טיפול בסרטן מעי גס מקומי MMR-D/MSI-H
האם ניתן לוותר על ניתוח?

דר' שחם שמואלי עינת

מנהלת יחידת גידולי מערכת העיכול

מרכז הסרטן, שיבא

Tasuku Honjo and James Allison 2018 Nobel Prize in Physiology/Medicine for their discovery of immune checkpoint proteins (CTLA-4 for Allison, PD-1 for Honjo)

The NEW ENGLAND JOURNAL of MEDICINE

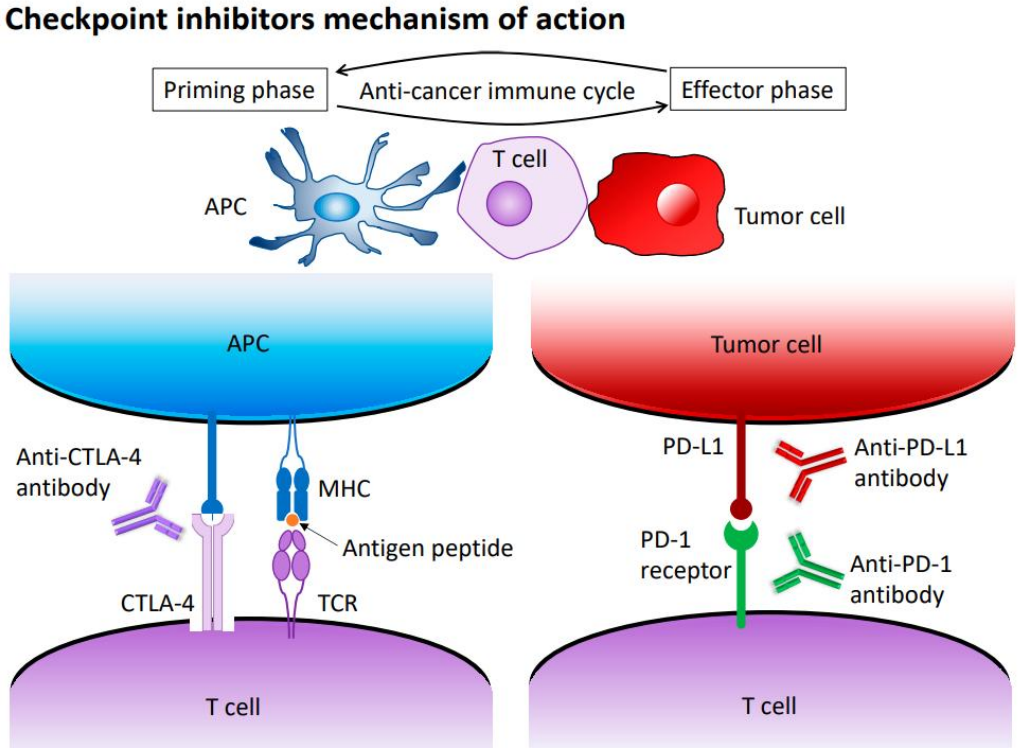
ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

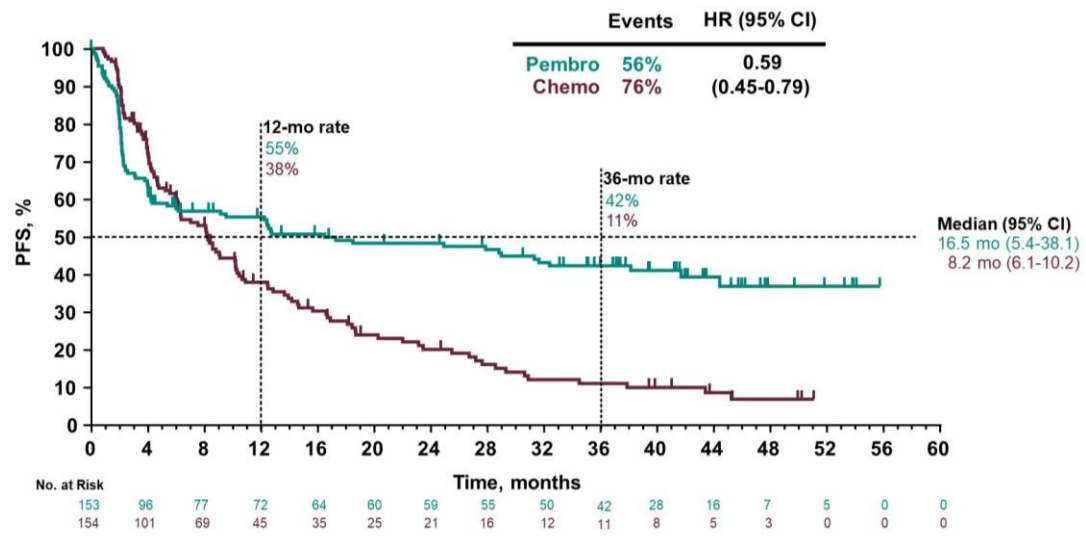
Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

Immunotherapy for MSI-H/MMR-D

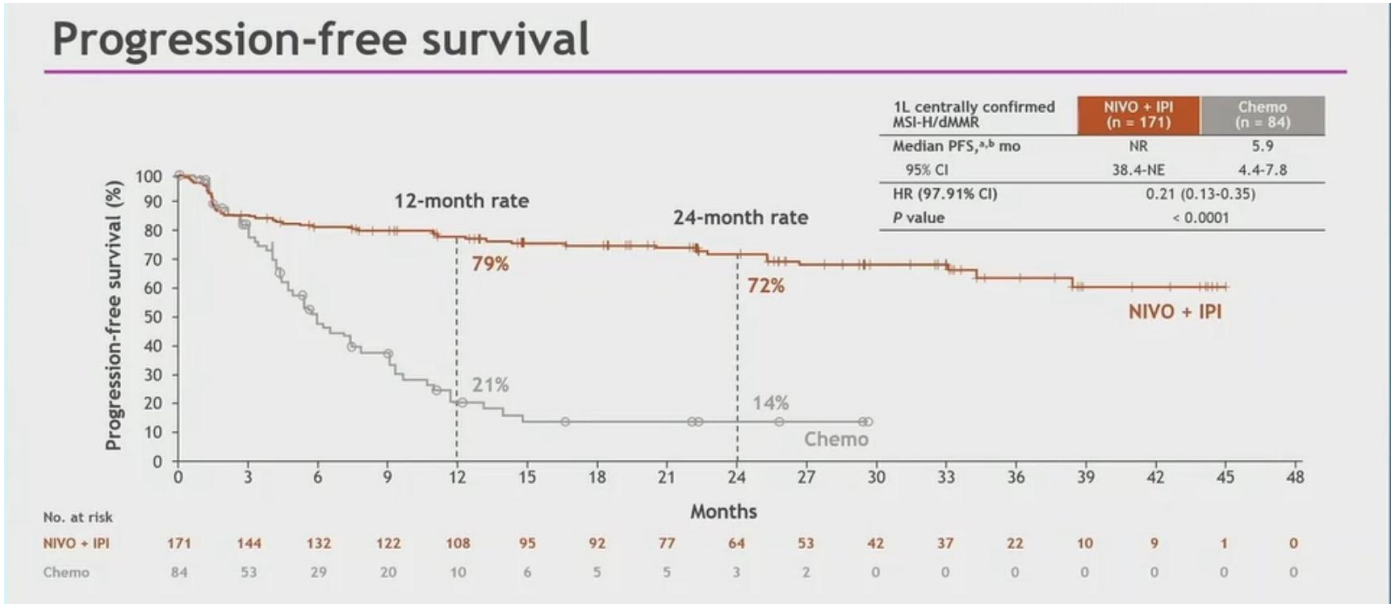
- High tumor mutational burden and immune cell infiltration are hallmarks
- Confer marked and durable response to immunotherapy
- 2017 1st FDA **agnostic** approval of Pembrolizumab for all **Metastatic** MSI-H tumors



KN177


Progression-Free Survival
Events
HR (95% CI)
Pembro 56%
Chemo 76%
0.59
(0.45-0.79)
12-mo rate
55%
38%
36-mo rate
42%
11%
Median (95% CI)
16.5 mo (5.4-38.1)
8.2 mo (6.1-10.2)
PFS, %
Time, months
No. at Risk
153 96 77 72 64 60 59 55 50 42 28 16 7 5 0 0
154 101 69 45 35 25 21 16 12 11 8 5 3 0 0 0

CM8HW


Progression-free survival
1L centrally confirmed MSI-H/dMMR
NIVO + IPI (n = 171)
Chemo (n = 84)
Median PFS,a,b mo
NR
5.9
95% CI
38.4-NE
4.4-7.8
HR (97.91% CI)
0.21 (0.13-0.35)
P value
< 0.0001
12-month rate
24-month rate
79%
72%
NIVO + IPI
21%
14%
Chemo
Progression-free survival (%)
Months
No. at risk
NIVO + IPI 171 144 132 122 108 95 92 77 64 53 42 37 22 10 9 1 0
Chemo 84 53 29 20 10 6 5 5 3 2 0 0 0 0 0 0 0

Immunotherapy for MSI-H **Non metastatic** cancer

Prevalence in GI malignancies

Colon cancer Stage 2-3 - 10– 15 %

Rectal cancer – low prevalence <5%

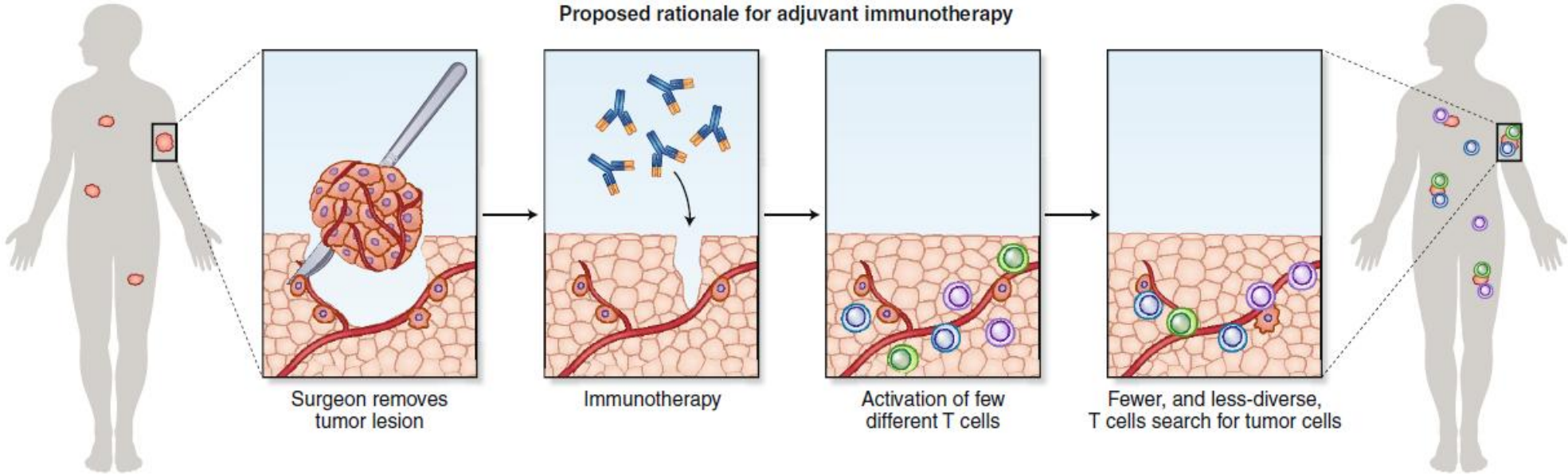
Gastric cancer – 10 %-20 %

1. Cercak A. et al.MMR rectal cancer and resistence to neoadjuvant chemotherapy 2020 1;26(13):3271-3279
2. RattiM. et al. microsatellite instability in gastric cancer .Cell Mol Life Sci 2018; 75(22): 4151–4162

Surgery

↓

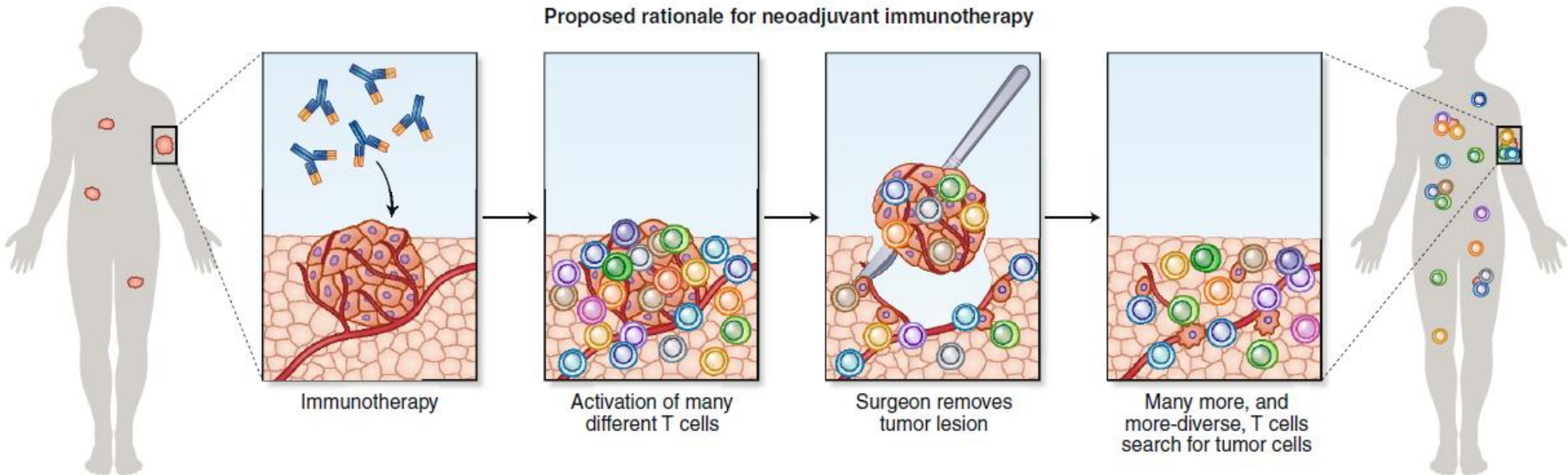
Adjuvant



Neo-adjuvant

↓

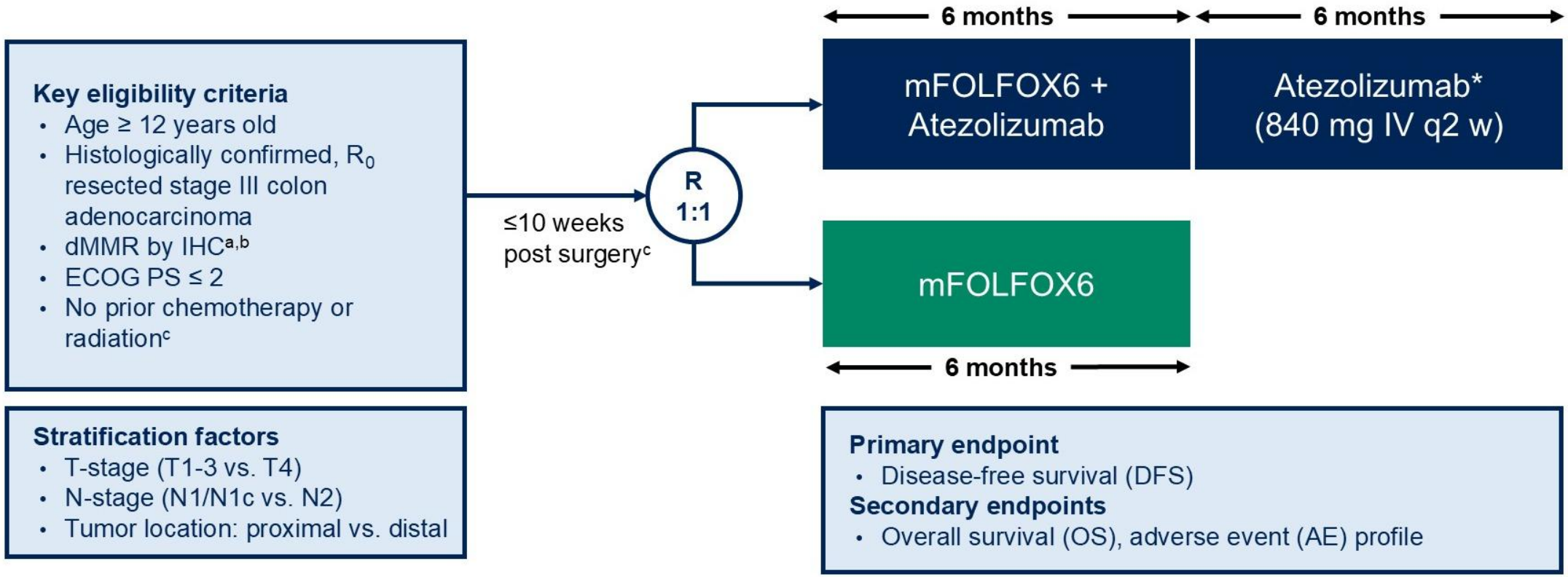
Surgery



Versulius et al. Nat Medicine 2020 p475

Adjuvant

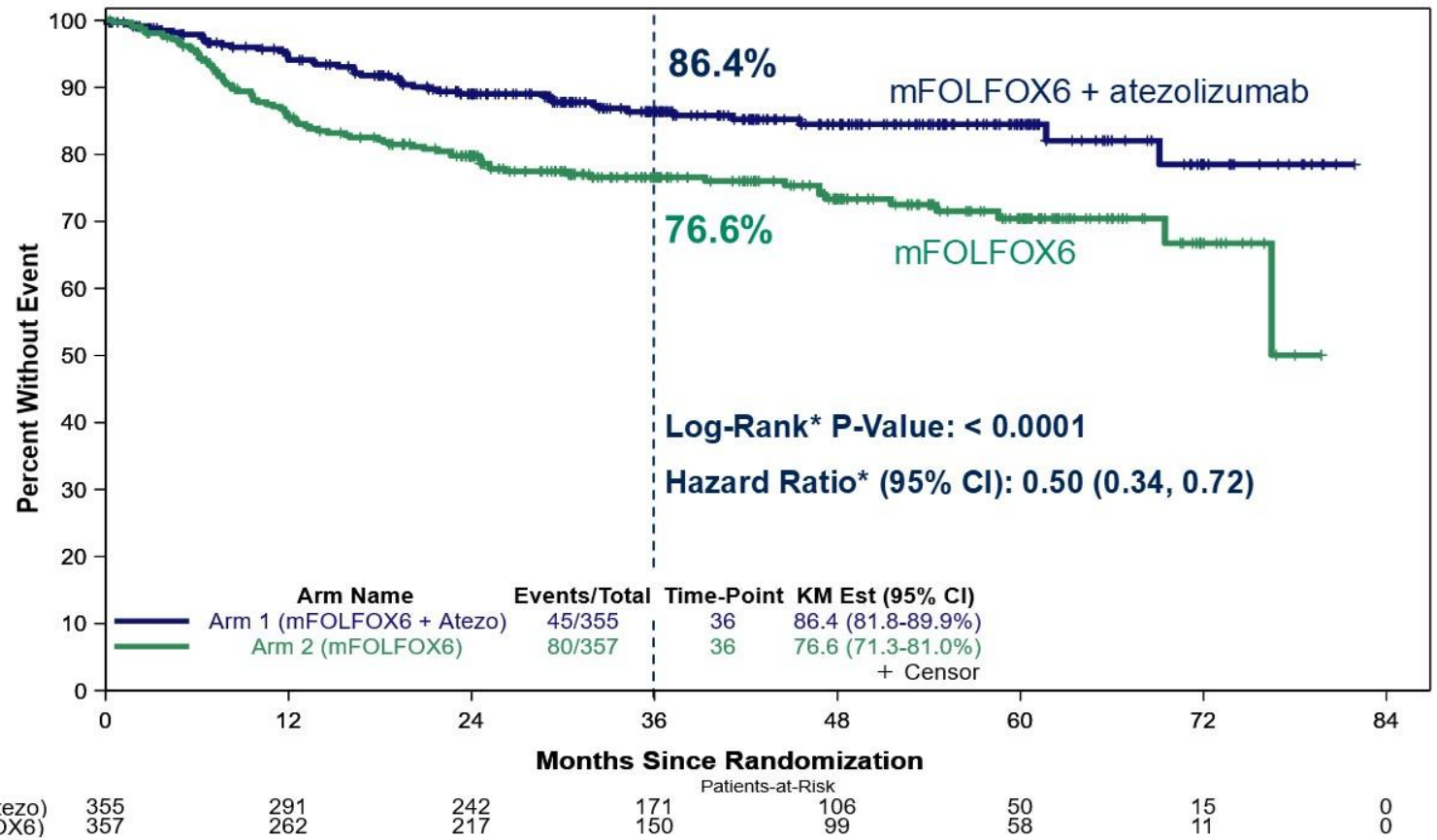
ATOMIC is a randomized, multicenter, open label phase 3 study



[a] **dMMR by immunohistochemistry (IHC) locally or at site-selected reference laboratory. Retrospective central confirmation of dMMR also performed.**
[b] Lynch syndrome included.
[c] One cycle of mFOLFOX6 prior to randomization permitted.

*Atezolizumab (anti-PD-L1)

Primary Endpoint: DFS



Confirmed dMMR by central reference laboratory: Log-Rank P-Value: 0.0007, Hazard Ratio (95% CI): 0.53 (0.36, 0.79)

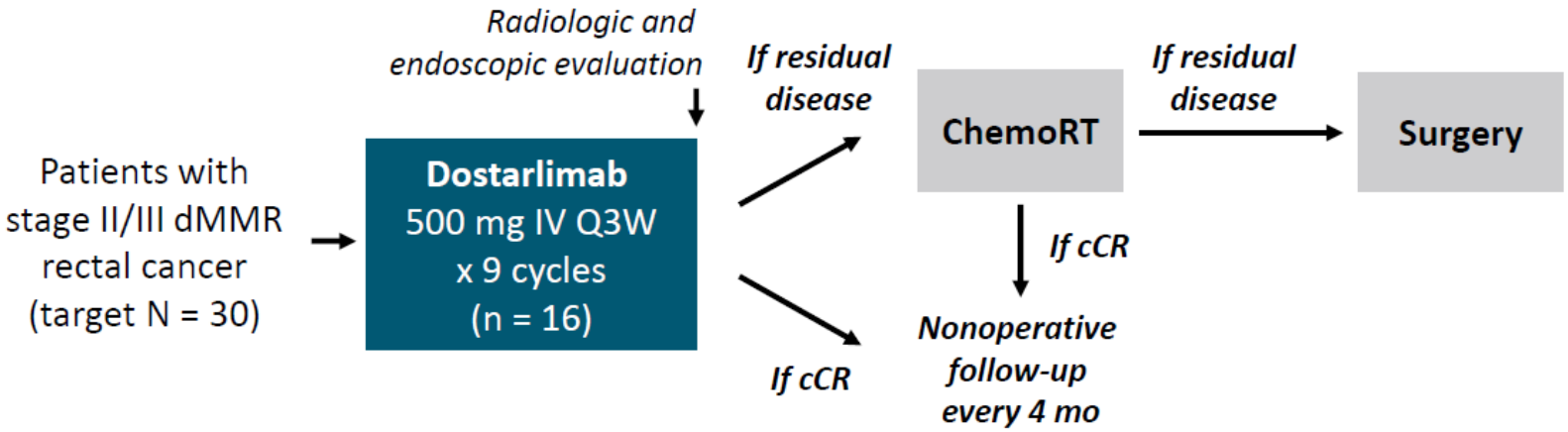
*Stratified by randomization factors

Median follow-up = 37.2 mos

Neo-adjuvant

Dostarlimab for Locally Advanced dMMR Rectal Cancer: Study Design

- Single-arm phase II study



Dostarlimab = anti pd-1

Cercek et al. N Engl J Med 2022;386

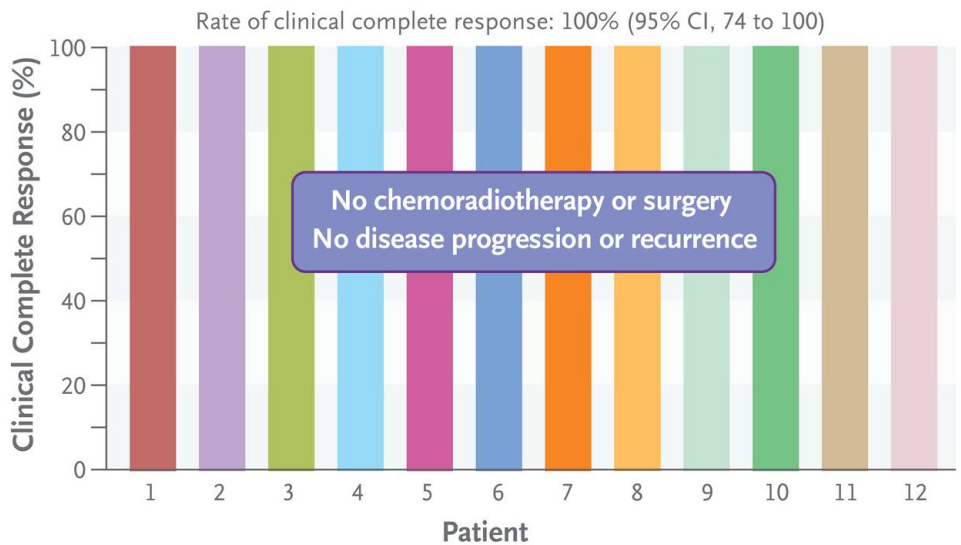
The NEW ENGLAND JOURNAL of MEDICINE

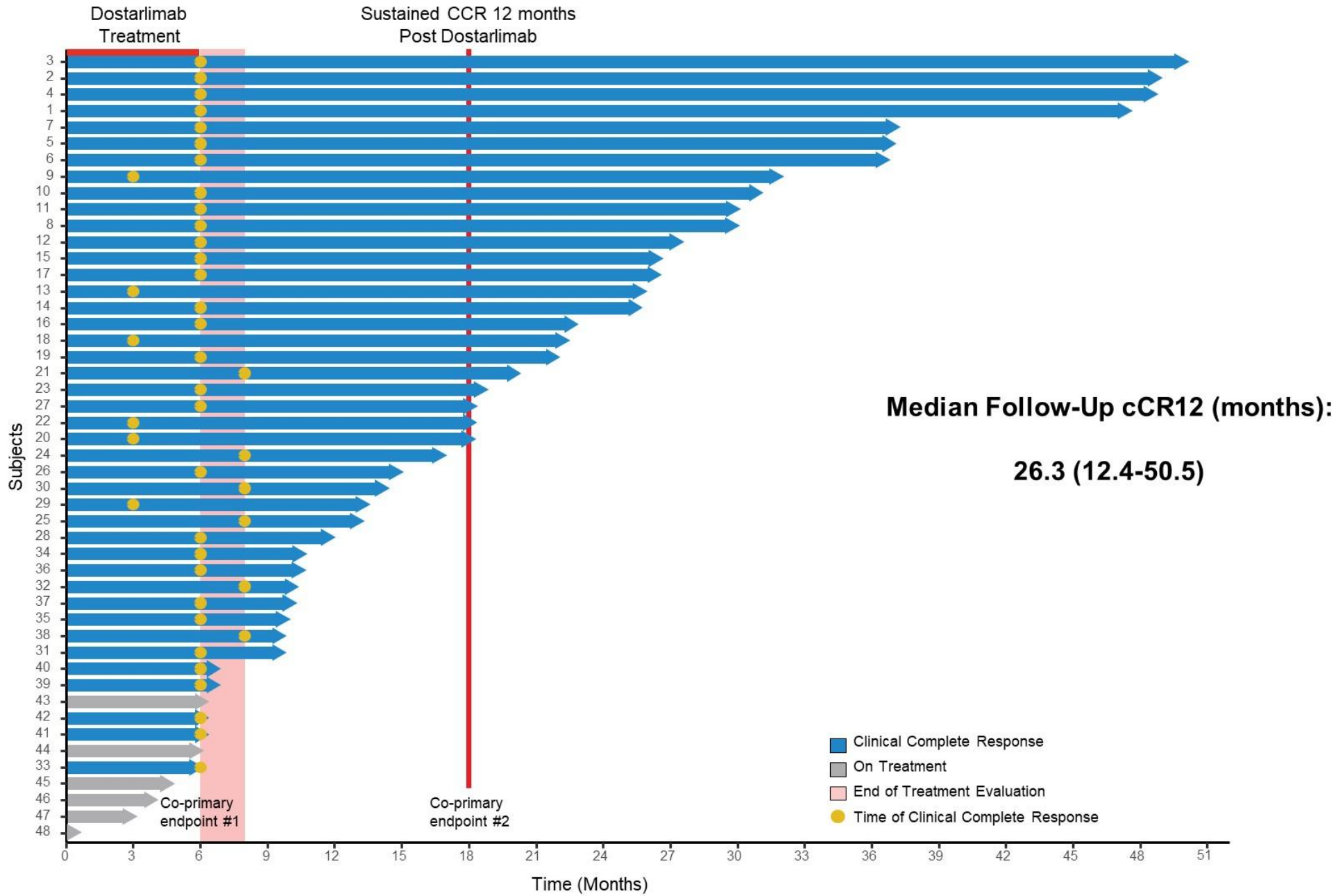
ESTABLISHED IN 1812 JUNE 23, 2022 VOL. 386 NO. 25

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.

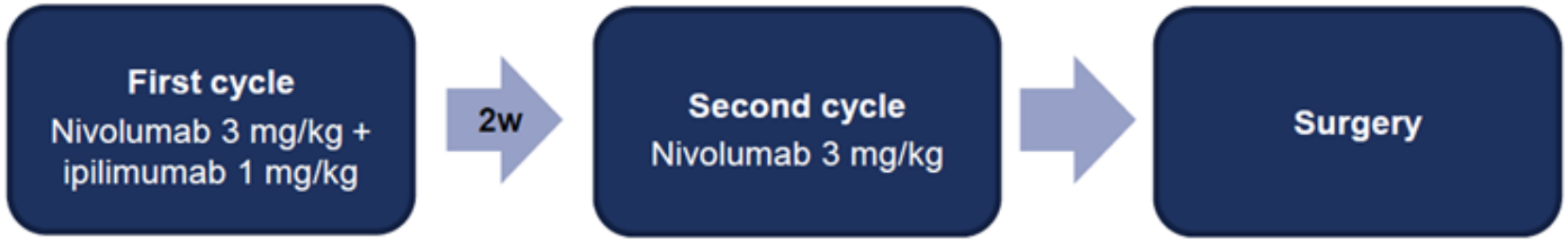
Overall Response to Dostarlimab in 12 Patients




Dostarlimab Treatment
Sustained CCR 12 months Post Dostarlimab
Subjects
3
2
4
1
7
5
6
9
10
11
8
12
15
17
13
14
16
18
19
21
23
27
22
20
24
26
30
29
25
28
34
36
32
37
35
38
31
40
39
43
42
41
44
33
45
46
47
48
Co-primary endpoint #1
Co-primary endpoint #2
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
48
51
Time (Months)
Clinical Complete Response
On Treatment
End of Treatment Evaluation
Time of Clinical Complete Response
Median Follow-Up cCR12 (months):
26.3 (12.4-50.5)

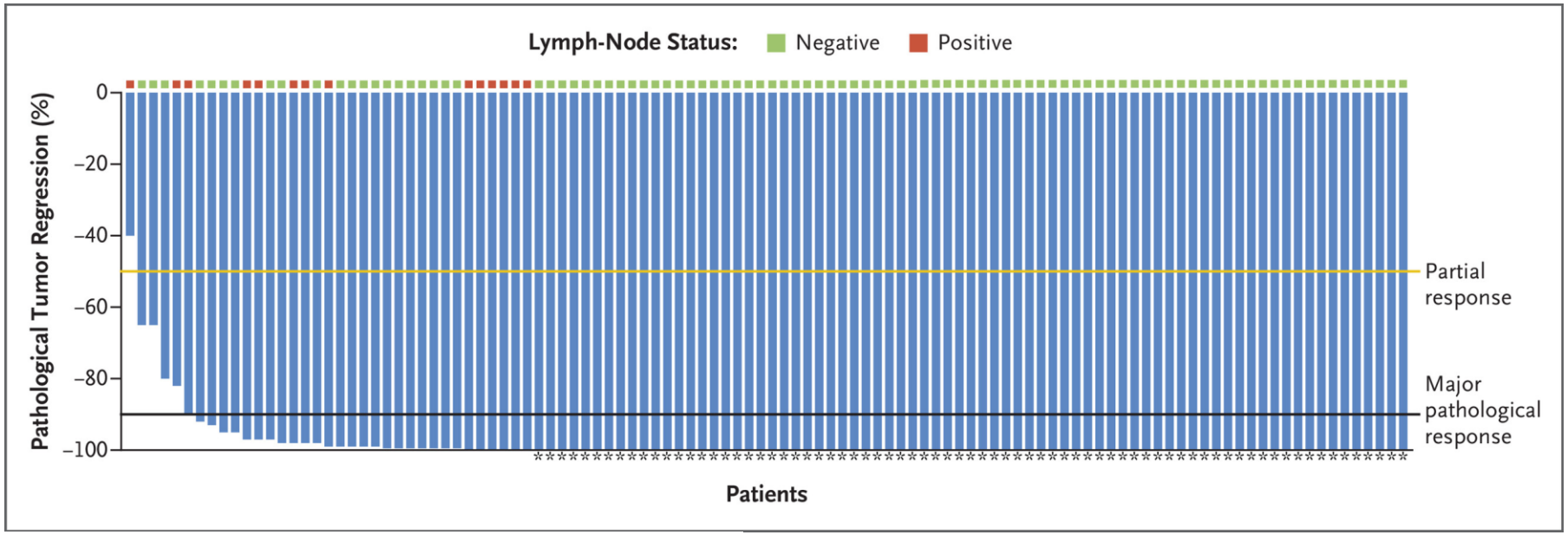
NICHE-2 study design

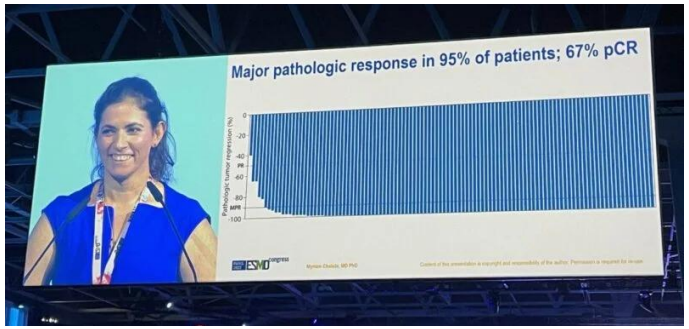
115 patients
locally advanced and previously untreated dMMR colon cancers

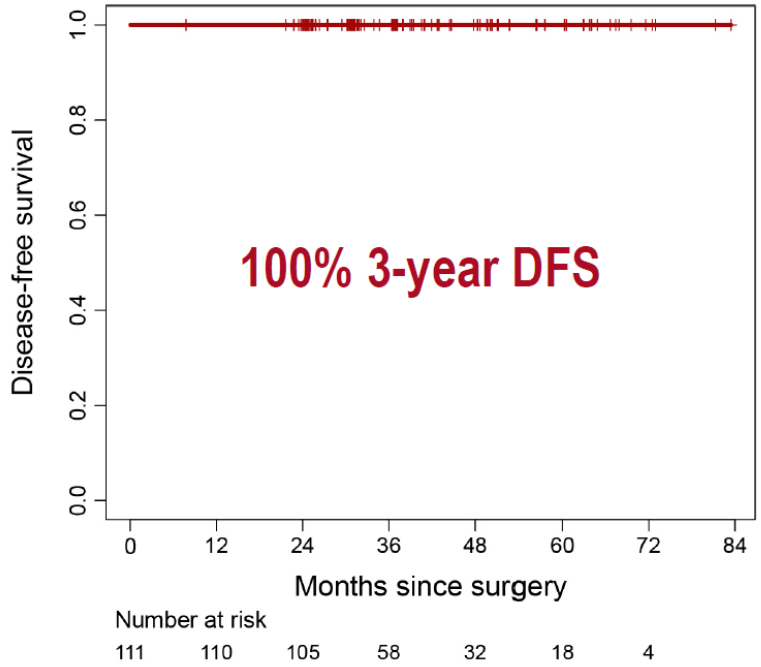


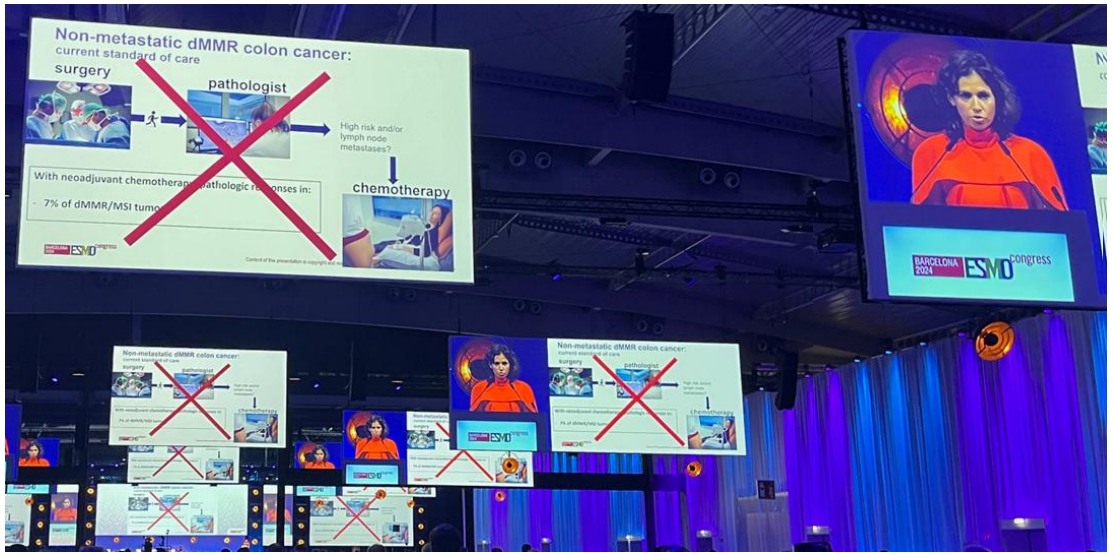
Nivolumab = Anti PD1
Ipilimumab = Anti CTLA4

Chalabi et al. N Engl J Med 2024;390:1949-1958


Lymph-Node Status: Negative Positive
Pathological Tumor Regression (%)
0
−20
−40
−60
−80
−100
Partial response
Major pathological response
Patients


Major pathologic response in 95% of patients; 67% pCR


Disease-free survival
1.0
0.8
0.6
0.4
0.2
0.0
100% 3-year DFS
0
12
24
36
48
60
72
84
Months since surgery
Number at risk
111
110
105
58
32
18
4


Non-metastatic dMMR colon cancer:
current standard of care
surgery
pathologist
chemotherapy
BARCELONA 2024 ESMO congress

Do we need surgery??

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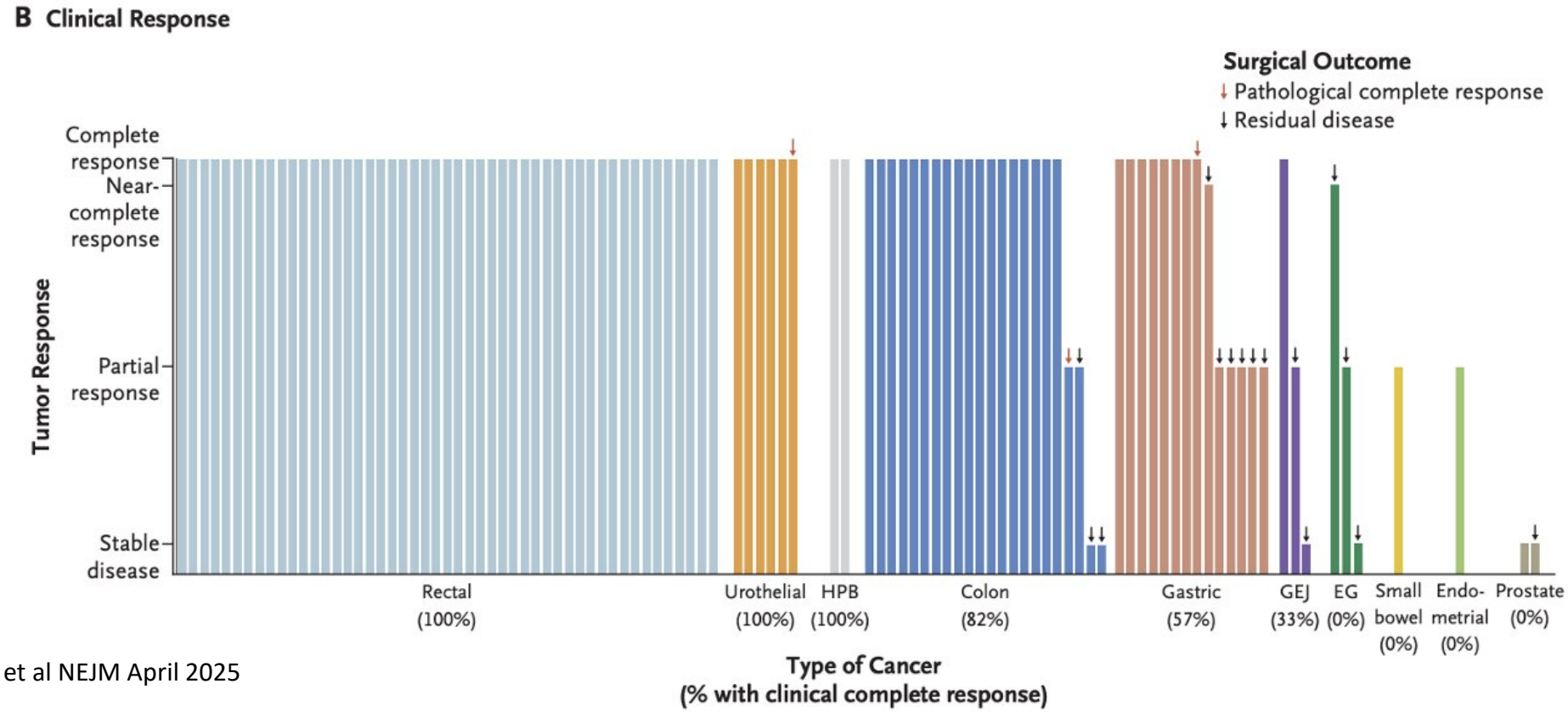
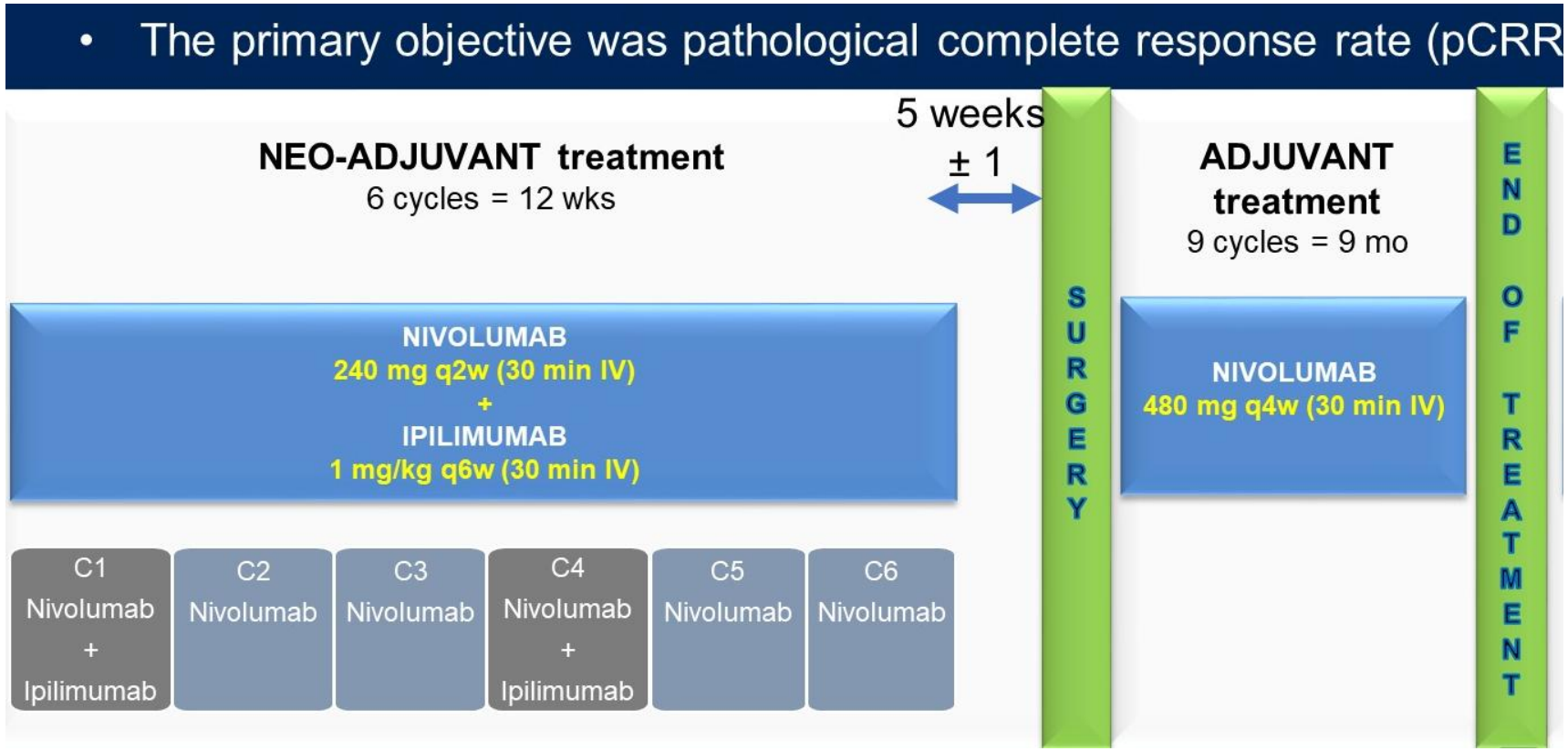
ORIGINAL ARTICLE

Nonoperative Management of Mismatch Repair–Deficient Tumors



Cercek et al NEJM April 2025

NEONIPIGA – Gastric/GEJ MSI-H

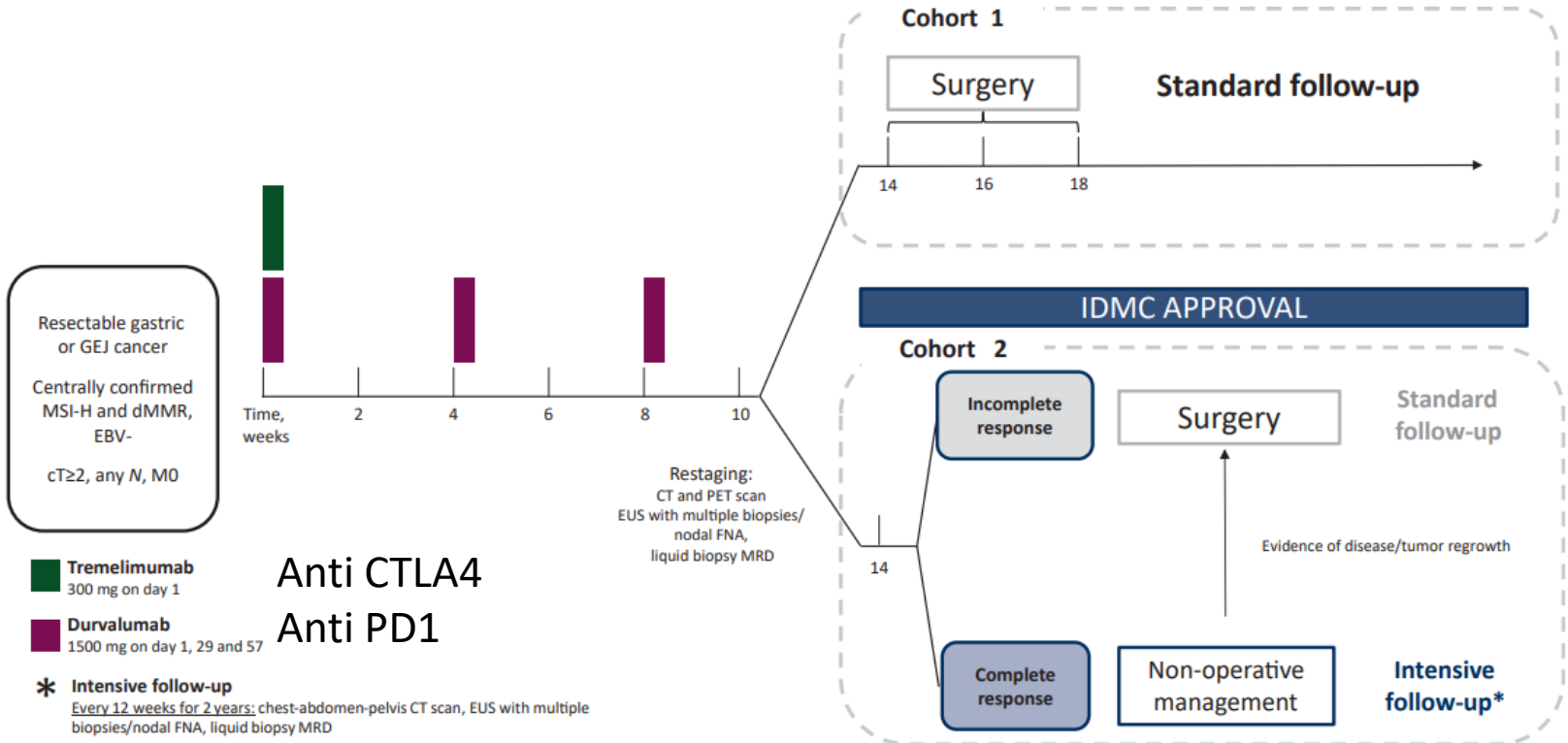


17 pts (58.6%) achieved pCR in primary & LN
2 pts T0, some tumoral cells in one node (MPR)

Nivolumab = Anti PD1
Ipilimumab = Anti CTLA4

Andre et al. JCO 2023, 41, 255-265

INFINITY – Gastric/GEJ Msi-H

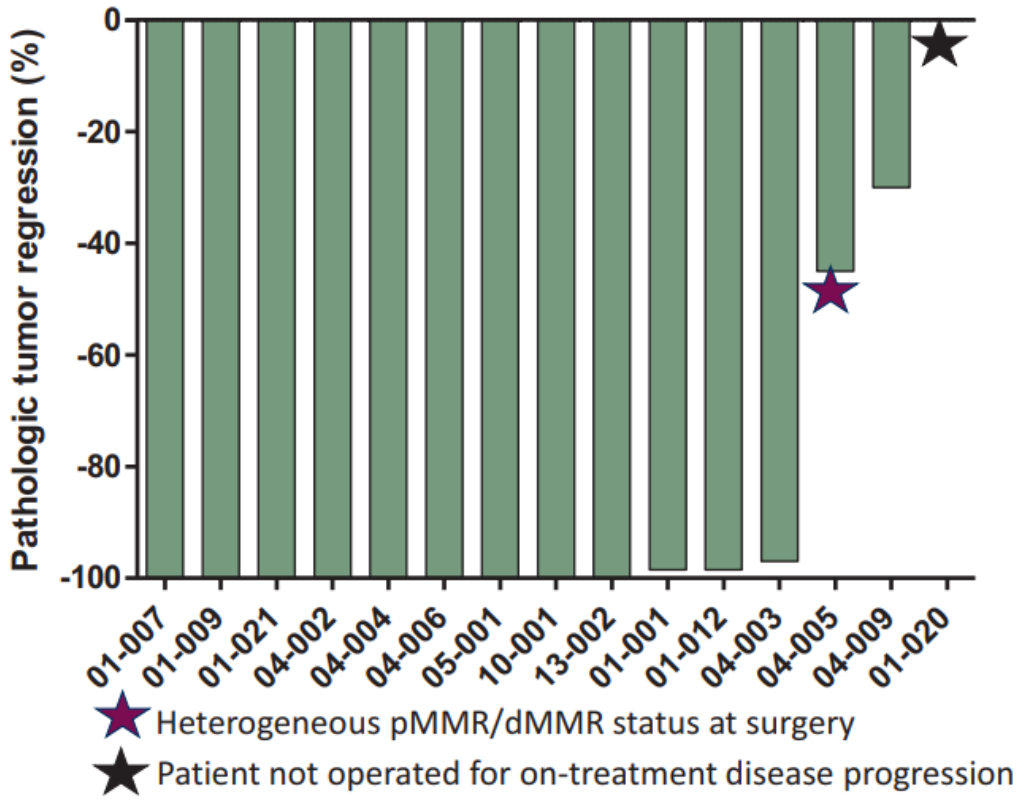


18 Pts

18 Pts

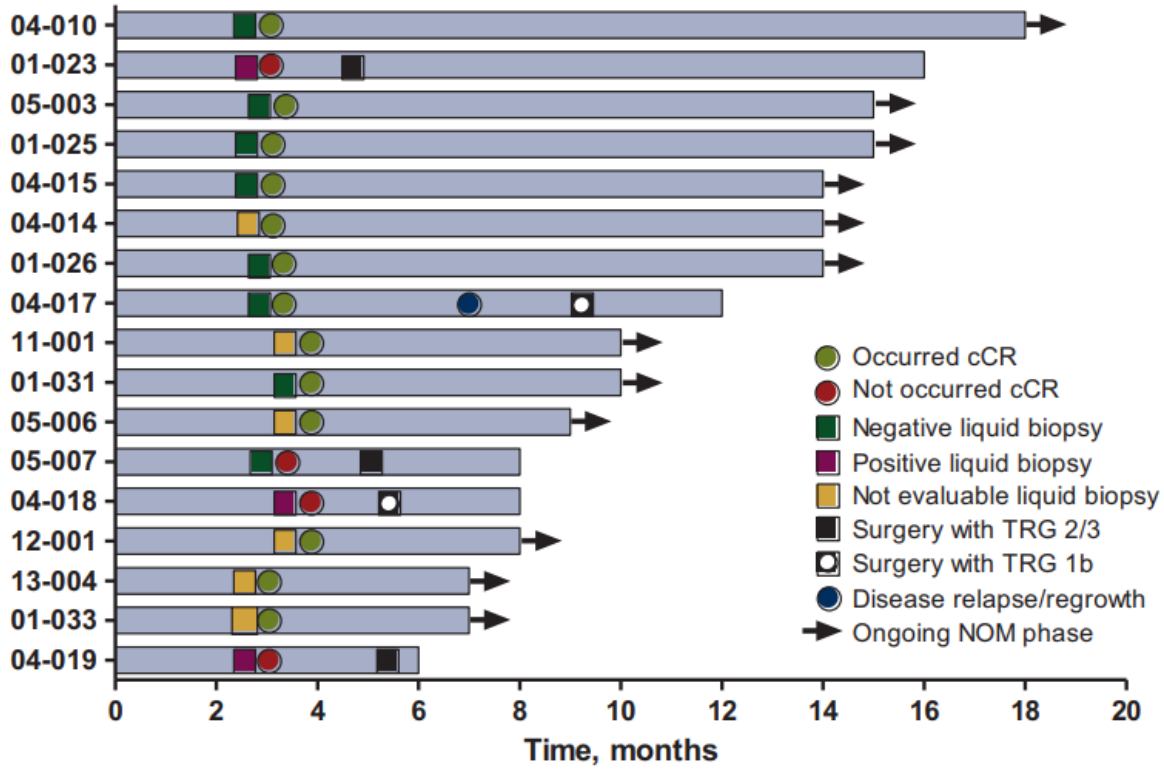
GONO trial. Rainmondi et al. Ann Of Oncol April 2025

Operative Management



60% pCR + 20% Major Path Respons (<10% viable cells)
2 y DFS 66%
2 y OS 73%

Nonoperative Management



76% cCR → NOM

1 y PFS 94%

1 y OS 100%

4 pts who did not reach cCR underwent salvage surgery (without disease relapse on short follow up)

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NCCN Guidelines Version 4.2025
dMMR/MSI-H Rectal Cancer

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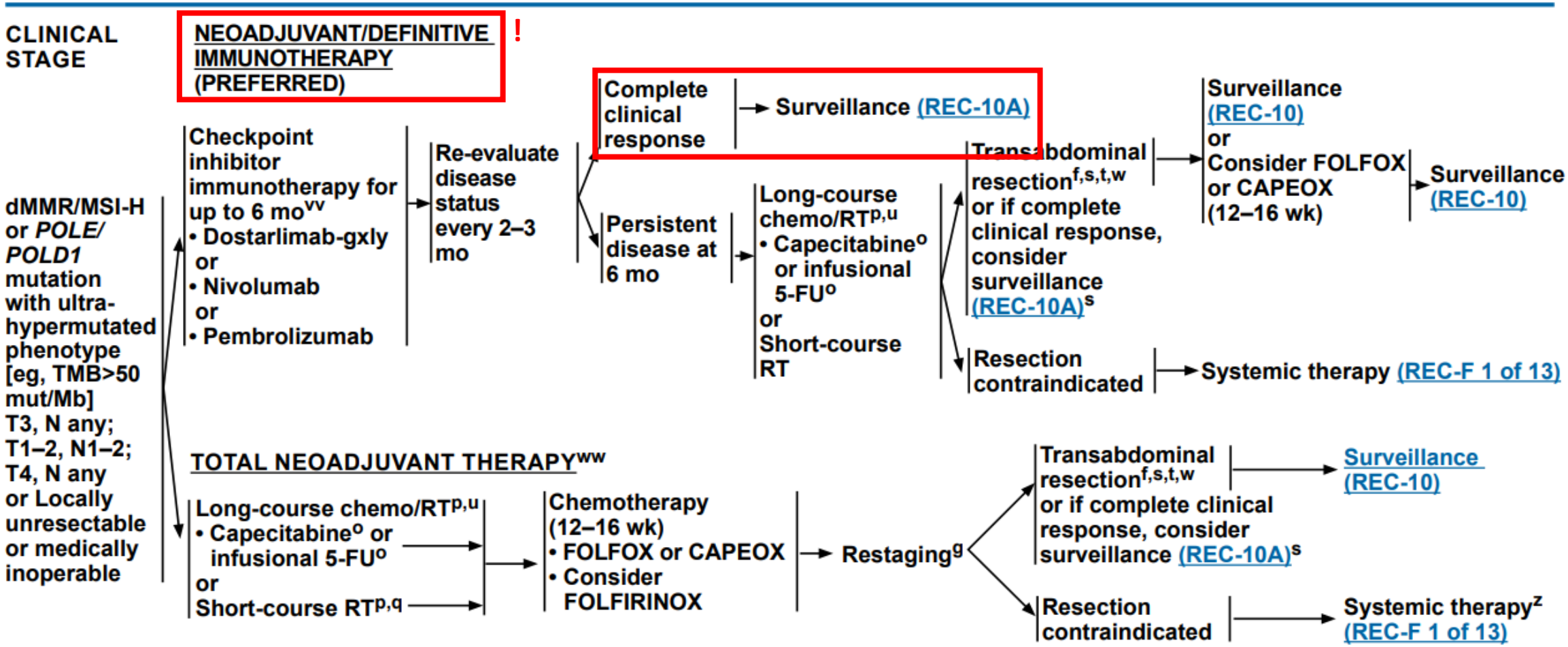

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dMMR/MSI-H Colon Cancer

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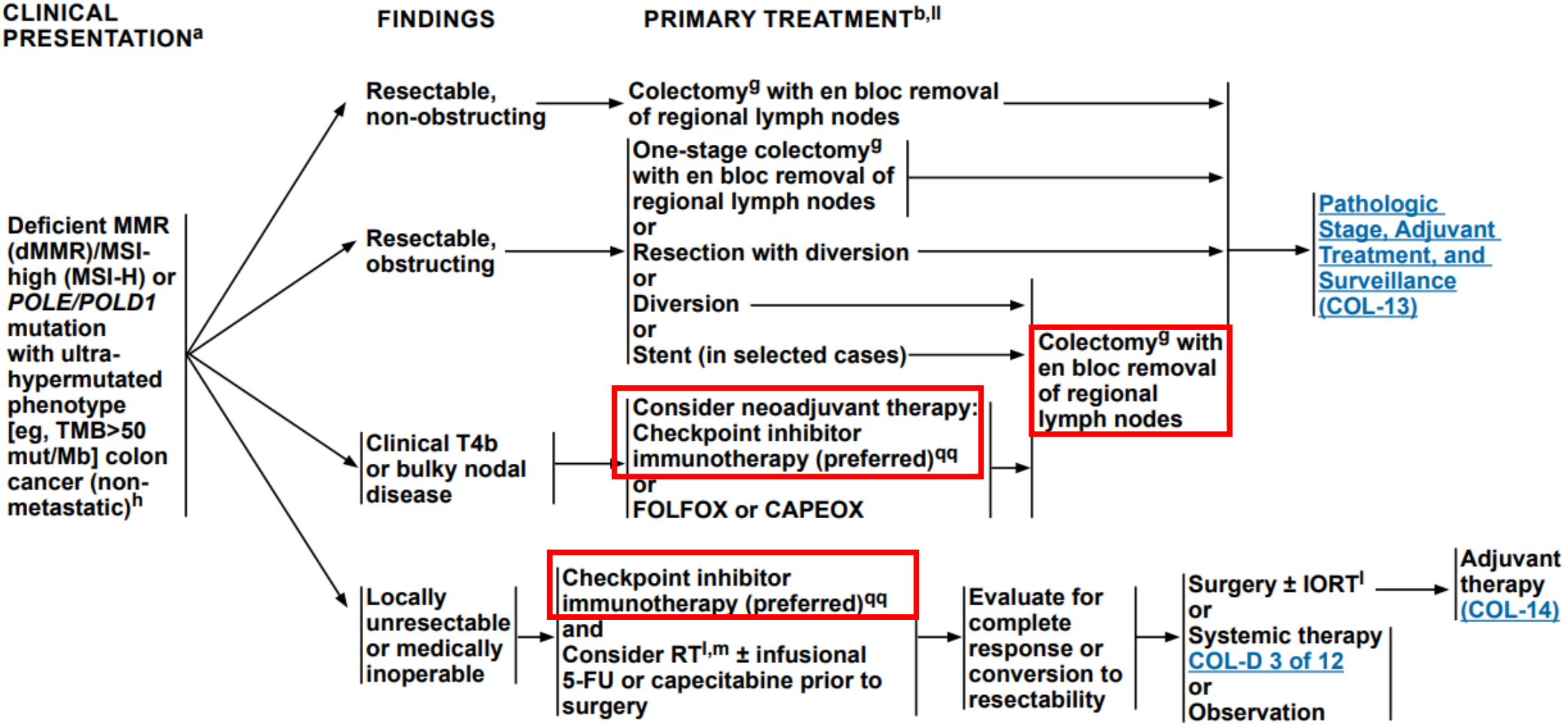

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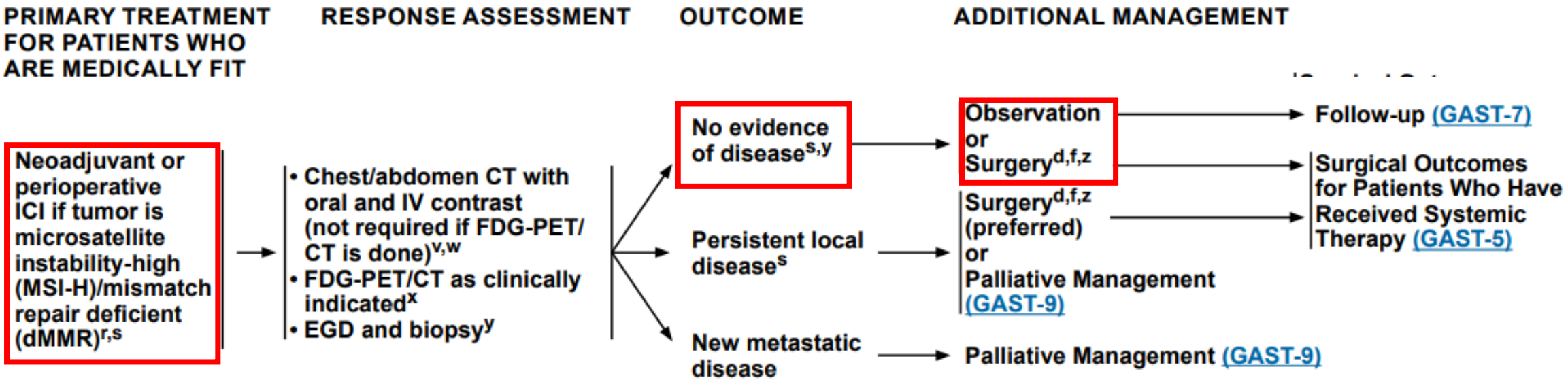
NCCN Guidelines Version 1.2026
Gastric Cancer



Take away

- Neoadjvant IO in MSI-H/MMR-D non metastatic tumors confers
  high (p)CR / major pathological response
- Non Operative Management is feasible

What's missing?

- Who will likely NOT respond? (T4, TMB↓, diffuse type…?)
- limited long term survival outcomes
- No clear treatment protocol (Anti PD1 ± Anti CTLA4, 1-3-6 mo?)
- No Clear protocol to establish cCR → NOM follow up (except in rectal ca)

Real new era