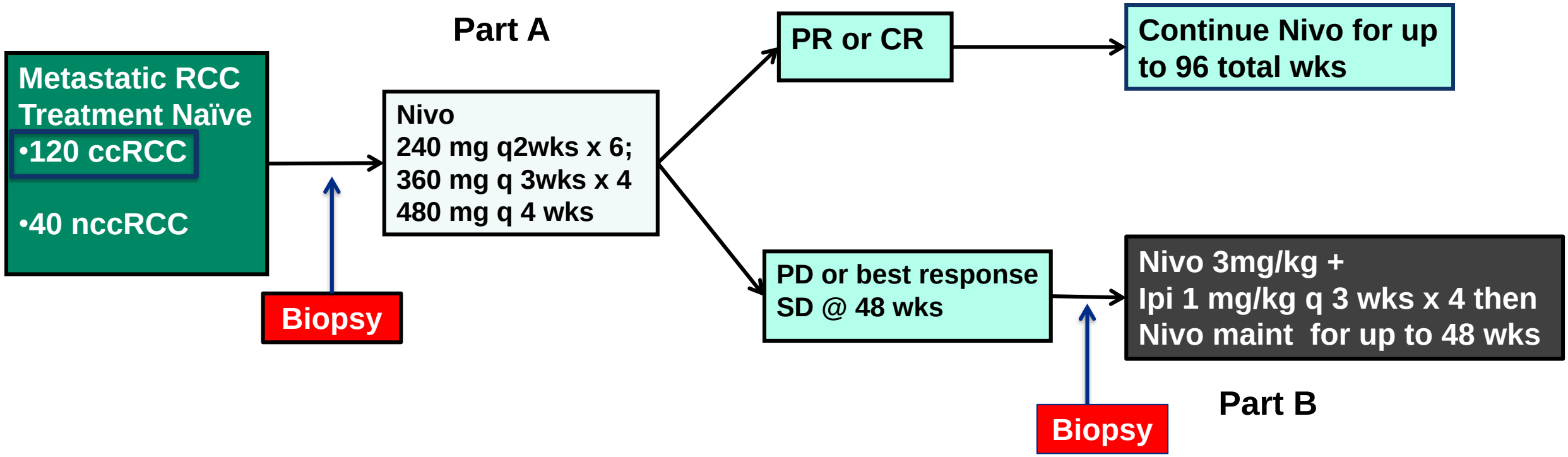
NIVO	410	379	345	305	266	238	205	182	167	152	138	128	113	111	104	96	89	63	25	5	0
EVE	411	351	301	268	235	188	163	137	126	110	102	91	84	76	69	65	58	36	21	4	0

[a]Number of events: NIVO = 308/410; EVE = 337/411; median follow-up, 72 months.

Motzer et al. Cancer 2020 Sep 15;126(18):4156-4167

HCRN GU16-260: Study Design

IIT at 12 sites conducted through the HCRN GU Group
(CM209-669)



Extensive Biomarker studies in collaboration with the DFHCC Kidney Cancer SPORE
DOD Translational Partnership Grant (Atkins, Wu)

Scans q12 weeks; Confirm response and PD;
Measurements by RECIST 1.1
Mandatory biopsies

Atkins M et al. Presented at: ASCO 2020; May 29-31, 2020; Virtual Meeting. Abstract 5006.

Objective Response Rates: Nivo Monotherapy (Part A)

Best Response N (%)	IMDC Risk Category (N)			Total (N= 123) N (%)
	Favor (30) N (%)	Interm (80) N (%)	Poor (12) N (%)	
CR	4 (13.3)	3 (3.8)	0	7 (5.7)
PR*	11 (36.7)	17 (21.2)	3 (25)	32 (26.0)
SD	15 (50.0)	26 (32.5)	5 (42)	46 (37.4)
PD	0	34 (42.5)	4 (33)	38 (30.9)
ORR	15/30 (50)	20/80 (25)	3/12 (25)	39/123 (31.7)
(95% CI) %	(31.3, 68.7)	(16.6, 35.1)		(23.6, 40.7)

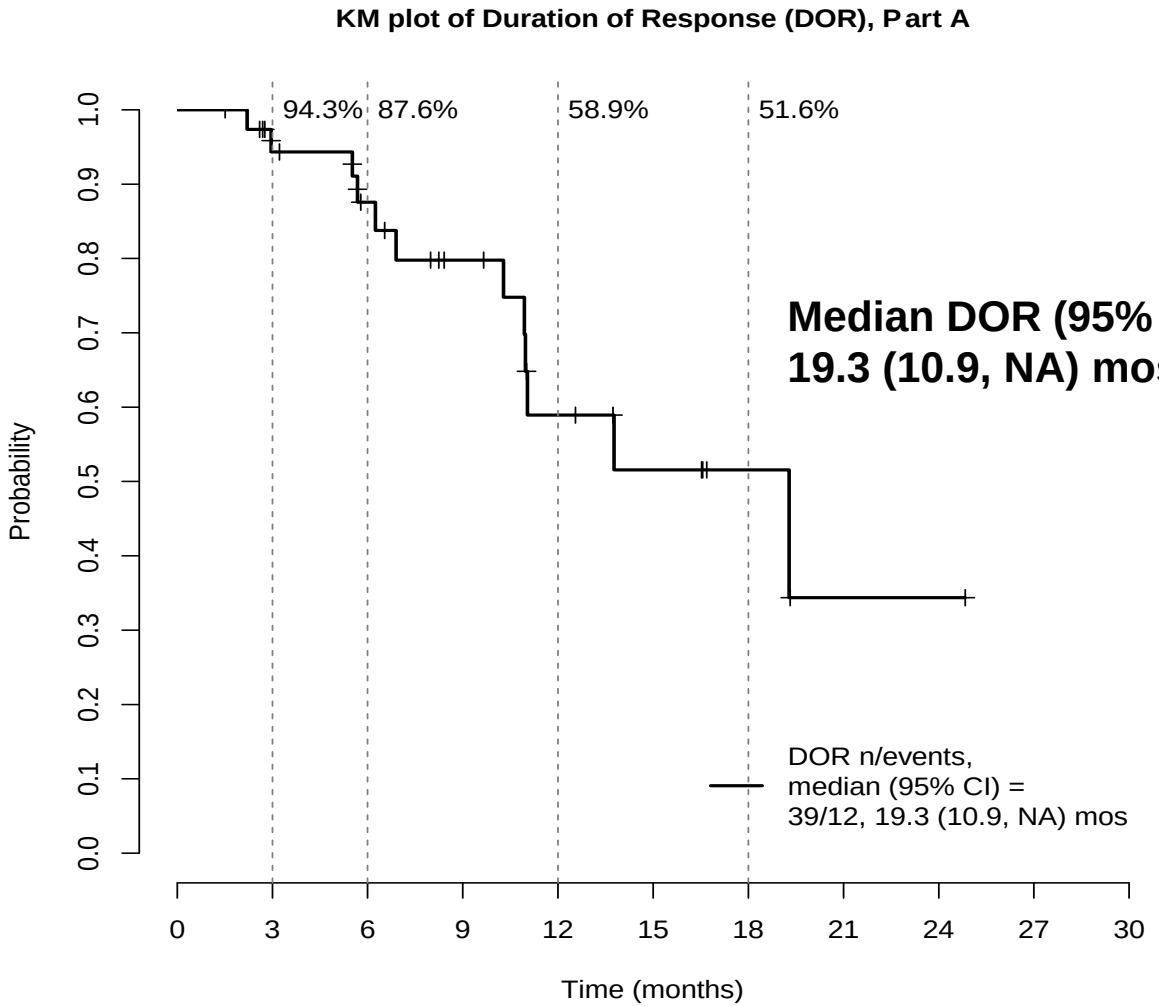
*** 1 PR with missing IMDC Risk Category**

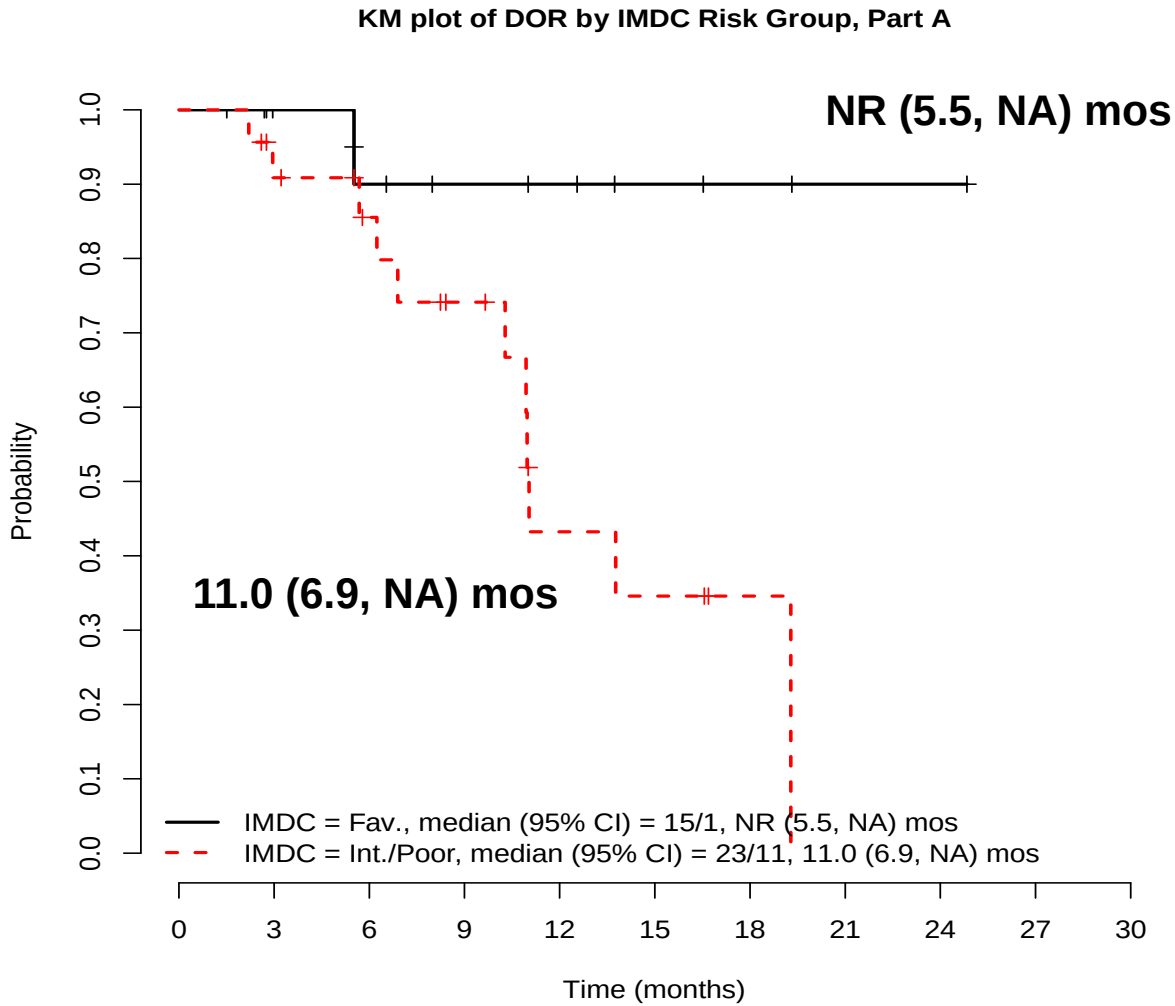
ORR: 39/123 = 31.7%
95% CI (23.6, 40.7%)

Sarcomatoid RCC ORR:
7/22 = 31.8% (all PRs)
95% CI (13.9, 54.9%)

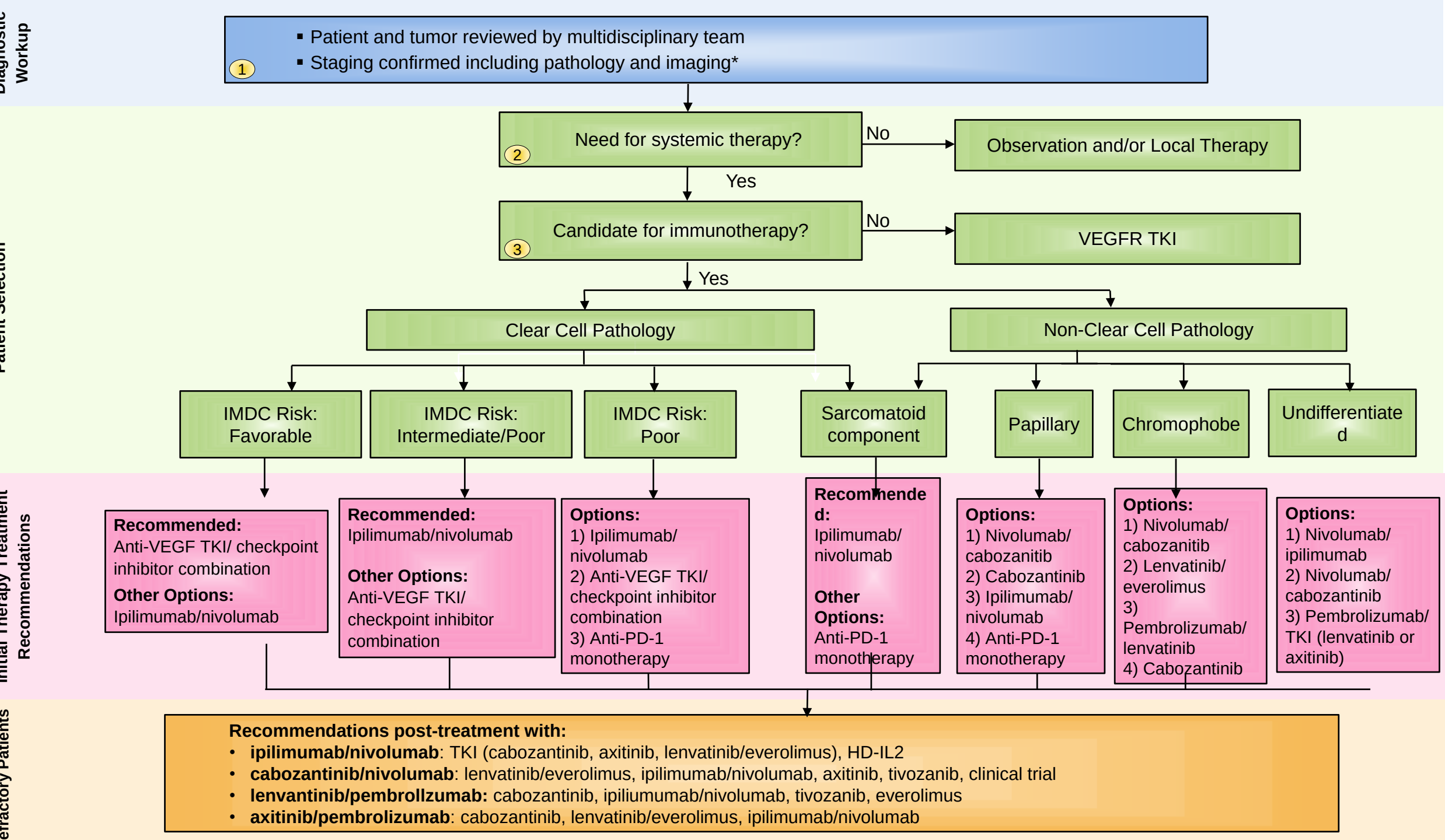
Atkins M et al. Presented at: ASCO 2020; May 29-31, 2020; Virtual Meeting. Abstract 5006.

Duration of Response: Nivo Monotherapy (Part A)



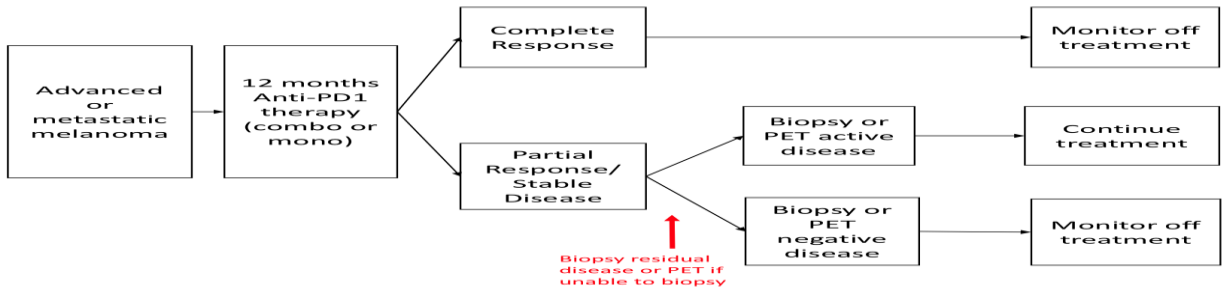


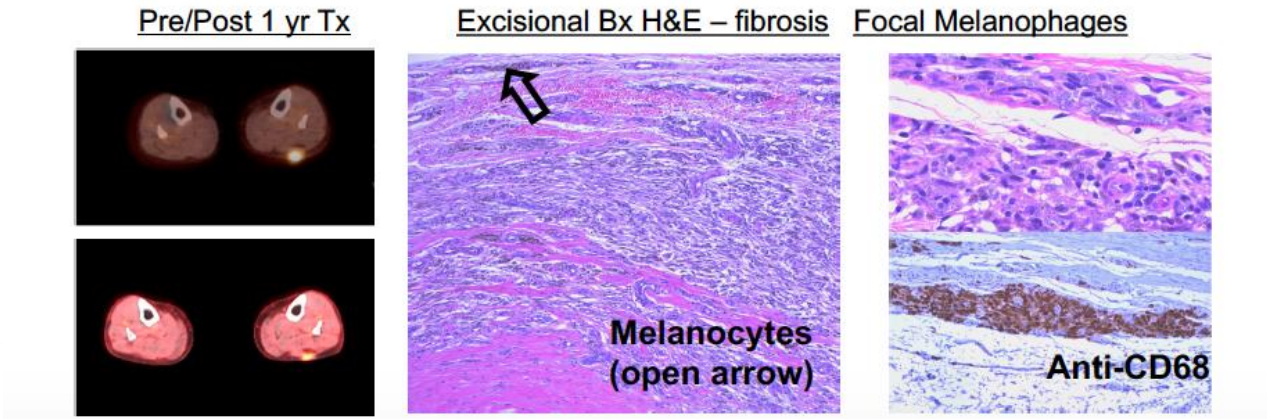
Atkins M et al. Presented at: ASCO 2020; May 29-31, 2020; Virtual Meeting. Abstract 5006.


Diagnostic Workup
Patient Selection
Initial Therapy Treatment Recommendations
Refractory Patients
1
Patient and tumor reviewed by multidisciplinary team
Staging confirmed including pathology and imaging*
2
Need for systemic therapy?
No
Observation and/or Local Therapy
Yes
3
Candidate for immunotherapy?
No
VEGFR TKI
Yes
Clear Cell Pathology
Non-Clear Cell Pathology
IMDC Risk: Favorable
IMDC Risk: Intermediate/Poor
IMDC Risk: Poor
Sarcomatoid component
Papillary
Chromophobe
Undifferentiated
Recommended: Anti-VEGF TKI/ checkpoint inhibitor combination
Other Options: Ipilimumab/nivolumab
Recommended: Ipilimumab/nivolumab
Other Options: Anti-VEGF TKI/ checkpoint inhibitor combination
Options: 1) Ipilimumab/ nivolumab 2) Anti-VEGF TKI/ checkpoint inhibitor combination 3) Anti-PD-1 monotherapy
Recommended: Ipilimumab/ nivolumab
Other Options: Anti-PD-1 monotherapy
Options: 1) Nivolumab/ cabozanitib 2) Cabozantinib 3) Ipilimumab/ nivolumab 4) Anti-PD-1 monotherapy
Options: 1) Nivolumab/ cabozanitib 2) Lenvatinib/ everolimus 3) Pembrolizumab/ lenvatinib 4) Cabozantinib
Options: 1) Nivolumab/ ipilimumab 2) Nivolumab/ cabozantinib 3) Pembrolizumab/ TKI (lenvatinib or axitinib)
Recommendations post-treatment with:
• ipilimumab/nivolumab: TKI (cabozantinib, axitinib, lenvatinib/everolimus), HD-IL2
• cabozantinib/nivolumab: lenvatinib/everolimus, ipilimumab/nivolumab, axitinib, tivozanib, clinical trial
• lenvantinib/pembrollzumab: cabozantinib, ipiliumumab/nivolumab, tivozanib, everolimus
• axitinib/pembrolizumab: cabozantinib, lenvatinib/everolimus, ipilimumab/nivolumab

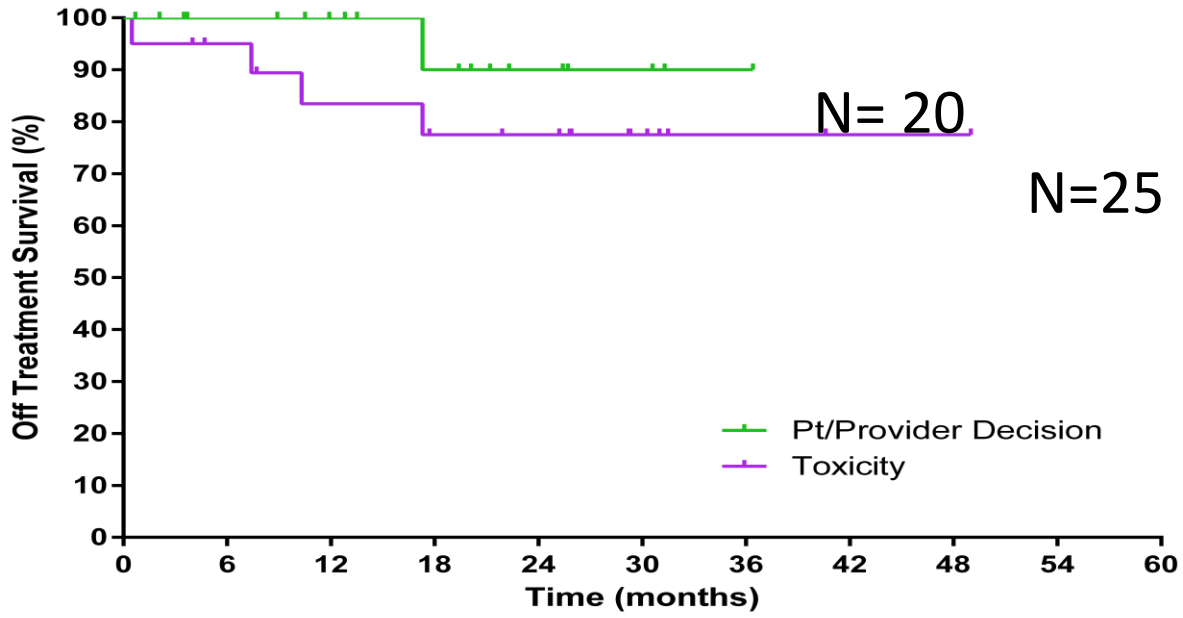
Stopping Therapy:
Lessons From Melanoma Population

MedStar Georgetown Approach – Create TFS

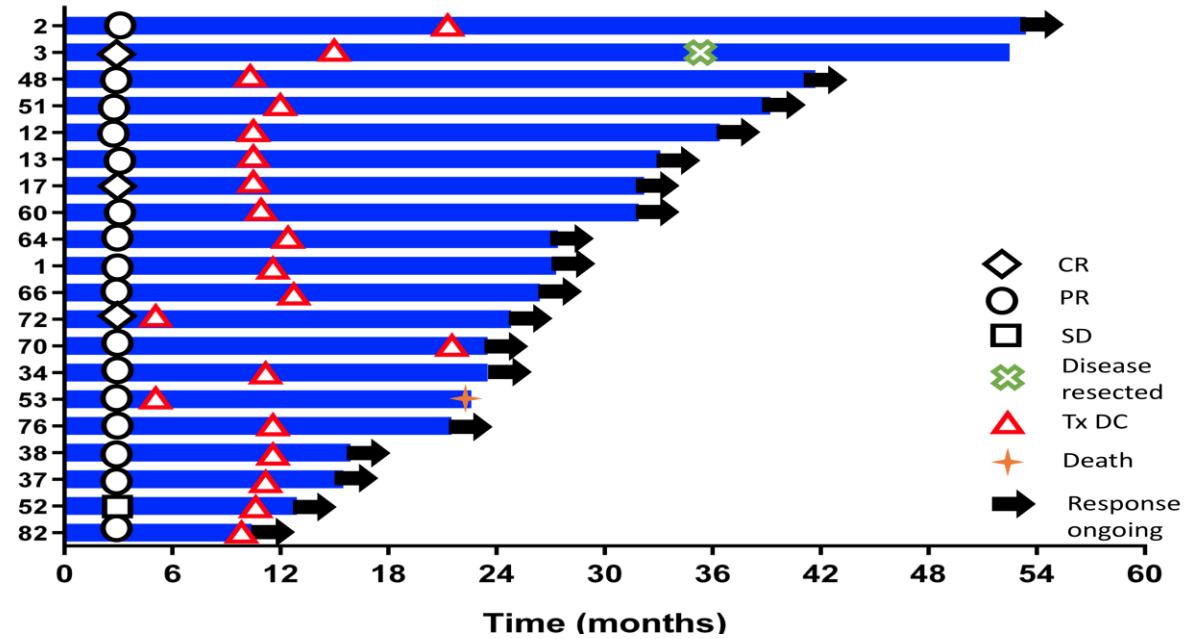




Melanoma pt off treatment survival (OTS) following Rx DC by reason

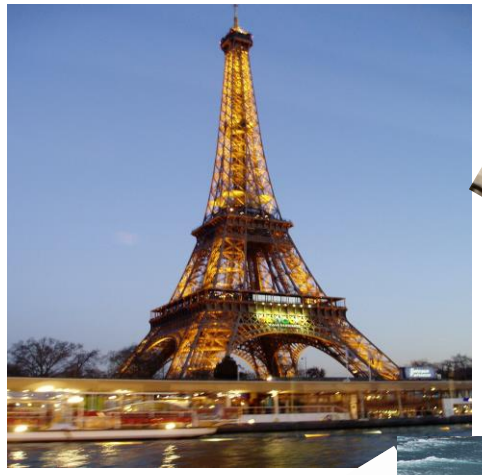


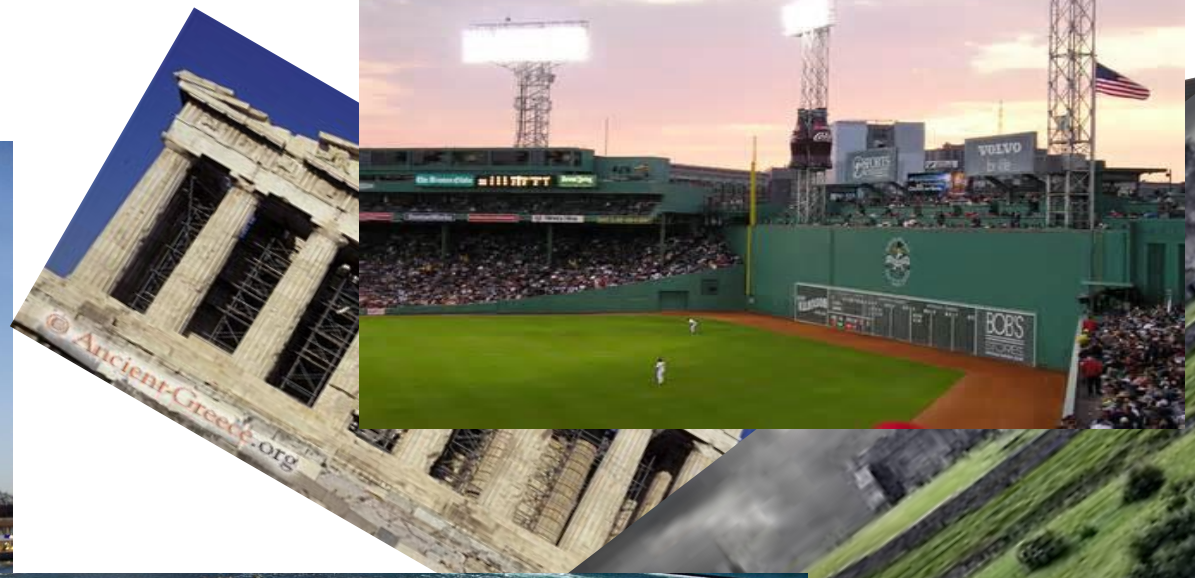
OS for pts with Tx DC for Pt/Provider decision (n=20: 1 PD, 1 death - non mel related)

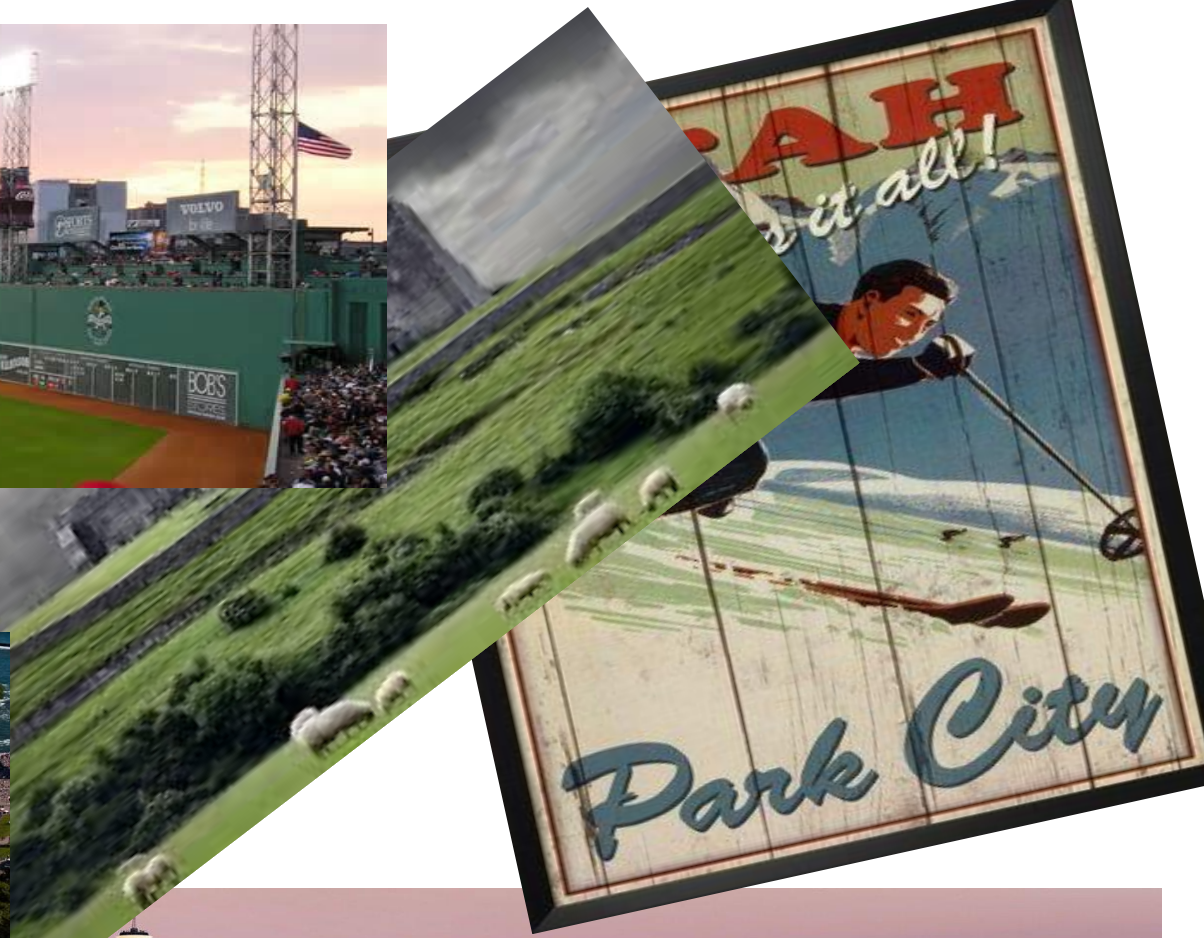


Gibney GT, Zaemes J, Shand S, *et al* PET/CT scan and biopsy-driven approach for safe anti-PD-1 therapy discontinuation in patients with advanced melanoma *Journal for ImmunoTherapy of Cancer* 2021;**9:**e002955. doi: 10.1136/jitc-2021-002955

TFS = Travel Full Survival- Survivors into “Thrivers”



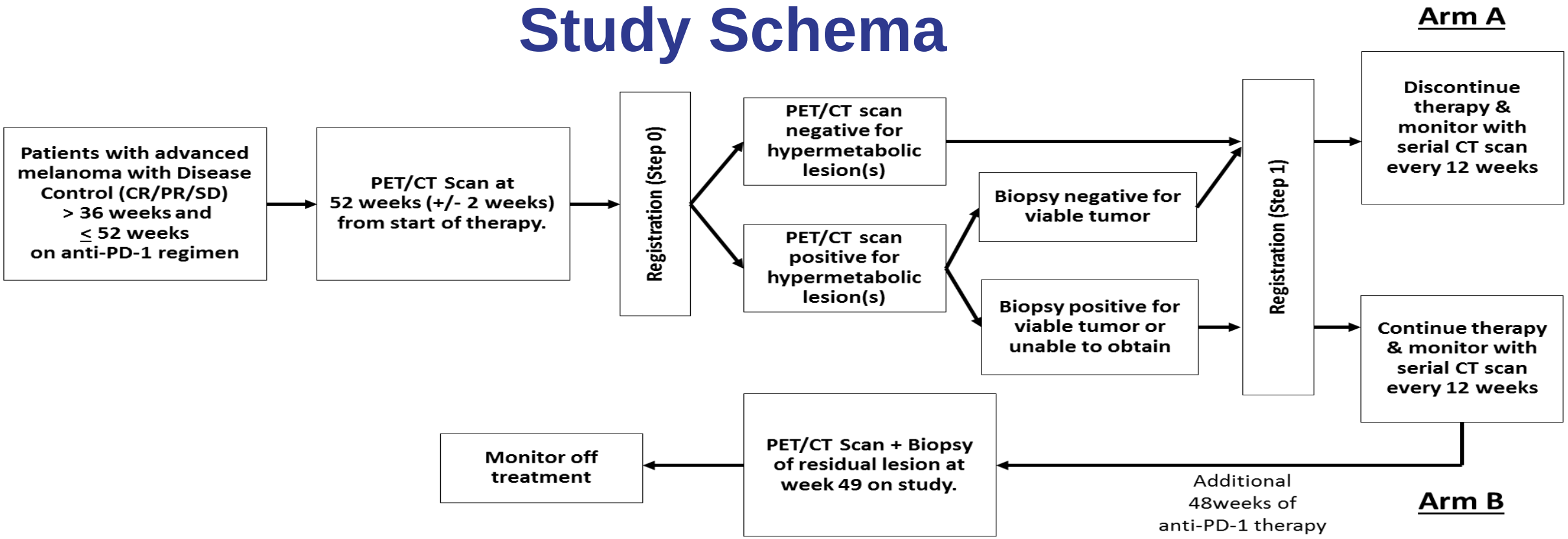




Georgetown | Lombardi

A Phase II Study of Biomarker Driven Early Discontinuation of Anti-PD-1 Therapy in Patients with Advanced Melanoma (PET-Stop):EA6192

Study Schema



https://www.clinicaltrials.gov/ct2/show/NCT04462406

Geoff Gibney PI- Open 9/2020

Take Home Messages

- Nivo monotherapy represents an alternative therapeutic approach
  - Particularly for patients at high risk of ipilimumab toxicity (e.g. autoimmune conditions)
- Stopping immunotherapy is possible in major responders and can turn survivors into thrivers
  - PET-CT and biopsy can aid decision making

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