

**DANSKE KRÆFTFORSKNINGSDAGE 2023**

**Hvordan bliver kræftbehandling  
mere effektiv gennem aktivering  
af immunrespons: Kirurgens  
perspektiv**

Ismail Gögenur, Prof og Overlæge på kirurgisk afd. Sjællands Universitets Hospital

#DKD2023

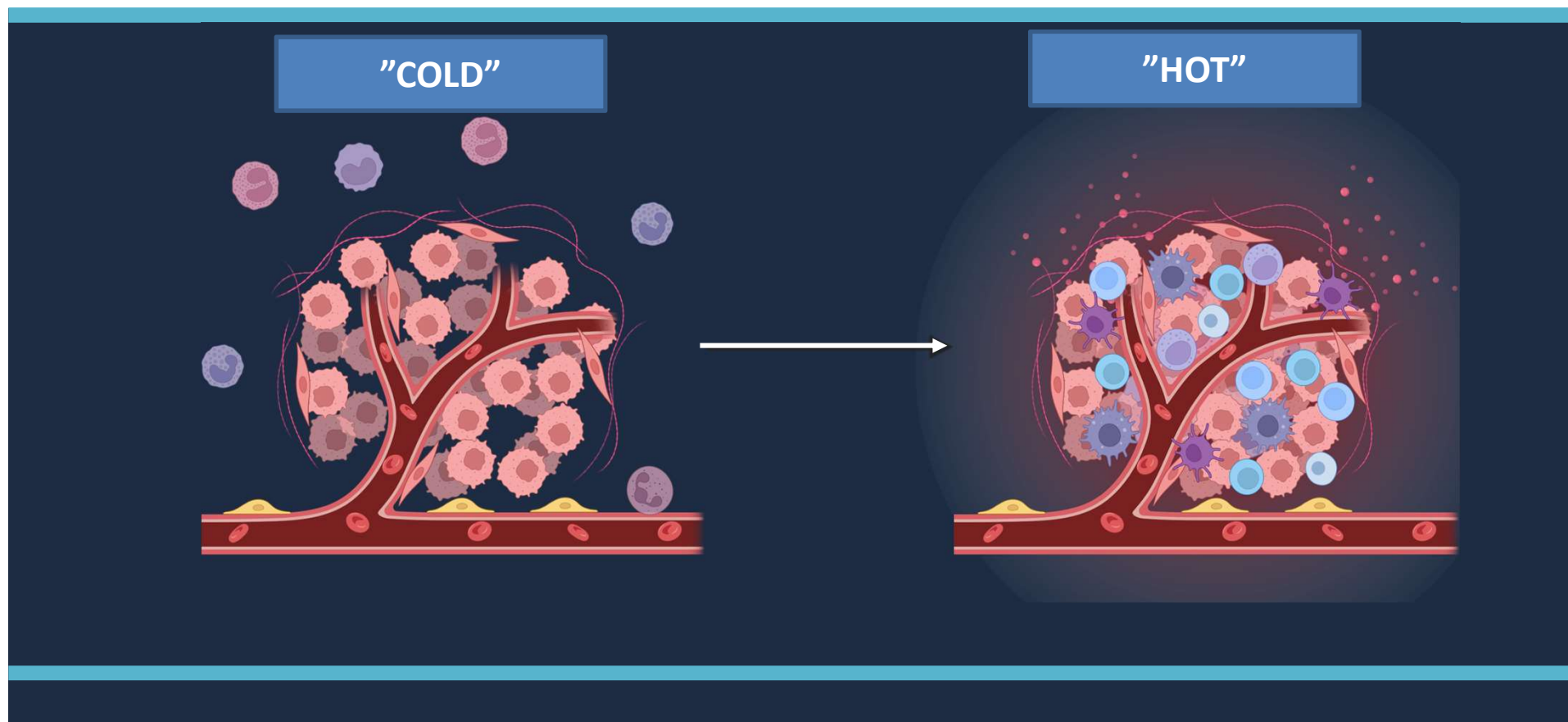
#SamarbejdeOmKræft



CENTER FOR  
SURGICAL  
SCIENCE

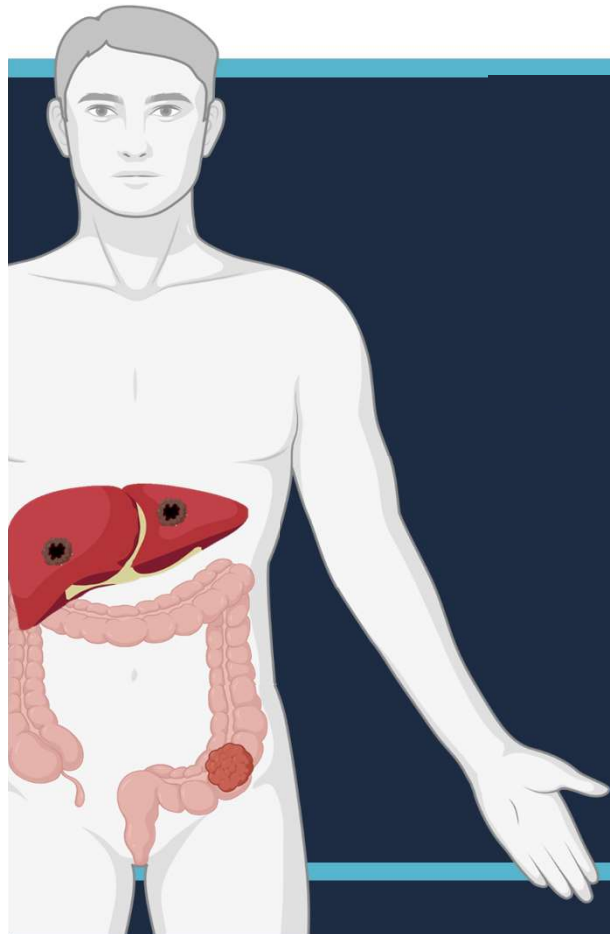
**Mellem 10-60 % => tilbagefald  
af sygdommen efter  
kræftkirurgi!**

# Ændre tumorens fænotype før kirurgi



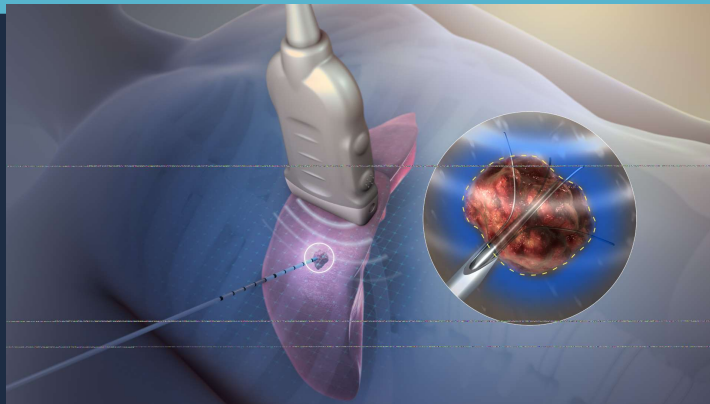
# Window of opportunity





Eksempler på **lokale**  
behandlinger der kan  
igangsætte et  
immunrespons

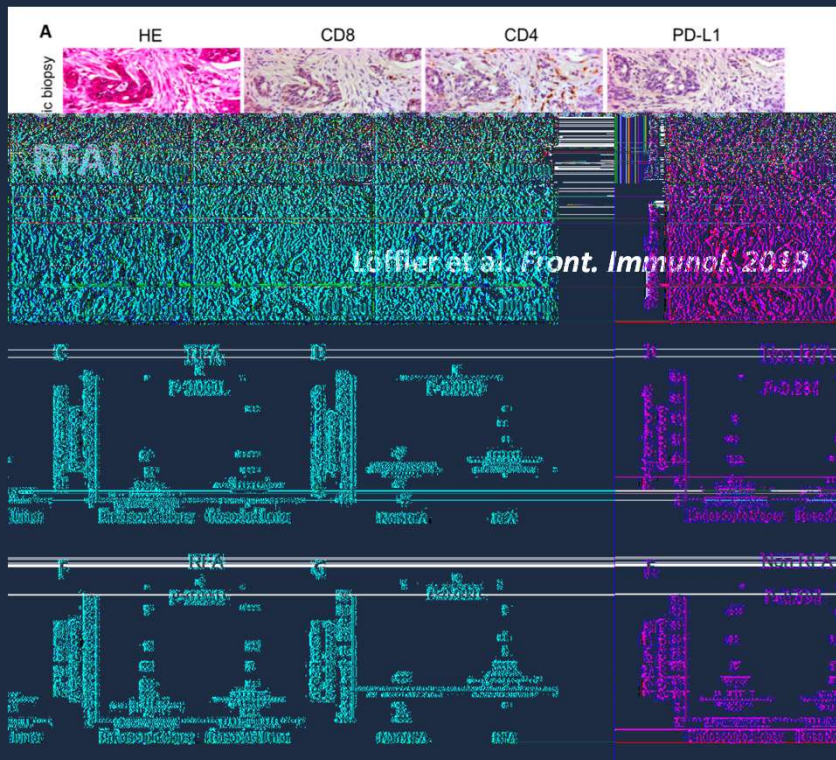
# Ablation før kirurgi



| Level of evidence | Method                 | Mechanism   | Probe Type               | Advantages   | Disadvantages   |
|-------------------|------------------------|---|--------------------------|--|---|
| High              | <b>Radiofrekvens</b>   | Expandable<br>Thermal conduction                                    | Monopolar and multipolar | <ul style="list-style-type: none"> <li>~90% of lesions reachable with RFA</li> <li>No-touch technique</li> <li>Well established</li> </ul>   | <ul style="list-style-type: none"> <li>Heat sink effect limits efficacy in nodules close to major vessels</li> <li>Thermal injury to adjacent structures</li> </ul> |
| Moderate          | <b>Mikrobølger</b>     | Active ablative zone<br>Passive zone                                | Monopolar and multipolar | <ul style="list-style-type: none"> <li>Less susceptible to heat sink effect</li> <li>Faster heating over large volume</li> </ul>             | <ul style="list-style-type: none"> <li>Thermal injury to adjacent structures</li> <li>Size of ablation zone harder to predict</li> </ul>                            |
| Moderate          | <b>Kryoablation</b>    | Argon circulation   | Monopolar and multipolar | <ul style="list-style-type: none"> <li>Real time monitoring of ablation zones</li> <li>Might be an option for tumors &gt; 2 cm</li> </ul>    | <ul style="list-style-type: none"> <li>Risk of bleeding</li> <li>Cryoshock as potentially severe complication</li> </ul>  |
| Low               | <b>Elektroporering</b> | Reversible electroporation probe<br>Nanosized pores in the membrane |                          | <ul style="list-style-type: none"> <li>Non-thermal method, less risk of injury to adjacent structures</li> <li>No-touch technique</li> </ul> | <ul style="list-style-type: none"> <li>Limited clinical experience</li> <li>Cardiac gating necessary</li> </ul>   |

Legend: □ Advantages    □ Disadvantages

# Ablation => betydelig immun aktivering

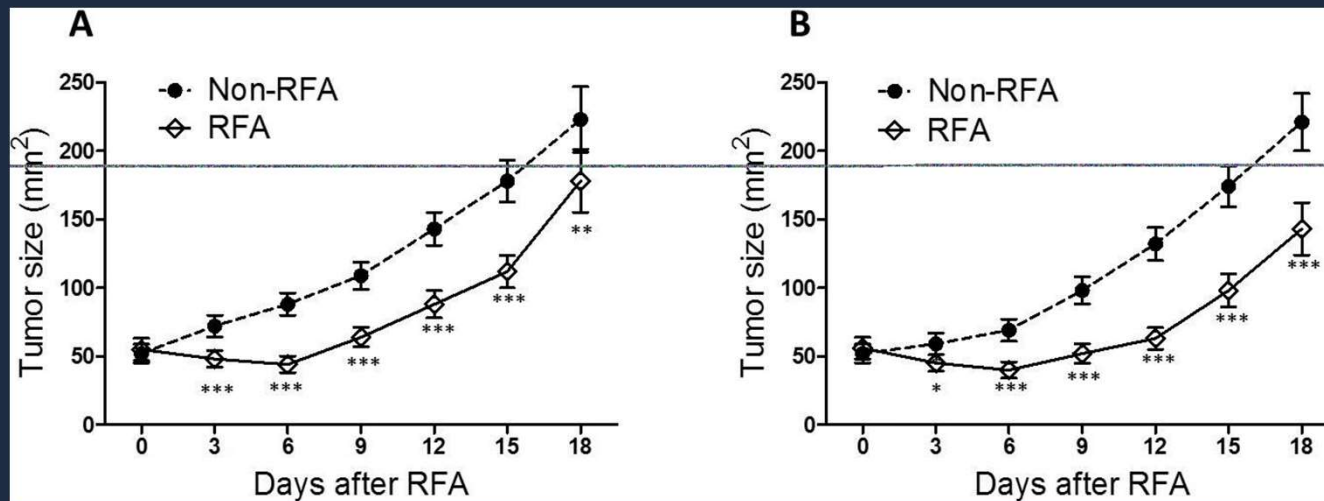


RFA + kirurgi grp (n = 38)  
Kun kirurgi (n = 40)

↑ Tumor infiltrerende lymfocytter  
↑ PD-L1 (tumorceller og T-celler)

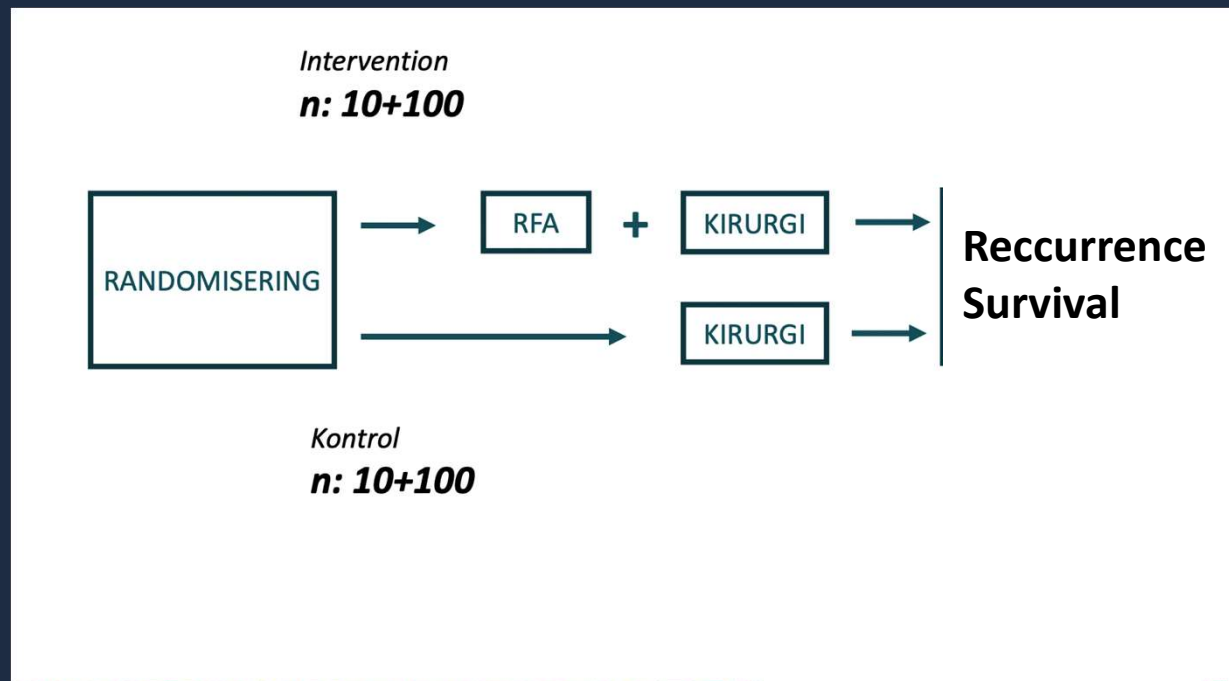
# Ablation + Immunoterapi => abskopal effect?

- RFA i sig selv effekt på kontralateral tumor (CT26 tumor bearing mice) effekt på mikrometastaser?



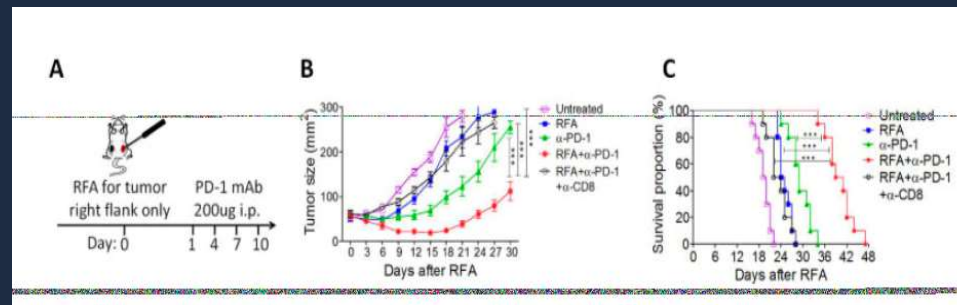
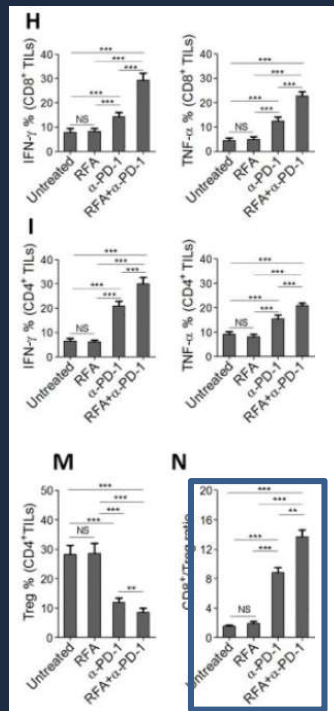


The ISCOLIM Trial:  
Improving Survival of Colo-rectal Liver Metastases  
by RFA-mediated Immuno-stimulation

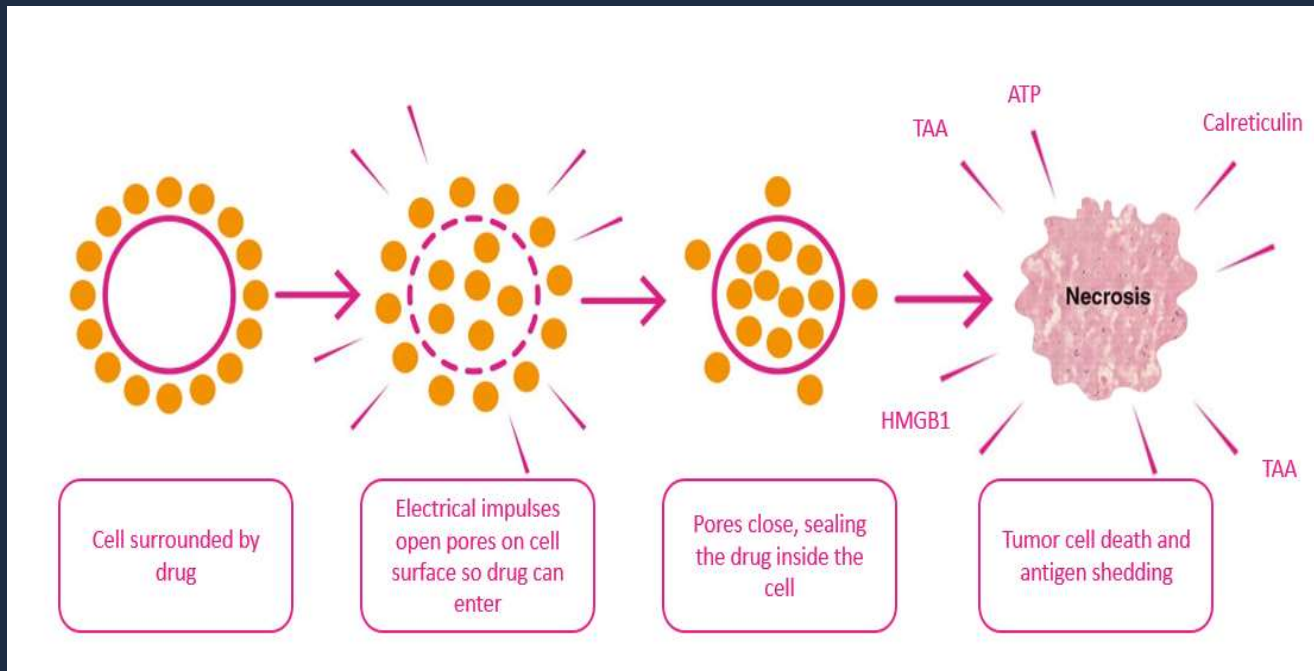


# Ablation + Immunoterapi + kirurgi

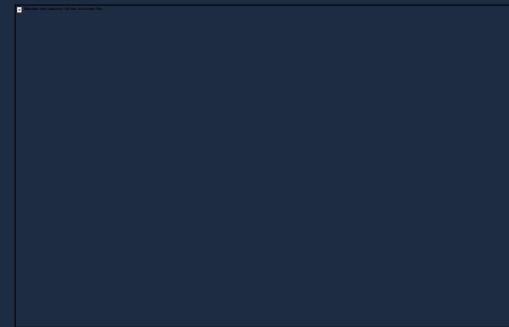
RFA + Immunoterapi synergistisk forbedret T cell-mediated antitumor immunitet!



# Elektroporation en mulighed?



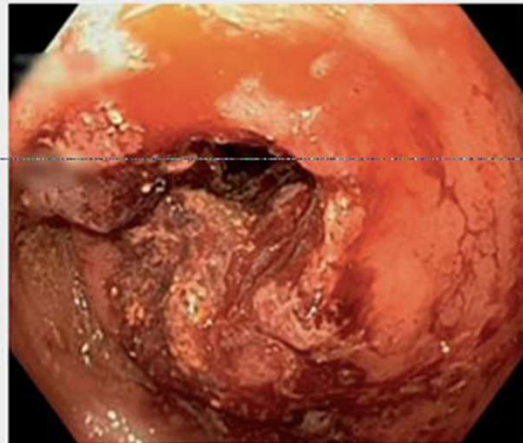
## Elektroporation (bleomycin efter kemoradioterapi)



- N= 16 (8 elektroporation Bleomycin og 8 standard radiokemo)
  - 3 ud af 6 patienter havde komplet patologisk response
  - 1 i watchfull waiting
  - 1 patient sygdomsprogression i ventetiden



# (Ca++)Elektroporation



Baseline



12 weeks follow-up

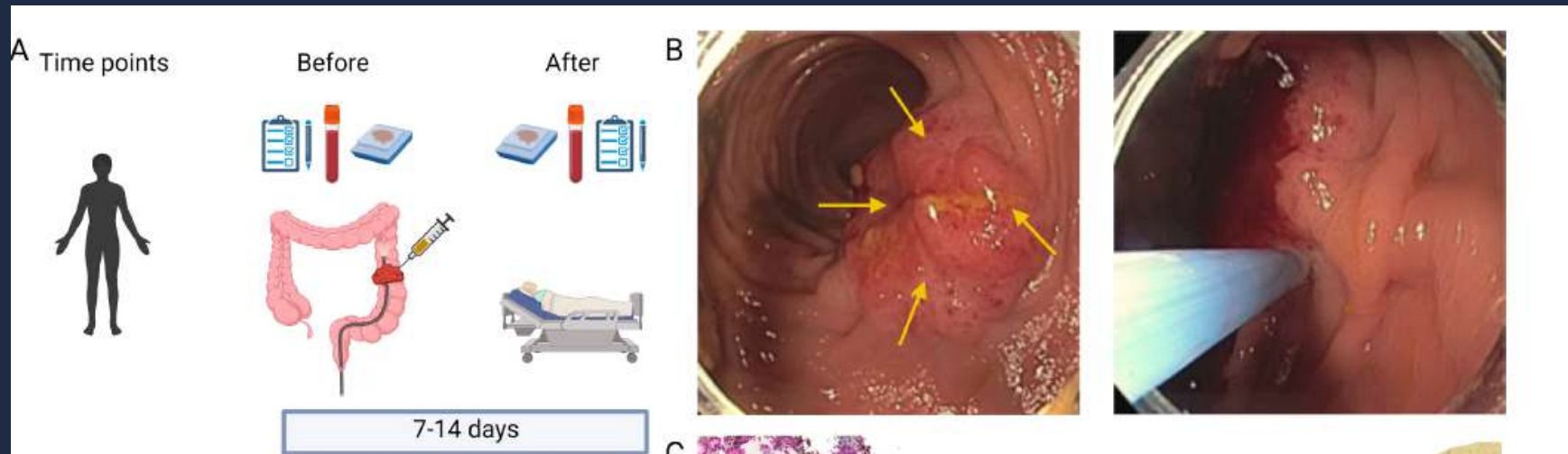


16 weeks follow-up

Broholm et al Endosc Int Open 2023

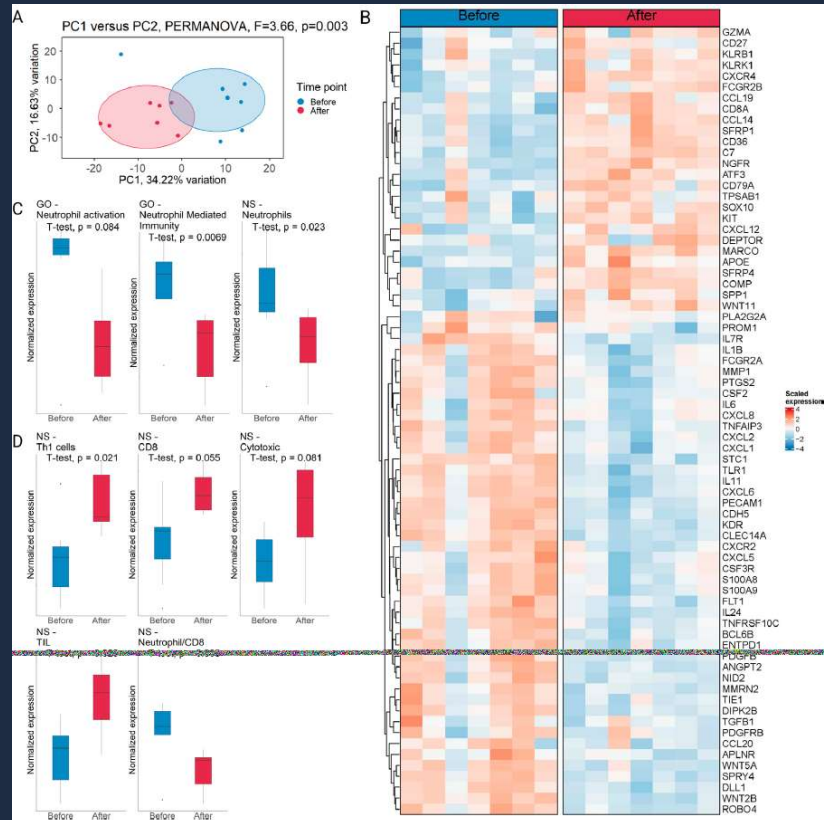


# Influenzavaccine før tarmkræft kirurgi





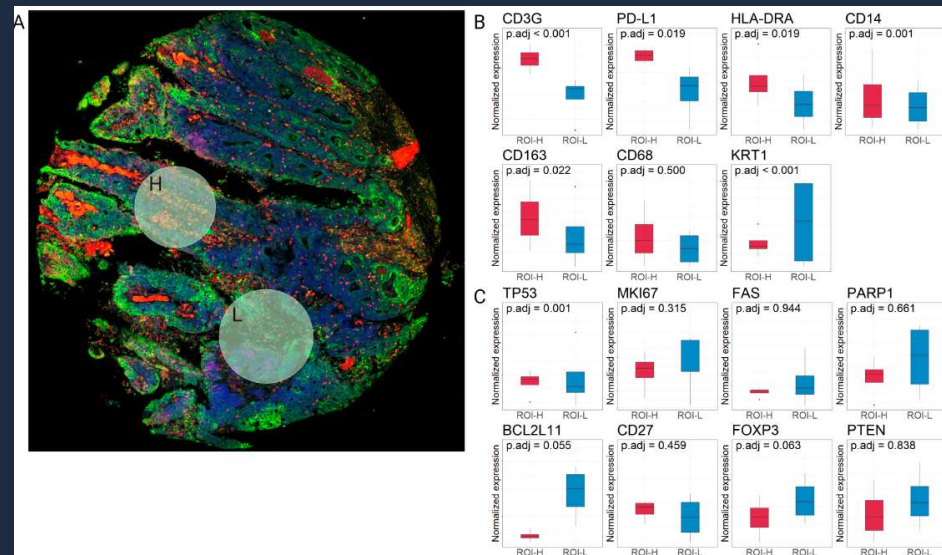
# Influenzavaccine før tarmkræft kirurgi





# Influenzavaccine før tarmkræft kirurgi

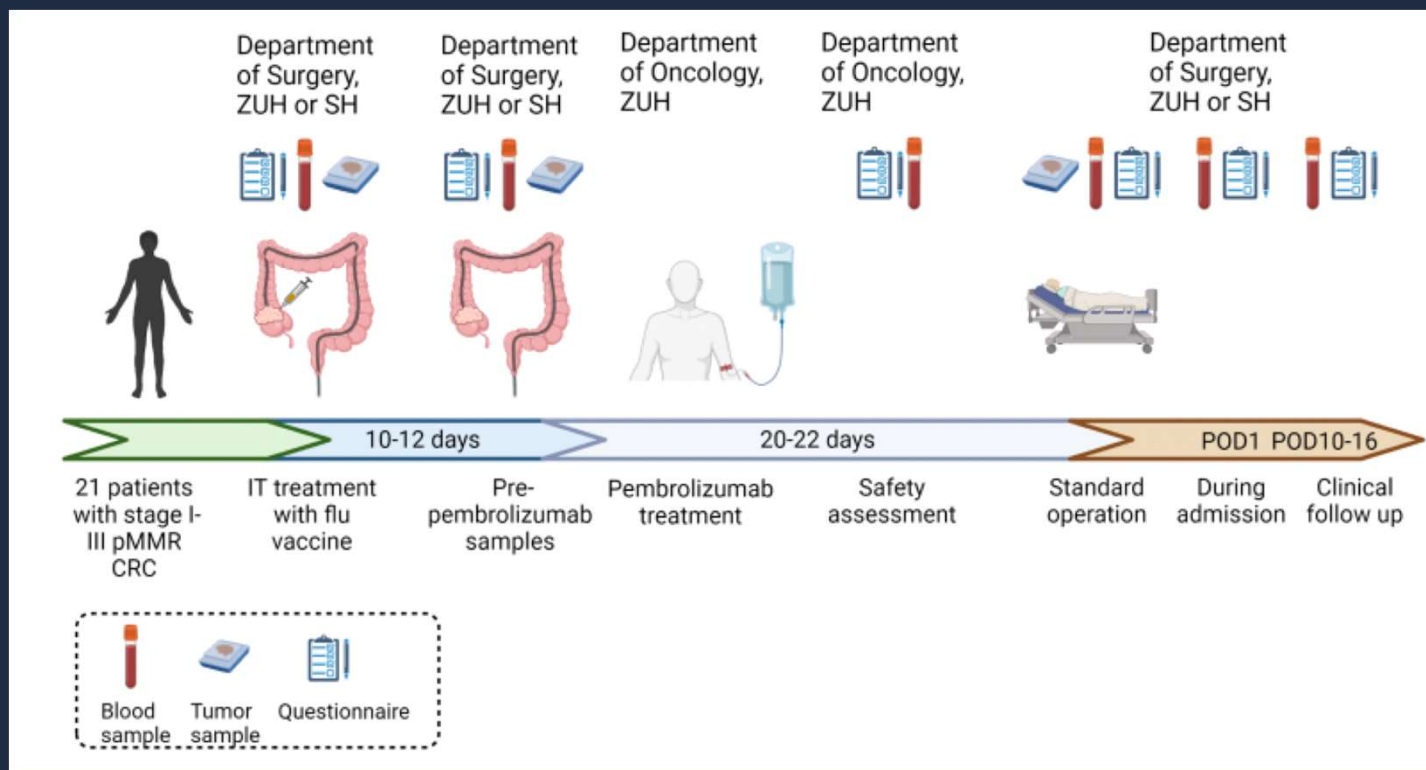
↑ Tumor infiltrerende lymfocytter  
↑ PD-L1

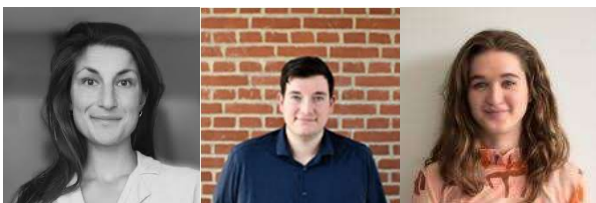




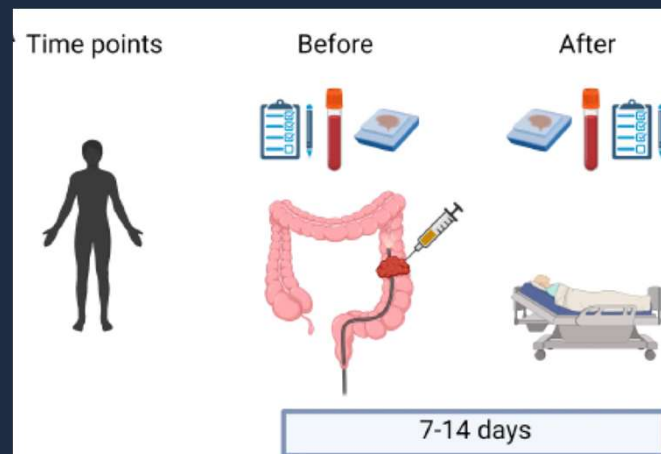


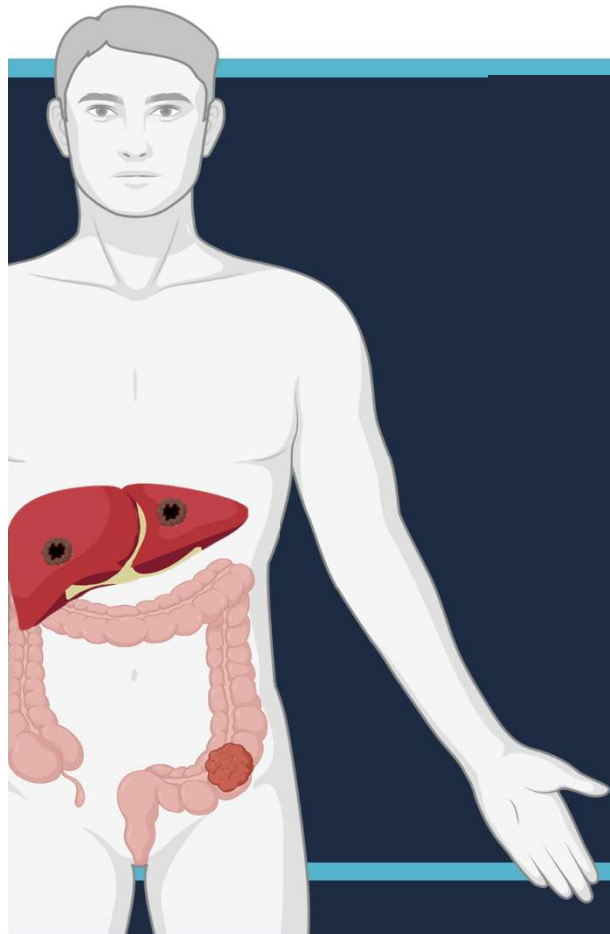
# Inflenzavaccine + immunterapi før tarmkræft kirurgi





- PLATFORMSTUDIE
  - mRNA baseret vaccine
  - Interferon-alfa intratumoralt før tarmkræft kirurgi

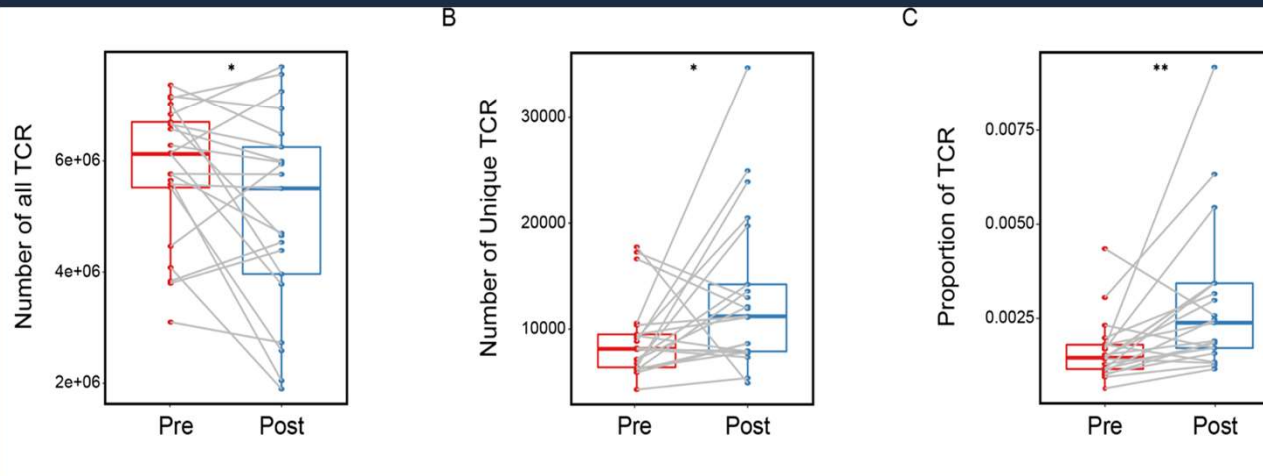
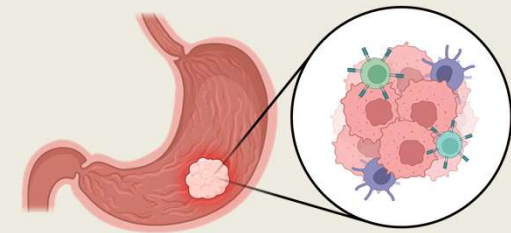




Eksempler **systemiske**  
behandlinger der kan  
igangsætte et  
immunrespons

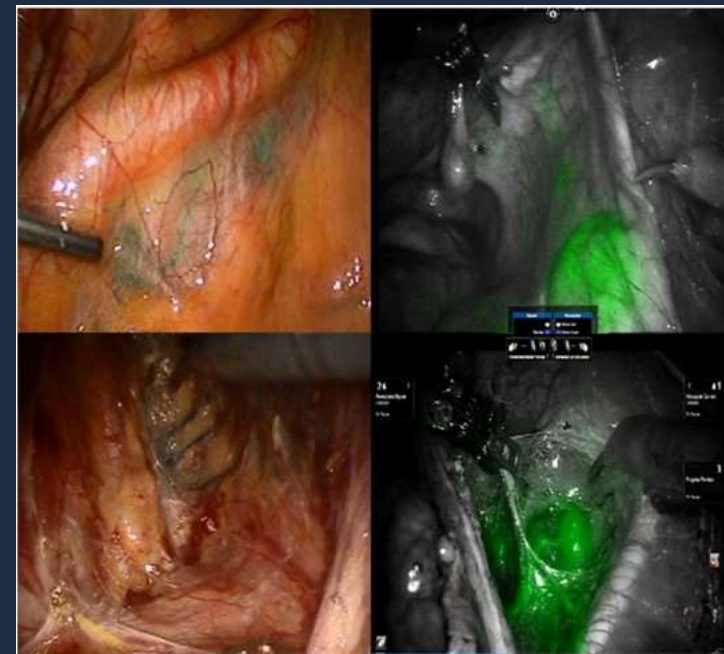
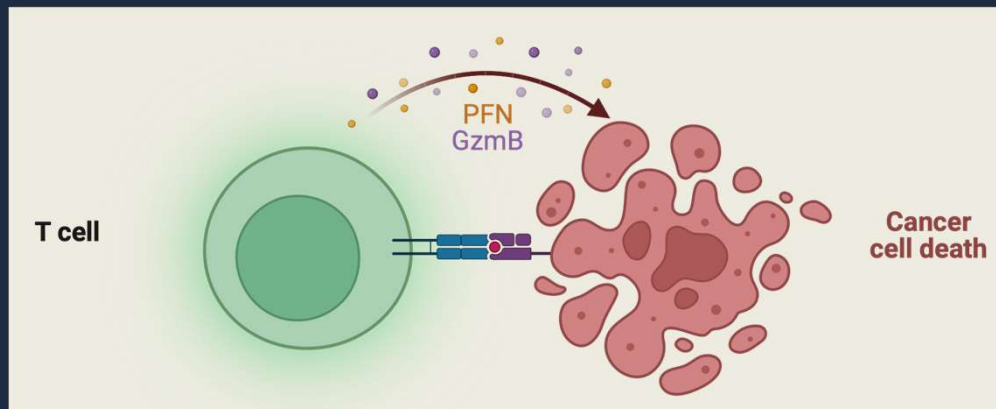
# Neoadjuvant kemoterapi før operation for ventrikel cancer

- ↓ forekomst af Tregs i stroma
- ↑ aktive CD8<sup>+</sup> T celler (↑ granzyme B)
- ↓ CD68 Makrofager



# Neoadjuvant kemoterapi før operation for muskelinvasiv blærecancer

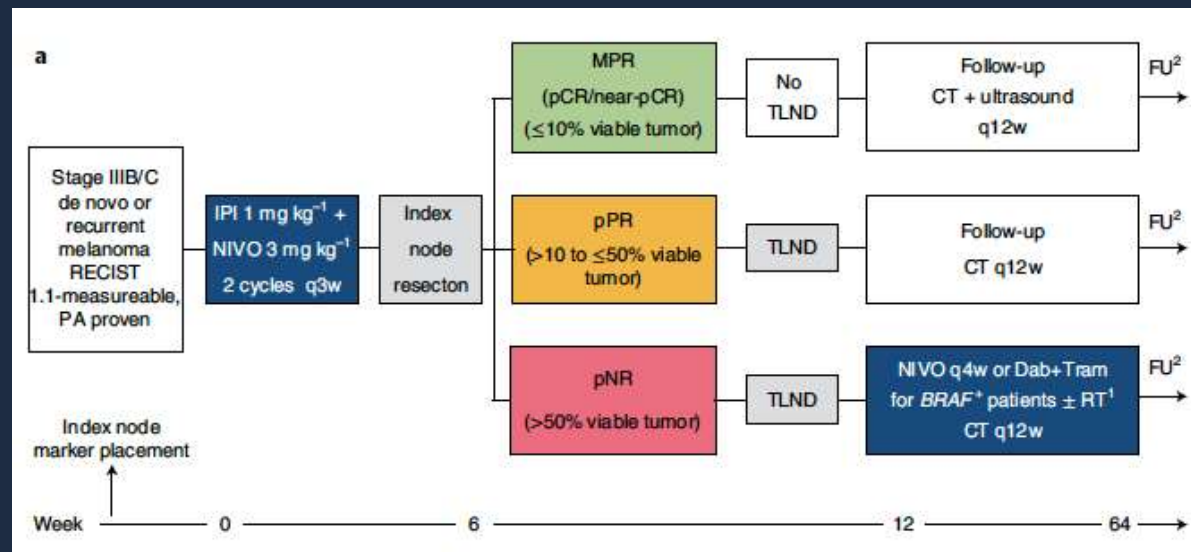
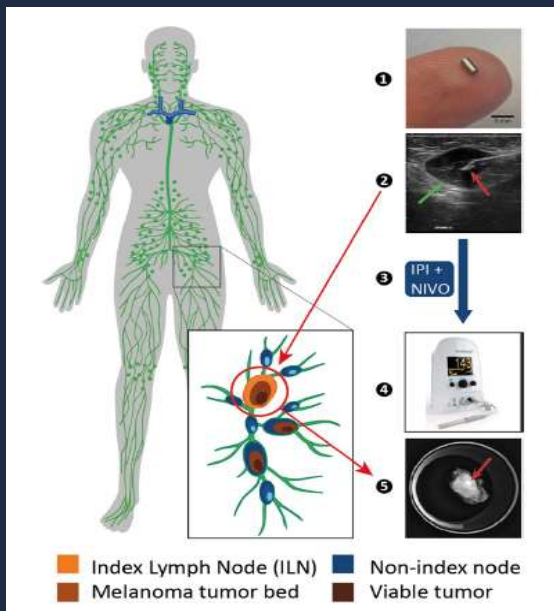
- ↓ forekomst af Tregs i sentinel nodes
- ↑ aktive CD8<sup>+</sup> T celler (udtrykkende granzyme B, perforin)
- ↑ CD4<sup>+</sup> T celler i sentinel nodes



### Surgical removal of the index node marked using magnetic seed localization to assess response to neoadjuvant immunotherapy in patients with stage III melanoma

B. Schermers<sup>1,6</sup>, V. Franke<sup>1</sup>, E. A. Rozeman<sup>2</sup>, B. A. van de Wief<sup>3</sup>, A. Bruining<sup>4</sup>, M. W. Wouters<sup>1</sup>, W. J. van Houdt<sup>1</sup>, B. ten Haken<sup>6</sup>, S. H. Muller<sup>5</sup>, C. Bierman<sup>3</sup>, T. J. M. Ruers<sup>1,6</sup>, C. U. Blank<sup>2</sup> and A. C. J. van Akkooi<sup>1</sup>

### Personalized response-directed surgery and adjuvant therapy after neoadjuvant ipilimumab and nivolumab in high-risk stage III melanoma: the PRADO trial



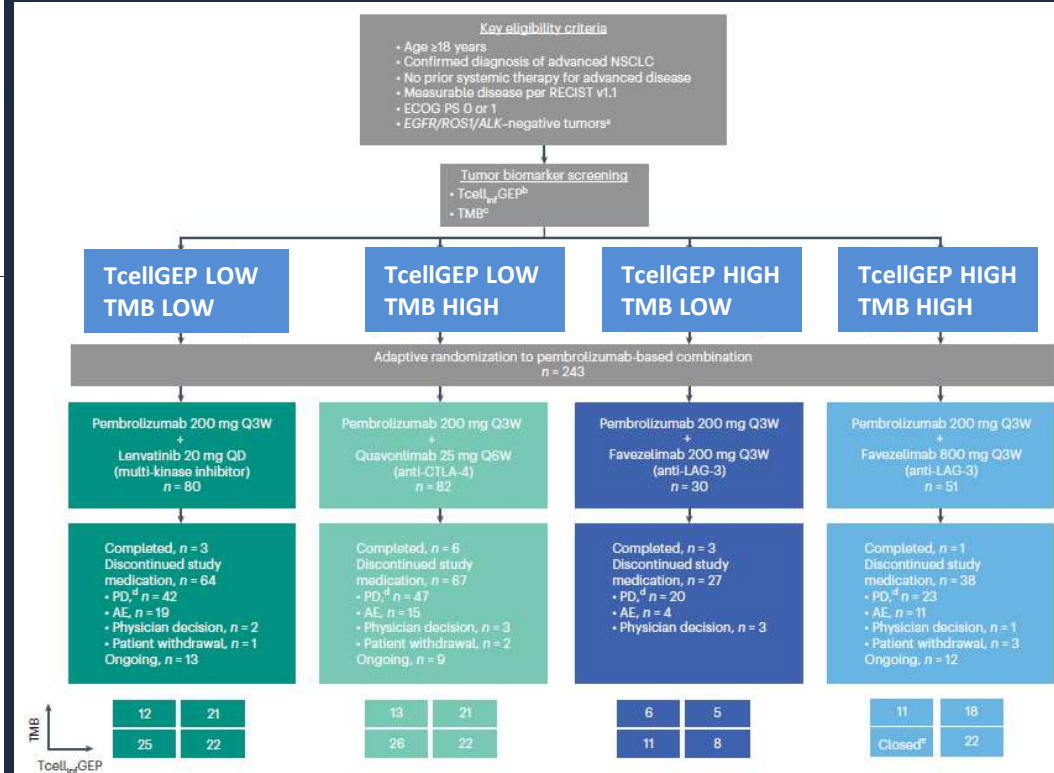
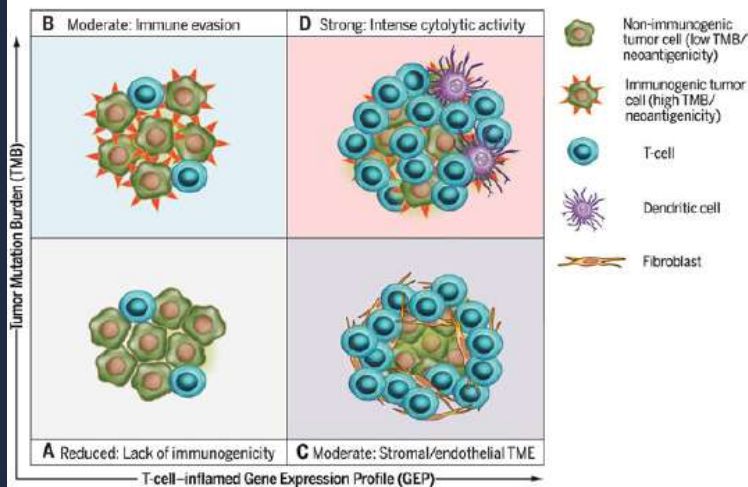
# Upfront biomarkør analyse inden immunterapi ved lungekræft

nature medicine

Article

<https://doi.org/10.1038/s41591-023-02385-6>

## Biomarker-directed, pembrolizumab-based combination therapy in non-small cell lung cancer: phase 2 KEYNOTE-495/KeyImPaCT trial interim results



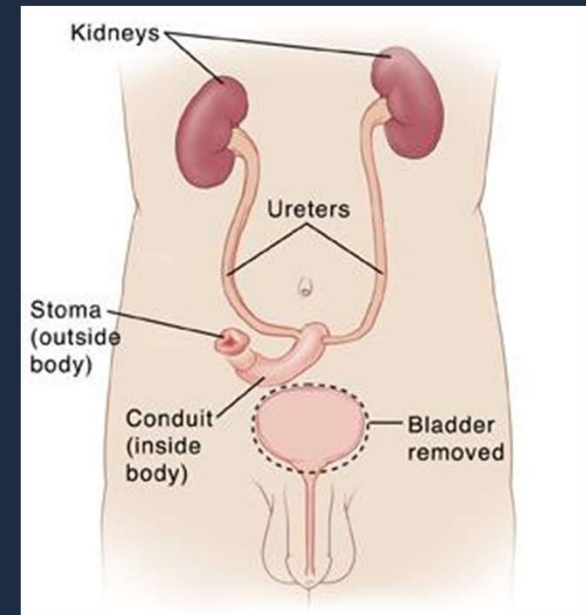
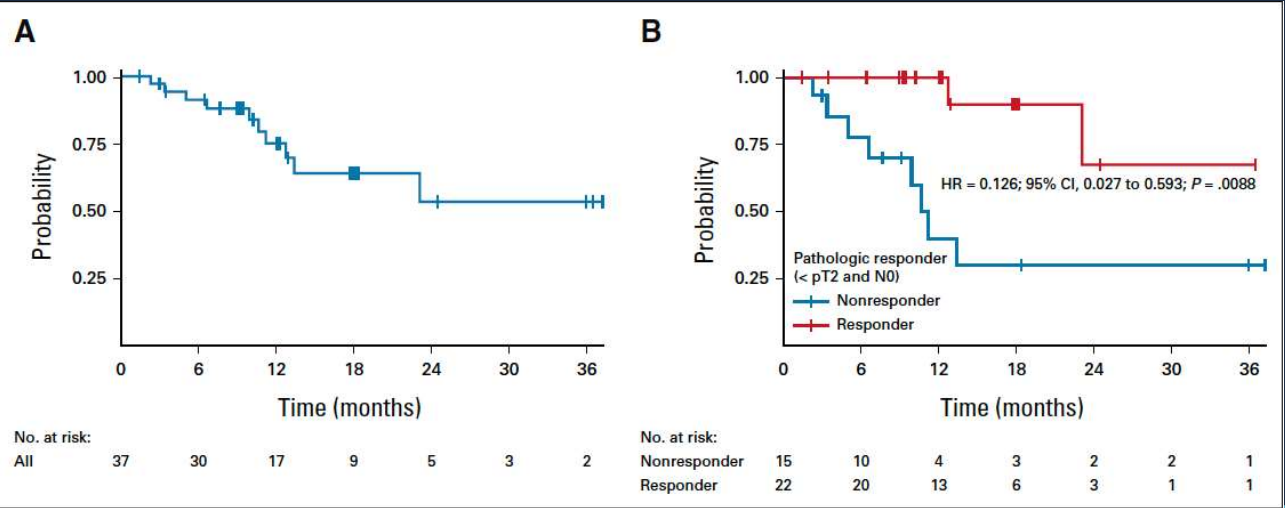
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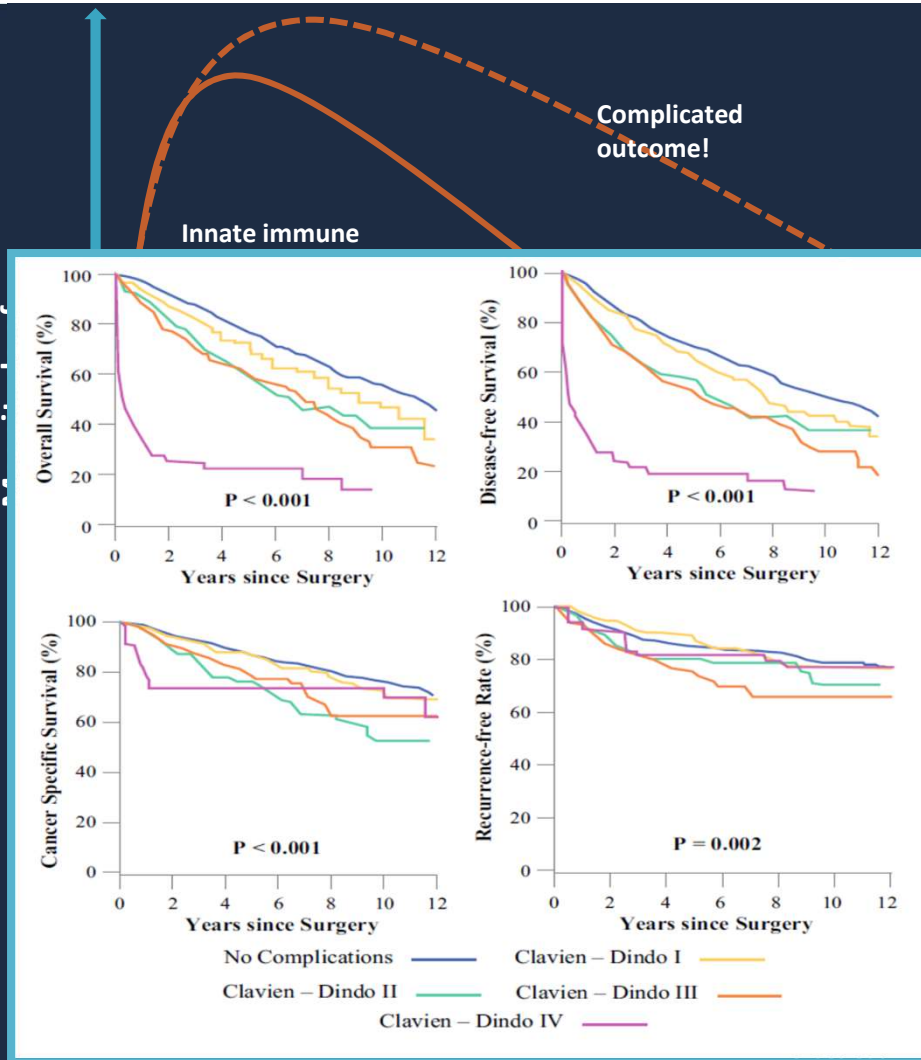
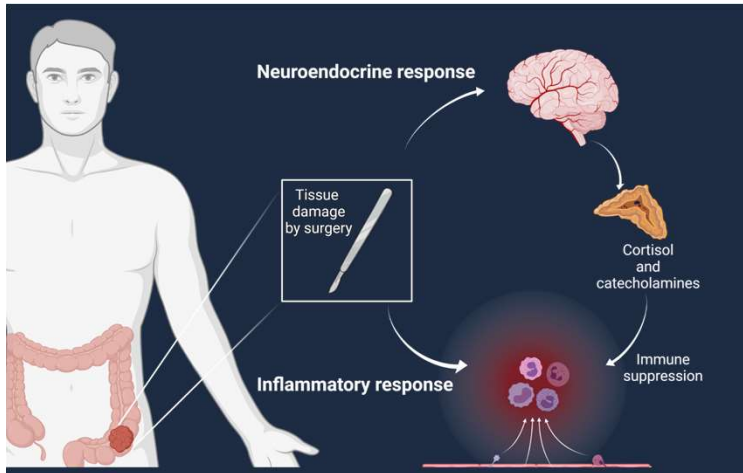
Gutierrez et al, Nat Med (2023)

# Neoadjuvant kemoterapi + immunterapi før operation for muskelinvasiv blærecancer (T2-4aN0/XM0)

- 56 % havde <pT2N0
- 36 % havde pT0N0 på operationstidspunktet



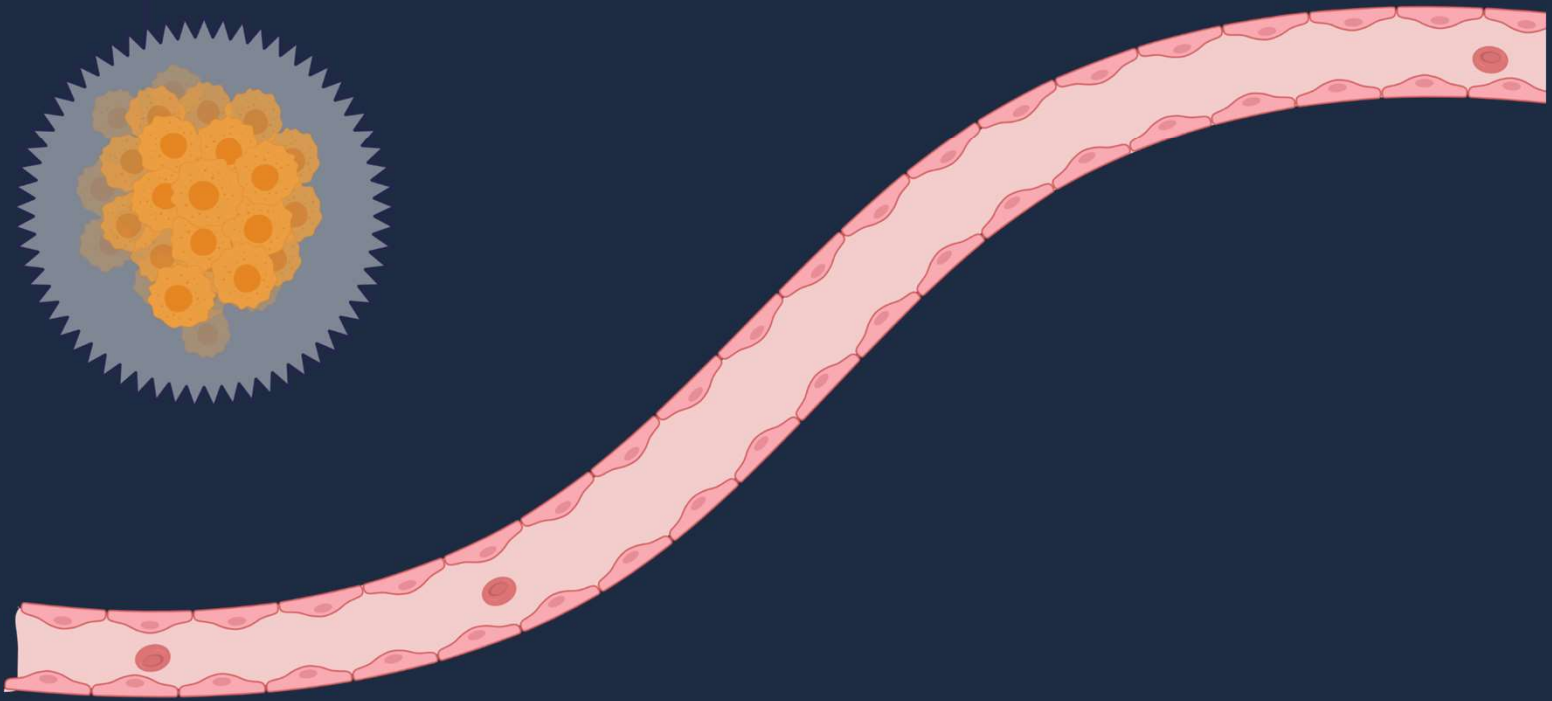
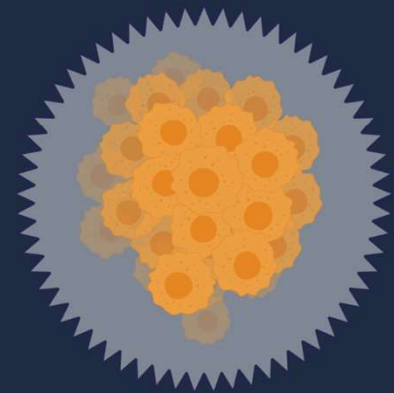


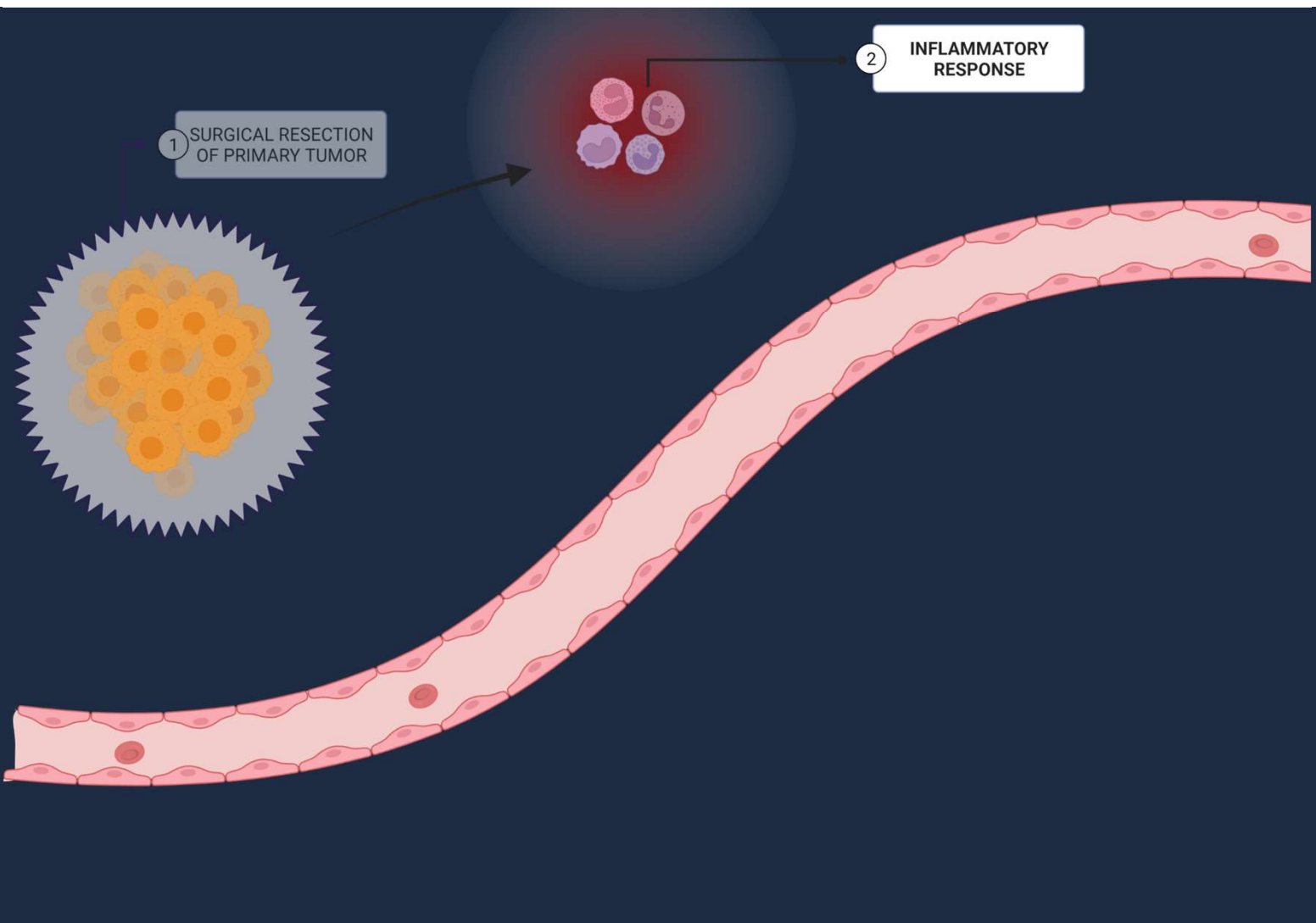


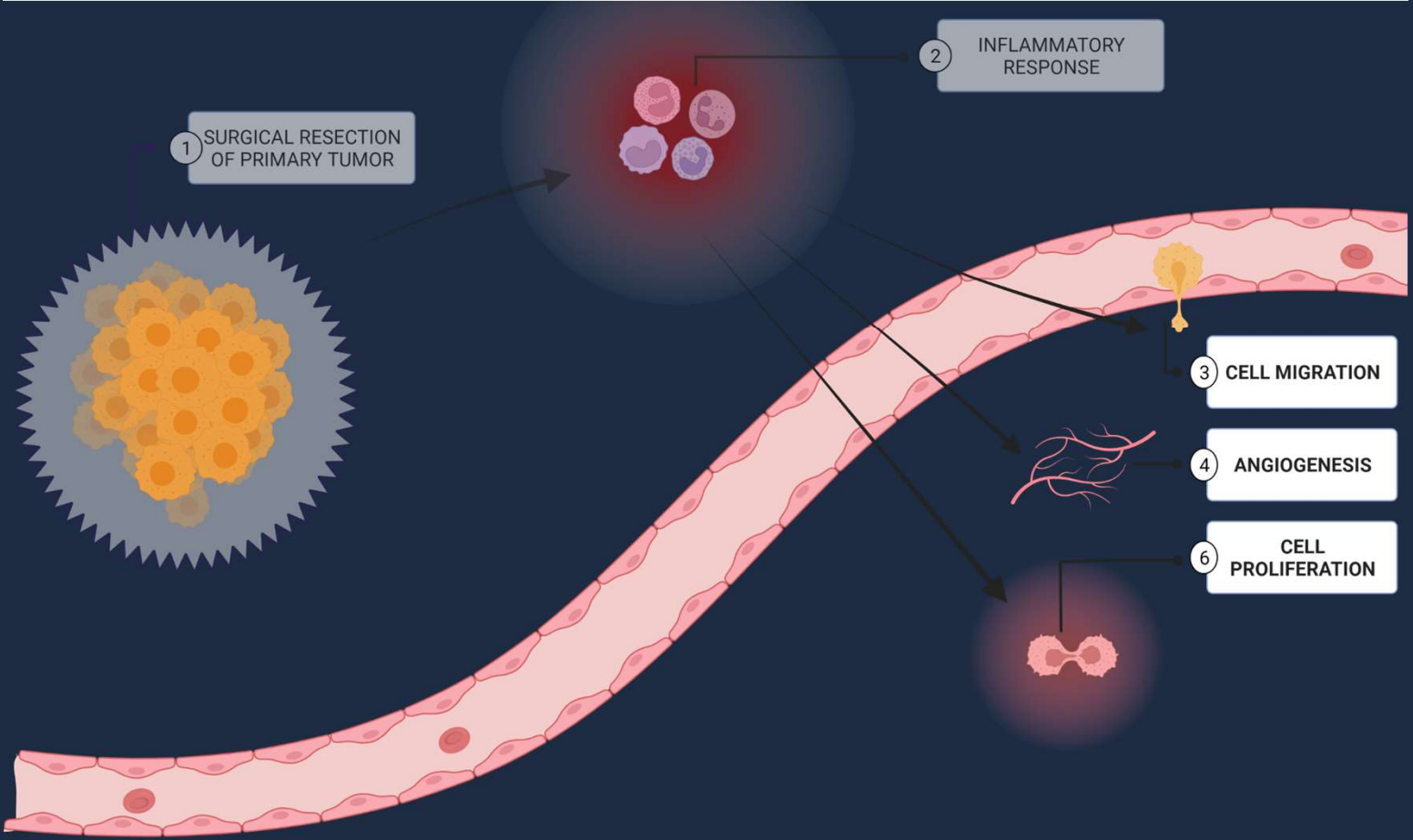
N=2266, whereof 669 (30%) had at least 1 Postoperative Complication

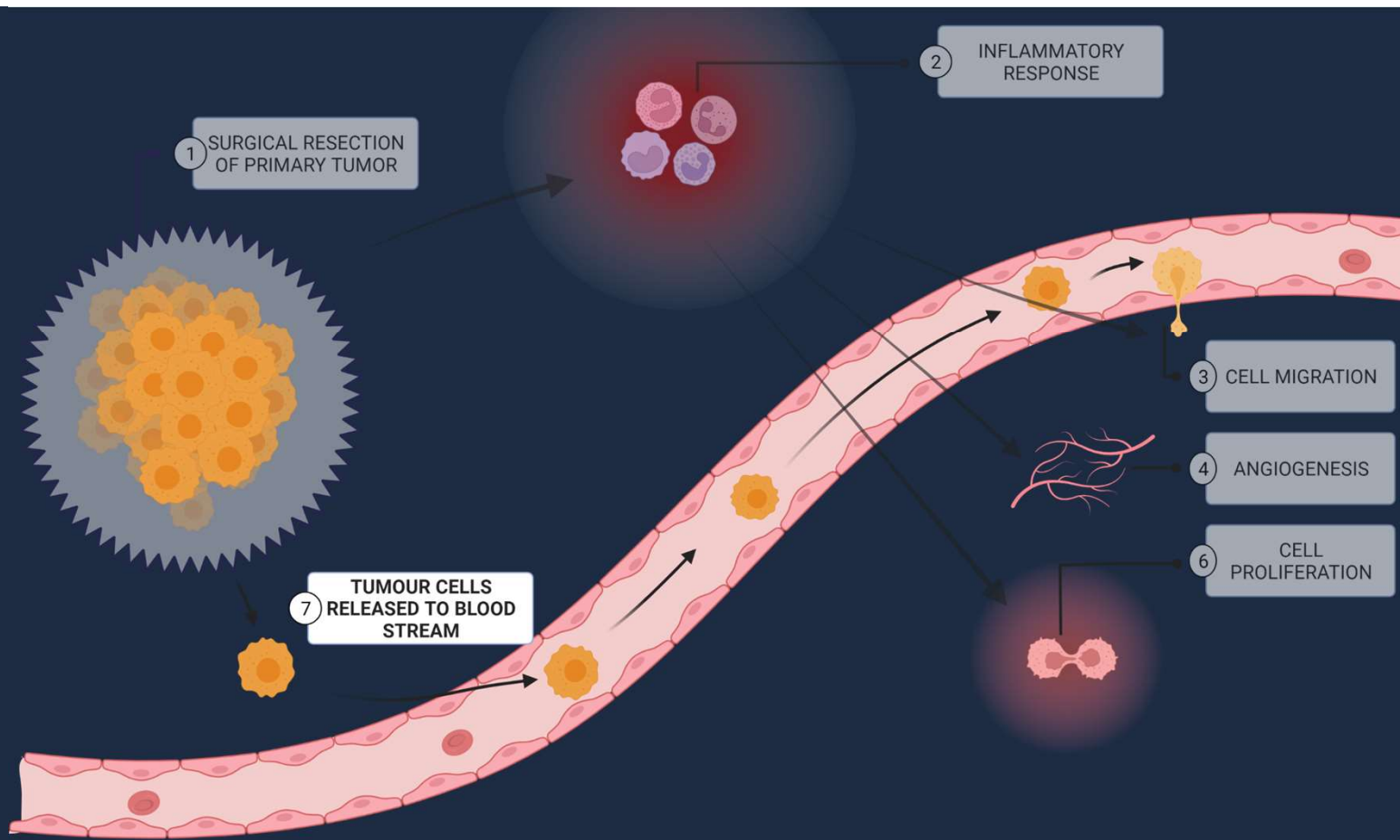
POC => reduced OS (60% vs 77%), DFS (53% vs 70%), CSS (81% vs 87%) and increased recurrence (19% vs 15%)

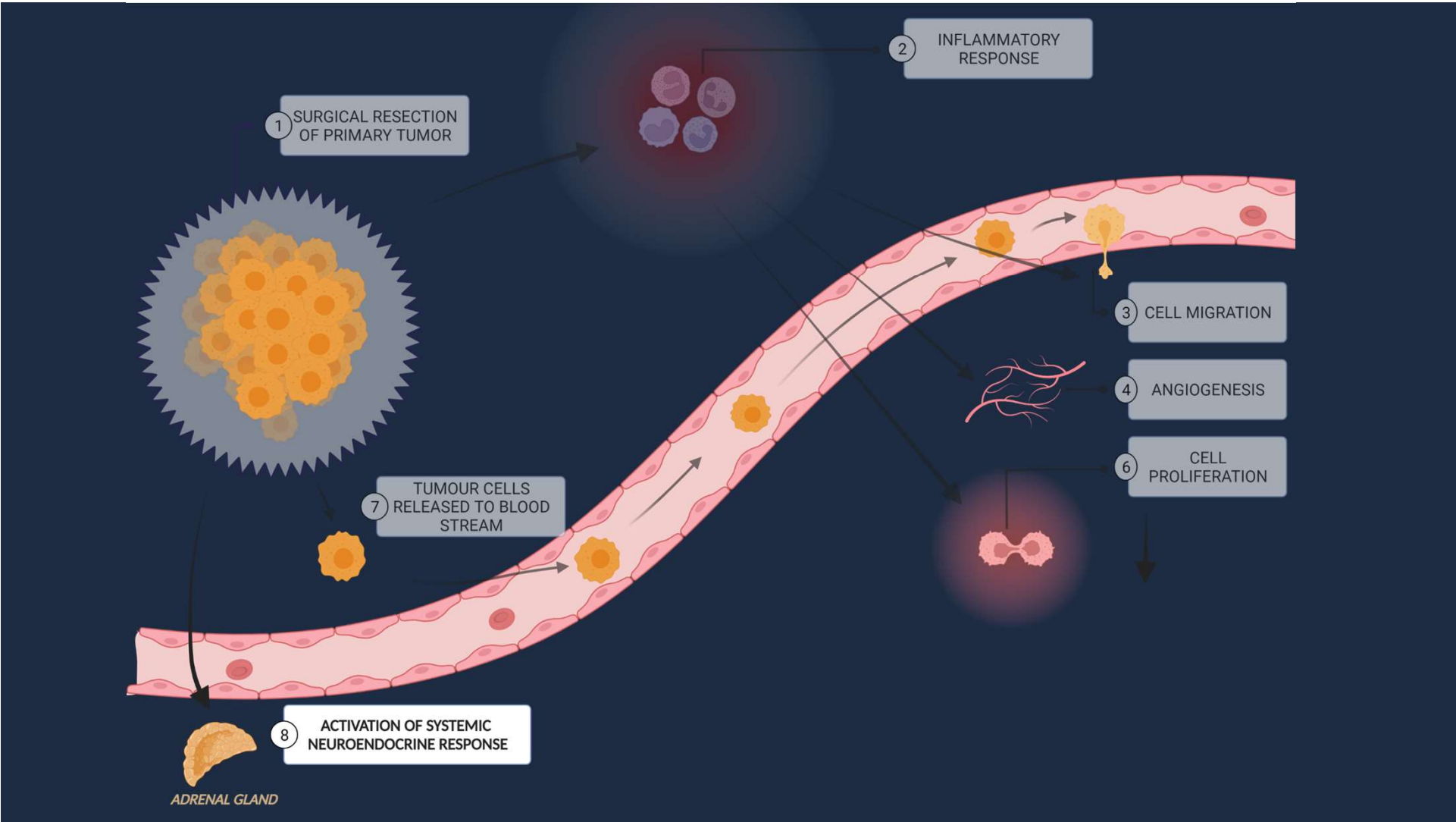
1 SURGICAL RESECTION  
OF PRIMARY TUMOR

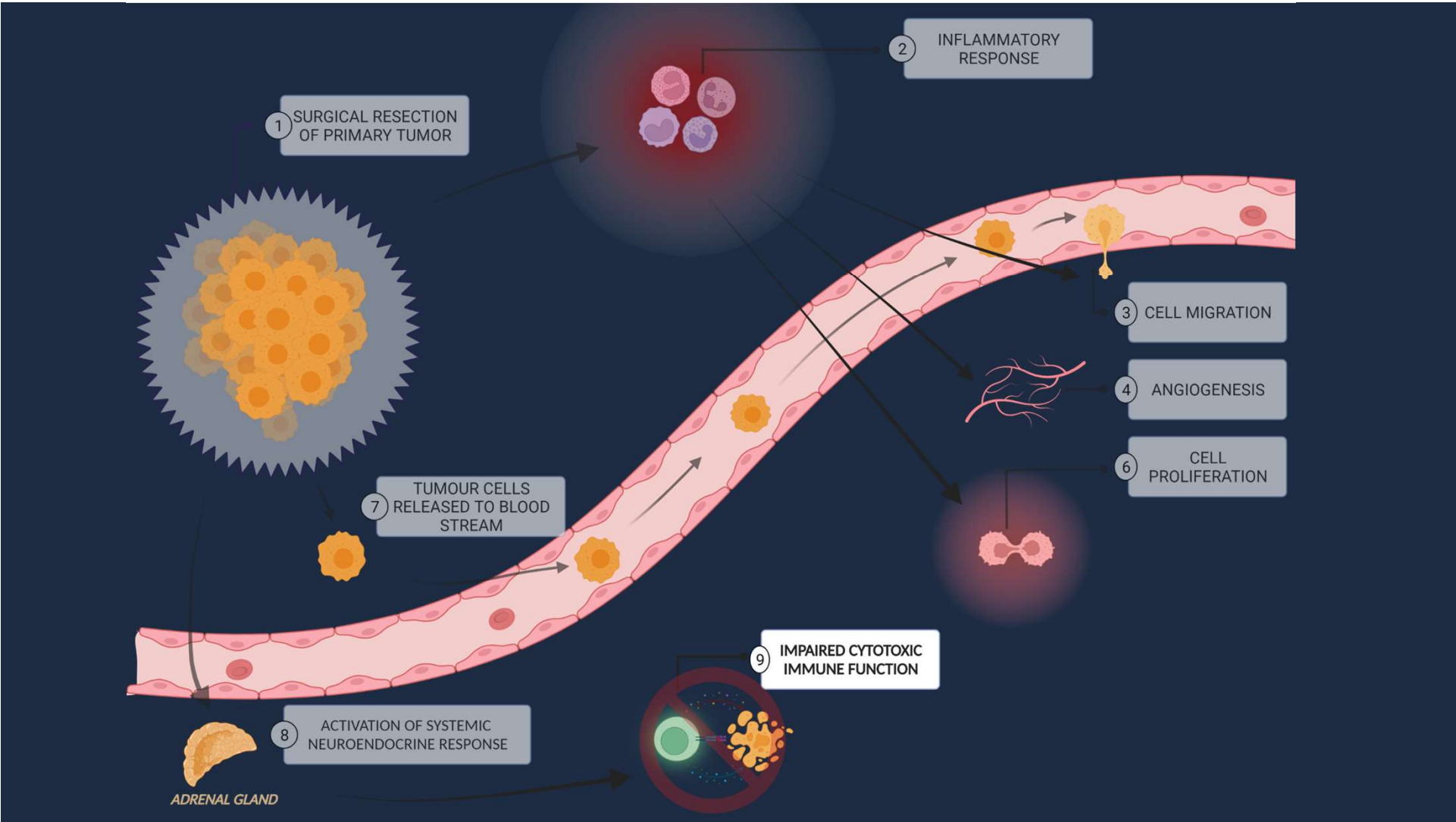


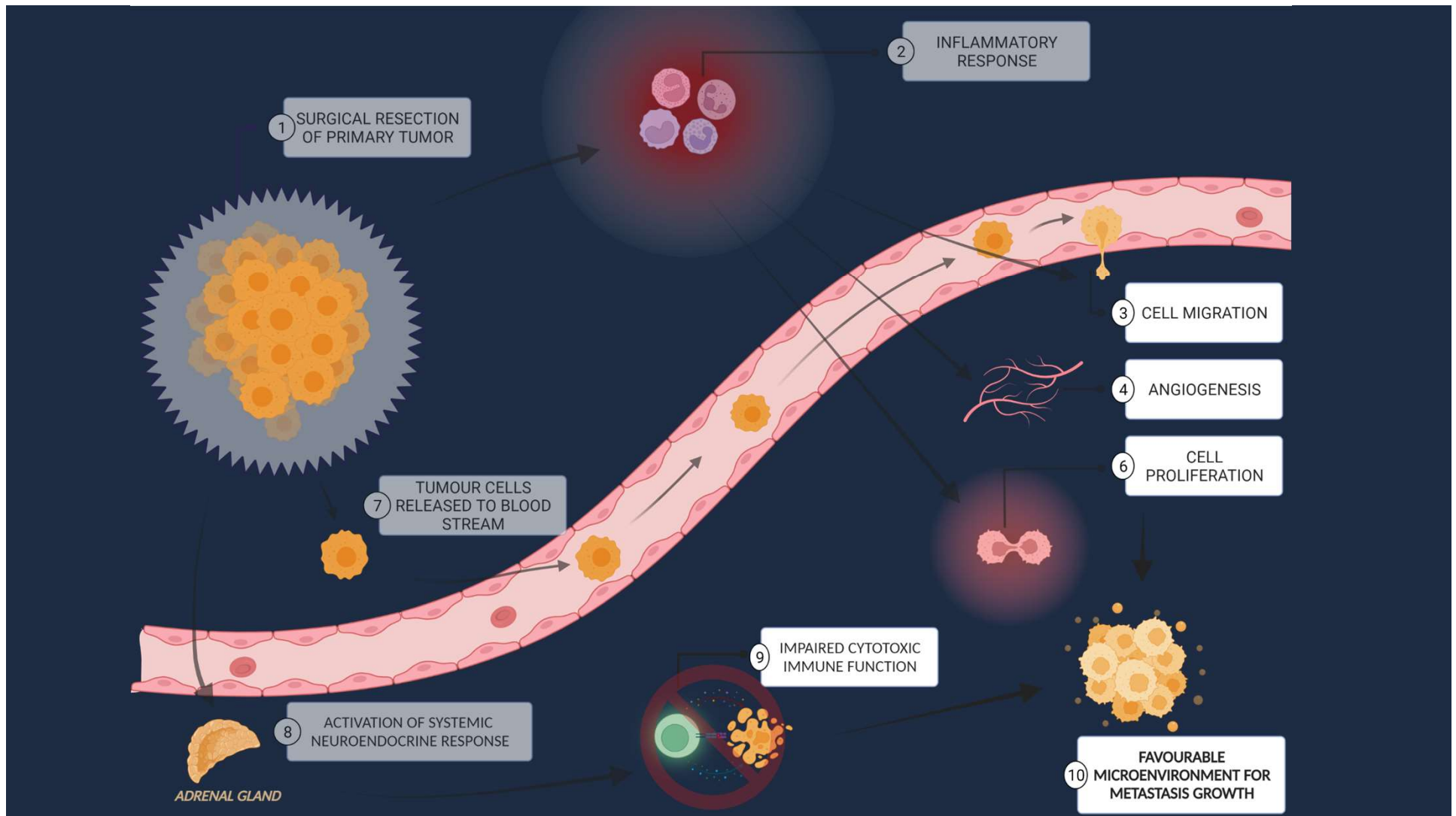






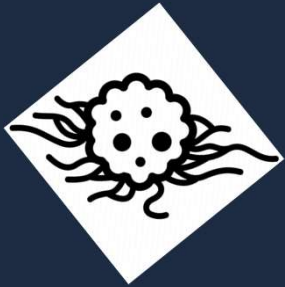








# Kliniske studier med betablokkere



Præoperativ propranolol hos patienter med brystkræft:  
↓ ekspression af biomarkører for invasion og metastasering.

(Hiller et al. 2020)



Patienter med PDAC som tager non-selektive beta-blokkere:  
↓ mortalitet

(Støer et al. 2021)



Patienter med CRC som tager beta-blokkere:  
↓ 90-dages, 1-års og 5-års cancer-specifik mortalitet.

(Ahl et al. 2021)



# Patienter planlagt til operation for pancreas cancer: IMPULS studiet

15 patienter



1:1

15 patienter



Diagnose



Propranolol

40 mg 2 x dagligt

Placebo

2 x dagligt

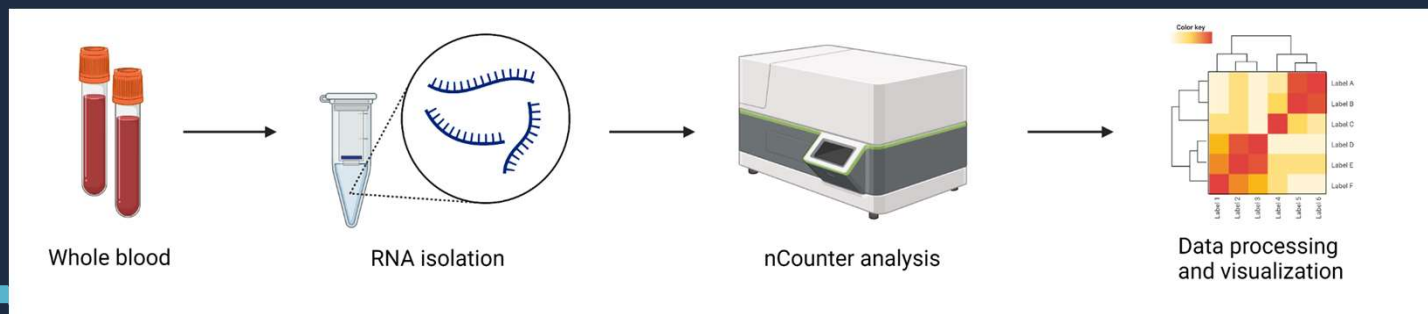
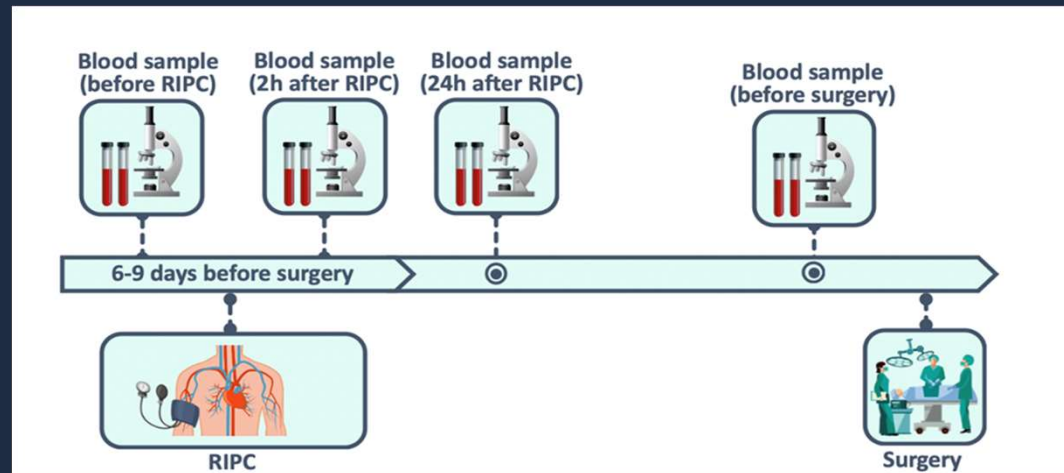
Kirurgi

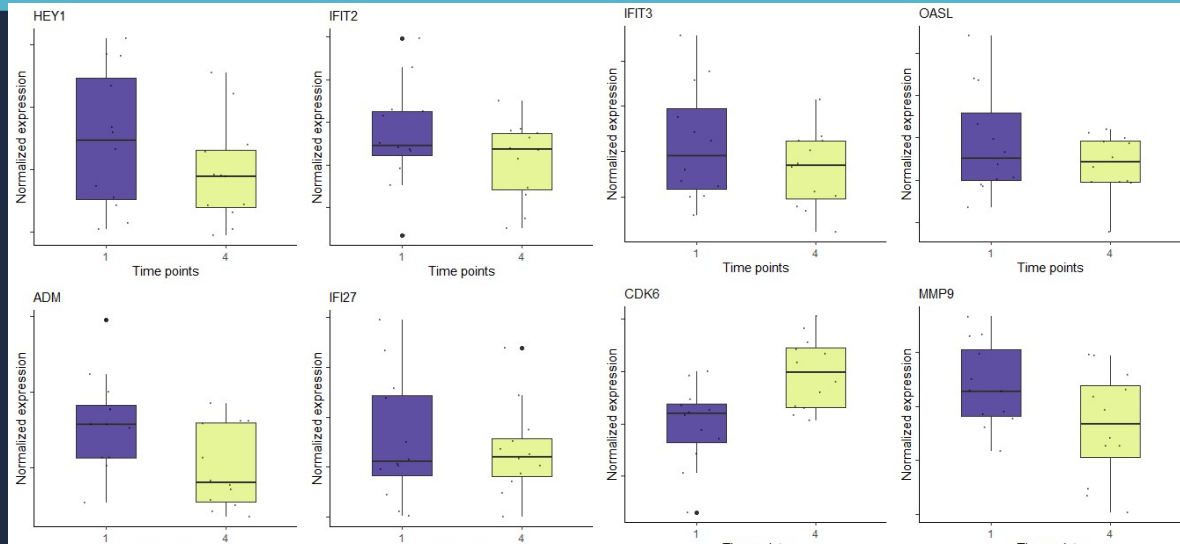
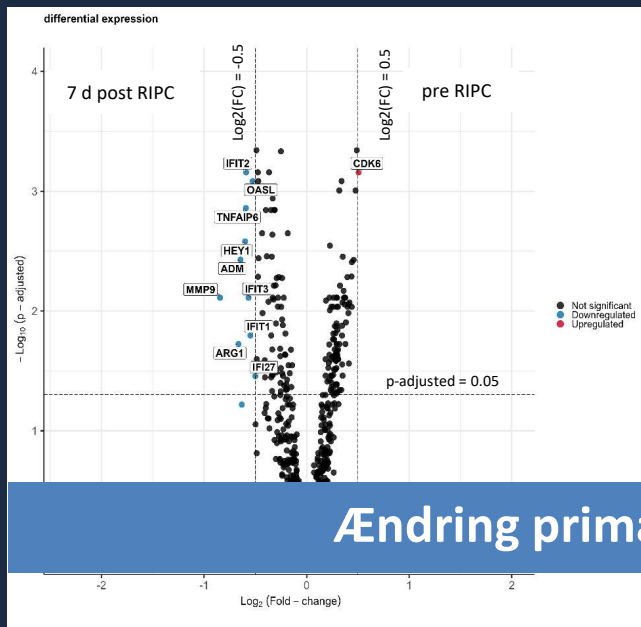


10 dages præoperativ behandling

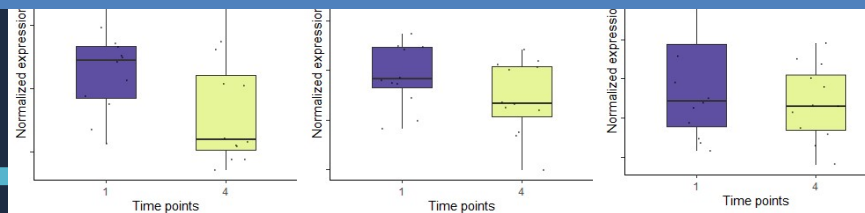


# Andre modaliteter – iskæmisk prækonditionering





## Ændring primært i interferon gamma + alfa pathways



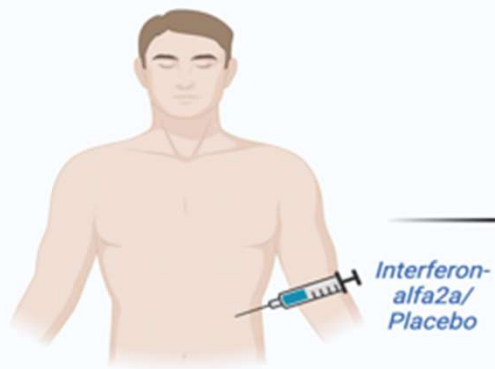
Timepoints  
1: pre RIP  
4: 7 days after RIP



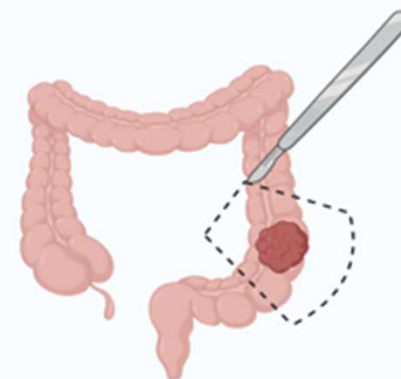
## RCT med Interferon-alfa systemisk før tarmkræft kirurgi



Colon cancer



Randomization and  
medication



Surgery

# Konklusion

**Patientrelaterede risikofaktorer**

**Mit mest vigtige mål**

**Kirurgiens plads i kræftbehandlingsforløb**

- Flere lovende resultater ift til igangsætning af immun respons før kirurgi
- Window studier en vigtig metodologi til drug/procedure udvikling
- Multimodal /multidisciplinær tilgang
- Selektion af patienter/respons evaluering afgørende (nye "responsmarkører")
- Dataintegration afgørende (AI-metoder)

#DKD2023  
#SamarbejdeOmKræft

# Tak til Center for Surgical Science (CSS) – Kirurgisk afdeling SUH



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