Management Issues For Patients with Advanced Renal Cell Carcinoma

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RCC Case Scenario (Case 1)

Choice of 1st line therapy for metastatic RCC:

- 58 yo, ccRCC resected 4 years ago; no evidence of metastasis
- Imaging reveals multiple pulmonary nodules and bone lesions; biopsy of lung lesion confirms metastatic ccRCC
- Serum Crt 1.2 mg/dl; other labs WNL
- ECOG PS 1
- Two weeks ago had a short course of radiation to metastatic site in thoracic spine which resulted in pain reduction
- What would you recommend now?

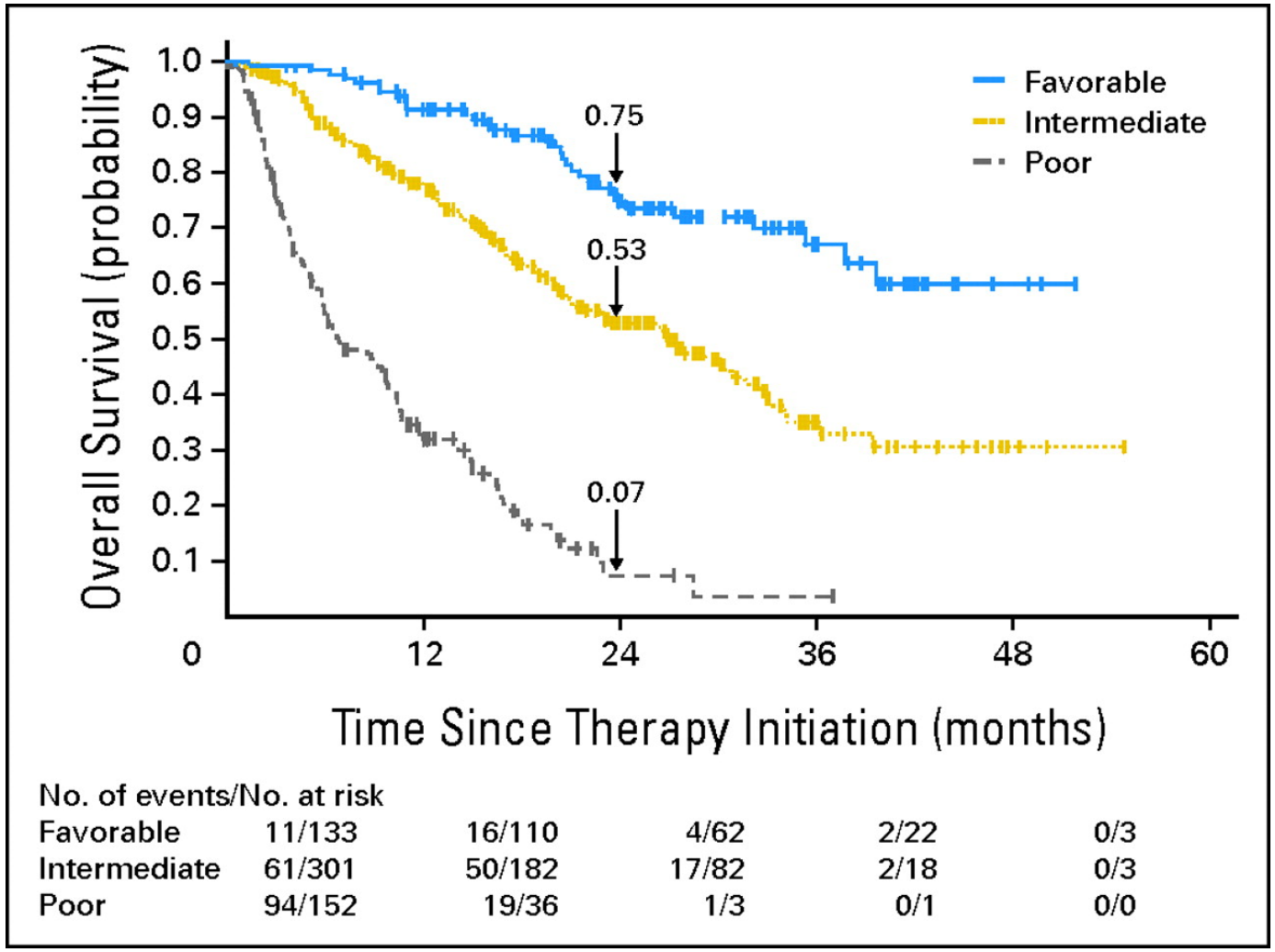
Choice of 1st line therapy for metastatic RCC when recurrence occurs 8 months following initial resection (rather than 4 years):

- If recurrence were at 8 months following initial resection (rather than 4 years), what would you recommend?

Courtesy of Thomas E Hutson, DO, PharmD

Overall Survival Probability for Patients with mRCC Treated with VEGF-Targeted Agents

According to time after therapy initiation and risk group



Heng DYC et al. JCO 2009;27:5794-5799

Courtesy of Thomas E Hutson, DO, PharmD

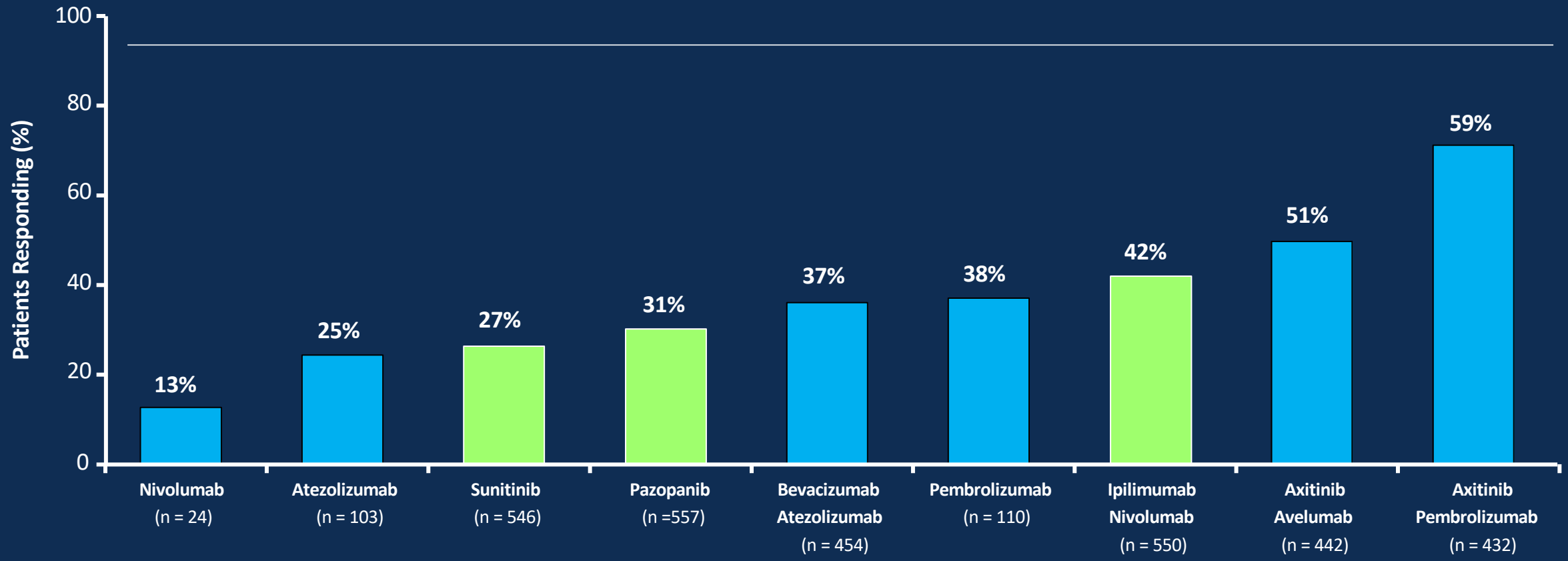
Endpoint summary table- indirect comparison

	COMPARZ PAZOP	COMPARZ SUN	CM214 IPI/NIVO Poor/Int	CM214 SUN Poor/Int	CABOSUN CABO	CABOSUN SUN	KN426 AXI/PEM	KN426 SUN	JAV101 AXI/AVE PD-L1+	JAV101 SUN PD-L1+	JAV101 AXI/AVEL ITT	JAV101 AXI/AVEL SUN ITT
Patient (n)	557	553	425	422	79	78	432	429	270	290	442	444
PFS	8.4m	9.5m	11.6m	8.4m	8.6m	5.3m	15.1m	11.1m	13.8m	7.2m	13.8	8.4
mOS	28.4m	29.3m	NR *HR 0.71*	26.0m	30.3m *HR 0.80*	21.8m	NR *HR 0.53*	NR	NR	NR	NR *HR 0.78*	NR
ORR	31%	25%	42%	27%	33%	12%	59%	36%	55%	26%	51%	26%
AEs (Grade 3/4)	NR	NR	46% (ITT pop)	63% (ITT pop)	67%	68%	76%	71%	71% (ITT pop)	72% (ITT pop)	71%	72%

NR: not reached or not recorded.

Motzer RJ *et al. N Engl J Med* 2013;369:722—31. Motzer RJ *et al. N Engl J Med* 2018;378:1277—90. Choueiri TK *et al. J Clin Oncol* 2016;35:591—7. Rini BI *et al. N Engl J Med* 2019;380:1116—27. Motzer RJ *et al. N Engl J Med* 2019;380:1103—15.

Response Rates in Frontline Metastatic ccRCC (ITT; All Risk Groups)



Courtesy of Thomas E Hutson, DO, PharmD

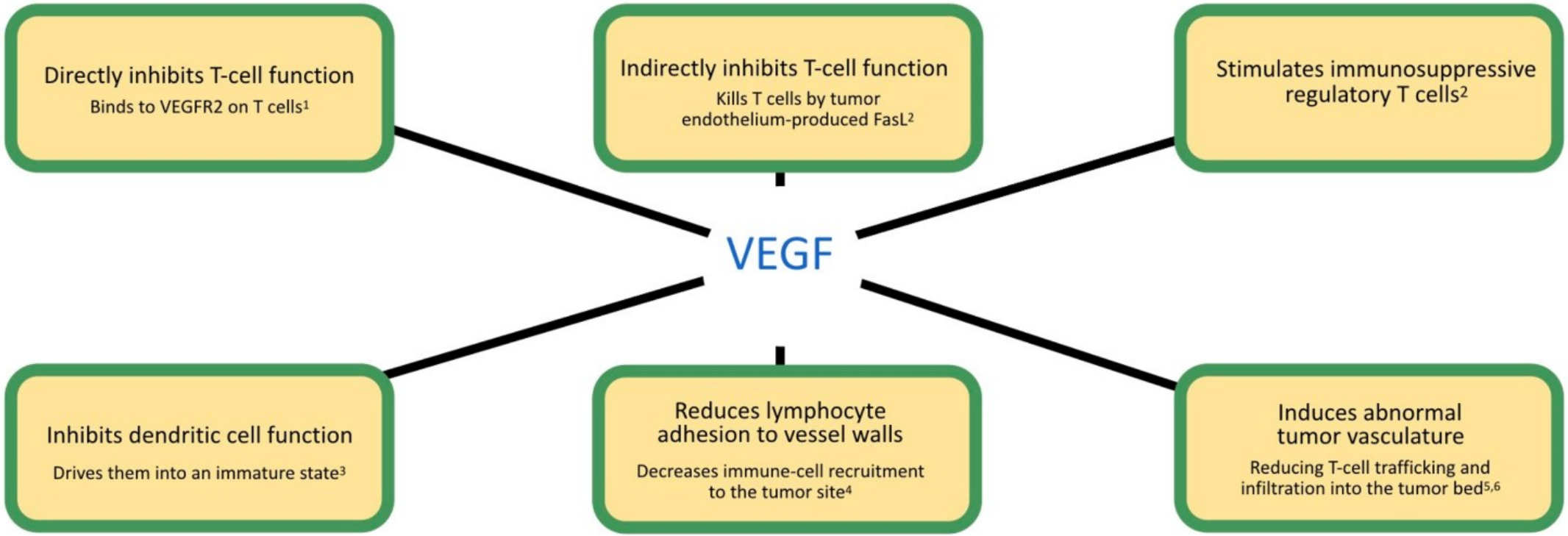
NEW IO/TKI COMBINATIONS ENTER TREATMENT PARADIGM

Setting		Preferred	Alternative
First-Line Therapy	Good risk*	Cabo/Nivo Len/Pembro Sunitinib/Pazopanib Pembrolizumab + axitinib? Avelumab + axitinib?	Ipilimumab + nivolumab Cabozantinib Axitinib Bevacizumab + IFNα HD IL-2
	Intermediate or poor risk*	Ipilimumab + nivolumab Cabozantinib Pembrolizumab + axitinib? Avelumab + axitinib?	Sunitinib Pazopanib Axitinib Bevacizumab + IFNα HD IL-2 Temsirolimus
Second-Line Therapy	Prior VEGFR inhibitor	Nivolumab Cabozantinib Lenvatinib + everolimus Axitinib Everolimus Ipilimumab + nivolumab	Sunitinib Pazopanib Sorafenib Bevacizumab HD IL-2 Temsirolimus
	Prior IO Agent	Same as above minus nivolumab	

Courtesy of Thomas E Hutson, DO, PharmD

RATIONALE FOR IO–TKI COMBINATIONS

EFFECTS OF VEGF ON THE TUMOR MICROENVIRONMENT

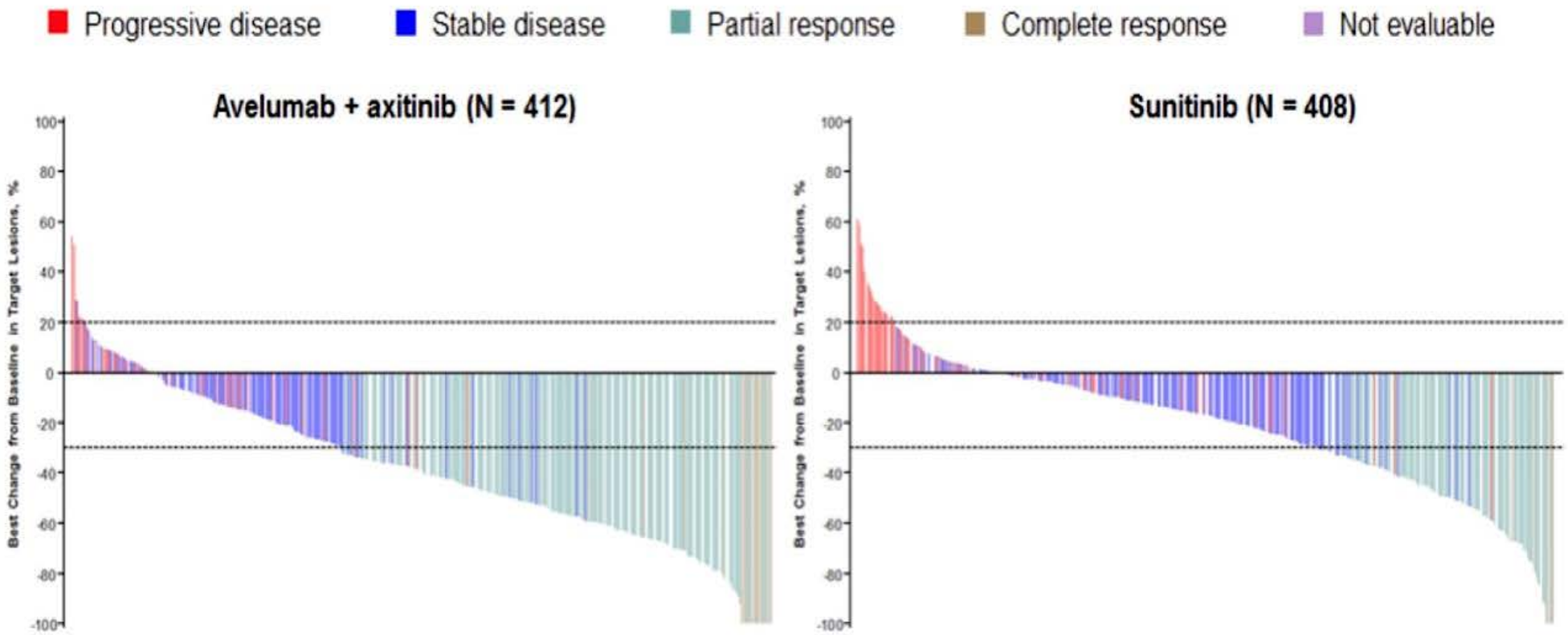


1. Gavalas NG et al. Br J Cancer 2012;107:1869–75; 2. Terme M et al. Cancer Res 2013;73:539–49; 3. Coukos G et al. Br J Cancer 2005;92:1182–7; 4. Bouzin C etal. J 5. Immunol 2007;178:1505–11; 5. Shrimali RK et al. Cancer Res 2010;70:6171–80; 6. Chen DS & Mellman I. Immunity 2013;39:1–10

Courtesy of Thomas E Hutson, DO, PharmD

IO+TKI DEMONSTRATED DEEP* TUMOR RESPONSES

JAVELIN RENAL 101 BEST PERCENTAGE CHANGE FROM BASELINE IN THE SUM OF THE LONGEST DIAMETERS OF TARGET LESIONS IN THE ITT POPULATION



* Characterized as ≥30% decrease in the sum of target-lesion diameters measured using RECIST v1.1 criteria

Adaptado de: Motzer RJ, et al. Ann Oncol. 2018;29(Suppl 8): Abstract LBA6

Courtesy of Thomas E Hutson, DO, PharmD

First-line IO Combination Trials in mRCC

	CheckMate 214 (Ipi/Nivo) [1] (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro)[2] (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo)[3] (n=323 vs n=328)	CLEAR (Len/Pembro)[4] (N=355 vs n=357)
mOS, months HR (CI);	NR vs 38.4 **0.69** (0.59–0.81);	NR vs 35.7 **0.68** (0.55-0.85);	NR vs NR **0.60** (0.40–0.89);	NR vs NR **0.66** (0.49-0.88)
Landmark OS 12 mo Landmark OS 24 mo	**83%** vs. 78% **71%** vs. 61%	**90%** vs. 79% **74%** vs. 66%	**87%** vs. 78% (est) **74%** vs 60% (est)	**90%** vs 79% (est.) **79%** vs. 70%
mPFS, months HR (CI)	**12.2** vs 12.3 0.89 (0.76–1.05)	**15.4** vs 11.1 0.71 (0.60–0.84)	**16.6** vs 8.3 0.51 (0.41–0.64)	**23.9** vs 9.2 0.39 (0.32-0.49)
ORR, %	**39** vs 32	**60** vs 40	**56** vs 27	**71** vs 36
CR, %	**11** vs 3	**9** vs 3	**8** vs 5	**16** vs 4
Med f/u, months	**55**	**30.6**	**18.1**	**27**
Prognostic risk, % Favorable Intermediate Poor	 23 61 17	 32 55 13	 23 58 19	 31 59 9
Prior nephrectomy	82%	83%	69%	74%
Subsequent systemic therapies for sunitinib arm, %	Overall (69%) IO (42%)	Overall (69%) IO (48%)	Overall (40%) IO (29%)	NR

1. Albiges et al. ESMO Open 2020
2. Powles et al. Lancet Oncology 2020
3. Choueiri et al. ESMO 2020
4. Motzer et al. ASCO GU 2021.

@brian_rini and @Uromigos (podcasts: https://anchor.fm/the-Uromigos)

Courtesy of Thomas E Hutson, DO, PharmD

RCC Case Scenario, Case 1 continued

Choice of 2nd line therapy for mRCC – recurrence at 4 months:

- Patient with bone and lung mets receives your 1st line therapy of choice.
- Imaging at 12 weeks documents stable disease; however, after 4 months of therapy, reimaging reveals increasing lung nodules bilaterally and several new retroperitoneal nodes
- Brain MRI is normal; ECOG PS is 1; Crt: 1.2; other labs are WNL
- What would you recommend as 2nd line therapy?

Choice of 2nd line therapy for mRCC – recurrence at 11 months:

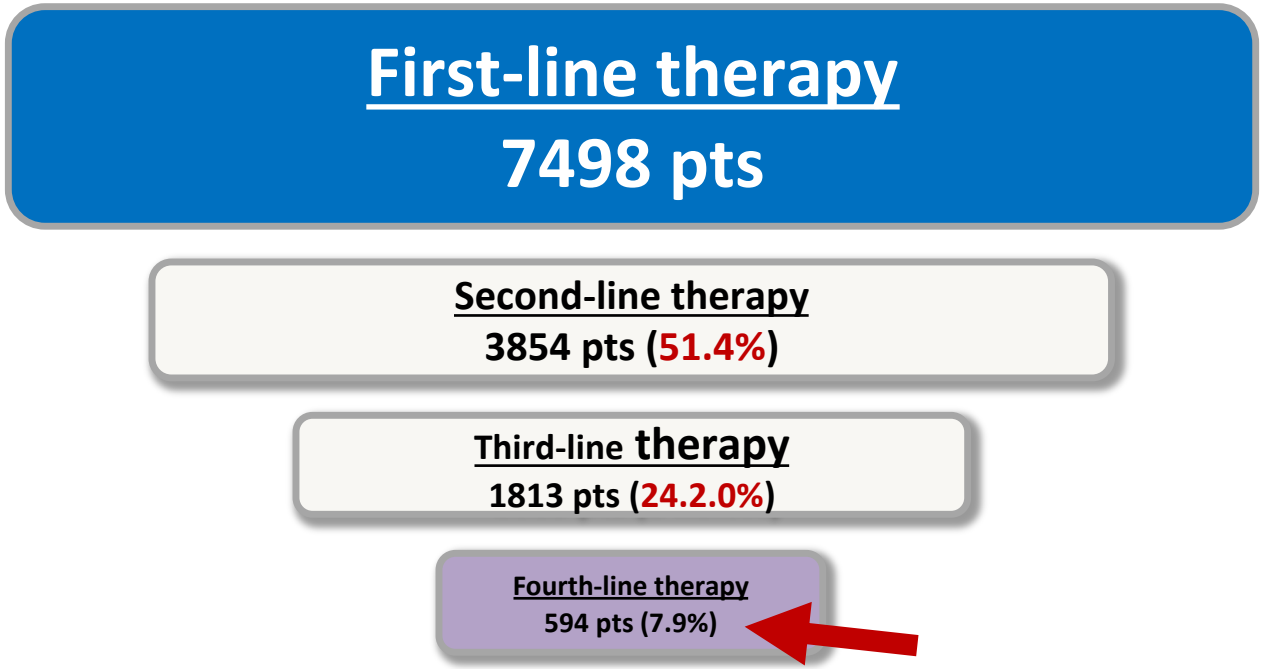
- If recurrence were at 11 months (rather than 4 months) what would you recommend as 2nd line therapy?

Choice of 3rd line therapy for mRCC – recurrence at 11 months:

- Receives your 2nd line therapy of choice; then recurs 5 months later
- ECOG PS remains 1

Courtesy of Thomas E Hutson, DO, PharmD

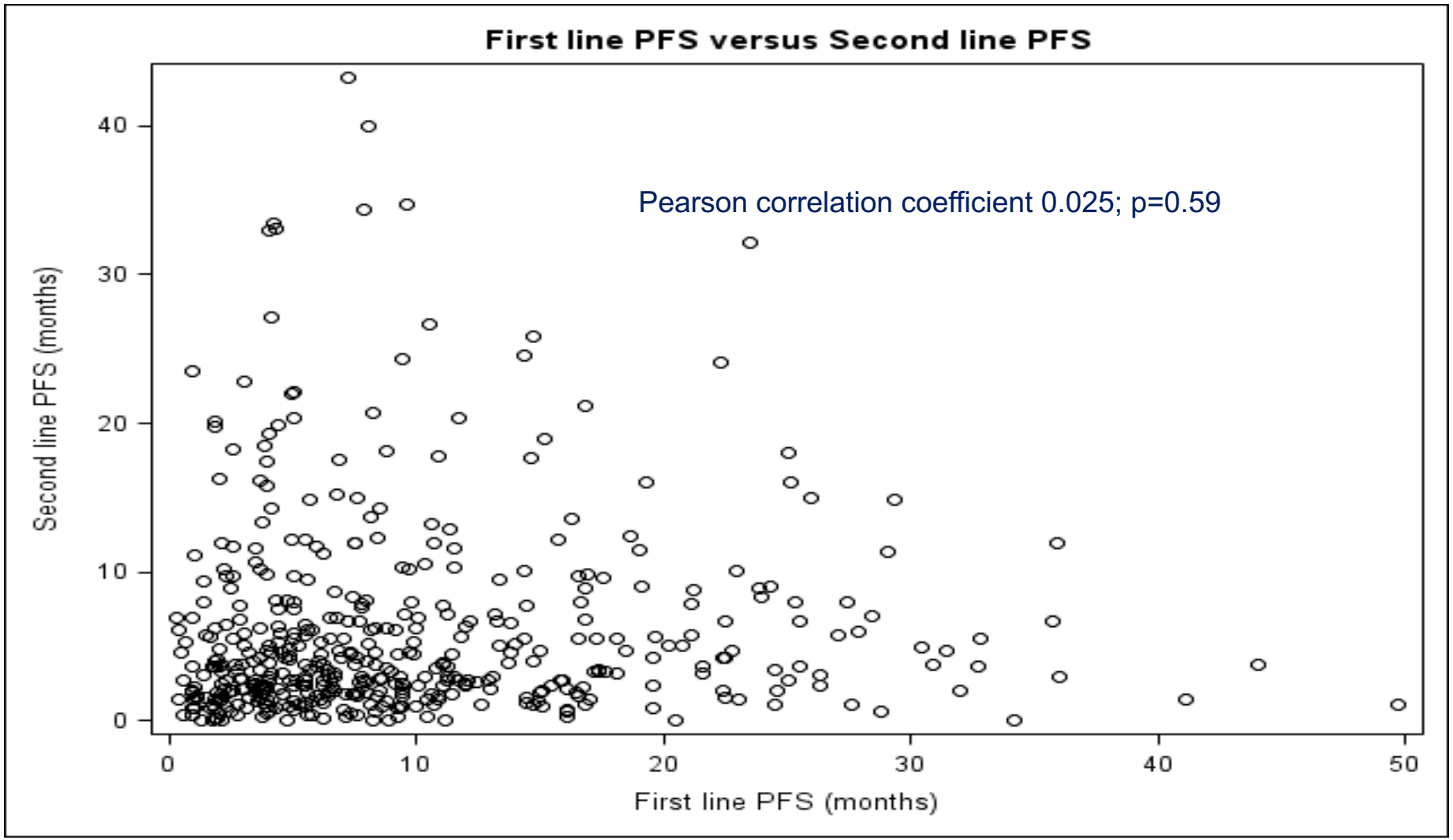
Attrition Across Lines of Therapy (IMDC Data)



Stukalin et al, Kidney Cancer, 2018

Courtesy of Thomas E Hutson, DO, PharmD

Correlation of first line PFS and second line PFS



Courtesy of Thomas E Hutson, DO, PharmD

Efficacy summary in the second line setting

Trial	AXIS	CheckMate-025	METEOR	HOPE 205
Arms	Axitinib vs Sorafenib	Nivolumab vs Eve	Cabozantinib vs Eve	Len + Eve vs Eve
Phase	3	3	3	2
No. of pts.	361 vs 362	406 vs 397	330 vs 328	51 vs 50
mPFS (months)	6.7 vs 4.7	4.6 vs 4.4	7.4 vs 3.9	14.6 vs 5.5
HR 95% CI P value	0.665 (0.544-0.812) P<0.0001	0.88 (0.75-1.03) P<0.11	0.58 (0.45-0.75) P<0.001	0.45 (0.27-0.79) P=0.029
mOS (months)	20.1 vs 19.2	25 vs 19.6	21.4 vs 16.5	25.5 vs 19.1
HR 95% CI P value	0.969 (0.800-1.174) p=0·3744	0.73 (0.57-0.93) P=0.002	0.66 (0.53-0.83) p-=0.00026	NA NA
ORR (%)	19 vs 9	25 vs 5	21 vs 5	43 vs 6
P value	P<0.0001	P<0.001	P<0.0001	P<0.0001

Courtesy of Thomas E Hutson, DO, PharmD

Safety summary in the second line

Trial	AXIS	CheckMate-025	METEOR	HOPE 205
Arms	Axitinib vs Sorafenib	Nivolumab vs Eve	Cabozantinib vs Eve	Len + Eve vs Eve
Phase	3	3	3	2
No. of pts.	361 vs 362	406 vs 397	330 vs 328	51 vs 50
Median treatment duration, months	8.2	5.5	8.3	7.6
Any Dose reduction (%)	34	NA	62	71
Discontinuation due to AE (%)	4	8.6	12	24
All causality AEs Grade 3/4 AE (%)	65.7	53	71	71

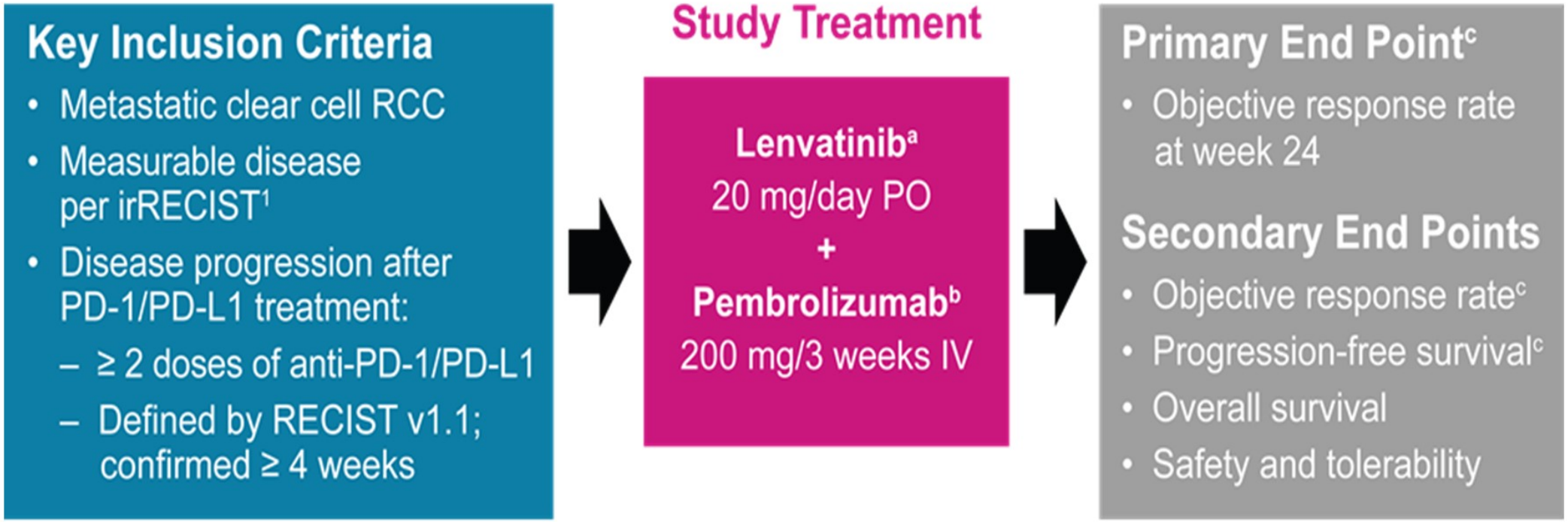
Courtesy of Thomas E Hutson, DO, PharmD

Phase 2 trial of lenvatinib plus pembrolizumab for disease progression after PD-1/PD-L1 immune checkpoint inhibitor (ICI) in metastatic clear cell renal cell carcinoma

Chung-Han Lee[1], Amishi Y. Shah[2], James J. Hsieh[3], Arpit Rao[4], Alvaro Pinto[5], Mehmet Asim Bilen[6], Allen Lee Cohn[7], Christopher Di Simone[8], David R. Shaffer[9], Regina Girones Sarrio[10], Sara Gunnestad Ribe[11], Jane Wu[12], Emmett V. Schmidt[13], Rodolfo Perini[13], Peter Kubiak[12], Alan D. Smith[14], Robert J. Motzer[1]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]MD Anderson Cancer Center, University of Texas, Houston, TX, USA; [3]Washington University School of Medicine, St. Louis, MO, USA; [4]Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA; [5]Hospital Universitario La Paz, Madrid, Spain; [6]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [7]Rocky Mountain Cancer Center, Denver, CO, USA; [8]Arizona Oncology Associates, Tucson, AZ, USA; [9]New York Oncology Hematology, Albany, NY, USA; [10]Medical Oncology Service, Hospital Universitari i Politècnic La FE, Valencia, Spain; [11]Sorlandet Hospital Kristiansand, Kristiansand, Norway; [12]Eisai Inc., Woodcliff Lake, NJ, USA; [13]Merck & Co. Inc., Kenilworth, NJ, USA; [14]Eisai Ltd., Hatfield, UK.

Study Design for the Phase 2 RCC Cohort



[a] Dose reductions to lenvatinib 14 mg/day, 10 mg/day, 8 mg/day and 4 mg/day were allowed to manage toxicities; dose reductions below 4 mg/day were discussed with the sponsor; [b] maximum of 35 treatments (approximately 2 years); [c] per irRECIST, by investigator assessment.

1. Perrone A. Immuno-Oncology 360° conference. New York, NY. 2016.
IV, intravenously; PO, by mouth; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1.

Presented By Chung-Han Lee

Courtesy of Thomas E Hutson, DO, PharmD

Previous Systemic Cancer Therapy

Characteristics	(N = 104)
Number of prior anticancer regimens[a], %	
1	39
≥ 2	62
Prior regimens[b], %	
Anti-PD-1/PD-L1[c]	100
Anti-PD-1/PD-L1 and Anti-VEGF[d]	65
Nivolumab + ipilimumab	37
Duration of prior ICI regimen, months	
Median (interquartile range)	7 (3–13)

[a] Percentages may not add up to 100% because of rounding; [b] patients can belong to > 1 category; [c] in combination or as monotherapy; [d] in combination or sequentially.

Presented By Chung-Han Lee

Courtesy of Thomas E Hutson, DO, PharmD

Tumor Response by Investigator Assessment

Parameter	irRECIST N = 104	RECIST v1.1[a] N = 104
ORR at week 24, % (95% CI)	51 (41–61)	–
ORR, % (95% CI)	55 (45–65)	52 (42–62)
Best objective response, %		
Partial response	55	52
Stable disease	36	38
Progressive disease	5	6
Not evaluable	5	5
Median DOR, months (95% CI)	12 (9–18)	12 (9–18)

[a] Up to 10 target lesions could be selected (up to 5 per organ).

DOR, duration of response.

Courtesy of Thomas E Hutson, DO, PharmD

Efficacy Results by Prior Anticancer Therapy Subgroup[a]

Parameter	Anti-PD-1/ PD-L1[b] (N = 104)	Anti-PD-1/PD-L1 and Anti-VEGF[c] (n = 68)	Nivolumab + Ipilimumab (n = 38)
ORR, % (95% CI)	55 (45–65)	59 (46–71)	47 (31–64)
Best objective response, %			
Partial response	55	59	47
Stable disease	36	31	42
Progressive disease	5	6	8
Not evaluable	5	4	3
Median duration of response, months (95% CI)	12 (9–18)	9 (7–17)	NR (7–NR)

[a] By irRECIST per investigator assessment. Patients can belong to > 1 category; [b] in combination or as monotherapy; [c] in combination or sequentially.

Presented By Chung-Han Lee

Courtesy of Thomas E Hutson, DO, PharmD

RCC Case Scenario, Case 1 continued

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Choice of 3rd line therapy for mRCC – recurrence at 11 months:

- Receives your 2nd line therapy of choice; then recurs 5 months later
- ECOG PS remains 1

Courtesy of Thomas E Hutson, DO, PharmD

Tivozanib in Patients with Advanced Renal Cell Carcinoma (aRCC) who have Progressed After Prior Treatment with Axitinib: Results from TIVO-3

Brian I. Rini, Sumanta K. Pal, Bernard Escudier, Michael B. Atkins, Thomas E. Hutson, Camillo Porta, Elena Verzoni, Michael N. Needle, David F. McDermott

Vanderbilt-Ingram Cancer Center, Nashville, TN; Department of Medical Oncology & Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA; Gustave Roussy, Villejuif, France; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; Texas A&M College of Medicine, Bryan, TX; University of Bari 'A. Moro', Bari, Italy; Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Aveo Oncology, Boston, MA; Beth Israel Deaconess Medical Center, Dana-Farber/Harvard Cancer Center, Boston, MA

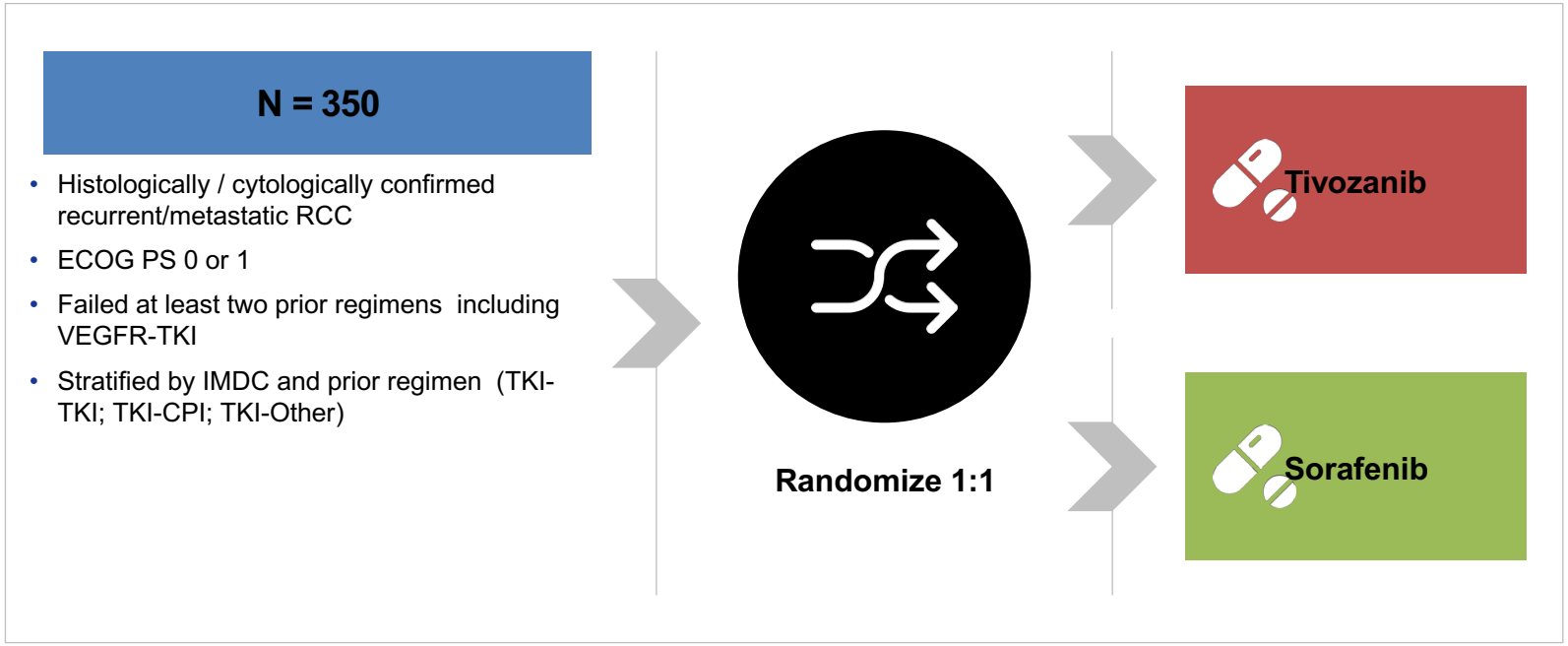
Courtesy of Thomas E Hutson, DO, PharmD

TIVO-3: Pivotal Trial in RCC

TIVO-3

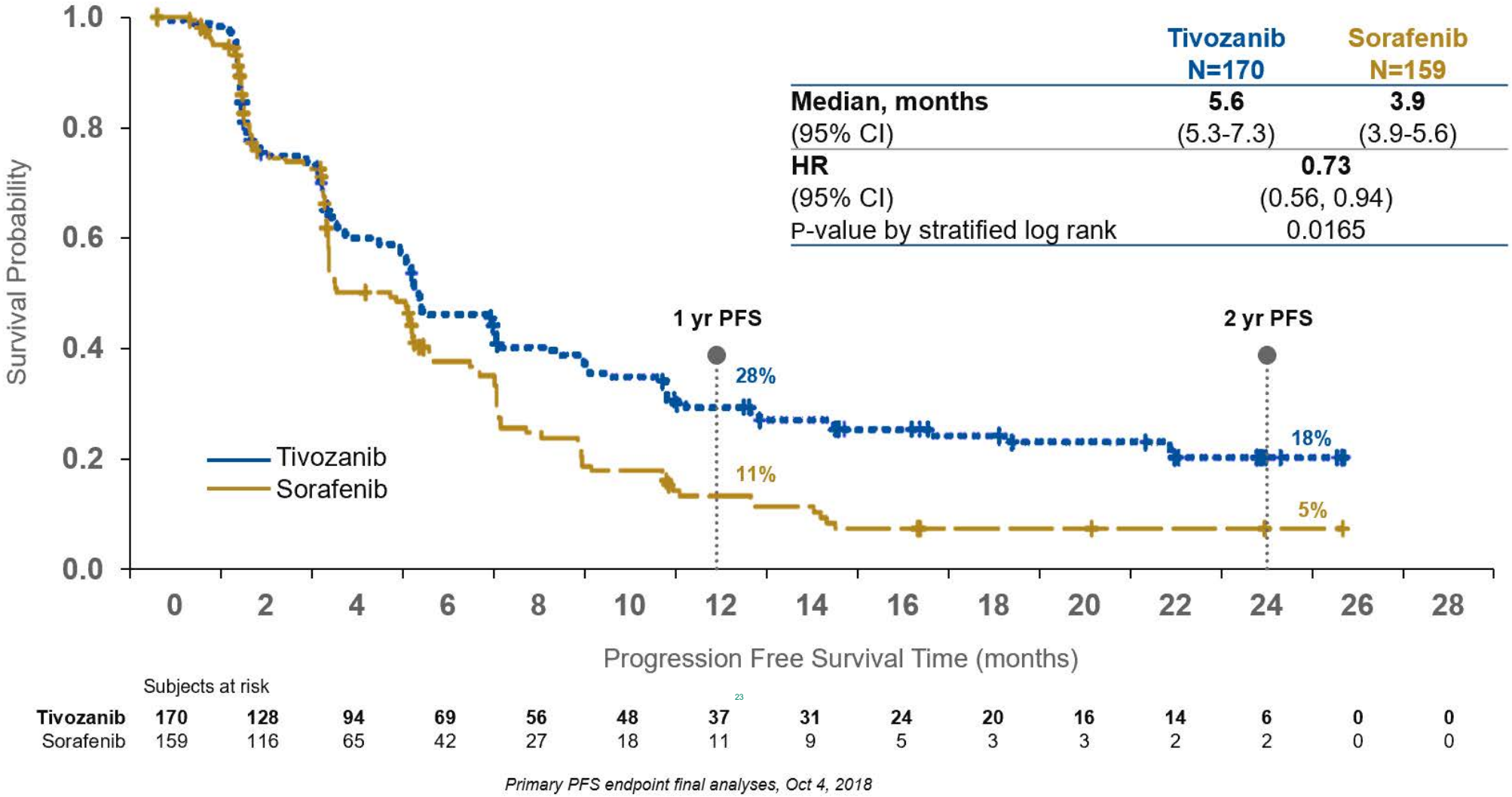
Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib to Sorafenib in Subjects With R/R RCC

Tivozanib is an orally bioavailable inhibitor of VEGFR-1/2/3.



Courtesy of Thomas E Hutson, DO, PharmD

TIVO-3: Met Primary Endpoint of Superior PFS in aRCC Patients treated with 2 or 3 prior regimens

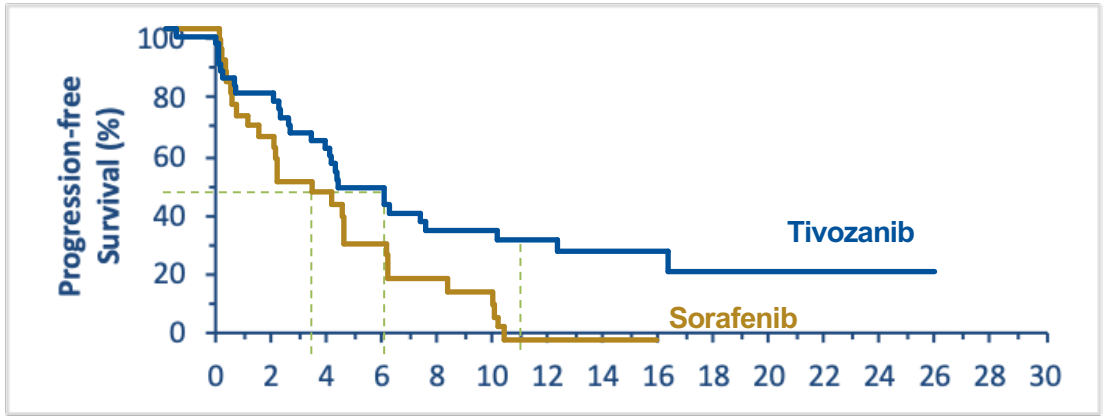


	Tivozanib N=170	Sorafenib N=159
Median, months	**5.6**	**3.9**
(95% CI)	(5.3-7.3)	(3.9-5.6)
HR	**0.73**	
(95% CI)	(0.56, 0.94)	
P-value by stratified log rank	0.0165	

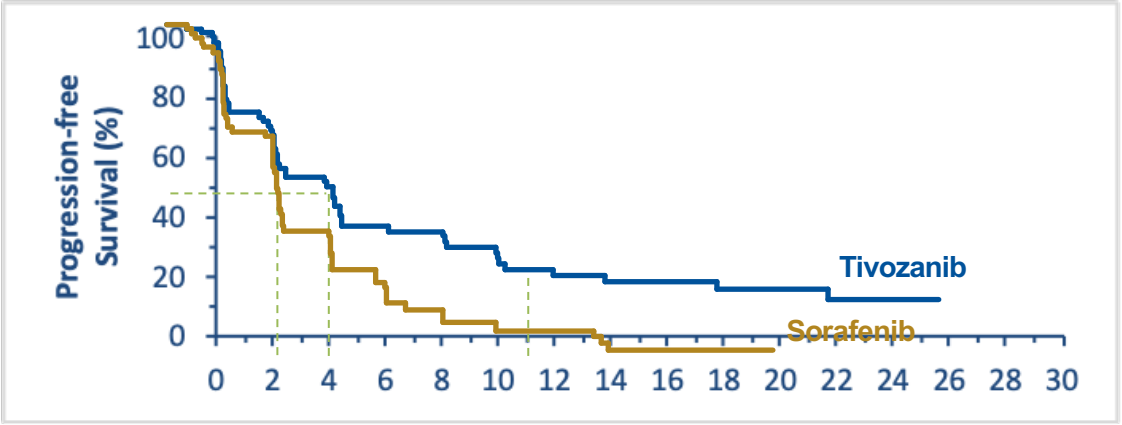
Primary PFS endpoint final analyses, Oct 4, 2018

Courtesy of Thomas E Hutson, DO, PharmD

TIVO-3: Progression-Free Survival – Prior Checkpoint Inhibitor and TKI/TKI



Prior Checkpoint Inhibitor & Prior VEGFR TKI		
	Tivozanib (n = 47)	Sorafenib (n = 44)
Median PFS, months	**7.3**	**5.1**
(95% CI)	(4.8, 11.1)	(3.2, 7.4)
HR	**0.55**	
(95% CI)	(0.32, 0.94)	
P Value	0.028	
ORR*	24.4%	6.8%



Two Prior VEGFR TKIs		
	Tivozanib (n = 79)	Sorafenib (n = 80)
Median PFS, months	**5.5**	**3.7**
(95% CI)	(3.6, 7.4)	(3.6, 3.9)
HR	**0.57**	
(95% CI)	(0.39, 0.83)	
P Value	0.003	
ORR*	15.2%	7.5%

Porta et al. ASCO 2019
Other + VEGFR TKI: (N=100) HR=0.98; 95% CI 0.62; 1.56, ASCO GI 2019

Courtesy of Thomas E Hutson, DO, PharmD

Tivozanib after Axitinib in the TIVO-3 Study

Clinical Outcome	No. of pts (n)	PFS HR	95% CI	Tivo ORR	Sora ORR
ITT	350	0.73	0.56, 0.94	18%	8%
Any prior axitinib	172	0.66	0.46, 0.93	13%	8%

Courtesy of Thomas E Hutson, DO, PharmD

Adverse Events in Prior Axitinib Patients

	Tivozanib	Sorafenib
Treatment-related AE	79.7%	92.3%
Reduction due to AE	22.8%	39.7%
Interruption due to AE	46.8%	56.4%
Discontinuation due to AE	20.3%	30.8%

Courtesy of Thomas E Hutson, DO, PharmD

Conclusions

- Tivozanib improved PFS and ORR vs. sorafenib in patients who have progressed after multiple VEGFR-TKIs, including patients with immediate prior axitinib treatment.
- The safety profile of tivozanib in prior axitinib patients was consistent with that of the ITT population
- These results suggest that a selective VEGFR inhibitor, tivozanib, has clinical benefit over the multi-targeted VEGFR-TKI, sorafenib, after prior axitinib.

Courtesy of Thomas E Hutson, DO, PharmD