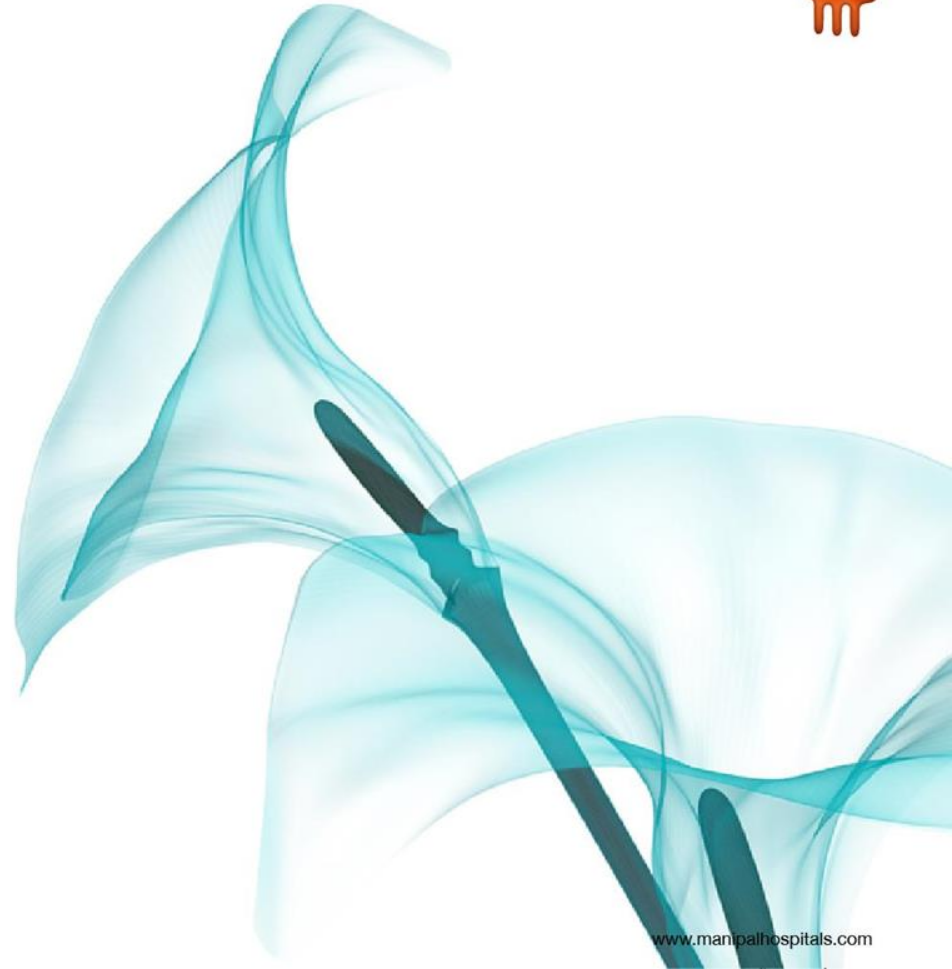




## **PANEL DISCUSSION – metastatic RCC**

**DR PEUSH BAJPAI  
CONSULTANT AND HEAD  
DEPARTMENT OF MEDICAL ONCOLOGY.**

**MANIPAL HOSPITAL, DELHI**



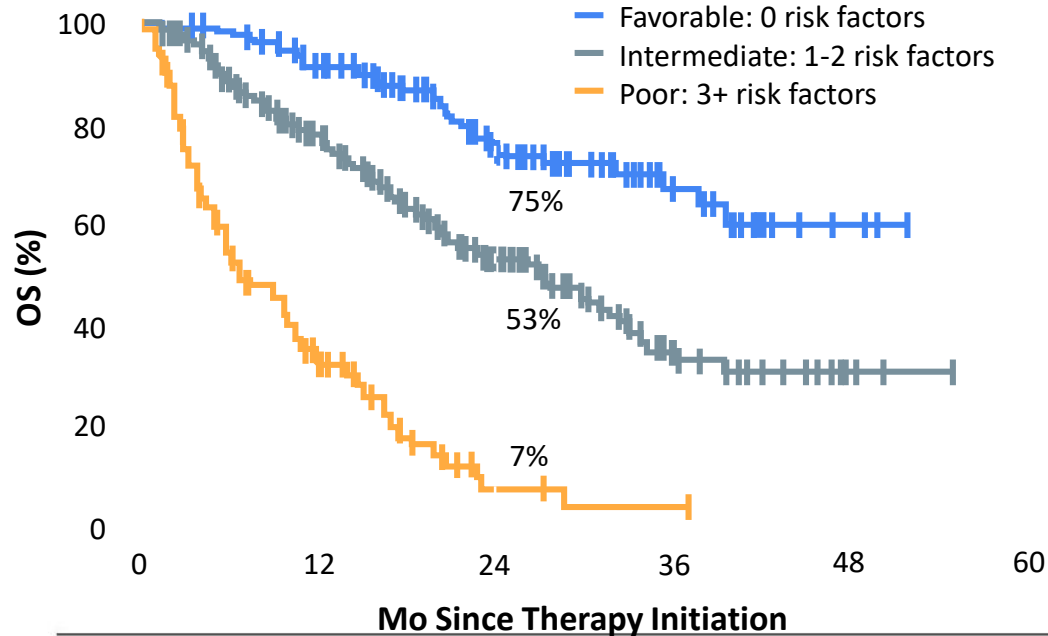
# Case

- 71 y old was diagnosed with Renal tumor in 2001 underwent left Nephrectomy.
- Currently , presents to me with a history of sternal bulge –no pain ( imaging sternal mets ( **Clear cell ca grd 2 –biopsy proven**) and mediastinal nodes approx 2 cm) with this being there for past 6 months ( previous 6 m imaging present).
- IMDC score 0 ( Hmg –Normal , Calcium 9.3 ,PS1)—Favorable
- Anxious family and patient

# For all Panelists ?

- Options
  - Pembro + Axitinib
  - Observation
  - Sunitinib
  - Any other

# IMDC Prognostic Criteria



Events, n/At Risk, n	0	12	24	36	48	60
Favorable	11/133	16/110	4/62	2/22	0/3	0/3
Intermediate	61/301	50/182	17/82	2/18	0/3	0/3
Poor	94/152	19/36	1/3	0/1	0/0	0/0

Heng. JCO. 2009;27:5794.

- Risk factors:
  - <1 year from diagnosis to treatment
  - Karnofsky PS <80%
  - Low hemoglobin (<LLN)
  - High calcium (>10 mg/dL)
  - High platelet count (>ULN)
  - High neutrophil count (>ULN)
- **75%-80% of patients with metastatic RCC are poor or intermediate risk**

manipalhospitals

Slide credit: [clinicaloptions.com](http://clinicaloptions.com)

# First-line Systemic Therapy for Advanced Clear-Cell RCC

## Favorable Risk

- **Axitinib + pembrolizumab**
- **Cabozantinib + nivolumab**
- Lenvatinib + pembrolizumab
- **Active surveillance (under certain circumstances)**

### Other regimens to consider for specific patients

- Ipilimumab + nivolumab
- Axitinib + avelumab
- **Pazopanib**
- **Sunitinib**
- Cabozantinib
- Axitinib

## Intermediate or Poor Risk

- Ipilimumab + nivolumab
- Axitinib + pembrolizumab
- Cabozantinib + nivolumab
- Lenvatinib + pembrolizumab
- Cabozantinib

### Other regimens to consider for specific patients

- Pazopanib
- Sunitinib
- Axitinib + avelumab
- Axitinib

# Are there any takers for Observation – For all Panelists

# Prospective Phase II Observational Study in Patients With Asymptomatic Metastatic RCC

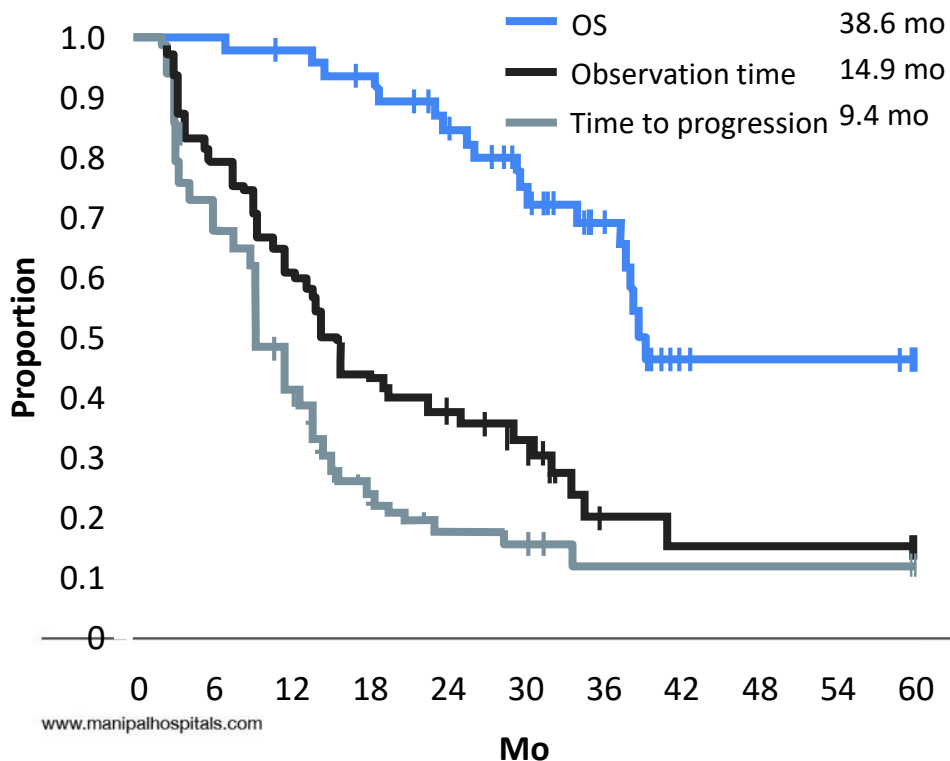
- Patients with clinically evident metastatic RCC of any histologic subtype (N = 48)
- First documentation (radiographic or histologic) of metastatic RCC up to 12 mo prior to registration on study
- No prior systemic therapy for RCC in the metastatic or neo/adjuvant setting
- Prior XRT (including for CNS metastases) and prior nephrectomy/metastasectomy permitted but not required
- No disease-related symptoms
- Measurable/evaluable disease per RECIST v1.0

CT every 3 mo in Yr 1, every 4 mo in Yr 2,  
then every 6 mo

Initiation of  
systemic  
treatment  
per doctor/  
patient  
discretion

- FKSI-DRS (QoL) and HADS (anxiety/depression) assessments administered at baseline and at every CT scan timepoint
- Peripheral blood for immune cell quantification drawn at baseline and at every CT scan time point

# Prospective Observation Study: Outcomes



- Median absolute change in tumor burden during surveillance: 1.3 cm
  - Relative change: 31%
  - Median growth rate: 0.09 cm/mo
- 23/43 (53%) patients with progressive disease immediately started systematic therapy after progression and 20/43 (47%) continued on surveillance
  - Median additional surveillance period for these patients: 15.8 mo



- This patient progresses lesion PD on CT after 6 months –remains asymptomatic
  - IMDC – Favorable still
  - Options ?
    - TKI +IO
    - Sunitinib
    - Pazopanib
    - Cabozantinib
- 
- Continue Observation

# ONLY VEGF TKI

## Nobel Loreate 2019:

William Kaelin, Gregg Semenza and Peter Ratcliff for their discoveries of how cells sense **and adapt to oxygen availability**



# VEGF TKI + IO

## Nobel Loreate 2019:

William Kaelin, Gregg Semenza and Peter Ratcliff for their discoveries of how cells sense **and adapt to oxygen availability**



## Nobel Loreate 2018:

James P. Allison and Tasuku Honjo for their discovery of **cancer therapy** by **inhibition of negative immune regulation**

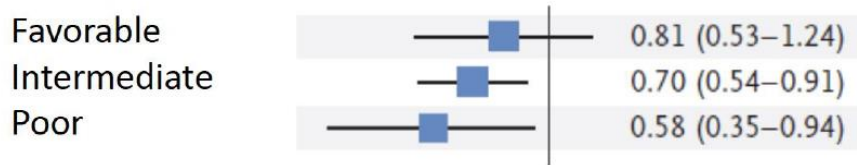


# IS SUTENT STILL IN THE RACE ? ( for all panelists)

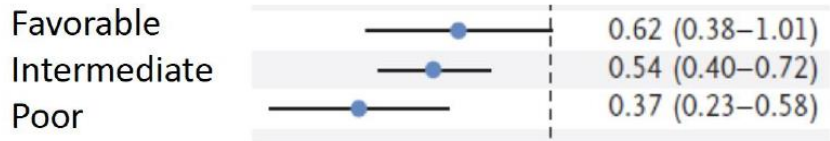
## Agents: Imune based combinations

TKI+IO combos

- PFS improvement across all subgroups



KN426: Axi+Pembro

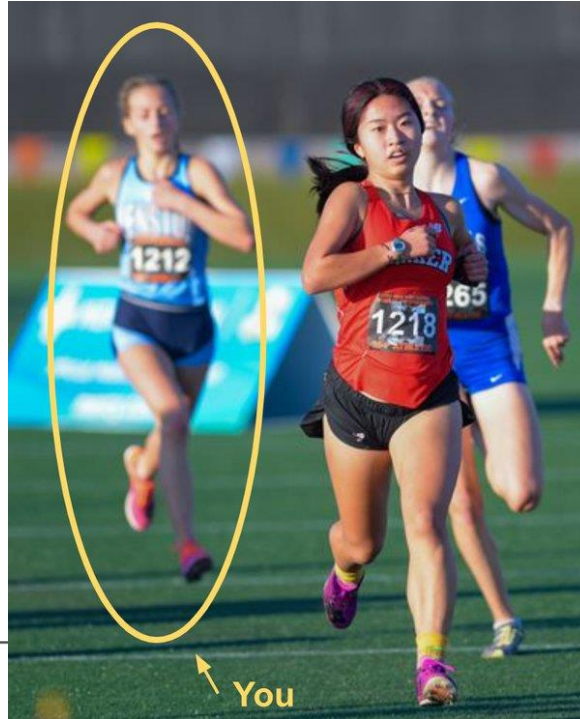


9ER: Cabo+Nivo



CLEAR: Len+Pembro

# IS SUTENT STILL IN THE RACE ? ( for all panelists)

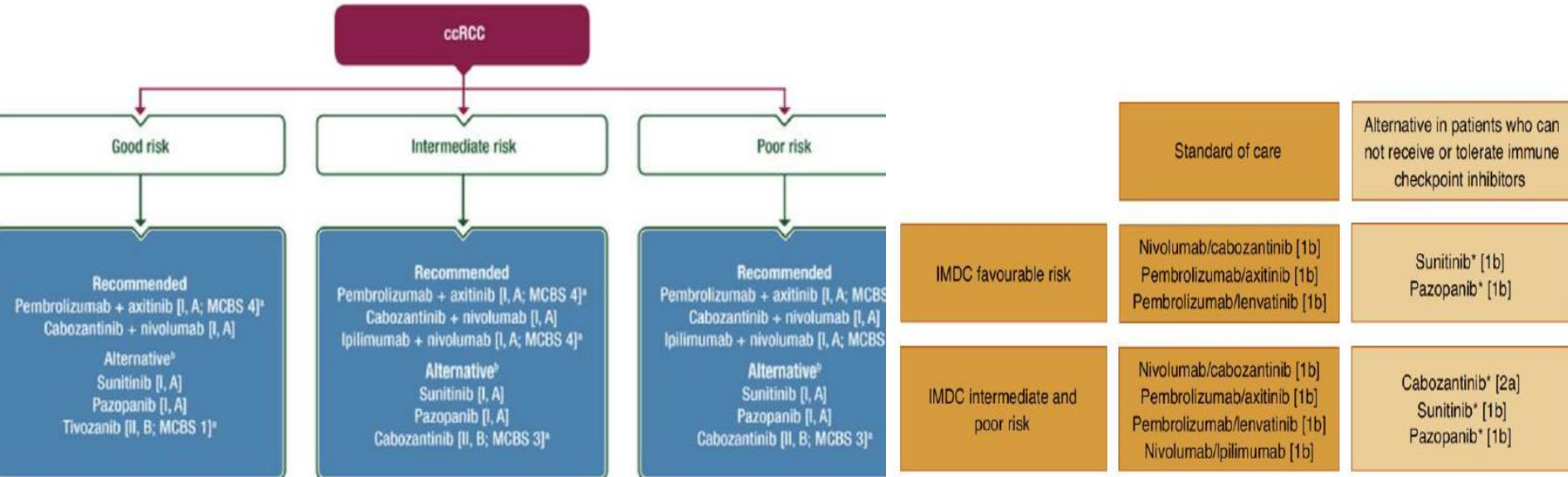




# SUTENT IS NOW STATED AS ALTERNATIVE

## ESMO

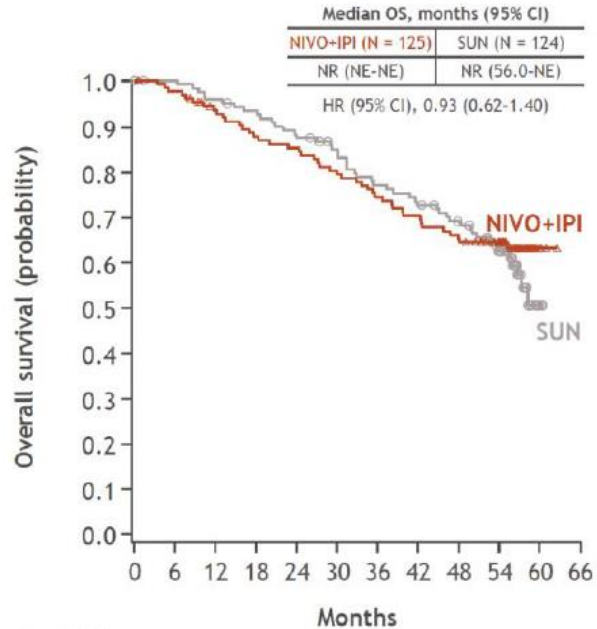
## EAU



# Sunitinib is not giving up easily in Favourable risk category

## Agents: Immune based combinations

### D. Favorable-risk population



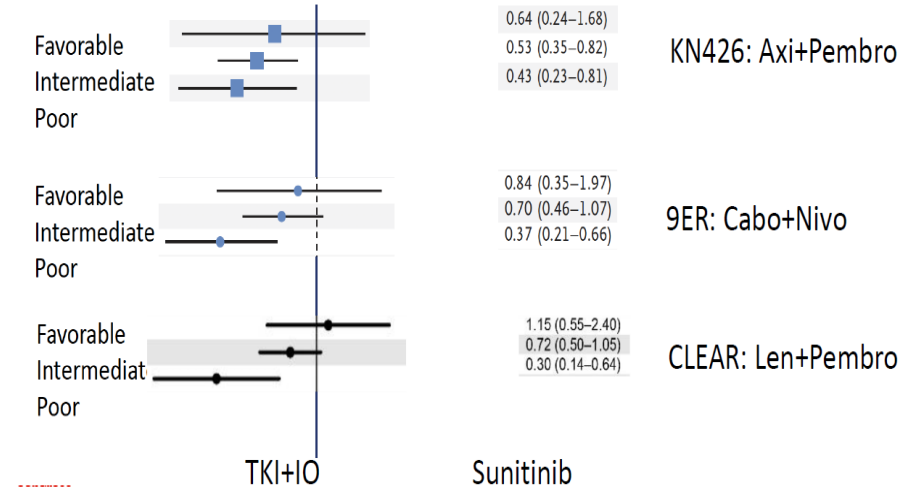
www.mai

No. at risk

NIVO+IPI	125	121	112	105	102	96	89	84	78	68	3	0
SUN	124	119	114	110	104	97	88	83	76	60	2	0

### TKI+IO combos

- OS maybe different across subgroups
- A question of minimum follow-up time?

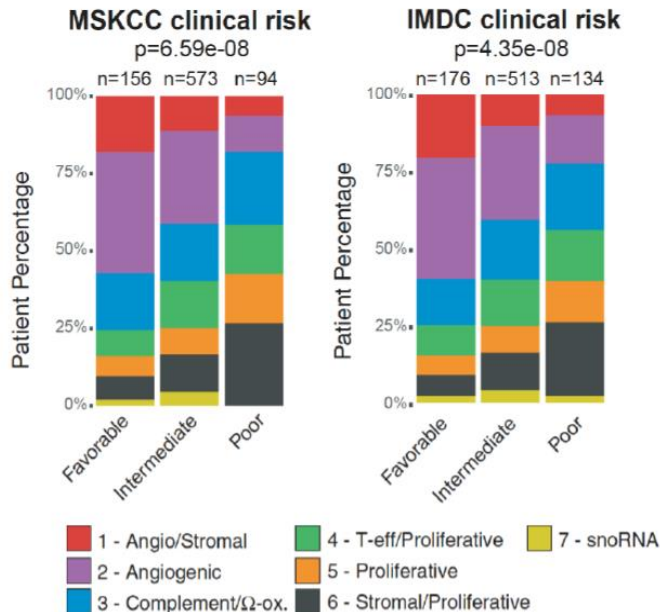
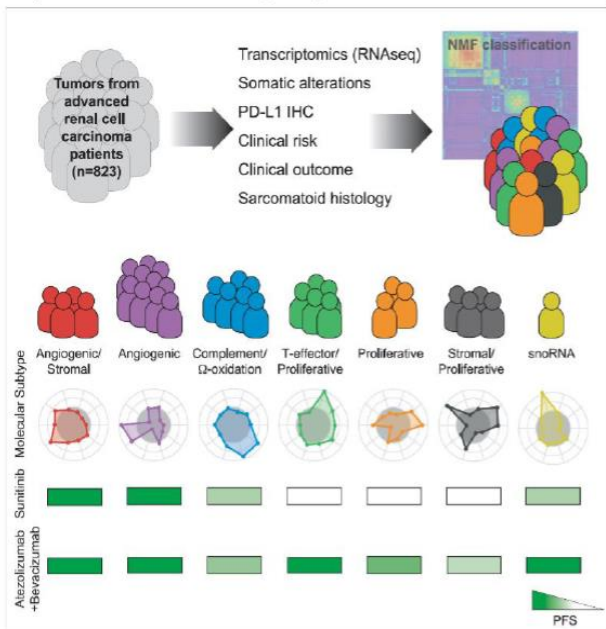


# FOR THOSE OPTING FOR ONLY VEGF TKI MAY NOT BE WRONG—SUTENT STILL IN THE RACE

## Emerging biomarkers:

Molecular Subsets in Renal Cancer Determine Outcome

to Checkpoint and Angiogenesis Blockade (IMmotion 151 cohort)



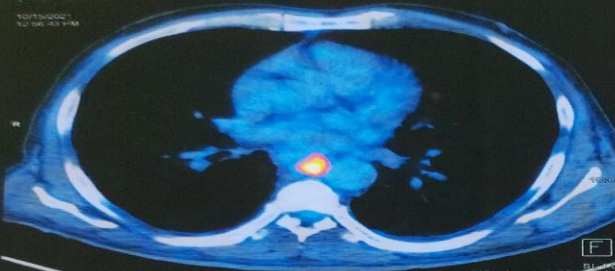


- Case 2

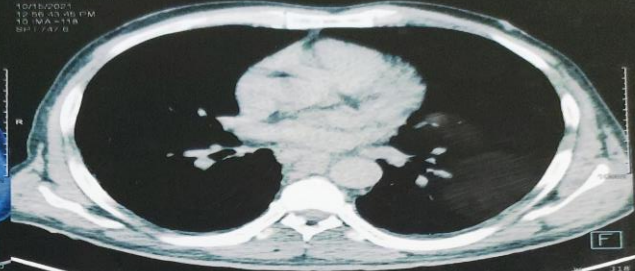
- 45 y old presenting with history of DM and recently diagnosed with Stg 4 RCC—clear cell grd 4/5 – Sarcomatoid histology focal
- Type 1 DM CONTROLLED
- Metastatic sites ---LN, Lung , patient had a Hb 8 g and is IMDC – POOR, HECTIC FEVER

# DELHI INSTITUTE OF FUNCTIONAL IMAGING

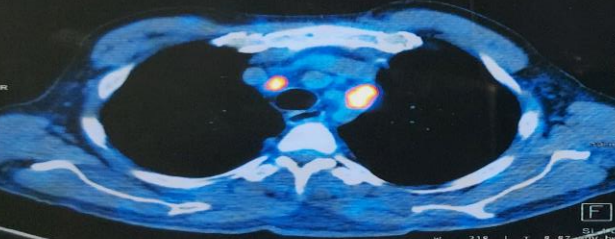
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10/15/2021  
12:56:43 PM



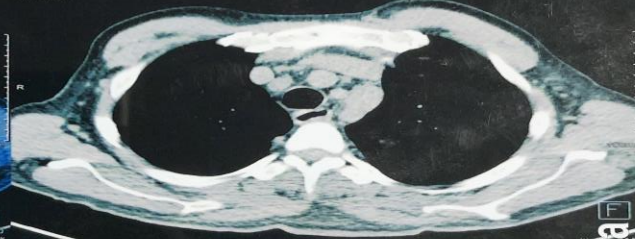
FATTAH MAHMOOD YASEEN 52Y/M, REG: FHN2282 A  
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SP: P/3.0



FATTAH MAHMOOD YASEEN 52Y/M, REG: FHN2282 A  
10/15/2021  
12:56:43 PM



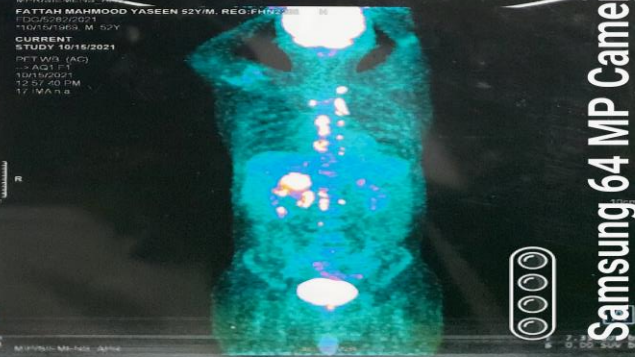
FATTAH MAHMOOD YASEEN 52Y/M, REG: FHN2282 A  
10/15/2021  
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12:56:43 PM  
SP: P/3.0



FATTAH MAHMOOD YASEEN 52Y/M, REG: FHN2282 M  
10/15/2021  
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STUDY 10/15/2021  
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12:57:40 PM  
10/15/2021  
12:57:40 PM  
SP: P/3.0



FATTAH MAHMOOD YASEEN 52Y/M, REG: FHN2282 M  
10/15/2021  
12:57:40 PM  
CURRENT  
STUDY 10/15/2021  
10/15/2021  
12:57:40 PM  
10/15/2021  
12:57:40 PM  
SP: P/3.0



Samsung 64 MP Camera  
Dr Peush Bajpai

# To all panelists

- **ROLE OF SURGERY—CYTOREDUCTIVE NEPHRECTOMY IS IT THERE ?**
- **If not now then when ?**

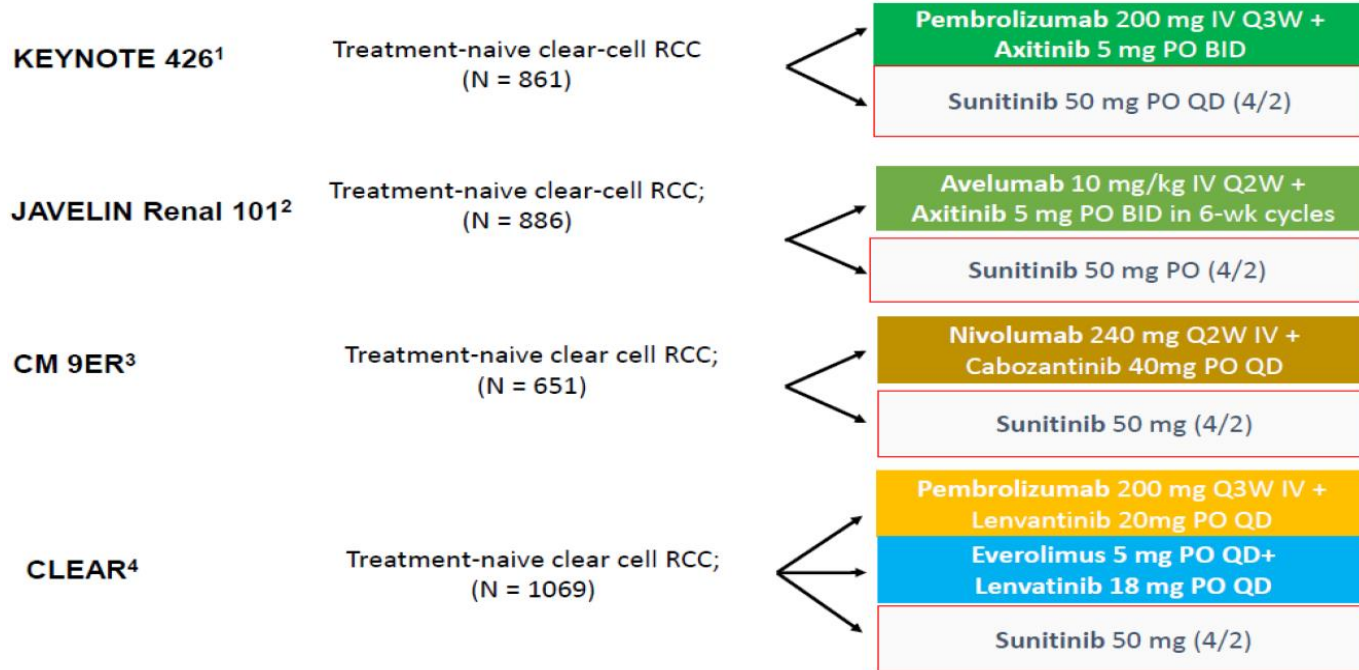
**Which regimen here and why?**

IO –TKI

IO – IO

IO –IO + TKI ( COSMIC 313)

# TKI + IO—WHICH ONE IS BETTER ? ( TO ALL PANELISTS)



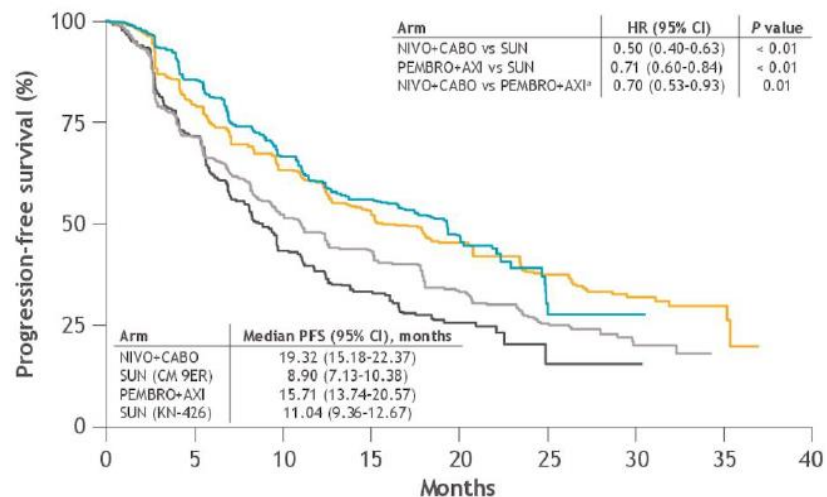
# Agents: Immune based combinations

## Can we compare cross-trial?

### Efficacy outcomes of nivolumab plus cabozantinib versus pembrolizumab plus axitinib in patients with advanced renal cell carcinoma: matching-adjusted indirect comparison

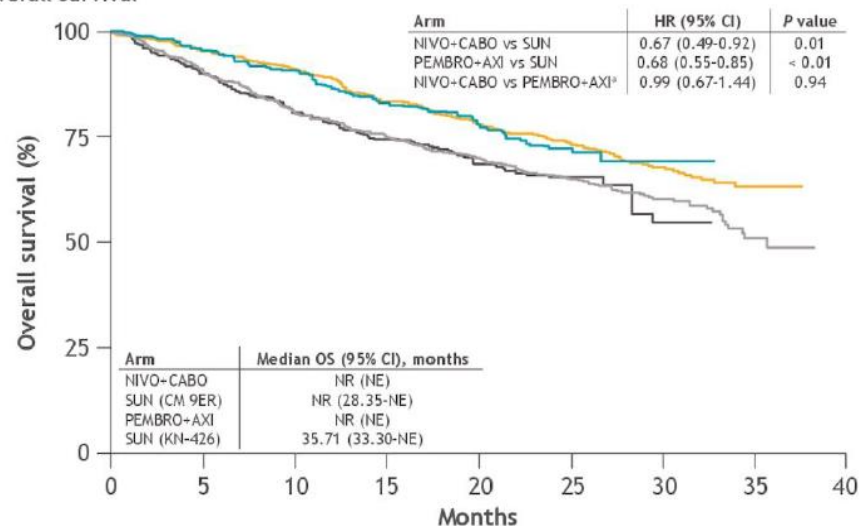
Bradley McGregor,<sup>1</sup> Daniel M. Geynisman,<sup>2</sup> Mauricio Burotto,<sup>3</sup> Camillo Porta,<sup>4</sup> Cristina Suarez,<sup>5</sup> Maria T. Bourlon,<sup>6</sup> Pedro C. Barata,<sup>7</sup> Shuchi Gulati,<sup>8</sup> Brian Stwalley,<sup>9</sup> Viviana Del Tejo,<sup>9</sup> Ella X. Du,<sup>10</sup> Aozhou Wu,<sup>10</sup> Andi Chin,<sup>10</sup>

#### A. Progression-free survival



Arm	NIVO+CABO	SUN (CM 9ER)	PEMBRO+AXI	SUN (KN-426)
No. at risk	323	328	432	429
NIVO+CABO	256	191	323	275
SUN (CM 9ER)	183	102	249	182
PEMBRO+AXI	145	61	203	138
SUN (KN-426)	61	18	158	96
	10	3	109	61
	2	1	37	19
	0	0	9	0
	0	0	0	0

#### C. Overall survival



Arm	NIVO+CABO	SUN (CM 9ER)	PEMBRO+AXI	SUN (KN-426)
No. at risk	323	328	432	429
NIVO+CABO	299	281	411	390
SUN (CM 9ER)	281	245	392	345
PEMBRO+AXI	281	217	359	320
SUN (KN-426)	180	145	332	295
	68	47	305	268
	10	4	163	134
	0	0	46	37
	0	0	0	0

# First-line IO Combination Trials in mRCC

	CheckMate 214 <sup>1</sup> Ipi/Nivo vs Sun (n = 550 vs n = 546)	KEYNOTE-426 <sup>2</sup> Axi/Pembro vs Sun (n = 432 vs n = 429)	CheckMate 9ER <sup>3</sup> Cabo/Nivo vs Sun (n = 323 vs n = 328)	CLEAR <sup>4</sup> Len/Pembro vs Sun (n = 355 vs n = 357)
mOS, mo HR (CI)	55.7 vs 38.4 <b>0.72</b> (0.62-0.85)	45.7 vs 40.1 <b>0.73</b> (0.60-0.88)	NR vs 29.5 <b>0.66</b> (0.50-0.87)	NR vs NR <b>0.72</b> (0.55-0.93)
Landmark OS 12 mo	<b>83%</b> vs 78%	<b>90%</b> vs 79%	<b>86%</b> vs 76%	<b>90%</b> vs 79% (est.)
Landmark OS 24 mo	<b>71%</b> vs 61%	<b>74%</b> vs 66%	<b>72%</b> vs 60% (est)	<b>79%</b> vs 70%
mPFS, mo HR (CI)	<b>12.2</b> vs 12.3 0.86 (0.73-1.01)	<b>15.7</b> vs 11.1 0.68 (0.58-0.80)	<b>17.0</b> vs 8.3 0.52 (0.43-0.64)	<b>23.9</b> vs 9.2 0.39 (0.32-0.49)
ORR, %	<b>39</b> vs 32	<b>60</b> vs 40	<b>55</b> vs 27	<b>71</b> vs 36
CR, %	<b>12</b> vs 3	<b>10</b> vs 4	<b>9</b> vs 4	<b>16</b> vs 4
Median f/u, mo	<b>67.7</b>	<b>42.8</b>	<b>23.5</b>	<b>33.7</b>
Primary PD, %	<b>18</b>	<b>11</b>	<b>6</b>	<b>5</b>
Prognostic risk, %				
Favorable	23	32	23	31
Intermediate	61	55	58	59
Poor	17	13	19	9
Prior nephrectomy	82%	83%	69%	74%

Subsequent systemic Tx

Overall (68%)

Overall (69%)

Overall (40%)

Overall (71%)

1. Motzer. ESMO 2021. Abstr 661P. 2. Rini. ASCO 2021. Abstr 4500.

3. Motzer. ASCO GU 2021. Abstr 308. 4. Motzer. ASCO GU 2021. Abstr 269.

IO (48%)  
Adapted from

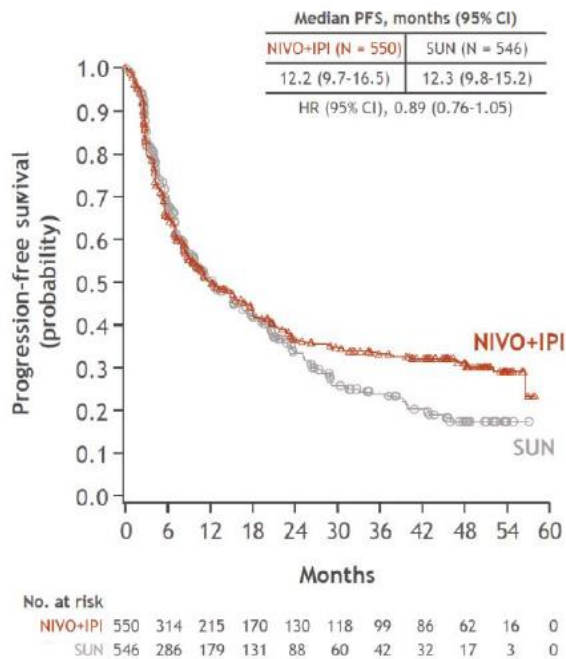


@brian\_rini and @Uromigos (podcasts: <https://anchor.fm/the-Uromigos>)

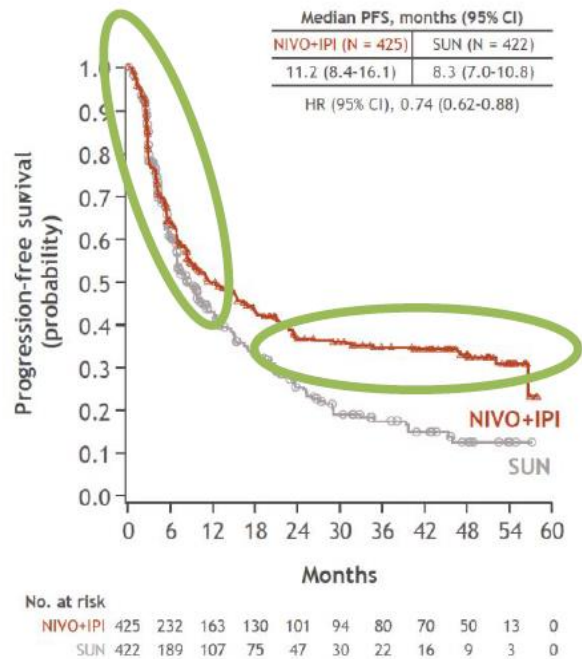


# CM214: Ipi+Nivo: Progression-free Survival

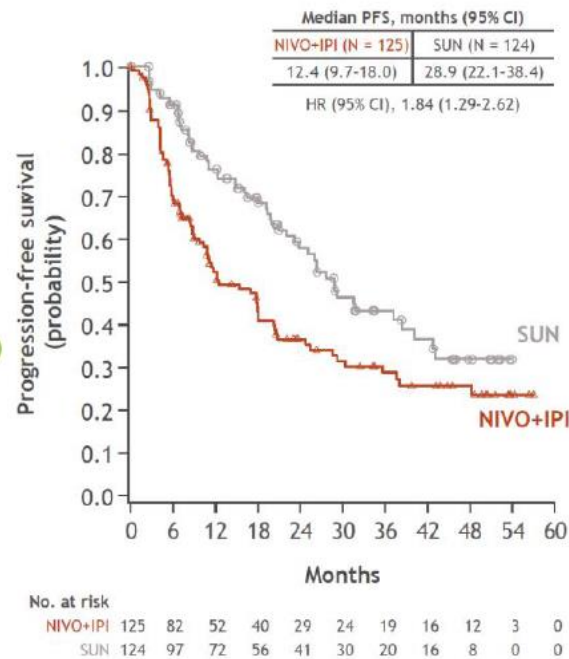
B. ITT population



C. I/P-risk population

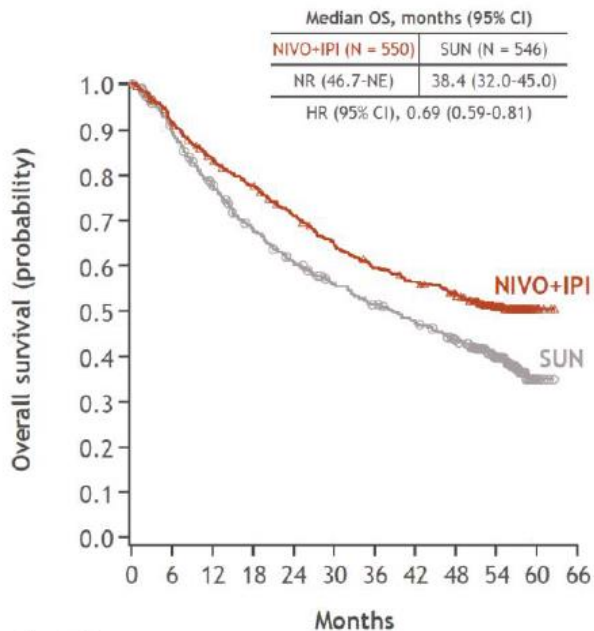


D. Favorable-risk population



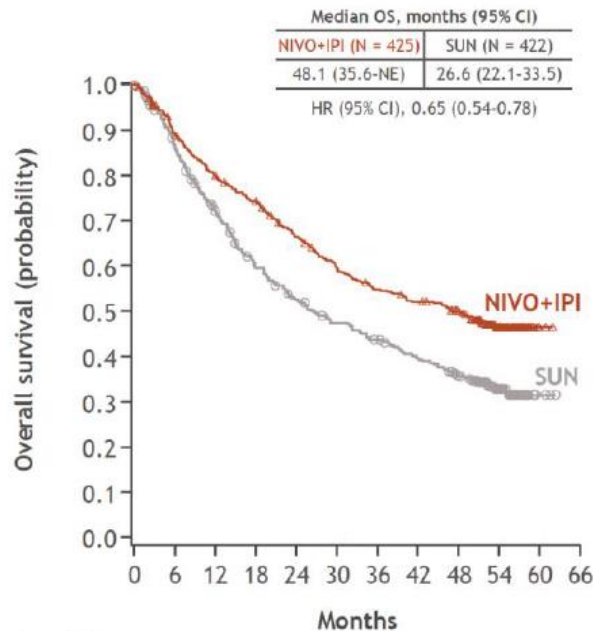
# OS in CHECKMATE 214—Nearly 48 months in intermediate /poor risk population---Longest median FUP

B. ITT population



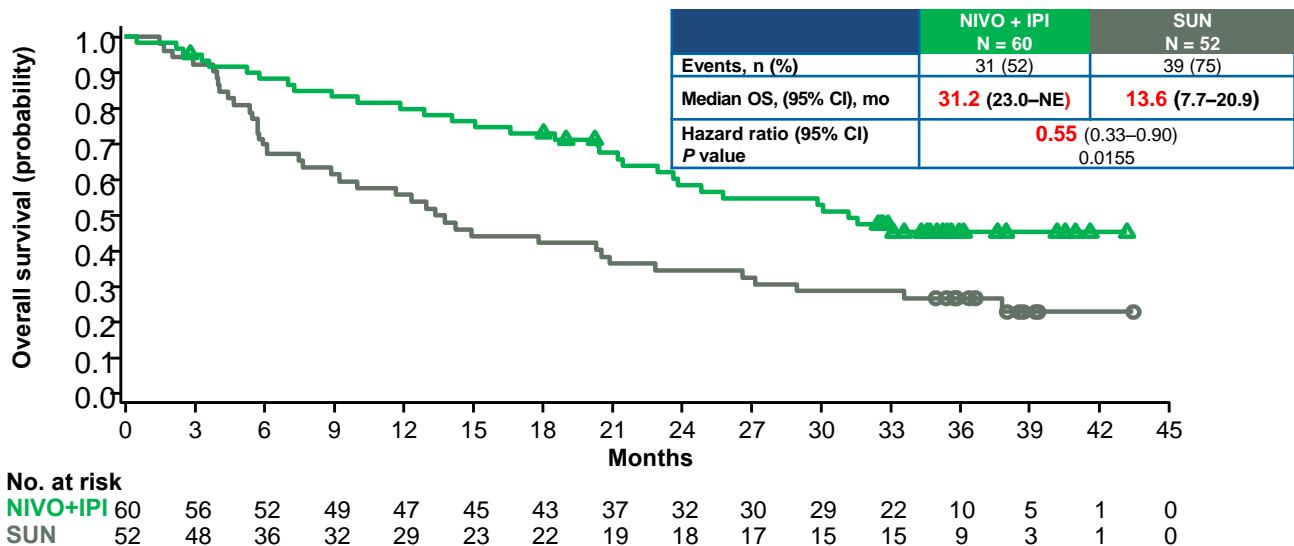
No. at risk	0	6	12	18	24	30	36	42	48	54	60	66
NIVO+IPI	550	493	444	411	372	337	309	292	271	154	6	0
SUN	546	472	405	347	310	281	257	234	209	126	5	0

C. I/P-risk population



No. at risk	0	6	12	18	24	30	36	42	48	54	60	66
NIVO+IPI	425	372	332	306	270	241	220	208	193	86	3	0
SUN	422	353	291	237	206	184	169	151	133	66	3	0

## OS: Intermediate/Poor-Risk Sarcomatoid Patients

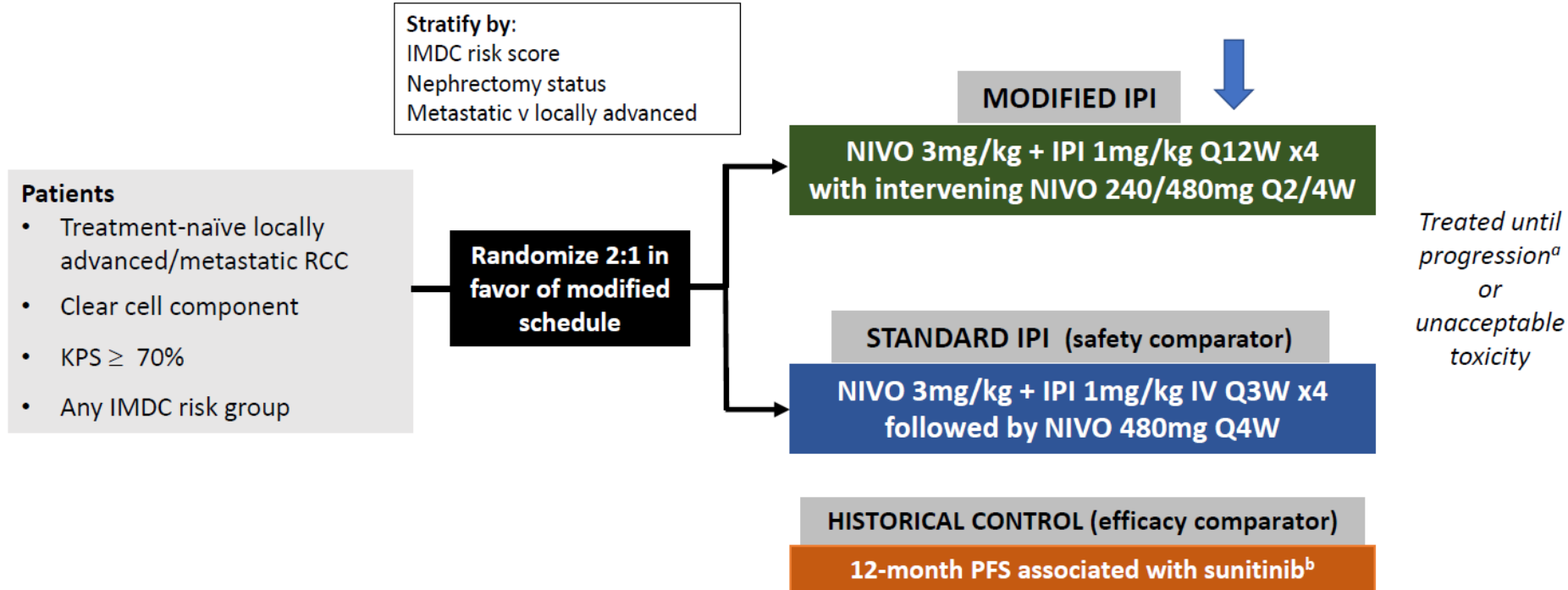


OS probability, % (95% CI)	NIVO + IPI N = 60	SUN N = 52
12 month	<b>80 (67–88)</b>	<b>56 (41–68)</b>
24 month	<b>58 (45–70)</b>	<b>35 (22–47)</b>
30 month	<b>53 (39–65)</b>	<b>29 (17–41)</b>

NE, not estimable

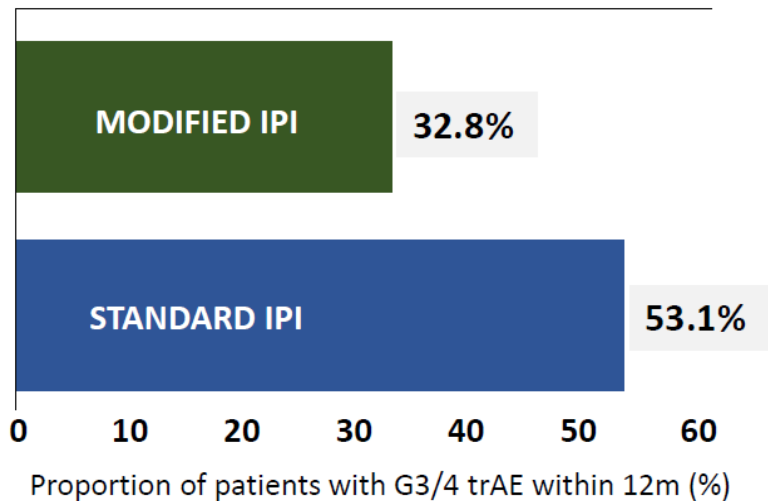
**In IO- IO dose of Ipi 1mg/kg Q 3 weekly x 4 cycles or the PRISM strategy ?**

# PRISM: Study design



- **Primary endpoint:** Proportion of patients experiencing at least one CTCAE (v 5.0) grade 3 or 4 treatment-related AE within 12 months of initiating therapy
- **Secondary endpoint:** PFS in the modified IPI arm at 12 months, tested against historical PFS with sunitinib

# Less frequent Ipi led to less toxicity and efficacy reasonably preserved



**Δ -20.3% (90%CI -32.6, -8.0)**

**OR 0.43 (90% CI 0.25-0.72); p = 0.0075**

Event (%)	Modified IPI (n=128)		Standard IPI (n=64)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Diarrhea	27.3	5.5	20.3	4.7
Colitis	6.3	3.9	9.4	6.3
Arthralgia	18.8	1.6	20.3	7.8
Hyperthyroidism	14.1	0.8	12.5	1.6
Hypothyroidism	12.5	0.0	10.9	0.0
ALT increased	10.9	4.7	15.6	3.1
AST increased	7.0	1.6	4.7	1.6
Creatinine increased	6.3	0.0	4.7	1.6
Lipase increased	5.5	1.6	9.4	9.4
Pneumonitis	5.5	0.8	6.3	1.6
Hypophysitis	0.8	0.8	3.1	3.1
D/C due to trAE, %	22.7		39.1	

PFS 11 months, ORR 45%, CR 6%

- **Post progression what are 2<sup>nd</sup> line options if patient has progressed on**
  - 1 TKI
  - 2 IO –TKI combination

# Therapies for Relapsed or Refractory Stage IV RCC

- Second-line treatments for advanced or metastatic RCC may include targeted therapies and immunotherapy combinations

## Immunotherapy-Based Regimens

- **Nivolumab**
- **Nivolumab + ipilimumab**
- Axitinib + pembrolizumab
- Axitinib + avelumab
- Cabozantinib + nivolumab
- Lenvatinib + pembrolizumab

## Targeted Therapies

- **Cabozantinib**
- Lenvatinib + everolimus
- Axitinib
- Everolimus
- Pazopanib
- Sunitinib
- Tivozanib

## Other Targeted Treatments for Select Circumstances

- Bevacizumab
- Sorafenib
- High-dose IL-12
- Temsirolimus



## Immunotherapy based t/t in Salvage setting—Issues ?

	TITAN RCC ESMO 2019 ASCO 2021	OMNIVORE ASCO 2020 JCO 2021	HCRN GU16-260 ASCO 2020	FRACTION ASCO 2020
Population ccRCC	207 100%	83 95%	34 100%	46 100%
Prior treatment	NIVO 100% VEGFR TKI 48%	NIVO 100% VEGFR TKI 49%	NIVO 100% VEGFR TKI 0%	PD-1/L1 100% Other ICB 40% VEGFR TKI 80%
Rescue strategy	NI X4	NI X2	NI X4	NI X4
ORR NIVO+IPI	7/102 (12%) N=3 CRs	2/57 (4%) No CR	4/30 (13%)	7/46 (15%) No CR

*A rescue strategy with CTLA addition to PD-1 in IO-VEGFR pretreated patients didn't induce CR*

# CONCLUSION--

- IMDC favourable risk –observation is an option in Favourable risk groups
- Sunitinib is still in race in Favourable risk IMDC
- I-O –IO if you want durable responses, CR's matter and without many SE of TKI with poor histology and site--SARCOMATOID HISTOLOGY / BRAIN METS)
- IO –TKI for quick and durable responses but quality of life issues
- If you want to use **NIVO-IPI** at some point then the best is **upfront**

Thank You

