Colon and Rectal Cancer: Novel Therapies and Future Approaches

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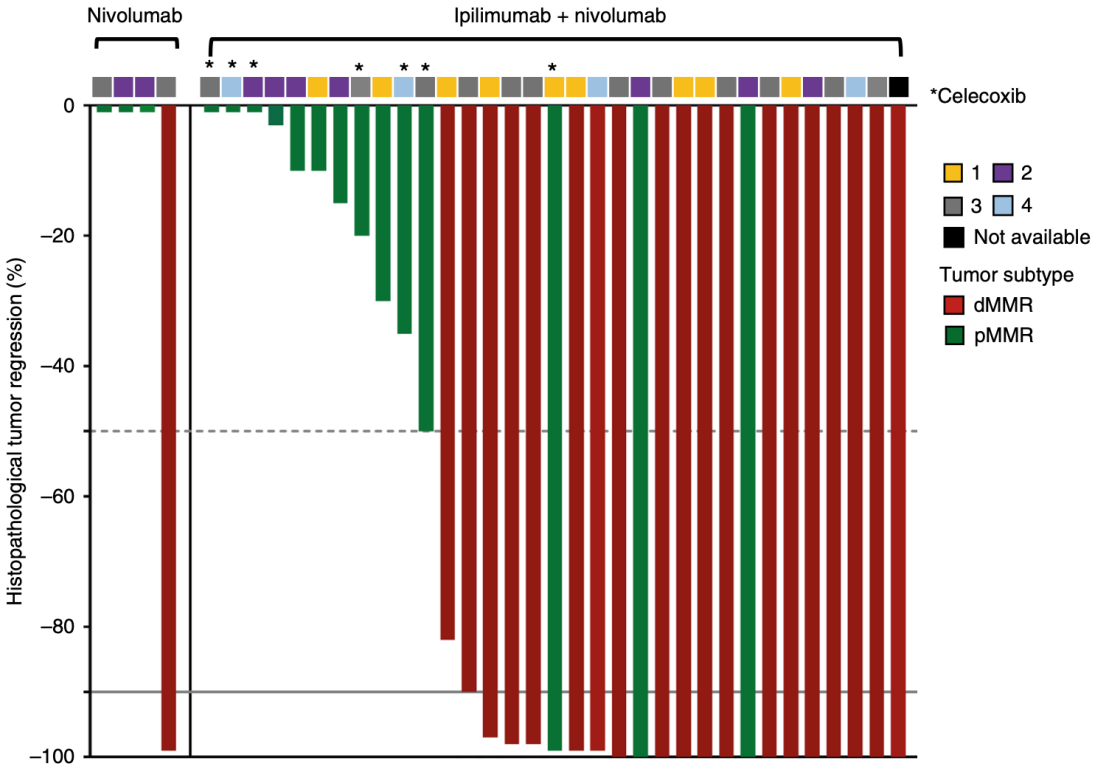
Neoadjuvant or definitive immunotherapy in rectal cancer?

Neoadjuvant therapy in rectal cancer by MMR status

Outcome	No. of patients (%)	
	dMMR	pMMR
FOLFOX as initial treatment	*n = 21*	*n = 63*
Progression of disease	6 (29)	0
Response or stable disease	15 (71)	63 (100)
Chemoradiation as initial treatment	*n = 16*	*n = 48*
Progression of disease	0	0
Complete pathologic response	2 (13)	8 (17)

Cercek et al, Clin Cancer Res 2020

Rectal Ca: Neoadjuvant IO Therapy



41 pts with rectal cancer treated with Nivo and Nivo/Ipi (35 assessable for reponse)

Path response in:

20/20 dMMR (12 pCR)

4/15 pMMR

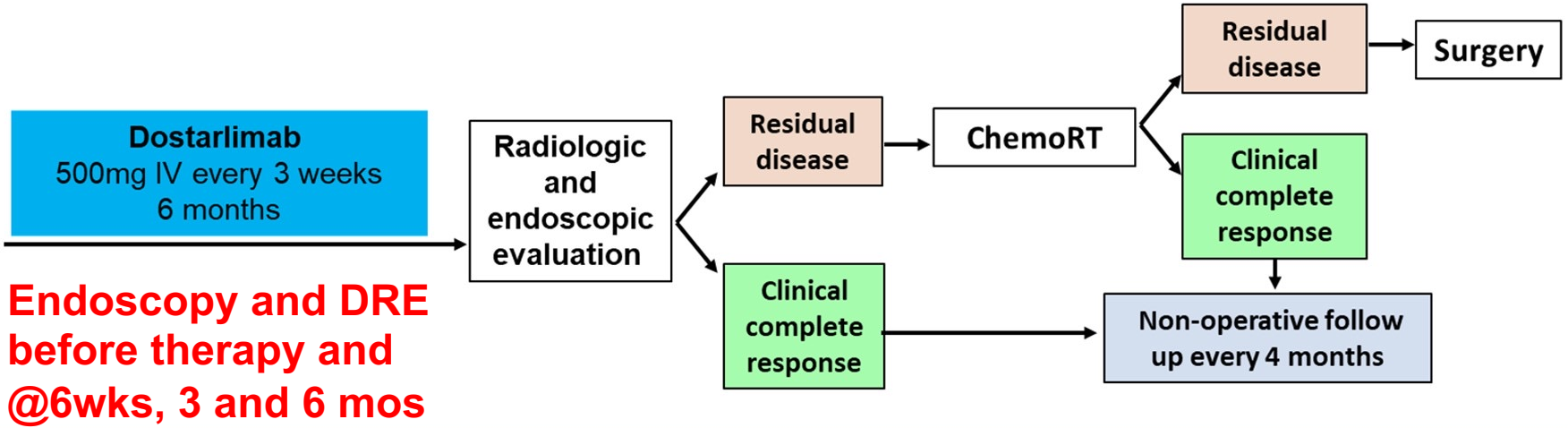
Chalabi et al., Nat Med 2020

2022 ASCO® ANNUAL MEETING

Late breaking abstract

PD-1 blockade as curative-intent therapy in mismatch repair deficient locally advanced rectal cancer

Andrea Cercek, MD
Head, Colorectal Cancer Section
Co-Director Center for Young Onset Colorectal and Gastrointestinal Cancers
Memorial Sloan Kettering Cancer Center



Patient population: Stage II and III mismatch repair deficient rectal cancer

Target Enrollment: 30 subjects

Target RR: 25%

Study Design: Simon's two stage minimax design

NCT04165772

Demographic and disease characteristics of the patients at baseline

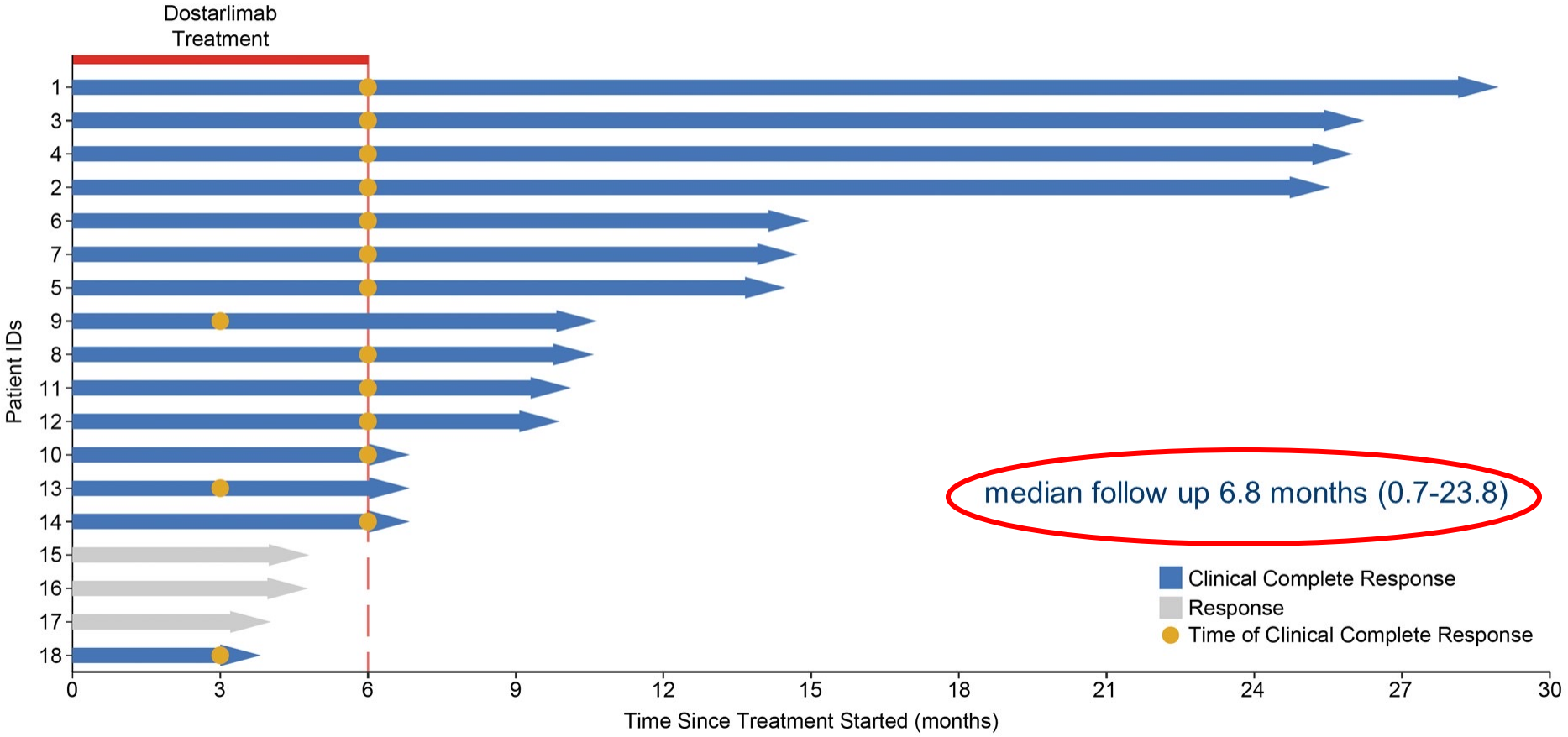
	Value (%)
Sex	
Male	6 (33)
Female	12 (67)
Age, median (range)	54 (26-78)
Race/Ethnicity	
White non-Hispanic	11 (61)
Hispanic	1 (6)
Black or African American	3 (17)
Asian-Far East/Indian Subcontinent	3 (17)
Tumor Staging	
T1/2	4 (22)
T3, T4	14 (78)
Nodal Staging	
Node-positive	17 (94)
Node-negative	1 (6)
Germline Mutation Status n=17	
MSH2, MLH1, MSH6, or PMS2	10 (59)
Negative	7 (41)
BRAF V600E wild type	18 (100)
Tumor Mutational Burden (mut/Mb), mean (range)	67 (36 -106)

Individual responses to PD-1 blockade with dostarlimab

Patients who completed 6-months of dostarlimab

ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response
1	38	T4	N+	23.8	CR	CR	CR	**cCR**
2	30	T3	N+	20.5	CR	CR	CR	**cCR**
3	61	T1/2	N+	20.6	CR	CR	CR	**cCR**
4	28	T4	N+	20.5	CR	CR	CR	**cCR**
5	53	T1/2	N+	9.1	CR	CR	CR	**cCR**
6	77	T1/2	N+	11.0	CR	CR	CR	**cCR**
7	77	T1/2	N+	8.7	CR	CR	CR	**cCR**
8	55	T3	N+	5.0	CR	CR	CR	**cCR**
9	68	T3	N+	4.9	CR	CR	CR	**cCR**
10	78	T3	N-	1.7	CR	CR	CR	**cCR**
11	55	T3	N+	4.7	CR	CR	CR	**cCR**
12	27	T3	N+	4.4	CR	CR	CR	**cCR**
13	26	T3	N+	0.8	CR	CR	CR	**cCR**
14	43	T3	N+	0.7	CR	CR	CR	**cCR**

Duration of response



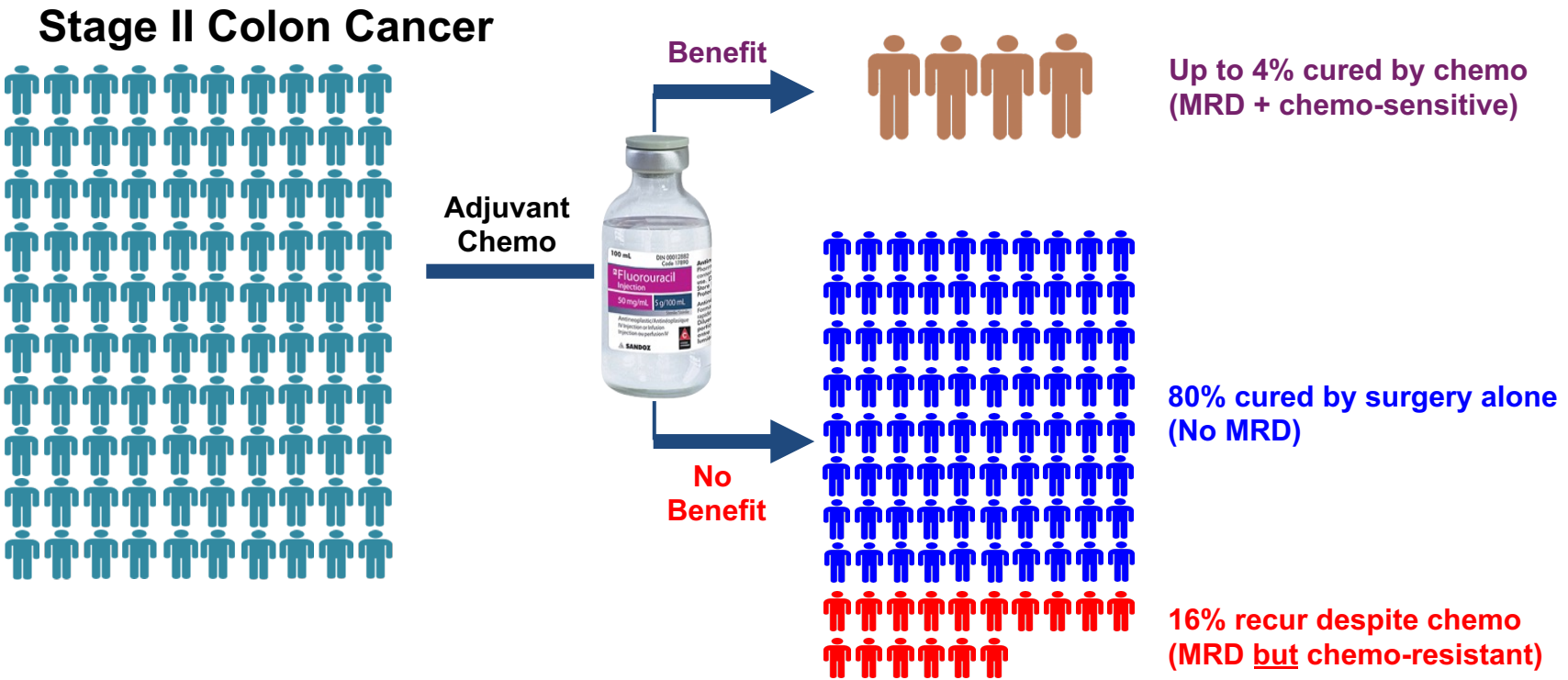
My Conclusions for Neoadjuvant IO Therapy in MSI-H/ dMMR colorectal cancer

- **Upfront, definitive IO therapy has emerged as SOC in MSI-H/ dMMR rectal cancer**
  - Hard to beat 14/14 cCR…
  - FOLFOX does not work well, if at all
  - Matches results in advanced disease and consistent with prior studies
- **But:**
  - Follow up still short (median: 6.8 mos)
  - What is the best IO therapy? PD-1 single agent? Combo?
  - Will it always lead to NOM? Role of radiation?
- **In locally advanced MSI-H/ dMMR colon cancer, I would also favor IO therapy as neoadjuvant treatment**

Role of ctDNA MRD in Management of Early Stage Colon Cancer?

Clinical Applications for ctDNA

The Crux of Adjuvant Therapy: Treat Many to Save a Few



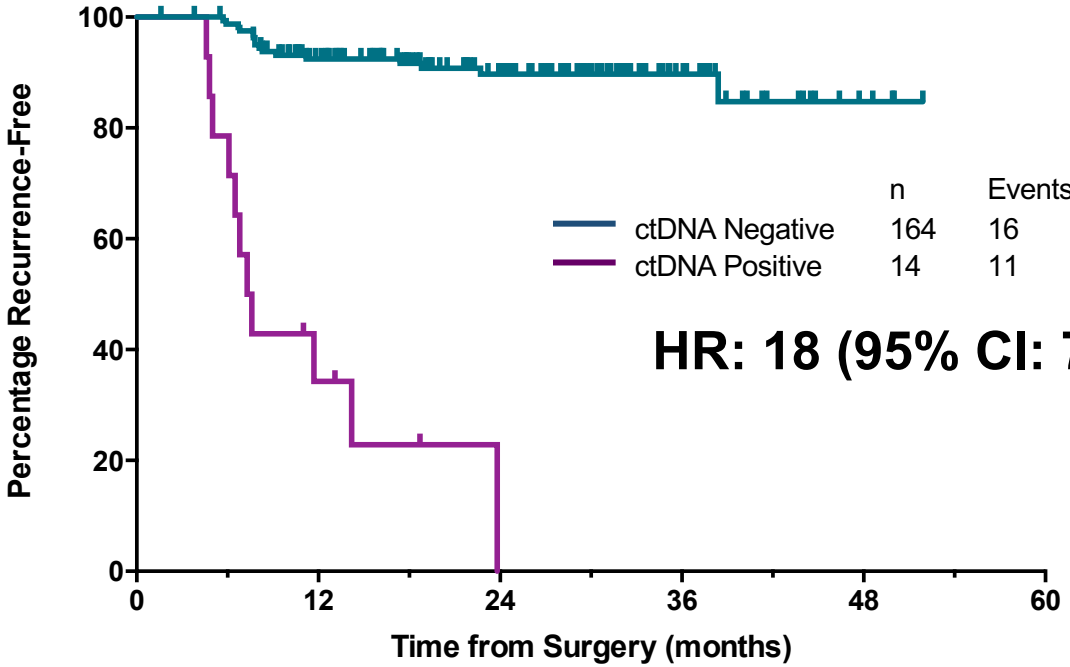
ctDNA as Marker for MRD (molecular residual disease)

- **Two main types of tests:**
  - **Tumor-agnostic, Disease-specific**
    - NGS or PCR panel of common mutations in CRC
    - Methylation markers

    Pro: easy logistics; Con: lower sensitivity
  - **Tumor-informed, Disease-agnostic**
    - NGS or PCR panel of mutations detected in patient's primary tumor

    Pro: high sensitivity; Con: logistics more complicated

Stage II Recurrence-Free Survival
(Patients *not* treated with chemotherapy)



HR: 18 (95% CI: 7.9–40), $p < 0.001$

Tie et al. Sci Transl Med 2016

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Adjuvant Chemotherapy Guided by Circulating Tumor DNA Analysis in Stage II Colon Cancer

The Randomized DYNAMIC Trial

Jeanne Tie

Peter MacCallum Cancer Centre and Walter & Eliza Hall Institute of Medical Research, Melbourne, Australia

On behalf of the DYNAMIC Investigators

Joshua Cohen, Kamel Lahouel, Serigne Lo, Yuxuan Wang, Rachel Wong, Jeremy Shapiro, Samuel Harris, Adnan Khattak, Matthew Burge, Marion Harris, James Lynam, Louise Nott, Fiona Day, Theresa Hayes, Nickolas Papadopoulos, Cristian Tomasetti, Kenneth Kinzler, Bert Vogelstein, Peter Gibbs

DYNAMIC Study Design

ACTRN12615000381583

Non-inferiority trial!

Stage II Colon Cancer

- R0 resection
- ECOG 0 – 2
- Staging CT within 8 weeks
- Provision of adequate tumor tissue within 4 weeks post-op
- No synchronous colorectal cancer

Plasma Collections

Week 4 + 7 post-op

R 2:1

ctDNA-Guided Management

- **ctDNA-Positive → Adjuvant Chemo** (oxaliplatin-based or single agent FP)
- **ctDNA-Negative → Observation**

ctDNA-Positive = Positive result at week 4 and/or 7

Standard Management

Adjuvant treatment decisions based on conventional clinico-pathologic criteria

Endpoints

Primary
- RFS rate at 2 years

Key Secondary
- Proportion receiving adjuvant chemo

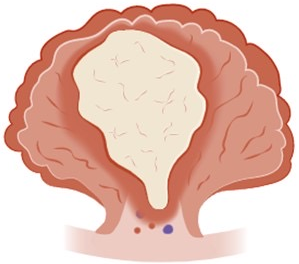
Secondary
- RFS by ctDNA status for ctDNA-guided arm
- TTR
- OS

Stratification Factors
- T stage (T3 vs T4)
- Type of participating center (metropolitan vs regional)

Surveillance:
- CEA → 3-monthly for 24M, then 6-monthly for 36M
- CT C/A/P → 6-monthly for 24M, then at 36M

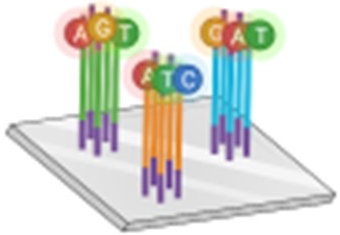
ctDNA Analysis: Tumor-Informed Personalized Approach

Resected tumor tissue



FFPE tissue from primary tumor

Targeted sequencing identifies mutation(s) unique to that cancer

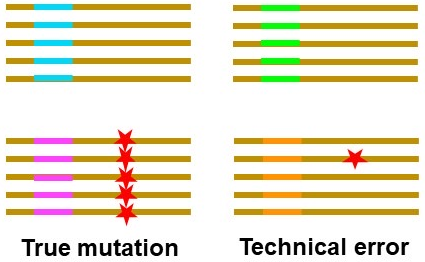


15 recurrently mutated genes in colorectal cancer

(APC, TP53, KRAS, PIK3CA, FBXW7, BRAF, SMAD4, RNF43, POLE, CTNNB1, ERBB3, NRAS, PPP2R1A, AKT1, HRAS)

Week 4 + 7 plasma

At least one patient-specific mutation assessed in plasma



ctDNA detection by Safe-Sequencing System*

(error reduction technology designed to detect low frequency mutations using unique molecular identifier)

*Kinde *et al*. Proc Natl Acad Sci U S A. 2011;108(23):9530-5

Baseline Characteristics

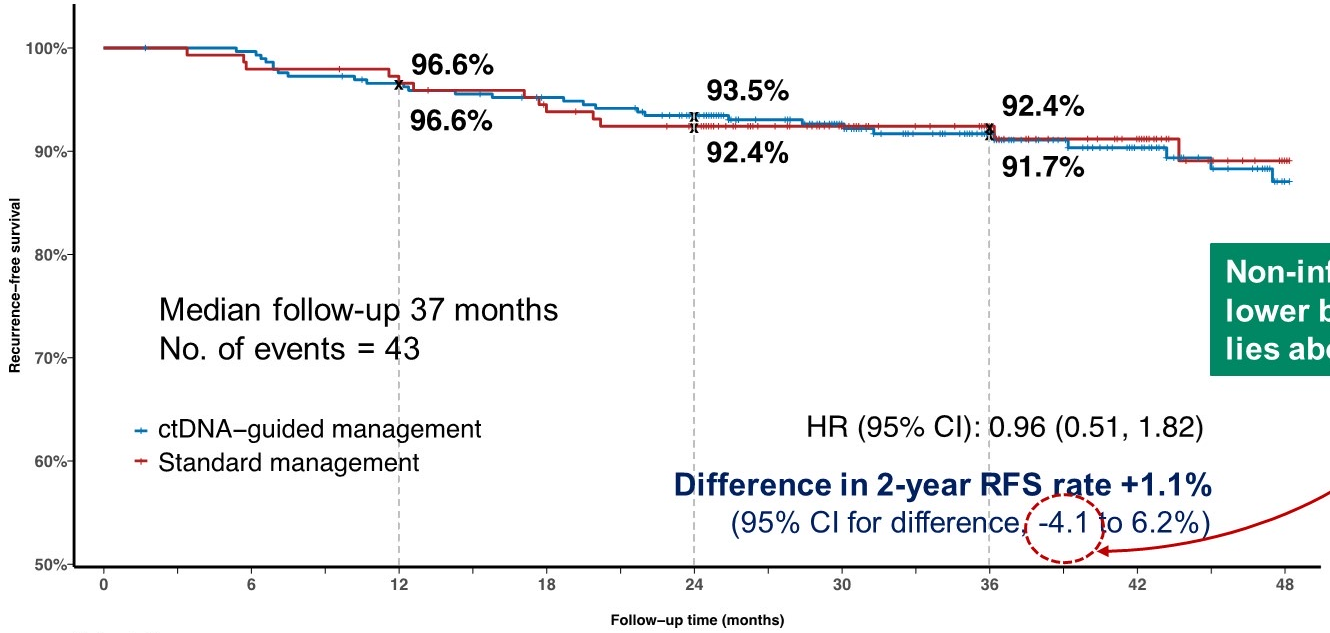
Characteristics	ctDNA-Guided Management N = 294, N (%)	Standard Management N = 147, N (%)
Age, median (range), years	65 (30 , 94)	62 (28 , 84)
Sex, Male	154 (52)	81 (55)
ECOG, 0	226 (77)	124 (84)
Center type, metropolitan	240 (82)	121 (82)
Primary tumor site, left-sided	126 (43)	78 (53)
Tumor stage, T3	250 (85)	127 (86)
Tumor differentiation, poor	43 (15)	17 (12)
Lymph node yield, < 12	13 (4)	7 (5)
Lymphovascular invasion, present	82 (28)	38 (26)
MMR, deficient	59 (20)	27 (18)
Clinical risk group, high*	116 (40)	60 (41)

*High clinical risk = proficient MMR + ≥1 high-risk feature (T4, poor tumor differentiation, <12 lymph node yield, LVI, tumor perforation and/or bowel obstruction)

Adjuvant Treatment Delivery

Treatment Information	ctDNA-Guided N = 294	Standard Management N = 147	P-value
Adjuvant Chemotherapy received, n	45 **(15%)**	41 **(28%)**	0.0017
Chemotherapy regimen received, n			
Oxaliplatin-based doublet	28/45 **(62%)**	4/41 **(10%)**	
Single agent fluoropyrimidine	17/45 **(38%)**	37/41 **(90%)**	<.0001
Time from surgery to commencing chemotherapy, median (IQR), days	83 (76, 89)	53 (49, 61)	<.0001
Treatment duration, median (IQR), weeks	24 (19, 24)	24 (21, 24)	0.9318
Completed planned treatment, n	38 (85%)	32 (78%)	0.7036
Percentage of full dose delivered, median (IQR)	78 (56, 100)	84 (64, 100)	0.6194

Recurrence-Free Survival

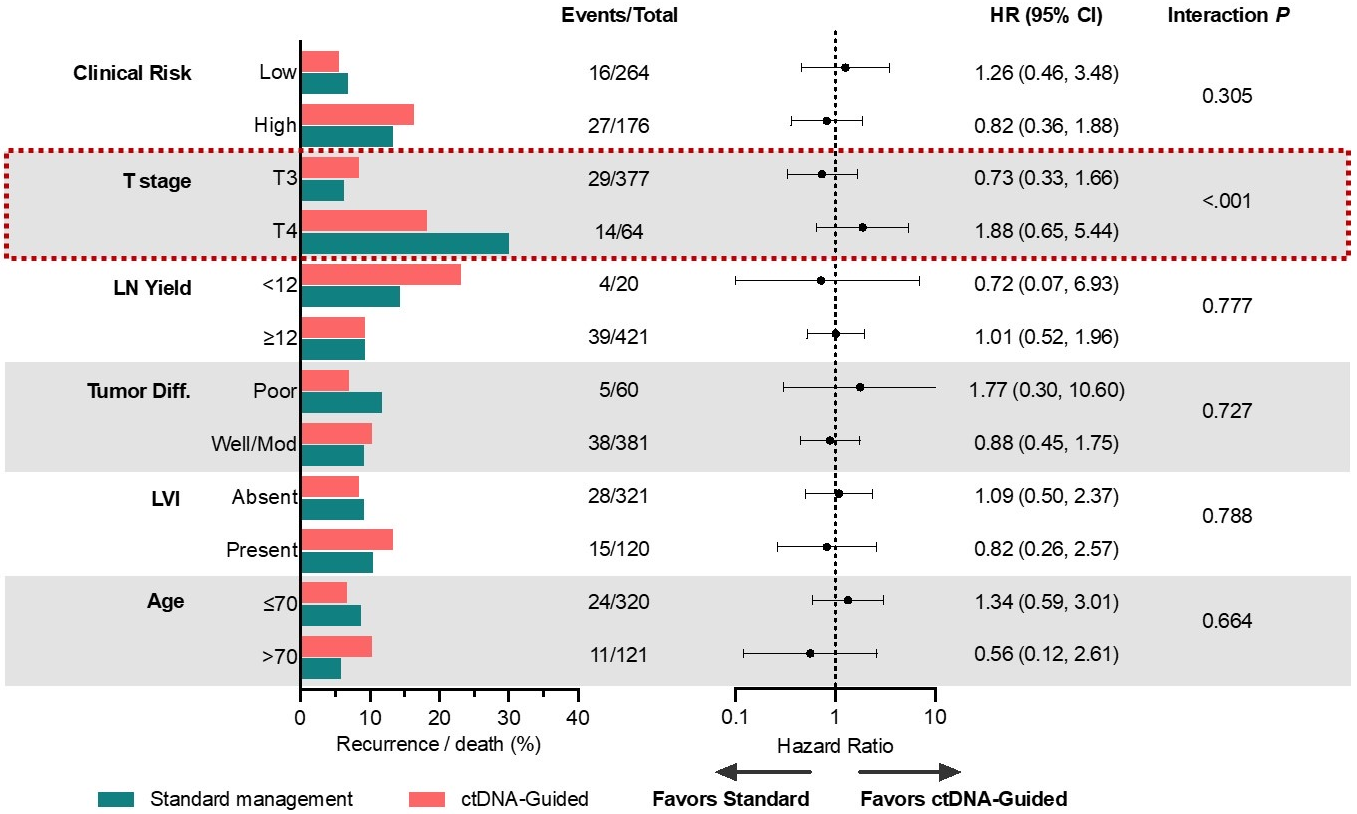


Non-inferiority confirmed: lower bound of 95% CI lies above -8.5%

Numbers at risk

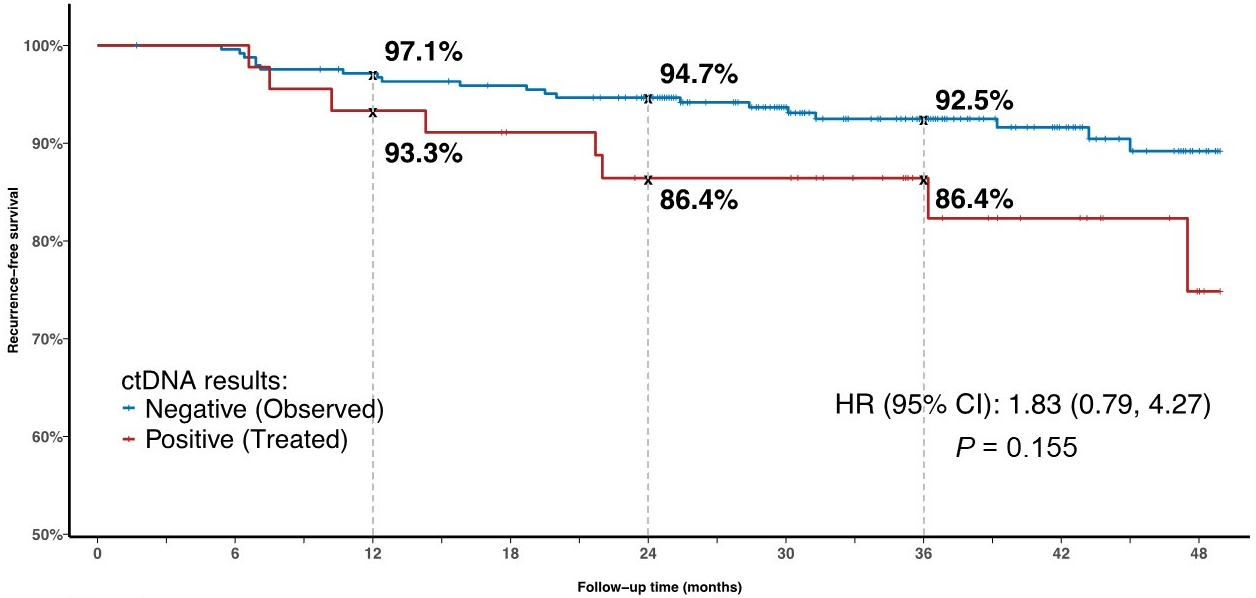
ctDNA-guided	294	292	281	273	259	207	155	109	64
Standard	147	144	142	136	128	97	78	57	33

Recurrence-Free Survival in Key Subgroups



Recurrence-Free Survival: ctDNA-Guided Management

ctDNA Negative vs Positive



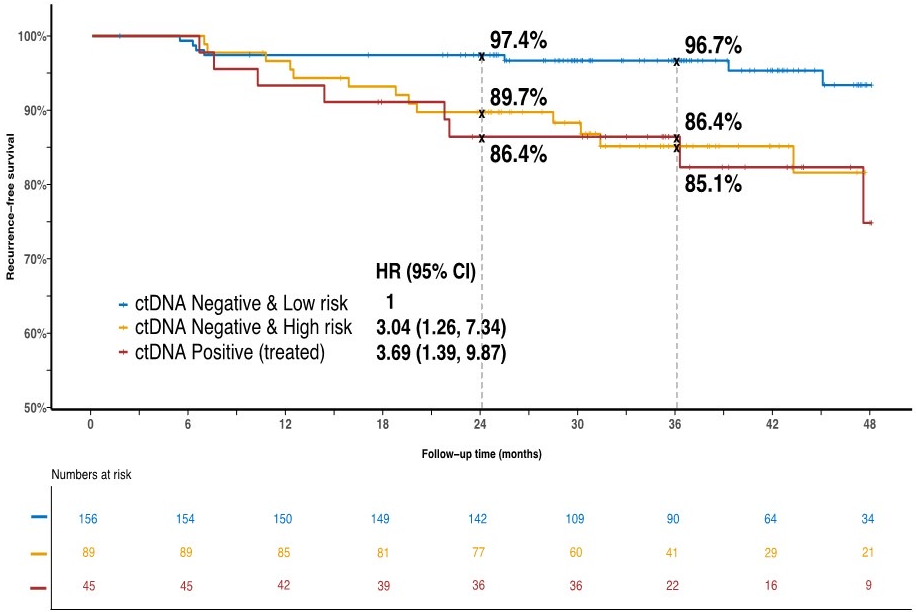
Numbers at risk

ctDNA-Negative	246	244	236	231	220	169	131	93	55
ctDNA-Positive	45	45	42	39	36	36	22	16	9

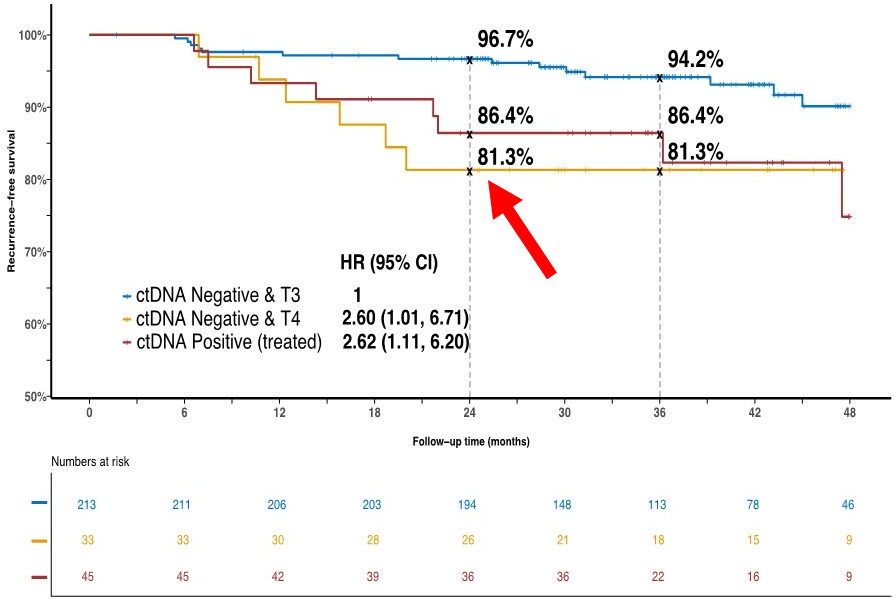
Recurrence-Free Survival: ctDNA-Guided Management

ctDNA, Clinical Risk and T Stage

ctDNA and Clinical Risk



ctDNA and T Stage



ASCO Gastrointestinal Cancers Symposium

CIRCULATE Japan

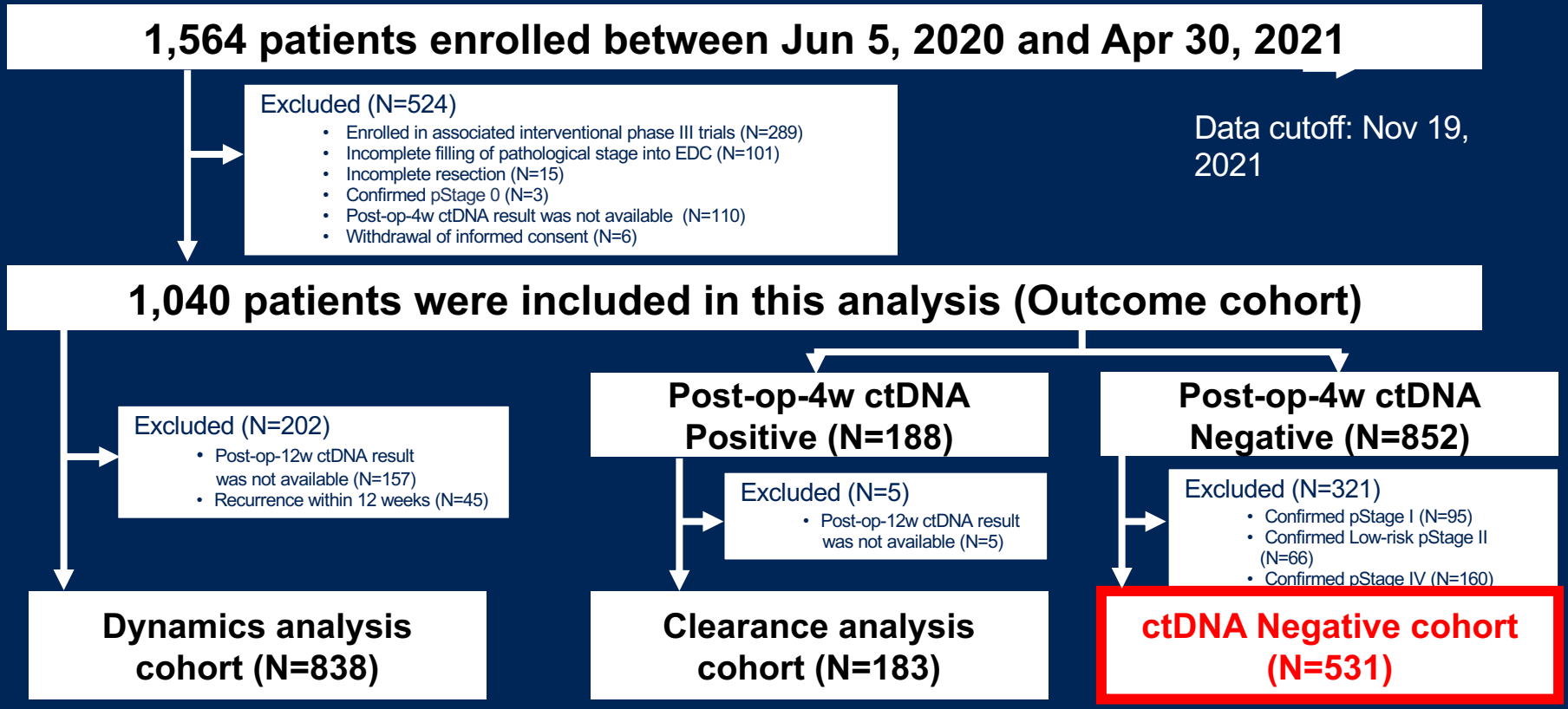
Association of circulating tumor DNA dynamics with clinical outcomes in the adjuvant setting for patients with colorectal cancer from an observational GALAXY study in CIRCULATE-Japan

Masahito Kotaka Gastrointestinal Cancer Center, Sano Hospital, Kobe, Japan

Co-authors; Hiromichi Shirasu, Jun Watanabe, Kentaro Yamazaki, Keiji Hirata, Naoya Akazawa, Nobuhisa Matsuhashi, Mitsuru Yokota, Masataka Ikeda, Kentaro Kato, Alexey Aleshin, Shruti Sharma, Daisuke Kotani, Eiji Oki, Ichiro Takemasa, Takeshi Kato, Yoshiaki Nakamura, Hiroya Taniguchi, Masaki Mori, Takayuki Yoshino

On behalf of the CIRCULATE-Japan Investigators

CONSORT diagram



op, operation; EDC, Electronic data

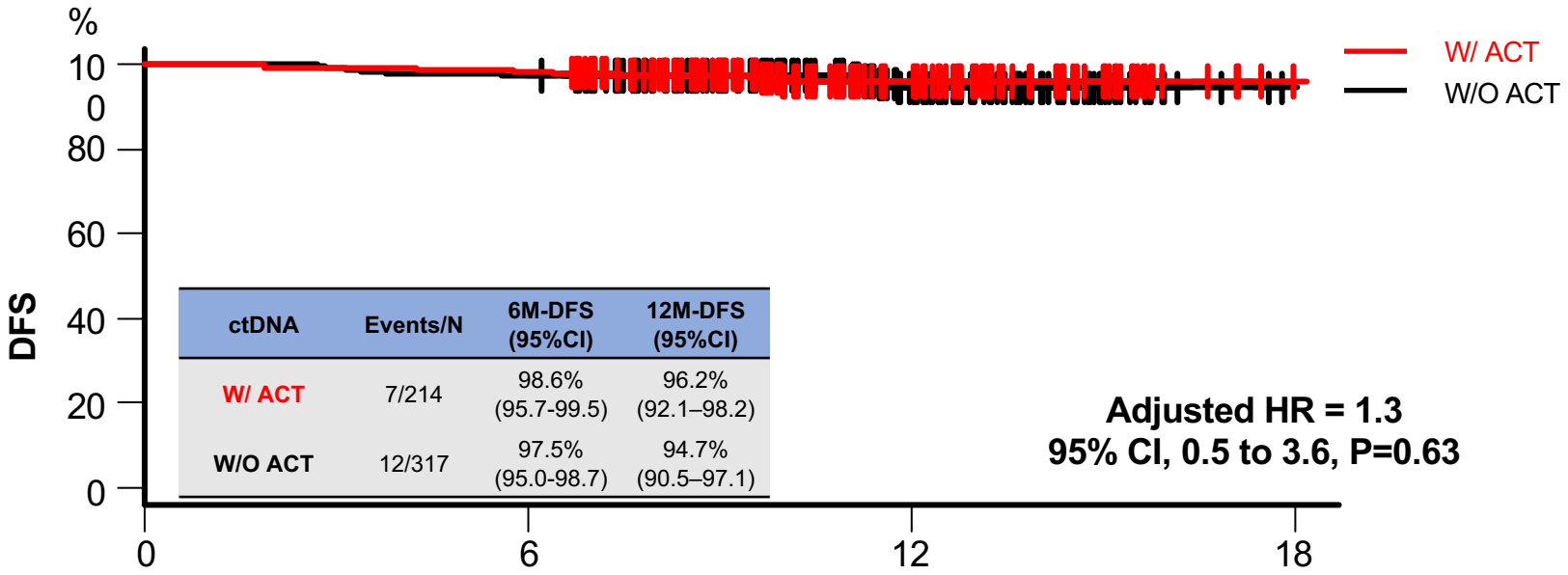
Patient characteristics in ctDNA negative cohort

	Patients W/ ACT (N=214)		Patients W/O ACT (N=317)		P
Sex					
Male/Female	106/108	50%/50%	159/158	50%/50%	0.93
Performance status					
0/1	196/18	92%/8%	258/59	81%/19%	**0.001**
pStage[1]					
pStage II (high-risk)	37	17%	188	59%	**<0.001**
pStage III	177	83%	129	41%	
ACT regimen: FP+Oxa / FP					
FP+Oxa / FP (High-risk pStage II)	24/13	65%/35%	-	-	-
FP+Oxa / FP (pStage III)	152/25	86%/14%	-	-	-

FP, fluoropyrimidine; Oxa, oxaliplatin; ACT, adjuvant chemotherapy; Comparisons between categorical variables were performed by Fisher's exact test.
High-risk Stage II is defined as having at least one of the following risk factors: (a) T4 (SE/SI/AI), (b) intestinal tract obstruction (clinical), (c) intestinal tract perforation/penetration (clinical), (d) less than 12 dissected lymph nodes, (e) poorly differentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous carcinoma, (f) positive for lymphatic invasion, venous invasion, or neuroinvasion.

1. Sobin LH,et al. International Union Against Cancer (UICC): TNM Classification of Malignant Tumours. 8th ed. Oxford: Wiley-Blackwell (2017)

DFS by ACT in post-op-4w ctDNA negative population (High-risk pStage II-III)



ctDNA	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
W/ ACT	7/214	98.6% (95.7-99.5)	96.2% (92.1–98.2)
W/O ACT	12/317	97.5% (95.0-98.7)	94.7% (90.5–97.1)

Number at risk

W/ ACT	214	211	79	0
W/O ACT	317	309	117	0

Median follow-up time: 11.4 months
Data cutoff: Nov 19, 2021

HR was adjusted by age, performance status, pStage, and MSI status that are imbalanced between two groups.
ACT, adjuvant chemotherapy; DFS, disease-free survival; HR, hazard ratio; CI, confidential interval.
DFS curve was estimated by the Kaplan-Meier method. HR and 95%CI were calculated by the Cox proportional hazard model.

What do we know about ctDNA in 2022?

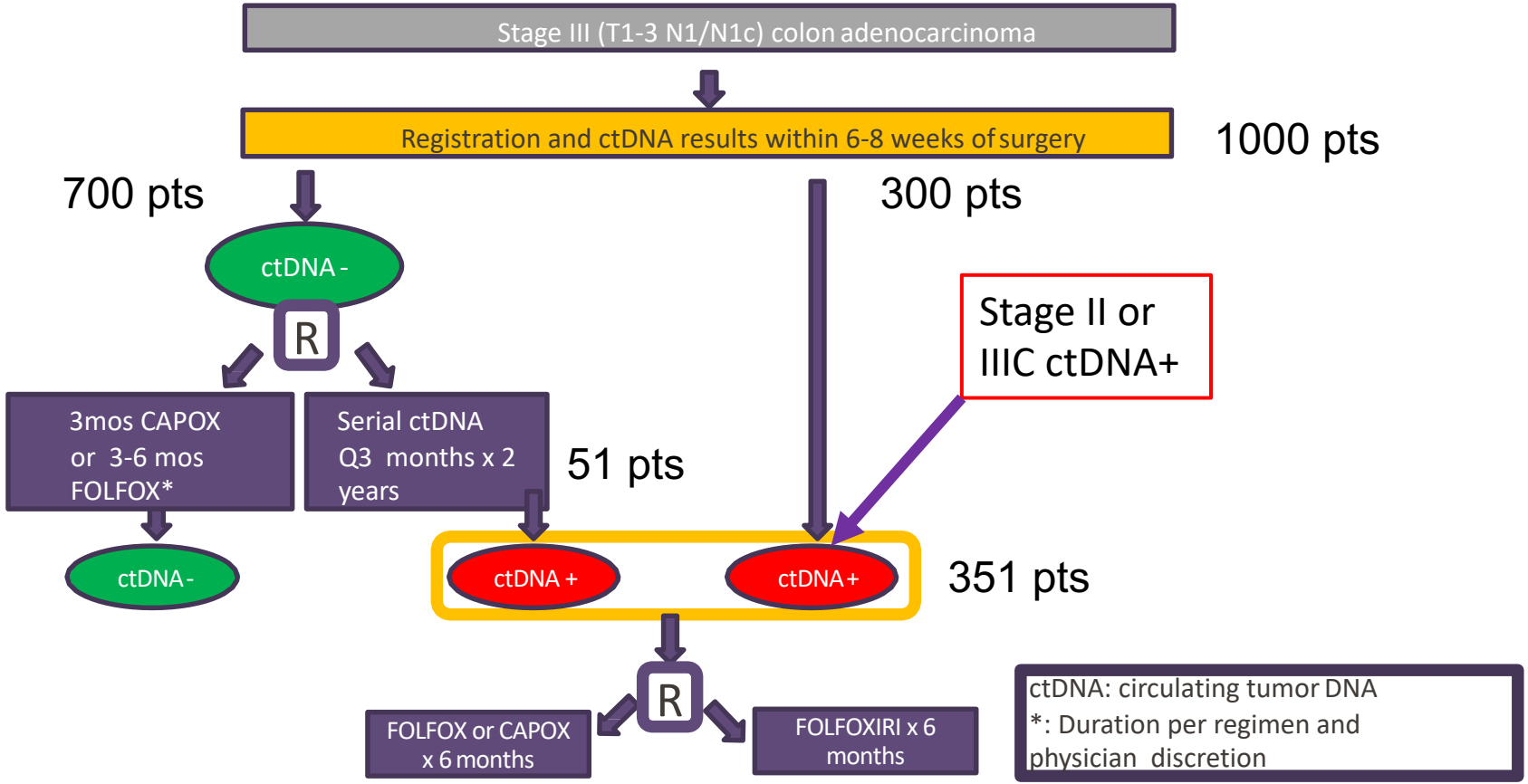
1. **The persistent presence of ctDNA after surgical resection is the strongest poor prognostic factor we have ever identified**
   - It is more important than T and/ or N stage
2. **Adjuvant therapy can decrease the likelihood for cancer recurrence in ctDNA positive cases**
   - ctDNA positivity is not a “point of no return”
3. **ctDNA kinetic is early marker of treatment response**
   - Validated for immunotherapy

What don't we know about ctDNA in 2022?

1. Can we use sequential ctDNA monitoring and only use "adjuvant therapy" when the ctDNA test turns positive? Would this compromise outcome?
2. Can we de-escalate the intensity or duration of adjuvant therapy in ctDNA negative cases? – are DYNAMIC II and CIRCULATE-Japan definitive for e.g. T4 N0 cancers?
3. Will ctDNA positive cases benefit from an escalation of the intensity or duration of adjuvant therapy? Can molecular targeted approaches be helpful in these cases?
4. Can we forgo routine surveillance scans *in lieu* of serial ctDNA monitoring?
5. Can ctDNA conversion be used as an endpoint for adjuvant trials?
6. Can ctDNA help predict or define the benefit or lack of benefit of local therapies?
7. Can ctDNA help us define the duration of immunotherapy when patients have reached a state of NED?

Various prospective clinical studies are addressing these issues
-> results of randomized trials expected in next 5-10 years – might be too late!

NRG GI-008 (CIRCULATE-US) Trial – Activated 03/2022



Co-PIs: C Lieu, T George

Optimized first-line therapy of mCRC in 2022

Overview of Precision Medicine Approaches in GI Cancers

GI Cancer	Negative predictive markers	Positive predictive markers	Cancer-agnostic markers
Gastroesophageal		HER-2 PD-L1 FGFR2 Claudin	**MSI-H/ dMMR** **NTRK fusions** **POLe/d** **TMB?** **RET fusions?** **NRG-1 fusions?**
CRC	**RAS mutations** **BRAF V600E** **Sidedness** **HER2**	**HER-2** **BRAF V600E** **KRAS G12C**	
Biliary cancers (IHCC!)		IDH-1 FGFR fusions HER-2 BRAF V600E mut	
Pancreas cancer		BRCA (-like) NRG-1 fusions	
HCC		(AFP high)	

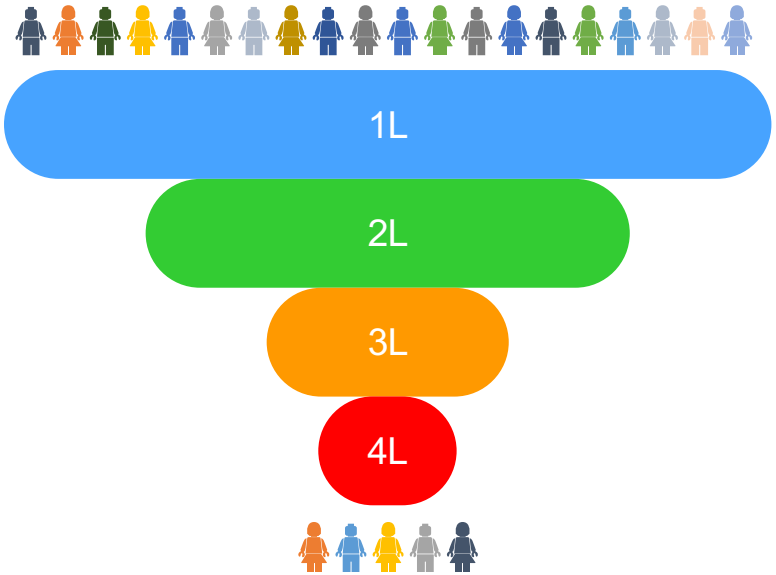
What influences treatment choices in mCRC?

Patient characteristics

- Comorbidities
- Prior adjuvant treatment
- Age
- Performance status

Tumor characteristics

- Tumor burden
- Resectability
- Tumor location



Molecular characteristics

- RAS
- BRAF
- MSI-high
- HER2

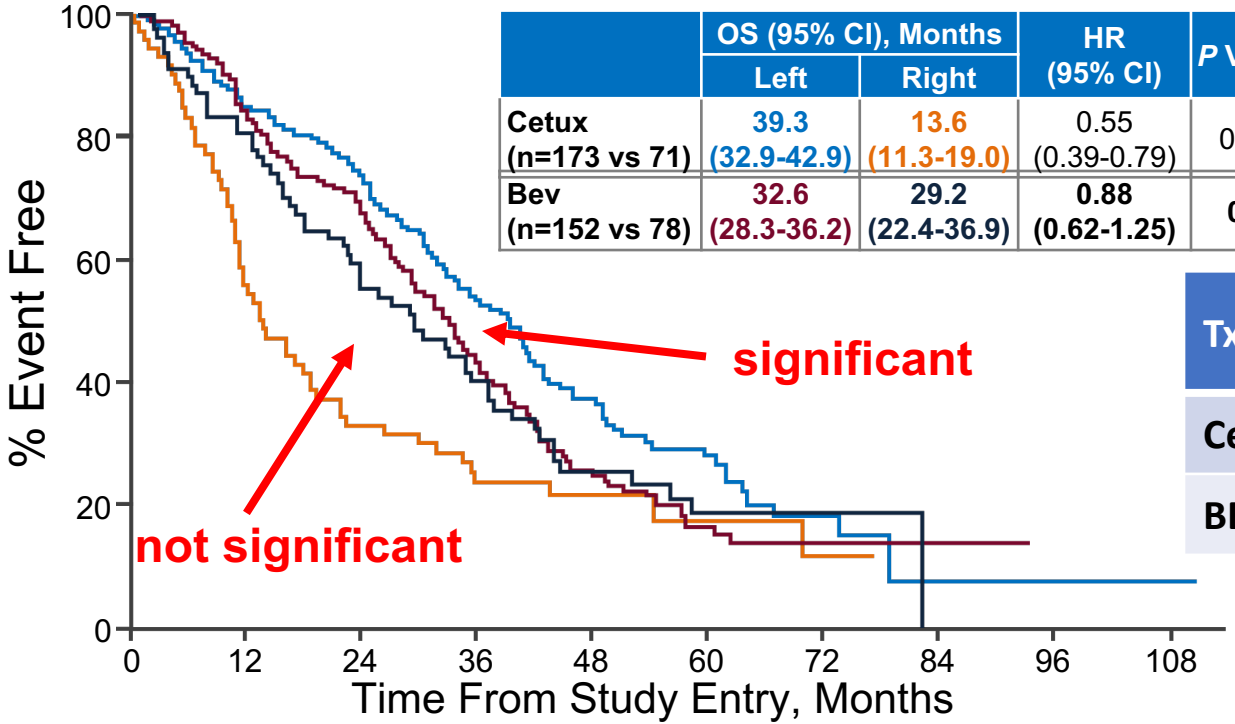
Patient preference

- Quality of life
- Toxicity profile

Goals of care

Therapy tailored according to individual patient needs

CALGB/SWOG 80405: OS by Tumor Location (*RAS* WT)



	OS (95% CI), Months		HR (95% CI)	*P* Value*
	Left	Right		
Cetux (n=173 vs 71)	39.3 (32.9-42.9)	13.6 (11.3-19.0)	0.55 (0.39-0.79)	0.001
Bev (n=152 vs 78)	32.6 (28.3-36.2)	29.2 (22.4-36.9)	0.88 (0.62-1.25)	0.50

Tx	ΔR vs L (mos)
Cetux	25.7
BEV	3.4

*Adjusted for biologic, protocol CT, prior adjuvant therapy, prior RT, age, sex, synchronous disease, in place primary, liver metastases.

Venook A, et al. Presented at: ESMO. 2016.

2022 ASCO® ANNUAL MEETING

Panitumumab plus mFOLFOX6 versus Bevacizumab plus mFOLFOX6 as first-line treatment in patients with *RAS* wild-type metastatic colorectal cancer: results from the phase 3 PARADIGM trial

Takayuki Yoshino[1], Jun Watanabe[2], Kohei Shitara[1], Kentaro Yamazaki[3], Hisatsugu Ohori[4], Manabu Shiozawa[5], Hirofumi Yasui[4], Eiji Oki[6], Takeo Sato[7], Takeshi Naitoh[8], Yoshito Komatsu[9], Takeshi Kato[10], Masamitsu Hihara[11], Junpei Soeda[11], Kouji Yamamoto[12], Kiwamu Akagi[13], Atsushi Ochiai[14], Hiroyuki Uetake[15], Katsuya Tsuchihara[16], Kei Muro[17]

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PARADIGM Trial Design

Phase 3, randomized, open-label, multicenter study (NCT02394795)

Patients with *RAS* WT mCRC

- Unresectable disease
- No previous chemotherapy[a]
- Age: 20–79 years
- ECOG performance status 0–1
- At least 1 evaluable lesion
- Adequate organ function
- Life expectancy ≥ 3 months

N=823

R
1:1

Panitumumab +mFOLFOX6[b]

Bevacizumab +mFOLFOX6[b]

Primary endpoint
- **OS: left-sided[c] population**; if significant, analyzed in overall population

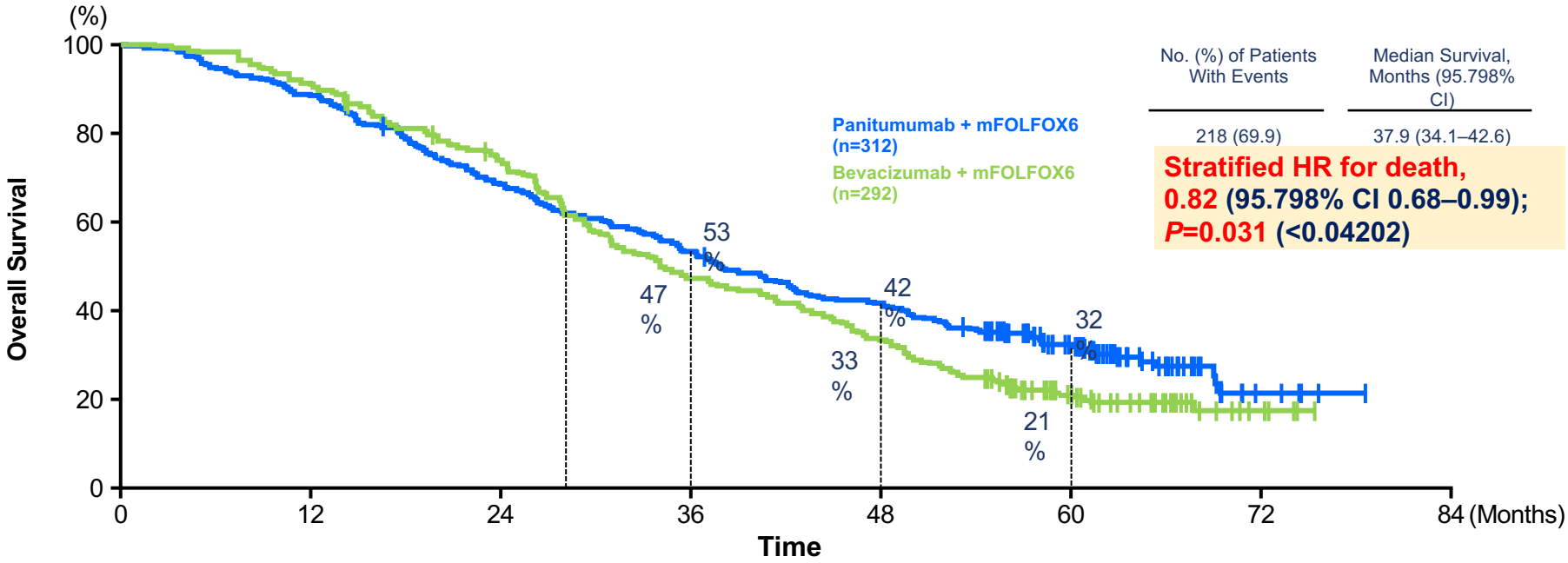
Secondary endpoints
- PFS, RR, DOR, R0 resection: left-sided[c] and overall populations
- Safety: all treated patients

Exploratory endpoints
- ETS, depth of response, DCR: left-sided[c] and overall populations

Stratification factors
- Institution
- Age: 20–64 vs 65–79 years
- Liver metastases: present vs absent

DCR, disease control rate; DOR; duration of response; ECOG, Eastern Cooperative Oncology Group; ETS, early tumor shrinkage; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression free survival; RR, response rate; R0, curative resection; WT, wild type.
[a]Adjuvant fluoropyrimidine monotherapy allowed if completed > 6 months before enrollment. [b]Until disease progression, unacceptable toxicity, withdrawal of consent or investigator's judgement or curative intent resection.
[c]Primary tumor in descending colon, sigmoid colon, rectosigmoid, and rectum.

Primary Endpoint-1; Overall Survival in Left-sided Population



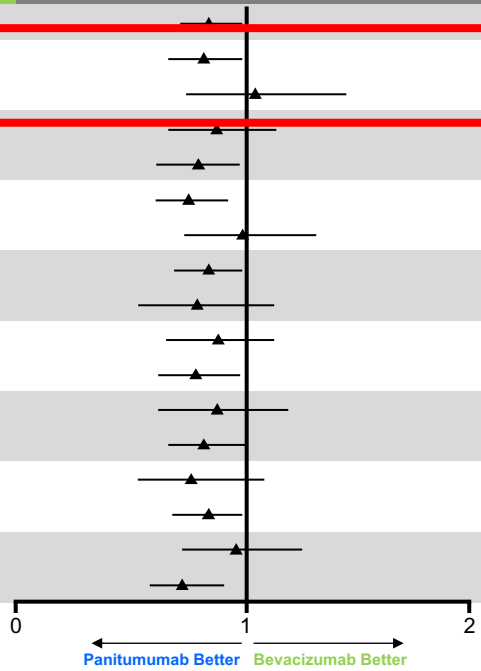
	No. (%) of Patients With Events	Median Survival, Months (95.798% CI)
Panitumumab + mFOLFOX6 (n=312)	218 (69.9)	37.9 (34.1–42.6)

Stratified HR for death, 0.82 (95.798% CI 0.68–0.99); *P*=0.031 (<0.04202)

No. at risk								
Panitumumab	312	276	213	166	129	68	5	0
Bevacizumab	292	266	212	136	96	40	5	0

Subgroup Analyses of Overall Survival in Overall Population

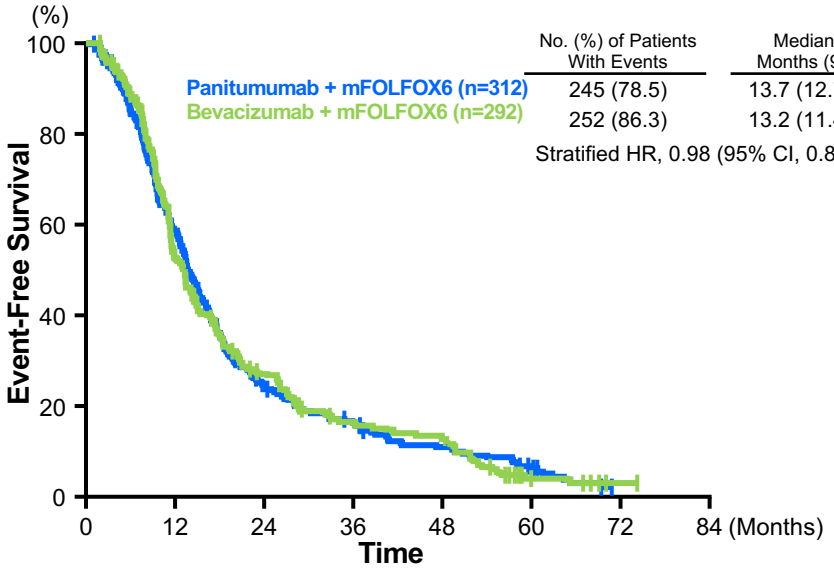
Subgroup		Events/Patients: Panitumumab + mFOLFOX6	Events/Patients: Bevacizumab + mFOFLFOX6	Hazard Ratio (95% CI)
	Overall*	291/400	322/402	0.84 (0.72–0.98)
Primary tumor location	Left-sided	218/312	230/292	0.83 (0.69–1.00)
	Right-sided	71/84	85/103	1.06 (0.77–1.45)
Age	20-64 yr	117/164	129/168	0.89 (0.69–1.14)
	65-79 yr	174/236	193/234	0.81 (0.66–1.00)
Sex	Male	185/252	221/268	0.77 (0.63–0.93)
	Female	106/148	101/134	1.00 (0.76–1.31)
ECOG PS	0	237/328	253/319	0.85 (0.71–1.02)
	1	53/71	69/83	0.79 (0.56–1.14)
No. of organs with metastasis	0-1	123/196	133/194	0.88 (0.69–1.13)
	≥2	168/204	189/208	0.79 (0.64–0.98)
Liver metastasis	No	83/125	89/124	0.88 (0.65–1.19)
	Yes	208/275	233/278	0.83 (0.68–1.00)
Organs with metastasis	Liver only	66/105	83/113	0.78 (0.56–1.08)
	Other	225/295	239/289	0.85 (0.71–1.02)
Primary tumor resection	No	132/161	110/130	0.97 (0.75–1.25)
	Yes	159/239	212/272	0.74 (0.60–0.91)



*Stratified Hazard Ratio is shown with 95% CI.

Progression-free Survival[a]

Left-sided Population

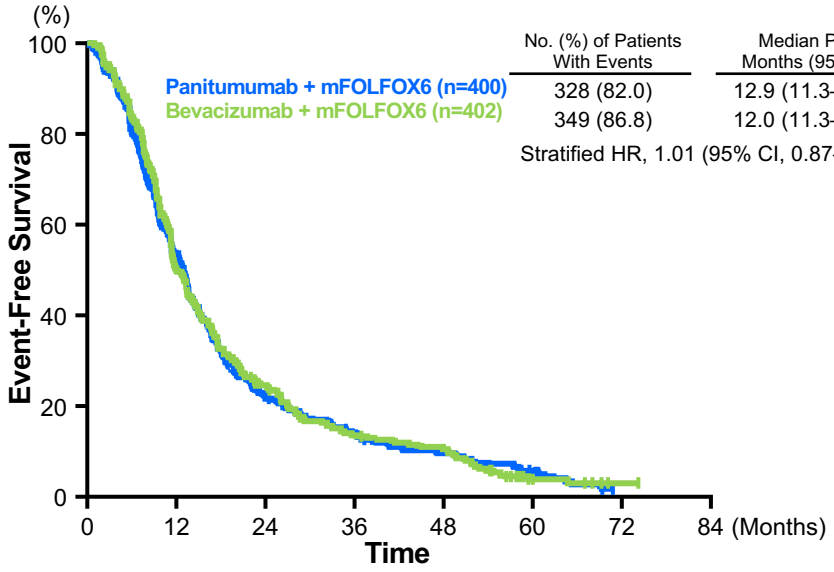


	No. (%) of Patients With Events	Median PFS, Months (95% CI)
Panitumumab + mFOLFOX6 (n=312)	245 (78.5)	13.7 (12.7–15.3)
Bevacizumab + mFOLFOX6 (n=292)	252 (86.3)	13.2 (11.4–14.5)

Stratified HR, 0.98 (95% CI, 0.82–1.17)

No. at risk								
Panitumumab	312	149	59	38	24	13	0	0
Bevacizumab	292	139	67	40	31	5	1	0

Overall Population



	No. (%) of Patients With Events	Median PFS, Months (95% CI)
Panitumumab + mFOLFOX6 (n=400)	328 (82.0)	12.9 (11.3–13.6)
Bevacizumab + mFOLFOX6 (n=402)	349 (86.8)	12.0 (11.3–13.5)

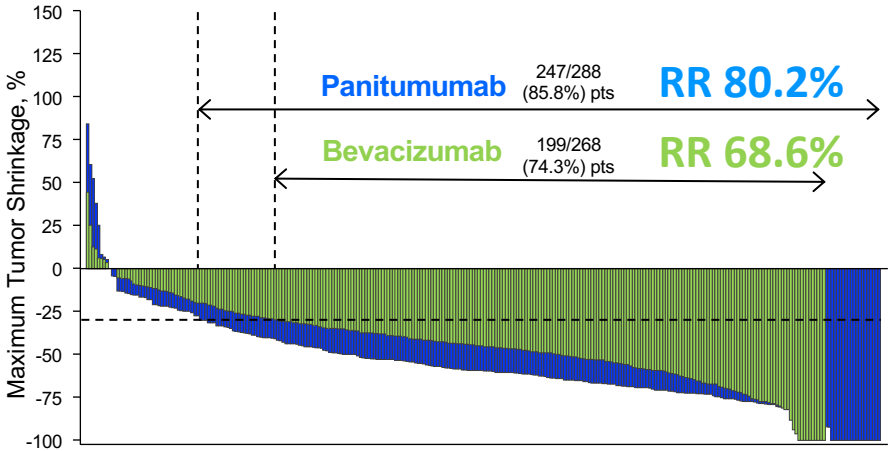
Stratified HR, 1.01 (95% CI, 0.87–1.18)

No. at risk								
Panitumumab	400	179	71	43	28	15	0	0
Bevacizumab	402	182	83	45	35	6	1	0

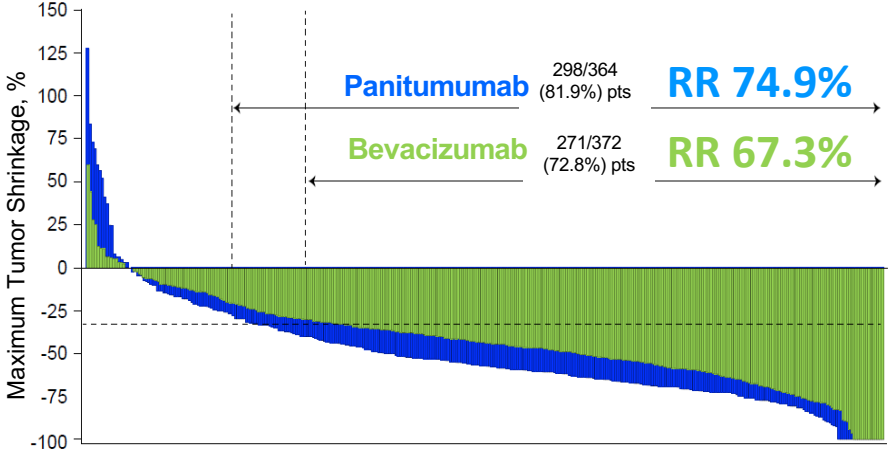
[a]Patients who underwent curative-intent resection were censored at the last tumor evaluable assessment date before the resection.

Other Efficacy Outcome: Depth of Response

Left-Sided Population



Overall Population

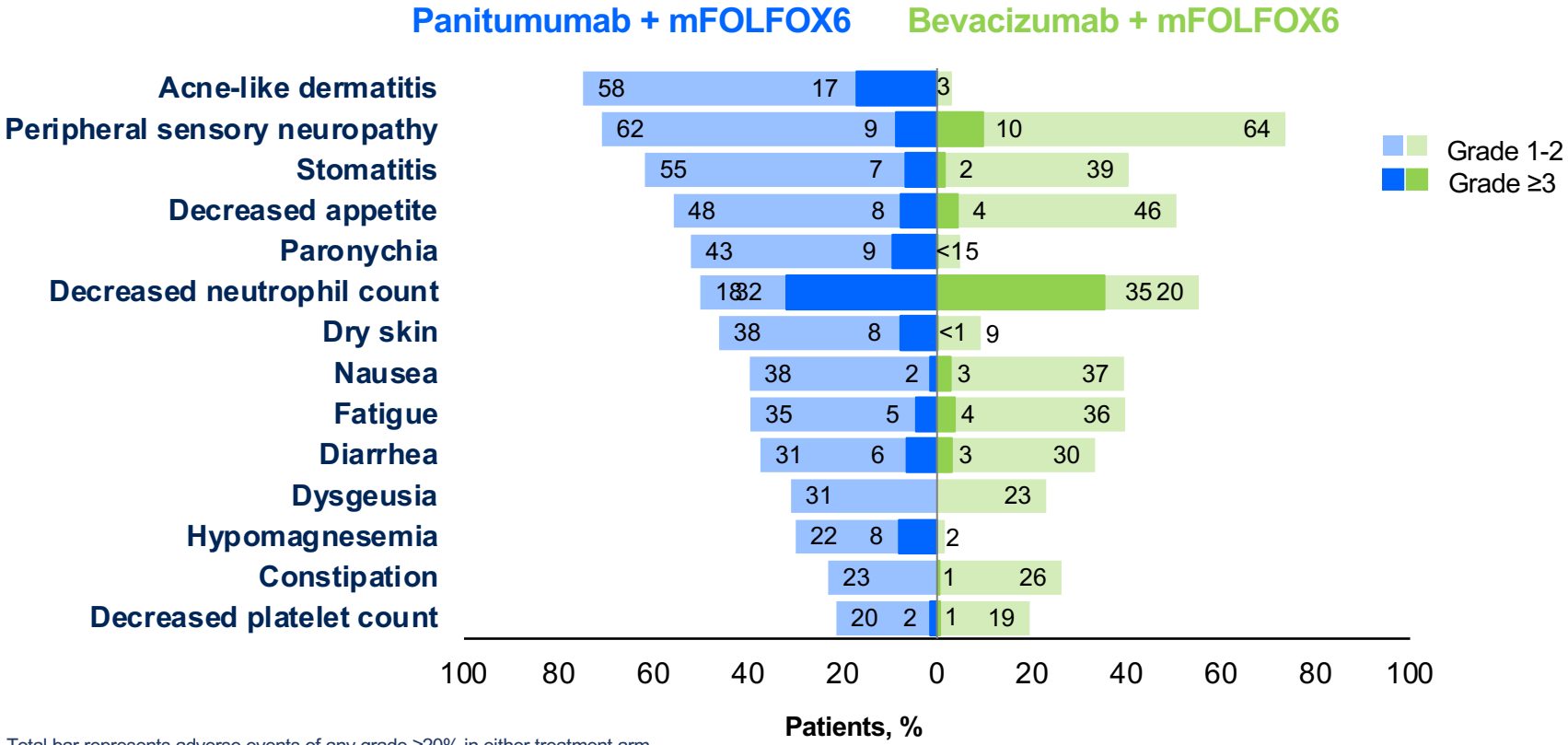


Horizontal dotted line at 30% indicates response per RECIST v1.1.

	Left-sided Population		Overall Population	
	Panitumumab + mFOLFOX6 (n=288)	Bevacizumab + mFOLFOX6 (n=268)	Panitumumab + mFOLFOX6 (n=364)	Bevacizumab + mFOLFOX6 (n=372)
Median, %	-59.4	-43.6	-57.3	-43.6

Depth of response was assessed in patients with measurable lesions at baseline.

Adverse Events Reported in ≥ 20% of Patients



Total bar represents adverse events of any grade ≥20% in either treatment arm.

2022 ASCO® ANNUAL MEETING

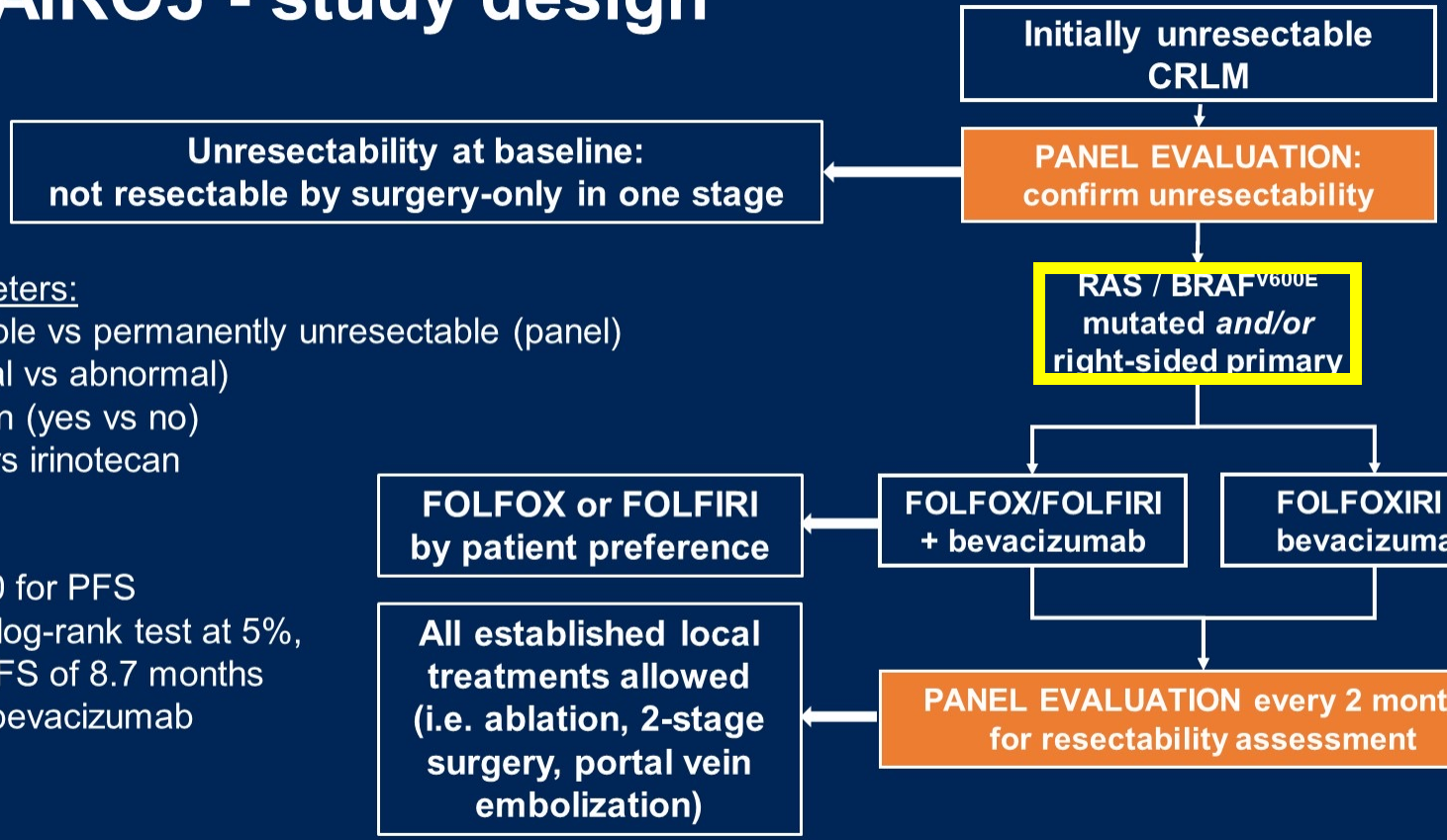
FOLFOXIRI + bevacizumab vs FOLFOX/FOLFIRI + bevacizumab in patients with initially unresectable colorectal liver metastases and right-sided and/or *RAS/BRAF*^{V600E} mutated primary tumor

Randomized phase III CAIRO5 study of the Dutch Colorectal Cancer Group

Cornelis J.A. Punt[1,2], M.J.G. Bond, K. Bolhuis, O.J.L. Loosveld, H.H. Helgason, J.W.B. de Groot, M.P. Hendriks, E.D. Kerver, M.S.L. Liem, A.M. Rijken, C. Verhoef, J.H.W. de Wilt, K.P. de Jong, G. Kazemier, M.J. van Amerongen, M.R.W. Engelbrecht, J.M. Klaase, A. Komurcu, M.I. Lopez-Yurda, R.J. Swijnenburg

[1] Julius Centre for Health Sciences and Primary Care, dept. of Epidemiology, University Medical Center Utrecht
[2] Amsterdam University Medical Center, dept. of Medical Oncology, The Netherlands

CAIRO5 - study design

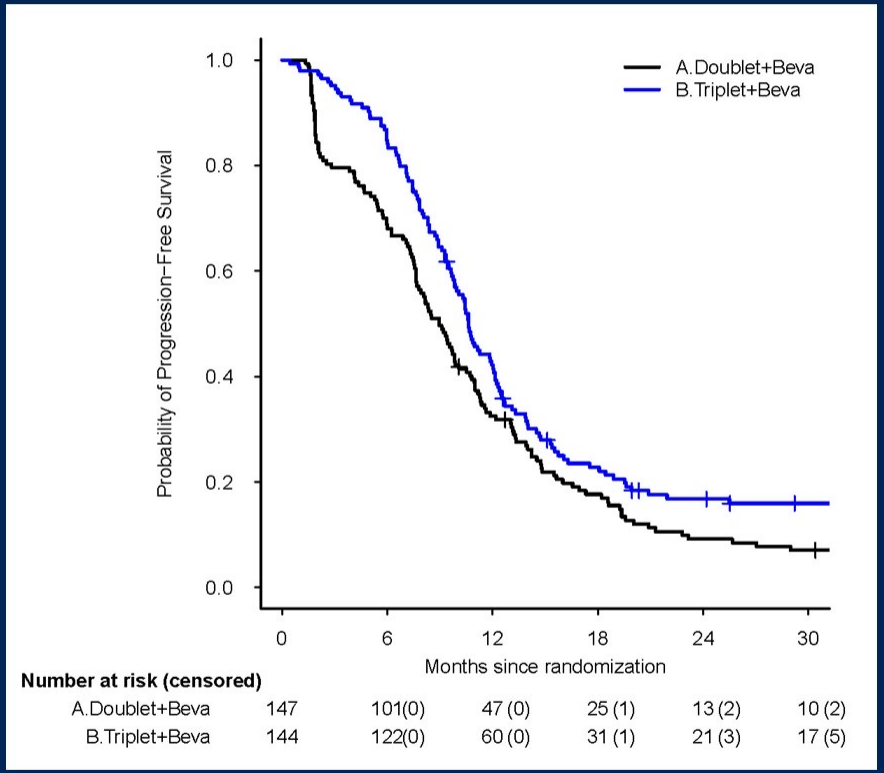


Stratification parameters:
- potentially resectable vs permanently unresectable (panel)
- serum LDH (normal vs abnormal)
- *BRAF*^{V600E} mutation (yes vs no)
- choice oxaliplatin vs irinotecan

Statistics:
257 events, HR 0.70 for PFS
80% power 2-sided log-rank test at 5%, assuming median PFS of 8.7 months for doublet chemo+bevacizumab

PRESENTED BY:
Prof. Cornelis J.A. Punt, MD, PhD

CAIRO5 – progression-free survival



Median follow up 41 months

FOLFOX/FOLFIRI + bevacizumab 9.0 months
FOLFOXIRI + bevacizumab 10.6 months

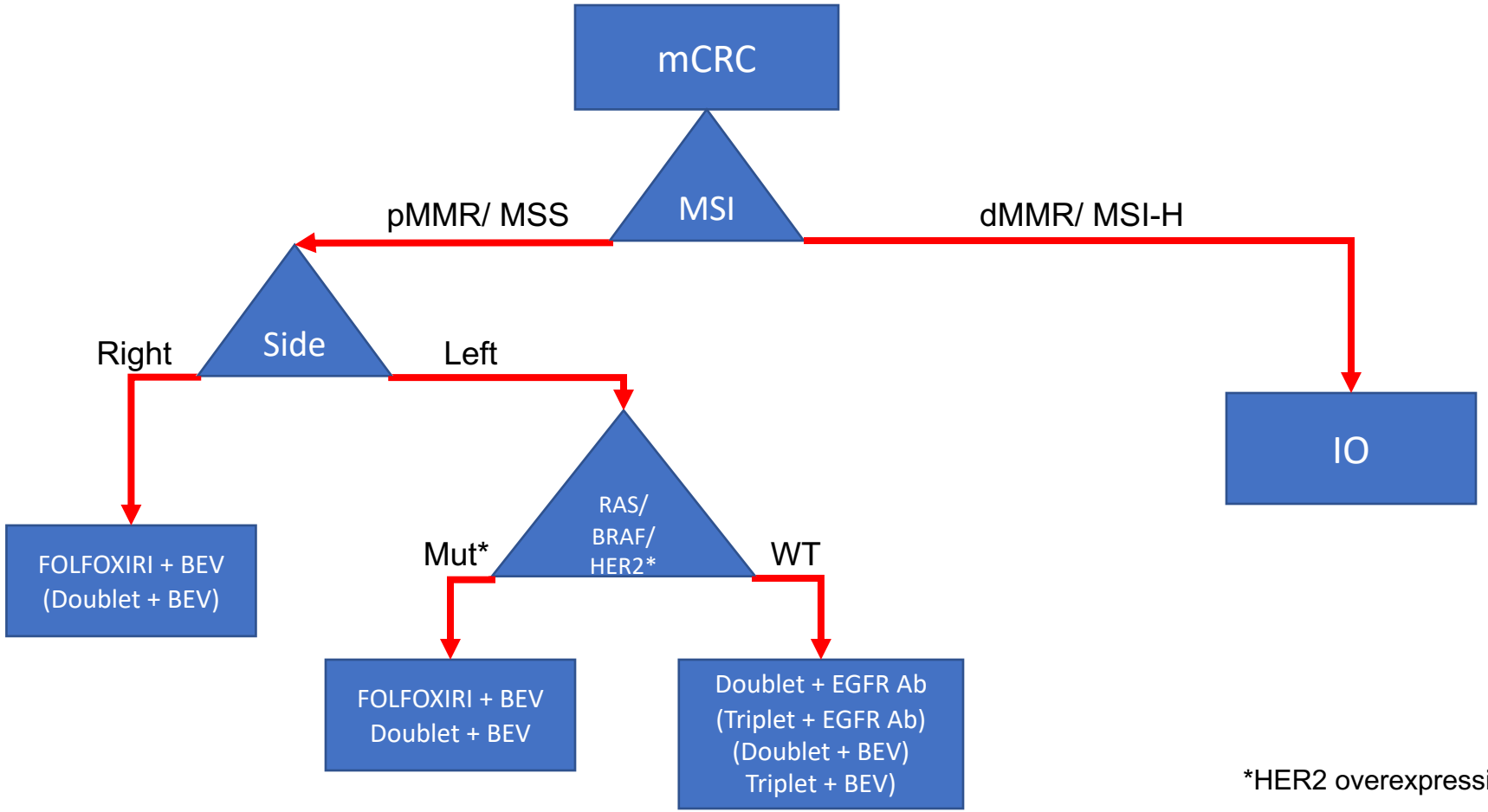
HR 0.77, 95% CI 0.60-0.99, p=0.038

Data on overall survival not yet mature

CAIRO5 – local treatment

	FOLFOX/FOLFIRI + beva	FOLFOXIRI + beva	
n	147	144	
Resection +/- ablation rate postoperative complications Clavien Dindo grade ≥3 grade 5 (death)	46% 40% 15% 0%	57% 51% 27% 2% (n=3)	p=0.08 p=0.19 p=0.08
Number of induction cycles (median, range)	7 (4-12)	6 (2-12)	
Adjuvant chemotherapy	38%	45%	
Number of adjuvant cycles (median, range)	6 (1-8)	4 (1-8)	
R0/1 resection +/- ablation rate 2-stage surgery +/- PVE	37% 16%	51% 32%	p=0.02 p=0.04

Optimized first-line therapy for mCRC



*HER2 overexpression

The Present and the Future

Where we are now		Where we will go
Early stage colon cancer		
Adjuvant therapy	Duration and intensity based on traditional TNM staging	**ctDNA as MRD marker** • to select patients for adjuvant therapy • to identify high-risk patients with distinct molecular profile for targeted intervention • to serve as endpoint in adjuvant trials
	No targeted agents or immunotherapy	
Advanced CRC		
Palliative therapy	Chemotherapy as backbone	**Identify more patients suitable for targeted therapies** • Characterize markers of secondary resistance • Immunotherapy for MSS/ pMMR cancers **Define the role of tumor microbiota** • in oncogenesis • as prognostic and predictive marker • as target for therapeutic intervention
	Targeted agents based on molecular profile and sidedness	
	Immunotherapy only for MSI-H/ dMMR cancers	

The Present and the Future

Where we are now		Where we will go
Early stage rectal cancer		
Neo-Adjuvant therapy	Ongoing shift from radio-chemotherapy followed by surgery and post-op adj Tx to TNT	**Firm establishment of TNT as SOC** • Best sequencing strategy TBD • ? SCRT vs LC-chemo-rads
	Increased use of short-course radiation therapy	
	Even in cCR surgery considered SOC	**Non-operative management as SOC in suitable cases** • Role of imaging, endoscopy and serial ctDNA testing to monitor response and in follow-up TBD
	Molecular markers largely ignored for treatment decisions	**Neoadjuvant or definitive IO therapy is SOC in dMMR/MSI-H rectal cancers**