Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

Renal Cell Carcinoma Webinar

Tuesday, January 7, 2020

11 a.m.–12 p.m. EST

Jointly provided by Postgraduate Institute for Medicine and the Society for Immunotherapy of Cancer

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Journal for ImmunoTherapy of Cancer

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*]

Webinar Agenda

11:00–11:05 a.m. EST	Welcome, Introductions and Overview
11:05–11:35 a.m. EST	Review of SITC Cancer Immunotherapy Guideline – Renal Cell Carcinoma
11:35-11:40 a.m. EST	Discussion
11:40–11:45 a.m. EST	Question and Answer Session
11:45-11:57 a.m. EST	Case Studies
11:57 a.m.–12:00 p.m. EST	Closing Remarks

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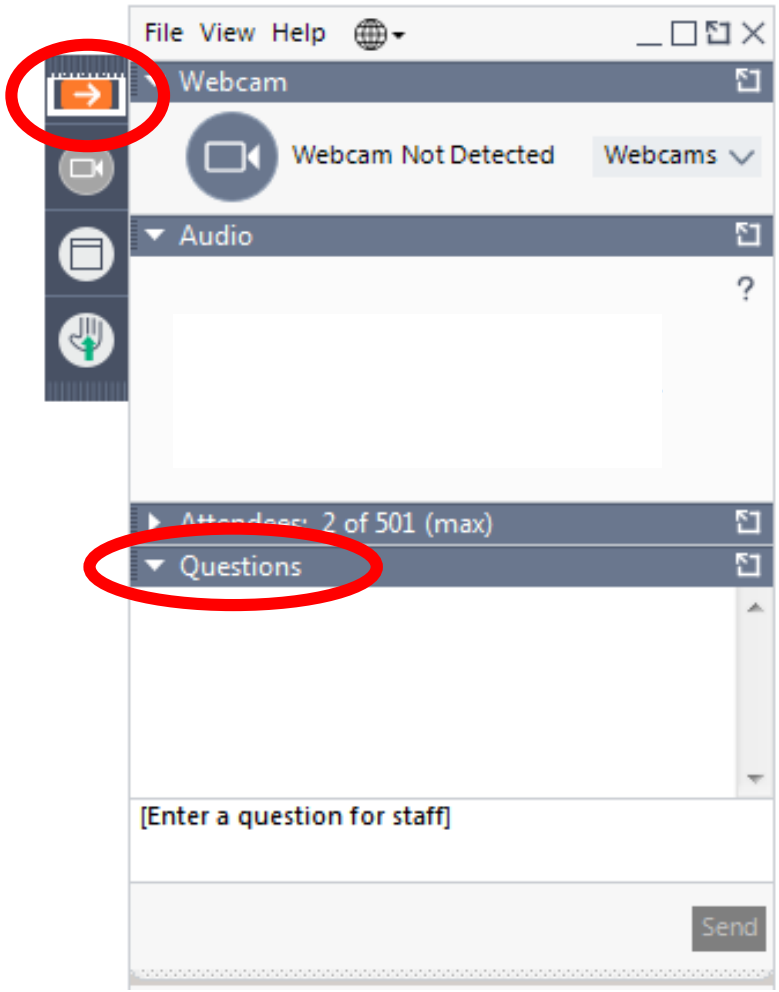
Cancer Immunotherapy GUIDELINES

How to Submit Questions

Computer



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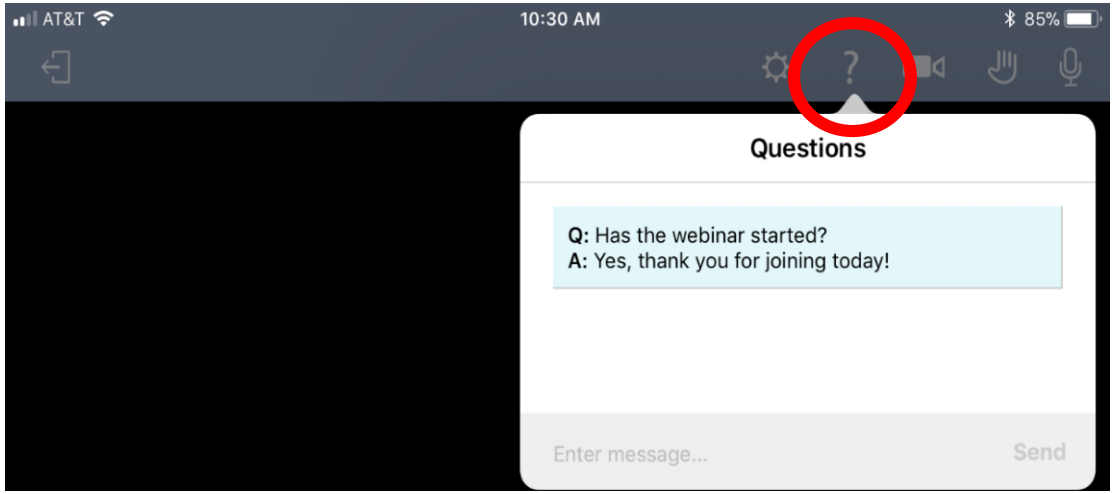


Webinar Faculty

Michael B. Atkins, MD
Georgetown-Lombardi Comprehensive Cancer Center

Dena Battle
KCCure

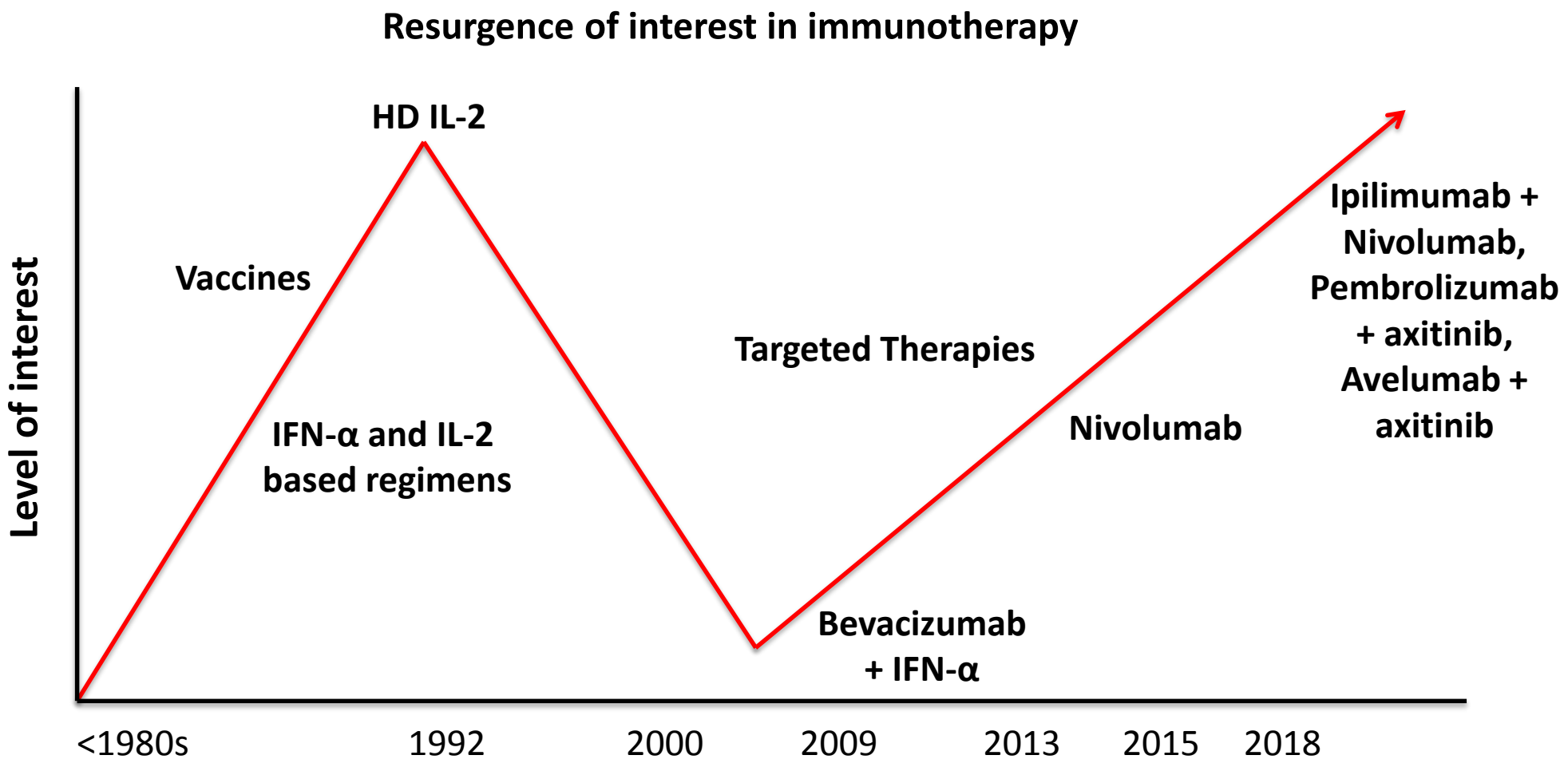
David McDermott, MD
Beth Israel Deaconess Medical Center

Brian Rini, MD
Vanderbilt University Medical Center

Previous standard-of-care treatment for aRCC

- Nephrectomy, if eligible
- Tyrosine kinase inhibitors (TKIs)
- mTOR inhibitors
- High-dose IL-2

Timeline of IO in RCC



Current immunotherapy approvals

Drug	Approved	Indication	Dose
High dose Interleukin-2	1992	Metastatic RCC	600,000 International Units/kg (0.037 mg/kg) IV q8hr infused over 15 minutes for a maximum 14 doses, THEN 9 days of rest, followed by a maximum of 14 more doses (1 course)
Interferon-a + bevacizumab	2009	Clear cell RCC	IFN 9 MIU s.c. three times a week + bev 10 mg/kg Q2W
Nivolumab	2015	Clear cell RCC refractory to prior VEGF targeted therapy	3mg/kg or 240mg IV Q2W or 480mg IV Q4W
Nivolumab +ipilimumab	2018	Clear cell RCC, treatment naïve	3mg/kg nivo plus 1mg/kg ipi Q3W x 4 doses then nivo maintenance at flat dosing
Pembrolizumab + axitinib	2019	Advanced RCC, Treatment naïve	200 mg pembro Q3W + 5 mg axitinib twice daily
Avelumab + axitinib	2019	Advanced RCC, Treatment naïve	800 mg avelumab Q2W + 5 mg axitinib twice daily

Key clinical questions

1. How should checkpoint inhibitors be integrated into the **first-line** treatment of advanced clear cell renal carcinoma (accRCC)?
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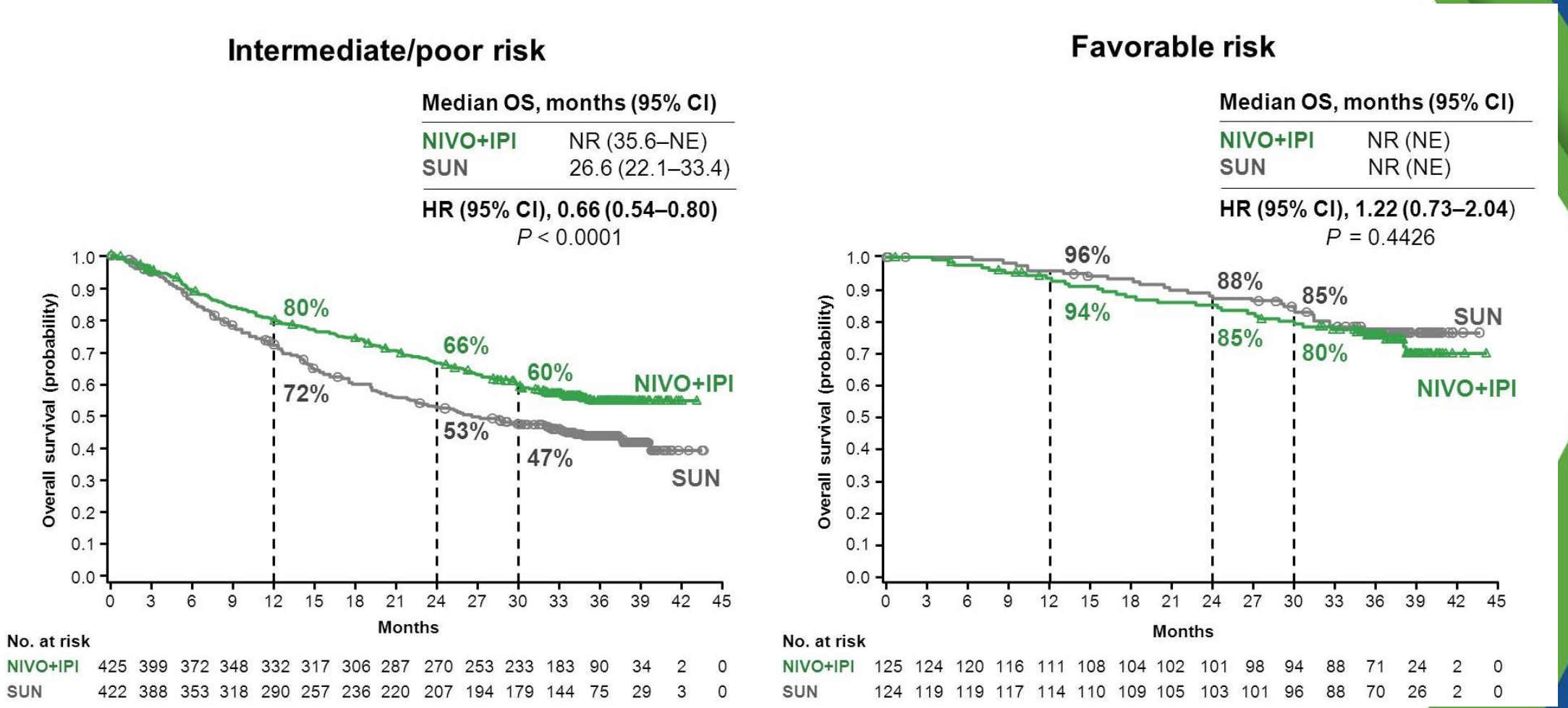
Summary of front-line phase 3 trials

	CheckMate 214	KEYNOTE-426	JAVELIN 101	IMmotion151
Intervention	Ipilimumab + Nivolumab	Pembrolizumab + Axitinib	Avelumab + Axitinib	Atezolizumab + Bevacizumab
Comparator	Sunitinib	Sunitinib	Sunitinib	Sunitinib
Primary Endpoint	OS, PFS, ORR in int/poor risk	OS, PFS	PFS, OS in PD-L1+	PFS in PD-L1+; OS
mPFS, months	9.7 vs 9.7	15.1 vs 11.1	13.8 vs 8.4	11.2 vs 8.4
ORR (ITT), %	41% vs 34%	59% vs 36%	51% vs 26%	37% vs 33%
12 month survival (ITT)	83% vs 77%	90% vs 78%	86% vs 83%	63% vs 60% (24-month)
IIT: Intent-to-Treat; PFS: progression-free survival; ORR: overall response rate; OS: overall survival				

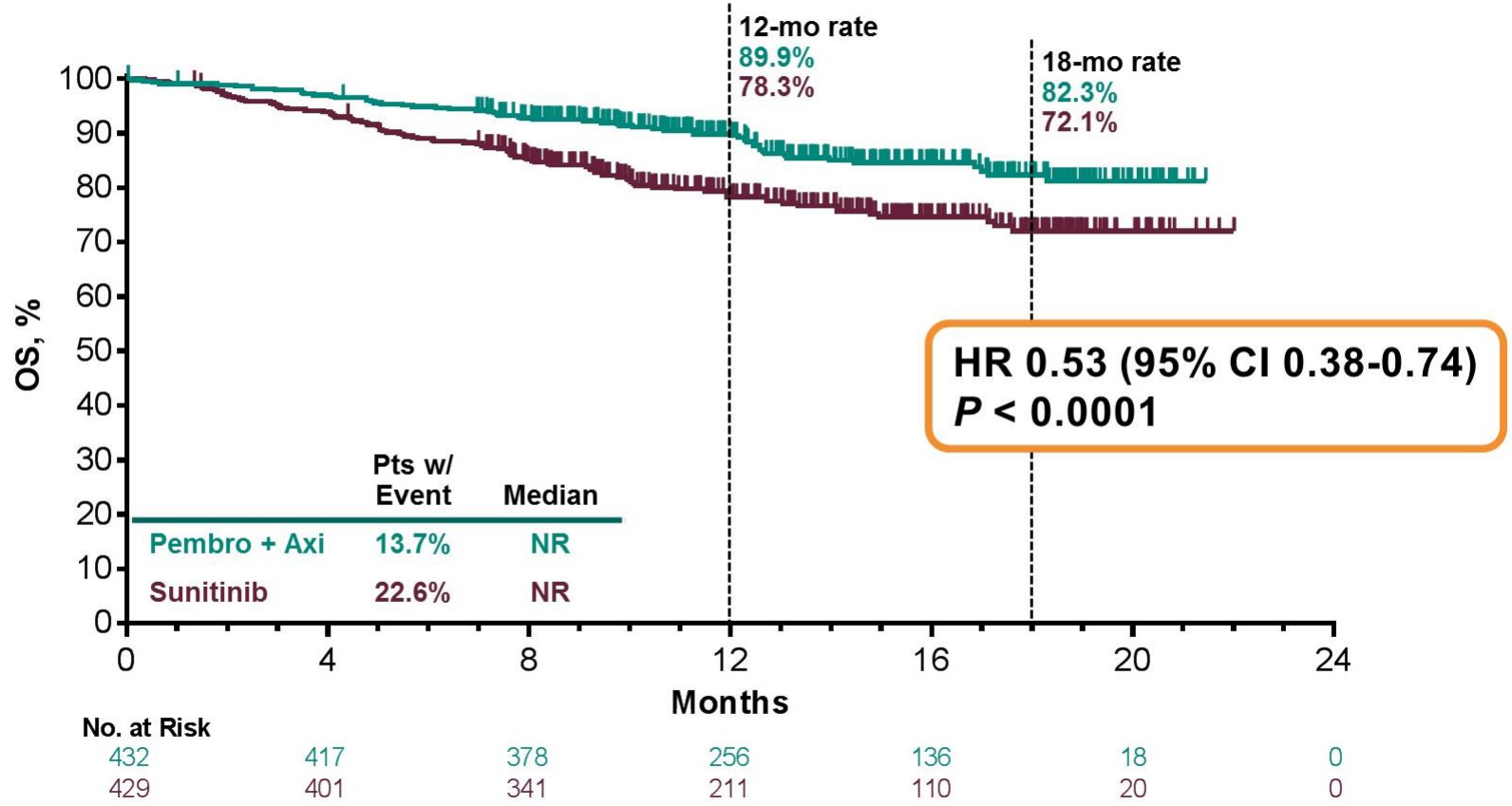
Tannir, ASCO GU 2019.
Rini, NEJM 2019.
Motzer, NEJM 2019.
Rini, Lancet 2019.

CheckMate 214



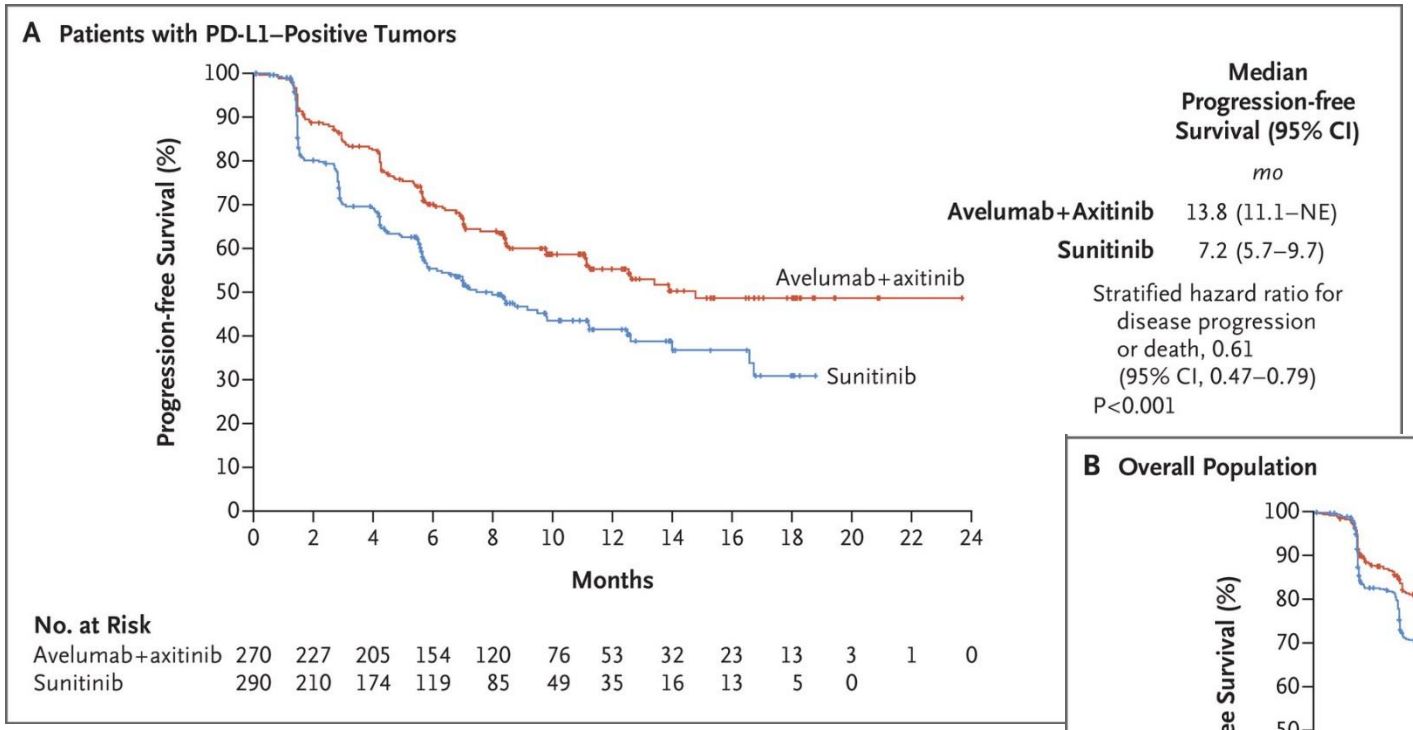
Tannir, ASCO GU 2019.

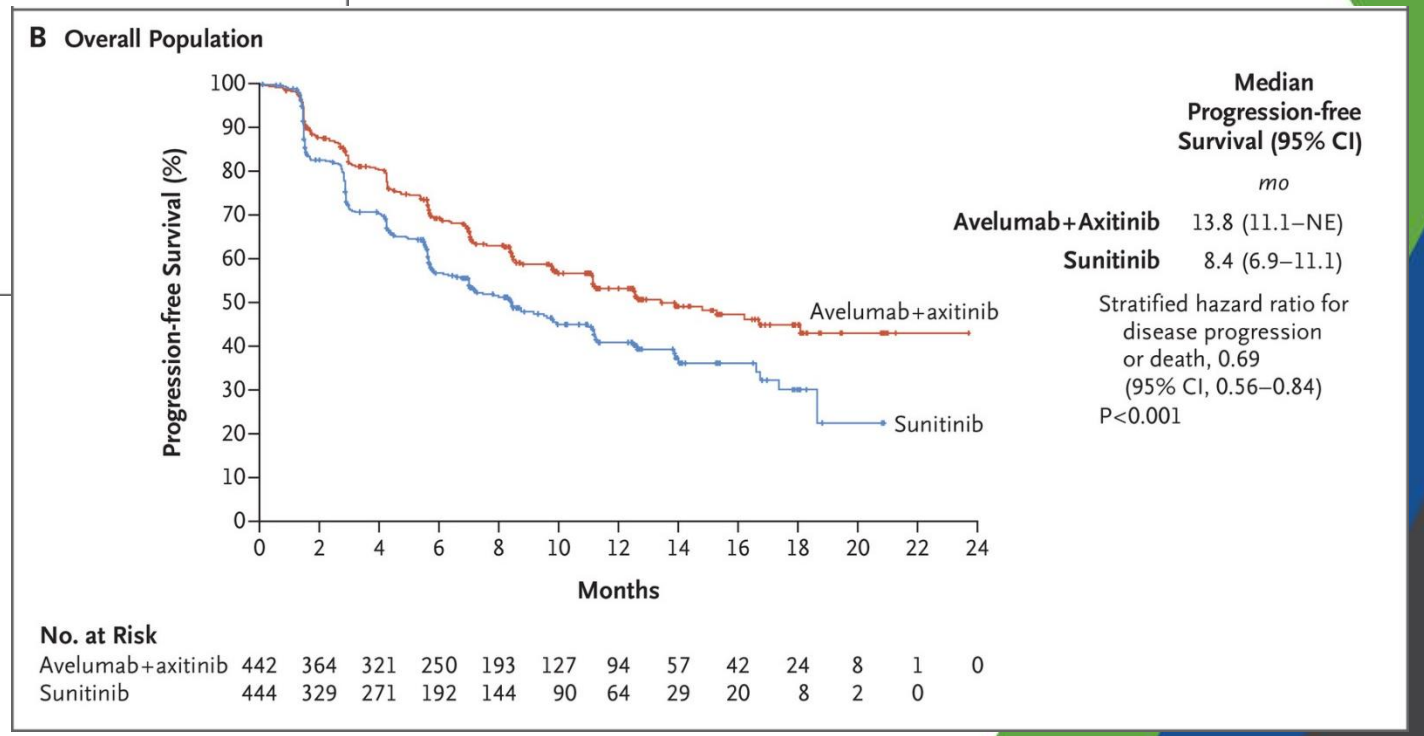
KEYNOTE-426



Rini, ASCO 2019

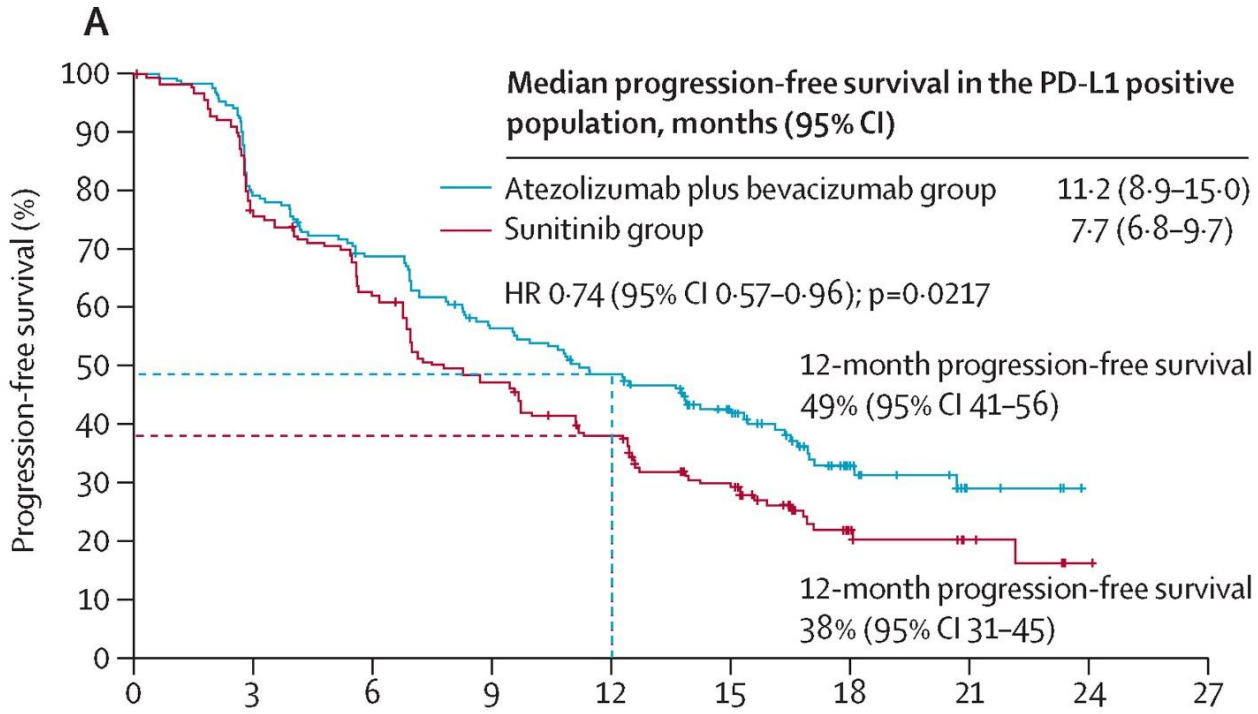
JAVELIN 101

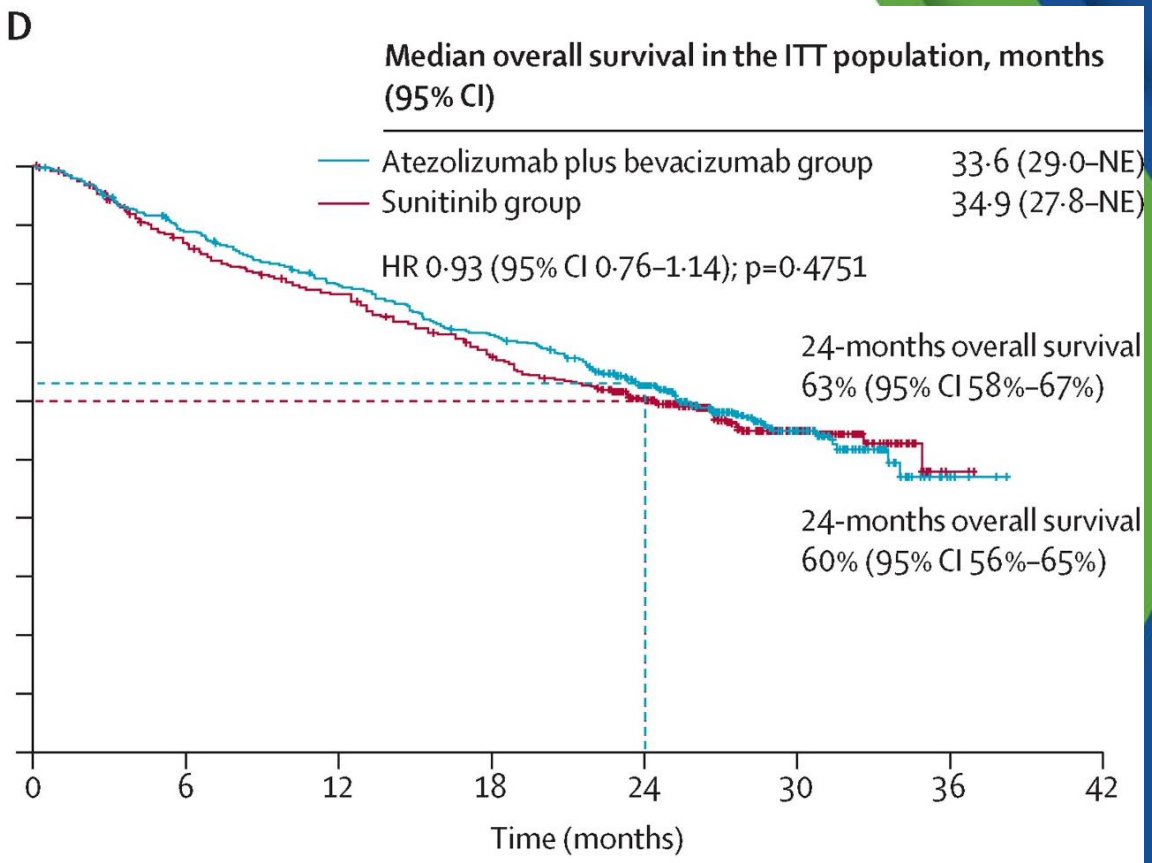




Motzer, NEJM 2019.

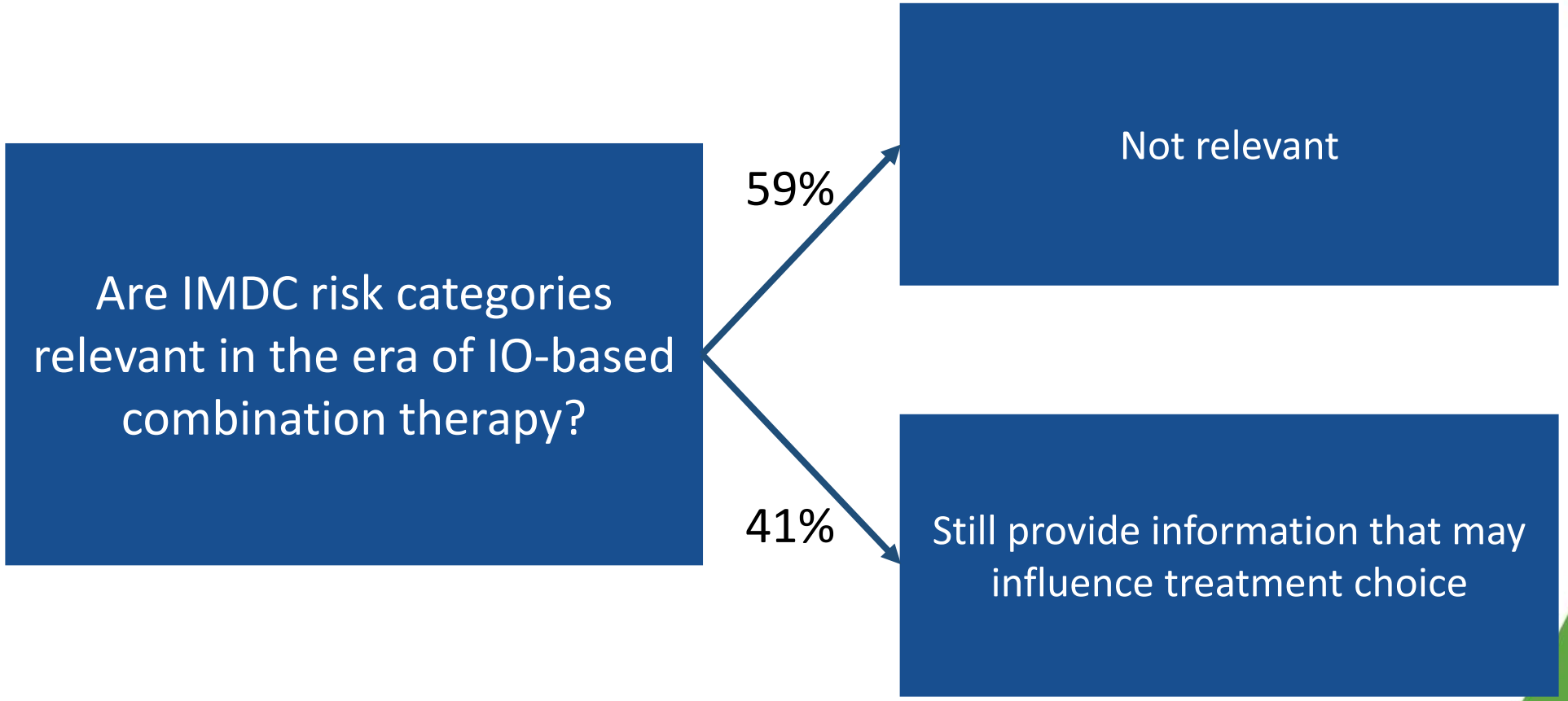
IMmotion151





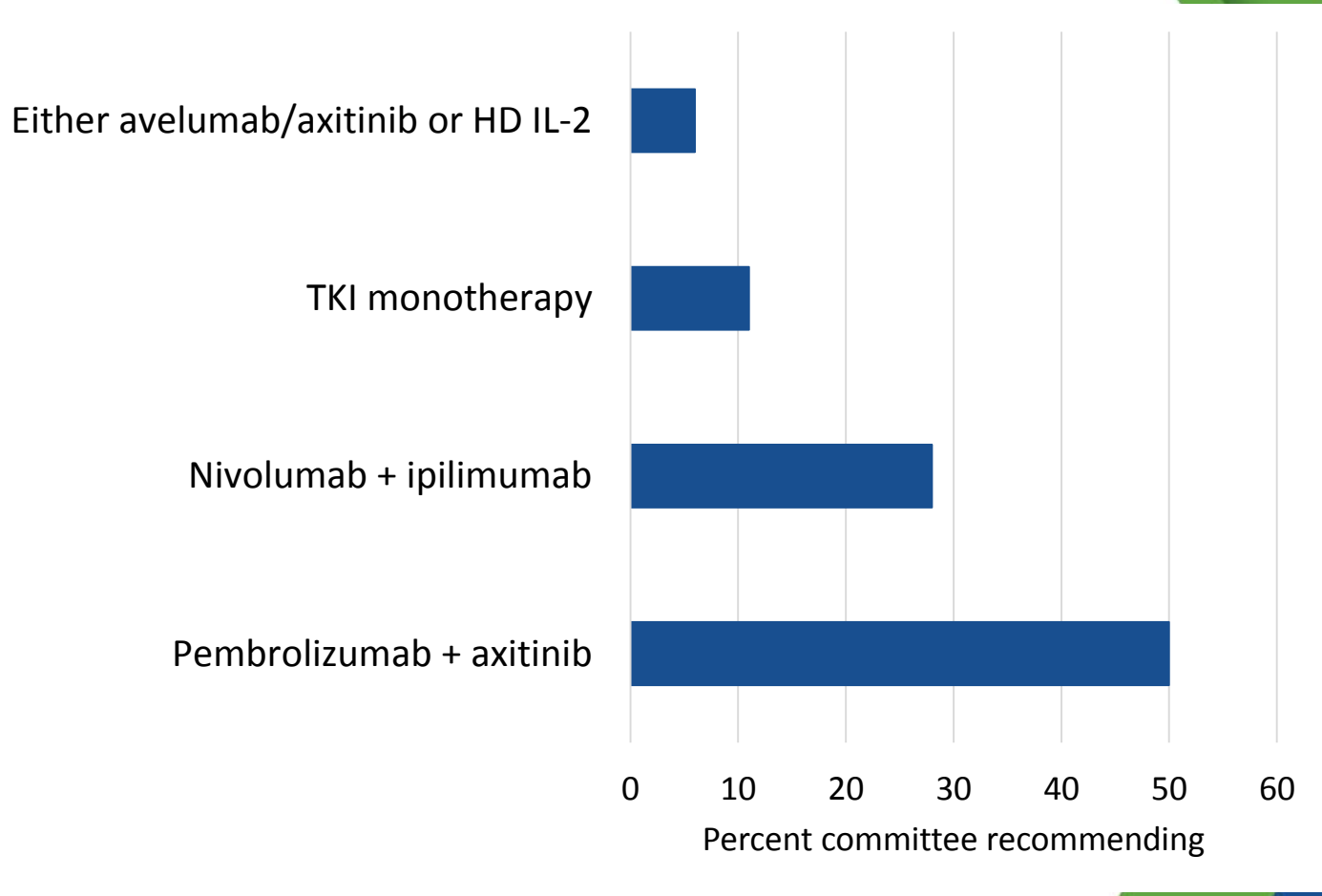
Rini, The Lancet 2019.

First-line treatment



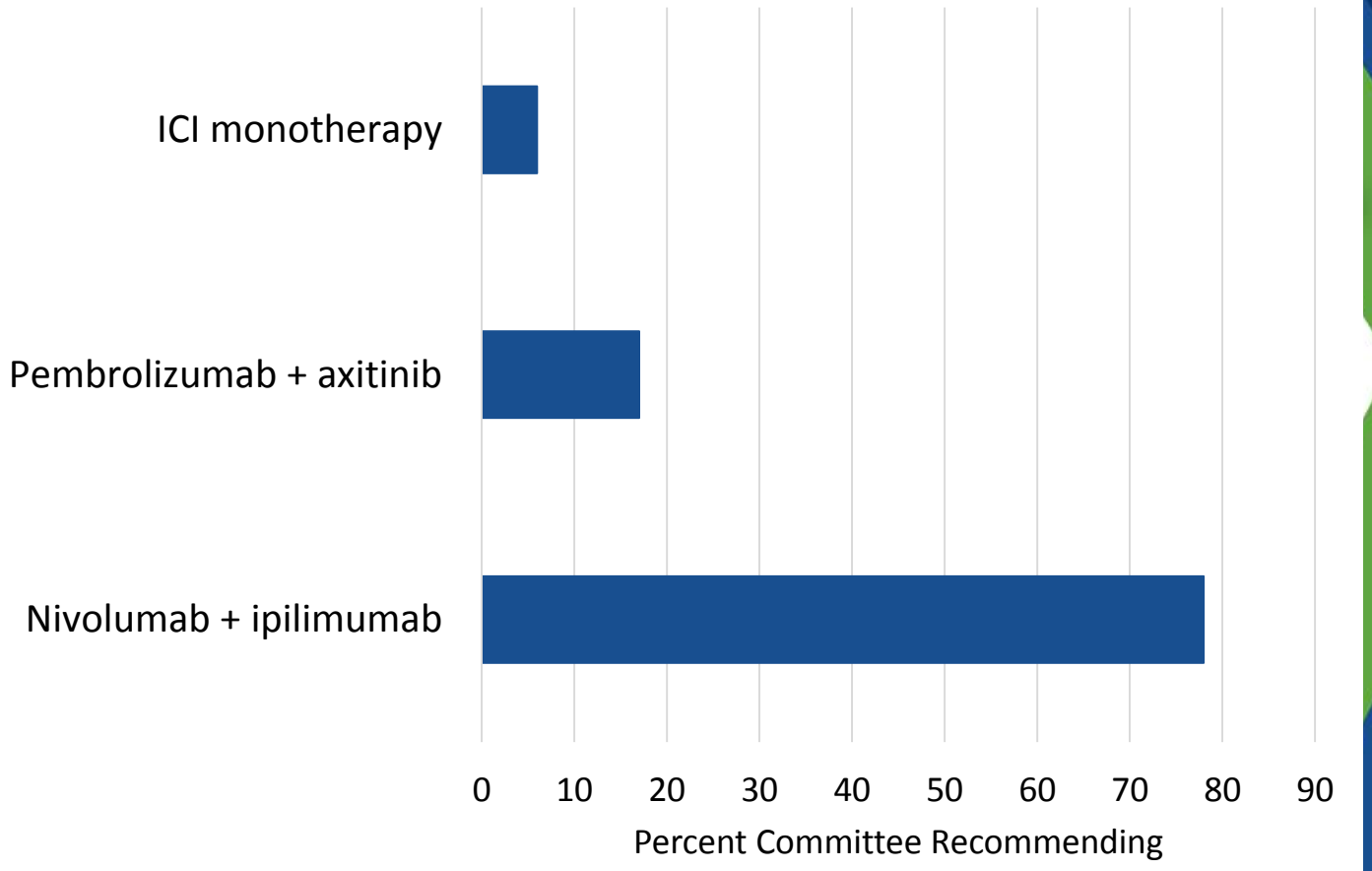
First-line treatment

Recommendations for:
Treatment naïve, ECOG 0, ccRCC patient with "favorable" risk per IMDC, who is determined to need systemic therapy and has no contraindication to receiving either an IO or an anti-VEGF therapy

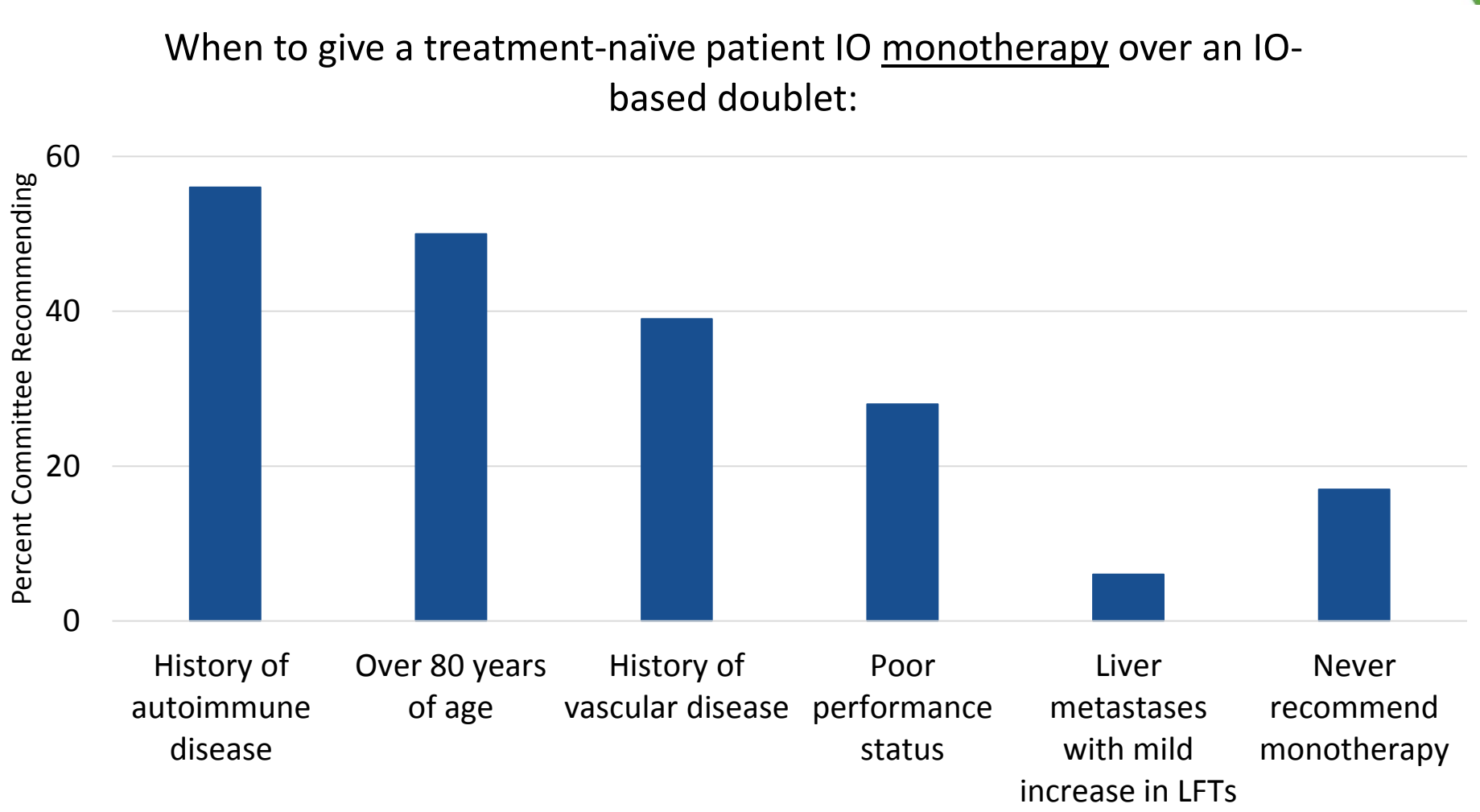


First-line treatment

Recommendations for:
Treatment naïve, ECOG 0 ccRCC patient with "intermediate/poor" risk per IMDC, who is determined to need systemic therapy and has no contraindication to receiving either an IO or an anti-VEGF therapy



First-line treatment



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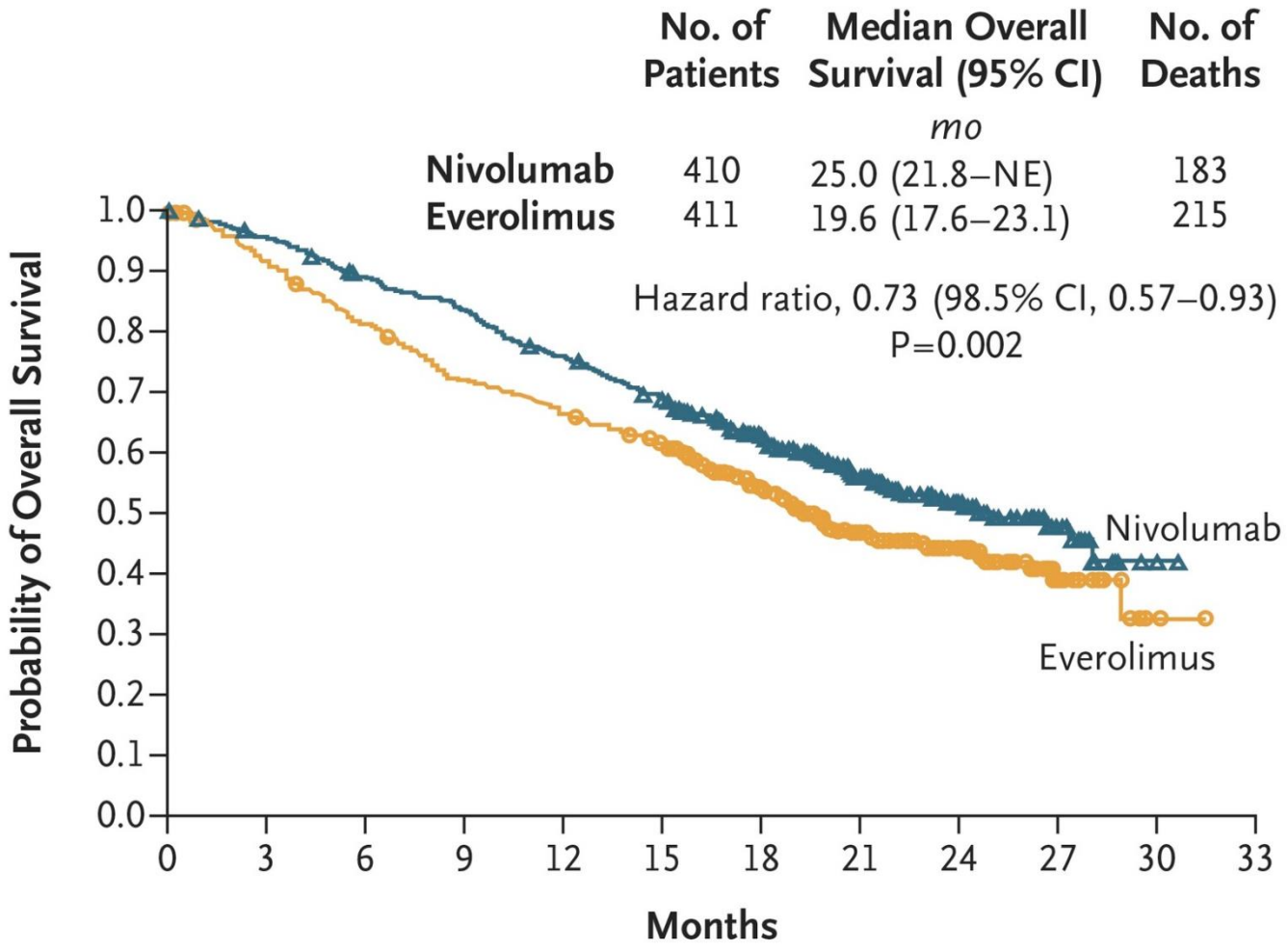
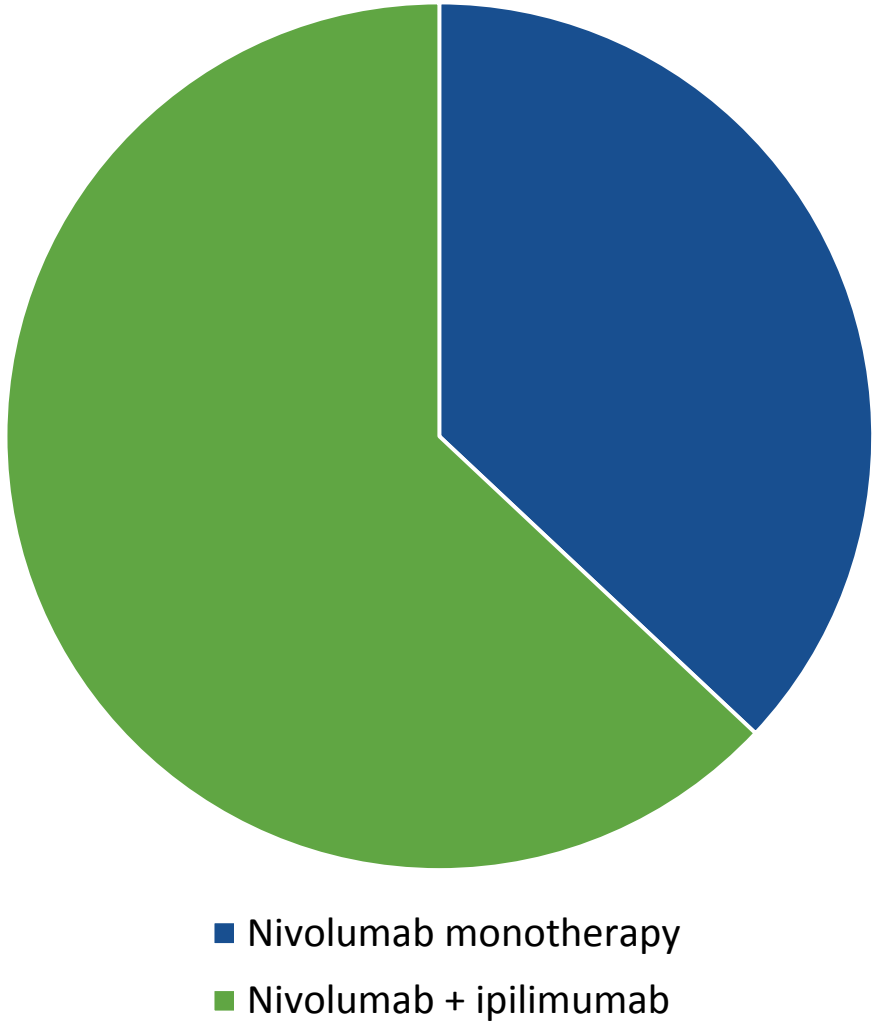
CheckMate 025



Motzer, NEJM 2015.

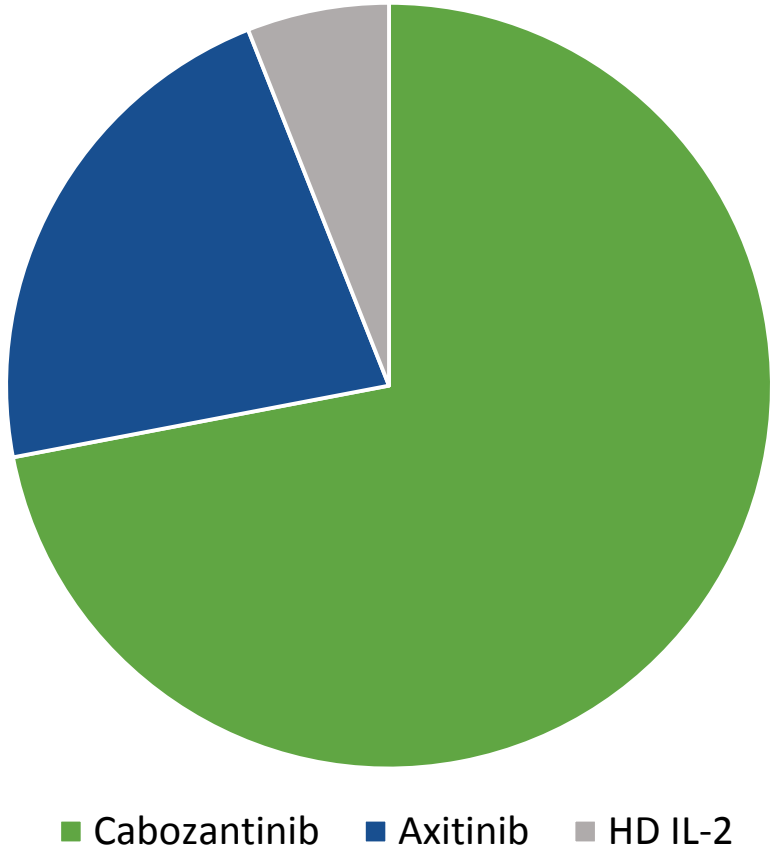
Second-line treatment

Recommendations for:
A previously treated, ECOG 0, clear cell mRCC patient with “favorable” risk whose tumors progressed on front-line therapy with sunitinib

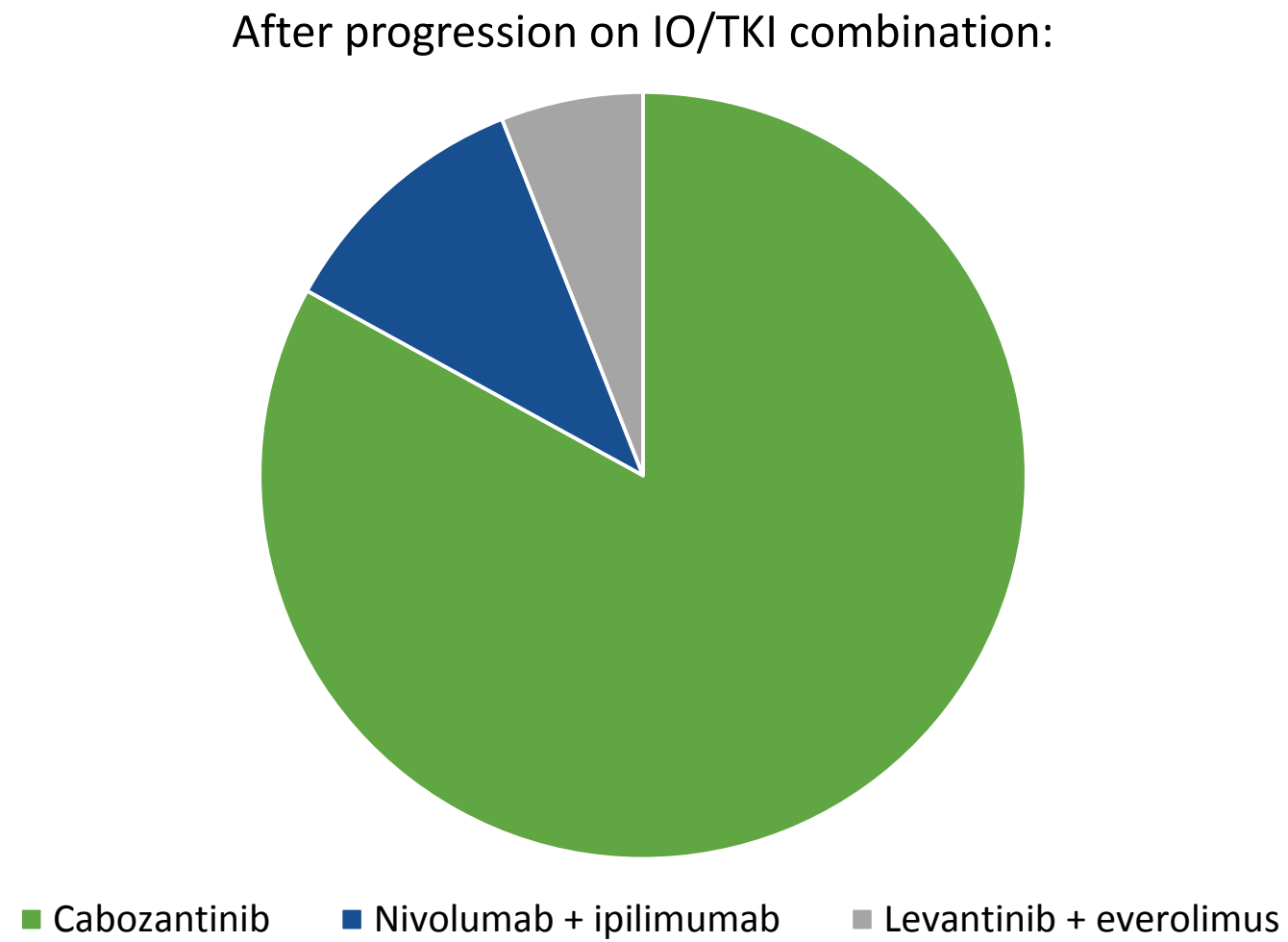


Second-line treatment

After progression on nivolumab/ipilimumab:



Second-line treatment



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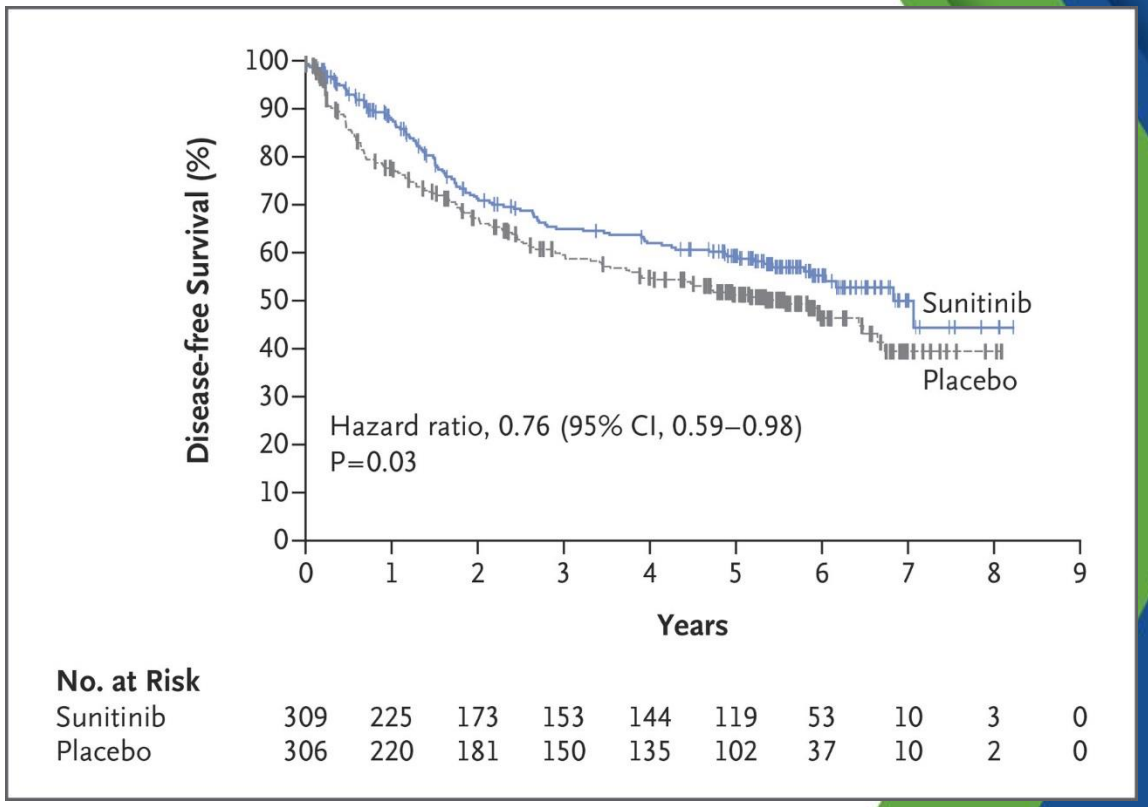
Sunitinib

- FDA-approved for RCC treatment post-nephrectomy in high-risk patients
- 50 mg/day
- Common AEs include diarrhea, palmar-plantar erythrodysesthesia, hypertension

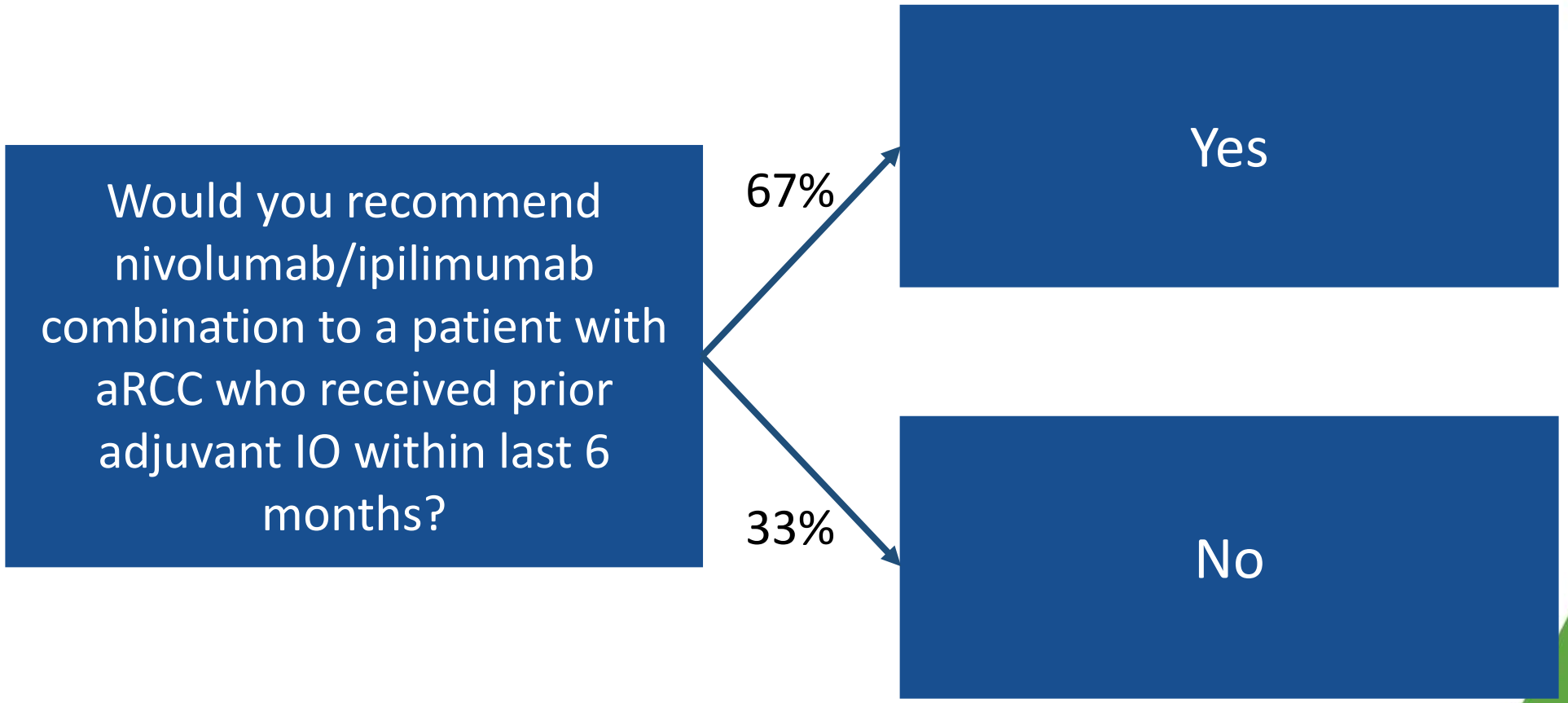


Ravaud, NEJM 2016.

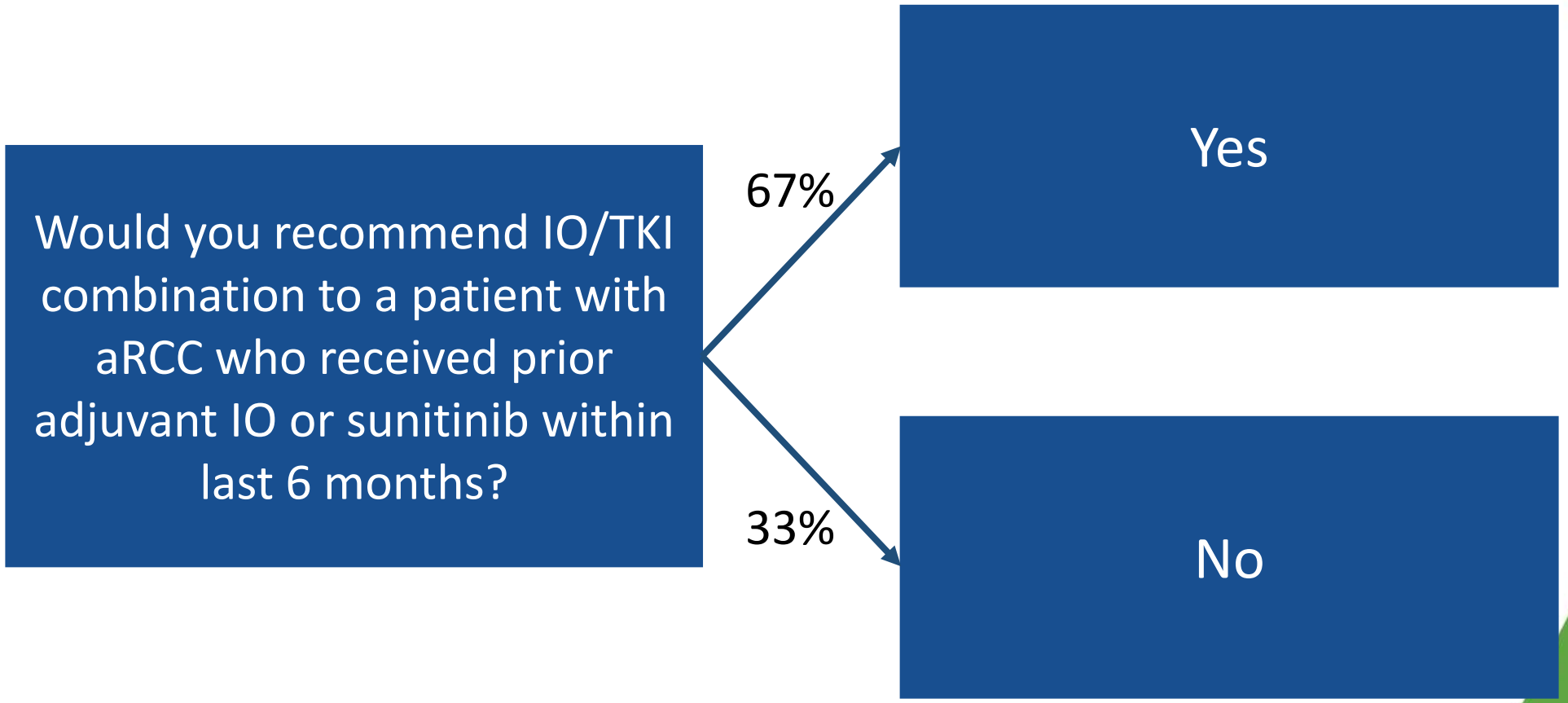
Adjuvant treatment

Trial	Treatment arms	Primary outcome	Current status
CheckMate 914	Nivolumab + Ipilimumab vs. placebo	DFS	Recruiting
IMmotion010	Atezolizumab vs. placebo	DFS	Active, not recruiting
KEYNOTE-564	Pembrolizumab vs. placebo	Safety, efficacy, DFS	Active, not recruiting
PROSPER RCC	Perioperative nivolumab vs. nephrectomy alone	RFS	Recruiting
RAMPART	Durvalumab vs. durvalumab + tremelimumab vs. active monitoring	DFS and OS	Recruiting

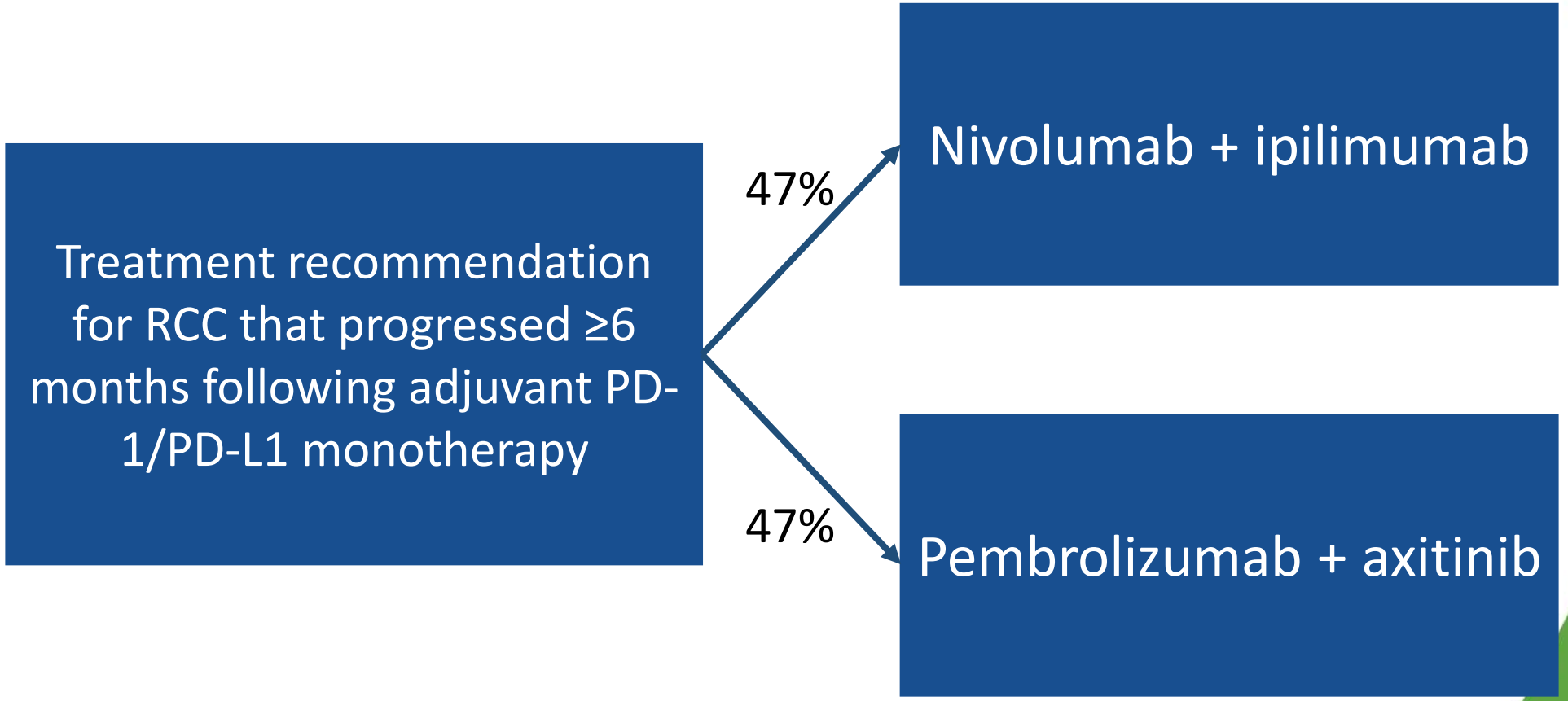
Adjuvant treatment



Adjuvant treatment

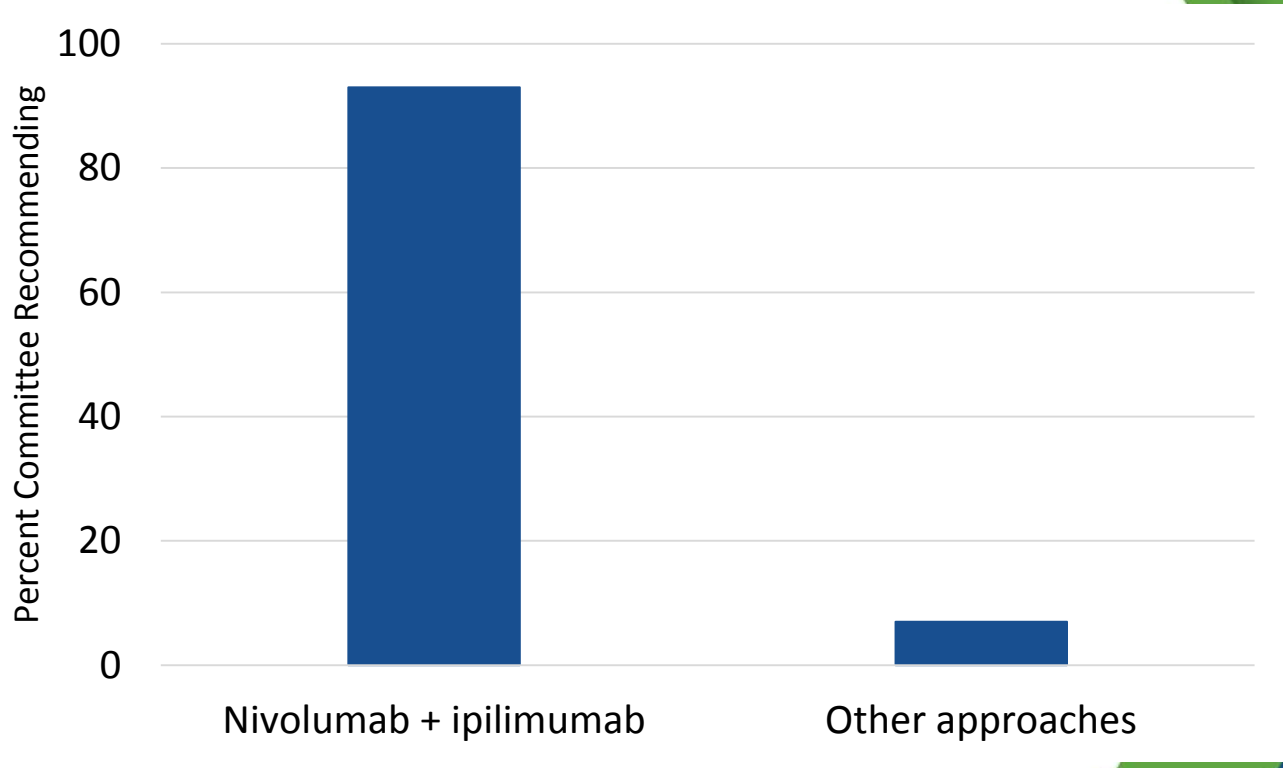


Adjuvant treatment



Adjuvant treatment

Recommendations for:
Patients whose disease has progressed >6 months following completion of adjuvant sunitinib



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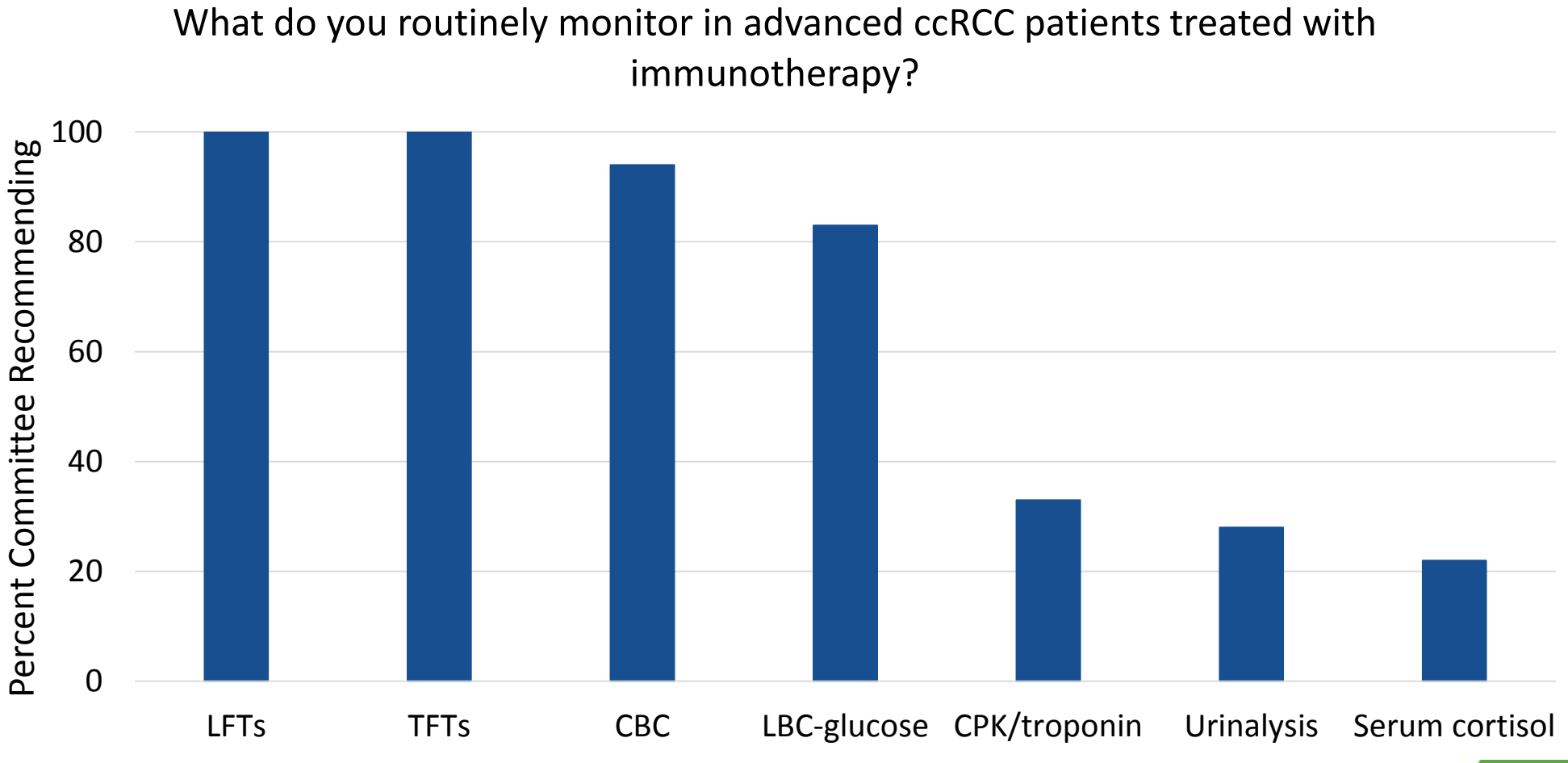
Evaluating response

Which endpoints are most important to you in evaluating a treatment for patients with advanced RCC?

Committee ranking:

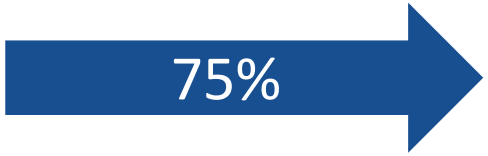
1. Landmark overall survival (OS)
2. Complete response (CR) rate
3. Median progression free survival (PFS)
4. Treatment free survival (TFS)
5. Overall response rate (ORR)
6. Disease control rate (DCR)
7. Quality of life
8. Cost effectiveness

Monitoring patients



Monitoring patients

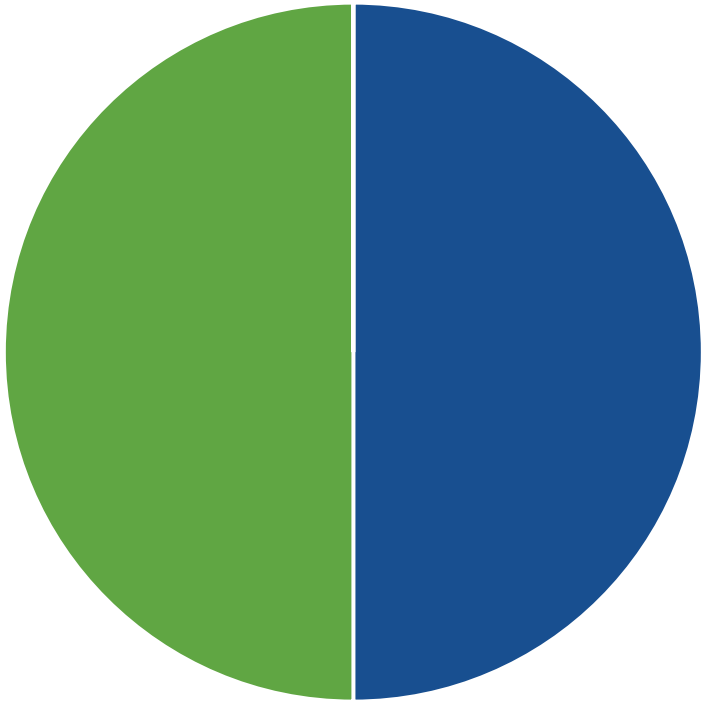
Recommendations for:
An aRCC patient on anti-PD-1 monotherapy (e.g. nivolumab) who experiences RECIST-defined PD (e.g. in maintenance phase of ipilimumab/nivolumab or on nivolumab monotherapy)



Repeat scans in 4-12 weeks and continue nivolumab if the patient is clinically well, until additional progression is documented.

Monitoring patients

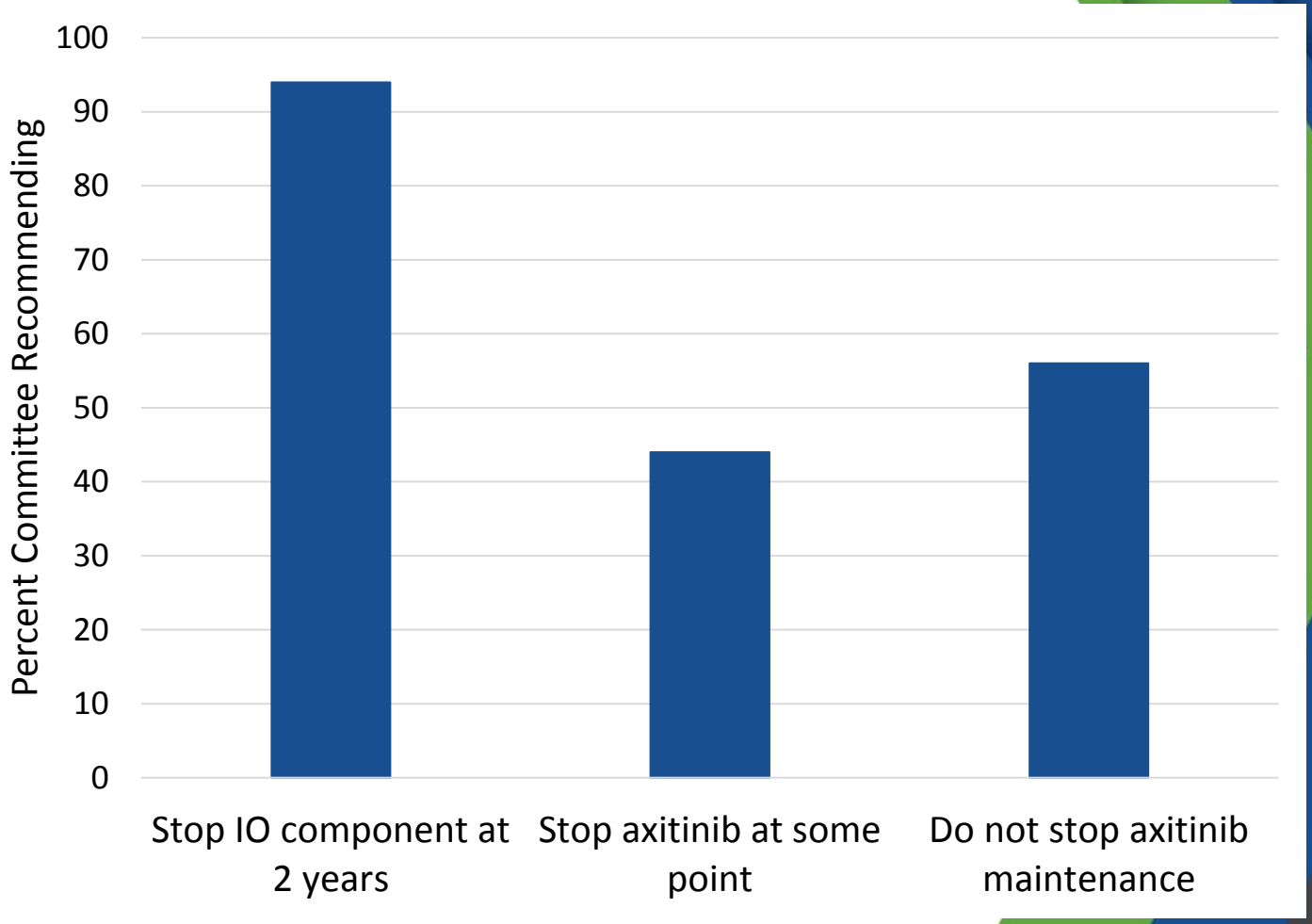
Recommendations for:
How long to continue therapy in a patient with a CR or near CR after ipilimumab plus nivolumab induction and 6-9 months of maintenance nivolumab therapy



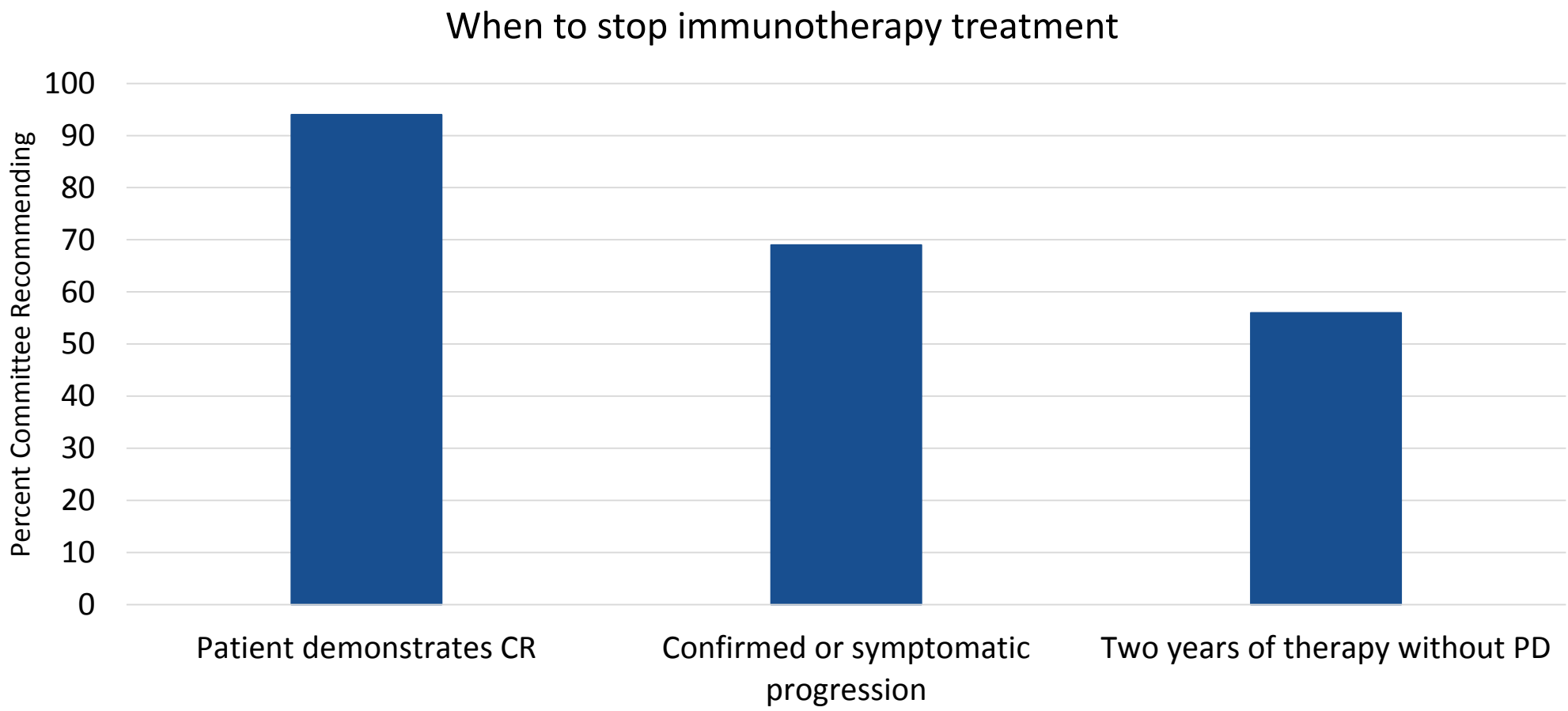
- Stop therapy at this point
- Treat patient for a given number of cycles after best response
- Treat indefinitely

Monitoring patients

Recommendations for:
In the absence of limiting toxicity, patient receives axitinib/IO combination therapy. At month 9 they have a CR/near CR/over 80% response.



Monitoring patients



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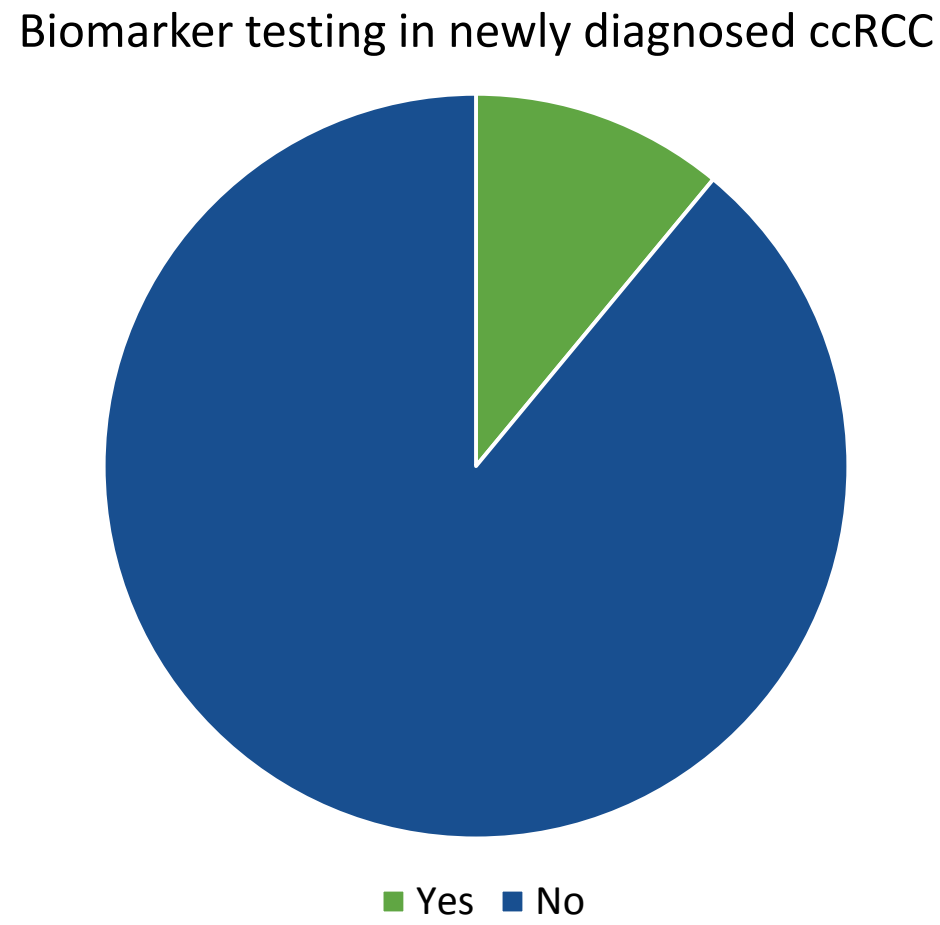
Biomarkers in aRCC

Study	Treatment arms	OS by PD-L1 status
CheckMate 025	Nivolumab vs everolimus	<1%: 27.4 vs 21.2 mo ≥1%: 21.8 vs 18.8 mo
CheckMate 214	Nivolumab/ipilimumab vs sunitinib	<1%: 80% vs 75% (@ 12 mo) ≥1%: 86% vs 66% (@ 12 mo)
KEYNOTE-426	Pembrolizumab/axitinib vs sunitinib	<1%: HR=0.59 ≥1%: HR=0.54
IMmotion151	Atezolizumab/bevacizumab vs sunitinib	≥1%: HR=0.68

The majority of the committee does not utilize PD-L1 testing in patients before immunotherapy, as the data is not conclusive.

Biomarkers in aRCC

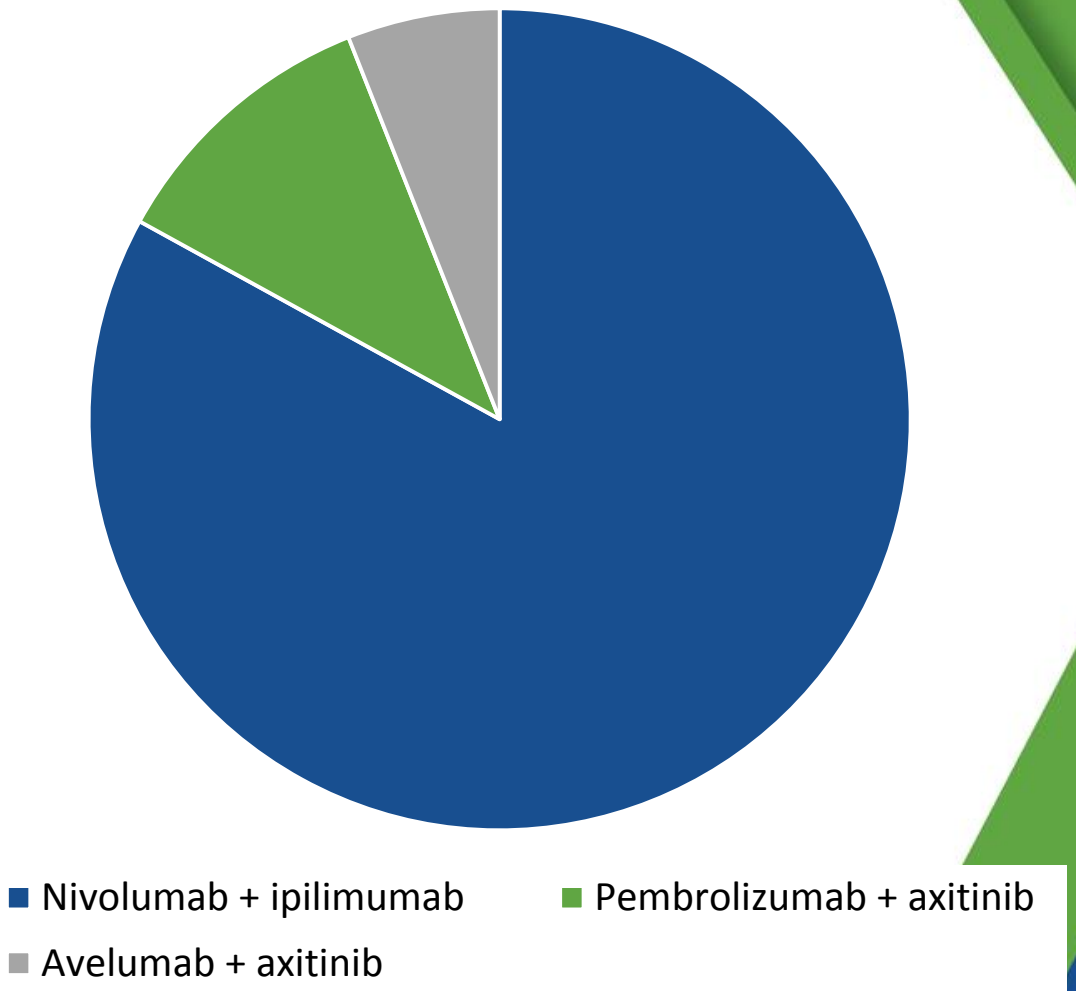


Studies in sarcomatoid histology

Study	Treatment arms	Overall Survival
CheckMate 214	Nivolumab + ipilimumab vs sunitinib	Median: 31.2 vs 13.6 months
KEYNOTE-426	Pembrolizumab + axitinib vs sunitinib	12-month: 83.4% vs 79.5%
JAVELIN RENAL 101	Avelumab + axitinib vs sunitinib	12-month: 83% vs 67%
IMmotion151	Atezolizumab + bevacizumab vs sunitinib	Median: 21.7 vs 15.4 months

Sarcomatoid RCC

Recommendations for:
First-line treatment for patients with sarcomatoid RCC irrespective of IMDC risk factors



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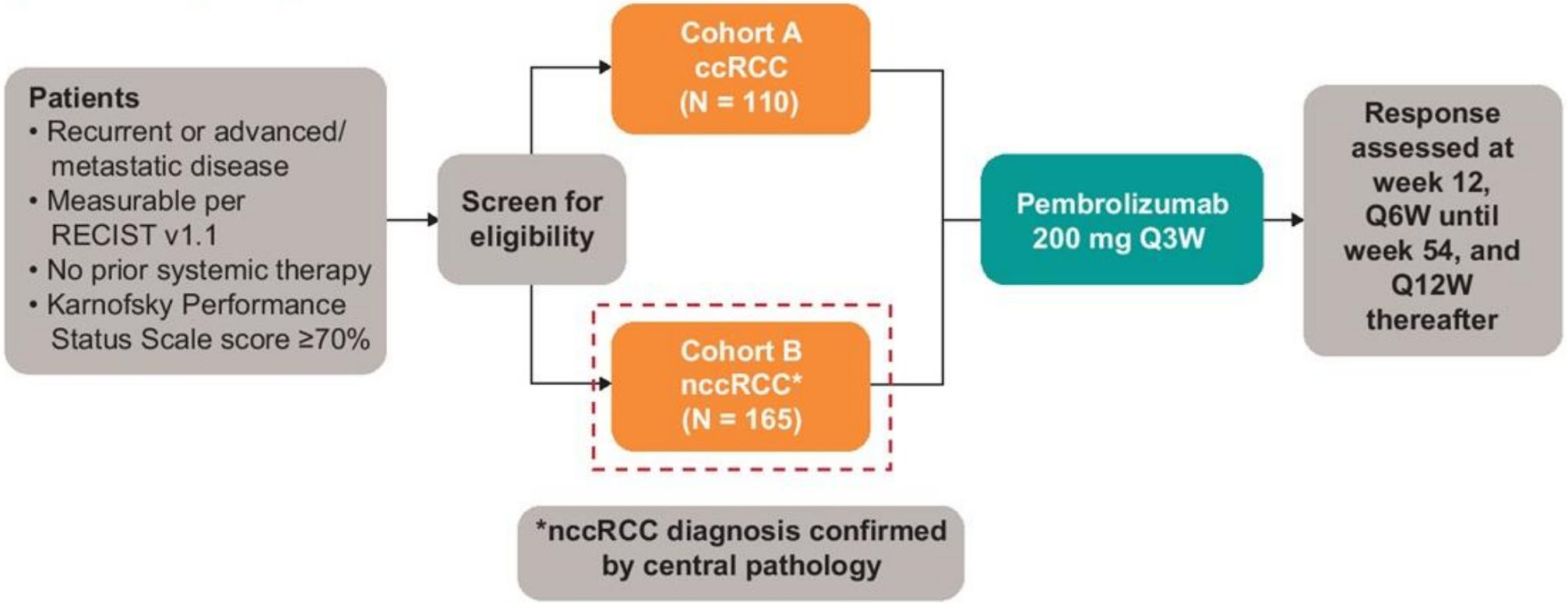
KEYNOTE-427 cohort B

Figure 1. Study Design

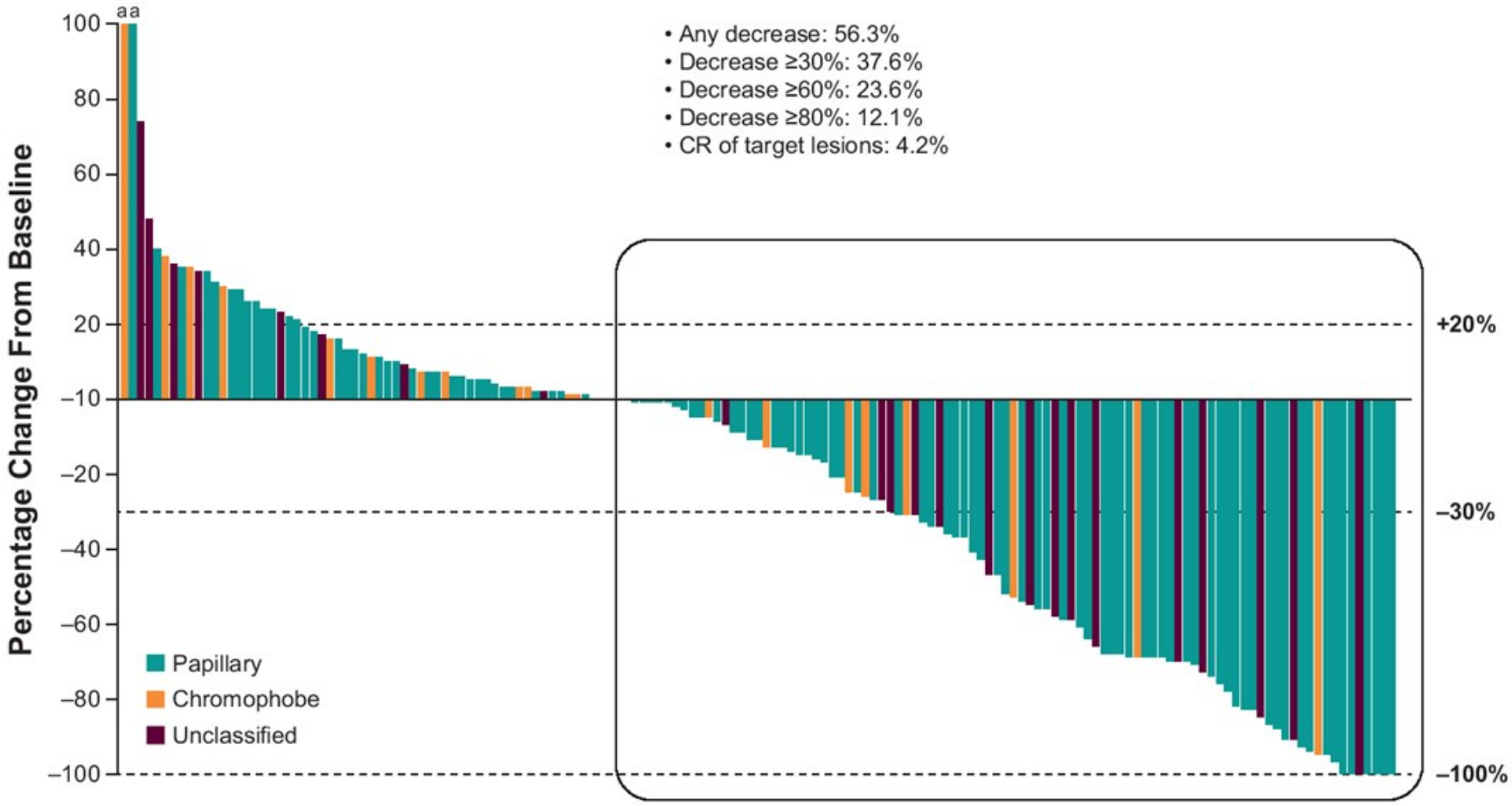


ccRCC, clear cell renal cell carcinoma; nccRCC, non–clear cell renal cell carcinoma; Q3W, every 3 weeks; Q6W, every 6 weeks; Q12W, every 12 weeks.

Lee, ASCO 2019.

KEYNOTE-427 cohort B

Figure 3. Maximum Change From Baseline in Target Lesions by BICR



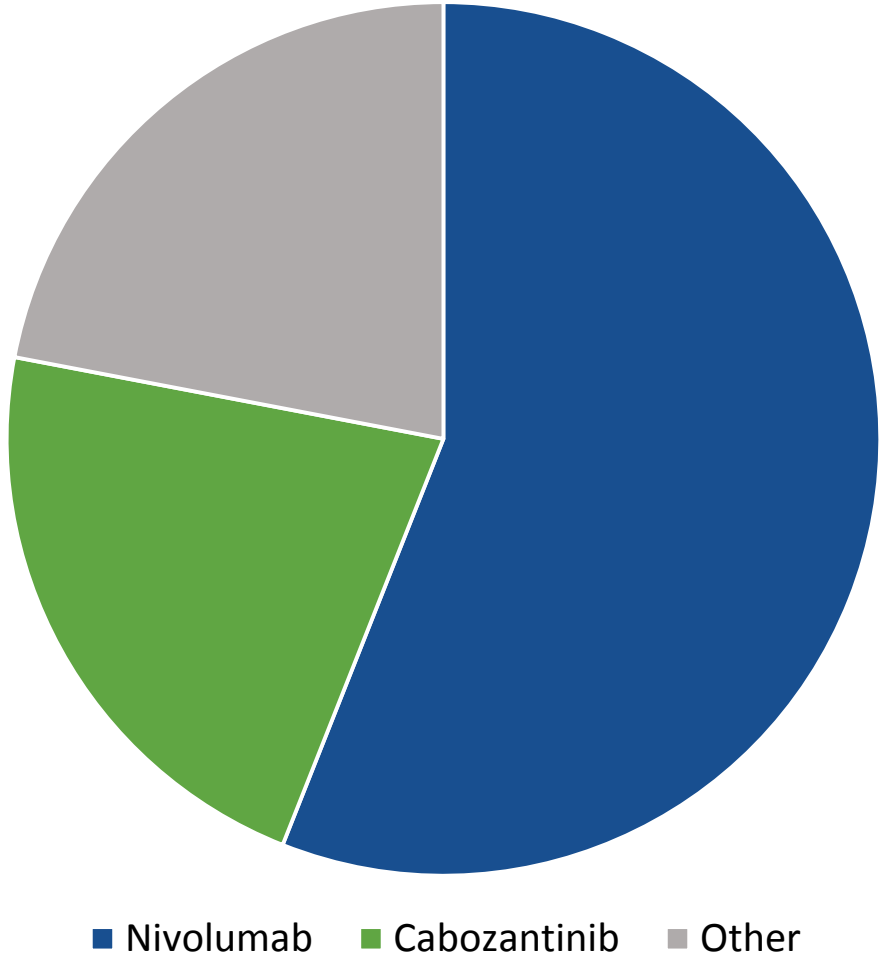
Lee, ASCO 2019.

Non-clear cell pathology

- Papillary or unclassified RCC:
  - Single-agent anti-PD-1
  - Nivolumab/ipilimumab possibly for unclassified
- Chromophobe RCC:
  - IO-based monotherapy
  - TKI

Non-clear cell pathology

Recommendations for:
Patient with non-clear cell RCC whose disease progressed on frontline VEGFR TKI



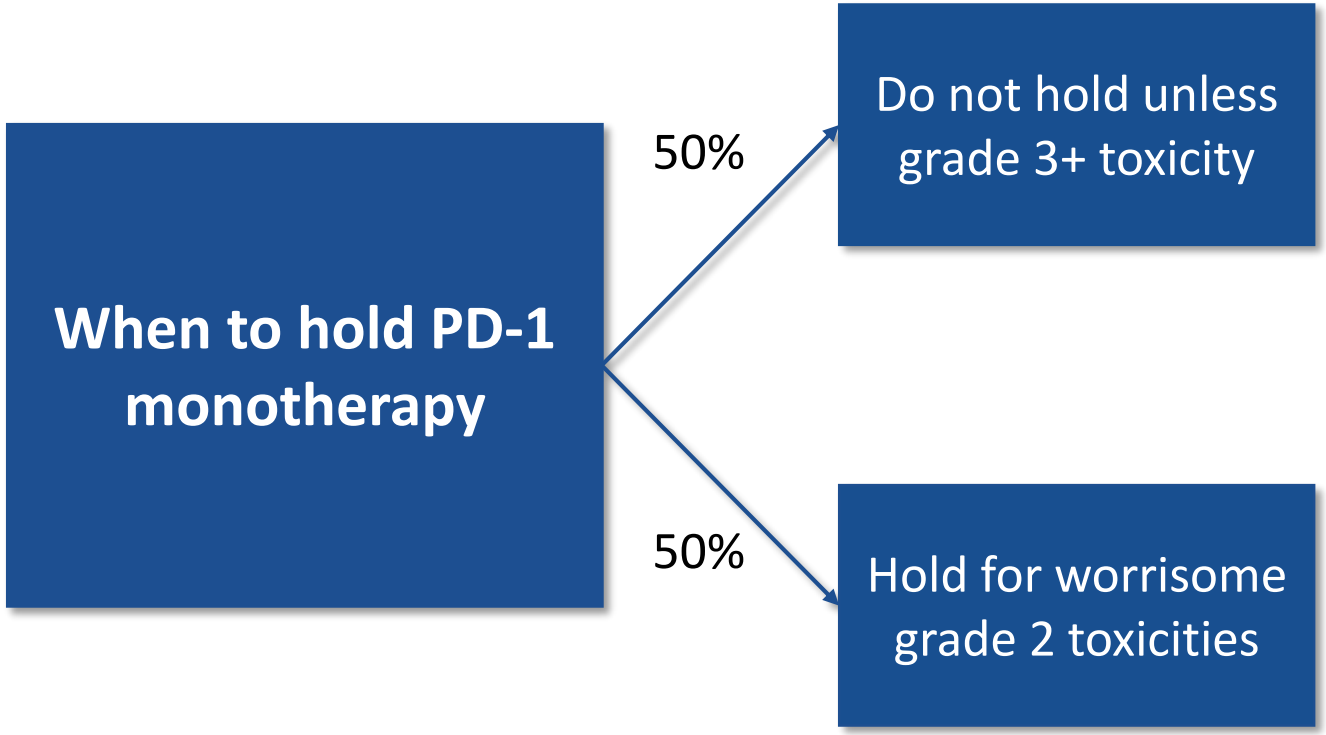
Key clinical questions

1. How should checkpoint inhibitors be integrated into the **first-line** treatment of advanced clear cell renal carcinoma (accRCC)?
2. How should checkpoint inhibitors be integrated into treatment of **refractory** accRCC?
3. How should **adjuvant therapy** and related failures be managed within an IO-related treatment paradigm for patients with accRCC?
4. How should **treatment response** to immunotherapy be evaluated, monitored and managed in patients with accRCC?
5. What is the role of **biomarker** testing in patients with aRCC?
6. What is the role of immunotherapy in **non-clear cell** pathology?
7. How should immune-related **adverse events** be recognized and managed in patients with accRCC?
8. Are there populations of patients with accRCC who **should not receive immunotherapy**?

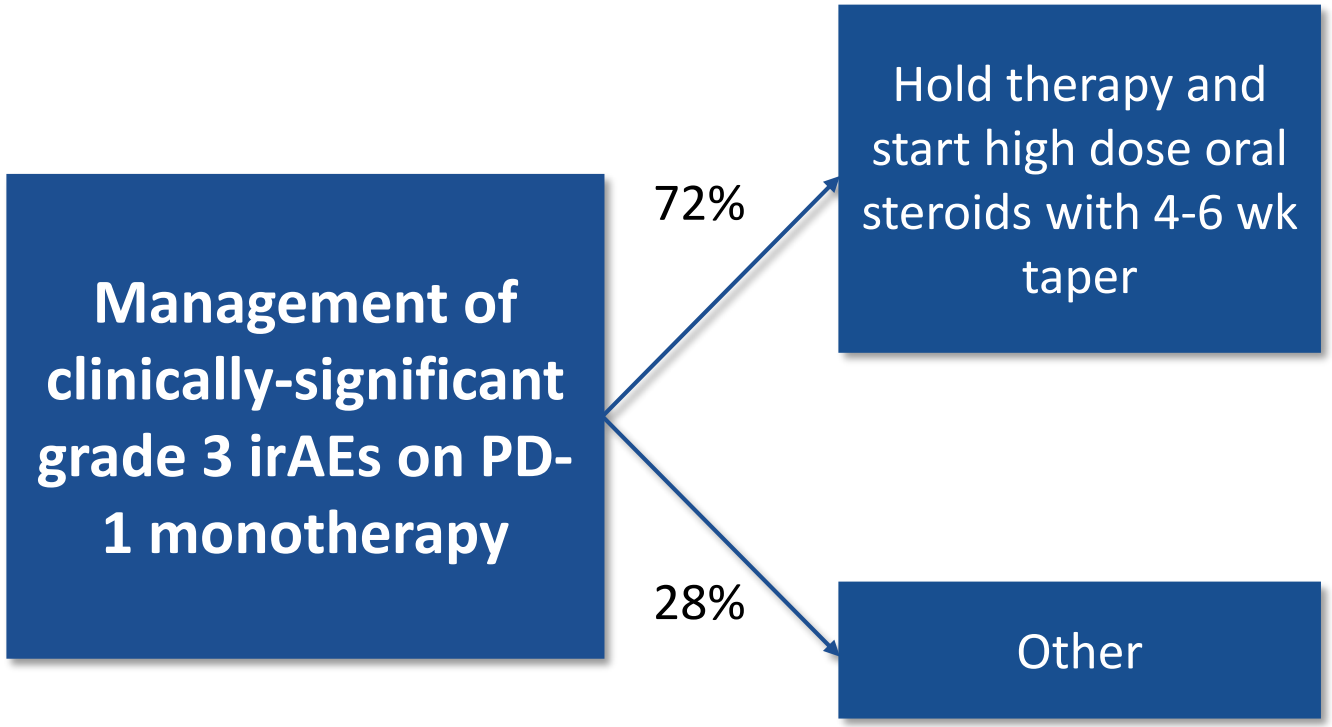
Adverse events in accRCC

	CheckMate 214	KEYNOTE-426	Javelin RENAL 101	IMmotion151	CheckMate 025
Any TRAE	93%	98.4%	95.4%	91%	79%
Grade 3-4 TRAE	46%	63%	56.7%	40%	19%
TRAE leading to discontinuation of both drugs	22%	10.7%	7.6%	5%	8%
Treatment-related deaths	1.5%	0.9%	0.7%	1.1%	0%
Most common TRAE	Fatigue (37%)	Diarrhea (54.3%)	Diarrhea (62.2%)		Fatigue (33%)
Most common grade 3-4 TRAE	Increased lipase (10%)	Hypertension (22.1%)	Hypertension (25.6%)	Hypertension (14%)	Fatigue (2%)

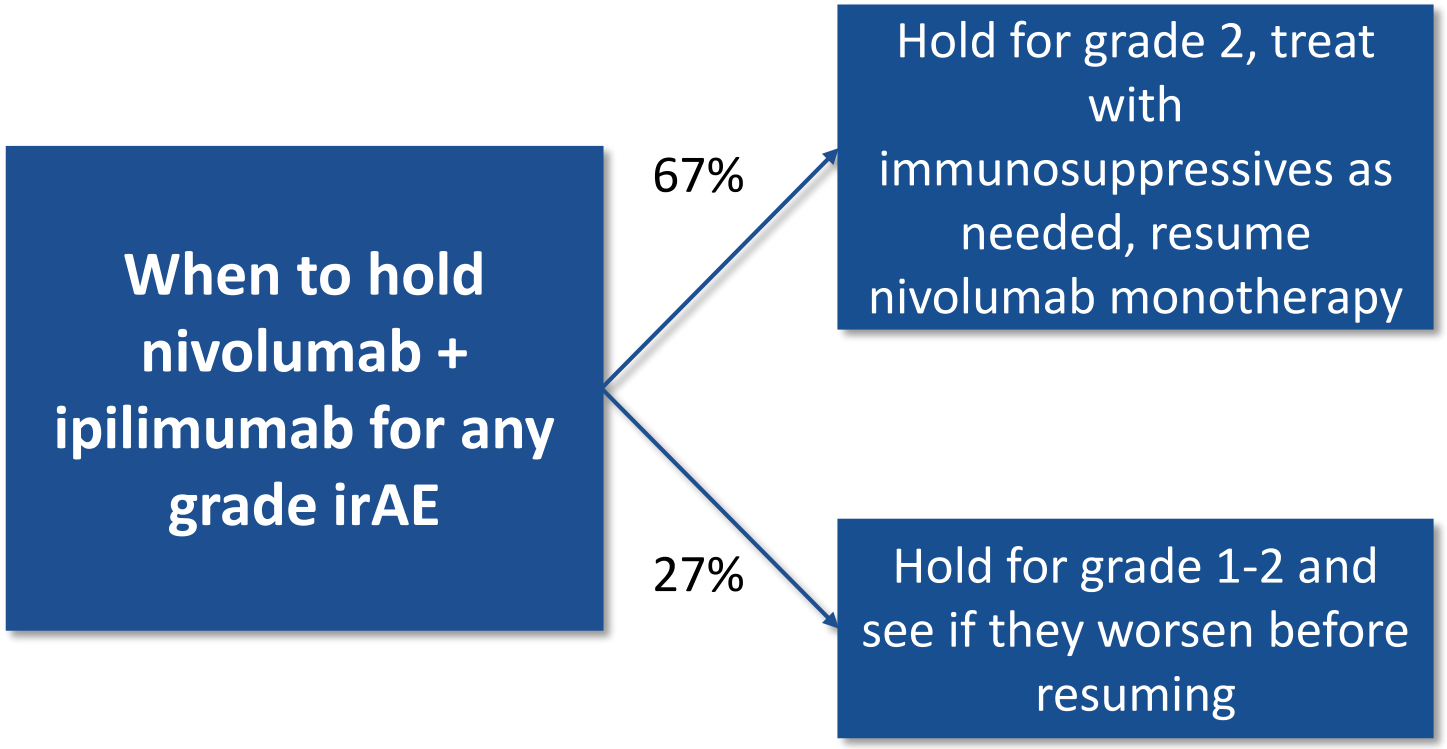
Adverse events in aRCC



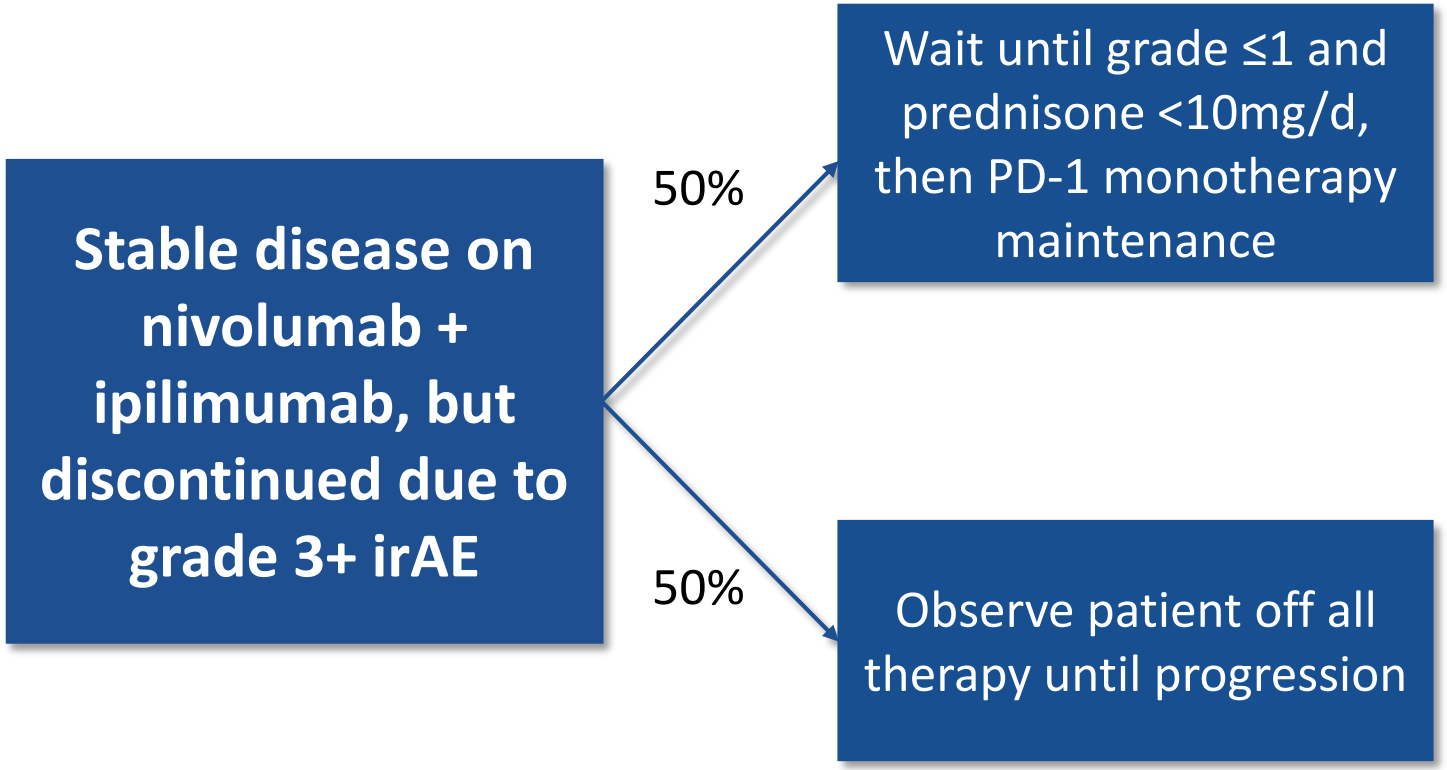
Adverse events in aRCC



Adverse events in aRCC

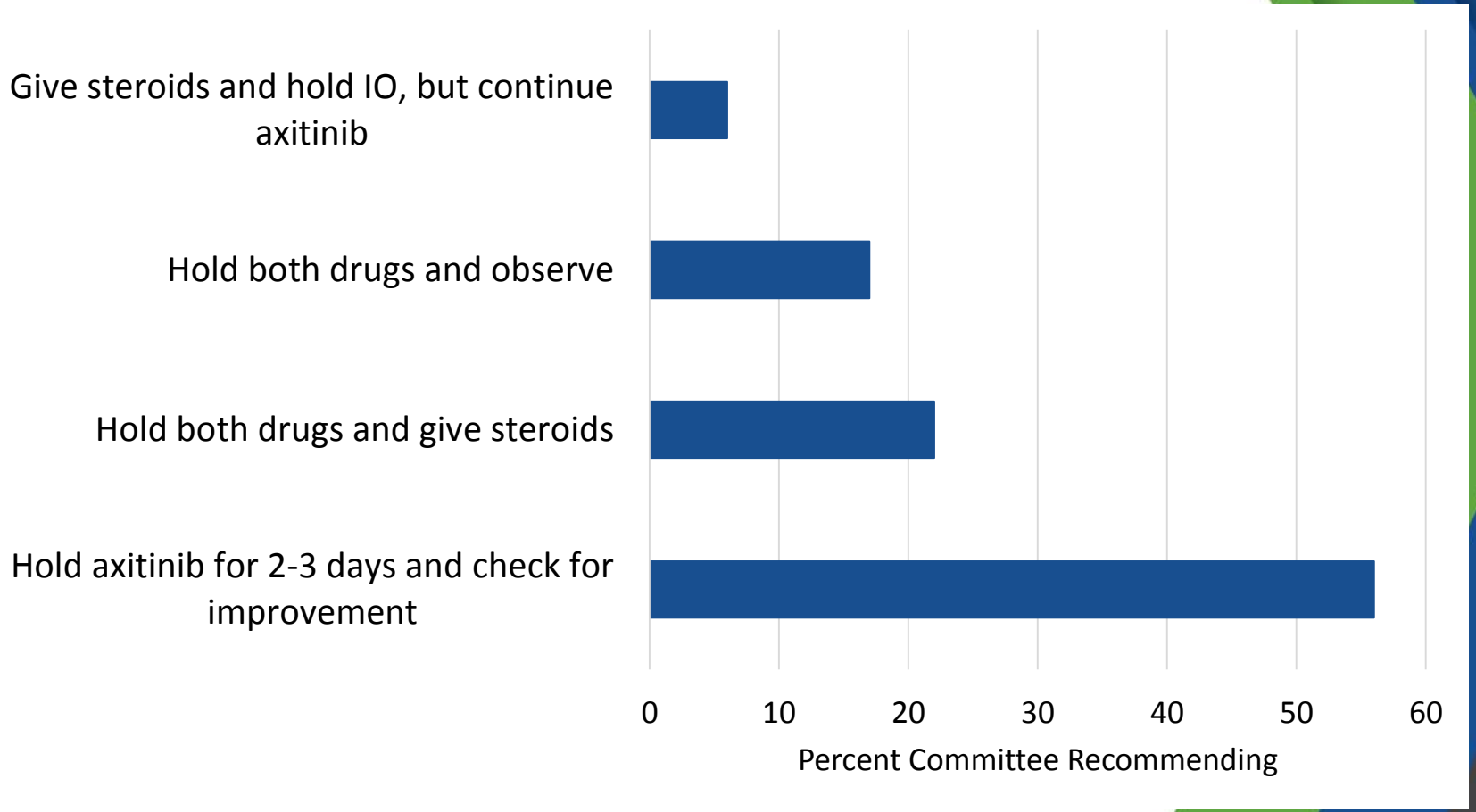


Adverse events in aRCC

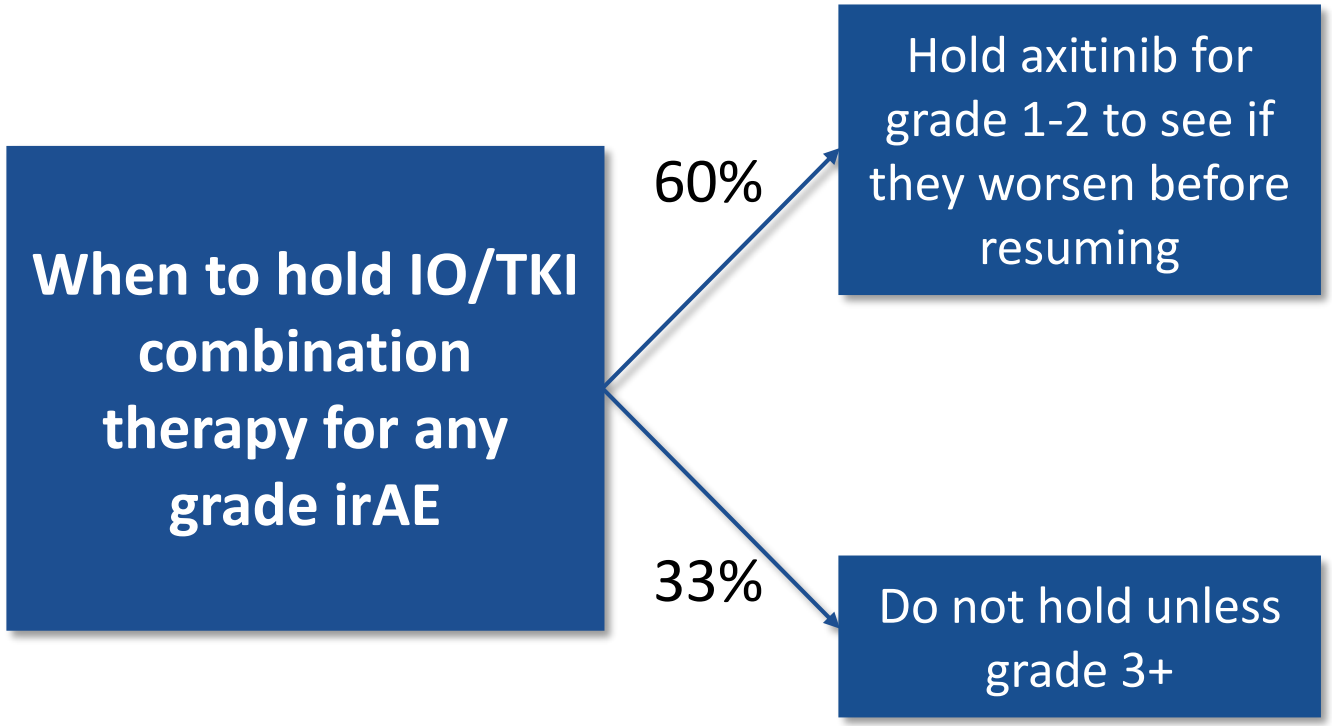


Adverse events in aRCC

When to hold IO/TKI combination therapy due to grade 3 toxicity that could result from either drug



Adverse events in aRCC



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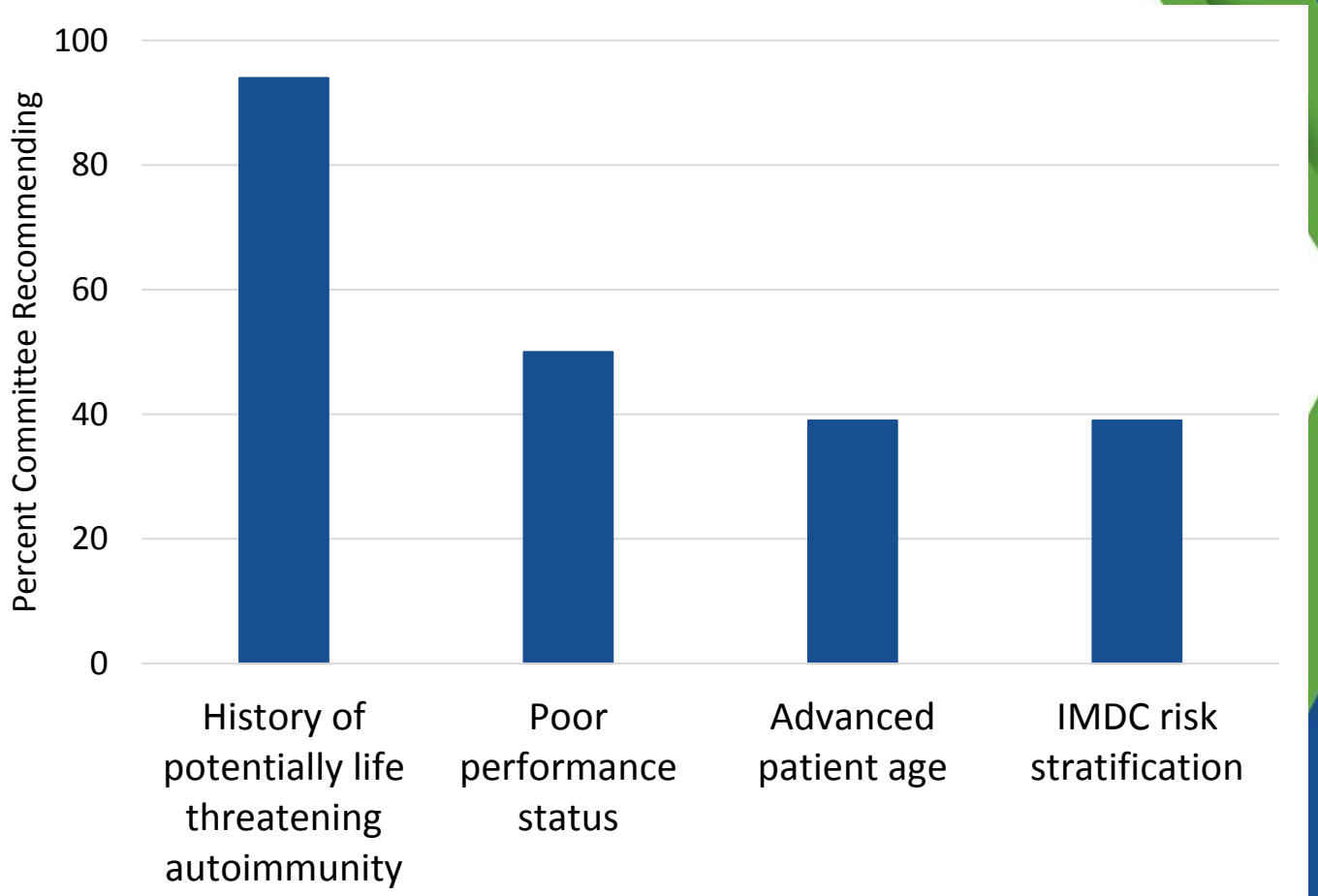
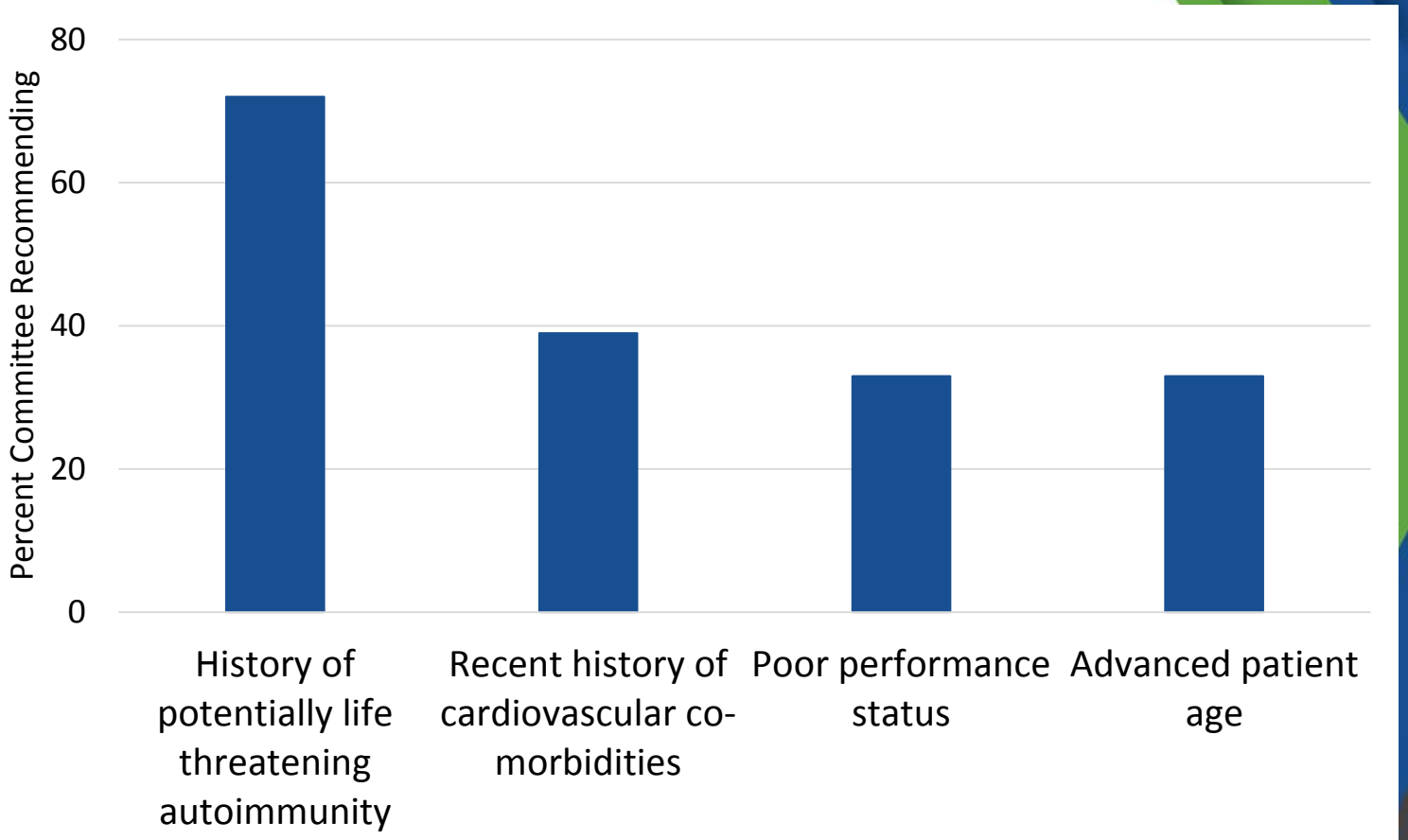
Excluded patient populations

Recommendations for:
The general factors to consider when determining NOT to give nivolumab/ipilimumab combination therapy in patients with aRCC



Excluded patient populations

Recommendations for:
The general factors to consider when determining NOT to give IO/TKI combination therapy in patients with aRCC



Excluded patient populations

- Other considerations:
  - Active autoimmune disease requiring medication
  - Receiving steroid dosing (for any reason) > 10mg per day prednisone equivalent
  - Significant burden and/or pace of disease
  - History of controlled HIV or hepatitis infection

Key clinical questions

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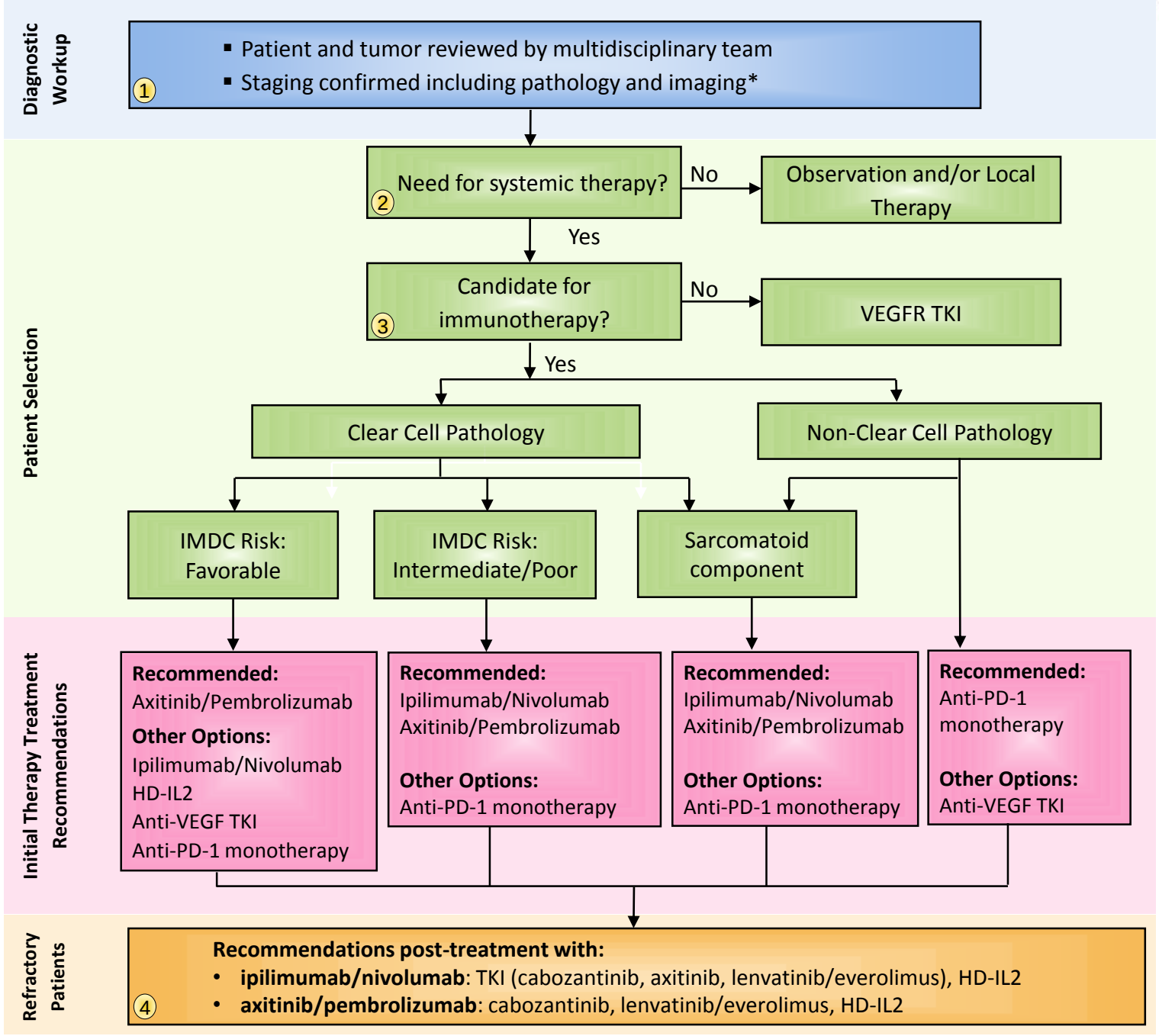
Guidelines process

In accordance with the National Academy of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines

1. Committee with range of relevant specialties
2. Systematic literature search
3. Survey development and completion
4. Manuscript draft
5. In-person meeting
6. Open comment period

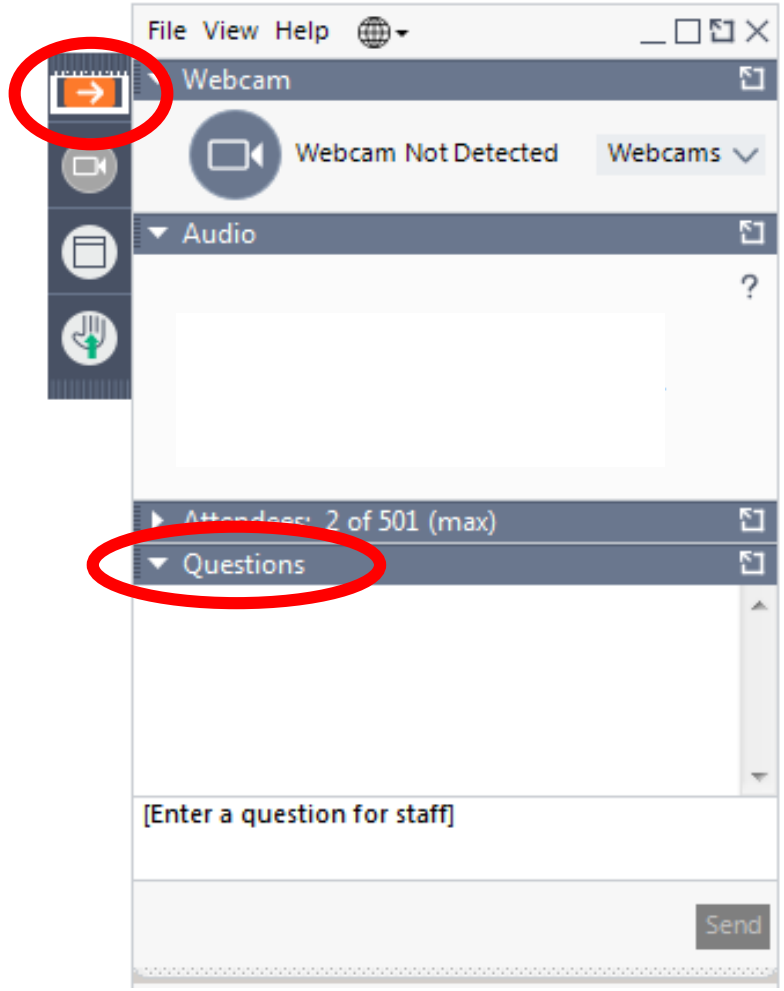


Notes: 1) Clinical Trials are always an option for any patient, in any category. 2) This recommendation may change as data matures.

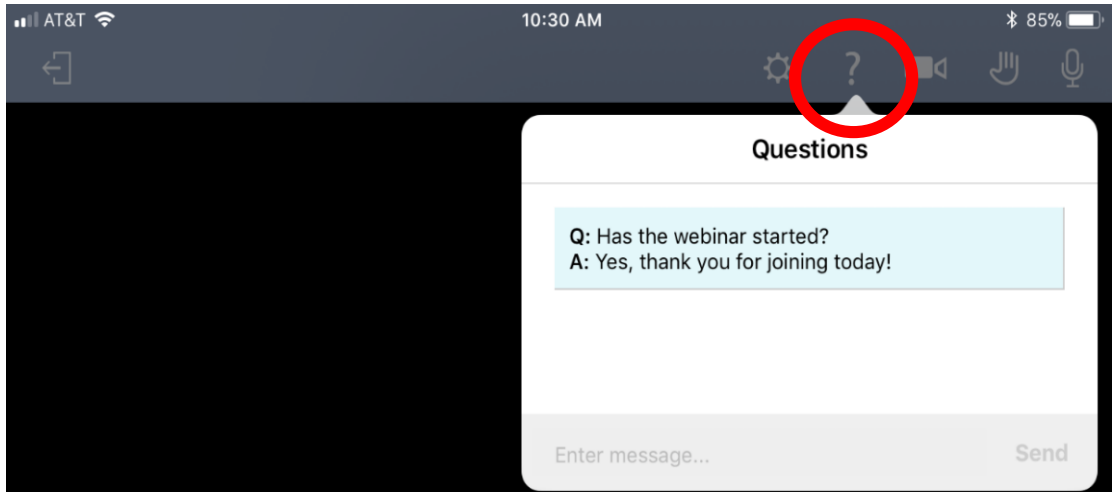
Questions and Answer Session

Submit your questions

Computer



Mobile Phone



Case study 1

- The patient is a 67yo male, former smoker
- In 2016, he presented with gross hematuria, work-up reveal a left renal mass (11cm)
- The patient underwent a laparoscopic nephrectomy, pathology clear cell renal cell carcinoma, grade 3
- The patient has been followed with regular CT scan, ECOG PS - 0
- In September 2019, CT scan reveals new lung lesions – incisional biopsy +RCC, sarcomatoid differentiation present
- Labs – CBC, Chem 20 – WNL
- **How would you treat this patient?**

Case study 2

- 73F presents with liver and lung mets after nephrectomy for clear cell RCC 10 months prior. IMDC intermediate risk (time to mets; anemia)
- Patient begins axitinib at 5mg BID and pembrolizumab 200mg IV q3 weeks
- Pt presents at 3 weeks for second dose. No fatigue or diarrhea. LFTs as follows:

	AlkPhos	ALT (ULN 54)	AST (ULN 40)	TBil
Baseline	90	24	24	0.4
3 wks after starting therapy	102	163	121	0.7

- Next steps?
  1. Hold axi; recheck LFTs in 3 days
  2. Hold axi and pembro; recheck LFTS in 3 days
  3. Continue both drugs and see patient in 3 weeks
  4. Hold both drugs and start prednisone 60mg/d

Questions and Answer Session

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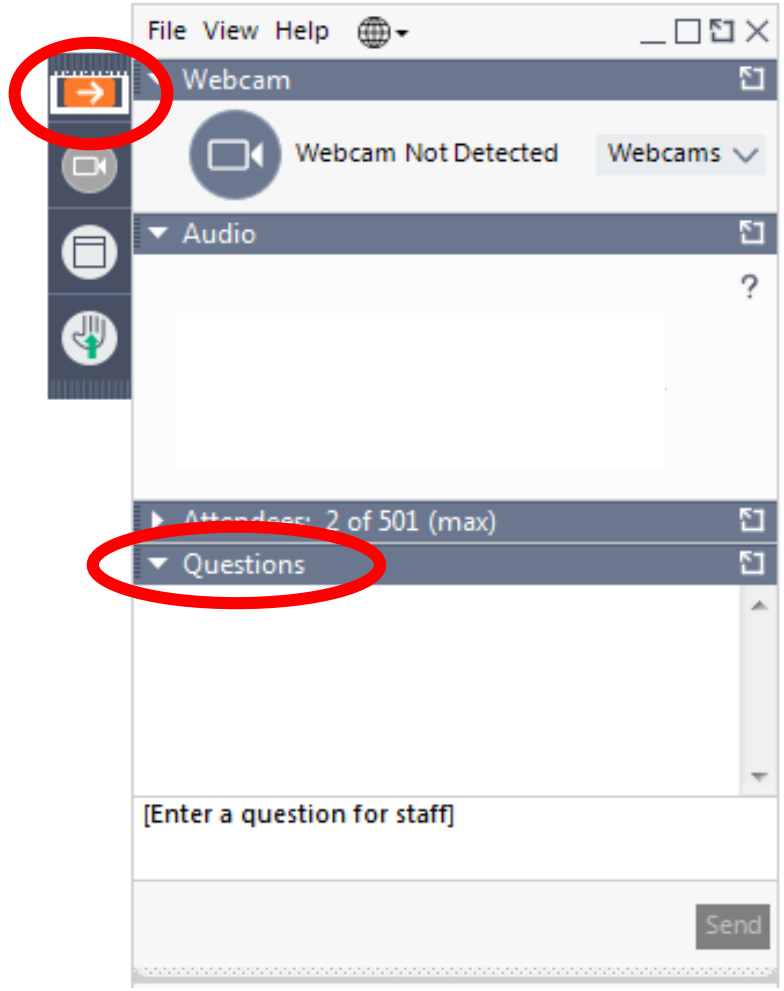

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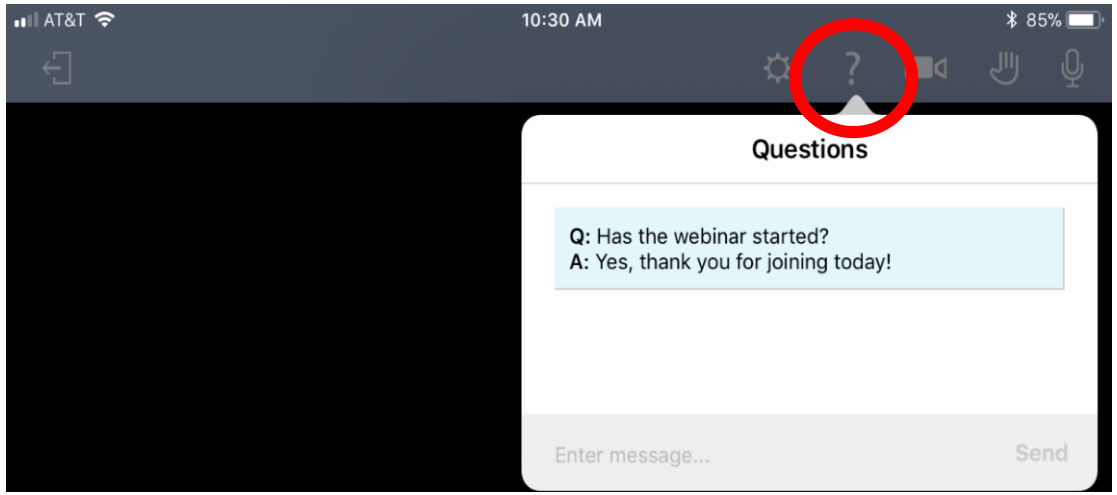

Additional Resources from SITC

Cancer Immunotherapy Guidelines:

www.sitcancer.org/guidelines

Free Online Courses (CE) for Healthcare Providers:

www.sitcancer.org/clinician

Webinar Recording and Slides:

After the webinar, you will receive an email with more information

Continuing Education Credits

- Continuing Education Credits are offered for Physicians, PA's, NP's, RN's and Pharmacists
- You will receive an email following the webinar with instructions on how to claim credit
- Questions and comments: connectED@sitcancer.org

Thank you for attending the webinar!

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