Updates in Metastatic Renal Cell Carcinoma

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Pembrolizumab vs Placebo as Post Nephrectomy Adjuvant Therapy for Patients with Renal Cell Carcinoma: Randomized, Double-Blind, Phase 3 KEYNOTE-564 Study

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KEYNOTE-564 Study Design

Key Eligibility Criteria

- Histologically confirmed clear cell renal cell carcinoma
- Nephrectomy ≤12 weeks prior to randomization
- No prior systemic therapy
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment

Stratification Factors

- M0 vs M1 NED
- M0 group further stratified:
  - ECOG PS 0 vs 1
  - US vs non-US

R (1:1)

- Pembrolizumab 200 mg Q3W for ~1 year[a]
- Placebo Q3W for ~1 year[a]

- Primary end point: DFS per investigator
- Key secondary end point: OS
- Other secondary end points: Safety

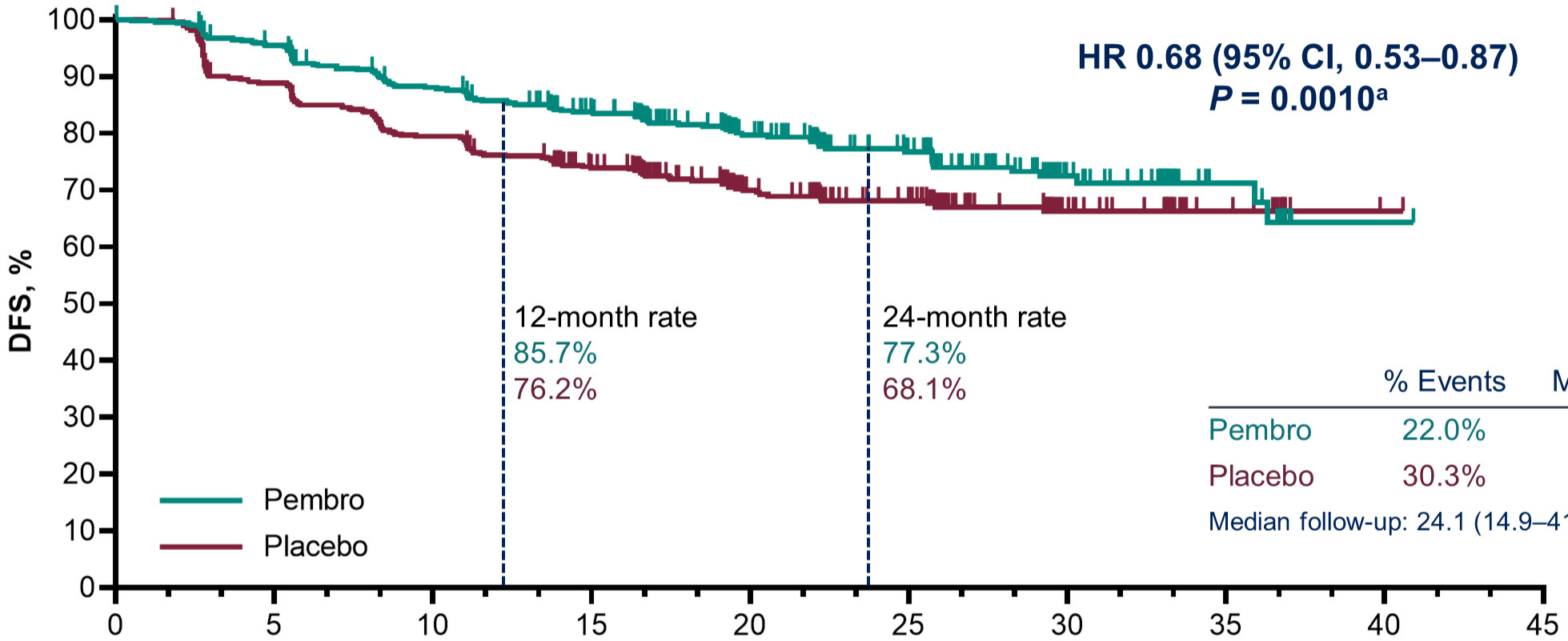
DFS, disease-free survival; Q3W, every 3 weeks.
[a]≤17 cycles of treatment were equivalent to ~1 year.

Prespecified Disease Risk Categories

Intermediate-High Risk		High Risk		M1 NED
pT2	pT3	pT4	Any pT	NED after resection of oligometastatic sites ≤1 year from nephrectomy
Grade 4 or sarcomatoid	Any grade	Any grade	Any grade	
N0	N0	N0	N+	
M0	M0	M0	M0	

NED, no evidence of disease.

DFS by Investigator, ITT Population



	% Events	Median (95% CI)
Pembro	22.0%	NR (NR–NR)
Placebo	30.3%	NR (NR–NR)

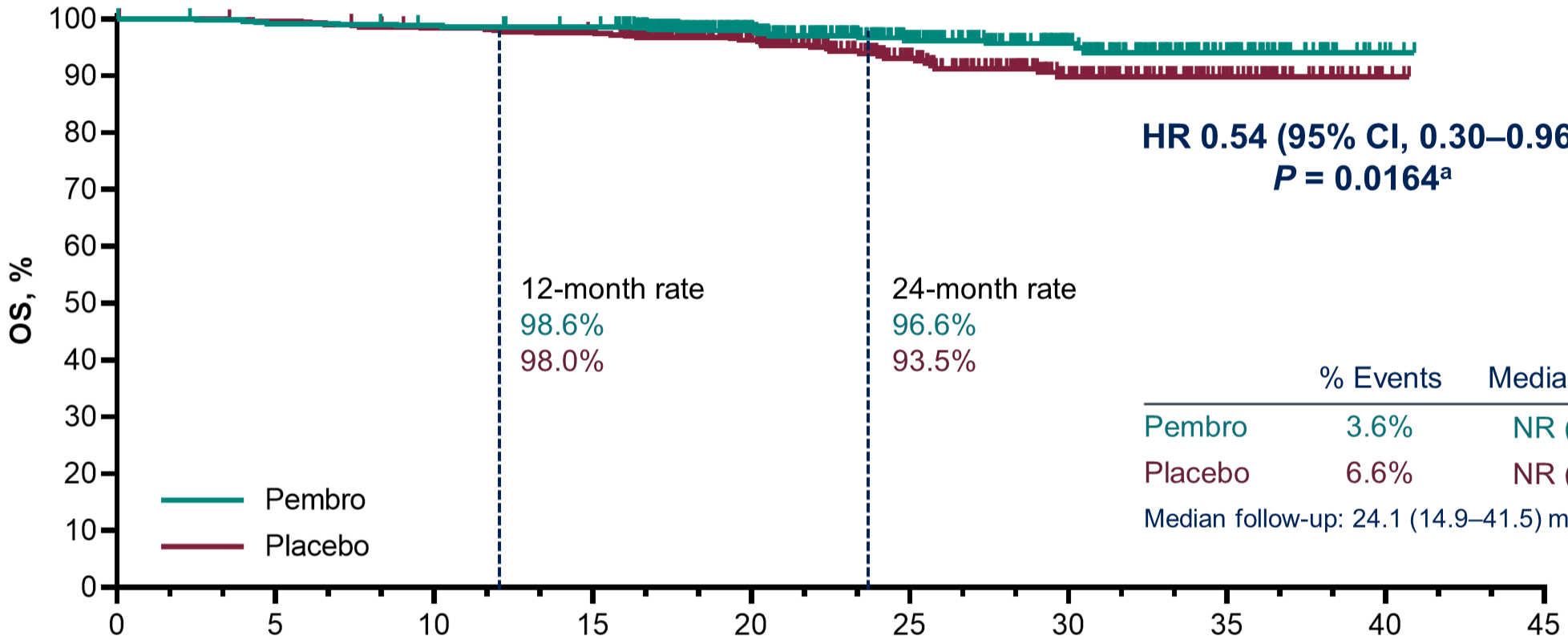
Median follow-up: 24.1 (14.9–41.5) months.

No. at Risk

Pembro	496	457	414	371	233	151	61	21	1	0
Placebo	498	436	389	341	209	145	56	19	1	0

[a]Crossed prespecified p-value boundary for statistical significance of 0.0114.
ITT population included all randomized participants. NR, not reached. Data cutoff date: December 14, 2020.

Interim OS Results, ITT Population



HR 0.54 (95% CI, 0.30–0.96)
***P* = 0.0164[a]**

	% Events	Median (95% CI)
Pembro	3.6%	NR (NR–NR)
Placebo	6.6%	NR (NR–NR)

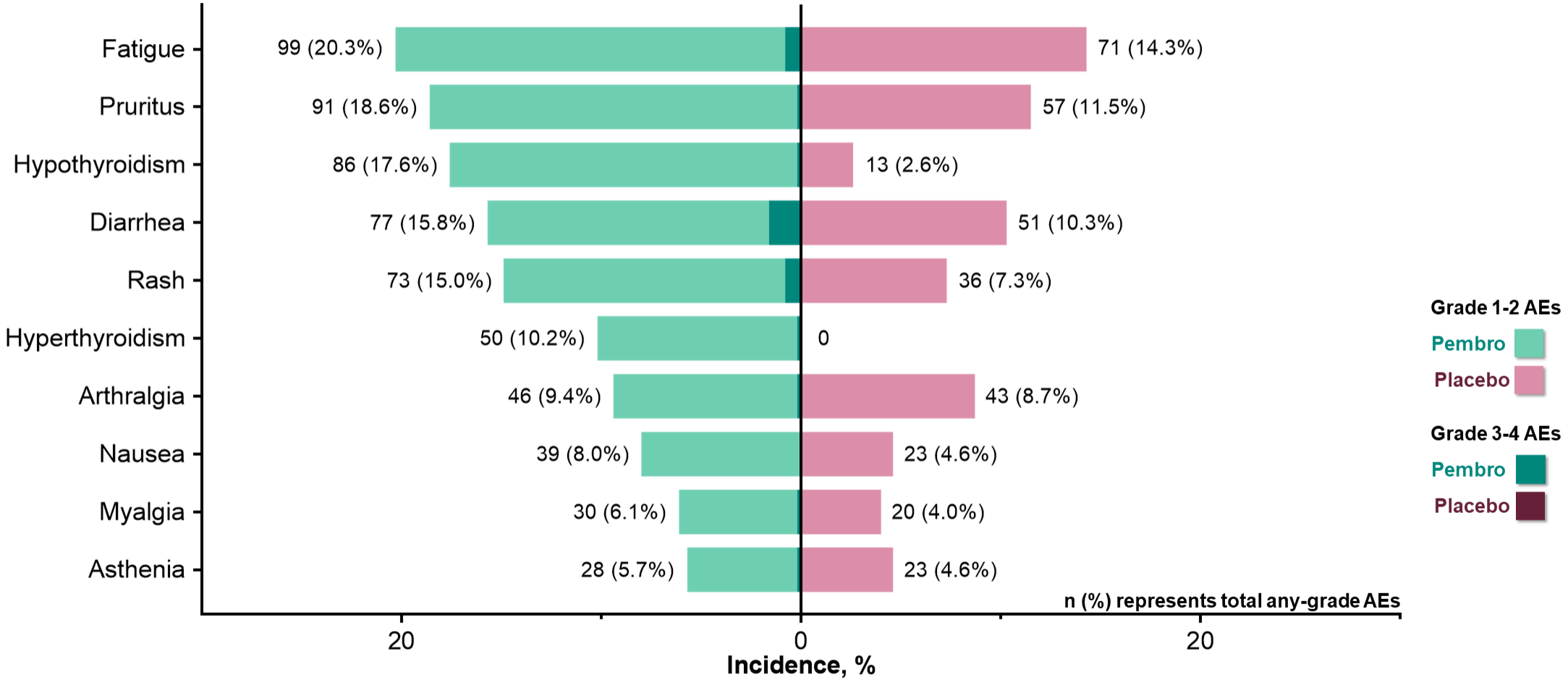
Median follow-up: 24.1 (14.9–41.5) months.

No. at Risk

Pembro	496	490	486	482	338	215	124	51	3	0
Placebo	498	494	485	480	336	209	117	48	3	0

[a]Did not cross prespecified p-value boundary for statistical significance of 0.0000093 for 51 events. Final analysis for OS to occur after approximately 200 OS events.
ITT population included all randomized participants. NR, not reached. Data cutoff date: December 14, 2020.

Treatment-Related AEs with Incidence ≥5%, As-Treated Population



As-treated population included all participants who received ≥1 dose of study treatment. No treatment-related deaths occurred. Data cutoff date: December 14, 2020.

Front-line mRCC

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)	45.7 vs 40.1 **0.73** (0.60-0.88)	NR vs 29.5 **0.66** (0.50–0.87)	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%	**86%** vs. 76% **72%** 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)	**15.7** vs 11.1 0.68 (0.58–0.80)	**17.0** vs 8.3 0.52 (0.43–0.64)	**23.9** vs 9.2 0.39 (0.32-0.49)
ORR, %	**39** vs 32	**60** vs 40	**55** vs 27	**71** vs 36
CR, %	**11** vs 3	**10** vs 4	**9** vs 4	**16** vs 4
Med f/u, months	**55**	**42.8**	**23.5**	**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%)	Overall (71%) IO (53%)

1. Albiges et al. ESMO Open 2020
2. Rini et al. ASCO 2021
3. Motzer et al. ASCO GU 2021
4. Motzer et al. ASCO GU 2021.

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

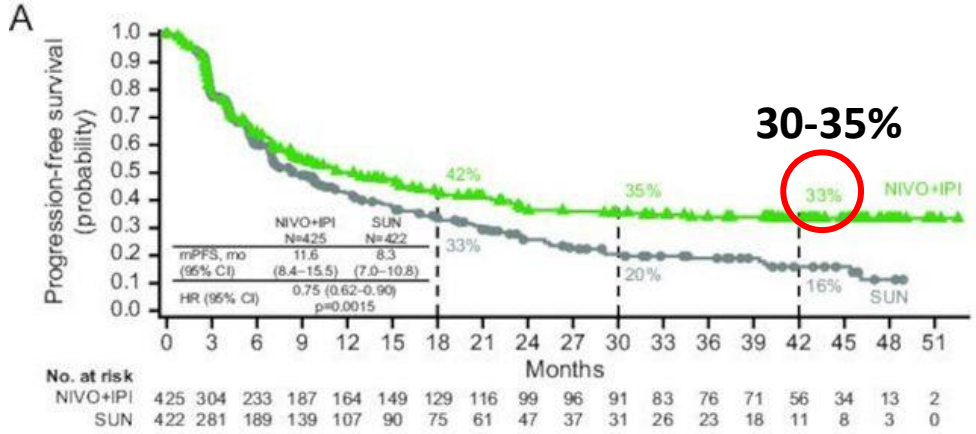
Progression-free survival and duration of response

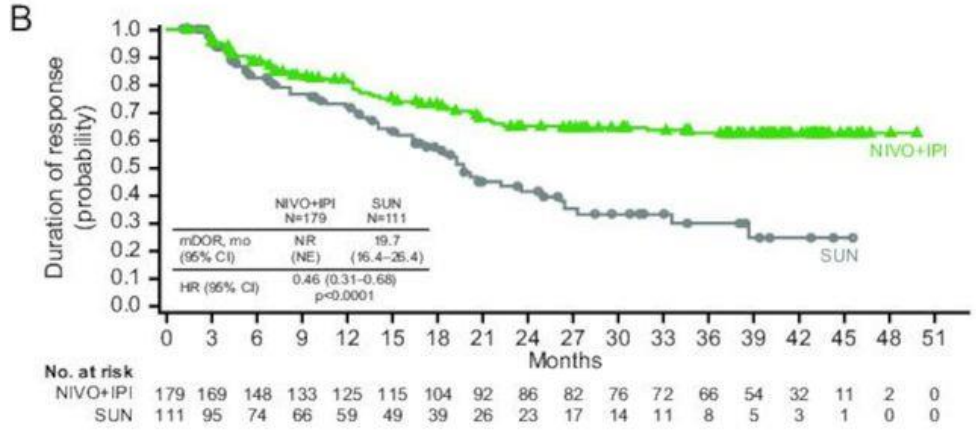
I/P

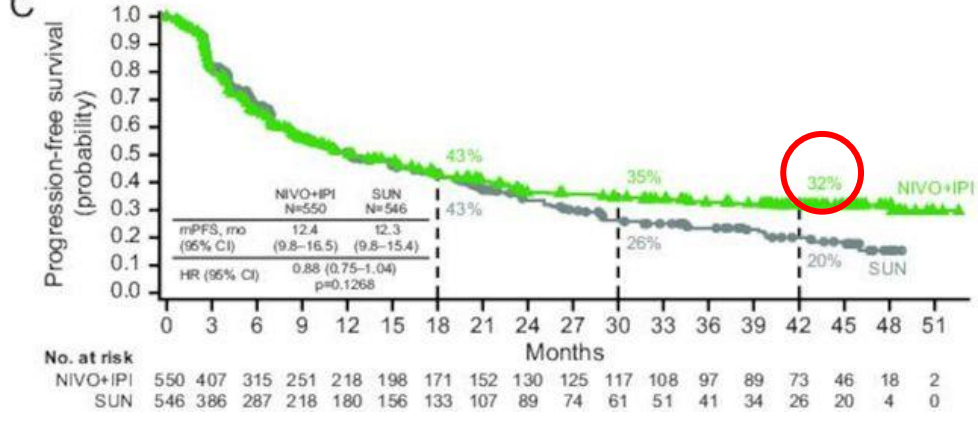
ITT

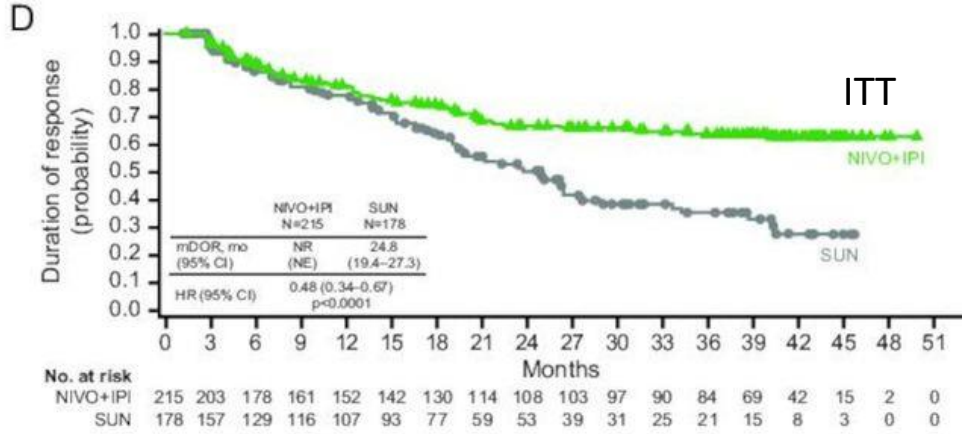
ITT

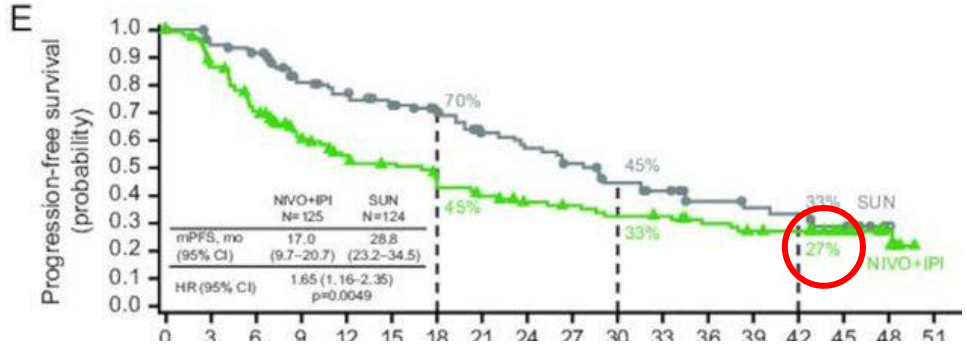
30-35%

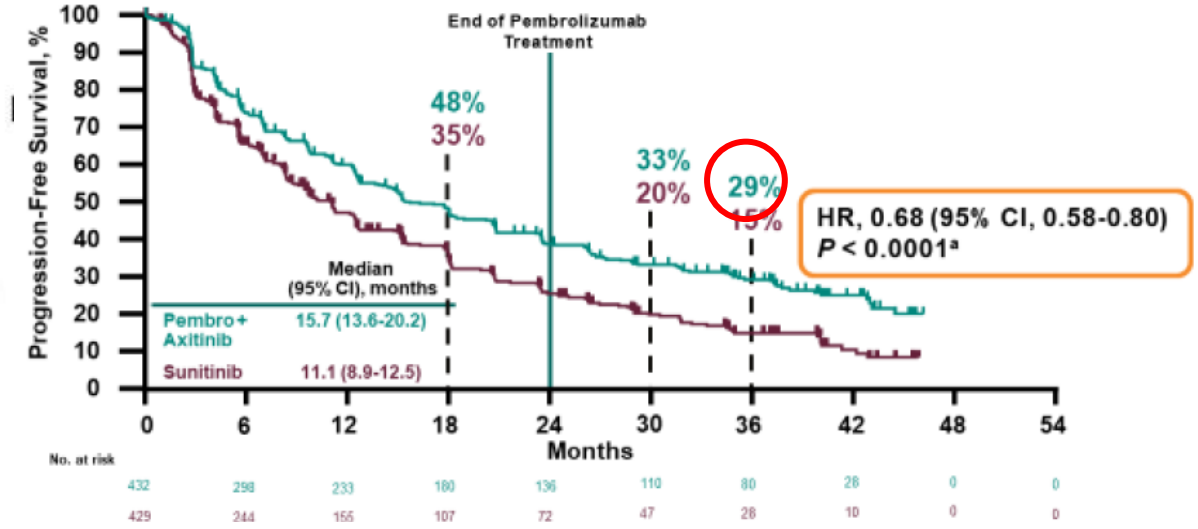






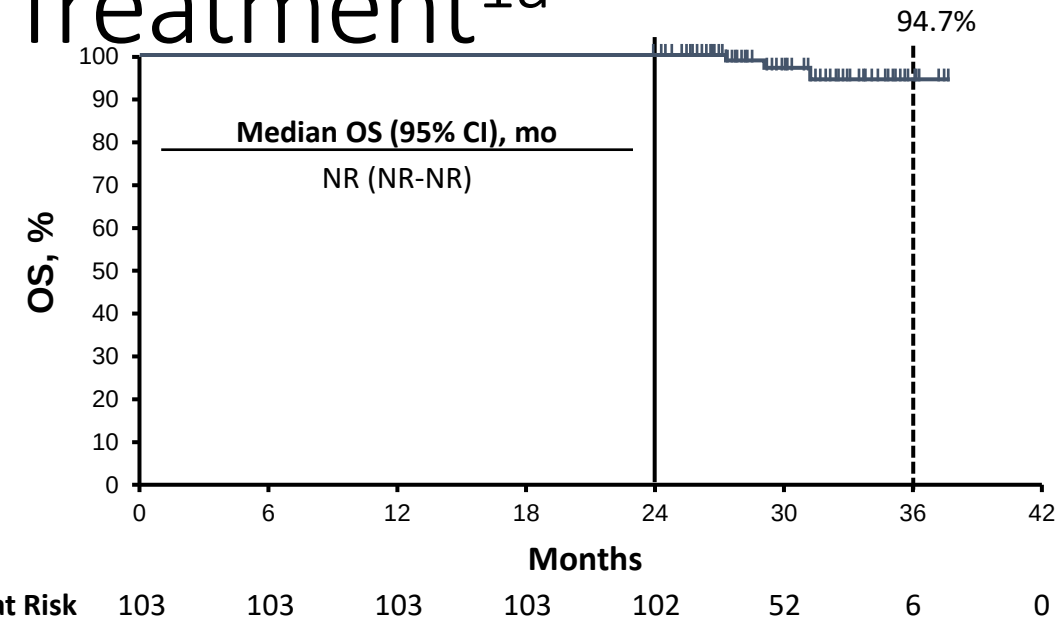


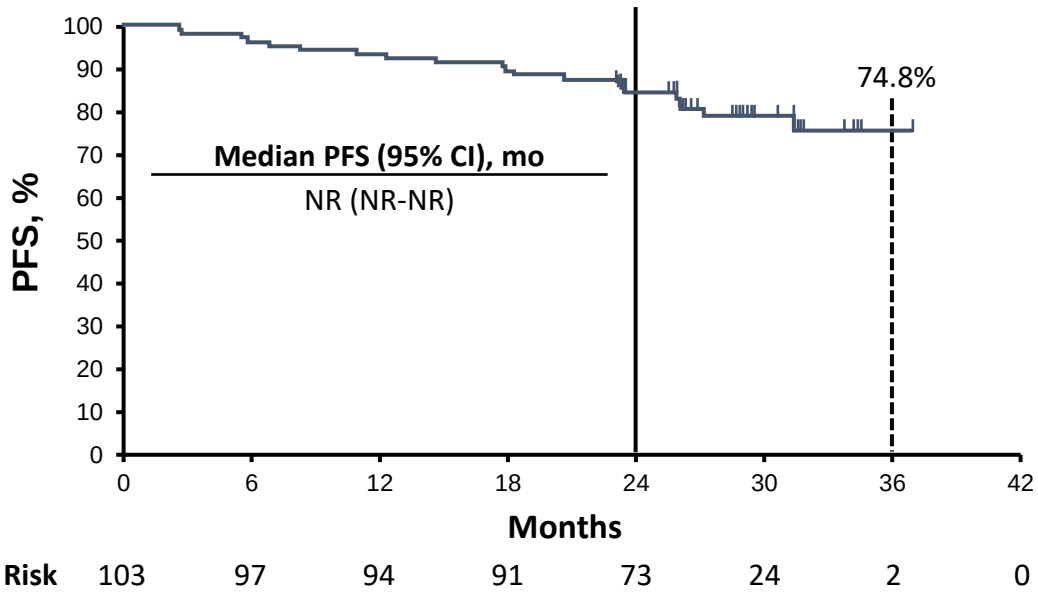




· 2020

KEYNOTE-426: Outcomes Following 2 Years of Treatment[1a]





- Of 432 patients randomly assigned to receive pembrolizumab + axitinib, 103 (23.8%) completed 2 years of treatment and did not discontinue because of progression
- In these 103 patients:
  - mOS[b] and PFS[b,c] have not been reached
  - 85% had either CR or PR; 16 CRs were seen at first assessment

Plimack et al. ASCO 2021

IO/TKI vs. IO/IO

	Pros	Cons
IO/TKI	• Consistent effects on OS, PFS and ORR across IMDC risk groups • Significant tumor burden reduction reflected in high ORR and long PFS • Manageable toxicity • QoL maintained vs TKI	• Long-term durability of response yet to be demonstrated • Potential for acute and chronic TKI toxicity
IO/IO	• OS and ORR advantages over TKI monotherapy • Durability of response / disease-control • Treatment-free interval possible • QoL improved vs TKI	• Sometimes significant initial toxicity • Lower ORR and shorter PFS compared with IO/TKI regimens • Less effect in favorable risk patients

2021 ASCO ANNUAL MEETING

Abstract #4501

CANTATA: Primary Analysis of a Global, Randomized, Placebo-Controlled, Double-Blind Trial of Telaglenastat (CB-839) + Cabozantinib vs. Placebo + Cabozantinib in Patients With Advanced/Metastatic Renal Cell Carcinoma that Progressed on Immune Checkpoint Inhibitor or Anti-Angiogenic Therapies

Nizar M. Tannir[1], Neeraj Agarwal[2], Camillo Porta[3], Nicola J. Lawrence[4], Robert Motzer[5], Richard J. Lee[6], Rohit K. Jain[7], Nancy Davis[8], Leonard Appleman[9], Oscar Goodman, Jr.[10], Walter M. Stadler[11], Sunil Gandhi[12], Daniel M. Geynisman[13], Roberto Iacovelli[14], Begona Mellado[15], Robert Figlin[16], Thomas Powles[17], Lalith Akella[18], Keith Orford[18], Bernard Escudier[19]

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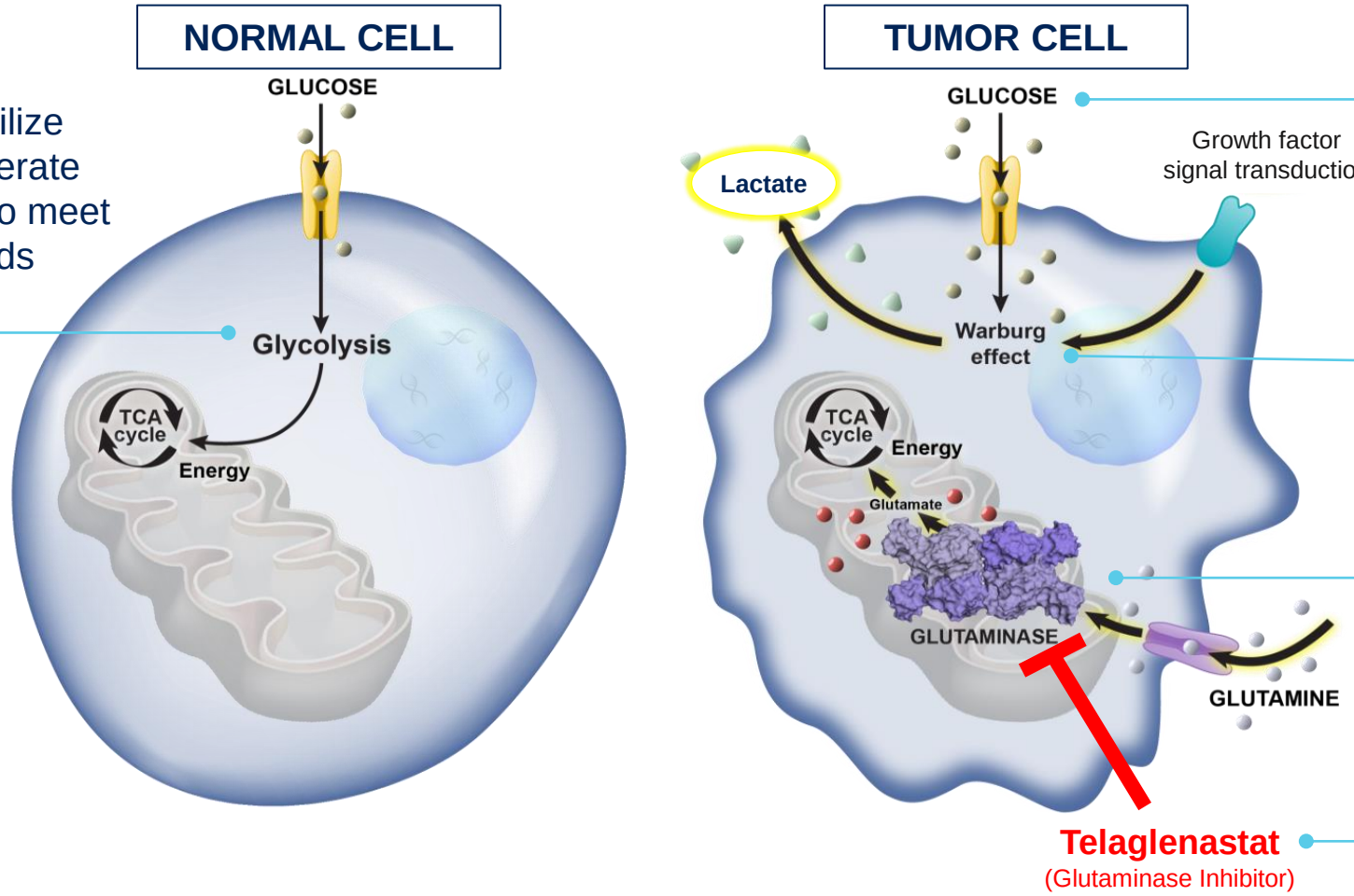
Altered Tumor Metabolism in Tumor Cells

Normal cells utilize glucose to generate sufficient ATP to meet cellular demands



Increased dependence on glutamine due to altered glucose metabolism in tumor cells

Oncogene-driven conversion of glucose to lactate via the Warburg Effect[1,2]

Conversion of glutamine to glutamate via glutaminase fuels proliferation and survival[3]

Inhibiting glutaminase deprives tumor cells of glutamate as a vital fuel source

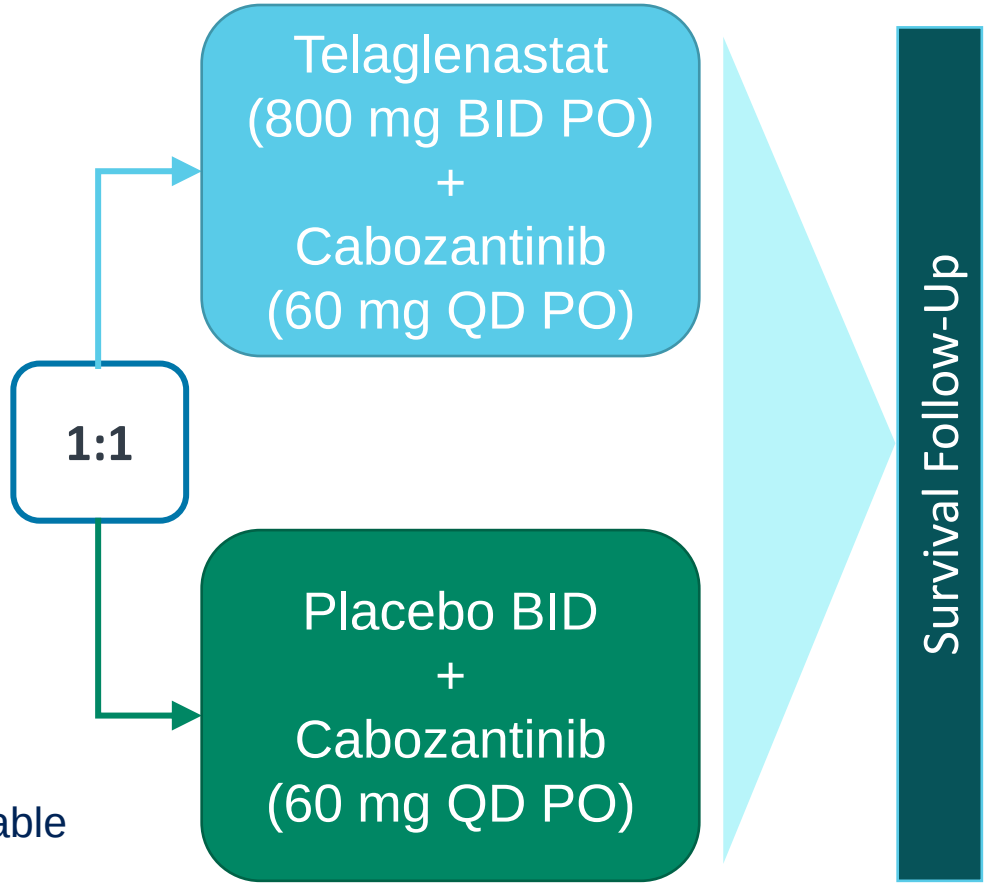
[1]Warburg O. J Cancer Res. 1925;9(1):148-163; [2]Warburg O. Science. 1956;123(3191):309-314; [3]Altman BJ et al. Nat Rev Cancer. 2016;16(10):619-634.

CANTATA Study Design

Key Eligibility Criteria

- Advanced/metastatic clear cell RCC
- KPS ≥ 70%
- 1-2 lines of prior therapy including at least 1 antiangiogenic therapy **or** nivolumab + ipilimumab

- N=444
- Stratification factors:
  - Prior ICI therapy (yes vs. no)
  - IMDC Prognostic Risk Group (favorable vs. intermediate vs. poor)



ENDPOINTS

Primary
IRC-adjudicated PFS per RECIST v1.1

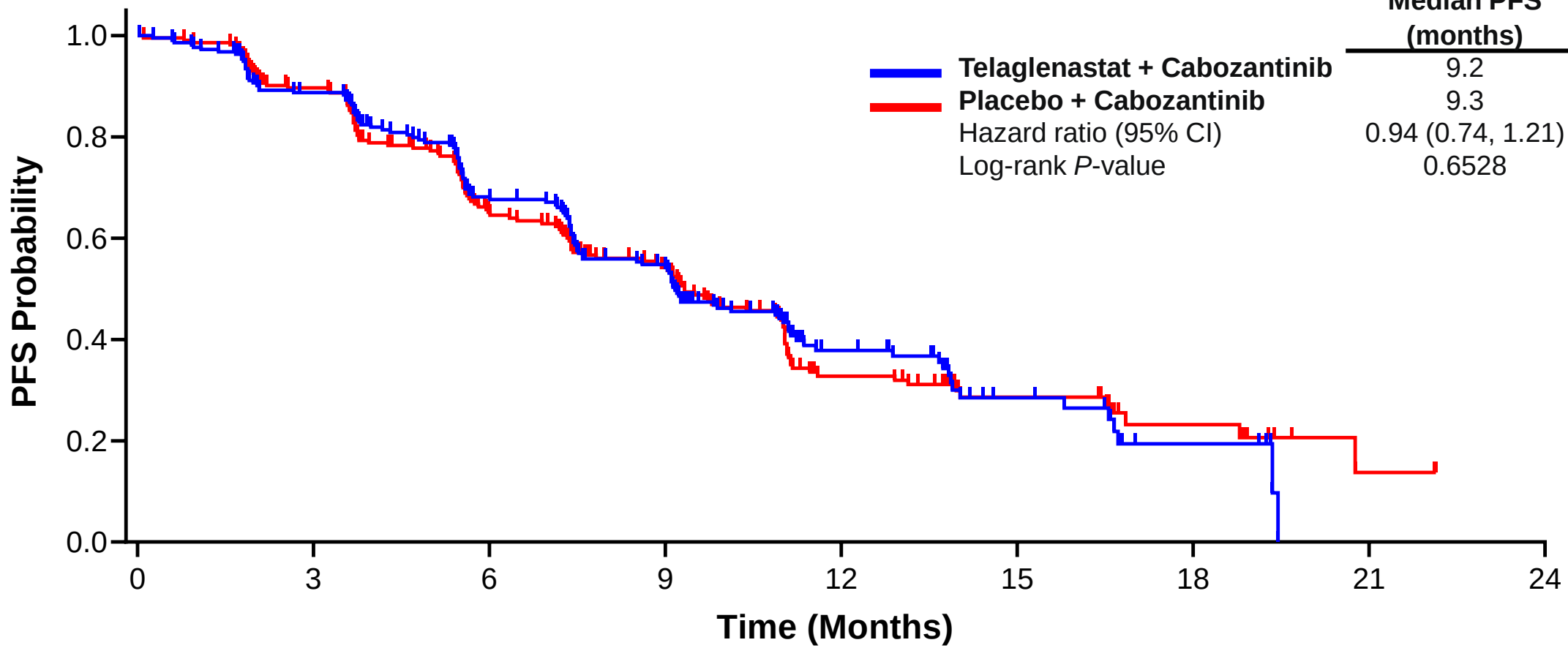
Secondary
Overall Survival

Investigator-assessed PFS

NCT03428217

BID, twice daily; ICI, immune checkpoint inhibitor; IMDC, International Metastatic RCC Database Consortium; IRC, independent review committee; KPS, Karnofsky Performance Status; PFS, progression-free survival; PO, per os; QD, once daily; QOL, quality of life; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors

IRC-Assessed Progression-Free Survival



	Median PFS (months)
Telaglenastat + Cabozantinib	9.2
Placebo + Cabozantinib	9.3
Hazard ratio (95% CI)	0.94 (0.74, 1.21)
Log-rank *P*-value	0.6528

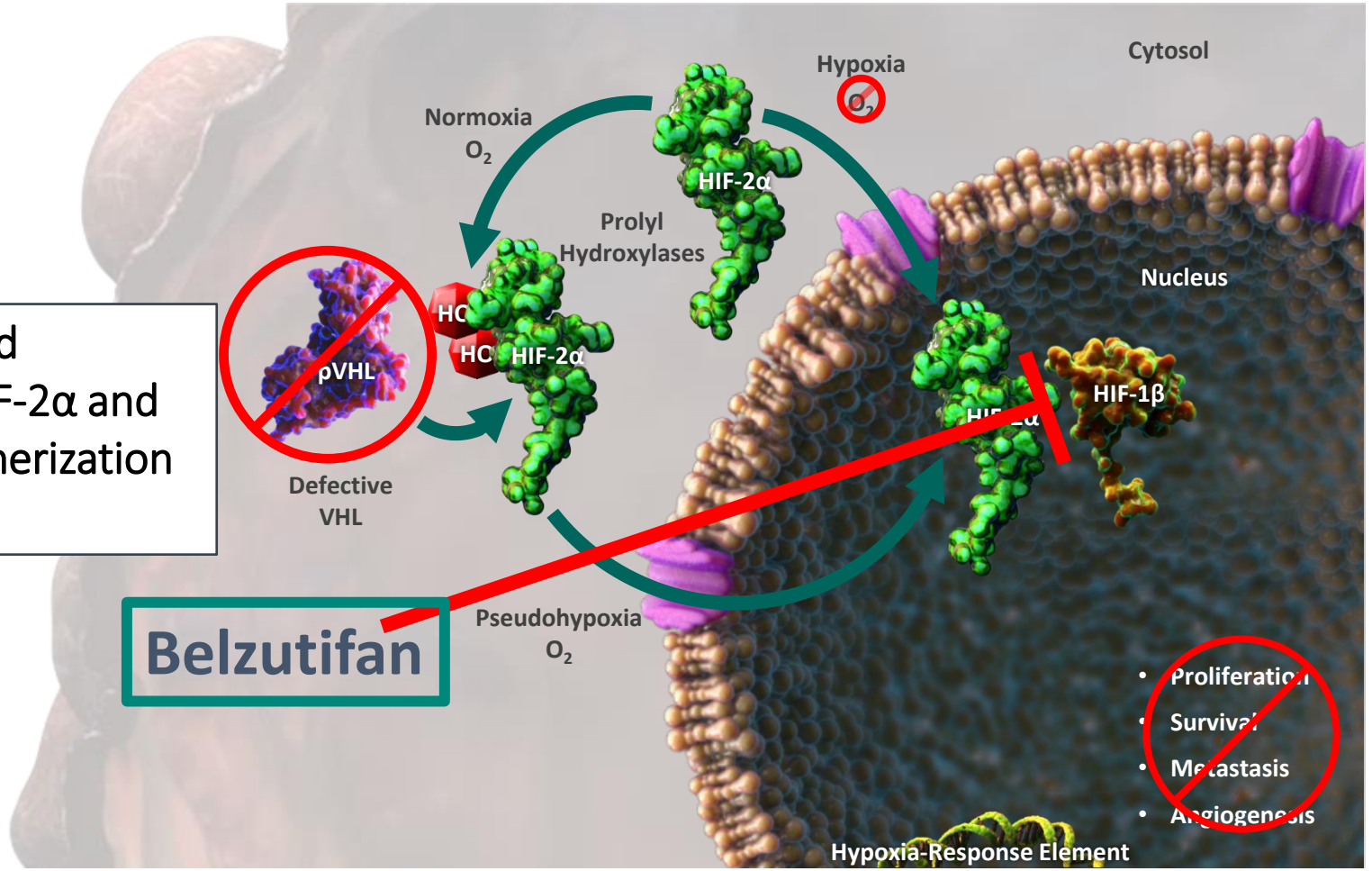
Number at risk

Telaglenastat + Cabozantinib:	221	185	131	97	37	15	6	0	0
Placebo + Cabozantinib:	223	184	117	90	40	21	9	2	0

CI, confidence interval; IRC, independent review committee; PFS, progression-free survival

PT2977: HIF-2α Inhibitor

Belzutifan potently and selectively binds to HIF-2α and prevents its heterodimerization with HIF-1β

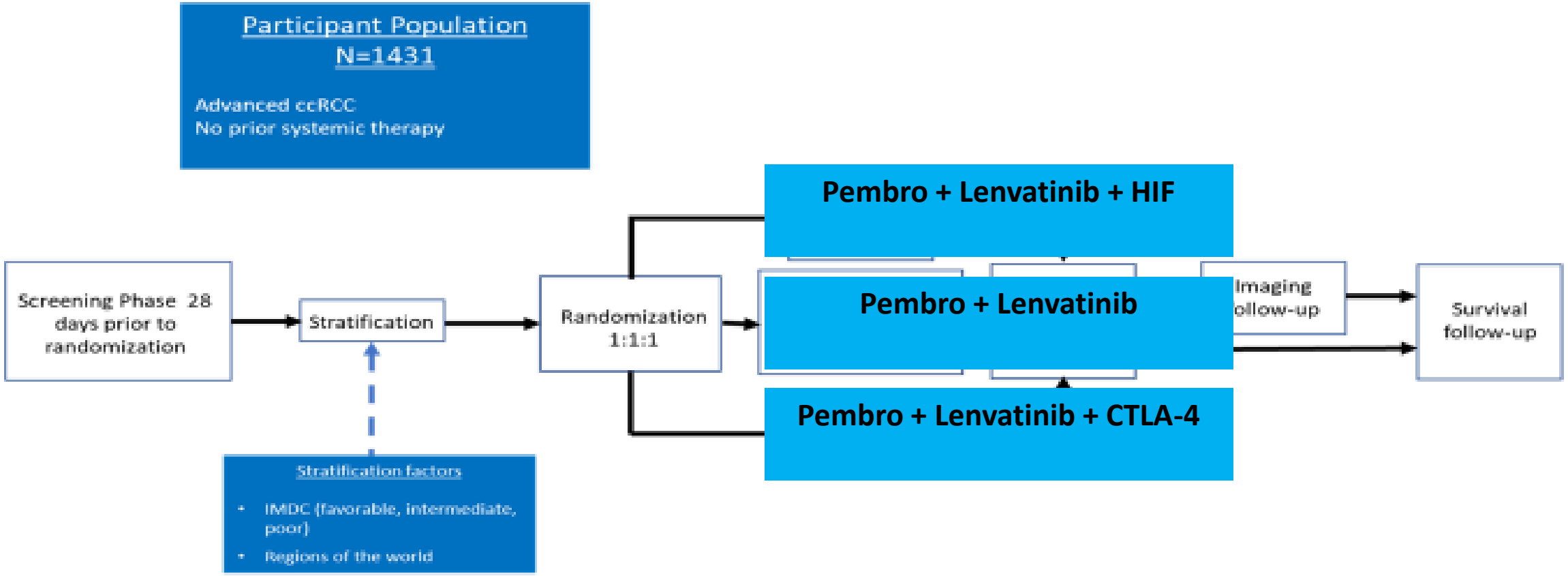


Best Confirmed Objective Response by RECIST v1.1 per Investigator Assessment (ccRCC cohort)

Efficacy Parameter, n (%) [95%CI]	All Patients N = 55	IMDC Favorable n = 13	IMDC Intermediate/Poor n = 42
Objective Response Rate	14 (25) [15-39]	4 (31) [9-61]	10 (24) [12-40]
Complete Response (CR)	0	0	0
Partial Response (PR)	14 (25)	4 (31)	10 (24)
Stable Disease (SD)	30 (54)	8 (62)	22 (52)
Disease Control Rate (CR + PR + SD)	44 (80) [67-90]	12 (92) [64-100]	32 (76) [61-88]
Progressive Disease	8 (15)	1 (8)	7 (17)
Not Evaluable	3 (5)	0	3 (7)

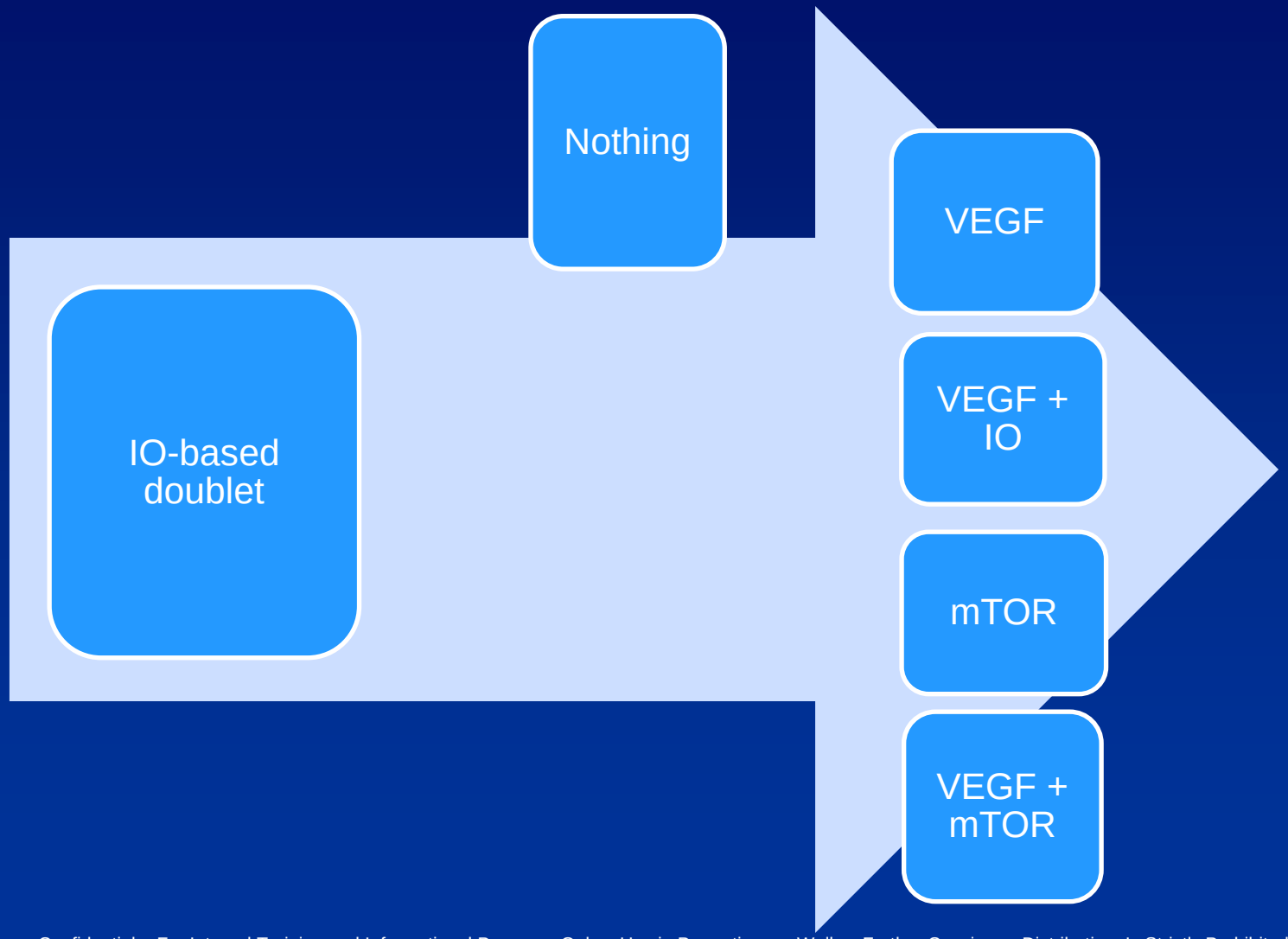
ata cutoff: June 1, 2020.

MK-6482-012 Study Design



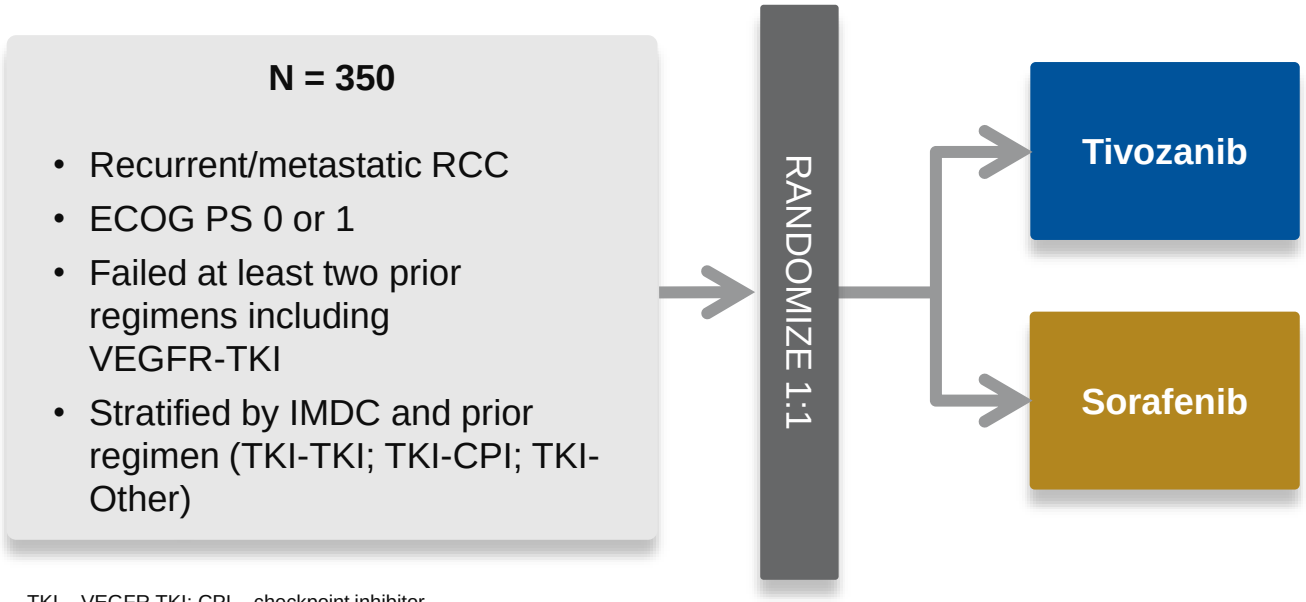
- Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ccRCC = clear cell renal cell carcinoma.
- a. The treatment arms are the HIF triplet (MK-6482 + pembrolizumab + lenvatinib), the CTLA4 triplet (MK-1308A + lenvatinib), and the doublet (pembrolizumab + lenvatinib). Note: MK-1308A is a coformulation of pembrolizumab and MK-1308
- Global Study- ~225 sites, 33 countries

Current Options in Refractory RCC



TIVO-3: Study Schema

Randomized Trial in Relapsed or Refractory Advanced Renal Cell Carcinoma

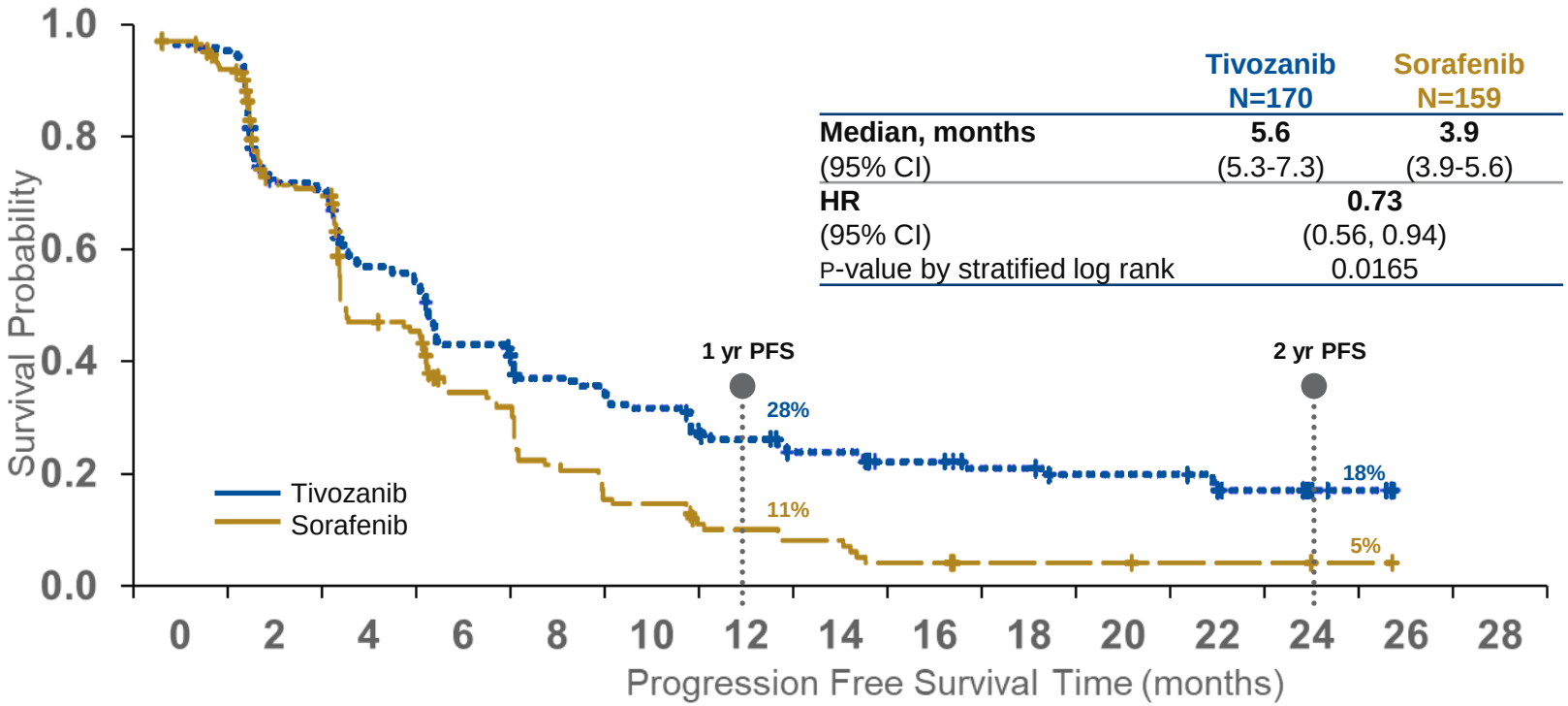


Endpoints

- **Primary**: PFS
- **Secondary**: OS, ORR, DoR, Safety and Tolerability for ITT

TKI – VEGFR TKI; CPI – checkpoint inhibitor

TIVO-3: Primary Endpoint of PFS



	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	

Subjects at risk

Tivozanib	**170**	**128**	**94**	**69**	**56**	**48**	**37**	**31**	**24**	**20**	**16**	**14**	**6**	**0**	**0**
Sorafenib	159	116	65	42	27	18	11	9	5	3	3	2	2	0	0

Primary PFS endpoint final analyses, Oct 4, 2018

Rini et al. Lancet Oncology 2020

TIVO-3: Dose Modifications

Characteristic	Tivozanib (N=173)^		Sorafenib (N=170)^
Mean Number of Cycles Initiated	**11.9**		**6.7**
AEs Leading to Dose Reductions (%)	25	P=0.0147	39
AEs Leading to Dose Interruption (%)	50	P=0.0164	64
ADRs Leading to Permanent Discontinuation (%)	8		15
Treatment Related SAEs (%)	12		11
Treatment Related Deaths (%)	0		0
Deaths within 30 days of Tx (N)	15		13
Exposure Adj Deaths per Month of Tx	0.72%		1.11%

^Safety population

Lenvatinib + Pembro in IO-refractory RCC

Tumor Response by Investigator Assessment

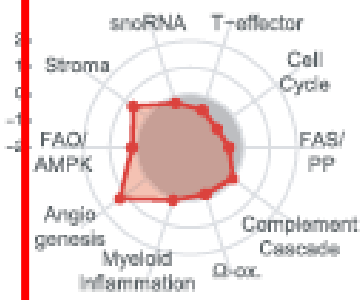
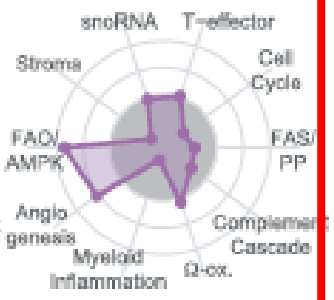
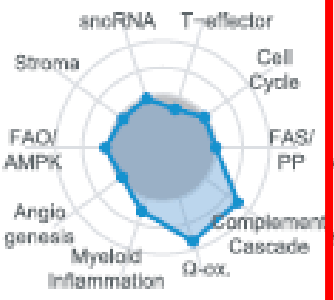
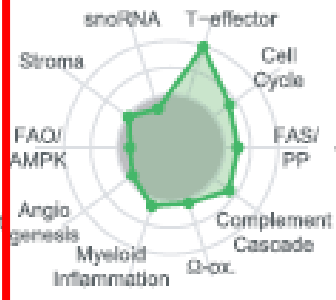
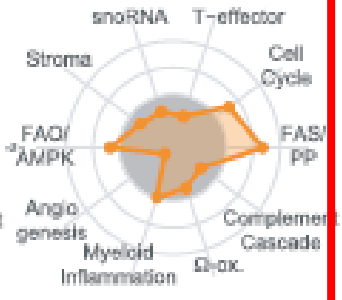
Parameter	irRECIST N = 104	RECIST v1.1[a] N = 104
ORR at week 24, % (95% CI)	51 (41–61)	–
ORR, % (95% CI)	55 (45–65)	52 (42–62)
Best objective response, %		
Partial response	55	52
Stable disease	36	38
Progressive disease	5	6
Not evaluable	5	5
Median DOR, months (95% CI)	12 (9–18)	12 (9–18)

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

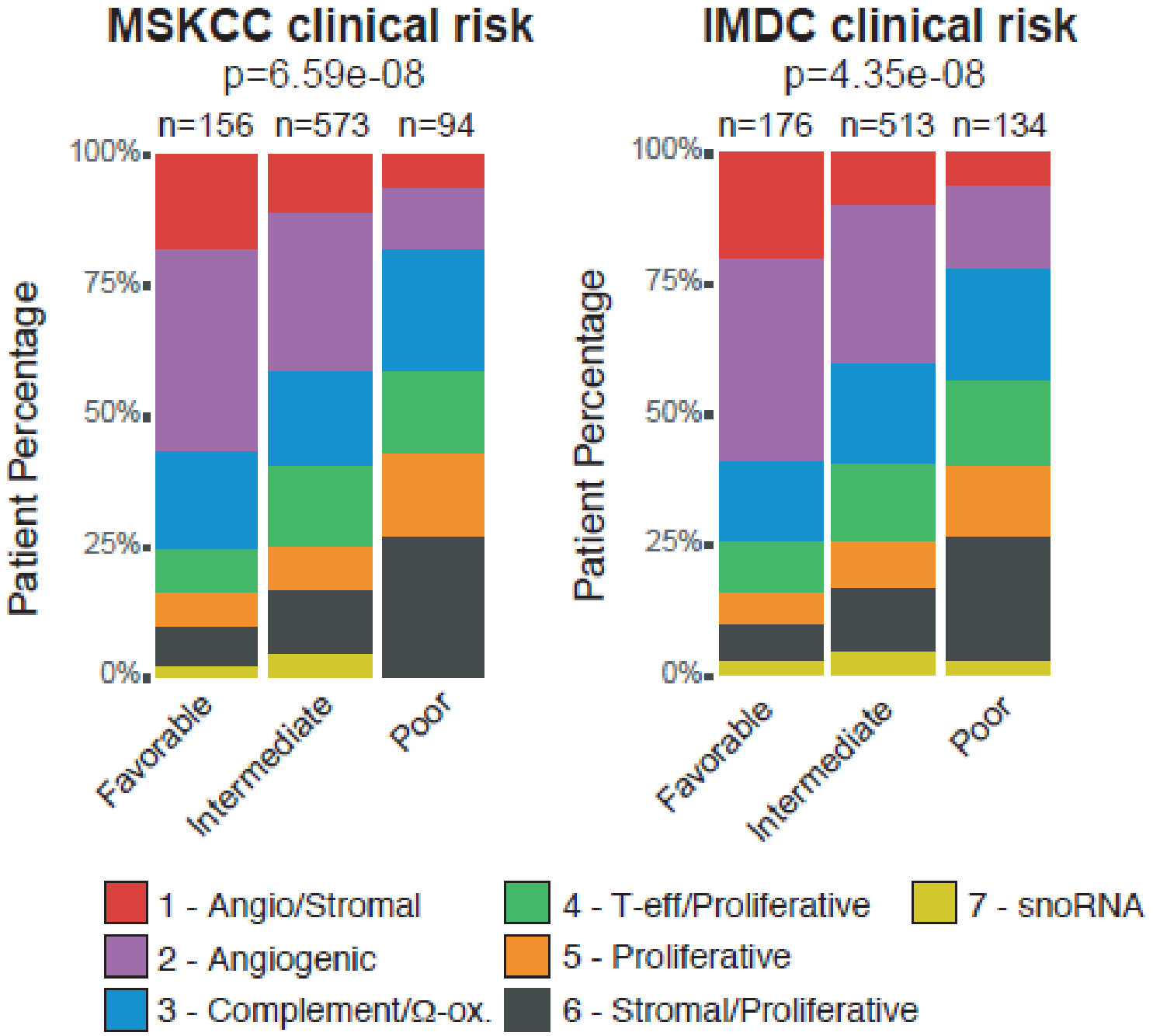
DOR, duration of response.

Presented By Chung-Han Lee at ASCO 2020

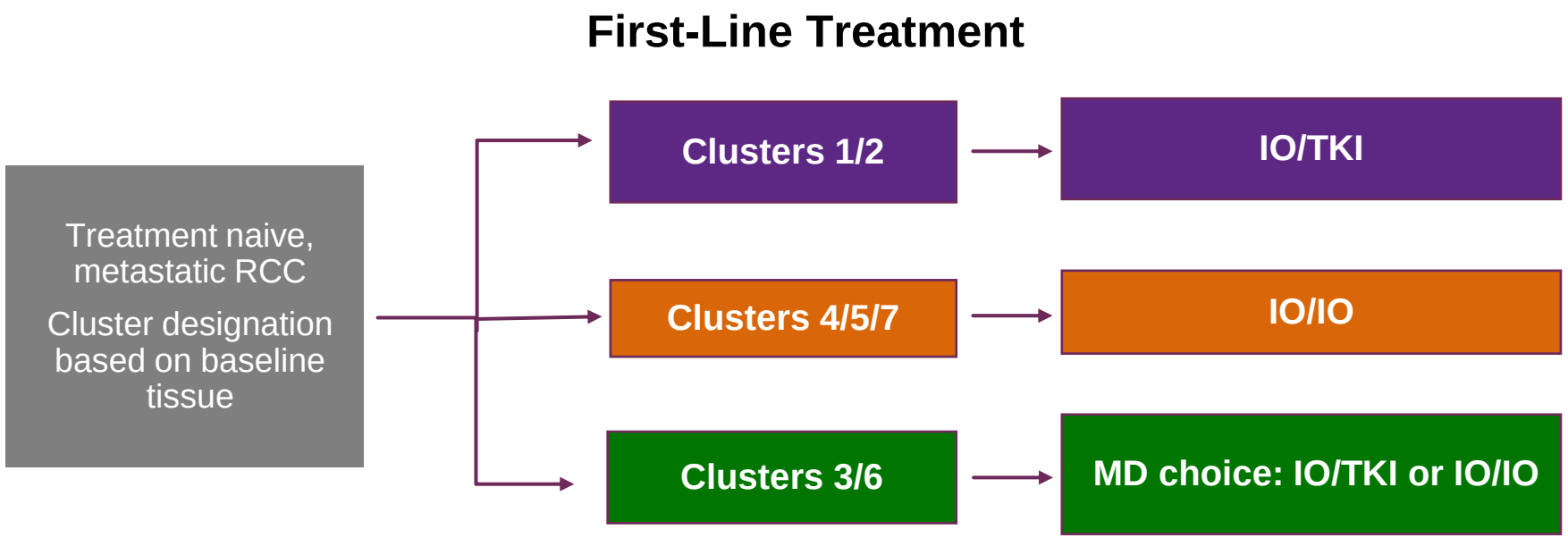
RCC is driven primarily (although not exclusively) driven by angiogenic and inflammatory pathways

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7
	98/823 (12%)	245/823 (30%)	156/823 (19%)	116/823 (14%)	74/823 (9%)	106/823 (13%)	28/823 (3%)
Pathways	Angiogenesis Stroma	Angiogenesis Fatty acid oxidation	Complement cascade Ω-oxidation	T-effector Cell Cycle Fatty acid synthesis	Cell Cycle Fatty acid synthesis	Stroma Cell Cycle	snoRNA
RNA profile							
DNA alts	VHL PBRM1 KDM5C PTEN	VHL PBRM1 KDM5C	VHL PBRM1 KDM5C PTEN BAP1	VHL CDKN2A/B BAP1	CDKN2A/B TP53	VHL CDKN2A/B TP53	VHL SETD2 PTEN

Motzer et al. *Cancer Cell* 2020


MSKCC clinical risk
p=6.59e-08
n=156
n=573
n=94
100%
75%
50%
25%
0%
Patient Percentage
Favorable
Intermediate
Poor
IMDC clinical risk
p=4.35e-08
n=176
n=513
n=134
100%
75%
50%
25%
0%
Patient Percentage
Favorable
Intermediate
Poor
1 - Angio/Stromal
2 - Angiogenic
3 - Complement/Ω-ox.
4 - T-eff/Proliferative
5 - Proliferative
6 - Stromal/Proliferative
7 - snoRNA

Future Trial Concept



Conclusions

- Adjuvant pembrolizumab prolongs DFS in high-risk resected RCC. OS effects uncertain.

- IO-based doublets with an anti-PD1 backbone are transforming the initial management of mRCC with IO +VEGF regimens leading to the highest ORR/longest PFS while IO/IO regimens are notable for durability of response/disease control and potential for disease control off therapy.
  - We are rapidly moving towards triplets

- Single agent VEGF TKI is the standard of care after an IO-based doublet, but early signals suggest IO can be active after failure of prior IO-based regimens, pending randomized, prospective investigation.

- Biologic insights in mRCC reinforces angiogenic and inflammatory pathways but uncover novel drug targets and may provide a path to more personalized therapy.