

How to approach the patient with MMR deficient locally advanced colon cancer

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No disclosures

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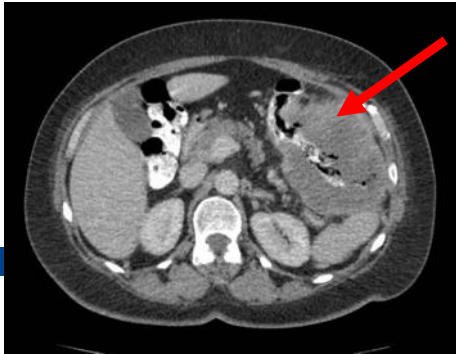
Immunotherapy trials CRC



- Basic concept of MSI – ICI
- Neoadjuvant ICI MSI colon cancer
 - Niche studies
 - Other studies
- Locally advanced MSI colon cancer
- Watch & Wait
- Toxicity ICI

Case 1

- 54 yr lady. locally advanced CRC, T4N+,M0
- Start neoadjuvant 5FU/oxaliplatin
- Complications – lap stoma – local perit M palliative??
- Restaging: some effect primary, progression perit M, mediast N
- Definitely palliative: continu capox



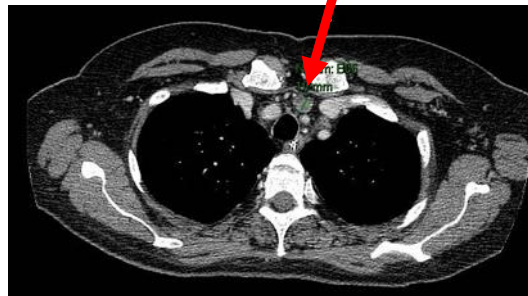
- imaging: progression locally, peritoneal, lung, mediastinal,..
- dMMR/MSI: loss of PMS2 expression, no mutations MMR genes



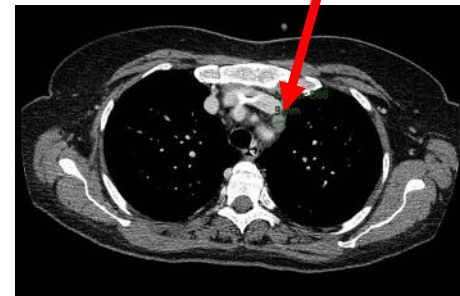
4 cycles ICI



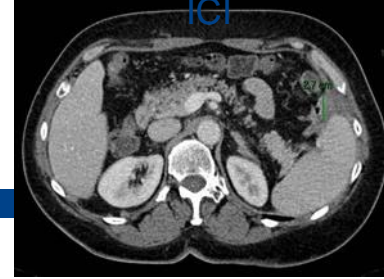
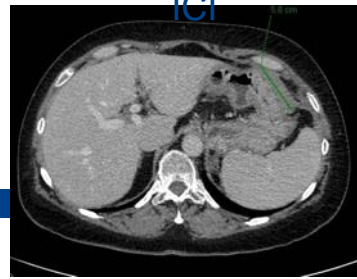
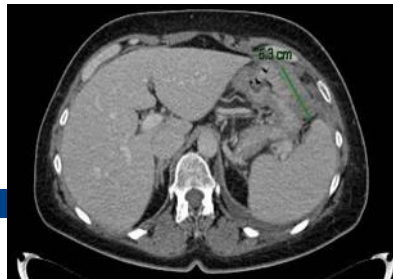
6 cycles ICI



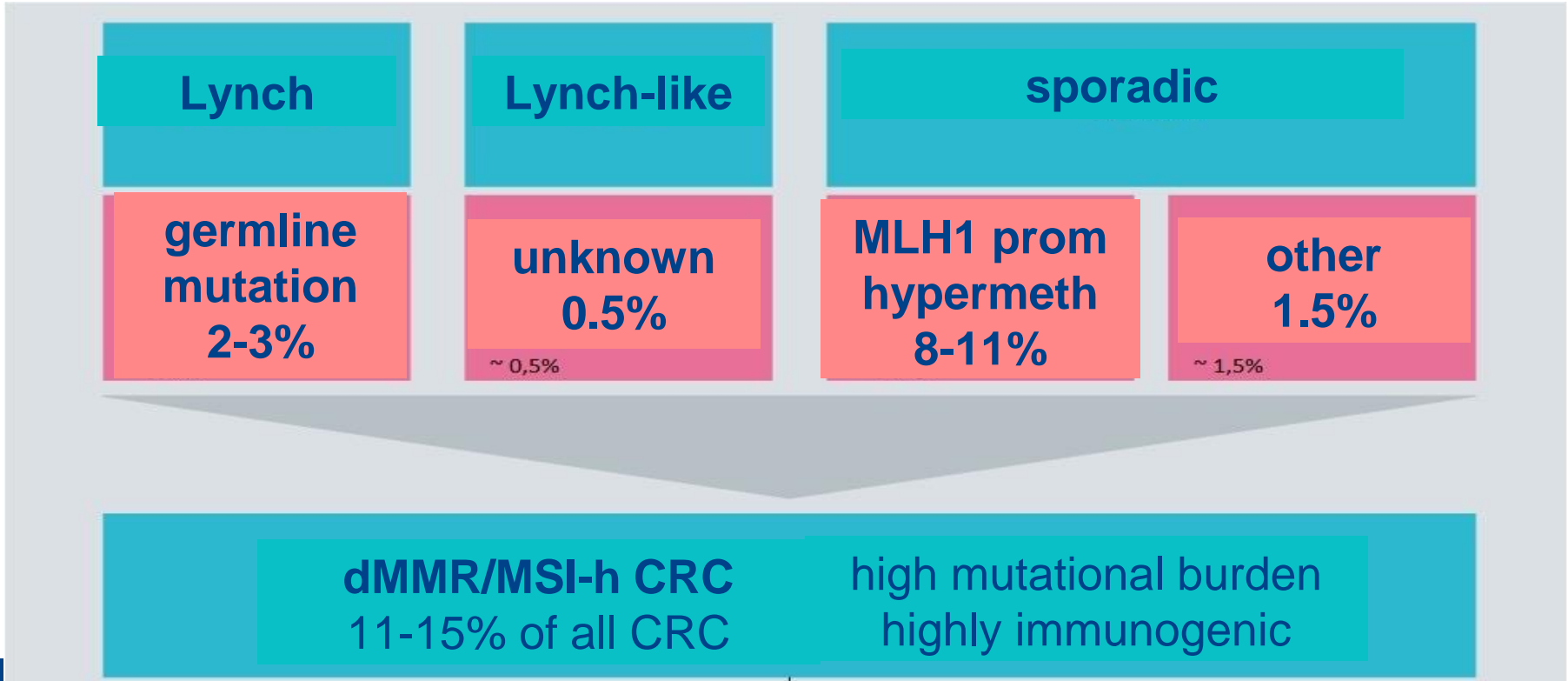
5 months after stop
ICI



10 months after stop
ICI

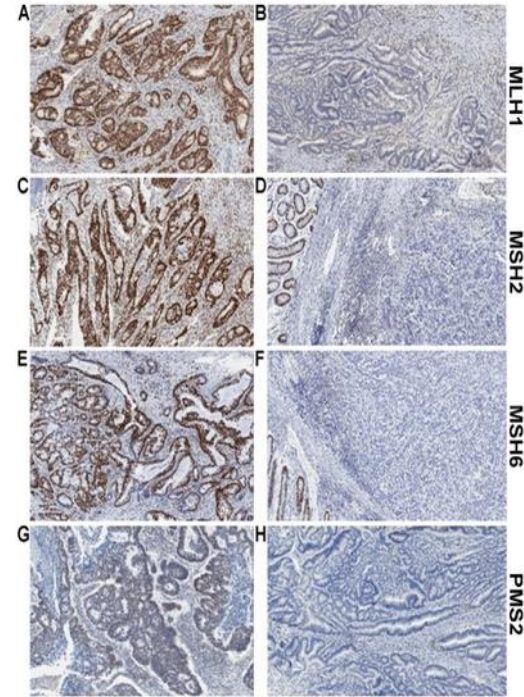


MSI/dMMR

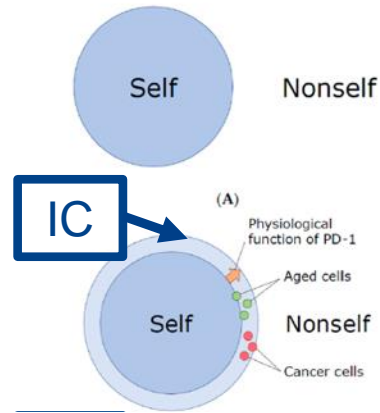
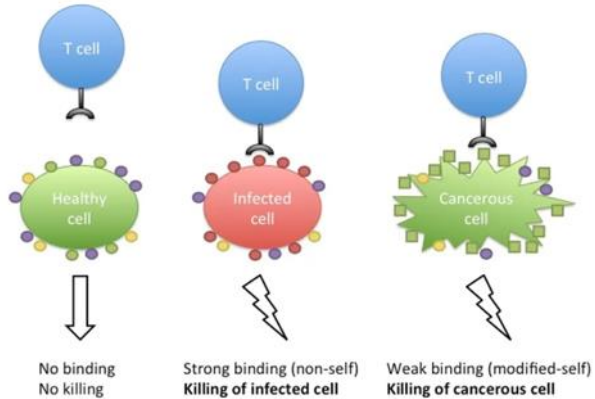


Universal MMR testing?

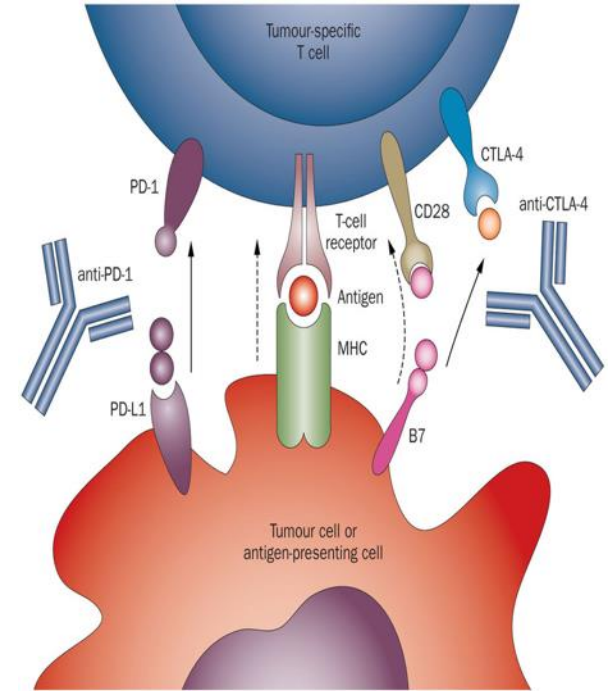
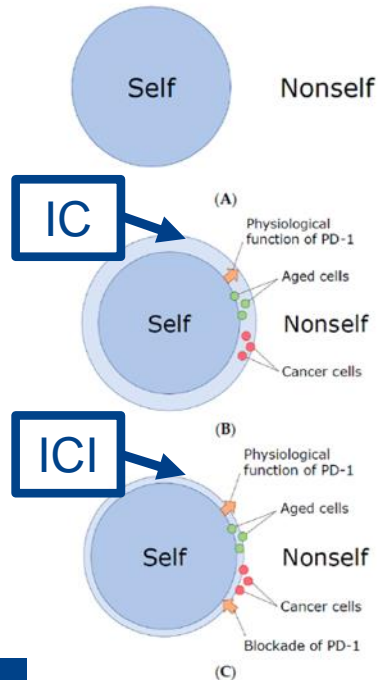
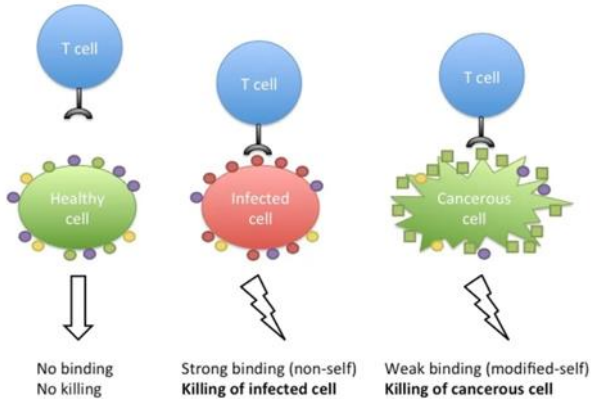
- Dutch guideline
 - all new CRC < age 70
 - whenever considering adjuvant ChTx
 - whenever considering treating M+ disease
- Why not all patients?
 - as suggested by ESMO guideline (?)



Immune checkpoint - inhibition

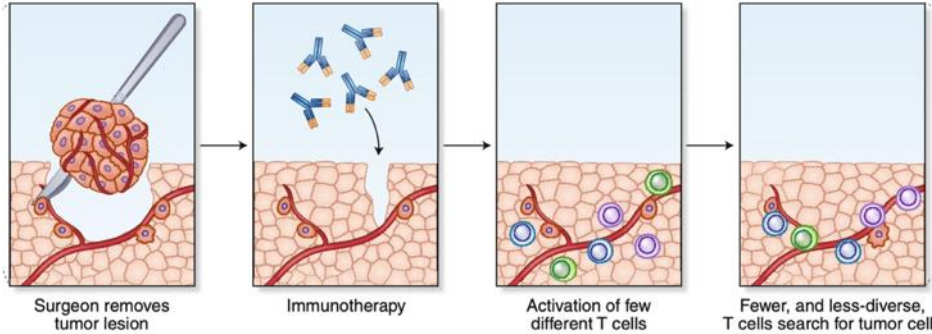


Immune checkpoint - inhibition

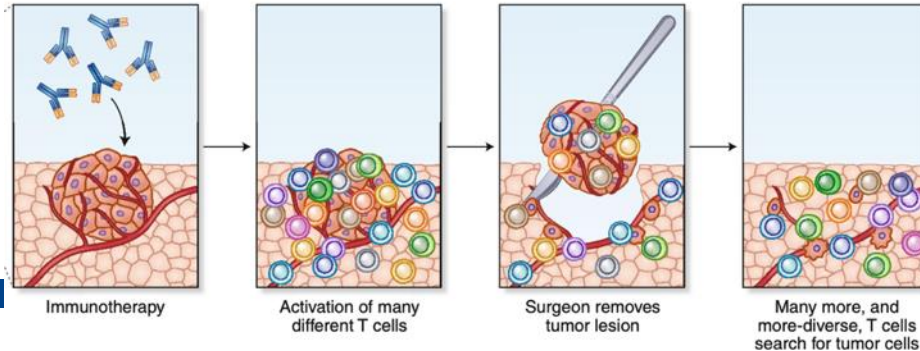


Immunotherapy: before or after

Proposed rationale for adjuvant immunotherapy



Proposed rationale for neoadjuvant immunotherapy



ery?

Neoadjuvant (before surgery)

Better recognition by the immune system when the tumor is still present

Treat micrometastases early

Easier removal of the tumor

Organ preservation

Potential for research and better understanding improve treatment

NICHE 1

Chalabi et. al, Nat Med 2020

ARTICLES

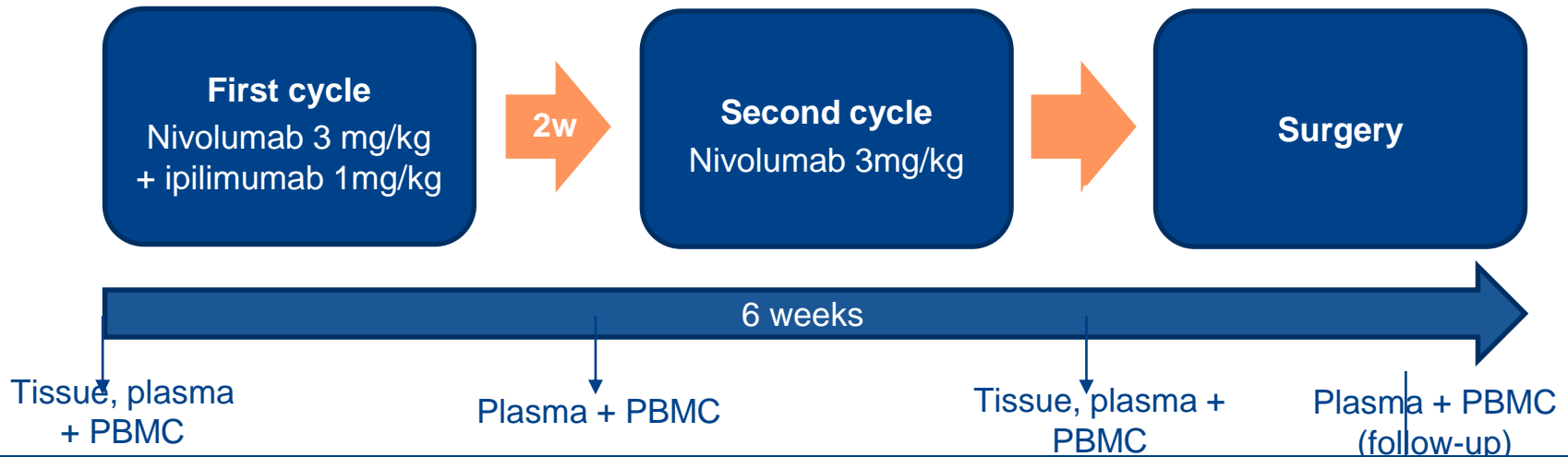
<https://doi.org/10.1038/s41591-020-0805-8>

nature
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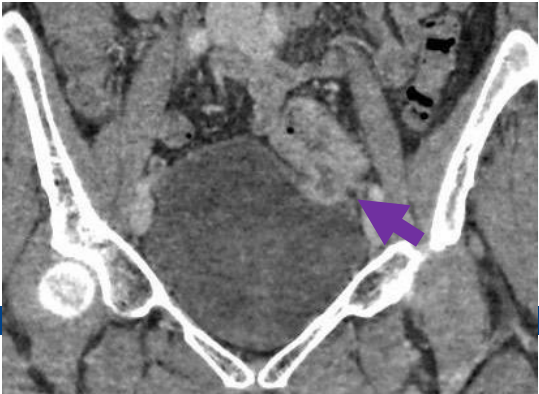
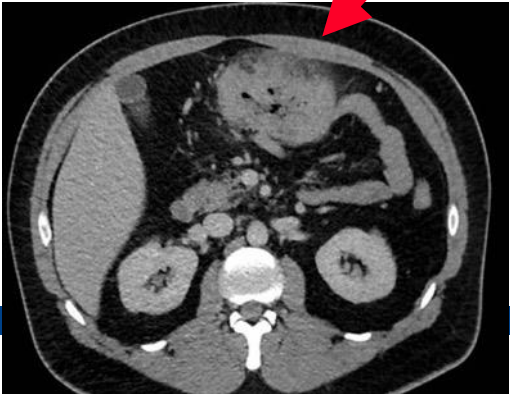
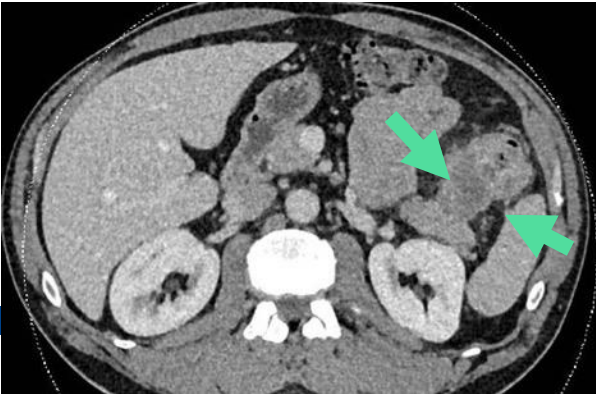
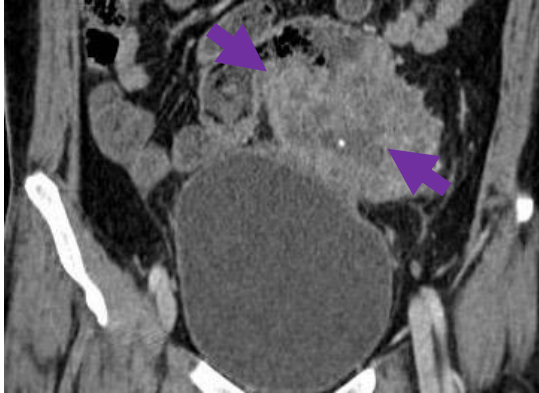
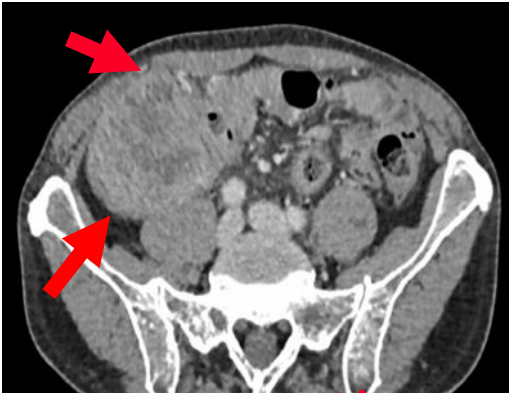
Check for updates

Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers

Myriam Chalabi^{1,2,3} , Lorenzo F. Fanchi^{2,4,17}, Krijn K. Dijkstra^{2,4,17}, José G. Van den Berg^{5,17}, Arend G. Aalbers⁶, Karolina Sikorska⁷, Marta Lopez-Yurda^{7,9}, Cecile Grootscholten¹, Geerard L. Beets^{6,9}, Petur Snaebjornsson⁶, Monique Maas¹⁰, Marjolijn Mertz¹¹, Vivien Veninga^{2,4}, Gergana Bounova^{4,12}, Annegien Broeks¹³, Regina G. Beets-Tan^{9,10}, Thomas R. de Wijkerslooth¹, Anja U. van Lent¹⁴, Hendrik A. Marsman¹⁵, Elvira Nuijten⁷, Niels F. Kok⁶, Maria Kuiper¹, Wieke H. Verbeek¹, Marleen Kok^{3,16}, Monique E. Van Leerdam¹, Ton N. Schumacher^{2,4}, Emile E. Voest^{1,2,4,17} , and John B. Haanen^{2,3,17} 

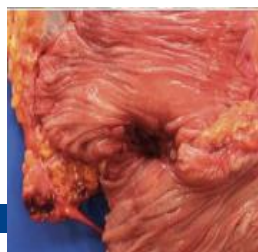
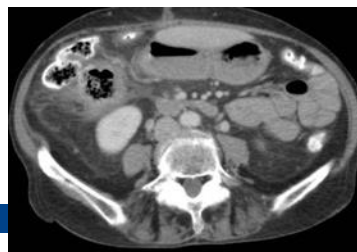


63% clinical T4a or T4b tumours



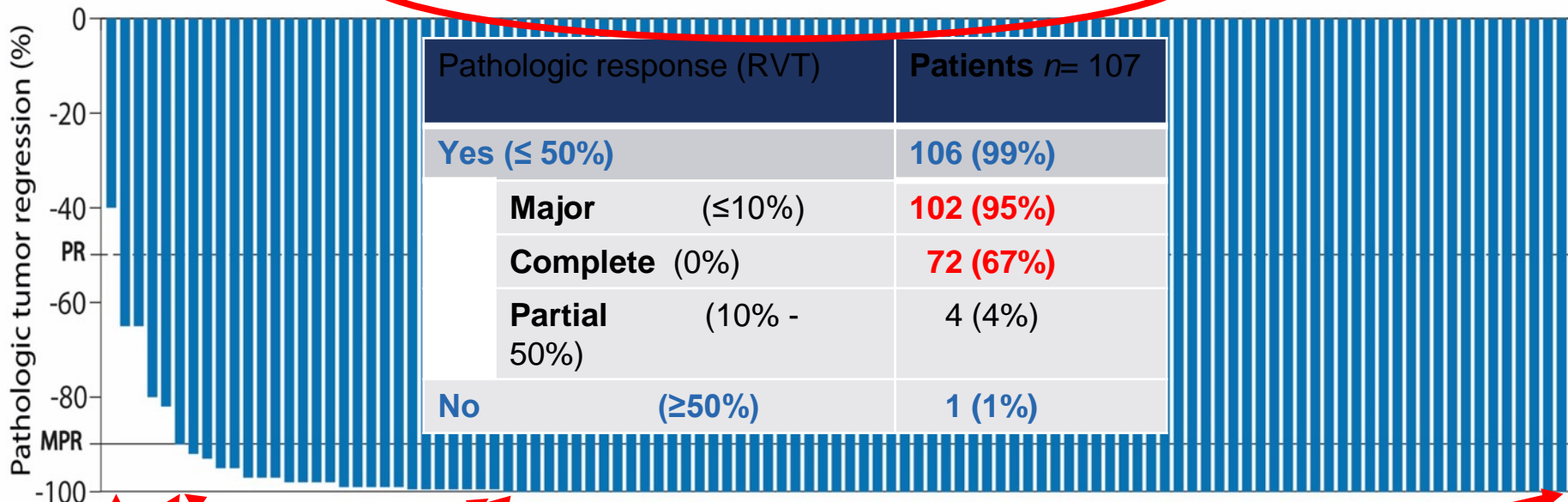
Case 2: early Niche patient

- 82 y/o lady large T3/4N1 right colonca, dMMR
- Niche study? "no, please, I don't want another colonoscopy"
- During surgery: invasion of duodenum and terminal ileum
 - telephone consultation study coordinator, family: only biopsy and discuss inclusion
- Niche study 4w ICI Resectie ypT0N0 FU 5yr
NED



Niche 2 waterfall plot: 99% response

Until now: no metastases!!



partial tricht major

Chalabi, 2024 NEJM

pCR

With a complete response after ICI for locally advanced MSI CRC

Should you still give adjuvant chemotherapy?

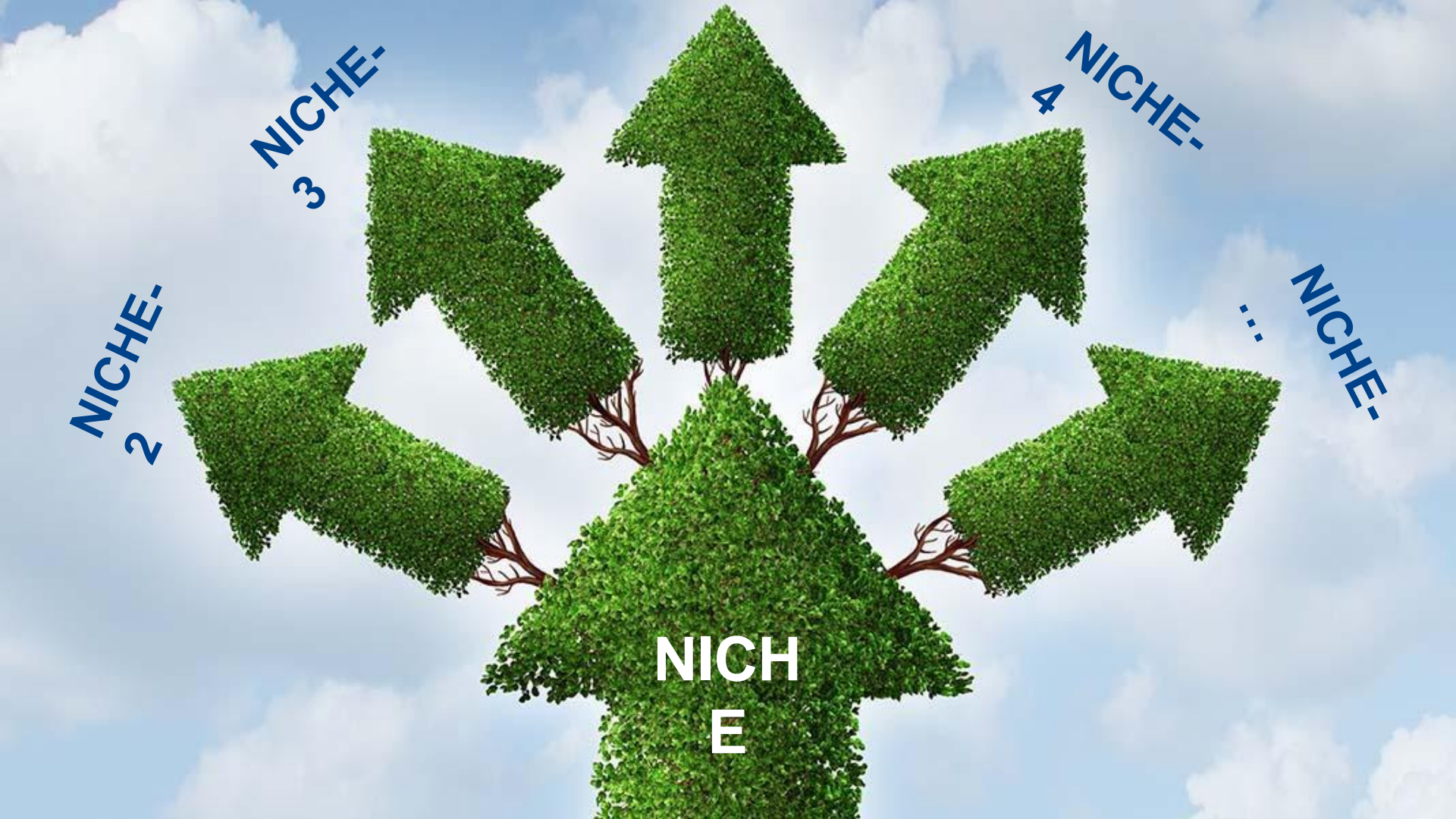
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2

NICHE-
3

NICHE-
4

...
NICHE-

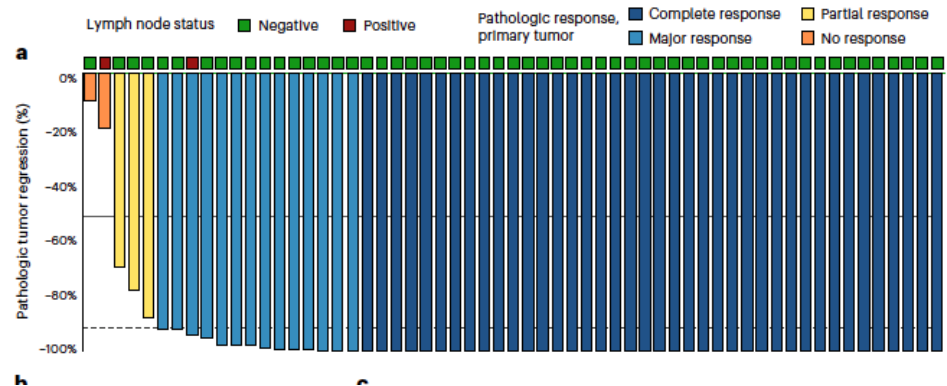
NICH
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Niche 3: MSI colon cancer: nivo + anti LAG3

- 59 patients
- 2 cycles – surgery 6 weeks

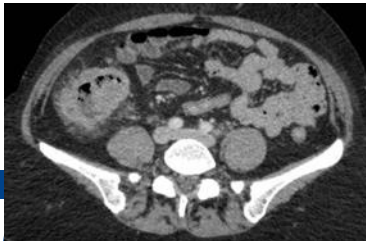
- 68%pCR
- 10% gr 3-4 tox
- 1 pt metastases



Case 3: what??

- 50 yr lady right colonic cancer, sporadic MSI. cT3/4N+M0
- Niche cohort 6: 2x nivolumab/relatlimab (LAG-3 inhibitor)
- 1 day after immunotherapy: fever, RLQ pain, peritoneal irritation

- **Imaging / clinical history: pT0N0**



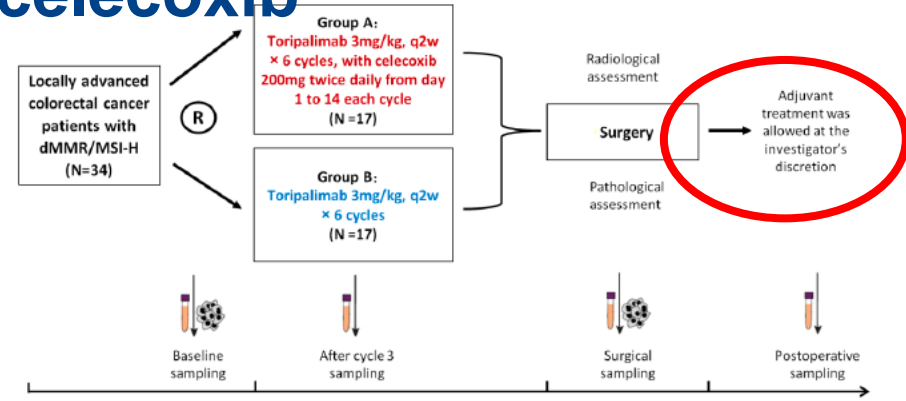
T0

T+1week

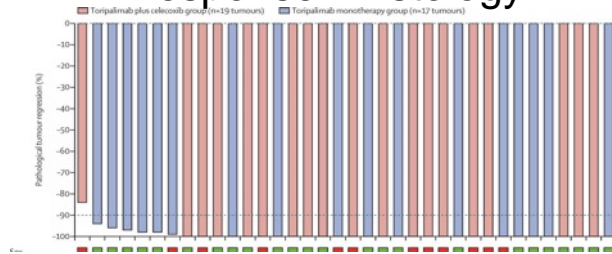
T+8week

PICC study loc adv MSI CRC anti PD1 +/- celecoxib

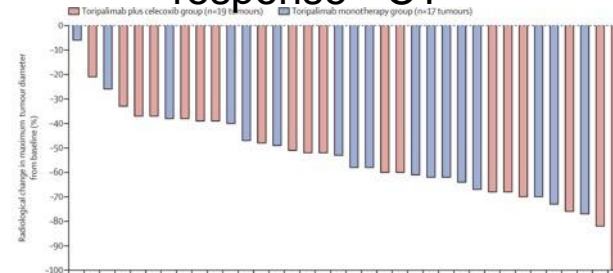
- 34 pts (6 rectal), stage II/III
- 3 months
- pCR 89% - 65%
- Tox gr 3-5: 1 pt + 1 pt



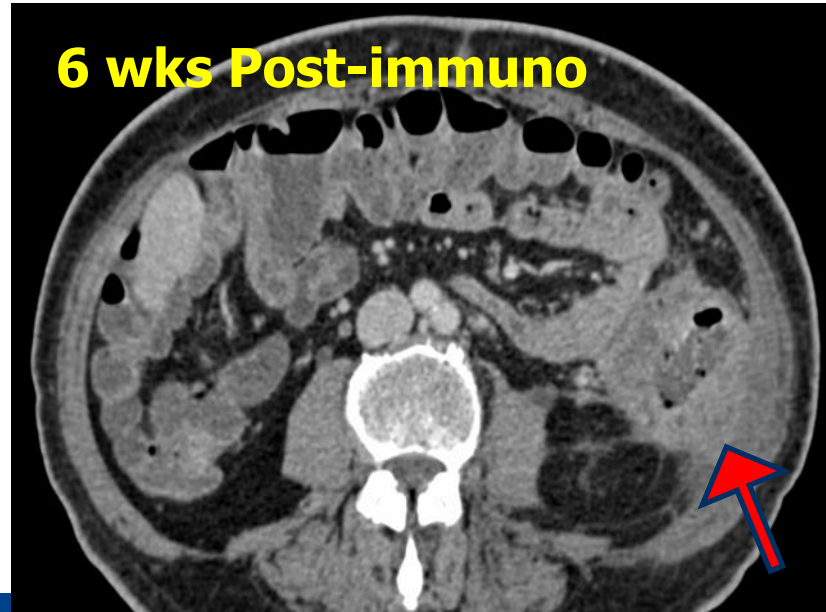
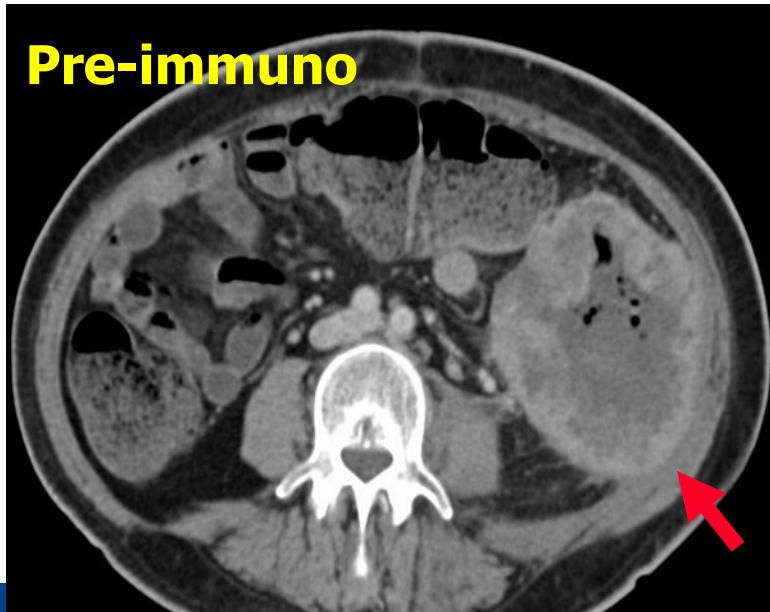
response - histology



response - CT



Difficulties short term assessment response CT

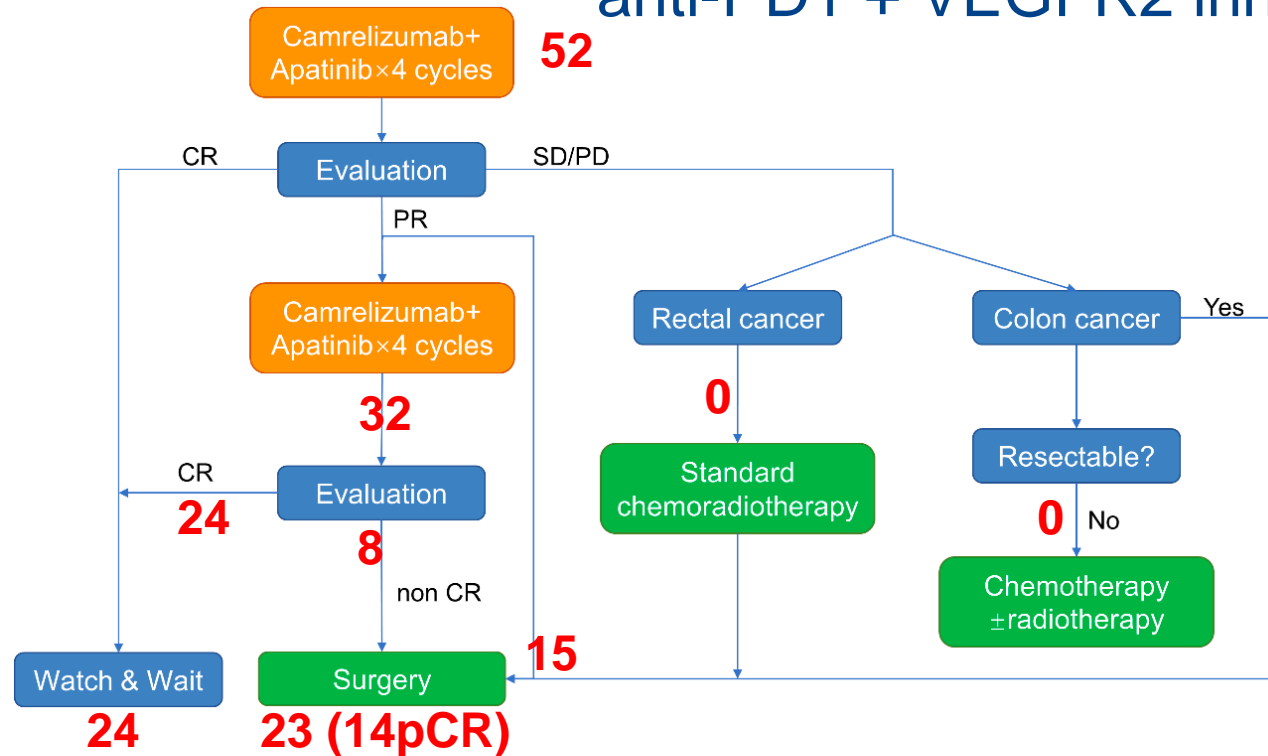


Should we try Watch&Wait?

- How to assess response?
- How to follow up?
- Small right colon tumor fit patient?
- Large left sided tumor frail patient?

NEOCAP ICI study loc adv MSI CRC

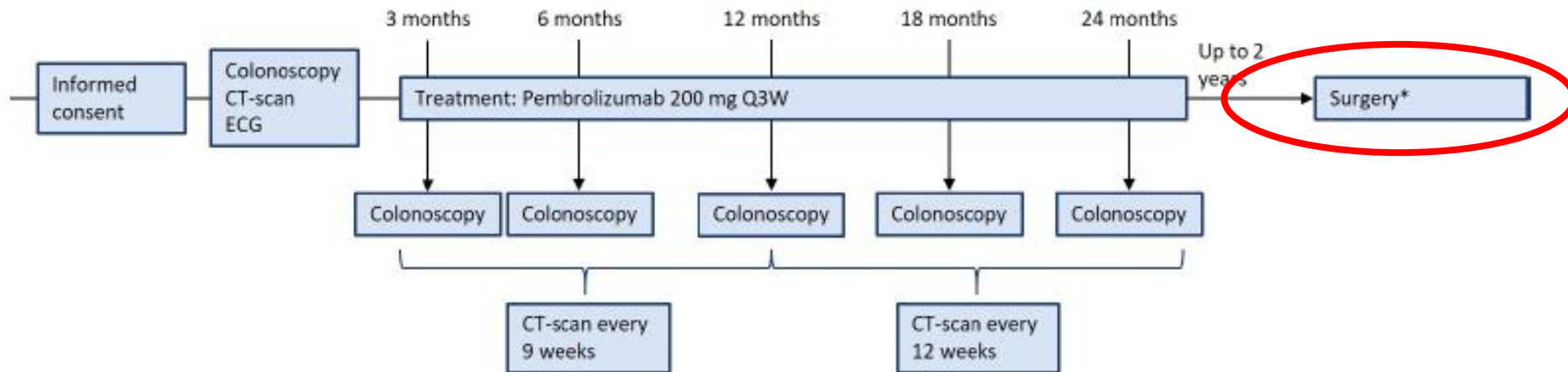
anti-PD1 + VEGFR2 inhib.



- 52 pts (12% rectal)
- T3-4, N+(96%)
- 3-6 months
- CR: 38/52: 73%
- Time to CR: 5.7 mths
- Toxicity gr 3-5: 38%
 - adrenal, diabetes
 - 1 death: hepatitis

PUMA –trial

Pembrolizumab for locally advanced ‘unresectable’ dMMR-CRC

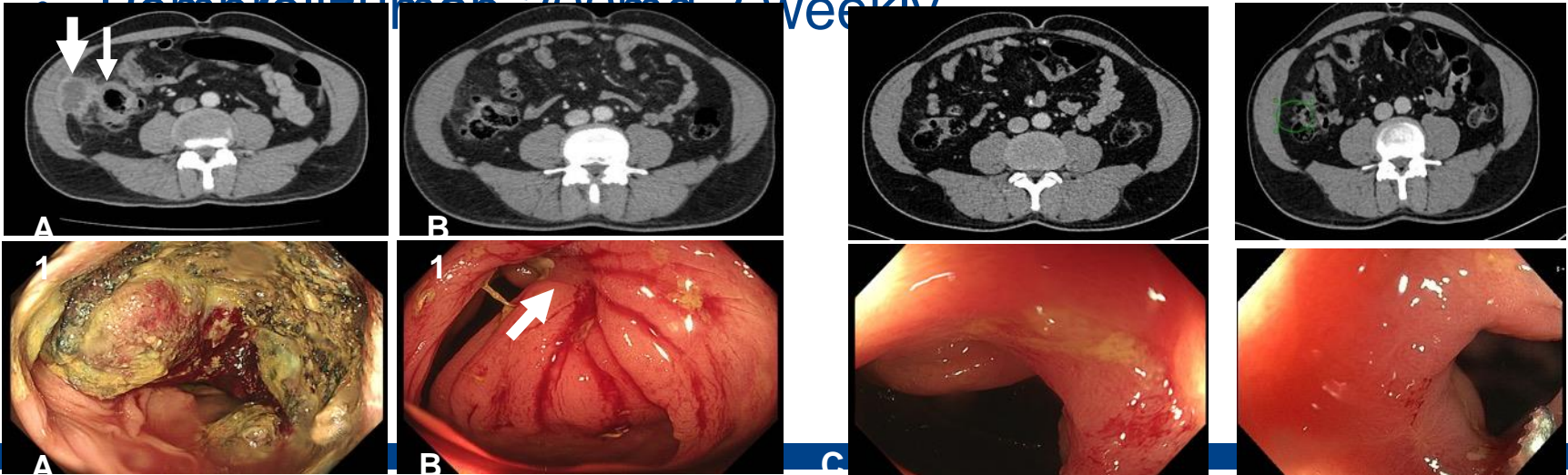


- Aim: more conversion to resectability than with standard chemotherapy
- Primary endpoint: objective response rates (RECIST)
- **Do we still require surgery?**

Case 4: perforated T4

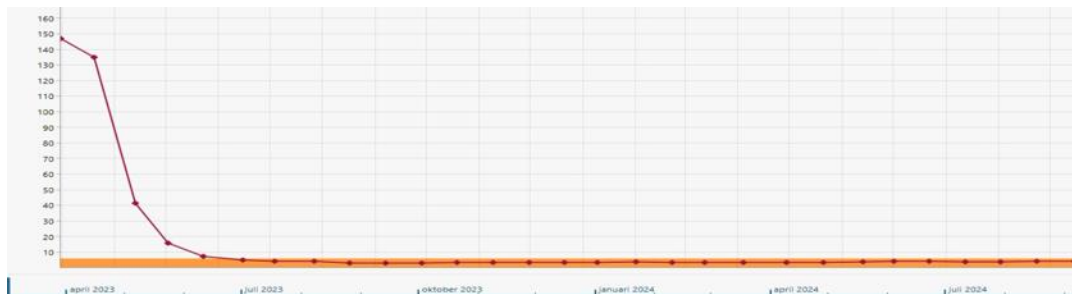
- 54 y/o man, some psychiatric history, dMMR sporadica right colon cancer cT4N0M0 with perforation/abscess abdo wall

Darbepoetin 200mg 2 weekly



Monitoring response

- CT, PET?
- Endoscopy, biopsy?
- CEA, ctDNA?



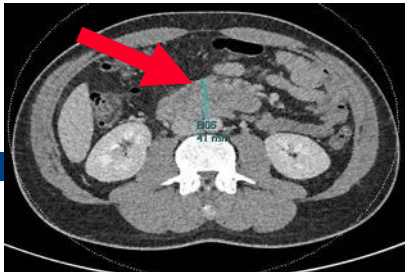
Would you have stopped earlier?

Case 5: Locally advanced or metastasized?

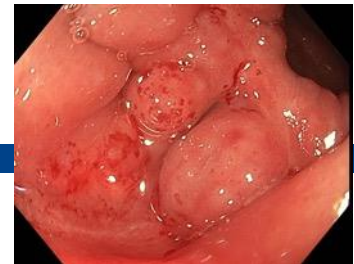
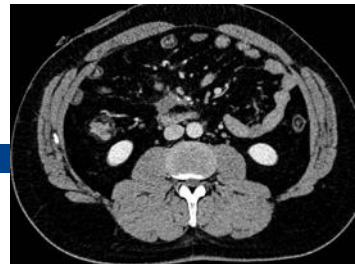
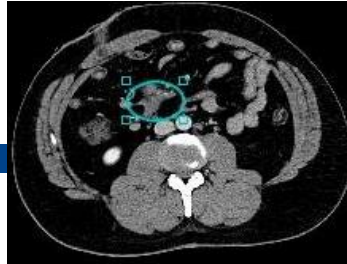
- 39 y/o man, large obstructing right tumor, ileostomy, Lynch
 - What do you tell him?
 - 2 yr pembro --> wants to get rid of stoma



du g



du g

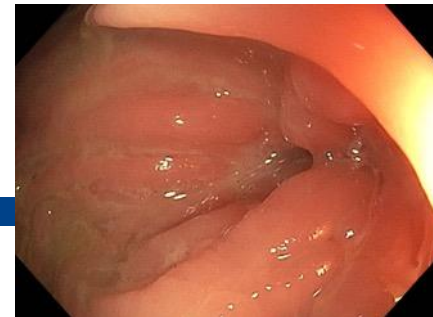
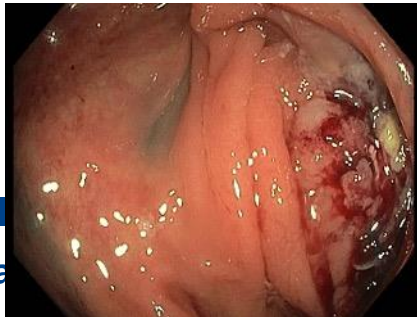


Case 6 – Surgical management

- 77 y/o lady right sided perforated sporadic MSI tumor
- Ileostomy, abces drain, double J □ pembro □ getting tired of it

complications

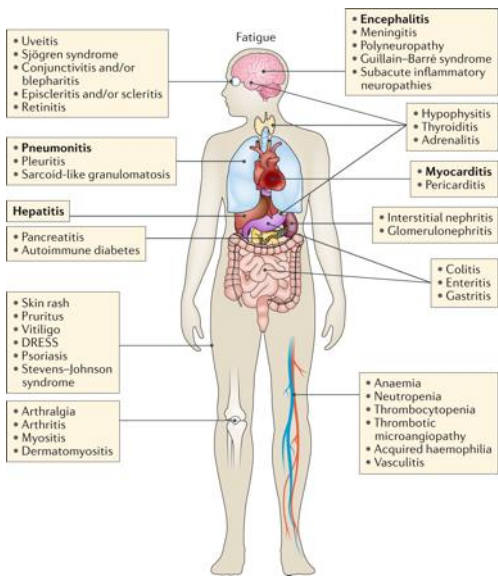
- [unclear] the [unclear]



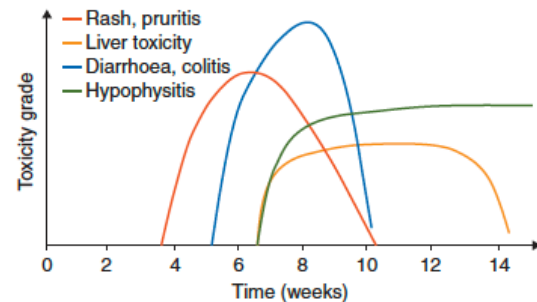


- Optimal schedule?
- Optimal duration?
- What is the goal?
 - Target metastases and improve survival?
 - Improve R0? Avoid surgery?
- Toxicity? 'generally well tolerated'

Toxicity immunotherapy



- Incidence: any AE 40-70%, mostly grade 1-2
 - which agent(s) – double > single
 - exposure time – patient factors
- Skin problems, fatigue, arthralgia,...
- Colitis, hypothyroidism,.
- Grade 3-5: 14-21%
- Fatal AE: 0.3-1.3%
- Early recognition!!



– Steroids, etc

Haanen 2017, Ann Onc

Martins 2019, Nature rev Clin Oncol

Toxicity ICI - Niche 2

- 4% grade 3-4 immune-related adverse events

Immune-related toxicity (112 patients)	Number of patients (%)
Patients with any adverse events	68 (61)
Grade ≥ 3	4 (4)
Toxicity leading to delay in surgery ≥ 2 weeks	2 (2)

Most common grade 1-2 toxicities:

- infusion reactions
- dry mouth
- hyper- or hypothyroidism
- fatigue
- flu-like symptoms

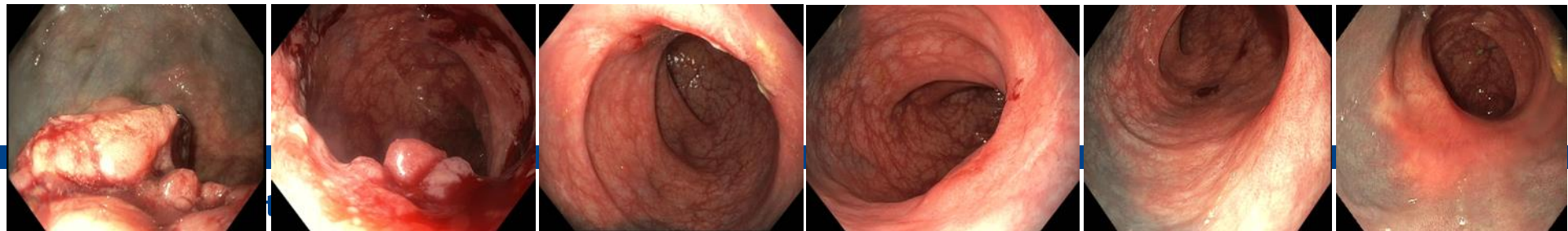
Safety

- 98% timely surgery
- CRM- 100%

Case – toxicity ICI

- 66 y/o man MSS sigmoid tumour. Study: nivo/ipi - nivo
- ICI complications: myositis □ prednisone, cellsept, tacrolimus

- Muscle weakness – walking problems
- Cardiac problems
- Eye problems
- Vocal chord problems



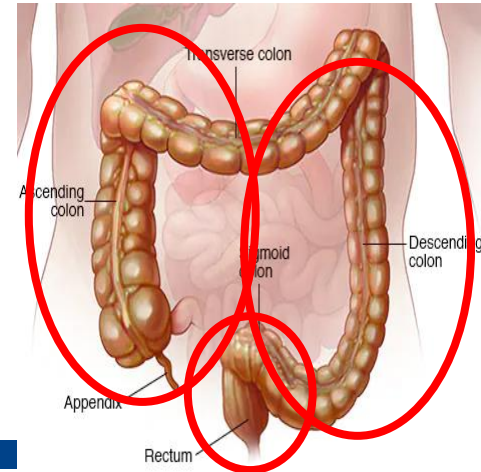
Benefit

Harm



Organ Preservation MSI/dMMR

- Rectal cancer: Yes
 - Framework/experience after neoadj Ch/RT
- Right sided colon: ?
 - Less functional problems
 - Assessment response? Follow up? Colonoscopy?
- Sigmoid/left colon: Maybe
- Respon assessment and follow up
 - Imaging: MRI – CT – PET
 - Endoscopy
 - ctDNA

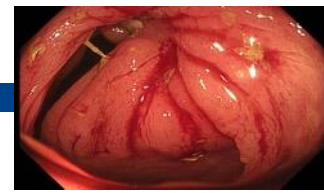


How long should we give ICI?

- 1 – 2 – 3 - 6 – 12 – 24 months?
- Just long enough to do the job
- micrometastases? short (1-2-3)
- organ preservation? intermediate (3-6)
- improve R0 intermediate (3-6)
- macrometastases intermediate/long (3-24)
- adaptive according to response

Conclusions

- Universal MSI/MMR testing
- Moving field: combinations, new drugs, duration
 - Toxicity very important factor
- Large MSI colon cancers: neoadj ICI
 - Target micrometastases – increase R0 – W&W?
- Early tumours: resection in good candidates
- Intermediate tumours? Neoadj ICI optional
- W&W: more practical for leftsided and sigmoid
 - Response assessment and follow up?



Thank you

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