2024 Updates in Colorectal Cancer

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Outline

- Circulating tumor DNA in localized CRC
  - GALAXY
  - COBRA
  - DYNAMIC RECTAL
- Immunotherapy in metastatic CRC
  - KEYNOTE-177 (1L pembrolizumab vs. chemo)
  - CHECKMATE 8HW (1L nivo/ipi vs. chemo)

Patient Case

- 51-year-old female with abdominal pain, change in bowels
- Went to PCP, Hg was 6 (previously normal)
- CT with large colonic mass at the hepatic flexure, no mets
- Colonoscopy confirmed ascending colon mass; biopsy: adenocarcinoma, dMMR; CEA WNL
- R hemicolectomy: 8.4 cm invasive moderately differentiated adenocarcinoma, invading to pericolonic tissue, LVI+/PNI-, 2/31 LN+, negative margins; pT3N1b, dMMR
- Discussed adjuvant therapy, ctDNA testing
- Restaging scans done prior to adjuvant therapy initiation

ASCO Gastrointestinal Cancers Symposium

Circulating tumor DNA (ctDNA) dynamics in colorectal cancer (CRC) patients with molecular residual disease: Updated analysis from GALAXY study in the CIRCULATE-JAPAN

Presenting Author: Hiroki Yukami, MD, PhD

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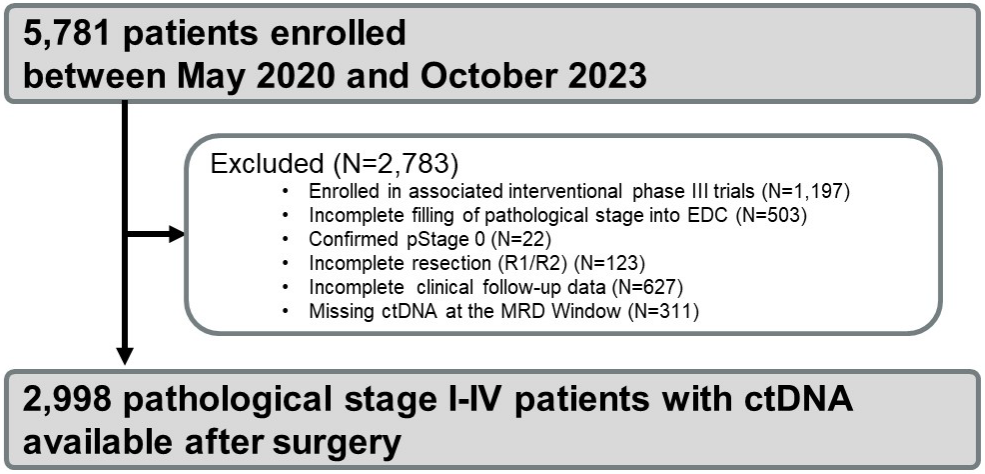
CONSORT diagram and patient characteristics

- Postoperative ctDNA-based molecular residual disease (MRD) is reported to be associated with a high risk of recurrence[1].
- Here, **we present an updated 24-month disease free survival (DFS)** analysis in stage I–IV patients with radically resected CRC participating in the prospective, observational GALAXY study (UMIN000039205).
- A personalized, tumor-informed assay (Signatera™, Natera, Inc.) was used for the detection and quantification of ctDNA in serial plasma samples collected at 1, 3, 6, 9, 12, 18, and 24 months after surgery until recurrence.
- We investigated the association between ctDNA status and recurrence.



Median Follow-up: 16.14 months (range: 0.23-42.14)

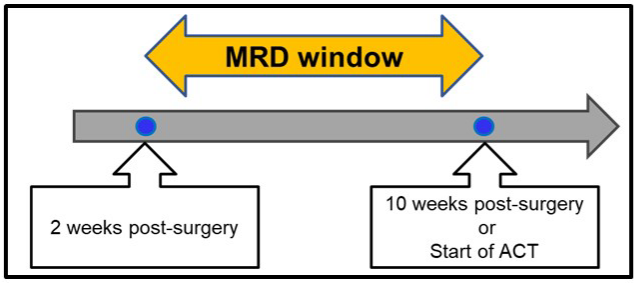
Characteristic	N = 2,998[1]
Age	69 (23 - 95)
Gender	
Male	1,622 (54%)
Female	1,376 (46%)
Performance Status	
0	2,700 (90%)
1	298 (10%)
Tumor Location	
Right-sided colon	938 (33%)
Left-sided colon	1,376 (48%)
Rectum	553 (19%)
Unknown	131
Pathological T Stage	
T1-T2	592 (20%)
T3-T4	2,351 (80%)
Unknown	55
Pathological N Stage	
N0	1,449 (49%)
N1-N2	1,493 (51%)
Unknown	56
Pathological Stage	
I	415 (14%)
II	901 (30%)
III	1,231 (41%)
IV	451 (15%)

Characteristic	N = 2,998[1]
Neoadjuvant Treatment	
Neoadjuvant Chemotherapy	315 (11%)
Upfront Surgery	2,683 (89%)
Adjuvant Treatment	
Adjuvant Chemotherapy	1,130 (38%)
Observation	1,868 (62%)
Adjuvant Treatment Duration	
3 months	361 (32%)
6 months	458 (40%)
<3 or >6 months	311 (28%)
***BRAF* status**	
BRAF^{wt}	2,638 (93%)
BRAF^{V600E}	205 (7%)
Unknown	155
***RAS* status**	
RAS^{wt}	1,622 (57%)
RAS^{mut}	1,231 (43%)
Unknown	145
MSI status	
MSS or MSI-Low	2,686 (91%)
MSI-High	280 (9%)
Unknown	32
Clinical or Radiological Recurrence	
Recurrence	530 (18%)
No Recurrence	2,468 (82%)
Total Follow-up (months)	16.1 (0.2 - 42)

[1]Median (Range); n (%)

1)Daisuke K, et al. Nat Med 2023.

DFS according to status in the MRD window in all stage

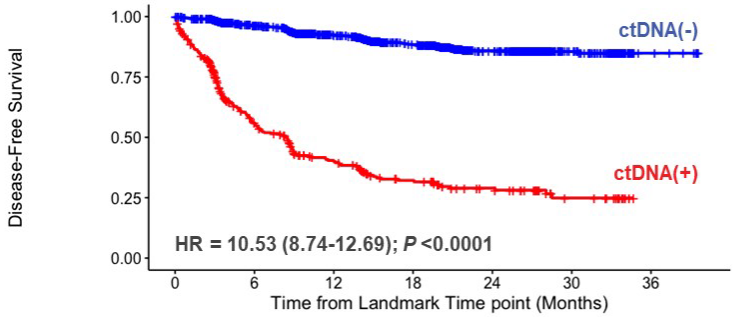


ACT: adjuvant chemotherapy

2,998 stage I-IV patients included in the outcome cohort

Excluded (N=138)
- DFS event prior to the 10 weeks landmark timepoint (n=138)

MRD Window analysis cohort (n=2,860)



Number at risk

ctDNA Negative	2491	2031	1441	1041	495	135	8
ctDNA Positive	369	165	98	59	35	13	0

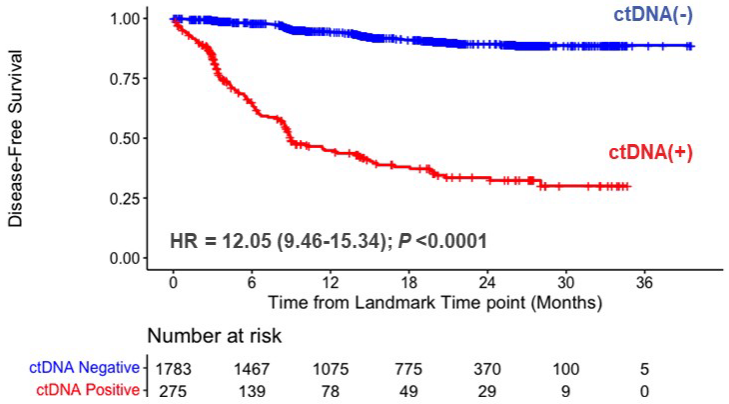
ctDNA status	Negative	Positive
Events %	9.4 (235/2491)	58.8 (217/369)
24M-DFS % (95% CI)*	85.9 (83.9–87.7)	28.9 (23.4–34.8)

**DFS % from landmark time point*

MRD window: 2-10 weeks post surgery, prior to start of any adjuvant therapy - Landmark 10 weeks post-surgery

ctDNA-positive in the MRD window is predictive inferior DFS

DFS according to status in the MRD window in pStage II/III

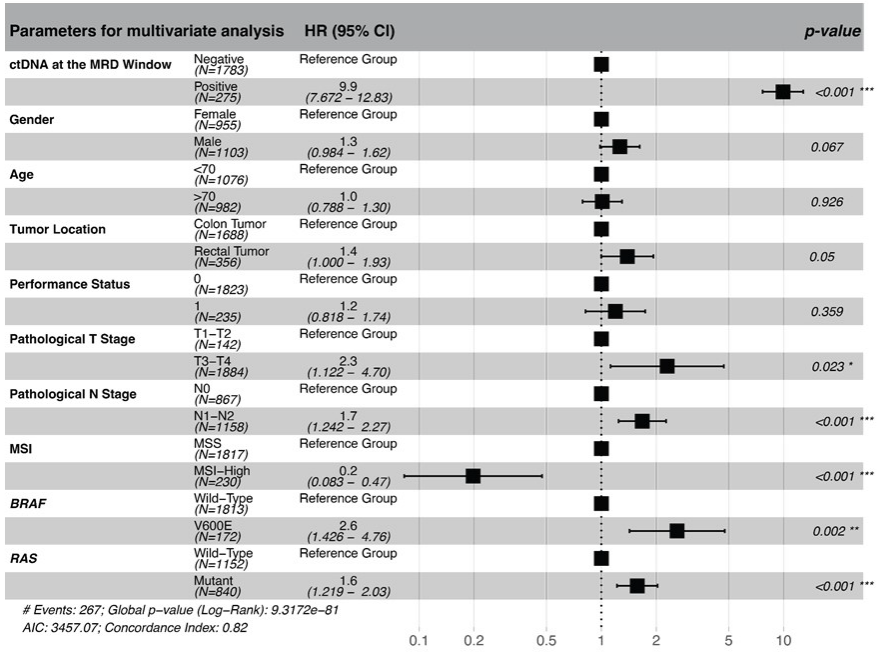


Dynamics	ctDNA Negative	ctDNA Positive
Events %	7.8 (126/1783)	56.5 (143/275)
24M-DFS % (95% CI)*	89.3 (87.2–91.1)	33.5 (26.5–40.7)

**DFS % from landmark time point*

MRD window: 2-10 weeks post surgery, prior to start of any adjuvant therapy - Landmark 10 weeks post-surgery

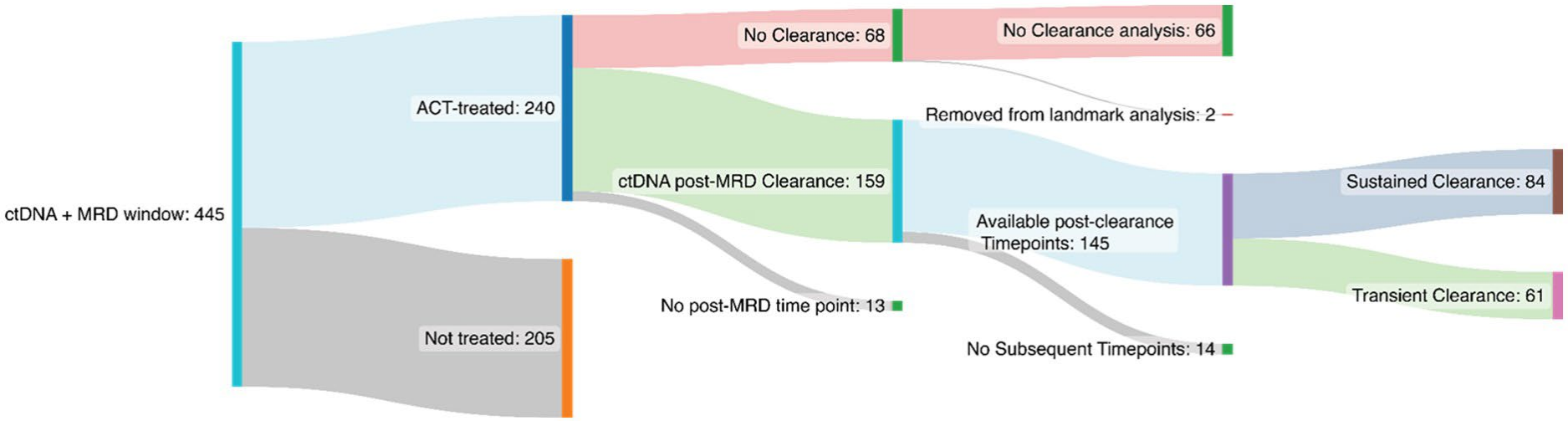
Multivariate Regression Model for DFS



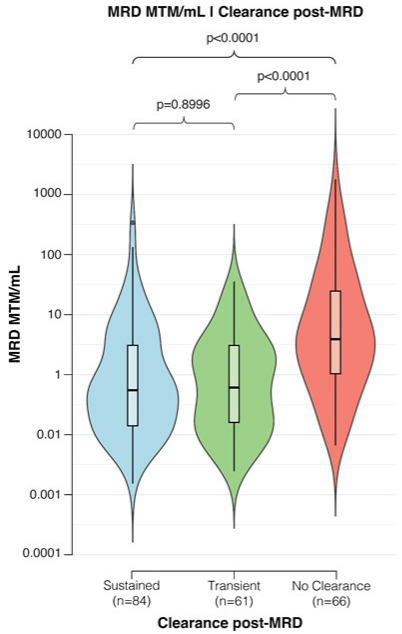
ctDNA-positive in the MRD window is predictive of inferior DFS (pStage II/III)

Sankey diagram of post MRD ctDNA clearance in the ACT treated cohort

Landmark 10 weeks post surgery



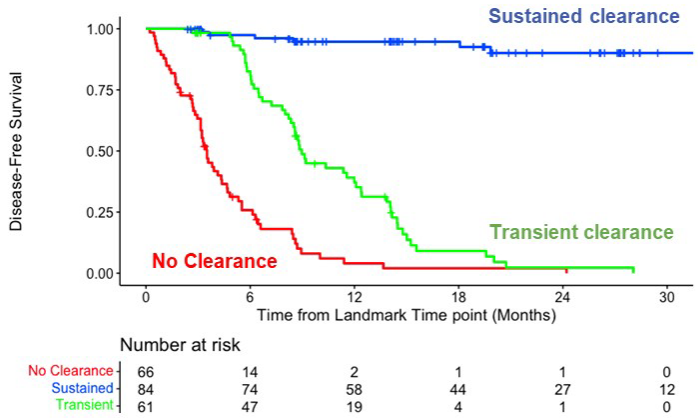
DFS according to ctDNA clearance in Patients with ctDNA positive in the MRD window



Group	Median MRD MTM/mL
Sustained	0.61
Transient	0.53
No Clearance	3.89

**P values from Wilcoxon rank-sum test*

Landmark 10 weeks post surgery



ctDNA Clearance	Sustained Clearance	Transient Clearance	No Clearance
Events %	7.1 (6/84)	85.2 (52/61)	89.4 (59/66)
Median DFS months (95% CI)	NR	9 (8.5–12.4)	3.5 (3.2–4.7)
24M-DFS % (95% CI)*	90.1 (78.6–95.6)	2.3 (0.02–10.3)	2 (0.02–9.2)
HR	**Reference**	**25.13**	**87.08**
95% CI	Not applicable	10.57–59.73	36.14–209.84
P	Not applicable	<0.0001	<0.0001

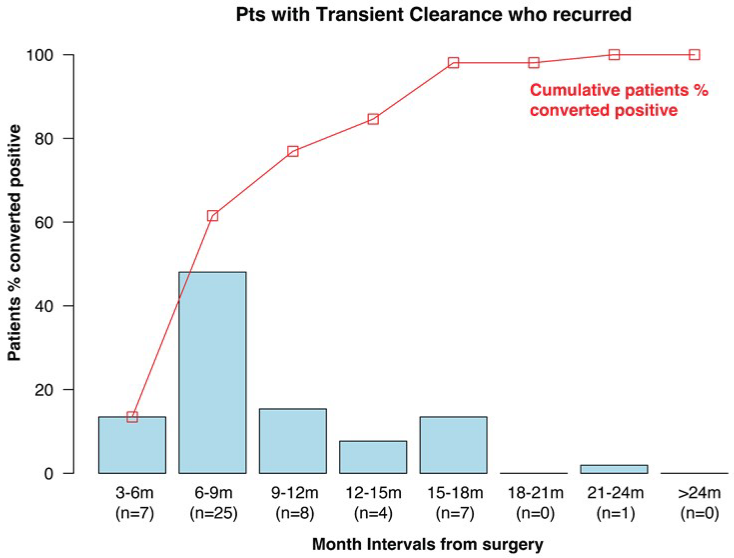
**DFS % from landmark time point*

Sustained clearance indicates superior DFS compared to Transient or No clearance

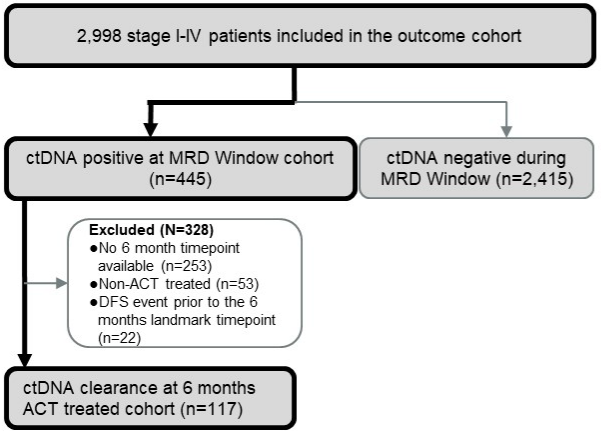
PRESENTED BY: Hiroki Yukami, MD, PhD

ctDNA dynamics of patients with transient clearance post-MRD with recurrence

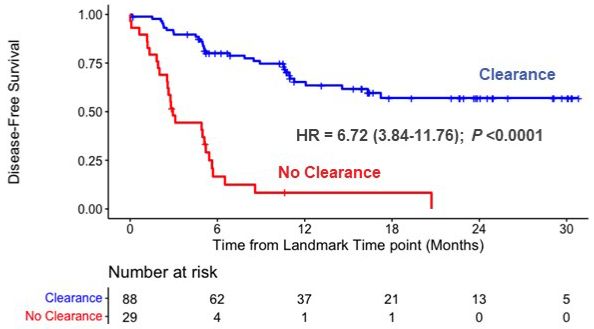
For recurrent pts with transient clearance, 98% of pts turned back positive by 18 months post-surgery.



Clearance and reduction in MTM/mL at 6 months in ACT treated patients

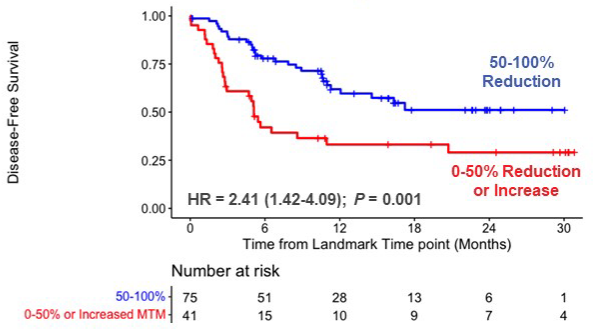


ctDNA clearance at 6 months



ctDNA Clearance	Clearance	No Clearance
Events %	35.2 (31/88)	89.7 (26/29)
24M-DFS % (95% CI)	57.1 (44–68.2)	NR

Positive at the MRD window to 6 months MTM/mL Reduction | ACT-treated



ctDNA Clearance	50-100% Reduction	0-50% Reduction or Increase
Events %	38.7 (29/75)	65.9 (27/41)
24M-DFS % (95% CI)	51.1 (36.4–64.1)	29 (15–44.6)

**DFS % from landmark time point*

Landmark 6 months post-surgery

ctDNA clearance and MTM/mL reduction on ACT is an indicator of treatment efficacy and results in better outcomes

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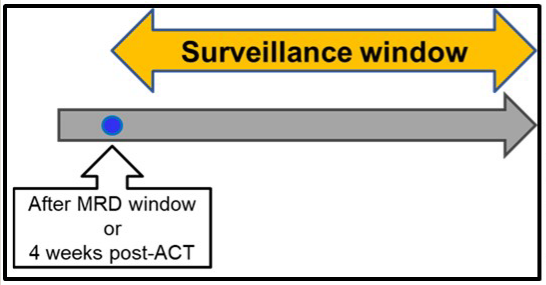
DFS according to ctDNA status in the Surveillance window

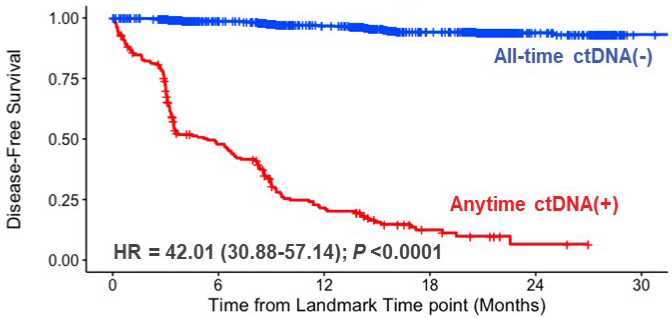


2,998 stage I-IV patients included in the outcome cohort

Excluded (N=1,212)
- No subsequent timepoints available (n=858)
- DFS event prior to the 8 months landmark timepoint (n=354)

Surveillance Window analysis cohort (n=1,786)

All stages

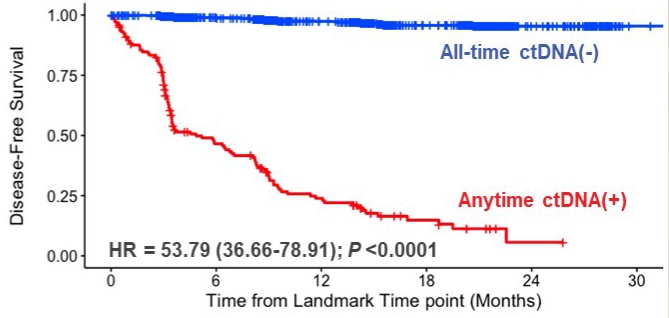


Number at risk

ctDNA Negative	1582	1211	885	432	125	8
ctDNA Positive	204	84	33	10	2	0

ctDNA status	All-time Negative	Anytime Positive
Events %	3.7 (58/1582)	77.5 (158/204)
24M-DFS % (95% CI)*	93.9 (92–95.4)	6.6 (2–14.9)

Stage II/III



Number at risk

ctDNA Negative	1326	1022	737	355	97	5
ctDNA Positive	146	57	26	9	1	0

ctDNA status	All-time Negative	Anytime Positive
Events %	2.7 (36/1326)	75.3 (110/146)
24M-DFS % (95% CI)*	95.4 (93.5–96.8)	5.6 (0.8–18.3)

**DFS % from landmark time point*

- *Surveillance window starts from 4 weeks post-ACT or at the end of MRD window if patient had no ACT, until the last follow up or relapse.*
- *Landmark 8 months post-surgery (2 months for ACT initiation + 6 months of ACT duration)*

ctDNA-positive in the surveillance window is predictive of inferior DFS

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Phase II results of circulating tumor DNA as a predictive biomarker in adjuvant chemotherapy in patients with stage II colon cancer: NRG-GI005 (COBRA) phase II/III study

Van K. Morris[1], Greg Yothers[2], Scott Kopetz[1], Shannon L. Puhalla[3], Peter C. Lucas[2], Atif Iqbal[4], Patrick M Boland[5], Dustin A. Deming[6], Aaron J. Scott[7], Howard J Lim[8], Theodore S. Hong[9], Norman Wolmark[2], Thomas J. George[10]

[1]The University of Texas -- MD Anderson Cancer Center; [2]NSABP Foundation, Inc.; [3]UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine; [4]Baylor College of Medicine; [5]Rutgers Cancer Institute of New Jersey; [6]University of Wisconsin; [7]University of Arizona Cancer Center; [8]BC Cancer - Vancouver, University of British Columbia; [9]Massachusetts General Hospital Cancer Center, Harvard Medical School; [10]UF Health Cancer Center, Gainesville, FL

January 20, 2024

NCI National Clinical Trials Network — a National Cancer Institute program

NCI Community Oncology Research Program — A program of the National Cancer Institute of the National Institutes of Health

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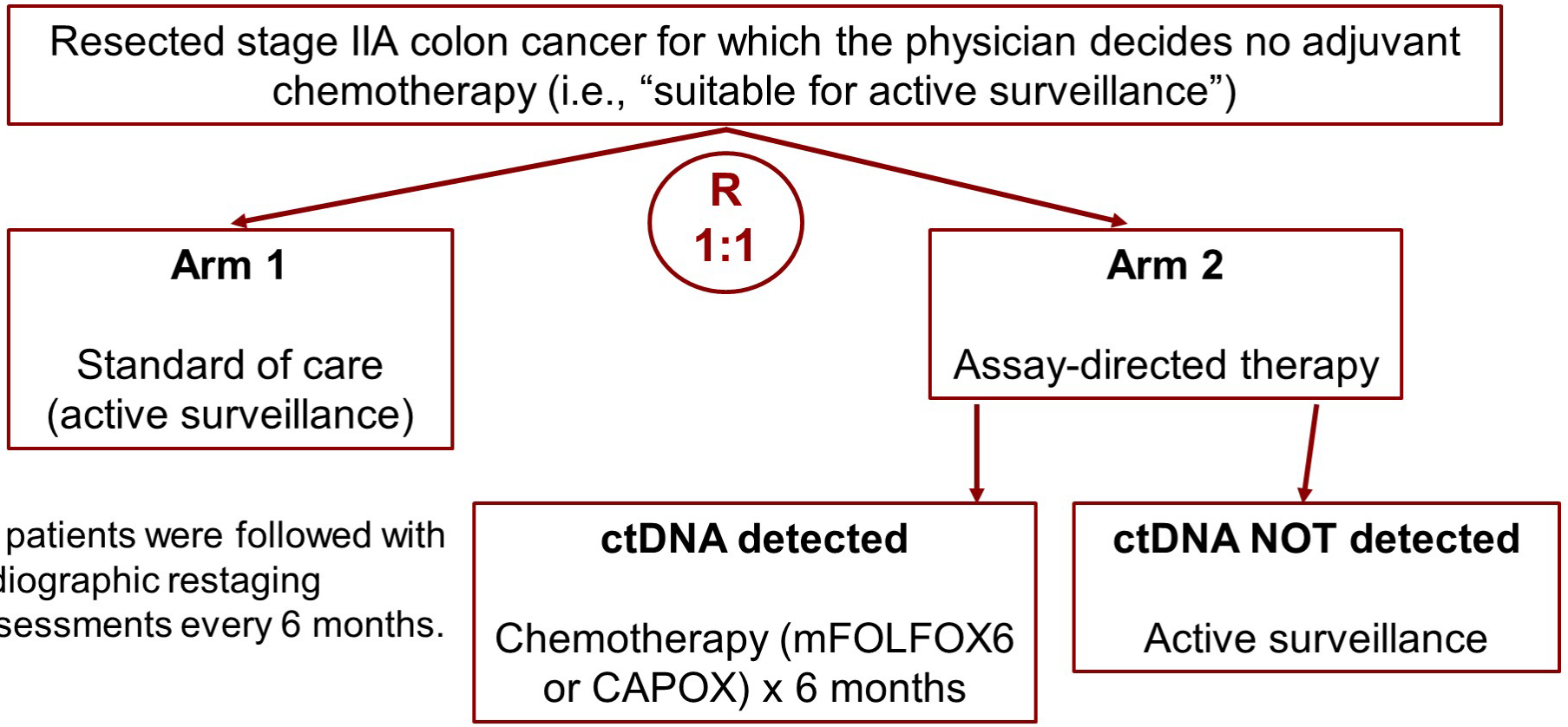
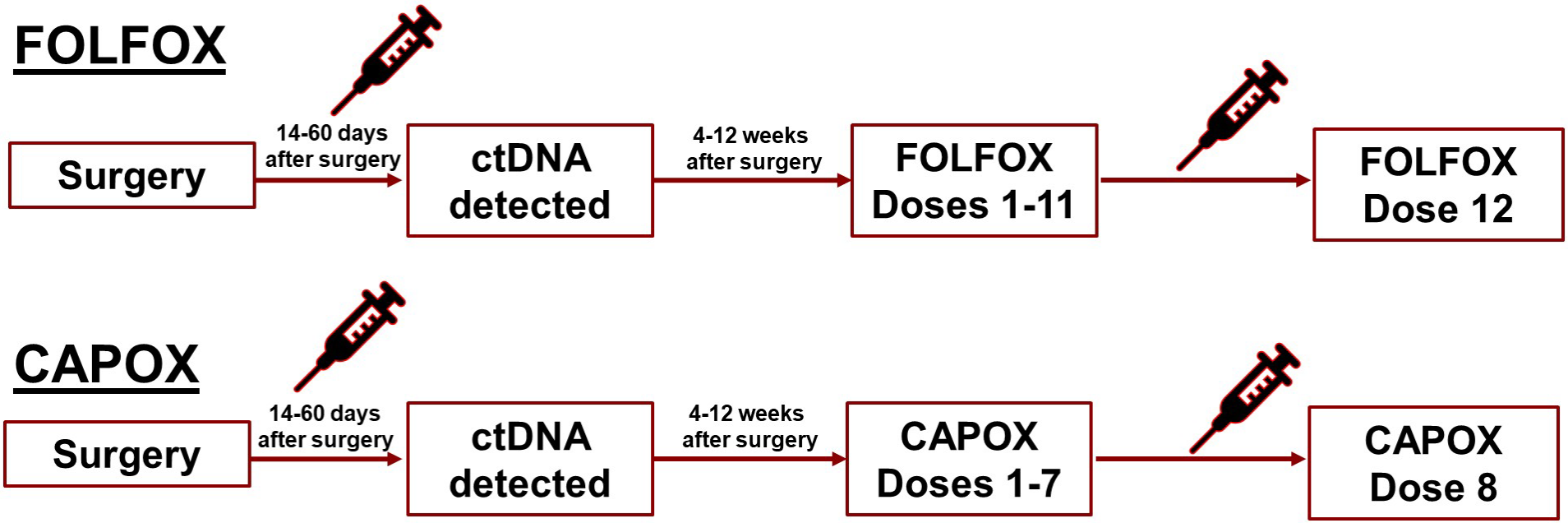
NRG-GI005 (COBRA) Study Schema

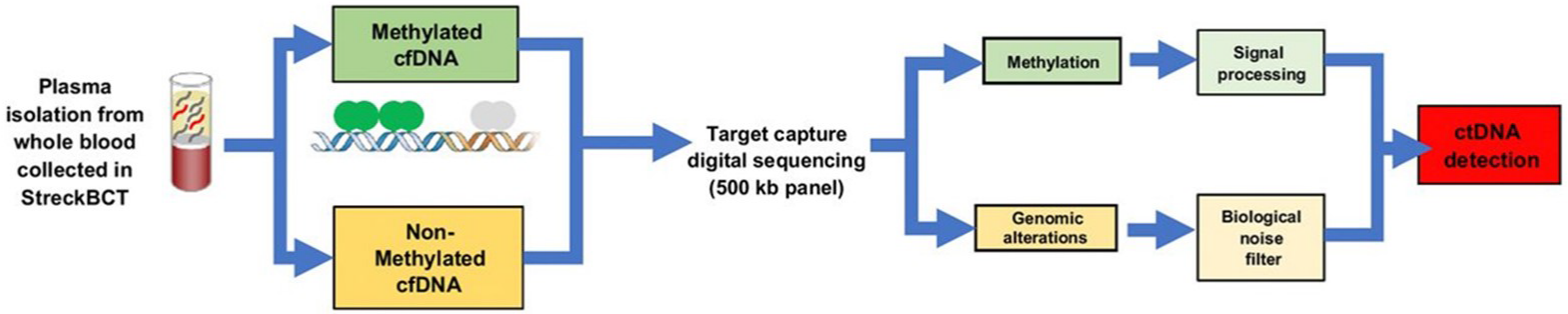


Treatment schema: Arm 2 “ctDNA detected”



The 6-month timepoint was collected two weeks after prior dose of chemotherapy/ immediately prior to the administration of the last dose of chemotherapy.

ctDNA assay



- Guardant LUNAR assay was selected for NRG GI005 through an open RFA and peer-reviewed process as a tissue-agnostic assay that incorporates mutation/genomic and methylation/epigenomic markers alike for detection of ctDNA.
- Guardant LUNAR had undergone previous clinical and analytic validation:
  - In a previously reported cohort of 70 patients with stage I-IV colorectal cancer, sensitivity and specificity for were 56% and 95% (100% for those with one year of follow-up), respectively, when drawn one month after completion of definitive therapy.
  - Adding epigenomic profiling improved sensitivity relative to mutation calling alone by 25%.

Parikh A et al, Clin Cancer Res 2021

Statistical Plan

Primary objective (phase II):

- Compare rates of ctDNA clearance between ctDNA (+) cohorts at 6 months after randomization.

Secondary objectives:

- Describe median OS, RFS, and TTR according to ctDNA status and treatment arm.
- Assess feasibility of trial design (compliance with adjuvant chemotherapy).
- Correlate ctDNA clearance/persistence with survival outcomes.

Statistical Design:

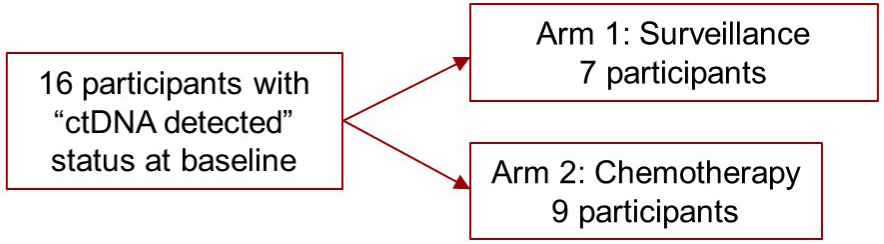
- For an assumed baseline ctDNA+ rate of 5.45%, the phase II/III decision rule (using a 1-sided p-value ≤ 0.35 from a Fisher exact test with 1-sided α= .072 and power .909) based on intention to treat,
  H_0: clearance 10% in each arm
  H_a: clearance 60% vs 10% (Arm 2 versus Arm 1)

- 1408 patients were anticipated to provide 55 RFS events in the subset of patients ctDNA+ at baseline in order to provide 92% power at one-sided α=.025 for the primary phase III endpoint.

- First 16 ctDNA(+) patients were evaluated after 6 months from randomization for phase II futility analysis.

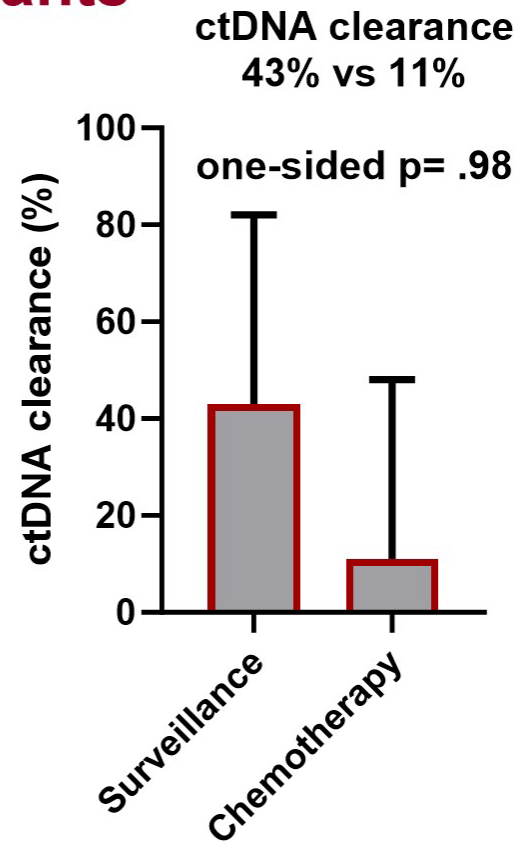
Phase II Endpoint Analysis: ctDNA(+) baseline participants

- Among 596 participants with baseline ctDNA status available, ctDNA(+) detection was observed in 33 (5.54%).

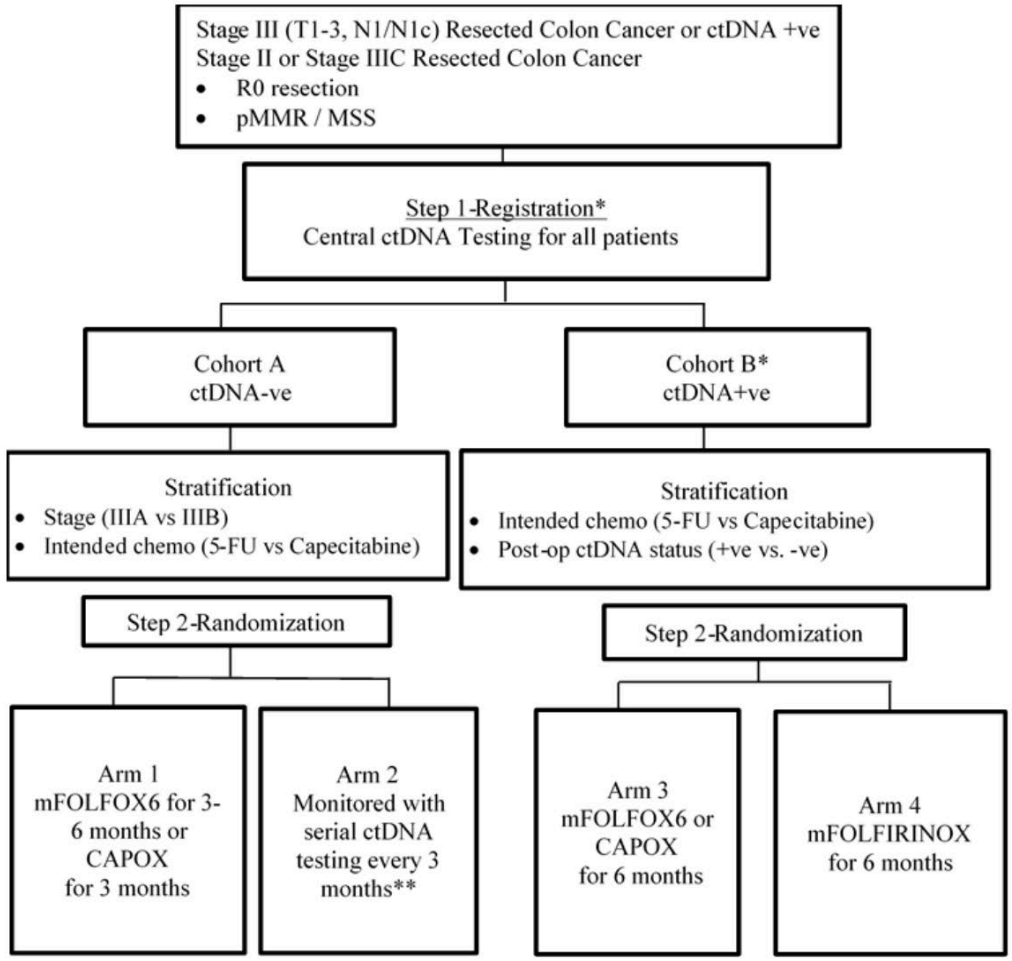


- Clearance of ctDNA at 6 months among ctDNA(+) participants at baseline was observed in:
  - **Arm 1 (surveillance):** 3 of 7 (43%, 95% CI 10 - 82%) participants
  - **Arm 2 (chemotherapy):** 1 of 9 patients (11%, 95% CI 0.3 - 48%) participants

- **Because the 1-sided Fisher's Exact Test yields p = 0.98 exceeded 0.35, H_o was not rejected, and the decision rule calls for early stopping due to futility.**



CIRCULATE-US (NRG-GI008)



High-risk stage II/stage III

Assay: Signatera (tumor-informed)

Primary Outcomes: TTPos (time from randomization until ctDNA+), DFS

Secondary Outcomes: baseline post-sx ctDNA+ rate, OS, time to recurrence, compliance with adjuvant chemo

Principal Investigators:
Dr. Arvind Dasari (MD Anderson)
Dr. Christopher Lieu (Colorado)

NCT04089631

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ASCO Gastrointestinal Cancers Symposium

AGITG
AUSTRALASIAN GASTRO-INTESTINAL TRIALS GROUP

Circulating Tumor DNA Analysis Informing Adjuvant Chemotherapy in Locally Advanced Rectal Cancer

The Randomized AGITG DYNAMIC-Rectal Study

Jeanne Tie

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

On behalf of the DYNAMIC-RECTAL Investigators

Joshua D Cohen, Yuxuan Wang, Chris Brown, Rachel Wong, Jeremy Shapiro, Rob Campbell, Fiona Day, Theresa Hayes, Morteza Aghmesheh, Christos Karapetis, Maria Popoli, Lisa Dobbyn, Janine Ptak, Natalie Silliman, Christopher Douville, Nickolas Papadopoulos, Kenneth Kinzler, Bert Vogelstein, Peter Gibbs

PRESENTED BY: Jeanne Tie, MBChB FRACP MD

DYNAMIC-Rectal Study Design

ACTRN12617001560381

Locally Advanced Rectal Cancer

- cT3-4 and/or N+
- Pre-op LCCRT
- R0 TME surgery
- ECOG 0 – 2
- No metastasis on CT CAP at diagnosis
- Provision of adequate tumor tissue within 5 weeks post-op

ctDNA Analysis
Week 4 + 7 post-op

R
2:1

Stratification
ypN stage
Participating site

ctDNA-Informed Management

- **ctDNA-Pos → 4M Adjuvant Chemo** (oxaliplatin-based or single agent FP)
- **ctDNA-Neg + ypN0 → Observation**
- **ctDNA-Neg + ypN+ → Clinician's choice**

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

Standard Management

Adjuvant treatment decisions at clinician's discretion

Endpoints

Primary
- Proportion receiving adjuvant chemo

Key Secondary
- 3-year RFS (non-inferiority)

Secondary
- OS
- ctDNA dynamics

- Target sample size 408: 80% power with 95% confidence to demonstrate non-inferiority margin of at most 10%
- Ceased recruitment early (due to COVID-19 and increasing adoption of TNT) → **230 eligible patients analyzed**

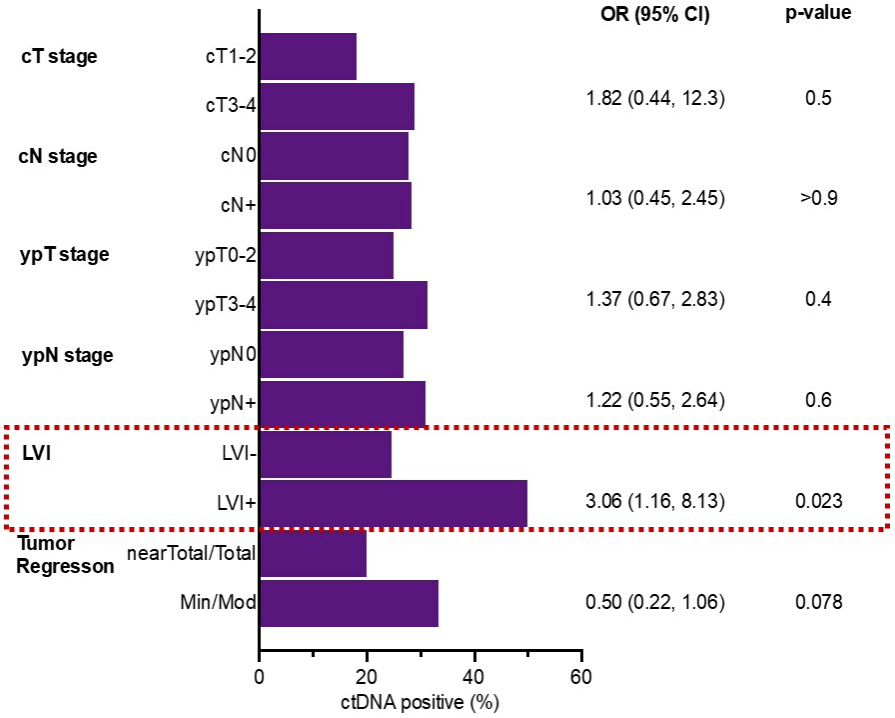
PRESENTED BY: Jeanne Tie, MBChB FRACP MD

Baseline Characteristics

Characteristics	ctDNA-Informed Management N = 155, N (%)	Standard Management N = 75, N (%)
Age, median (range), years	69 (29 - 85)	62 (34 - 84)
Sex, Male	109 (70)	57 (76)
ECOG, 0	96 (62)	50 (67)
Distance from anal verge, < 5 cm	39 (26)	15 (21)
Baseline T stage, cT4	17 (11)	6 (8)
Baseline N stage, cN2	39 (25)	15 (20)
Pathologic T stage, ypT4	2 (1.3)	2 (2.7)
Pathologic N stage, ypN+	45 (29)	23 (31)
Lymphovascular invasion, present	21 (14)	8 (11)
Pathologic complete response	26 (17)	9 (12)
Post-op CEA, > 5 ug/L	4 (2.6)	0 (0)
Surgery to randomization, median (range), days	38 (21 - 63)	39 (24 - 57)

ctDNA Detection in Key Subgroups

- ctDNA analysis completed in 150/155 **(97%)**
- ctDNA-positive in 42/150 **(28%)**



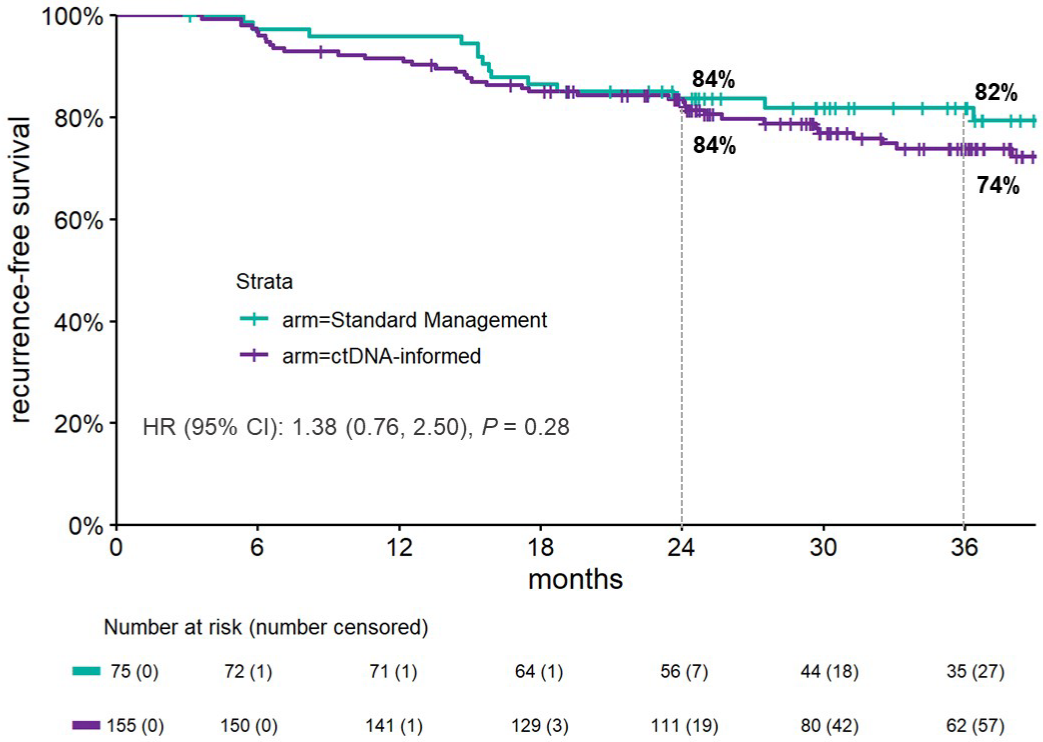
Adjuvant Treatment Delivery

Treatment Information	ctDNA-Informed N = 155	Standard N = 75	*P*
Adjuvant chemo commenced, n	71 **(46%)**	58 **(77%)**	<0.001
ctDNA +ve ctDNA –ve ctDNA unknown	42 (27%) 25 (16%) 4 (3%)		
Chemo regimen, n			
Oxaliplatin-based doublet	43/155 **(28%)**	19/75 **(25%)**	--
Single agent	28/155 **(18%)**	39/75 **(52%)**	
Time to commencing chemotherapy, median (IQR), days	69 (54, 80)	56 (49, 62)	--
Treatment duration, median (IQR), weeks	15 (11, 18)	14 (11, 17)	--
Completed planned treatment, n	57/71 (80%)	41/58 (71%)	--

PRESENTED BY: Jeanne Tie, MBChB FRACP MD

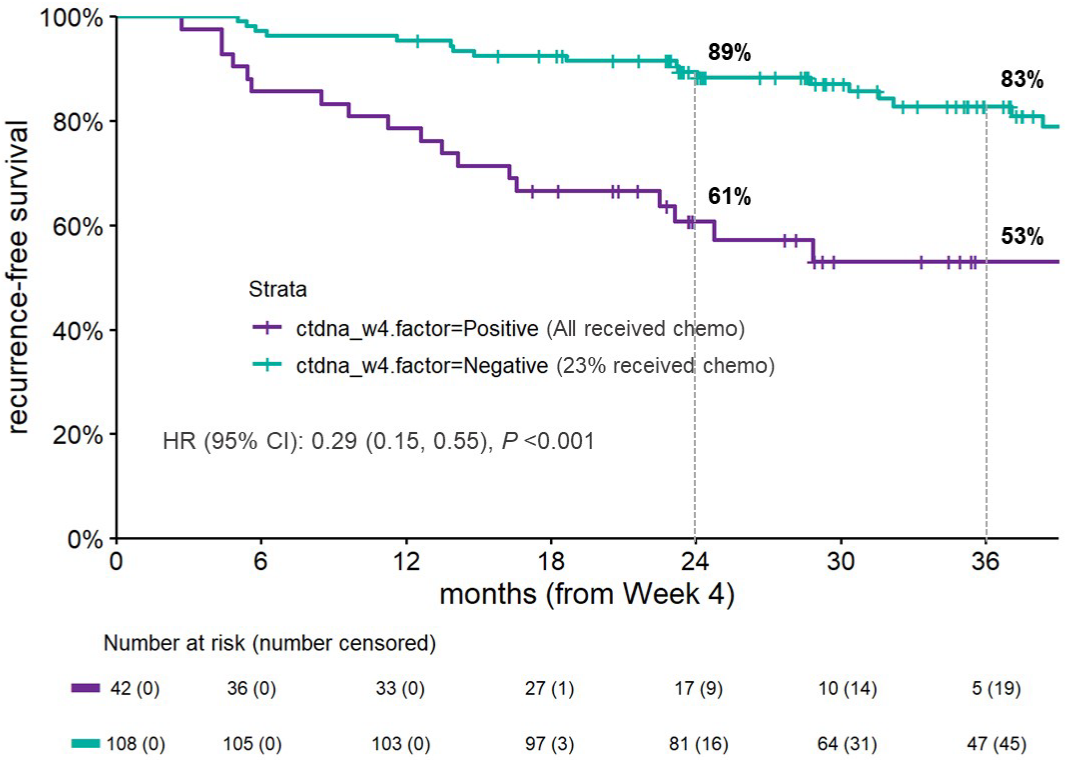
Recurrence-Free Survival

Median follow-up 36 months



PRESENTED BY: Jeanne Tie, MBChB FRACP MD

Recurrence-Free Survival and ctDNA Status



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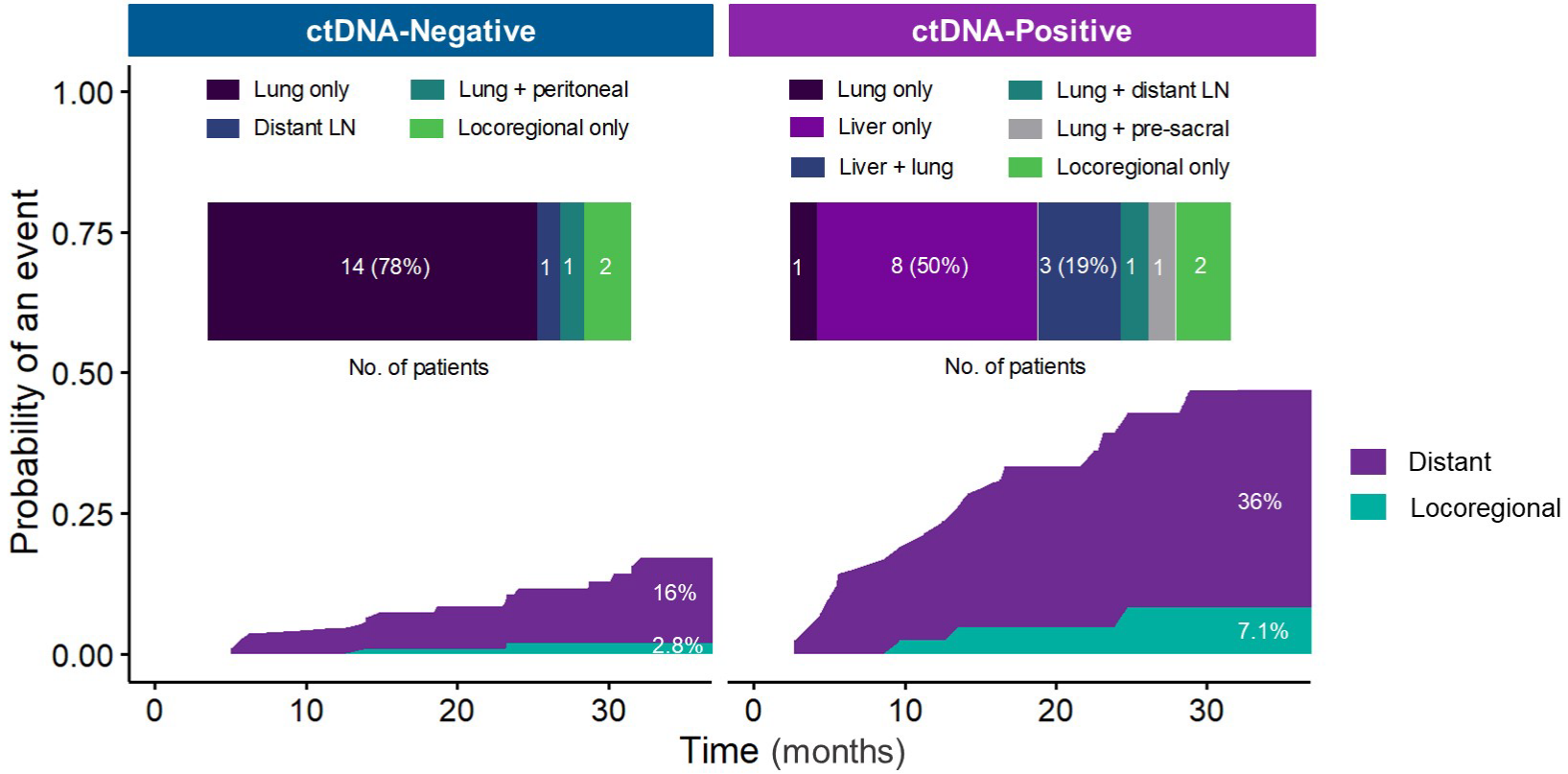
Sites of Relapse by Post-Op ctDNA Status



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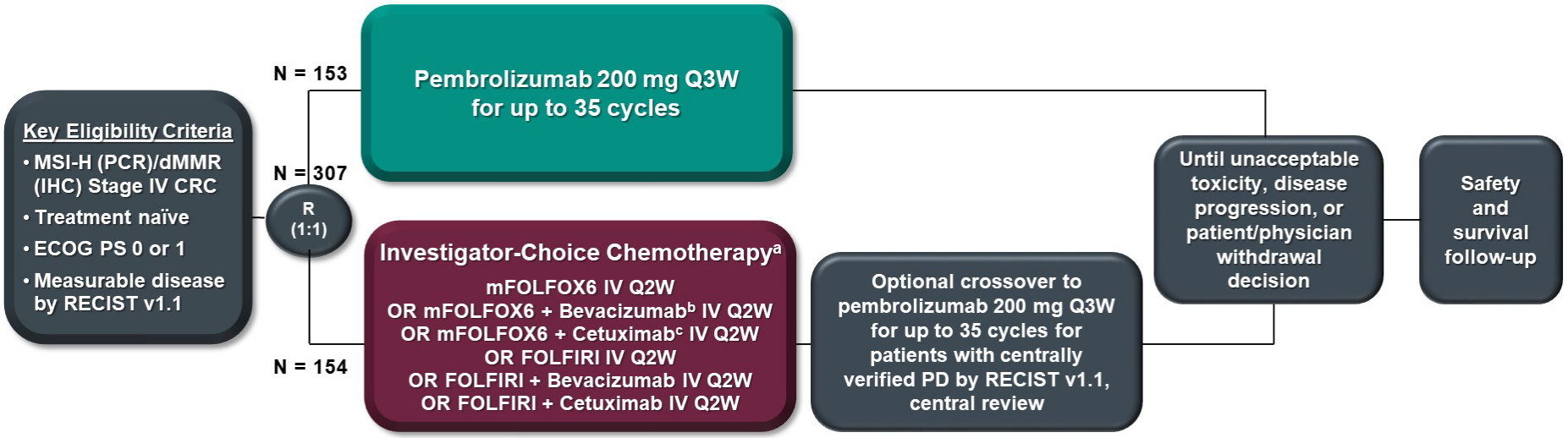
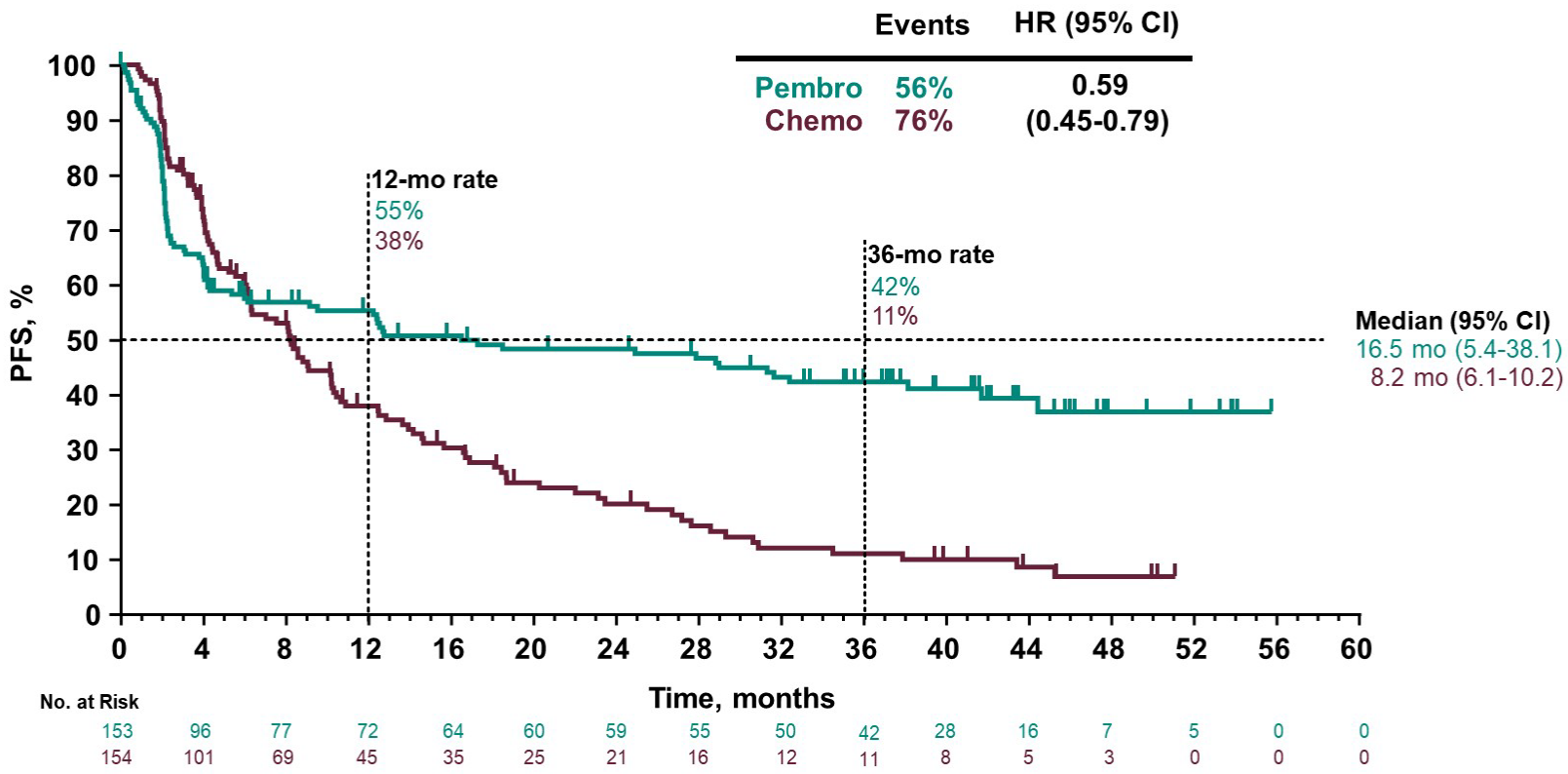
KEYNOTE-177 Study Design
(NCT02563002)



- Dual-Primary endpoints: PFS per RECIST v1.1, BICR; OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, PFS2, HRQoL, safety
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

[a]Chosen before randomization; [b]Bevacizumab 5 mg/kg IV; [c]Cetuximab 400 mg/m2 over 2 hours then 250 mg/mg^2 IV over 1 hour weekly.
BICR, blinded independent central review; IHC: immunohistochemistry with hMLH1, hMSH2, hMSH6, PMS2; PCR: polymerase chain reaction; PFS, progression-free survival; OS: overall survival; ORR: overall response rate; Q9W: every 9 weeks.

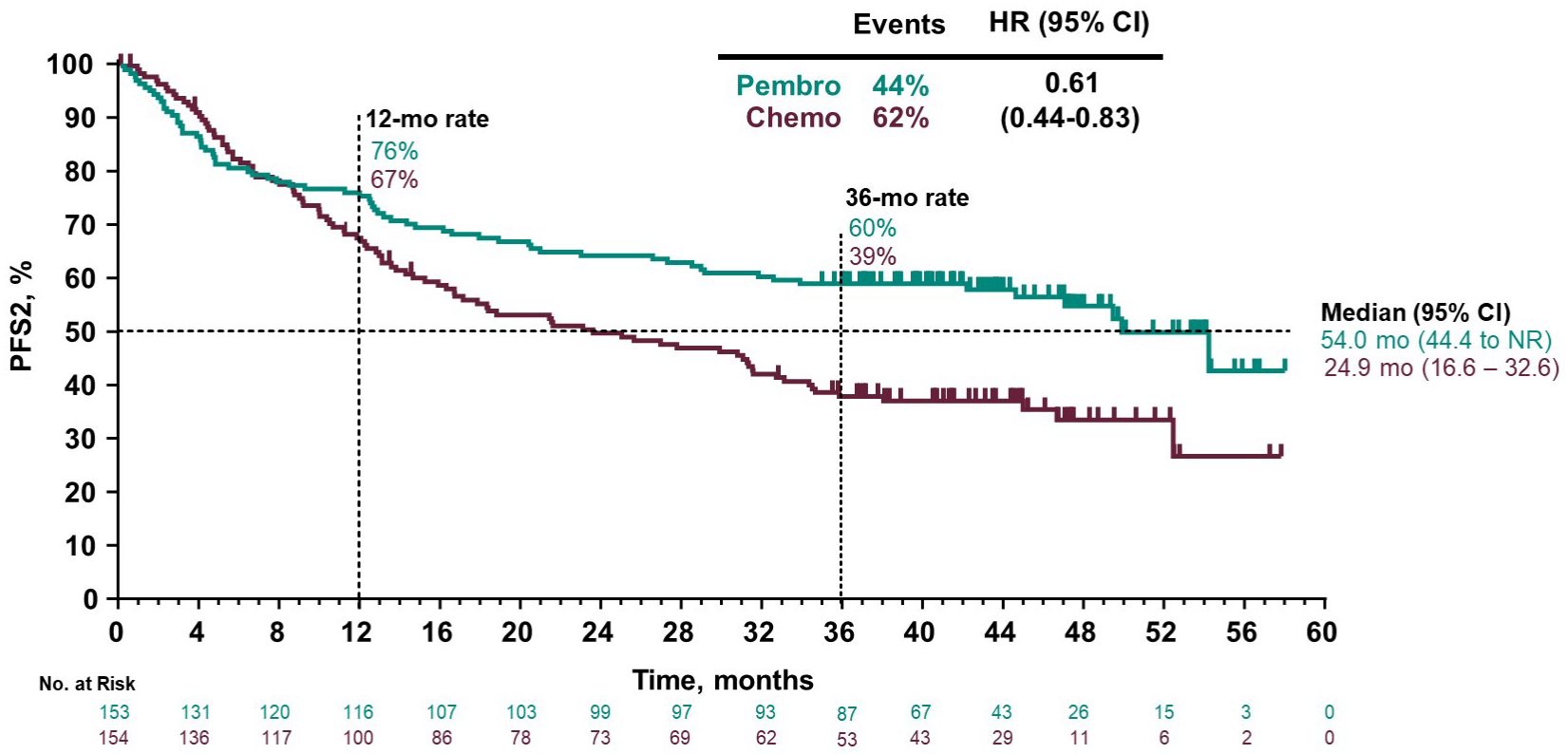
Progression-Free Survival



Data cut-off: 19Feb2021.

Progression-Free Survival 2

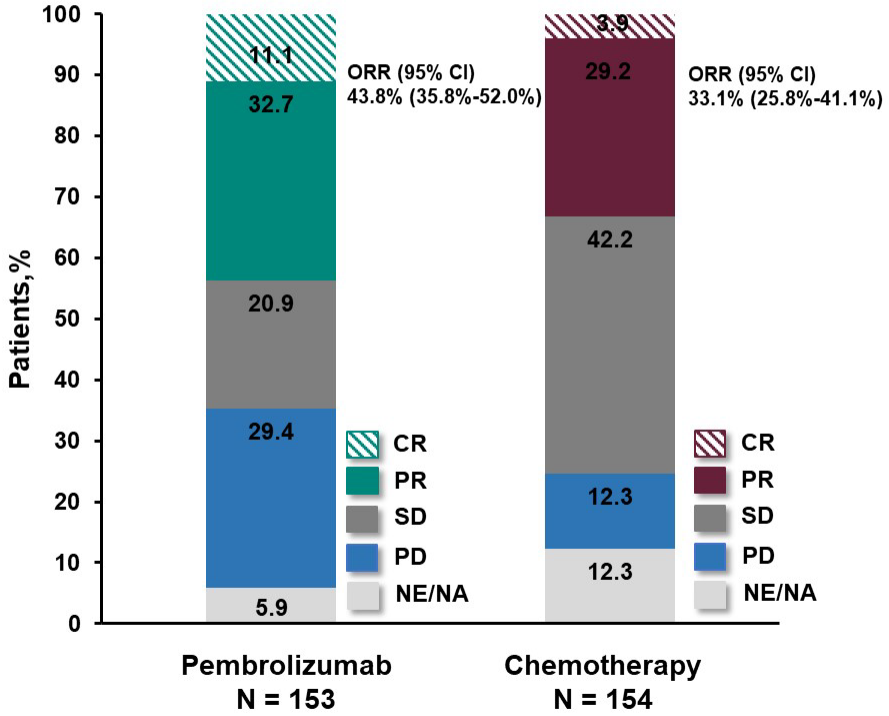
Time from randomization to progression on next line therapy or any cause death

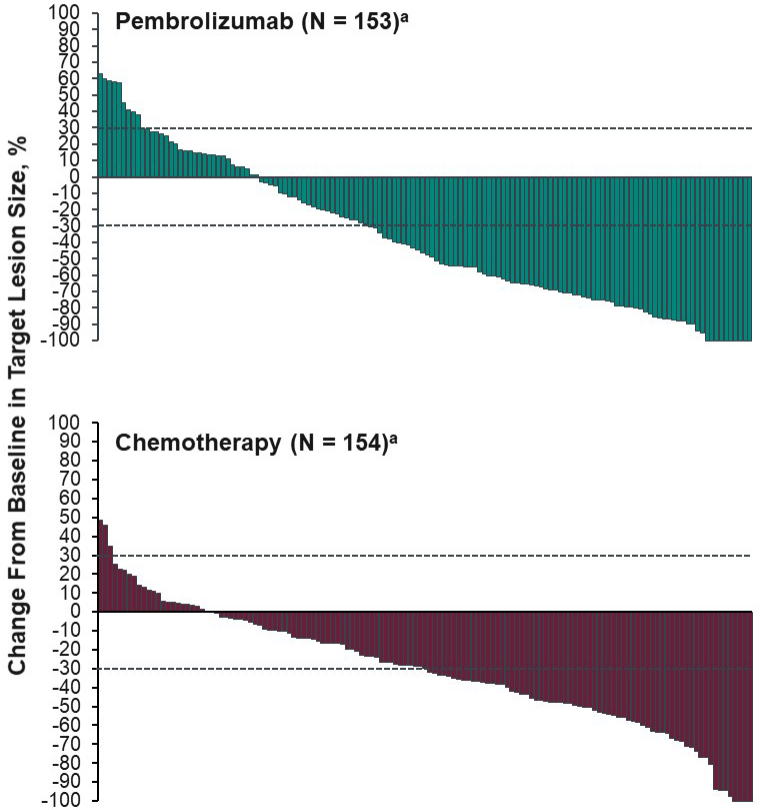


Data cut-off: 19Feb2021.

Summary of Best Anti-Tumor Response

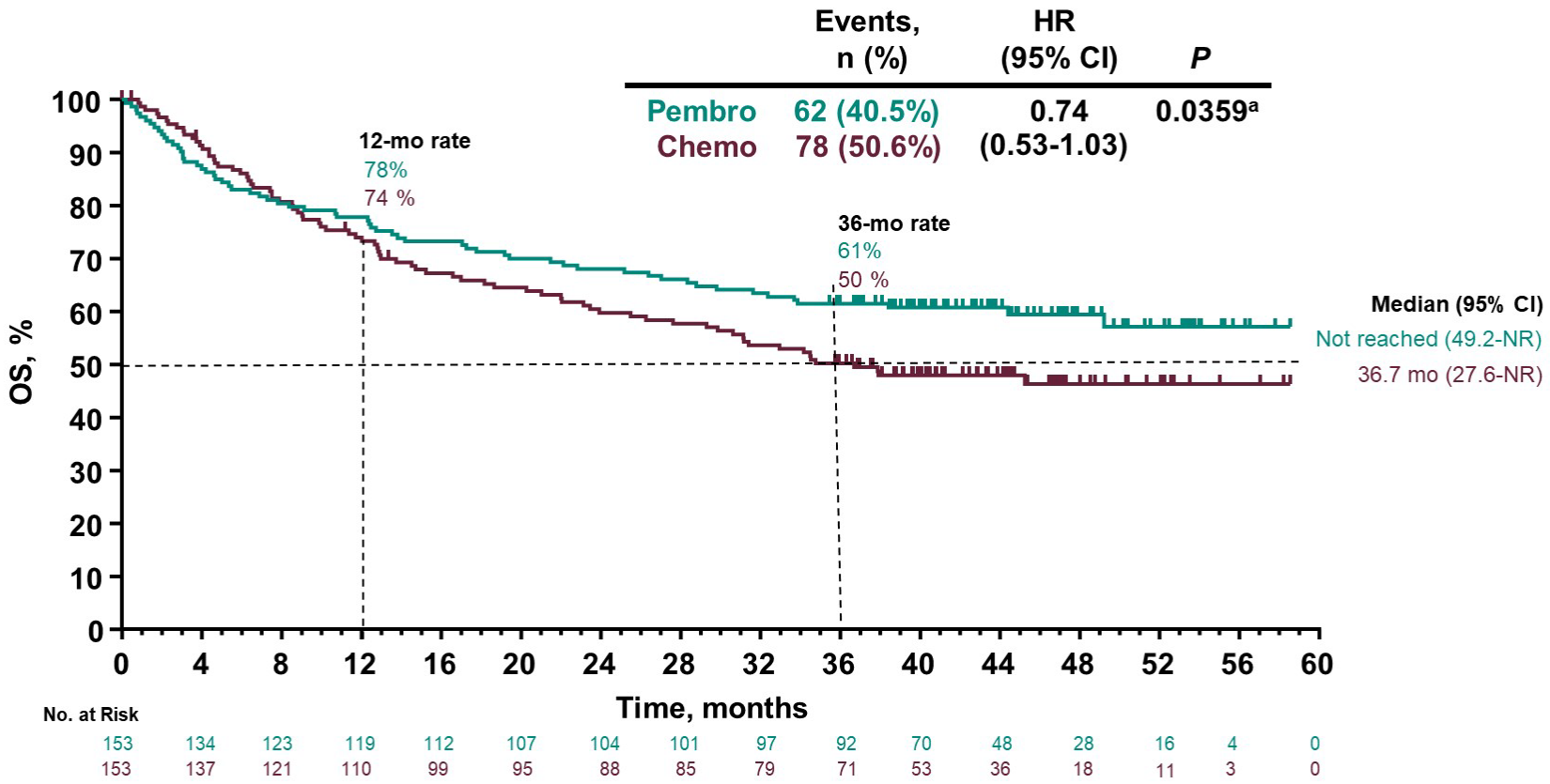
Place video here





9 (6%) patients in the pembrolizumab arm and 19 (12%) in the chemotherapy arm were not evaluable (NE) or had no assessment (NA); [a]104 of 138 (75%) evaluable patients in the pembrolizumab arm and 111 of 135 (82%) evaluable patients in the chemotherapy arm had a reduction from baseline in target lesion size. Evaluable patients include those with ≥1 post-baseline target lesion imaging assessment in the intention-to-treat population; Data cut-off: 19Feb2020.

Overall Survival



[a]**Pembrolizumab was not superior to chemotherapy for OS as one-sided α > 0.0246. Pre-specified sensitivity analyses to adjust for crossover effect by rank-preserving structure failure time model and inverse probability of censoring weighting showed OS HRs of 0.66 (95% CI 0.42-1.04) and 0.77 (95% CI 0.44-1.38).** Data cut-off: 19Feb2021.

ASCO Gastrointestinal Cancers Symposium

Nivolumab plus ipilimumab vs chemotherapy as first-line treatment for microsatellite instability-high/ mismatch repair-deficient metastatic colorectal cancer: first results of the CheckMate 8HW study

Thierry Andre,[1] Elena Elez,[2] Eric Van Cutsem,[3] Lars Henrik Jensen,[4] Jaafar Bennouna,[5] Guillermo Ariel Mendez,[6] Michael Schenker,[7] Christelle de la Fouchardiere,[8] Maria Luisa Limon,[9] Takayuki Yoshino,[10] Jin Li,[11] Heinz-Josef Lenz,[12] Jose Manzano Mozo,[13] Giampaolo Tortora,[14] Rocio Garcia-Carbonero,[15] Elvis Cela,[16] Yingsi Yang,[16] Ming Lei,[16] Lixian Jin,[16] Sara Lonardi[17]

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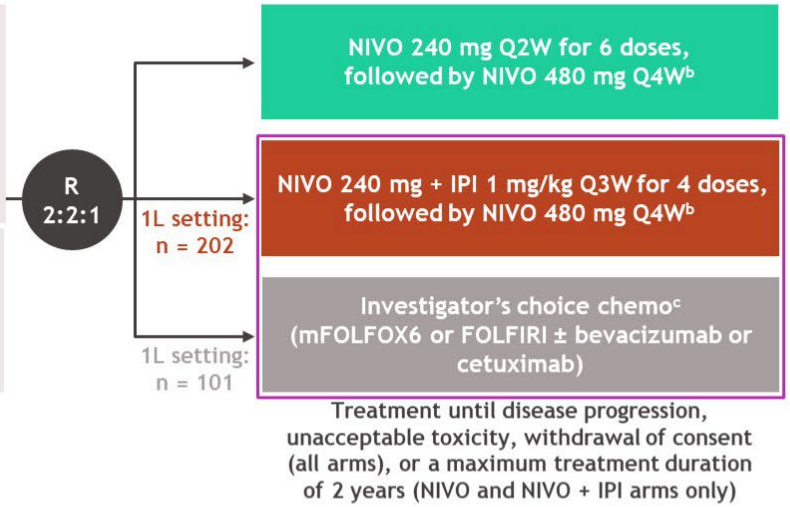
Abstract number LBA768

CheckMate 8HW study design

- CheckMate 8HW is a randomized, multicenter, open-label phase 3 study[a]

Key eligibility criteria:
- Histologically confirmed unresectable or metastatic CRC
- MSI-H/dMMR status by local testing
- ECOG PS 0 or 1

Stratification factors:
- Prior lines of treatment (0 vs 1 vs ≥ 2)
- Primary tumor location (right vs left)



Dual primary endpoints in patients with centrally confirmed MSI-H/dMMR status[d]:
- PFS by BICR[e] (NIVO + IPI vs chemo in the 1L setting)
- PFS by BICR[e] (NIVO + IPI vs NIVO across all lines)

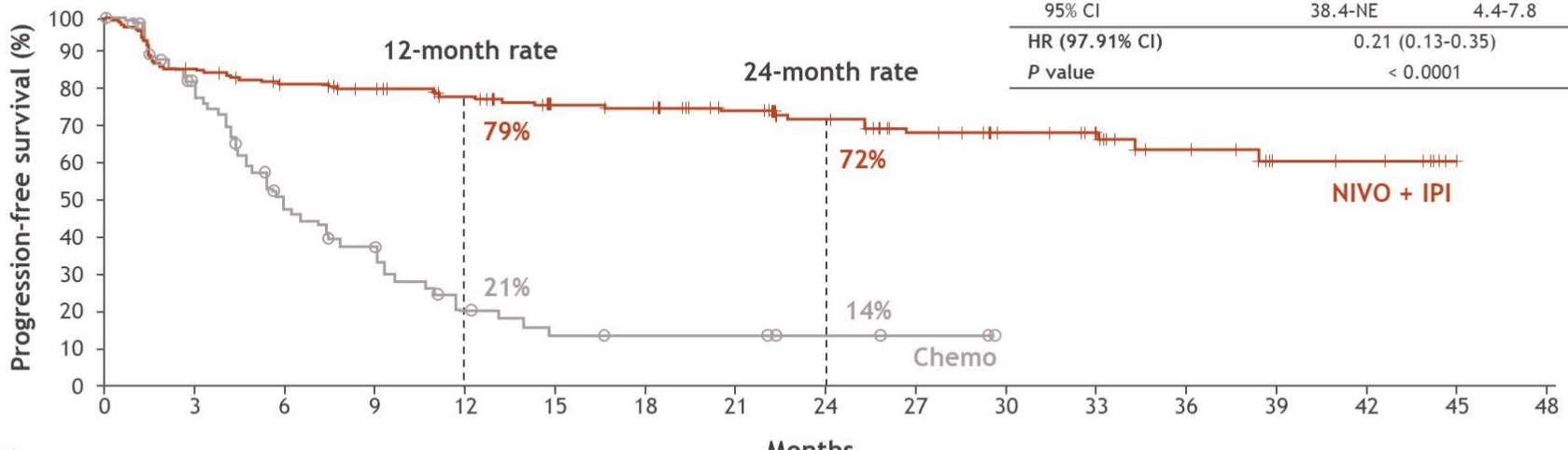
Other select endpoints:
- Safety
- OS; ORR by BICR[e]; PROs

- At data cutoff (October 12, 2023), the median follow-up[f] was 24.3 months

[a]ClinicalTrials.gov. NCT04008030. [b]Patients with ≥ 2 prior lines are randomized only to the NIVO or NIVO + IPI arms. [c]Patients receiving investigator's choice of chemotherapy are eligible to receive NIVO + IPI upon progression (crossover treatment). [d]Confirmed using either immunohistochemistry and/or polymerase chain reaction-based tests. [e]Evaluated using RECIST v1.1. [f]Time between randomization and last known date alive or death.

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	



No. at risk

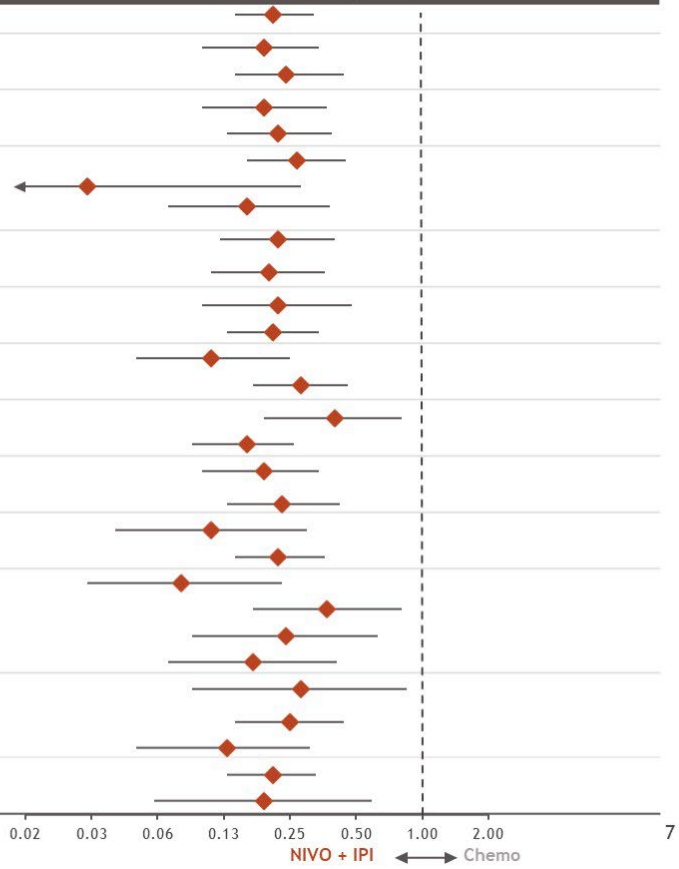
NIVO + IPI	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemo	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

- PFS benefit with NIVO + IPI vs chemo was robust and consistent across the sensitivity analyses, including PFS by BICR in 1L all randomized patients (HR, 0.32; 95% CI, 0.23-0.46)

[a]Per BICR. [b]Median follow-up, 24.3 months.

Progression-free survival subgroup analysis

Category (1L centrally confirmed MSI-H/dMMR)	Subgroup	Median PFS,[a] mo		Unstratified HR
		NIVO + IPI	Chemo	
Overall (N = 255)		NR	5.9	0.21
Age, years	< 65 (n = 138)	NR	5.7	0.19
	≥ 65 (n = 117)	NR	5.9	0.24
Sex	Male (n = 117)	NR	5.9	0.19
	Female (n = 138)	NR	6.2	0.22
Region	US/Canada/Europe (n = 167)	NR	5.7	0.27
	Asia (n = 28)	NR	7.4	0.03
	Rest of world (n = 60)	NR	6.2	0.16
ECOG PS	0 (n = 142)	NR	9.0	0.22
	≥ 1 (n = 113)	NR	4.2	0.20
Tumor sidedness	Left (n = 70)	NR	4.4	0.22
	Right (n = 185)	NR	7.1	0.21
Liver metastases[a]	Yes (n = 87)	NR	5.9	0.11
	No (n = 166)	NR	5.4	0.28
Lung metastases[a]	Yes (n = 53)	13.2	4.9	0.40
	No (n = 200)	NR	6.2	0.16
Peritoneal metastases[a]	Yes (n = 115)	NR	4.4	0.19
	No (n = 138)	NR	7.4	0.23
Tumor cell PD-L1 expression	≥ 1% (n = 55)	NR	3.4	0.11
	< 1% (n = 191)	NR	6.5	0.22
BRAF/KRAS/NRAS mutation status	*BRAF/KRAS/NRAS* all wild type (n = 58)	34.3	5.4	0.08
	BRAF mutant (n = 72)	NR	9.2	0.37
	KRAS or *NRAS* mutant (n = 45)	NR	5.7	0.24
	Unknown (n = 74)	NR	4.9	0.17
Lynch syndrome	Yes (n = 31)	NR	7.4	0.28
	No (n = 152)	NR	6.2	0.25
	Unknown (n = 66)	NR	5.5	0.13
Prior surgery related to current cancer	Yes (n = 222)	NR	7.1	0.21
	No (n = 33)	NR	3.0	0.19

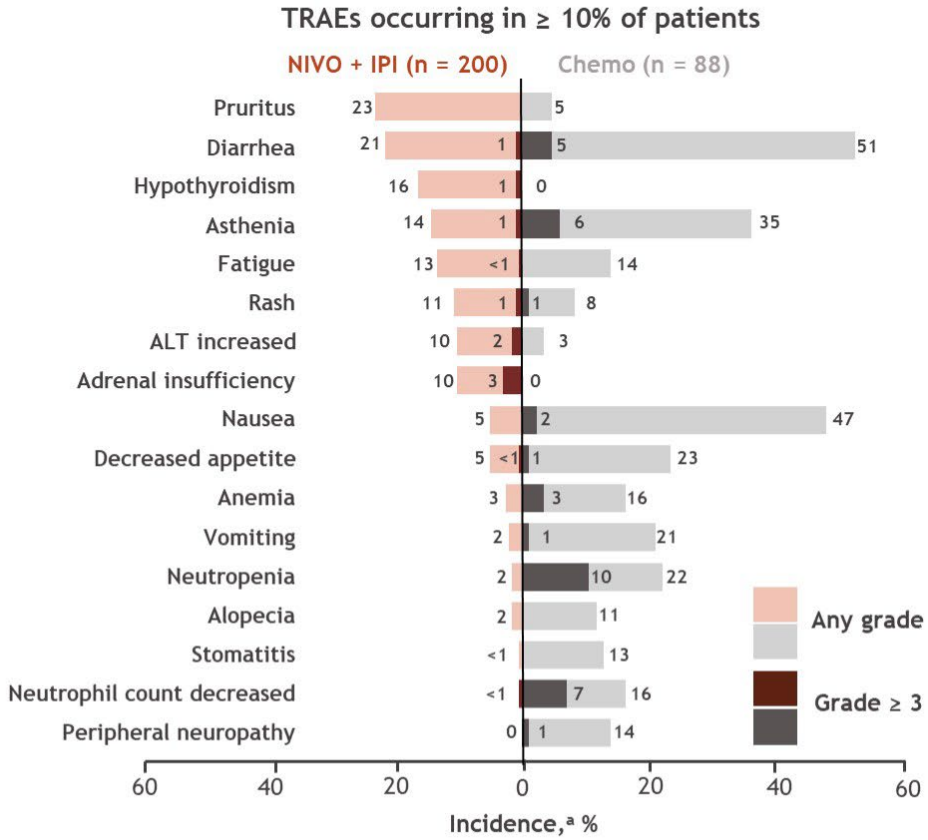


[a]Per BICR.

VANDERBILT UNIVERSITY MEDICAL CENTER

Andre, ASCO GI 2024

Treatment-related adverse events



1L all treated patients	NIVO + IPI (n = 200)		Chemo (n = 88)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs,[a] n (%)				
Any TRAEs	160 (80)	46 (23)	83 (94)	42 (48)
Serious TRAEs	38 (19)	32 (16)	17 (19)	14 (16)
TRAEs leading to discontinuation	33 (17)	23 (12)	28 (32)	9 (10)
Treatment-related deaths, n (%)	2 (1)[b]		0 (0)[c]	
IMAEs,[d] n (%)				
Non-endocrine events				
Diarrhea/colitis	13 (7)	9 (5)	1 (1)	0
Hepatitis	11 (6)	6 (3)	0	0
Rash	11 (6)	3 (2)	0	0
Pneumonitis	4 (2)	3 (2)	0	0
Endocrine events				
Hypothyroidism/thyroiditis	34 (17)	3 (2)	1 (1)	0
Adrenal insufficiency	21 (11)	7 (4)	0	0
Hyperthyroidism	18 (9)	0	1 (1)	0
Hypophysitis	10 (5)	5 (3)	0	0

[a]Includes events reported between first dose and 30 days after last dose of study therapy. [b]Includes 1 event each of myocarditis and pneumonitis. [c]One death (acute myocarditis) was related to crossover treatment. [d]Includes events reported within 100 days of last dose of study therapy reported in ≥ 2% of patients.

Update on Patient Case

- After discussion of pros and cons, decided to send ctDNA (tumor-informed) and start adjuvant FOLFOX
- Obtained new postop staging scans -> omental deposits
- Diagnostic laparoscopy with biopsy confirmed presence of metastatic disease
- Of note, tumor-informed ctDNA testing negative
- Started pembrolizumab – patient having great response to therapy, minimal side effects

Key Takeaways

- Circulating tumor DNA assays are in rapid development phase, more clinical trial data needed
  - Each assay must be validated for use!
  - Pros and cons (including usefulness and potential for incorrect information) must be discussed with patients
  - Current limitations in how ctDNA can be helpful in making treatment decisions
- Both IO monotherapy and doublet combinations are SOC in MSI-H mCRC
  - Awaiting head to head nivo/ipi vs. nivo data (CM 8HW)
  - Risk/benefit ratio including toxicity and efficacy must be considered in treatment decisions