Progression in neoadjuvant immunotherapy for local advanced CRC

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CONTENTS

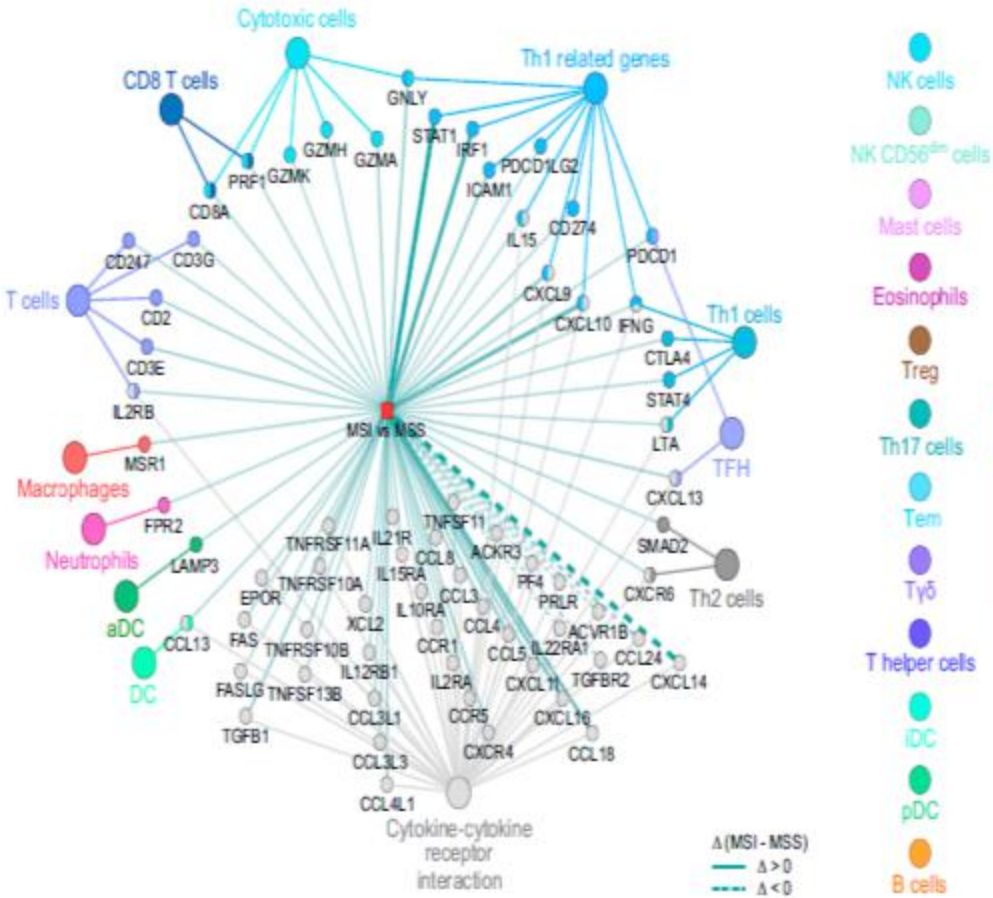
01 Immune microenvironment in CRC and current state of immunotherapy in mCRC

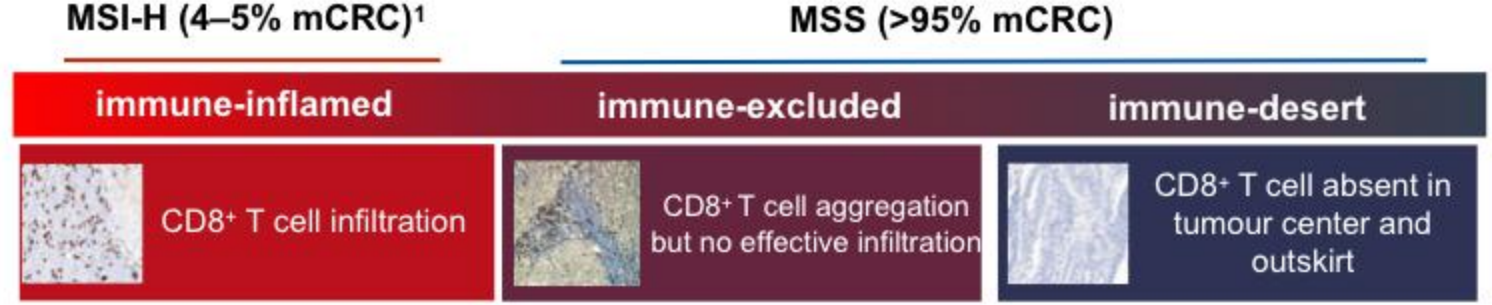
02 neoadjuvant immunotherapy for locally advanced colon cancer

03 neoadjuvant immunotherapy for locally advanced rectal cancer

04 Hotspots and chanllenge of immunotherapy for locally advanced CRC

Immune microenvironment of CRC: MSI-H vs. MSS

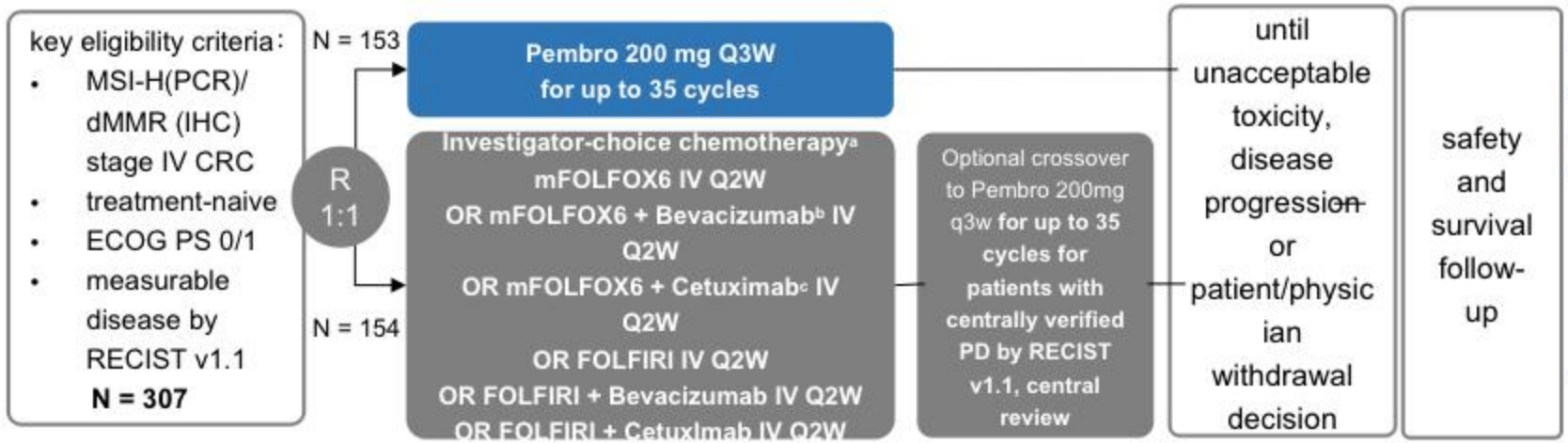




- **Cytotoxic cells, CD8, Th1, Th2, Tfh and other T cell markers: higher in MSI than in MSS tumours**
- **Tumour mutation burden,mismatch/frame-shifting mutations, number of tumour neoepitopes: MSI higher than MSS tumours**

Immunity 2016；BJC 2009

first-line IO for MSI-H mCRC： KEYNOTE-177 study pembrolizumab superior to traditional chemotherapy



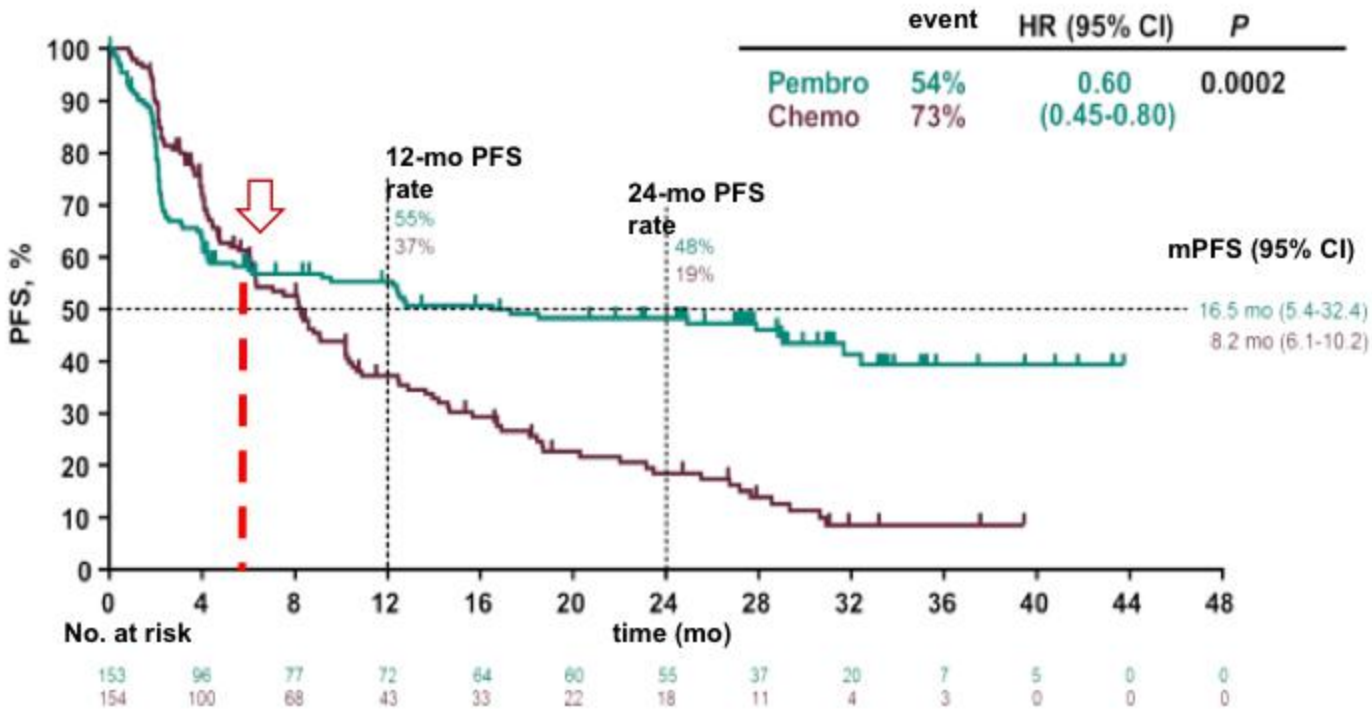
- **double primary endpoints：PFS & OS (blinded independent centre review, RECIST v1.1)**
- **secondary endpoint：ORR & safety (BICR, RECIST v1.1)**
- **Tumour evaluation at week 9 (BICR, RECIST v1.1). Follow-up interval: 9 weeks.**

	Pembro N = 153	chemo N = 154
median age (span), yr	63.0 (24-93)	62.5 (26-90)
male	71 (46)	82 (53)
ECOG PS 0	75 (49)	84 (55)
metachronous dis	80 (52)	74 (48)
liver metastasis	71 (46)	54 (35)
Region		
Asia	22 (14)	26 (17)
Western Europe/NA	**109 (71)**	**113 (73)**
Rest of world	22 (14)	15 (10)
Primary location		
right-sided	102 (67)	107 (70)
left-sided	46 (30)	42 (27)
others/NA	5 (3)	5 (3)
Previous systemic therapy		
Adjuvant	33 (22)	37 (24)
Neoadjuvant(perioperative period)	5 (3)	8 (5)
none	115 (75)	109 (71)
mutation state		
BRAF/KRAS/NRAS WT	34 (22)	35 (23)
BRAF V600E mut	**34 (22)**	**43 (28)**
KRAS/NRAS mut	**33 (22)**	**41 (27)**
unassessable	52 (34)	38 (25)

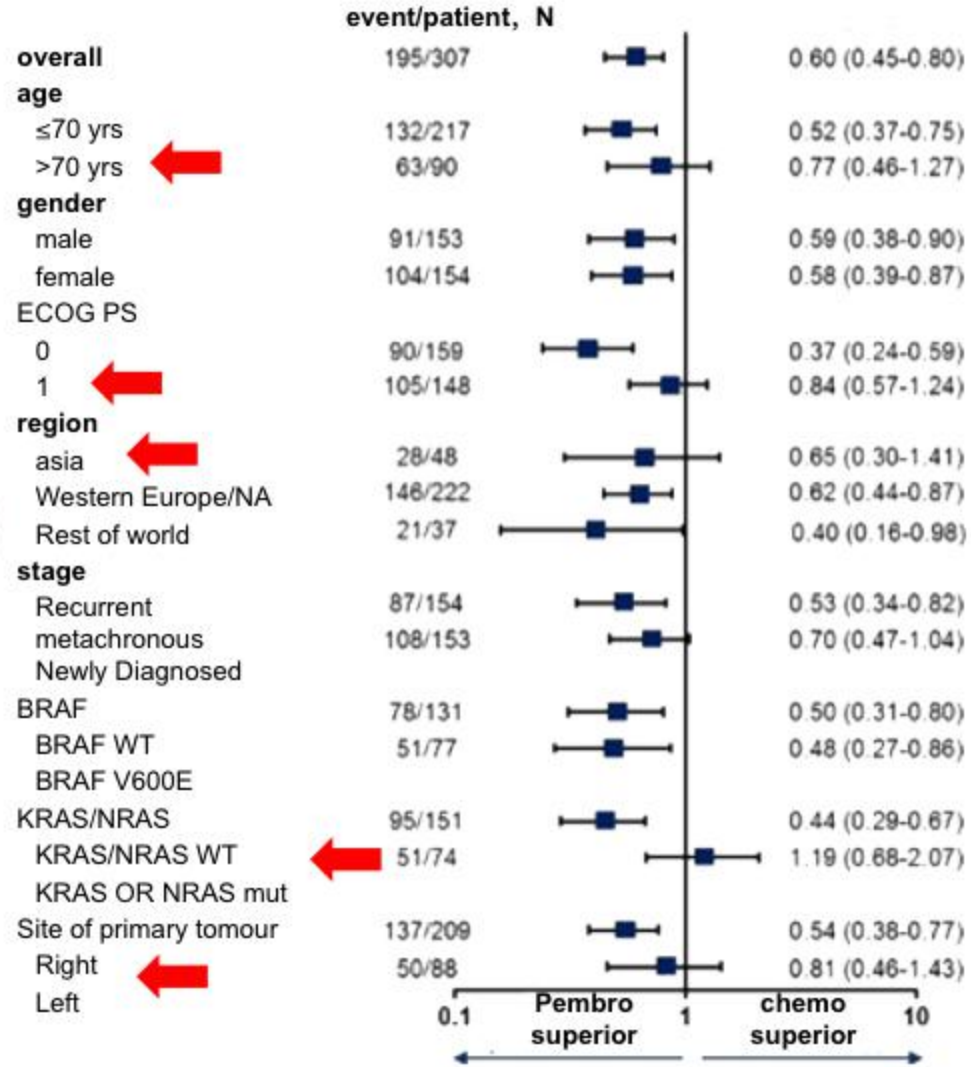
Thierry Andre ,et al. 2020 ASCO abs LBA4

Pembro: 24-mo PFS=48%, mPFS=16.5 months

Pemvro vs. chemo: initial crossing of the progression-free survival curve at 6-month



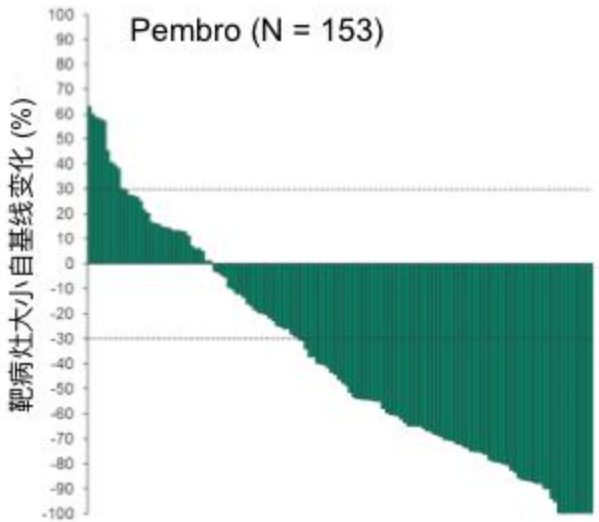
the median trial follow-up was 32.4 months (range, 24.0 to 48.3).

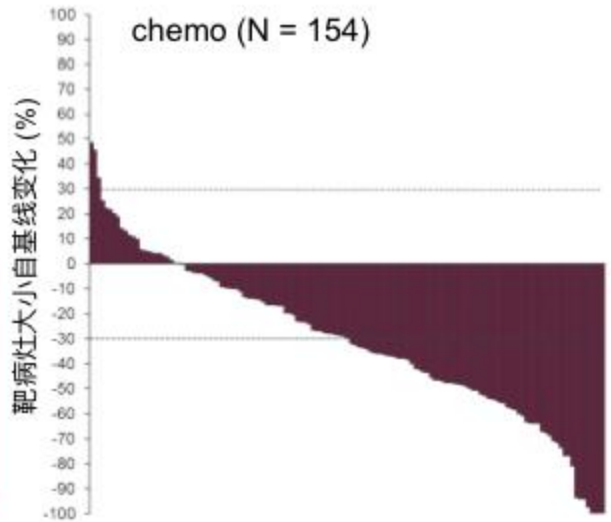


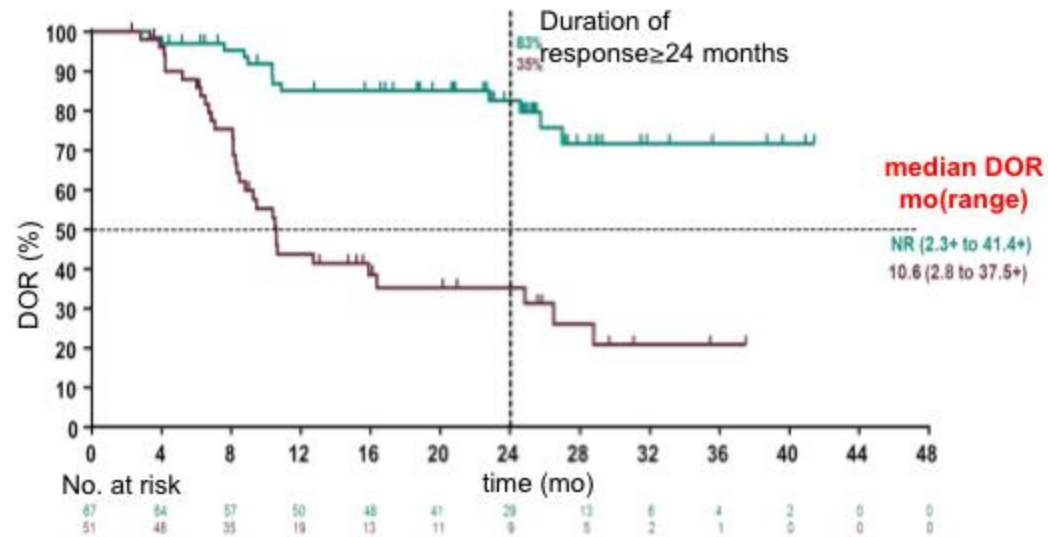
Thierry Andre ,et al. 2020 ASCO abs LBA4

Pembro has a higher ORR, but lower DCR and higher PD rate compared to chemotherapy

	Pembro N = 153	化疗 N = 154
ORR，n (%)	**67 (43.8)**	**51 (33.1)**
Difference (95% CI)	10.7 (-0.2-21.3)	
P value	0.0275	
Best response，n (%)		
Complete response	17 (11.1)	6 (3.9)
Partial response	50 (32.7)	45 (29.2)
Stable disease	32 (20.9)	65 (42.2)
Disease Control Rate(CR+PR+SD)	**99 (64.7)**	**116 (75.3)**
progression of disease	**45 (29.4)**	**19 (12.3)**
Could not be evaluated	3 (2.0)	2(1.3)
no assessment was made	6 (3.9)	17 (11.0)
Median time to response (range), mo	2.2 (1.8-18.8)	2.1 (1.7-24.9)







Thierry Andre ,et al. 2020 ASCO abs LBA4

Checkmate 142：nivolumab plus low-dose ipilimumab as first-line therapy in MSI-H/dMMR mCRC

- metastatic or recurrent CRC
- MSI-H/dMMR per local laboratory
- No prior treatment for metastatic disease

→

NIVO3 Q2W
+
IPI1 Q6W[a]

Primary endpoint：
- **ORR by investigator (RECIST v1.1)**

Other key endpoints：
- **ORR by BICR,DCR,DOR、PFS、OS、AE**

[a]直到疾病进展或因患者接受研究治疗出现超进展停止治疗，因毒性停止治疗，同意知情退出，或研究结束
[b]CR、PR或SD持续≥12周的患者数除以接受治疗患者数
BICR，盲法独立中心评审；CR，完全缓解；CRC，结直肠癌；DCR，疾病控制率；IPI1，ipilimumab 1 mg/kg；NIVO3，纳武利尤单抗 3 mg/kg；PR，部分缓解；RECIST，实体瘤缓解评估标准；SD，疾病稳定

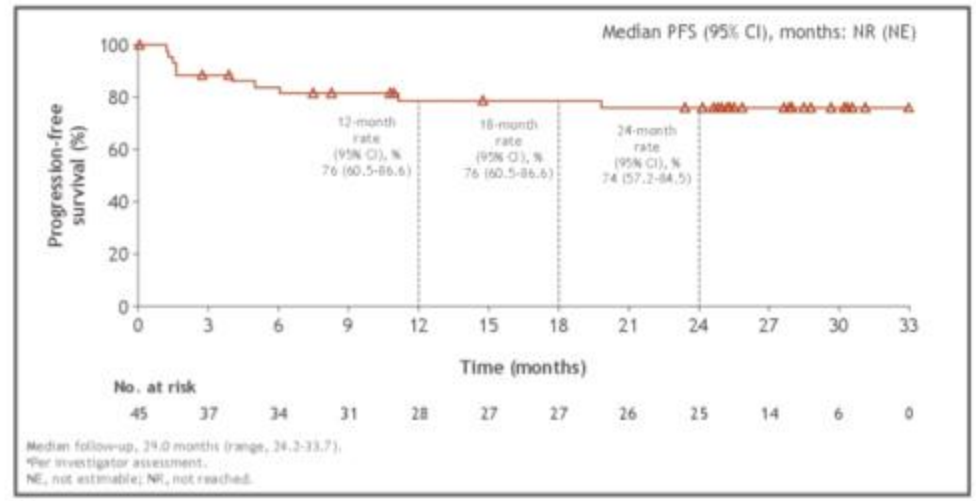
Lenz H,et al. 2020 ASCO abs 4040.

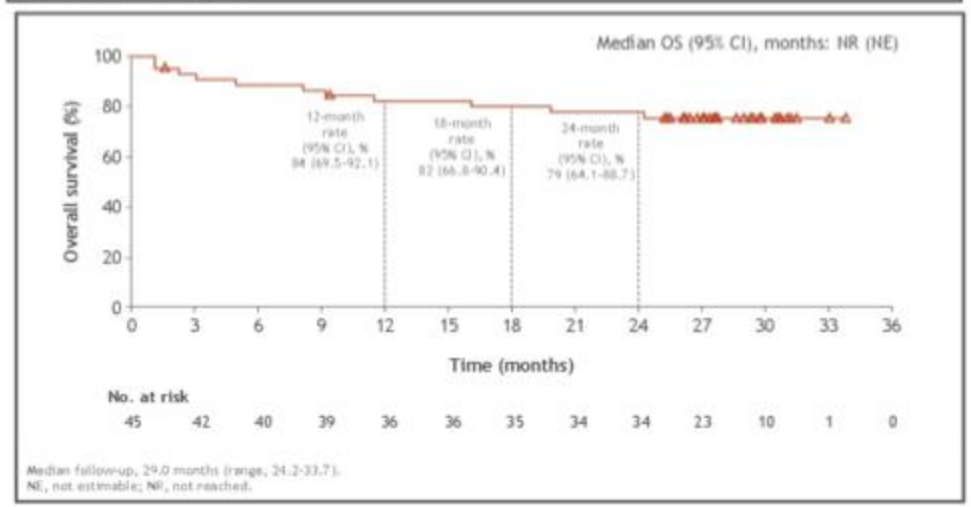
Results：ORR

- With median follow-up of 29.0months, the investigat-associated ORR was 69%,the CR rate was 13%
- Median DOR was NR
- At 24 months, PFS and OS rate were 74% and 79%,respectively

	NIVO3 (Q2W) + IPI1 (Q6W) N = 45 Investigator assessed	
Data cutoff	July 2018	October 2019
Median follow-up (range), months	13.8 (9.0-18.5)	29.0 (24.2-33.7)
ORR,[a] n (%) [95% CI]	27 (60) [44 -74]	**31 (69)** [53-82]
Best overall response, n (%)		
CR	3 (7)	**6 (13)**
PR	24 (53)	25 (56)
SD	11 (24)	7 (16)
PD	6 (13)	6 (13)
Not determined	1 (2)	1 (2)
DCR,[b] n (%) [95% CI]	38 (84) [70.5-93.5]	38 (84) [70.5-93.5]
Median TTR (range), months	2.6 (1.2-13.8)	2.7 (1.2-27.7)
Median DOR (range), months	NR (1.4+ to 15.4+)	NR (1.4+ to 29.0+)

[a]Patients with CR or PR divided by the number of treated patients; [b]Patients with CR, PR, or SD for ≥ 12 weeks divided by the number of treated patients. PD, progressive disease; TTR, time to response.





1. https://clinicaltrials.gov/ct2/show/NCT02060188.
2. Heinz-Josef Lenz,et al . ASCO 2020. Poster abstract 4040.

CONTENTS

01 Immune microenvironment in CRC and current state of immunotherapy in mCRC

02 **neoadjuvant immunotherapy for locally advanced colon cancer (LACC)**

03 **neoadjuvant immunotherapy for locally advanced rectal cancer (LARC)**

04 Hotspots and chanllenge of immunotherapy for locally advanced CRC

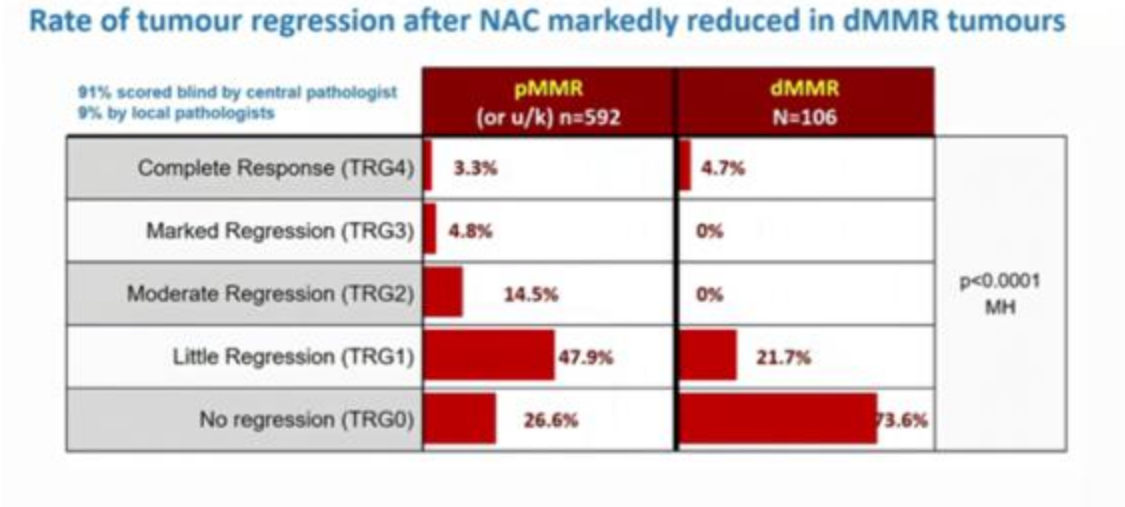
Goals of neoadjuvant therapy for locally advanced CRC

- ✔ Increasing R0 resection rate
- ✔ Improving DFS and OS of population at high risk of recurrence
- ✔ Detecting chemosensitivity before adjuvant chemotherapy
- ✔ Reducing or eliminating subclinical lesions
- ✔ Biological behaviour
- ✔ Organ-preservation (e.g. low rectal cancer)

neoadjuvant chemotherapy or radiotherapy for local CRC：dMMR and pMMR varies greatly in sensitivity to RT or CT

neoadjuvant chemotherapy for LACC

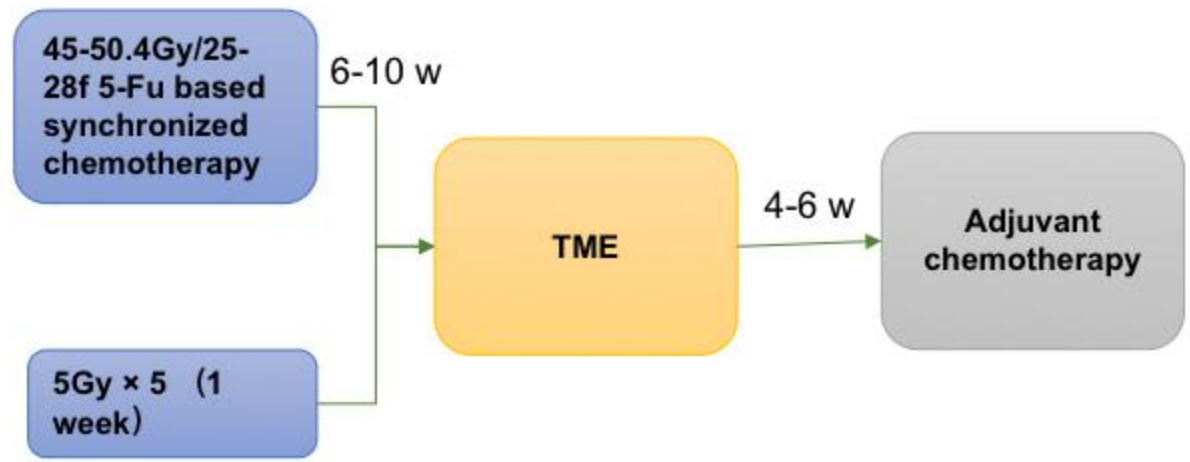
- FOxTROT study



Tumor regression: dMMR inferior to pMMR

neoadjuvant chemoradiotherapy for LARC

- Neo-CRT



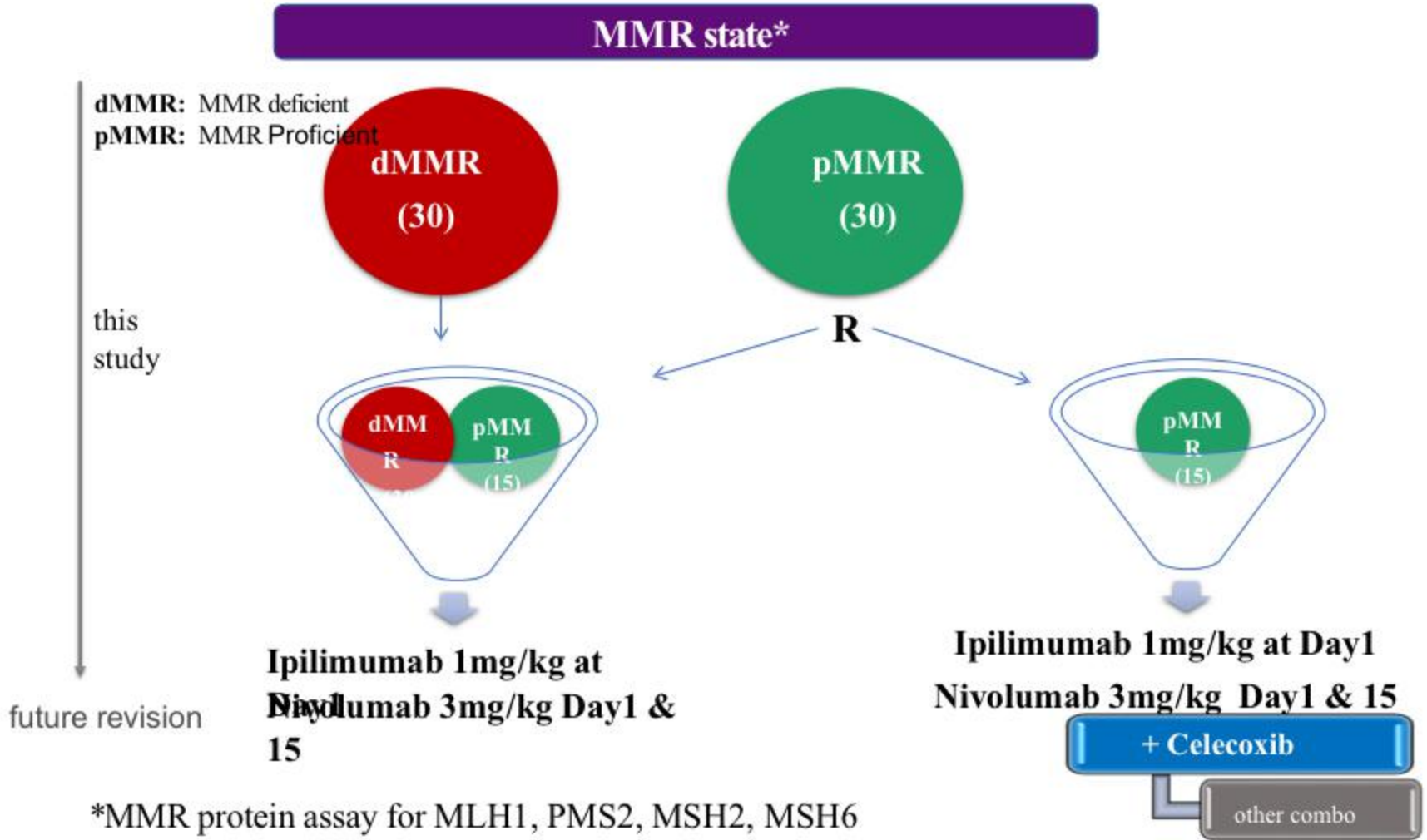
NCDB data-- pCR rate: dMMR inferior to pMMR

ASCO 2018
Ann of surg 2018

neoadjuvant immunotherapy for locally advanced colon cancer

NICHE : nivolumab plus low-dose ipilimumab as neoadjuvant-therapy

Phase 2 study in patients with stage I-III MSS or MSI colon cancer with no signs of distant metastases



*MMR protein assay for MLH1, PMS2, MSH2, MSH6

nature medicine

SUPPLEMENTARY INFORMATION

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

In the format provided by the authors and unedited.

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

2018 ESMO oral presentation

dMMR (n=7)

clinical stage before treatment	pathological stage	obvious residual tumour
cT2N2a	ypT0N0	0 %
cT2N0	ypT0N0	0 %
cT2N0	ypT0N0	0 %
cT3N0	ypT0N0	0 %
cT3N2a	ypT1N0	1 %
cT4aN2a	ypT2N0	2 %
cT4aN1a	ypT3N1	2 %

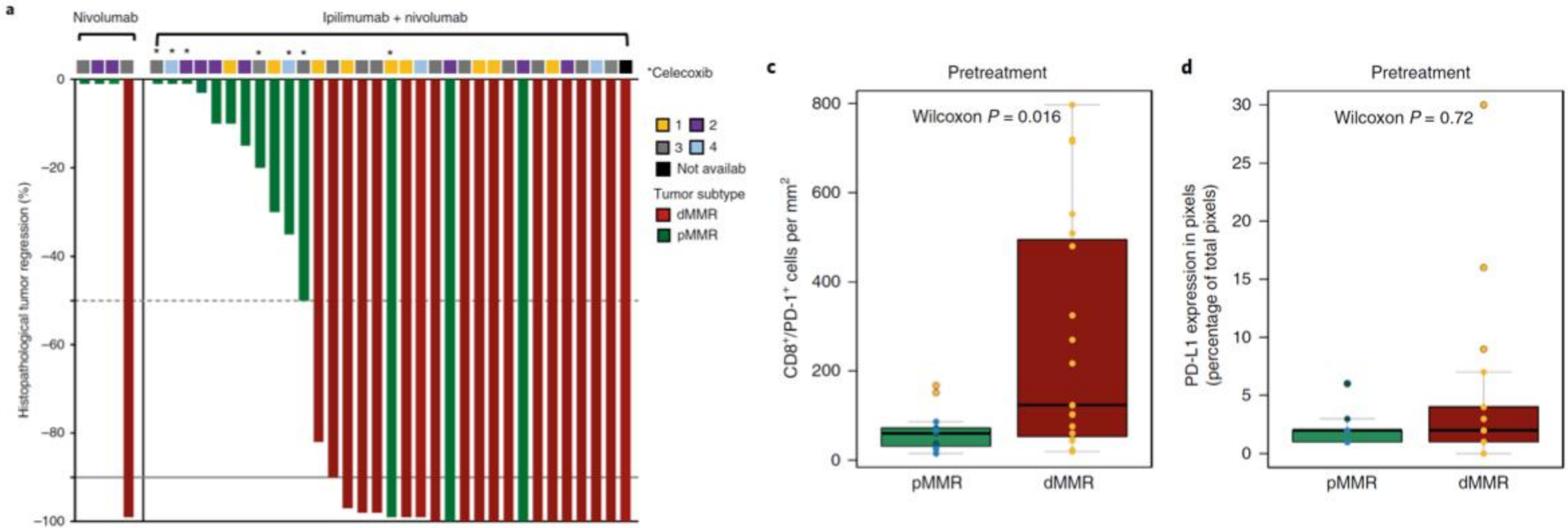
pMMR (n=8)

clinical stage before treatment	pathological stage	obvious residual tumour
cT3N1a	ypT3N2	85 %
cT3N0	ypT3N0	90 %
cT2N0	ypT3N1	90 %
cT2N0	ypT3N0	90 %
cT3N1b	ypT3N1	90 %
cT3N1b	ypT3N2	95 %
cT3N0	ypT3N0	100%
cT2N0	ypT2N0	100 %

2020 Nat Med final results

	dMMR tumors (*n* = 21)	pMMR tumors (*n* = 19)
Age at enrollment (years)		
Median (range)	58.4 (22–82)	65.9 (44–77)
Sex (*n* (%))		
Female	12 (57)	10 (53)
Male	9 (43)	9 (47)
Eastern Cooperative Oncology Group performance status		
0	21 (100)	19 (100)
Clinical disease stage (*n* (%))		
I	2 (9.5)	5 (20)
II	2 (9.5)	7 (35)
IIIA	1 (4.8)	1 (5)
IIIB	10 (47.6)	6 (30)
IIIC	6 (28.6)	1 (5)
Primary tumor location (*n* (%))		
Right colon	14 (67)	8 (42)
Left colon	5 (24)	11 (58)
Transverse colon	2 (10)	1 (5)
Lynch syndrome	7 (33)	0 (0)

NICHE Results：



- 20 dMMR：20/20 (100%) pathological responses, including 19/20 (95%) MPR and 12/20 (60%) pCR；
- 15 pMMR：4/15 (27%) pathological responses, including 3/15 (20%) MPR and 1/20 (5%) pCR（nonPOLE mut）。
- presence of T cell co-expressing CD8+PD-1+ may predict response in pMMR

Safety: all treatment-related adverse events

Treatment-related adverse events, n (%)	Grade 1-2	Grade 3	Grade 4
Any adverse event	**23 (58)**	**4 (10)**	**1 (2)**
Rash or pruritus	3 (8)	2 (5)	–
Dry skin	3 (8)	–	–
Infusion-related reaction	8 (20)	–	–
Dry mouth	5 (12)	–	–
Thyroiditis or hypothyroidism	4 (10)	–	–
Fever	1 (2)	–	–
Gastrointestinal			
Diarrhea	3 (8)	–	–
Nausea	1 (2)	–	–
Colitis	–	1[a] (2)	–
Musculoskeletal			
Arthralgia	1 (2)	–	–
Arthritis	2 (2)	–	–
Myalgia	2 (2)	–	–
Adrenal insufficiency	1 (2)	–	–
Respiratory			
Dyspnea	1 (2)	–	–
Sarcoid-like reaction	1 (2)	–	–
Fatigue	3 (8)	–	–
Laboratory tests			
Lipase increase	1 (2)	1[b] (2)	1[b] (2)
Amylase increase	–	1[b] (2)	–
Alkaline phosphatase increase	1 (2)	–	–

Surgery-related adverse events, n (%)	Grade 1-2	Grade 3
Any adverse event	**1 (2)**	**8 (20)**
Wound/abdominal infection	1 (2)	4 (10)
Post-operative ileus	—	1 (2)
Anastomotic leak	—	4 (10)
Small bowel injury	—	1 (2)
Pneumonia	—	1 (2)

- Five patients (13%) experienced grade 3/4 treatment -related toxicity
- Surgery- related, grade 3 AEs were observed in 8 patients

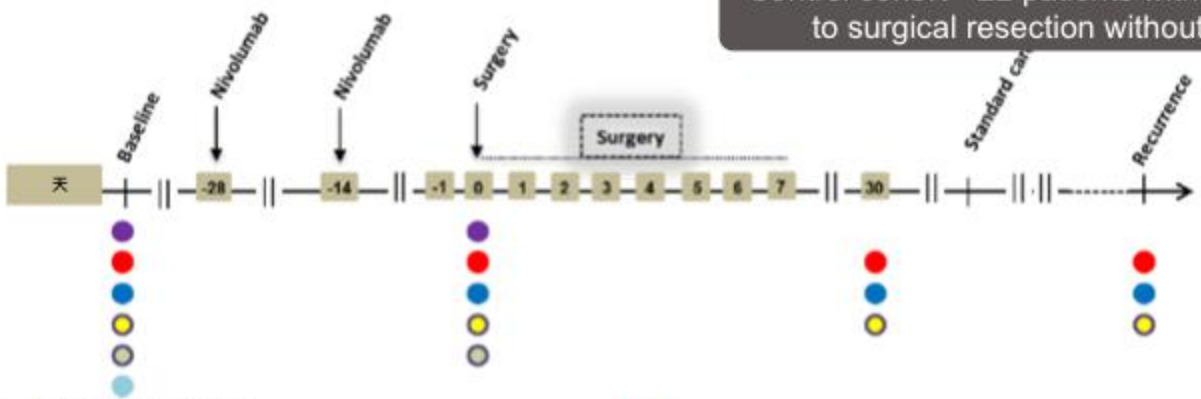
Percentages for all grade adverse events total more than 100% due to more AEs per patients. Some AEs may be related to 1 another and were reported simultaneously. All patients experiencing respiratory adverse events underwent CT-scans of the chest and there were no signs of pneumonitis in any of the patients. Grade 3/4 AEs: [a]Colitis was diagnosed in 1 patient 8 weeks after surgery. Patient was treated with a single dose of infliximab, after which symptoms resolved completely. Two grade 3 rash for which steroids (1x oral and 1x topical) were given with complete resolution. [b]Two grade 3 and the only grade 4 AEs were asymptomatic laboratory findings of increased lipase or amylase, which resolved without intervention. Reproduced with permission from Chalabi M et al. *Nat Med* 2020;26:566-576.

NICOLE study: Nivolumab (single-drug) neoadjuvant treatment for early-stage colon cancer

- NICOLE(Preoperative Nivolumab in Patients With Locally Advanced Colon Cancer， NCT04123925)
- First trial of anti-PD-1 drug (Nivolumab) as neoadjuvant treatment on non-selective MMR early-stage colon cancer

22 participants of clinical T3/T4 resectable colon cancer → **An initial 6-patients safety run-in cohort + an 16-patient expansion cohort.** → **Nivolumab received twice, fixed dose of 240mg, Q2W** → **surgery within 5 weeks after onset of treatment**

Control cohort：22 patients with LACC (T3-T4) who proceed to surgical resection without preoperative anti-PD-1



- tissue (tumour/normal)
- blood biomarkers
- CBT, biochemistry, electrolyte, coagulation, urine assay
- TAC t.b.
- PET-FDG
- microbiota

blood biomarkers
systemic cytokines and chemokines; myeloid derived suppressing cells; Immune cell subtypes; Lymphocyte activation; metabolomics

tissue biomarkers
immune scales; PD-L1 expression; inflammation; TCR sequencing and expression; Nanostring assay; MSI and RAS/Raf state; Tumour mutation burden

Primary outcomes：
- feasibility of Nivolumab in the preoperative setting in patients with T3-T4 colon cancer
- Objective Tumor Response Rate (ORR) as defined by Response Evaluation Criteria In Solid Tumors
- molecular and immunophenotypic changes in tumor and peripheral blood evaluating several biomarkers.

Secondary Outcome：
- the degree of pathologic regression
- Metabolic Response(FDG-PET)
- Postoperative complications (occurring within 60 days from surgery)Relapse-Free Survival
- Overall Survival

Avallone A, et al. ESMO 2020. Poster No.491P.

baseline characteristics

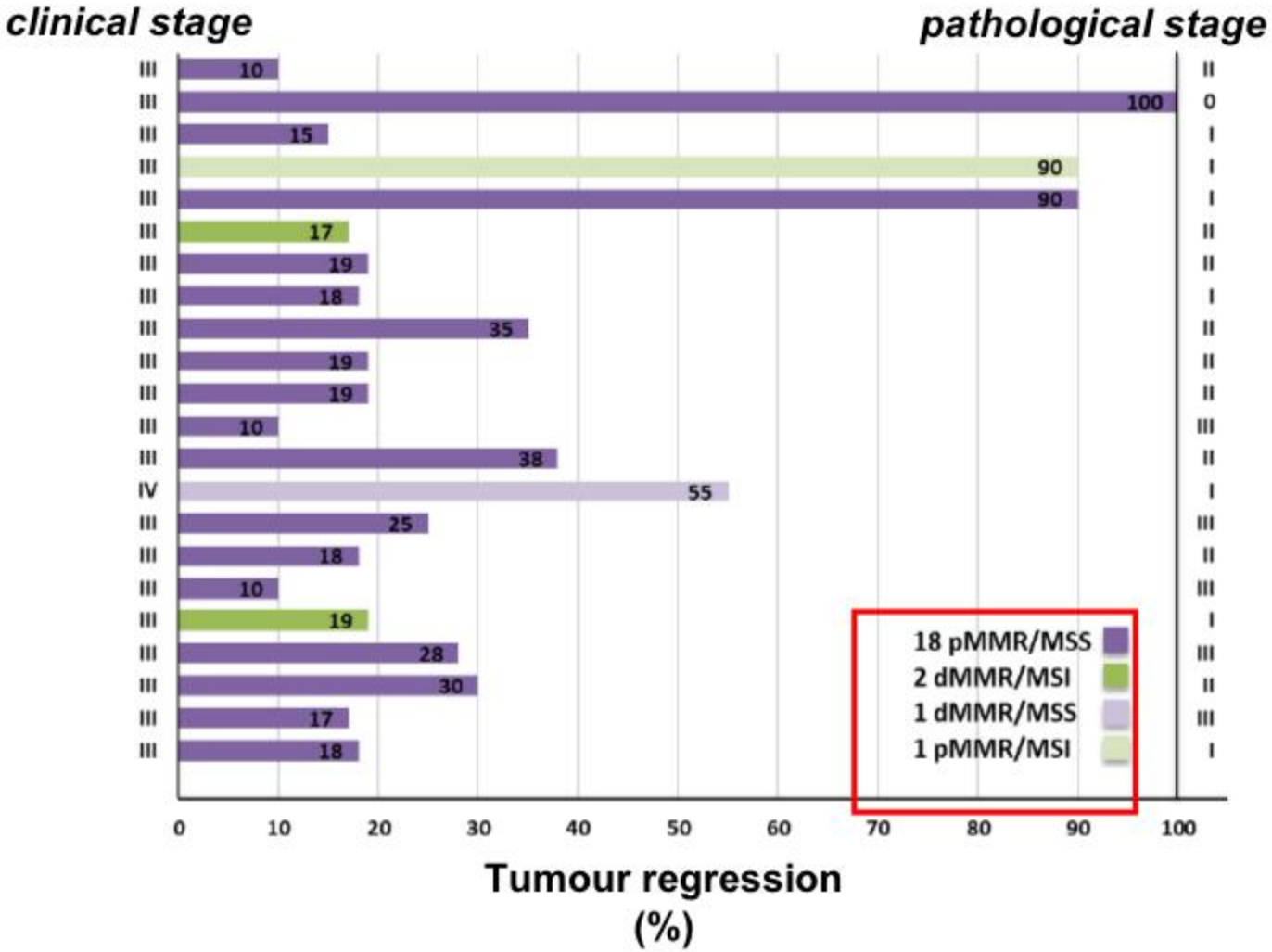
- **Similar between Nicole cohort and control cohort (except for age and gender);**
- **NICOLE cohort patients are younger and had more males.**
- **No difference of intratumoural number of CD8+ T cells between two cohorts (IHC digital staining)**

	Nicole cohort(N=22)	control cohort(N=22)	*P* value
age, yr			
median (range)	63 (25-73)	73 (42-86)	0.01
gender, n(%)			
male	16 (73%)	9 (41%)	
femail	6 (17%)	13 (59%)	0.03
primary site, n(%)			
right	10 (45%)	12 (55%)	
left	12 (55%)	10 (45%)	0.76
clinical stage, n(%)			
II	-	4 (18%)	
III	22* (100%)	18 (82%)	0.66
RAS, n(%)			
wild type	10 (45%)	7 (32%)	
mutation	12 (55%)	15 (68%)	0.35
BRAF, n(%)			
wild type	21 (96%)	19 (86%)	
mutation	1 (4%)	3 (14%)	0.33
MMR, n(%)			
proficient	19€ (86%)	17 (77%)	
deficient	3§ (14%)	5§ (23%)	0.45
baseline CD8+ cells/mm²			
median (IQR range)	222 (115-310)	178 (75-323)	0.74

*1 patient is stage IV ; €MSI of 1 patient by PCR; §MSS of 1 patient by PCR

Results：

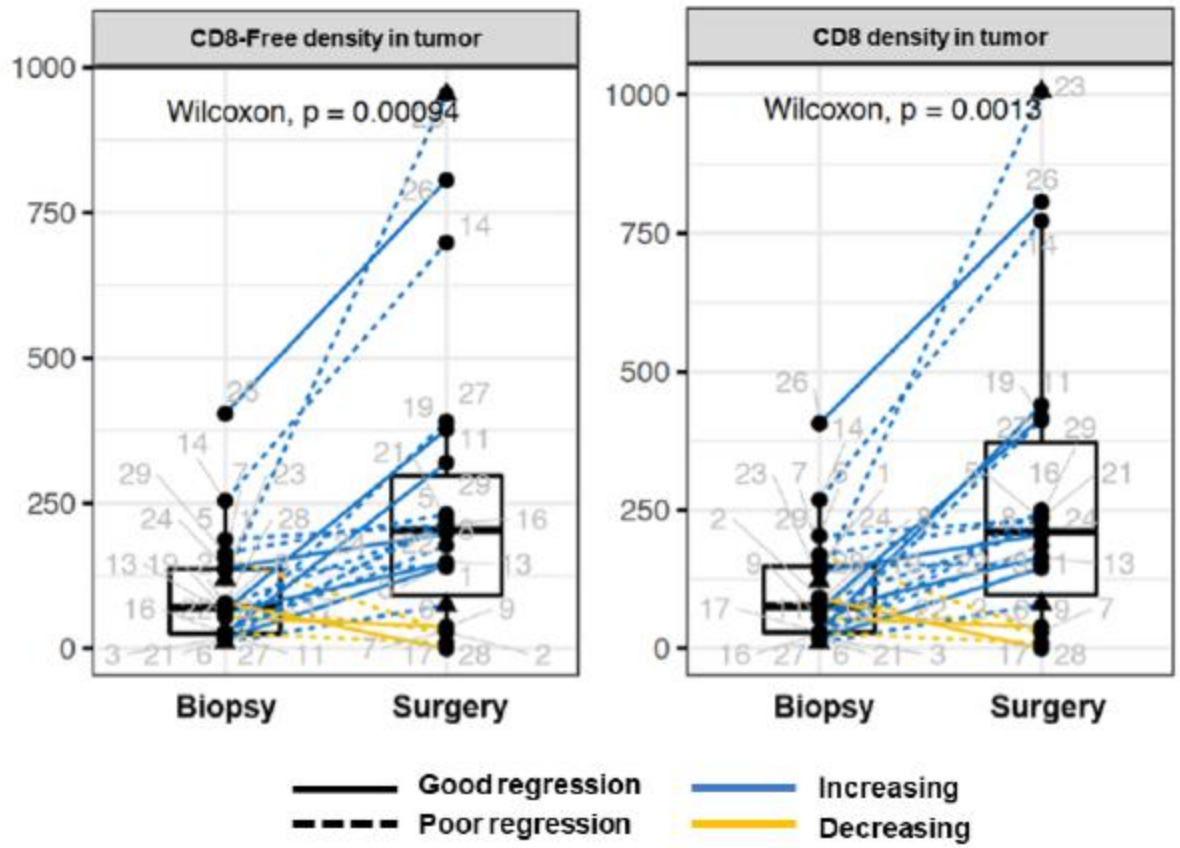
objective pathological response in 6/19 pMMR/ MSS and 1/4 dMMR /MSI-H



- Tumour regression defined by no alive tumour cells
- Major pathological regression (MPR) observed in 2 pMMR/MSS (including 1 CR) and 1 pMMR/MSI
- ≥30% tumour regression seen in 4 confirmed MSS tumours
- no MPR observed in 2 dMMR/MSI tumours
- A downstaging was observed in 70% of Nicole cohort patients

Results: NICOLE cohort CD8+T infiltration—biopsy vs. surgery

- biomarkers from biopsy and surgery samples show that CD8+ cell infiltration significantly increased
- on the contrary, radiological and metabolic assessment at baseline/pre-operative time point show no significant differences (data not shown)



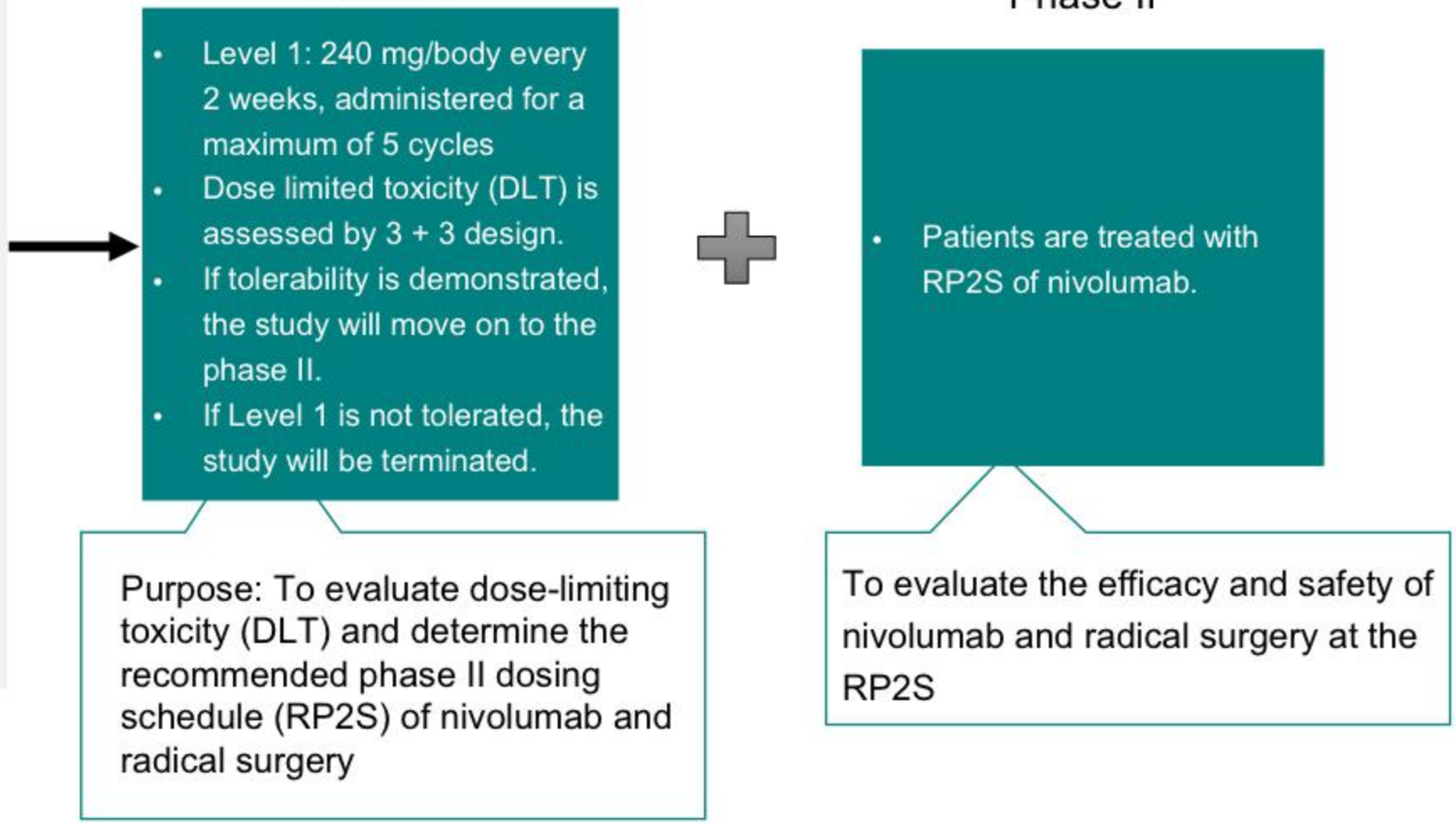
neoadjuvant immunotherapy for locally advanced rectal cancer

Voltage：Nivolumab monotherapy and subsequent radical surgery following preoperative chemoradiotherapy in patients with microsatellite stable and microsatellite instability-high locally advanced rectal cancer.

- an open-labeled, single-arm, multi-centre, phase I/II clinical trial
- phase II：**cohort A1：37 MSS patients (including patients receiving RP2S treatment in phase I); cohort A2:** 5 MSI-H patients

Key Eligibility Criteria：

- Treatment-naïve patients with rectal cancer located within 12 cm from their anal verge
- Clinical stage of T3 –4 N -any M0
- Age ≥ 20 to < 80 years
- ECOG PS of 0 or 1
- 50.4 Gy of concurrent CRT with daily 1,650 mg/m2 of capecitabine was completed
- CRT-associated AEs will be recovered to grade ≤ 1 when study treatment starts
- Sufficient organ functions



2019 ASCO. Abstract # 3606

Primary endpoint: pCR by central assessment

AJCC tumor regression grading	Cohort A1* Primary endpoint (MSS, N = 37)	Cohort A1 (MSS, N=39)	Cohort A2 (MSI -H, N = 2)
0(pCR)	11(30%)	11(28%)	2(100%)
1	3(8%)	4(10%)	0(0%)
2	15(41%)	15(38%)	0(0%)
3	7(19%)	8(21%)	0(0%)
Not evaluated	1(3%)	1(3%)	0(0%)

Totally, 39 patients were included in cohort A1. Primary endpoint was analyzed for first consecutive 37 patients.; Surgical resection was not performed in one case showing clinical CR due to patient' s refusal

- The primary endpoint of this study was met (**pCR rate=30%**; 90% CI 18-44%)
- As 3 patients (8%) had the AJCC Grade 1 response, 14 patients (38%) had the major pathologic response.
    - **Median RFS and OS were not reached.**
    - As of Dec 7th 2018, only one case with lung metastasis was observed 18.9 months after surgery in cohort A1.

Key Subgroup Analysis for pCR and Major Pathologic Response (MPR)

	no. of patients	AJCC grade 0	AJCC grade 1	pCR rate	MPR (0 or 1)
all patients	39	11	4	28%	38%
stage II	30	7	4	23%	37%
stage III	9	4	0	44%	44%
T3 and N	27	6	4	22%	37%
T4 and/or N+	12	5	0	42%	42%
<5cm from AV	9	2	0	22%	22%
≥5cm from AV	30	9	4	30%	43%

- **VOLTAGE regimen suggested to be effective for rectal cancer with T4 and/or N+ as well.**

AVANA study: preoperative chemoradiotherapy +Avelumab treating LARC, a phase II study

phase II study

LARC (N=101)

- high-risk cT3
- cT4
- cN+

→ **CRT + Avelumab**

standard CRT+
Avelumab 10mg/kg
q2w，6 cycles

→ **surgery**

TME
8-10 weeks after CRT

→ **adjuvant chemo**

according to the state of pathological remission (XELOX+capecitabine, 6 cycles)

Primary endpoint：pCR

secondary endpoints：

- R0 resection rate
- tumor downstaging
- local recurrence
- sphincter preservation rate
- progression-free survival
- overall survival
- safety profile
- evaluation of exploratory predictive and/or prognostic biomarkers

statistical analysis

Assuming as null hypothesis p0 a pCR rate of 15%, a significance level of 5% (one-side), and a power of 80%

↓

The experimental regimen will be considered for further studies if in at least 22 pts we observe a pCR

注：CTRT, chemoradiotherapy; CT, chemotherapy; pCR, pathological complete remission; PFS, progression-free survival; OS, overall survival;

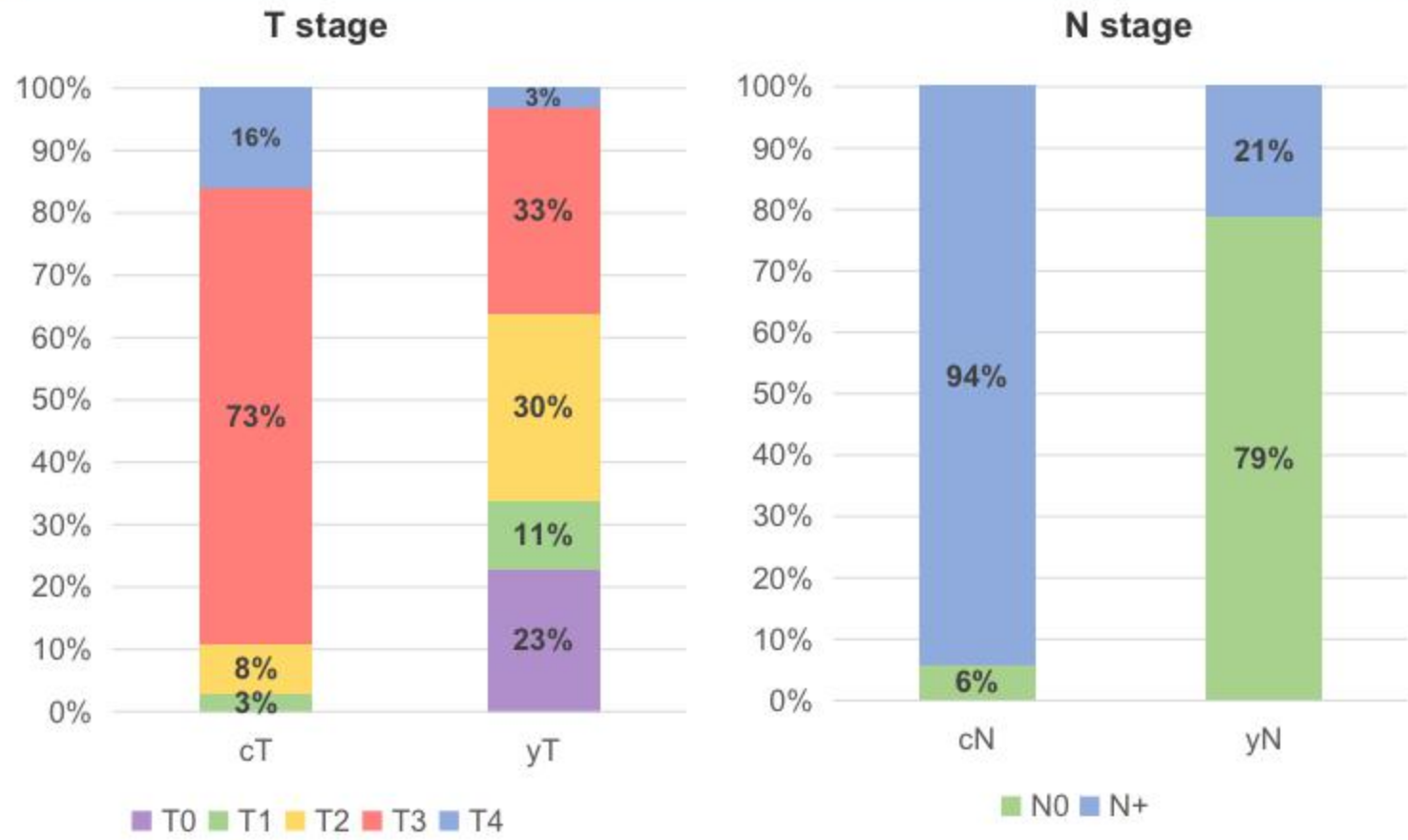
anti-tumour efficacy: pCR 23%，MRP 60%

	N=100*，%
yT stage	
yT0	23%
yT1	11%
yT2	30%
yT3	33%
yT4	3%
yN stage	
yN0	79%
yN+	21%
pathologic remission	
pCR	23%
MRP	60%
no response	17%

*1 patient refused surgery

pCR：23/100(23%)

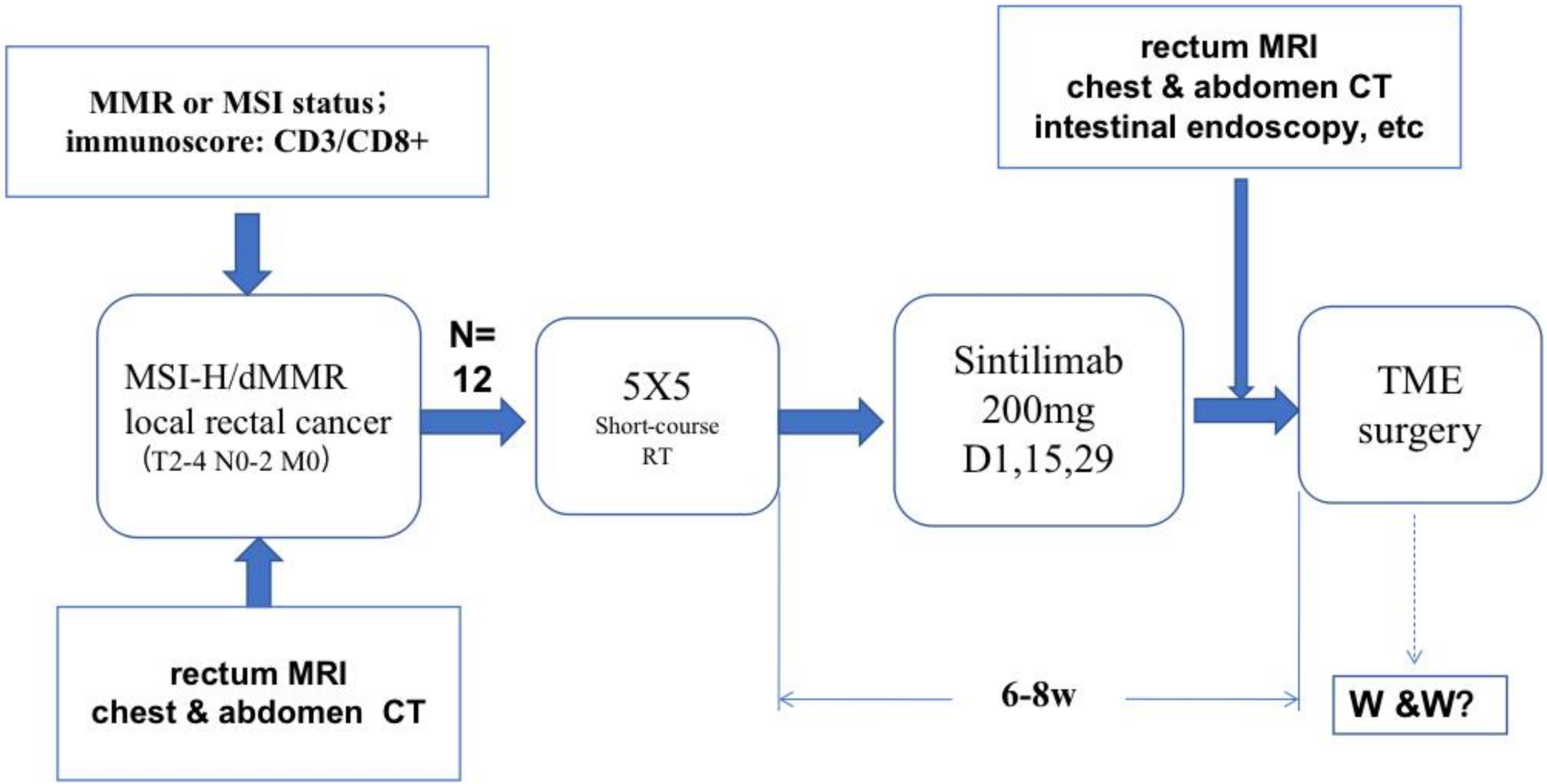
MRP：60/100(60%)



Ongoing studies of LARC

Identifier/reference	Study title	Study design	Population	Status	Trial description	Primary endpoints
			ICIs and chemotherapy			
NCT04262687	POCHI	Phase II	First-line MSS/P-MMR CRC	Soon-to-start	XELOX + bevacizumab + pembrolizumab, single arm. All patients will be prospectively assessed by immunoscore/TuLIP score	OS
NCT03626922	-	Phase IB	First-line MSS/P-MMR CRC	Recruiting	Pemetrexed + oxaliplatin + pembrolizumab, single arm	ORR
			ICIs and radiotherapy			
NCT02921256	-	Random Phase II	LARC untreated	Enrollment suspended	Randomised 3-arm treatment: standard treatment with FOLFOX-based CRT vs FOLFOX-based CRT + pembrolizumab vs FOLFOX-based CRT + veliparib + pembrolizumab	ORR
NCT04109755	PEMREC	Phase II	LARC untreated	Recruiting	Short course radiotherapy followed by pembrolizumab monotherapy	TRG grade
NCT02948348	-	Phase IB/II	LARC untreated	Recruiting	Standard CRT (with capecitabine + RT) followed by sequential nivolumab therapy	Safety/ORR
NCT04124601	CHINOREC	Phase II	LARC untreated	Recruiting	Standard CRT (with capecitabine + RT) followed by sequential nivolumab + ipilimumab therapy	Safety
NCT03921684	-	Phase II	LARC untreated	Recruiting	Standard CRT (with capecitabine + RT) followed by FOLFOX + nivolumab combination therapy	pCR rate
NCT04017455	TARZAN	Phase II	LARC untreated	Recruiting	Short course radiotherapy followed by atezolizumab + bevacizumab combination	ORR
NCT03127007	R-IMMUNE	Phase IB/II	LARC untreated	Recruiting	Standard CRT (with 5FU + RT) with concomitant atezolizumab	Safety/ORR
NCT03299660	-	Phase II	LARC untreated	Recruiting	Standard CRT (with capecitabine + RT) followed by avelumab	pCR rate

Neoadjuvant immunotherapy for rectal cancer, West China Hospital (Registered on ClinicalTrials: NCT04636008)



CONTENTS

01 Immune microenvironment in CRC and current state of immunotherapy in mCRC

02 neoadjuvant immunotherapy for locally advanced colon cancer

03 neoadjuvant immunotherapy for locally advanced rectal cancer

04 **Hotspots and chanllenge of immunotherapy for locally advanced CRC**

Challenges to neoadjuvant immunotherapy in local CRC

■ optimal population?

--select high-risk population with MSI-H locally advanced CRC at stage III

--accuracy of pre-operative staging and response evaluation in MSI-H locally advanced CRC: PET/CT

--based on goals: increase R0 resection rate? surgery-free or organ-preserving, exp. for lower rectal cancer?

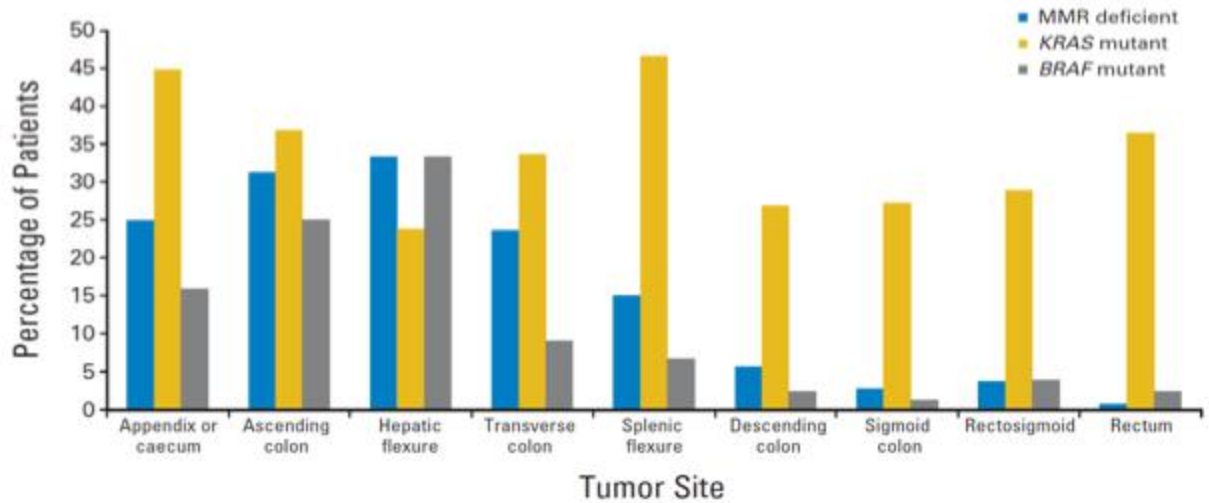
■ accuracy of MSI test

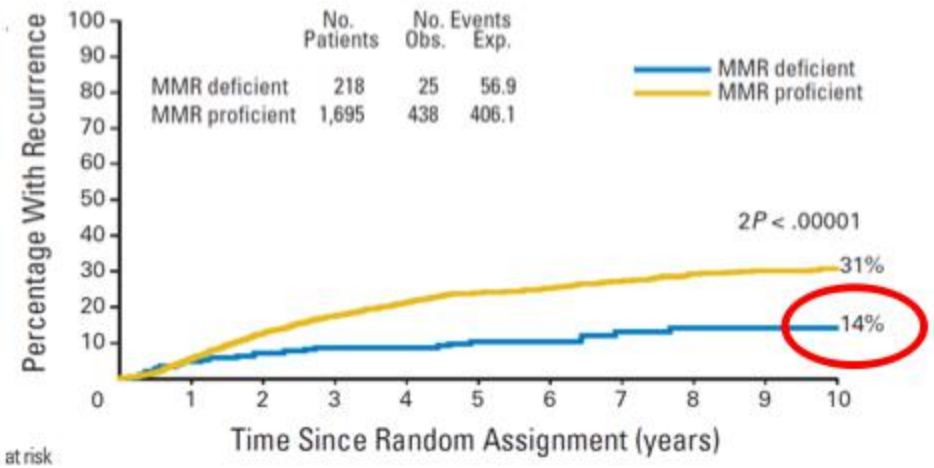
■ timing of treatment: neoadjuvant vs. adjuvant?

■ treatment strategies: immune monotherapy or combination treatment?

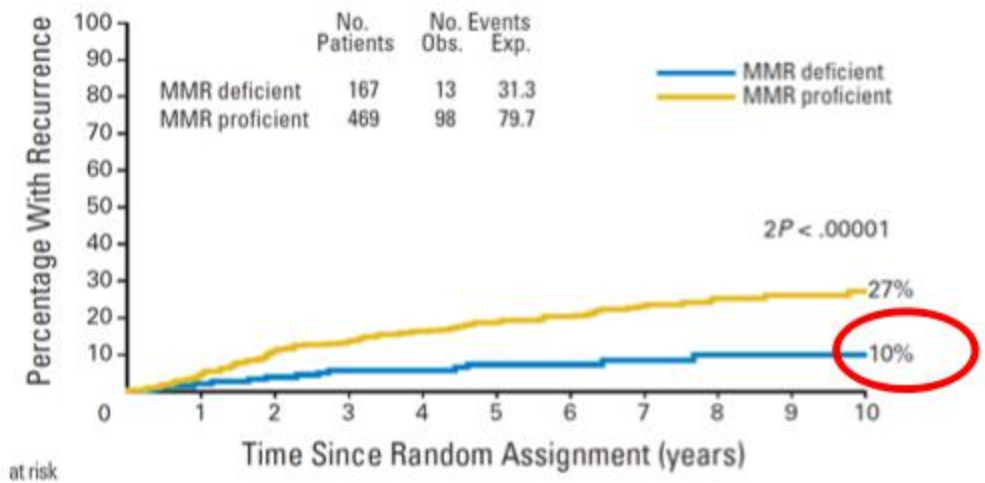
■ duration of perioperative immunotherapy? balance of efficacy and safety

QUASAR study: dMMR stage II/III CRC have good prognosis





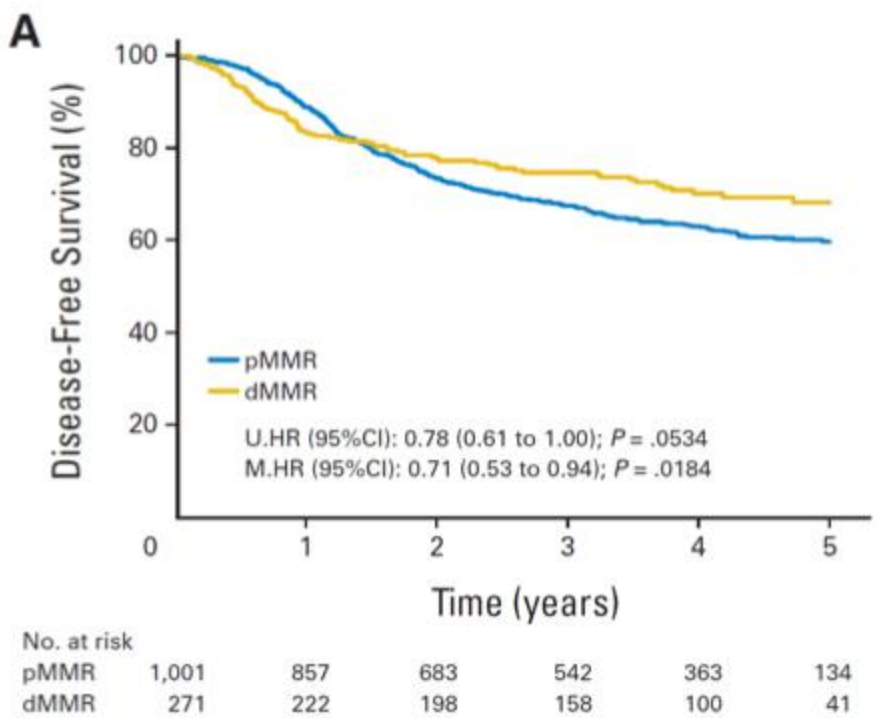
stage II/III



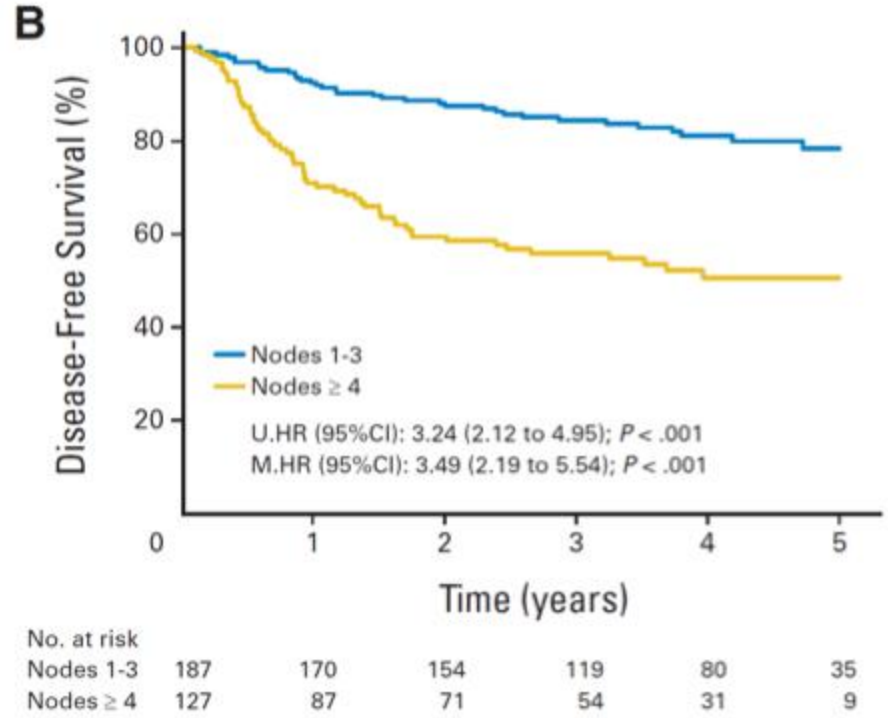
stage II

J Clin Oncol 2011 ; 29:1261-1270.

Meta-analysis: prognosis of stage III dMMR colon cancer is correlated with primary site and N2



proximal colon cancer



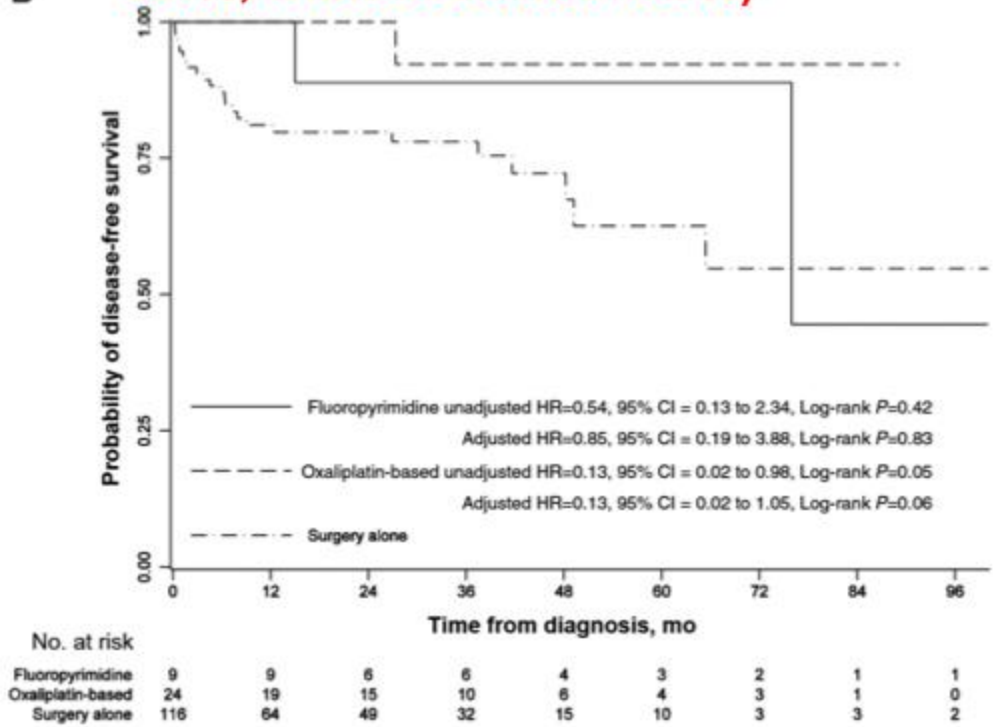
N1/2

JCO 2013

high-risk dMMR stage II CRC: adjuvant therapy containing oxaliplatin is not beneficial?

stage II (overall RFS 5.7%; with chemo 2.4%; without chemo 6..3%)

B

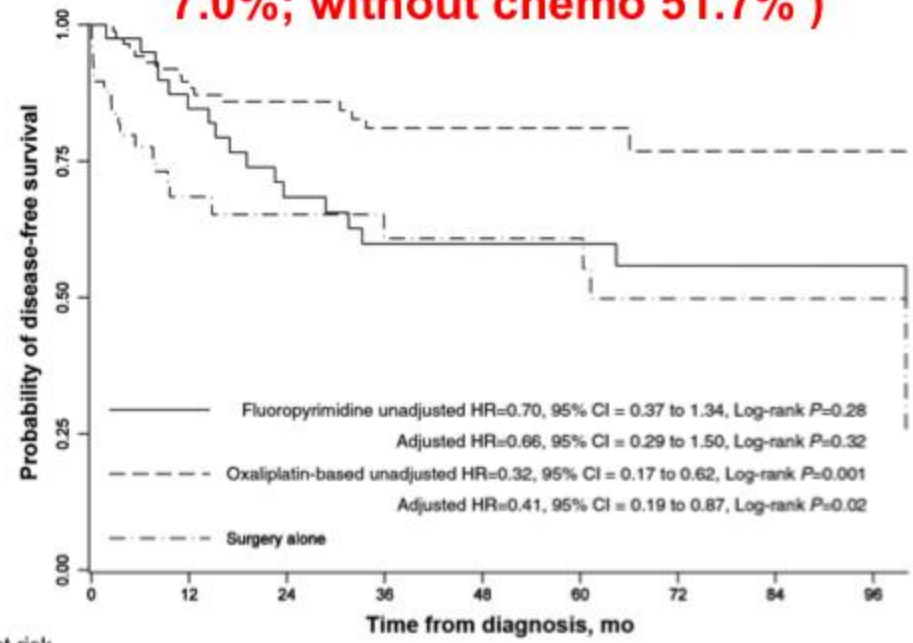


No. at risk

Fluoropyrimidine	9	9	6	6	4	3	2	1	1
Oxaliplatin-based	24	19	15	10	6	4	3	1	0
Surgery alone	116	64	49	32	15	10	3	3	2

stage III (overall RFS 20.9%; with chemo 7.0%; without chemo 51.7%)

A



No. at risk

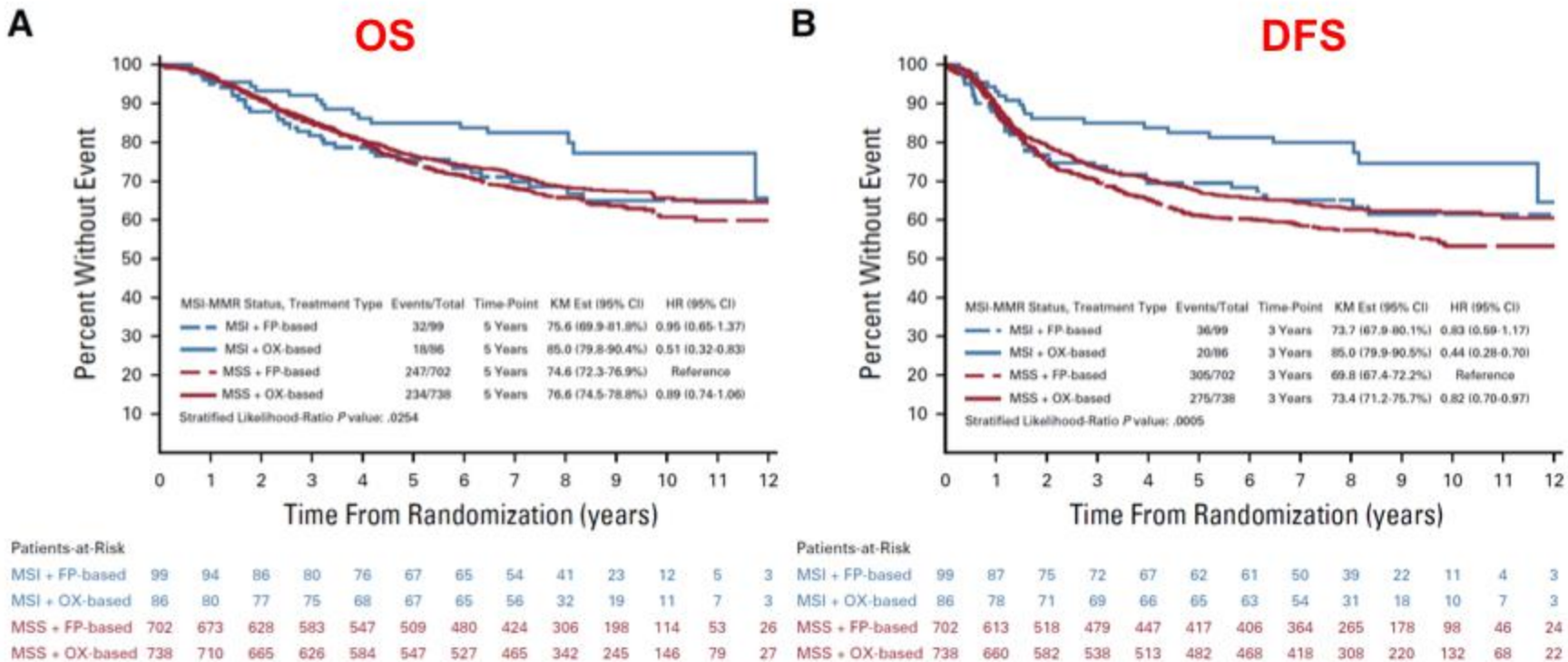
Fluoropyrimidine	40	32	25	20	17	16	13	12	9
Oxaliplatin-based	89	75	60	46	32	22	14	7	6
Surgery alone	58	24	17	14	13	11	8	7	4

		Disease-free survival			
		Univariate analysis		Multivariable analysis*	
Variable	No. of patients (3-year survival rates, %)	HR (95% CI)	P†	HR (95% CI)	P†
High-risk stage II					
Surgery alone	116 (78.0)	1		1	
Fluoropyrimidine-based	9 (88.9)	0.54 (0.13 to 2.34)	.41	0.85 (0.19 to 3.88)	.83
Oxaliplatin-based	24 (92.3)	0.13 (0.02 to 0.98)	.05	0.13 (0.02 to 1.05)	.06

JNCI 2016

adjuvant chemotherapy for dMMR stage III colon cancer: regimens containing oxaliplatin may be beneficial?

meta-analysis of 12 clinical trials in ACCENT database: N=5457, dMMR=609

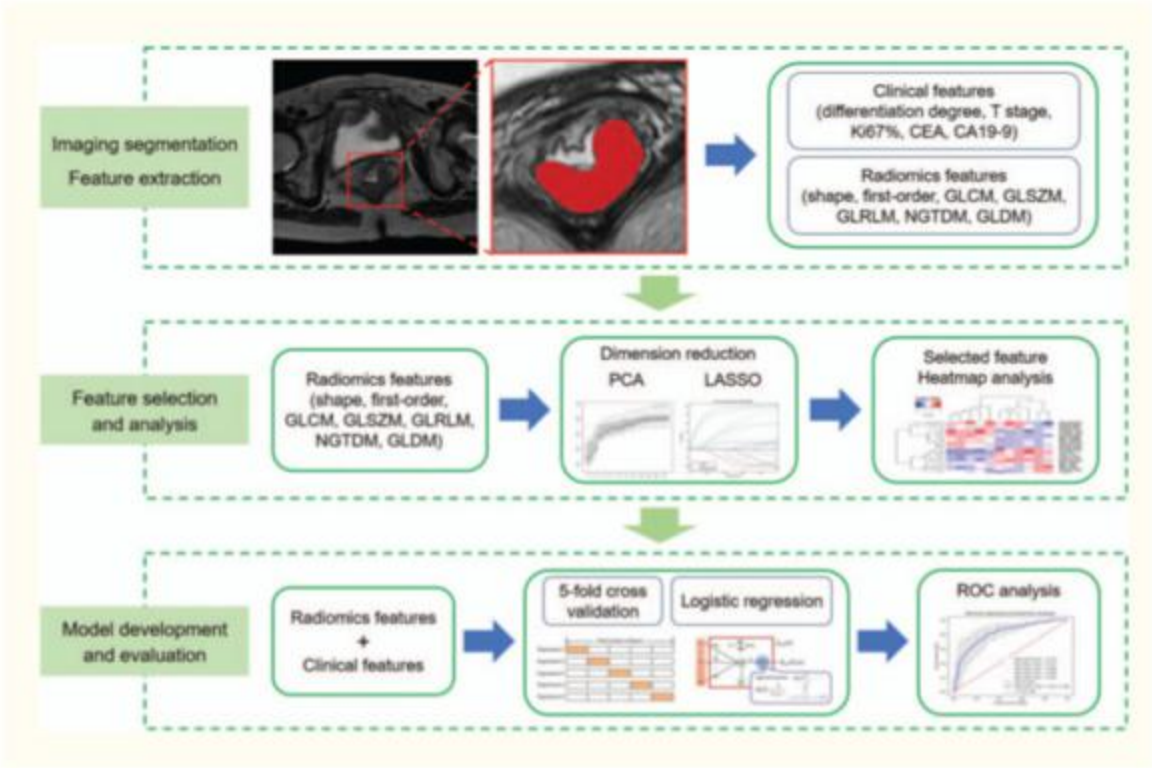


better prognosis factors of oxaliplatin-containing chemo: N1, low-risk stage III

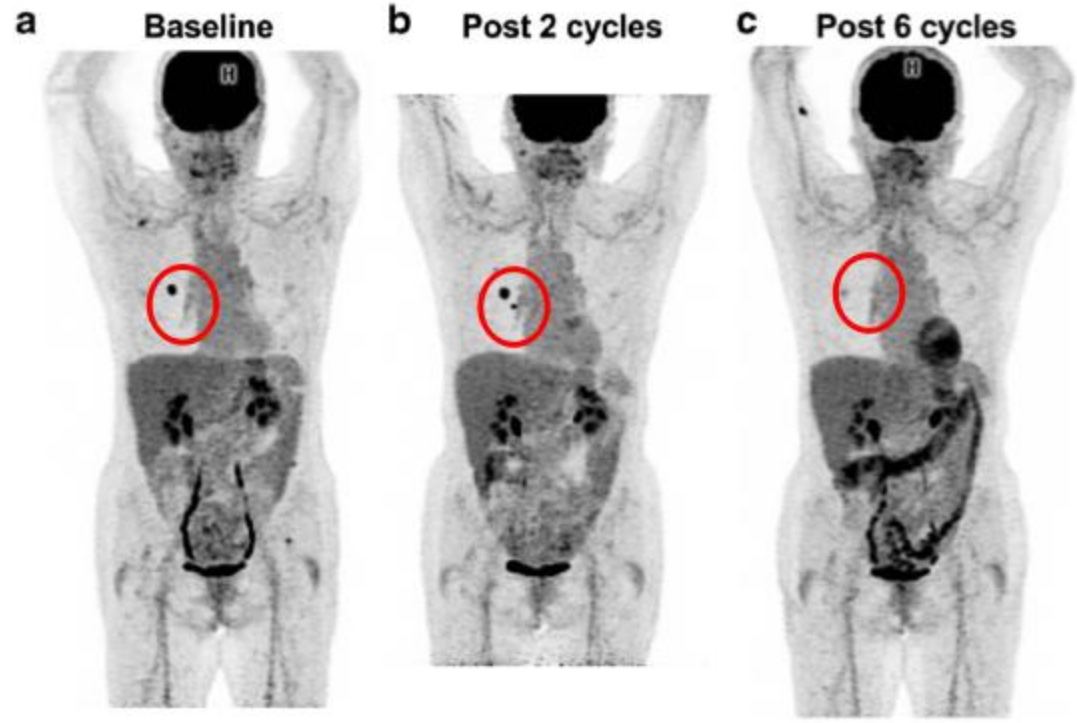
JCO2020

optimal imaging test for MSI-H CRC pre-operative staging and response evaluation

Stage interpretation by CT/MRI radiomics



Response interpretation in images by tumour metabolism



NICHE study: **Poor correlation** between primary tumour treatment response by radiography and pathologic downstaging

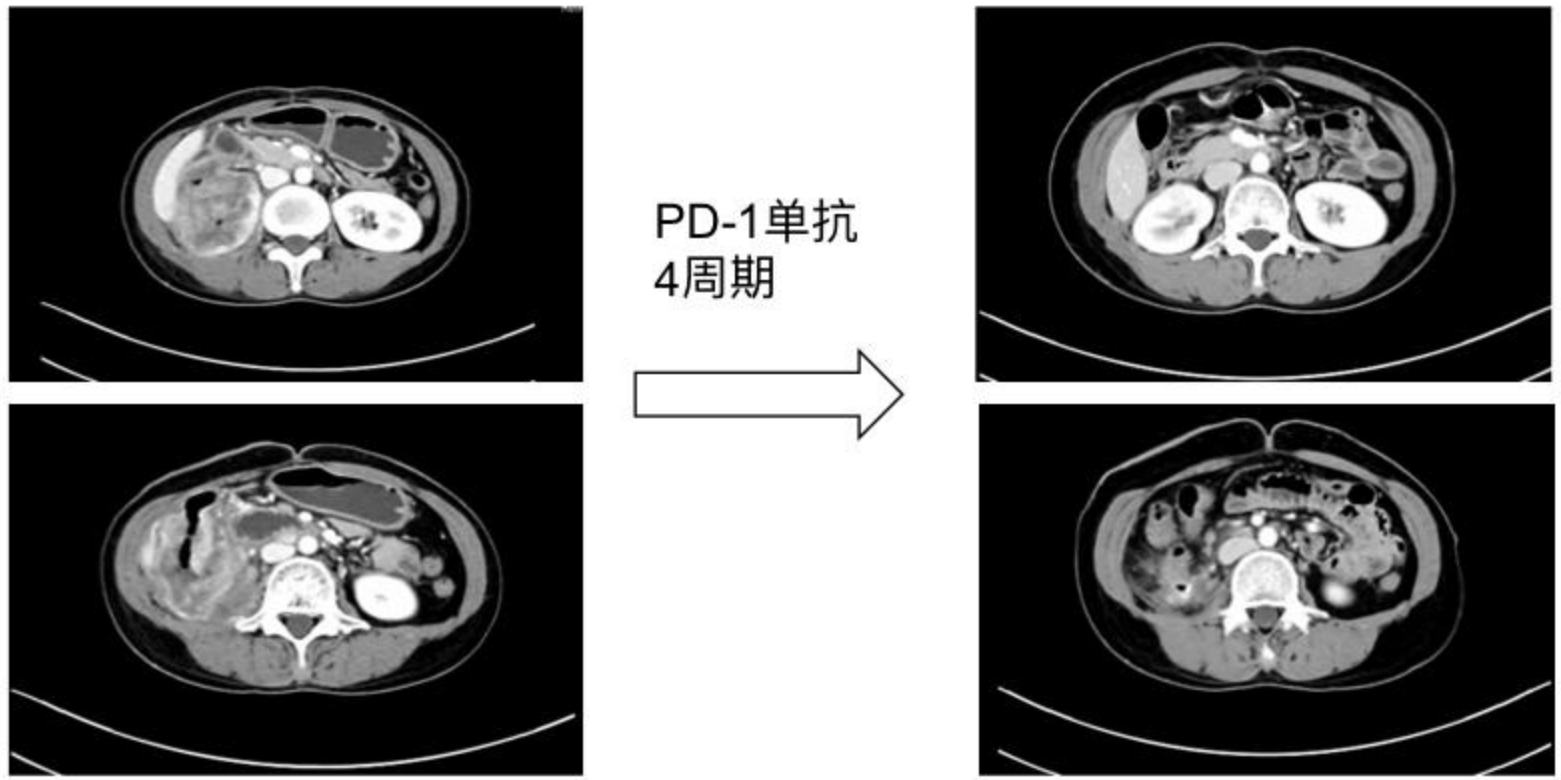
ycT3-4N1-2

dMMR tumors	Pre- treatment clinical TNM staging (stage)	Post- treatment radiological staging Stage; TNM	Post-treatment residual viable tumor (%)	Post-treatment pathological TNM staging (Mandard)	Tumor mutational burden	Driver mutations
3* (run-in)	cT3N2a (IIIb)	-	1	ypT1N0 (2)	2130	*APC; BRAF; NRAS*
5	cT2N2a (IIIb)	-	0	ypT0N0 (1)	1324	*KRAS*
6	cT2N0 (I)	-	0	ypT0N0 (1)	3290	*APC; PIK3CA*
10	cT2N0 (I)	-	3	ypT2N0 (2)	1338	*APC; BRAF*
12	cT4aN2a (IIIc)	ycT4aN0	0	ypT0N0 (1)	1460	*APC; KRAS*
14	cT4aN1a (IIIc)	-	2	ypT2N1 (2)	4458	*APC; BRAF*
15	cT3N0 (IIa)	-	0	ypT0N0 (1)	1556	*APC*
16	cT4aN2a (IIIc)	-	0	ypT0N0 (1)	2226	*BRAF*
19	cT4aN2b (IIIc)	-	10	ypT3N1b (2)	824	*TP53; BRAF*
21	cT3N1a (IIIb)	-	1	ypT3N0 (2)	648	--
23	cT4aN2a (IIIc)	ycT4aN1b	0	ypT0N0 (1)	1108	--
24	cT3N2a (IIIb)	ycT3N1b	18	ypT3N1 (3)	1416	*BRAF*
25	cT3N1a (IIIb)	ycT2N0	8	ypT1N0 (3)	2737	*APC; BRAF*
27	cT3N2 (IIIb)	ycT3N2	0	ypT0N0 (1)	1161	*APC; PIK3CA*
29	cT3N2 (IIIb)	ycT2N2	0	ypT0N0 (1)	1754	*APC; KRAS; PIK3CA*
30	cT2N0 (II)	-	0	ypT0N0 (1)	709	*APC*
32	cT3N1b (IIIb)	ycT2N0	0	ypT0N0 (1)	1696	*APC; BRAF*
35	cT4aN1b (IIIb)	ycT4aN1b	0	ypT0N0 (1)	1689	*APC; PIK3CA*
36	cT4aN2a (IIIc)	-	2	ypT3N0 (2)	1186	*BRAF*
40	cT4bN1b (IIIb)	ycT4aN1b	1	ypT1N0 (2)	2581	*TP53; PIK3CA*
43	cT2N1b (IIIa)	ycT2N0	0	ypT0N0 (1)	N/A	N/A

ypT0N0

Case： li xx，F，33y，Lynch syndrome

- First gene test in other hospital: pMMR (IHC)
- 1st line: FOLFOX；2nd line: FOLFIRI+bev，rapid progression，PS score 2
- MSI PCR annalysis：confirmed MSI-H，3rd line： PD-1 antibody q3w monotherapy x 4cycles
- Objective Respnse：PR，degree of pathologic regression: pCR



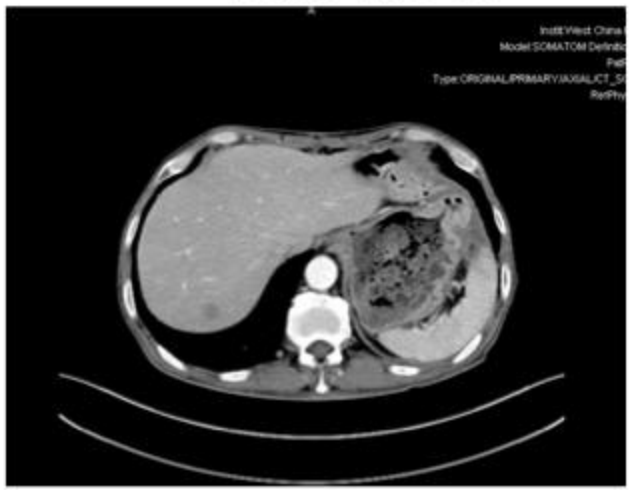
Case：Dong xx，M，56y，right colon cancer with liver metastases，MSI-H，

- stage of primary tumor：stage III

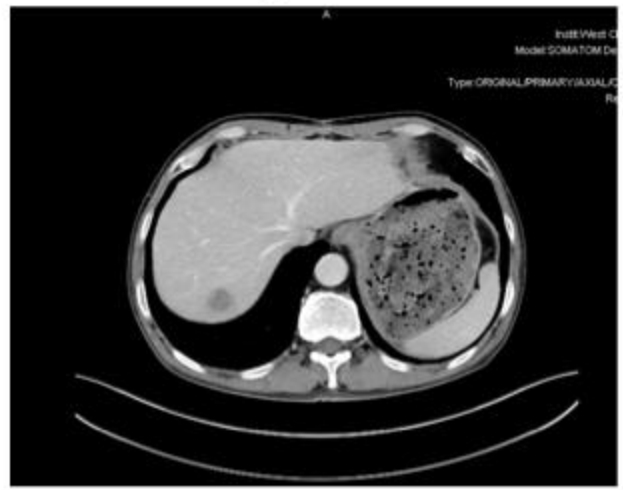
-Isolated liver metastases occurred rapidly during postoperative adjuvant chemotherapy (XELOX)

-false progression was observed after receiving PD-1 mab treatment

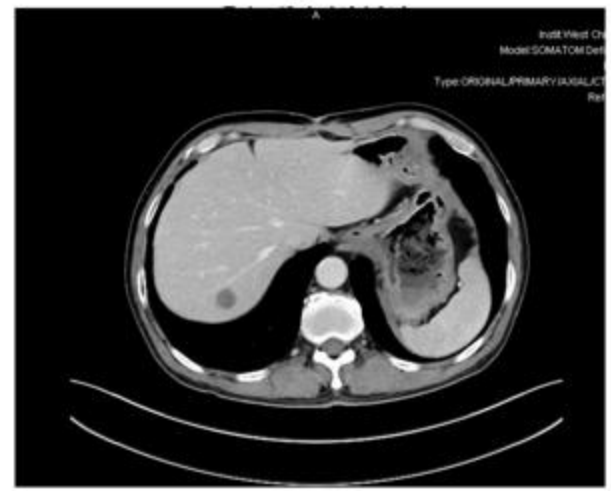
Base-line CT



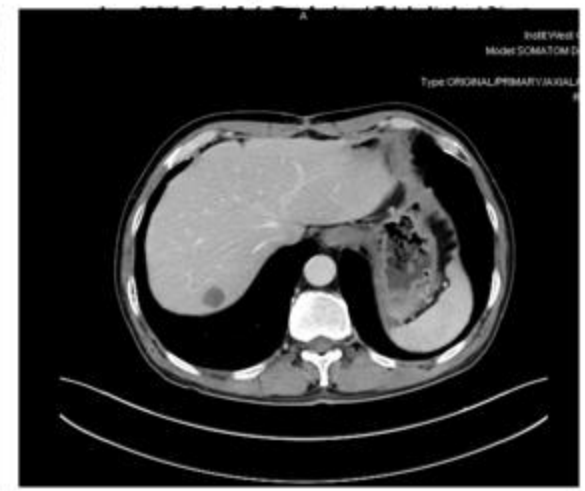
2cycles



4cycles



6cycles



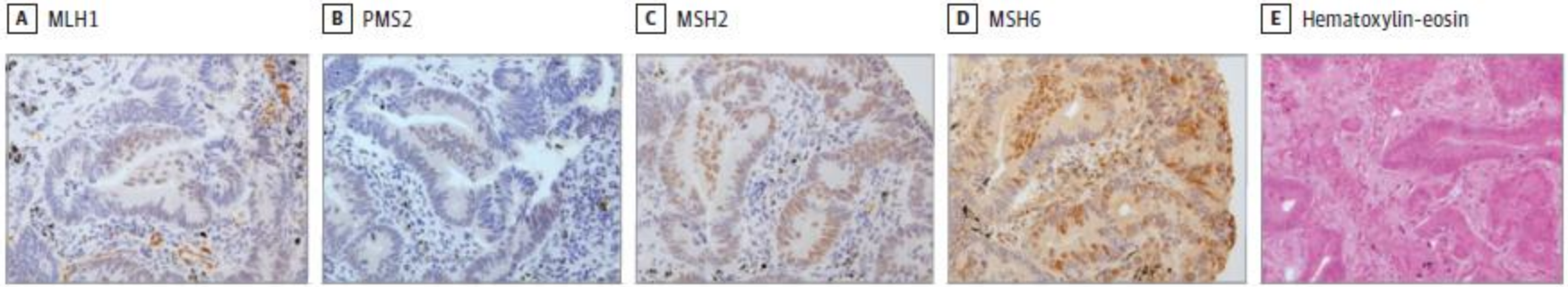
TRG 0：pCR

Misdiagnosis of MSI-H is one reason of ineffective immunotherapy

JAMA Oncol 2018

	Local Assessment		Central Review		
Sample No.[a]	IHC	PCR	IHC	PCR	Best Response Under Immunotherapy
Patients included in immunotherapy trials (n = 38)					
47	pMMR	MSI	pMMR	MSS	Disease progression
115	NE	MSI	pMMR	MSS	Disease progression
181	dMMR	NE	pMMR	MSS	Disease progression
Retrospective historical cohort (n = 93)					
29	pMMR	MSI	pMMR	MSS	NA[b]
41	NE	MSI	pMMR	MSS	NA
42	NE	MSI	pMMR	MSS	NA
43	NE	MSI	pMMR	MSS	NA
46	NE	MSI	pMMR	MSS	NA
56	NE	MSI	pMMR	MSS	NA
64	pMMR	MSI	pMMR	MSS	NA
94	pMMR	MSI	pMMR	MSS	NA
106	NE	MSI	pMMR	MSS	NA

False-Positive Tumor Due to Rare Microsatellite Polymorphisms:



MMR IHC / MSI PCR inconsistency

Series *	Number of Patients	Population	MMR IHC	Molecular MSI Testing	Discordance Rates
Lindor NM et al., 2002 [54]	1144	From multiple centers from the Cooperative Family Registry for Colon Cancer Studies: USA, Australia, and Canada	2 proteins (MLH1 and MSH2)	10 markers: *BAT25, BAT26, BAT40, BAT34C4, D5S346, D17S250, ACTC, D18S55, D10S197,* and *MYCL.* or 6 markers: *D5S346, TP53, D18S34, D18S49, D18S61, ACTC* and *BAT 26*	2.4%
Hatch et al., 2005 [55]	262	CRC with complete resection	4 proteins (MLH1, MSH2, MSH6 and PMS2)	NCI panel (*D5S346, BAT25, BAT26, D2S123,* and *D17S250*)	5.4%
Pinol et al., 2005 [56]	1222	CRC in Spain	2 proteins (MSH2 and MLH1)	*BAT26* ± *BAT-25, D5S346, D2S123,* and *D17S250*	2.8%
Watson et al., 2007 [57]	Cohort 1: 68 Cohort 2: 208	CRC patients younger than 60 years (*BRAF* mutated CRC are excluded in cohort 1)	4 proteins (MLH1, MSH2, MSH6 and PMS2)	Single microsatellite: *BAT26*	Cohort 1: 1.4% Cohort 2: 1%
Yuan L et al., 2015 [58]	296	CRC patients fulfilled revised Bethesda criteria	4 proteins (MLH1, MSH2, MSH6 and PMS2)	Bethesda panel	1%
Chen et al., 2018 [59]	569	Chinese monocentric study with only CRC	4 proteins (MLH1, MSH2, MSH6 and PMS2)	Bethesda panel	8.1%
Cohen et al., abstract ESMO 2018 [60]	92	CRC only	4 proteins (MLH1, MSH2, MSH6 and PMS2)	Pentaplex panel	9.1%
Jaffrelot M et al., abstract JFHOD 2019 [61]	2528	Patients with dMMR tumors (CRC, endometrium, non-colorectal digestive cancers and others)	4 proteins (MLH1, MSH2, MSH6 and PMS2)	Pentaplex panel	1.1%

causes：

- Few tumour cells
- Pre-test factors
- Accuracy of interpretation
- after-treatment samples
- gene polymorphism
- intratumour heterogeneity
- spatiotemporal heterogeneity

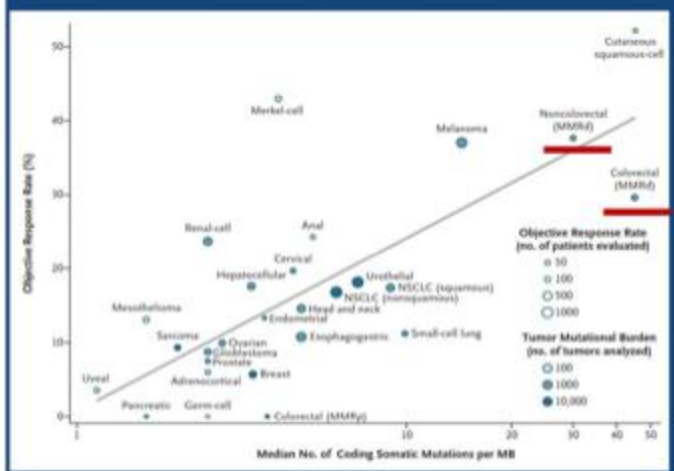
Neoadjuvant immunotherapy: monotherapy or combination?

late stage dMMR CRC:

- **immune checkpoint inhibitor (single OR combination): good and lasting effect**
  - **ORR: ~30-60%; DCR: 60%-80%; PFS rate at 12 mo: 40%~80%**
  - **KN177: pemb ORR 43.8%**
  - **Checkmate 142: Nivo+ipi ORR 69%**

Anti-PD1 Benefit Across Tumor Types

Response Rate



12 month Progression-free Survival

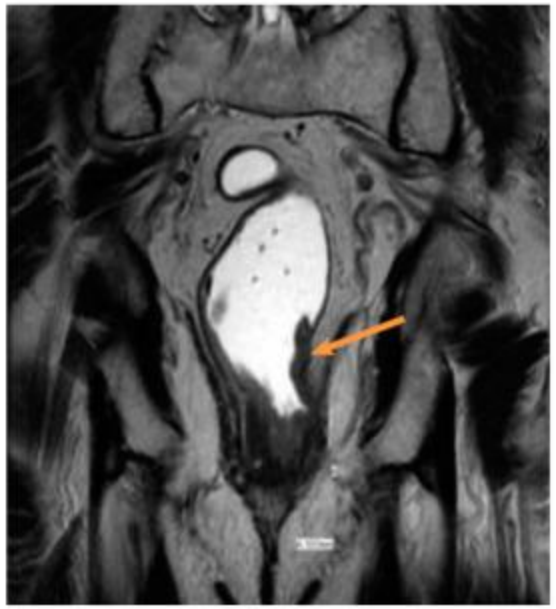
	Nivo	Pembro	Atezo	Durva
dMMR (MSI-high)	48	65		
NSCLC PDL1+	24	45		
Hodgkin's	35	45		
Merkel		45		
Melanoma	42	40		
Head and Neck PDL1+		22		
Urothelial	15	20	22	15
Renal Cell	22			
NSCLC	19		18	
Head and Neck	5			
Gastroesophageal PDL1+		5		

Registered researches： combo of immunotherapy and radiotherapy / chemoradiotherapy

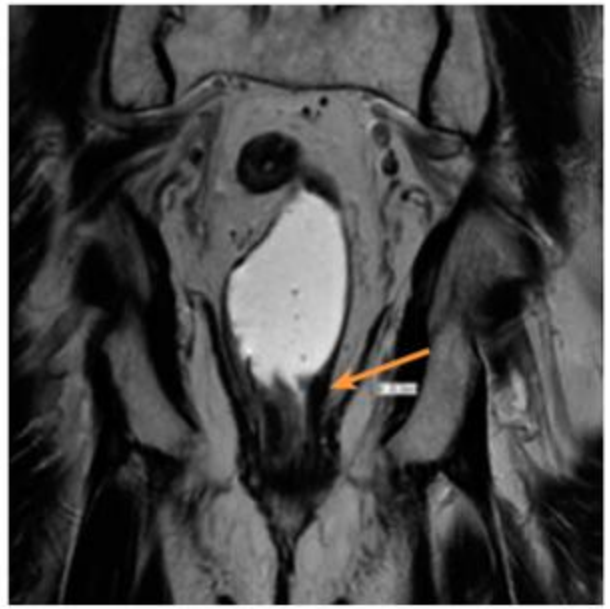
☐	Not yet recruiting	The Combination of **Immunotherapy** and Neoadjuvant Chemoradiotherapy in **MSI-H** Locally Advanced **Rectal Cancer**	• Locally Advanced **Rectal Cancer**	
☐	Not yet recruiting NEW	Watch and Wait in PD-1 Monoclonal Antibody Treated dMMR/**MSI-H** Distal **Rectal Cancer**	• **Rectal Cancer**	
☐	Recruiting	Toripalimab With or Without Celecoxib as **Neoadjuvant** Therapy in Resectable dMMR/**MSI-H Colorectal Cancer**	• **Colorectal Cancer** • Mismatch Repair-deficient (dMMR) • **Microsatellite Instability-high** (**MSI-H**) • **Neoadjuvant** Therapy	• Drug: **Neoadjuvant** therapy with PD-1 inhibitor plus COX inhibitor • Drug: **Neoadjuvant** therapy with PD-1 inhibitor
☐	Recruiting NEW	Sintilimab Plus Hypofractionated Radiotherapy for MSI-H/dMMR Rectal Cancer	• Anti-PD-1 Antibody • Radiotherapy • Rectal Cancer • (and 2 more...)	• Drug: Sintilimab • Radiation: Hypofractionated Radiotherapy

Low rectal cancer: organ preserving?

Pre-treatment

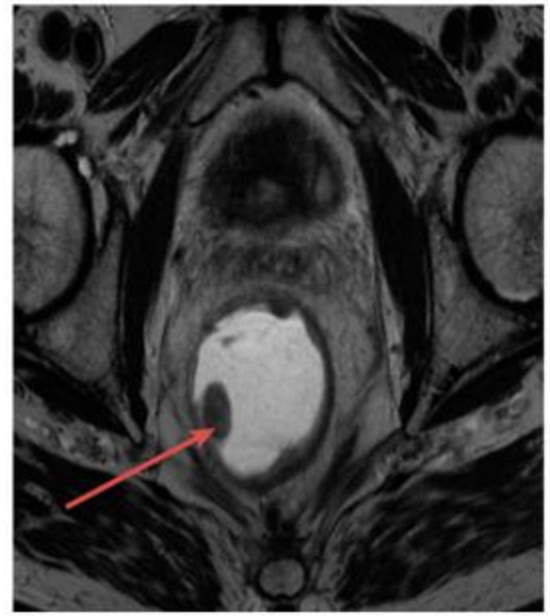


Post-treatment

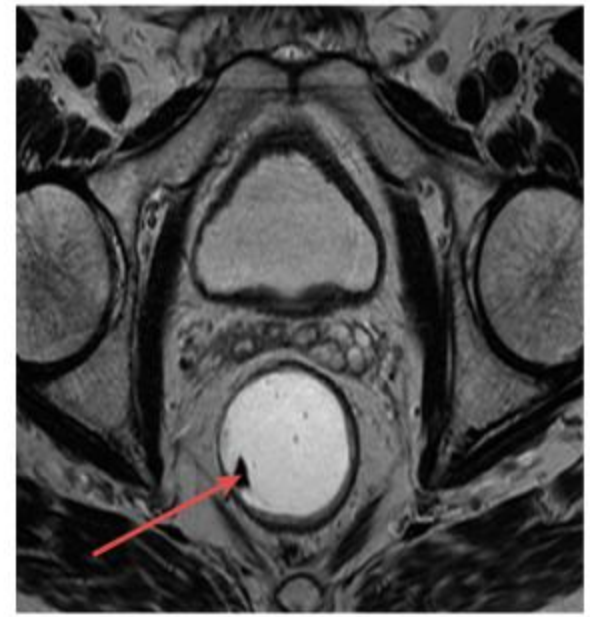


cCR > 17mo
cCR followed by
peb 6 mo

Pre-treatment



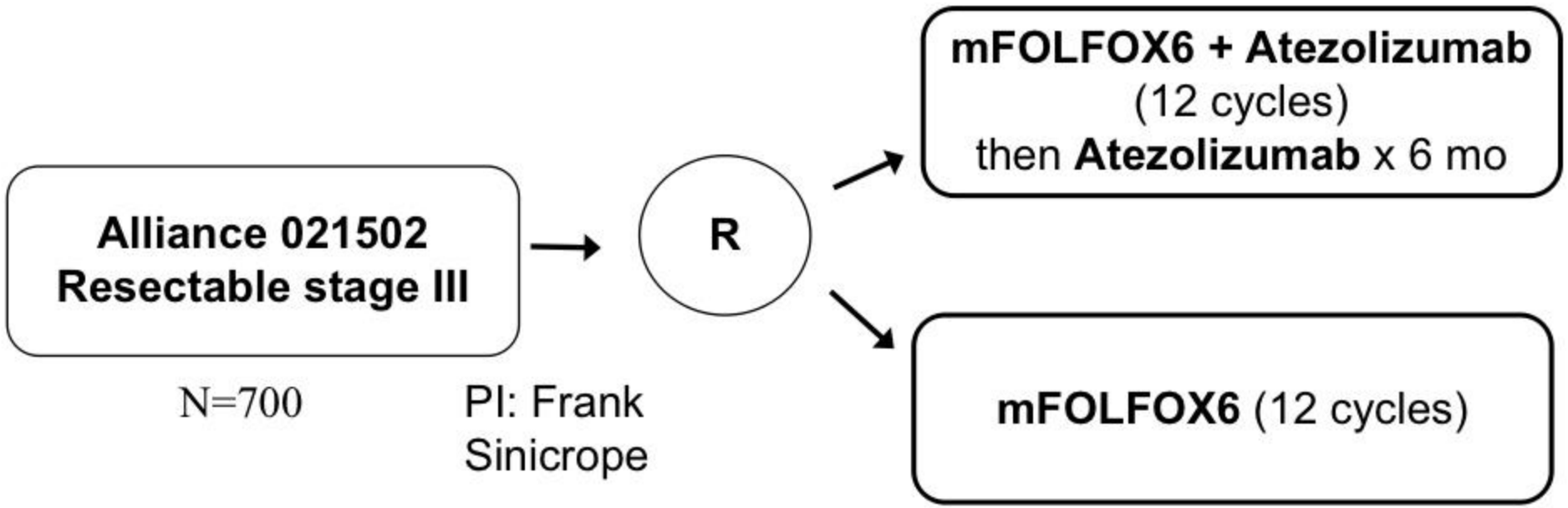
Post-treatment



cCR > 10m
cCR followed by
Niv 14 weeks

J Natl Compr Canc Netw 2020;18(7):798–804

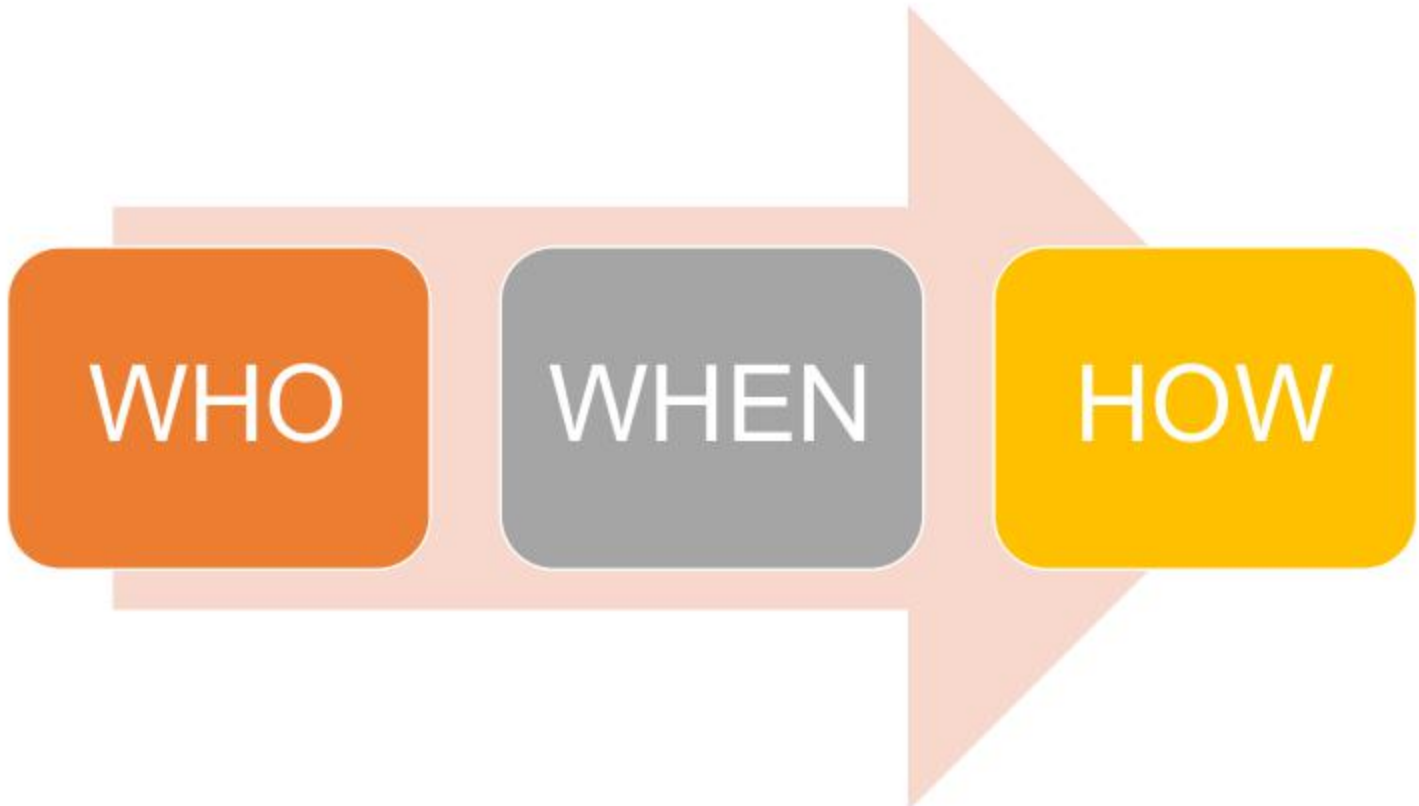
MSI-H CRC adjuvant treatment:
Combination therapy or immune-targeted monotherapy? Duration?



N=700

PI: Frank Sinicrope

Finding optimal population and treatment strategies




終
感謝觀賞
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