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Neoadjuvant Therapy for GI Cancers

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ACS Cancer Programs

American College of Surgeons

Disclosures

- I have no relevant disclosures

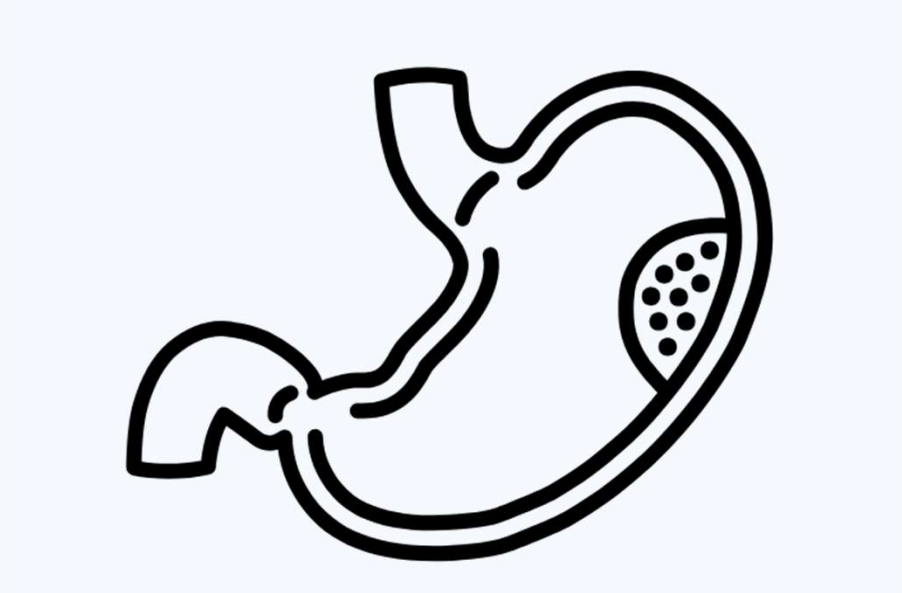
Benefits of Neoadjuvant Immunotherapy

- Reduce Tumor Burden
- Enhanced immune response due to increased tumor antigens from intact tumors
- Increased understanding of tumor biology
- Increasing chance of complete response or decreasing tumor burden to allow higher chance of R0 Resection
- Potential for improved long-term survival

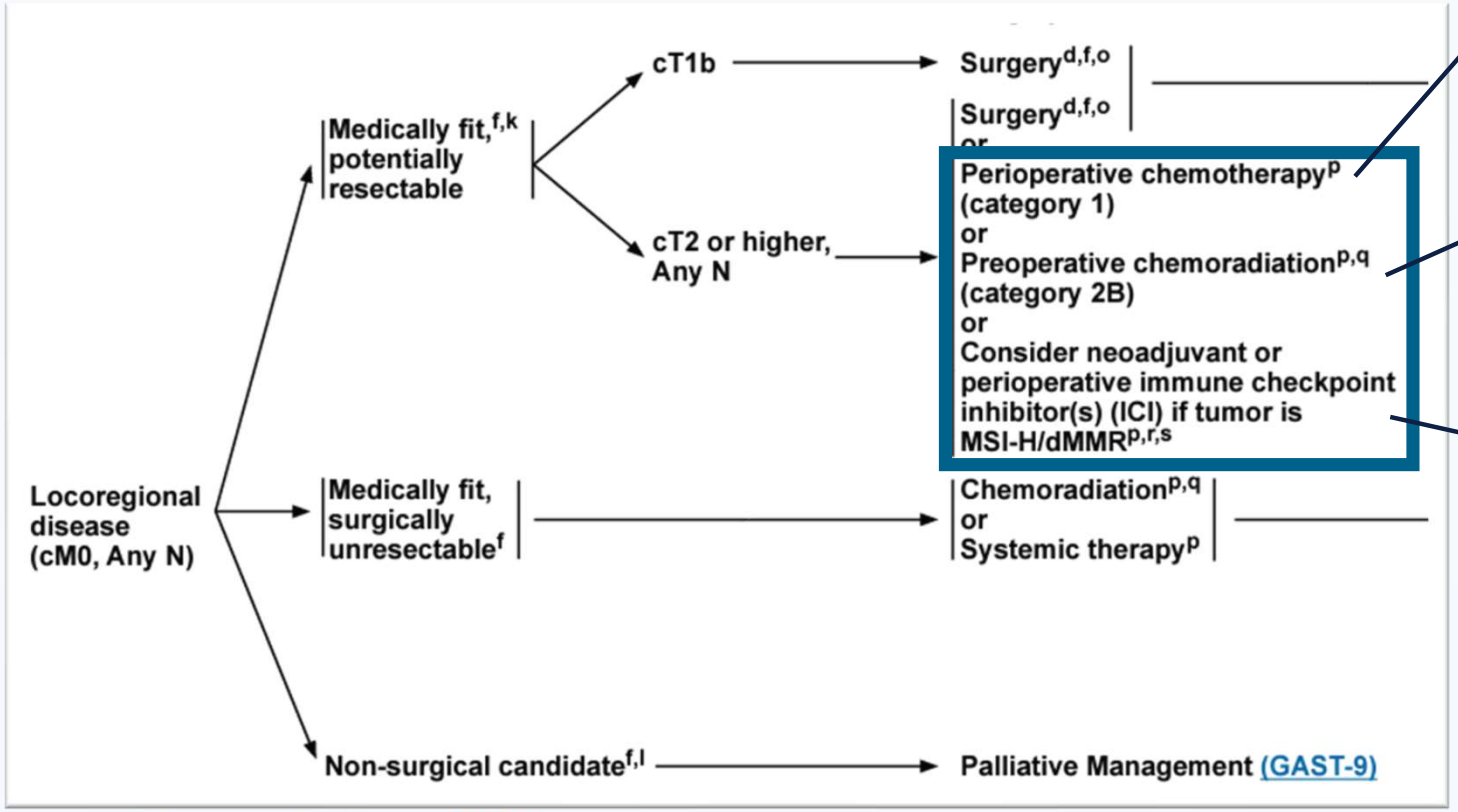
GI Tumor Types

- Gastric
- Colon
- Rectal

GASTRIC CANCER



Adjuvant therapy for gastric cancer



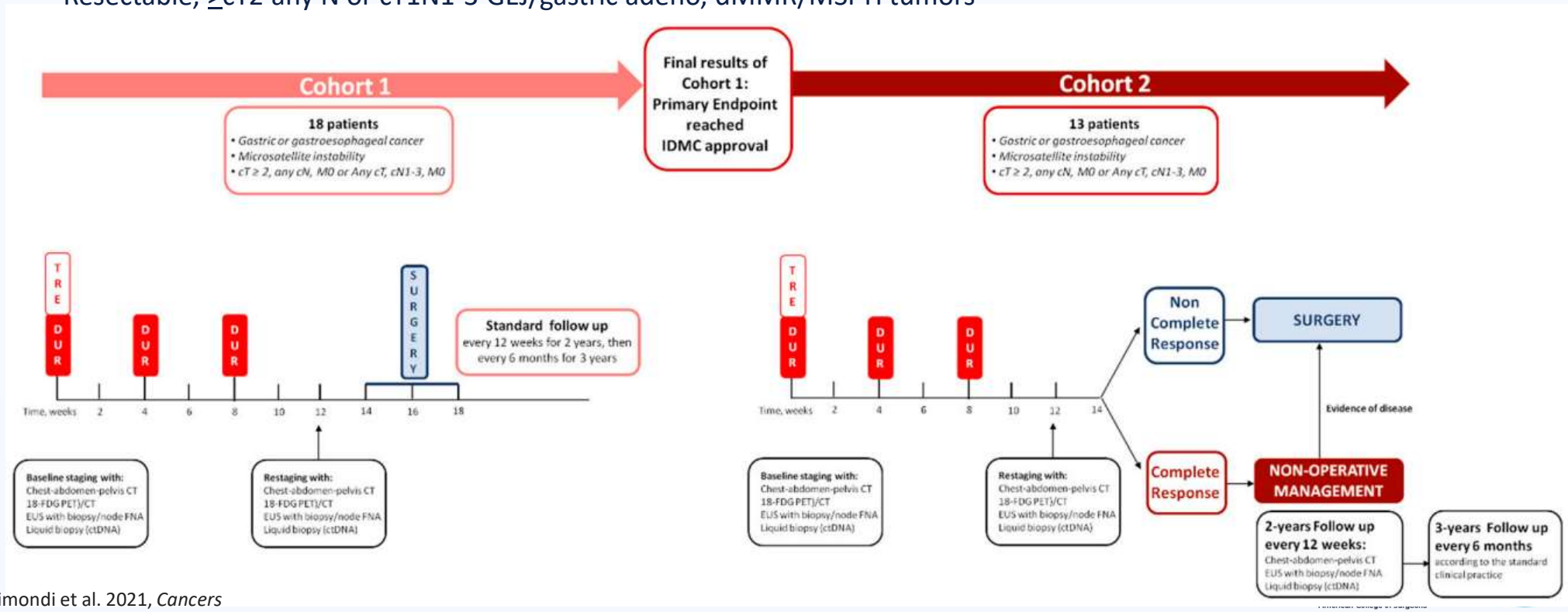
MAGIC
FLOT Trial

CRITICS 1/2
ARTIST 1/2
TOPGEAR

INFINITY
NEONIPIGA
MATTERHORN
KEYNOTE-585

INFINITY Trial: Immunotherapy for MSI-H tumors

- Phase II, multi-center, single-arm study from Italy
- Tremelimumab (anti-CTLA4) and Durvalumab (PD-L1)
- Resectable, ≥cT2 any N or cT1N1-3 GEJ/gastric adeno, dMMR/MSI-H tumors



Raimondi et al. 2021, *Cancers*

INFINITY Trial:

- Promising results thus far from 2023 ASCO Abstract
  - N=18 enrolled
  - Two clinical CR→ refused surgery
  - 14/15 evaluable patients underwent surgery
    - 1 progressed
  - No disease relapses to date → follow up ongoing

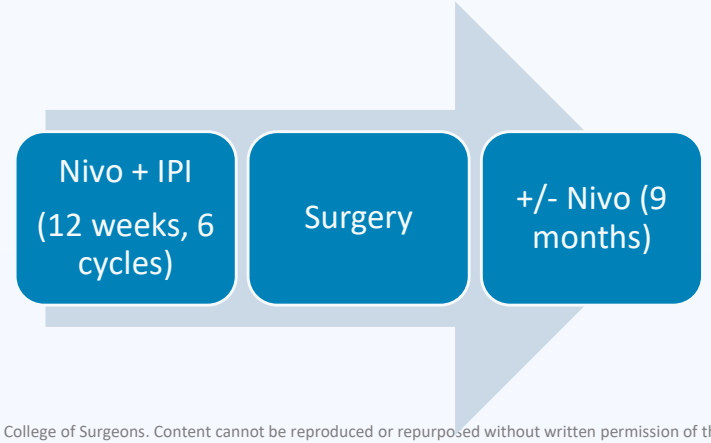
	N=18
pCR	**60%**
Major pathologic response*	80%
≥ Grade III AE's	17%

Vs. 17% in TOPGEAR (chemoXRT + chemo)

*<10% viable cells

NEONIPIGA Trial: Immunotherapy for MSI-H tumors

- Phase II, multi-center, single-arm study from France
- Resectable, ≥cT2 N *any* GEJ/gastric adeno, dMMR/MSI-H tumors
- Investigator choice for adjuvant therapy = 9 months of additional Nivo



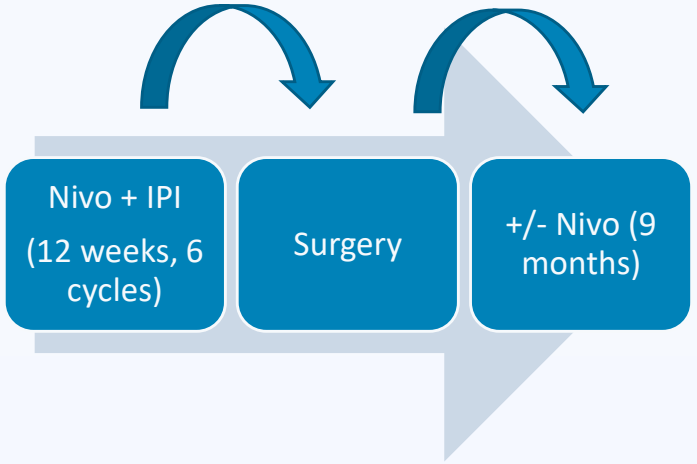
- Primary endpoint = pCR of 20%

Andre et al. 2023, *J Clin Oncol*

NEONIPIGA Trial: Immunotherapy for MSI-H tumors

84% completed all 6
91% underwent surgery
(2 pts refused surgery)

79%



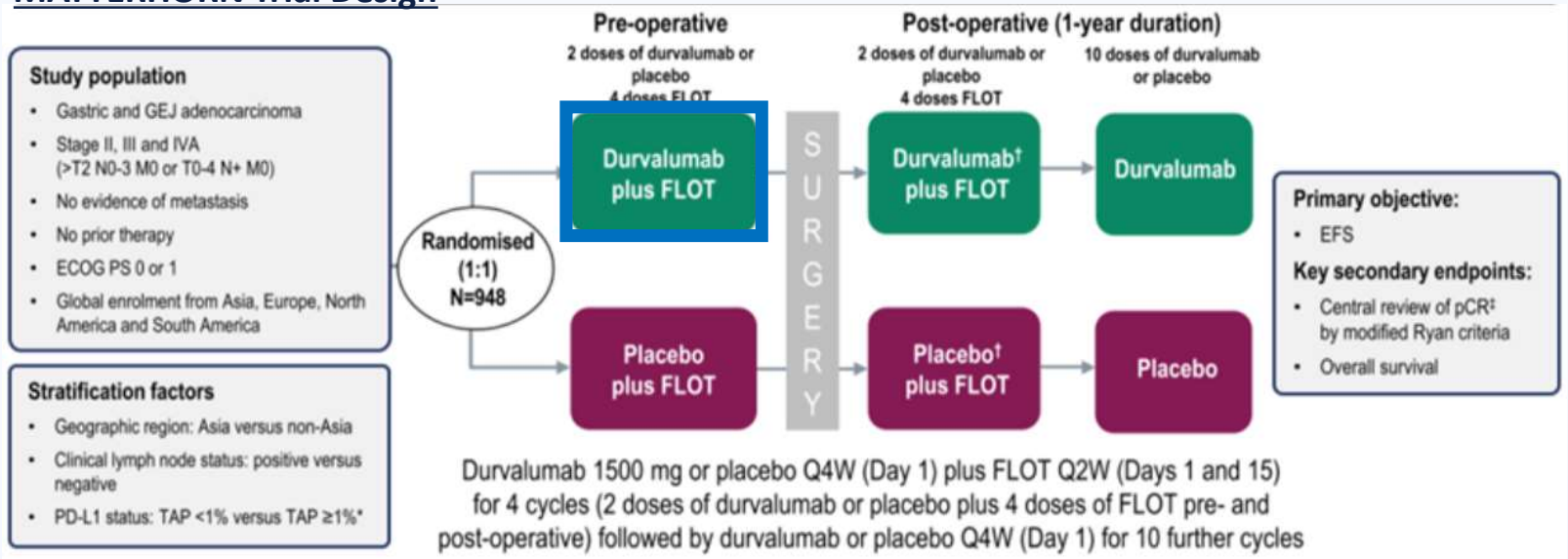
	N=29
pCR	**59%**
≥ Grade III AE's	19%
Clavien-Dindo ≥ 3 surgical complications	47%

6/29 (21%) postop fistula

Andre et al. 2023, *J Clin Oncol*

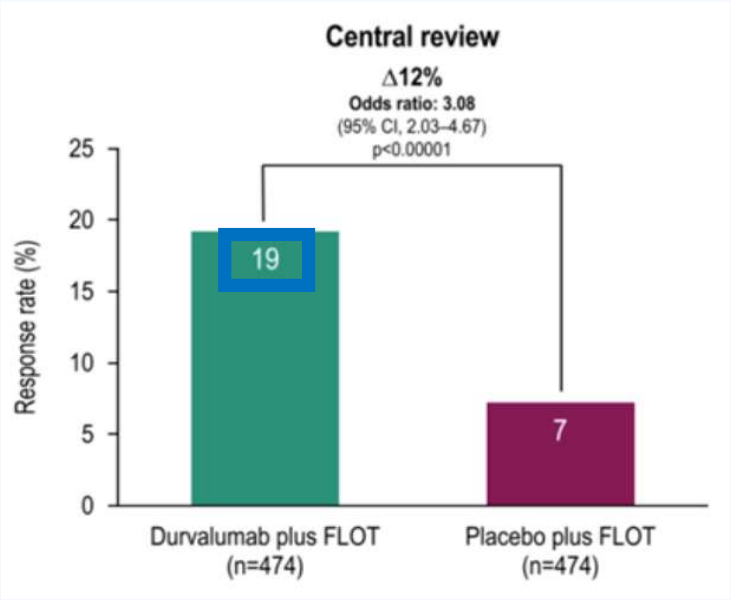
MATTERHORN and Keynote-585: Immunotherapy + peri-op chemo

MATTERHORN Trial Design



Janjigian YY et al. 2022, *Future Oncol*

MATTERHORN study: Immunotherapy + peri-op chemo

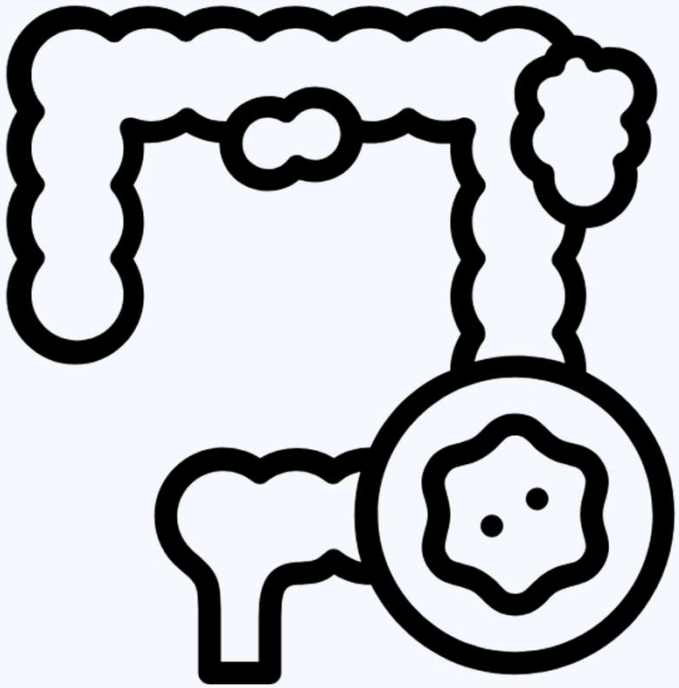


ASCO 2024 Updated results (global)

Region	D + FLOT: pCR, n/N; % (95% CI)	P + FLOT: pCR, n/N; % (95% CI)	Odds Ratio (95% CI)
Global	91/474; 19 (15.7–23.0)	34/474; 7 (5.0–9.9)	3.08 (2.03–4.67)
Asia	17/90; 19 (11.4–28.5)	5/90; 6 (1.8–12.5)	3.96 (1.39–11.26)
Japan	7/40; 18 (7.3–32.8)	3/46; 7 (1.4–17.9)	3.04 (0.73–12.66)
Europe	47/256; 18 (13.8–23.7)	21/250; 8 (5.3–12.6)	2.45 (1.42–4.24)
Germany	14/47; 30 (17.3–44.9)	9/70; 13 (6.1–23.0)	2.88 (1.13–7.35)
Spain	6/37; 16 (6.2–32.0)	3/24; 13 (2.7–32.4)	1.35 (0.30–6.03)
Poland	9/37; 24 (11.8–41.2)	3/22; 14 (2.9–34.9)	2.04 (0.49–8.51)
North America	12/42; 29 (15.7–44.6)	3/40; 8 (1.6–20.4)	4.93 (1.27–19.10)
USA	4/24; 17 (4.7–37.4)	3/29; 10 (2.2–27.4)	1.73 (0.35–8.64)
South America	15/86; 17 (10.1–27.1)	5/94; 5 (1.7–12.0)	3.76 (1.30–10.84)
Brazil	7/24; 29 (12.6–51.1)	1/30; 3 (0.1–17.2)	11.94 (1.35–105.54)

Janjigian YY et al. 2022, *Future Oncol*

COLON CANCER

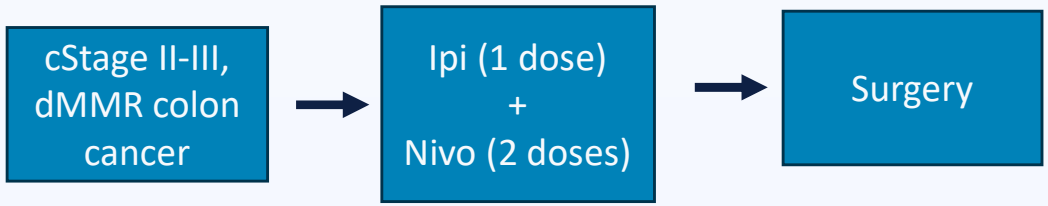


NICHE Trial

- Built upon recent FOxTROT study supporting use of neoadjuvant therapy for locally advanced colon ca
  - Highly dependent on MMR status → only 7% of dMMR responded to chemotherapy
- Prospective, Phase II study of dual agent neoadjuvant IO (Nivo + Ipi)) for locally advanced, dMMR colon cancer
- Two primary endpoints
  - Safety → defined as timely surgery within 2 weeks of planned date
  - 3-year DFS

98% met the safety primary endpoint

6 weeks target



**amendment in Oct 2020 to only include cT3 or cN+ to enrich for "high-risk disease"*

NICHE Trial

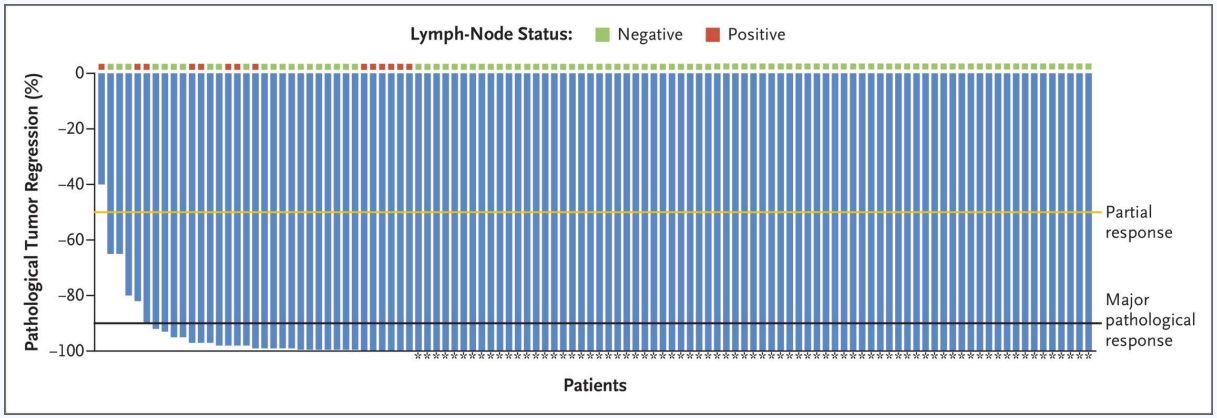
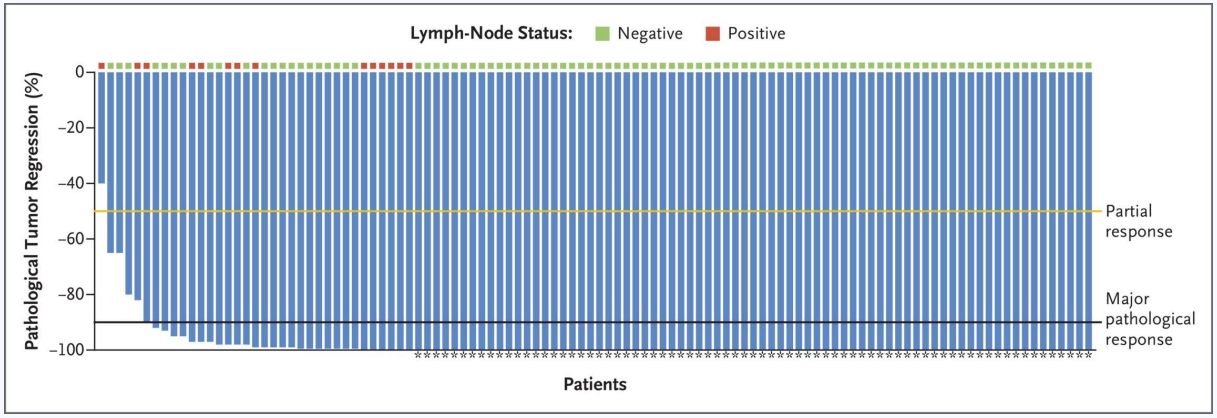


Table 2. Pathological Responses among Patients in the Efficacy Analysis.*

Residual Viable Tumor	Patients (N = 111)
	no. (%)
≤50% Residual viable tumor	109 (98)
≤10% Residual viable tumor: major pathological response	105 (95)
0% Residual viable tumor: complete pathological response	75 (68)
11–49% Residual viable tumor: partial pathological response	4 (4)
≥50% Residual viable tumor, indicating lack of pathological response	1 (1)
Unable to be evaluated†	1 (1)

* For patients with a synchronous second tumor in the colon, the response observed in the tumor with the highest baseline stage is shown.
† In one patient, the tumor bed could not be determined, and therefore, the percentage of residual viable tumor could not be calculated.

NICHE Trial



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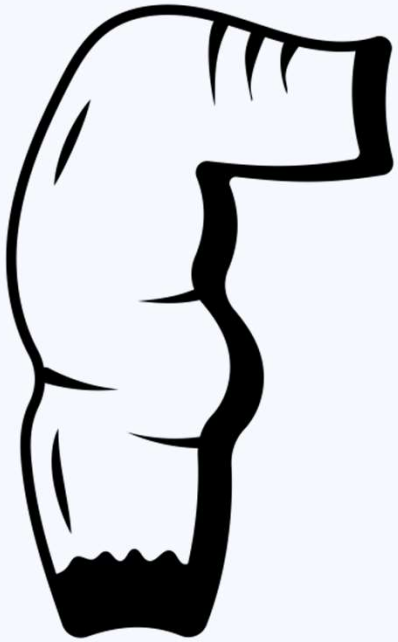
Unable to be evaluated†	1 (1)

* For patients with a synchronous second tumor in the colon, the response observed in the tumor with the highest baseline stage is shown.
† In one patient, the tumor bed could not be determined, and therefore, the percentage of residual viable tumor could not be calculated.

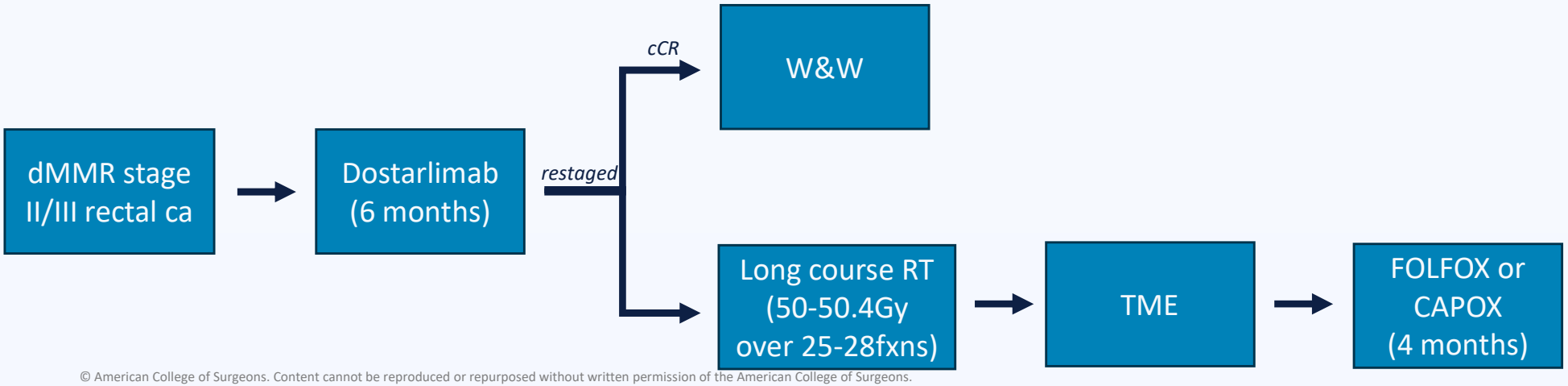
- No disease recurrences at median of 26.2 months
- None of the patients beyond 36 months have recurred at 1st publication

RECTAL CANCER

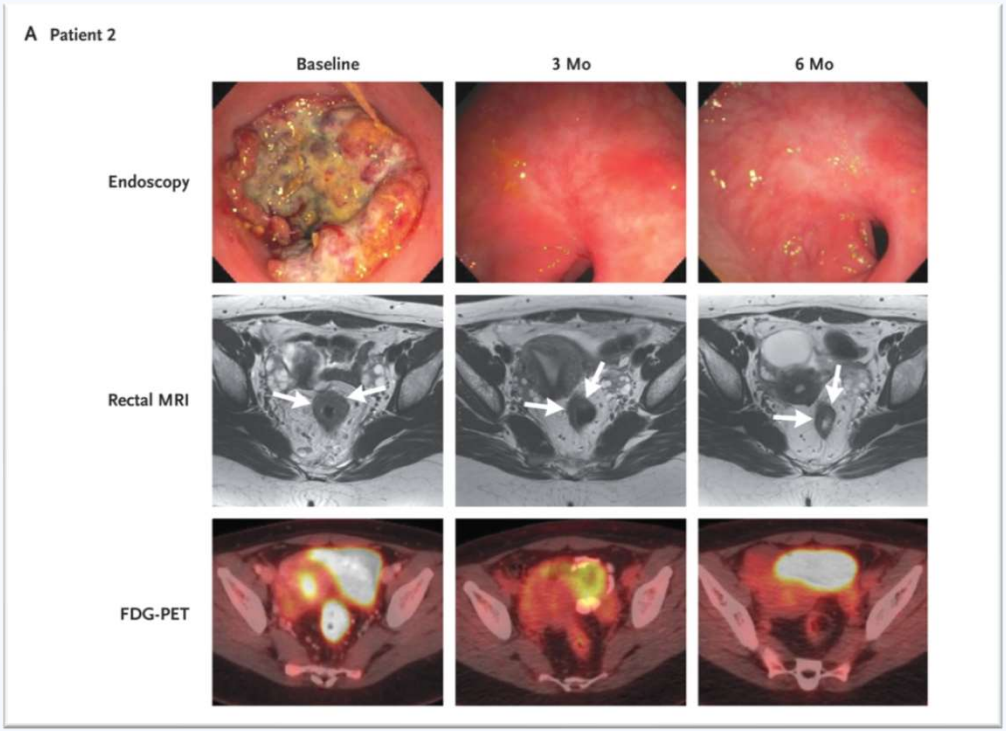


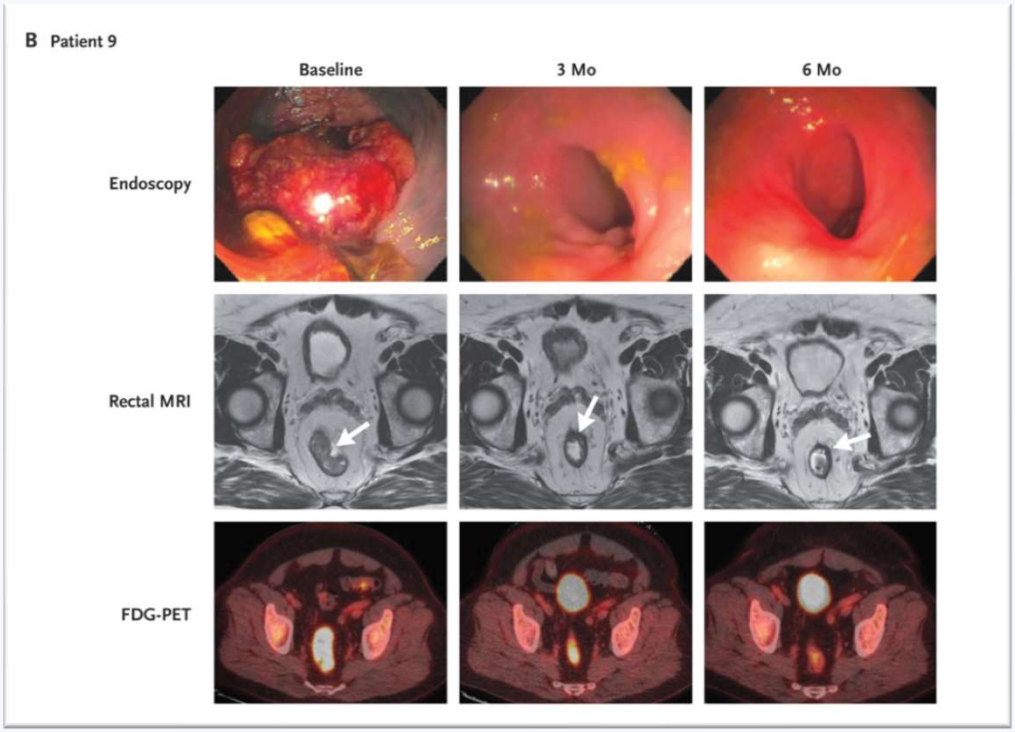
Neoadjuvant IO in dMMR Rectal Cancer

- Prospective, single center, Phase II study of IO (dostarlimab) for dMMR rectal cancer
- Primary endpoint → cCR 12 months after completion of IO or pCR post-TME



Evolution of Endoscopic and Radiographic Response in Representative Patients Treated with Dostarlimab.

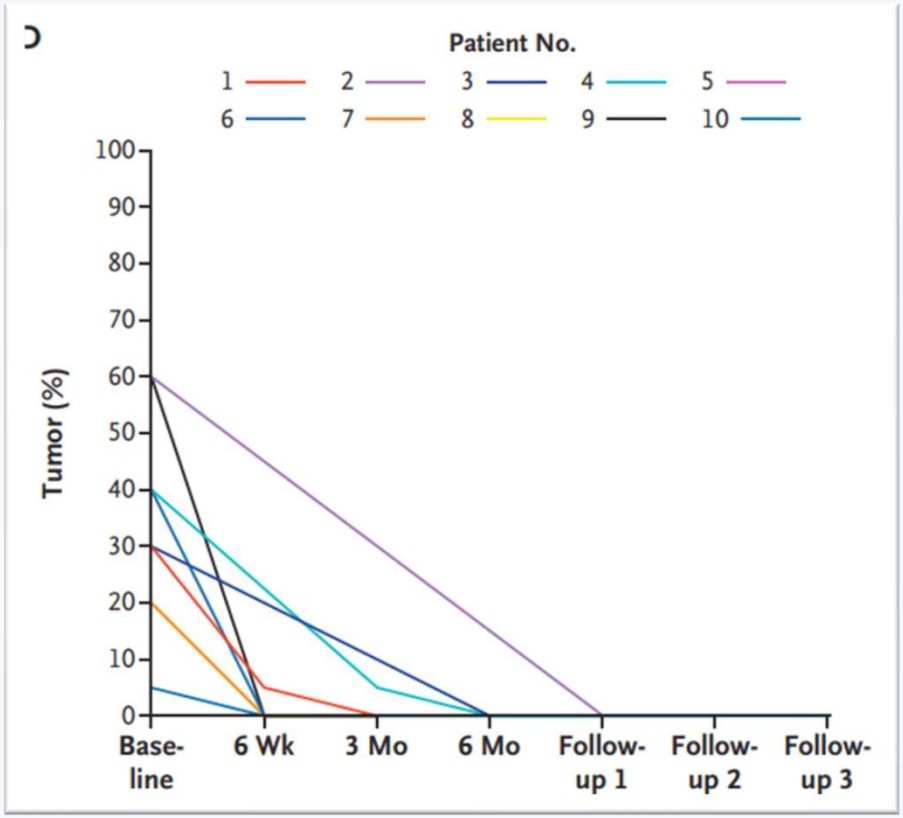




The NEW ENGLAND JOURNAL of MEDICINE

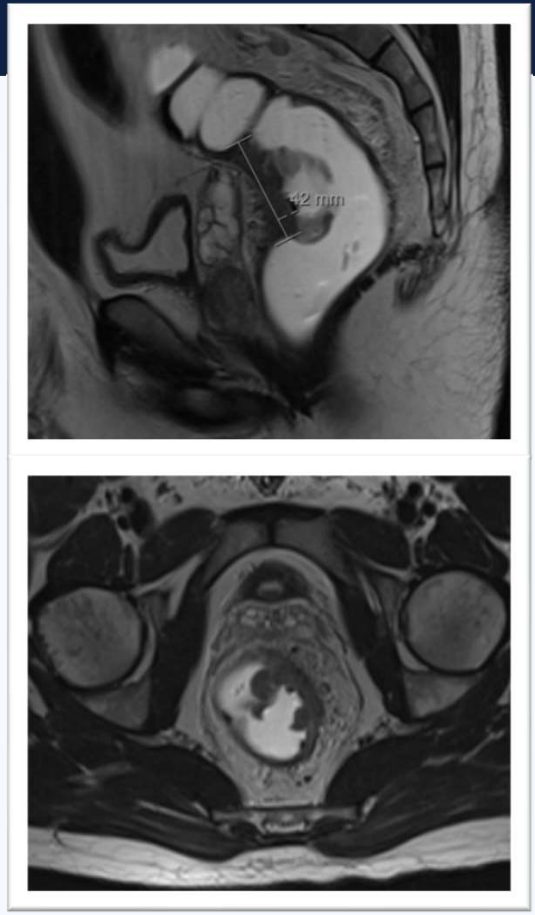
Cercek A et al. N Engl J Med2022;386:2363-2376

Neoadjuvant IO in dMMR

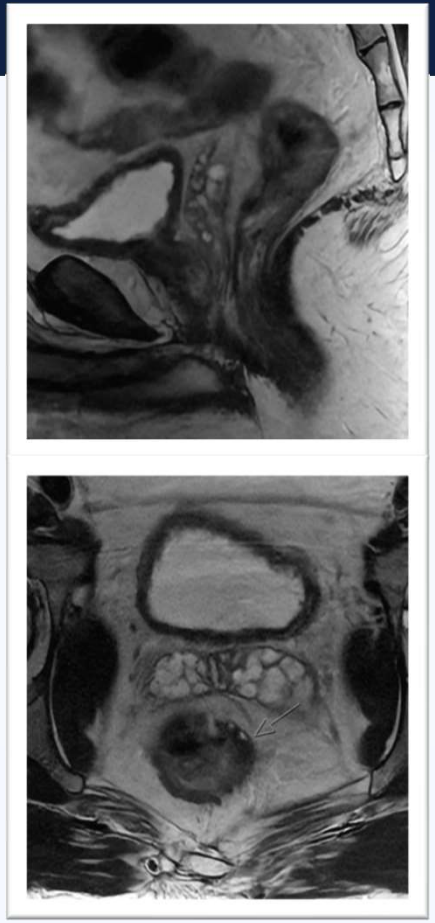


- All 12 patients had cCR upon restaging post-IO
- None went on to chemoradiation or surgery
- No adverse events ≥ grade 3 reported

April 2024



February 2025



Conclusion

- Amazing promise and responses in subset of GI patients with dMMR and Immunotherapy, but many ongoing questions to answer.
- Long term outcomes
- Recurrence patterns
- Retreatment with IO if recurrence
- Surveillance strategies, timing, modality
- How do we expand these results to treat a wider range of patients
- Do we need to operate

THANK YOU

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