City of Hope

ANNUAL

Advances and Innovations in Endoscopic Oncology and Multidisciplinary Gastrointestinal Cancer Care

Unleashing the Power of Immunotherapy: A New Dawn for Primary Colorectal Cancer Treatment

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City of Hope

Disclosures

- Consultant for AbbVie, Adagene, Bayer, Bristol Myers Squibb, Entos, Janssen, Merck, Microbial Machines, Mirati, Nouscom, Pfizer, Roche/Genentech, Summit, Taiho, Tempus, and Totus

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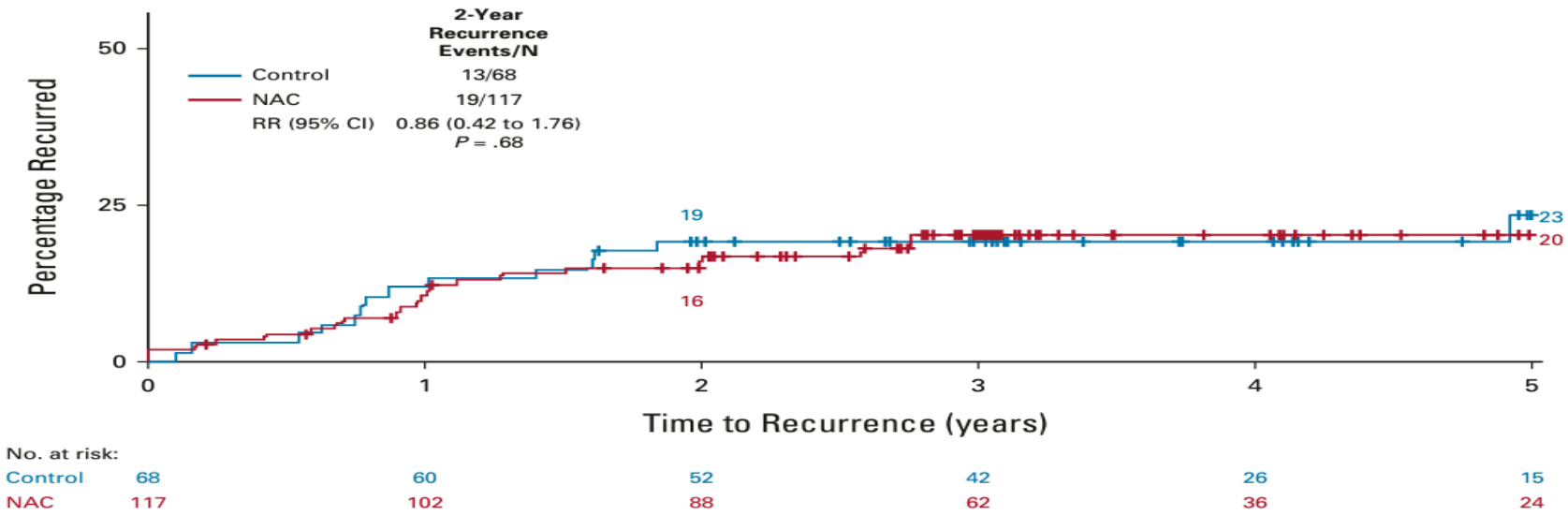
This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

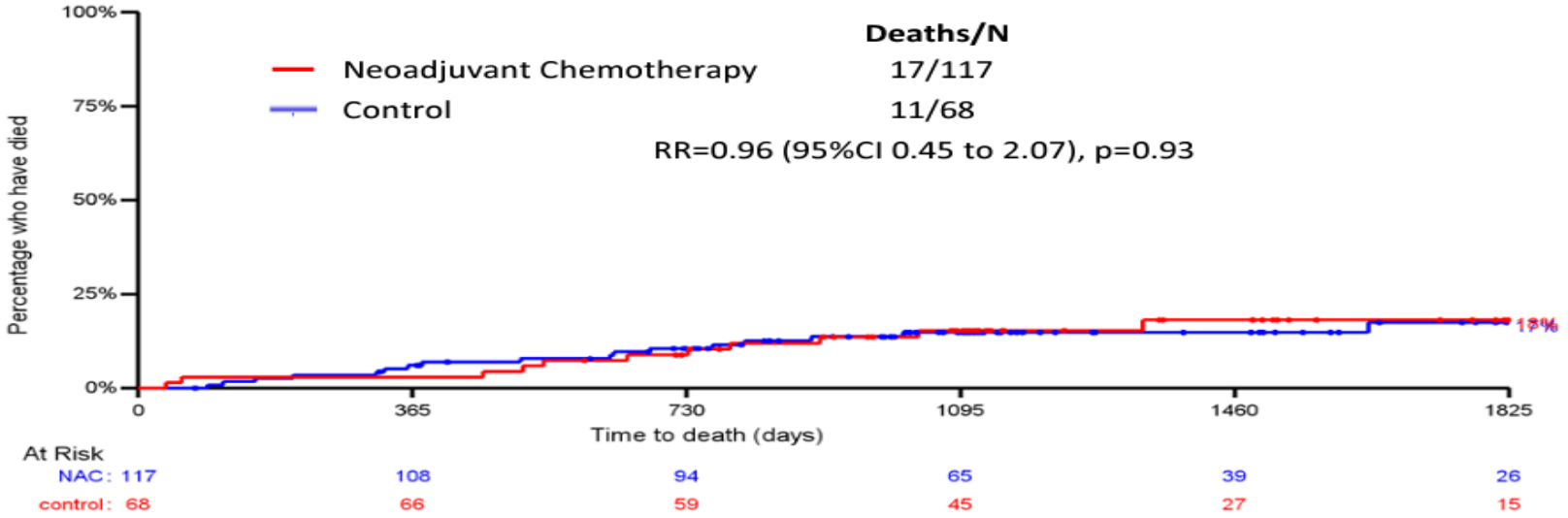
This presentation has been peer-reviewed and no conflicts were noted.

MSI-H Colorectal Cancer

- MSI-H colorectal cancer incidence decreases by stage of disease
  - 20% of stage 1-2
  - 10-15% of stage 3
  - 4-5% of stage 4 disease
- Risk of recurrence is substantially reduced in stage 1-2 disease and slightly reduced in stage 3 disease
- For locally advanced disease, there remains an unmet need given the risk of distant and locoregional recurrence

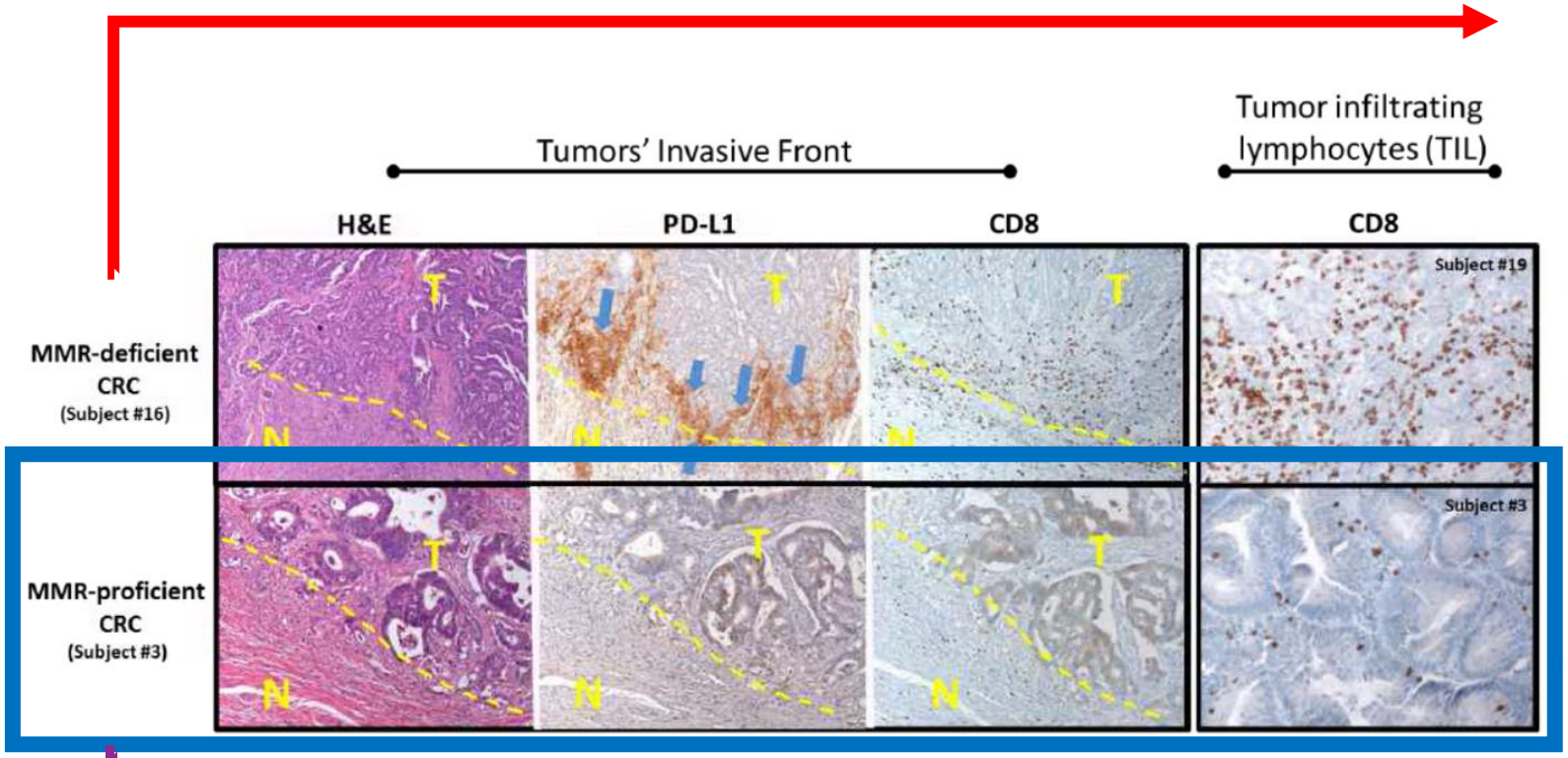
Recurrence and OS in MMRD CRC Treated with FOLFOX perioperatively or in the adjuvant setting

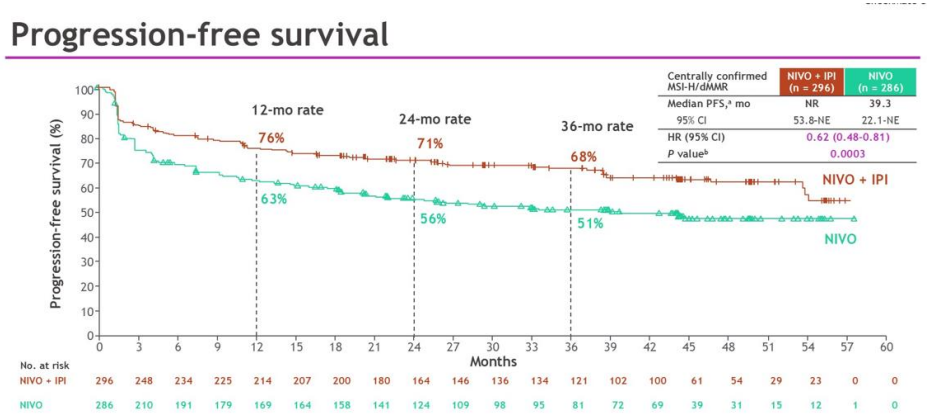




Morton D, J Clin Oncol 2023

Colorectal Cancer and Microsatellite Instability Status





MSI-H: 4% of Metastatic CRC

- Highly responsive to immunotherapy (Checkpoint Inhibitors)
- ~70% without progression after immunotherapy with Dual CPI
- ~50% or more cures are expected

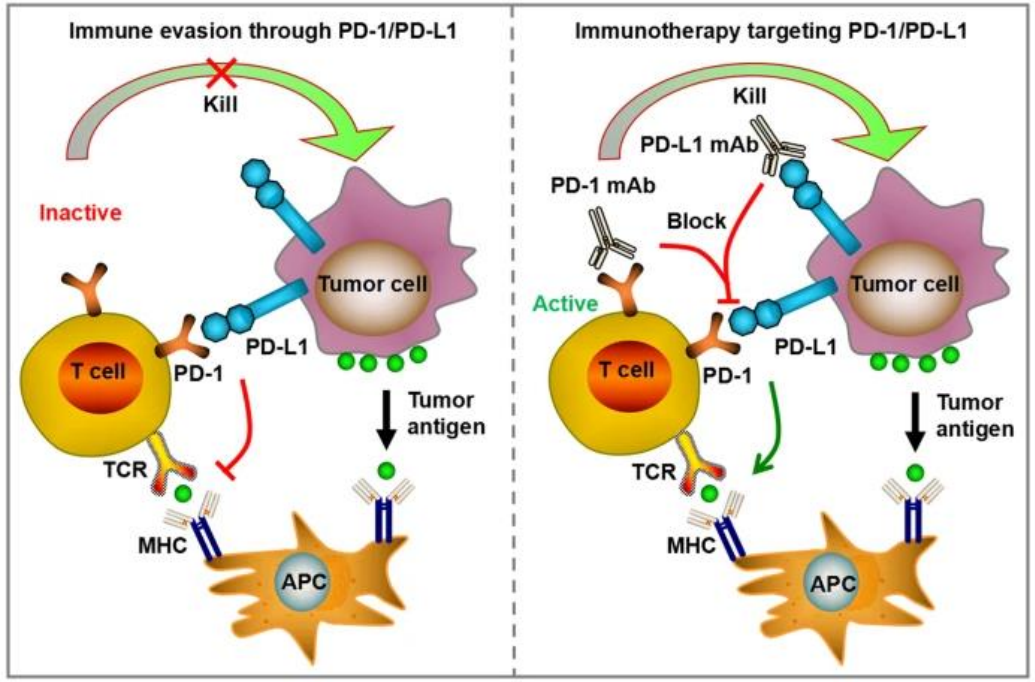
MSS: not hyper-mutated, cold tumors with poor infiltration with T-cells, unresponsive to immunotherapy

UNMET NEED: 96% of metastatic colorectal cancer

T Andre, GI ASCO 2025. Llosa, N. Cancer Discovery. 2015; 5: 43-51

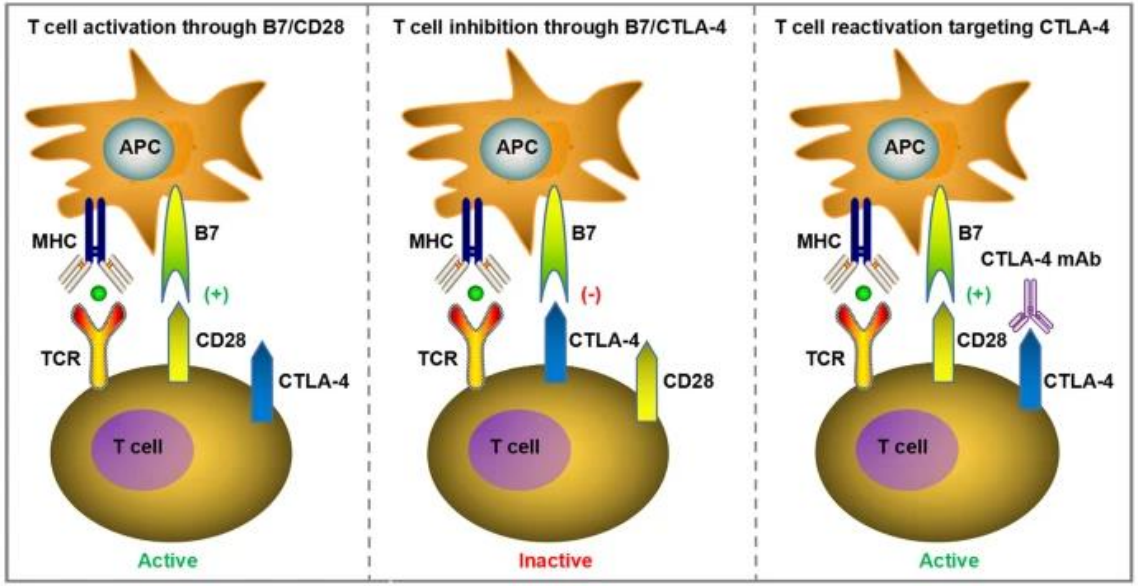
PD-1 and CTLA-4 Targeting

Fig. 1: PD-1/PD-L1 pathway contributes to tumor immune escape, enabling tumors resistant to immune response.



When PD-1 binds to PD-L1 on the surface of immune effector cells such as T cells, T cell receptor (TCR) signaling transduction was suppressed. Monoclonal antibodies (mAbs) blocking the PD-1/PD-L1 pathway have been widely applied for clinical immunotherapy to fight against a fraction of advanced cancer.

Fig. 2: CTLA-4 negative regulates T cell responses through several ways, such as attenuating T cell receptor (TCR) and CD28 signaling by competively binding to B7 with CD28.



The application of mAbs to block CTLA-4 can relieve its inhibitory effects on T cells, reactivate T cell proliferation and differentiation into cytotoxic T lymphocytes (CTLs), thereby exerting anti-tumor immune effects.

Meng, L. Cell Death and Disease. 2024

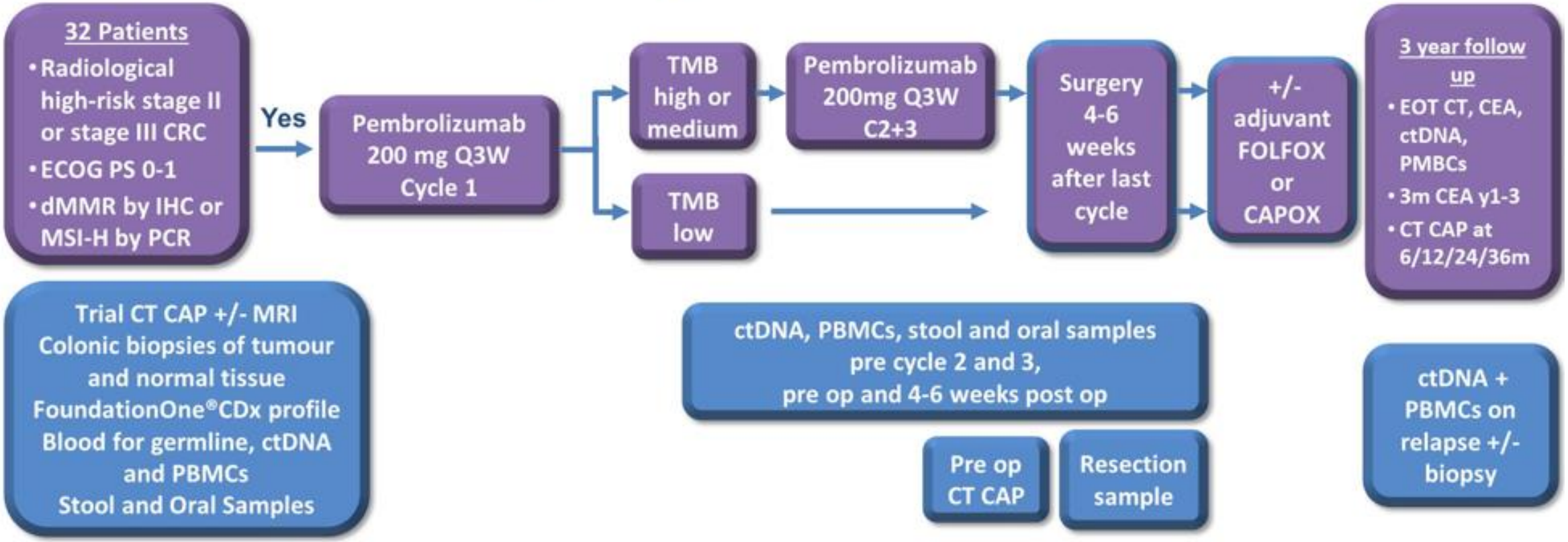
Can we achieve a curative outcome in primary colorectal cancers?

- Role of PD-1 Inhibition in MSI-H tumors
- Role of Dual Checkpoint Inhibition (PD-1 and CTLA-4) in MSI-H tumors
- What about MSS?

PD-1 Targeting

- Duration of treatment and timing of surgery impact pathological response

NEOPRISM-CRC Study Design



Primary endpoint: Pathological complete response rate

Secondary endpoints: 3-year RFS, OS, Safety, Health-related Quality of Life

Exploratory endpoints: ctDNA response to neoadjuvant therapy, minimal residual disease monitoring, genomic and microbiome biomarker signatures

NCT05197322

Kai-Keen Shiu. ASCO 2024

Patient Characteristics

Characteristic	N=32
Age, median (range)	60 (34-78)
Sex, N (%)	
Male	19 (59)
Female	13 (41)
Race, N (%)	
White	27 (84.4)
Asian	3 (9.4)
Black	2 (6.2)
ECOG PS, N (%)	
0	22 (68.7)
1	10 (31.3)
Lynch Syndrome, N (%)	
Yes	10 (31.3)
No	17 (53.1)
Pending	5 (15.6)
Mutational status, N (%)	**N=34***
BRAF V600E mut	14 (41.2)
KRAS or NRAS mut	9 (26.5)
RAS-RAF wild type	11 (32.3)

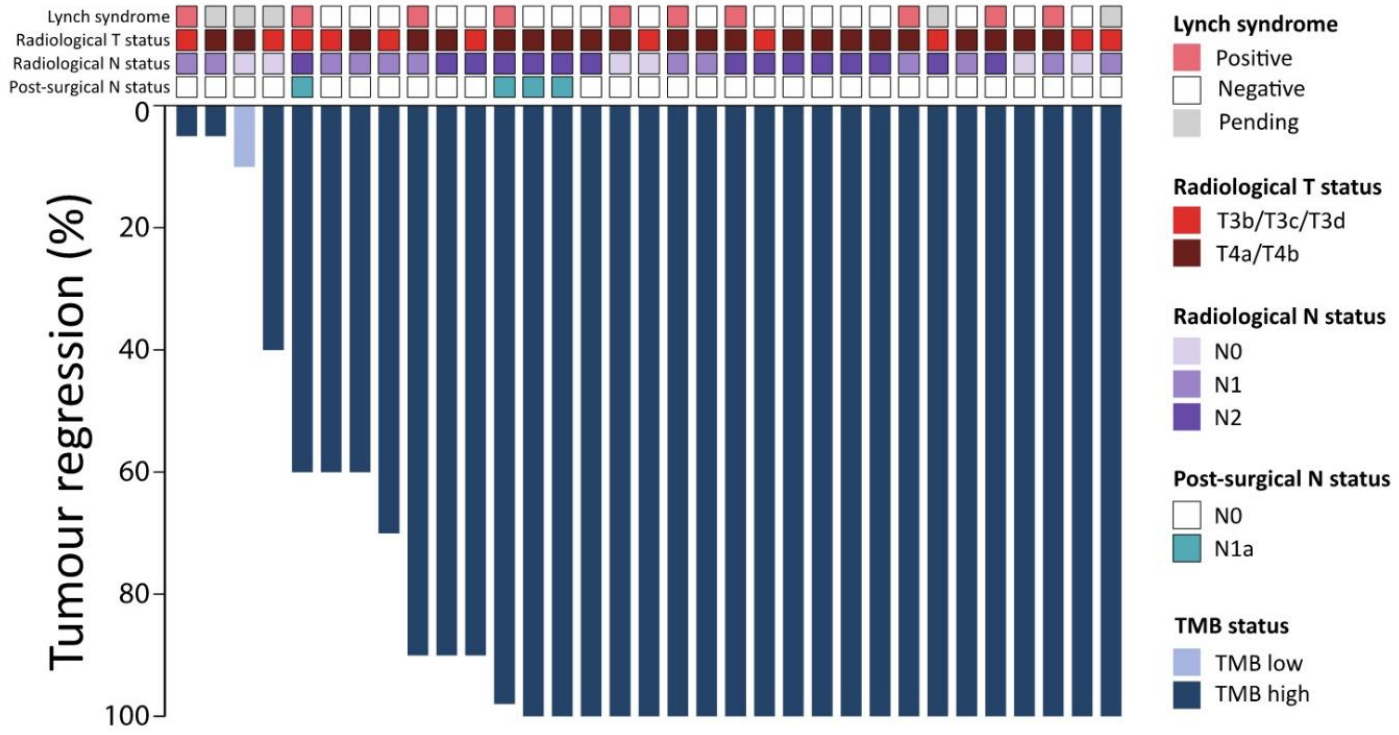
Primary tumour location, N (%)	N=34*
Right side	24 (70.6)
Left side	7 (20.6)
Transverse colon	3 (8.8)

Radiological stage, N (%)	N=32
II A	
T3c/d N0 M0	3 (9.4)
II B	
T4a N0 M0	2 (6.2)
II C	
T4b N0 M0	1 (3.1)
IIIB	
T3 -T4 N1 M0	12 (37.5)
T2-T3 N2 M0	4 (12.5)
IIIC	
T4a N2 M0	9 (28.1)
T4b N2 M0	1 (3.1)

* One patient had 3 synchronous BRAF V600E mutated primary tumours in ascending, transverse and descending colon

High Complete Path Response with Favorable Toxicity (9 weeks of Pembro)

pCR seen in 59% of 32 TMB-high resected primaries



Immune-Related Adverse Events in >5% of patients

Immune-Related AE	Any	Grade 1-2	Grade 3-4
	N° of patients (%)		
Any Immune-Related AE	**20 (62.5)**	**18 (56.3)**	**2[a,b] (6.2)**
Fatigue	9 (28.1)	8 (25.0)	1[a] (3.1)
Hypothyroidism	5 (15.6)	5 (15.6)	0 (0)
Rash	5 (15.6)	5 (15.6)	0 (0)
Hyperthyroidism	4 (12.5)	4 (12.5)	0 (0)
ALT increase	3 (9.4)	2 (6.3)	1[b] (3.1)
Arthralgia	3 (9.4)	3 (9.4)	0(0)
Dry Skin	3 (9.4)	3 (9.4)	0 (0)
Pruritus	3 (9.4)	3 (9.4)	0 (0)
Myalgia	2 (6.3)	1 (3.1)	1[b] (3.1)
Infusion reaction	2 (6.3)	2 (6.3)	0 (0)
ALP increase	2 (6.3)	2 (6.3)	0 (0)
Dry mouth	2 (6.3)	2 (6.3)	0 (0)
Nausea	2 (6.3)	2 (6.3)	0 (0)

Duration of PD-1 Therapy and cPR

Study	Number of Pts	Treatment	Duration	cPR
IMHOTEP	50	Pembrolizumab	6 weeks	46%
NEOPRISM	32	Pembrolizumab	9 weeks	59%
IMHOTEP	22	Pembrolizumab	12 weeks	68.2%
PICC	17	Toripalimab	12 weeks	65%
PICC	17	Toripalimab + Celecoxib	12 weeks	88%

Kai-Keen Shiu, ASCO 2024; Christelle de la Fouchardiere, ESMO 2024; Hu H, Lancet Gastroenterology and Hepatology 2022.

Pembrolizumab monotherapy can be associated with G3 Toxicities

IMHOTEP

Results : Safety (N=89)

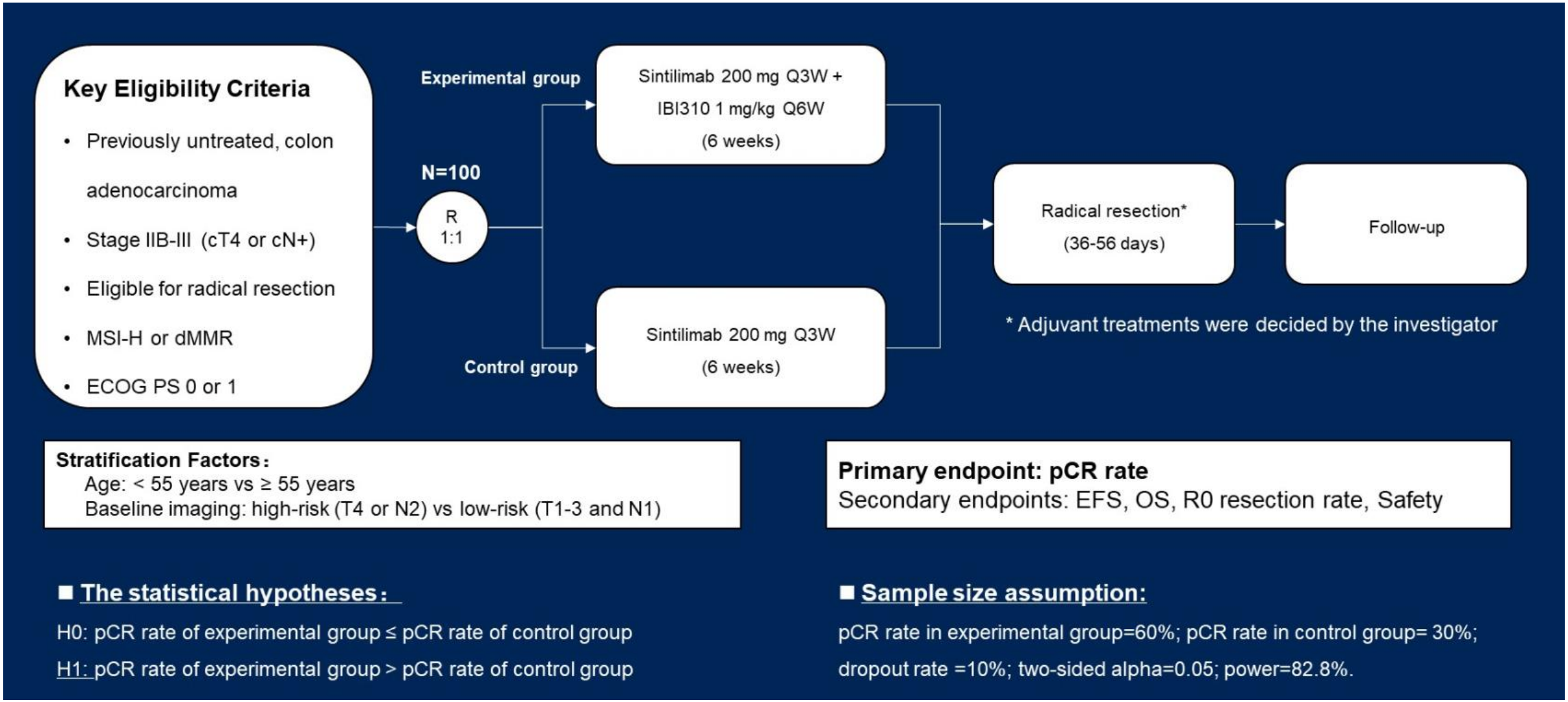
Adverse Events (AE)	N (patients)	%
Patients with any AE	87	97.8
Grade ≥ 3 AE	36	40.4
Ir-Grade ≥ 3 AE	12	13.5
Grade 5 AE	5	5.6
Ir- Grade 5 AE	1	1.1

Ir-grade ≥ 3 AE	N (events)
Pancreatitis	1
Colitis	1
Hepatitis	2
Adrenal insufficiency	1
Rash	1
Myasthenia	1
Abdominal pain	2
Drug reaction with eosinophilia and systemic symptoms (DRESS)	1
Ptosis	1
Fatigue	2
Arthralgia	1
Diarrhea	1
Hepatocellular Injury	1
Abscess	1

Christelle de la Fouchardiere, ESMO 2024

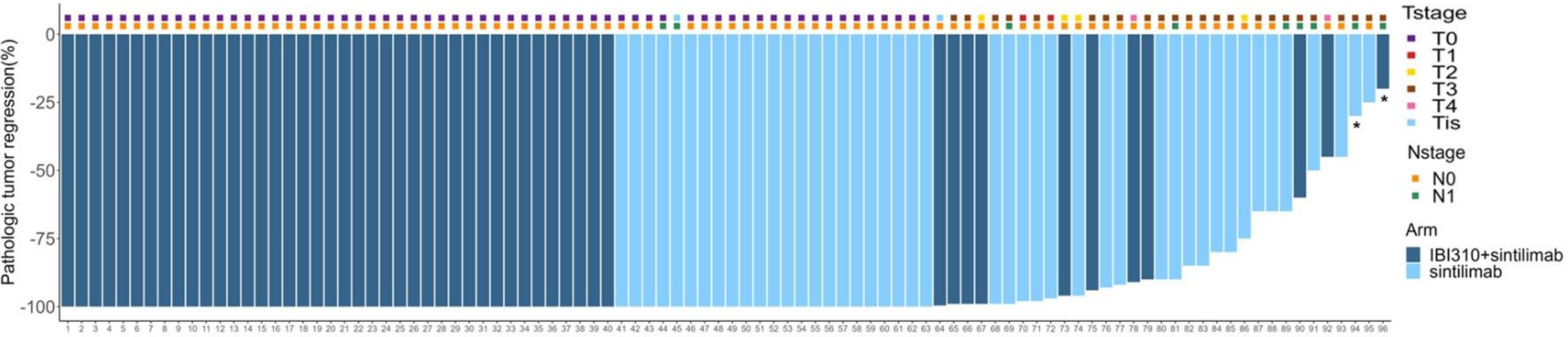
Can we improve on cPR with dual Checkpoint Inhibition?

IBI310 (CTLA-4) + Sintilimab (PD-1) vs. Sintilmab in MSI-H CRC



Rui Hua Xu. ASCO 2024

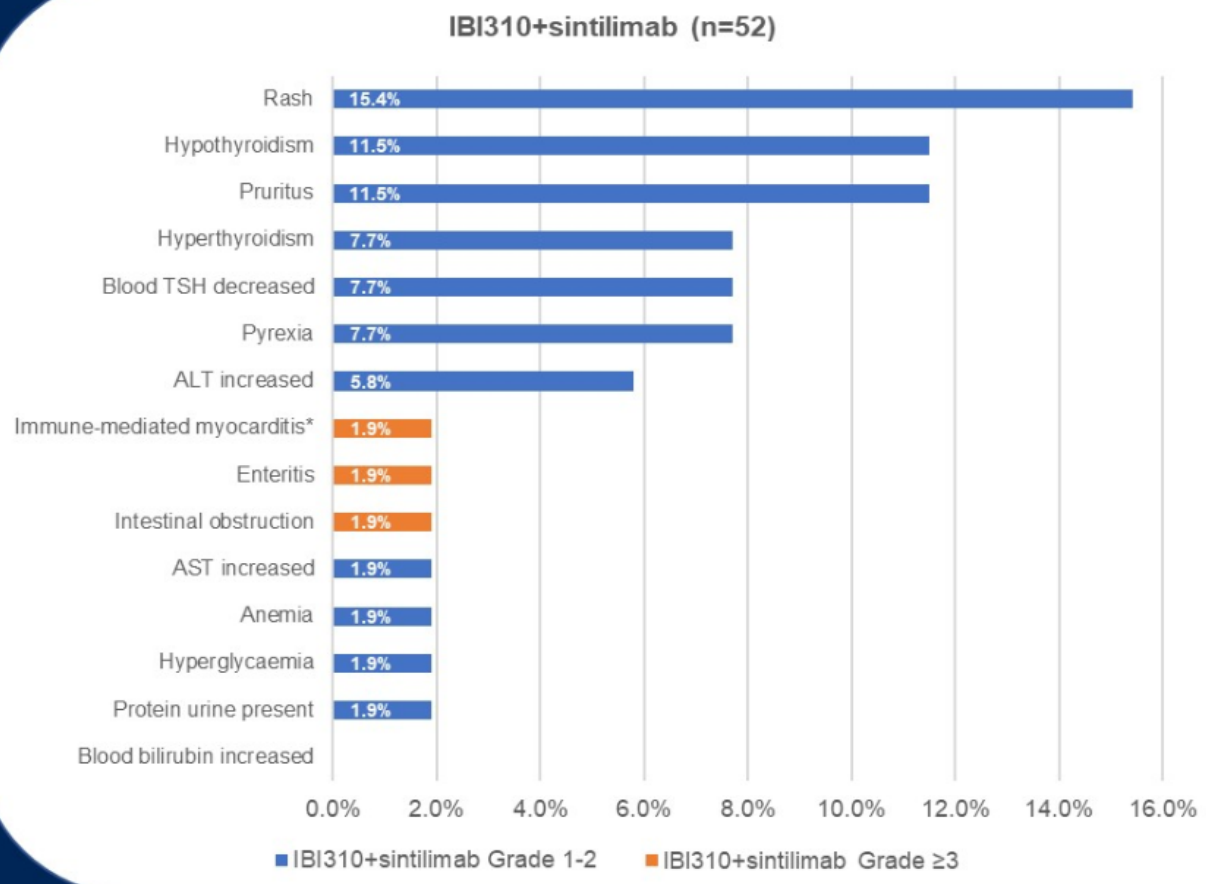
Higher cPR with CTLA-4/PD-1 targeting than PD-1 monotherapy

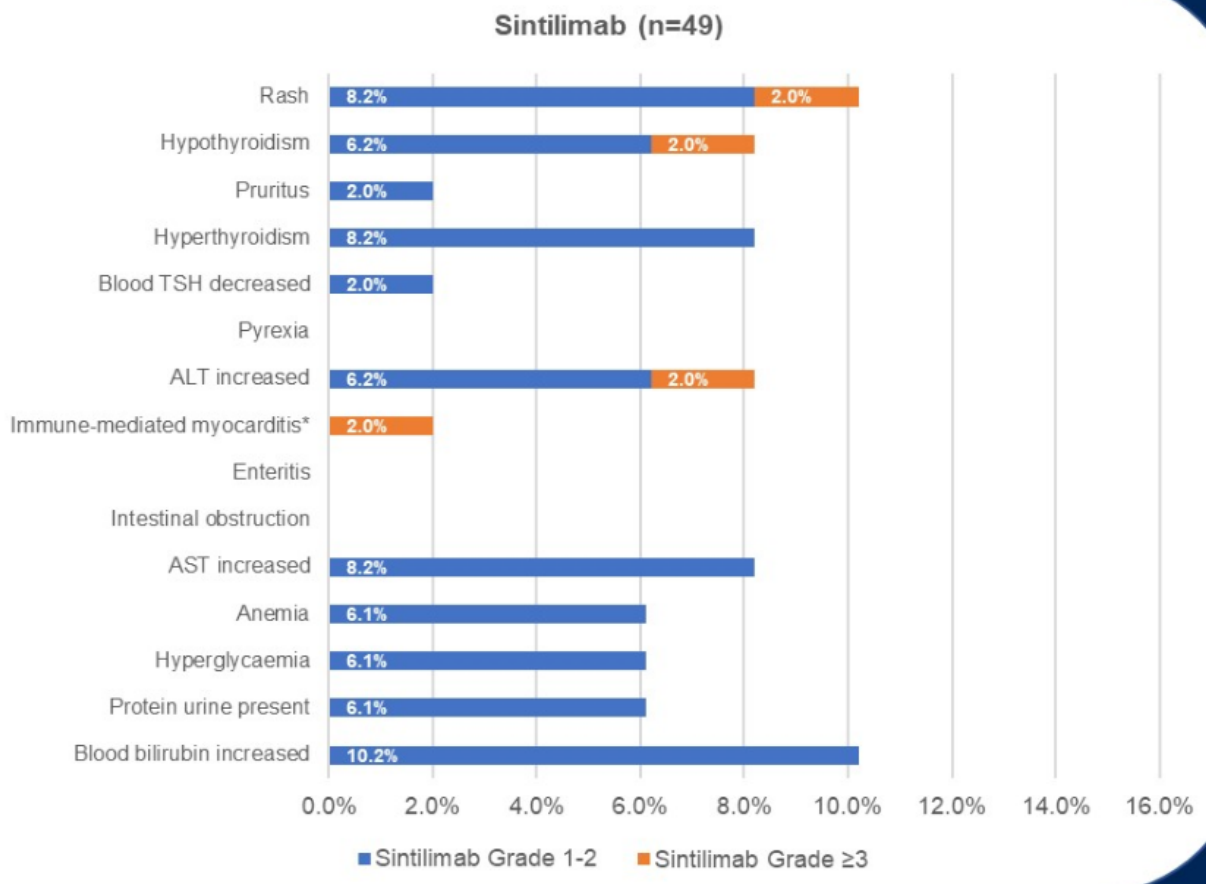


- In mITT set, pCR was observed in patients with neoadjuvant IBI310 plus sintilimab (40/51) and sintilimab alone (21/45) with significant improved pCR rates (78.4% versus 46.7%, p=0.0015).

* Patient 96 in experimental arm and patient 94 in control arm were found to be pMMR according to postoperative evaluation, and were considered as major protocol deviation.

Immune-Related AE with Sintilimab +/- IBI310





* Immune-mediate myocarditis: 1 patient in experimental group (grade 3, asymptomatic and recovered without steroids therapy), and 1 patient in control group (grade 5, died on day 46).

NICHE-2 (4 weeks course of Nivo-Ipi) on MSI-H CRC

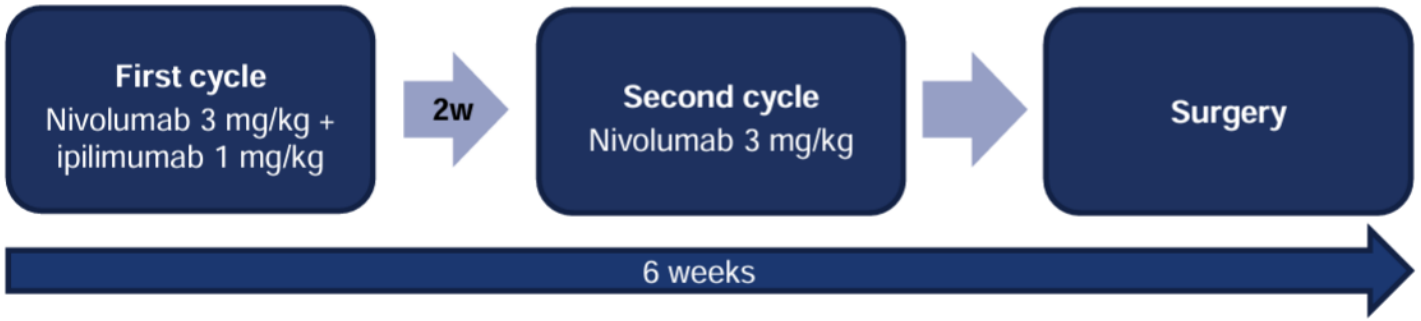


Table 2. Pathological Responses among Patients in the Efficacy Analysis.*

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)

Table 1. Demographic and Disease Characteristics of the Patients.

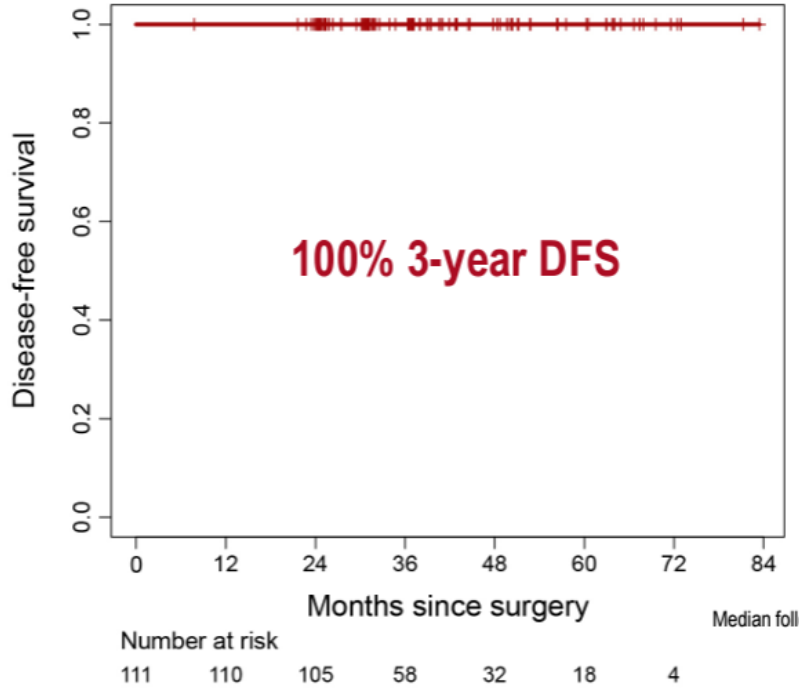
Characteristic	Patients (N=115)
Female sex — no. (%)	67 (58)
Median age (range) — yr	60 (20–82)
WHO performance-status score — no. (%)*	
0	100 (87)
1	15 (13)
Race or ethnic group — no. (%)†	
White	97 (84)
Asian	6 (5)
Black	5 (4)
Other	7 (6)
Tumor stage — no. (%)‡	
cT2	17 (15)
cT3 or cT3–T4a	24 (21)
cT4a	41 (36)
cT4b	33 (29)
Nodal status — no. (%)§	
cN–	38 (33)
cN+	77 (67)
Primary tumor location — no. (%)	
Right	78 (68)
Transverse	17 (15)
Left	20 (17)
Lynch syndrome — no. (%)	37 (32)
Unexplained dMMR — no. (%)¶	2 (2)
Non–Lynch syndrome dMMR — no. (%)	76 (66)

Chalabi, M. NEJM 2024

NICHE-2 Results: Balancing Efficacy and Toxicity

Immune-related adverse events of any grade were observed in 73 patients (63%; 95% CI, 54 to 72), and most were grade 1 or 2 events. The most common grade 1 or 2 adverse events included infusion-related reactions (37 patients; 32%), thyroid function disorders (14 patients; 12%), and dry mouth (10 patients; 9%). Nine patients (8%) with thyroid function disorders and 4 patients (3%) with adrenal insufficiency received long-term replacement therapy. Five patients (4%; 95% CI, 1 to 10) had grade 3 or 4 adverse events, which included rash (1 patient), asymptomatic increase in amylase and lipase levels (1 patient), myositis (1 patient), hepatitis (1 patient), and hyponatremia (1 patient) (Table S3). Surgery-related adverse events of any grade were observed in 22 patients (19%; 95% CI, 12 to 28) (Table S4), and surgery-related grade 3 events occurred in 12 patients (10%; 95% CI, 6 to 18). Anastomotic leakage occurred in 4 patients (3%).

Results – 3-year disease-free survival 100%



Median follow-up after surgery: 36.6 months (7.8 - 83.4)

BARCELONA 2024 ESMO congress

Data cut-off: 11 September 2024

Chalabi, M. NEJM 2024; Chalabi, M. ESMO 2024

NICHE-3: Nivolumab + Relatlimab (LAG-3) in MSI-H CRC

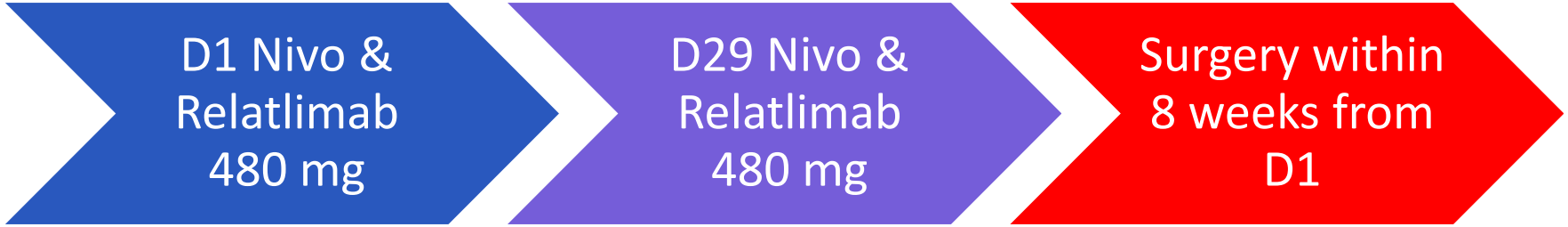


Table 3 | Pathologic response in all treated patients (*n*=59)

Pathologic response (RVT)	Full cohort *n*=59	cT2–3 *n*=19	cT4a *n*=26	cT4b *n*=14	cN0 *n*=22	cN+ *n*=37
Yes (≤50%)	57 (97%)	19 (100%)	25 (96%)	13 (93%)	22 (100%)	35 (95%)
Major (≤10%)	54 (92%)	17 (89%)	25 (96%)	12 (86%)	20 (91%)	34 (92%)[a]
Complete (0%)	40 (68%)	14 (74%)	18 (69%)	8 (57%)	16 (73%)	24 (65%)
Partial (11–50%)	3 (5%)	2 (11%)	0	1 (7%)	2 (9%)	1 (3%)
No (>50%)	2 (3%)	0	1 (4%)	1 (7%)	0	2 (5%)[a]

[a]One patient had lymph node metastases in the resection specimen.

- Results largely consistent with Nivo + IPI (NICHE-2)
- IO toxicity mostly G1-2 with a higher rate of thyroid dysfunction and a higher incidence of hepatitis (but longer duration of treatment)
- G3 hepatitis 5% and G3 colitis 3%

Peter de Gooyer. Nature Medicine 2024

Neoadjuvant IO Therapy in MSI-H CRC

Excellent dowstaging

Surgery-sparing in UNFIT individuals

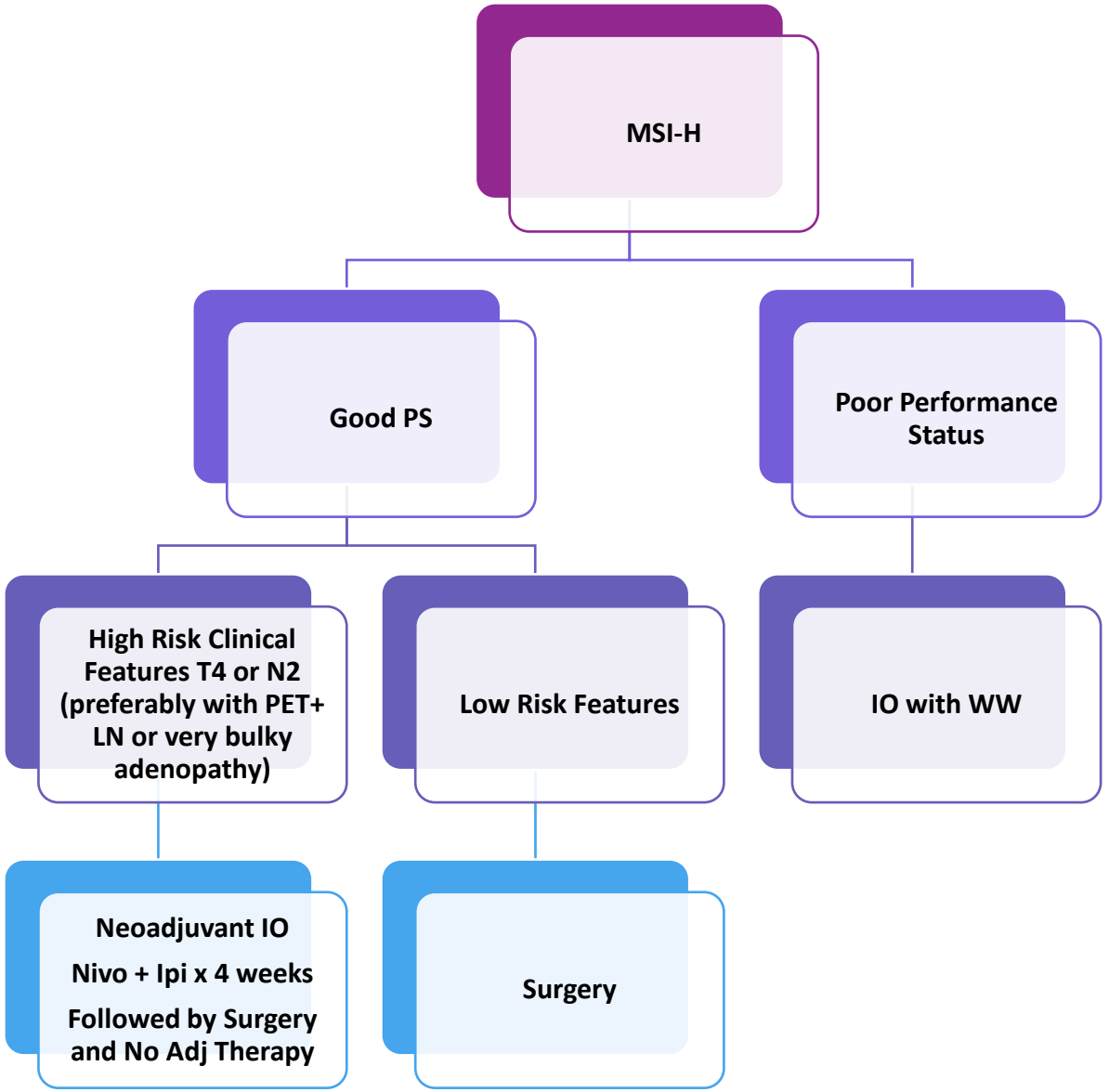
Excellent DFS (100%)

IO toxicities

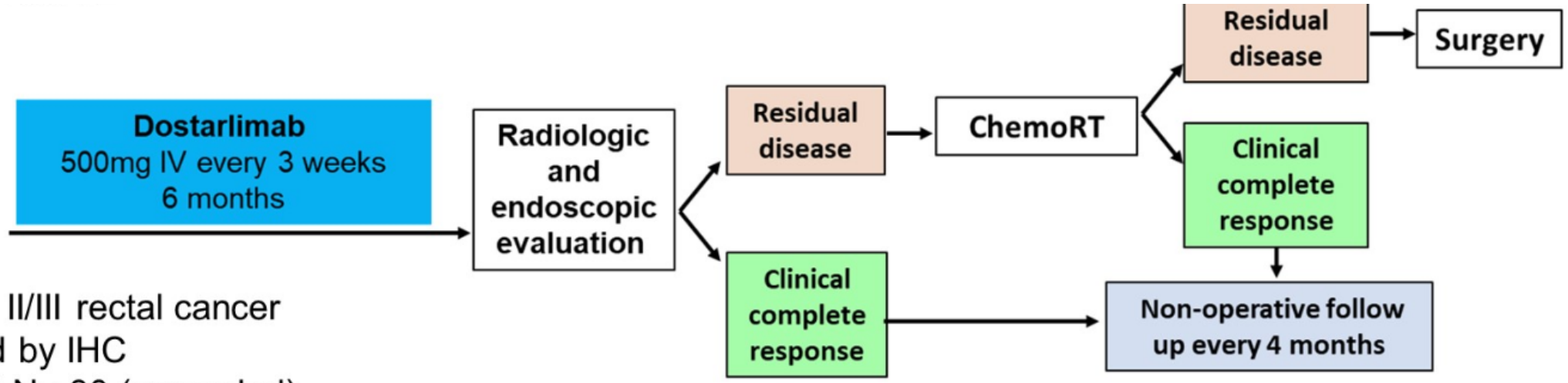
Lifelong thyroxine replacement

Rare severe toxicities (colitis/ hepatitis/ myositis/ myocarditis/hypoadrenalism)

Proposed Algorithm in Managing MSI-H Locoregional Colon cancer



PD-1 Blockade in Primary Rectal Cacer



Stage II/III rectal cancer
MMRd by IHC
Target N= 30 (expanded)

Primary Endpoints:

- ORR after completion of PD-1 alone or in combination with chemoRT
- pCR or sustained cCR for 12 mo after completion of PD1 alone or in combination with chemoRT

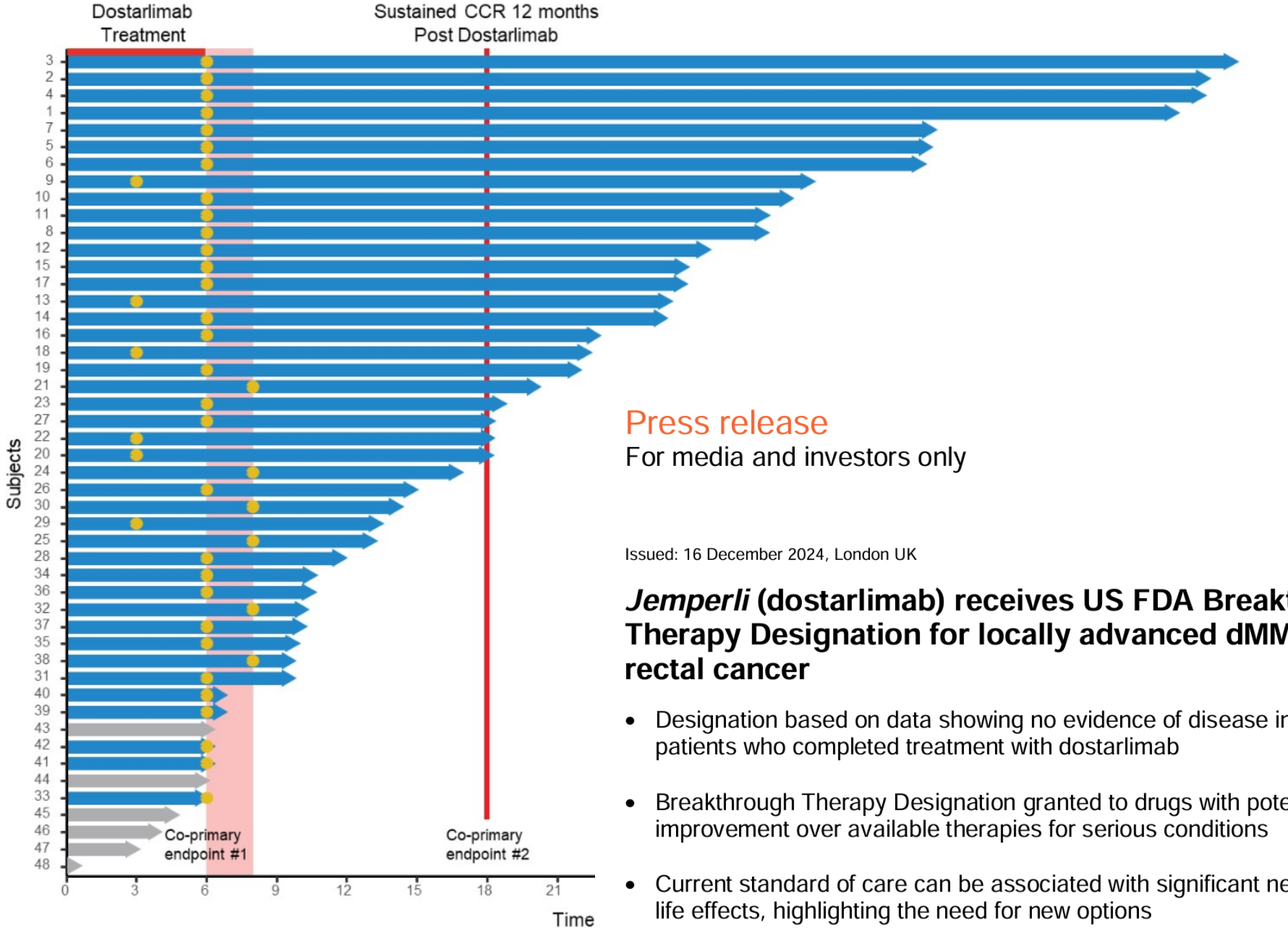
Cercek, A. ASCO 2024

cCR Definition

- Normal rectal exam and lack of evidence of disease on endoscopic assessment
- No abnormal signal on DWI with scar on T2WI
- Each target LN should have decreased to < 0.5 cm on short axis

Patient Characteristics

Patient Demographics N= 48	N (%)
Female Sex	**28 (58)**
Median Age (range)	**51 (26,78)**
Race	
White	**37 (77)**
Asian	**5(10)**
Black	**6 (13)**
Non Hispanic/Latino	**42 (85)**
Hispanic/Latino	**6 (13)**
Tumor Stage	
T 0/1/2	**10 (21)**
T 3	**23 (48)**
T 4	**15 (31)**
N +	**41 (85)**
Median Distance from anal verge (cm)	**5.1 (0, 14.8)**



Press release

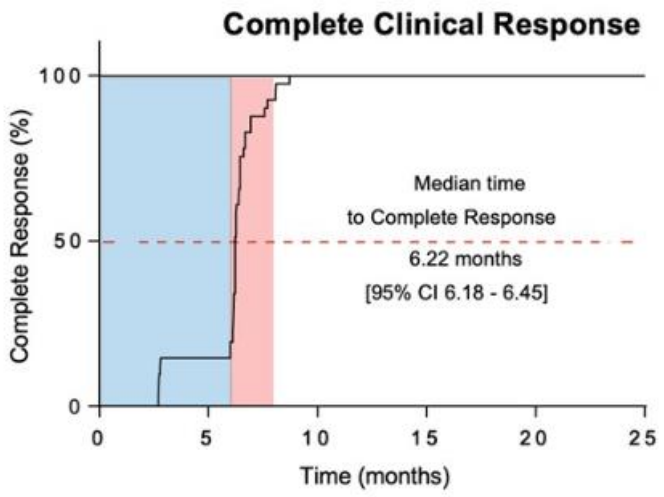
For media and investors only

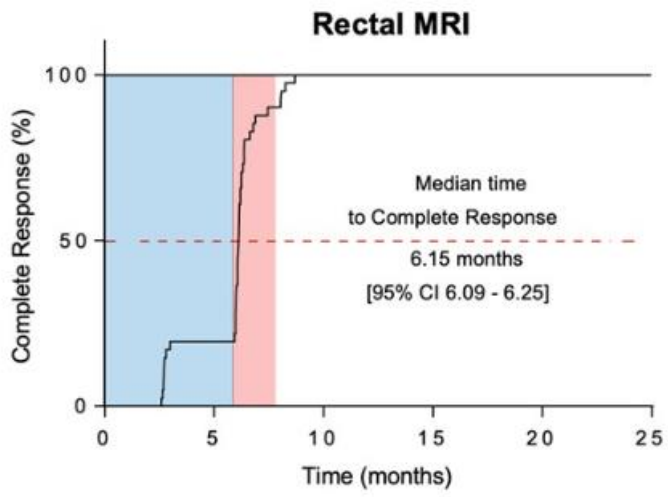
Issued: 16 December 2024, London UK

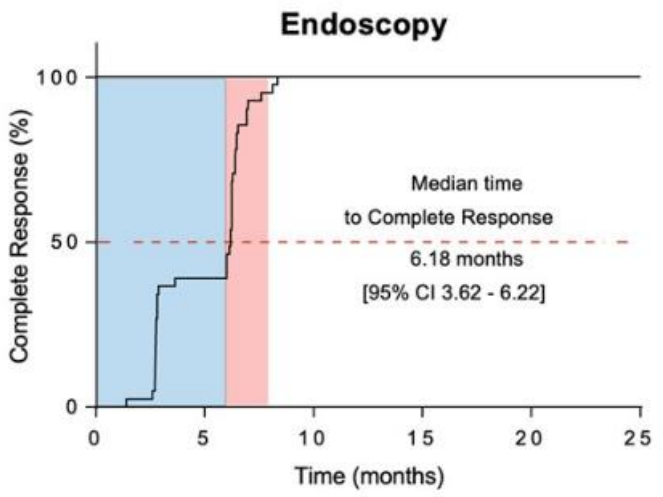
Jemperli (dostarlimab) receives US FDA Breakthrough Therapy Designation for locally advanced dMMR/MSI-H rectal cancer

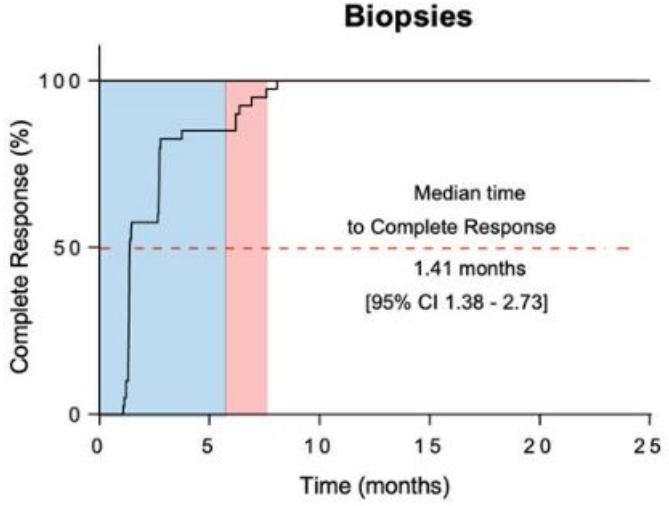
- Designation based on data showing no evidence of disease in 100% of all 42 patients who completed treatment with dostarlimab
- Breakthrough Therapy Designation granted to drugs with potential to show improvement over available therapies for serious conditions
- Current standard of care can be associated with significant negative quality-of-life effects, highlighting the need for new options

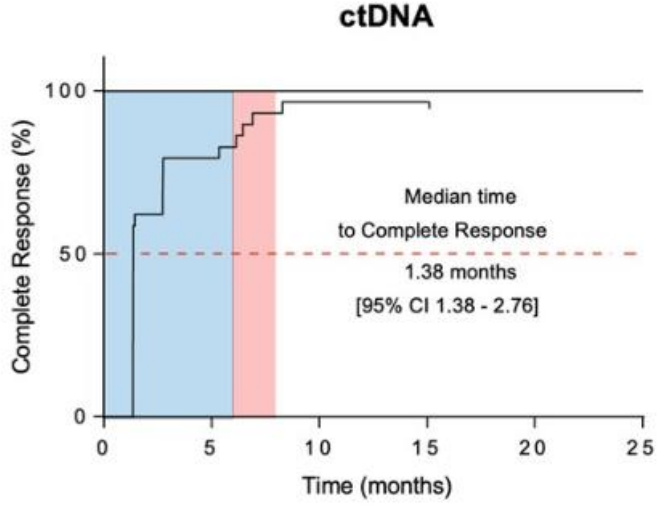
Time to cCR

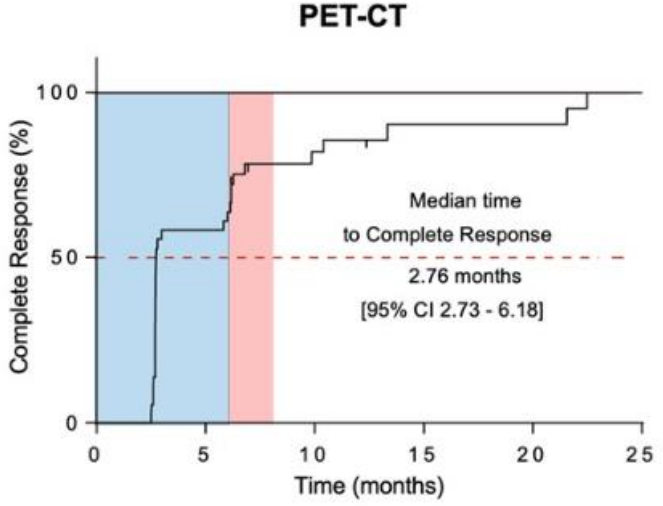

Complete Clinical Response
Complete Response (%)
100
50
0
0
5
10
15
20
25
Time (months)
Median time
to Complete Response
6.22 months
[95% CI 6.18 - 6.45]


Rectal MRI
Complete Response (%)
100
50
0
0
5
10
15
20
25
Time (months)
Median time
to Complete Response
6.15 months
[95% CI 6.09 - 6.25]


Endoscopy
Complete Response (%)
100
50
0
0
5
10
15
20
25
Time (months)
Median time
to Complete Response
6.18 months
[95% CI 3.62 - 6.22]


Biopsies
Complete Response (%)
100
50
0
0
5
10
15
20
25
Time (months)
Median time
to Complete Response
1.41 months
[95% CI 1.38 - 2.73]


ctDNA
Complete Response (%)
100
50
0
0
5
10
15
20
25
Time (months)
Median time
to Complete Response
1.38 months
[95% CI 1.38 - 2.76]


PET-CT
Complete Response (%)
100
50
0
0
5
10
15
20
25
Time (months)
Median time
to Complete Response
2.76 months
[95% CI 2.73 - 6.18]


Time on Treatment
End of Treatment Evaluation

How About MSS CRC?

Chemo-IO (PD-1) following SCRT in Rectal Cancer

Study	N	Stage	Treatment Arm	cPR
UNION Phase 3	113	T3-4/N+	SCRT + CAPOX x 2 cycles + camrelizumab	**39.8%**
TORCH Phase 2	62	T3-4/N+	SCRT + CAPOX x 6 + toripalimab	**50%**
TORCH Phase 2	59	T3-4/N+	CAPOX x 2 + toripalimab then SCRT than 4 cycles of CAPOX + toripalimab	**50%**
NeoCaCRT	27	T3-4/N+	SCRT + FOLFOX x 6 + cadonilimab	**37%**
UNION-TNT	45	T3/4/N+	SCRT + fruquintinib + CAPOX + adebralimab	**65% (12/19)**

Compares favorably to RAPIDO (SCRT followed by CAPOX) and PRODIGE 23 (FOLFOXIRI followed by CRT)

MSS CRC: Dual CPI Blockade and Pathological Response

Potent CTLA4/PD-1 inhibition is associated with high pathological response in pMMR tumors

Need mature DFS data, need mature LR data, need larger sample size, and need control arms

Risk/Benefits?

UNICORN

Molecular status	n°	Treatment	pCR, n (%)	pMR, n (%)	pR, n (%)
pMMR	14	BOT	0 (0)	0 (0)	6 (43)
	14	BOT/BAL	4 (29)	5 (36)	10 (71)
dMMR	14	BOT	4 (29)	5 (36)	9 (64)
	14	BOT/BAL	13 (93)	14 (100)	14 (100)

NEST

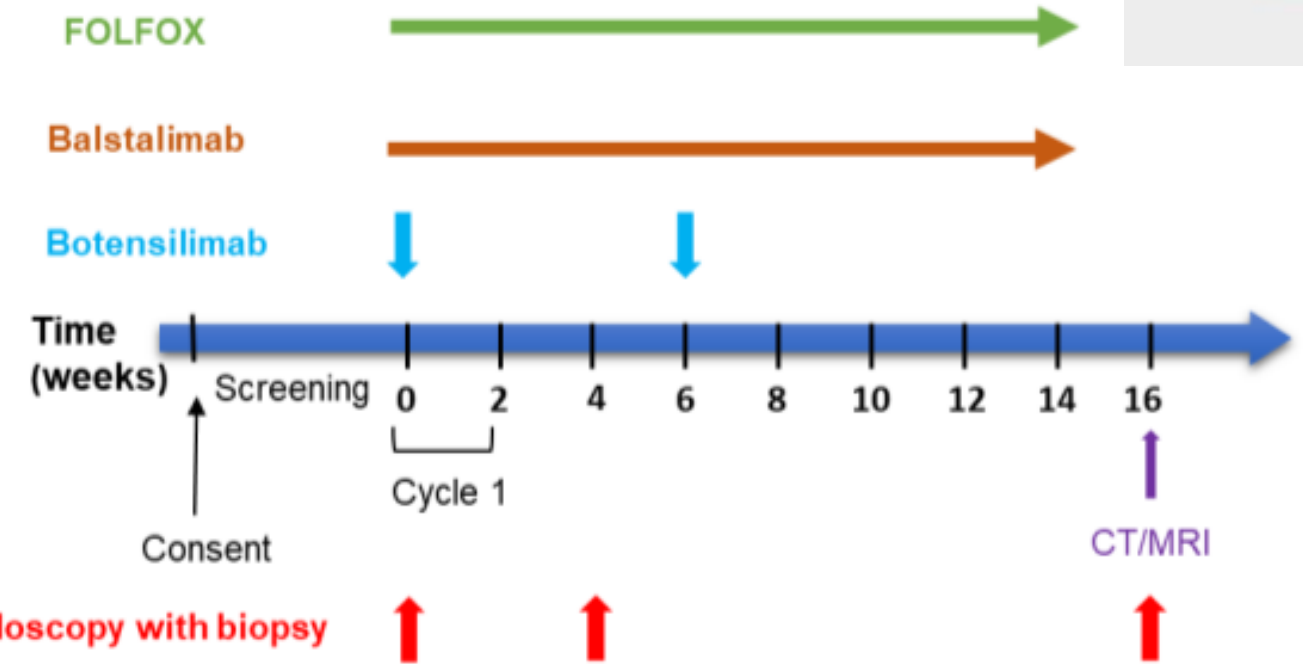
Pathologic Response	NEST 1 n=7 MSS tumors	NEST 2 n=15 MSS tumors	MSI-H (3 NEST1, 1 NEST2)
100% (CR%, 95%CI)	1 (14%, 0.4-58%)	6* (40%, 16-68%)	3** (75%, 19-99%)
≥ 90% (MPR%, 95%CI)	2 (29%, 4-71%)	7 (47%, 21-73%)	4^ (100%, 40-100%)
≥ 50%	4 (57%)	9 (60%)	4 (100%)
Median days to Surgery (range)	29 (21-37)	57 (45-104)	46 (34-78)

Hissong E. GI ASCO 2025; Ghelardi F. GI ASCO 2025

COH FOLFOX-2B TNT for Rectal Cancer

GATEWAY FOR CANCER RESEARCH

STUDY SCHEMA



Each cycle is 2 weeks

FOLFOX will be given every 2 weeks for 8 cycles

Botensilimab (75mg fixed dose), will be given on D1C1 and D1C4, for a total of 2 doses

Balstilimab will be given at fixed dose at 240 mg (D1 of each cycle) every 2 weeks for 8 cycles

Upon completion of treatment, MRI of the pelvis, CT chest and abdomen will be performed within 2 weeks after cycle 8.

Endoscopic assessment with endoscopy will be performed at baseline (with biopsy), at 4 weeks, and within 4 weeks from last cycle of chemotherapy

Conclusions

- MSI-H status should be determined in ALL colorectal cancer patient prior to any treatment planning
- In localized MSI-H colon cancer, the SOC remains surgical intervention, HOWEVER:
  - 6 weeks of doublet immunotherapy is associated with >95% response and ~70% cPR
    - Further delay in surgical intervention would have resulted in higher cPR
  - Neoadjuvant IO therapy is associated with an exception DFS
  - Neoadjuvant IO therapy should be considered in T4/N2 tumors
  - Definitive IO with close observation in poor surgical candidates is appropriate
    - Optimal testing strategy (ctDNA, endoscopy, CT, PET/CT) and frequency is not well-defined
- In MSI-H rectal cancer, definitive immunotherapy is the SOC
  - cCR may not be achieved until 6 months
  - Definitive surgical intervention should not be considered before 6 mo in responding patients
- Research in ongoing in colon and cancer MSS localized disease to determine the role of CPI in definitive and adjuvant therapy

Thank you!