

THE NORDIC SUN TRIAL

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Cytoreductiv nefrectomi: YES or NO?

The New England Journal of Medicine

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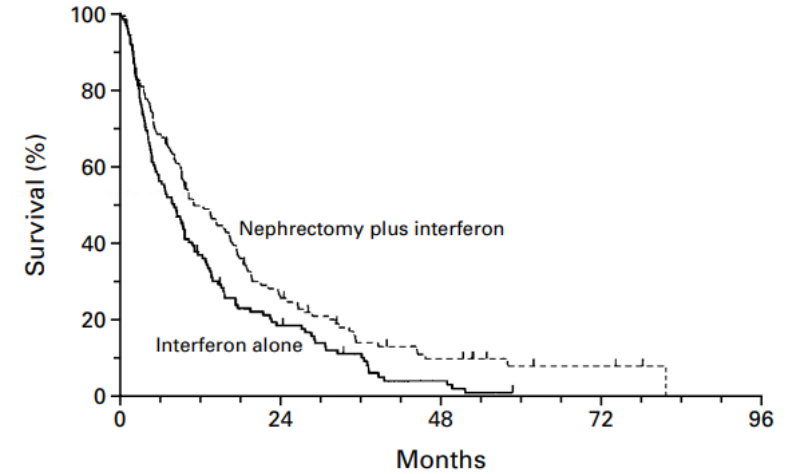
NUMBER 23



NEPHRECTOMY FOLLOWED BY INTERFERON ALFA-2b COMPARED WITH INTERFERON ALFA-2b ALONE FOR METASTATIC RENAL-CELL CANCER

ROBERT C. FLANIGAN, M.D., SYDNEY E. SALMON, M.D., BRENT A. BLUMENSTEIN, PH.D., SCOTT I. BEARMAN, M.D.,
VIVEK ROY, M.D., PATRICK C. McGRATH, M.D., JOHN R. CATON, JR., M.D., NIKHIL MUNSHI, M.D.,
AND E. DAVID CRAWFORD, M.D.

The New England Journal of Medicine



No. AT RISK		0	24	48	72	96
Interferon alone	121	21	4	0		
Nephrectomy plus interferon	120	29	9	3	0	

Figure 1. Actuarial Survival among All Eligible Patients, According to Treatment-Group Assignment. In the interferon-only group, there were 115 deaths and median survival was 8.1 months. In the surgery-plus-interferon group, there were 106 deaths and median survival was 11.1 months.

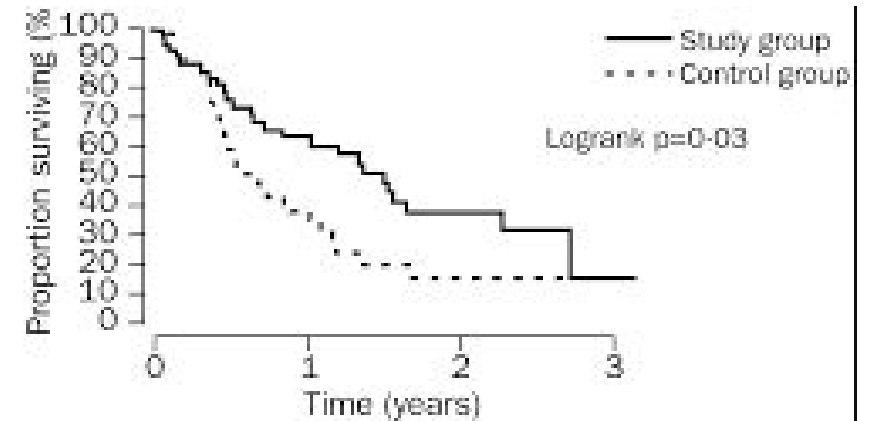
Median OS 11,1 month vs 8,1 month

Cytoreductiv nefrectomi: YES or NO?

Clinical Trial > Lancet. 2001 Sep 22;358(9286):966-70. doi: 10.1016/s0140-6736(01)06103-7.

Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial

G H Mickisch ¹, A Garin, H van Poppel, L de Prijck, R Sylvester;
European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group



	Observed number of events		Number of patients at risk		
Study group	25	42	22	7	1
Controls	30	42	12	2	0

Median OS 17 month vs 7 month

CN in ptt. Treated with TKI:cRetrospektiv study IMDC



European Urology

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Platinum Priority – Kidney Cancer

Editorial by Stephen H. Culp on pp. 711–712 of this issue

Cytoreductive Nephrectomy in Patients with Synchronous Metastases from Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium

Daniel Y.C. Heng^{a,†}, J. Connor Wells^{a,†}, Brian I. Rini^b, Benoit Beuselinck^c, Jae-Lyun Lee^d, Jennifer J. Knox^e, Georg A. Bjarnason^f, Sumanta Kumar Pal^g, Christian K. Kollmannsberger^h, Takeshi Yuasaⁱ, Sandy Srinivas^j, Frede Donskov^k, Aristotelis Bamias^l, Lori A. Wood^m, D. Scott Ernstⁿ, Neeraj Agarwal^o, Ulka N. Vaishampayan^p, Sun Young Rha^q, Jenny J. Kim^r, Toni K. Choueiri^s

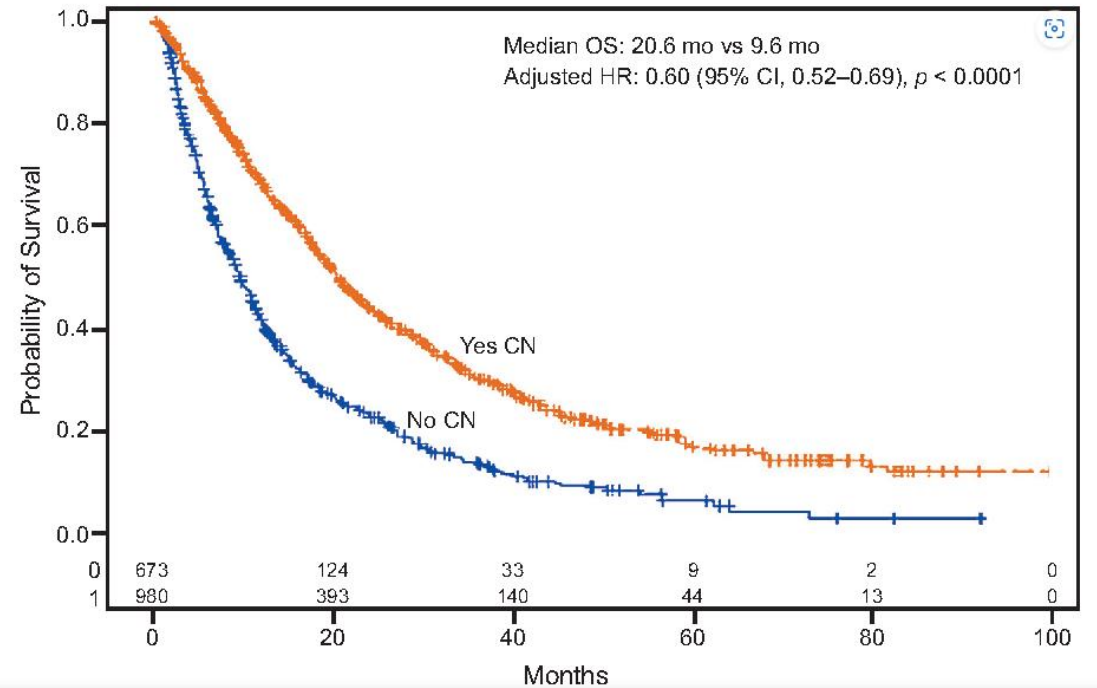


Fig. 1 – Kaplan-Meier curve depicting the overall survival from the initiation of targeted therapy for 1633 metastatic renal cell carcinoma patients who did or did not receive a cytoreductive nephrectomy. CI... Expand

Do not operate patients with >3 IMDC risk factors

No. of IMDC criteria met	No CN OS, mo (n)	CN OS, mo (n)	p value
0	92% of patients (65/71) had CN, insufficient number to compare		
1	22.5 (n = 72)	30.4 (n = 178)	0.002
2	10.2 (n = 143)	20.2 (n = 253)	<0.001
3	10.0 (n = 113)	15.9 (n = 106)	<0.001
4	5.4 (n = 103)	6.0 (n = 67)	0.166
5	3.6 (n = 36)	2.8 (n = 14)	0.504
6	25% of patients (3/12) had CN, insufficient number to compare		







Overall, 1168 of 1658 subjects (70%) had complete information about prognostic factors, nephrectomy, and outcomes and were used in this complete case analysis; the rest were excluded. Shaded rows indicate patient groups that may not benefit from cytoreductive nephrectomy. CN = cytoreductive nephrectomy; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; OS = overall survival.

Understanding IMDC Criteria for Metastatic RCC

(Heng criteria)

Step 1

Before treatment

		Yes (1) / No (0)
Time from initial diagnosis to treatment	 < 1 Year	1 / 0
		+
Karnofsky Performance Score (KPS)	 < 80%	1 / 0
		+
Low Hemoglobin	 < LLN	1 / 0
		+
High Calcium	 > 10mg/dL	1 / 0
		+
High Platelet	 > ULN	1 / 0
		+
High Neutrophil	 > ULN	1 / 0

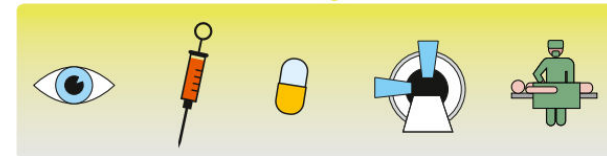
Step 2

Risk Categories



Step 3

Treatment Selection



About IMDC Risk Categories

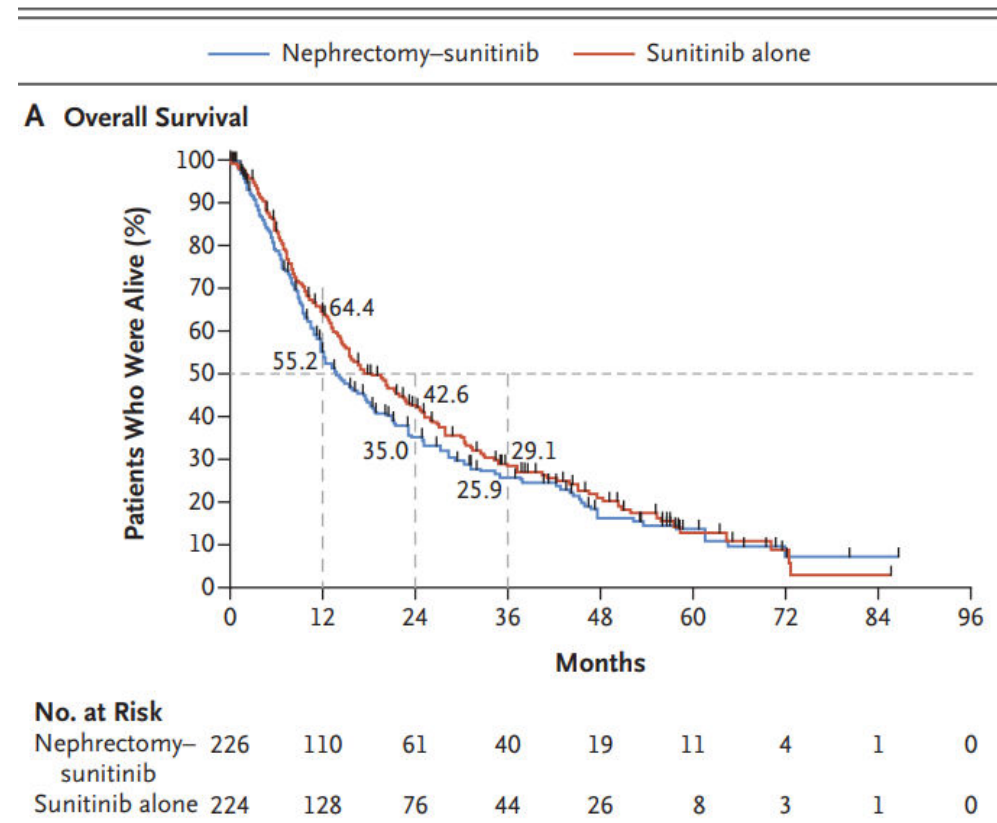
75 – 80% of patients selecting 1st line mRCC treatment options have at least 1 of these risk factors, therefore classifying their mRCC as intermediate/poor risk. Risk classification may change over time and may help in selecting treatments such as immunotherapy.

The CARMENA trial



Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma

A. Méjean, A. Ravaud, S. Thezenas, S. Colas, J.-B. Beauval, K. Bensalah, L. Geoffrois, A. Thierry-Vuillemin, L. Cormier, H. Lang, L. Guy, G. Gravis, F. Rolland, C. Linassier, E. Lechevallier, C. Beisland, M. Aitchison, S. Oudard, J.-J. Patard, C. Theodore, C. Chevreau, B. Laguerre, J. Hubert, M. Gross-Goupil, J.-C. Bernhard, L. Albiges, M.-O. Timsit, T. Le Bret, and B. Escudier



Large prospective study but::

<1 pt per center!

44% of the patients had 3+ risk factors

17% in the control arm had delayed nephrectomy

18,4 months vs 13,9 months (advantage for Sunitinib)
HR 0.89 (95% CI 0.71-1.10)

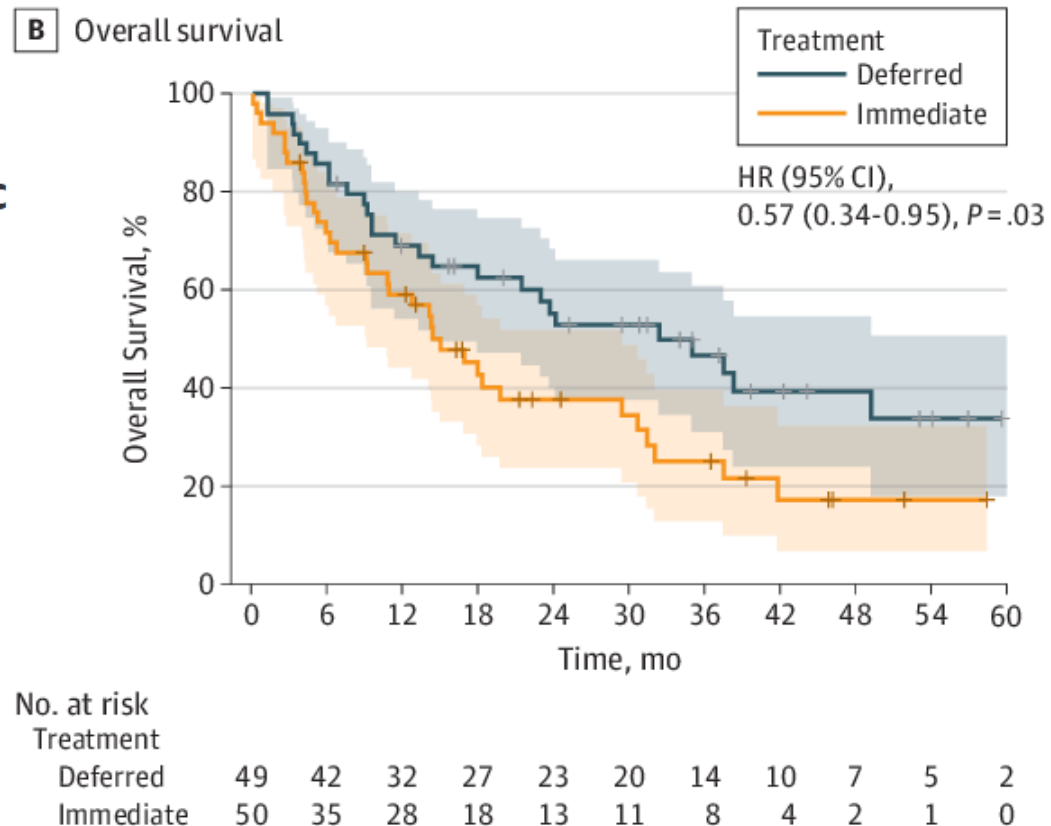
The SURTIME trial

Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients With Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib The SURTIME Randomized Clinical Trial

Axel Bex, MD, PhD¹; Peter Mulders, MD, PhD²; Michael Jewett, MD³; et al

» Author Affiliations | Article Information

JAMA Oncol. 2019;5(2):164-170. doi:10.1001/jamaoncol.2018.5543



Nephrectomy after 3 months of Sunitinib is better than up-front nephrectomy

Multicenter Randomized Trial of Deferred Cytoreductive Nephrectomy
in Synchronous Metastatic Renal Cell Carcinoma Receiving Checkpoint Inhibitors:
a DaRenCa and NoRenCa Trial Evaluating the Impact of Surgery or No Surgery.
The NORDIC-SUN-Trial

Main question:

Does primary metastatic patients in treatment with double immune therapy or TKI/IO be offered delayed cytoreductive nephrectomy?

PI: Niels Frstrup, Aarhus University Hospital, DK.

A Darenca and Norenca study

NORDIC SUN TRIAL

Figure 1

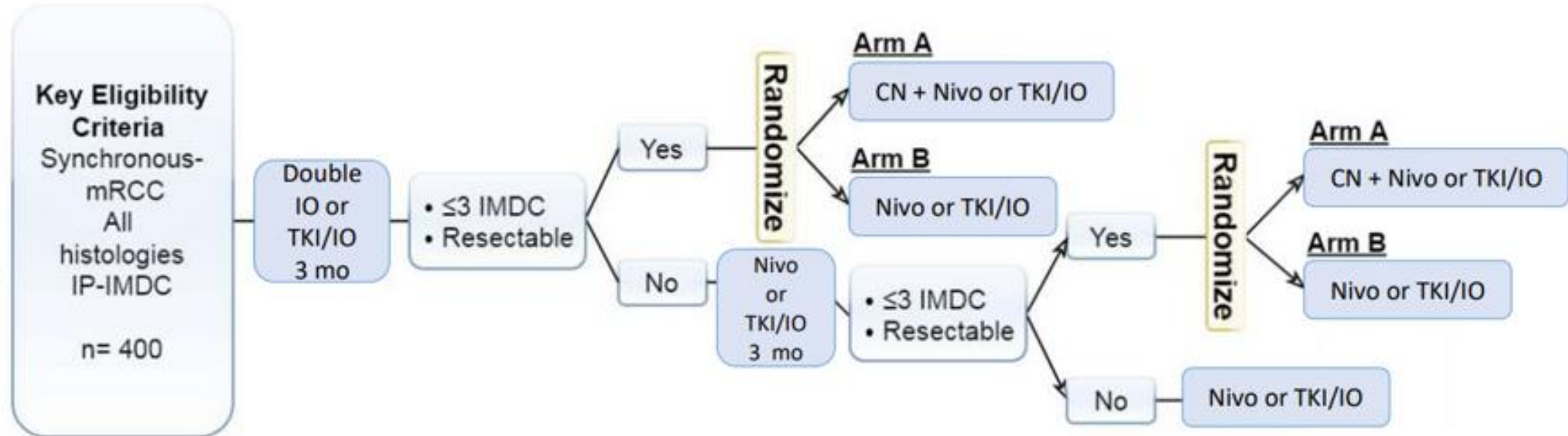


Figure 1: mRCC (metastatic Renal Cell Carcinoma), n (number), mo (months), Nivo (Nivolumab), Ipi (ipilimumab), IP-IMDC (Intermediate and poor International Metastatic Renal Cell Carcinoma Database Consortium Classification), CN (Cytoreductive Nephrectomy)

Workflow at the department of urology

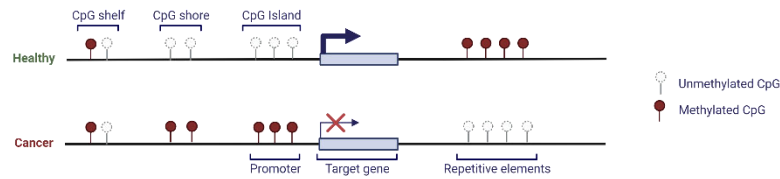
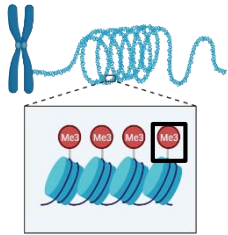
1. Obtaining written consent for biopsy of primary tumor for RBGB

Workflow at the department of clinical oncology

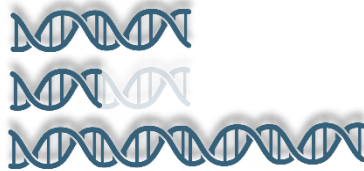
1. Informing about the NORDIC SUN trial
2. Obtaining written consent to the NORDIC SUN trial
3. Ordering research blood sampling at baseline, 12 w and 24 w.
4. Do a Rectal Swap in the outpatient clinic at baseline + 12 w.
5. Give 3 months of doublet therapy and send the patient to a MDT
 - If not possible to operate at this timepoint, then another 3 months of doublet therapy and a new MDT
 - A third look at 9 months is now also possible
6. Resuming oncological treatment after cytoreductive nephrectomy

Detection of ctDNA using cfMeDIP seq

DNA methylation changes



+ Copy number alterations

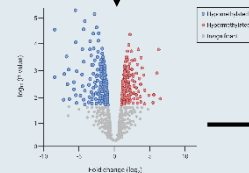
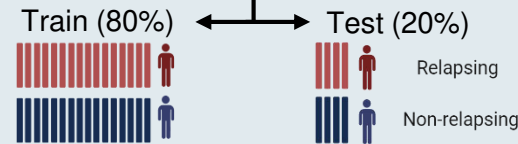
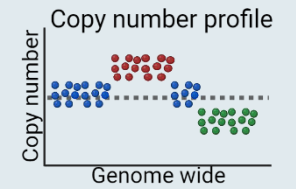
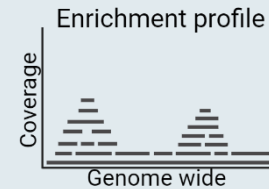


cfMeDIPseq classifier

Cell-free methylated DNA immunoprecipitation and high-throughput sequencing

Immunoprecipitation

Input control



Me-ctDNA level

CNV-ctDNA level

Analyzing circulating tumor DNA as a marker for response to treatment in the NORDIC-SUN clinical trial

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RENAL CANCER

LYSKJÆR GROUP



THE NORDIC SUN TRIAL

Present status:

Around 80 patients included.

!8 patients randomised

Center Aarhus and center Aalborg is open and recruiting

Center Gødstrup opened April 2024

Center Odense opened in July 2024

Center Herlev opened in August 2024

After starting full Danish recruiting we will aim at opening the trial in the nordic countries during 2025. Norway is expected to open in the spring 2025. Sweden and Finland later in 2025.

THE NORDIC SUN TRIAL

Primary endpoint: OS

Secondary endpoints: PFS, TST, ORR, DCR
30-day surgery complication and mortality
Recist outcome
Clear vs non-clear histology

Explorative part:

Biopsy at diagnosis + nefrectomy sampling

Rectal swap: Baseline + 12 w

Blood samples: Baseline + 12 w + 24 w

-MoMA (ctDDA analysis, microbiome analysis, DNA+RNA-seq etc)

-Biomedicin at AU (PBMCs)

NORDIC SUN received 400.000 DKK from Nordic Cancer Union

NORDIC SUN received 1.650.000 DKK from the Danish Cancer Institute

NORDIC SUN received 500.000 DKK from DCC ctDNA Research Center

Spørgsmål

