Treatment of Non-Clear Cell Kidney Cancer

Past, Present, and Future

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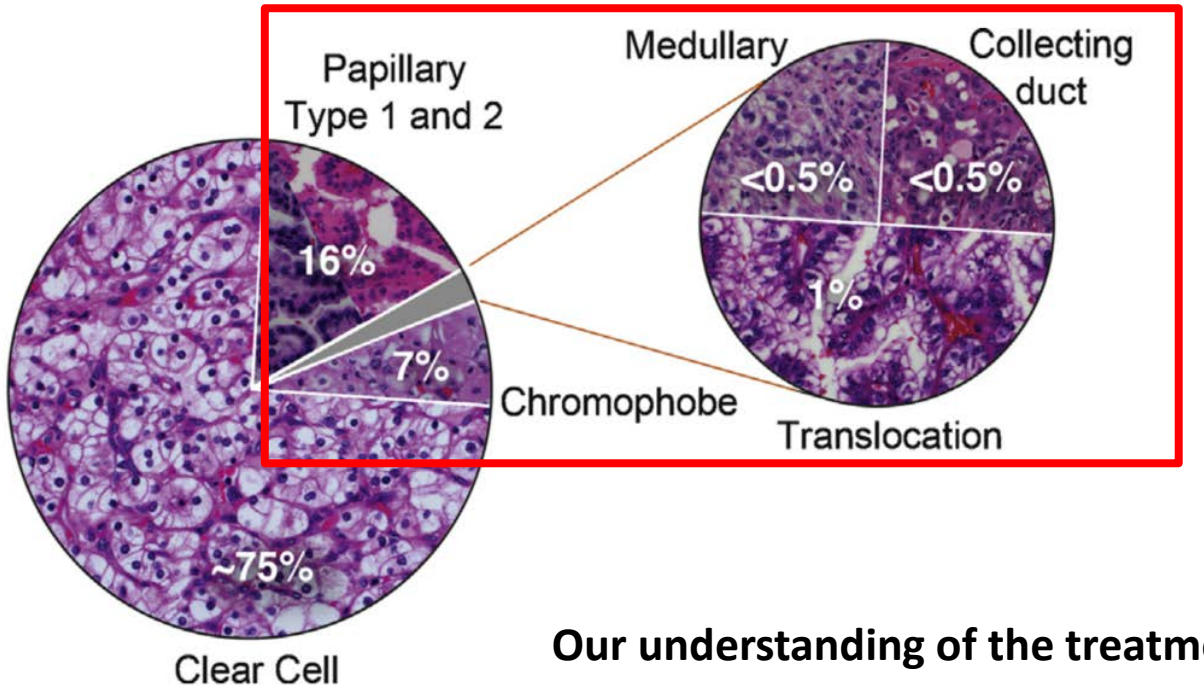
Histologic Classification of Renal Cell Carcinoma



<u>Non-clear cell Kidney Cancers:</u>

- 15 – 20% of all kidney cancers
- Major types of Non-Clear Cell RCC:
  - Papillary type 1 and type 2
  - Chromophobe
  - Unclassified
- Several additional less common subtypes
- Sarcomatoid – admixed with any RCC subtype

Our understanding of the treatment of Non-Clear Cell RCC is *evolving*.

Single uniform entity → spectrum of different diseases:

- **distinctive molecular and genetic alterations**
- **differing clinical courses**
- **variable responses to treatment**

Shuch B et al. *Eur Urol.* 2015;67:85-97.
Linehan WM et al. *J Urol.* 2003;170:2163-2172.

Treatment of Non-Clear Cell RCC: the PAST

Majority of initial studies for the treatment of RCC evaluated agents for Clear Cell Disease (80% of patients).

Little consensus regarding best practice for treatment of Non Clear Cell Disease (~20% of patients).

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	Preferred regimens	Other recommended regimens	Useful under certain circumstances
Favorable[a]	• Axitinib + pembrolizumab • Pazopanib • Sunitinib	• Ipilimumab + nivolumab • Cabozantinib (category 2B) • Axitinib + avelumab	• Active surveillance[b] • Axitinib (category 2B) • High-dose IL-2[c]
Poor/ intermediate[a]	• Ipilimumab + nivolumab (category 1) • Axitinib + pembrolizumab (category 1) • Cabozantinib	• Pazopanib • Sunitinib • Axitinib + avelumab	• Axitinib (category 2B) • High-dose IL-2[c] • Temsirolimus[d]

Treatment of Non-Clear Cell RCC: the PAST

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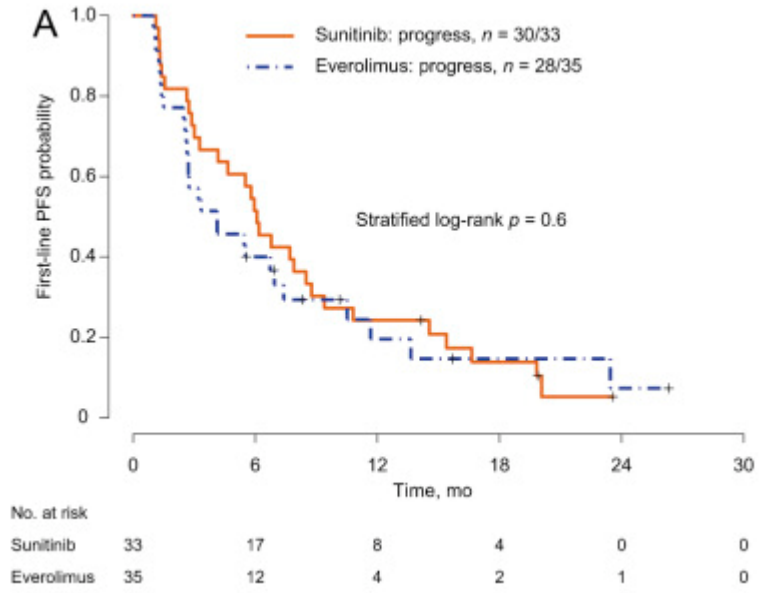
SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY[f]		
Preferred regimens	**Other recommended regimens**	**Useful under certain circumstances**
• Clinical trial • Sunitinib	• Cabozantinib • Everolimus	• Axitinib • Bevacizumab or biosimilar[e] • Erlotinib • Lenvatinib + everolimus • Nivolumab • Pazopanib • Bevacizumab or biosimilar[e] + erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC) • Bevacizumab or biosimilar[e] + everolimus • Temsirolimus[d] (category 1 for poor-prognosis risk group; category 2A for other risk groups)

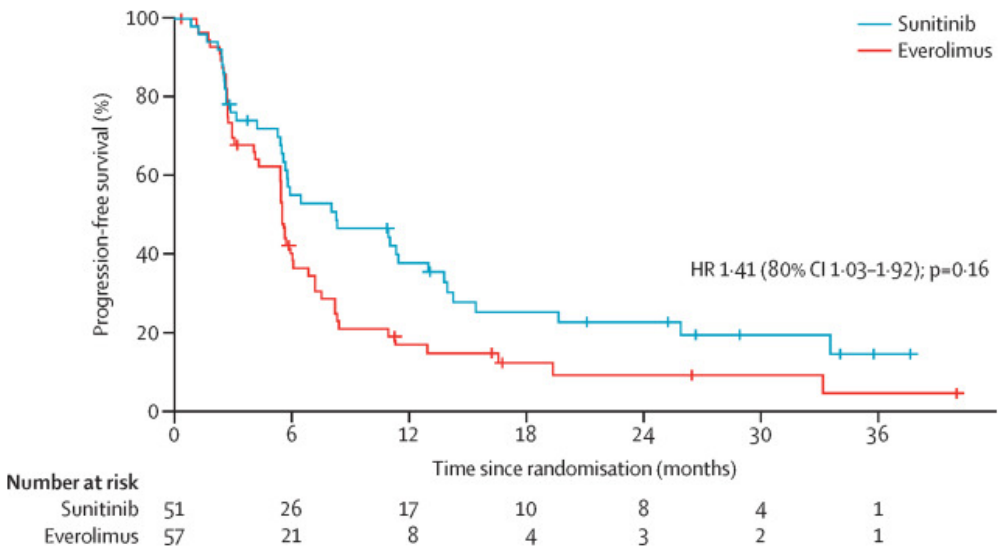
Treatment of Non-Clear Cell RCC: the PAST

Two trials evaluated systemic treatments specifically in Non Clear Cell Disease.
Head to Head comparison: Sunitinib versus Everolimus

ESPN Trial (68 patients)

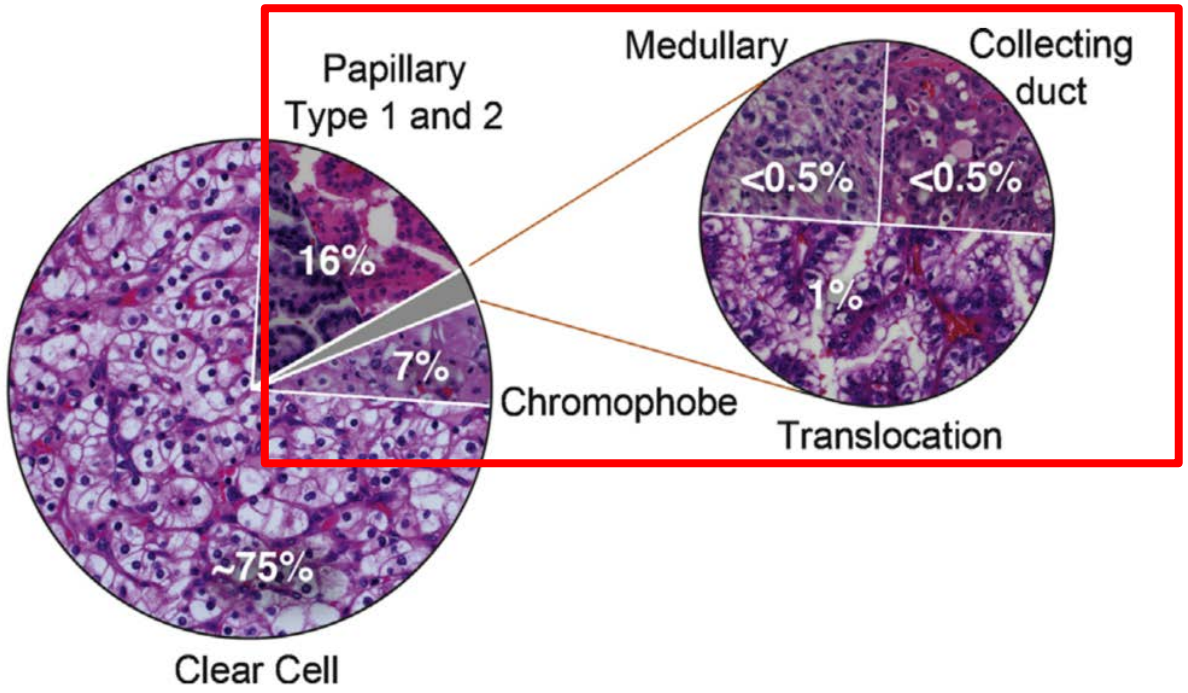


ASPEN Trial (108 patients)



Conclusion: VEGF-directed therapies are the 'standard' treatment for Non Clear Cell Disease (but with very modest clinical outcomes)

Treatment of Non-Clear Cell RCC: the PRESENT



- Non-clear cell RCC is a heterogeneous disease group
  - SPLITTERS (not LUMPERS)
- Each subtype bears a distinct biology
- Improved understanding of the molecular underpinnings of each subtype
- Defining characteristics based on chromosomal alterations, tumor metabolism, etc.

Treatment of Non-Clear Cell RCC: the PRESENT

The Cancer Genome Atlas

Collaborative project to create comprehensive “maps” of the key genomic changes in various cancers

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Clear Cell RCC

- Inactivation of VHL
- Mutations in chromatin remodeling pathways (PBRM1, SETD2, BAP1)
- Mutations in PI3K-Akt-mTOR pathway
- Loss of CDKN2A

Chromophobe RCC

- Alterations in TERT promoter region
- Mitochondrial function
- TP53, PTEN mutations
- Loss of CDKN2A
- Mutations in PI3K-Akt-mTOR pathway

Papillary RCC

Type 1

- Activating mutations, copy number alterations MET protooncogene

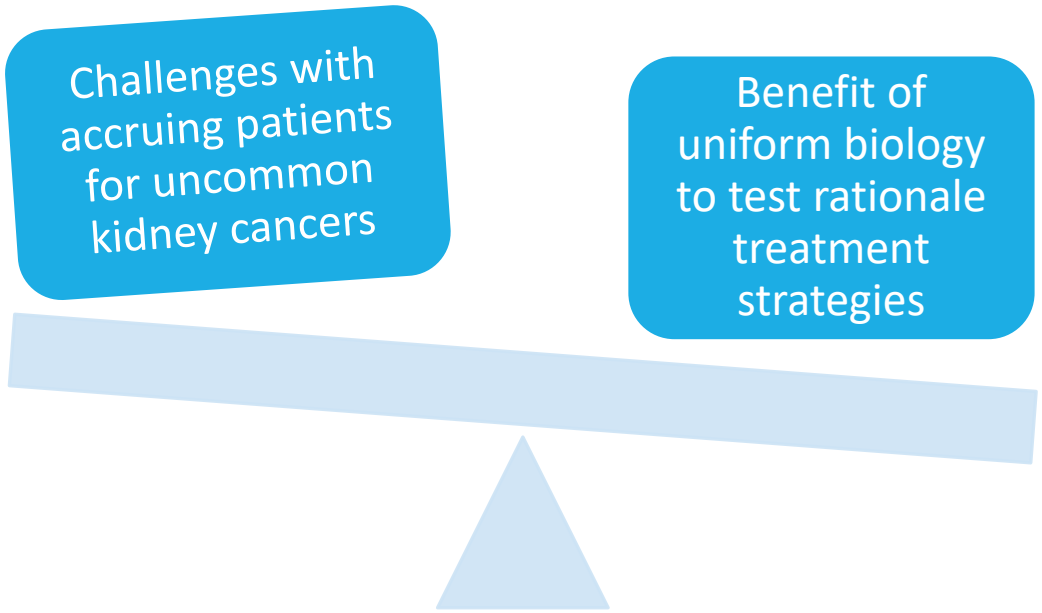
Type 2

- NRF2-ARM
- NF2, SMARCB1
- Loss of CDKN2A
- MET mutation

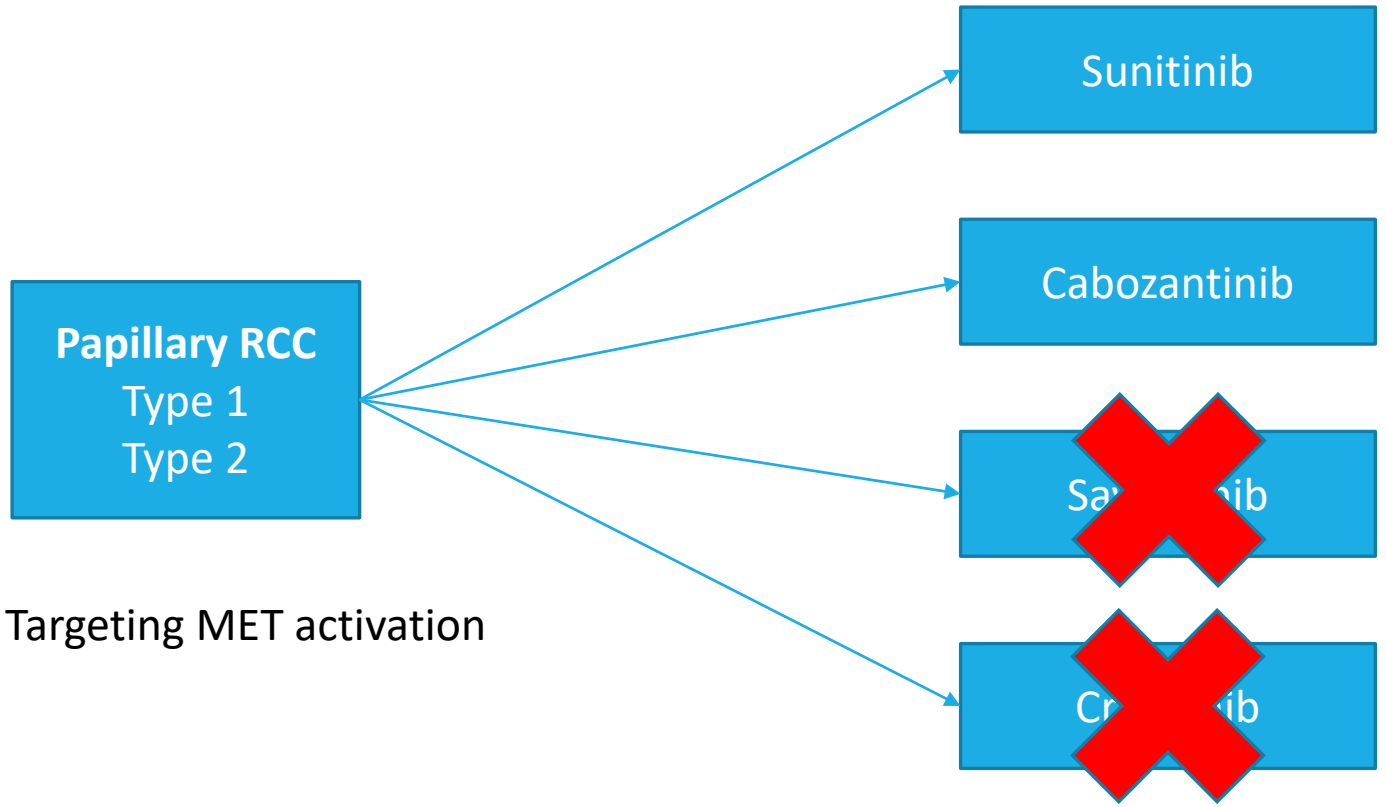
Treatment of Non-Clear Cell RCC: the FUTURE

Change in Treatment Paradigm:

Extrapolating from Clear Cell RCC → Biology-Driven Clinical Trials for Specific Non-Clear Cell RCC Subtypes



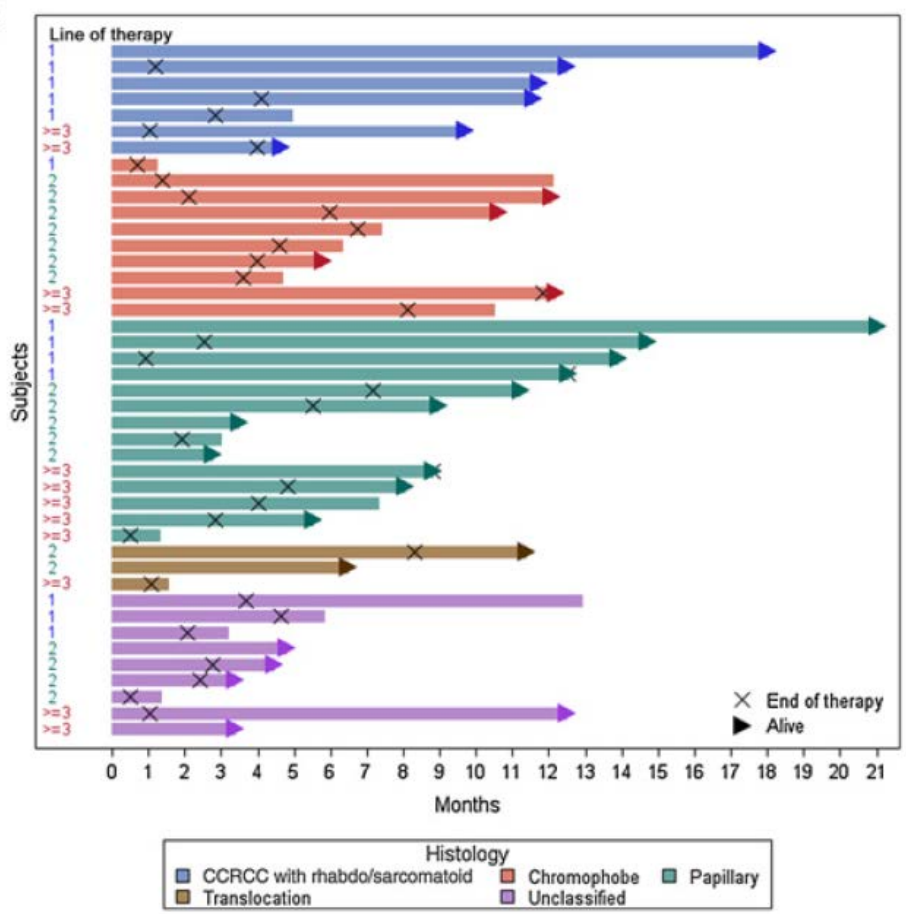
Treatment of Non-Clear Cell RCC: the FUTURE



Targeting MET activation

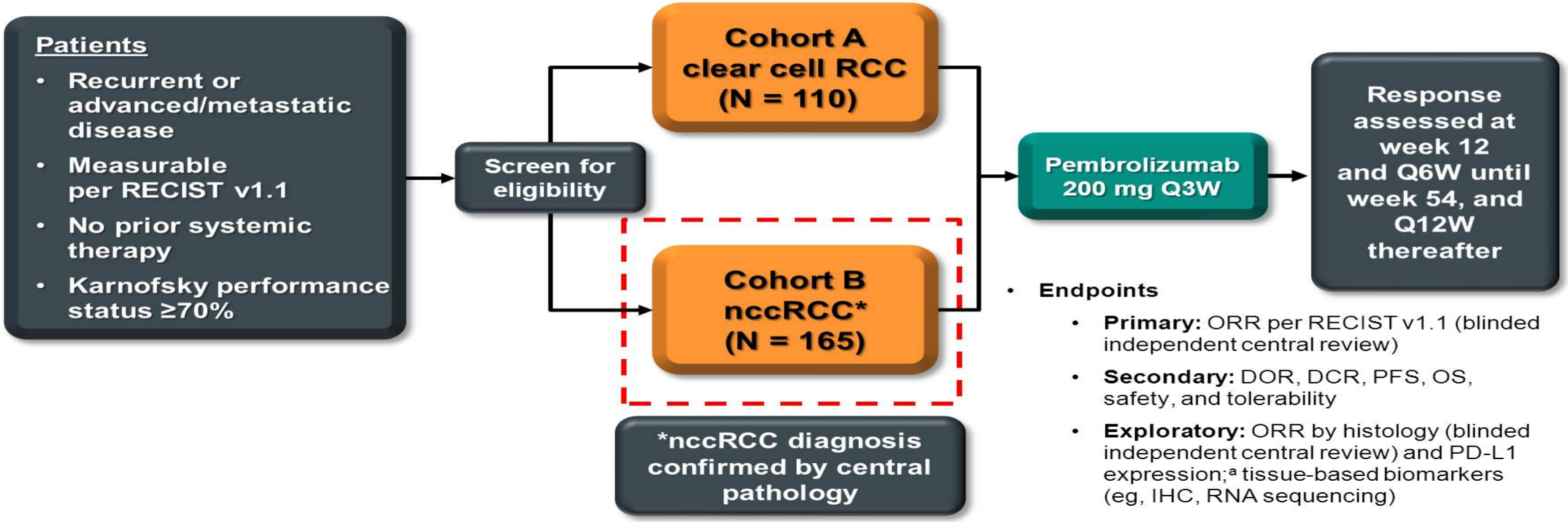
Treatment of Non-Clear Cell RCC: the FUTURE

Immune Checkpoint Inhibitors:



McKay RR. et al. Cancer Immun Res. 2018;6(7):758-765.

KEYNOTE-427: (NCT02853344)



[a]PD-L1 positive defined as combined positive score [CPS] ≥1.

Baseline Characteristics

Characteristic, n (%)	N = 165
Age, median (range), years	62 (22-86)
≥65 years	59 (36)
Men	109 (66)
Race	
White	145 (88)
Asian	17 (10)
Black or African American	1 (1)
Other	1 (1)
Karnofsky performance scale	
90-100	124 (75)
70-80	41 (25)

Characteristic, n (%)	N = 165
Confirmed RCC histology	
Papillary	118 (71)
Chromophobe	21 (13)
Unclassified	26 (16)
IMDC risk category	
Favorable	53 (32)
Intermediate/poor	112 (68)
PD-L1 status	
CPS ≥1	102 (62)
CPS <1	58 (35)
Missing	5 (3)

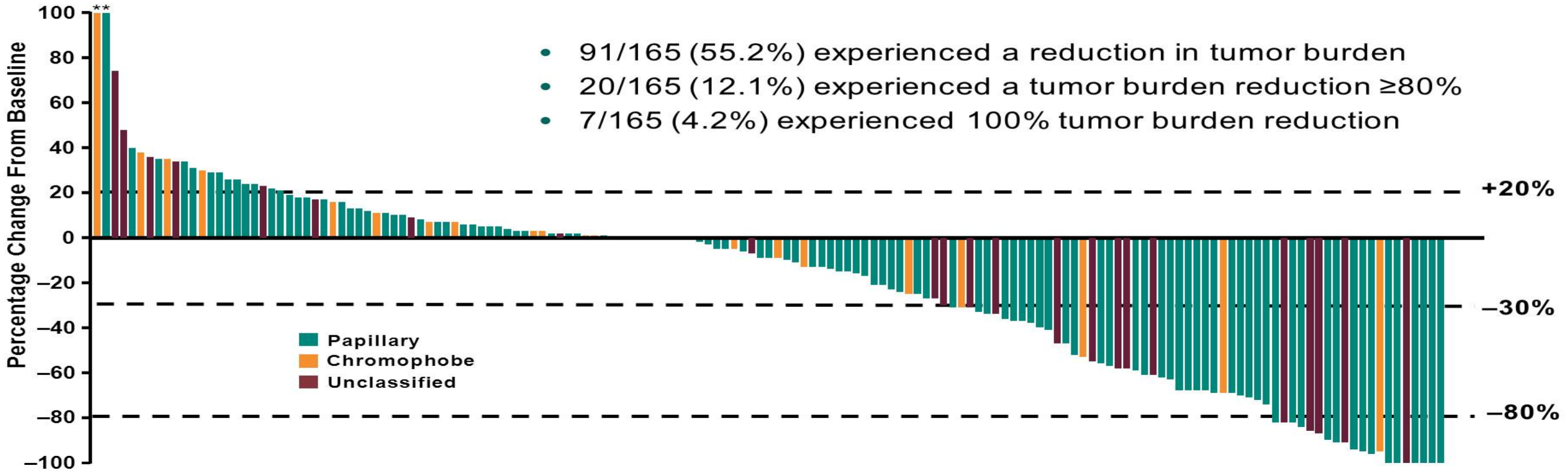
Database cutoff: September 7, 2018.

ORR by Confirmed RCC Histology per Blinded Independent Central Review

	Papillary n = 118	Chromophobe n = 21	Unclassified n = 26
Confirmed ORR, % (95%CI)	**25.4 (17.9-34.3)**	**9.5 (1.2-30.4)**	**34.6 (17.2-55.7)**
DCR, % (95%CI)[a]	**43.2 (34.1-52.7)**	**33.3 (14.6-57.0)**	**34.6 (17.2-55.7)**
Confirmed BOR, %			
CR	4.2	4.8	7.7
PR	21.2	4.8	26.9
SD	34.7	47.6	7.7
PD	33.9	42.9	46.2
No assessment[b]	5.1	0.0	7.7
Not evaluable[c]	0.8	0.0	3.8

[a]DCR = CR + PR + SD ≥6 months. [b]Includes patients who discontinued or died before first postbaseline scan. [c]Includes patients with insufficient data for response assessment. Database cutoff: September 7, 2018.

Maximum Change From Baseline in Target Lesions by Central Review

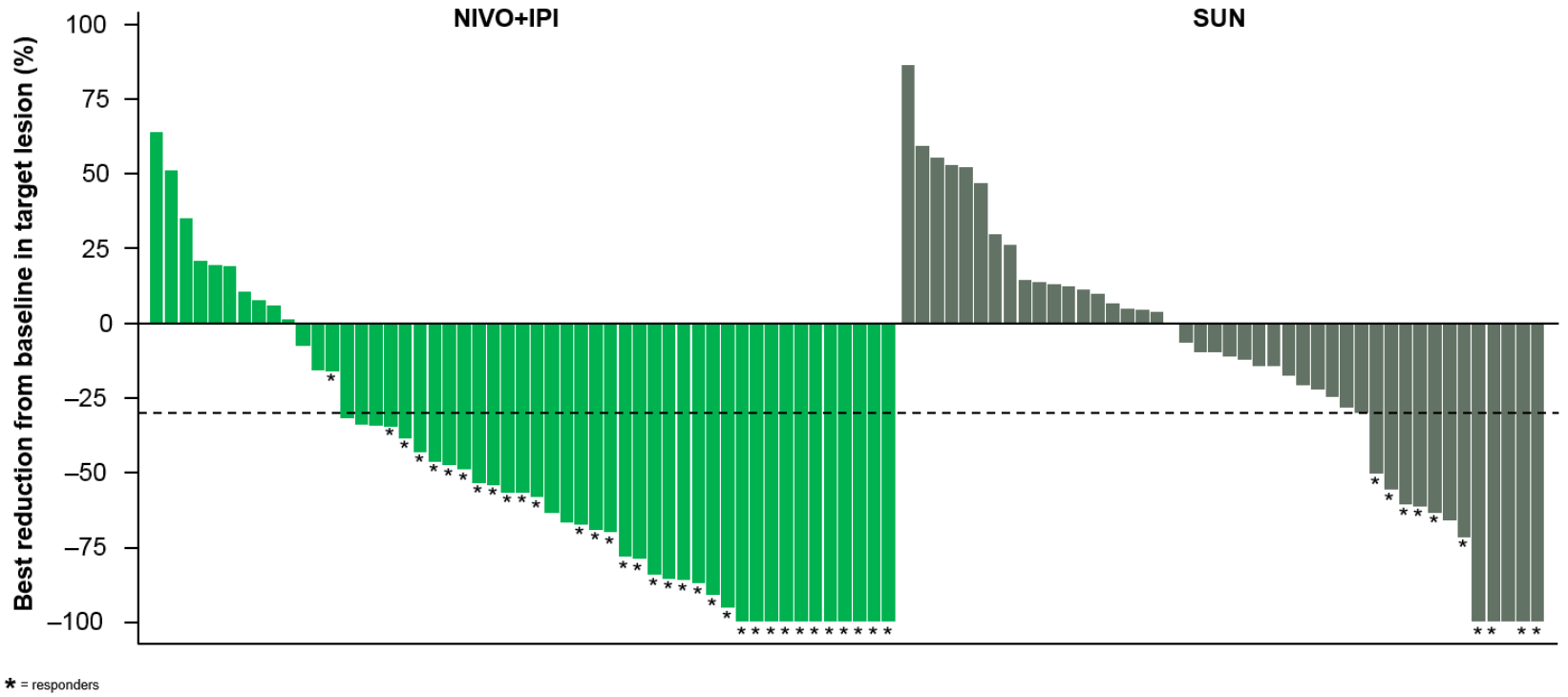


- 91/165 (55.2%) experienced a reduction in tumor burden
- 20/165 (12.1%) experienced a tumor burden reduction ≥80%
- 7/165 (4.2%) experienced 100% tumor burden reduction

Includes patients who received ≥1 dose of pembrolizumab, had a baseline scan with measurable disease per RECIST v1.1, and had a postbaseline assessment (n = 155).
*Patient had an increase in target lesions above 100%.
Database cutoff: September 7, 2018.

Treatment of Non-Clear Cell RCC: the FUTURE

Immune Checkpoint Inhibitors: Sarcomatoid RCC



Treatment of Non-Clear Cell RCC: the FUTURE

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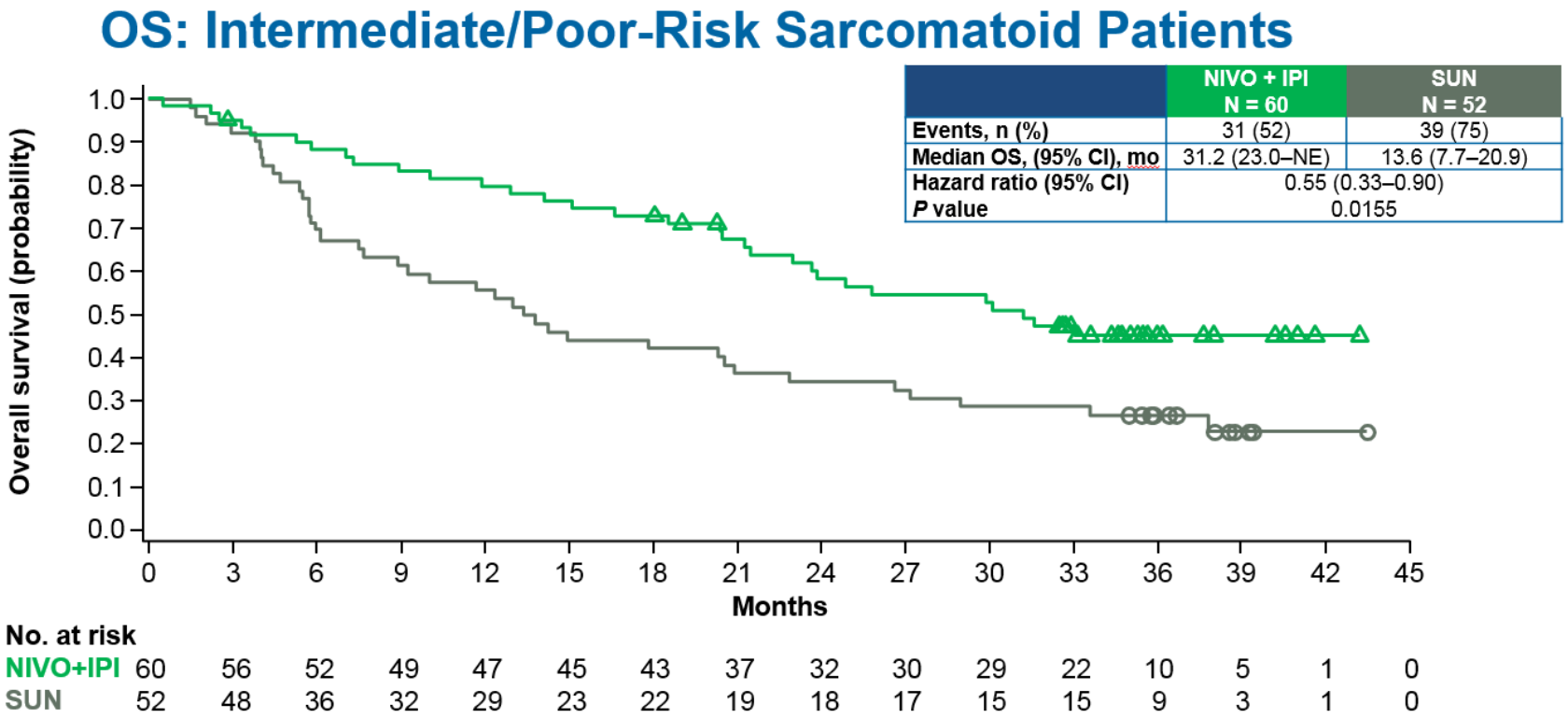

Treatment of Non-Clear Cell RCC: CONCLUSIONS

- Our understanding of non-clear cell RCC is evolving

- Non-clear cell RCC represents unique subtypes with distinct molecular alterations and clinical courses
  - We are now understanding the areas of overlap and difference with conventional clear cell RCC

- Ongoing and Future Studies will evaluate treatment strategies targeting the unique biology of each subtype

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