Developments in Colorectal Cancer: 2021

VANDERBILT-INGRAM CANCER CENTER

- Cathy Eng, MD, FACP, FASCO
- David H. Johnson Chair in Surgical and Medical Oncology
- Professor of Medicine, Hematology and Oncology
- Co-Director, GI Oncology
- Co-Leader, Gastrointestinal Cancer Research Program
- Director, Young Adults Cancer Program

- June 19, 2021

- Contact Info: cathy.eng@vumc.org
- Twitter: @cathyengmd
- FB: cathy eng-mdcancer
- www.youngadultswithcancer.org

Disclosures:

- Consulting
  - Apexigen
  - Bayer
  - Gilead
  - GSK
  - Hookipa
  - Karyopharm Merck
- Research grants:
  - Hutchmed
  - Merck
  - Pfizer

Discussion Points:

- mCRC subsets:
  - MSI-H
    - Keynote 177
    - Checkmate 042
  - BRAF MT
    - BEACON
    - BREAKWATER
  - HER-2 amplified
    - DESTINY
  - EGFR resistance:
    - Chronos
  - All-comers:
    - FRESCO-2
- Rectal cancer - OPRA

KEYNOTE-177: Phase 3 Randomized Study of Pembrolizumab Versus Chemotherapy for Microsatellite Instability-High Advanced Colorectal Cancer

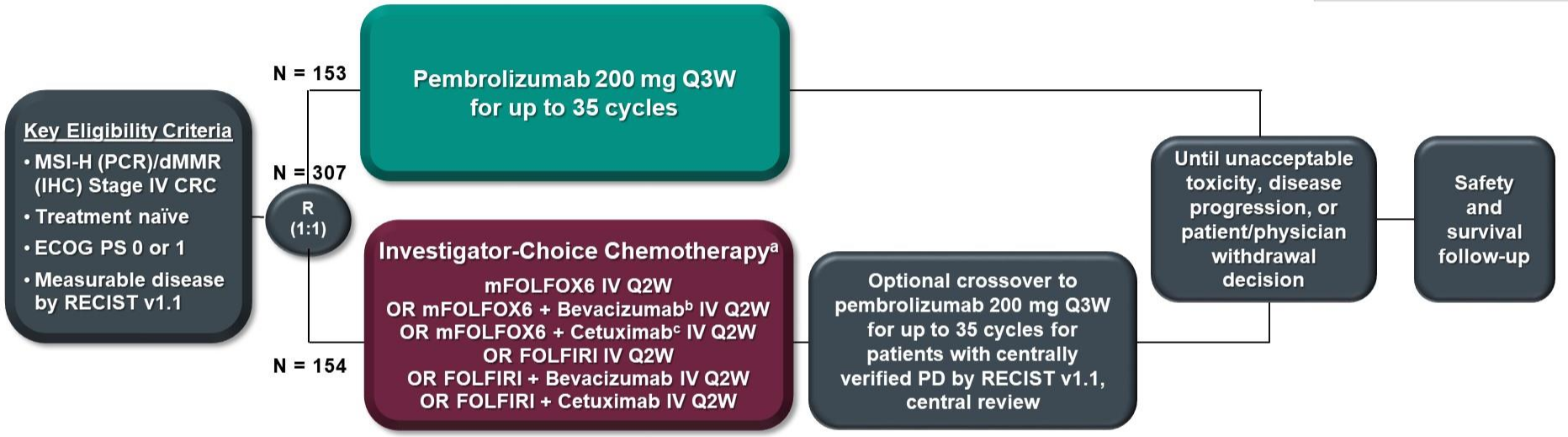
Kai-Keen Shiu,[1] Thierry André,[2] Tae Won Kim,[3] Benny Vittrup Jensen,[4] Lars Henrik Jensen,[5] Cornelis Punt,[6] Denis Smith,[7] Rocio Garcia-Carbonero,[8] Manuel Benavides,[9] Peter Gibbs,[10] Christelle de la Fouchardiere,[11] Fernando Rivera,[12] Elena Elez,[13] Johanna Bendell,[14] Dung T. Le,[15] Takayuki Yoshino,[16] Ping Yang,[17] Mohammed Farooqui,[18] Patricia Marinello,[18] and Luis A. Diaz Jr[19]

[1]University College Hospital, NHS Foundation Trust, London, United Kingdom; [2]Sorbonne Université and Hôpital Saint Antoine, Paris, France; [3]Asan Medical Center, University of Ulsan, Seoul, Republic of Korea; [4]Herlev and Gentofte Hospital, Herlev, Denmark; [5]University Hospital of Southern Denmark, Vejle, Denmark; [6]Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, Netherlands; [7]Bordeaux University Hospital, Bordeaux, France; [8]Hospital Universitario 12 de Octubre, Imas12, CNIO, UCM, Madrid, Spain; [9]Hospital Regional Universitario de Malaga, Malaga, Spain; [10]Western Health, St Albans, Australia; [11]Léon Bérard Center, Lyon, France; [12]Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain; [13]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [14]Sarah Cannon Research Institute, Nashville, TN, USA; [15]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [16]National Cancer Center Hospital East, Kashiwa, Japan; [17]MSD China, Beijing, China; [18]Merck & Co., Inc. Kenilworth, NJ, USA; [19]Memorial Sloan Kettering Cancer Center, New York, NY, USA

Presented By Kai-Keen Shiu at 2021 Gastrointestinal Cancers Symposium

KEYNOTE-177 Study Design (NCT02563002)

Place video here



- Dual-Primary endpoints: PFS per RECIST v1.1 per blinded independent central review (BICR) and OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, safety
- Exploratory endpoints: DOR per RECIST v1.1 by BICR, PFS2, HRQoL
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

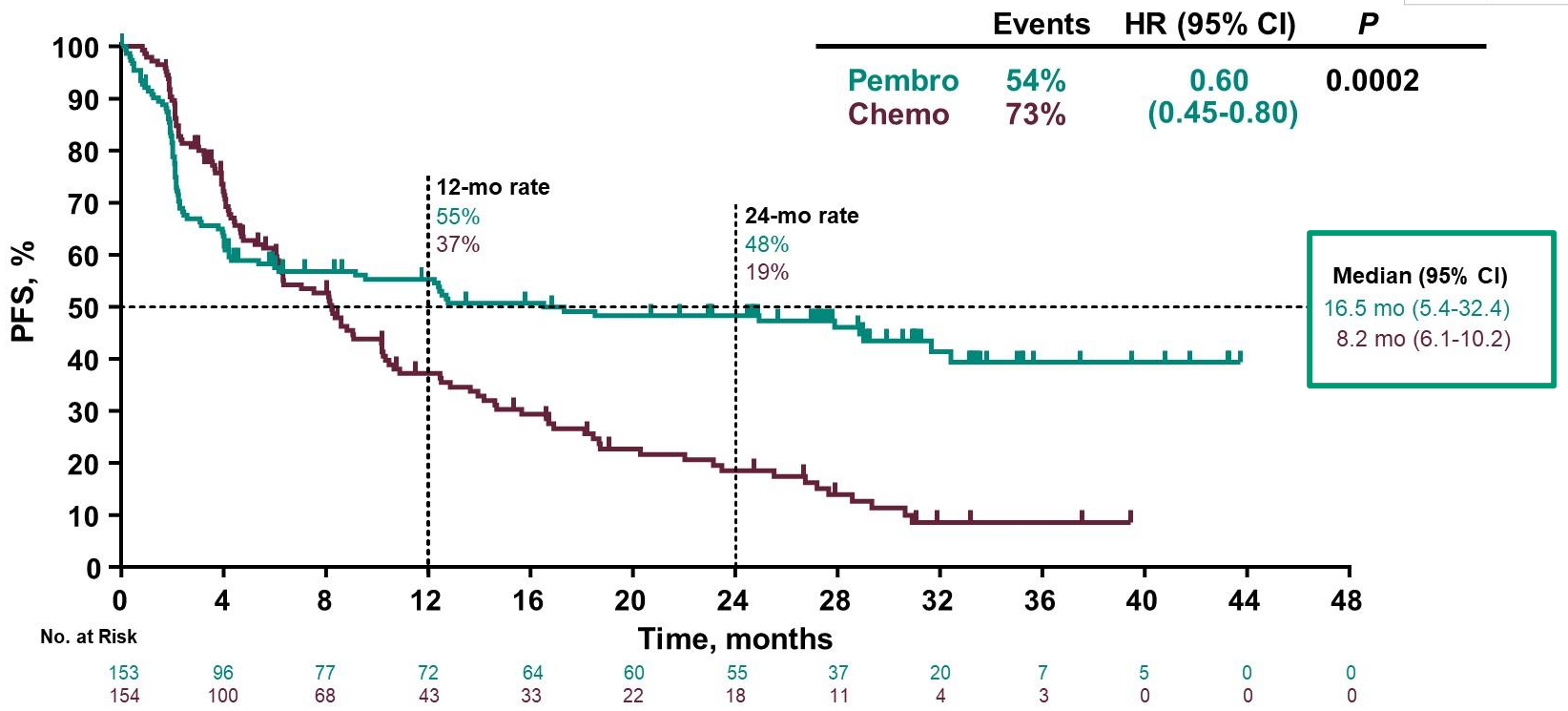
Baseline Characteristics

	Pembrolizumab N = 153	Chemotherapy N = 154
Age, median (range), years	63.0 (24-93)	62.5 (26-90)
Male	71 (46)	82 (53)
ECOG PS 0	75 (49)	84 (55)
Metachronous disease	80 (52)	74 (48)
Hepatic metastases	71 (46)	54 (35)
Region		
Asia	22 (14)	26 (17)
Western Europe/North America	109 (71)	113 (73)
Rest of World	22 (14)	15 (10)
Primary tumor location		
Right	102 (67)	107 (70)
Left	46 (30)	42 (27)
Other/Missing	5 (3)	5 (3)
Prior systemic therapy		
Adjuvant	33 (22)	37 (24)
Neoadjuvant (peri-operative)	5 (3)	8 (5)
None	115 (75)	109 (71)
Mutation status		
BRAF, KRAS, NRAS all wildtype	34 (22)	35 (23)
BRAF V600E mutant	34 (22)	43 (28)
KRAS or *NRAS* mutant	33 (22)	41 (27)
Not evaluable[a]	52 (34)	38 (25)

[a]Patients not evaluable for *BRAF, KRAS, NRAS* mutation if at least one of the mutation statuses was undetermined or missing, or the type of *BRAF* mutation was non V600E. Data cut-off: 19Feb2020.

Progression-Free Survival

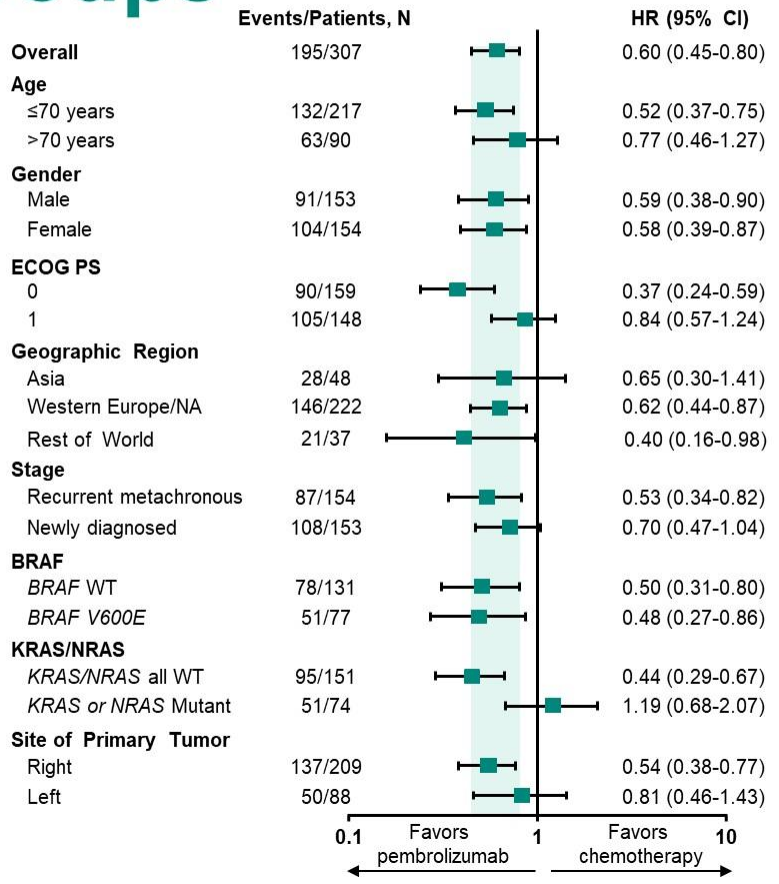
Place video here



Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR. Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

Progression-Free Survival in Key Subgroups

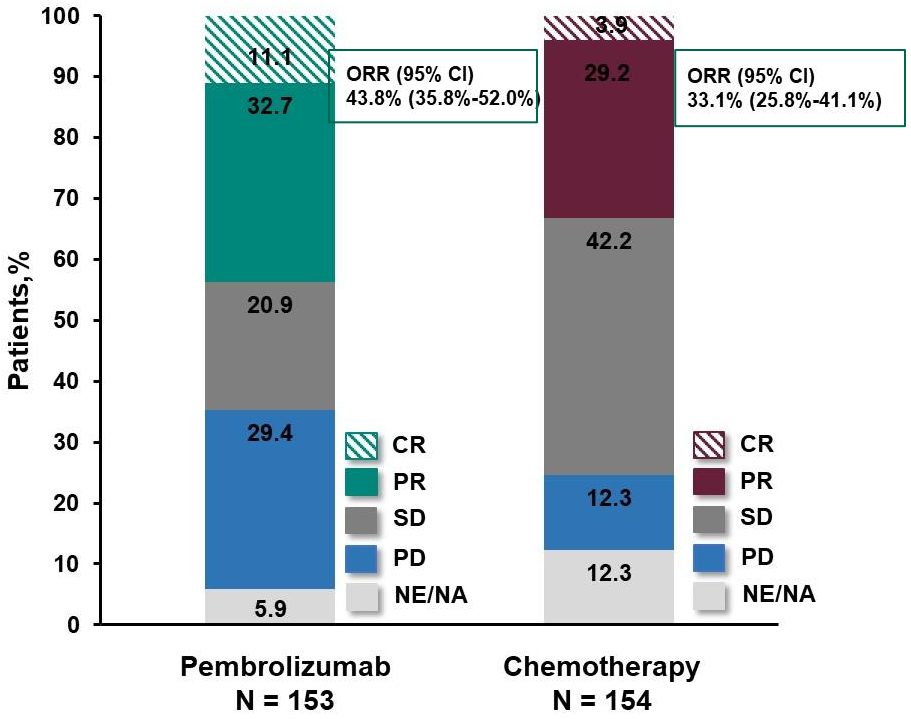
Place video here

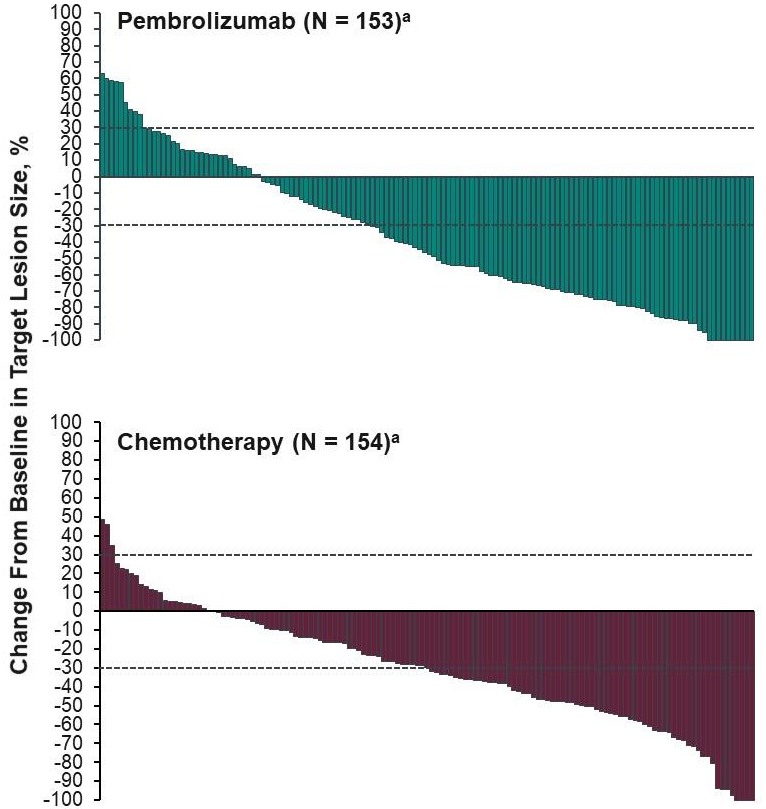


NA, North America; Data cut-off: 19Feb2020.

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.

Final Overall Survival for the Phase 3 KN177 Study: Pembrolizumab Versus Chemotherapy in Microsatellite Instability-High/Mismatch Repair Deficient (MSI-H/dMMR) Metastatic Colorectal Cancer (mCRC)

Thierry André,[1] Kai-Keen Shiu,[2] Tae Won Kim,[3] Benny Vittrup Jensen,[4] Lars Henrik Jensen,[5] Cornelis Punt,[6] Denis Smith,[7] Rocio Garcia-Carbonero,[8] Julia Alcaide-Garcia,[9] Peter Gibbs,[10] Christelle de la Fouchardiere,[11] Fernando Rivera,[12] Elena Elez,[13] Johanna Bendell,[14] Dung T. Le,[15] Takayuki Yoshino,[16] Wenyan Zhong,[17] David Fogelman,[18] Patricia Marinello,[18] Luis A. Diaz Jr[19]

[1]Sorbonne Université and Hôpital Saint Antoine, Paris, France; [2]University College Hospital, NHS Foundation Trust, London, United Kingdom; [3]Asan Medical Center, University of Ulsan, Seoul, Republic of Korea; [4]Herlev and Gentofte Hospital, Herlev, Denmark; [5]University Hospital of Southern Denmark, Vejle, Denmark; [6]Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, Netherlands; [7]Bordeaux University Hospital, Bordeaux, France; [8]Hospital Universitario 12 de Octubre, Imas12, CNIO, UCM, Madrid, Spain; [9]Hospital Regional Universitario de Malaga, Malaga, Spain; [10]Western Health, St Albans, Australia; [11]Léon Bérard Center, Lyon, France; [12]Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain; [13]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [14]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [15]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [16]National Cancer Center Hospital East, Kashiwa, Japan; [17]MSD China, Beijing, China; [18]Merck & Co., Inc. Kenilworth, NJ, USA; [19]Memorial Sloan Kettering Cancer Center, New York, NY, USA

Cross Over and Subsequent Therapy

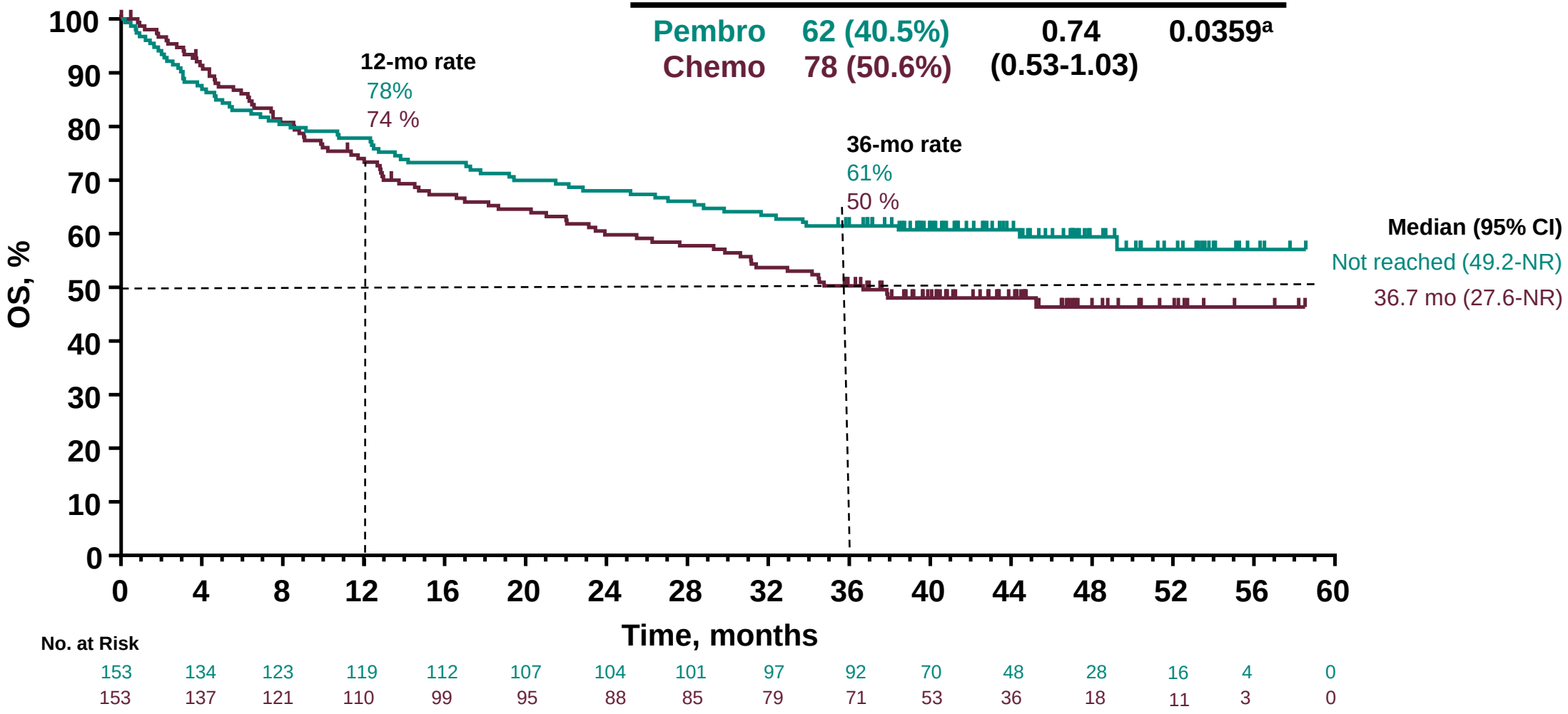
- 56 of 154 (**36%**) patients in the chemotherapy arm crossed over to receive pembrolizumab after confirmed disease progression
  - 37 additional patients received anti-PD-1/PD-L1 therapy outside of the study for an effective crossover rate of **60%** in the ITT

	Pembrolizumab N = 153	Chemotherapy N = 154
Any anti-PD-1/PD-L1 therapy, n (%)	14 (9.2)	93 (60.4)
On protocol therapy - pembrolizumab[a]	8 (5.2)	56 (36.4)
Off protocol therapies	6 (3.9)	37 (24.0)
Any non-anti-PD-1/PD-L1 therapy, n (%)	38 (24.8)	28 (18.2
Chemotherapy	35 (22.9)	20 (13.0)
VEGF inhibitor	22 (14.4)	13 (8.4)
EGFR inhibitor	9 (5.9)	5 (3.2)
Nucleosoide analog/thymidine phosphorylase inhibitor	2 (1.3)	2 (1.3)
CTLA-4 inhibitor	0	5 (3.2)
ICOS agonist	1 (0.7)	1 (0.6)
LAG-3 inhibitor	1 (0.7)	0
TIM3 inhibitor	1 (0.7)	1 (0.6)
Vaccine/viral therapy	0	2 (1.3)

[a]Including 2nd course treatment for patients randomized to pembrolizumab arm. Data cut-off: 19Feb2021.

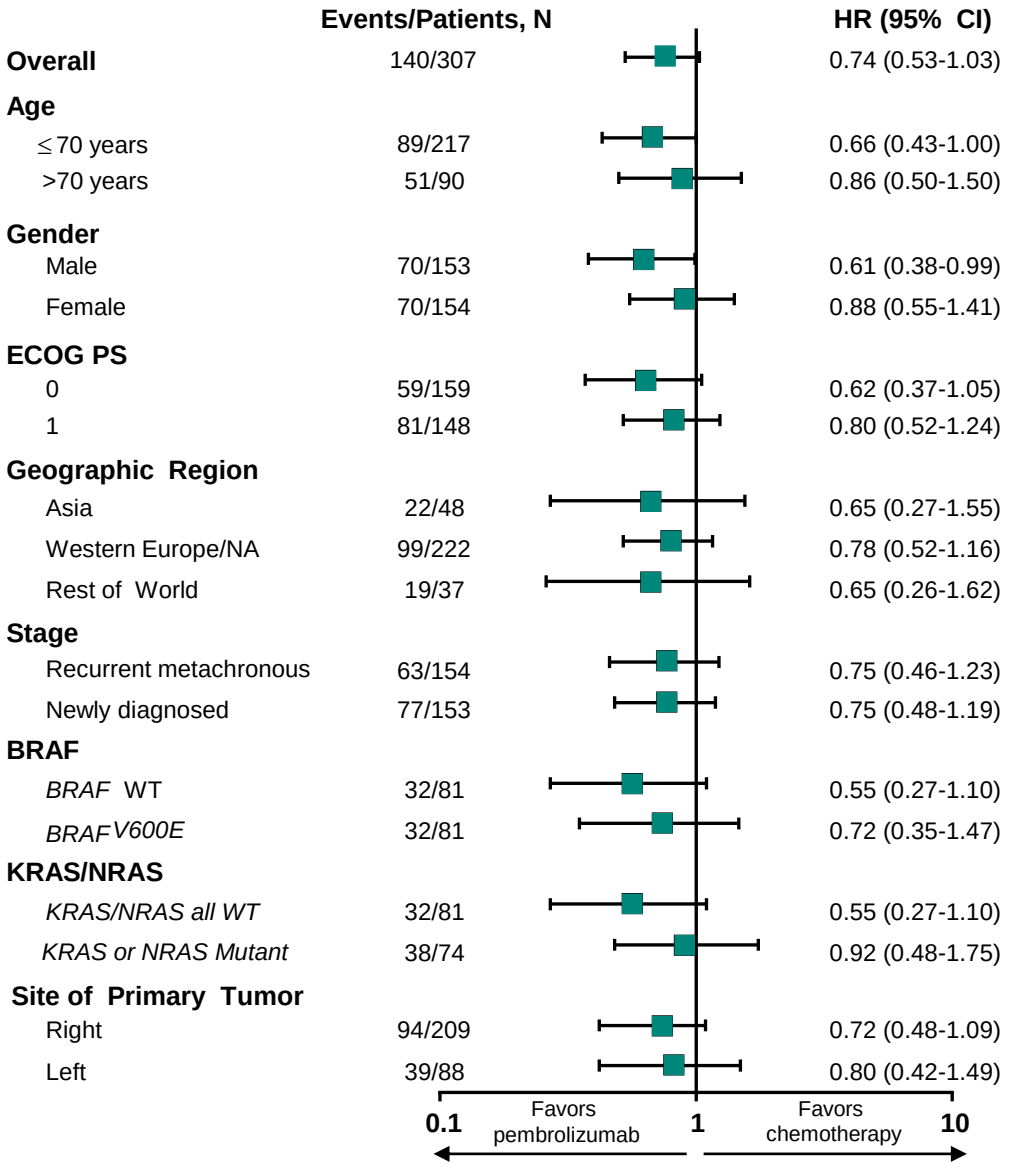
Overall Survival

	Events, n (%)	HR (95% CI)	*P*
Pembro	62 (40.5%)	0.74 (0.53-1.03)	0.0359[a]
Chemo	78 (50.6%)		



[a]**Pembrolizumab was not superior to chemotherapy for OS as one-sided α > 0.0246. Pre-specified sensitivity analyses to adjust for crossover 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-

OS in Key Subgroups



Data cut-off: 19Feb2021.

Summary and Conclusions (1)

- Pembrolizumab versus chemotherapy provided statistically superior PFS as first-line therapy for patients with MSI-H mCRC
  - Pembrolizumab versus chemotherapy met the criteria for superiority in PFS at IA2[1]
  - Superiority was not formally tested at final analysis
- Fewer treatment-related adverse events observed with pembrolizumab versus chemotherapy: grade ≥3 treatment-related events (22% vs 66%)[1]
- Pembrolizumab monotherapy provided clinically meaningful improvements in HRQoL versus chemotherapy in this population[1]
  - Limitations include open label trial and PROs as exploratory end points
  - Results are mostly limited to treatment period in first line
- Treatment with pembrolizumab versus chemotherapy is associated with a non-statistically significant reduction in mortality
  - HR for OS: 0.74 (*P* = 0.0359; did not meet threshold for significance)
  - High crossover rate from chemotherapy to anti-PD-1/PD-L1 therapies in second line of 60%

1. André T et al; *N Eng J Med* 2020;383:2207-18.

CheckMate 142 NIVO3 + IPI1 1L cohort study design

- CheckMate 142 is an ongoing, multicohort, nonrandomized phase 2 trial evaluating the efficacy and safety of NIVO-based therapies in patients with mCRC[a]

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

→ NIVO3 Q2W + IPI1 Q6W[b]

Primary endpoint:

- ORR per investigator assessment (RECIST v1.1)

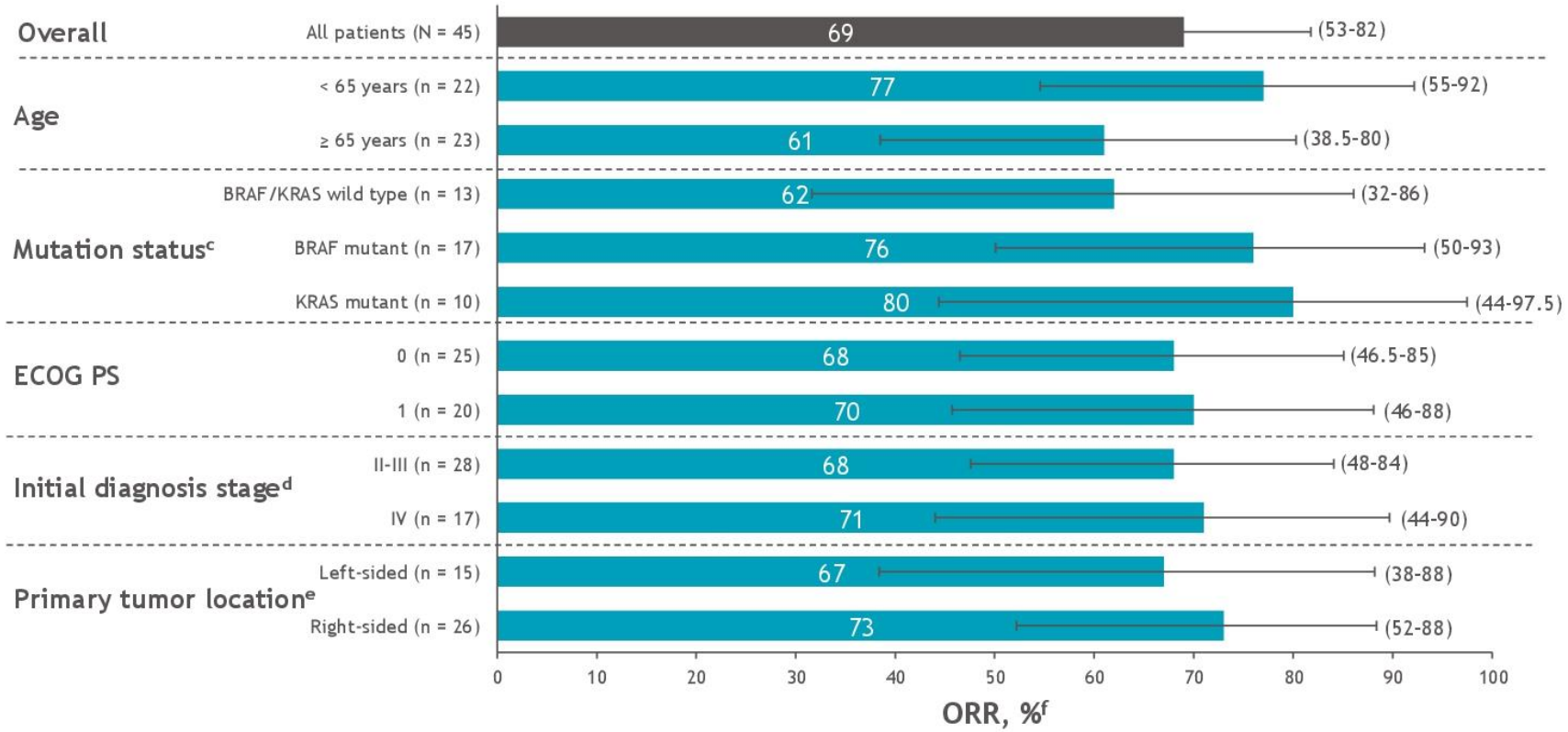
Other key endpoints:

- ORR per BICR, DCR,[c] DOR, PFS, OS, and safety

- At data cutoff (October 2019), the median duration of follow-up was 29.0 months (range, 24.2-33.7)[d]

[a]ClinicalTrials.gov number, NCT02060188. [b]Until disease progression or discontinuation in patients receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study end. [c]Patients with CR, PR, or SD for ≥ 12 weeks divided by the number of treated patients. [d]Median follow-up was defined as time from first dose to data cutoff. BICR, blinded independent central review; CR, complete response; CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; NIVO3, nivolumab 3 mg/kg; IPI1, ipilimumab 1 mg/kg; PR, partial response; SD, stable disease.

Objective response rate by subgroup[a,b]



- ORR was generally similar across evaluated subgroups and consistent with that of the overall study population

[a]Median follow-up, 29.0 months. [b]Per investigator assessment. [c]Excluded 5 patients with unknown mutation status. [d]All patients had stage IV disease at study entry. [e]Excluded 4 patients with uncategorized primary tumor location. [f]Error bars and numbers in parentheses indicate 95% CIs; evaluated subgroups had overlapping 95% CIs for ORR.

BRAF MT V600E

Encorafenib plus Cetuximab With or Without Binimetinib for *BRAF* V600E Metastatic Colorectal Cancer:

Updated Survival Results from a Randomized, 3-Arm, Phase 3 Study vs Choice of Either Irinotecan or FOLFIRI plus Cetuximab (BEACON CRC)

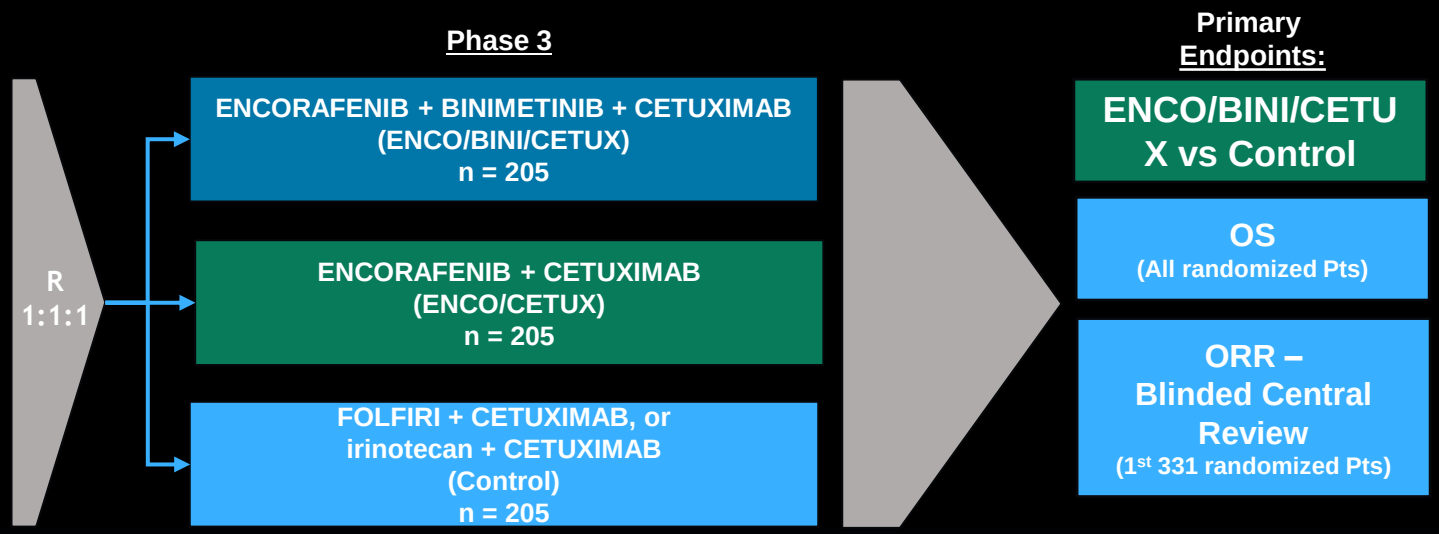
Scott Kopetz, Axel Grothey, Eric Van Cutsem, Rona Yaeger, Harpreet Wasan, Takayuki Yoshino, Jayesh Desai, Fortunato Ciardiello, Fotios Loupakis, Yong Sang Hong, Neeltje Steeghs, Tormod Kyrre Guren, Hendrik-Tobias Arkenau, Pilar Garcia-Alfonso, Ashwin Gollerkeri, Kati Maharry, Janna Christy-Bittel, and Josep Tabernero

BEACON CRC: **B**inimetinib, **E**ncorafenib, **A**nd **C**etuximab C**O**mbi**N**ed to Treat *BRAF*-mutant **C**olo**R**ectal **C**ancer

VANDERBILT-INGRAM CANCER CENTER

Study Design: BEACON

Patients with *BRAF* V600E-mutant mCRC with disease progression after 1 or 2 prior regimens; ECOG PS of 0 or 1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor



Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved)

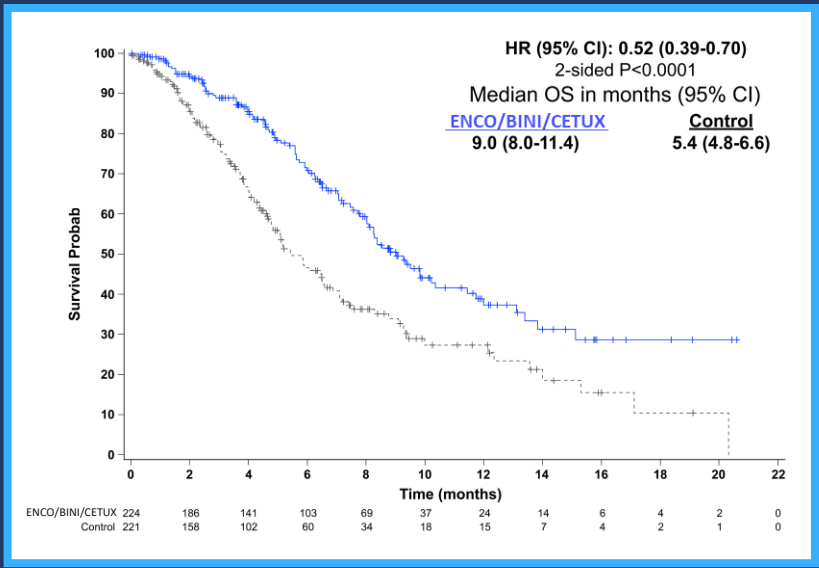
Secondary Endpoints: ENCO/CETUX vs Control and ENCO/BINI/CETUX vs ENCO/CETUX - OS & ORR, PFS, Safety, QOL

Post hoc Updated Analysis: includes 6 months of additional follow-up since cut off for primary analysis

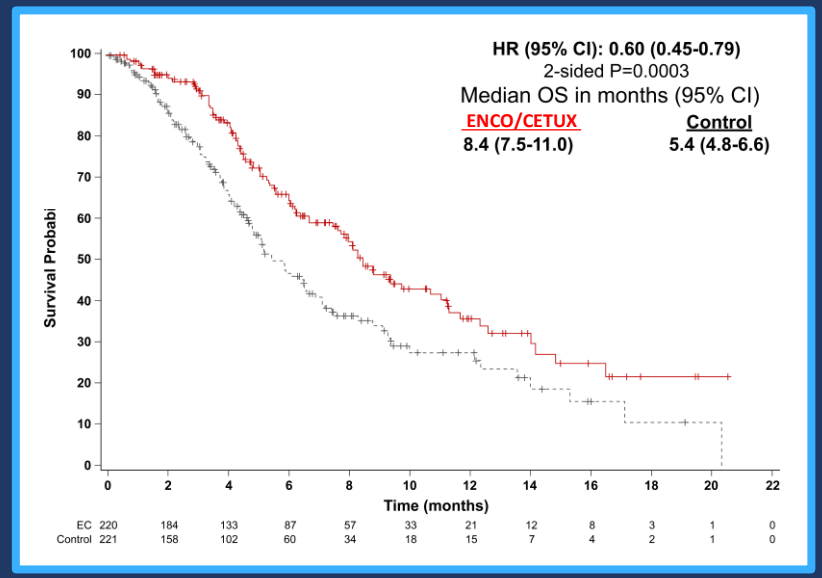
Kopetz et al: NEJM, 2019

Primary Analysis: Overall Survival and Objective Response Rate

ENCO/BINI/CETUX vs Control*



ENCO/CETUX vs Control*



Objective Response Rate (First 331 Randomized Patients)

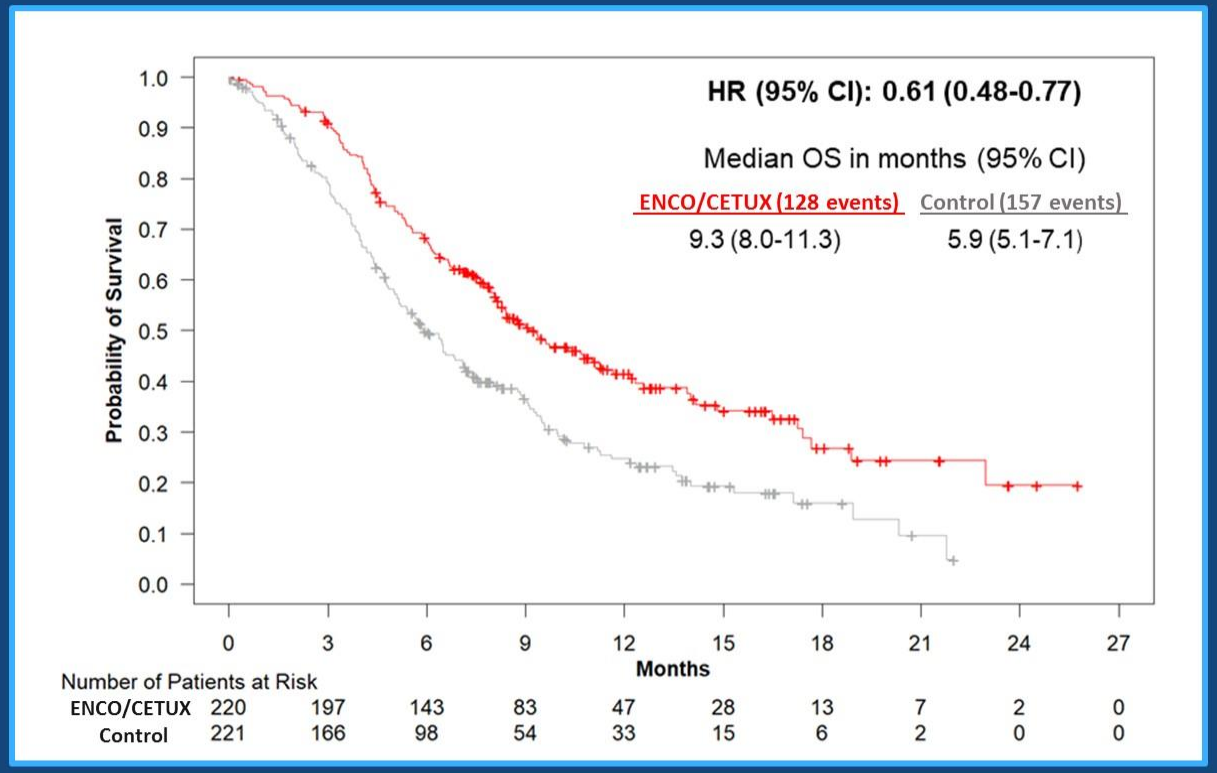
Confirmed Response by blinded central review	ENCO/BINI/CETUX N=111	ENCO/CETUX N=113	Control N=107
Objective Response Rate	**26%**	**20%**	**2%**
95% (CI)	(18%, 35%)	(13%, 29%)	(<1%, 7%)
p-value vs. Control	<0.0001	<0.0001	

Kopetz et al. N Engl J Med 2019; 381:1632-1643

*Overall survival analysis conducted in all randomized patients.

Revised FDA Indication for BRAFTOVI (4/8/2020)

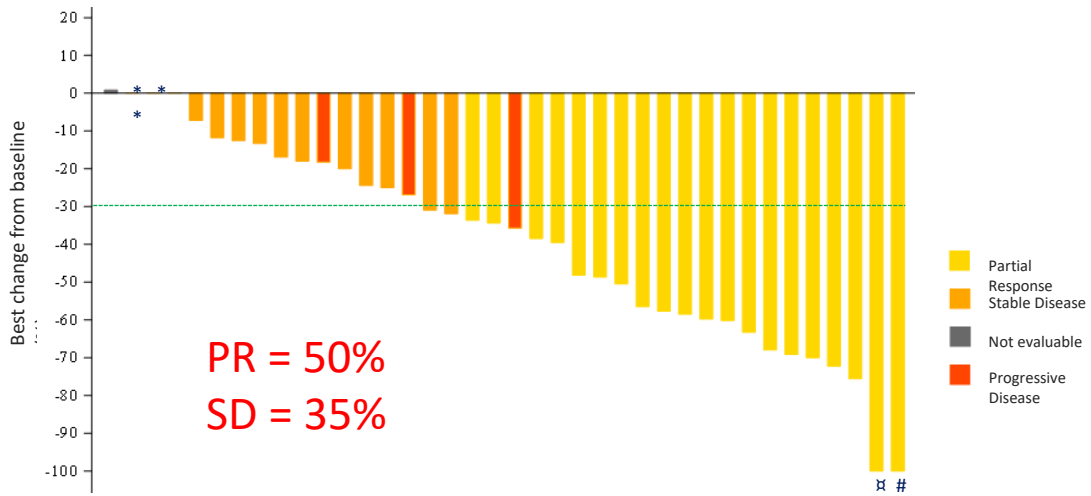
Updated Overall Survival: ENCO/CETUX vs Control



J Tabenero et al: JCO 2021

Best Percentage Change in Tumor Measurements for Stage 1: ANCHOR

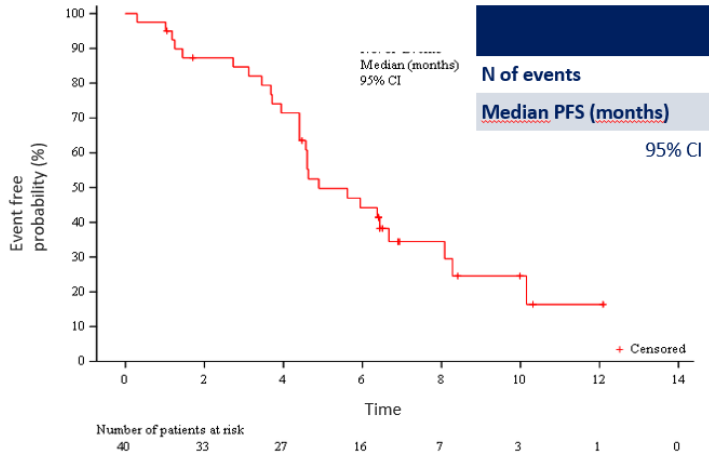
Investigator's assessment, patients evaluable for efficacy



*3 patients with best percent change from baseline=0% and have Confirmed Best Overall Response=stable disease
¤ Complete Response on target lesion but non target lesion still present
Complete Response was not confirmed at the subsequent tumor evaluation

Progression Free Survival for Stage 1: ANCHOR

Investigator's assessment, median follow-up: 4.6 months

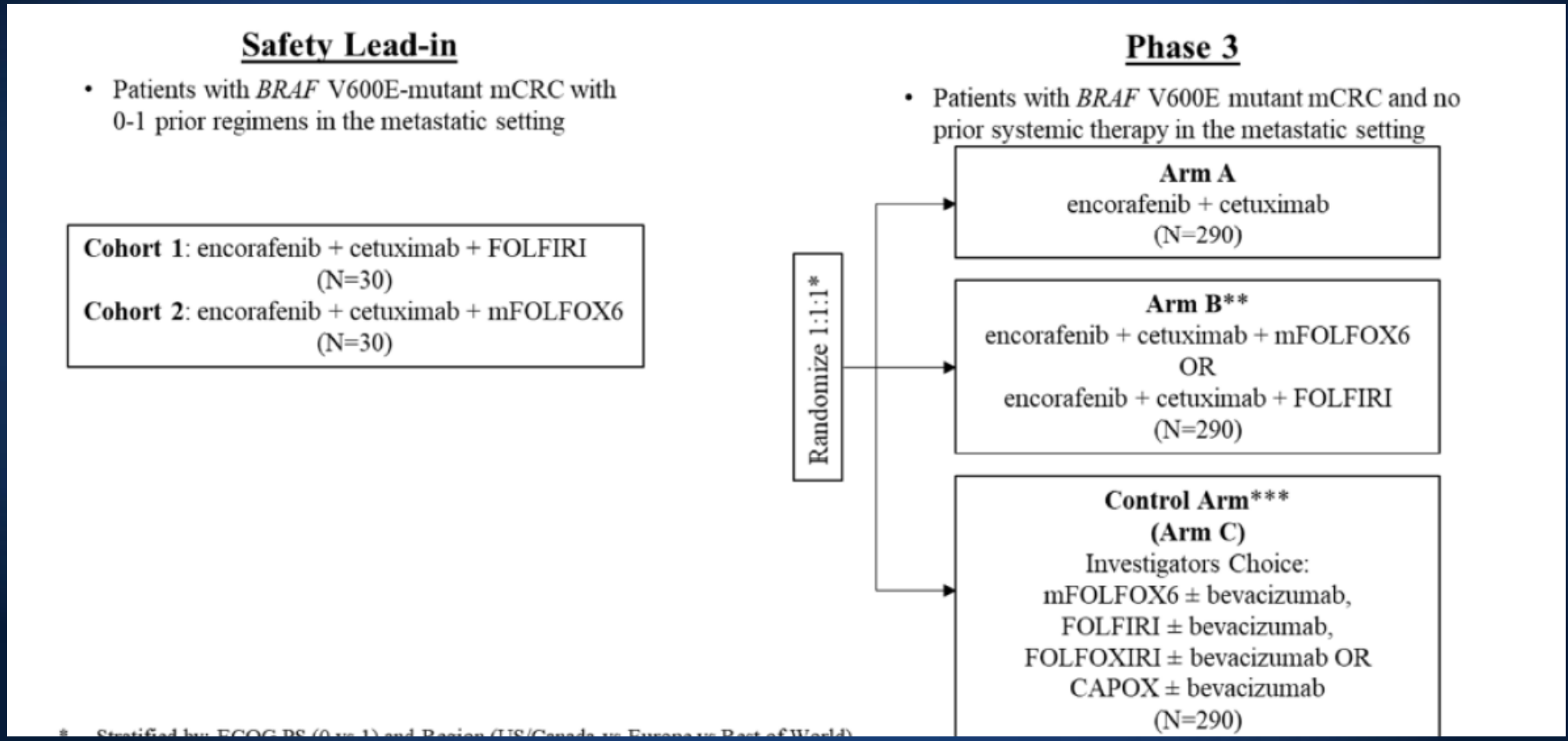


	Patients (N=40#)
N of events	27 (68%)
Median PFS (months)	4.9
95% CI	[4.4 ; 8.1]

1 patient has been excluded from the efficacy analysis as the BRAF mutation was not confirmed by central lab

Note: the data have not been fully cleaned due to Covid-19 pandemic.

FIRST-LINE ENCORAFENIB PLUS CETUXIMAB +/- CHEMOTHERAPY VERSUS Chemotherapy METASTATIC BRAF V600E-MUTANT COLORECTAL CANCER: BREAKWATER Trial



NCT04607421

HER-2 AMPLIFICATION

DESTINY-CRC01 Study Design

An open-label, multicenter, phase 2 study (NCT03384940)

6.4 mg/kg dose of T-DXd administered Q3W (all cohorts)

Patients

- Unresectable and/or metastatic CRC
- HER2 expressing (central confirmation)
- *RAS/BRAF*^{V600E} wild type
- ≥2 prior regimens
- Prior anti-HER2 treatment was allowed
- Excluded patients with a history of or current/suspected interstitial lung disease

Cohort A:
HER2 Positive
(IHC3+ or IHC2+/ISH+)
n = 53

Cohort B[a]:
HER2 IHC2+/ISH−
n = 15

Cohort C[a]:
HER2 IHC1+
n = 18

Primary endpoint

- ORR[b] (cohort A)

Secondary endpoints

- ORR[b] (cohorts B and C)
- PFS
- OS
- DOR
- DCR
- Safety and tolerability

Primary analysis
(Data cutoff: August 9, 2019)

Final analysis
(Data base lock: December 28, 2020)

Primary analysis of cohort A[1]

- Results yielded promising antitumor activity and a manageable safety profile
- The median follow-up was 27.1 weeks at data cutoff

Patient disposition at final analysis[c]

- No patients remain on treatment
- At the end of the study, median follow-up was 62.4 weeks for cohort A, 27.0 weeks for cohort B and 16.9 weeks for cohort C

CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; q3w, every three weeks; RECIST, Response Evaluation Criteria in Solid Tumors; T-DXd, trastuzumab deruxtecan.

[a]A futility monitoring analysis was done after ≥20 patients in Cohort A had 12 weeks of follow-up to inform opening of Cohorts B and C. [b]ORR was based on RECIST version 1.1 in all cohorts. [c]Data presented are from the full analysis set.

1. Siena S et al. *Lancet Oncol*. 2021;S1470-2045(21)00086-3.

Baseline Characteristics

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 86)
Age, median (range), years	57.0 (27-79)	62.0 (37-78)	58.5 (43-79)	58.5 (27-79)
Female, %	52.8	33.3	38.9	46.5
Region, %				
Europe	52.8	60.0	50.0	53.5
Asia	28.3	20.0	44.4	30.2
North America	18.9	20.0	5.6	16.3
ECOG performance status, %				
0	69.8	53.3	50.0	62.8
1	30.2	46.7	44.4	36.0
2	0	0	5.6	1.2
Sum of target lesions, median, cm	8.1	8.1	10.2	9.0
Primary tumor site, %[a]				
Left	88.6	93.3	94.4	90.7
Right	11.4	6.7	5.6	9.3

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.
[a]Left: rectum, sigmoidal, descending; Right: cecum, ascending, transverse.

Baseline Characteristics (cont)

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 86)
Microsatellite status, %[a]				
MSI-H	0	0	0	0
Microsatellite stable	81.1	93.3	66.7	80.2
Unknown	18.9	6.7	33.3	19.8
***RAS* wild type, %[a,b]**	98.1	93.3	100	97.7
***BRAF*^{V600E} wild type, %[a,c]**	100	100	94.4	98.8
HER2 status, %[d]				
IHC 3+	75.5	0	0	46.5
IHC 2+	24.5	100	0	32.6
IHC 1+	0	0	100	20.9
ISH+	98.1[e]	0	22.2	65.1
ISH–	0	100	77.8	33.7

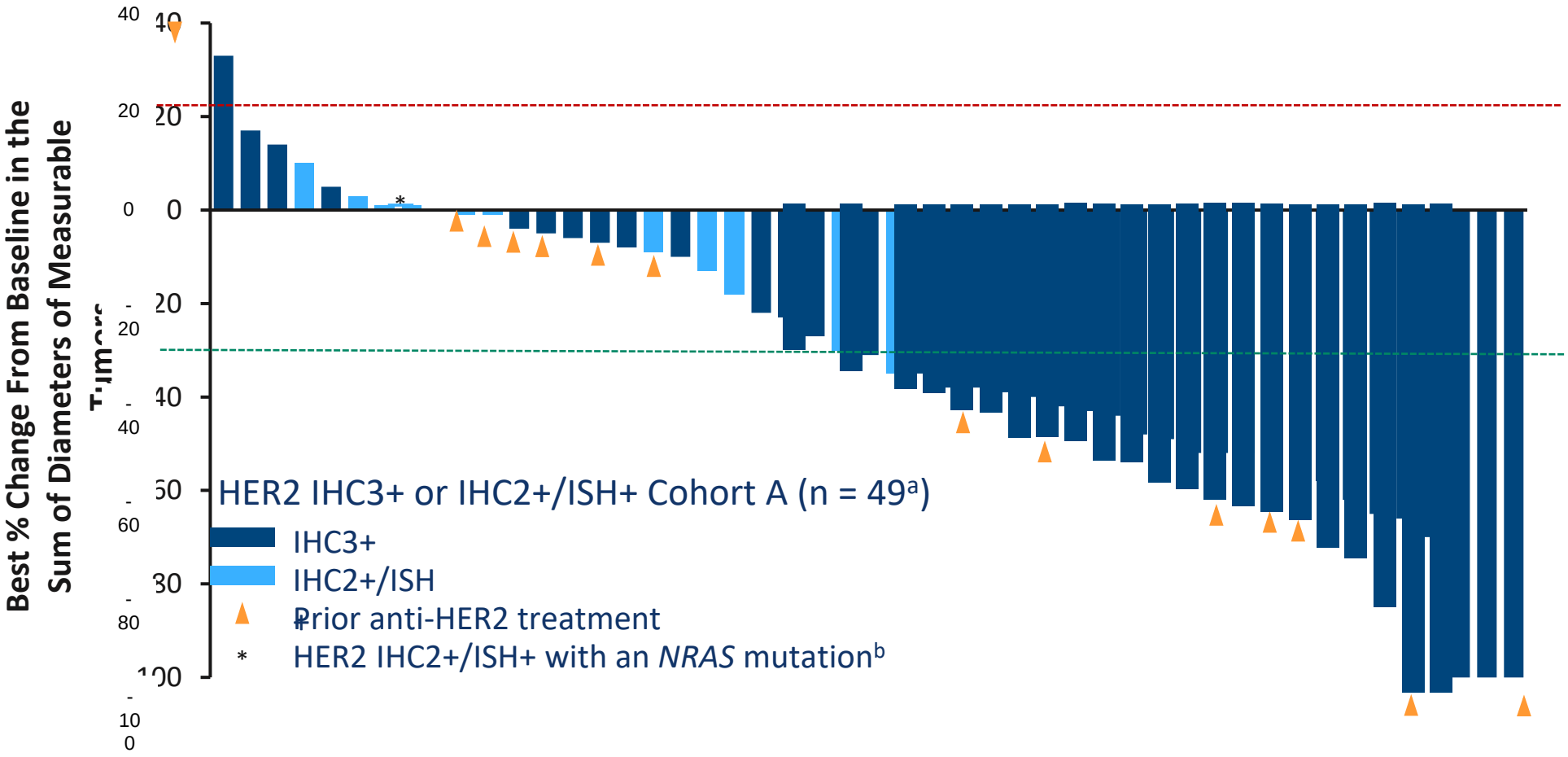
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; MSI-H, microsatellite instability status-high.
[a]By local assessment. [b]1 patient cohort A had an *NRAS* mutation; 1 patient in cohort B was not examined. [c]1 patient in cohort C was not examined. [d]By central assessment. Sums may not total 100% due to rounding. [e]1 patient was non-evaluable for ISH testing.

Efficacy Results

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
Confirmed ORR by ICR, n (%) [95% CI]	**24 (45.3)** [31.6-59.6]	0 [0.0-21.8]	0 [0.0-18.5]
CR	0	0	0
PR	24 (45.3)	0	0
SD	20 (37.7)	9 (60.0)	4 (22.2)
PD	5 (9.4)	5 (33.3)	10 (55.6)
Not evaluable[a]	4 (7.5)	1 (6.7)	4 (22.2)
Disease control rate, % (95% CI)	83.0 (70.2-91.9)	60.0 (32.3-83.7)	22.2 (6.4-47.6)
Median duration of response, (95% CI) months	7.0 (5.8-9.5)	NE (NE-NE)	NE (NE-NE)
Median treatment duration, (95% CI) months	5.1 (3.9-7.6)	2.1 (1.4-2.6)	1.4 (1.3-1.5)

CR, complete response; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; NE, non-evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Patients were missing postbaseline scans.

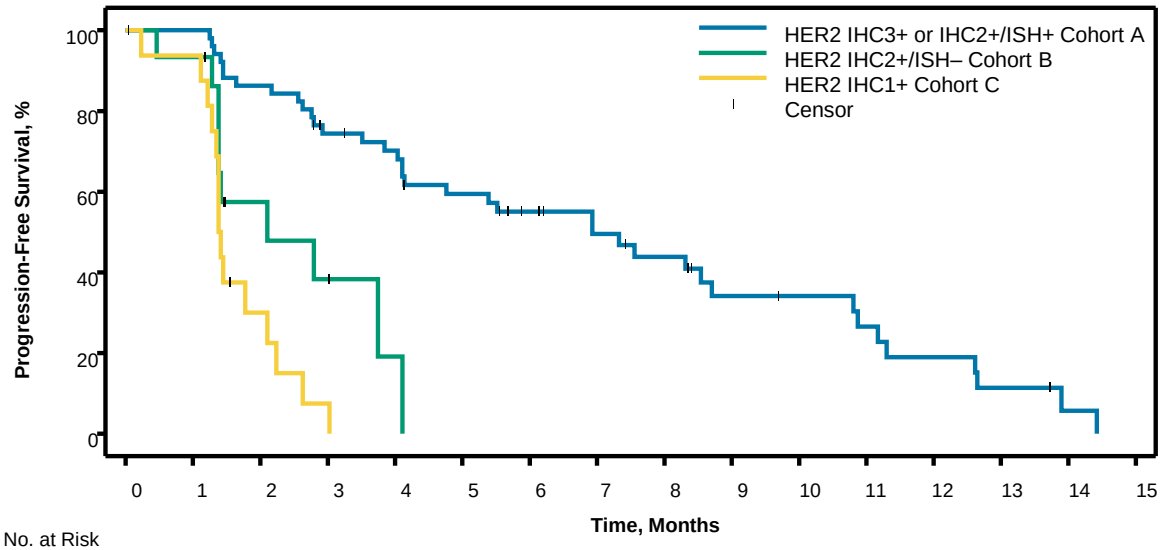
Best Change in Tumor Size in Cohort A



HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.
The line at 20% indicates progressive disease. The line at -30% indicates partial response. [a]4 patients from the full analysis set were excluded since 1 patient had no measurable target lesion and 3 patients had no postbaseline data. [b]By local assessment.

Progression-Free and Overall Survival

Progression-Free Survival

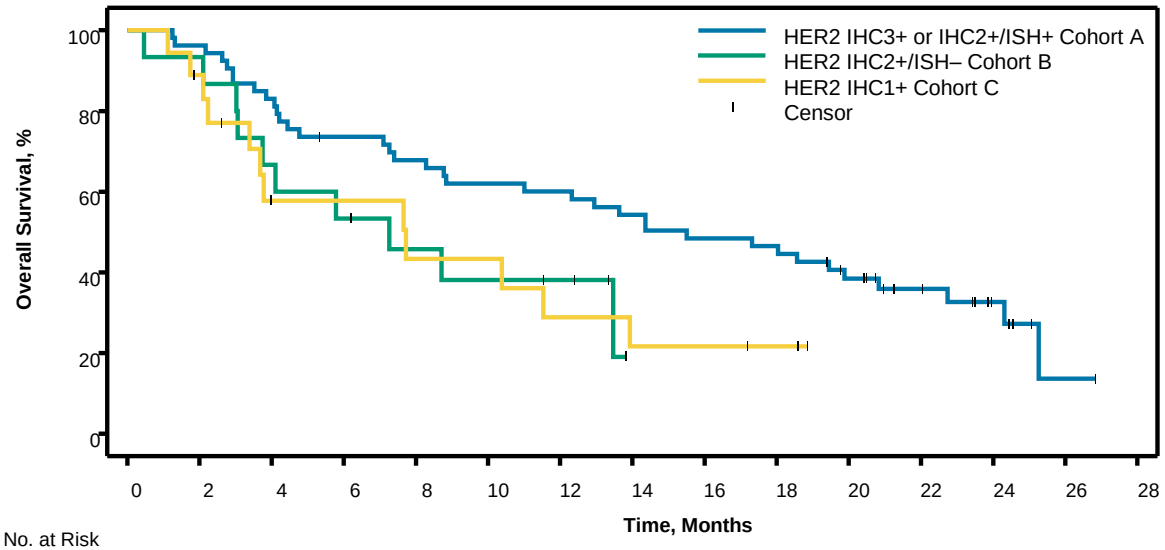


No. at Risk

Cohort A	53	51	44	36	33	27	22	18	15	10	9	7	5	3	1	0
Cohort B	15	14	6	4	1	0	0	0	0	0	0	0	0	0	0	0
Cohort C	18	15	4	1	0	0	0	0	0	0	0	0	0	0	0	0

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
mPFS (95% CI), months	6.9 (4.1-8.7)	2.1 (1.4-4.1)	1.4 (1.3-2.1)

Overall Survival



No. at Risk

Cohort A	53	51	44	38	35	32	31	28	25	24	18	12	6	1	0	
Cohort B	15	14	10	8	6	5	4	0	0	0	0	0	0	0	0	
Cohort C	18	15	8	8	6	6	4	3	3	2	0	0	0	0	0	

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
mOS (95% CI), months	15.5 (8.8-20.8)	7.3 (3.0-NE)	7.7 (2.2-13.9)

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mOS, median overall survival; mPFS, median progression-free survival; NE, not-evaluable.

TEAEs in ≥20% of Patients

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 86)	
n (%)	Any Grade	Any Grade	Any Grade	Any Grade	Grade ≥3
Patients with any TEAE	**53 (100)**	**15 (100)**	**18 (100)**	**86 (100)**	**56 (65.1)**
Nausea	37 (69.8)	9 (60.0)	7 (38.9)	53 (61.6)	5 (5.8)
Anemia	21 (39.6)	4 (26.7)	6 (33.3)	31 (36.0)	12 (14.0)
Fatigue	21 (39.6)	7 (46.7)	3 (16.7)	31 (36.0)	1 (1.2)
Decreased appetite	18 (34.0)	5 (33.3)	7 (38.9)	30 (34.9)	0
Platelet count decreased	17 (32.1)	4 (26.7)	7 (38.9)	28 (32.6)	8 (9.3)
Vomiting	23 (43.4)	3 (20.0)	1 (5.6)	27 (31.4)	1 (1.2)
Neutrophil count decreased	20 (37.7)	2 (13.3)	4 (22.2)	26 (30.2)	19 (22.1)
Diarrhea	19 (35.8)	0	4 (22.2)	23 (26.7)	1 (1.2)

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; TEAE, treatment-emergent adverse events.

DESTINY CRC-01: AEs of Special Interest - Interstitial Lung Disease

All Patients (N=86)	n (%)
Grade 1	0
Grade 2	4 (4.7)
Grade 3	1 (1.2)
Grade 4	0
Grade 5	3 (3.5)[a]
Any Grade/Total	8 (9.3)[b,c]

Adjudicated drug-related ILDs:

- Median time to adjudicated onset was 61.0 days (range, 9-165 days)
- 8 of 8 patients received corticosteroids
- 4 patients with grade 2 recovered and 1 patient with grade 3 did not recover (later died due to disease progression)
- Median time from adjudicated onset date to initiation of steroid treatment in the 8 ILD cases was 3.5 days, (range 0-50)

Grade 5 ILDs:

- In the 3 fatal cases adjudicated as drug-related ILD, onset was from 9 days to 120 days (median: 22 days); and death occurred 6-19 days after diagnosis (median: 6 days)

Updated ILD/pneumonitis guidelines recommend to monitor for symptoms, interrupt or discontinue T-DXd, conduct imaging (as clinically indicated), and start steroids as soon as ILD is suspected.

AE, adverse events; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.
[a]2 patients were from cohort A, 1 from cohort B. [b]4 patients were from cohort A, 3 from cohort B and 1 from cohort C. [c]ILD grades are the highest/most severe grade recorded in a patient.

Anti-EGFR Resistance

2021 ASCO ANNUAL MEETING

PHASE II STUDY OF ANTI-EGFR RECHALLENGE THERAPY WITH PANITUMUMAB DRIVEN BY CIRCULATING TUMOR DNA MOLECULAR SELECTION IN METASTATIC COLORECTAL CANCER: THE CHRONOS TRIAL

Andrea Sartore-Bianchi, Filippo Pietrantonio, Sara Lonardi, Benedetta Mussolin, Francesco Rua, Elisabetta Fenocchio, Alessio Amatu, Salvatore Corallo, Chiara Manai, Federica Tosi, Paolo Manca, Francesca Daniel, Valter Torri, Angelo Vanzulli, Giovanni Cappello, Caterina Marchiò, Anna Sapino, Silvia Marsoni, Salvatore Siena, Alberto Bardelli

June 7th, 2021

Ospedale Niguarda Cancer Center

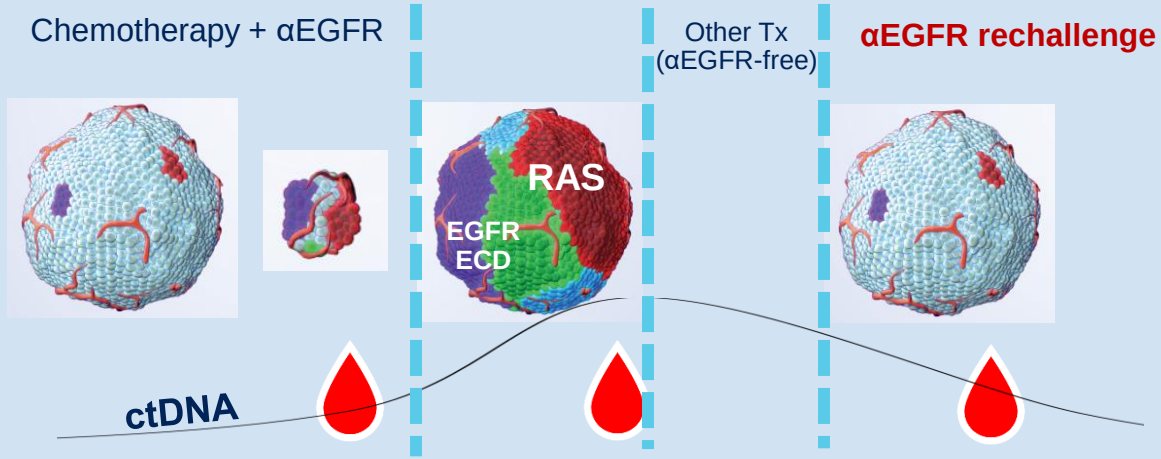
ISTITUTO DI CANDIOLO - IRCCS

Fondazione IRCCS Istituto Nazionale dei Tumori

I.O.V. ISTITUTO ONCOLOGICO VENETO I.R.C.C.S.

IFOM

Background and rationale (II)



Anti-EGFR rechallenge strategies:

Clinical-based rechallenge ~ 20% ORR

Could ctDNA-driven rechallenge do better?

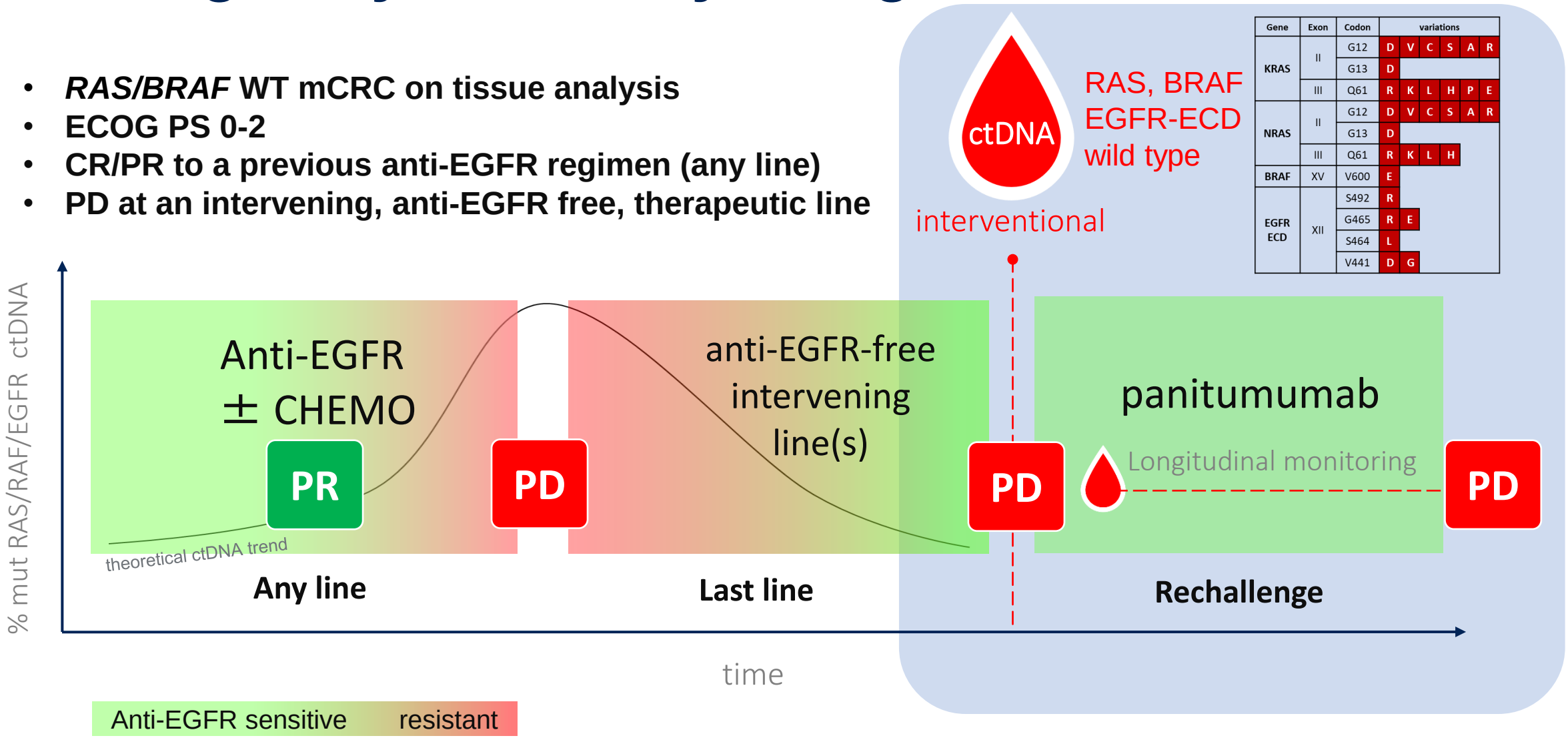
- **Resistance to anti-EGFR moAbs is predominatly driven by mutant RAS and EGFR ectodomain clones**[1,2]
- **Resistance can be monitored by ctDNA in plasma**[3]
- **RAS/EGFR alleles decline upon anti-EGFR therapy withdrawal, leading the tumor to regain sensitivity**[3,4]
- **Clinical-based rechallenge has shown promising results**[5,6]
- **No data are available regarding the interventional use of ctDNA**

1. Misale et al, Nature 2012; 2. Diaz et al, Nature 2012; 3. Siravegna et al, Nat Med 2015; 4. Parseghian et al, Ann Oncol 2019; 5. Santini et al, Ann Oncol 2012; 6. Cremolini et al, JAMA Oncol 2018

Trial eligibility and study design

Phase II trial single-stage

- ***RAS/BRAF* WT mCRC on tissue analysis**
- **ECOG PS 0-2**
- **CR/PR to a previous anti-EGFR regimen (any line)**
- **PD at an intervening, anti-EGFR free, therapeutic line**



Gene	Exon	Codon	variations
KRAS	II	G12	D V C S A R
		G13	D
	III	Q61	R K L H P E
NRAS	II	G12	D V C S A R
		G13	D
	III	Q61	R K L H
BRAF	XV	V600	E
EGFR ECD	XII	S492	R
		G465	R E
		S464	L
		V441	D G

Trial eligibility, objectives and statistics

Eligibility

Main criteria:

- RAS/BRAF WT mCRC on tissue biopsy at diagnosis
- At least PR to previous anti-EGFR containing regimen
- RAS/BRAF/EGFR WT at molecular screening by ctDNA
- ECOG ≤2
- FFPE genotyping on archival solid tissue derived before anti-EGFR rechallenge

Endpoints

Primary:

- Response rate (RECIST, centrally reviewed)

Secondary:

- PFS
- OS
- Toxicity

Translational:

- ctDNA RAS/BRAF/EGFR dynamics
- ctDNA landscapes (baseline and PD)
- tDNA landscape (baseline)

Statistics

Design:
Phase II trial single-stage Fleming-A'Hern

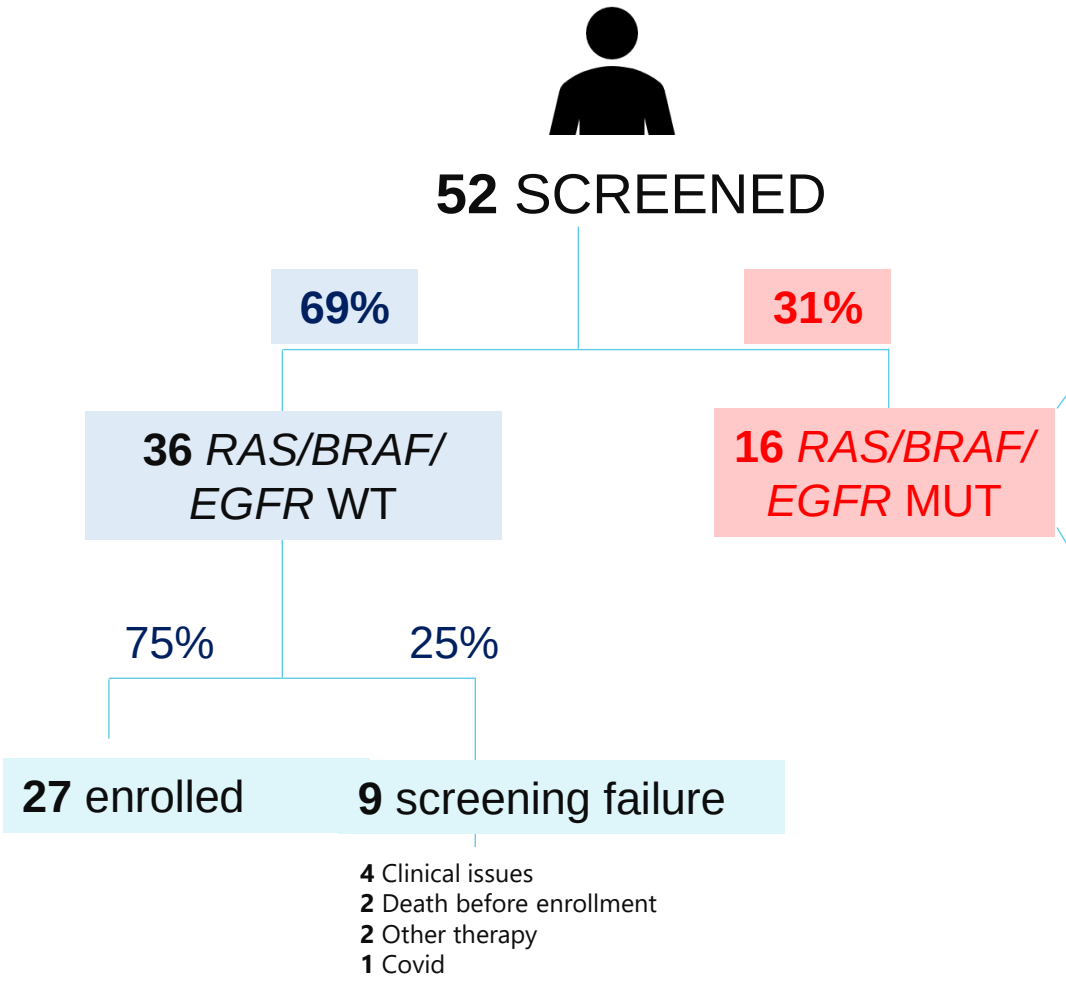
Assumption:
H_0 10% ORR
H_1 ≥30% ORR
$\alpha=0.05$; $\beta=0.15$

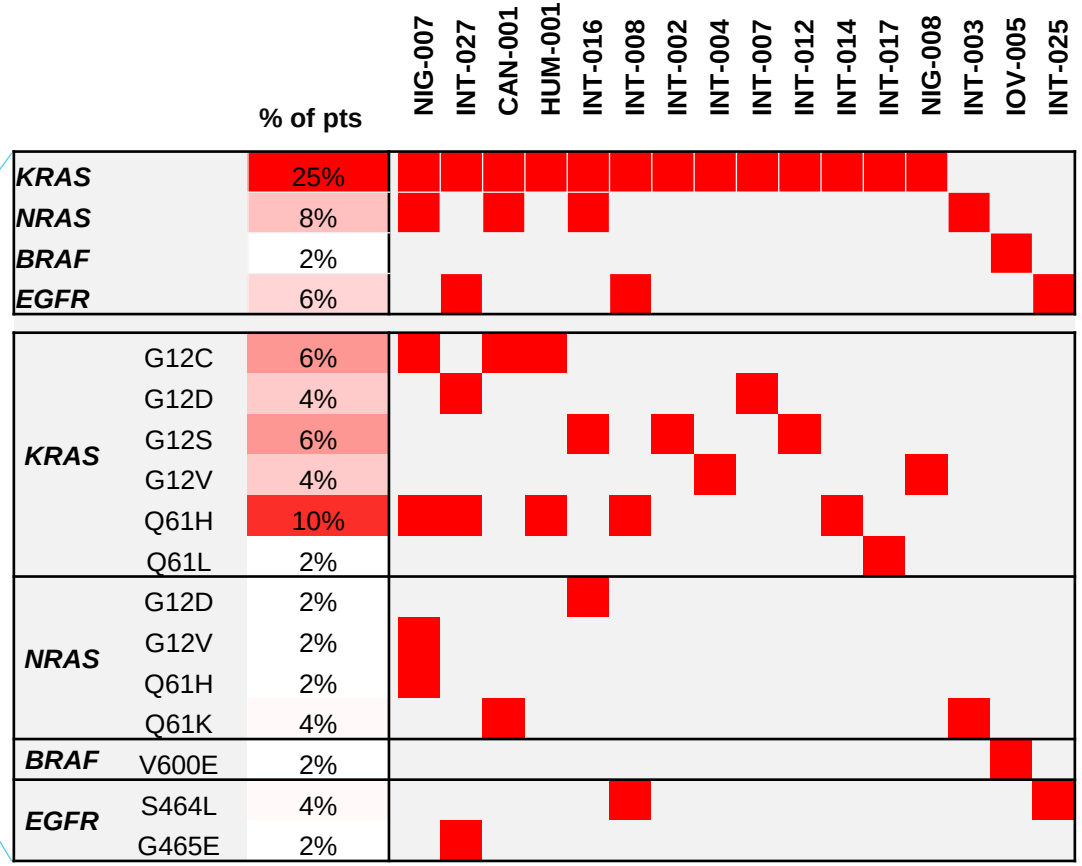
Sample size:
27 patients; ≥ 6 PR required to declare the study positive

Data lock:
April 15, 2021

Molecular screening: results

Liquid biopsy avoids ineffective treatment in 30% of clinically eligible cases

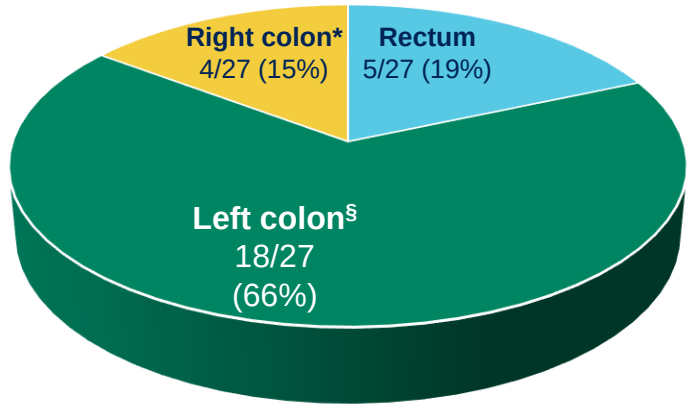




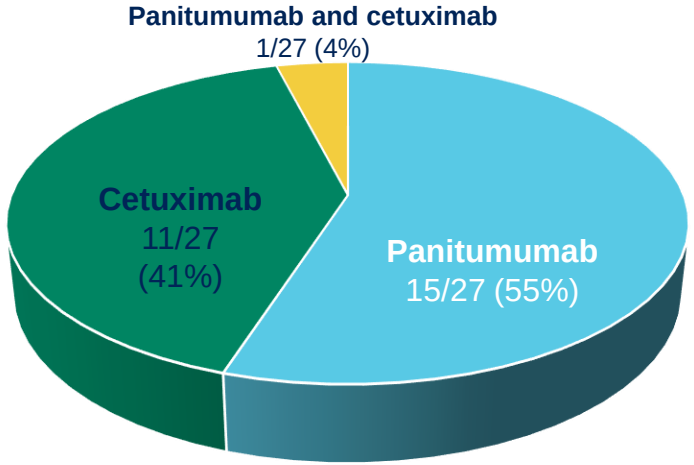
Baseline characteristics

Characteristic	Study population (N=27)
Age (median; range of years)	64 (42-80)
Gender (n; %)	
Male	16 (59)
Female	11 (41)
ECOG status (n; %)	
0-1	26 (96)
2	1 (4)
Stage at initial diagnosis (n; %)	
Stage I-III	12 (44)
Stage IV	15 (56)
Mismatch repair status (n;%)	
MSI	0 (0)
MSS	26 (96)
Unknown	1 (4)
Number of previous lines of therapy (median; range)	3 (2-6)
oxaliplatin-containing regimens (n;%)	27 (100)
irinotecan-containing regimens (n; %)	25 (93)
anti-VEGF (n; %)	16 (59)
Previous anti-EGFR treatment	
combination with chemotherapy (n;%)	27 (100)
anti-EGFR monotherapy (n; %)	0 (0)

Primary tumor sidedness



Previous anti-EGFR antibody

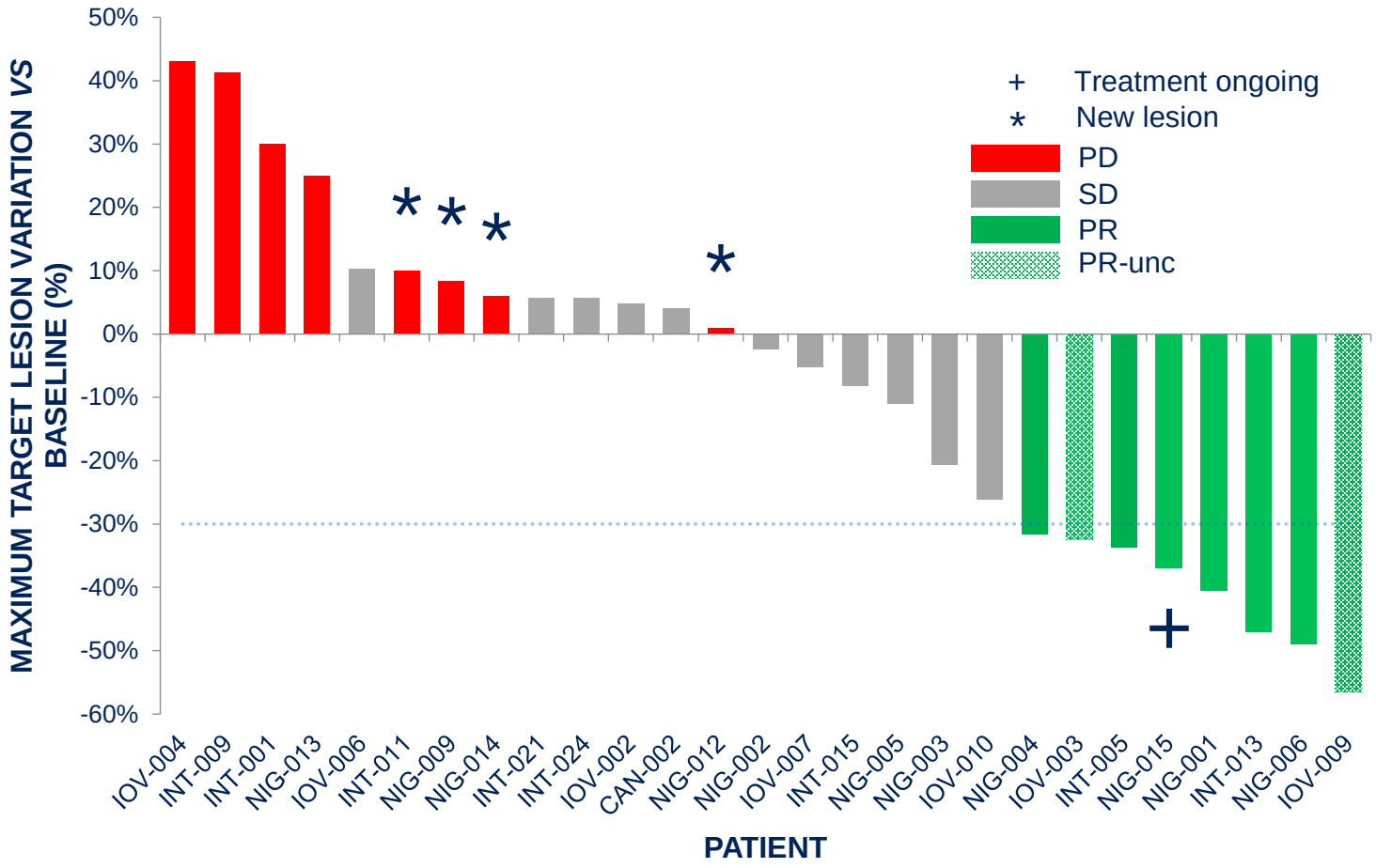


*Located in caecum, ascending colon, liver flexure, and transverse colon. §Located in splenic flexure, descending colon, and sigmoid colon.

Objective response rate

Best Response RECIST 1.1 by centralized revision	N	%
Responses (PR+CR)	**8**	**30%**
Partial Response	8*	30%
Stable Disease ≥4 mos	9	33%
Stable Disease <4 mos	2	7%
Control of disease (PR+SD≥4 mos)	**17**	**63%**
Progressive Disease	8	30%
Total	27	100%

* Two PR were unconfirmed

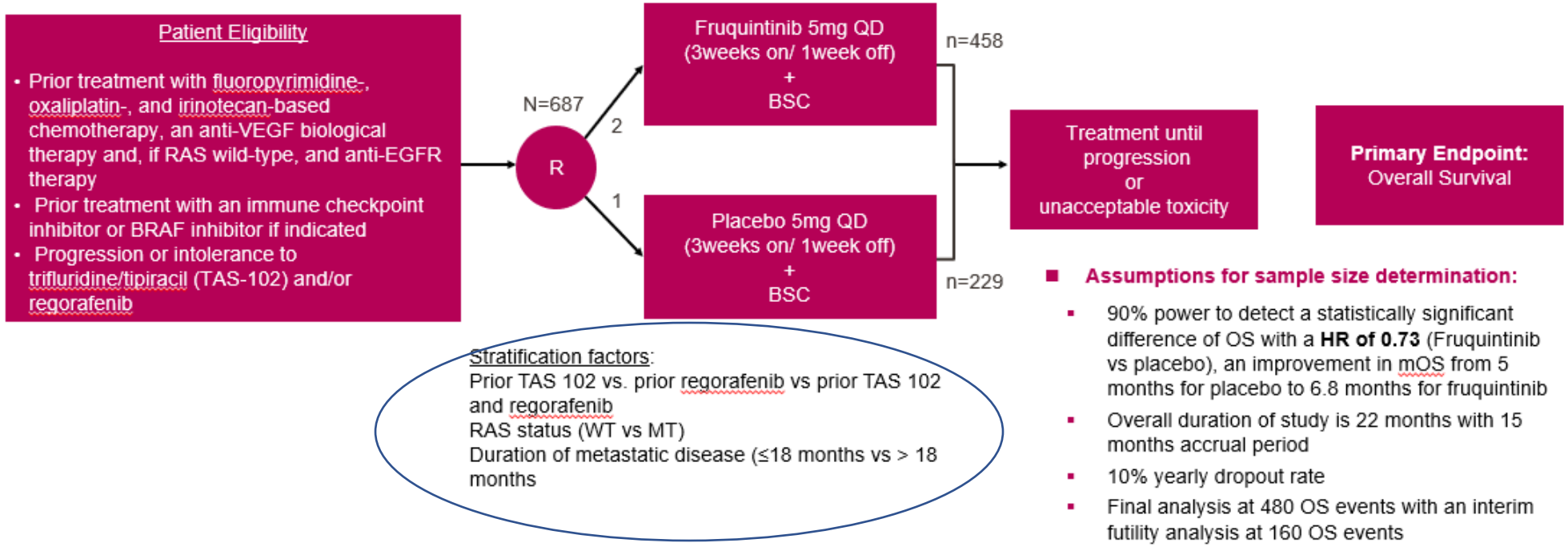


Phase III trial for all mCRC

Phase III: A Study of Efficacy and Safety of Fruquintinib (HMPL-013) in Patients With mCRC(FRESCO-2)
PI's Drs. Dasari and Eng

NCT04322539

FRESCO-2 STUDY DESIGN



Neoadjuvant Approaches

Pioneer: Watch + Wait Approach

Patterns of failure and survival for nonoperative treatment of stage co distal rectal cancer following neoadjuvant chemoradiation therapy

Angelita Habr-Gama [1], Rodrigo O Perez, Igor Proscurshim, Fábio G Campos, Wladimir Nadalin, Desiderio Kiss, Joaquim Gama-Rodrigues

Affiliations + expand

PMID: 17175450 DOI: 10.1016/j.gassur.2006.09.005

Abstract

Neoadjuvant chemoradiation therapy (CRT) is the preferred treatment option for distal rectal cancer. Complete pathological response after CRT has led to the proposal of nonoperative approach as an alternative treatment for highly selected patients with complete clinical response. However, patterns of failure following this strategy remains undetermined. Three hundred sixty-one patients with distal rectal cancer were managed by neoadjuvant CRT including 5-FU, leucovorin, and 5040 cGy. Tumor response assessment was performed at 8 weeks following CRT. Patients with complete clinical response were not immediately operated on and were closely followed. One hundred twenty-two patients were considered to have complete clinical response after the first tumor response assessment. Of these, only 99 patients sustained complete clinical response for at least 12 months and were considered stage c0 (27.4%) and managed nonoperatively. Mean follow-up was 59.9 months.

Preliminary results of the Organ Preservation in Rectal Adenocarcinoma (OPRA) trial

Julio Garcia-Aguilar, Sujata Patil, Jin K. Kim, Jonathan B. Yuval, Hannah Thompson, Floris Verheij, Meghan Lee, Leonard B. Saltz,
on behalf of the OPRA Consortium

Memorial Sloan Kettering Cancer Center
New York

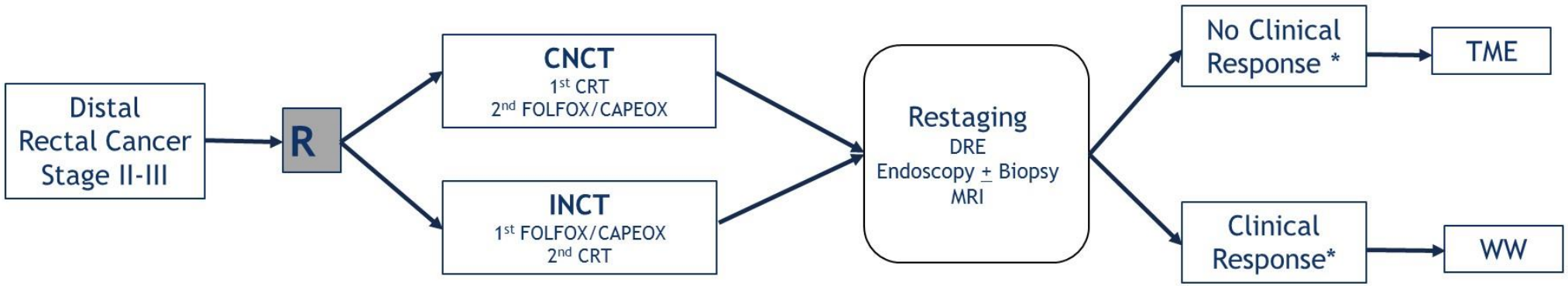
PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Julio Garcia-Aguilar

Protocol Schema

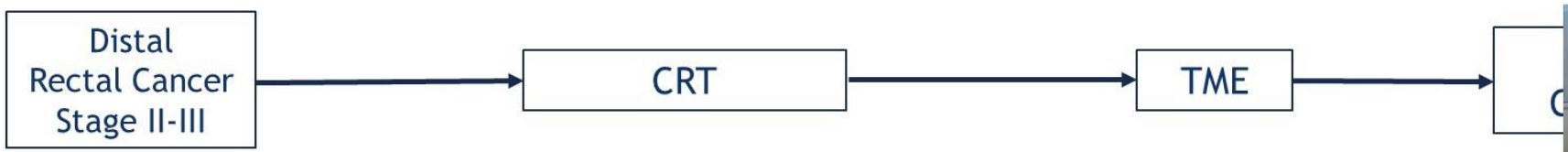
NCI trial registration: NCT02008656
NIH-funded (R01): 1R01CA182551-01

Investigational Arm

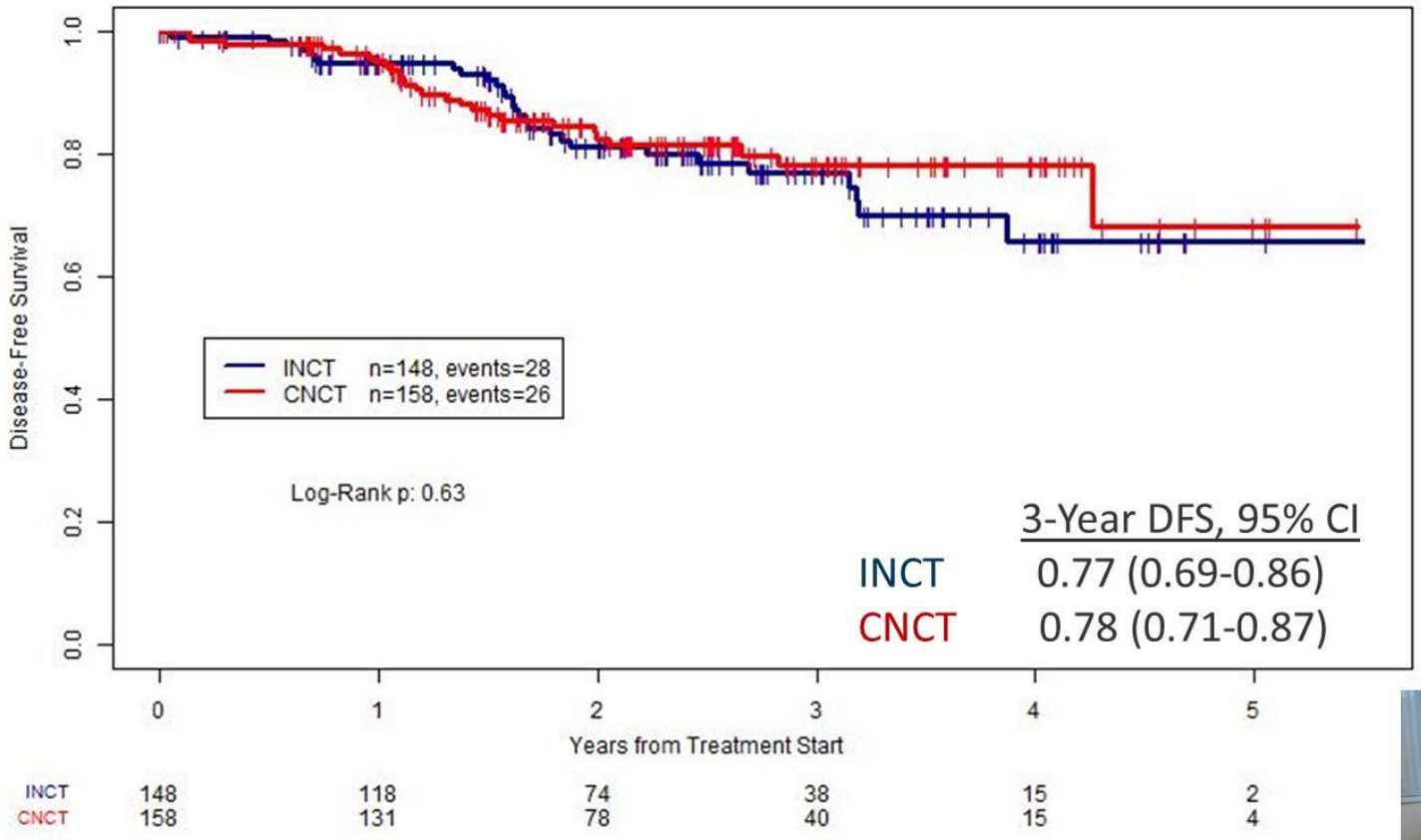


(*) Smith J et al, BMC Cancer 2015;15:767.

Control Arm (Historical Controls)



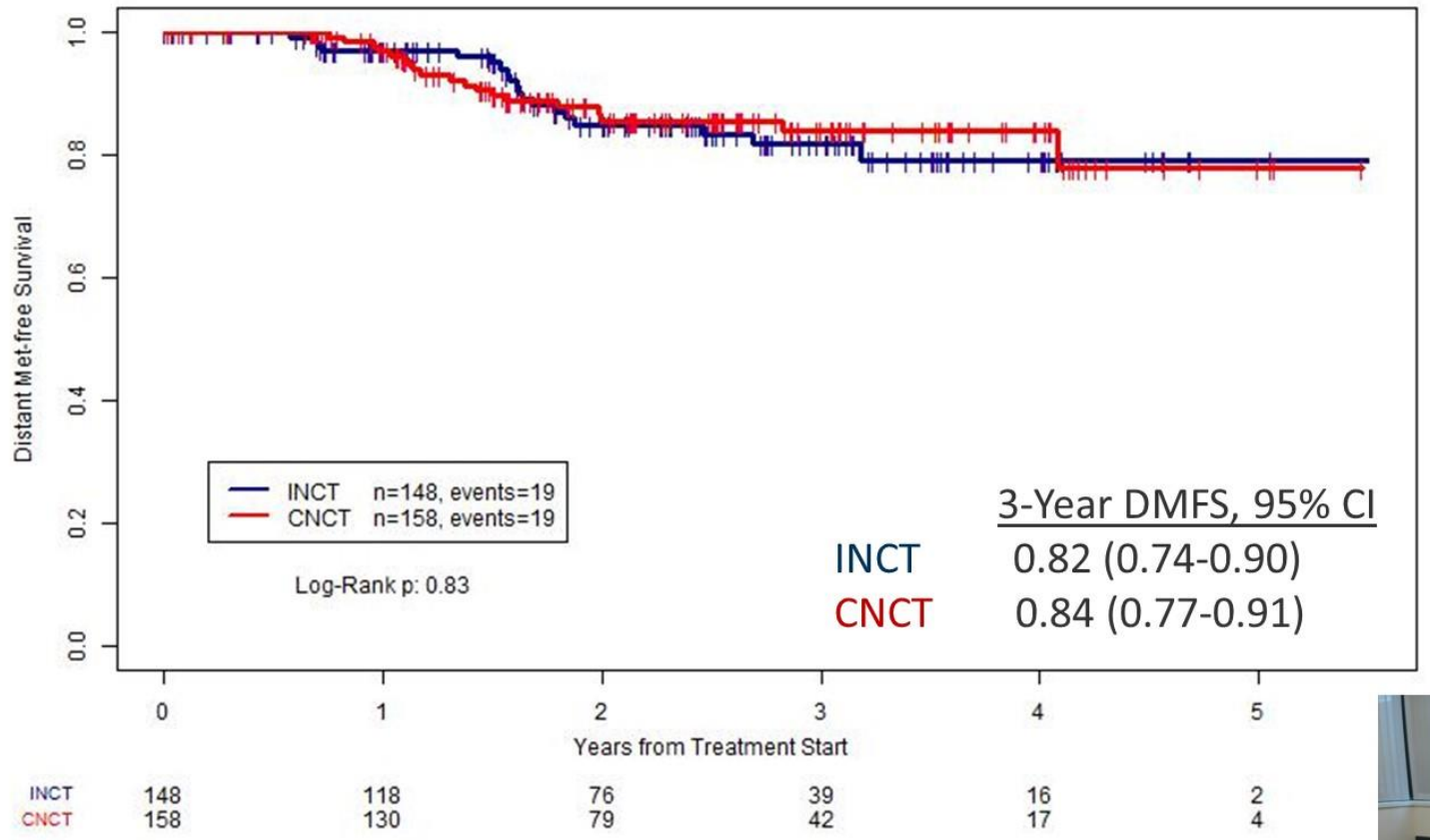
Results: DFS by Treatment Group



	3-Year DFS, 95% CI
INCT	0.77 (0.69-0.86)
CNCT	0.78 (0.71-0.87)

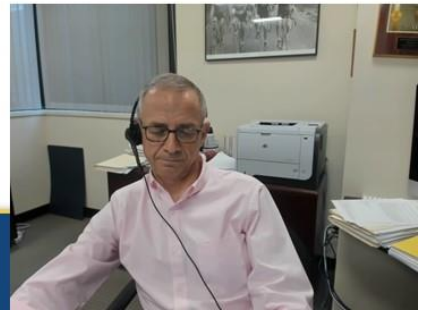
Median follow-up 2.26 years (min=0.003, max=5.6)

Results: Distant Metastasis-Free by Treatment Group

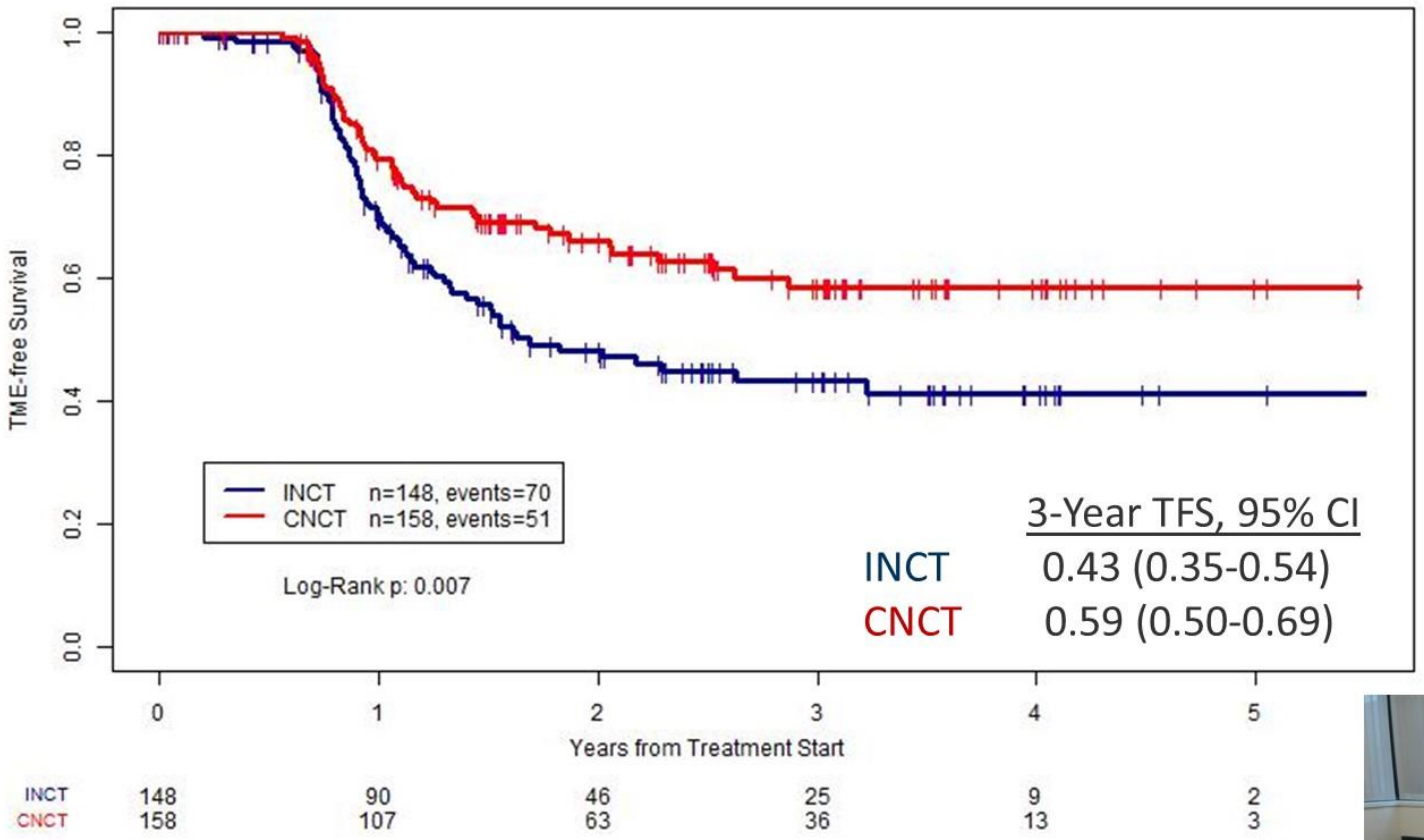


3-Year DMFS, 95% CI	
INCT	0.82 (0.74-0.90)
CNCT	0.84 (0.77-0.91)

Median follow-up 2.26 years (min=0.003, max=5.6)



Results: TME-Free by Treatment Group

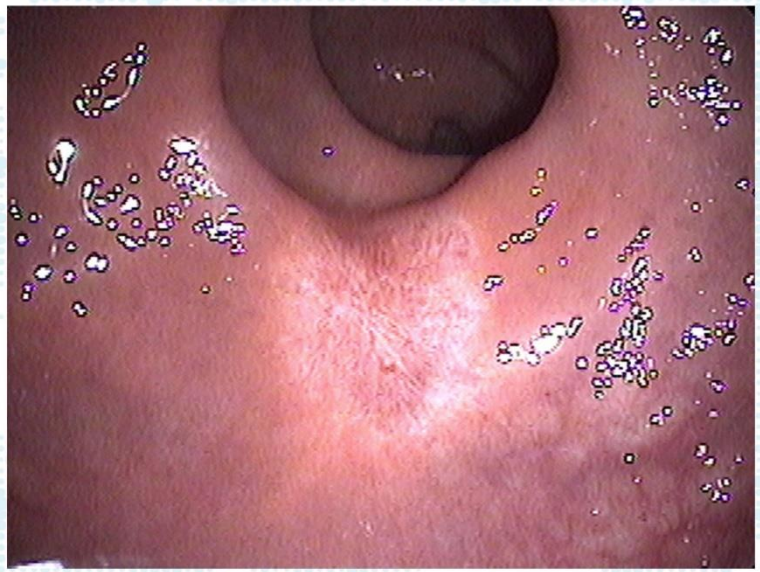


	3-Year TFS, 95% CI
INCT	0.43 (0.35-0.54)
CNCT	0.59 (0.50-0.69)

Median follow-up 2.26 years (min=0.003, max=5.6)

2021 ASCO ANNUAL MEETING

SURVIVAL AND ORGAN PRESERVATION ACCORDING TO CLINICAL RESPONSE AFTER TOTAL NEOADJUVANT THERAPY IN LOCALLY ADVANCED RECTAL CANCER PATIENTS: A SECONDARY ANALYSIS FROM THE OPRA TRIAL



Memorial Sloan Kettering Cancer Center

June 6, 2021

Methods

Rectal Adenocarcinoma stage II-III

Randomized to total neoadjuvant therapy (TNT):

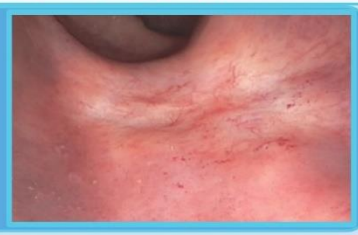
- **Consolidation (CNCT)**
  OR
- **Induction (INCT)**

8 +/- 4 weeks

Three-Tier Clinical Response Assessment Schema

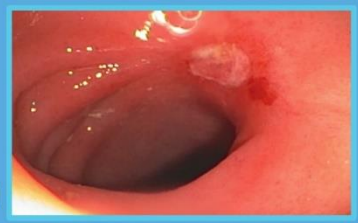
Clinical Complete Response (cCR)

- Flat, white scar
- Telangiectasia
- No ulceration or nodularity
- Digital rectal exam (DRE): normal



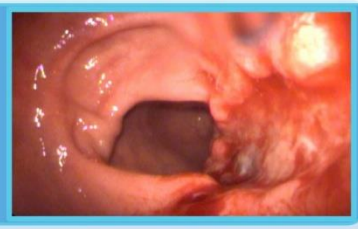
Near Complete Clinical Response (nCR)

- Irregular mucosa
- Small nodules/minor mucosal abnormality
- Superficial ulceration
- Mild persisting erythema
- DRE: smooth induration/minor mucosal abnormality on DRE



Incomplete Clinical Response (iCR)

- Visible Tumor
- DRE: palpable tumor nodules



Recommend WW

or

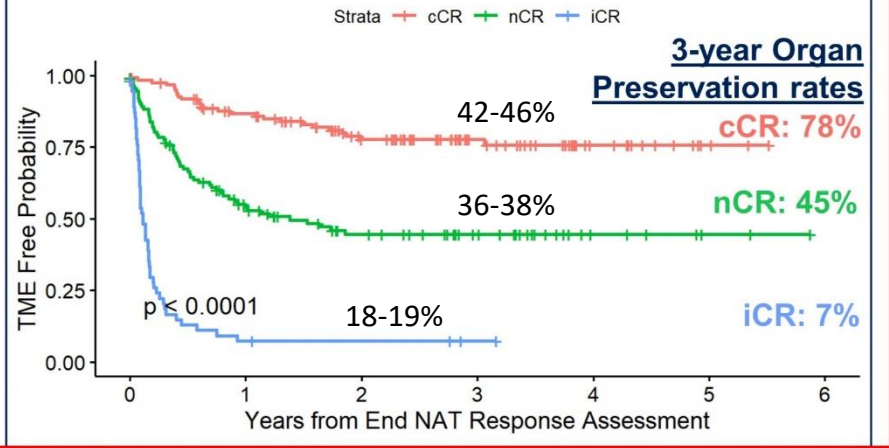
Recommend TME

Patient Characteristics and Treatment by Clinical Response

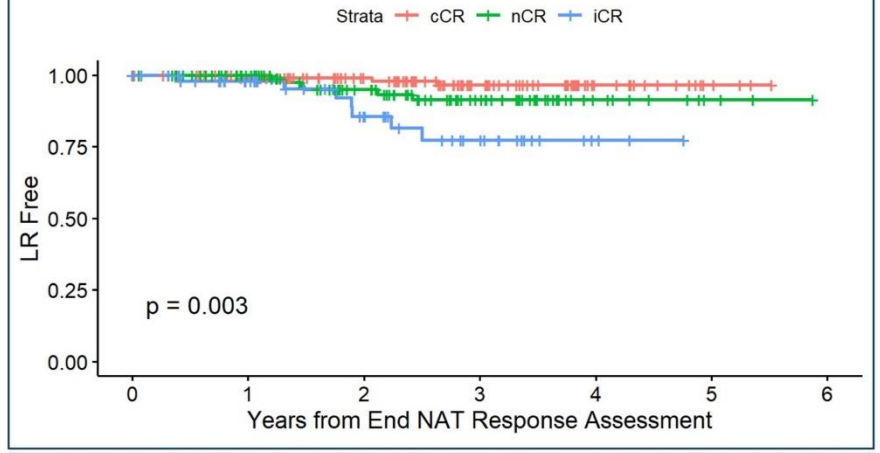
	cCR (n=124)	nCR (n=114)	iCR (n=55)	p-value
Treatment				0.3
INCT	54 (44%)	60 (53%)	28 (51%)	
CNCT	70 (56%)	54 (47%)	27 (49%)	
Median Tumor Distance from Anal Verge (cm)	4.5	4.0	4.5	0.3
Male Sex	75 (60%)	80 (70%)	37 (67%)	0.3
Median Age (years)	60	58	55	0.09
cT Classification				0.7
1/2	16 (13%)	11 (10%)	4 (7%)	
3	94 (76%)	87 (76%)	45 (82%)	
4	14 (11%)	16 (14%)	6 (11%)	
cN Classification				0.08
Negative	45 (36%)	28 (25%)	13 (24%)	
Positive	79 (64%)	86 (75%)	42 (76%)	
Median Time to Assessment (weeks)	7.5	8.0	7.7	0.3
Treatment Recommended after Reassessment				-
WW	122 (98%)	94 (82%)	8 (15%)	
TME	2 (2%)	20 (18%)	47 (85%)	

Organ Preservation and Survival Outcomes by Clinical Response

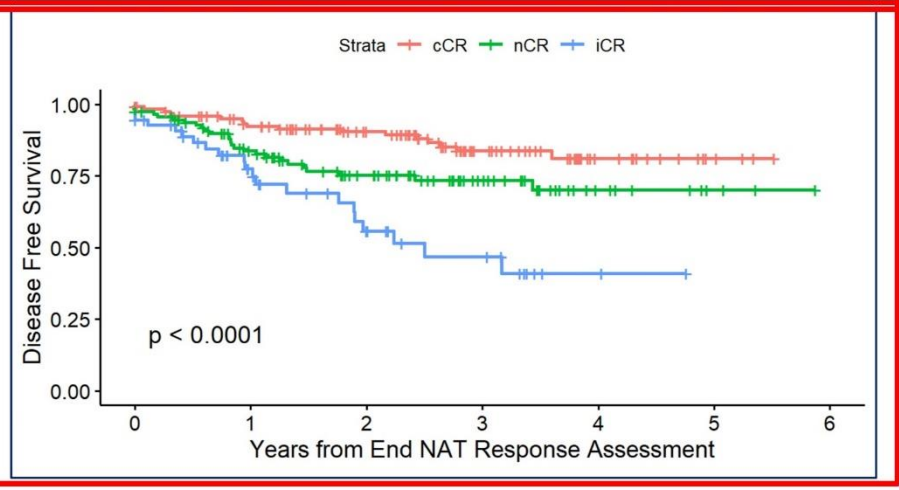
Organ Preservation



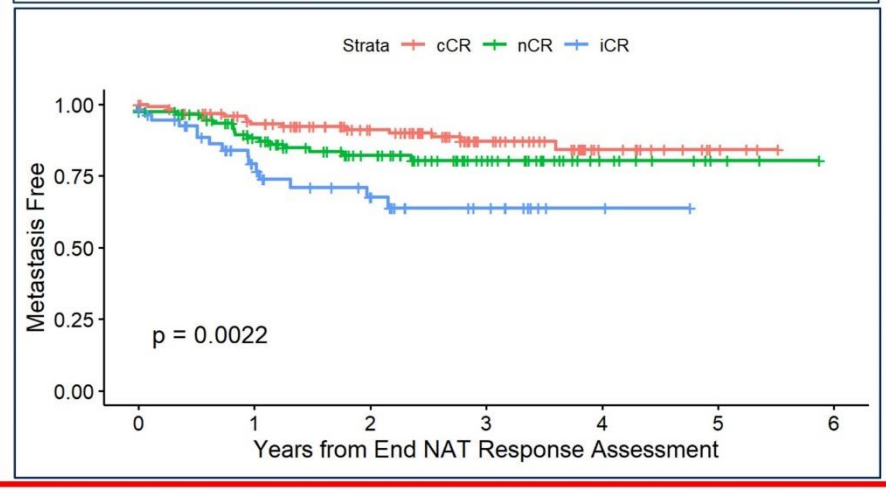
Local Recurrence-Free Survival



Disease-Free Survival



Metastasis-Free Survival



EA2201: Neoadjuvant nivo/ipi + 5X5 RT in dMMR/MSI-H Rectal Cancer (PI: Ciombor) NCT04751370

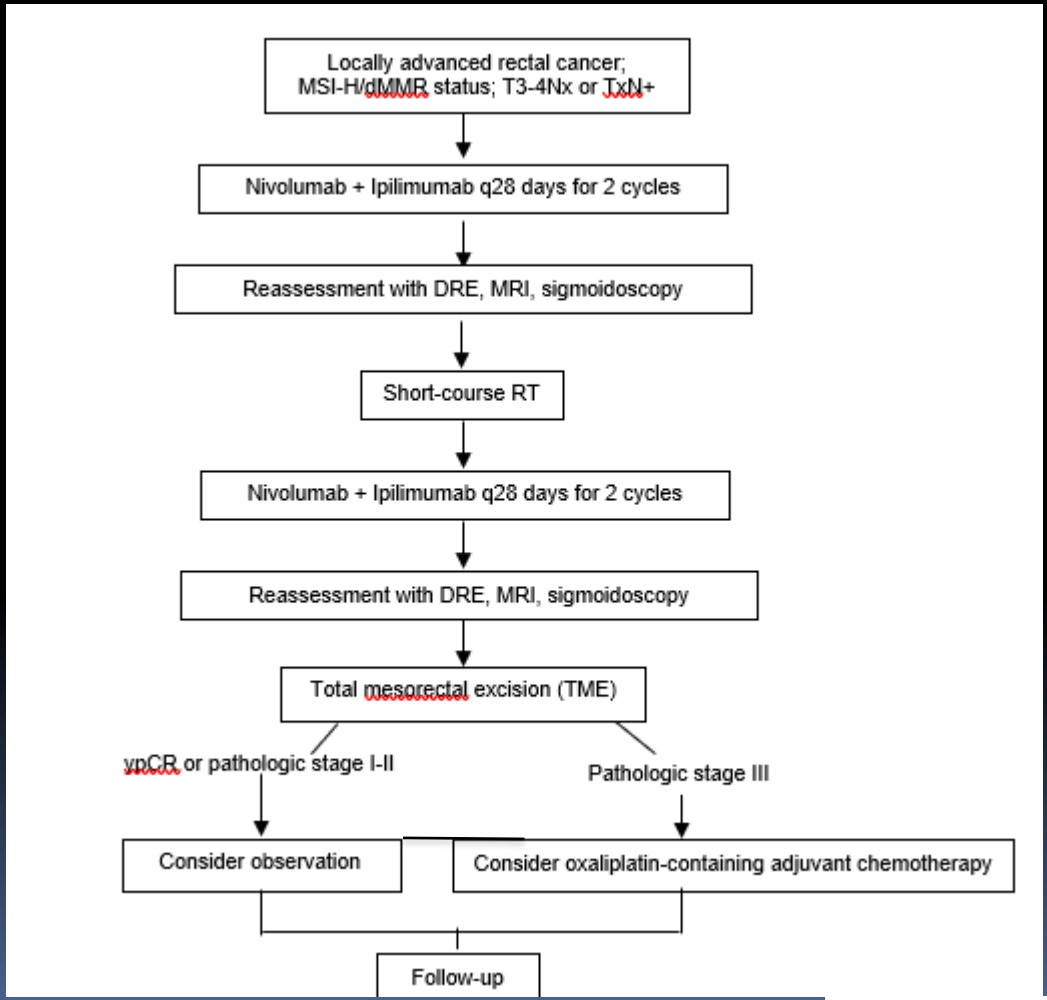
Eligibility:
- T3-4Nx or TxN+ rectal cancer
- dMMR or MSI-H

Primary endpoint:
- pCR rate

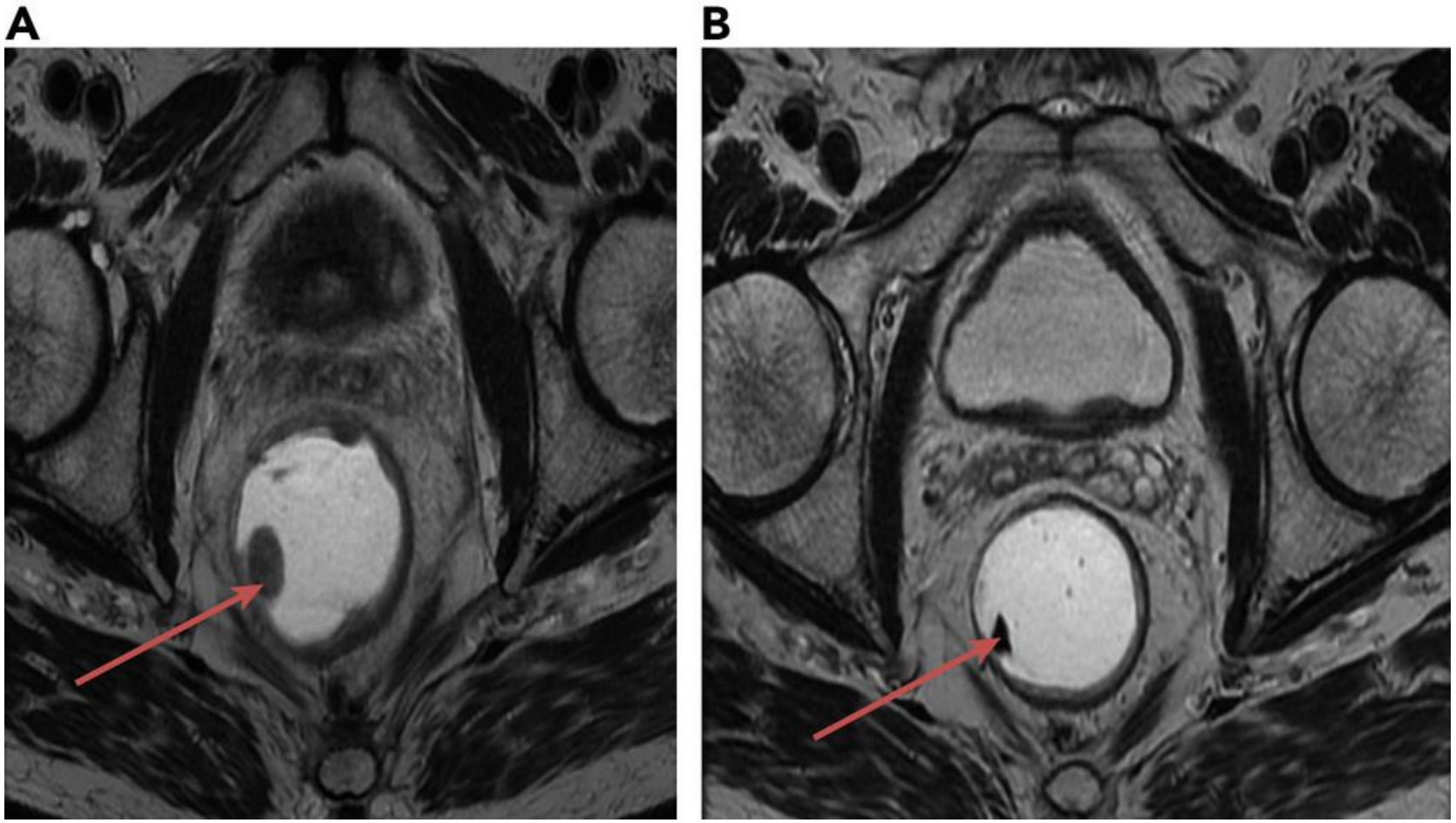
Secondary endpoints:
- DFS, OS
- Safety/tolerability
- Tumor regression grade
- Sphincter preservation rate for distal tumors

Exploratory endpoints:
-ctDNA

Statistical design:
- Two-stage single-arm phase II study (n=31)
- Null hypothesis: pCR = 25%
- Alternative hypothesis: pCR = 50%



Neoadjuvant Immunotherapy–Based Systemic Treatment in MMR-Deficient or MSI-High Rectal Cancer: Case Series



(A) Baseline axial T2-weighted image after administration of rectal gel in Case 1, with a polypoid mass seen at approximately 8:00. (B) After 6 cycles of pembrolizumab, axial T2-weighted image after administration of rectal gel at the level of previously seen polypoid mass shows no residual mass, compatible with tumor regression grade 1.

Demisse…Eng…et al: JNCCN, 2020

Conclusions:

- Pembrolizumab in tx naïve mCRC resulted in NS in OS but superior PFS
  - 60% crossover
- BRAFTOVI is the standard of care for refractory BRAF MT mCRC
  - Tx naïve: BREAKWATER enrolling
- HER-2 amplification should be evaluated in all mCRC pts
- ctDNA may assist in anti-EGFR resistance rechallenge
- Total neoadjuvant therapy (TNT) in locally advanced rectal cancer is promising for non-operative management
- **Clinical trial enrollment is ALWAYS encouraged whenever possible**