Herlev og Gentofte Hospital

Nye behandlinger til patienter med nyrekræft

Nyrecancer Symposium

7. Januar 2025

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Behandling af nyrekræft

Målrettet (targeteret) behandling

- Hæmmer dannelsen af nye blodkar til kræftcellerne. Derved forhindres tilførsel af ilt og næring, så kræften stopper med at vokse og sprede sig yderligere.

Immunterapi

- Øger aktiviteten af eget immunsystem
  - Styrke immunforsvarets evne til at genkende og angribe kræftceller
  - Svække kræftcellernes evne til at forsvare sig

Kombination af immunterapi + målrettet behandling

Forebyggende (adjuverende) behandling

Formål

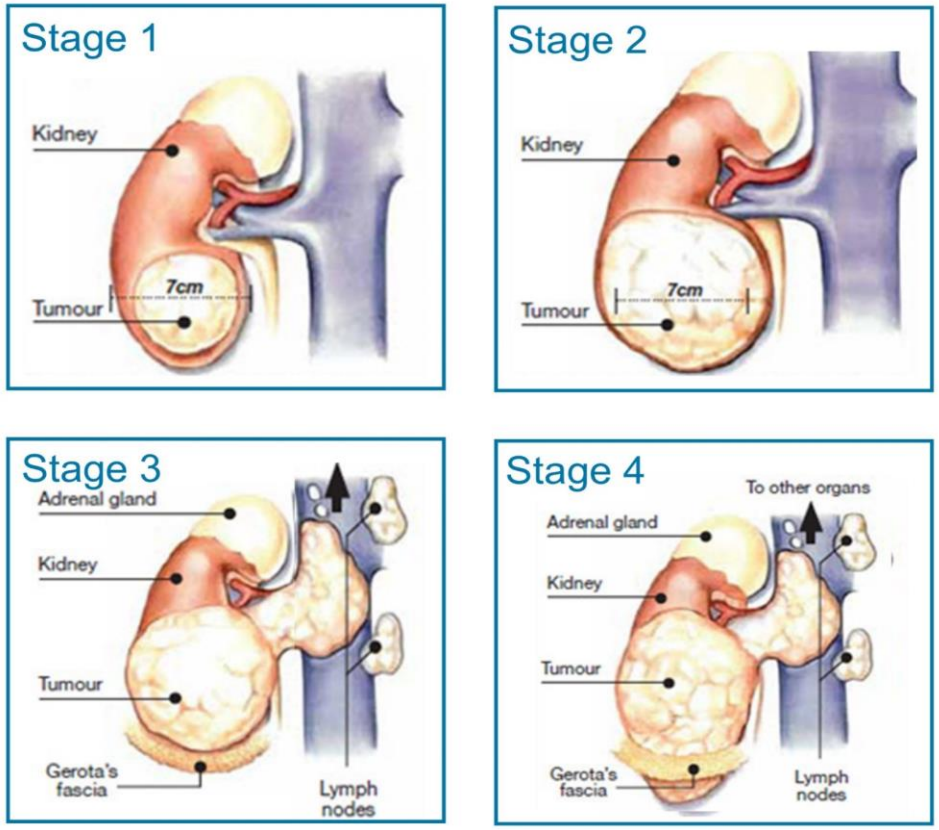
- At nedsættte risikoen for at kræftsygdommen vender tilbage (lokalt eller til andre organer) og derved nedsætte andelen af patienter der skal reopereres/modtage livsforlængende kræftbehandling (forbedre livskvaliteten) og forbedre overlevelsen

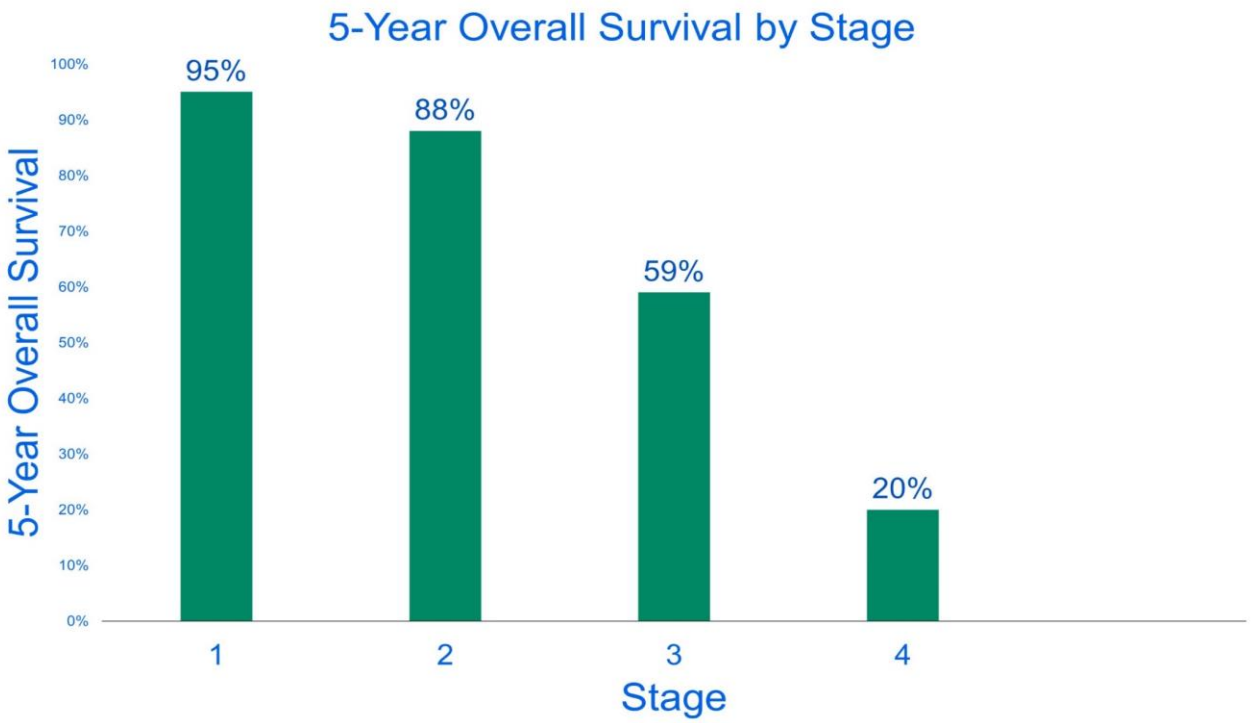
Krav til studier der undersøger forebyggende behandlinger

- Kun patienter med højest risiko for tilbagefald skal indgå
- Samme inklusionskriterier mellem studier
- Vigtigt at have fokus på livskvalitet og bivirkninger
- Endepunkterne skal være klinisk relevante

B Gyawali and V Prasad. Ann Oncol 2019

Risiko for tilbagefald afhænger af stadiet

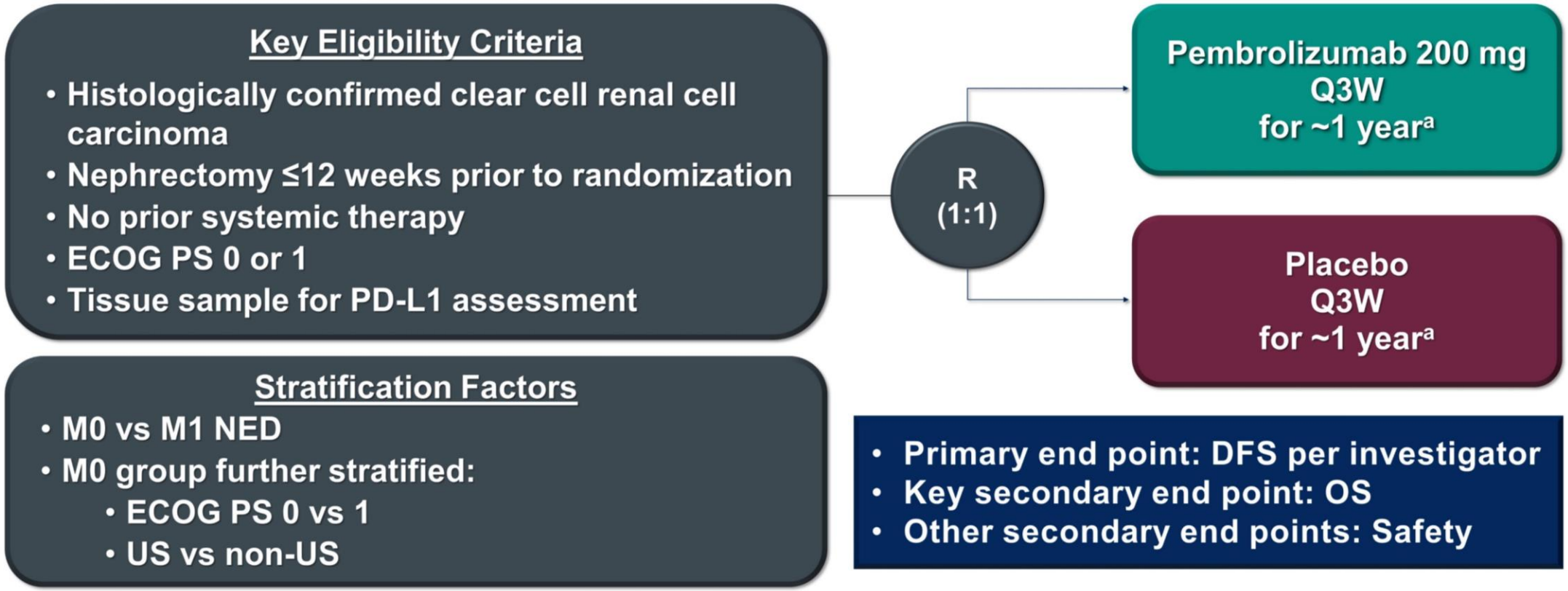




AJCC (TNM) Stage Grouping for RCC[4]		
Stage	**Description**	**Stage Definition**
I	• Tumour ≤7 cm • Limited to the kidney	T1, N0, M0
II	• Tumour >7 cm • Limited to the kidney	T2, N0, M0
III (either of these conditions)	• Tumour of any size • Spread to regional lymph nodes but not to other parts of the body	T1 or T2, N1, M0
	• Tumour grown into the major veins or perinephric tissue, may or may not have spread to lymph nodes • Has not spread to other parts of the body	T3, any N, M0
IV (either of these conditions)	• Tumour has spread beyond Gerota's fascia, extends into the adrenal gland on the same side of the body as tumour • Possibly spread to lymph nodes	T4, any N, M0
	• Tumour has spread to any other organ	Any T, any N, M1

Cohen et al, NEJM, 2005
Javidan et al, J Urol, 1999

KEYNOTE-564 Study Design



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

Choueiri et al. NEJM. 2021

Inkluderede patientgrupper i KN-564

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	
80% 5-year DFS UISS	55-80% 5-year DFS UISS	55% 5-year DFS UISS	32% 5-year DFS UISS	20% 3-year DFS E2810

NED, no evidence of disease.

Choueiri et al. NEJM. 2021

Patient karakteristika

Characteristic, n (%)	Pembro N = 496	Placebo N = 498
Age, median (range), yrs	60 (27–81)	60 (25–84)
Male	347 (70.0)	359 (72.1)
ECOG PS		
0	421 (84.9)	426 (85.5)
1	75 (15.1)	72 (14.5)
Disease risk category		
M0 intermediate-high risk	427 (86.1)[a]	433 (86.9)
M0 high risk	40 (8.1)	36 (7.2)
M1 NED	29 (5.8)	29 (5.8)

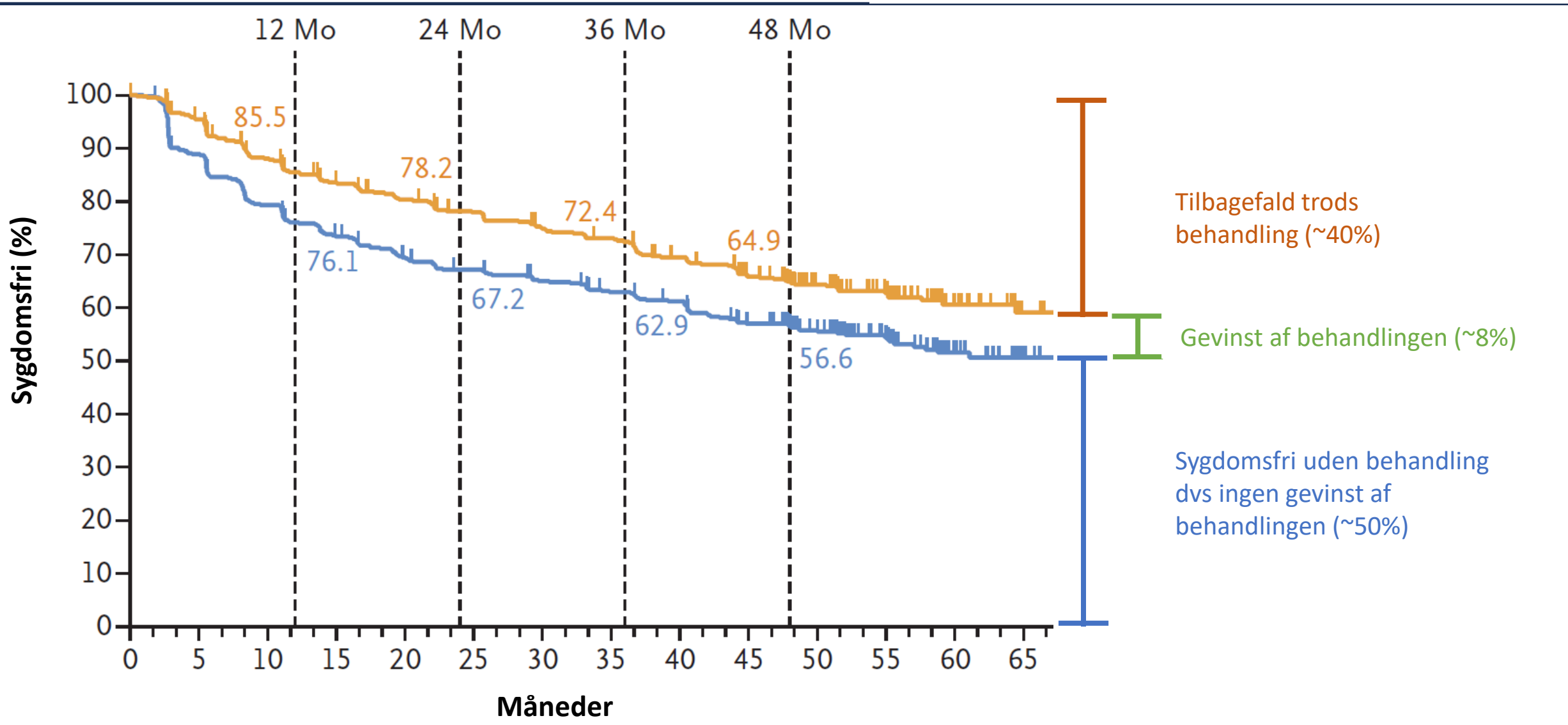
Characteristic, n (%)	Pembro N = 496	Placebo N = 498
Geographic location		
North America	113 (26.8)	125 (25.1)
European Union	188 (37.9)	187 (37.6)
Rest of the world	175 (35.3)	186 (37.3)
PD-L1 status[b]		
CPS <1	124 (25.0)	113 (22.7)
CPS ≥1	365 (73.6)	383 (76.9)
Missing	7 (1.4)	2 (0.4)
Sarcomatoid features		
Present	52 (10.5)	59 (11.8)
Absent	417 (84.1)	415 (83.3)
Unknown	27 (5.4)	24 (4.8)

Intermediate-high risk: pT2, grade 4 or sarcomatoid, N0 M0; or pT3, any grade, N0 M0
High risk: pT4, any grade, N0 M0; or pT any stage, any grade, N+ M0
M1 NED: No evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy
[a]Included 5 participants with T2, grade ≤3, N0 M0 or T1 N0 M0. [b]Assessed using the PD-L1 IHC 22C3 pharmDx assay. CPS (combined positive score) is the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100. Data cutoff date: December 14, 2020.

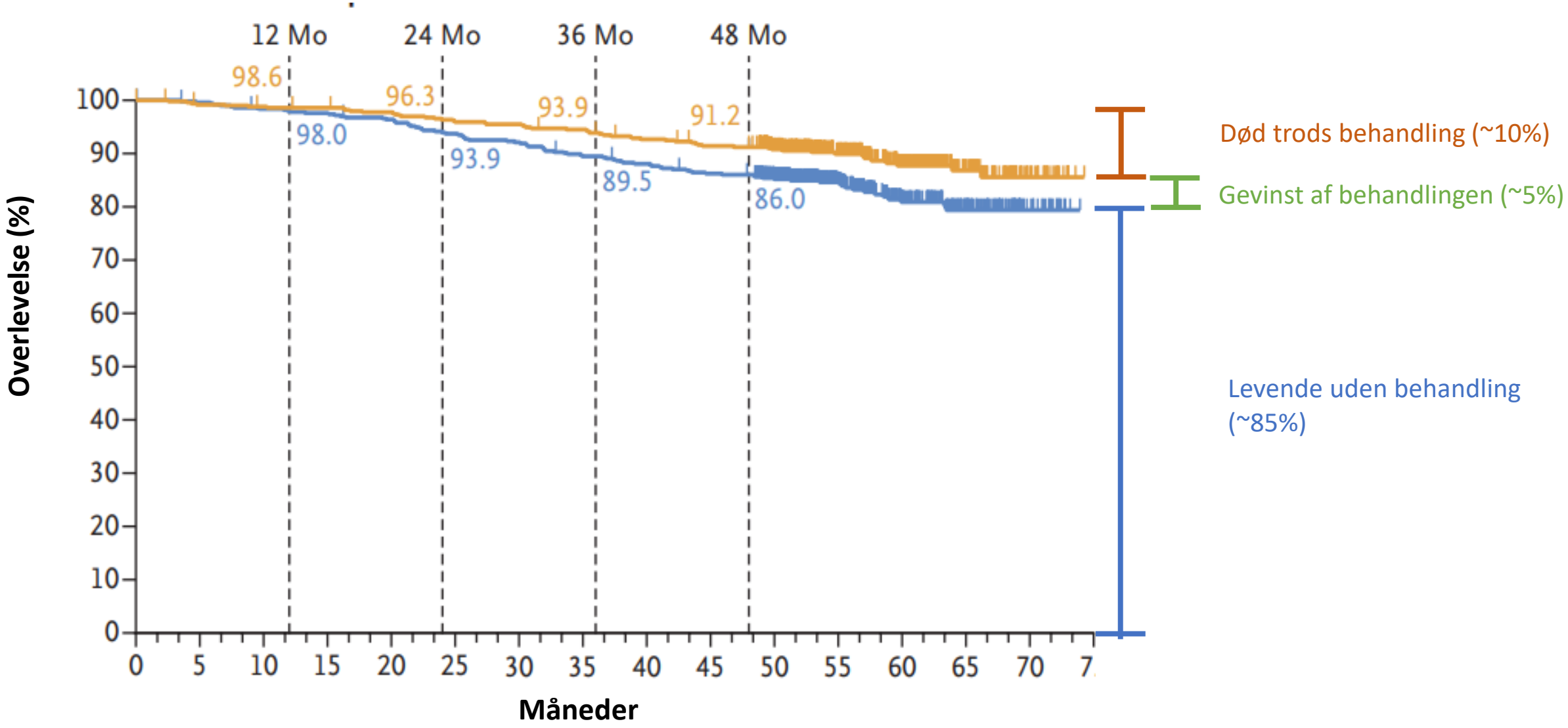
80% 5-year DFS UISS	55-80% 5-year DFS UISS

Choueiri et al. NEJM. 2021

Adj. Pembrolizumab gav signifikant længere DFS

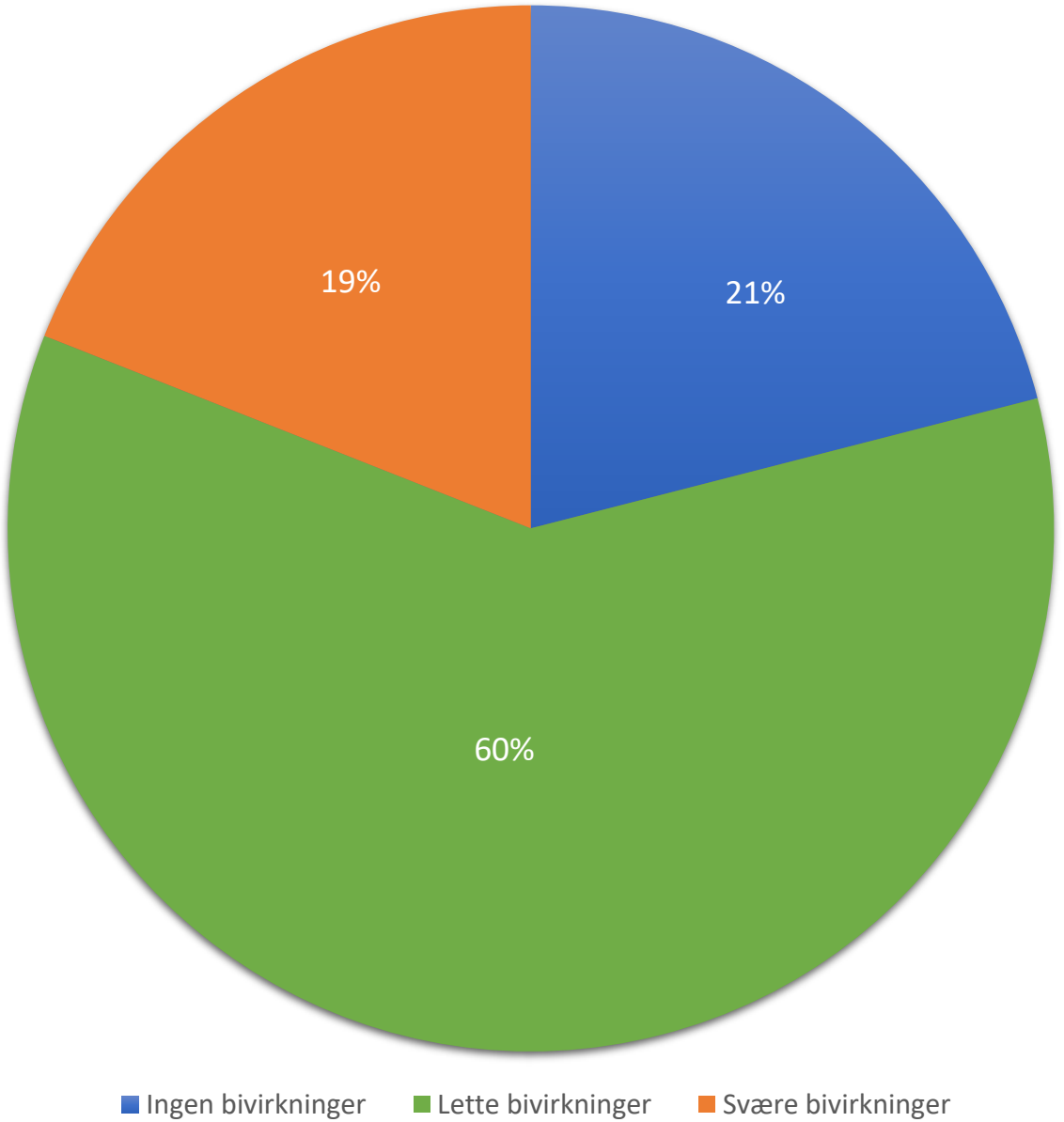


Adj. Pembrolizumab gav signifikant længere OS



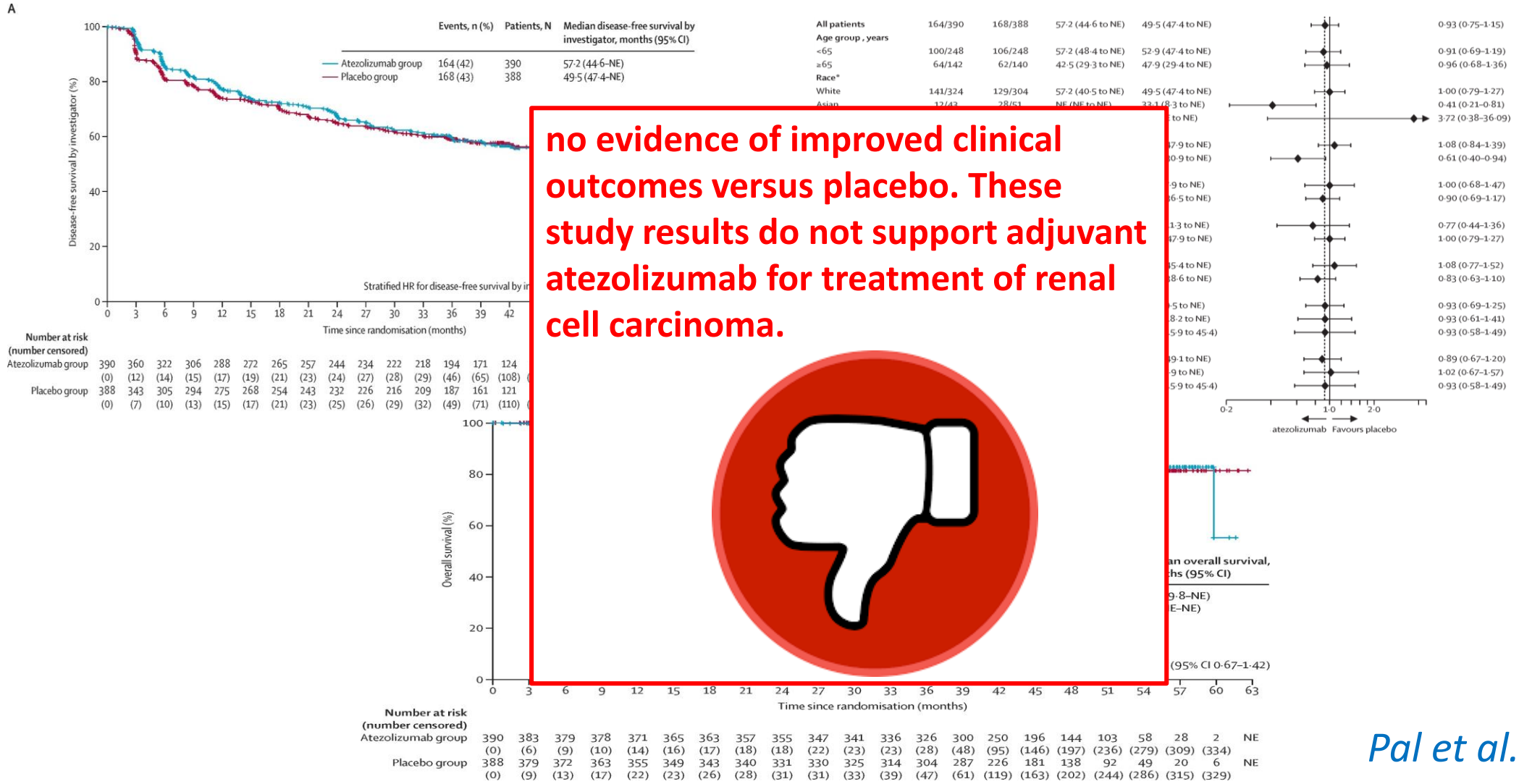
Bivirkninger til adj. Pembrolizumab

21 ud af 100 patienter får ingen bivirkninger
60 ud af 100 patienter får milde bivirkninger
19 ud af 100 patienter får svære bivirkninger
10 ud af 100 patienter får alvorlige immunrelaterede bivirkninger
Minimal risiko for at dø af bivirkninger



Andre adjuverende studier med immunterapi

Immotion010 – Atezolizumab vs Placebo



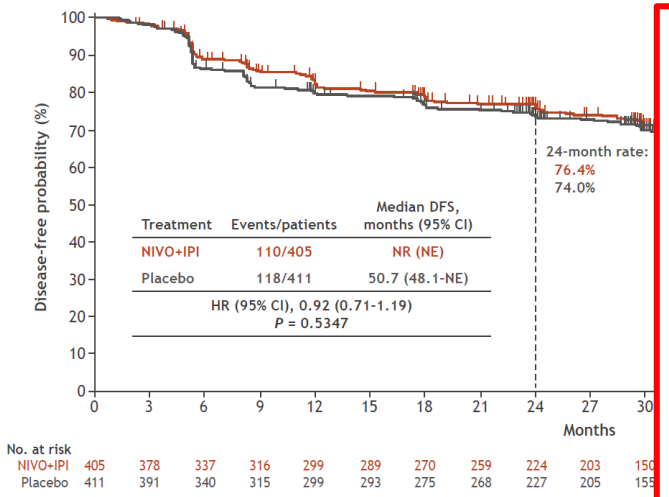
no evidence of improved clinical outcomes versus placebo. These study results do not support adjuvant atezolizumab for treatment of renal cell carcinoma.

Pal et al. Lancet. 2022

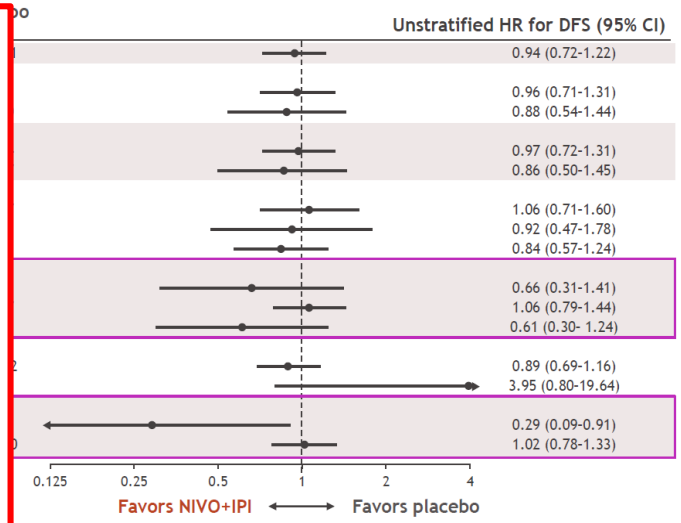
Andre adjuverende studier med immunterapi

Checkmate 914 – Ipi+Nivo vs Placebo

Primary endpoint: disease-free survival per BICR

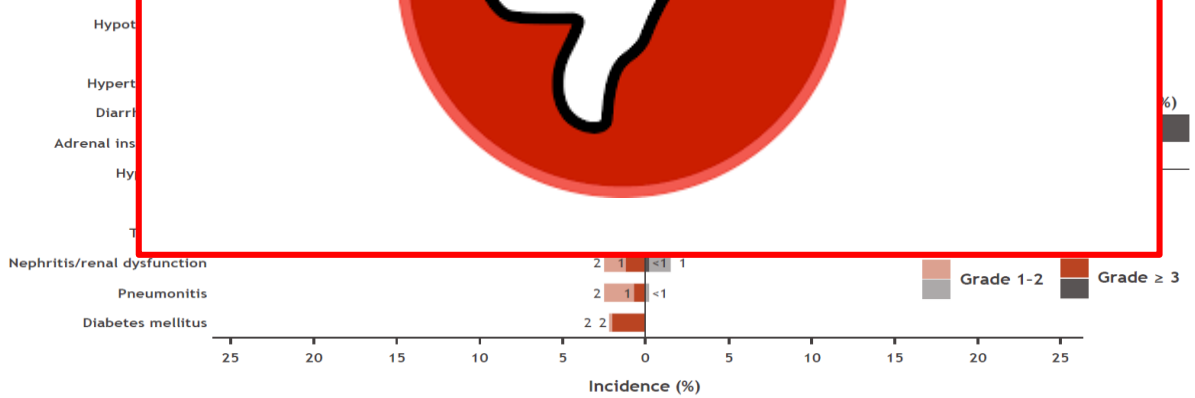


Disease-free survival per BICR in subgroups



- **Did not meet the primary endpoint of DFS**
- **The rate of discontinuation due to treatment related AEs was considerable with IPI+NIVO in the adjuvant setting**

Immu



Motzer et al. Lancet. 2023

Ongoing adjuverende studier med immunterapi

Table 3 – On-going clinical trials investigating adjuvant and neoadjuvant/perioperative therapy in RCC [a]

Trial	Trial design	Strategy	Stage (pathological or clinical)	*n*	Histology	Arms	Primary endpoint	Primary completion date (estimated)
Adjuvant								
NCT03288532 (RAMPART)	Phase 3 Randomised Multiarm multistage design Open label	Adjuvant IO monotherapy or IO combo. Multiarm multistage design	Leibovich score 3–11	1750	All subtypes of RCC, except for pure oncocytoma, collecting duct, medullary	No intervention: arm A: active monitoring Experimental: arm B: durvalumab 1500 mg Q4W monotherapy for 1 yr Experimental: arm C: durvalumab 1500 mg Q4W for 1 yr + tremelimumab 75 mg on day 1 and week 4 visits (ie, two cycles)	DFS, OS (arm C vs A and arm B vs A)	Closed to recruitment in June 2023
NCT05239728 (MK-6482-022)	Phase 3 Randomised Double blind	Adjuvant IO + HIF-2α inhibitor	Intermediate-high-risk RCC (pT2, Gr 4 or sarcomatoid, N0, M0; pT3, any grade, N0, M0) High-risk RCC (pT4, any Gr, N0, M0; pT any stage, any Gr, N+, M0) M1 NED RCC (solid, isolated, soft tissue metastases completely resected, synchronous) or ≤2 yr from nephrectomy	1800	Clear cell	Experimental: belzutifan 120 mg once daily + pembrolizumab Q6W (up to ~54 wk) Active comparator: placebo + pembrolizumab Q6W (up to ~54 wk)	DFS	October 2026
NCT06146777	Phase 3 Randomised Open label	Adjuvant IO in papillary RCC at high risk according to a multiclassifier system created by the investigators	Stage III, high risk by multiclassifier system created by the investigators	468	Papillary	Experimental: pembrolizumab 200 mg Q3W for up to 17 cycles Comparator: placebo	DFS	December 2030
NCT06005818 (MRD GATE RCC)	Phase 2 Nonrandomised Open label	Treatment de-escalation study based on MRD	Intermediate-high-risk RCC (pT2, Gr 4 or sarcomatoid, N0, M0; pT3, any G, N0, M0) High-risk RCC (pT4, any Gr N0, M0; pT any stage, any Gr, N+, M0)	100	Clear cell	No intervention: arm 1: MRD-negative patients Active comparator: arm 2: MRD-positive patients: pembrolizumab 400 mg Q6W for a total of 1 yr	DFS	December 2024
NCT06307431 (V940-004)	Phase 2 Randomised Double blind	Combination of IO with an mRNA-based personalised cancer vaccine	Intermediate-high-risk RCC (pT2 Gr4, N0, M0; pT3 Gr3/4, N0, M0) High risk (pT4, N0, M0; pT any stage, N1, M0) M1 NED RCC (solid, isolated, soft tissue metastases, completely resected, synchronous, or ≤2 yr from nephrectomy)	272	Clear cell or papillary	Experimental: V940 (Q3W) for up to nine doses + pembrolizumab 400 mg Q6W for nine cycles (up to ~54 wk) Active comparator: placebo + pembrolizumab 400 mg Q6W for nine cycles (up to ~54 wk)	DFS	January 2028 (Not yet recruiting. Study start estimated in April 2024)

Marandino et al. Eur Jour Oncol. 2024

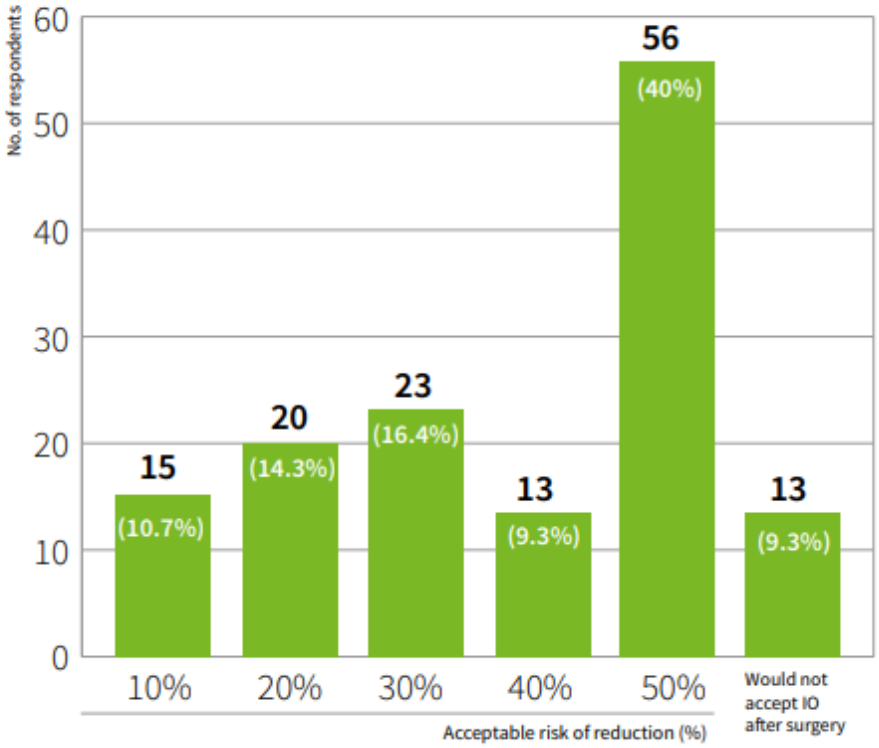
Hvad tænker patienterne?

Question 1

Imagine, you (or your loved one) have had surgery to remove your kidney cancer, but you still have a high risk that your kidney cancer will come back later on. Your doctor offers you a systemic immune checkpoint inhibitor treatment (also called immunotherapy). What would you, as a patient in that situation, consider the necessary reduction of risk of your kidney cancer coming back to accept immunotherapy after your surgery?

141 RCC Patients

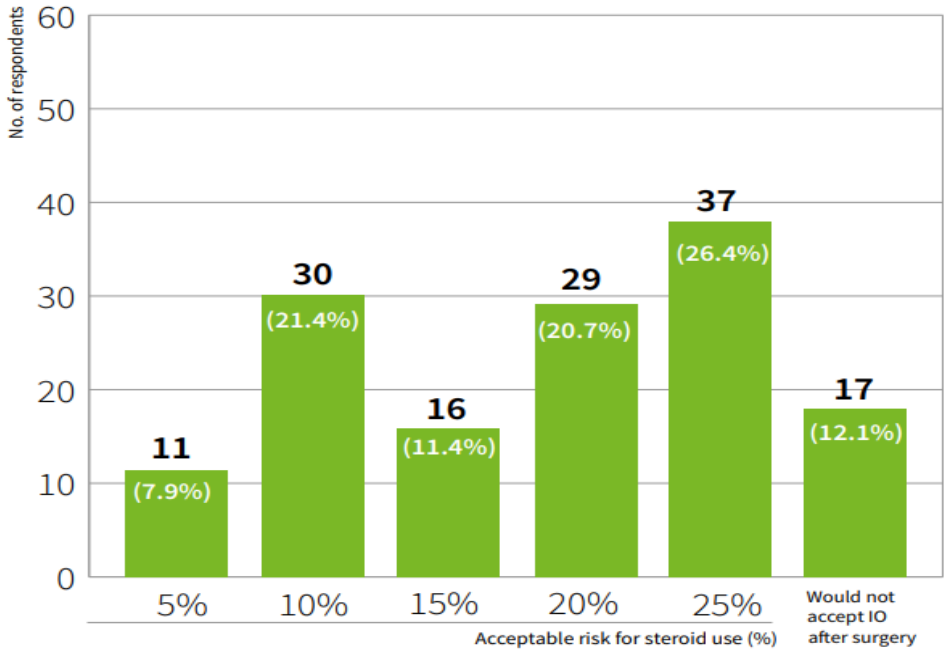
140 out of 141 people answered this question



Question 2

Treatment with immune checkpoint inhibitors often causes side effects, which can usually be managed by taking steroids so that you can finish the therapy. Steroids, in turn, can also have side effects, such as water retention (puffiness), weight gain, and even permanent side effects like diabetes, or fibrosis (tissue scarring). Knowing that there is a risk you may need high dose steroid treatment in addition to the immunotherapy, what level of risk for steroid use would be acceptable for you?

140 out of 141 people answered this question

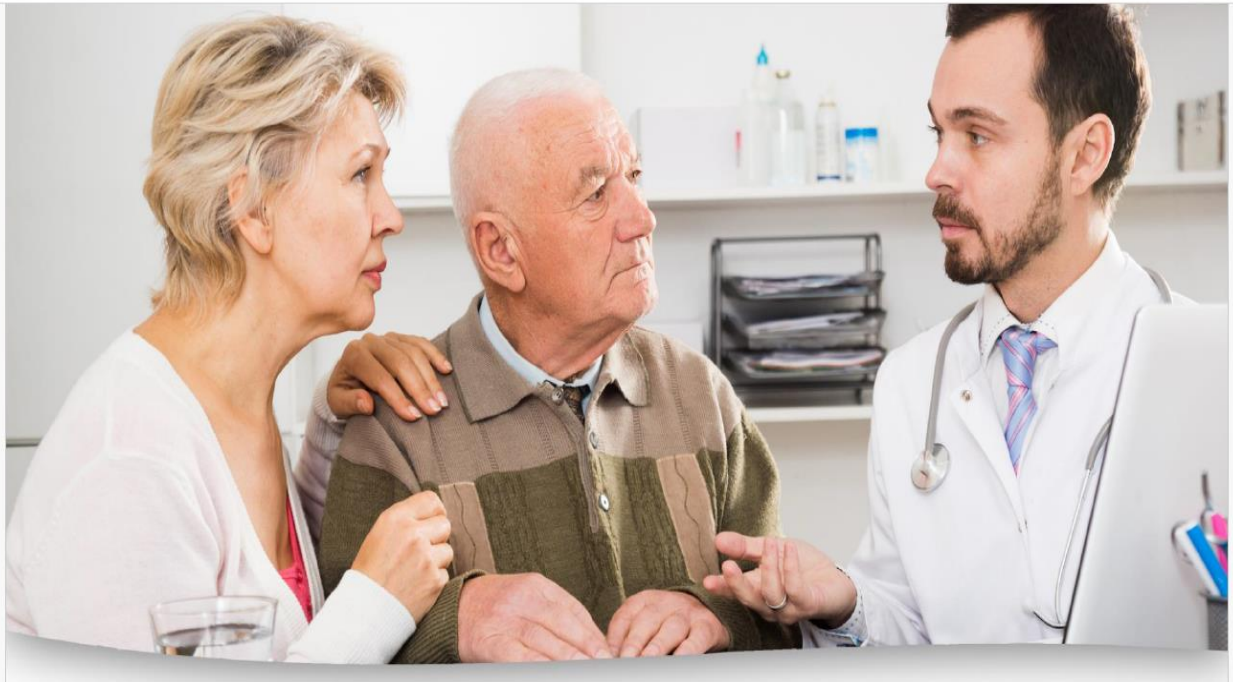


IKCC International Kidney Cancer Coalition

www.ikcc.org ikcc @ikcc.org @IKCCtrials

Hvad tænker patienterne?

Bør være en fælles beslutning mellem patient og læge

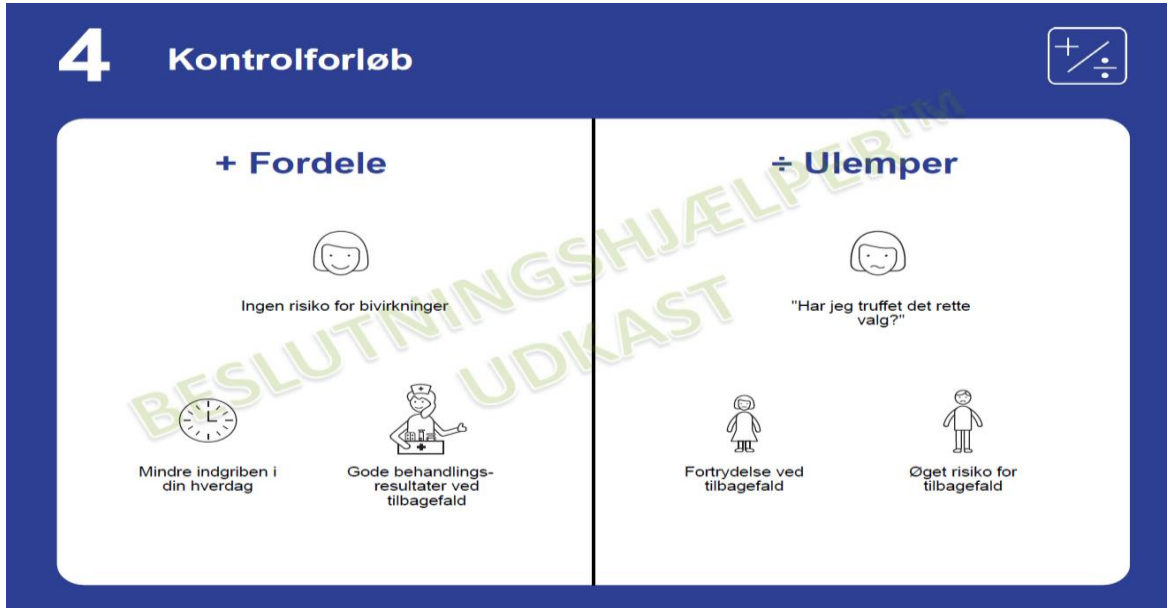


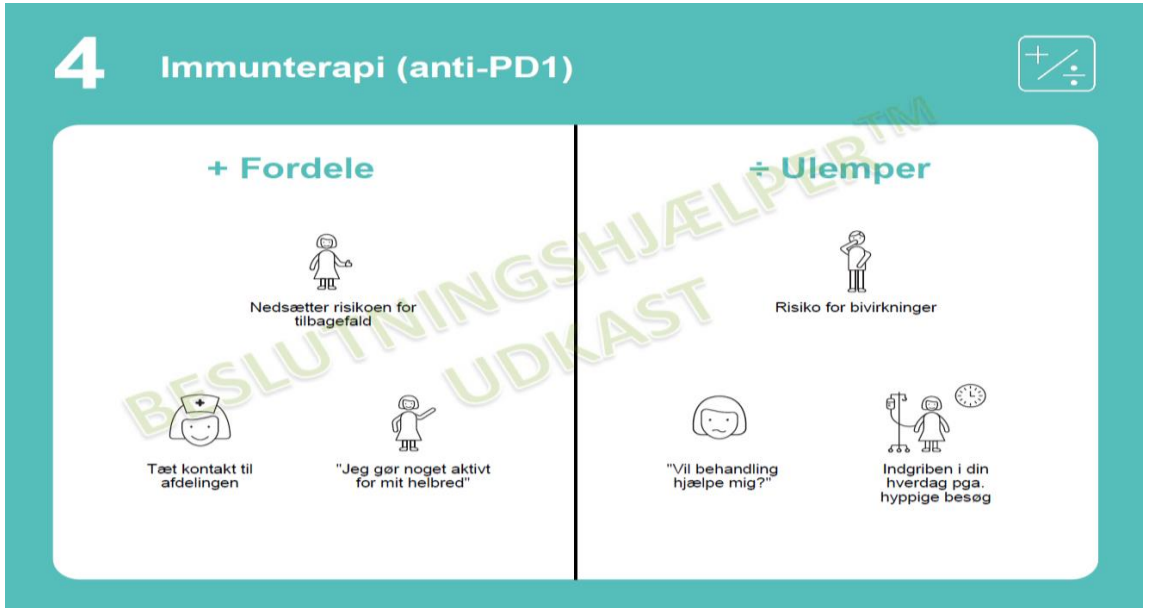
Cancer du rein CANADA Kidney Cancer CANADA

Should I receive pembrolizumab after kidney cancer surgery to prevent the cancer from coming back

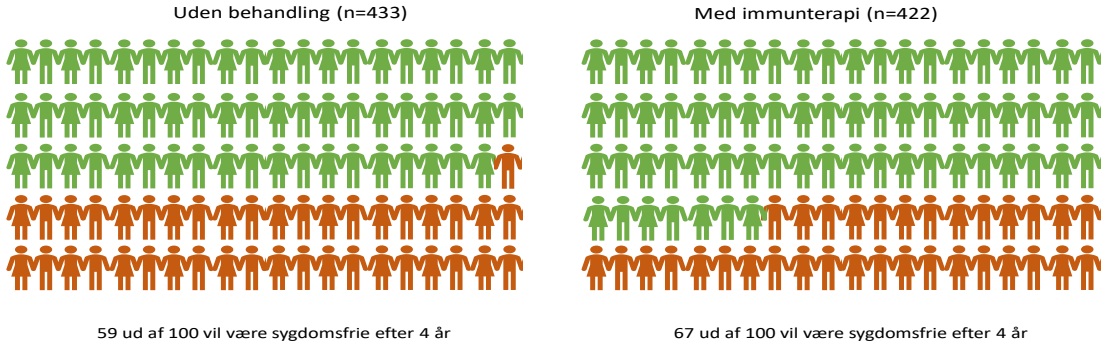
A decision aid to discuss a medical treatment option with your doctor

Fælles beslutningshjælper





Immunterapi (anti-PD1)
Intermediær/high risk (T2, grade 4 eller T3, any grade)



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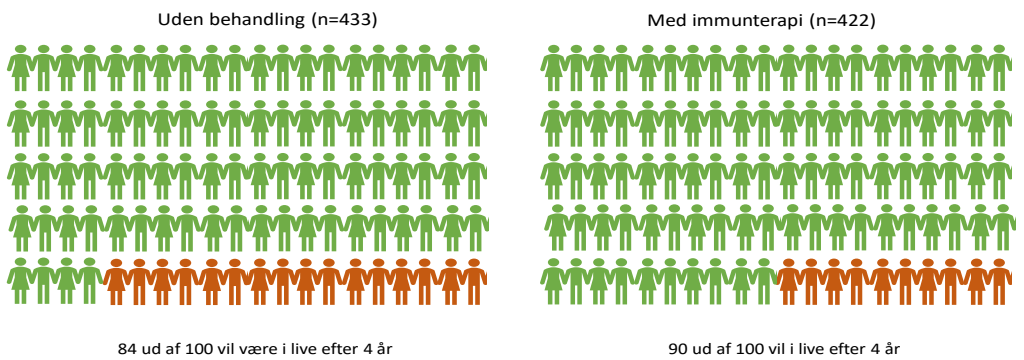
Intermediær/high risk (T2, grade 4 eller T3, any grade)



Charlson Comorbidity Index (CCI)

J Chron Dis Vol. 40, No. 5, pp. 373–383, 1987
Printed in Great Britain.

0021-9681/87 $3.00 + 0.00

A NEW METHOD OF CLASSIFYING PROGNOSTIC COMORBIDITY IN LONGITUDINAL STUDIES: DEVELOPMENT AND VALIDATION

MARY E. CHARLSON,* PETER POMPEI, KATHY L. ALES and C. RONALD MACKENZIE

Clinical Epidemiology Unit, Department of Medicine, Cornell University Medical College, 1300 York Avenue, New York, NY 10021, U.S.A.

(*Received in revised form* 2 *September* 1986)

Abstract—The objective of this study was to develop a prospectively applicable method for classifying comorbid conditions which might alter the risk of mortality for use in longitudinal studies. A weighted index that takes into account the number and the seriousness of comorbid disease was developed in a cohort of 559 medical patients. The 1-yr mortality rates for the different scores were : "0", 12% (181); "1–2", 26% (225); "3–4", 52% (71); and "≥5", 85% (82). The index was tested for its ability to predict risk of death from comorbid disease in the second cohort of 685 patients during a 10-yr follow-up. The percent of patients who died of comorbid disease for the different scores were: "0", 8% (588); "1", 25% (54); "2", 48% (25); "≥3", 59% (18). With each increased level of the comorbidity index, there were stepwise increases in the cumulative mortality attributable to comorbid disease (log rank $\chi^2 = 165$; $p < 0.0001$). In this longer follow-up, age was also a predictor of mortality ($p < 0.001$). The new index performed similarly to a previous system devised by Kaplan and Feinstein. The method of classifying comorbidity provides a simple, readily applicable and valid method of estimating risk of death from comorbid disease for use in longitudinal studies. Further work in larger populations is still required to refine the approach because the number of patients with any given condition in this study was relatively small.

Comorbidity	Score
Prior myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Rheumatologic disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes	1
Cerebrovascular (hemiplegia) event	2
Moderate-to-severe renal disease	2
Diabetes with chronic complications	2
Cancer without metastases	2
Leukemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
Acquired immuno-deficiency syndrome (AIDS)	6

Hvad med risikoen for død af komorbiditet?

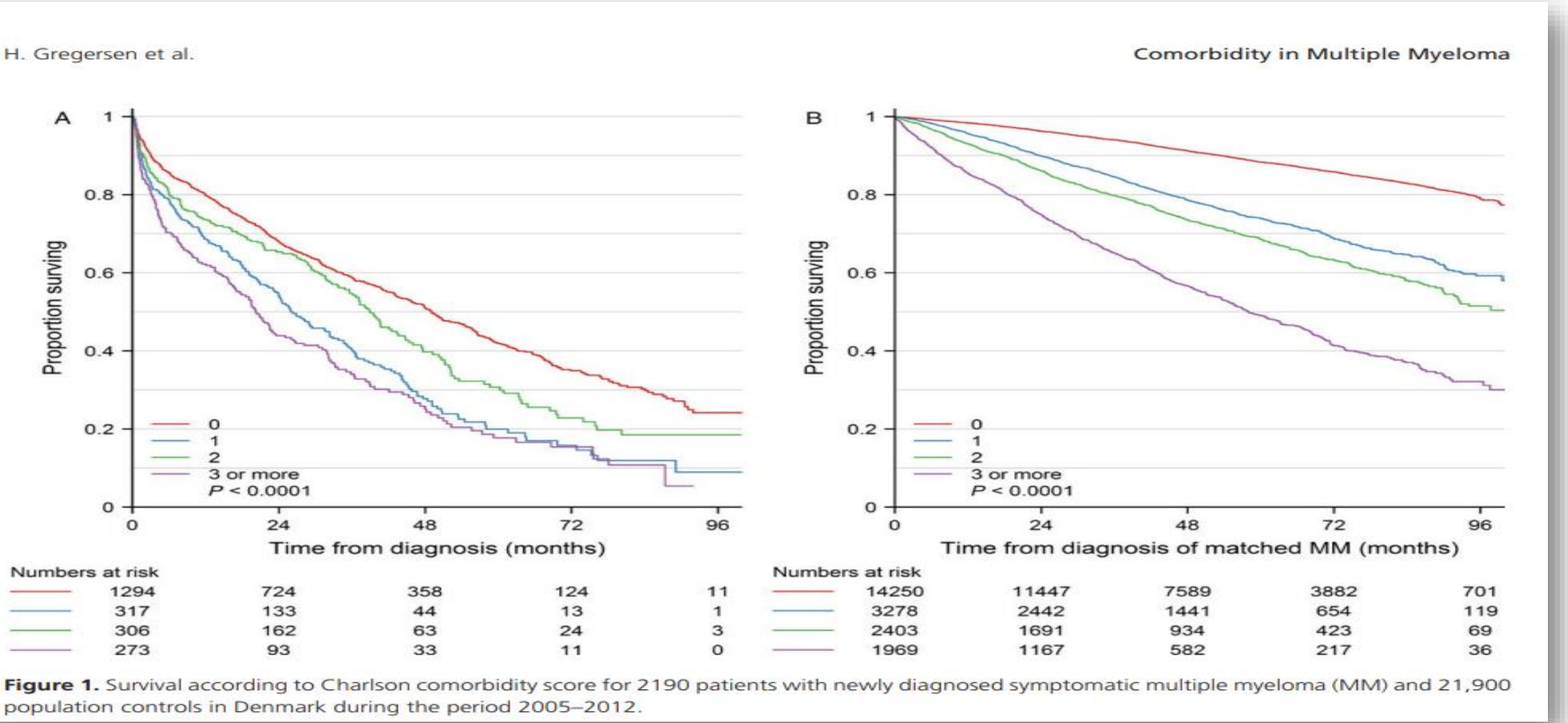


Figure 1. Survival according to Charlson comorbidity score for 2190 patients with newly diagnosed symptomatic multiple myeloma (MM) and 21,900 population controls in Denmark during the period 2005–2012.

Gregersen et al. Cancer Medicine. 2017

Europæiske guidelines omkring adj. pembrolizumab

EAU guidelines

** pT2 G4 or pT3 any G; pT4 any G; pN+ any G; M1, NED after resection of metastases.*

Recommendations	Strength rating
Do not use neoadjuvant therapy outside a clinical trial setting.	Weak
Discuss the contradictory results of the available adjuvant ICI trials with patients to facilitate shared decision making.	Strong
Inform patients about the potential risk of overtreatment and immune related side effects if adjuvant therapy is considered.	Strong
Do not offer adjuvant therapy with sorafenib, pazopanib, everolimus, girentuximab, or axitinib.	Strong
Do not offer adjuvant sunitinib following surgically resected high-risk clear-cell renal cell carcinoma (ccRCC).	Weak
Offer adjuvant pembrolizumab to ccRCC patients, preferably within 12-16 weeks post-nephrectomy, with a recurrence risk as defined in the Keynote-564 trial: • Intermediate-high risk: - pT2, grade 4 or sarcomatoid, N0 M0 - pT3, any grade, N0, M0 • High risk: - pT4, any grade, N0, M0 - any pT, any grade, N+, M0 • M1 no evidence of disease (NED): - NED after resection of oligometastatic sites ≤ 1 year from nephrectomy	Weak

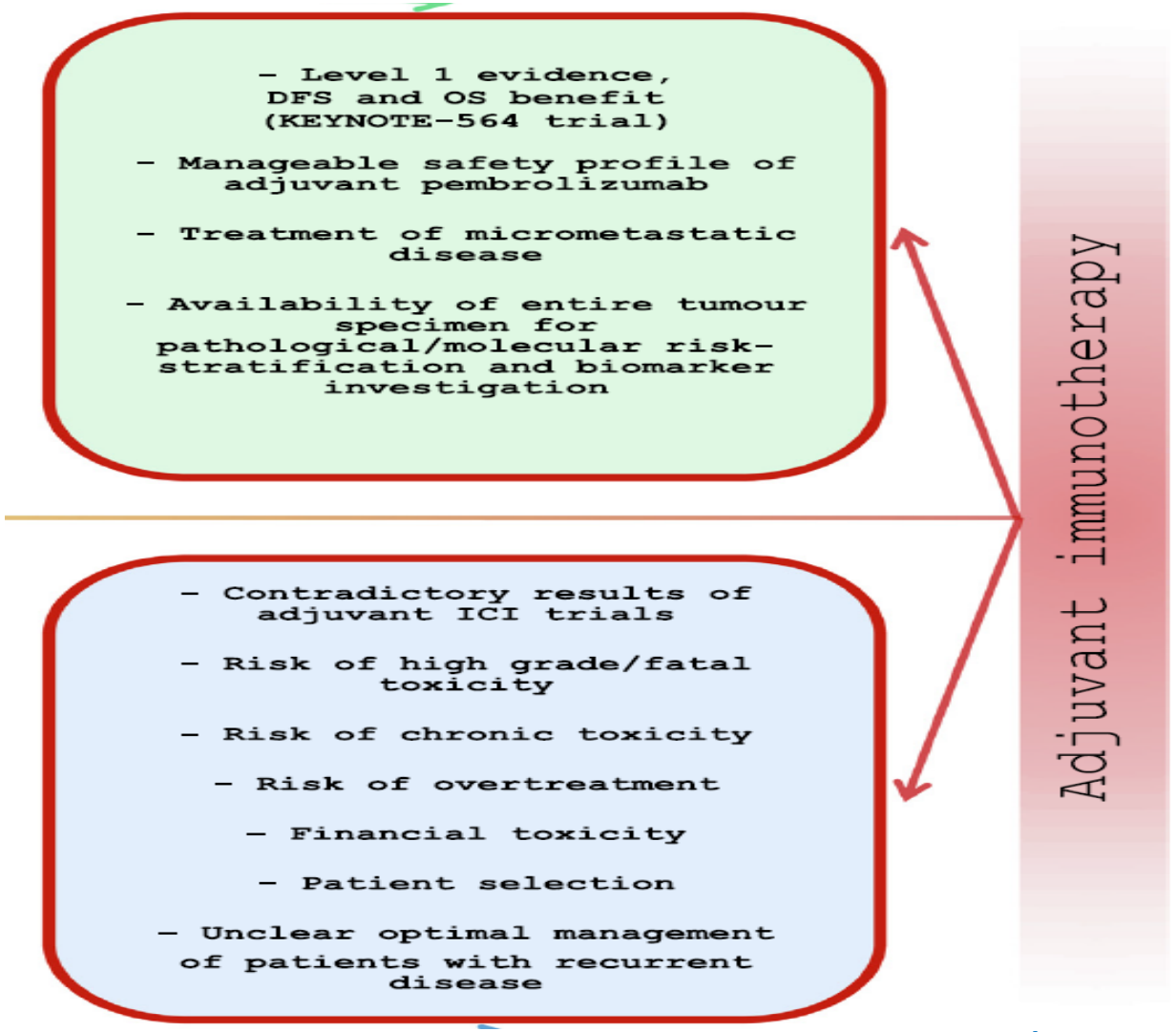
ESMO guidelines

Adjuvant pembrolizumab should be considered for patients with intermediate-high- or high-risk operable ccRCC (as defined by the KEYNOTE-564 criteria) after careful patient counselling regarding potential longterm AEs [I, A; ESMO-MCBS v1.1 score: A]. Treatment should start within 12 weeks of surgery and continue for up to 1 yea

Overvejelser om adj. Pembrolizumab

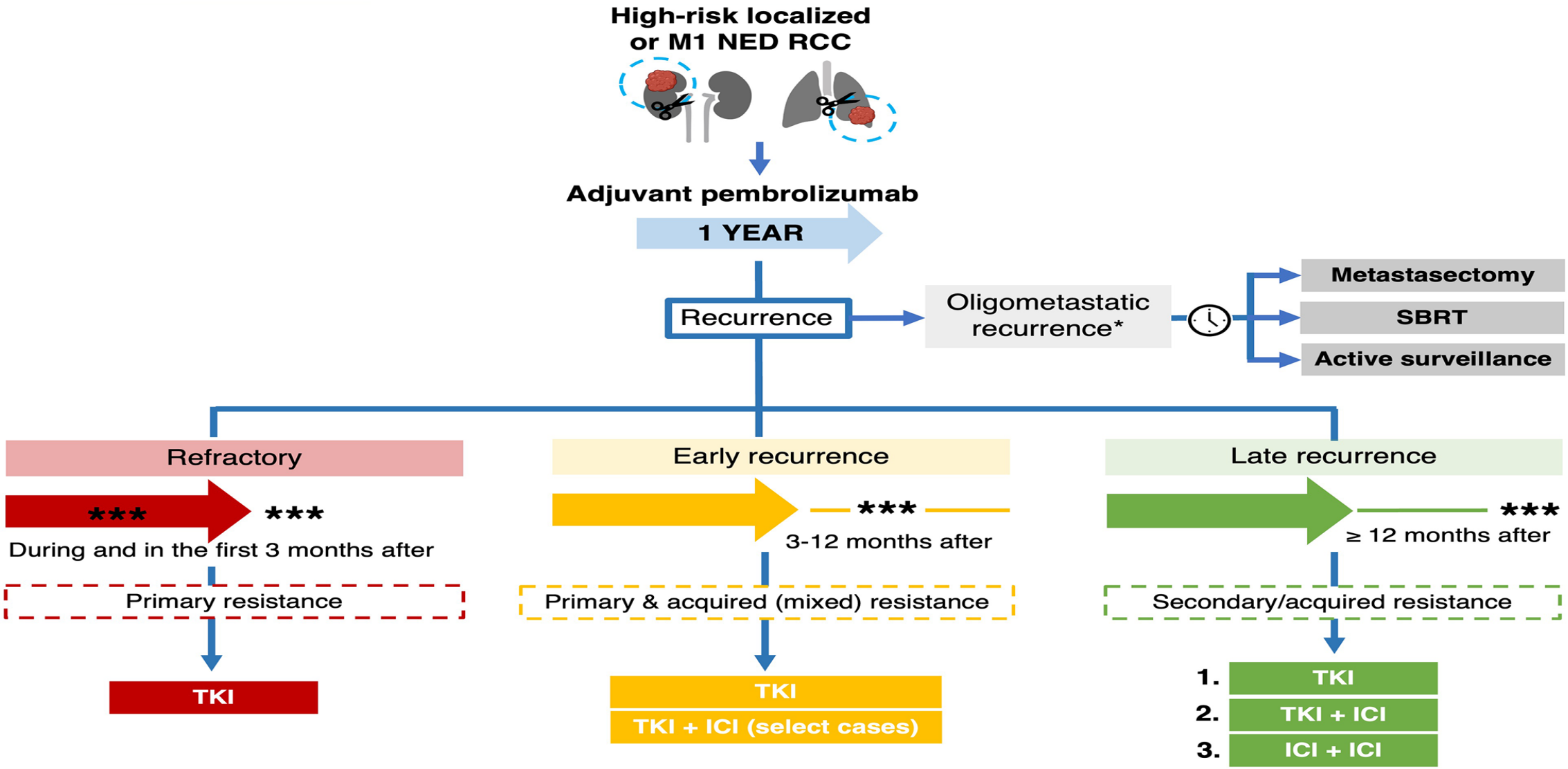
Styrker og muligheder

Begrænsninger og udfordringer



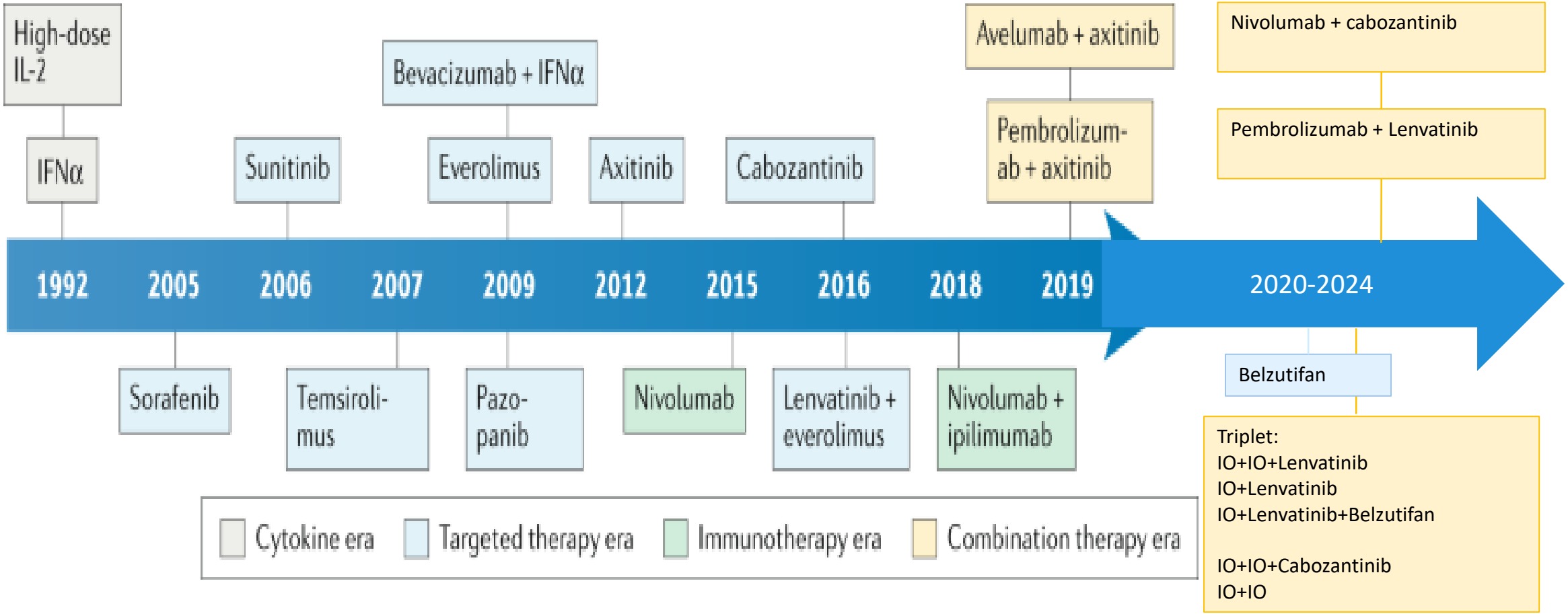
Marandino et al. Eur Jour Oncol. 2024

Proposed Algorithm on How to Treat Recurrent Renal Cell Carcinoma After Adjuvant Pembrolizumab

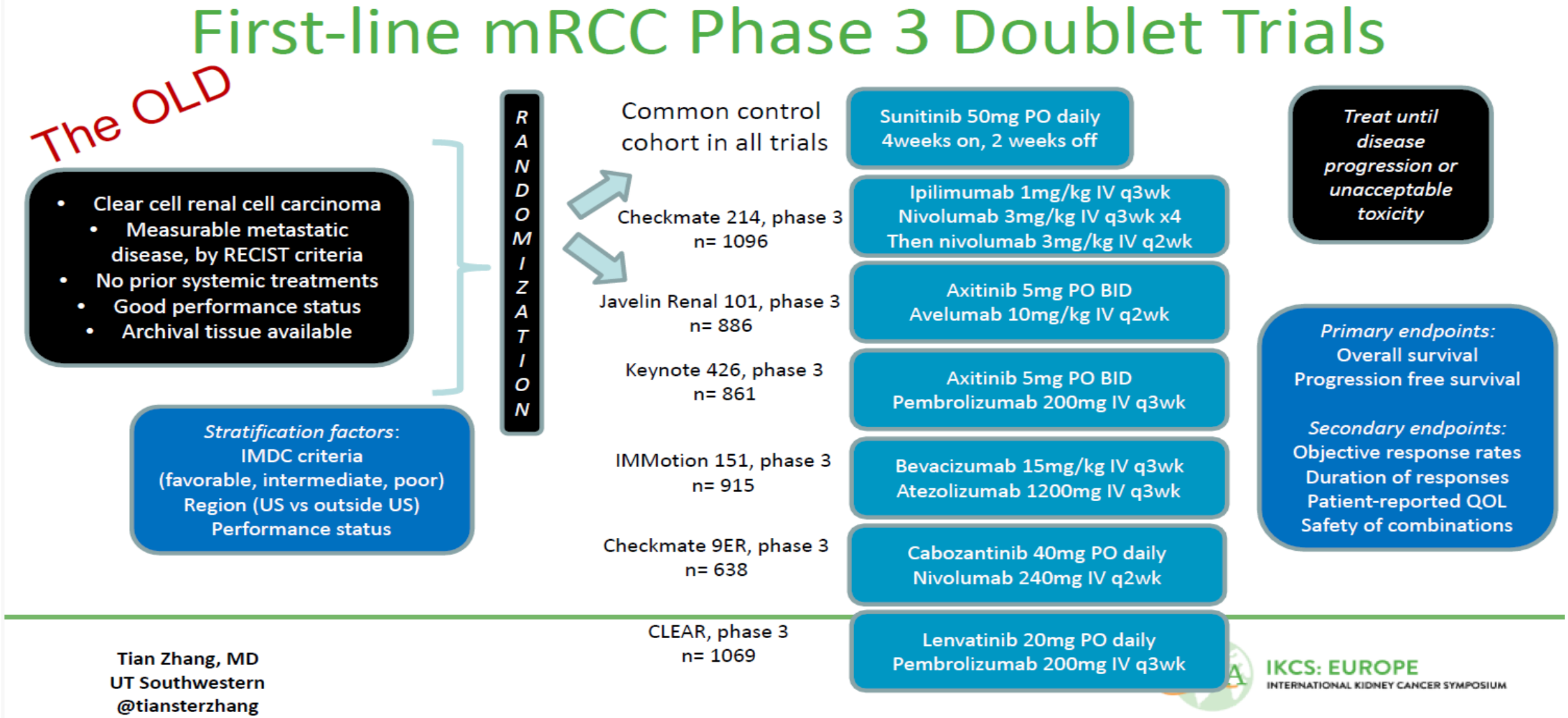


Behandlingsmuligheder ved metastatisk nyrekræft

Behandlingsmulighederne for nyrekræft er forbedret betydeligt indenfor for en kort periode



1. linje behandling til metastatisk nyrekræft



Tian Zhang, MD
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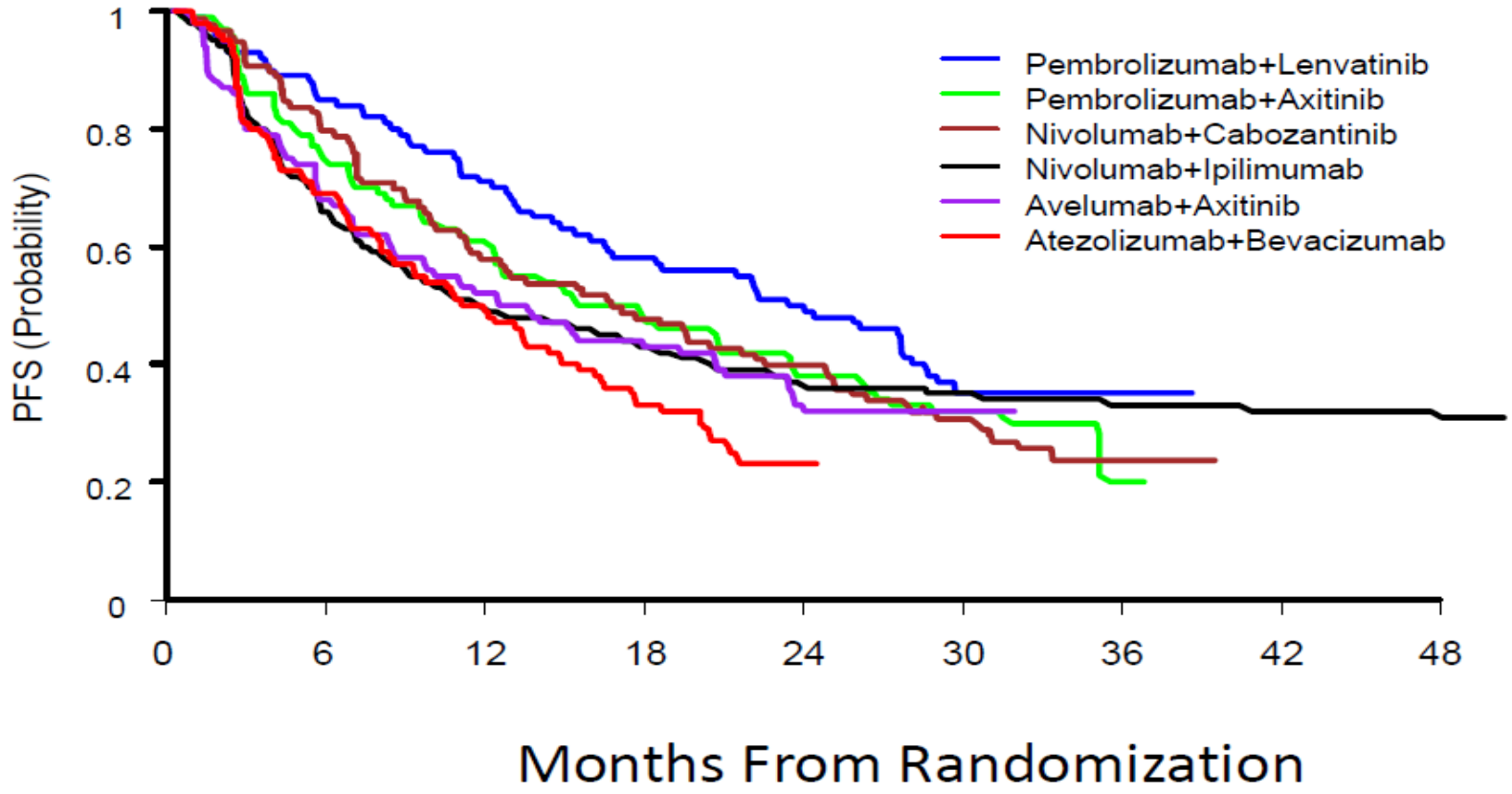
IKCS: EUROPE
INTERNATIONAL KIDNEY CANCER SYMPOSIUM

1. linje behandling til metastatisk nyrekræft

Studienavn	KEYNOTE-426	JAVELIN Renal 101	CHECKMATE-214	**CLEAR**	**Checkmate 9ER**
	Axitinib+Pembrolizumab vs Sutent (N=861)	**Axitinib+Avelumab vs. Sutent (N=886)**	**Ipilimumab+Nivolumab vs. Sutent (N=1096)**	**Lenvatinib + Pembrolizumab vs. Everolimus + Lenvatinib vs. Sutent (N= 1069)**	**Cabozantinib + Nivolumab vs. Sutent (N=651)**
Variable					
IMDC prognosegrupper					
• God	31,2	21,4	23	31	22,6
• Intermediær	56,2	61,8	61	59,2	57,6
• Dårlig	12,6	16,2	17	9,3	19,7
Overall survival					
• Hazrad ratio for død	0,53	0,79	0,68	0,66	0,60
• CI	95% CI 0,38-0,74	95% CJ 0,55-1,08	99,8% CI 0,49-0,95	95% CI 0,49-0,88	98,89% CI 0,4-0,89
• P-værdi	0,0001	0,14	0,001	0,005	0,0010
mPFS (måneder)					
• Kombinationsbehandling	15,1	13,8	12,4	23,9	16,6
• Sutent	11,1	8,4	12,3	9,2	8,3
Objektiv respons (%) i kombinationsbehandling	59,3	51,4	39	71,0	55,7
CR (%) i kombinationsbehandling	5,8	3,4	10,2	16,1	8
Progression som bedste respons	10,9	11,5	20	5,4	6,5

1. linje behandling til metastatisk nyrekræft

1L mRCC PFS: Phase III Data

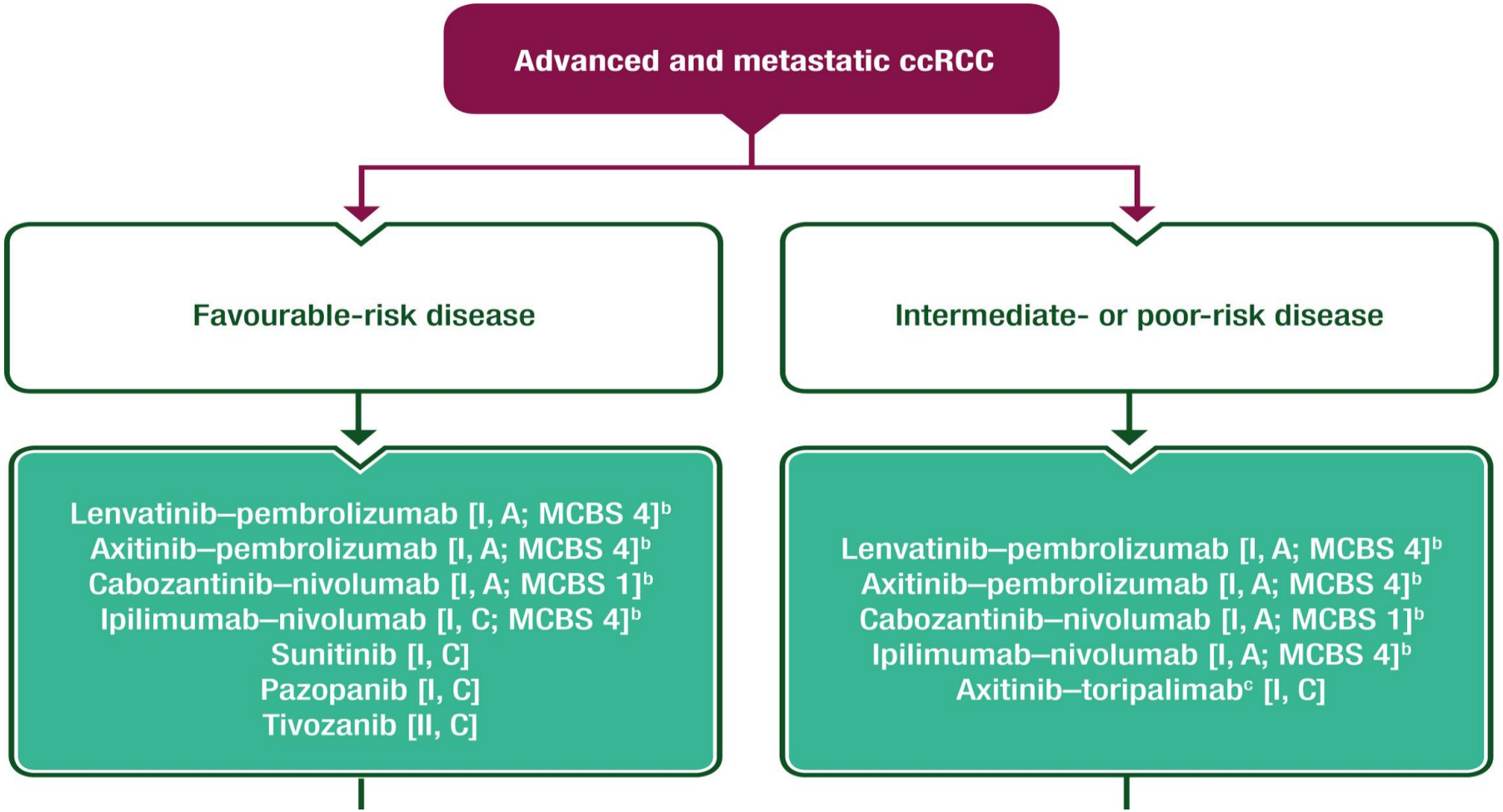


Still TKI Naive

No Data TFS for IO/TKI

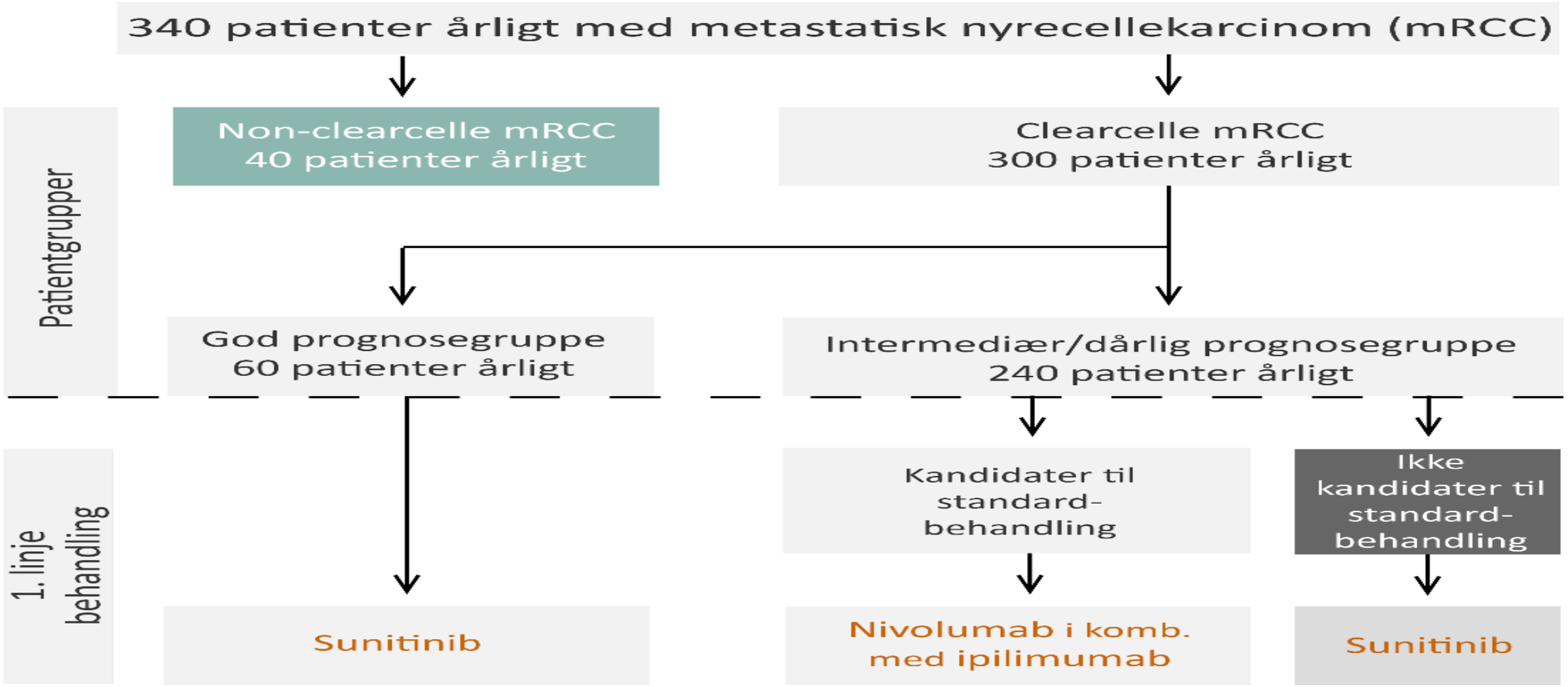
W. Xie
R.M. Saliby
T.K. Choueiri

ESMO guideline - behandling af metastatisk nyrekræft

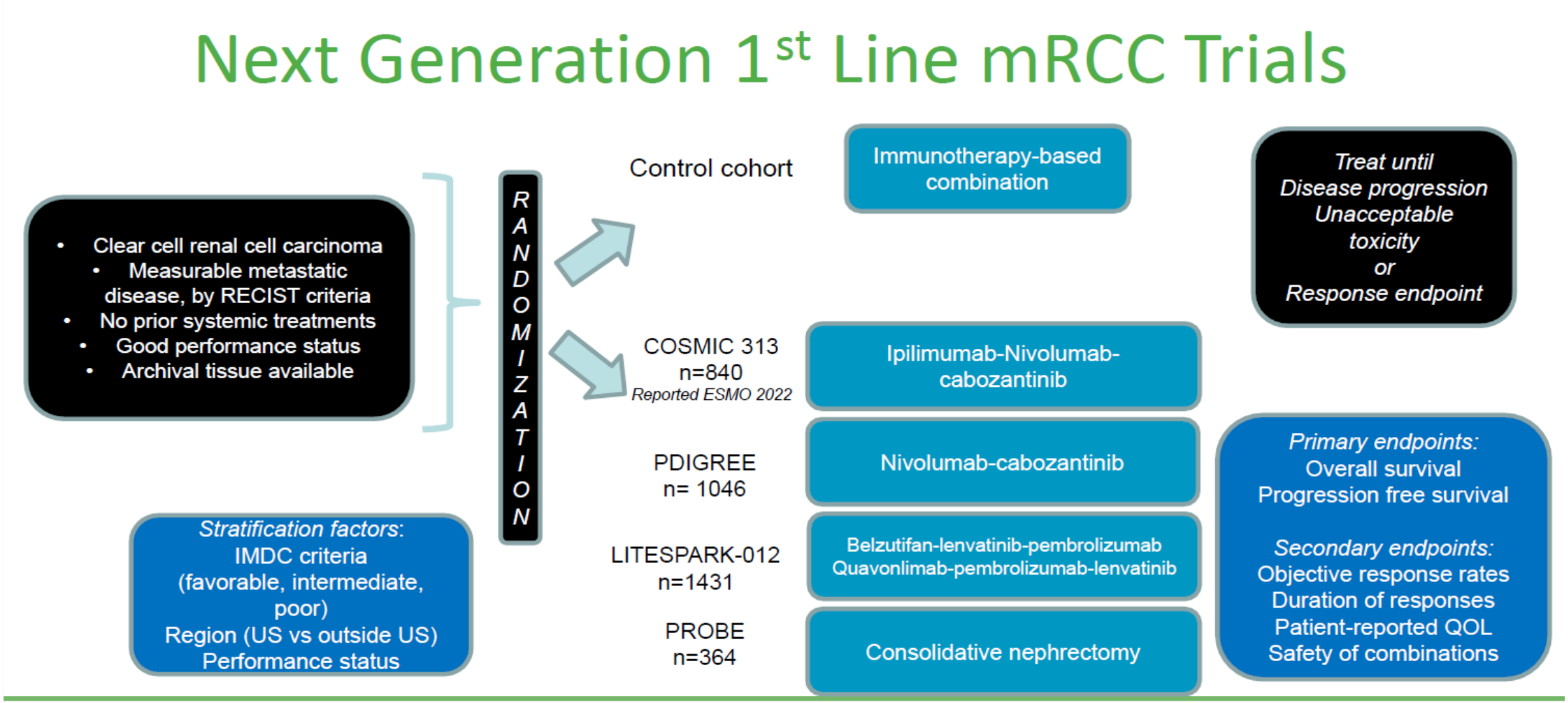


ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. 2024

Medicinrådets behandlingsvejledning for nyrekræft i DK

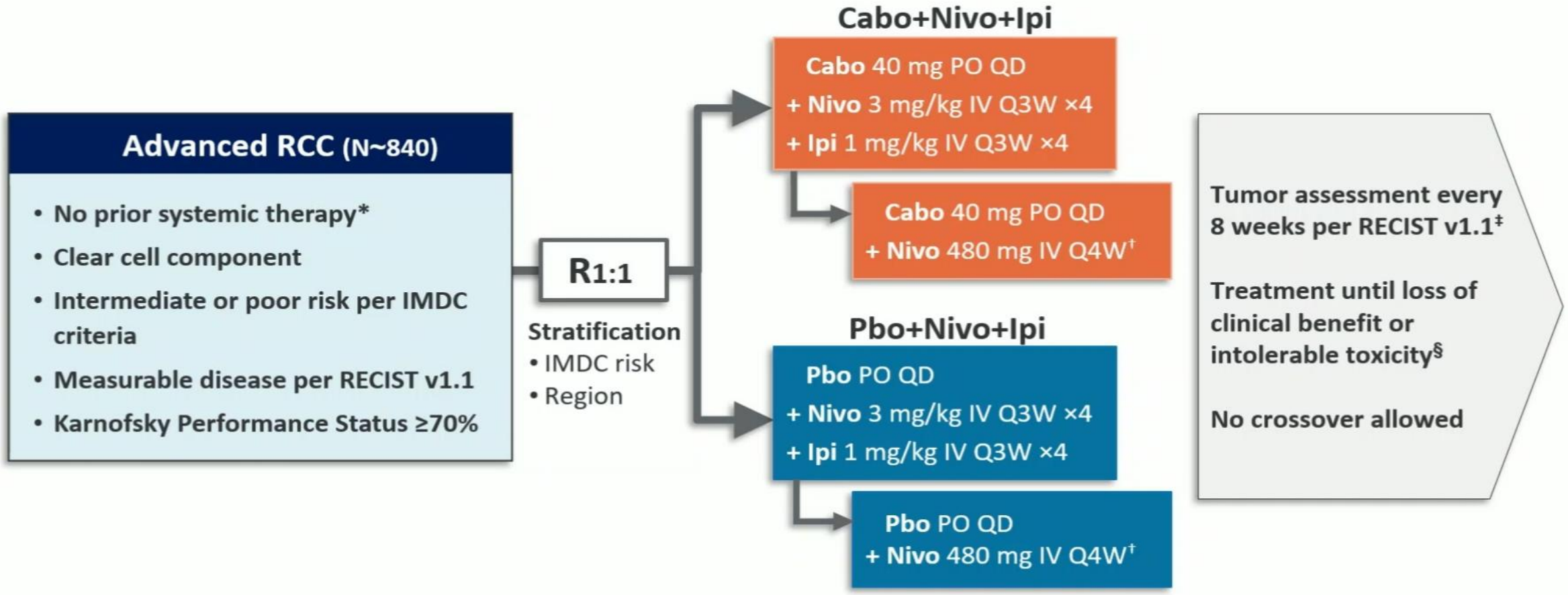


Nye 1. linje studier – triplet kombinationer



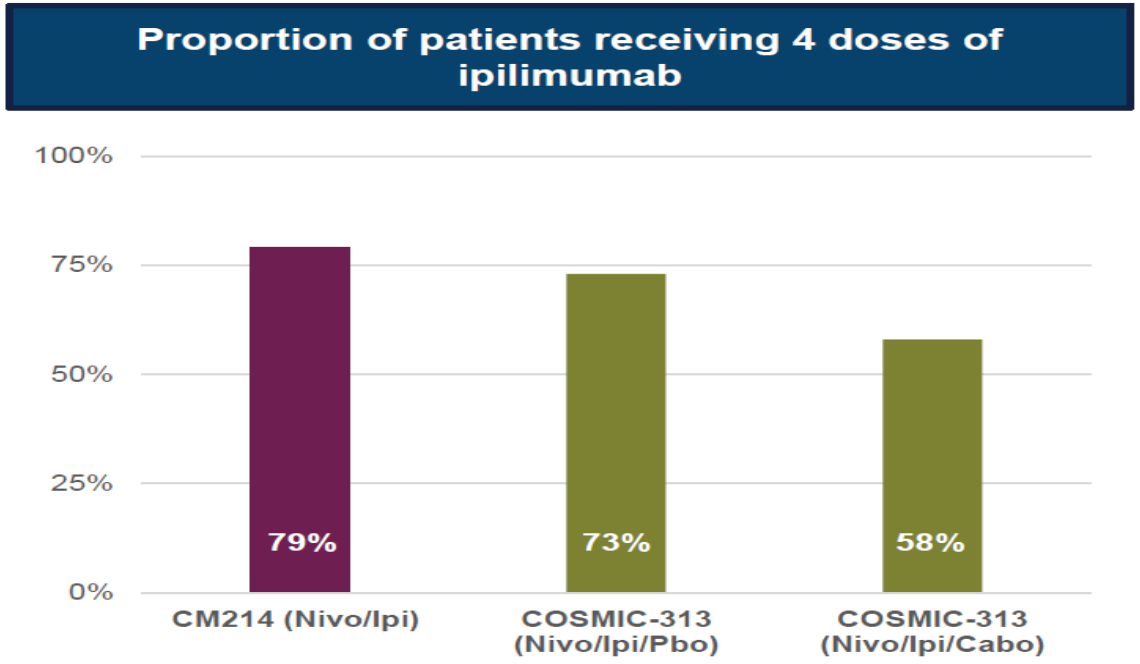
Nye 1. linje studier – triplet kombinationer

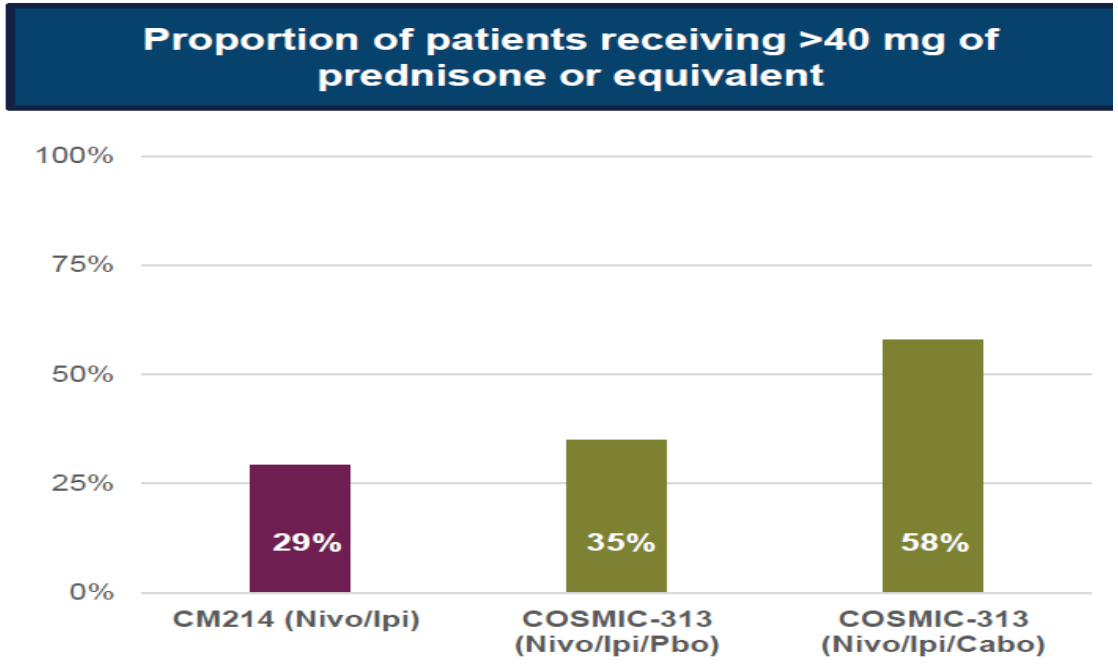
COSMIC-313 Study Design



Nye 1. linje studier – triplet kombinationer

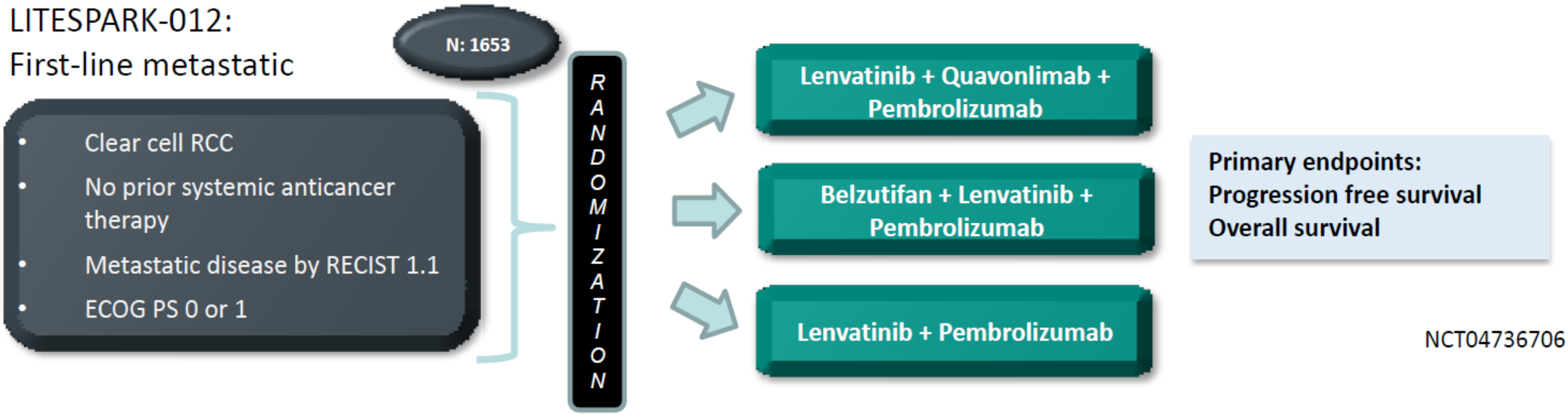
Does toxicity stand in the way of treatment?





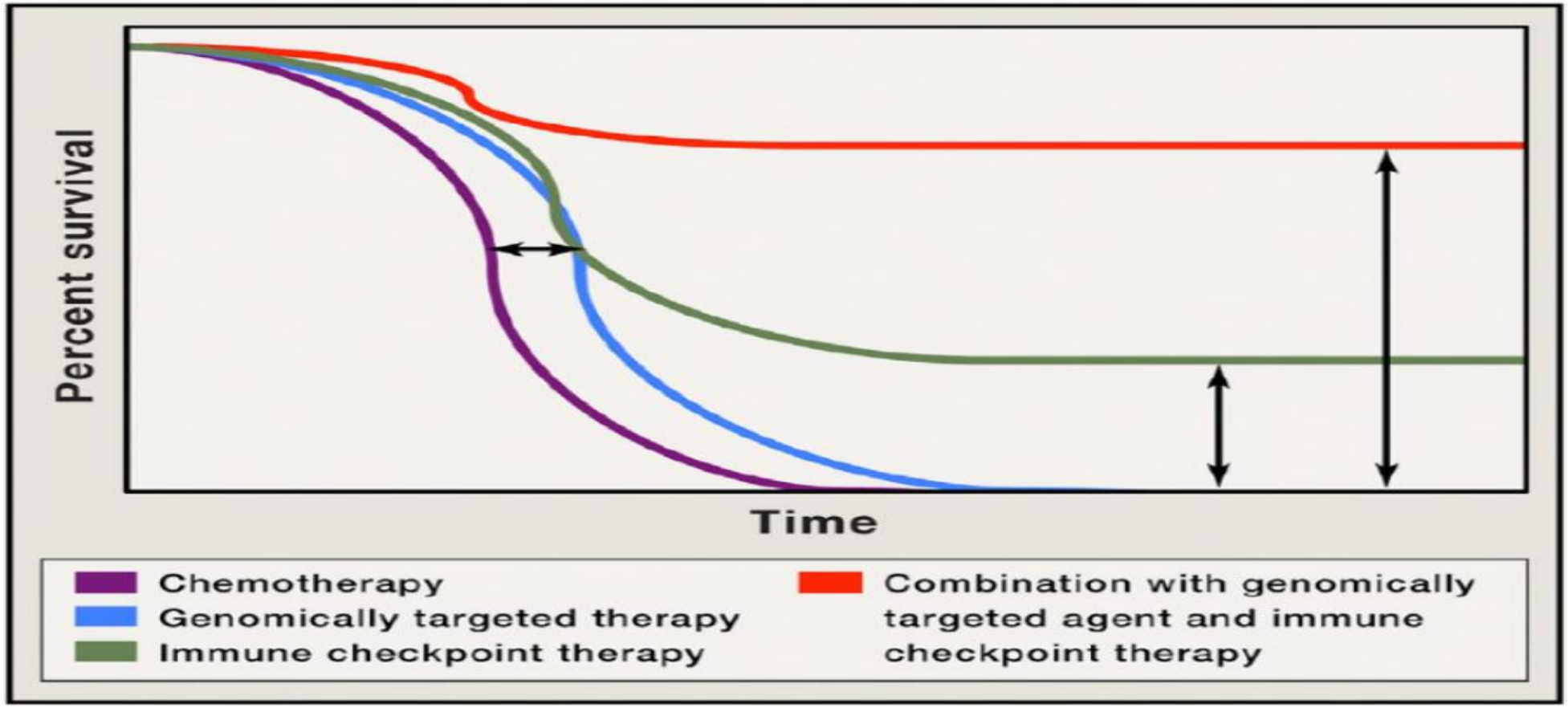
Nye 1. linje studier – triplet kombinationer

And Other Triplet Trials in First-line mRCC



Håbet med de nye behandlinger

Immunotherapy + Targeted Therapy

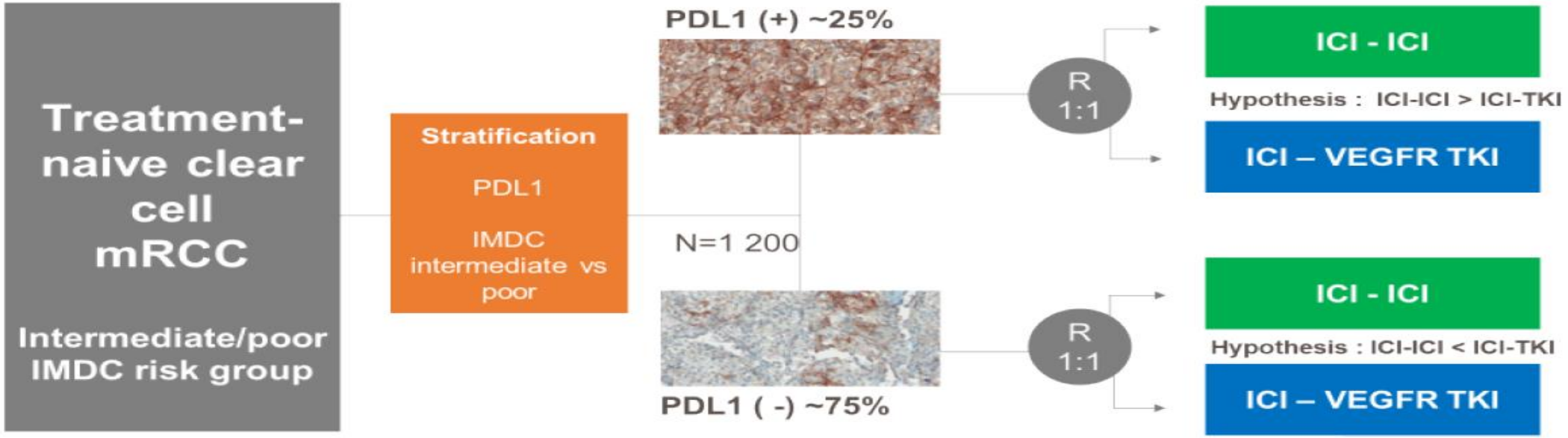


Sharma and Allison, Cell 2015

Anvendelse af biomarkører i valget af behandling

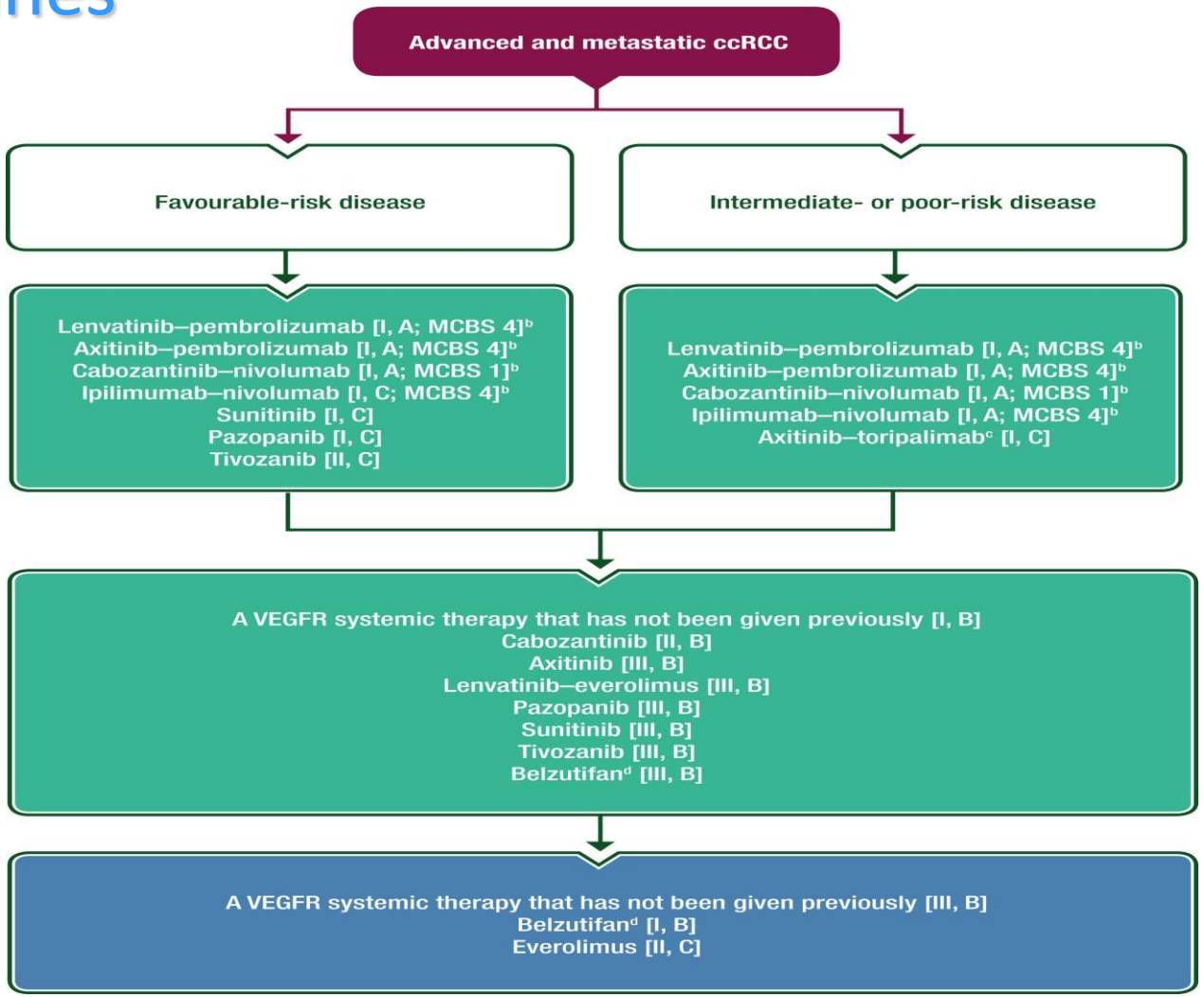
Until We Can Integrate a Biomarker to Decide!

CARE-1 RLT
FIRST LINE RANDOMISED STUDY PLATEFORM TO OPTIMIZE TREATMENT IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA



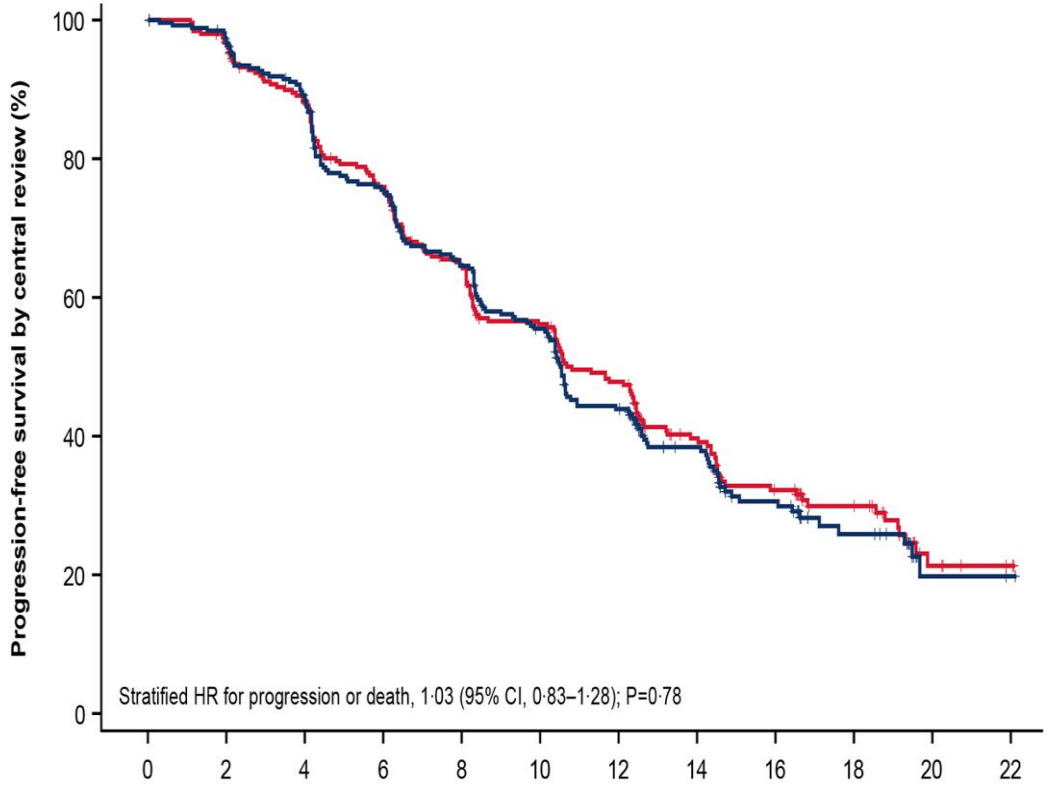
Senere behandlinger til metastatisk nyrekræft

ESMO guidelines

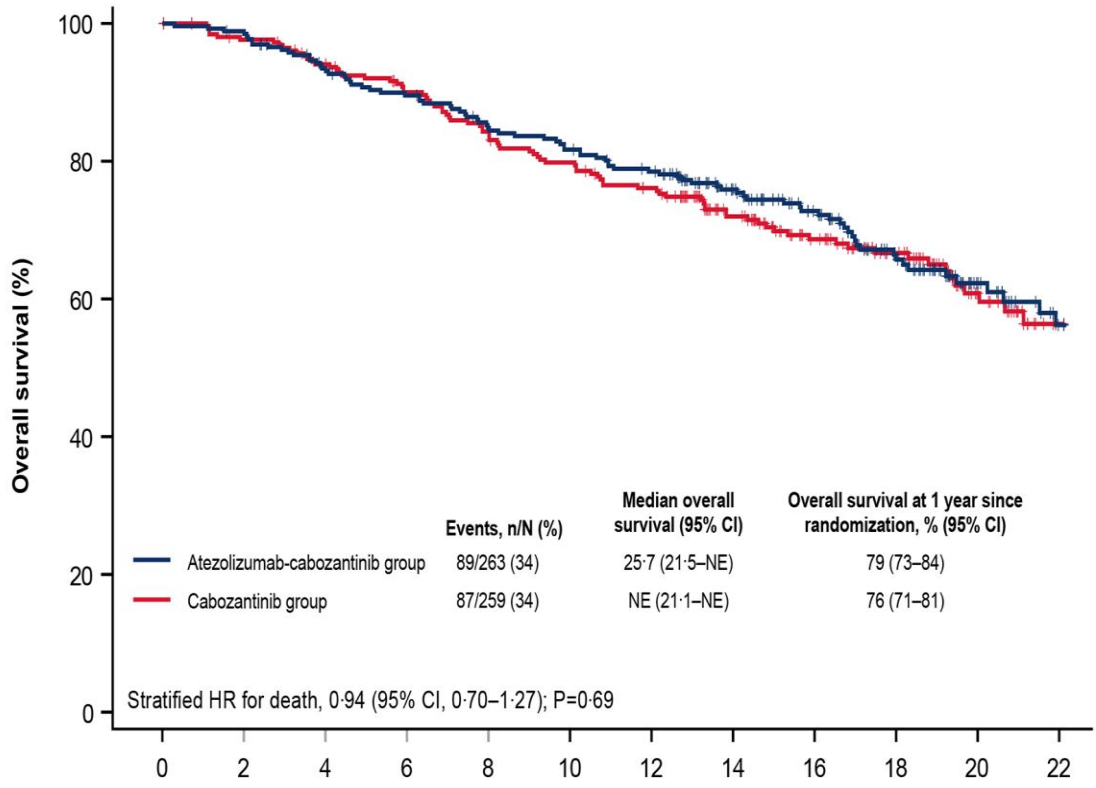


Senere behandlinger til metastatisk nyrekræft

Er der effekt ved at kombinere immunterapi med targeteret behandling efter 1. linje immunterapi?



Number at Risk												
Atezolizumab-cabozantinib group	263	253	226	188	158	133	100	68	43	22	7	6
Cabozantinib group	259	242	216	183	153	130	109	71	52	34	12	8

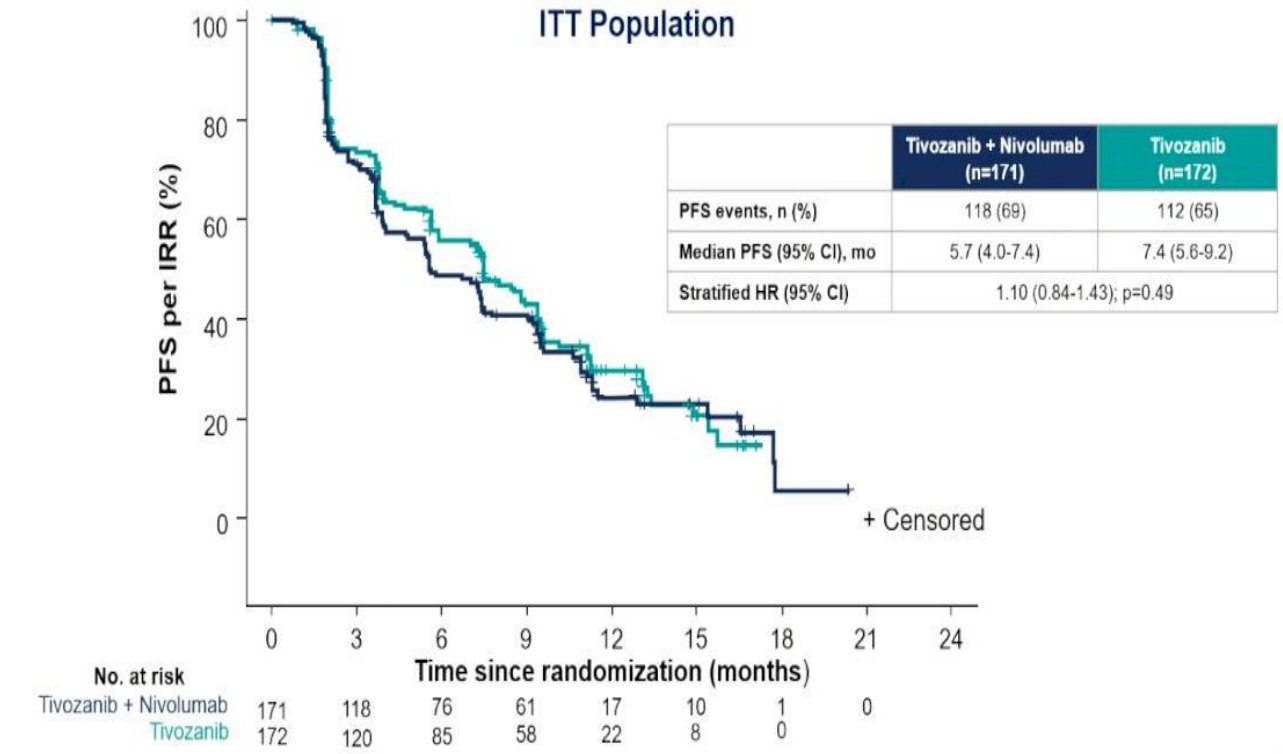


Number at Risk												
Atezolizumab-cabozantinib group	263	259	240	229	215	207	196	157	127	91	50	31
Cabozantinib group	259	247	235	221	207	195	182	145	113	88	50	22

Senere behandlinger til metastatisk nyrekræft

Er der effekt ved at kombinere immunterapi med targeteret behandling efter 1. linje immunterapi?

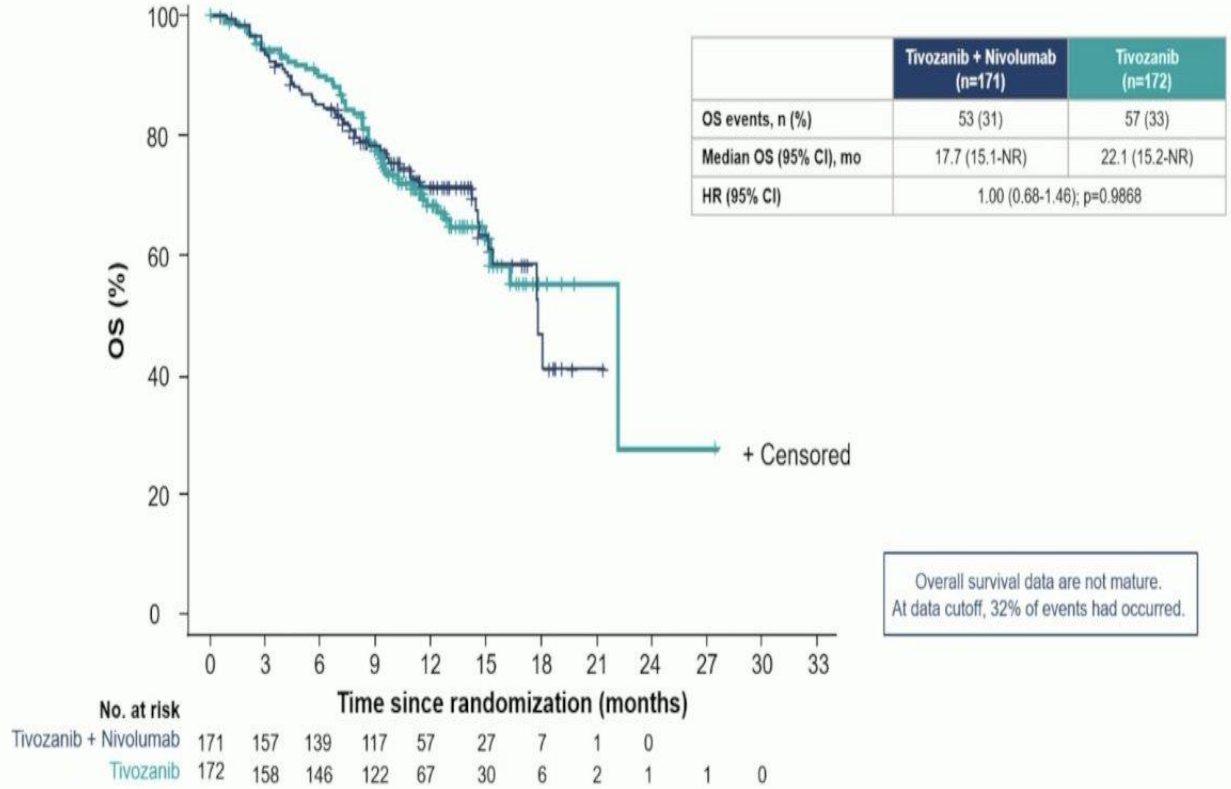
Primary Analysis of Centrally Reviewed PFS (primary endpoint)



	Tivozanib + Nivolumab (n=171)	Tivozanib (n=172)
PFS events, n (%)	118 (69)	112 (65)
Median PFS (95% CI), mo	5.7 (4.0-7.4)	7.4 (5.6-9.2)
Stratified HR (95% CI)	1.10 (0.84-1.43); p=0.49	

Median follow-up was 11.8 months in the tivozanib + nivolumab cohort and 12.5 months in the tivozanib monotherapy arm

Overall Survival



	Tivozanib + Nivolumab (n=171)	Tivozanib (n=172)
OS events, n (%)	53 (31)	57 (33)
Median OS (95% CI), mo	17.7 (15.1-NR)	22.1 (15.2-NR)
HR (95% CI)	1.00 (0.68-1.46); p=0.9868	

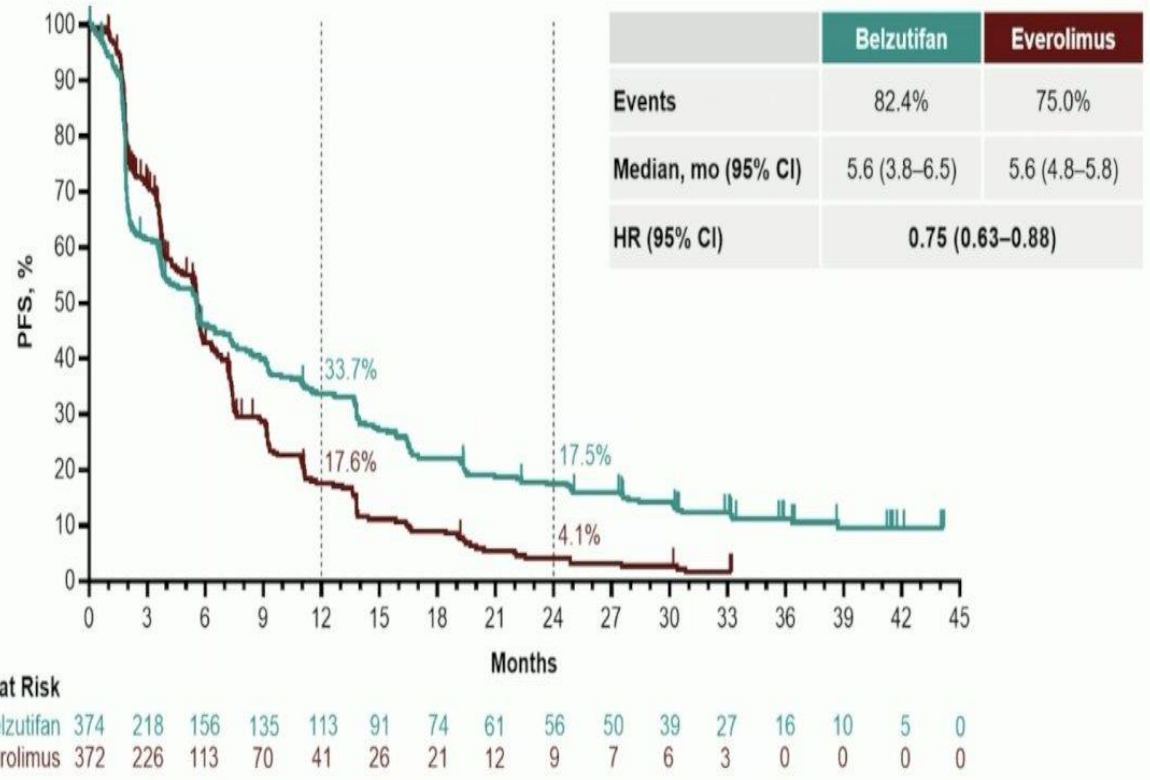
Overall survival data are not mature.
At data cutoff, 32% of events had occurred.

Senere behandlinger til metastatisk nyrekræft

Nye målrettede behandlinger – Belzutifan (HIF-α hæmmer)

LITESPARK-005 Study (NCT04195750)

Primary Endpoint: PFS per RECIST 1.1 by BICR

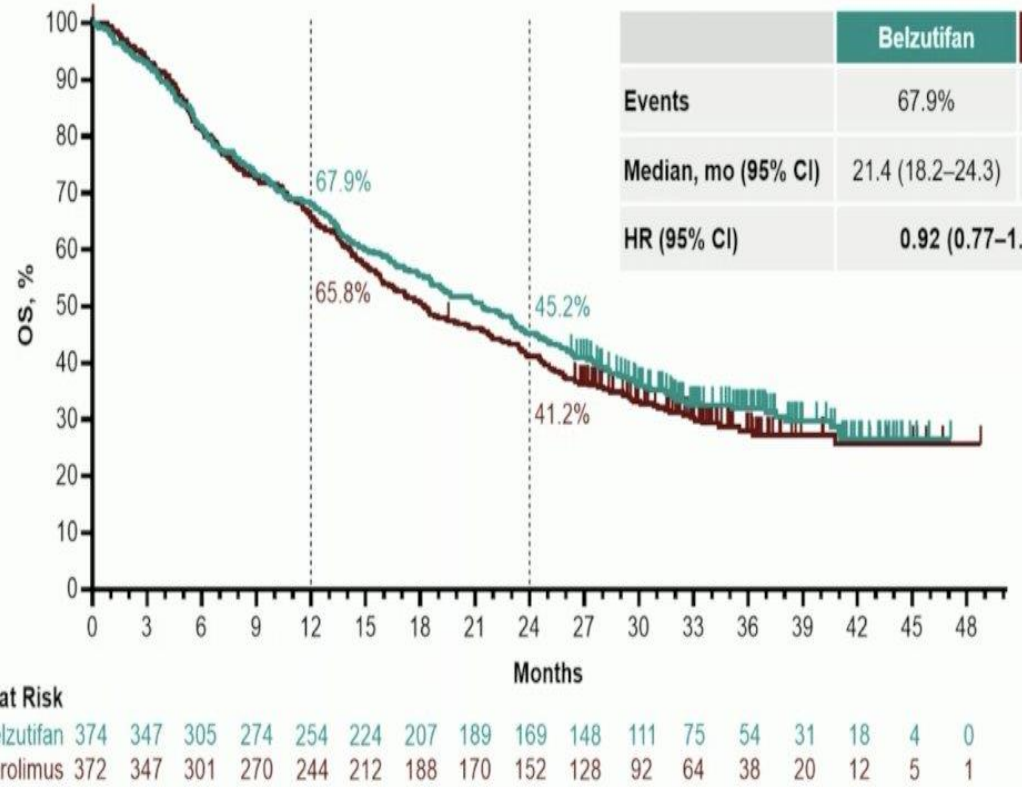


	Belzutifan	Everolimus
Events	82.4%	75.0%
Median, mo (95% CI)	5.6 (3.8–6.5)	5.6 (4.8–5.8)
HR (95% CI)	0.75 (0.63–0.88)	

No. at Risk

Belzutifan	374	218	156	135	113	91	74	61	56	50	39	27	16	10	5	0
Everolimus	372	226	113	70	41	26	21	12	9	7	6	3	0	0	0	0

Primary Endpoint: OS



	Belzutifan	Everolimus
Events	67.9%	69.6%
Median, mo (95% CI)	21.4 (18.2–24.3)	18.2 (15.8–21.8)
HR (95% CI)	0.92 (0.77–1.10); *P*=0.18	

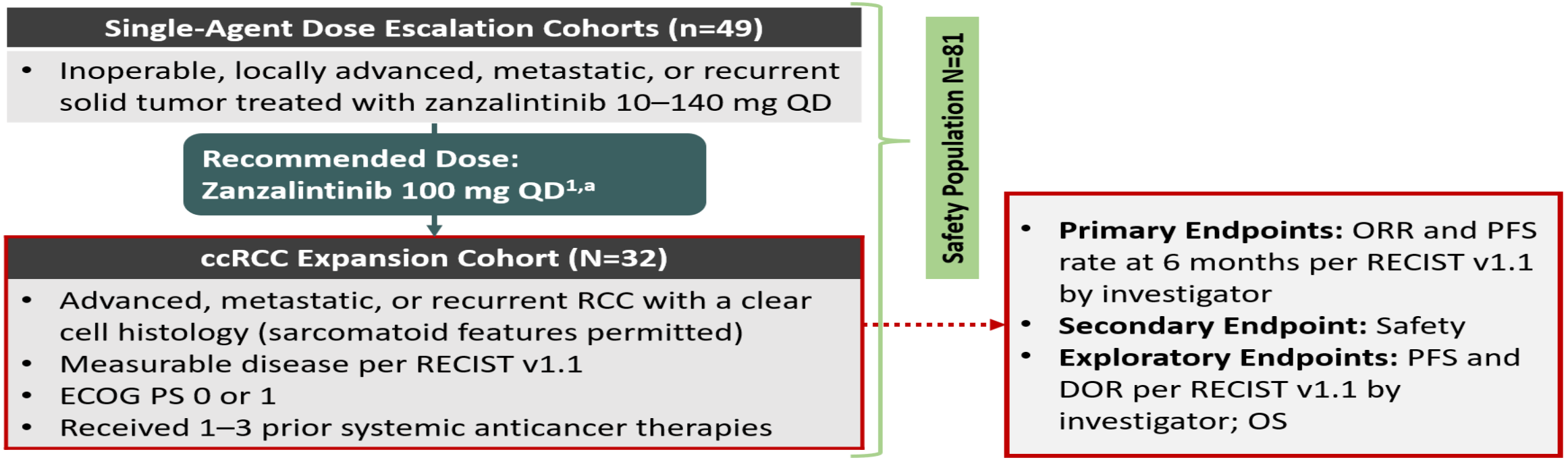
No. at Risk

Belzutifan	374	347	305	274	254	224	207	189	169	148	111	75	54	31	18	4	0
Everolimus	372	347	301	270	244	212	188	170	152	128	92	64	38	20	12	5	1

Senere behandlinger til metastatisk nyrekræft

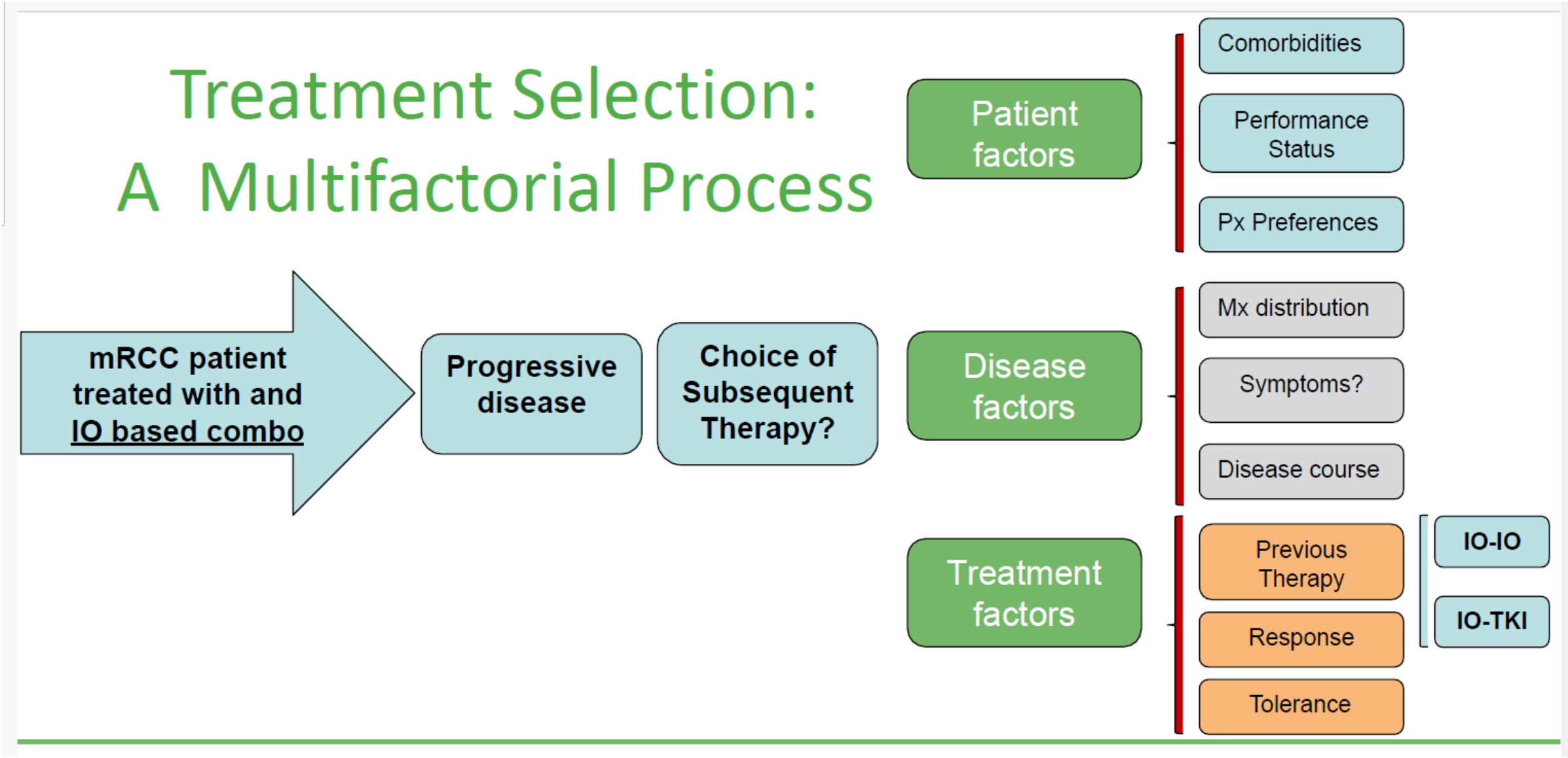
Nye målrettede behandlinger – Zanzalintinib – multi-hæmmer

STELLAR-001: ccRCC Expansion Cohort



1. Sharma M, et al. *Ann Oncol.* 2022;33(7_suppl):Abstract 481P. [a]Treatment until lack of clinical benefit or unacceptable toxicity; treatment post-progression allowed if there was clinical benefit per the investigator.

Senere behandlinger til metastatisk nyrekræft



Spørgsmål