Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma treated with Immune Checkpoint Inhibitors or Targeted Therapy – A Propensity Score-Based Analysis

Ziad Bakouny, Wanling Xie, Shaan Dudani, Connor Wells, Chun Loo Gan, Frede Donskov, Julia Shapiro, Ian Davis, Francis Parnis, Praful Ravi, John A. Steinharter, Neeraj Agarwal, Ajjai Alva, Lori Wood, Anil Kapoor, Jose M Ruiz Morales, Christian Kollmannsberger, Benoit Beuselinck, Daniel Y.C. Heng, and Toni K. Choueiri

@ZiadBakouny, @DrDanielHeng, @DrChoueiri

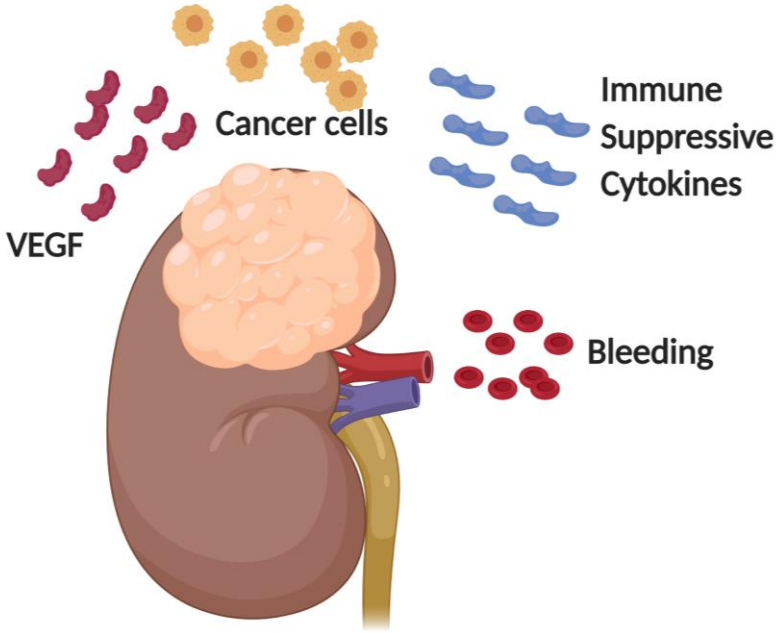
Disclosures

- None

Continued Role with More Effective Agents?

- Role of CN established in cytokine era

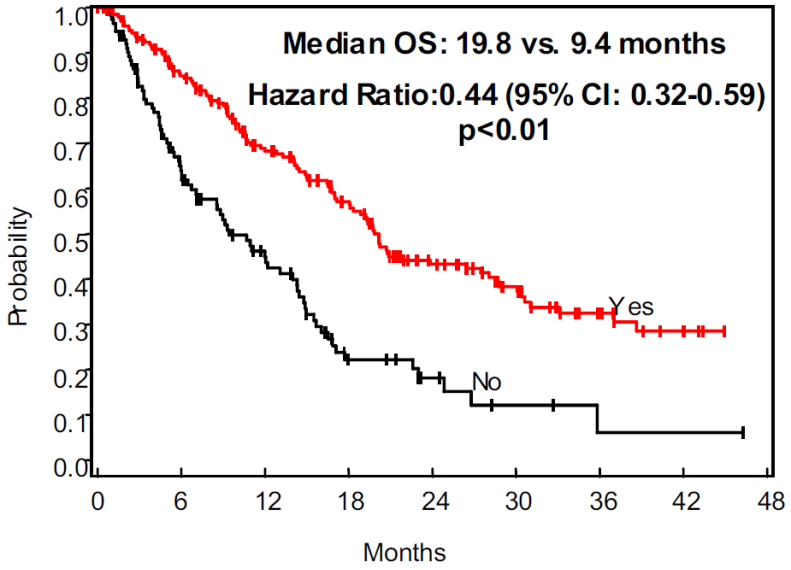
- More effective agents are now available
  - Why are still doing cytoreductive nephrectomies (CN)?



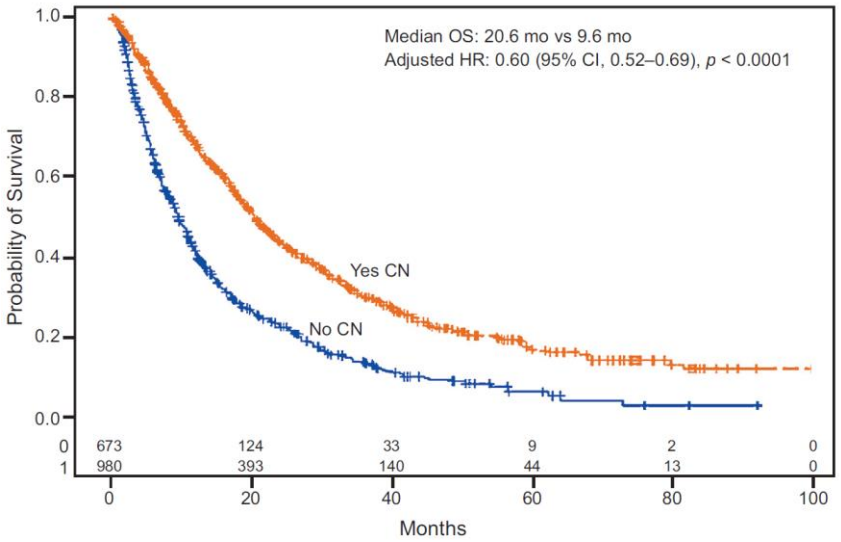
Flanigan et al., CCR, 2004
Marcus et al., J Urol, 1993

Targeted Therapy Era – Controversies and Patient Selection

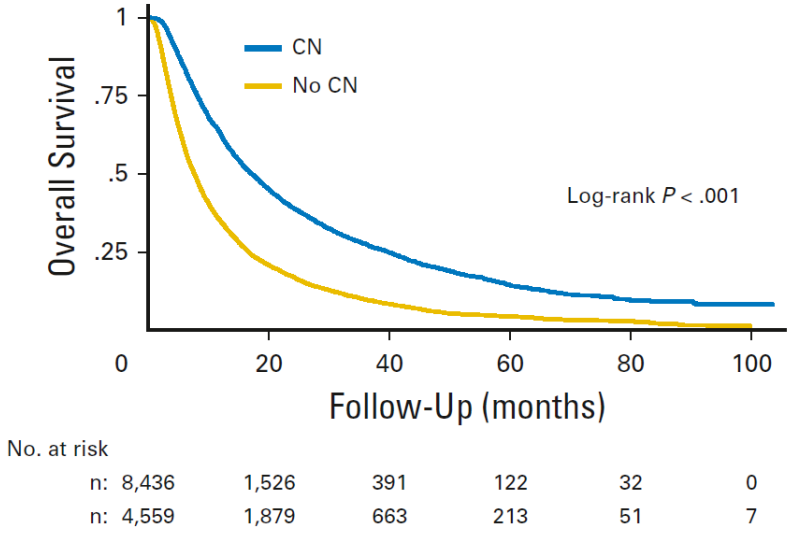
Choueiri et al, J Urol, 2011



Heng et al, Eur Urol, 2014



Hanna et al, JCO, 2016



Caveats:

- Retrospective
- Inherent Selection Bias with CN

CARMENA – RCT = Gold Standard

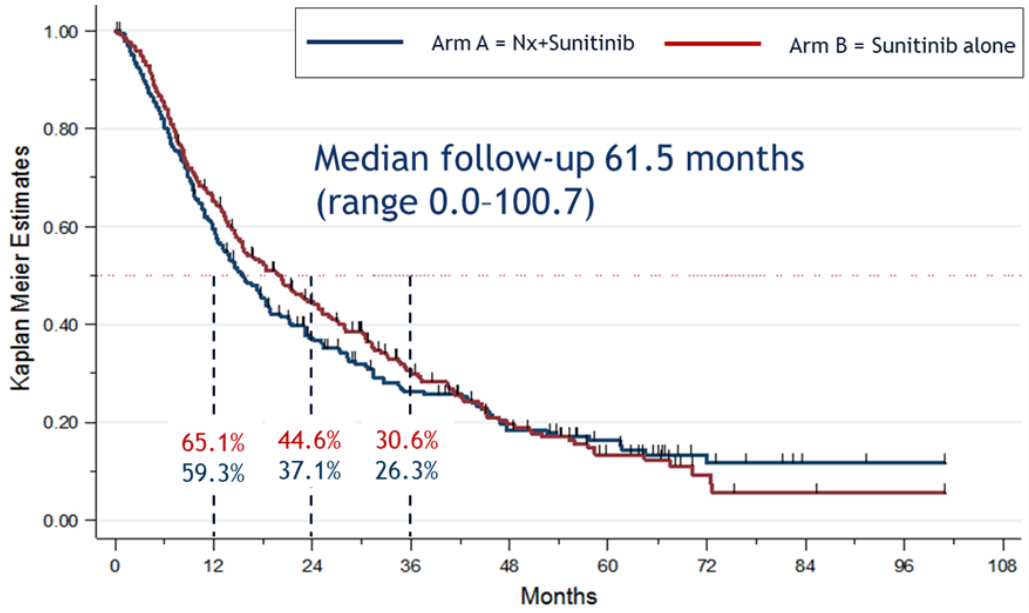
Key Eligibility Criteria:
- Metastatic Clear Cell RCC
- Treatment-naive
- MSKCCC Int/Poor Risk Disease

N= 450

RANDOMIZATION 1:1

- **CN** → **Sunitinib**
- **Sunitinib**

Primary endpoint: Overall Survival
Design: Non-Inferiority (HR OS <1.20)
PI: Arnaud Méjean



Potential Caveats:

- Lower Median OS than expected in both arms
- Potential benefit to CN in patients w/ IMDC criteria= 1

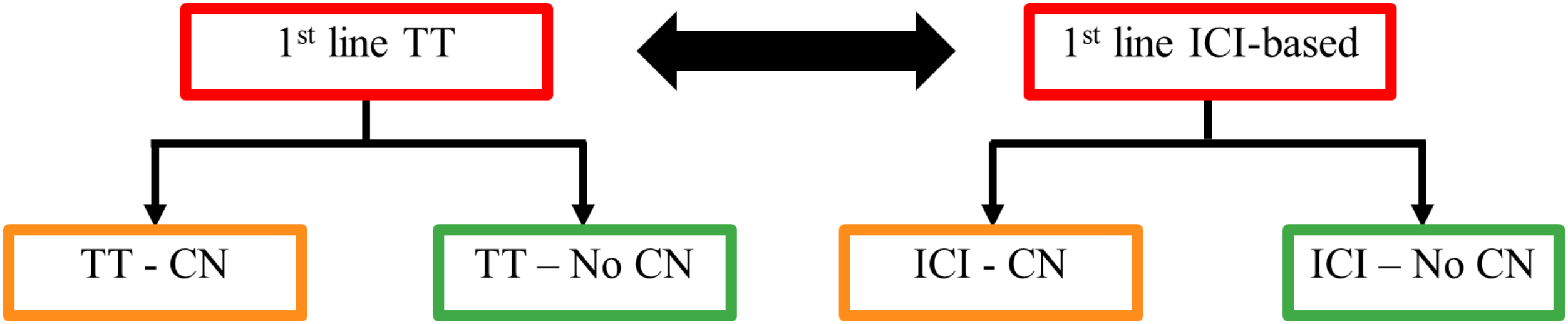
Méjean et al, ASCO, 2019

Motzer et al, NEJM, 2018

Questions

1) Is there still a benefit to CN in the ICI Era?

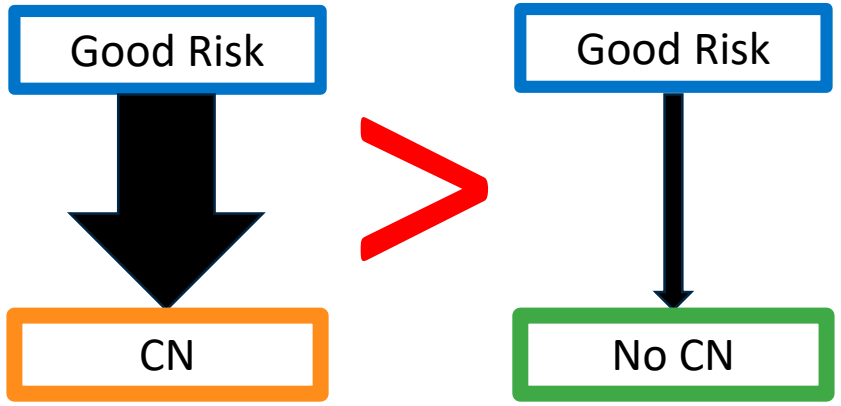
2) How does this benefit compare to that in the TT Era?



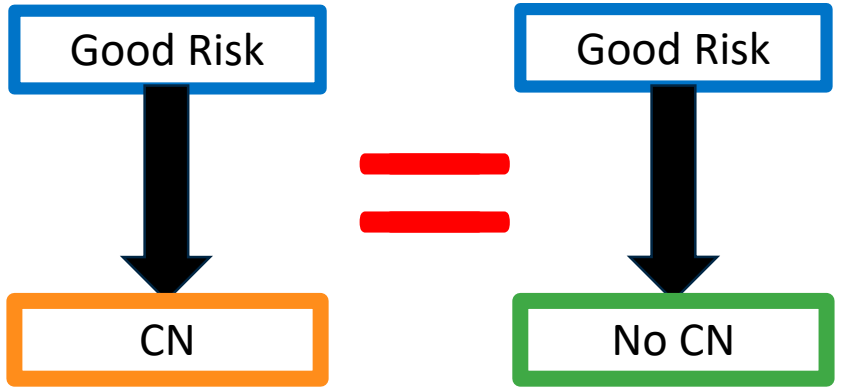
Methods

- IMDC
  - Consecutive patients with mRCC from 40+ centers across the world.
- CN
  - Defined as nephrectomy occurring after the development of metastases.
- OS
  - Defined from start of systemic therapy until death or last FU
- Adjustment for confounding factors
  - Variables
    - Age, Histology, Sarcomatoid features, IMDC group, Bone/Brain/Liver Metastases, and Regimen Type
  - Multivariable Model
  - Propensity-score based
    - Inverse Probability of Treatment Weighting (IPTW)

Univariable



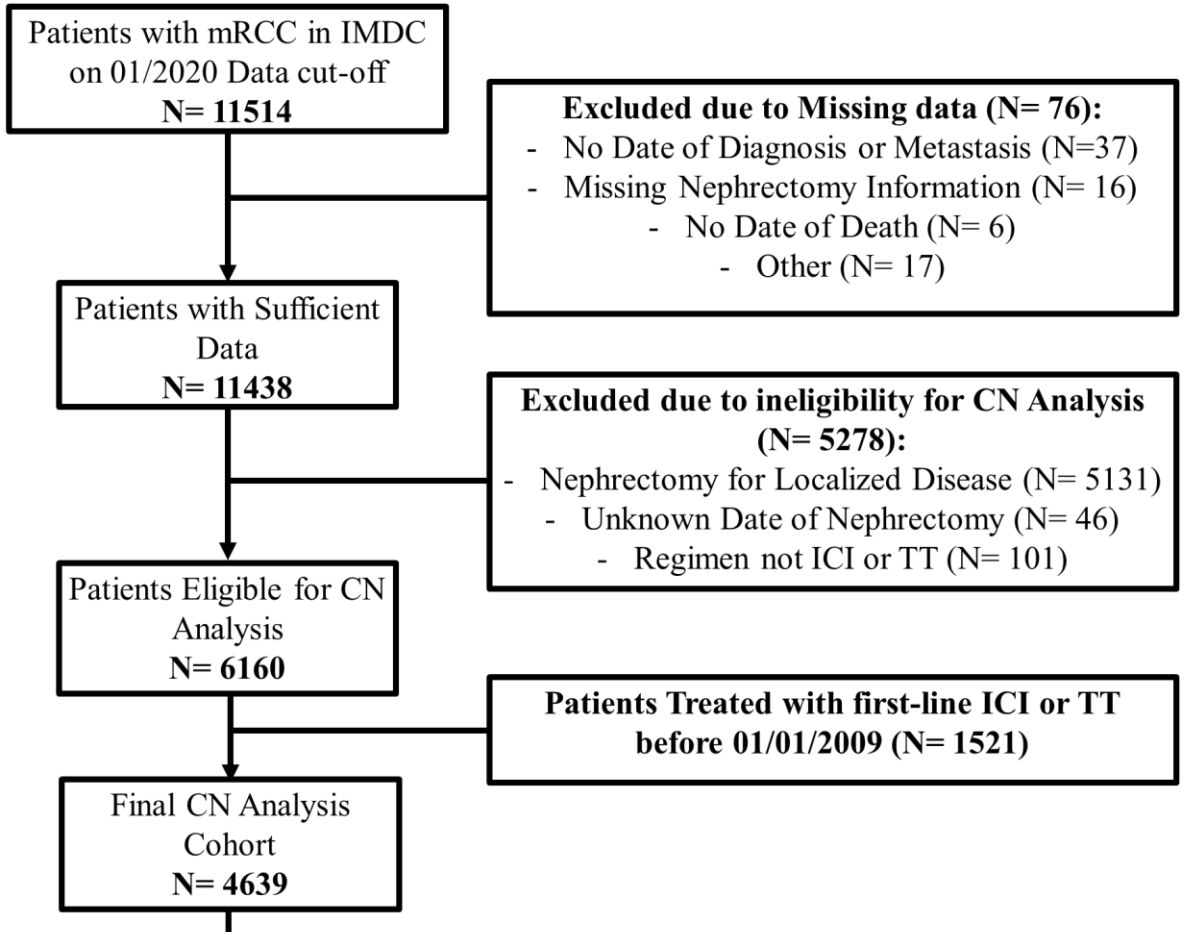
IPTW



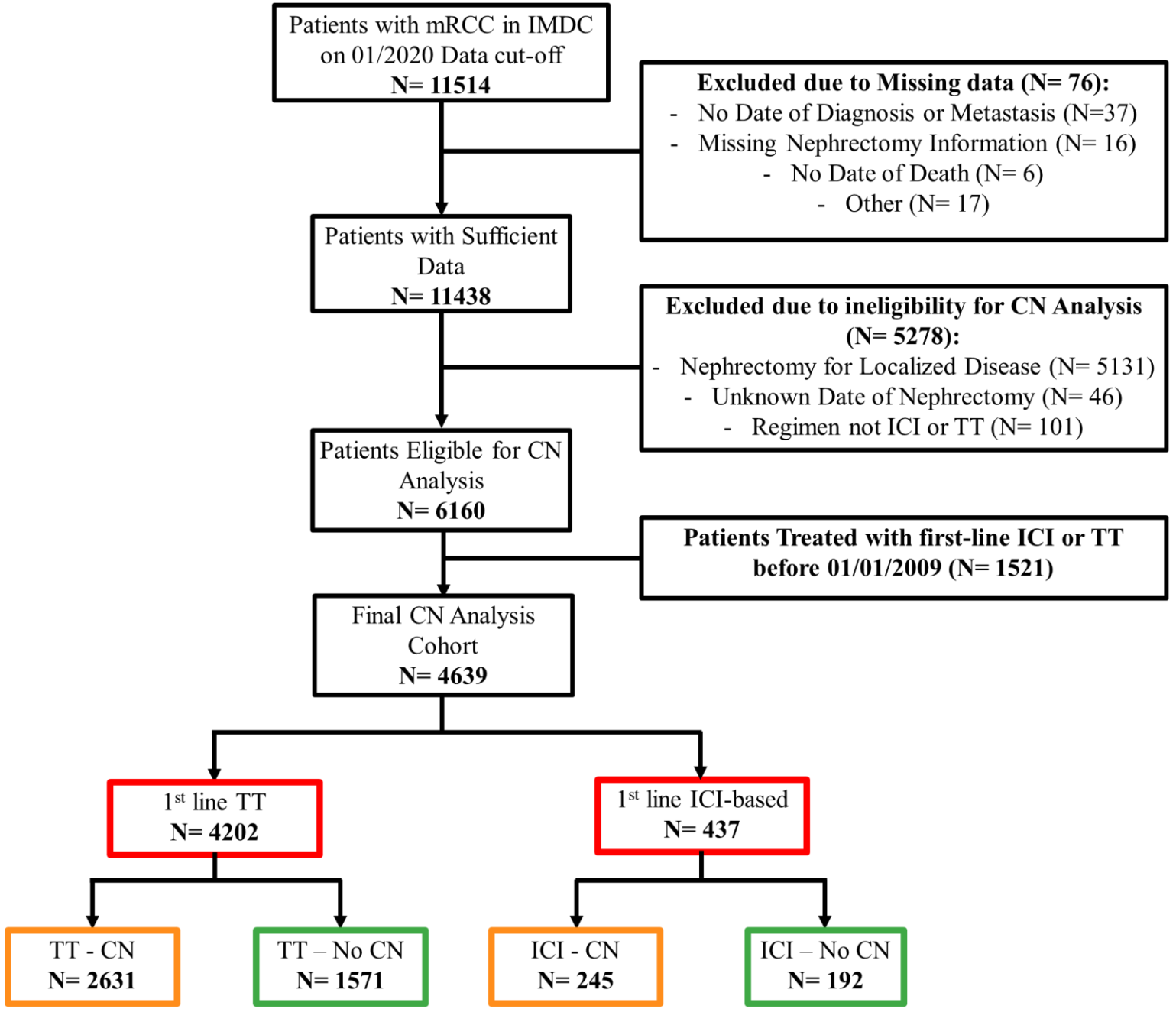
Patients with mRCC in IMDC
on 01/2020 Data cut-off
N= 11514

Flow Chart

Flow Chart


Patients with mRCC in IMDC on 01/2020 Data cut-off
N= 11514
Excluded due to Missing data (N= 76):
- No Date of Diagnosis or Metastasis (N=37)
- Missing Nephrectomy Information (N= 16)
- No Date of Death (N= 6)
- Other (N= 17)
Patients with Sufficient Data
N= 11438
Excluded due to ineligibility for CN Analysis (N= 5278):
- Nephrectomy for Localized Disease (N= 5131)
- Unknown Date of Nephrectomy (N= 46)
- Regimen not ICI or TT (N= 101)
Patients Eligible for CN Analysis
N= 6160
Patients Treated with first-line ICI or TT before 01/01/2009 (N= 1521)
Final CN Analysis Cohort
N= 4639

Flow Chart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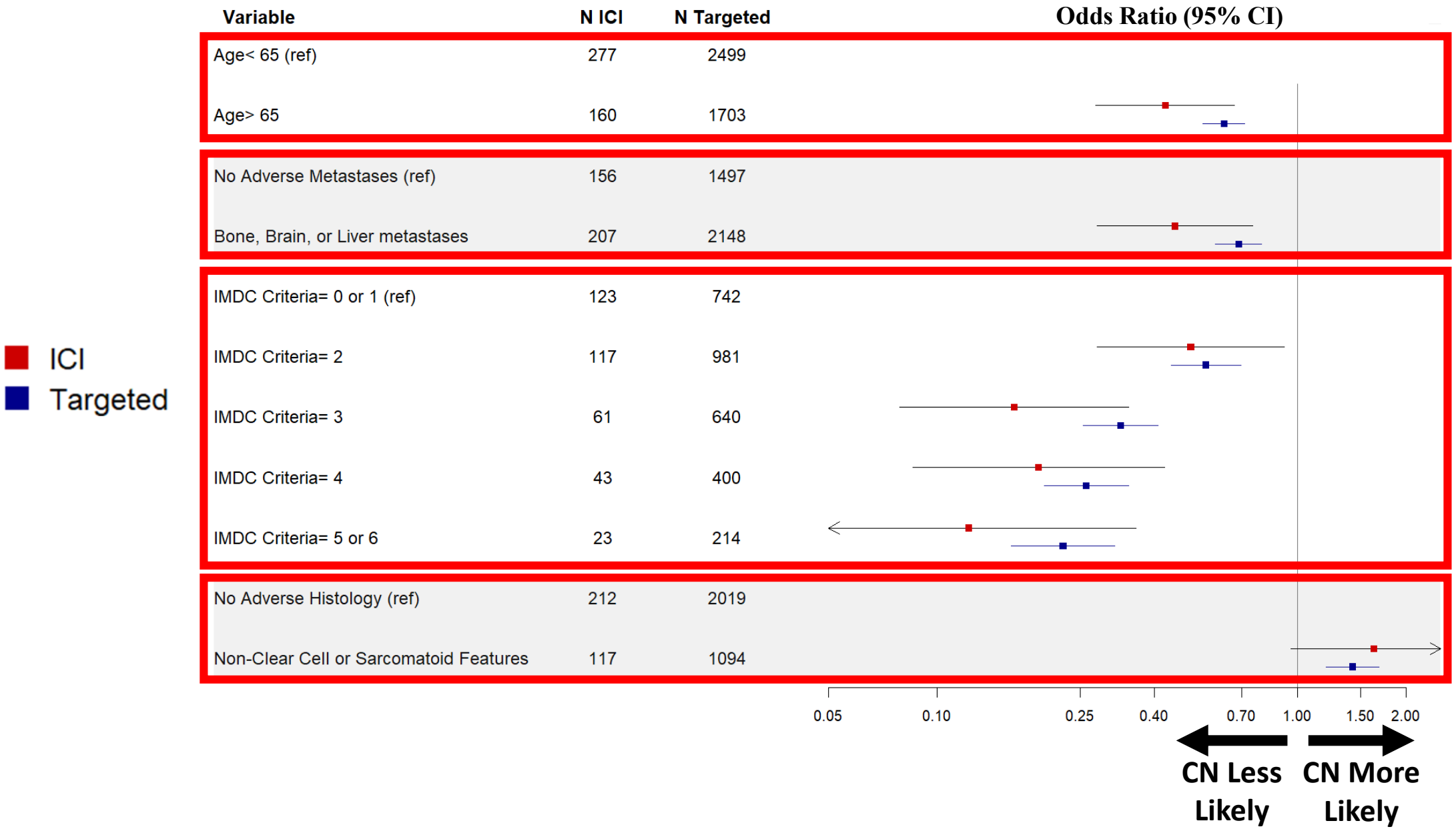
N= 4639
1st line TT
N= 4202
1st line ICI-based
N= 437
TT - CN
N= 2631
TT – No CN
N= 1571
ICI - CN
N= 245
ICI – No CN
N= 192

Baseline Characteristics

1st Line Targeted Therapies	CN (n=2631)	No CN (n=1571)
Age		
Mean (SD)	60.9 (10.5)	63.6 (11.5)
IMDC Group		
Favorable	112 (6.1%)	16 (1.4%)
Intermediate	1100 (60.2%)	495 (43.1%)
Poor	616 (33.7%)	638 (55.5%)
Histology		
Clear Cell	2197 (85.4%)	896 (77.0%)
Non-Clear Cell	376 (14.6%)	268 (23.0%)
Sites of Metastasis		
1 Site	844 (33.2%)	322 (21.6%)
≥2 Sites	1697 (66.8%)	1172 (78.4%)
1st line Regimen		
TKI	2410 (91.6%)	1397 (88.9%)
mTORi	159 (6.0%)	156 (9.9%)
VEGFi	29 (1.1%)	6 (0.4%)
Other	33 (1.3%)	12 (0.8%)

1st Line ICI-based	CN (n=245)	No CN (n=192)
Age		
Mean (SD)	59.4 (10.6)	63.9 (10.6)
IMDC Group		
Favorable	18 (8.6%)	1 (0.6%)
Intermediate	151 (72.2%)	70 (44.3%)
Poor	40 (19.1%)	87 (55.1%)
Histology		
Clear Cell	211 (87.6%)	103 (73.6%)
Non-Clear Cell	30 (12.4%)	37 (26.4%)
Sites of Metastasis		
1 Site	56 (24.0%)	35 (19.0%)
≥2 Sites	177 (76.0%)	149 (81.0%)
1st line Regimen		
ICI	51 (20.8%)	29 (15.1%)
ICI + ICI	98 (40.0%)	122 (63.5%)
ICI + VEGFi	94 (38.4%)	39 (20.3%)
Other	2 (0.8%)	2 (1.0%)

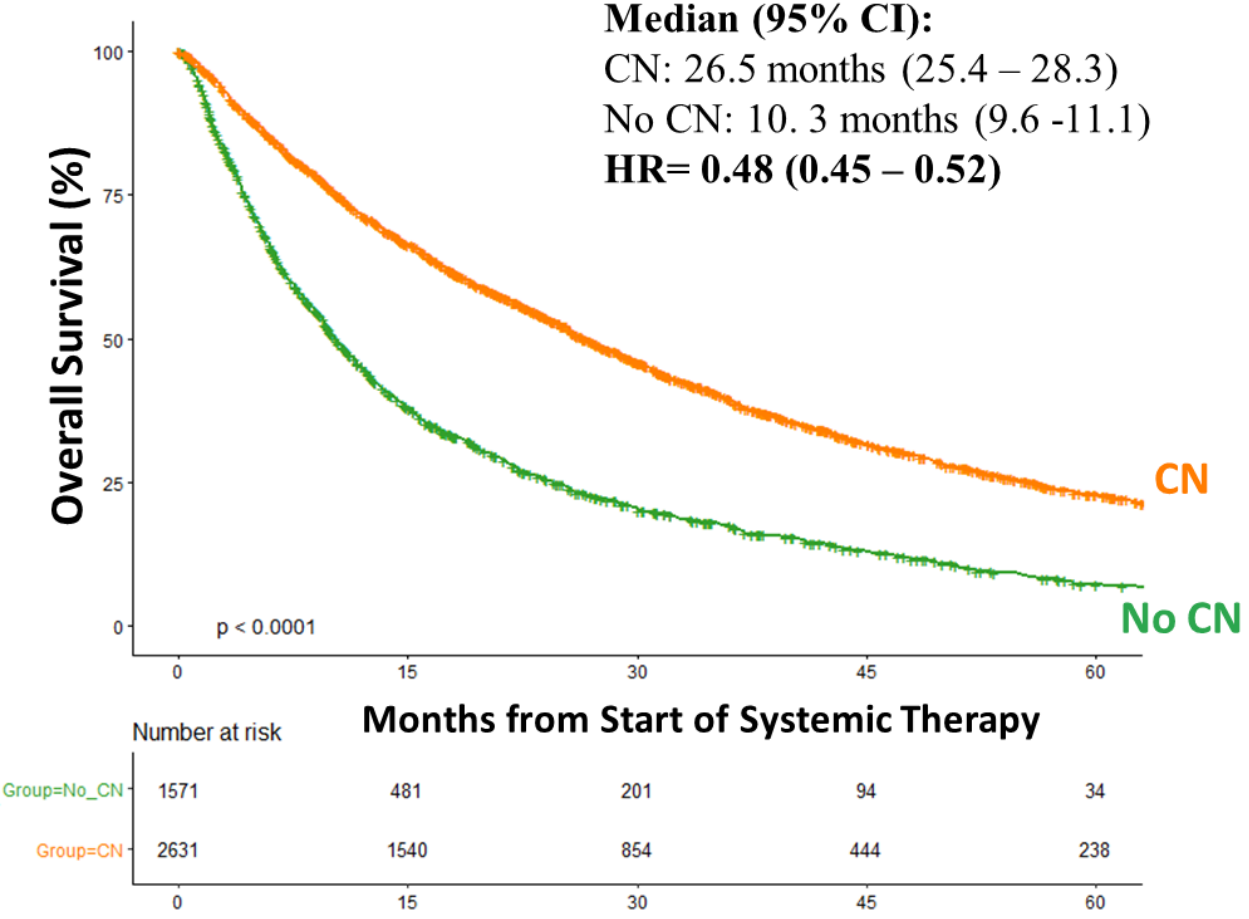
Profile of Patients Getting CN



CN in Patients Treated by TT or ICI

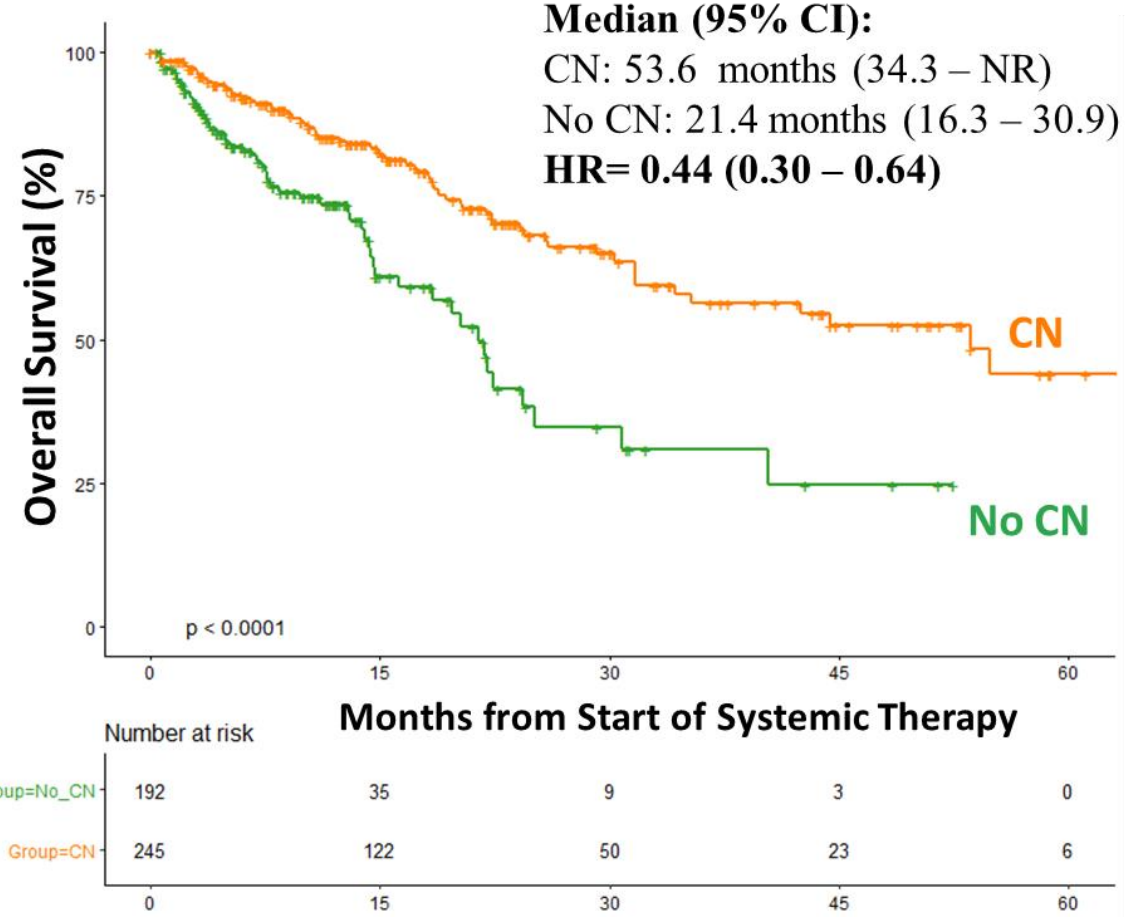
Targeted Therapies

FU: 42.0 months (39.6 – 44.0)



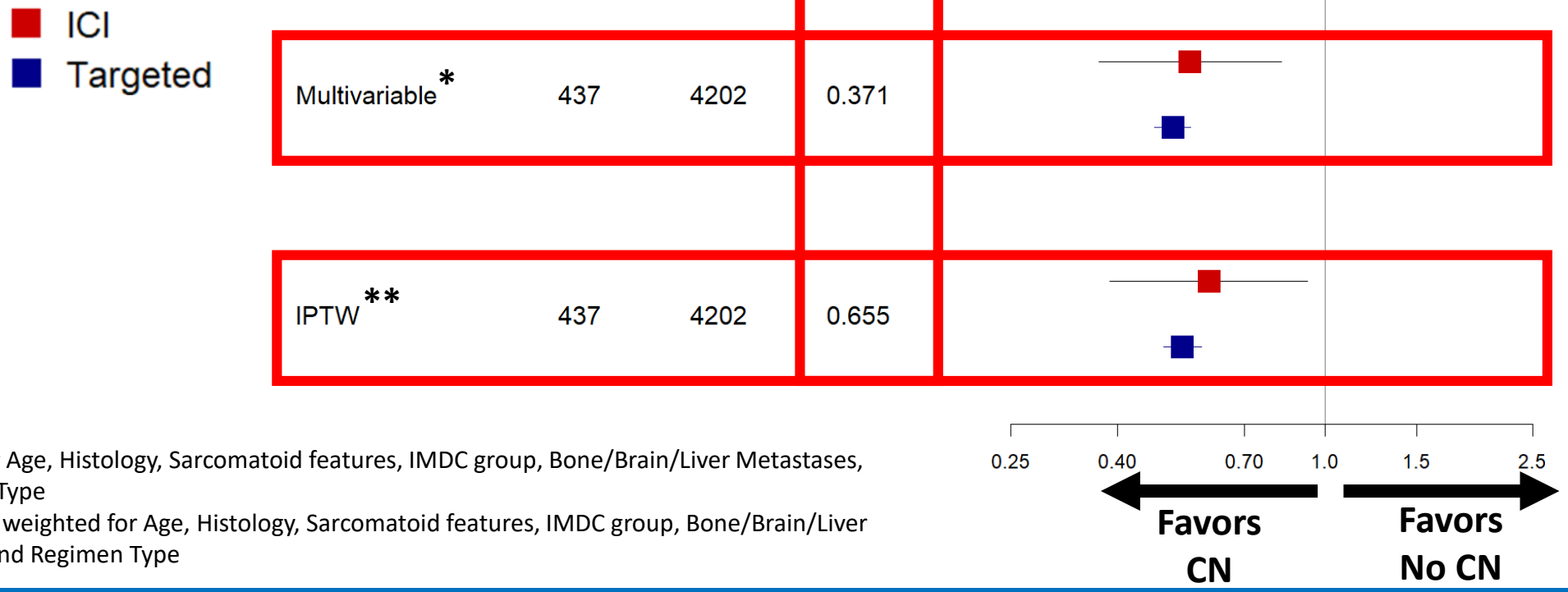
Immune Checkpoint Inhibitors

FU: 14.1 (12.9 – 16.5)



Adjusting for Covariates

Statistical Model	N ICI	N Targeted	Interaction P-Value
Univariable	437	4202	0.902
Multivariable*	437	4202	0.371
IPTW**	437	4202	0.655



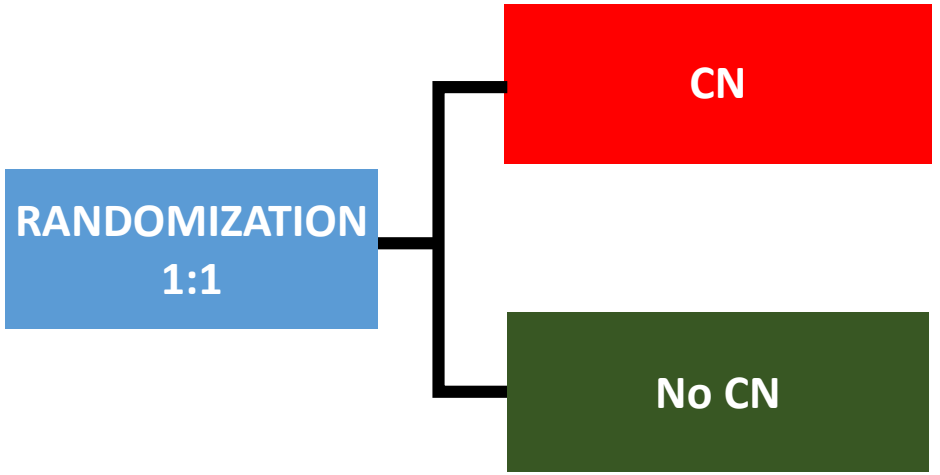
* Adjusted for Age, Histology, Sarcomatoid features, IMDC group, Bone/Brain/Liver Metastases, and Regimen Type

** Propensity weighted for Age, Histology, Sarcomatoid features, IMDC group, Bone/Brain/Liver Metastases, and Regimen Type

Limitations

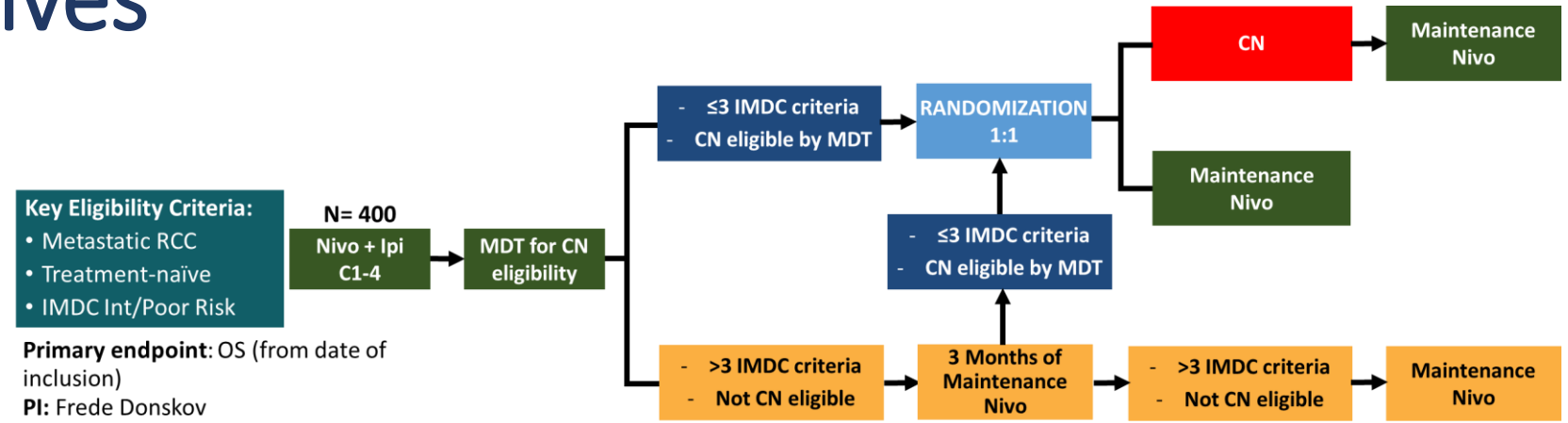
- Not a Randomized Controlled Trial
  - Selection bias for CN
  - Unmeasured confounders
  - Data from large academic centers

- Need more data in the ICI era…



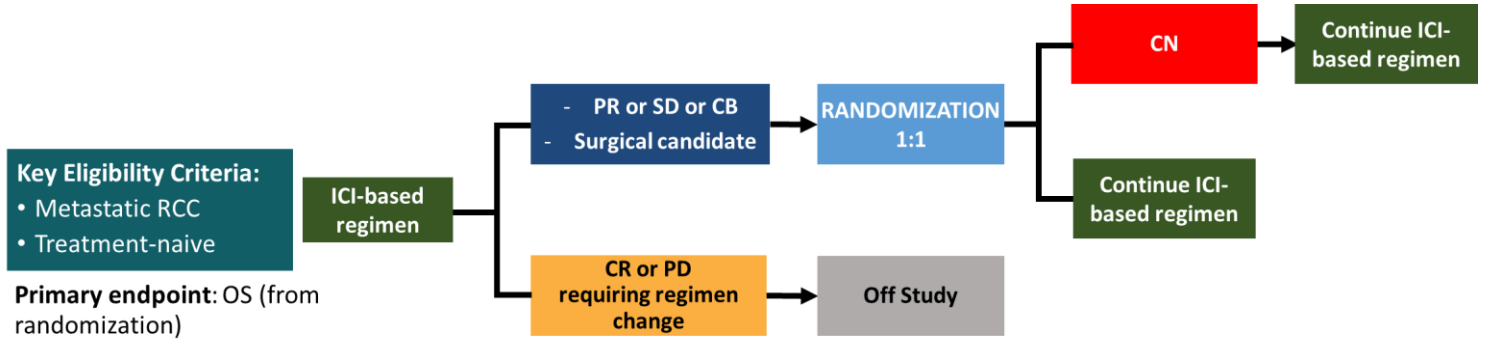
Perspectives

NORDIC-SUN *(NCT03977571)*



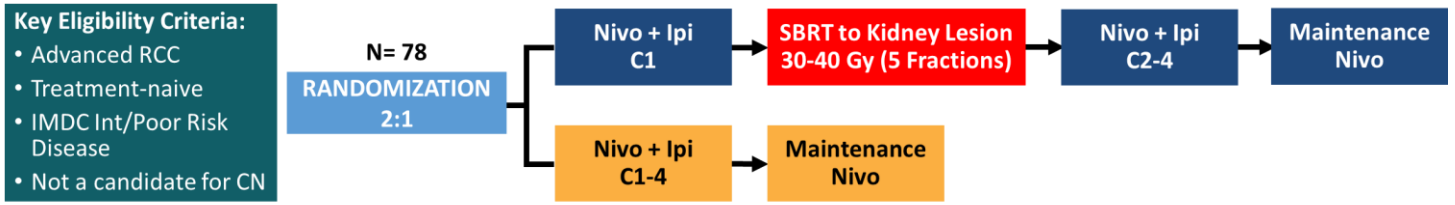
Primary endpoint: OS (from date of inclusion)
PI: Frede Donskov

PROBE Trial *(SWOG – Under Development)*



Primary endpoint: OS (from randomization)
PI: Ulka Vaishampayan & Hyung Kim

CYTOSHRINK *(NCT04090710)*



Primary endpoint: PFS
PI: Aly-Khan Lalani

Conclusions

- Large retrospective consecutive series.
- The benefit seen with CN seems to be similar across the ICI and TT eras.
- But patient selection remains key…

Overall Recommendations – Irrespective of Systemic Therapy

- CN should **rarely** be performed in
  - Patients with poor risk disease.
  - Patients with rapidly progressive disease or high disease burden who need systemic therapy.

- **Upfront CN** should be considered in
  - Patients with Favorable/Intermediate risk disease who are candidates for active surveillance.
  - Candidates for oligo-metastasectomy → NED.
  - Symptomatic kidney masses.

- **Deferred CN** should be considered in patients with strong responses to systemic therapy.

ASCO Daily News

Question: Which patients do you consider for cytoreductive nephrectomy (CN) in metastatic renal cell carcinoma (mRCC)?

Dr. Shaan Dudani

Answer: Deciding whom to offer CN to can be a considerable clinical challenge in the contemporary management of patients with mRCC.

The role of surgical resection of the primary renal tumor in synchronous mRCC was established in the historical cytokine era, with two randomized clinical trials demonstrating an overall survival (OS) benefit with the addition of upfront CN to standard interferon-based therapy.[1] These trials established CN as an integral component of the multimodal treatment of de novo mRCC.

Acknowledgements

IMDC

Daniel Heng

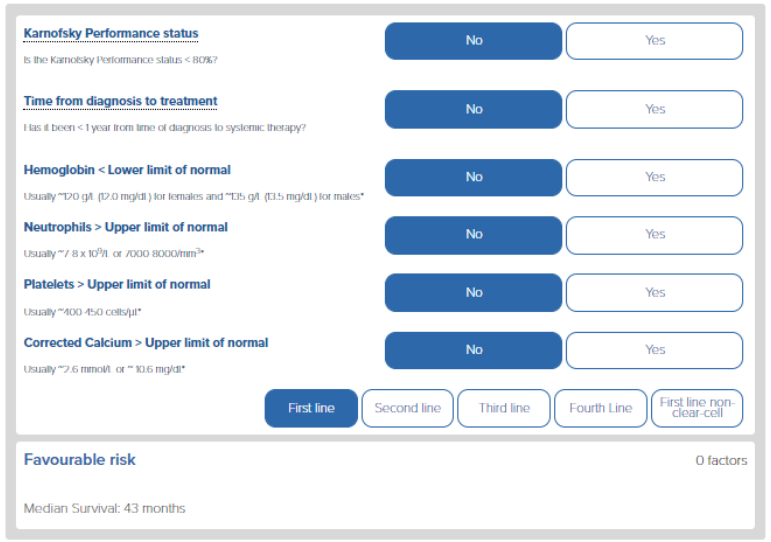
Toni Choueiri

Wanling Xie
Shaan Dudani
Connor Wells
Chun Loo Gan
Praful Ravi
John Steinharter
All 40+ Institutions
All 11000+ Patients

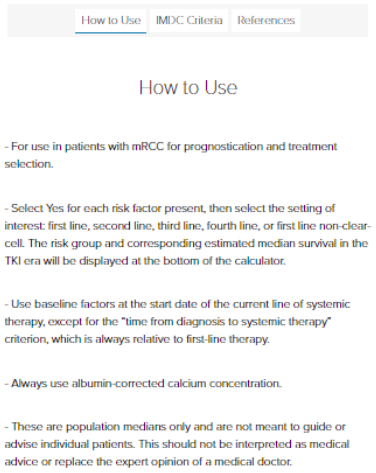
International mRCC Database Consortium

WORKING TOGETHER AGAINST KIDNEY CANCER

IMDC Risk Calculator



Instructions



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