ASCO Direct Highlights: Colorectal and Anal Cancer

VANDERBILT-INGRAM CANCER CENTER

South Carolina Oncology Society (SCOS) Annual Conference

- Cathy Eng, MD, FACP, FASCO
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- Professor of Medicine, Hematology and Oncology
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- Co-Director, GI Oncology
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- August 7, 2021

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Disclosure of Conflict(s) of Interest

Cathy Eng, MD, FACP, FASCO reported the following relevant financial relationships or relationships with ineligible companies of any amount during the past 24 months.

- *Consultant:*
  - Apexigen
  - Bayer
  - Gilead
  - GSK
  - Hookipa
  - Karyopharm Merck

- *Research grants:*
  - Hutchmed
  - Merck
  - Pfizer

Discussion Points:

- MCRC
  - MSI-H: Update
  - BRAF MT
  - HER-2 Refractory: Destiny CRC-01
  - EGFR resistance
- Rectal
  - OPRA
- Anal cancer
  - Trials Pending Results or in Progress

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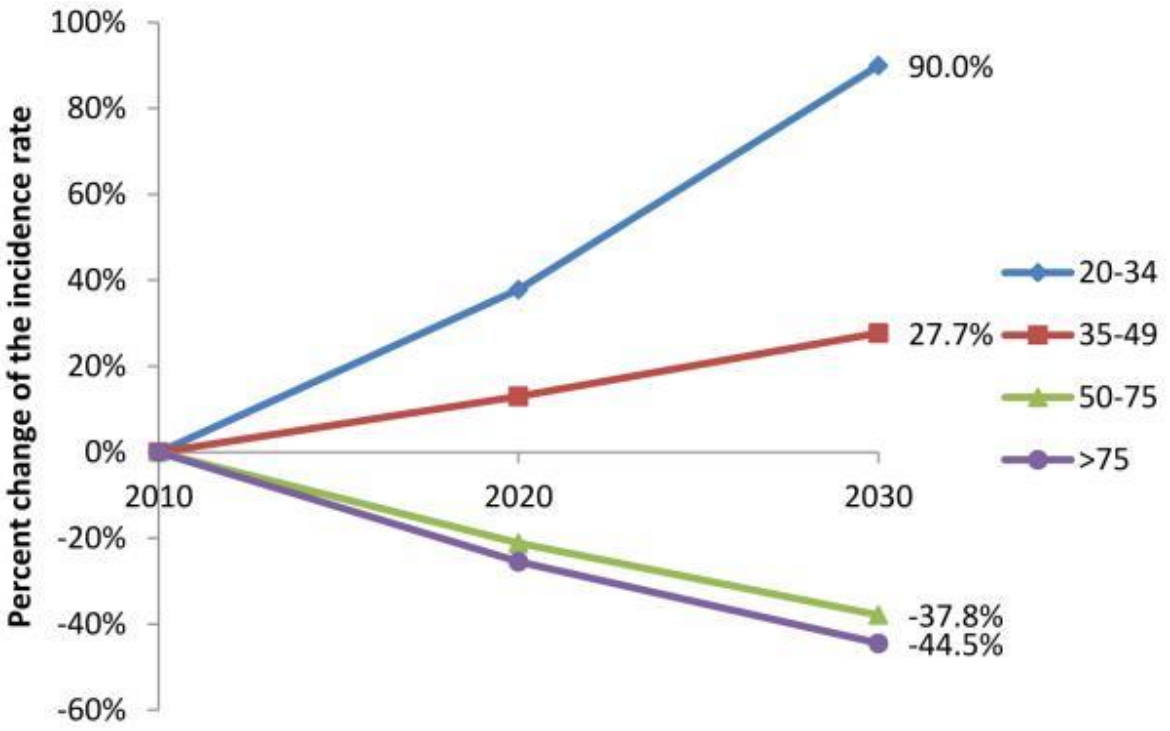
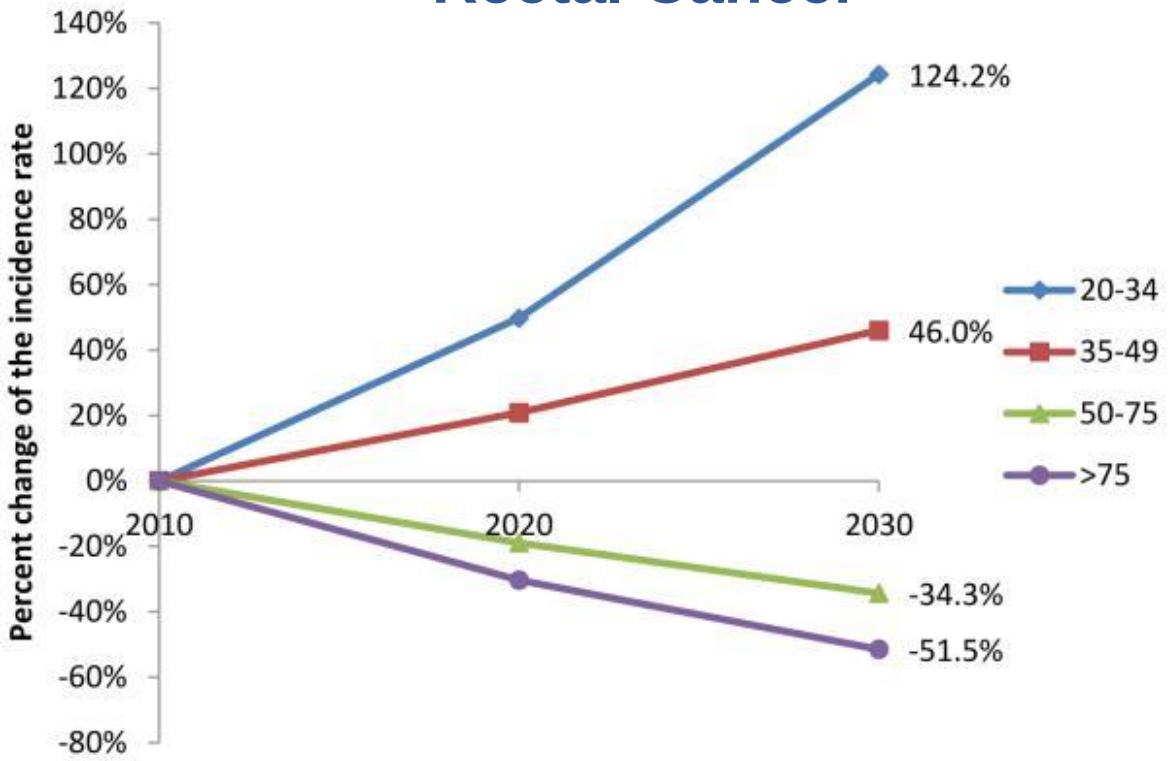
Fast Facts about Colorectal Cancer

- 2021: 149,500 new cases
  - 45, 230 cases are rectal cancer
  - Total = 52,980 deaths
- 2nd leading cause of cancer death for men and women combined

Colon Cancer



Rectal Cancer



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Bailey et al: Jama Surgery, 2015

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]

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Presented By Kai-Keen Shiu at 2021 Gastrointestinal Cancers Symposium

KEYNOTE-177 Study Design (NCT02563002)

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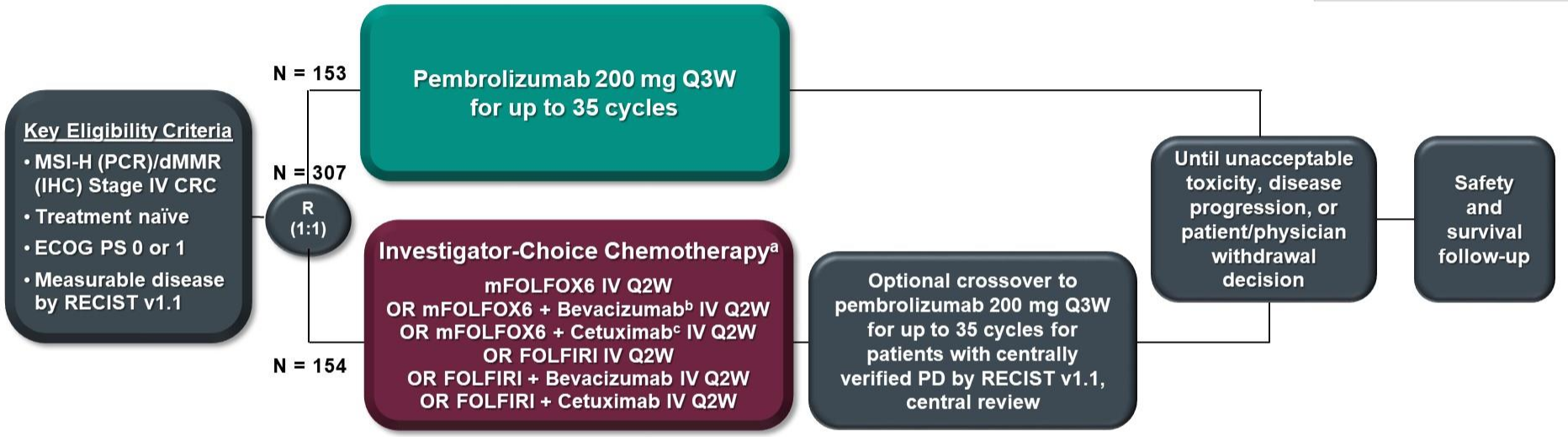

- Dual-Primary endpoints: PFS per RECIST v1.1 per blinded independent central review (BICR) and OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, safety
- Exploratory endpoints: DOR per RECIST v1.1 by BICR, PFS2, HRQoL
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

Progression-Free Survival

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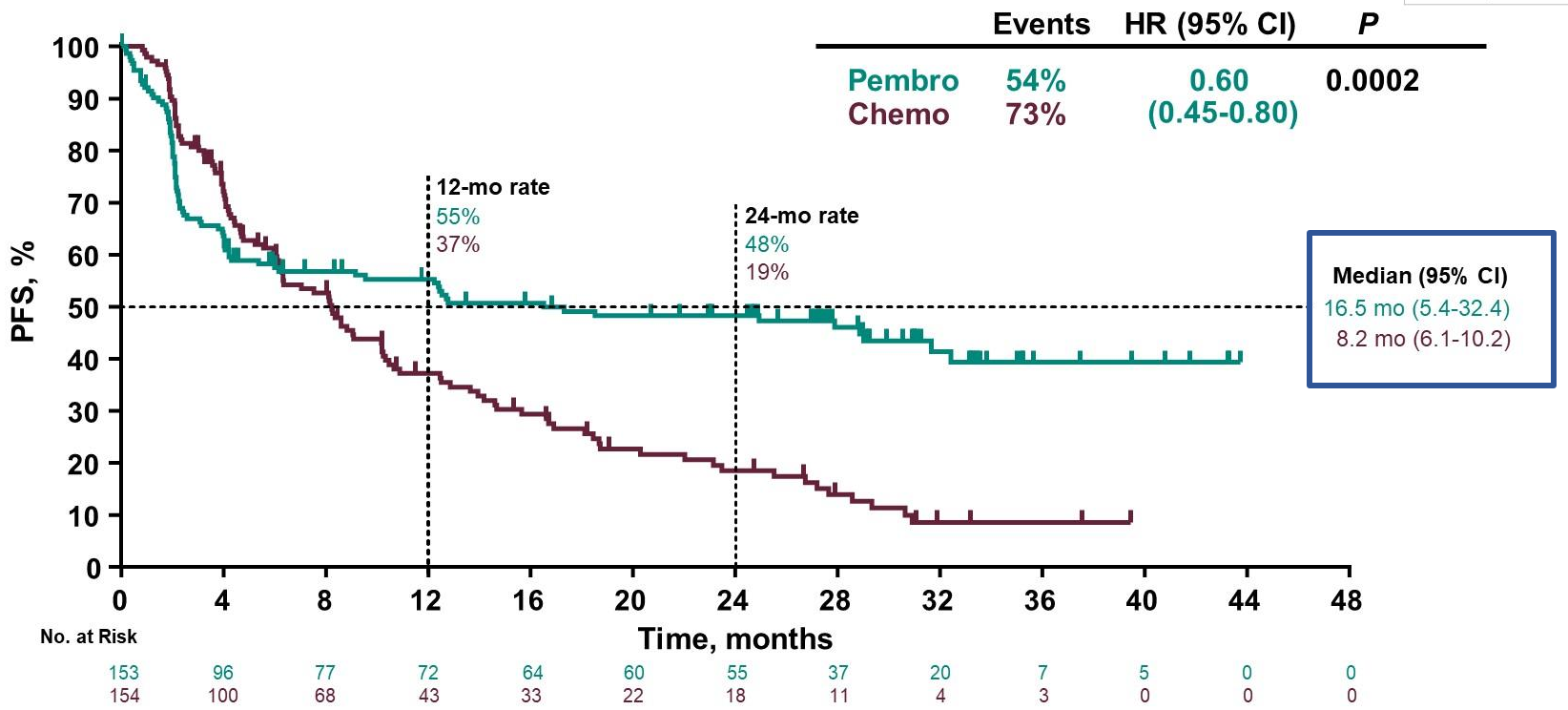

Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR. Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

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]

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Cross Over and Subsequent Therapy

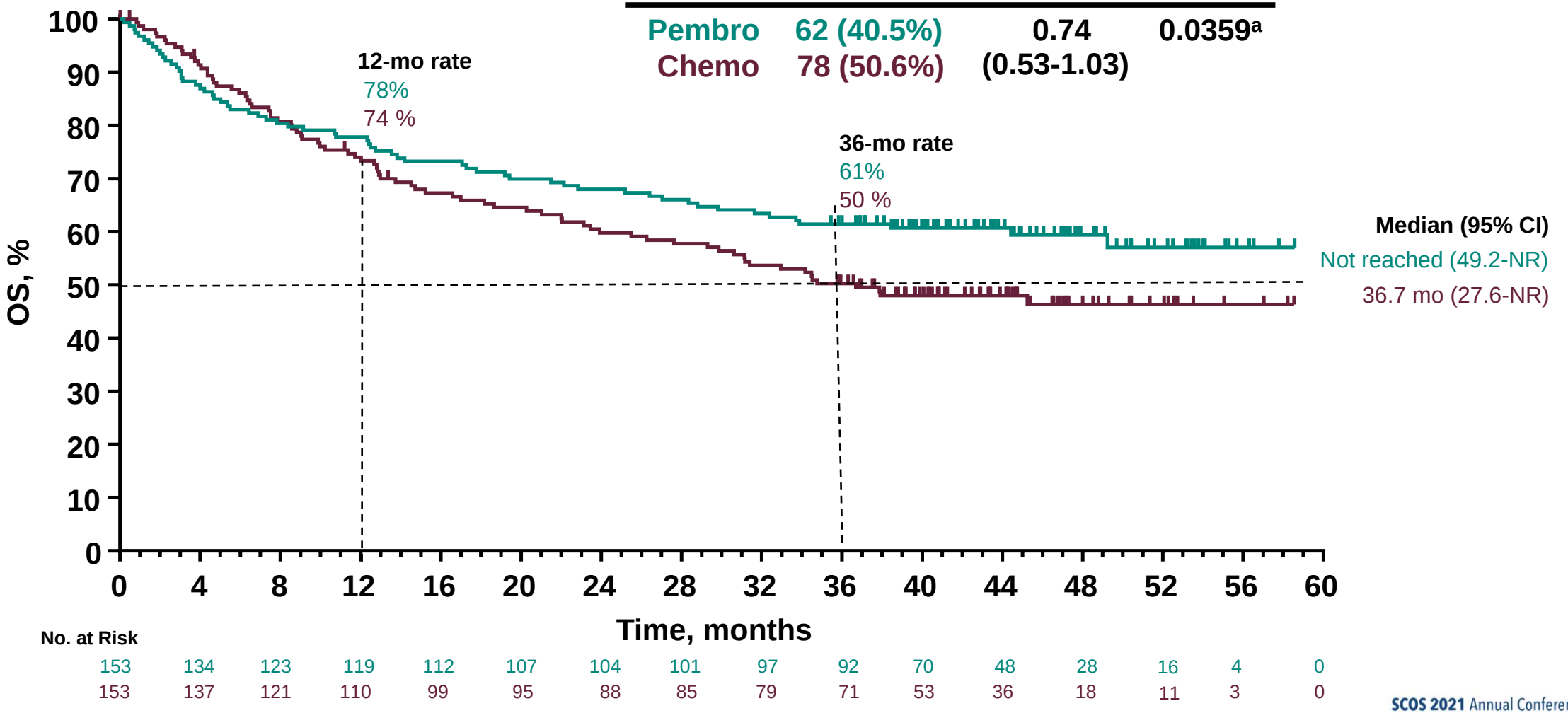
- 56 of 154 (**36%**) patients in the chemotherapy arm crossed over to receive pembrolizumab after confirmed disease progression
  - 37 additional patients received anti-PD-1/PD-L1 therapy outside of the study for an effective crossover rate of **60%** in the ITT

	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 effect by 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.

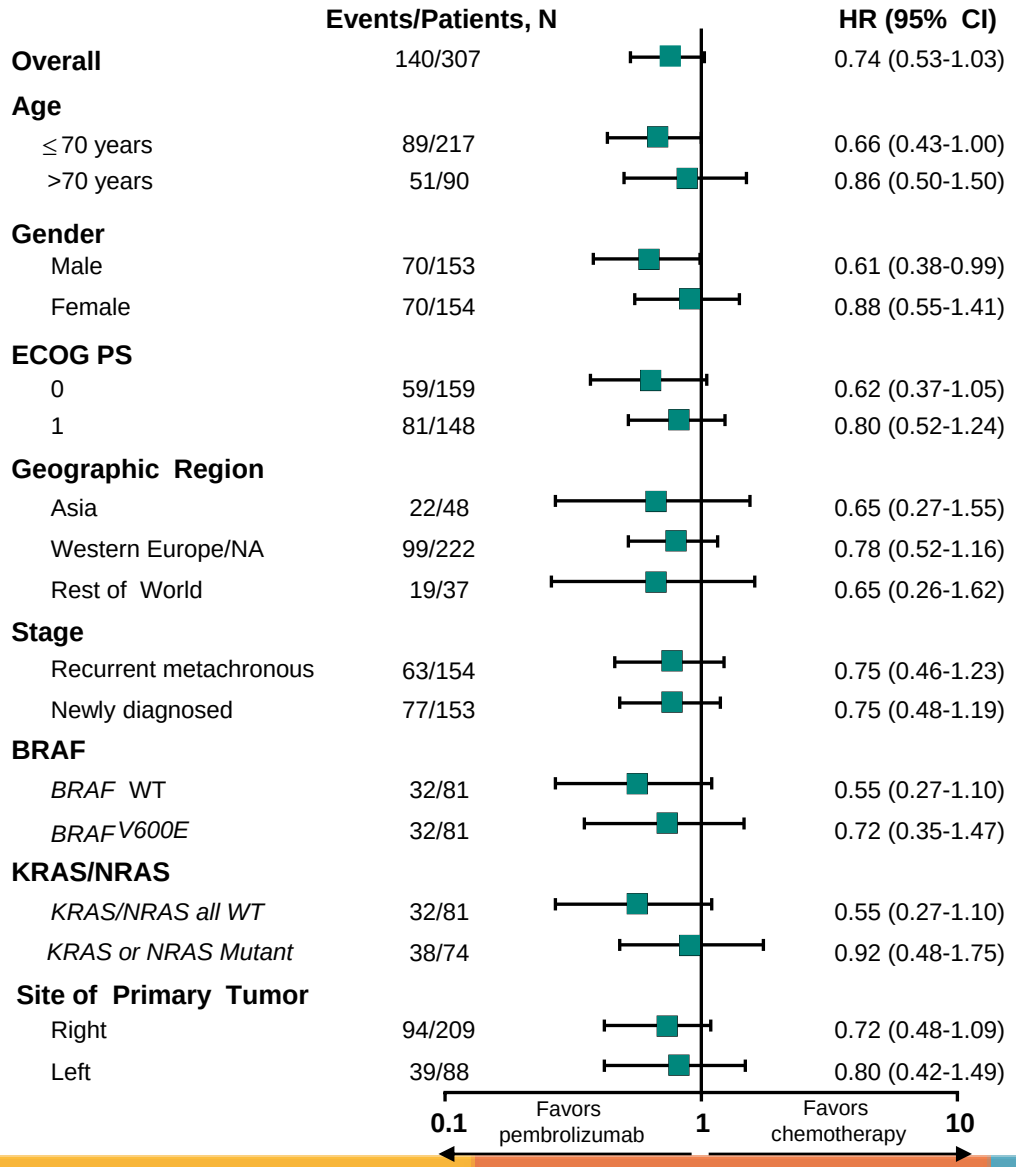
Antitumor Response

	Pembrolizumab N = 153	Chemotherapy N = 154
ORR, n (%)	**69 (45.1)[a]**	**51 (33.1)**
Best Overall Response, n (%)		
Complete response	20 (13.1)[b]	6 (3.9)
Partial response	49 (32.0)[c]	45 (29.2)
Stable disease	30 (19.6)	65 (42.2)
Disease control rate (CR+PR+SD)	99 (64.7)	116 (75.3)
Progressive disease	45 (29.4)	19 (12.3)
Not evaluable	3 (2.0)	2 (1.3)
No assessment	6 (3.9)	17 (11.0)
Median duration or response (range), mo	NR (2.3+ to 53.5+)	10.6 (2.8 to 48.3+)
≥ 24 months response duration, %	83.5	33.6

[a]ORR 43.8%; [b]CR rate 11.1%; [c]PR rate 32.7% at IA2 (data cut-off 19Feb2020).

Data cut-off: 19Feb2021.

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]

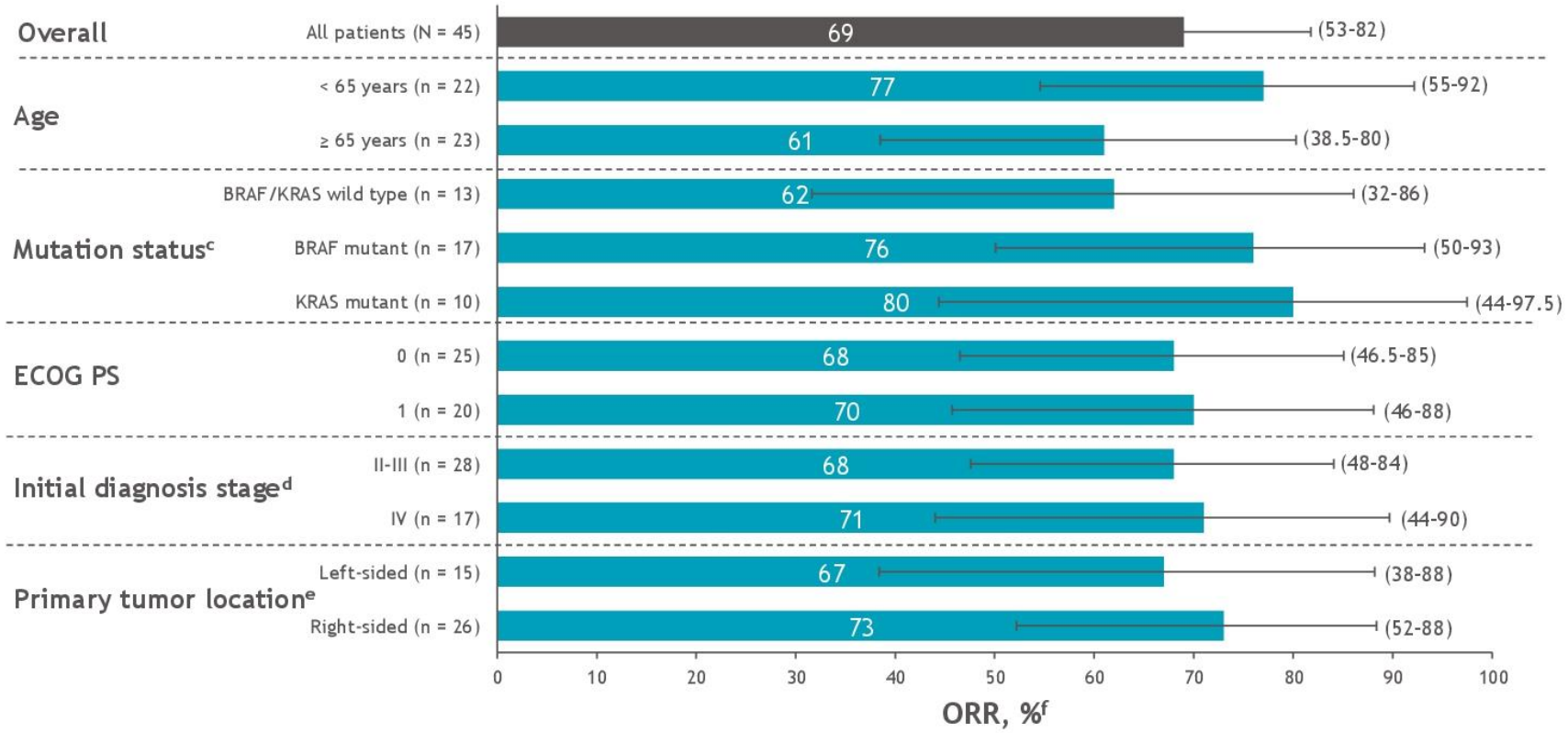
Primary endpoint:
- ORR per investigator assessment (RECIST v1.1)

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]

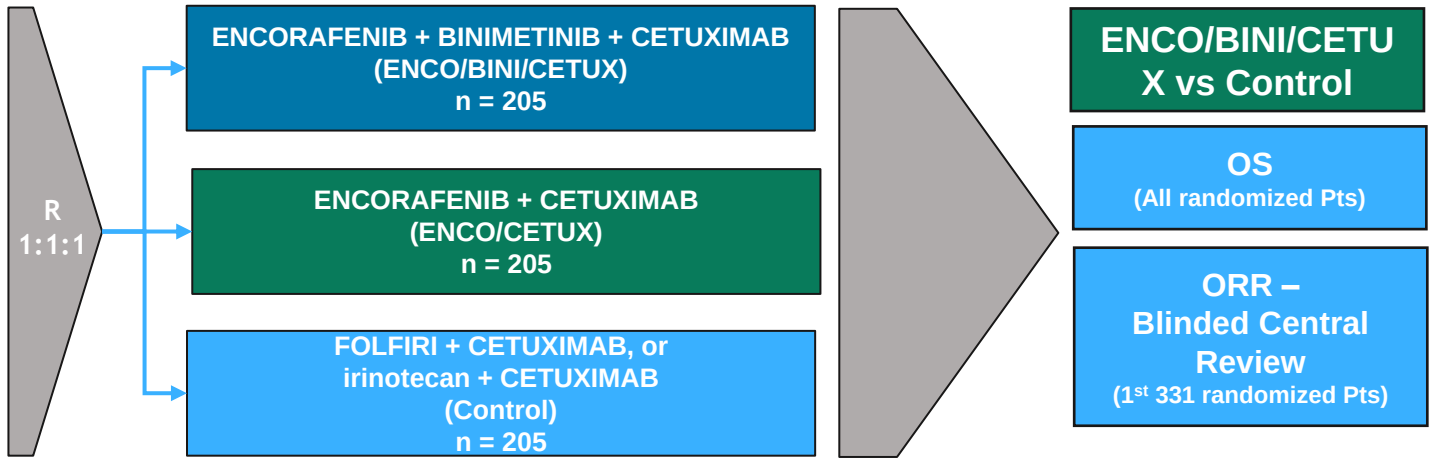


- ORR was generally similar across evaluated subgroups and consistent with that of the overall study population

[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

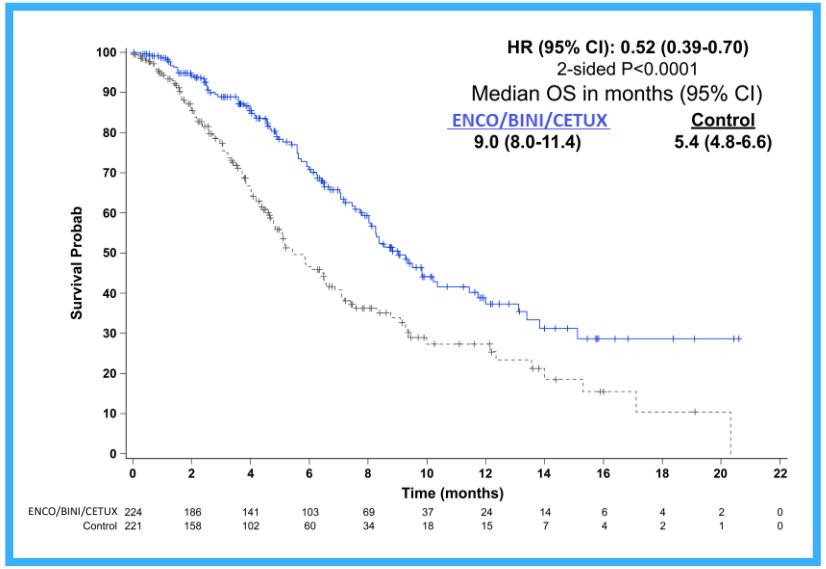
Patients with *BRAF* V600E-mutant mCRC with disease progression after 1 or 2 prior regimens; ECOG PS of 0 or 1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor

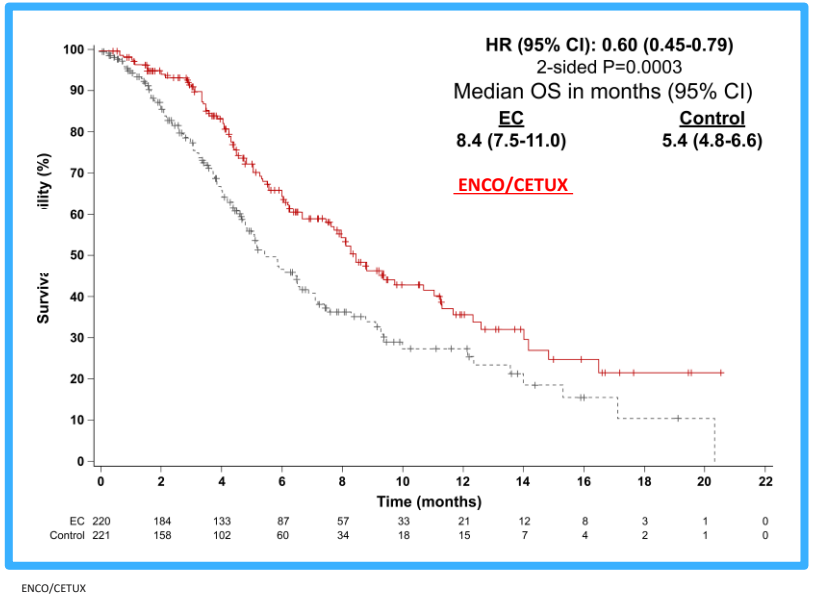


Post hoc Updated Analysis: includes 6 months of additional follow-up since cut off for primary analysis

Kopetz et al: NEJM, 2019

ENCO/BINI/CETUX vs Control*





ENCO/CETUX

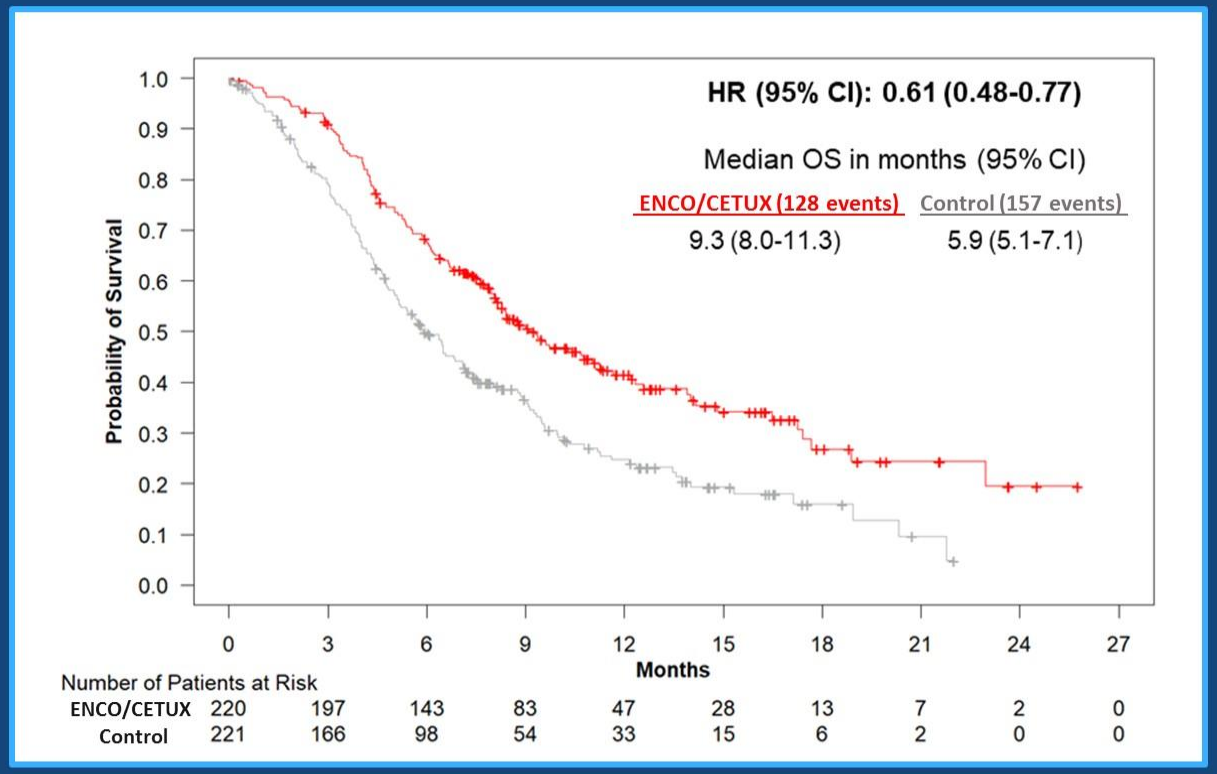
Objective Response Rate (First 331 Randomized Patients)

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	

*Overall survival analysis conducted in all randomized patients.

Revised FDA Indication for Enco/Cetux (4/8/2020)

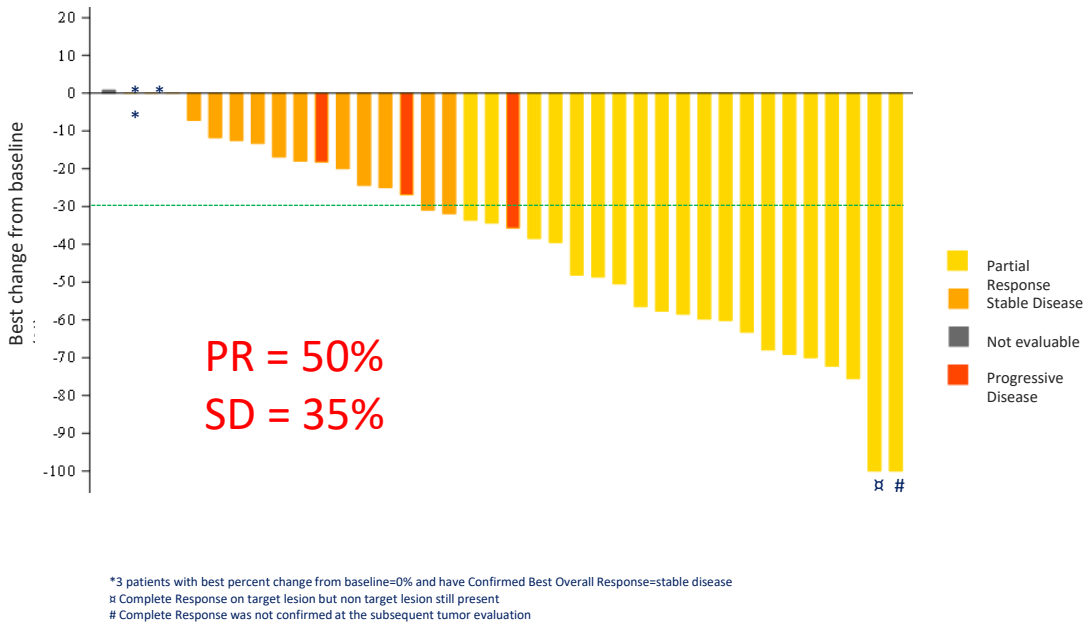
Updated Overall Survival: ENCO/CETUX vs Control



J Tabenero et al: JCO 2021

Best Percentage Change in Tumor Measurements for Stage 1: ANCHOR

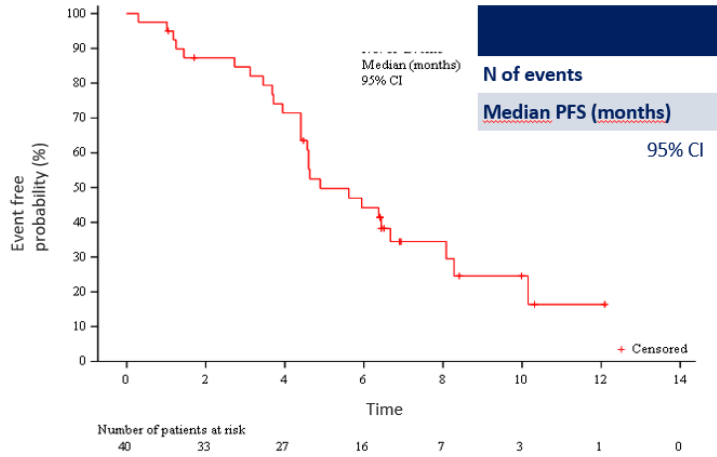
Investigator's assessment, patients evaluable for efficacy



*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.

World GI Congress ESMO 2021: Stage 2 update

- N=92
- The investigator-assessed **cORR was 47.8%** (95% confidence interval [CI] 37.3-58.5). There were no meaningful differences in cORR in subgroup analysis. The DCR was 88%.
- Regarding survival, **median PFS was 5.8 months** (95% CI 4.6-6.4) and **median OS was 17.2 months** (95% CI 14.1-NE

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

Safety Lead-in

- Patients with *BRAF* V600E-mutant mCRC with 0-1 prior regimens in the metastatic setting

Cohort 1: encorafenib + cetuximab + FOLFIRI (N=30)
Cohort 2: encorafenib + cetuximab + mFOLFOX6 (N=30)

Phase 3

- Patients with *BRAF* V600E mutant mCRC and no prior systemic therapy in the metastatic setting

Randomize 1:1:1*

Arm A
encorafenib + cetuximab
(N=290)

Arm B**
encorafenib + cetuximab + mFOLFOX6
OR
encorafenib + cetuximab + FOLFIRI
(N=290)

Control Arm* (Arm C)**
Investigators Choice:
mFOLFOX6 ± bevacizumab,
FOLFIRI ± bevacizumab,
FOLFOXIRI ± bevacizumab OR
CAPOX ± bevacizumab
(N=290)

* Stratified by: ECOG PS (0 vs 1) and Region (US/Canada vs Europe vs Rest of World)

VANDERBILT-INGRAM CANCER CENTER

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.

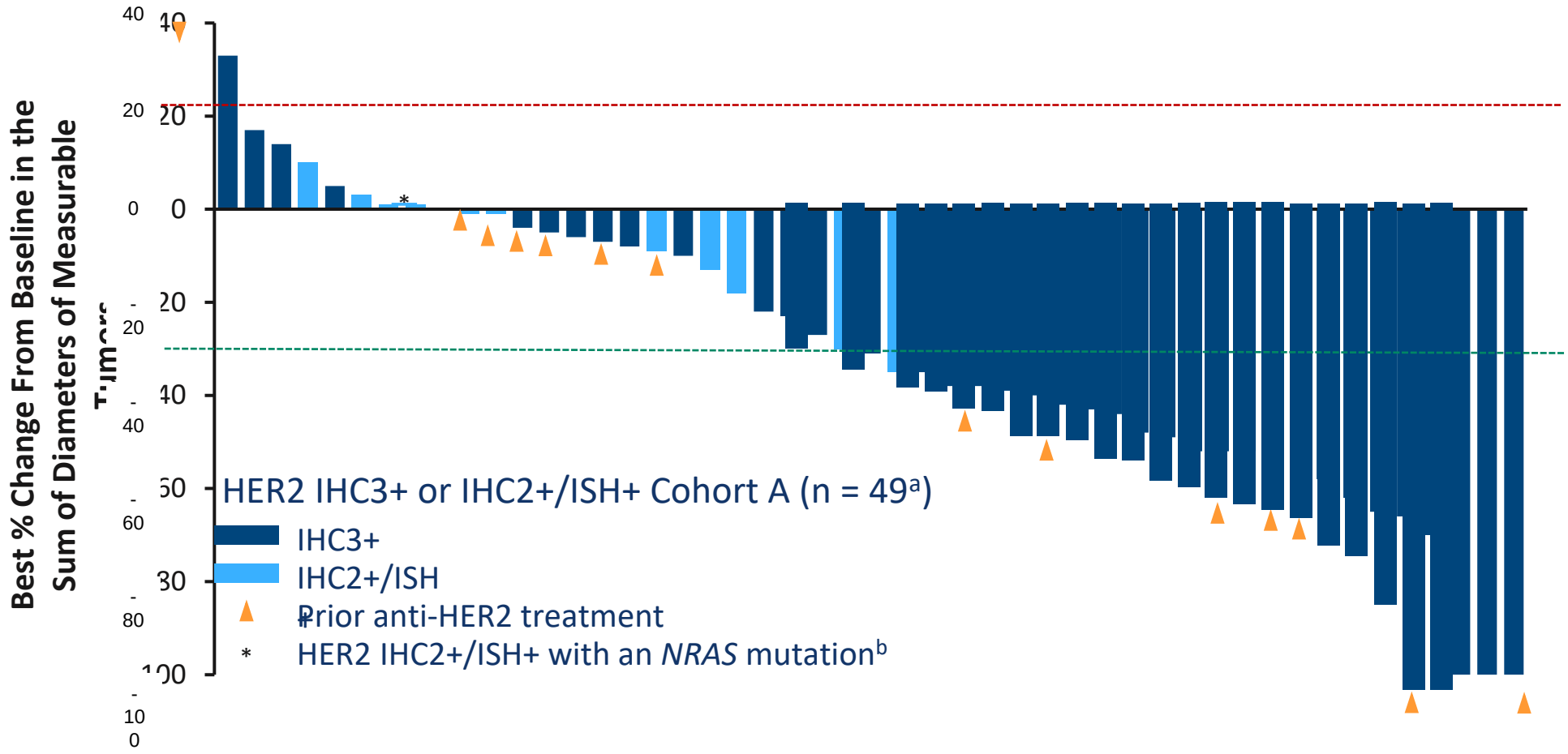
1. Siena S et al. *Lancet Oncol*. 2021;S1470-2045(21)00086-3.

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.

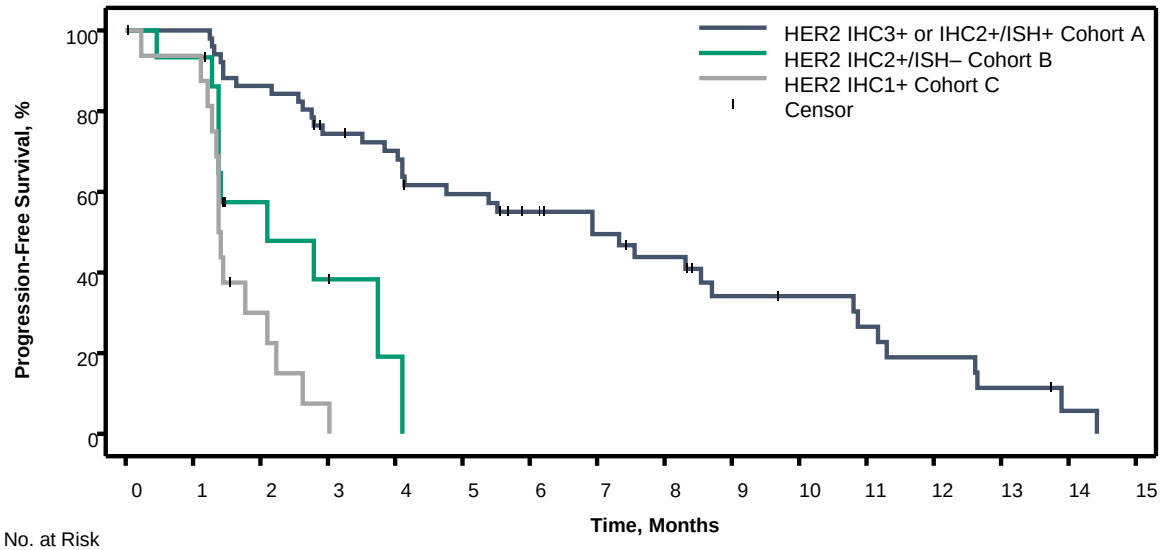
Best Change in Tumor Size in Cohort A



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

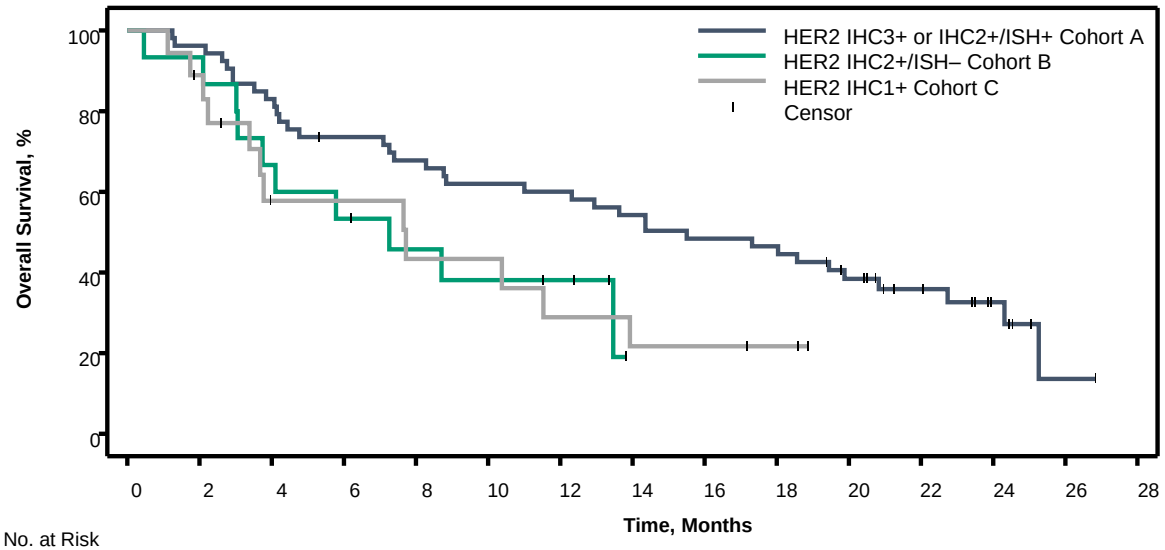


No. at Risk

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.

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

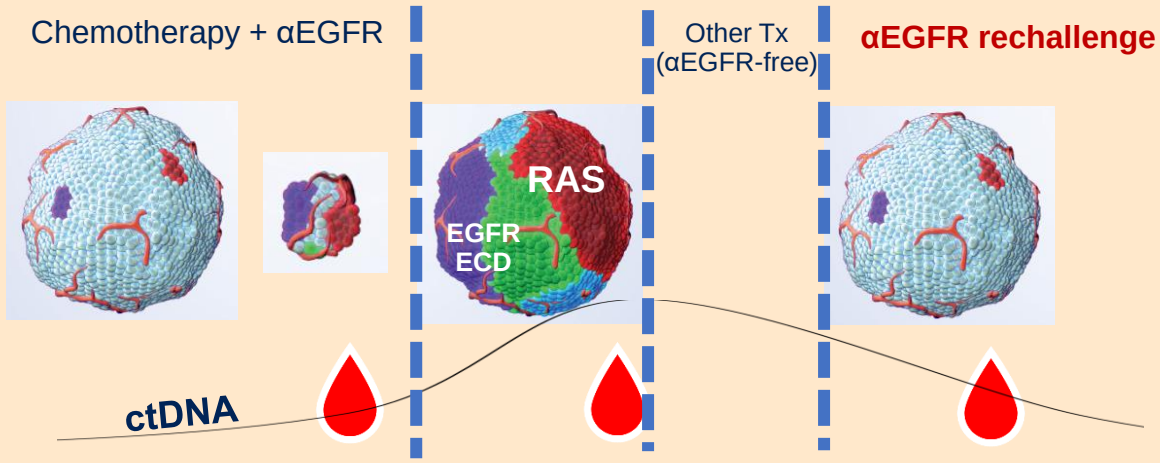
ISTITUTO DI CANDIOLO - IRCCS

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?

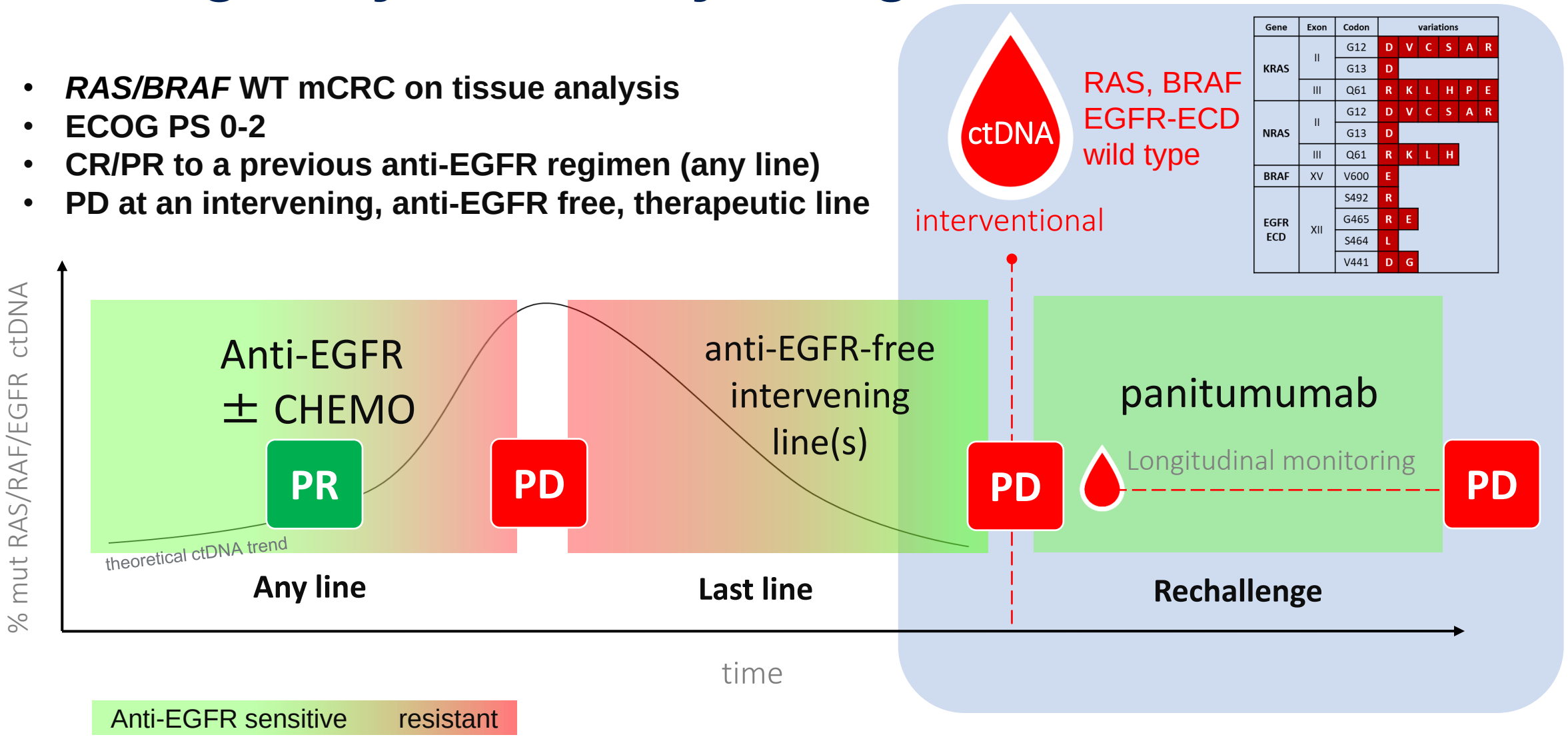
- **Resistance to anti-EGFR moAbs is predominatly driven by mutant RAS and EGFR ectodomain clones**[1,2]
- **Resistance can be monitored by ctDNA in plasma**[3]
- **RAS/EGFR alleles decline upon anti-EGFR therapy withdrawal, leading the tumor to regain sensitivity**[3,4]
- **Clinical-based rechallenge 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

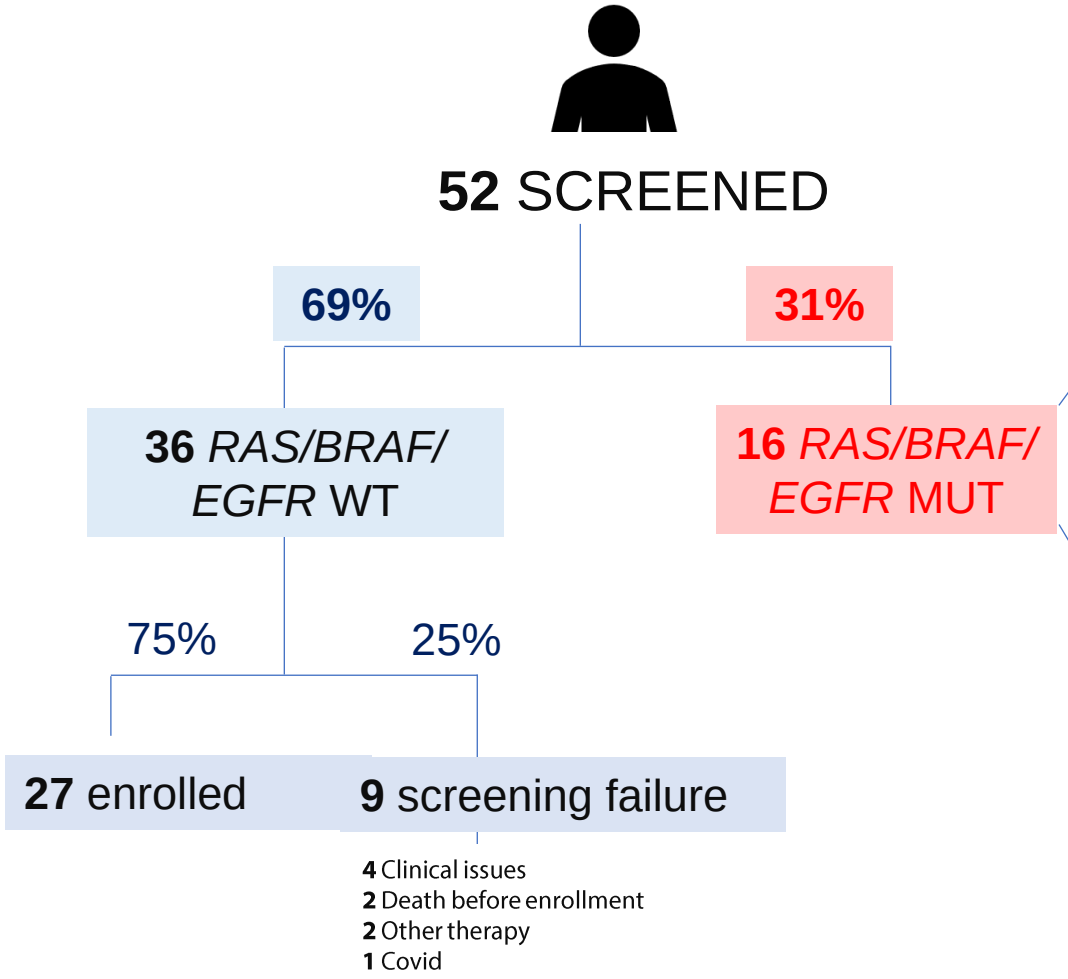
- ***RAS/BRAF* WT mCRC on tissue analysis**
- **ECOG PS 0-2**
- **CR/PR to a previous anti-EGFR regimen (any line)**
- **PD at an intervening, anti-EGFR free, therapeutic line**

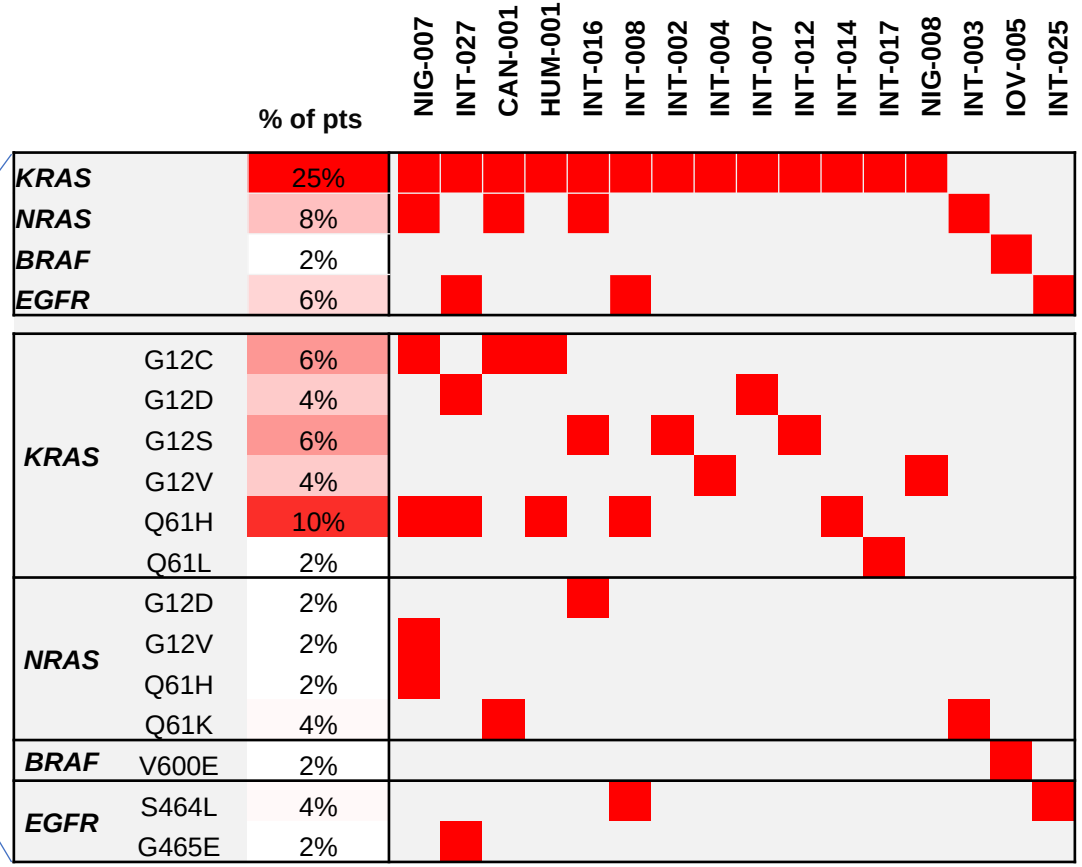


Gene	Exon	Codon	variations
KRAS	II	G12	D V C S A R
		G13	D
	III	Q61	R K L H P E
NRAS	II	G12	D V C S A R
		G13	D
	III	Q61	R K L H
BRAF	XV	V600	E
EGFR ECD	XII	S492	R
		G465	R E
		S464	L
		V441	D G

Molecular screening: results

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

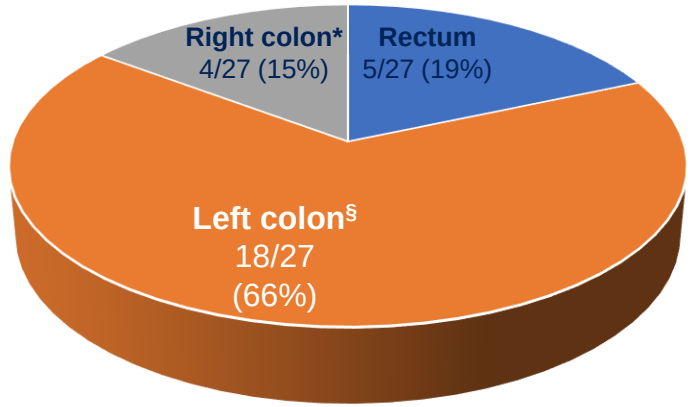




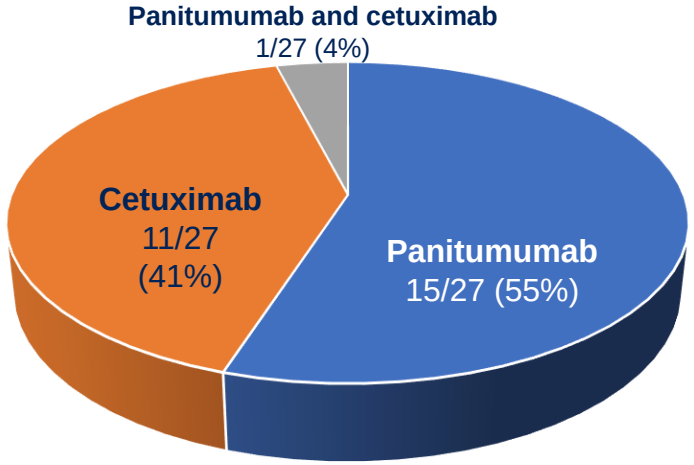
Baseline characteristics

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

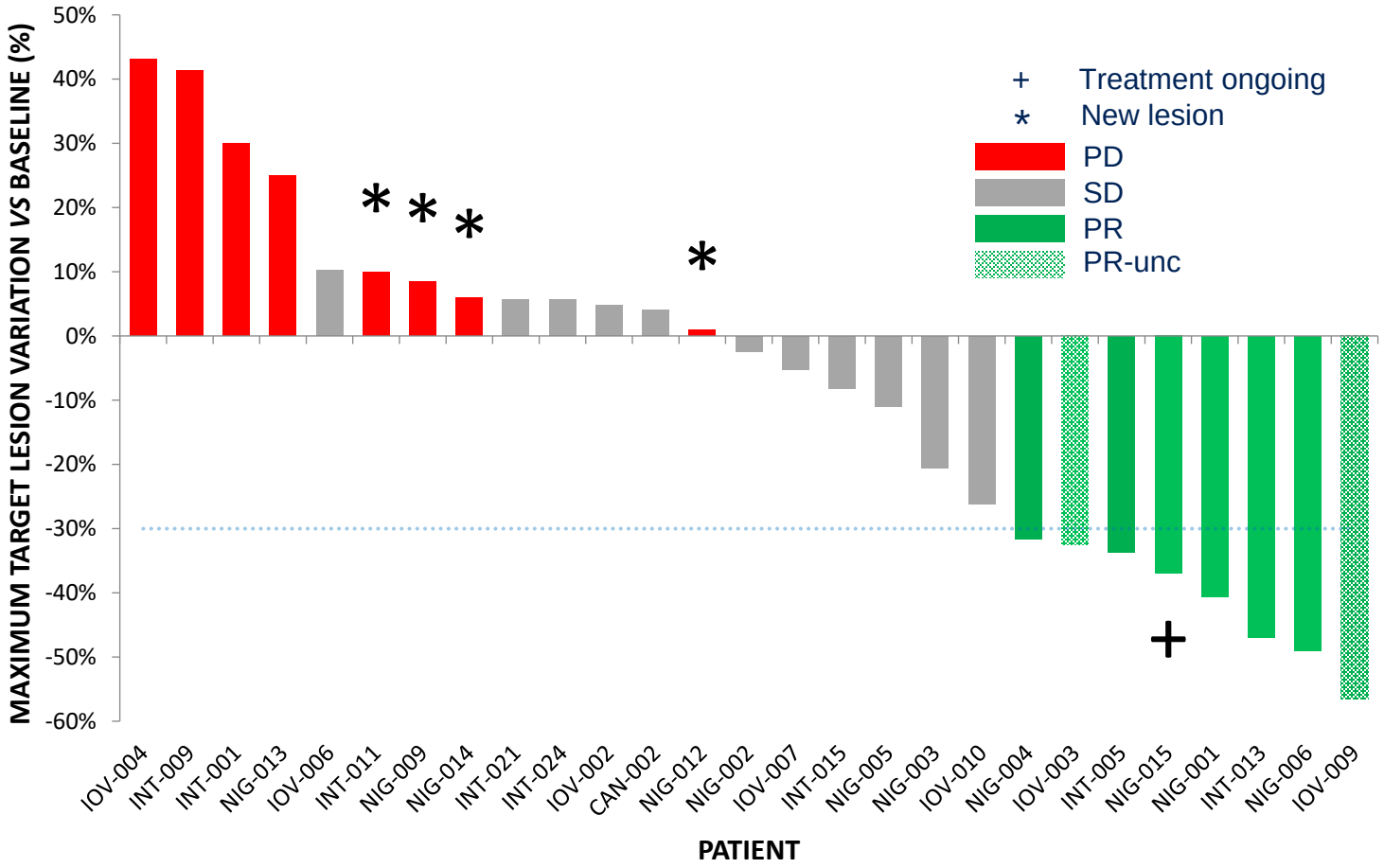


*Located in caecum, ascending colon, liver flexure, and transverse colon. §Located in splenic flexure, descending colon, and sigmoid colon.

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

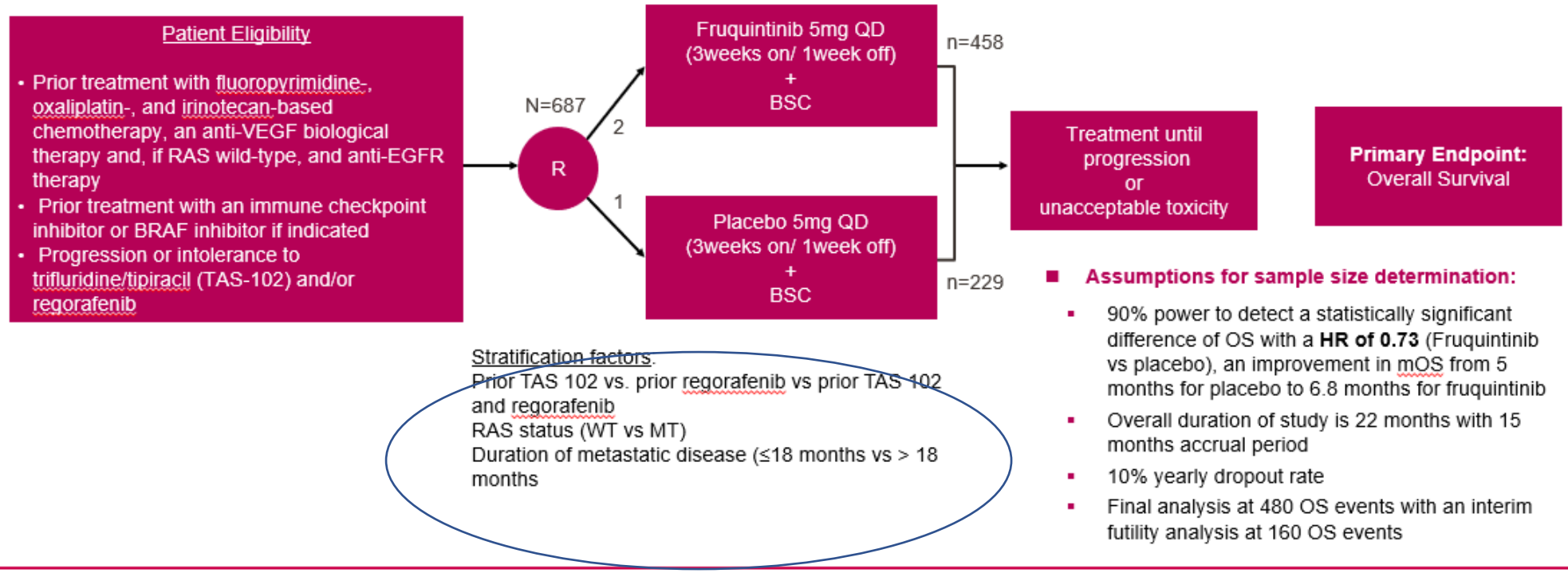


Phase III trial for all mCRC

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

NCT04322539

FRESCO-2 STUDY DESIGN



Non-operative Management (NOM) Rectal Cancer

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

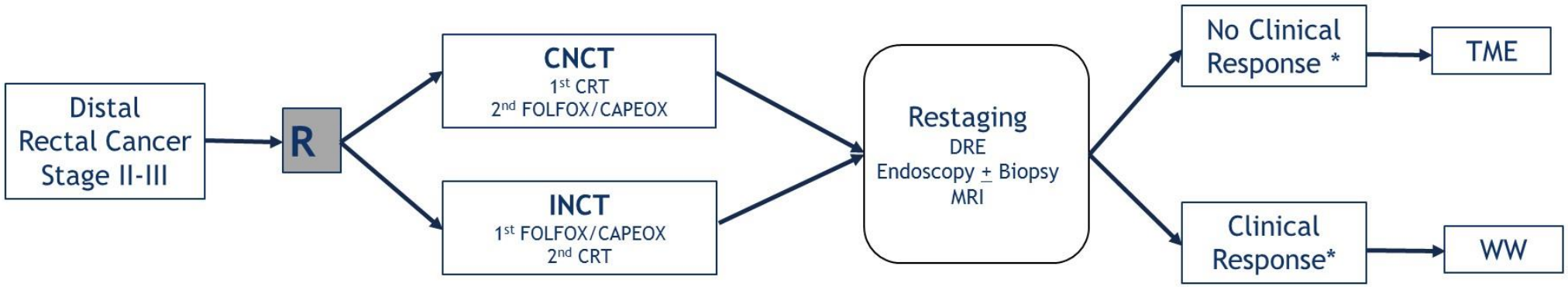
PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Julio Garcia-Aguilar

Protocol Schema

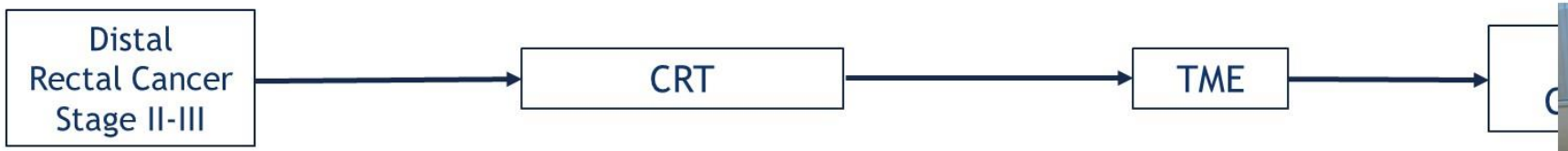
NCI trial registration: NCT02008656
NIH-funded (R01): 1R01CA182551-01

Investigational Arm

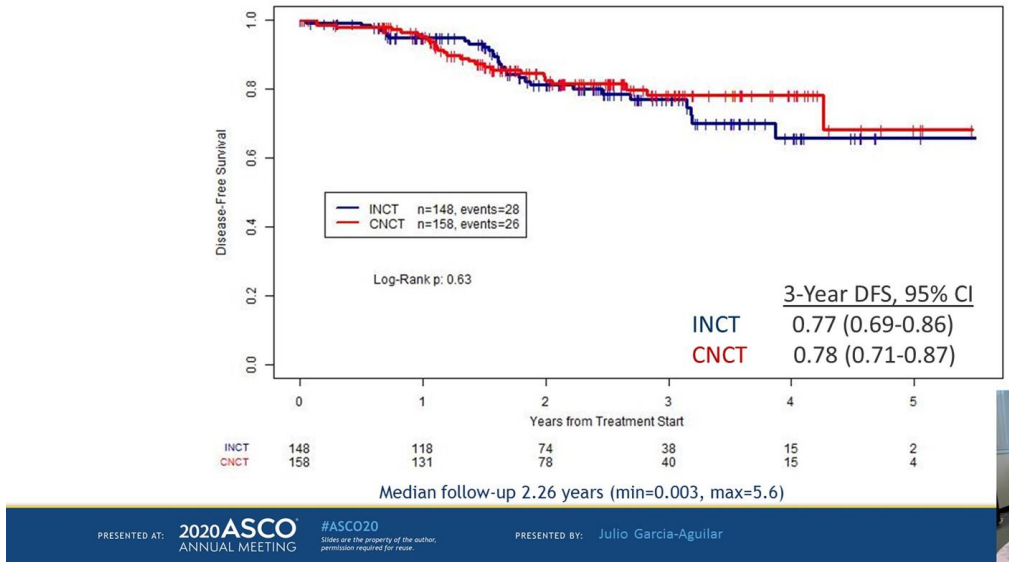


(*) Smith J et al, BMC Cancer 2015;15:767.

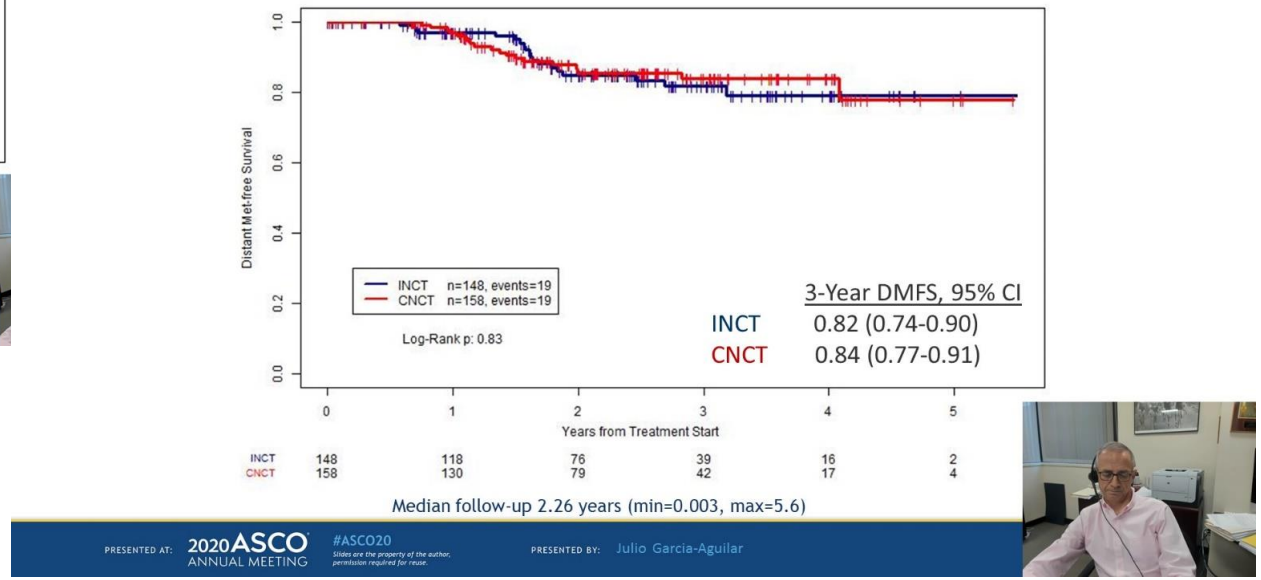
Control Arm (Historical Controls)



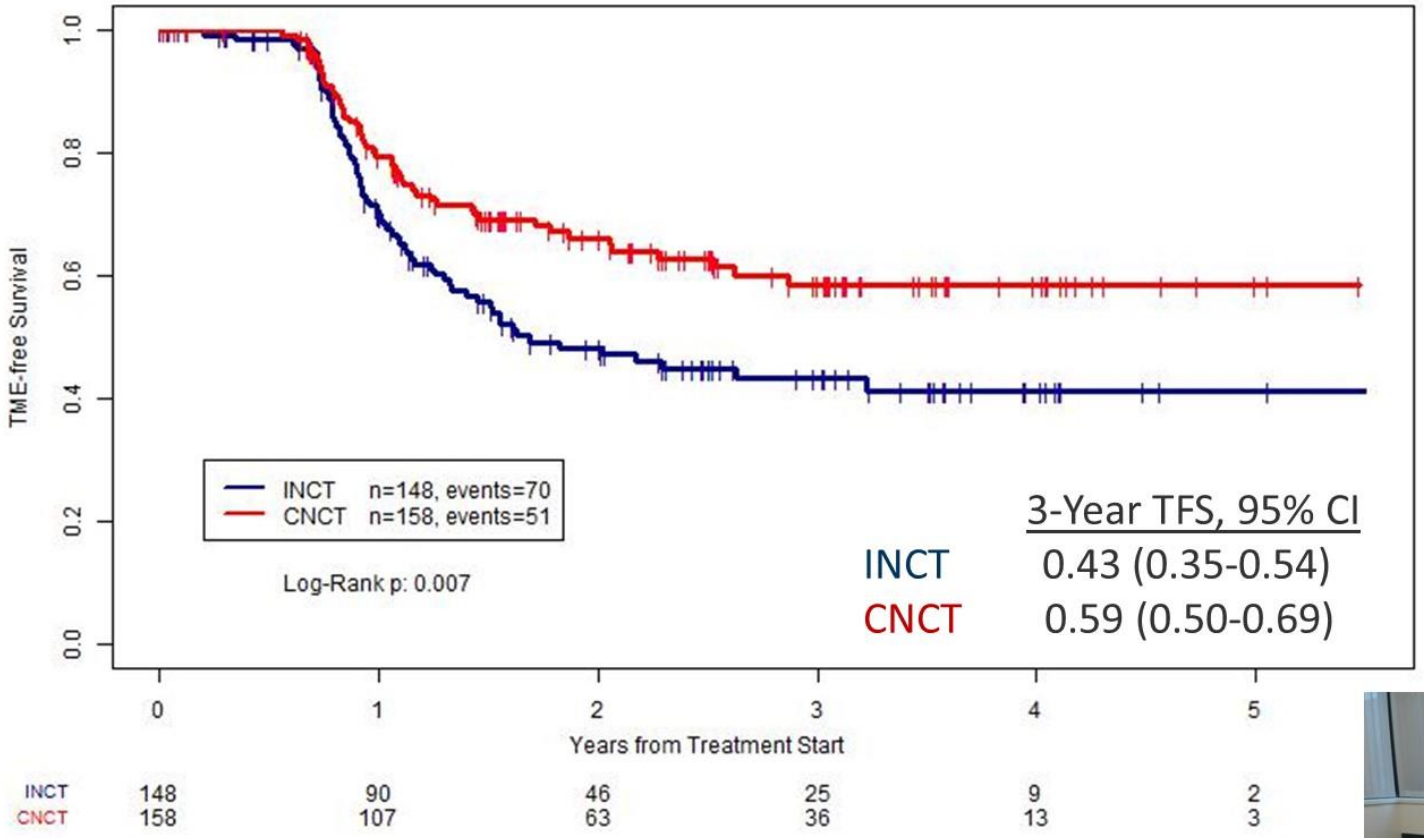
Results: DFS by Treatment Group



Results: Distant Metastasis-Free by Treatment Group



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)

Methods ASCO 2021 Update

Rectal Adenocarcinoma stage II-III

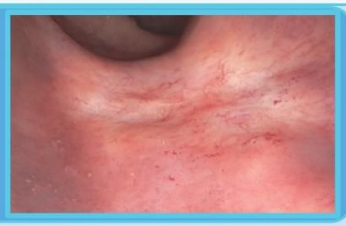
Randomized to total neoadjuvant therapy (TNT):
- **Consolidation (CNCT)**
OR
- **Induction (INCT)**

8 +/- 4 weeks

Three-Tier Clinical Response Assessment Schema

Clinical Complete Response (cCR)

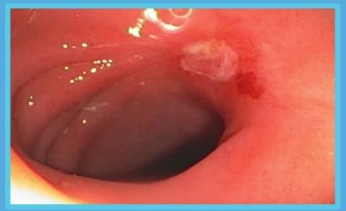
Flat, white scar
Telangiectasia
No ulceration or nodularity
Digital rectal exam (DRE): normal



→ Recommend WW

Near Complete Clinical Response (nCR)

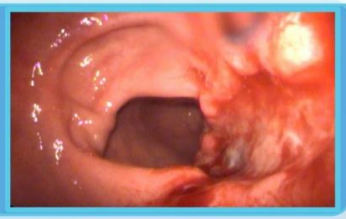
Irregular mucosa
Small nodules/minor mucosal abnormality
Superficial ulceration
Mild persisting erythema
DRE: smooth induration/minor mucosal abnormality on DRE



or

Incomplete Clinical Response (iCR)

Visible Tumor
DRE: palpable tumor nodules



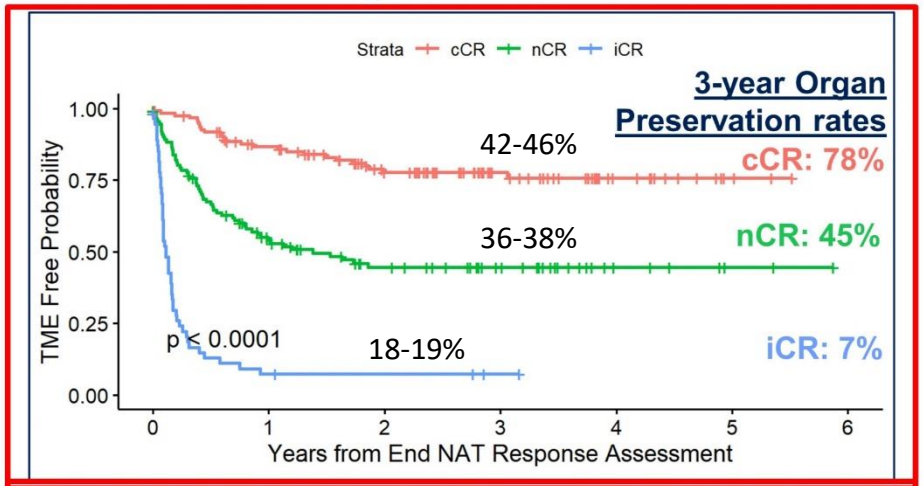
→ Recommend TME

Patient Characteristics and Treatment by Clinical Response

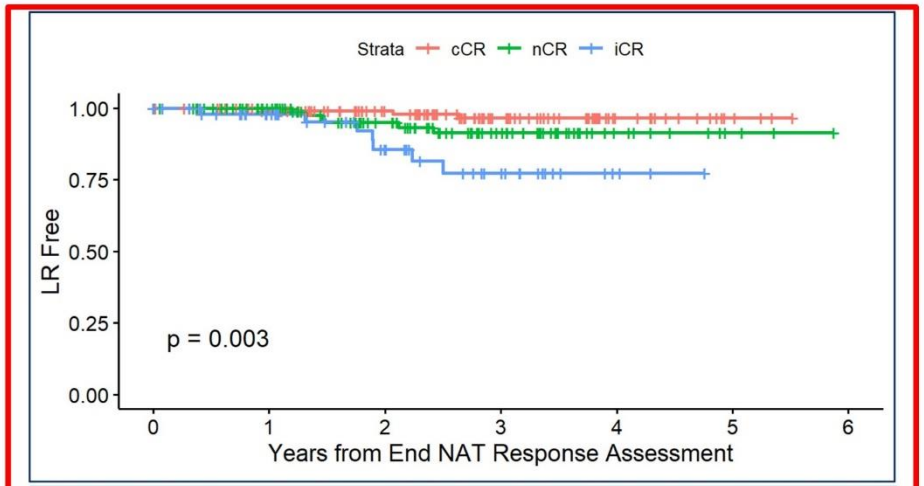
	cCR (n=124)	nCR (n=114)	iCR (n=55)	p-value
Treatment				0.3
INCT	54 (44%)	60 (53%)	28 (51%)	
CNCT	70 (56%)	54 (47%)	27 (49%)	
Median Tumor Distance from Anal Verge (cm)	4.5	4.0	4.5	0.3
Male Sex	75 (60%)	80 (70%)	37 (67%)	0.3
Median Age (years)	60	58	55	0.09
cT Classification				0.7
1/2	16 (13%)	11 (10%)	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

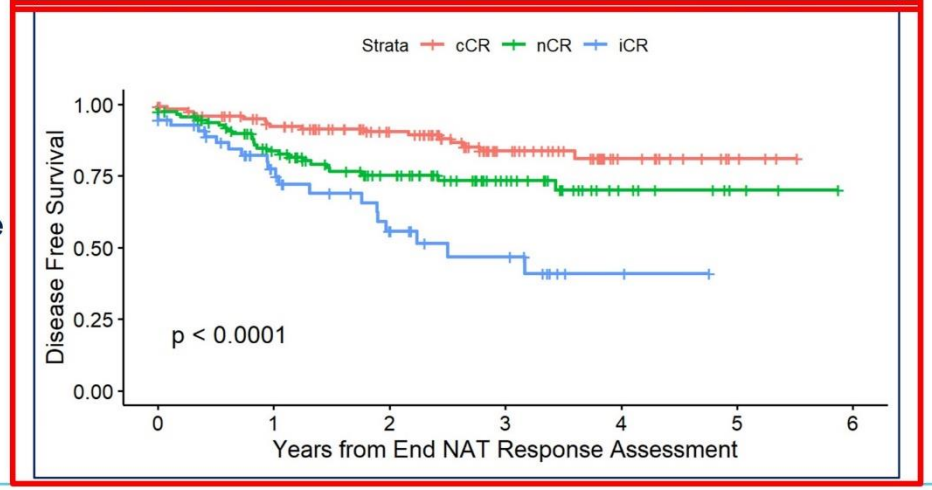
Organ Preservation



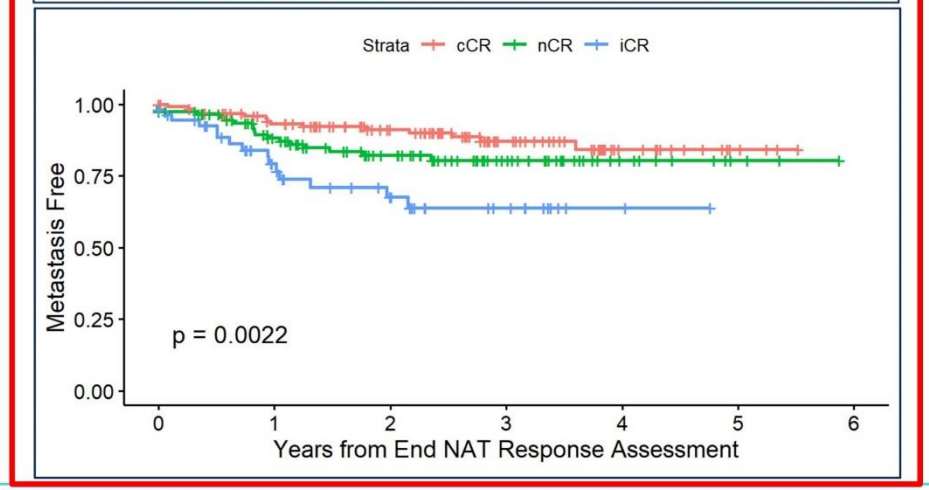
Local Recurrence-Free Survival



Disease-Free Survival



Metastasis-Free Survival



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

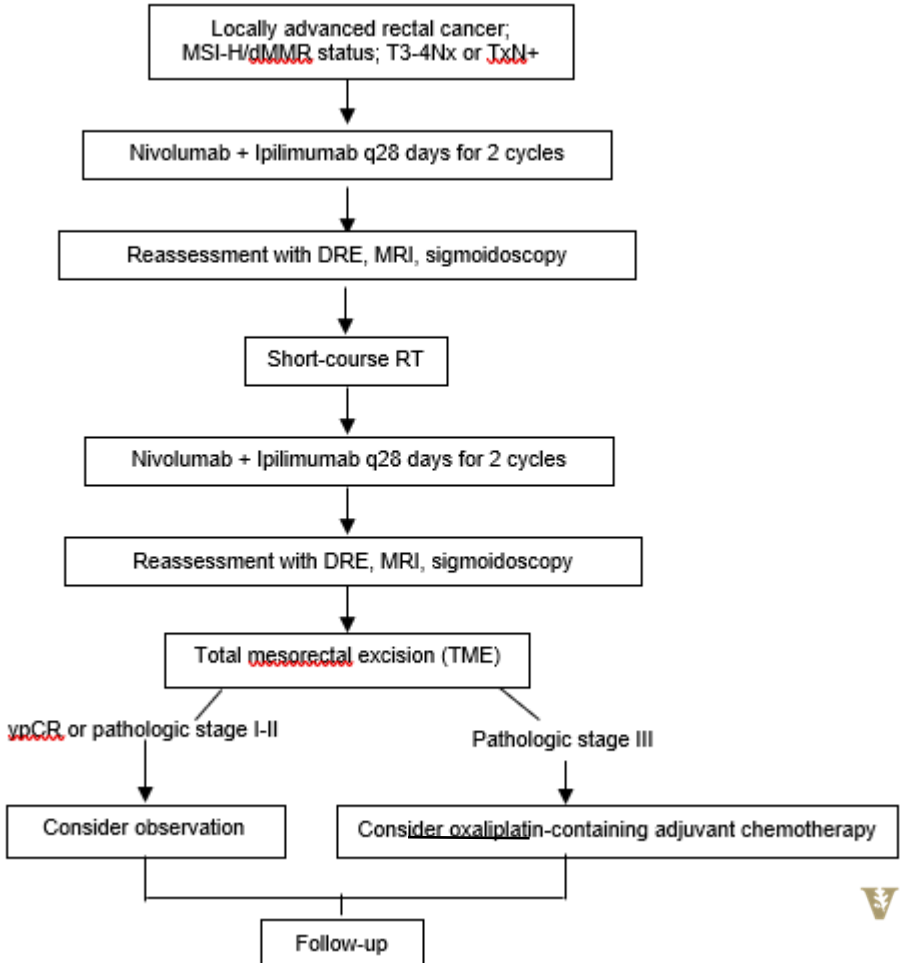
Eligibility:
- T3-4Nx or TxN+ rectal cancer
- dMMR or MSI-H

Primary endpoint:
- pCR rate

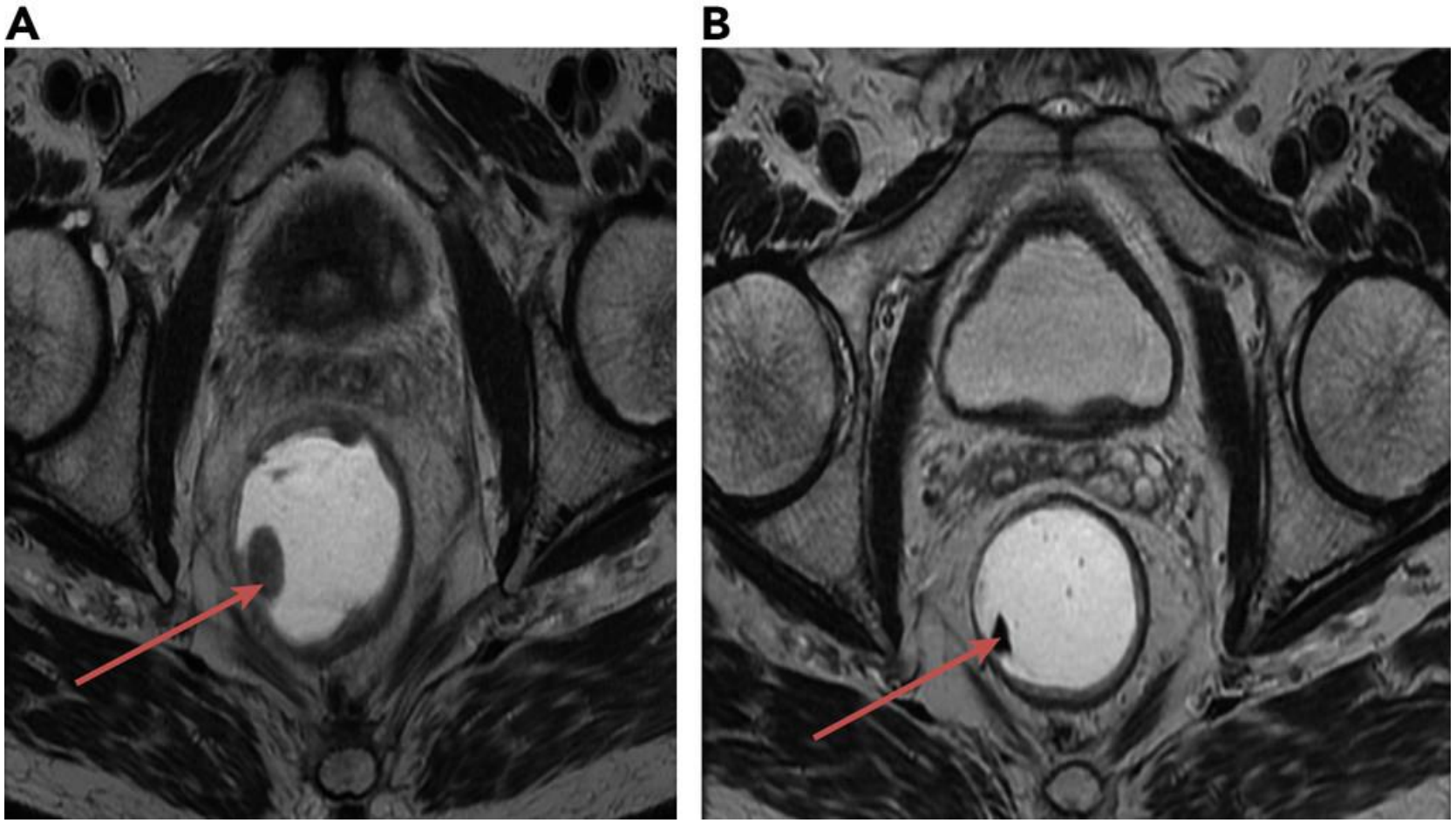
Secondary endpoints:
- DFS, OS
- Safety/tolerability
- Tumor regression grade
- Sphincter preservation rate for distal tumors

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

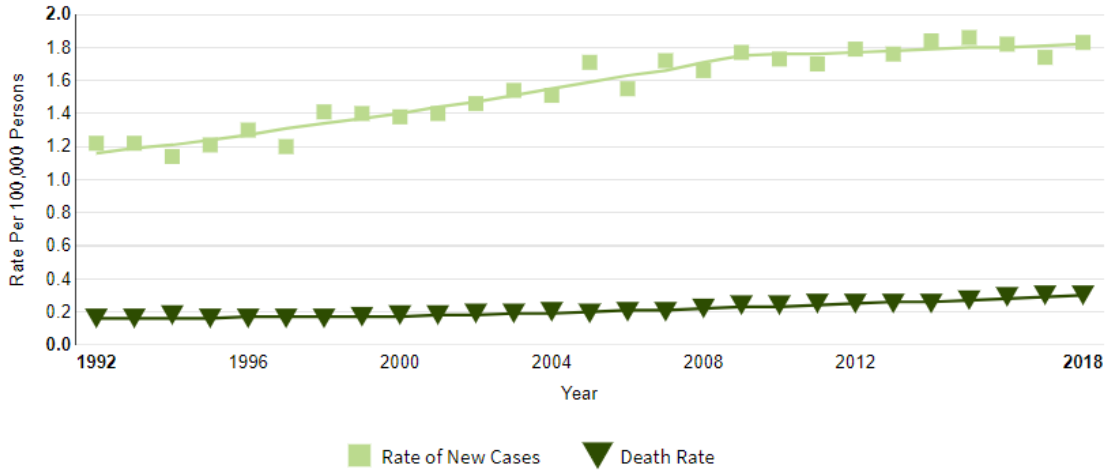
Fast Facts about Anal Cancer

Rising in incidence by 2.7% per year (2001-2015)

Estimated New Cases in 2021	9,090
% of All New Cancer Cases	0.5%

Estimated Deaths in 2021	1,430
% of All Cancer Deaths	0.2%

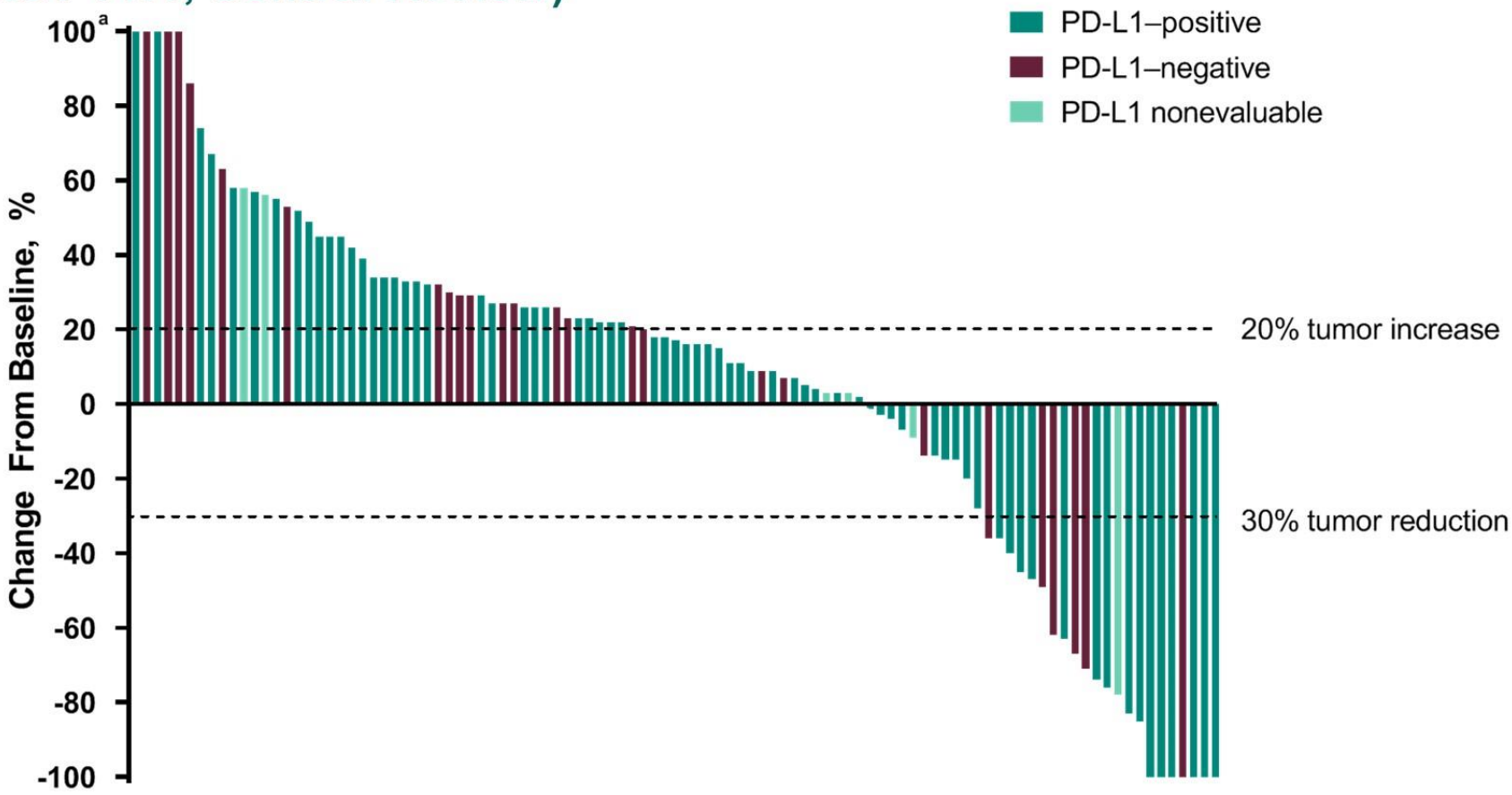
5-Year Relative Survival
68.7%
2011–2017



*Limited treatment options for advanced disease

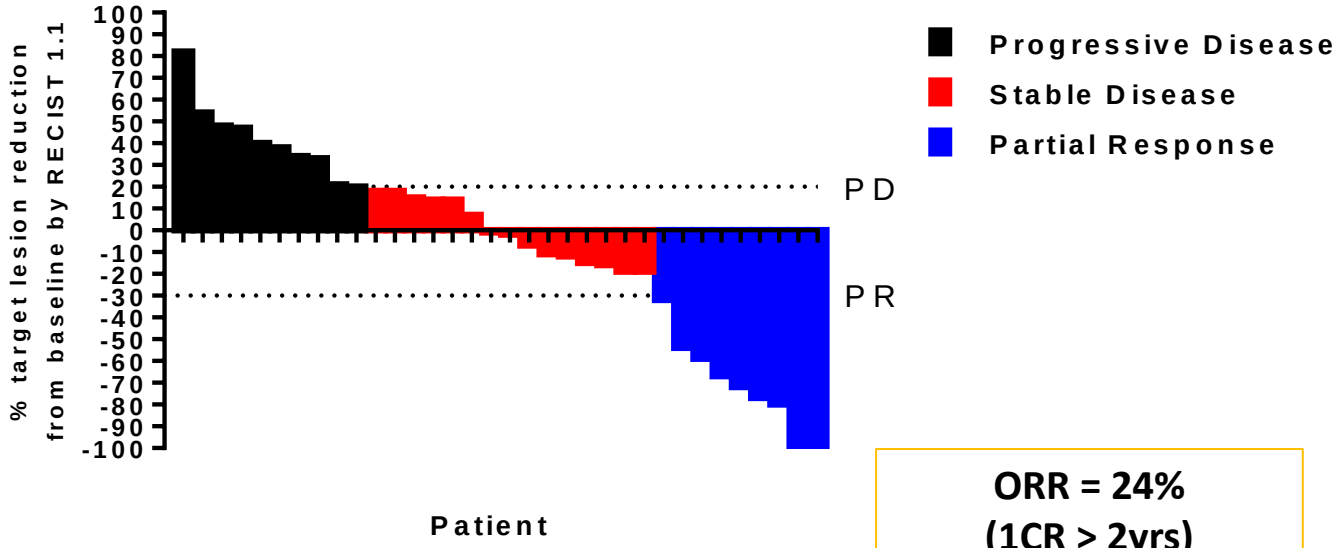
Phase II Study of Pembrolizumab in Metastatic Anal Cancer

Best percentage change from baseline in target lesion size
(RECIST v1.1, Central Review)



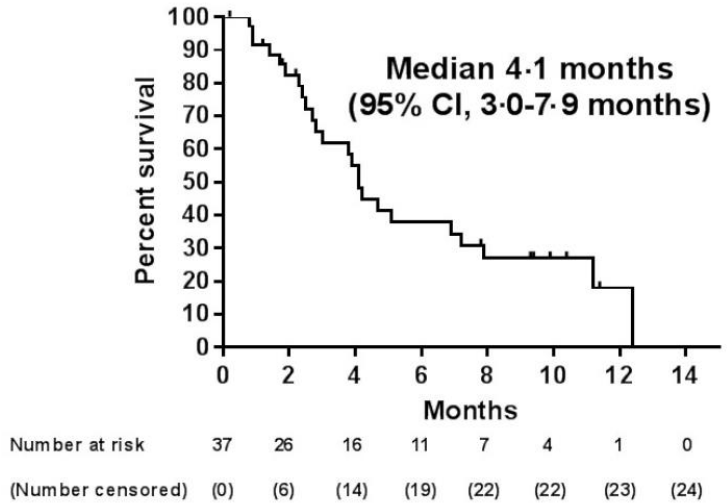
[a]Percentage changes from baseline >100% are presented as 100%.
Data cutoff date: June 27, 2019.

NCI9673 (Part A): Secondary Endpoints - PFS and OS

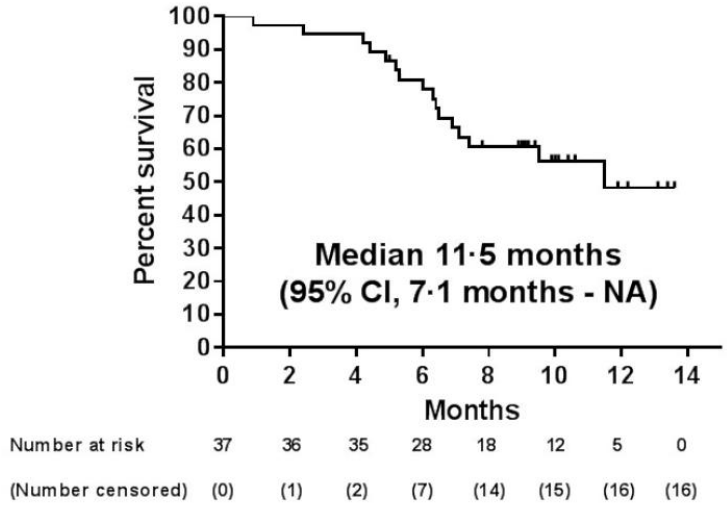


ORR = 24%
(1CR > 2yrs)

A



B

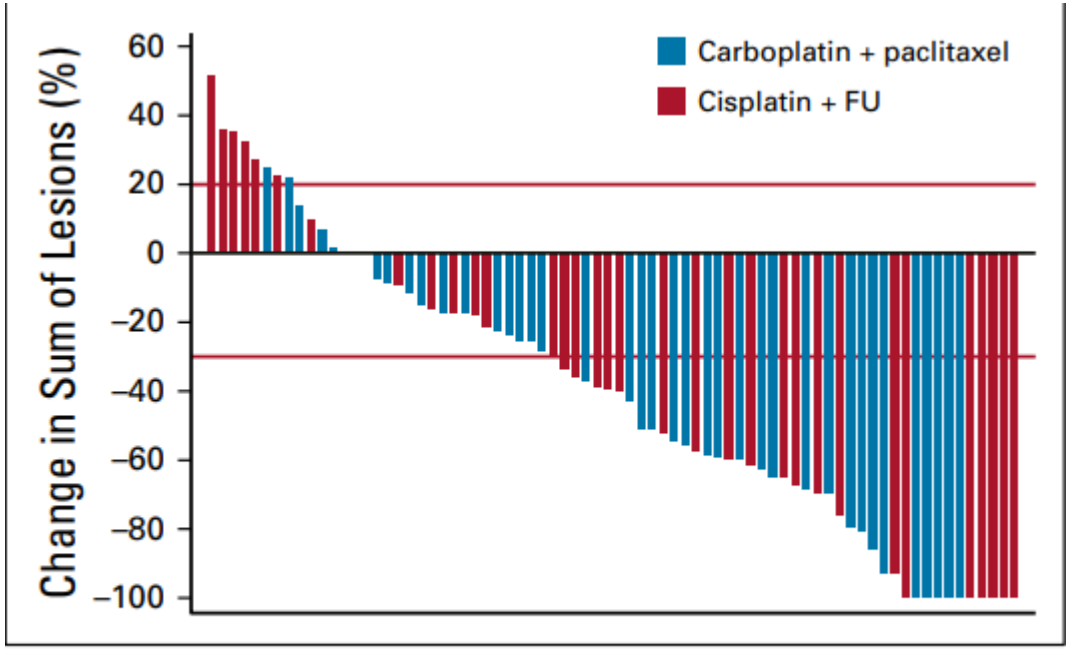


Morris et al: Lanc Onc, 2017

original reports

International Rare Cancers Initiative Multicent Randomized Phase II Trial of Cisplatin and Fluorouracil Versus Carboplatin and Paclitaxel in Advanced Anal Cancer: InterAAct

Sheela Rao, MD[1]; Francesco Sclafani, MD, PhD[1]; Cathy Eng, MD[2]; Richard A. Adams, MD[3]; Marianne G. Guren, MD, PhD[4]; David Sebag-Montefiore, MD[5]; Al Benson, MD[6]; Annette Bryant[1]; Clare Peckitt, MSc[1]; Eva Segelov, PhD[7]; Amitesh Roy, MSc, MD[8]; Matt T. Seymour, MA, MD[5]; Jack Welch, MD, PhD[9]; Mark P. Saunders, PhD[10]; Rebecca Muirhead, MD[11]; Peter O'Dwyer, MD[12]; John Bridgewater, PhD[13]; Shree Bhide, MRCP, PhD[14]; Rob Glynne-Jones, MD[15]; Dirk Arnold, MD[16]; and David Cunningham, MD FRCP[1]



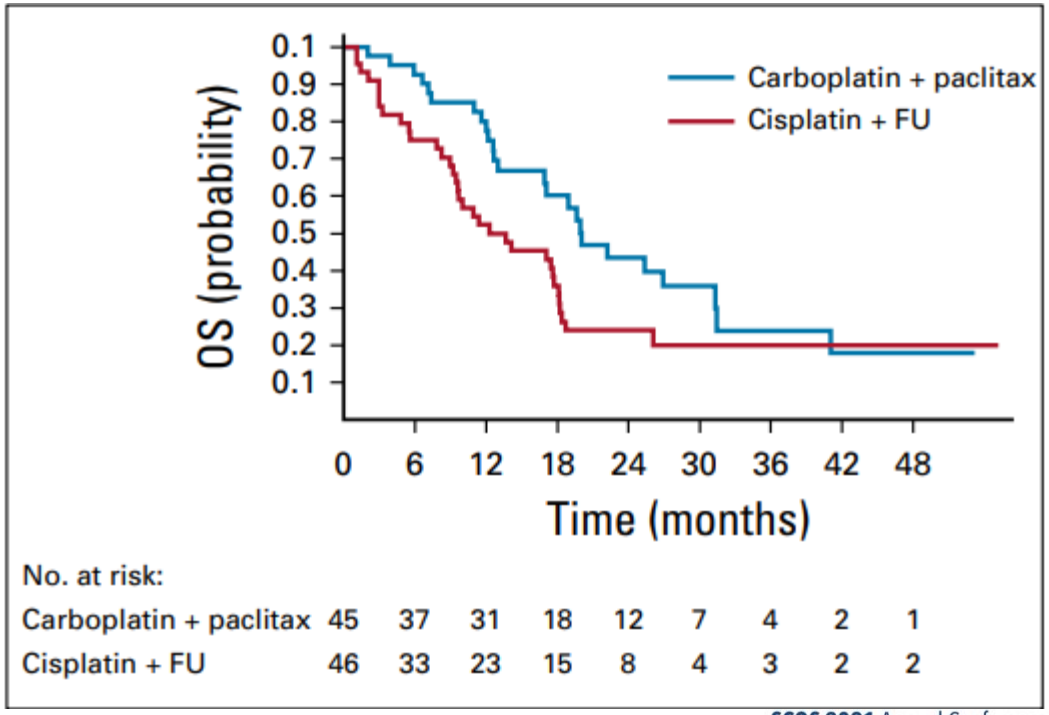
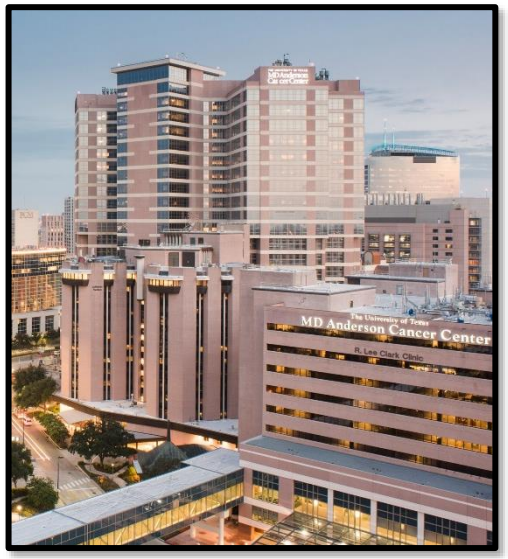


FIG 2. Waterfall plot of objective response. FU, fluorouracil.



Atezolizumab in combination with bevacizumab for patients with unresectable/metastatic anal cancer

Van K. Morris[1], Suyu Liu[2], Benny Johnson[1], Seema Prasad[1], Armeen Mahvash[3], Priya Bhosale[3], M. Laura Rubin[2], Nicole Rothschild[1], Andrew Futreal[4], Ignacio Wistuba[5], Patrick Hwu[6], James Yao[1], Cathy Eng[7]*, Daniel Halperin[1]*

Departments of [1]Gastrointestinal Medical Oncology, [2]Biostatistics, [3]Radiology, [4]Genomic Medicine, [5]Pathology, [6]Melanoma, MD Anderson Cancer Center, Houston, TX; [7]Department of Hematology/Oncology, Vanderbilt-Ingram Cancer Center, Nashville, TN

Abstract #2888

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

SCOS 2021 Annual Conference featuring ASCO Direct Highlights

*denotes equal contribution

Study Schema

Inclusion Criteria:

- Histologically confirmed SCCA
- ECOG PS 0-1
- Adequate hepatic, renal, and hematopoietic function

Exclusion Criteria:

- Prior immunotherapy (e.g., anti-PD-1/PD-L1/CTLA-4 antibodies)
- Prior immunosuppressive medications within 2 weeks of study treatment
- Active or prior autoimmune disease
- History of TIA/CVA or significant vascular disease (< prior 6 months)
- Current use of anti-platelet therapy (besides aspirin)
- History of GI perforation (< prior 6 months) or GI obstruction

N = 20

Atezolizumab (1200 mg)
+
Bevacizumab (7.5 mg/kg)
IV every 3 weeks,

Until progression, drug intolerance, or patient/provider decision

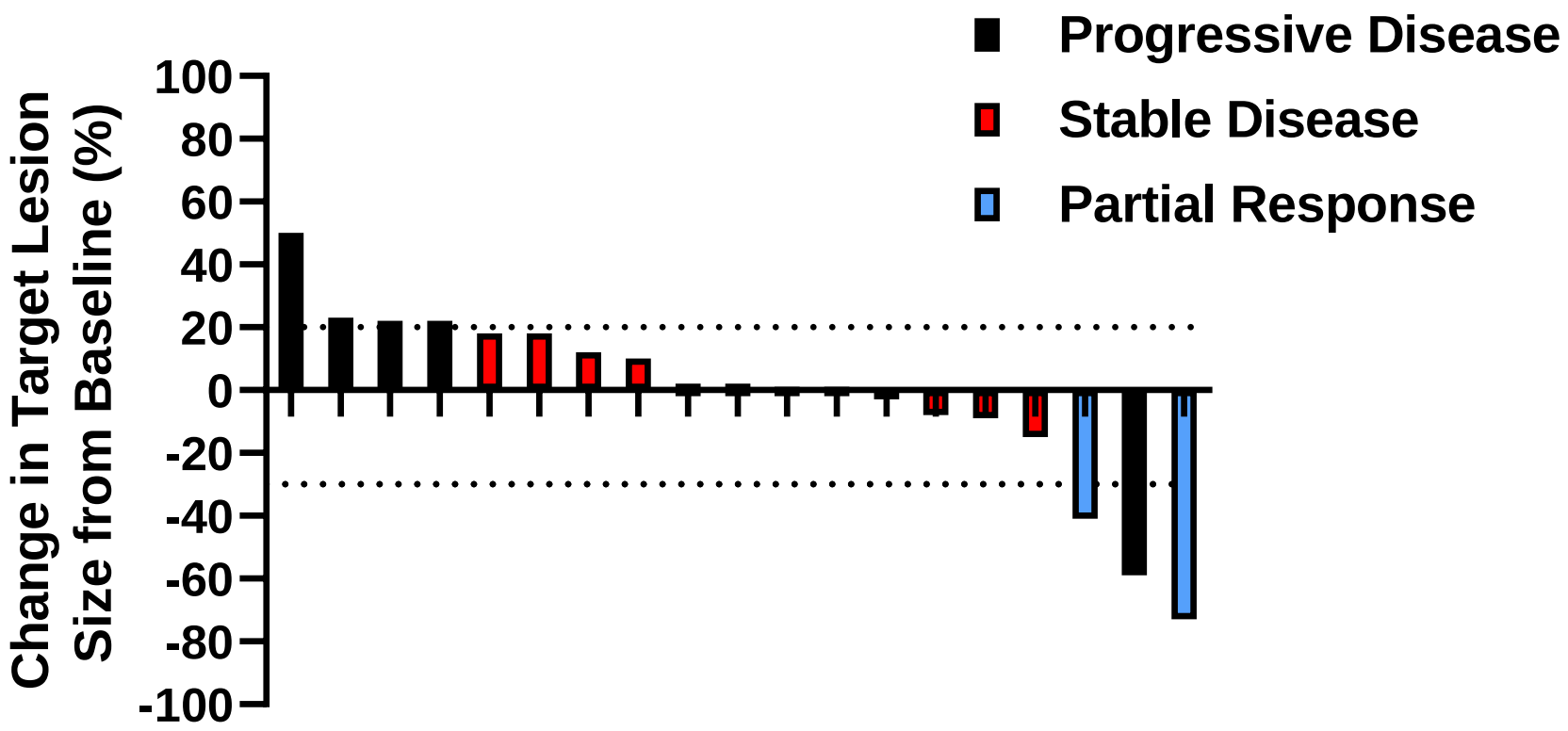
Response Assessment: every 9 weeks

Primary Endpoint:
- Radiographic response (RECIST 1.1)

Secondary Endpoints:
- Progression-free survival
- Overall survival
- Toxicity (CTCAE v 4.0)

*Serial blood and tissue collected for correlative studies.

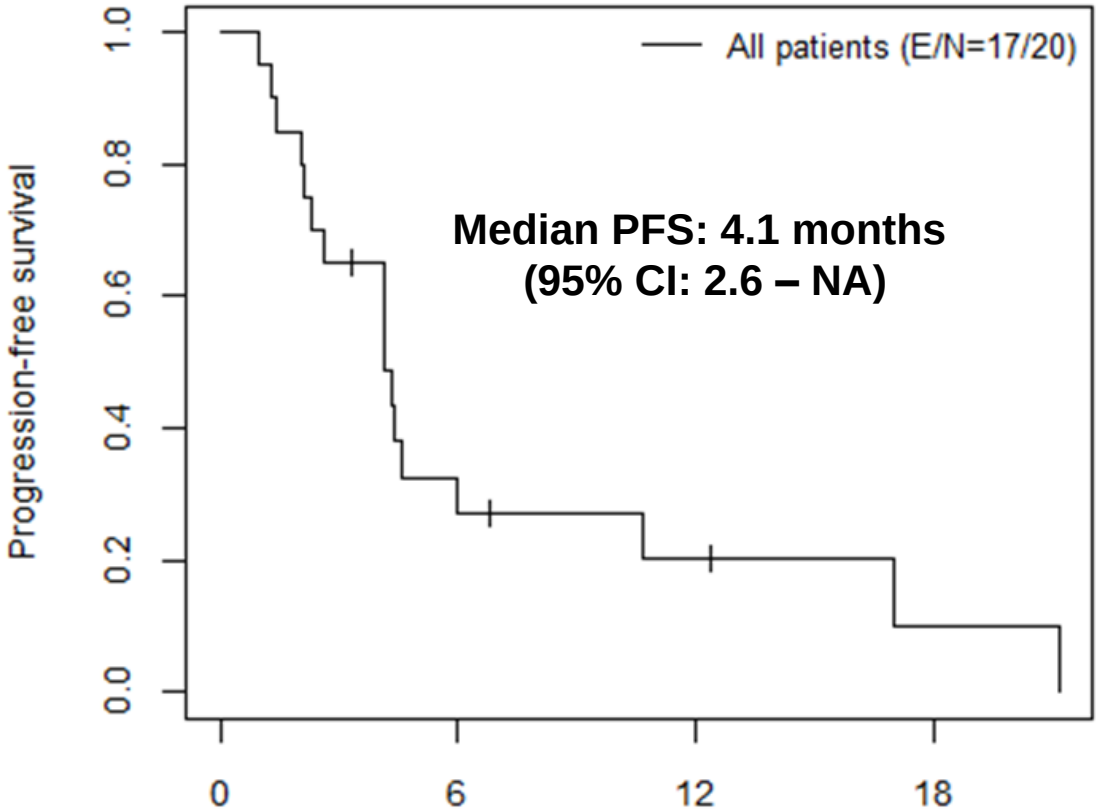
Treatment response



ORR: 10%
(95% CI: 1-32%)

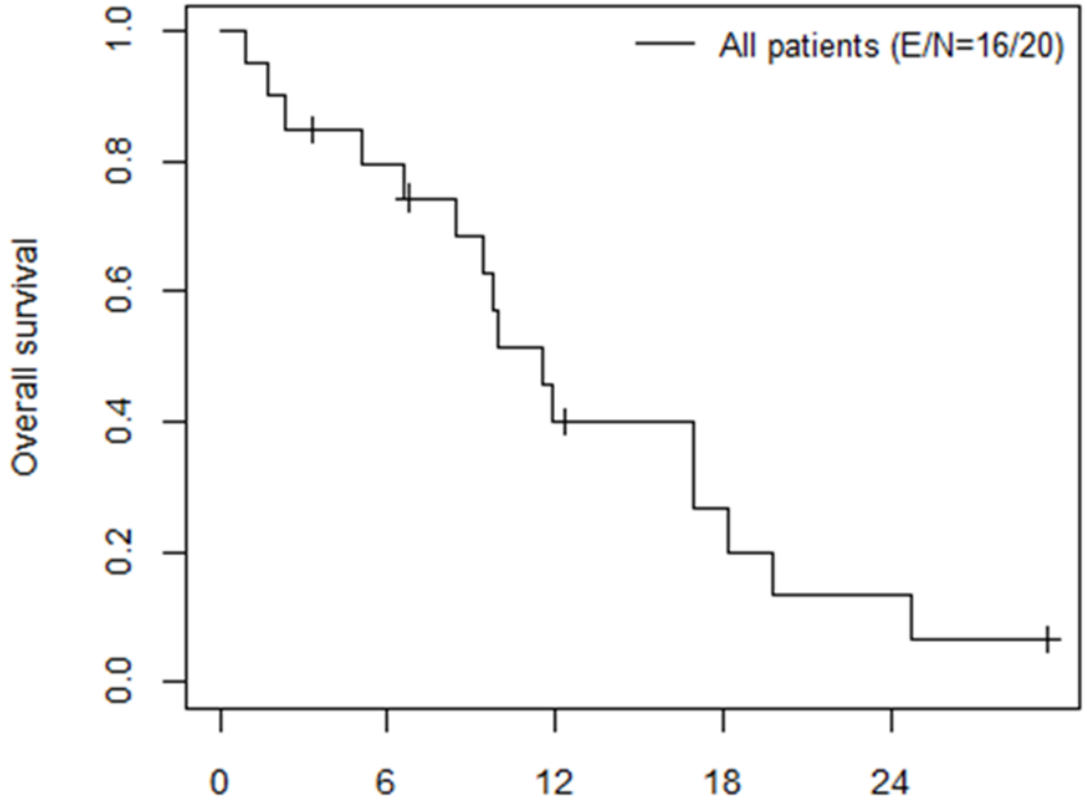
N=19 (evaluable)	N	%
Partial Response	2	10
Stable Disease	11	55
Progressive Disease	6	30

Progression-free Survival and Overall Survival



Median PFS: 4.1 months
(95% CI: 2.6 – NA)

12-month PFS rate: 20%
(95% CI: 8-52%)



12-month OS rate: 40%
(95% CI: 23-71%)

Pending and Ongoing Studies

EA 2182: Low Dose ChemoXRT in Early Stage (T1-2N0M0) Anal Cancer - The DECREASE Study

Inclusion:

- SCC of anal canal / margin
- T1-T2 N0 M0 ≤ 4cm
- N0 by PET/CT and pelvic CT/MRI criteria
- HIV negative or positive (CD4 ≥300)

Design:

- Phase II trial
- *n* = 252
- Stratified by T1 vs. T2 and HIV status

Primary endpoint:

- 2-year Disease Control ≥ 85%

RANDOMIZE

1:2

Standard-Dose Chemoradiation

- Primary tumor:
  50.4 Gy in 28 fractions
- Elective nodal regions: full pelvis + inguinal
  42 Gy in 28 fractions
- MMC X 1; 5-FU CI X 2 cycles OR Capecitabine

De-intensified Chemoradiation

- Primary tumor:
  T1: 36 Gy in 20 fractions
  T2: 41.4 Gy in 23 fractions
- Elective nodal regions: true pelvis + inguinal
  T1: 32 Gy in 20 fractions
  T2: 34.5 Gy in 23 fractions
- MMC X 1; 5-FU CI X 1 cycle OR Capecitabine

Concurrent Chemo

- MMC 10 mg/m^2 on day 1
- 5-FU CI 1000mg/m^2/d days 1-4 (c1), days 29-32 (c2) OR
  Capecitabine 825 mg/m^2 BID M-F on days of RT

Randomized Phase 2 Trial of Avelumab +/- Cetuximab for Unresectable, Locally Advanced or Metastatic Squamous Cell Anal Carcinoma (SCCAC)

Closed to Enrollment

Key Eligibility Criteria:

- Surgically unresectable, locally advanced/recurrent or metastatic squamous cell carcinoma patients of the anal canal

≥ 1 Prior Therapy

NCT0394425

Study PI's: Lonardi, Buggin

HIV+ CD4 > 300

N=54

Arm 1: Avelumab (10 mg/kg) q2 wks

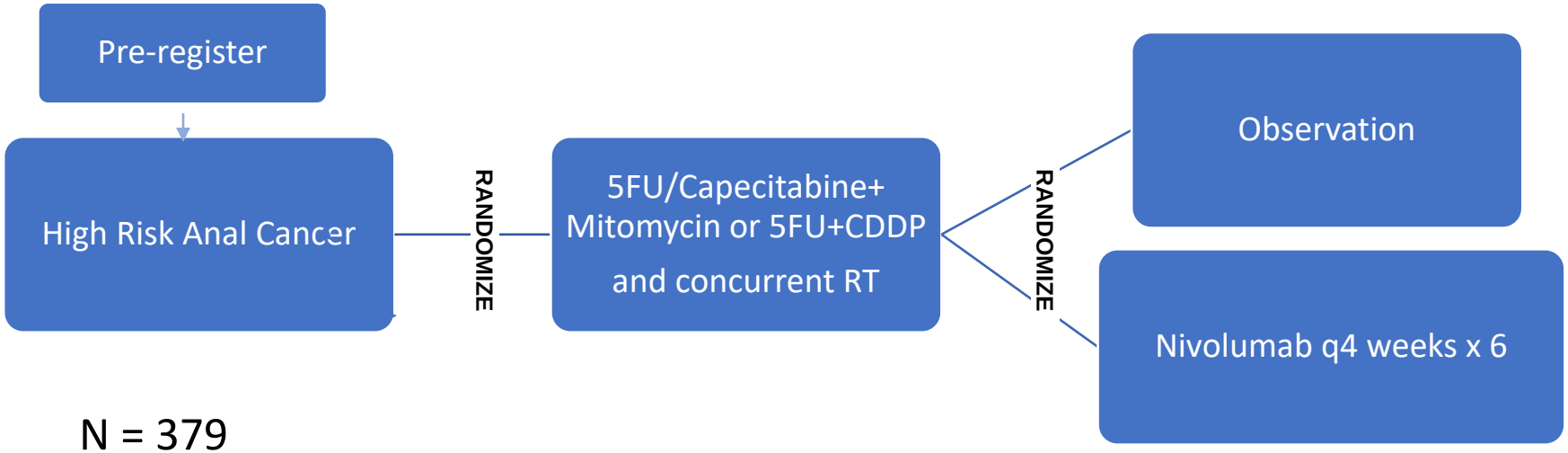
Arm 2:

Avelumab + Cetuximab q 2 wks

Primary Endpoint:
RR

Secondary Endpoints:
PFS, OS

EA2165: Randomized Phase II/III Trial of Nivolumab Following ChemoXRT in High-Risk Locally Advanced Anal Cancer (T ≥ 4 cm, N+)

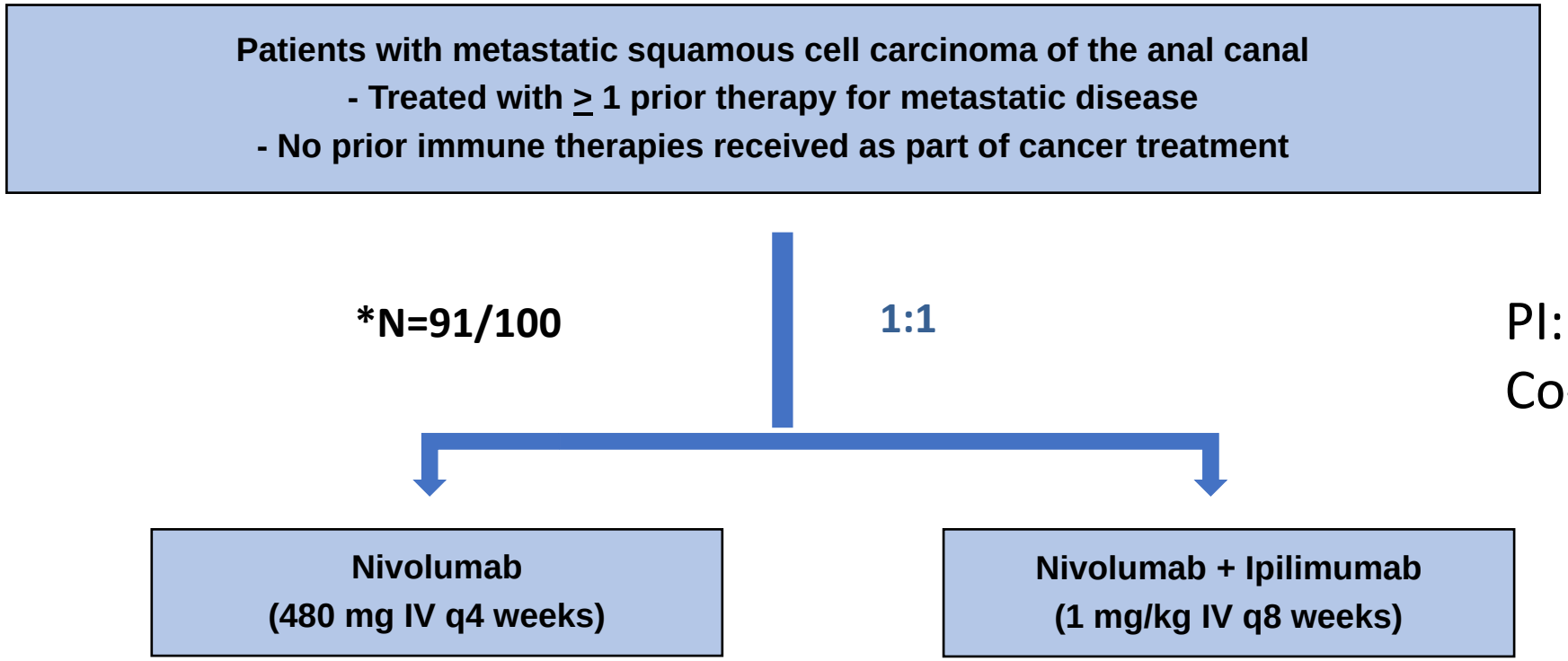


N = 379

Stratification Factors: Nodal status, HIV, RT dose
N=248/344

Primary endpoint: 2-yr DFS (Goal of 62.5% vs. 45%)
Secondary endpoints: CFS, OS, Toxicity

NCI9673 (Part B): Randomized Phase II ETCTN Study of Nivolumab +/- Ipilimumab in Metastatic SCCA of the Anal Canal

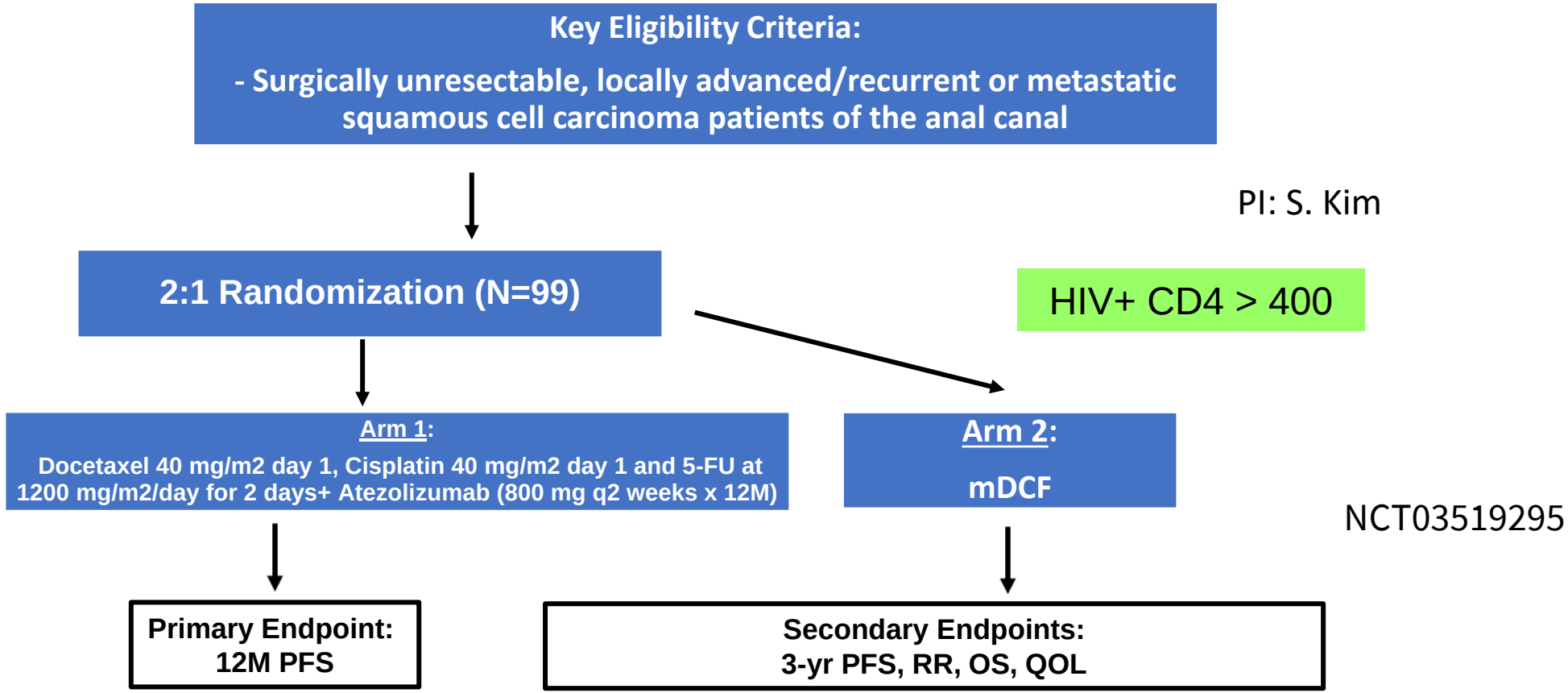


PI: C. Eng
Co-PI: V. Morris

Primary endpoint: PFS
Secondary endpoints: OS, RR, and SAE's
Exploratory correlatives to be collected

NCT02314169

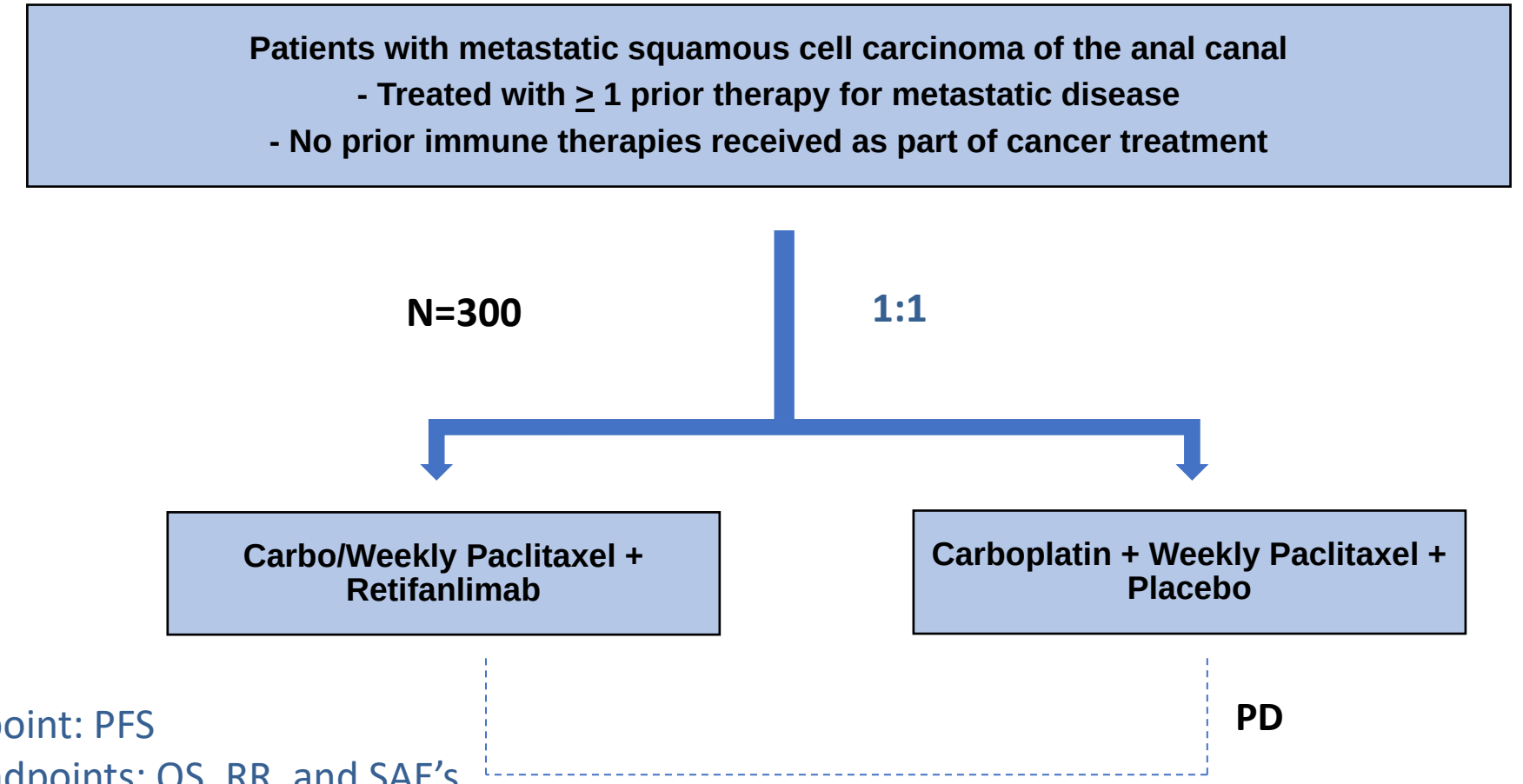
A Phase II Study of mDCF +/- Atezolizumab in Treatment-Naïve Metastatic Squamous Cell Anal Carcinoma (SCARCE)



PI: S. Kim

NCT03519295

Phase 3 Carboplatin-paclitaxel With Retifanlimab or Placebo in Participants With Locally Advanced or Metastatic Squamous Cell Anal Carcinoma (POD1UM-303/InterAACT 2)



PI: S. Rao

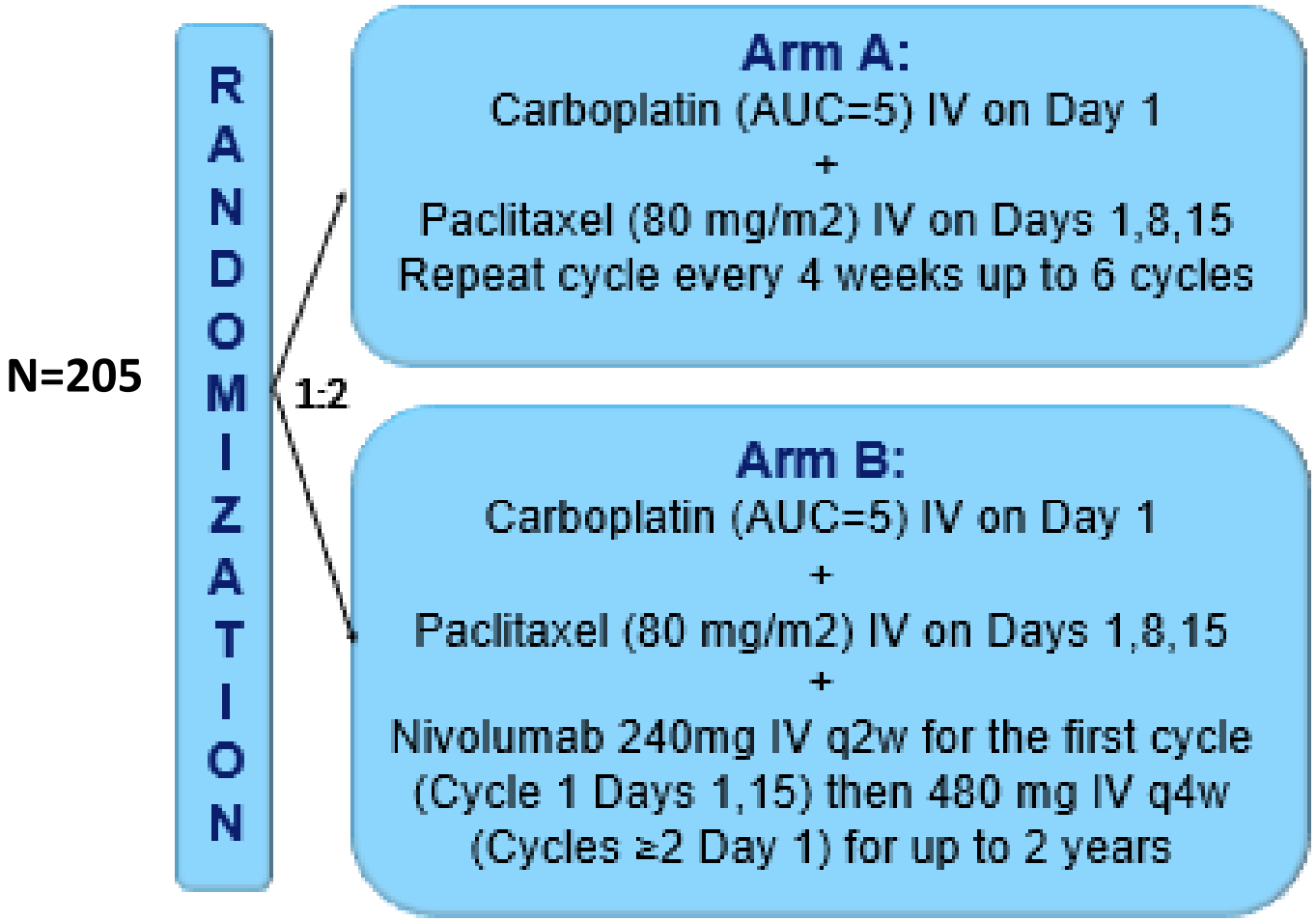
Primary endpoint: PFS
Secondary endpoints: OS, RR, and SAE's
Exploratory correlatives to be collected

NCT04472429

EA2176: Phase III Carboplatin + Paclitaxel +/- Nivolumab

Key Eligibility Criteria:

- Inoperable, recurrent, or metastatic anal squamous cell carcinoma
- ≥ 18 years of age
- ECOG Performance Status ≤ 0-1
- RECIST v1.1 measurable disease
- Patients with asymptomatic brain lesions are eligible if treatment ended >3 months
- HIV+ patients on effective anti-retroviral therapy with undetectable viral load are eligible
- No prior systemic chemo or other investigational therapy; no prior immunotherapy



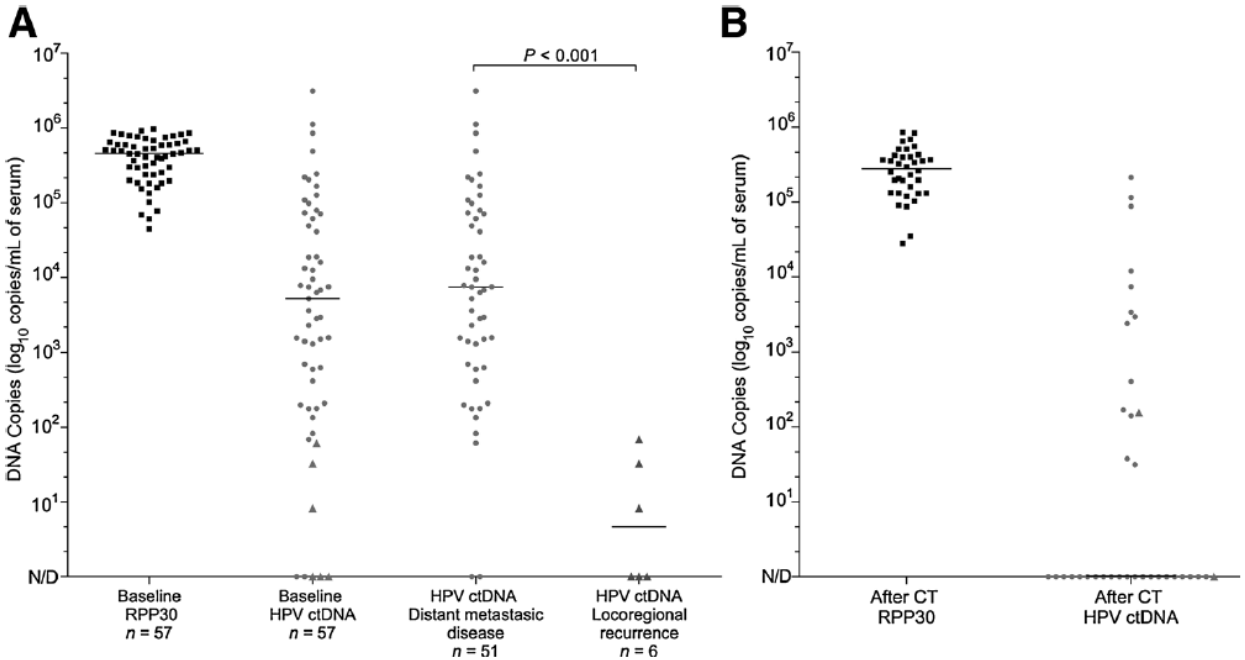
NCT04444921

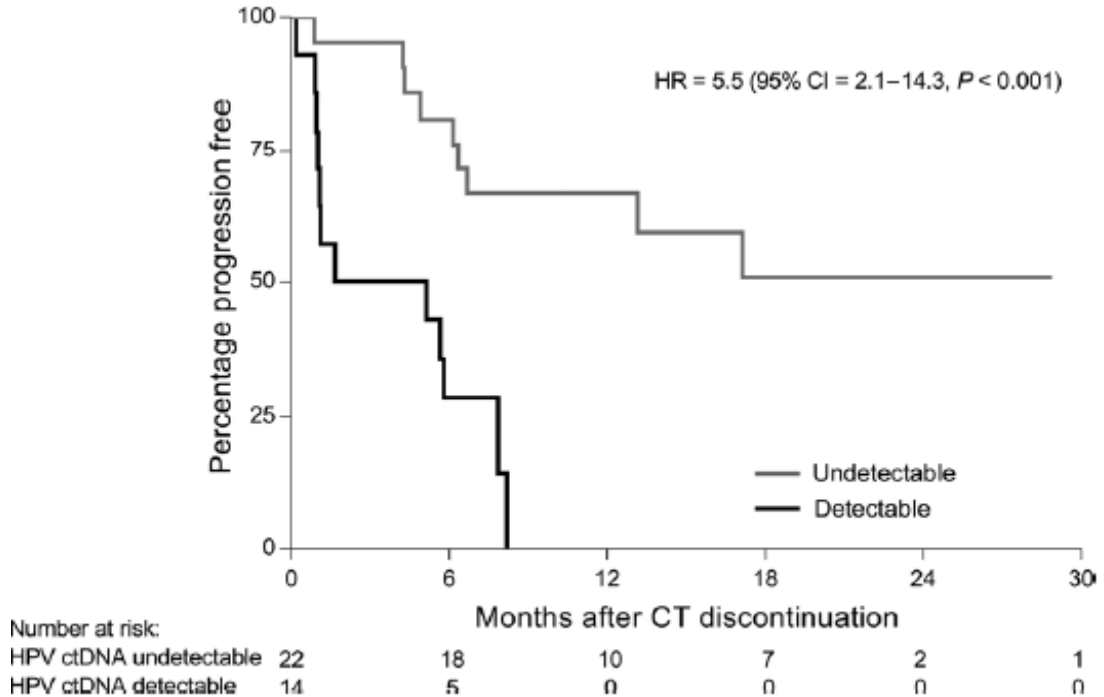
EA2176 Statistical Design and Correlatives:

- The study assumes a median PFS of **8** months in the control arm and will target a **PFS hazard ratio** of **0.625** under exponential failure which translates to an experimental PFS median of **12.8** months.
- For the PFS endpoint, to maintain at least 80% power using a stratified two-sided overall 0.05 level log-rank test as the primary analysis will require **160 total PFS events** and accrual of **205** patients (195 patients plus 5% to allow for drop-out) over 26 months with 14 months of follow-up (40 months total).
- HPV ctDNA has been correlated with tumor response in other HPV-driven malignancies
- EA2176 investigators, in collaboration with Sysmex, and as supported by the FF Foundation, will utilize SafeSEQ NGS to quantify serum HPV ctDNA during treatment at various timepoints (up to 5 collections per patient)

NCT04444921

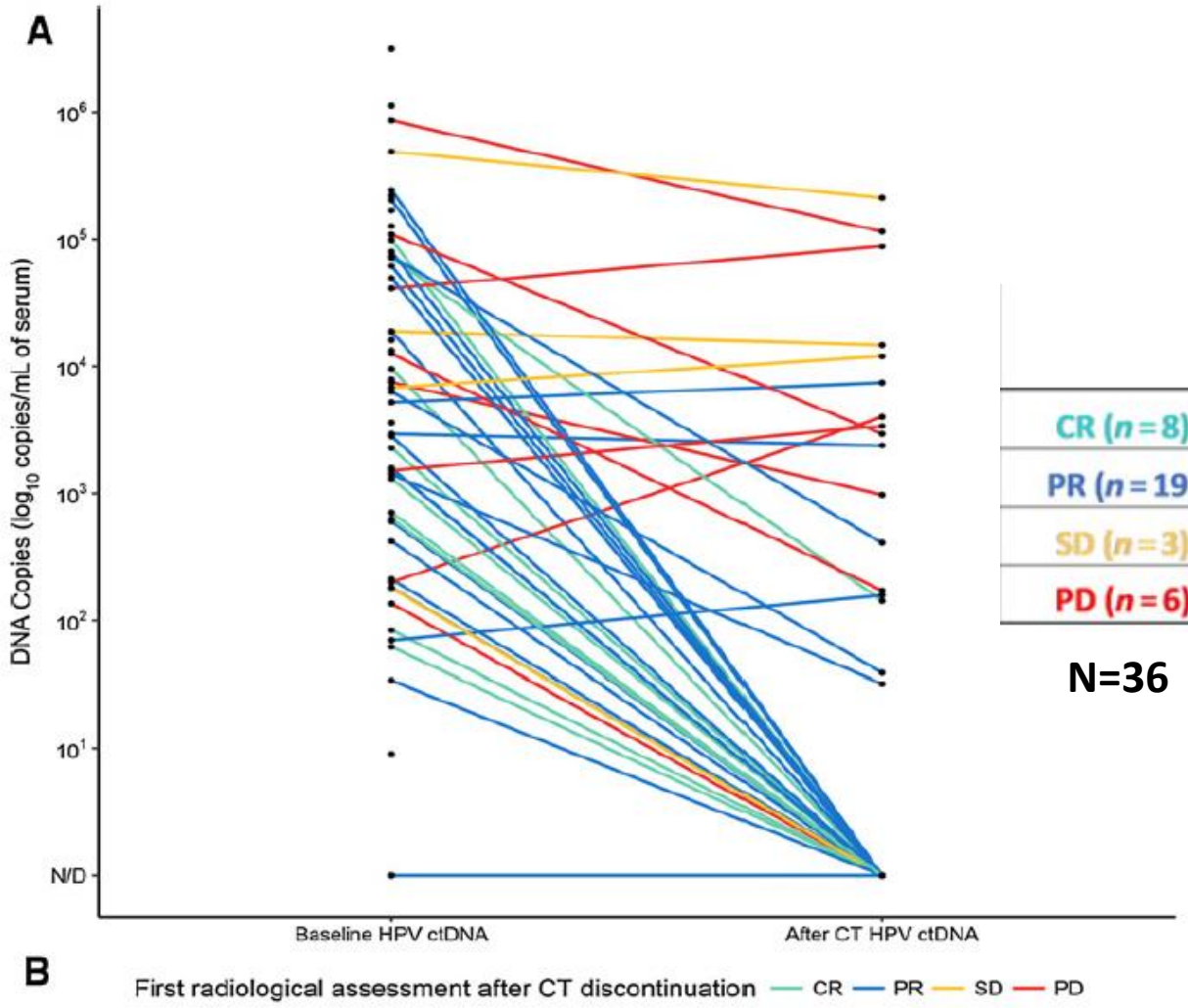
Role for HPV ctDNA in Metastatic Anal Cancer





Bernard-Tessier at al: CCR, 2019

Role for HPV ctDNA in Metastatic Anal Cancer



	Baseline HPV ctDNA median (range)	Median change during CT (%) (range)	*P*
CR (*n* = 8)	1792 (61; 98950)	-100% (-99.8; -100)	0.008
PR (*n* = 19)	2940 (0; 243750)	-100% (-100; 127)	0.0004
SD (*n* = 3)	6910 (178; 488700)	-57% (-100; 76)	0.75
PD (*n* = 6)	26825 (135; 865500)	-92% (-100; 124)	0.44

N=36

Bernard-Tessier at al: CCR, 2019

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
- Several ongoing or pending result trials utilizing immunotherapy for high risk recurrence and metastatic anal cancer
- **Clinical trial enrollment is ALWAYS encouraged whenever possible**