# Adjuvant treatment after surgery for localised renal cell carcinoma:
## *guidelines and early experiences*

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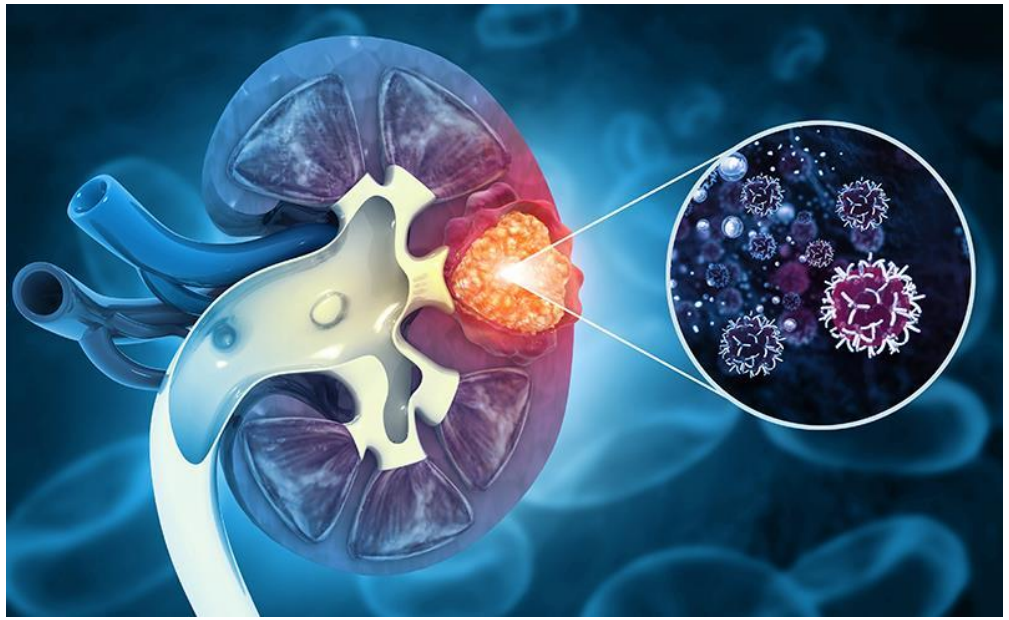

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# Disclosures

Invited lecturer: MSD, Ipsen, Pfizer, BMS

Advisory Board: BMS, Ipsen, MSD, Pfizer, Eisai

Research grant: Ipsen

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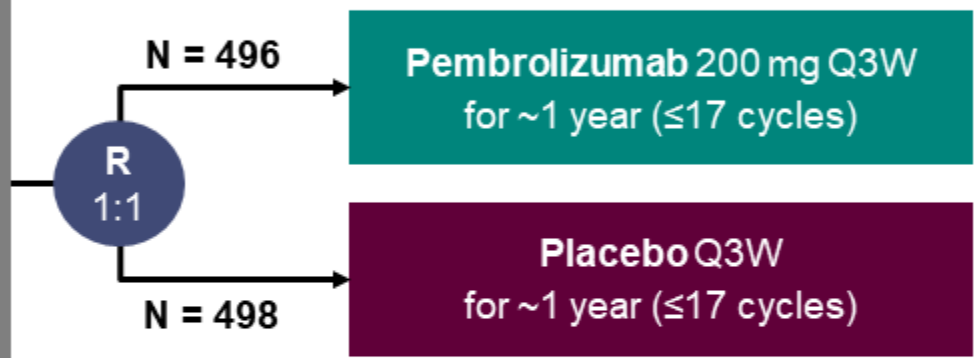
# **Conclusions** Adjuvant immunotherapy in RCC

- 1 yr of pembrolizumab (PD-1 inhibitor)
- Indications: clear cell RCC with T3-T4 /or/N1/or/Grade 4
- Increases DFS (HR 0.72)
- Increases OS (absolute nbrs 5%, HR 0.62)
- MDT!
- Avoid in frail patients
- Careful discussion with pt: pros vs cons
- RWD should be collected to understand feasiibilty/toxicity/benefit

# KEYNOTE-564 Study (NCT03142334)

**Key Eligibility Criteria**

- Histologically confirmed clear cell RCC with no prior systemic therapy
- Surgery ≤12 weeks prior to randomization
- Postnephrectomy intermediate-high risk of recurrence (M0):
  - pT2, grade 4 or sarcomatoid, N0
  - pT3, any grade, N0
- Postnephrectomy high risk of recurrence (M0):
  - pT4, any grade, N0
  - Any pT, any grade, N+
- Postnephrectomy + complete resection of metastasis (M1 NED)
- ECOG PS 0 or 1




**Stratification Factors**

- M stage (M0 vs. M1 NED)
- M0 group further stratified:
  - ECOG PS 0 vs. 1
  - US vs. non-US

**Primary Endpoint**

- Disease-free survival by investigator

**Key Secondary Endpoint**

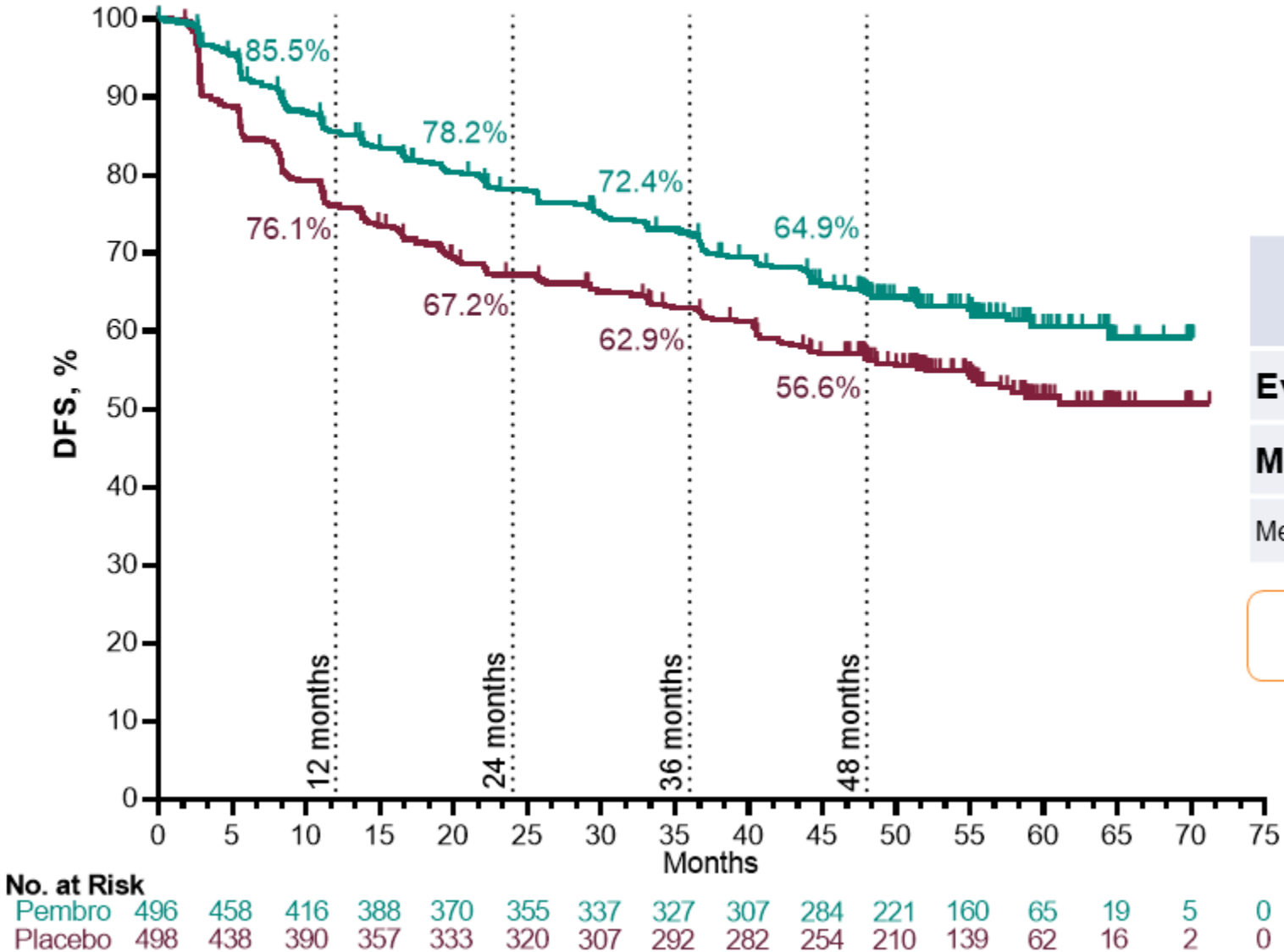
- Overall survival

**Other Secondary Endpoints**

- Safety

NED, no evidence of disease.

# Updated Disease-Free Survival by Investigator, Intention-to-Treat Population




| | Pembro (N = 496) | Placebo (N = 498) |
|---|---|---|
| **Events, n** | 174 | 224 |
| **Median, mo (95% CI)** | NR (NR–NR) | NR (54.9–NR) |

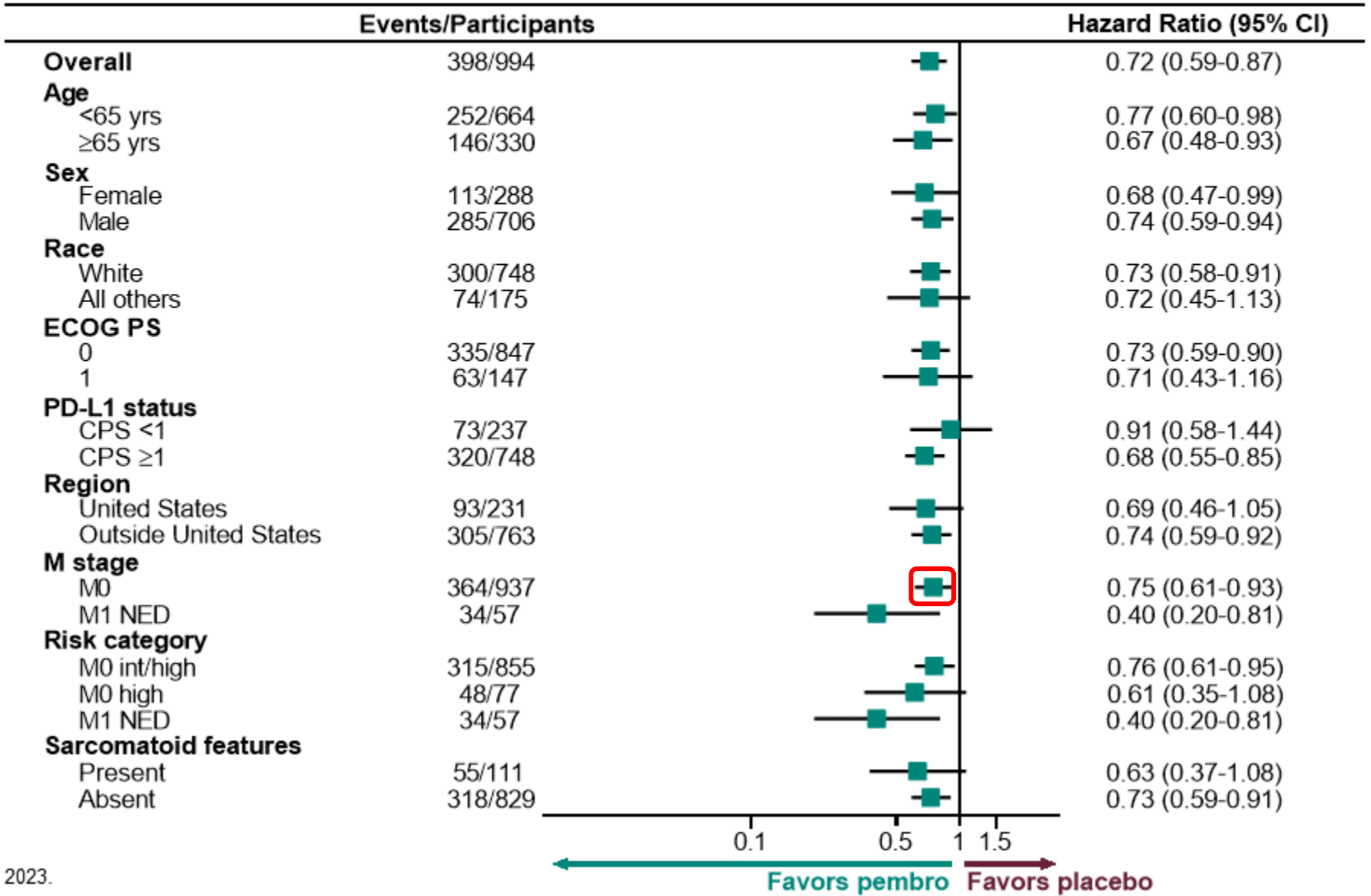
Median follow-up was 57.2 months (range, 47.9–74.5)

**HR 0.72 (95% CI 0.59–0.87)**

Primary DFS endpoint was met at IA1 and was not formally statistically tested thereafter.

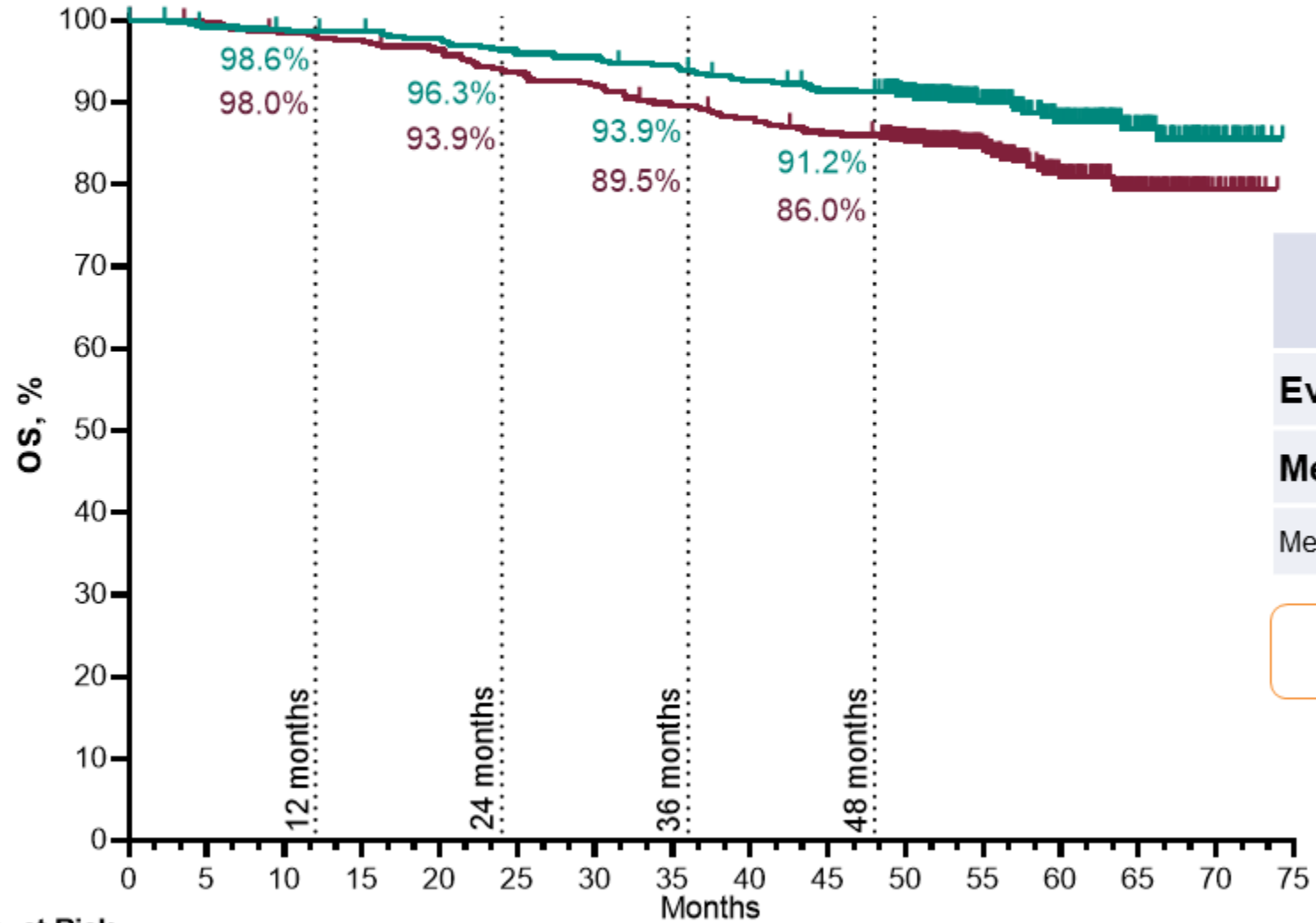
Data cutoff date: September 15, 2023.

# Disease-Free Survival by Subgroups




Data cutoff date: September 15, 2023.

# Overall Survival, Intention-to-Treat Population




**No. at Risk**

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembro | 496 | 489 | 486 | 484 | 479 | 470 | 468 | 462 | 451 | 443 | 397 | 270 | 168 | 81 | 22 | 0 |
| Placebo | 498 | 494 | 487 | 483 | 476 | 463 | 455 | 441 | 433 | 423 | 382 | 248 | 155 | 79 | 22 | 0 |

| | Pembro (N = 496) | Placebo (N = 498) |
|---|---|---|
| **Events, n** | 55 | 86 |
| **Median, mo (95% CI)** | NR (NR–NR) | NR (NR–NR) |

Median follow-up was 57.2 months (range, 47.9–74.5)

**HR 0.62 (95% CI 0.44–0.87); *P* =.002***

* **denotes statistical significance**. P-value boundary for OS at IA3 was 0.0072 (1-sided) per Lan-DeMets O'Brien-Fleming spending approximation α-spending function. As this key secondary endpoint was formally met, any future OS analyses will be descriptive only.

Data cutoff date: September 15, 2023.

The NEW ENGLAND JOURNAL of MEDICINE



ORIGINAL ARTICLE

# Overall Survival with Adjuvant Pembrolizumab in Renal-Cell Carcinoma

**Authors**: Toni K. Choueiri, M.D., Piotr Tomczak, M.D., Ph.D., Se Hoon Park, M.D., Balaji Venugopal, M.D., Tom Ferguson, M.D., Stefan N. Symeonides, M.D., Ph.D., Jaroslav Hajek, M.U.Dr., +26, for the KEYNOTE-564 Investigators* Author Info & Affiliations

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# Aduvant pembrolizumab in RCC in Sweden:

- Recommended since March 2022
- Supposedly implemented in clinical practise nationwide
- In reality, variabel! (uncertainties - patient selection, attitude to the data)

- Stockholm region: 2.4 mil inhabitants
- 4 hospitals perform RCC surgery
- Oncological treatment centralised to Karolinska

- Adjuvant pembro implemented in Stockholm since spring of 2022 (6-week schedule)
- MDT mandatory for pts fulfilling criteria (KN-564)
- Oncology appointment for all these pts (if not obviously too frail)

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# Follow-up Adjuvant Pembrolizumab at Karolinska


- Curatively intended surgery for RCC March 2022 – July 2024
- Matching at least 1 of the trial criteria (T3-T4 / N+ / T2 ISUP 4 / M1 NED)
- Discussed at MDT
- **N=77 patienter** considered for adjuvant treatment and referred to uro-oncologist

<u>Efter assessment by uro-oncologist (*if resident dr, discussed with specialist*)</u>

- n=45 patients (58%) ➡ started adjuvant pembrolizumab
- n=32 patients (42%) ➡ decision to refrain from adjuvant treatment ➡ monitoring

# Feasibility of adjuvant pembrolizumab at Karolinska

- Median follow-up 9.4 months

- **25 of the 45 pts who started on pembrolizumab had completed/discontinued treatment at analysis:**

➢ **52 %** completed treatment **according to plan at 1 yr** (13 out of 25 pt )
[61 % in KN-568]

➢ **32 %** discontinued due to **side effects** (8 out of 25 pt) after a median of 95 days (range 42-209 d)
[21 % in KN-568]**14 patients (31 %) in need of corticosteroid at some point, 1 recived tociluzumab*

➢ **16 %** discontinued due to **recurrence** (4 av 25 pt) after a median of 294 days (range 76-370 d)
[10.5 % in KN-568]

# Treatment-related side effects

34 out of 45 patients had a FU of  at least 3 months and were retrospectively evaluated fort TOX

| Treatment-related toxicity | Number of pts | Percent of pts with FU ≥ 3 mo |
|---|---|---|
| **Any** | 28 | **82 %** (79 %) |
| **Grade 3-4** | 7 | **21 %** (19 %) |
| **Skin** | 16 | **47 %** |
| **Endocrine** | 12 | **35 %** |
| **Reuma** | 8 | **24 %** |
| Fatigue/affected general condition | 7 | 21 % |
| Neurological/psychiatric | 4 | 12 % |
| Cardiac | 3 | 9 % (cardiac MRI normal in 3/3 pt) |
| Pulmonary | 2 | 6 % |
| Hepatic | 4 | 12 % |
| Gastrointestinal | 4 | 12 % |
| Oral | 4 | 12 % |
| Tox involving ≥ 3 organ | 13 | 38 % |

# Reported reasons for refraining from adjuvant treatment despite fulfilling formal criteria (n=32)

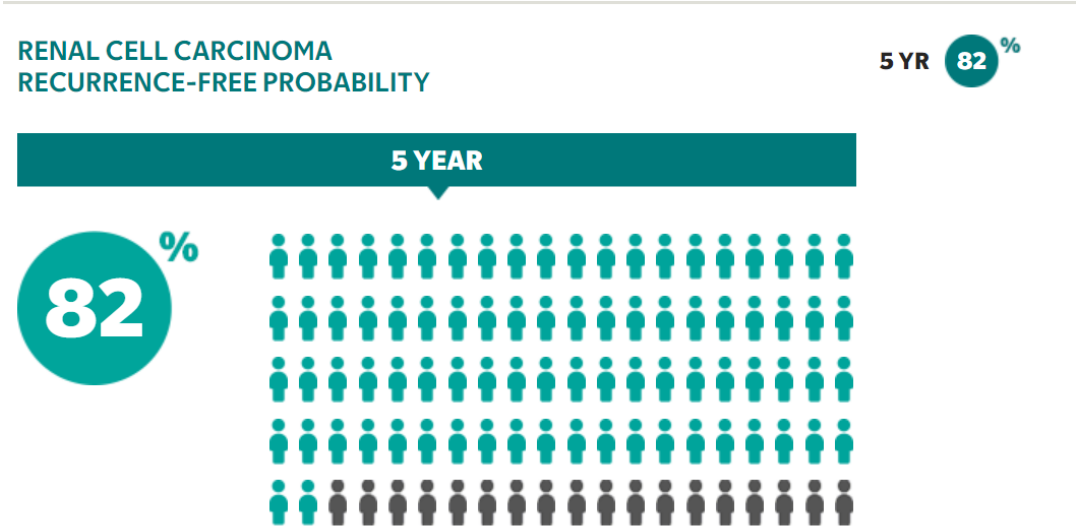
- Comorbidity – 14 patients (44 %)
- Patient's wish folloeing information from uro-oncologist – 11 patients (34 %)
- Inadequate recovery following surgery – 5 patients (16 %)
- Small pulmonary nodules of uncertain siggnificance, mets not ruled out – 6 patients (19 %)
- Favorable tumor biology (low ISUP grade) – 5 patienter (16 %)
- Criteria for adjuvant pembrolizumab not met – 2 patienter (6 %)

What is the
**optimal** patient selection
for adjuvant treatment?

# In the Karolinska cohort, 64 out of 77 patients (83 %) considered for adjuvant pembrolizumab were pT3aN0M0

*Theoretical patient:*

- No or local symptoms only
- Clear cell
- pT3a
- 55 mm

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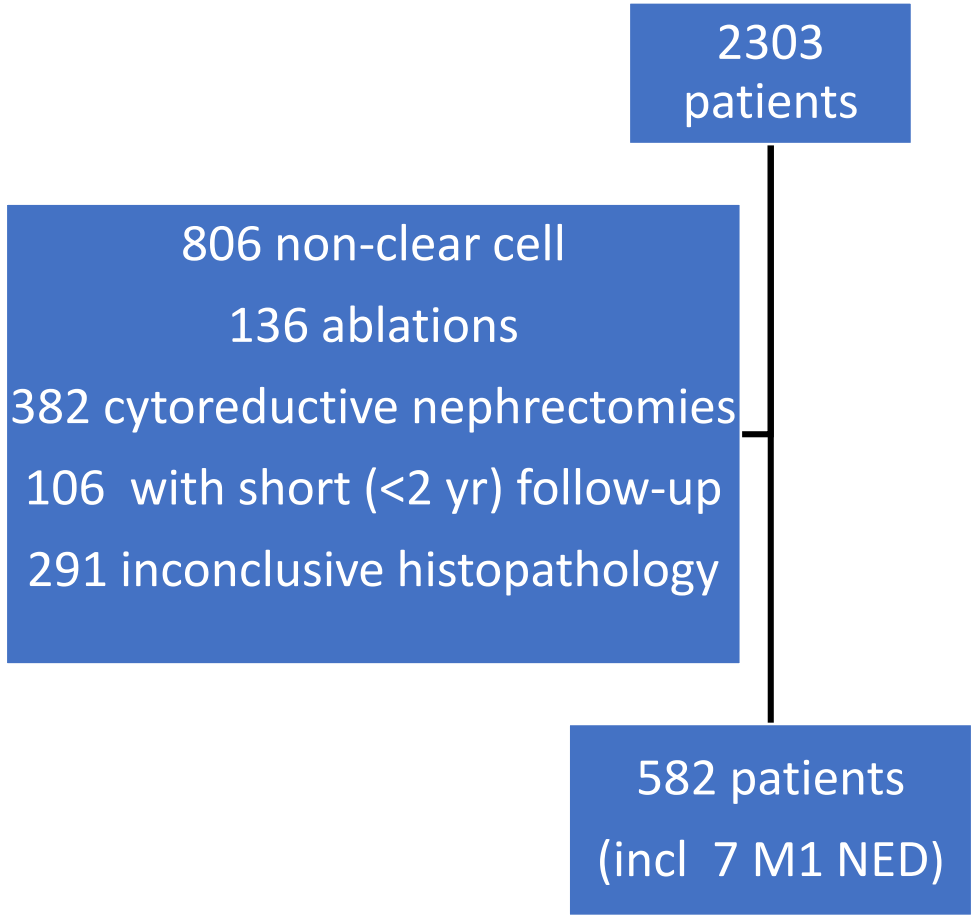
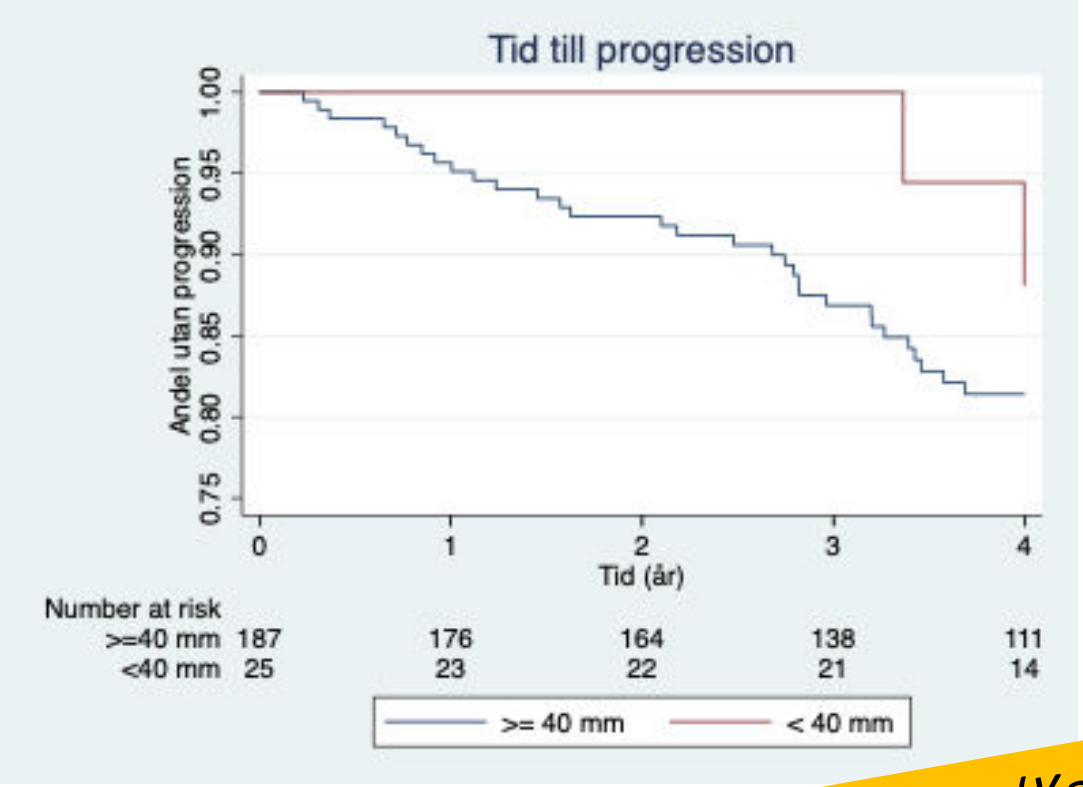
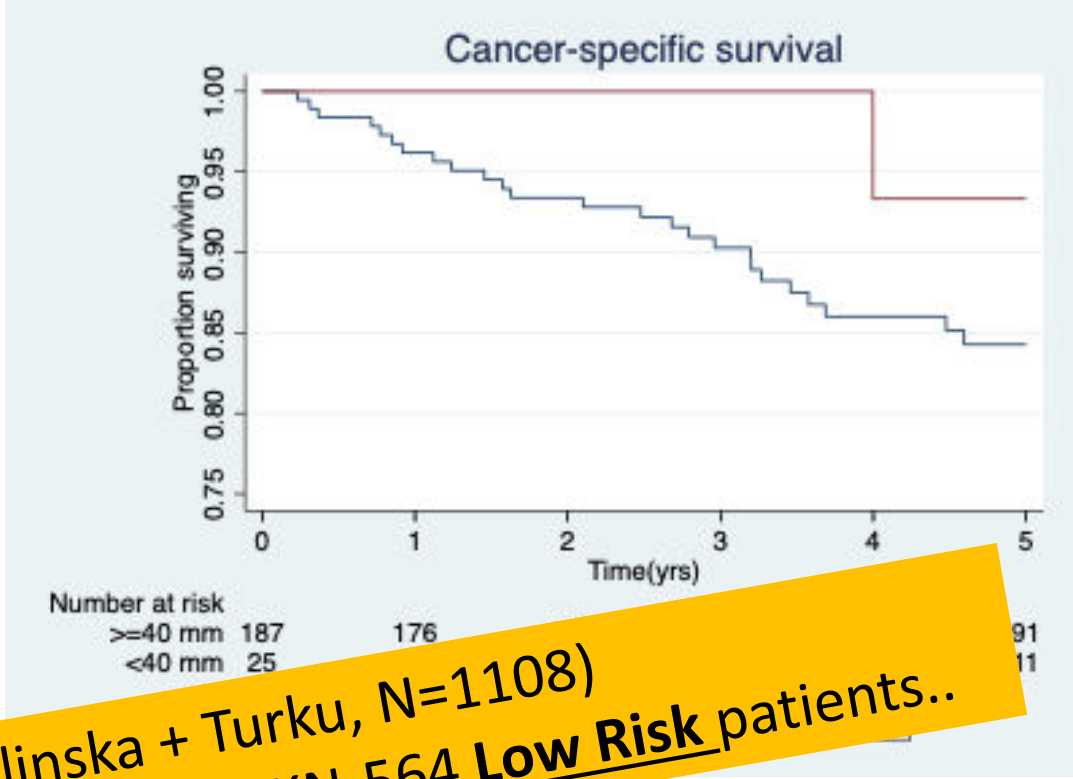
# RCC recurrences at Karolinska

- Institutional database
- Recurrences
- RCC-related deaths
- No adjuvant treat (surgery prior to 2021)
- Median follow-up 5.1 yrs



# Results: pT3a stratified for tumor diameter




➢ According to unpublished data (Karolinska + Turku, N=1108)
**41 % of RCC-related deaths** were seen among KN-564 **Low Risk** patients..

Ref: Brännbäck et al, manuscript in preparation
Competing risk of death in patients with low, intermediate, and high risk of recurrence after radical surgery for clear cell renal cell carcinoma

# Finnish cohort study

- Three viarables associated with recurrence risk:
  - Tumor diameter
  - Tumor grade
  - Microvascular invasion

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## A three-feature prediction model for metastasis-free survival after surgery of localized clear cell renal cell carcinoma

Kalle E. Mattila[1,7✉], Teemu D. Laajala[2,3,7], Sara V. Tornberg[4], Tuomas P. Kilpeläinen[4], Paula Vainio[5], Otto Ettala[6], Peter J. Boström[6], Harry Nisen[4], Laura L. Elo[3,8] & Panu M. Jaakkola[1,3,8]

After surgery of localized renal cell carcinoma, over 20% of the patients will develop distant metastases. Our aim was to develop an easy-to-use prognostic model for predicting metastasis-free survival after radical or partial nephrectomy of localized clear cell RCC. Model training was performed on 196 patients. Right-censored metastasis-free survival was analysed using LASSO-regularized Cox regression, which identified three key prediction features. The model was validated in an external cohort of 714 patients. 55 (28%) and 134 (19%) patients developed distant metastases during the median postoperative follow-up of 6.3 years (interquartile range 3.4–8.6) and 5.4 years (4.0–7.6) in the training and validation cohort, respectively. Patients were stratified into clinically meaningful risk categories using only three features: tumor size, tumor grade and microvascular invasion, and a representative nomogram and a visual prediction surface were constructed using these features in Cox proportional hazards model. Concordance indices in the training and validation cohorts were

What is the **optimal** patient selection?

The question **not just who** is likely to reccur..

..but also **if** that indvidual has a tumor **sensitive** to PD-1 inhibition..

Need for **translational studies in real-world** RCC cohorts!!!


*"I'm not sure what kind of luck this is."*