aRCC Script Concordance Test (SCT) Learning Program

Disclosure of Commercial Support

This program has received financial support from Ipsen in the form of an educational grant.

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Steering Committee Disclosures

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- Jeff Graham, MD
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Expert Panel Disclosures

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- Georg Bjarnason, MD
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  - Grant/Honorarium: Amgen, Novartis, Pfizer.
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  - Grant/Honorarium: Eisai clinical trial: Ayala, Eisai, Merck, Roche

Script Concordance Test

Program Objectives

- Evaluate the evolving standard of care in the management of metastatic renal cell carcinoma (mRCC)
- Reflect on the sequencing of treatments in a changing landscape and how
  this may impact decisions in the first-line setting
- Assess how previous treatment and patient characteristics impact decision-making

What Is SCT?

A different approach to case-based learning

- Educational tool based on clinical scenarios to assess and evaluate clinical reasoning
- Similar to a case study
  - Simulates clinical situations in which a physician must make decisions about diagnosis, treatment or management
- Unlike a case study
  - Emphasis is not on establishing a single “right answer”
  - Examines multiple solutions/considerations required in complex and uncertain situations, thereby exploring overall clinical reasoning process

How Does SCT Work?

- Brief case description
- 3 questions, divided into 3 parts
  A. Proposed action (“If you were thinking of…”)
     - Diagnostic possibility, investigative option or therapeutic alternative
  B. New information (“And then you find…”)
     - Physical examination sign, imaging study, laboratory test result
  C. Question
     - How does the new information impact the proposed action?

SCT

Important points

- The 3 questions in each case are
  - Completely independent of each other
  - *NOT sequential*
- The question asked of participants is NOT
  - Whether they agree with the proposed action
- The question asked of participants is
  - How does the new information impact the proposed action?

SCT Example

- You are an avid cook and your brother-in-law is stopping by October 31, which happens to be his birthday

Proposed action If you were thinking of…	**New information** And then you find…	**Question*** The new info makes the proposed action…
Making him a pumpkin birthday cake	Pumpkins cost $36/kg	-2 -1 0 +1 +2

*The new information makes the proposed action:
-2 very inappropriate; -1 inappropriate; 0 neither more nor less appropriate;
+1 more appropriate; +2 very appropriate.

Script Concordance Test

Case 1

Case 1: First-line Treatment in Metastatic RCC

Question 1

- A 65-year-old male patient with de novo metastatic RCC (mRCC) presents for his first consultation. He has biopsy-proven clear cell RCC with sarcomatoid features. CT and bone scan demonstrate an 8×8 cm left renal mass; 2 pulmonary nodules (both <2 cm); one lytic bone metastasis on the sternum; one lytic bone metastasis on the pelvis

Proposed action If you were thinking of…	**New information** And then you find…	**Question*** The new info makes the proposed action…
Recommending cytoreductive nephrectomy	• Karnofsky performance status (KPS) is 90% • Hemoglobin is 100 g/L • Platelet count is 500 (high) • Calcium, LDH, and neutrophil are within normal limits	-2 -1 0 +1 +2

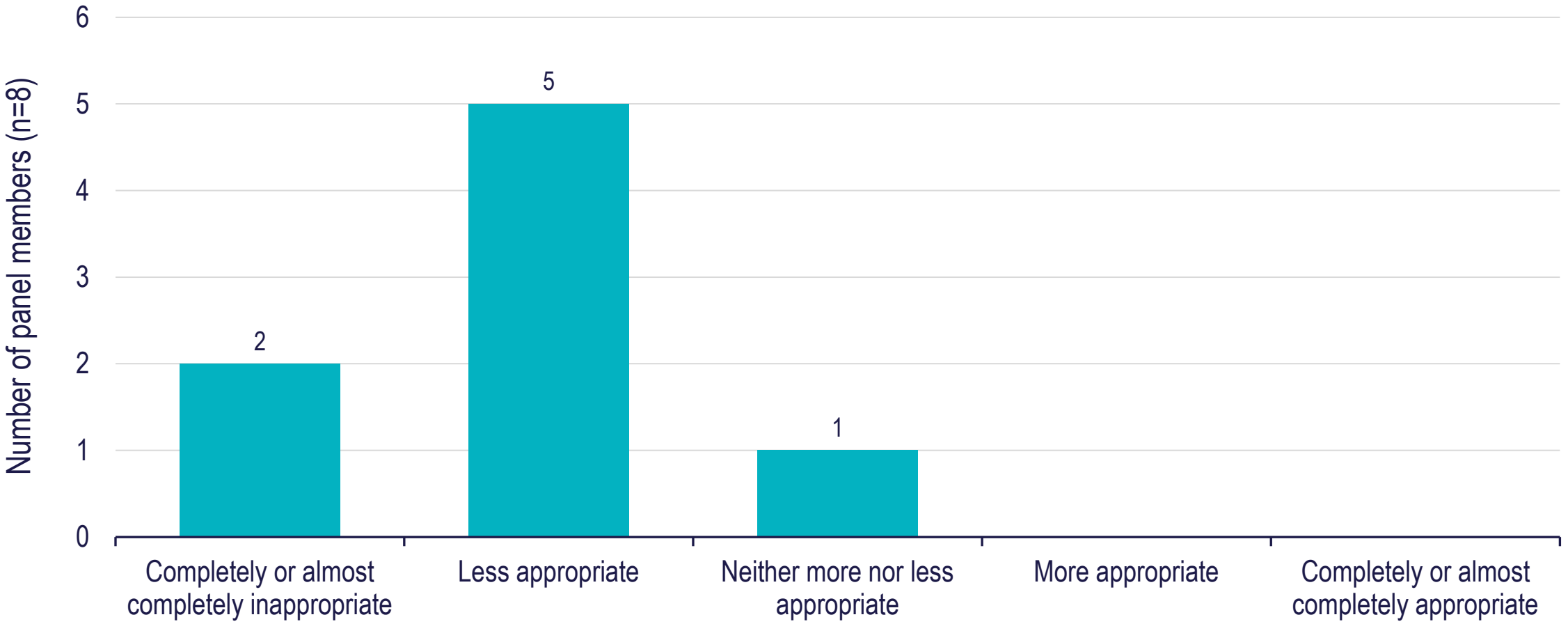
*The new information makes the proposed action:
-2 very inappropriate; -1 inappropriate; 0 neither more nor less appropriate;
+1 more appropriate; +2 very appropriate.

CT, computed tomography; LDH, lactic dehydrogenase; RCC, renal cell carcinoma

Individual Voting

5 minutes

Summary of Expert Panel Responses



Summary of Expert Panel Responses

-2	Intermediate risk with sarcomatoid features and lung and bone mets—would advise against cytoreductive nephrectomy due to the high risk of rapid progression systemically. Propose starting systemic therapy and consider nephrectomy later in case of a good response.
-2	This patient has IMDC poor-risk disease (3 risk factors). Based on data from retrospective studies and the CARMENA trial, we would not recommend upfront CN for this patient.
-1	Intermediate IMDC, but limited metastatic disease – so nephrectomy might well be sage and have benefits.
-1	Although burden of mets is not high outside of the kidney, and patient performance status is quite good, the patient has 3/6 IMDC criteria, which would put him in the poor prognosis category. I would consider deferring plans for a CN pending response to systemic therapy.
-1	Given that this individual has IMDC poor risk with visceral metastasis, I am more inclined to initiate systemic therapy. Especially given that it is sarcomatoid pathology.
-1	3/6 IMDC criteria—poor-risk prognostic criteria—CN not indicated upfront. Start systemic therapy first.
-1	Based on IMDC criteria, this patient has at least intermediate risk (or poor if the intention is to start systemic therapy sooner rather than later), so systemic therapy should be the initial treatment consideration. In addition, our local multidisciplinary team is often hesitant to recommend CN in the context of bony metastatic disease.
0	This patient has intermediate prognosis disease and immunotherapy-based primary systemic treatment is reasonable. If this is the plan, then CN is unnecessary. However, as he has oligometastatic disease, at my centre we might offer local treatment for all lesions (ie, SBRT to lung and bones, and CN) to then observe and delay systemic therapy.

CN, cytoreductive nephrectomy; IMDC, International Metastatic RCC Database Consortium; SBRT, stereotactic body radiation therapy

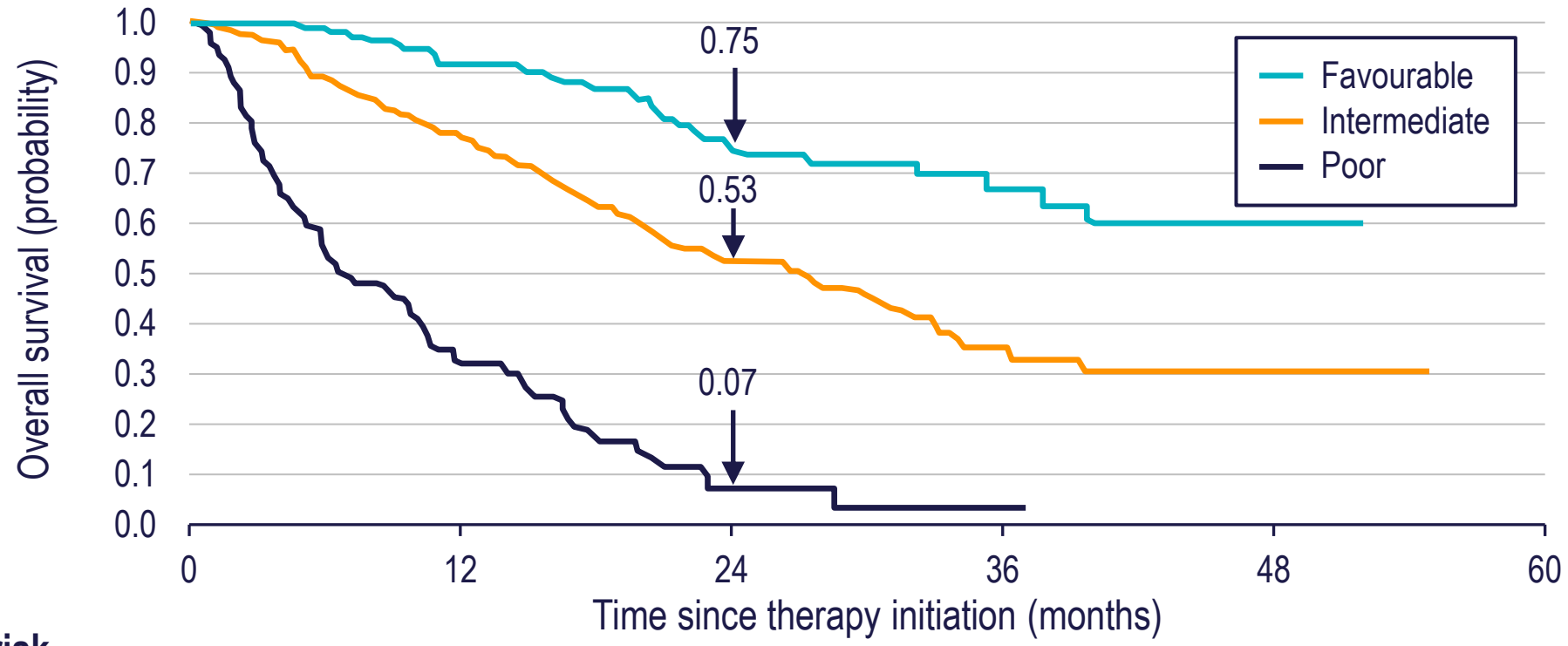
Summary of Risk Factors and Stratification

Risk factor	MSKCC risk factors	IMDC risk factors
Time from diagnosis to systemic treatment <1 year	X	X
Hemoglobin less than lower limit of normal	X	X
Calcium greater than upper limit of normal	X	X
Performance status (Karnofsky) <80%	X	X
LDH greater than 1.5× upper limit of normal	X	
Neutrophil count greater than upper limit of normal		X
Platelet count greater than upper limit of normal		X

IMDC, International Metastatic RCC Database Consortium; LDH, lactic dehydrogenase; MSKCC, Memorial Sloan-Kettering Cancer Center

Heng DY et al. *Lancet Oncol* 2013;14:141-8; Motzer RJ et al. *J Clin Oncol* 1999;17:2530-40

Overall Survival According to IMDC Risk Group



No. of events/no. at risk

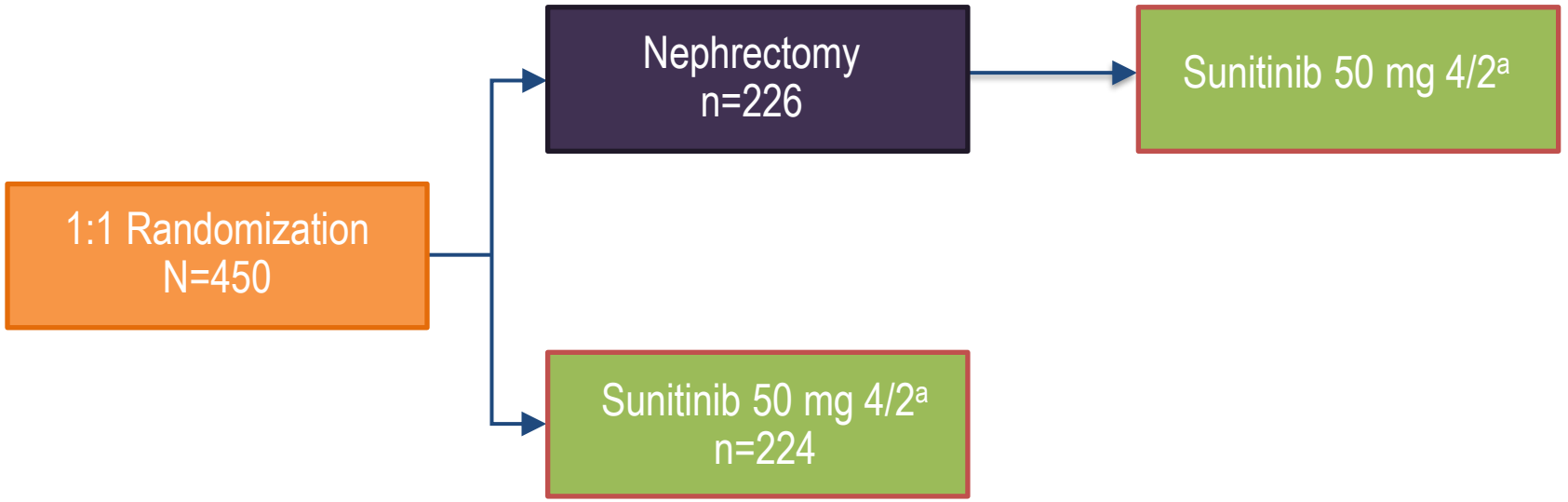
Favourable	11/133	16/110	4/62	2/22	0/3
Intermediate	61/301	50/182	17/82	2/18	0/3
Poor	94/152	19/36	1/3	0/1	0/0

IMDC, International Metastatic RCC Database Consortium

Heng DY et al. *J Clin Oncol* 2009;27:5794-9

CARMENA

Study design



Primary objective:

- OS; designed to demonstrate noninferiority of sunitinib alone vs nephrectomy followed by sunitinib

[a]28 days (4 weeks) on, 14 days (2 weeks) off.
OS, overall survival
Méjean A et al. *N Engl J Med* 2018;379:417-27

CARMENA

Key demographics at baseline

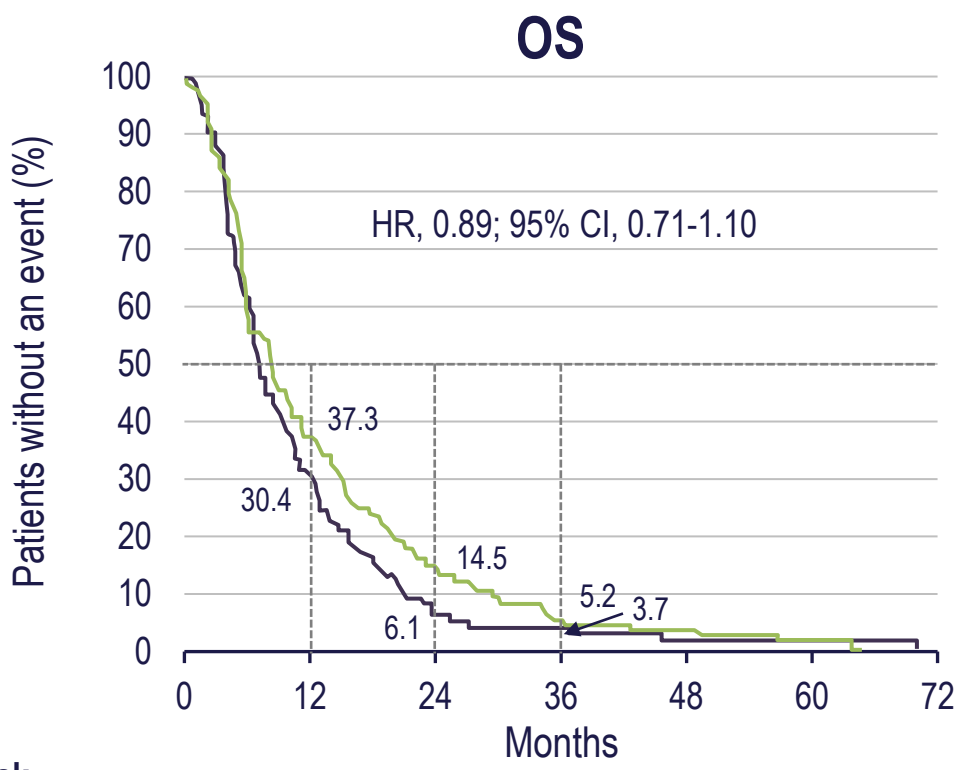
Characteristic	Nephrectomy-sunitinib (n=226)	Sunitinib alone (n=224)
MSKCC risk category, n/N (%) Intermediate risk Poor risk	125/225 (55.6) 100/225 (44.4)	131/224 (58.5) 93/224 (41.5)
ECOG 0, n (%)	130 (57.5)	122 (54.5)
ECOG 1, n (%)	96 (42.5)	102 (45.5)
Median primary tumour size (range), mm	88 (6-200)	86 (12-190)
Median no. of metastatic sites (range)	2 (1-5)	2 (1-5)
Median tumour burden (range), mm	140 (23-399)	144 (39-313)

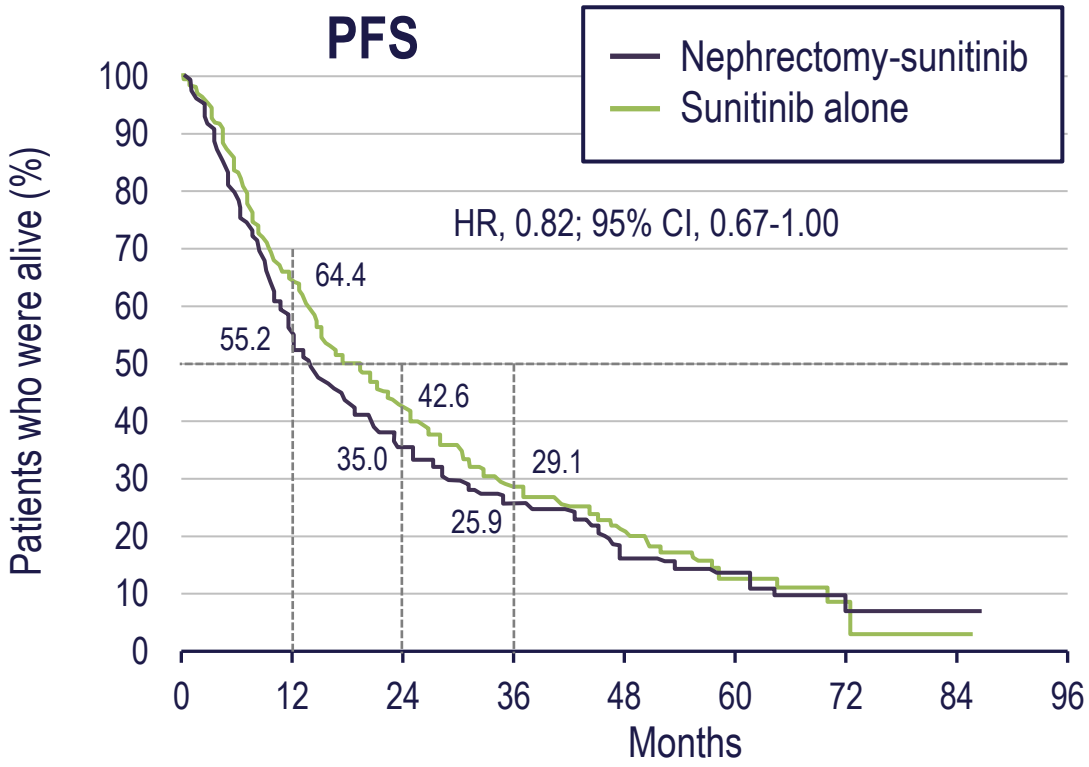
ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan-Kettering Cancer Center

Méjean A et al. N *Engl J Med* 2018;379:417-27

CARMENA

Sunitinib alone not inferior to CN followed by sunitinib





Number at risk

Nephrectomy-sunitinib	226	59	10	6	2	1	0
Sunitinib alone	224	74	28	9	6	2	0

226	110	61	40	19	11	4	1	0
224	128	76	44	26	8	3	1	0

CN, cytoreductive nephrectomy; HR, hazard ratio; OS, overall survival; PFS, progression-free survival

Méjean A et al. *N Engl J Med* 2018;379:417-27

CARMENA

OS longer with sunitinib alone regardless of risk group

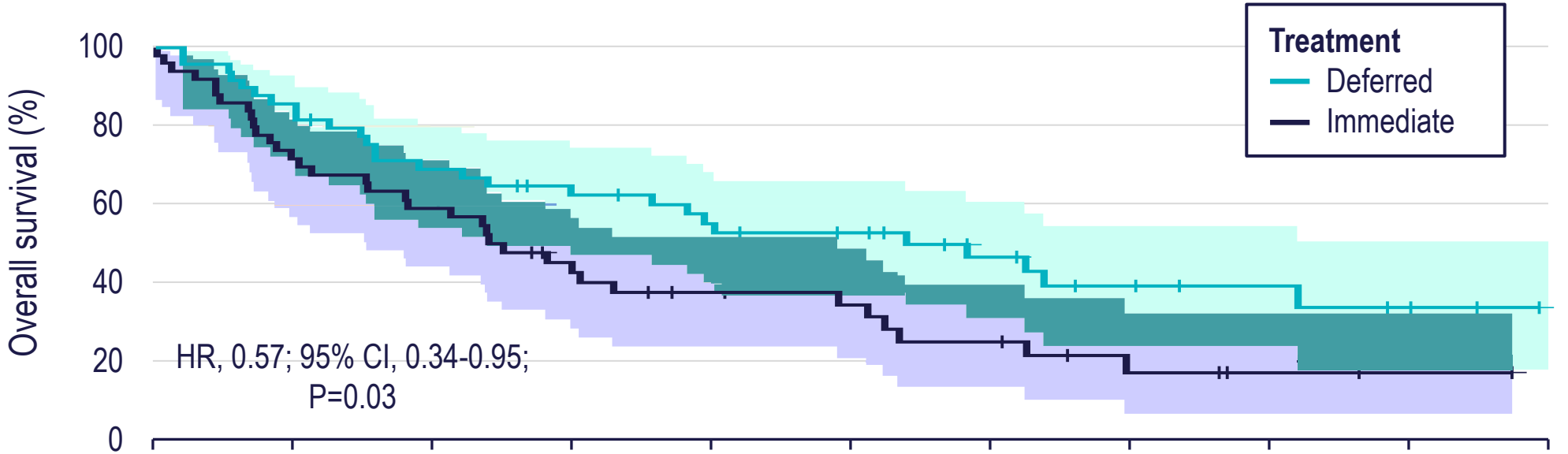
Risk group	OS (months)		HR (95% CI) for death
	Nephrectomy-sunitinib	Sunitinib alone	Sunitinib-alone vs nephrectomy-sunitinib
Intermediate	19.0	23.4	0.92 (0.68-1.24)
Poor	10.2	13.3	0.86 (0.62-1.17)

HR, hazard ratio; OS, overall survival

Méjean A et al. *N Engl J Med* 2018;379:417-27

SURTIME

OS numerically but not statistically significantly better in deferred vs immediate CN



No. at risk

Treatment:											
Deferred	49	42	32	27	23	20	14	10	7	5	2
Immediate	50	35	28	18	13	11	8	4	2	1	0

CN, cytoreductive nephrectomy; HR, hazard ratio; OS, overall survival

Bex A et al. *JAMA Oncol* 2019;5:164-70

KCRNC Consensus Statement for CN

Patient profile	Recommendation
All of the following: • ECOG ≤1 or KPS ≥80% • Minimal symptoms from metastatic disease • Resectable primary tumour • Limited burden of metastatic disease	• Upfront CN • Followed by appropriate therapy
Any of the following: • Significant systemic symptoms from metastatic disease • Active central nervous system metastases • Limited burden of disease within the kidney relative to the cumulative extrarenal volume of metastases • Rapidly progressing disease • ECOG >1 or KPS <80% • Limited life expectancy	• Should not undergo CN
Other patients	• Initial systemic therapy • Consider CN if significant clinical response

CN, cytoreductive nephrectomy; ECOG, Eastern Cooperative Oncology Group; KCRNC, Kidney Cancer Research Network of Canada; KPS, Karnofsky performance status

Mason RJ et al. *Can Urol Assoc J* 2019;13:166-74

Case 1: First-line Treatment in Metastatic RCC

Question 2

- A 65-year-old male patient with de novo metastatic RCC (mRCC) presents for his first consultation. He has biopsy-proven clear cell RCC with sarcomatoid features. CT and bone scan demonstrate an 8×8 cm left renal mass; 2 pulmonary nodules (both <2 cm); one lytic bone metastasis on the sternum; one lytic bone metastasis on the pelvis

Proposed action If you were thinking of…	**New information** And then you find…	**Question*** The new info makes the proposed action…
Prescribing axitinib/pembrolizumab	The patient has hypercalcemia, declining ECOG performance status, fever, and weight loss. You are concerned that he would not be fit to receive a subsequent line of therapy if he does not benefit from his first-line agents.	-2 -1 0 +1 +2

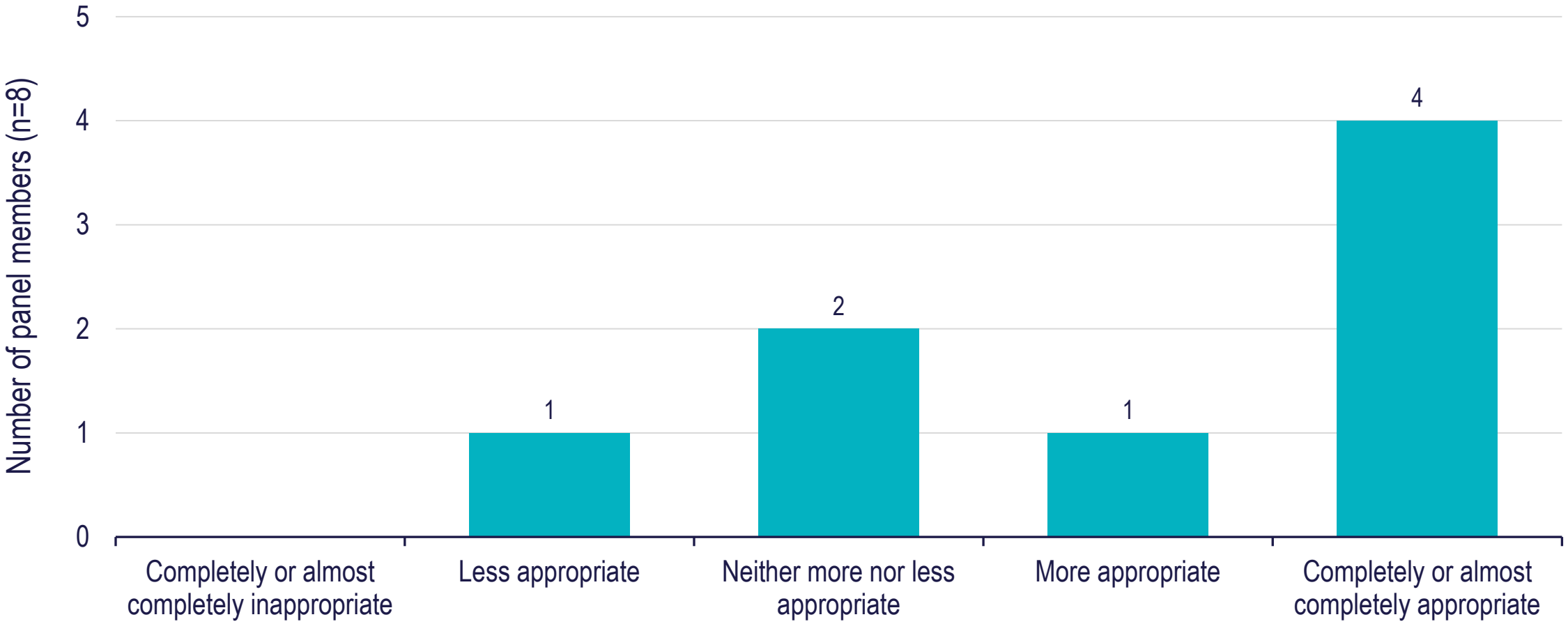
*The new information makes the proposed action:
-2 very inappropriate; -1 inappropriate; 0 neither more nor less appropriate;
+1 more appropriate; +2 very appropriate.

CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; RCC, renal cell carcinoma

Individual Voting

5 minutes

Summary of Expert Panel Responses



Summary of Expert Panel Responses (1 of 2)

-1	I think the important thing is to have a patient investigated when they have rapidly declining function and fever. What is the fever from? I would not start the patient on systemic therapy (even first line) unless the patient is stable. However, if the patient is well enough for initiation of treatment, first-line IO/TKI certainly has evidence and would be my first choice.
0	This patient is intermediate/poor prognosis by IMDC. Either axi/pembro or ipi/nivo is an option for this patient. However, if the patient is declining rapidly and there is concern about getting only one line of therapy for him, then it would be reasonable to consider IO+VEGF combo to cover both mechanisms of action for a mRCC case. A frank discussion with the patient to review both options would have to happen though, as ipi/nivo has proven benefit with longer-term follow-up in this patient population.
0	Axi/pembro and ipi/nivo both have shown benefit in poor-risk patients, and cabozantinib is an appropriate next line of therapy following either regimen.

axi, axitinib; IMDC, International Metastatic RCC Database Consortium; IO, immunotherapy; ipi, ipilimumab; mRCC, metastatic renal cell carcinoma; nivo, nivolumab; pembro, pembrolizumab; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor

Summary of Expert Panel Responses (2 of 2)

+1	The benefit of using axitinib and pembrolizumab in this setting is that you're hitting the disease using 2 completely different mechanisms of action (VEGF TKI and PD-1 inhibitor). With all the caveats of not comparing across trials, the objective response rate (ORR) for axi/pembro was 59.3% (all comers) and the ORR for ipi/nivo was 42% for intermediate-/poor-risk patients.
+2	Theoretically, both ipi/nivo and axi/pembro are options. Axi/pembro has a much lower primary progression rate of 11% vs 25% with ipi/nivo. Hence, it would be my first choice for a patient in whom I think I only get "one shot."
+2	This patient has poor prognosis disease and requires optimal first-line treatment. I would prefer TKI/IO in this setting, as it may have more immediate anticancer activity, may be more effective than IO/IO in sarcomatoid RCC, and TKI is dose titratable.
+2	Based on KEYNOTE-426, solid data support axi/pembro in this population. In patients who may not be fit enough to receive subsequent therapy, combining an IO agent and a VEGF-targeted agent provides early exposure to 2 different classes of drugs.

axi, axitinib; IO, immunotherapy; ipi, ipilimumab; nivo, nivolumab; ORR, objective response rate; PD-1, programmed cell death 1; pembro, pembrolizumab; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor

Summary of BOR

Rate of PD lower with pembro/axi vs sunitinib

Study results are not comparative

	KEYNOTE 426[1,2]		CHECKMATE 214[3,4]	
	Pembrolizumab/axitinib	Sunitinib	Nivolumab/ipilimumab	Sunitinib
Patient population	**All risk groups**		**Intermediate-/poor-risk groups**	
Median follow-up (mo)	30.6[1]		32.4[3] or 55[4]	
ORR (%)	60[1]	40[1]	41.9[4]	26.8[4]
BOR (%)				
CR	9[1]	3[1]	10.4[4]	1.4[4]
PR	51[1]	37[1]	31.5[4]	25.4[4]
SD	23[1]	35[1]	30.8[4]	44.3[4]
PD	11[1]	17[1]	19.3[4]	16.8[4]
Median time to confirmed objective response (95% CI), mo	2.8 (1.5-16.6)[2]	2.9 (2.1-15.1)[2]	2.8 (2.7-3.1)[3]	4.0 (2.8-5.5)[3]

axi, axitinib; BOR, best overall response; CR, complete response; ORR, objective response rate; PD, progressive disease; pembro, pembrolizumab; PR, partial response; SD, stable disease

1. Powles T et al. *Lancet Oncol* 2020;21:1563-73; 2. Rini BI et al. *N Engl J Med* 2019;380:1116-27; 3. Motzer RJ et al. *Lancet Oncol* 2019;20:1370-85; 4. Albiges L et al. *ESMO Open* 2020;5:e001079

Summary of PFS/OS

Study results are not comparative

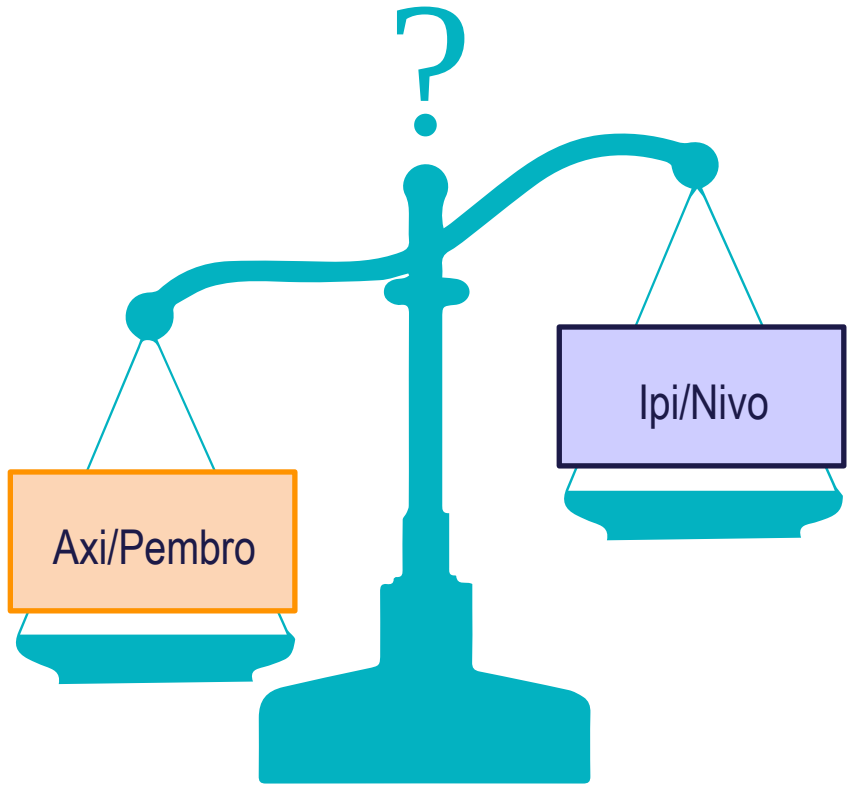
	KEYNOTE 426[1]		CHECKMATE 214[2]	
	Pembrolizumab/axitinib	Sunitinib	Nivolumab/ipilimumab	Sunitinib
Patient population	**All risk groups**		**Intermediate/poor risk groups**	
Median follow-up (m)	30.6[1]		55[2]	
Median OS (m)	NR[1]	35.7 (33.3-NR)[1]	48.1 (35.6-NE)[2]	26.6 (22.1-33.5)[2]
OS HR (95%CI)	0.68 (0.55-0.85), P <0.0003[1]		0.65 (0.54-0.78)[3]	
Median PFS (m)	15.4 (12.7-18.9)[1]	11.1 (9.1-12.5)[1]	11.2 (8.4-16.1)[2]	8.3 (7.0-10.8)[2]
PFS HR (95%CI)	0.71 (0.60-0.84), P <0.0001[1]		0.74 (0.62-0.88)[2]	

OS, Overall survival; PFS, Progression-free survival

1. Powles T et al. *Lancet Oncol* 2020;21:1563-73; 2. Albiges L et al. *ESMO Open* 2020;5:e001079

Treatment Choice Should Be Based on Patient Characteristics

- In patients with large tumour burden and high risk of rapid deterioration, treatment choice may be balanced slightly in favour of axitinib/pembrolizumab vs ipilimumab/nivolumab



axi, axitinib; ipi, ipilimumab; nivo, nivolumab; pembro, pembrolizumab

Discussion Question

?

- Do the available options in second line and beyond influence how you select treatment in the first line?

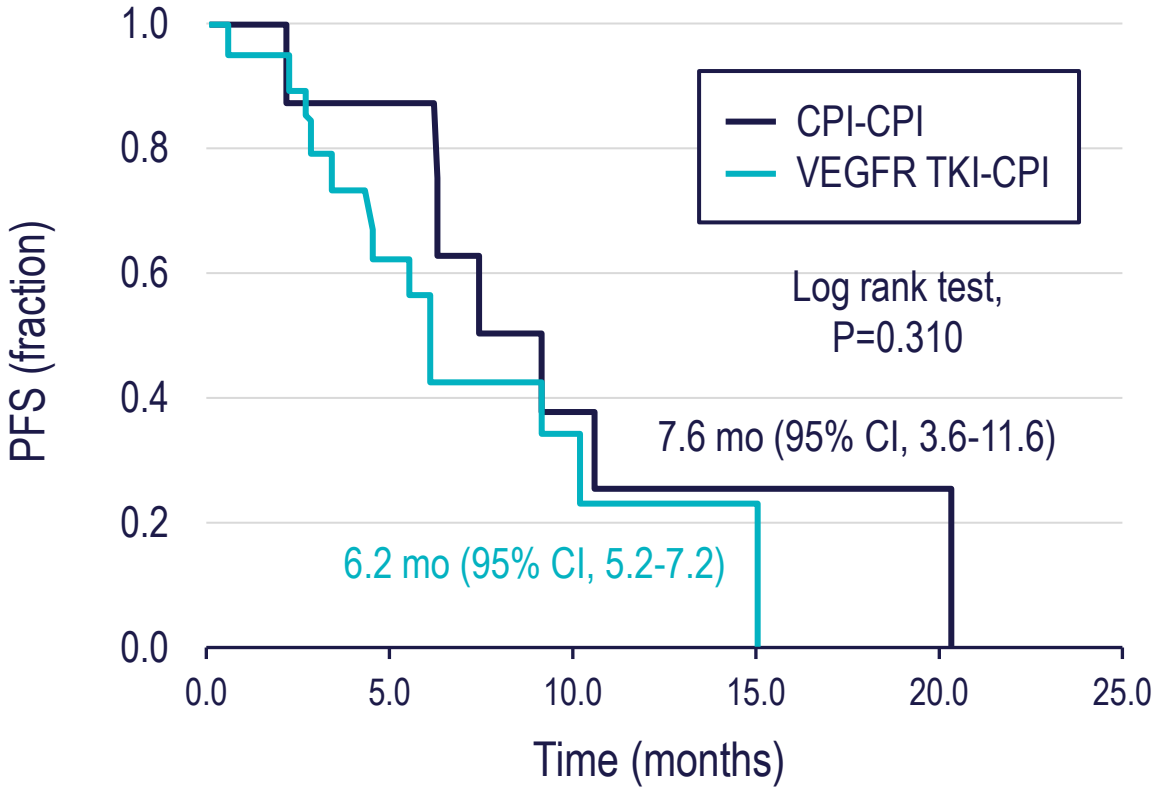
KCRNC Consensus Statement Treatment Recommendations by Risk and Line of Therapy

Setting	Patients	Preferred	Options
Untreated	Favourable risk (IMDC)	• Cabozantinib + nivolumab* • Axitinib + pembrolizumab • Lenvatinib + pembrolizumab*	• Sunitinib • Pazopanib • Axitinib + avelumab* • Active surveillance
	Intermediate-/poor-risk (IMDC)	• Ipilimumab + nivolumab • Cabozantinib + nivolumab* • Axitinib + pembrolizumab • Lenvatinib + pembrolizumab*	• Cabozantinib • Sunitinib • Pazopanib • Axitinib + avelumab* • Active surveillance
Second-line and beyond	Prior VEGF inhibitor	• Cabozantinib • Nivolumab	• Lenvatinib + everolimus • Everolimus • Axitinib
		Options	
	Prior immune checkpoint inhibitor	• Cabozantinib • Axitinib • Sunitinib	• Pazopanib • Lenvatinib + everolimus
	Prior VEGF and immune checkpoint inhibitor†	• Cabozantinib • Sunitinib • Pazopanib	• Axitinib • Lenvatinib + everolimus

Preferred options originated from studies that have demonstrated OS improvements. Options have usually demonstrated a progression-free survival advantage but not necessarily OS survival.
*Not yet approved in Canada. †If not previously used.
IMDC, International Metastatic RCC Database Consortium; OS, overall survival; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor
Canil C, et al. *Can Urol Assoc J* 2021;15:84-97

VEGFR TKIs Demonstrate Efficacy Post IC

PFS with at least one TKI by type of immunotherapy combination



N=89

Prior IC regimens:

- CPI-CPI: Ipilimumab/nivolumab: 33%
- VEGFR TKI-CPI:
  - Atezolizumab/bevacizumab: 64%
  - Axitinib/avelumab: 3%

CPI, checkpoint inhibitor; IC, immunotherapy combination; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor

Barata PC et al. *Br J Cancer* 2018;119:160-3

TKIs Demonstrate Efficacy After IO Treatment

	Total N	Time to treatment discontinuation		Overall survival		Physician-assessed best response Objective response rate, n (%)
		No. of discontinuations	Median, mo (95% CI)	No. of deaths	1-y probability, % (95% CI)	
Axitinib						
Received in 2nd line	12	7	10.2 (6.5-NR)	1	89 (45-98)	7 (58.3)
Received in 3rd line	49	30	5.7 (3.6-10.2)	12	61 (42-76)	5 (17.9)
Received in ≥4th line	22	16	4.7 (2.4-12.7)	8	49 (22-71)	2 (16.7)
Cabozantinib						
Received in 2nd line	7	4	11.4 (6.8-15.0)	1	83 (27-97)	3 (50.0)
Received in 3rd line	24	10	7.0 (3.0-16.4)	6	47 (16-73)	4 (26.7)
Received in ≥4th line	33	10	9.2 (5.3-NR)	6	59 (26-82)	10 (41.7)
Sunitinib						
Received in 2nd line	17	12	5.5 (3.2-14.8)	3	78 (46-92)	7 (53.8)
Received in 3rd line	8	6	11.6 (2.8-NR)	2	75 (31-93)	2 (25.0)
Received in ≥4th line	6	4	7.2 (0.7-NR)	3	40 (5-75)	1 (33.3)

- A retrospective, longitudinal cohort study using data from 8 international cancer centres
- Patients with mRCC (n=314) received IO therapy in any line and initiated targeted therapy after IO therapy discontinuation

IO, immunotherapy; mRCC, metastatic renal cell carcinoma; TKI, tyrosine kinase inhibitor

Graham J et al. *Eur Urol Oncol* 2019;S2588-9311(19)30160-9

Case 1: First-line Treatment in Metastatic RCC

Question 3

- A 65-year-old male patient with de novo metastatic RCC (mRCC) presents for his first consultation. He has biopsy-proven clear cell RCC with sarcomatoid features. CT and bone scan demonstrate an 8×8 cm left renal mass; 2 pulmonary nodules (both <2 cm); one lytic bone metastasis on the sternum; one lytic bone metastasis on the pelvis

Proposed action If you were thinking of…	**New information** And then you find…	**Question*** The new info makes the proposed action…
Prescribing ipilimumab/nivolumab	The patient has a remote history of Crohn's disease, 7 years ago. He is currently not taking medication for his Crohn's disease and reports no recent exacerbations.	-2 -1 0 +1 +2

*The new information makes the proposed action:
-2 very inappropriate; -1 inappropriate; 0 neither more nor less appropriate;
+1 more appropriate; +2 very appropriate.

CT, computed tomography; RCC, renal cell carcinoma

Individual Voting

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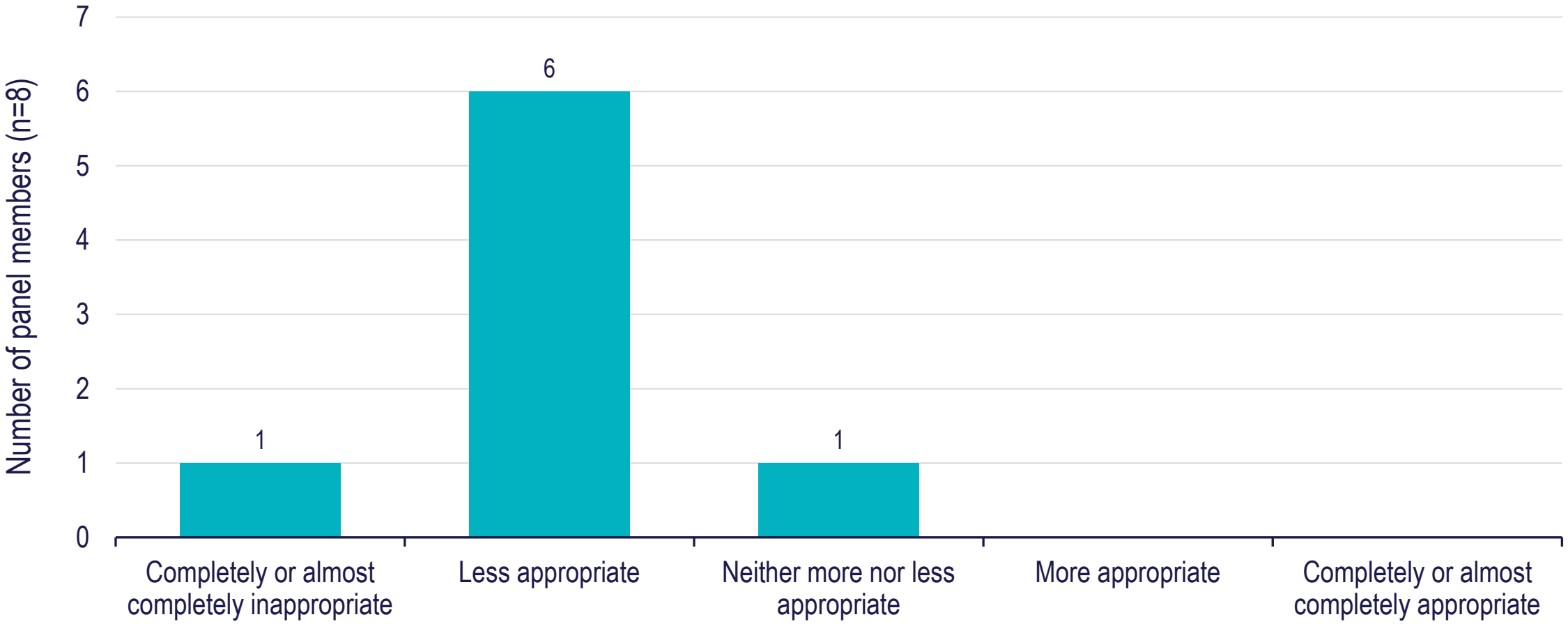


Summary of Expert Panel Responses (1 of 2)

-2	His Crohn's might get reactivated by ipi/nivo. This is less likely with axi/pembro.
-1	Would want to touch base with patient's gastroenterologist to get more details of patient's history and current state of disease. Would even consider endoscopic evaluation prior to starting therapy, if possible, to set a "baseline." Would also discuss the option of axi/pembro as an alternative to ipi/nivo as it's perhaps less likely to have severe autoimmune colitis toxicity.
-1	Preexisting autoimmune disease is a contraindication. Having said that, he has been in remission and is not on active therapy. Hence, if the patient was in agreement and understood the risks and potential benefits and had a preference for IO/IO, I would do it.
-1	Still a reasonable choice, but use of CTLA-4 inhibitor increases the risk of GI toxicity for this patient.
-1	The main toxicity of ipi would be diarrhea, and perhaps ipi/nivo is not the best choice because of the history of Crohn's disease, even with no recent exacerbations. Perhaps axi/pembro would be a better choice now that there are 2 choices available.

axi, axitinib; CTLA-4, cytotoxic T-lymphocyte antigen-4; GI, gastrointestinal; IO, immunotherapy; ipi, ipilimumab; nivo, nivolumab; pembro, pembrolizumab

Summary of Expert Panel Responses (2 of 2)

-1	Use of immune checkpoint inhibitors in the context of preexisting autoimmune disease has not been as challenging as we had once anticipated it would be. If the patient has stable autoimmune disease and is not on high doses of steroid or a biologic, I typically proceed (but ensure that the patient's gastroenterologist or rheumatologist is aware and in agreement with troubleshooting any flares). Having said that, a good option is available in this setting that may confer less risk of flaring up underlying autoimmune disease (ie, axi/pembro).
-1	This patient would likely be at increased risk of irAEs and for a flare of the underlying Crohn's, but this treatment is not absolutely contraindicated. The patient should be monitored carefully, with early steroid therapy if flare or irAE.
0	Patients with autoimmune disease (even in the setting of being on immunosuppressive agents) should not be disqualified from receiving checkpoint inhibition. Evidence suggests that even patients who are on immunosuppressive regimens fare well despite treatment with IO-targeted therapy (ie, the Crohn's does not flare). We have seen case reports from patients with advanced melanoma on IO therapy with background history of Crohn's. It would require an open discussion with the patient regarding risks and very close clinical monitoring. Steroids work well to negate potential toxicity if problems arise. The risk of not being on treatment far outweighs the risks of having a flare of their primary autoimmune disorder.

axi, axitinib; IO, immunotherapy; ir AE, immune-related adverse event; pembro, pembrolizumab

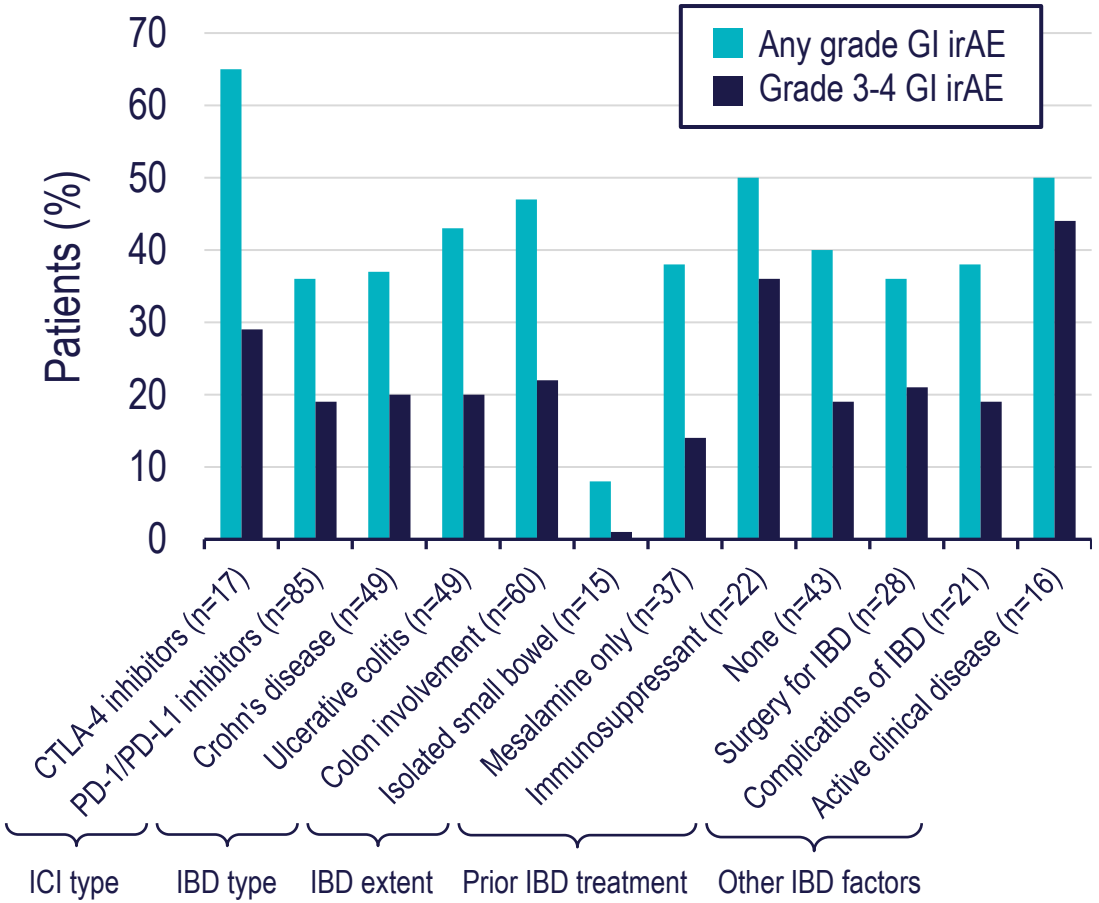
Preexisting IBD Increases Risk of Severe GI AEs in Patients Treated With IO

Patient characteristics

Characteristic	No. of patients (%) (N=102)
Type of IBD	
Crohn's disease	49 (48)
Ulcerative colitis	49 (48)
Unclassified	4 (4)
Median time from IBD diagnosis to immunotherapy initiation, years (IQR)	19 (8-28)
Median time from last active IBD episode to immunotherapy initiation, years (IQR)	5 (3-12)

42% of patients had not received IBD treatment within 3 months before IO

GI Immune-related AEs by subgroup

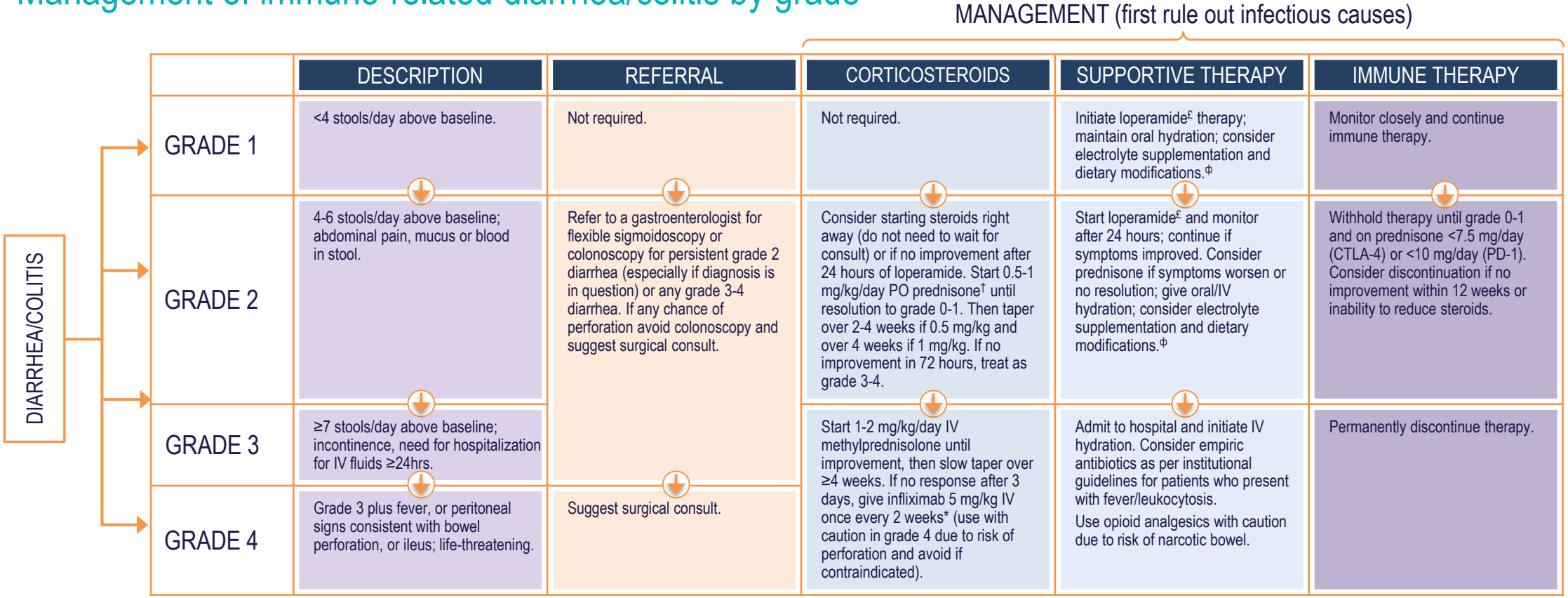


AE, adverse event; CTLA-4, cytotoxic T-lymphocyte antigen-4; GI, gastrointestinal; IBD, inflammatory bowel disease; ICI, immune checkpoint inhibitor; IO, immunotherapy; IQR, interquartile range; irAE, immune-related AE; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1

Abu-Sbeih H et al. *J Clin Oncol* 2020;38:576-83

Clinical Care Ontario Clinical Practice Guideline

Management of immune-related diarrhea/colitis by grade



£Loperamide 4 mg followed by 2 mg q4h or after every loose BM until diarrhea-free for 12hrs (max 16 mg/day). †Or equivalent. ΦRefer to CCO Diarrhea Guidelines: https://www.cancercareontario.ca/en/symptom-management/3151. *If infliximab is contraindicated (possibility of perforation, sepsis, TB, NYHA 3/4 CHF), consider mycophenolate mofetil or other immunosuppressive agents.
CTLA-4, cytotoxic T-lymphocyte antigen-4; IV, intravenous; PD-1, programmed cell death 1; PO, orally

Cancer Care Ontario. Immune Checkpoint Inhibitor Toxicity Management: clinical practice guideline. Published March 21, 2018. Accessed May 29, 2020. https://www.cancercareontario.ca/en/content/immune-checkpoint-inhibitor-toxicity-management-clinical-practice-guideline

Case 2

Case 2: Subsequent Treatment in mRCC

Question 1

- A 60-year-old female patient with clear cell mRCC has progressed on first-line ipilimumab/nivolumab and second-line sunitinib. Restaging scans after 6 months of sunitinib show progression of her disease.

Proposed action If you were thinking of…	**New information** And then you find…	**Question*** The new info makes the proposed action…
Prescribing axitinib	Restaging shows multiple bone and liver metastases	-2 -1 0 +1 +2

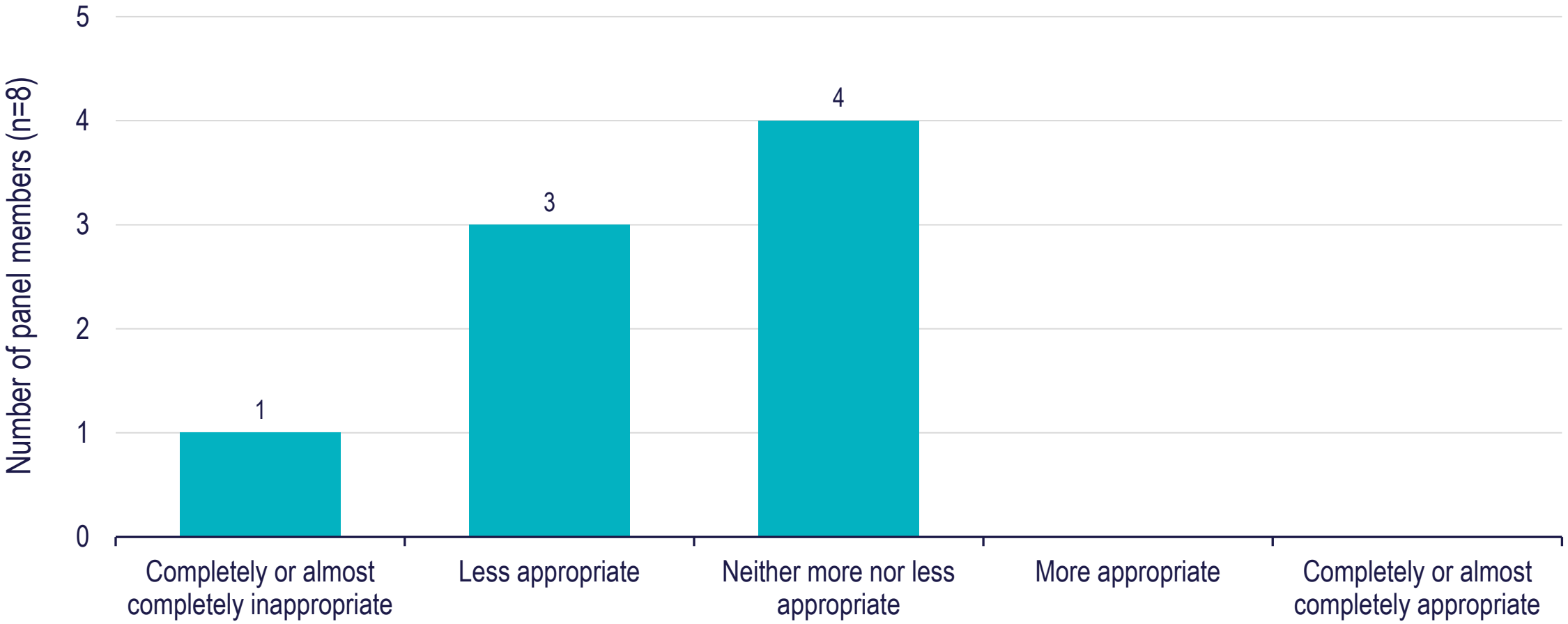
*The new information makes the proposed action:
-2 very inappropriate; -1 inappropriate; 0 neither more nor less appropriate;
+1 more appropriate; +2 very appropriate.

mRCC, metastatic renal cell carcinoma

Individual Voting

5 minutes

Summary of Expert Panel Responses



Summary of Expert Panel Responses

-2	I think my preference when patients have bone metastases and have progressed on TKI as second line would be to target pathways like MET inhibition. Data suggest that cabozantinib would be efficacious in this patient population (with better effect on skeletal metastases). My preference is not axitinib in this situation.
-1	Cabozantinib may be a better choice than axitinib for next-line therapy in patients with bone metastases.
-1	Although there is ample level 1 evidence for efficacy of a VEGF TKI after progression on a drug from the same class, my instinct is often to switch to an agent with a different mechanism of action. Particularly in the setting of bone metastases, I would be more inclined to consider cabozantinib in this setting.
-1	There are better data showing benefit of cabozantinib postprogression on sunitinib than for axitinib in this setting, particularly given bone metastases (METEOR subgroup analysis). Axitinib still an option but, given evidence with cabozantinib, I would introduce the option of cabozantinib to the patient with a tendency to prescribe that over axitinib.
0	We do not know which TKI or any treatment is best for third-line therapy after IO/IO followed by TKI. Both axitinib and cabozantinib are options. My personal preference would probably be cabozantinib in this situation due to the METEOR results.
0	Axitinib has activity after sunitinib; however, the benefit is unpredictable and the effect of prior IO therapy is uncertain.
0	Retrospective data suggest there is activity of axitinib post-IO therapy. Would need to monitor liver function closely while on therapy.
0	Axitinib may work post-sunitinib, but is not very active for bone metastases.

IO, immunotherapy; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor

KCRNC Consensus Statement Treatment Recommendations for Second-Line and Beyond

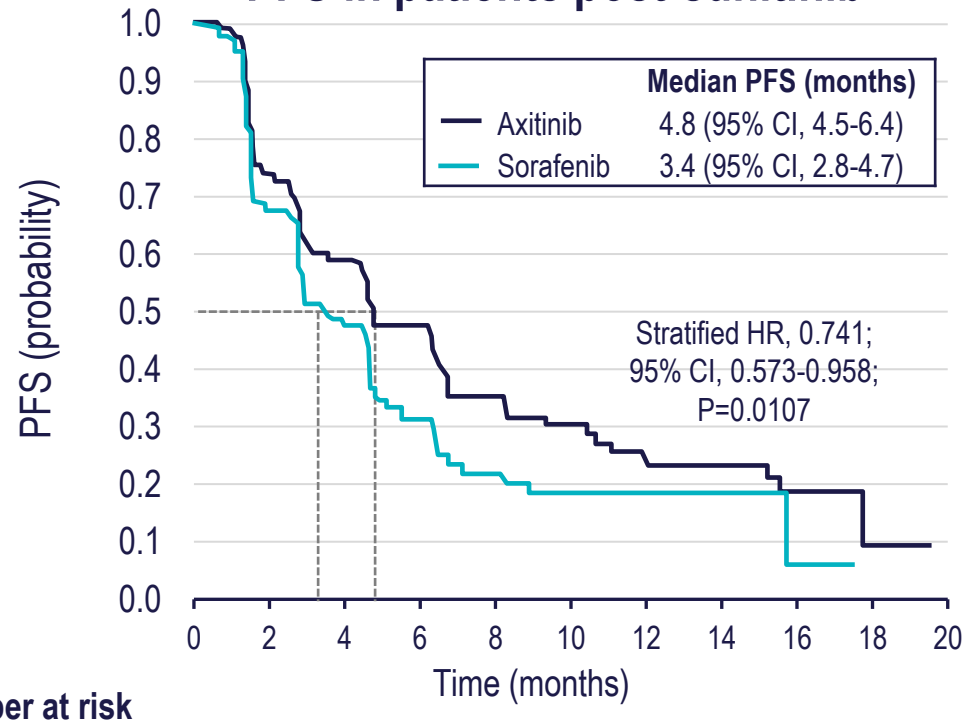
Setting	Patients	Preferred	Options
Untreated	Favourable risk (IMDC)	• Cabozantinib + nivolumab* • Axitinib + pembrolizumab • Lenvatinib + pembrolizumab*	• Sunitinib • Pazopanib • Axitinib + avelumab* • Active surveillance
	Intermediate-/poor-risk (IMDC)	• Ipilimumab + nivolumab • Cabozantinib + nivolumab* • Axitinib + pembrolizumab • Lenvatinib + pembrolizumab*	• Cabozantinib • Sunitinib • Pazopanib • Axitinib + avelumab* • Active surveillance
Second-line and beyond	Prior VEGF inhibitor	• Cabozantinib • Nivolumab	• Lenvatinib + everolimus • Everolimus • Axitinib
		Options	
	Prior immune checkpoint inhibitor	• Cabozantinib • Axitinib • Sunitinib	• Pazopanib • Lenvatinib + everolimus
	Prior VEGF and immune checkpoint inhibitor†	• Cabozantinib • Sunitinib • Pazopanib	• Axitinib • Lenvatinib + everolimus

Preferred options originated from studies that have demonstrated OS improvements. Options have usually demonstrated a progression-free survival advantage but not necessarily OS survival.
*Not yet approved in Canada. †If not previously used.
IMDC, International Metastatic RCC Database Consortium; OS, overall survival; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor
Canil C, et al. *Can Urol Assoc J* 2021;15:84-97

AXIS

Axitinib significantly increased PFS vs sorafenib; no difference in OS

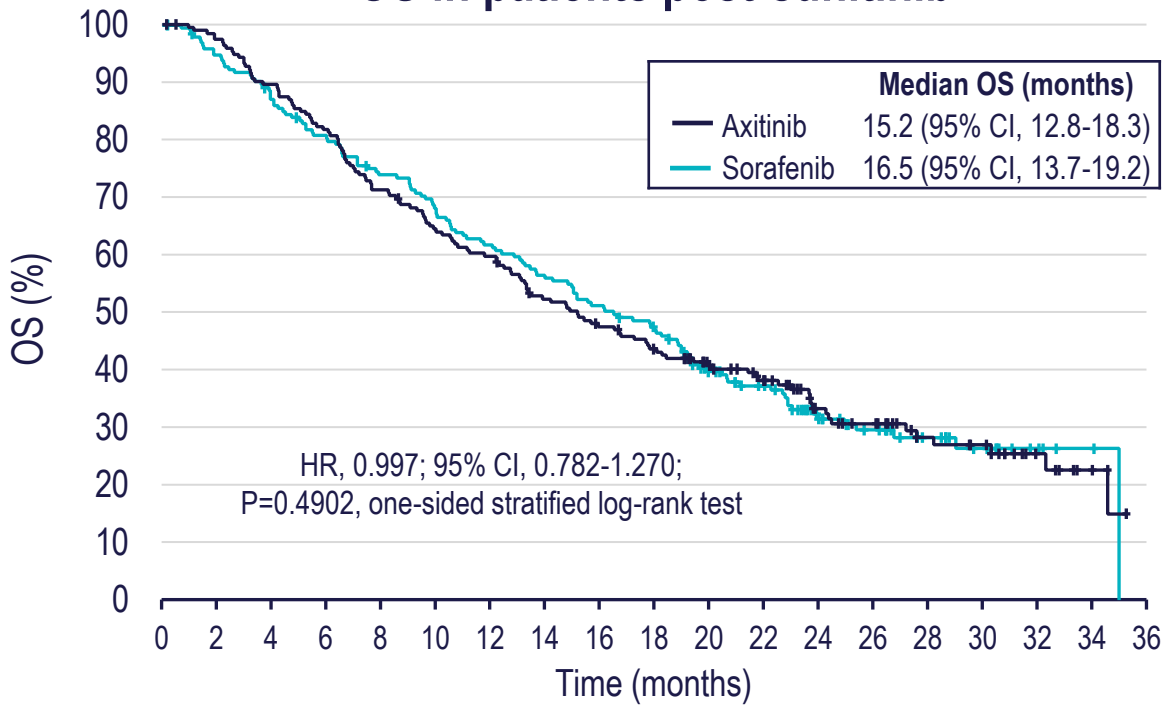
PFS in patients post-sunitinib[1]



Number at risk

Axitinib	184	132	97	60	34	24	11	10	6	1	0
Sorafenib	185	104	67	37	20	13	5	3	1	0	0

OS in patients post-sunitinib[2]



Axitinib	194	187	172	157	137	123	114	98	88	80	67	56	38	32	22	19	10	4	0
Sorafenib	195	183	167	154	140	129	117	106	97	88	66	56	39	28	19	12	5	2	0

HR, hazard ratio; OS, overall survival; PFS, progression-free survival

1. Rini BI et al. *Lancet* 2011;378:1931-9; 2. Motzer RJ et al. *Lancet Oncol* 2013;14:552-62

AXIS: Prior Liver or Bone Metastases Associated With Shorter OS

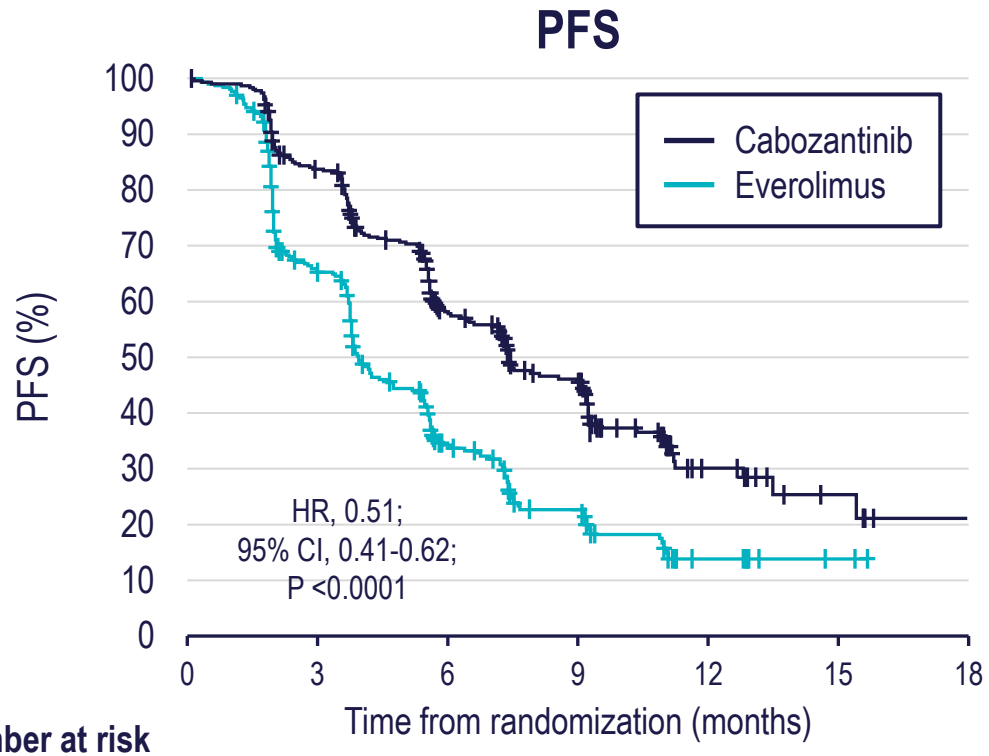
Multivariable analysis for baseline prognostic factors for OS

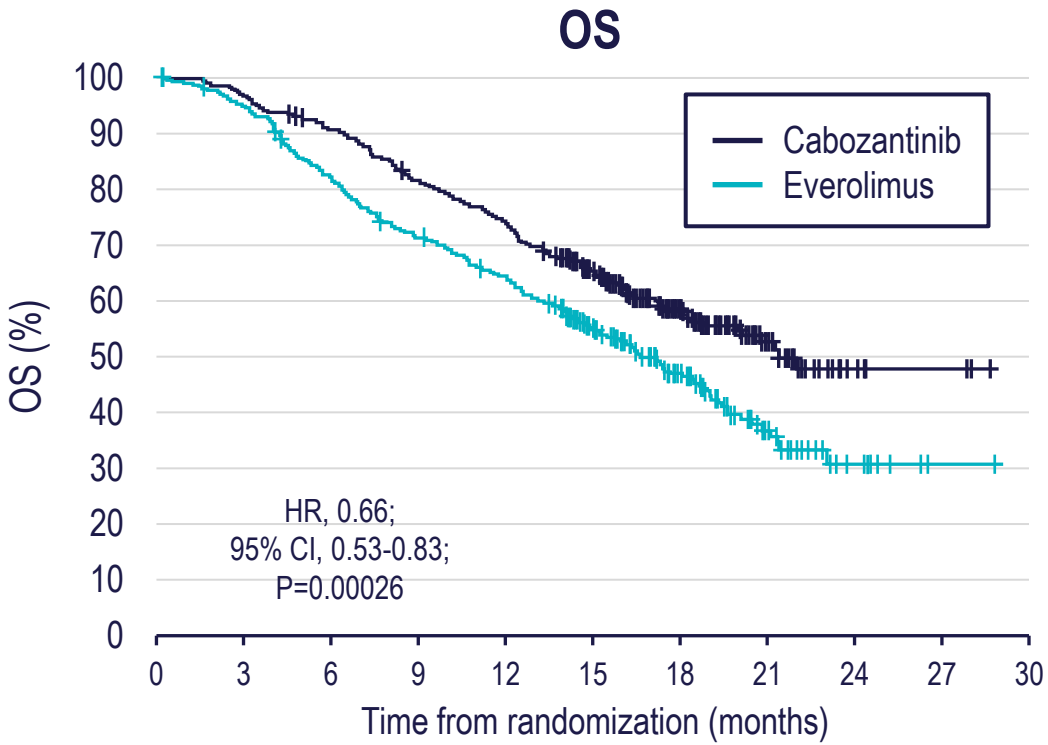
	Two-sided P value	HR (95% CI)
Previous treatment		
Bevacizumab vs sunitinib	0.2921	0.821 (0.568-1.185)
Cytokine vs sunitinib	<0.0001	0.503 (0.395-0.641)
Temsirolimus vs sunitinib	0.8046	1.065 (0.647-1.754)
ECOG PS (1 vs 0)	0.0005	1.452 (1.177-1.790)
Time from diagnosis to treatment on AXIS study (<1 vs ≥1 year)	0.0001	1.554 (1.240-1.947)
Metastatic sites (>1 vs 1)	0.0057	1.744 (1.176-2.588)
Liver metastases (yes vs no)	0.0204	1.298 (1.041-1.618)
Bone metastases (yes vs no)	0.0056	1.357 (1.093-1.685)
Corrected calcium (>10 mg/dL vs ≤10 mg/dL)	<0.0001	2.743 (1.971-3.817)
Alkaline phosphatase (>ULN vs ≤ULN)	0.0059	1.412 (1.104-1.805)
LDH (>1.5 × ULN vs ≤1.5 × ULN)	<0.0001	2.677 (1.764-4.062)
Hemoglobin (<LLN vs ≥LLN)	<0.0001	1.689 (1.352-2.111)
Neutrophils (>ULN vs ≤ULN)	0.0048	1.688 (1.173-2.428)

ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactic dehydrogenase; LLN, lower limit of normal; OS, overall survival; PS, performance status; ULN, upper limit of normal

Motzer RJ et al. *Lancet Oncol* 2013;14:552-62

METEOR: Cabozantinib Improved PFS and OS Compared With Everolimus





Number at risk

Cabozantinib	330	261	148	88	20	6	2
Everolimus	328	174	72	37	10	2	0

Cabozantinib	330	318	296	264	239	178	105	41	6	3	0
Everolimus	328	307	262	229	202	141	82	32	8	1	0

Number censored

Cabozantinib	0	17	37	32	47	12	3
Everolimus	0	51	24	13	16	8	2

Cabozantinib	0	0	3	1	0	35	57	56	32	3	3
Everolimus	0	3	2	1	2	34	42	36	20	7	1

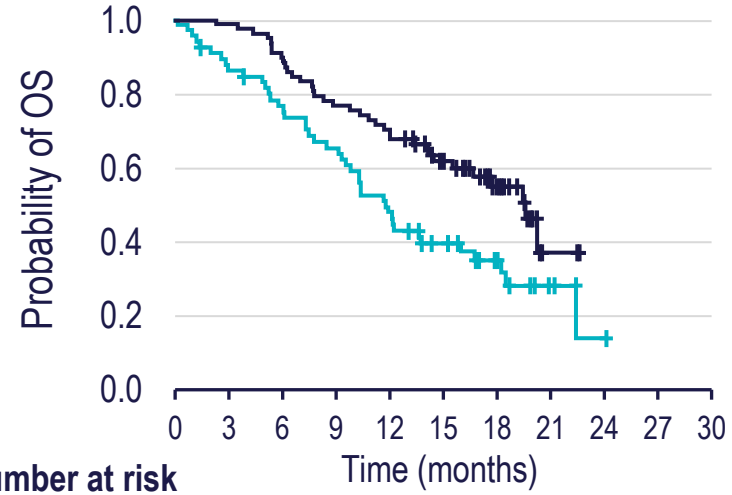
HR, hazard ratio; OS, overall survival; PFS, progression-free survival

Choueiri TK et al. *Lancet Oncol* 2016;17:917-27

METEOR

Cabozantinib improved OS in patients with and without bone metastases

Patients with bone metastases



Number at risk

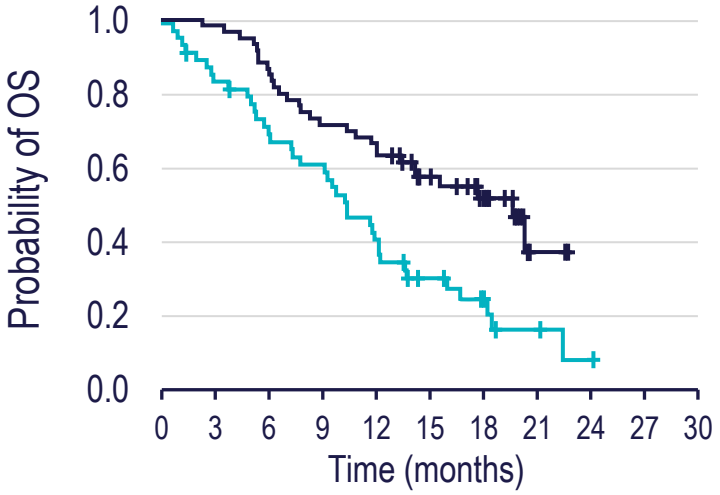
Cabozantinib	77	76	70	60	55	38	22	3	0	—	—
Everolimus	65	56	48	41	32	21	14	5	1	0	—

Months, median (95% CI)

Cabozantinib (n=77)	20.1 (14.9-NE)
Everolimus (n=65)	12.1 (9.6-16.4)

HR, 0.54; 95% CI, 0.34-0.84

Patients with bone and visceral metastases



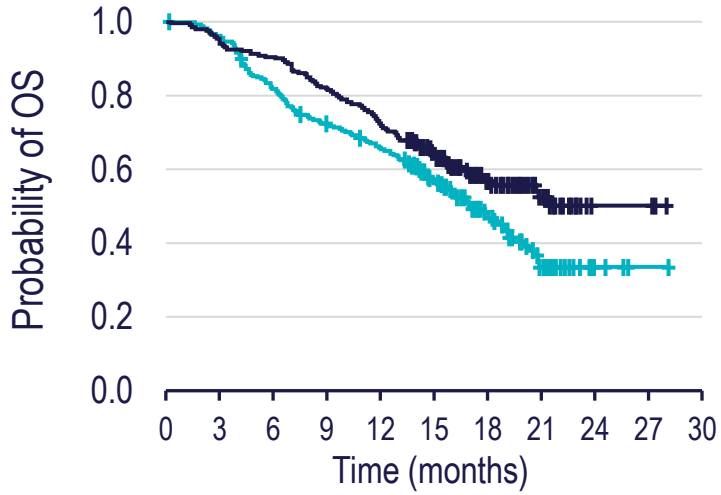
	60	59	53	44	41	25	18	3	0	—	—
	52	43	35	30	22	12	9	3	1	0	—

Months, median (95% CI)

Cabozantinib (n=60)	20.1 (12.4-NE)
Everolimus (n=52)	10.7 (7.5-12.5)

HR, 0.45; 95% CI, 0.28-0.72

Patients without bone metastases



	253	242	226	204	184	140	83	38	6	3	0
	263	251	214	188	170	120	68	27	7	1	0

Months, median (95% CI)

Cabozantinib (n=253)	NE (18.4-NE)
Everolimus (n=263)	17.5 (15.7-19.6)

HR, 0.71; 95% CI, 0.55-0.91

HR, hazard ratio; NE, not evaluable; OS, overall survival

Escudier B et al. *J Clin Oncol* 2018;36:765-72

Case 2: Subsequent Treatment in mRCC

Question 2

- A 60-year-old female patient with clear cell mRCC has progressed on first-line ipilimumab/nivolumab and second-line sunitinib. Restaging scans after 6 months of sunitinib show progression of her disease.

Proposed action If you were thinking of…	**New information** And then you find…	**Question*** The new info makes the proposed action…
Prescribing 60 mg cabozantinib daily	Patient needed individualized dosing for grade 3 hand-foot syndrome and grade 3 fatigue while on fixed dose of sunitinib.	-2 -1 0 +1 +2

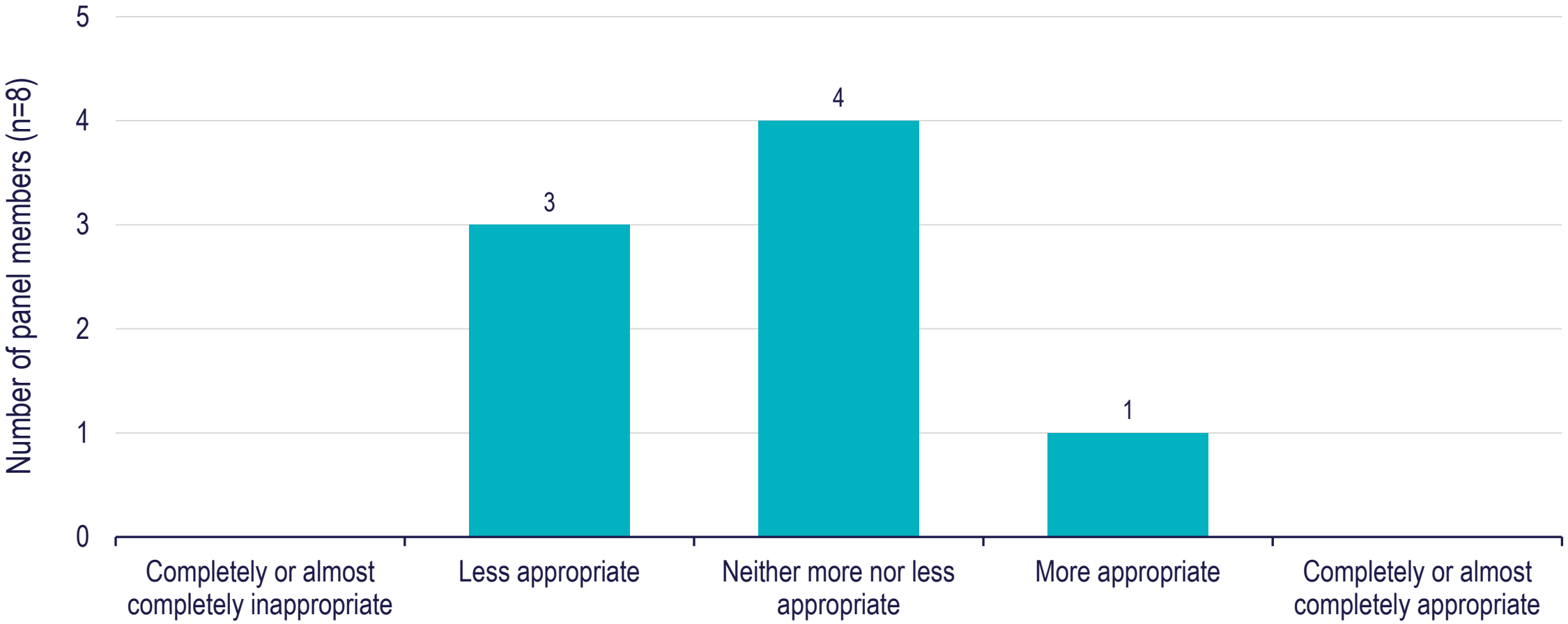
*The new information makes the proposed action:
-2 very inappropriate; -1 inappropriate; 0 neither more nor less appropriate;
+1 more appropriate; +2 very appropriate.

mRCC, metastatic renal cell carcinoma

Individual Voting

5 minutes

Summary of Expert Panel Responses



Summary of Expert Panel Responses

-1	I would start at 40 mg daily with plans to increase the dose if the patient tolerates therapy after a few weeks.
-1	In this situation, starting at a dose of 40 mg and titrating up would be reasonable.
-1	We can easily dose adjust the cabozantinib as well. I would just start at a lower dose and monitor very closely.
0	Just means that she might have a risk of hand-foot syndrome again and might need a dose reduction.
0	I might consider starting with a lower dose and titrating upward if well tolerated.
0	Cabozantinib can also be individualized for such patients.
0	Although toxicity with one agent does not always predict for toxicity with another, I would be very cautious in this situation. I would not dose reduce if the toxicity from the sunitinib had adequately resolved before starting cabozantinib. I would, however, increase the frequency of telephone and in-person assessments in the first few months of treatment so that any early toxicity could be addressed.
+2	Cabozantinib can be dose individualized.

The thoughts expressed here are those of the expert panel and may not align with Health Canada–approved dosing.
Ipsen Canada does not recommend the use of its products in a manner that is inconsistent with the approved product monograph.

Summary of Dosing and Key Characteristics

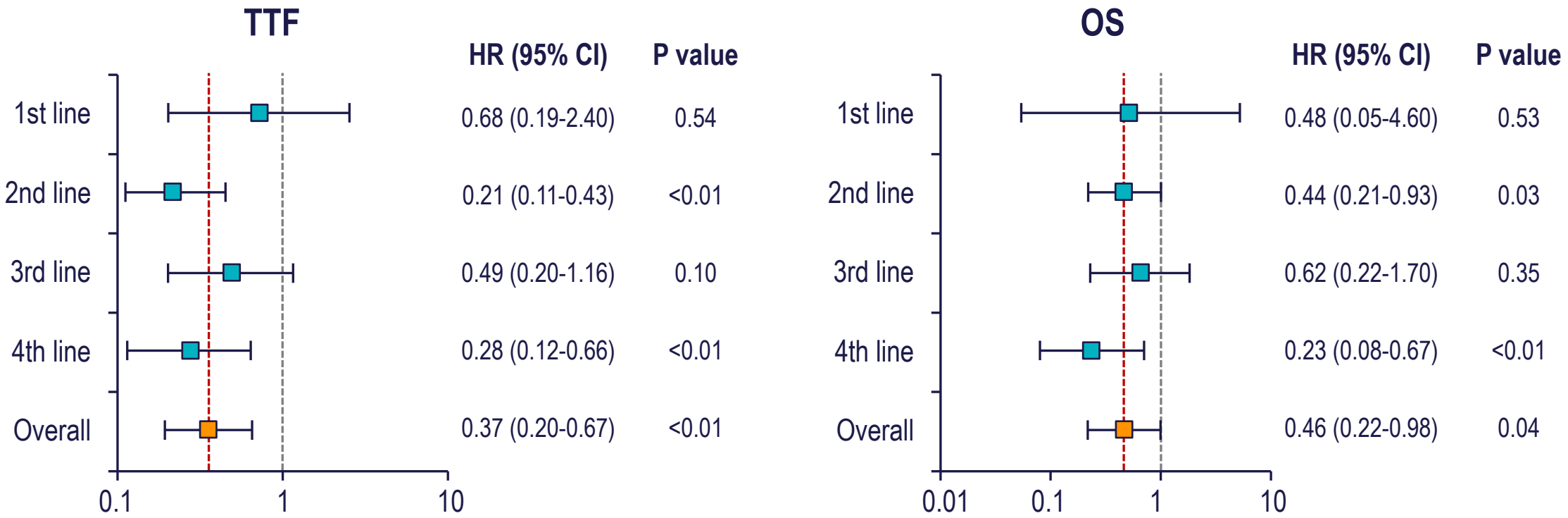
	Cabozantinib[1]	Axitinib[2]	Lenvatinib + everolimus[3,4]
Indication	Advanced RCC following prior VEGF-targeted therapy	Metastatic RCC following cytokine or sunitinib	Advanced RCC following one prior VEGF-targeted therapy (everolimus: sunitinib or sorafenib)
Mode of action	Inhibitor of multiple RTKs (including VEGFR, MET, and AXL)	TKI (including VEGFR-1, -2, and -3)	Lenvatinib: Multiple receptor TKI Everolimus: mTOR kinase inhibitor
Administration	60 mg tablet once daily	5 mg twice daily	18 mg lenvatinib + 5 mg everolimus once daily
Dose adjustments	• In case of AEs, reduce to 40 mg daily, then to 20 mg daily • Dose interruptions are recommended for management of AEs ≥ grade 3 or intolerable grade 2 toxicities	• Patients who tolerate 5 mg may have their dose increased to 7 mg, then 10 mg • If dose reduction necessary, the INLYTA® dose may be reduced from 5 mg twice daily to 3 mg twice daily, and further to 2 mg twice daily	• Management of AEs may require interruption of therapy • Upon resolution/improvement of an AE, lenvatinib should be resumed at the following reduced doses: - First occurrence: 14 mg/d - Second occurrence: 10 mg/d - Third occurrence: 8 mg/d
Half-life	99 hours	2.5-6.1 hours	Lenvatinib: 28 hours Everolimus: n/a

AE, adverse event; mTOR, mammalian target of rapamycin; n/a, not available; RCC, renal cell carcinoma;
RTK, receptor tyrosine kinase; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor

1. CABOMETYX® (cabozantinib) Product Monograph, Nov 7, 2019; 2. INLYTA® (axitinib) Product Monograph, Jan 3, 2020; 3. LENVIMA® (lenvatinib) Product Monograph, Sept 19, 2019;
4. AFINITOR® (everolimus) Product Monograph, November 16, 2017

Dose Reduction of Cabozantinib Due to Toxicity Associated With Improved TTF and OS

Effect on TTF and OS when dose reduction due to toxicity was required



HRs adjusted by IMDC prognostic group. HR <1 in favour of patients requiring dose reduction.

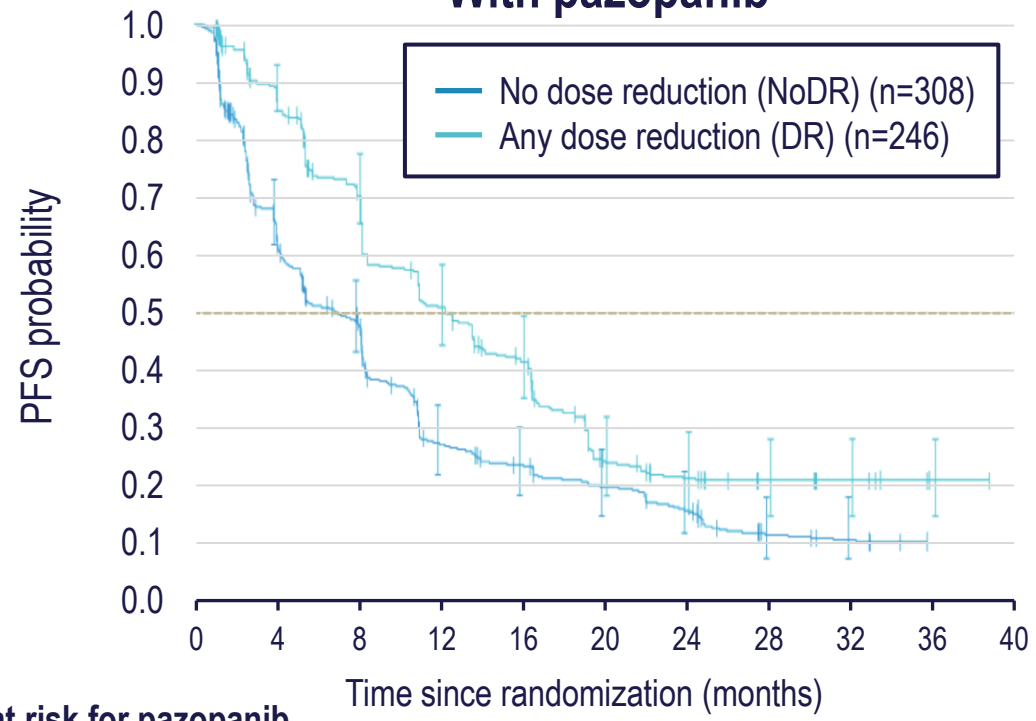
HR, hazard ratio; IMDC, International Metastatic RCC Database Consortium; OS, overall survival; TTF, time to treatment failure

Gan CL et al. *Cancer Med* 2021;10:1212-21

TKI Dose Reductions Associated With Greater Efficacy

PFS in patients with and without dose reductions

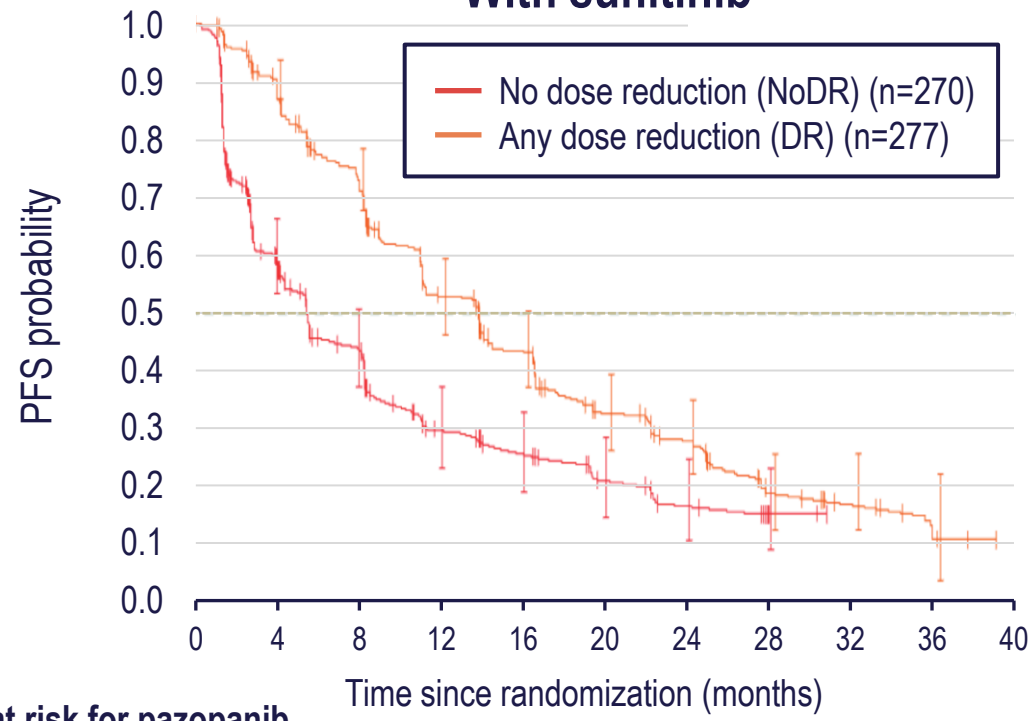
With pazopanib



No. at risk for pazopanib

NoDR	308	166	107	48	38	30	24	9	7	0	0
DR	246	195	138	88	67	31	22	10	6	1	0

With sunitinib



No. at risk for pazopanib

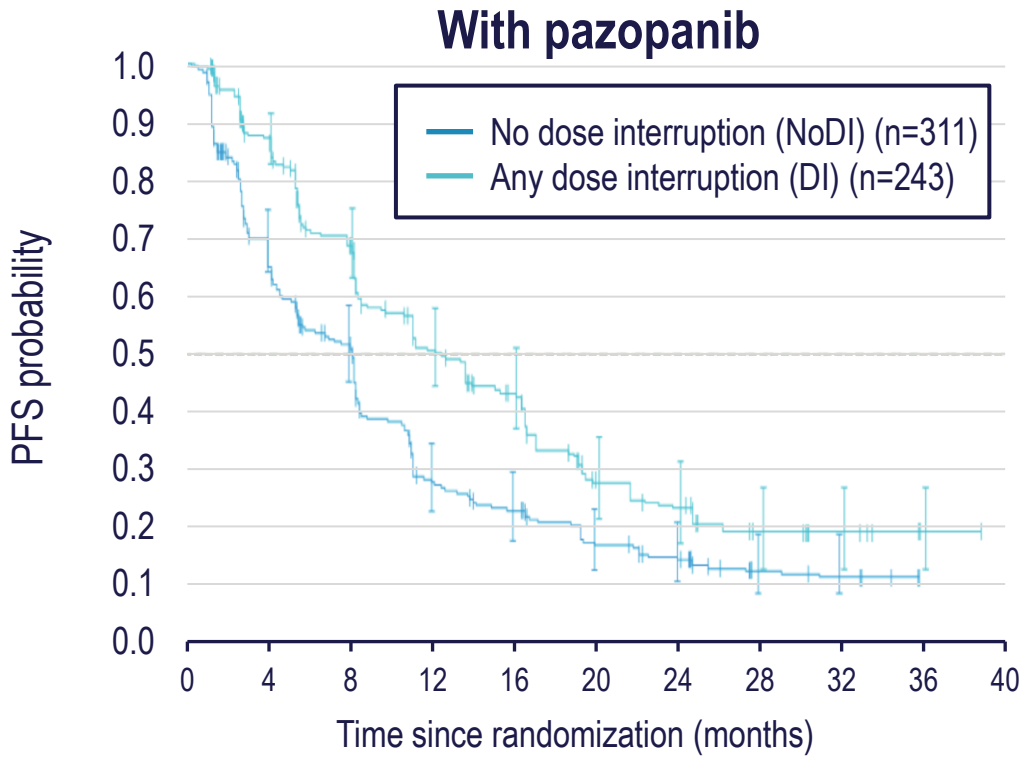
NoDR	270	118	74	39	29	18	11	2	0	0	0
DR	277	233	175	108	82	51	37	16	10	3	0

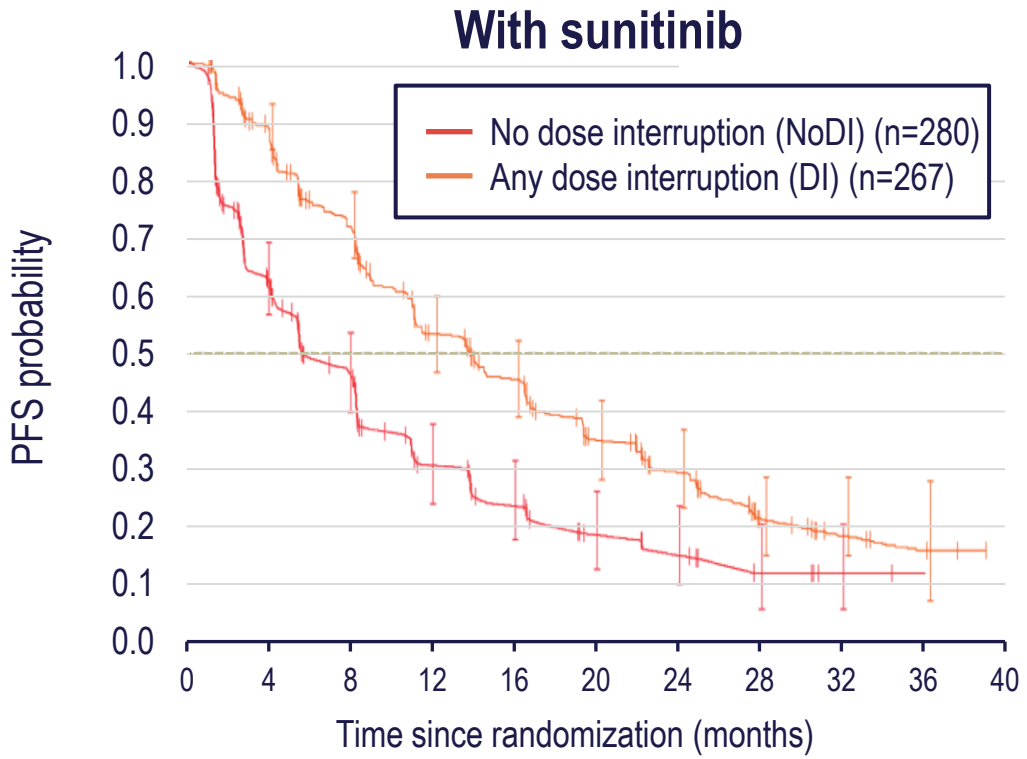
PFS, progression-free survival; TKI, tyrosine kinase inhibitor

Sternberg CN et al. *Clin Genitourin Cancer* 2019;17:425-35

TKI Dose Interruptions Associated With Greater Efficacy

PFS in patients with and without dose interruptions

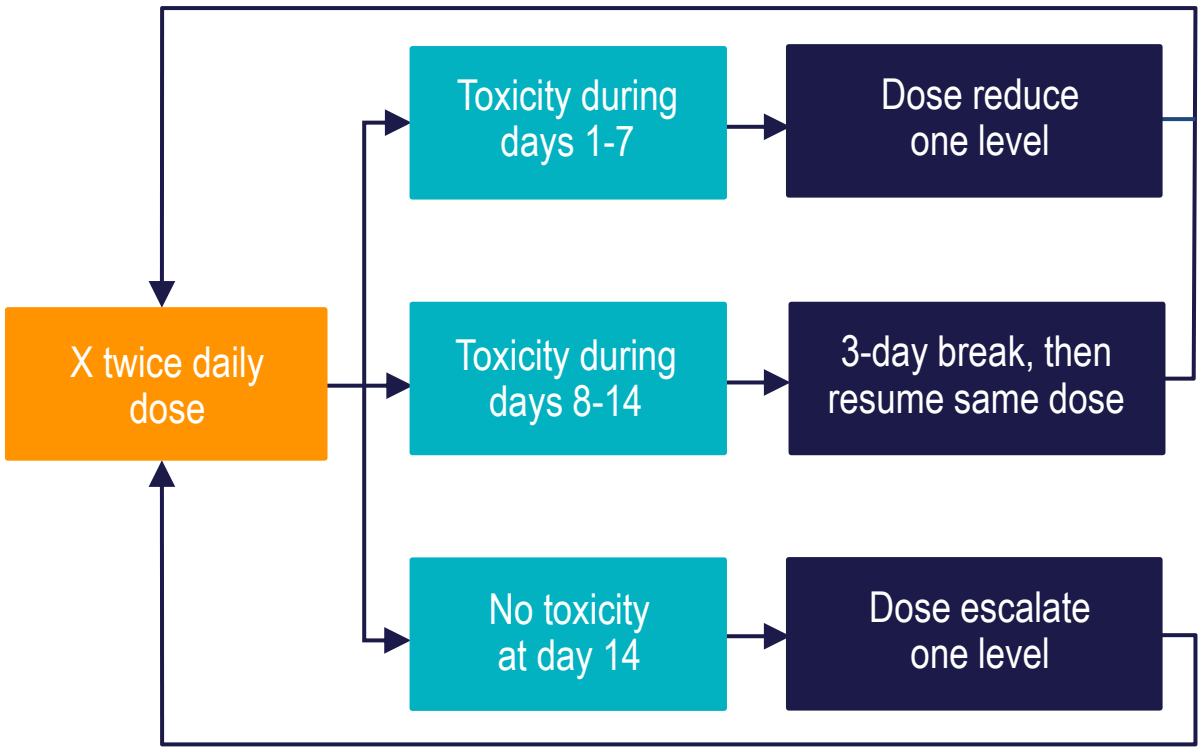




PFS, progression-free survival; TKI, tyrosine kinase inhibitor

Sternberg CN et al. *Clin Genitourin Cancer* 2019;17:425-35

Individualized Axitinib Dosing After IO Should Be Considered



- Multicentre, phase 2 trial of axitinib given on an individualized dosing algorithm (N=40)
- Toxicity-based titration, including dose escalations and reductions by 1 mg twice daily
- Although study did not meet the prespecified threshold for PFS, these data show that this individualized titration scheme is feasible and has robust clinical activity
- Optimizing axitinib exposure with refined titration and breaks should be strongly considered

IO, immunotherapy; PFS< progression-free survival

Ornstein MC et al. *Lancet Oncol* 2019;20:1386-94

Dose and Schedule of VEGF TKIs Should Be Optimized

Adjusting dose for individual toxicities is associated with improved outcomes

- Individualized sunitinib therapy has been proven to be a safe and effective method to manage sunitinib toxicity, with one of the best efficacies seen for oral VEGF inhibitors in mRCC and no decline in quality-of-life scores during therapy[1]
- Improved outcomes have been demonstrated for patients experiencing AEs requiring dose modifications compared with patients who do not require dose modification during treatment with VEGF TKIs[2-4]
- KCRNC recommends starting with the standard dosing schedule as outlined in the individual product monographs. After evaluation of type and timing of toxicities, patients may require adjustments to the schedule and/or dose[5]

AE, adverse event; KCRNC, Kidney Cancer Research Network of Canada; mRCC, metastatic renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor

1. Bjarnason GA et al. *Eur J Cancer* 2019;108:69-77; 2. Gan CL et al. Poster at ASCO 2020 Genitourinary Cancers Symposium; February 13-15, 2020; San Francisco, CA;
3. Sternberg CN et al. *Clin Genitourin Cancer* 2019;17:425-35; 4. Ornstein MC et al. *Lancet Oncol* 2019;20:1386-94; 5. Hotte SJ et al. *Can Urol Assoc J* 2019;13:343-54

Case 2: Subsequent Treatment in mRCC

Question 3

- A 60-year-old female patient with clear cell mRCC has progressed on first-line ipilimumab/nivolumab and second-line sunitinib. Restaging scans after 6 months of sunitinib show progression of her disease.

Proposed action If you were thinking of…	**New information** And then you find…	**Question*** The new info makes the proposed action…
Prescribing axitinib	Resistance pathways may be activated post-sunitinib	-2 -1 0 +1 +2

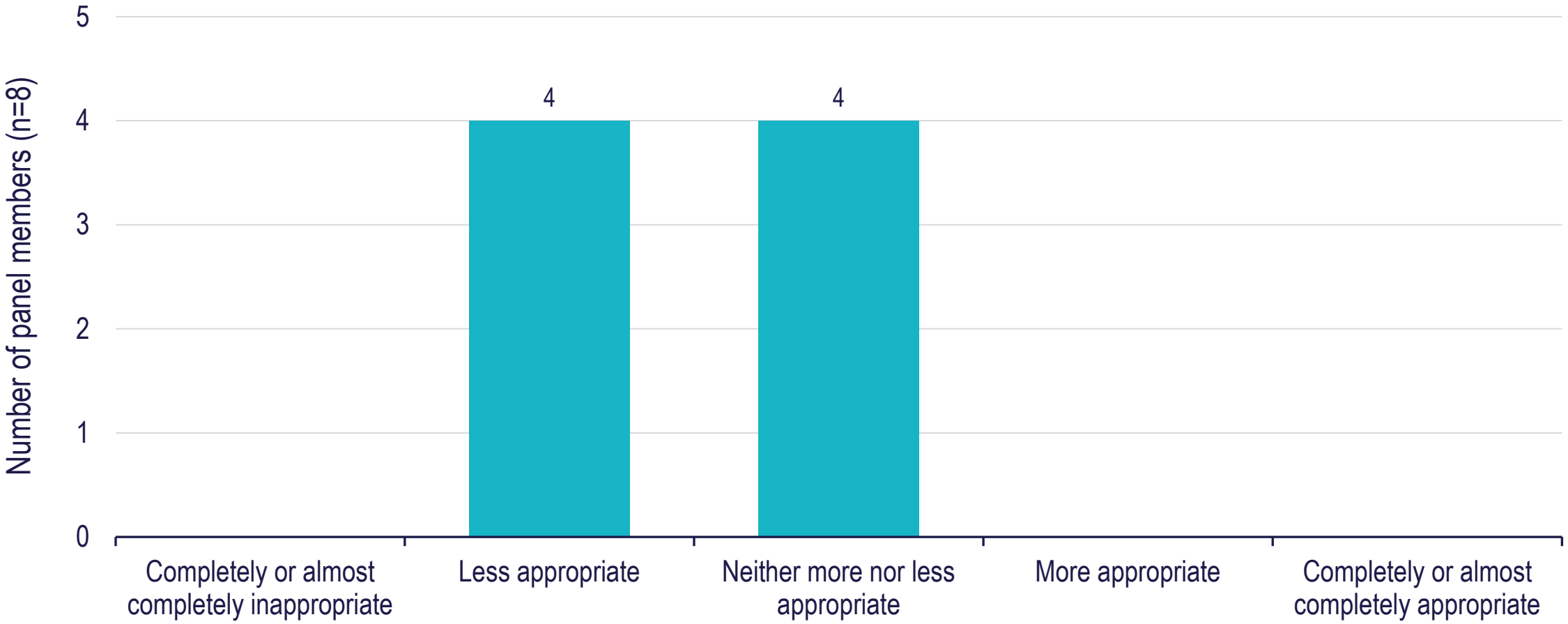
*The new information makes the proposed action:
-2 very inappropriate; -1 inappropriate; 0 neither more nor less appropriate;
+1 more appropriate; +2 very appropriate.

mRCC, metastatic renal cell carcinoma

Individual Voting

5 minutes

Summary of Expert Panel Responses



Summary of Expert Panel Responses

-1	We don’t know much about the resistance pathways and their impact on activity.
-1	I would like to target the MET pathway here. I would give cabozantinib for sure.
-1	Cabozantinib is a better option than axitinib based on the MoA of cabozantinib overcoming resistance pathways.
-1	Prior studies have suggested incomplete cross-resistance between these agents.
0	This would not change my thinking, since this may impact the activity of both axitinib and cabozantinib.
0	Patients progressing on sunitinib must have some resistance pathway activated. Choice of therapy is not based on this. There is evidence for efficacy of axitinib postprogression on sunitinib. Therefore, learning about "activated resistance pathways" would not affect my decision if I had already chosen to give axitinib in this setting.
0	Agree, but therapeutic options are limited.
0	Since we do not assess for this in routine clinical use, it would not necessarily alter my choice of agent.

MoA, mechanism of action

Target Pathways of Current TKIs in mRCC

TKI	VEGFR	PDGFR	RAF	MET	AXL
Axitinib	X	X			
Cabozantinib	X			X	X
Lenvatinib	X	X			
Pazopanib	X	X			
Sorafenib	X	X	X		

mRCC, metastatic renal cell carcinoma; PDGFR, platelet-derived growth factor receptor; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor

Choueiri TK, Motzer RJ. *N Engl J Med* 2017;376:354-66

Roles of Resistance and MoA Unclear

- No data available to guide subsequent therapy for patients who progress on IO
- Several retrospective reviews show TKIs have activity after IO
- Only one prospective study has demonstrated VEGF TKI (axitinib) activity after IO
- Based on METEOR, cabozantinib is also a preferred option in this setting
- Roles of the MoA and treatment resistance are unclear

IO, immunotherapy; MoA, mechanism of action; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor

Hotte SJ et al. *Can Urol Assoc J* 2019;13:343-54

KCRNC Consensus Statement Treatment Recommendations by Risk and Line of Therapy

Setting	Patients	Preferred	Options
Untreated	Favourable risk (IMDC)	• Cabozantinib + nivolumab* • Axitinib + pembrolizumab • Lenvatinib + pembrolizumab*	• Sunitinib • Pazopanib • Axitinib + avelumab* • Active surveillance
	Intermediate-/poor-risk (IMDC)	• Ipilimumab + nivolumab • Cabozantinib + nivolumab* • Axitinib + pembrolizumab • Lenvatinib + pembrolizumab*	• Cabozantinib • Sunitinib • Pazopanib • Axitinib + avelumab* • Active surveillance
Second-line and beyond	Prior VEGF inhibitor	• Cabozantinib • Nivolumab	• Lenvatinib + everolimus • Everolimus • Axitinib
		Options	
	Prior immune checkpoint inhibitor	• Cabozantinib • Axitinib • Sunitinib	• Pazopanib • Lenvatinib + everolimus
	Prior VEGF and immune checkpoint inhibitor†	• Cabozantinib • Sunitinib • Pazopanib	• Axitinib • Lenvatinib + everolimus

Preferred options originated from studies that have demonstrated OS improvements. Options have usually demonstrated a progression-free survival advantage but not necessarily OS survival.
*Not yet approved in Canada. †If not previously used.
IMDC, International Metastatic RCC Database Consortium; OS, overall survival; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor
Canil C, et al. *Can Urol Assoc J* 2021;15:84-97