Metastatic Colorectal Cancer Therapy

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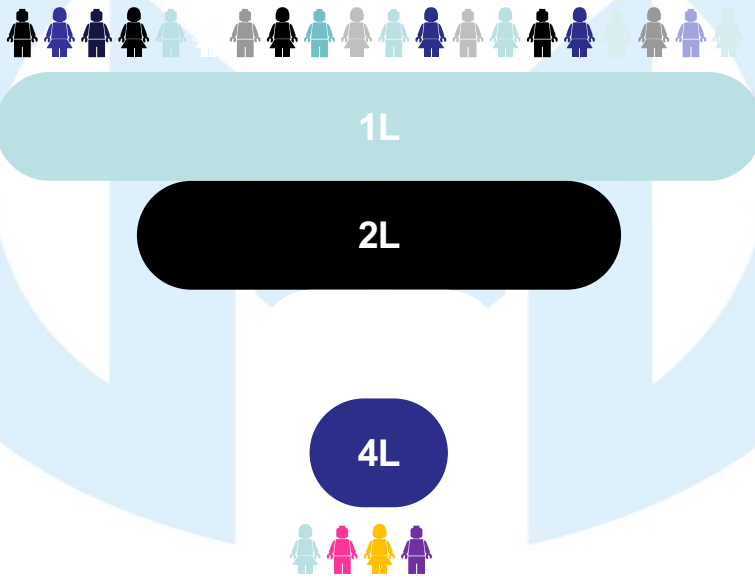
Topics for Discussion

- Latest data with IO for MSI-H mCRC
- Is KRAS druggable?
  - KRAS G12C inhibitors
- Impact of BRAF V600E mutations in mCRC
  - Targeted treatment options
- HER2 overexpression in mCRC
  - HER2-directed strategies

What Influences Treatment Choices in mCRC?



Patient characteristics

- Comorbidities
- Prior adjuvant treatment
- Age
- Performance status

Molecular characteristics

- RAS
- BRAF
- MSI-high
- HER2

Tumor characteristics

- Tumor burden
- Resectability
- Tumor location

Patient preference

- Quality of life
- Toxicity profile

Therapy tailored according to individual patient needs

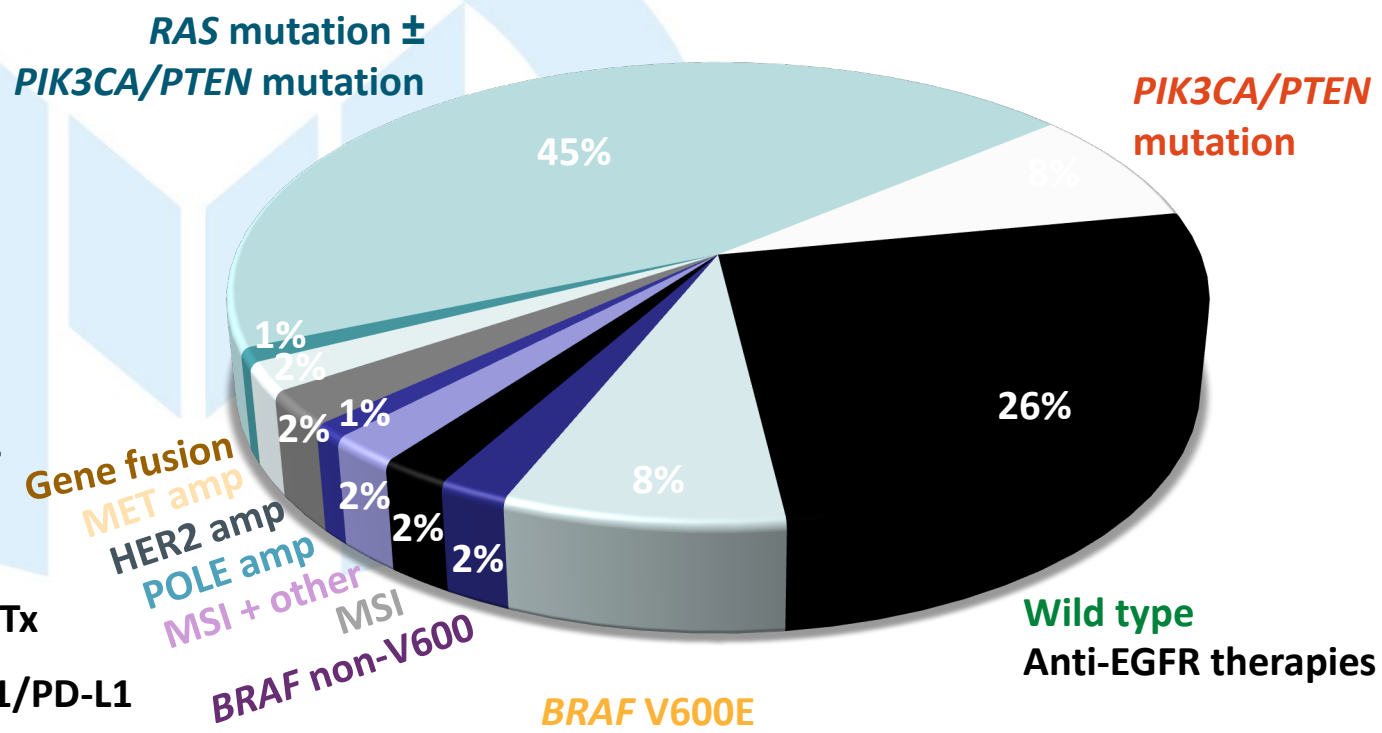
Modified from Van Cutsem. Ann Oncol. 2016;27:1386.

Biomarker Testing in CRC

- For all colon cancers:
  - **MMR**
  - **Microsatellite stability**
- Metastatic disease:
  - ***RAS***
  - ***BRAF*** → Kinase inhibitor
  - ***HER2*** → MET inhibitor
  - ***NTRK*** → Anti-HER2 Tx

Anti–PD-1/PD-L1

Molecular Classification of CRC and Associated Targeted Therapies

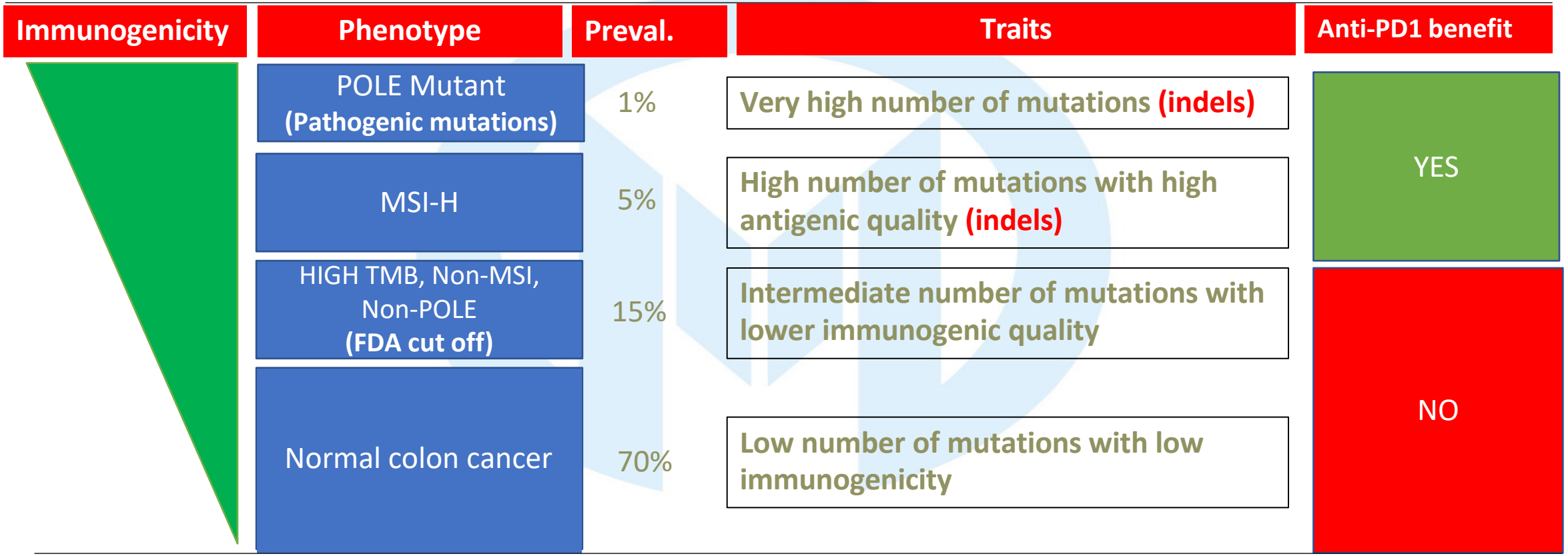


Dienstmann. Am Soc Clin Oncol Educ Book. 2018;38:231.

We will start with conclusions !!

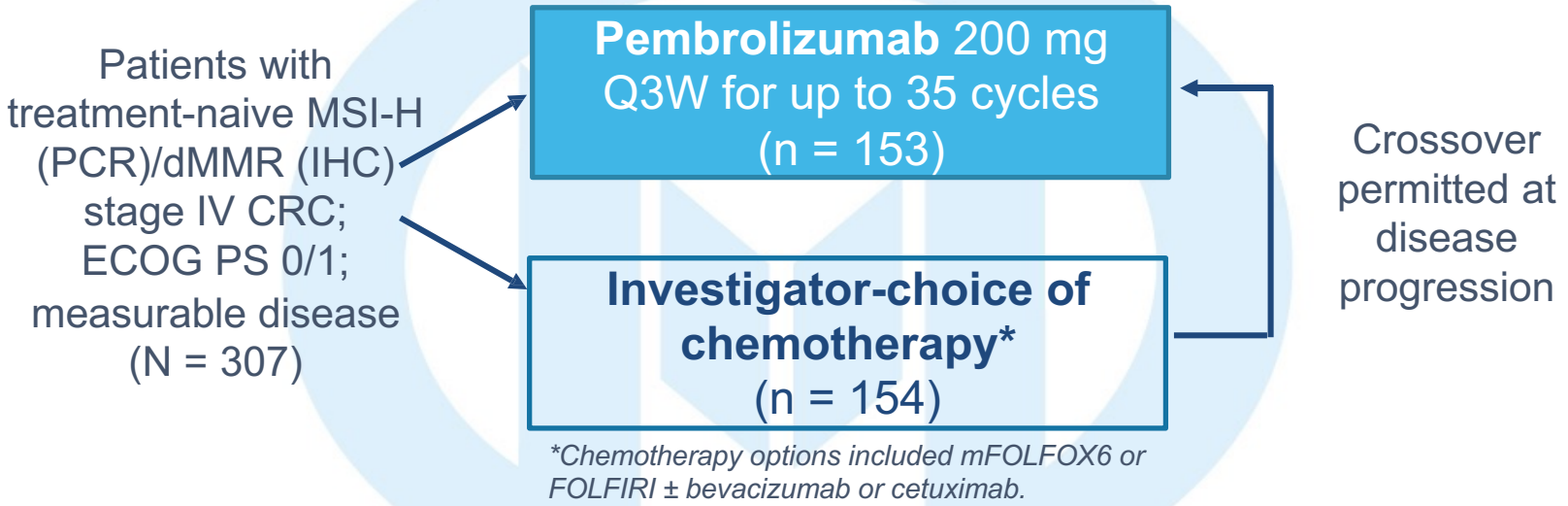
- MMR / MSI testing is now mandatory
- Immunotherapy is approved in the 2nd line setting for all dMMR/MSI-H solid tumors
- Pembrolizumab is approved in the first-line setting for dMMR/MSI-H CRC
- Nivolumab ± ipilimumab is approved in second-line dMMR/MSI-H CRC

MSI-H CRC among CRC Immune-Subgroups:



TCGA, Nat 2012, B. Rousseau ESMO 2020, T Andre NEJM 2020, M.J. Overman J Clin Oncol 2018, B. Rousseau NEJM 2021

Keynote-177 First-line Pembrolizumab for MSI-H/dMMR mCRC



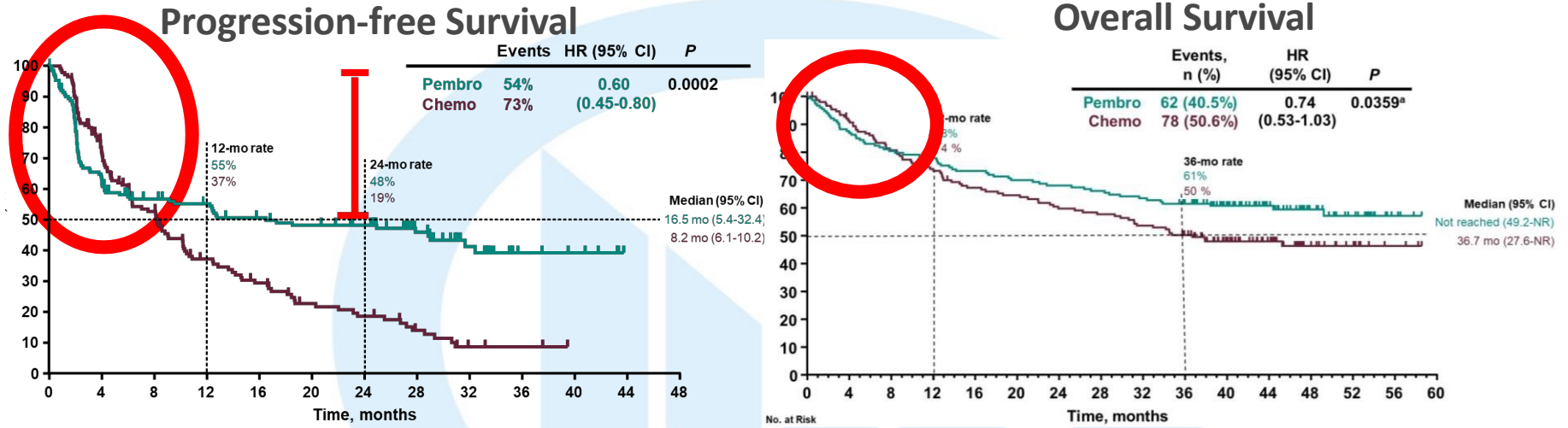
Pembrolizumab led to significantly longer PFS than chemotherapy when received as first-line therapy for MSI-H–dMMR metastatic colorectal cancer. FDA approval for first-line treatment based on KEYNOTE-177.

Andre T et al. N Engl J Med. 2020 Dec 3;383(23):2207-2218.

	Pembrolizumab		
Trial	KEYNOTE-177	KEYNOTE-164 (B)/(A)	
Population	1st L	≥2nd L	≥3rd L
Size	307 (III RCT v. chemo)	63	61
ORR	45.1% *v. 33.1%*	33%	33%
median PFS/ 12 mo PFS %	16.5m *v. 8.2m*	41%	34%
median OS/ 12 mo Surv %	NR *v. 36.7m.* HR 0.74. p=0.0359	76%	72%

Andre. NEJM. 2020; Andre. ASCO (#3500). 2021; Le. JCO. 2020;

Keynote-177 First-line Pembrolizumab for MSI-H/dMMR mCRC



	Pembrolizumab N = 153	Chemotherapy N = 154
Progressive disease	45 (29.4)	19 (12.3)

Andre T et al. *NJEM 2020*

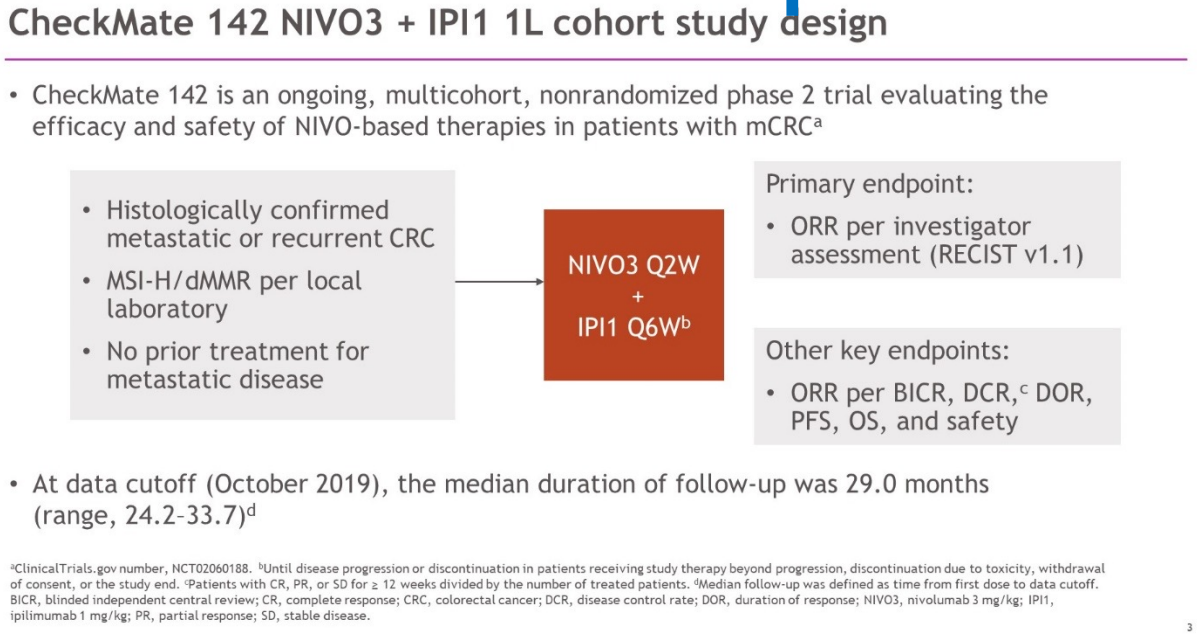
Andre T et al. N Engl J Med. 2020 Dec 3;383(23):2207-2218.

KEYNOTE-177: Adverse Events

AEs (≥ 20% in Either Arm, or ≥ 5% if Immune Mediated), %	Pembrolizumab (n = 153)		Chemotherapy (n = 143)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Diarrhea	25	2	52	10
Fatigue	21	2	44	9
Nausea	12	0	55	2
Decreased appetite	8	0	34	2
Stomatitis	5	0	30	4
Alopecia	3	0	20	0
Vomiting	3	0	28	4
Decreased neutrophil count	1	0	23	17
Neutropenia	0	0	21	15
Peripheral sensory neuropathy	0	0	20	2
Hypothyroidism	12	0	2	0
Colitis	7	3	0	0
Infusion reactions	2	0	8	1

Andre T et al. N Engl J Med. 2020 Dec 3;383(23):2207-2218.

Nivolumab and Ipilimumab for untreated MSI-H mCRC



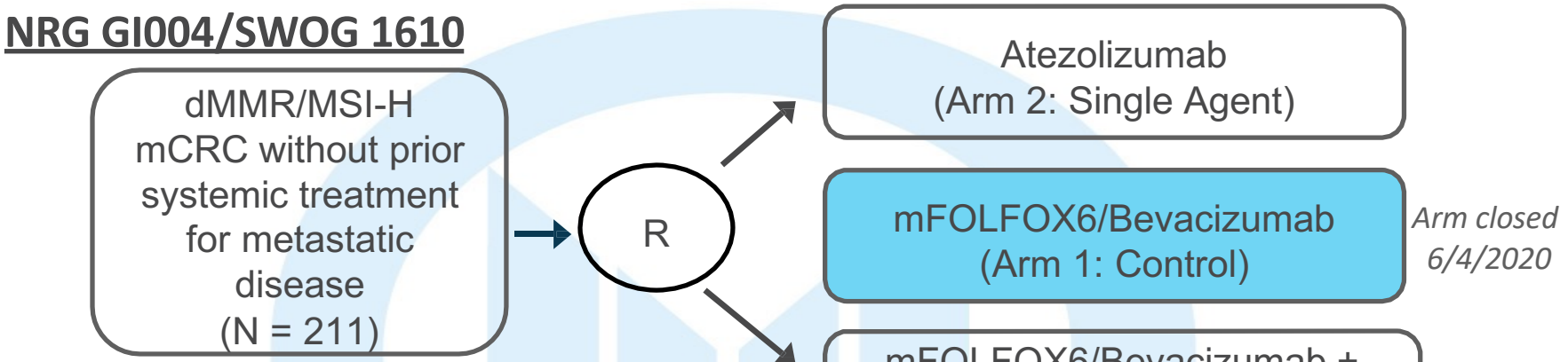
- CheckMate 142
  - ORR = 69%
  - 24-month PFS = 74%
  - OS = not reached

	Nivolumab	Nivolumab + Ipilimumab	
Trial	Checkmate-142		
Population	≥2nd L		*1st L (cont ipi)*
Size	74	119	*45*
ORR	31.1%	55%	*69%*
median PFS/ 12 mo PFS %	50%	71%	*76%*
median OS/ 12 mo Surv %	73%	85%	*84%*

;Overman. JCO. 2018; Lenz. ASCO (#4040). 2020. Overman. Lancet Oncology. 2017;
Lenz et al. ASCO GI 2021. Abstract #58

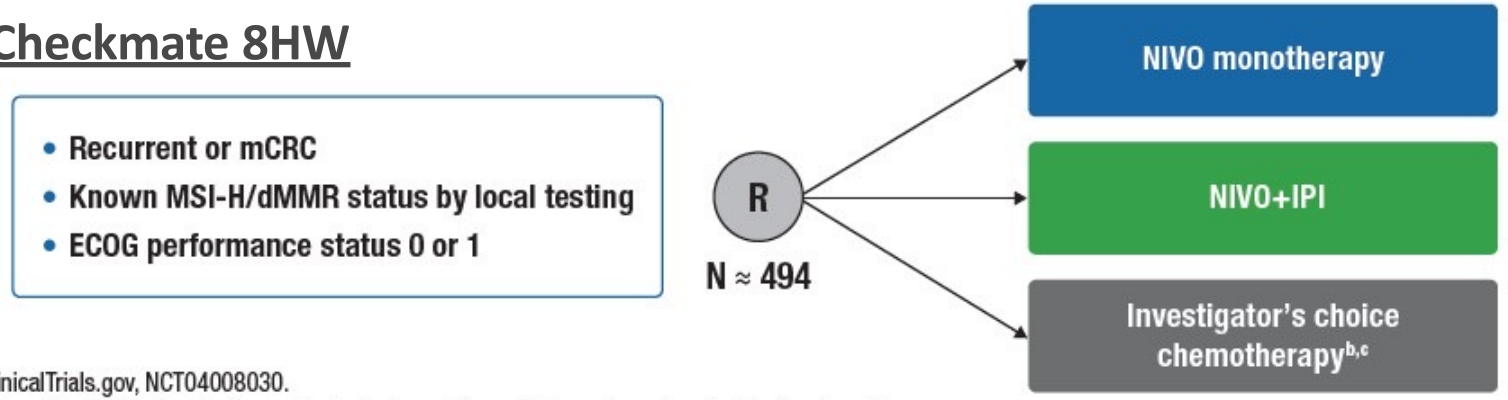
Ongoing Phase III Trials First Line dMMR mCRC

NRG GI004/SWOG 1610



PI: (SWOG): Michael Overman, MD
PI: (NRG Oncology):Caio Max Sao Pedro Rocha LIma MD

Checkmate 8HW



[a]ClinicalTrials.gov, NCT04008030.
[b]Only patients with 0 or 1 prior systemic treatments for mCRC can be randomized to the chemotherapy arm.

1. Rocha Lima et al. GI ASCO 2022. Abstract TPS232. 2. Abdullaev et al. GI ASCO 2021. Abstract TPS266

PD-1 blockade alone for mismatch repair deficient (dMMR) locally advanced rectal cancer

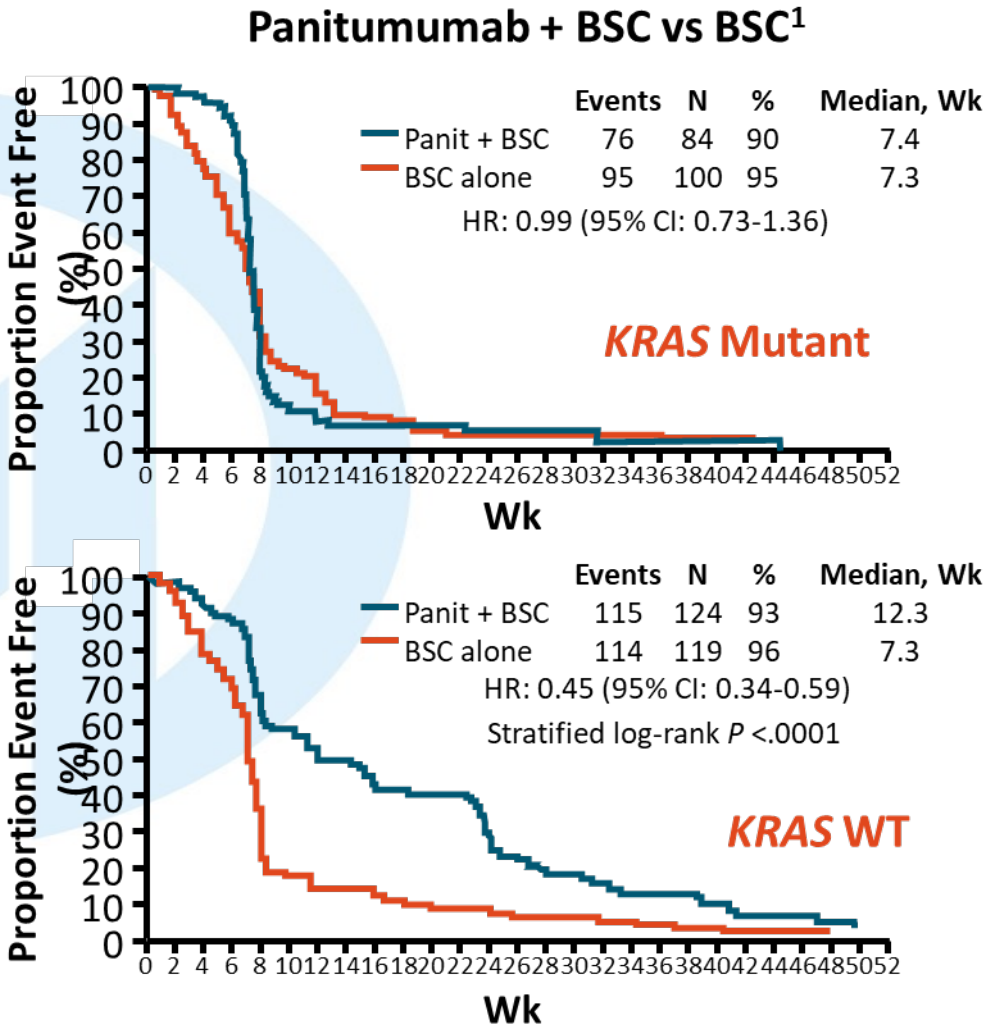
- Neoadjuvant dostarlimab (anti PD1) alone is effective in dMMR locally advanced rectal cancer
- Clinical complete response rate was 100%
- Patient may avoid chemoradiation and surgery
- Potential new paradigm for treatment of dMMR rectal cancer

Lumish M et al. GI ASCO 2022.

Moving on to targeted Therapies

RAS Mutations (*KRAS*, *NRAS*, *HRAS*)

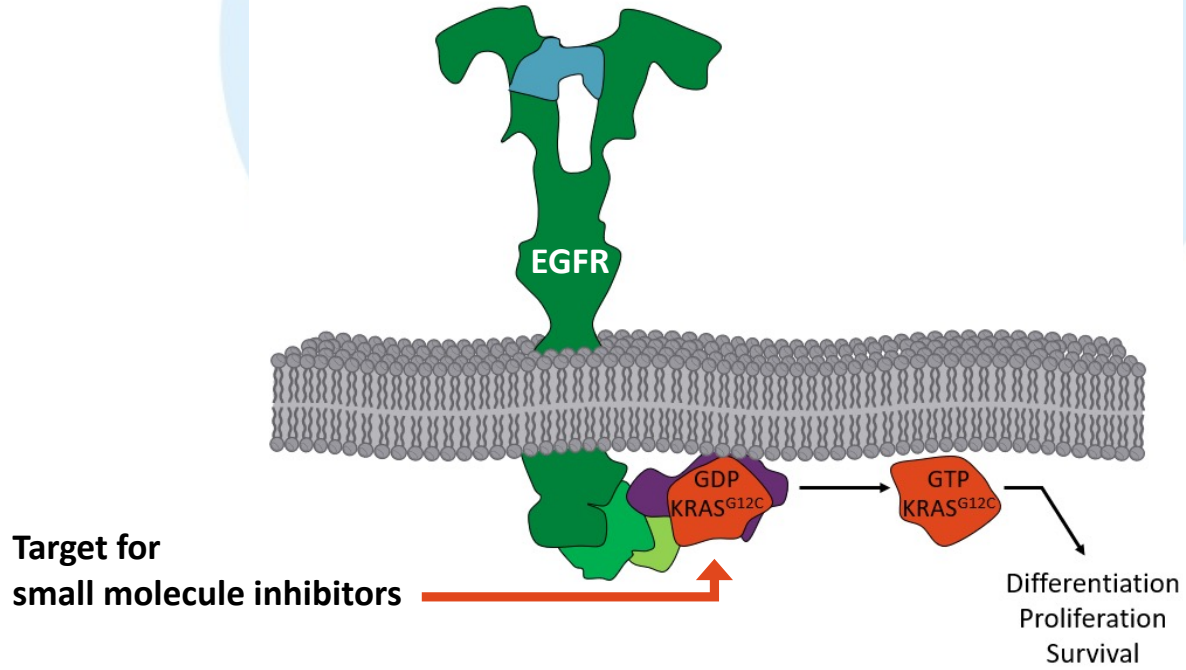
- Most frequently mutated oncogenes[1]
  - 90% of pancreatic cancers, 45% of colo
  - *KRAS* most prevalent in these tumor types
- In CRC, RAS testing is required prior to anti-EGFR therapy (eg, cetuximab or panitumumab)
  - Patients with *KRAS* and *NRAS* mutations should not be treated with anti-EGFR therapy[2-4]
  - *HRAS* mutations are much less common (1.7%) but likely have the same negative predictive value



1. Porru. J Exp Clin Cancer Res. 2018;37:57. 2. Allegra. JCO. 2016;34:179.
3. Al-Shamsi. J Gastrointest Oncol. 2015;6:314. 4. Gong. J Gastrointest Oncol. 2016;7:687.

KRAS p.G12C Mutation: Background

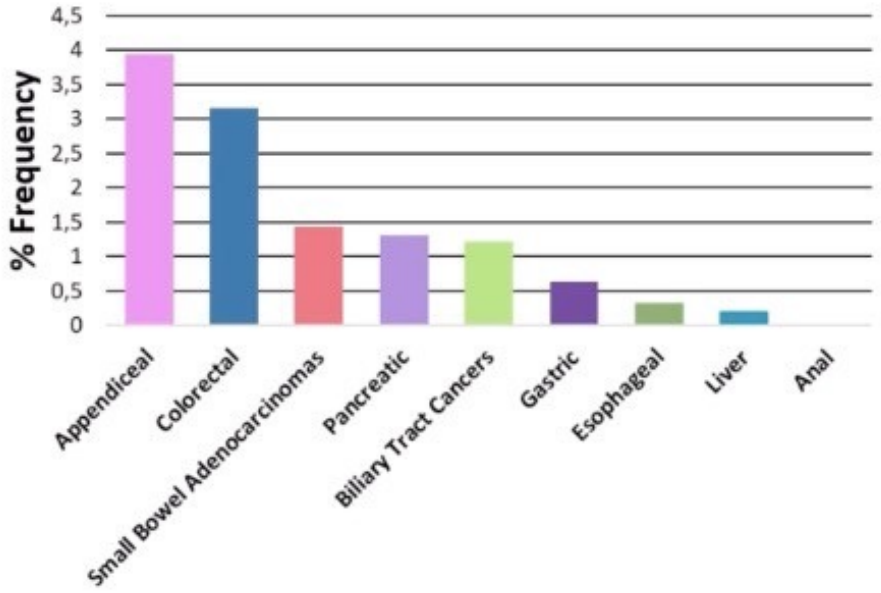
- GTP-bound $KRAS^{G12C}$ enhances downstream signaling and drives tumor growth[1,2]
- *KRAS* p.G12C mutation in 13% of NSCLC, and 1% to 3% of CRC and other solid tumors[3]
- Sotorasib (AMG 510) and Adagrasib (MRTX849) are the small molecule inhibitors with known clinical efficacy inhibiting this pathway[3,4]



1. Muñoz-Maldonado. Front Oncol. 2019;9:1088. 2. McCormick. Ann Rev Cancer Biol. 2018;2:81. 3. Hong. NEJM. 2020;383:1207. 4.Jänne. AACR-NCI-EORTC 2019. Abstr CS5.

KRAS-G12C in Gastrointestinal Malignancies

Cancer types included in the analysis	N
Colorectal Cancers	6586
Pancreatic Adenocarcinoma	5029
Biliary Tract Cancers	1481
Stomach Cancers	1401
Esophageal Cancers	941
Small Bowel Adenocarcinomas	630
Hepatocellular Carcinoma	467
Appendiceal Cancer	279
Anal Cancer	195
Total	17009



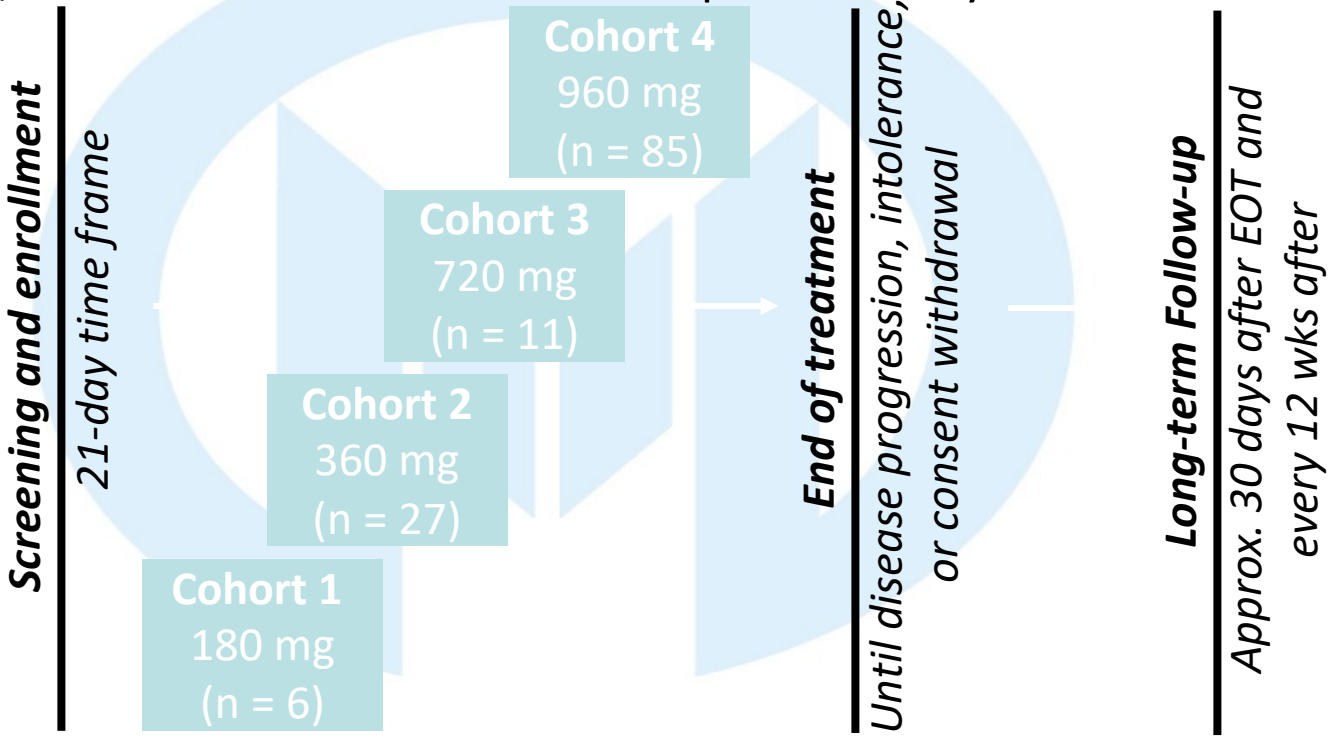
Tumor Type		Appendiceal (n= 279)	CRC (n= 6586)	SBA (n= 630)	Pancreatic (n= 5029)	Biliary Tract (n= 1481)	Gastric (n= 1401)	Esophageal (n= 941)	HCC (n= 467)	Anal (n= 195)
KRAS Mutation	G12C	11 (3.9%)	208 (3.1%)	9 (1.4%)	66 (1.3%)	18 (1.2%)	9 (0.6%)	3 (0.3%)	1 (0.21%)	0 (0.0%)
	Non-G12C	125 (44.8%)	2763 (42.0%)	142 (22.5%)	3627 (72.1%)	242 (16.3%)	168 (12.0%)	136 (14.5%)	23 (4.9%)	8 (4.1%)

Salem M, Van Cutsem E et al. ASCO 2021 & ESMO WCGI 2021

CodeBreaK100: Sotorasib in Patients With Previously Treated Cancers With *KRAS* p.G12C Mutation

- Multicenter, open-label, first-in-human dose-escalation phase I study

Adult patients with locally advanced or metastatic *KRAS* p.G12C–mutant solid tumors, ECOG PS ≤ 2 who could not tolerate, or previously received appropriate therapy for tumor type and stage, with no active brain metastases or severe cardiac history



- Primary endpoint: Safety and tolerability including the incidence of AEs and DLTs
- Secondary endpoints: PK, best response, ORR, DoR, PFS, duration of stable disease

Hong. NEJM. 2020;383:1207.

CodeBreaK100: Colorectal Cancer Patient Cohort

- Multicenter, open-label, first-in-human phase I/II trial (data cutoff: June 1, 2020)

Adult patients with locally advanced/metastatic *KRAS* p.G12C–mutant solid tumors and PD on prior SoC therapy specific to tumor/disease stage; no active brain metastases (N = 129*)

→ **CRC Escalation Cohort (n = 42)†**
Sotorasib PO QD‡
180 mg (n = 3), 360 mg (n = 10),
720 mg (n = 4), 960 mg (n = 25)

→ ***Evaluable for tumor response as of the data cutoff***

*Includes NSCLC (n = 59), CRC (n = 42), pancreatic cancer (n = 12), appendiceal cancer (n = 4), unknown primary cancer (n = 2), endometrial cancer (n = 2), and n = 1 in each of the following: ampullary cancer, small bowel cancer, sinonasal cancer, esophageal cancer, bile duct cancer, SCLC, gastric cancer, and melanoma. †2-4 patients enrolled on each cohort to evaluate safety, with additional enrollment at any dose deemed safe. Intrapatient dose escalation permitted. Radiographic scans Q6W on treatment, 30 days after end of treatment, then Q12W.

- Median follow-up: 12.8 mos (range: 9.0-20.9)
- At current data cutoff: 3 patients remain on treatment, 37 discontinued due to progression/death, and 2 discontinued per request of patient

Hong. NEJM. 2020;383:1207.

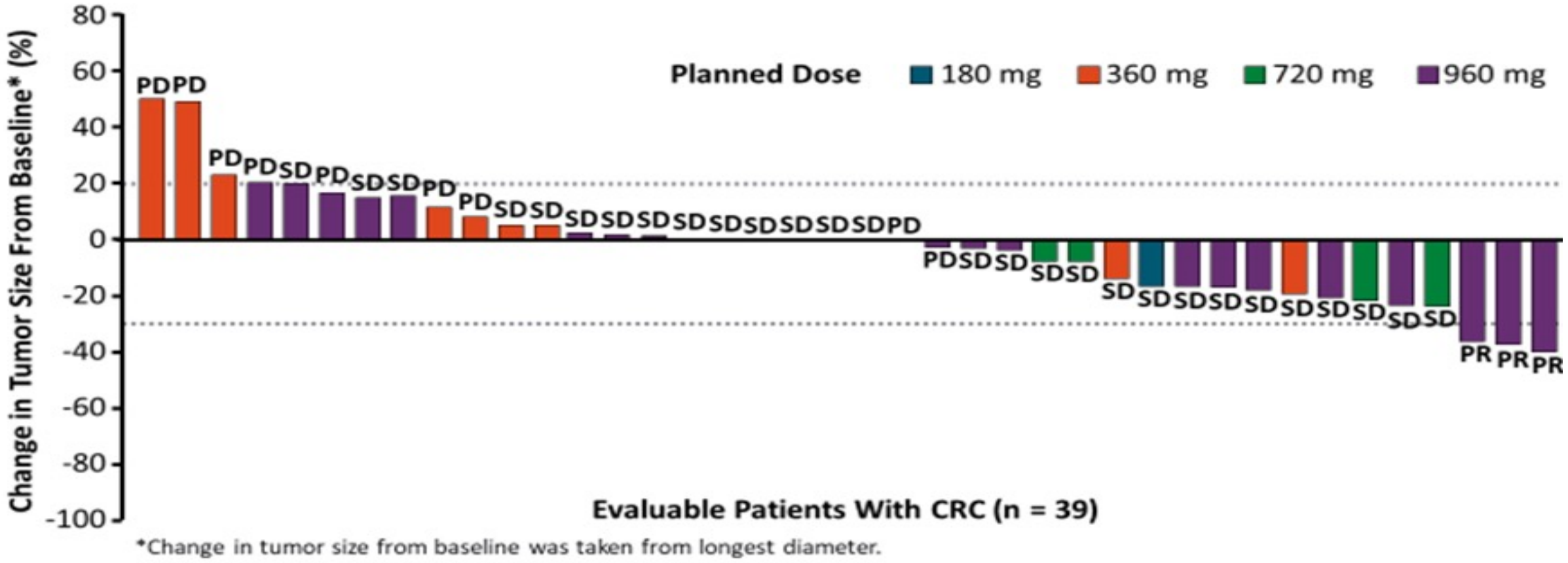
CodeBreaK100: Tumor Response in CRC Cohort

Tumor Response[1]	All Dose Levels (n = 42)	960-mg Dose (n = 25)
Best overall response, n (%)		
▪ PR	3 (7.1)	3 (12.0)
▪ SD	28 (66.7)	17 (68.0)
▪ PD	10 (23.8)	3 (12.0)
▪ Not done	1 (2.4)	1 (4.0)
ORR, % (95% CI)	7.1 (1.50 to 19.48)	12.0 (2.55 to 31.22)
DCR,§ % (95% CI)	73.8 (57.96 to 86.14)	80.0 (59.30 to 93.17)
Median DoR (n = 3), mos (range)	NR (4.9+ to 9.9+)	NR (4.9+ to 9.9+)
Median duration of stable disease, mos (range)	5.4 (2.5* to 11.1*)	4.2 (2.6 to 5.7*)[2]

*Censored value.

1. Hong. NEJM. 2020;383:1207. 2. Fakih. ASCO 2020. Abstr 4018.

CodeBreaK100: Tumor Burden Change From Baseline in CRC Cohort



- 3 patients missing postbaseline tumor data not included (1 PD, 1 SD, 1 not done with clinical progression)

Hong. NEJM. 2020;383:1207.

CodeBreaK100: PFS and OS in CRC Cohort

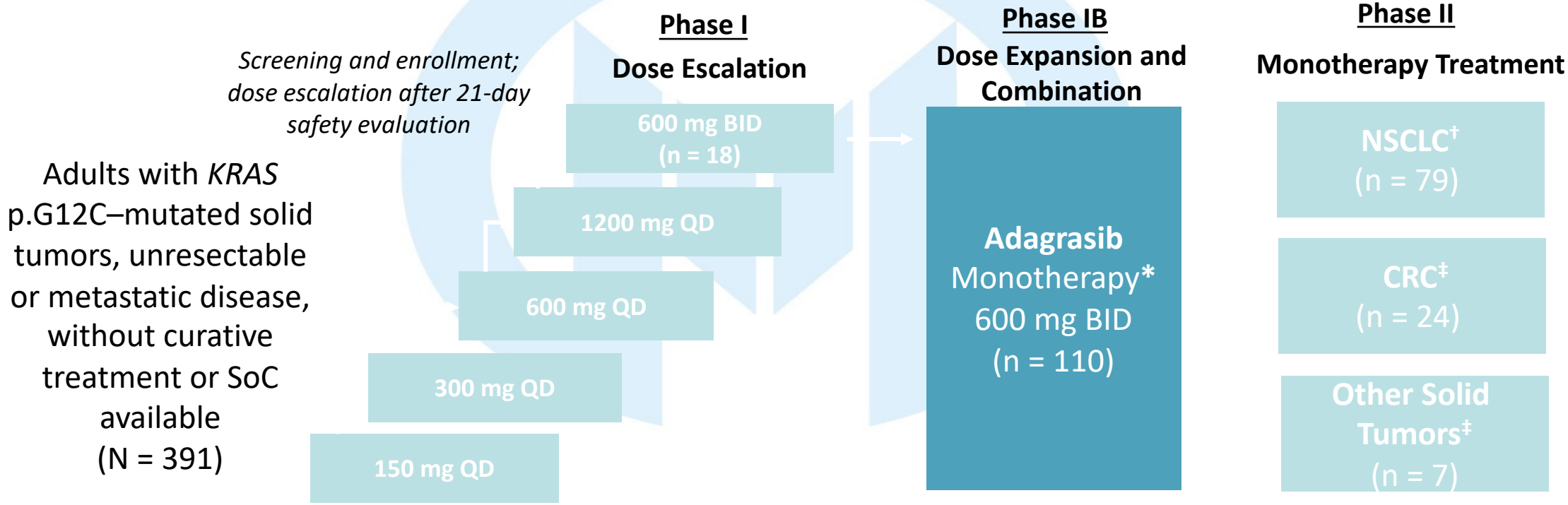
Survival	All Dose Levels (n = 42)	960-mg Dose (n = 25)
Median PFS, mos (95% CI)*	4.0 (2.8 to 5.5)[1]	4.2 (2.8 to NE)[2]
PFS range, min-max*	0+ to 11.1+[1]	1.2 to 5.7†[2]
KM PFS estimate, % (95% CI)[2]		
▪ At 3 mos	58.5 (41.9 to 71.9)	59.7 (38.1 to 76.0)
▪ At 6 mos	20.6 (7.3 to 38.7)	NE (NE to NE)
Median OS, mos (95% CI)[2]	10.1 (7.7 to NE)	NE (NE to NE)
OS range, min-max[2]	1.3† to 11.4†	2.3 to 8.0†
KM OS estimate, % (95% CI)[2]		
▪ At 3 mos	92.7 (79.0 to 97.6)	96.0 (74.8 to 99.4)
▪ At 6 mos	76.4 (57.7 to 87.7)	82.9 (53.3 to 94.6)

*Data collected from 2 different time points (January and June 2020) consistent with respective citation. †Censored value.

1. Hong. NEJM. 2020;383:1207. 2. Hong. ASCO 2020. Abstr 3511.

KRYSTAL-1: Adagrasib (MRTX849) in Patients With Cancer Having a *KRAS* p.G12C Mutation

- Potent, selective, and covalent inhibitor of $KRAS^{G12C}$ that selectively binds to mutant cysteine 12 in GDP-bound $KRAS^{G12C}$ and inhibits signaling[1]
- Nonrandomized, open-label phase I/II study to establish safe dosing and assess ORR

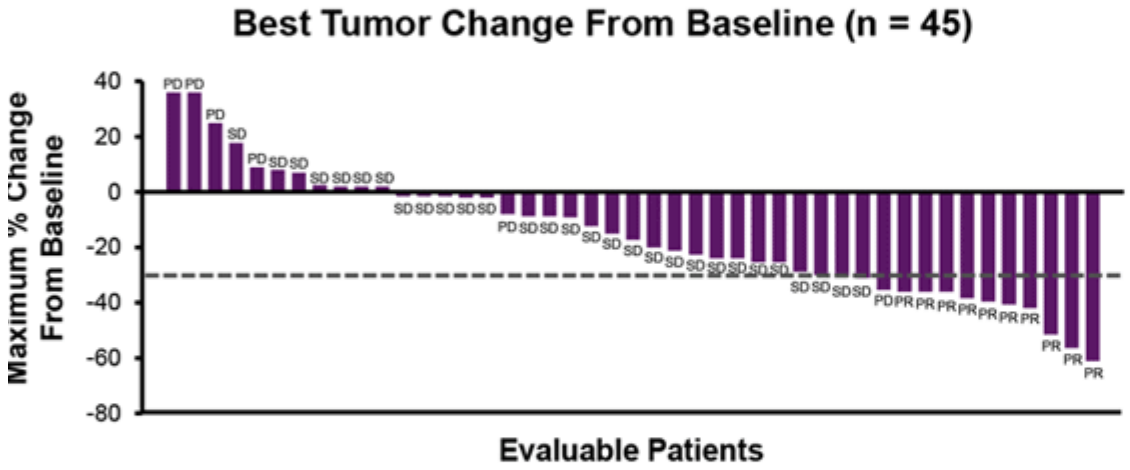


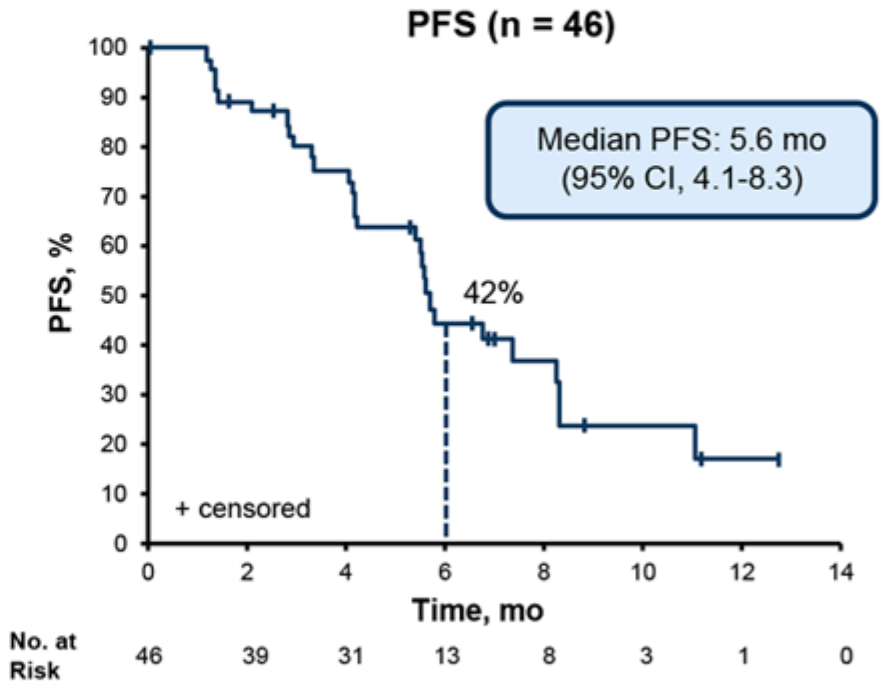
*Ongoing trials are evaluating adagrasib in combination with either pembrolizumab or afatinib in pts with NSCLC, and cetuximab in patients with CRC. †For phase II NSCLC cohort, patients must have received prior treatment with platinum-based chemotherapy and a PD-1/PD-L1 inhibitor. ‡CRC/other solid tumor cohort eligibility based on tissue or plasma test; $KRAS^{G12C}$ testing for entry was performed locally or centrally using a sponsor preapproved test. Data cutoff as of August 30, 2020.

1. Jänne. AACR-NCI-EORTC 2020. Abstr LBA-03. 2. Johnson. AACR-NCI-EORTC 2020. Abstr LBA-04. 3. NCT03785249.

Adagrasib Targeting *KRAS*^{G12C} in Patients With CRC

- Adagrasib monotherapy demonstrated promising clinical activity (response rate: 22%) and broad disease control (DCR: 87%) in heavily pretreated patients with CRC harboring a *KRAS* G12C mutation



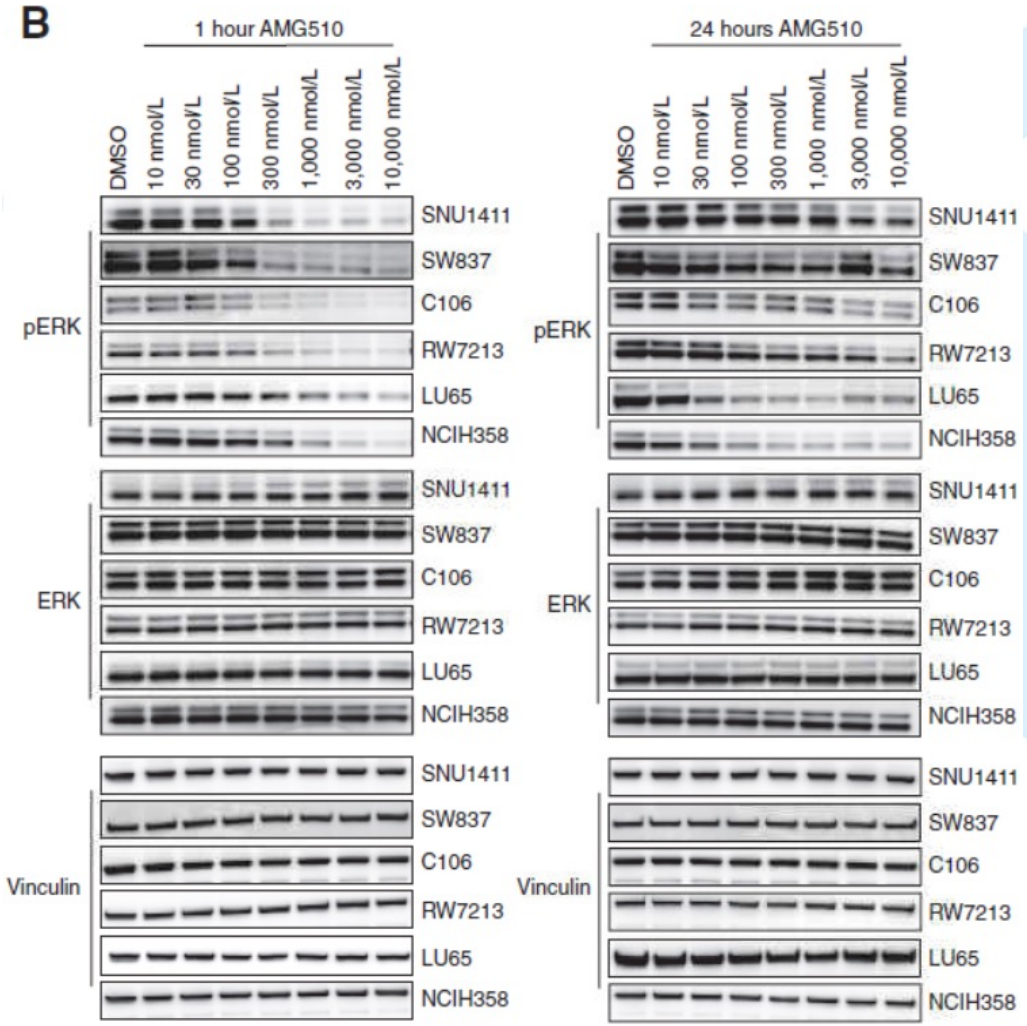


- Response rate was 22% (10/45), including 1 unconfirmed PR
- SD was observed in 64% (29/45) of patients
- Clinical benefit (DCR) was observed in 87% (39/45) of patients
- No apparent association between response rate and molecular status was shown in an exploratory analysis

Data as of 9 July 2021 (median follow-up: 7 months).
Weiss J, et al. ESMO 2021. Abstract LBA6.

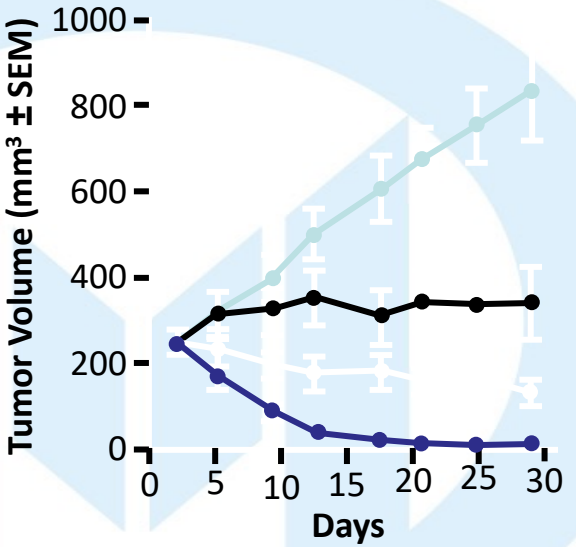
Addressing Resistance in *KRAS* p.G12C–Mutant CRC

ERK Activation in CRC Cell Lines

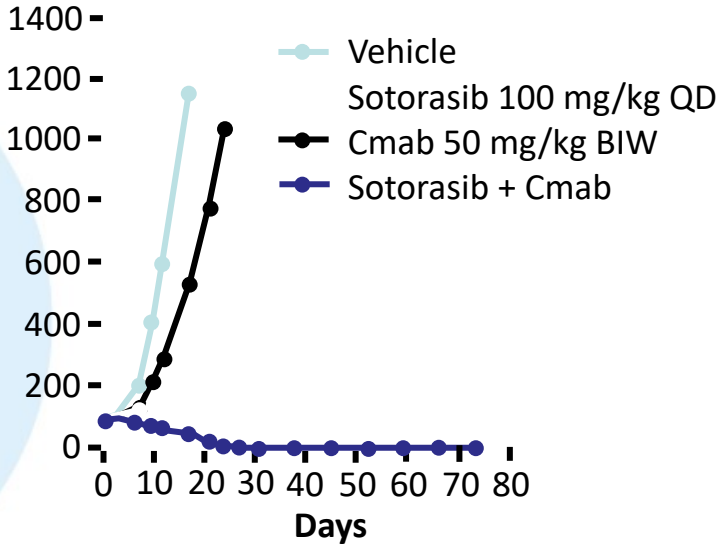


Amodio. Cancer Disco. 2020;10:1129.

CRC0051 *KRAS*^{G12C}–Mutant CRC PDX



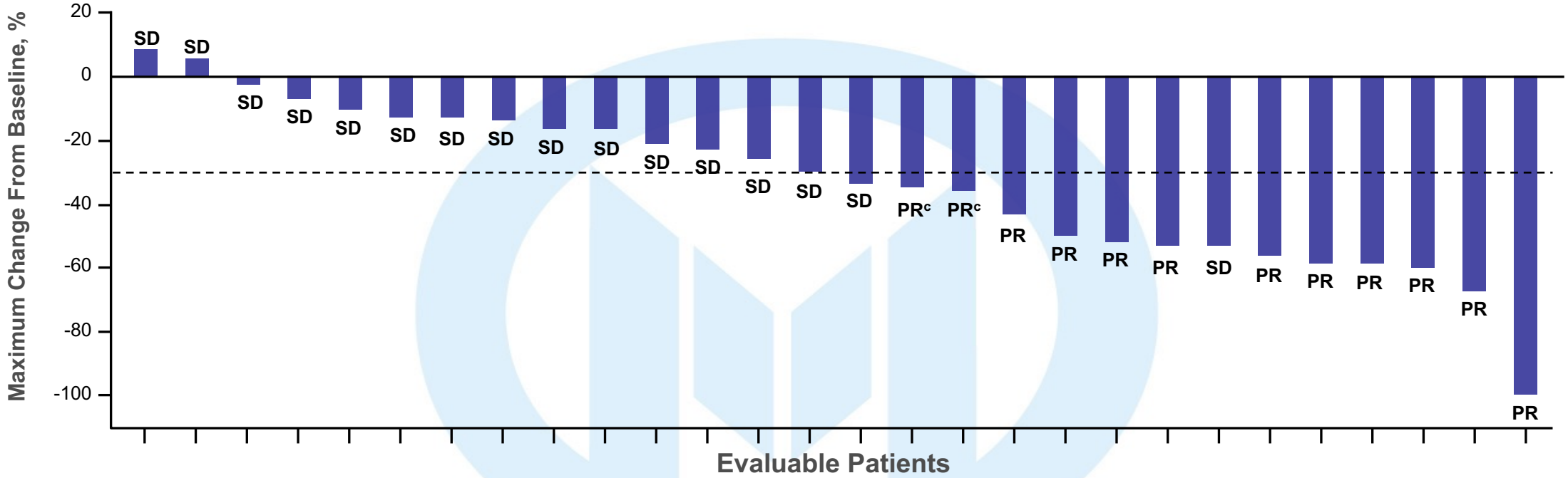
CLR113a *KRAS*^{G12C}–Mutant CRC PDX



- In contrast to NSCLC, CRC cell lines with *KRAS* p.G12C mutation experience rebound ERK phosphorylation after 24 hrs of exposure to Sotorasib;this is related to compensatory EGFR activation
- Dual anti-EGFR and KRAS^{G12C} inhibition with sotorasib leads to synergistic antitumor activity in CRC KRAS^{G12C} PDX models

Adagrasib + Cetuximab in Patients With Advanced CRC

Best Tumor Change From Baseline (n = 28)[a,b]



- Response rate was 43% (12/28), including 2 unconfirmed PRs
- SD was observed in 57% (16/28) of patients
- Clinical benefit (DCR) was observed in 100% (28/28) of patients
- No apparent association between response rate and molecular status was shown in an exploratory analysis[e]

[a]All results are based on investigator assessments. [b]Evaluable population (n = 28) excludes 4 patients who withdrew consent prior to the first scan. [c]At the time of the 9 July 2021 data cutoff, 2 patients had uPRs. [e]Molecular status (*BRAF* V600E mutation, MSI-H or dMMR, *EGFR* amplification, *TP53* mutation, *PIK3CA* mutation) includes patients with conclusively evaluable test results.
Data as of 9 July 2021 (median follow-up: 7 months).
Weiss J, et al. ESMO 2021. Abstract LBA6.

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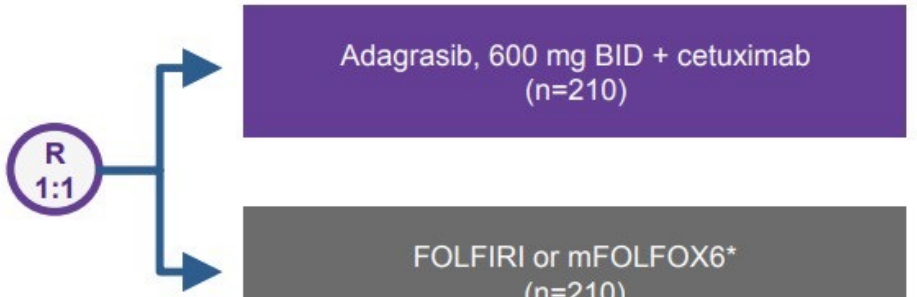
KRYSTAL-10 (849-010): Phase 3 Randomized, Open-Label Trial of 2L Adagrasib + Cetuximab vs Chemotherapy in mCRC With KRAS^{G12C} Mutation

Key Eligibility Criteria

- Histologically confirmed diagnosis of metastatic CRC
- Confirmed KRAS^{G12C} mutation in tumor
- Progression on 1L fluoropyrimidine-based oxaliplatin or irinotecan regimen



*A VEGF/VEGFR inhibitor may be given per Investigator discretion

Outcome Measures

Primary: PFS, OS
Secondary: Safety, ORR (RECIST 1.1), DOR, PROs

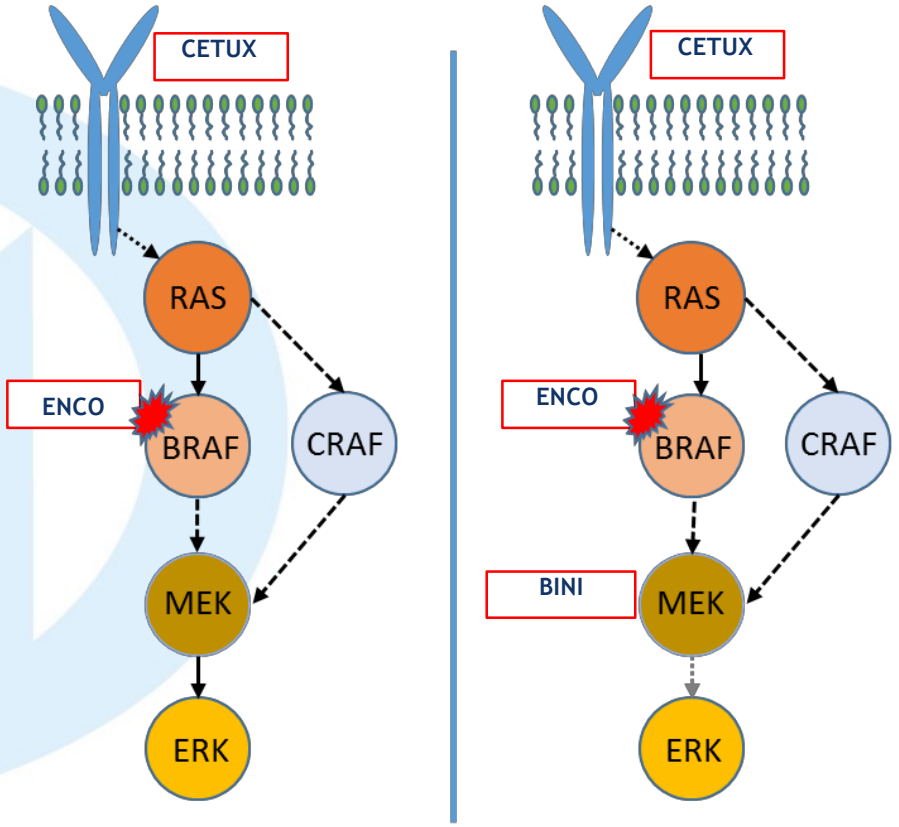
Dosing: cetuximab, 500 mg/m2 q2w, FOLFIRI q2w [irinotecan, 180 mg/m2, 5-FU/LV with fluorouracil given as 400 mg/m2 IV bolus followed by a further 2400 mg/m2 dose given as continuous infusion over 46-48 hours], mFOLFOX6 q2w [oxaliplatin, 85 mg/m2, 5-FU/LV, with fluorouracil given as 400 mg/m2 IV bolus followed by a further 2400 mg/m2 dose given as continuous infusion over 46-48 hours].

1L, first line; 2L, second line; 5-FU/LV, 5-fluorouracil + leucovorin; BID, twice daily; mCRC, metastatic colorectal cancer; mFOLFOX6, modified FOLFOX6; OS, overall survival; PFS, progression free survival; q2w, every two weeks.

$BRAF^{V600E}$ Mutation in mCRC

- Occurs in 10%–15% of patients and confers a poor prognosis[1-3]
- Recent studies with irinotecan-based chemotherapy have poor outcomes[3-4]
  - Expected median OS with 2nd and 3rd-line irinotecan-based chemotherapy standard of care is 5.9 months, median PFS of 4 months, and ORR of 4%[4]
- BRAF inhibitors are not effective alone due to the feedback activation of EGFR in *BRAF*-mutant CRC, leading to continued cell proliferation[5,6]
  - Feedback may be overcome by targeting multiple nodes in the pathway
- New effective therapies are urgently needed

MAPK Signaling in Colorectal Cancer[7]



CETUX=cetuximab; EGFR=epidermal growth factor receptor; ENCO=encorafenib; MAPK=mitogen-activated protein kinase; mCRC=metastatic colorectal cancer; PFS=progression-free survival; ORR=objective response rate; OS=overall survival.

1. De Roock W, et al. *Lancet Oncol*. 2010;11(8):753. 2. Sorbye H, et al. PLoS One. 2015;10:e0131046. 3. Loupakis F, et al. *Br J Cancer*. 2009;101:715. 4. Kopetz S, et al. *J Clin Oncol*. 2017;35(15):3505. 5. Corcoran RB, et al. *Cancer Disc*. 2012;2(3):227. 6. Prahallad A, et al. *Nature* 2012;100:100. 7. Adapted From: Strickler JH. *Cancer Treatment Reviews*. 2017; 60:109.

BEACON CRC: Encorafenib + Cetuximab ± Binimetinib for *BRAF* V600E–Mutant mCRC

- A multicenter, randomized, open-label, 3-arm phase III trial

Patients with *BRAF* V600E+ mCRC with PD after 1-2 prior regimens (no prior RAF/MEK/EGFR inhibitors); no symptomatic brain mets

Safety Lead-in

Binimetinib 45 mg BID
Encorafenib 300 mg QD
Cetuximab 400 mg/m^2 → 250 mg/m^2 QW

N = 30

Binimetinib 45 mg BID
Encorafenib 300 mg QD
Cetuximab 400 mg/m^2 → 250 mg/m^2 QW
(n = 224)

Encorafenib 300 mg QD
Cetuximab 400 mg/m^2 → 250 mg/m^2 QW
(n = 220)

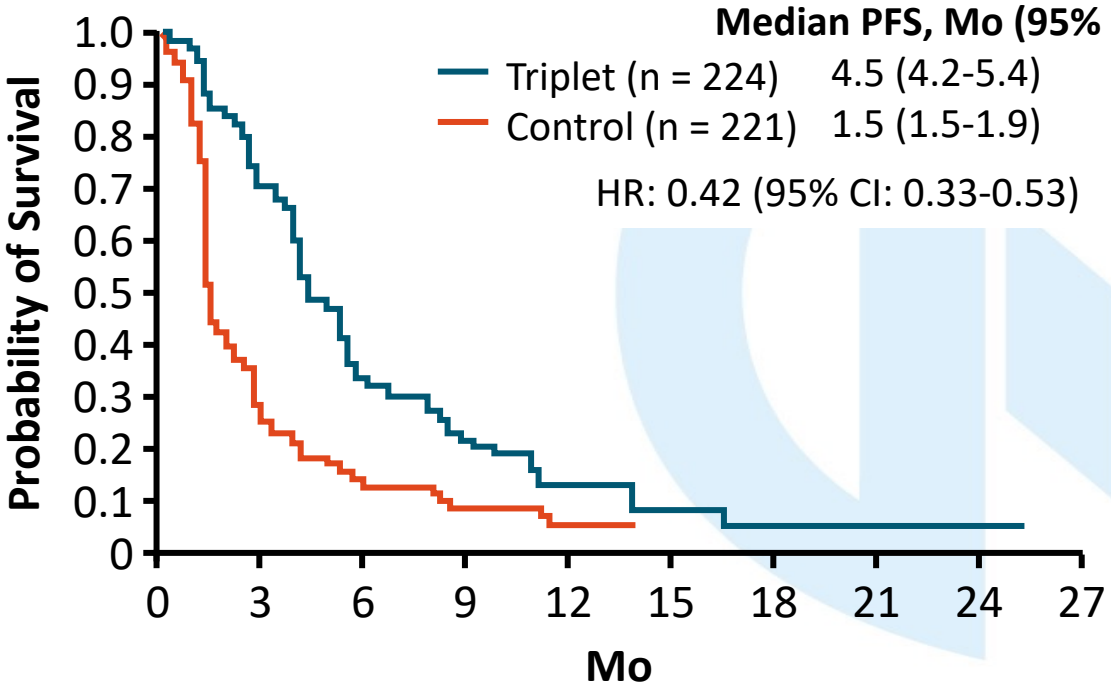
Investigator's Choice
FOLFIRI/Cetuximab or Irinotecan/Cetuximab
(n = 221)

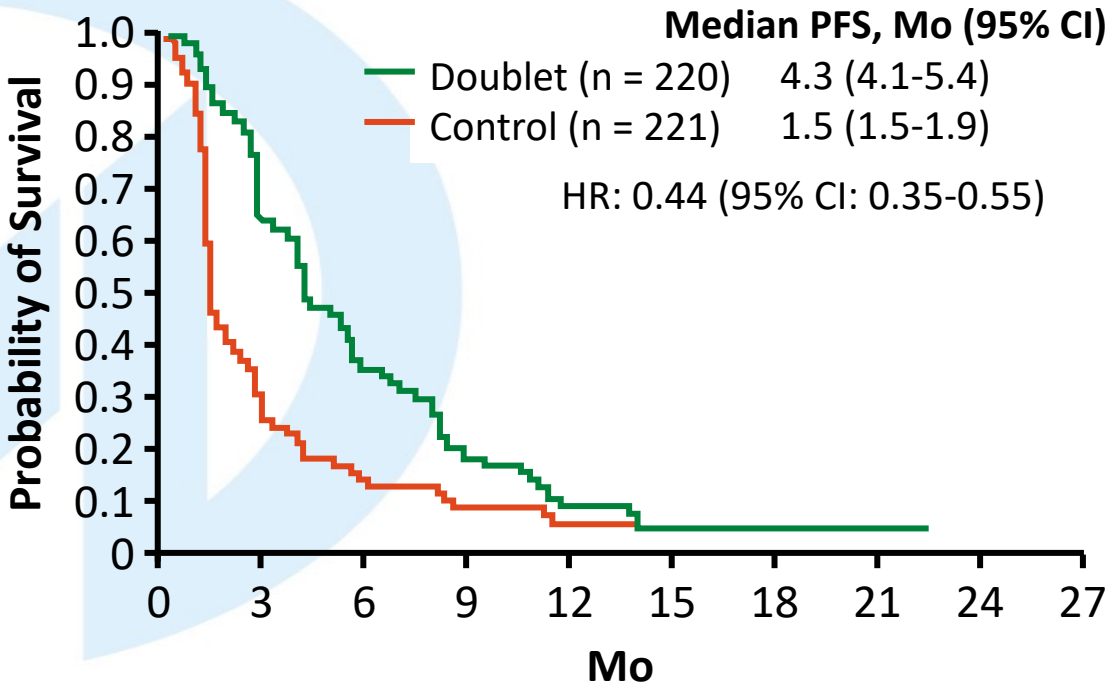
Patients followed for OS beyond progression

- Primary endpoints: OS and ORR for triplet vs control; secondary endpoints: OS and ORR for doublet vs control, triplet vs doublet; PFS; safety

Van Cutsem. JCO. 2019;10;37:1460. Kopetz, Van Cutsem. NEJM. 2019;381:1632.
Tabernero, Van Cutsem. JCO. 2021;39:273. NCT02928224.

BEACON CRC: PFS (BICR)



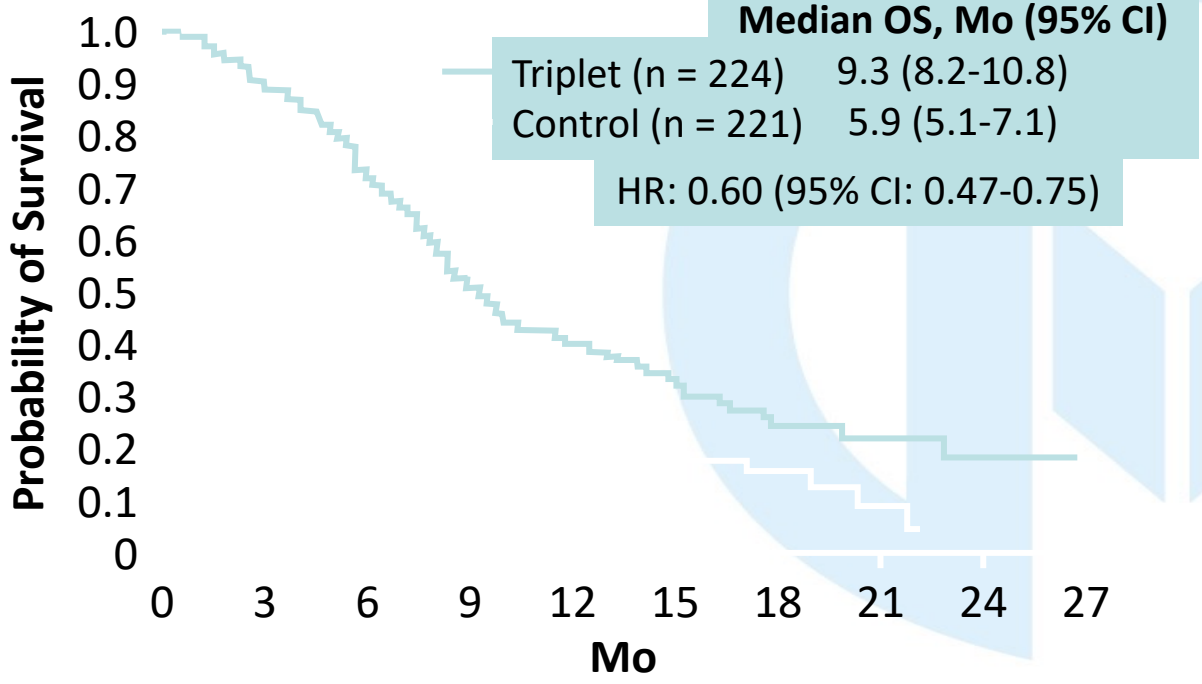


- FDA/EMA indication: encorafenib + cetuximab for *BRAF* V600E-mutated mCRC after previous systemic therapy

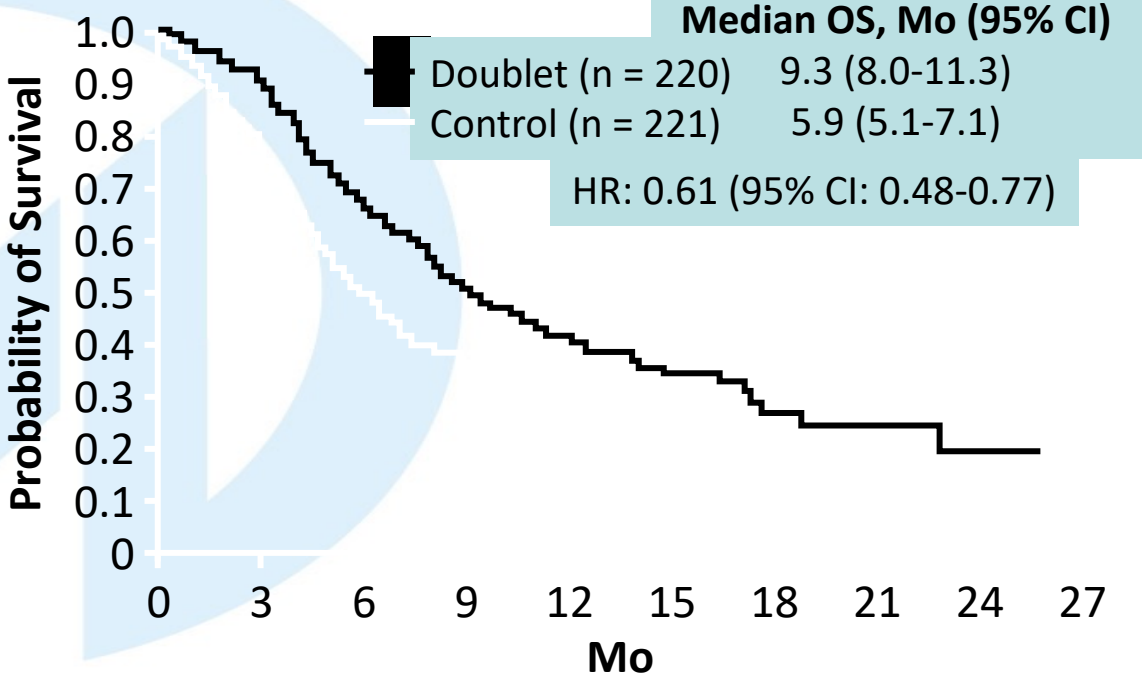
Tabernero, Van Cutsem. JCO. 2021;39:273.

BEACON CRC: OS and ORR

Triplet vs Control (Primary Endpoint)



Doublet vs Control



Confirmed Response by BICR	Triplet Regimen (n = 224)	Doublet Regimen (n = 220)	Control (n = 221)
ORR, % (95% CI)	27 (21-33)	20 (15-25)	2 (<1-5)
P value (vs control)	<.0001	<.0001	

Tabernero, Van Cutsem. JCO. 2021;39:273.

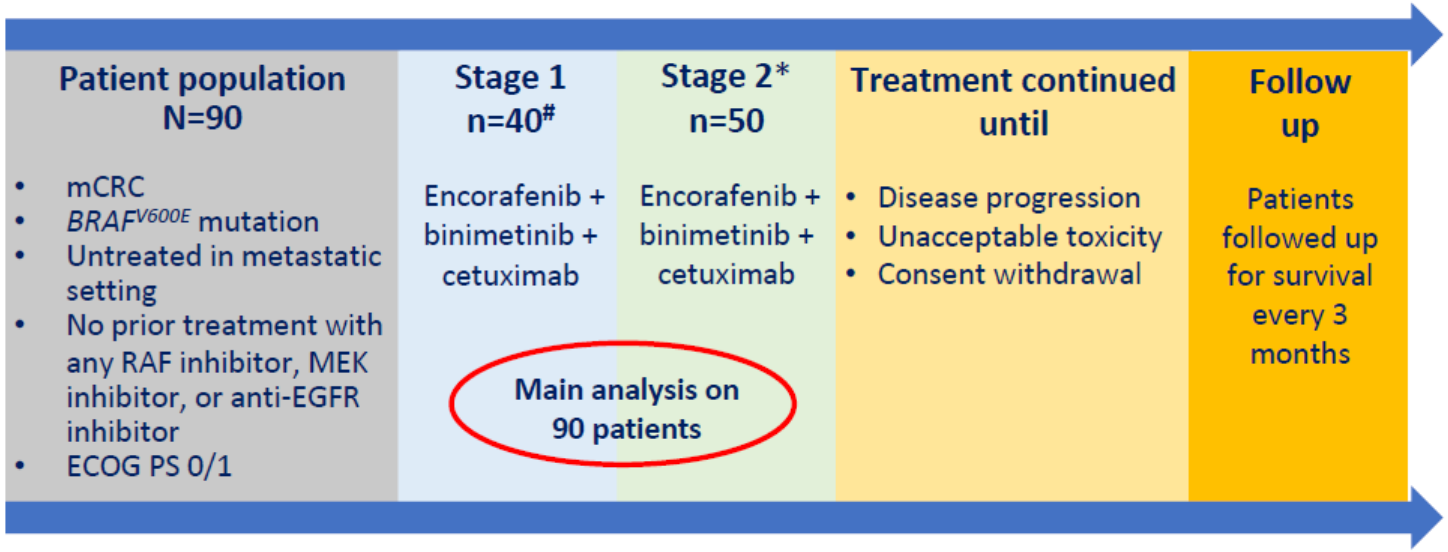
BEACON CRC: AEs

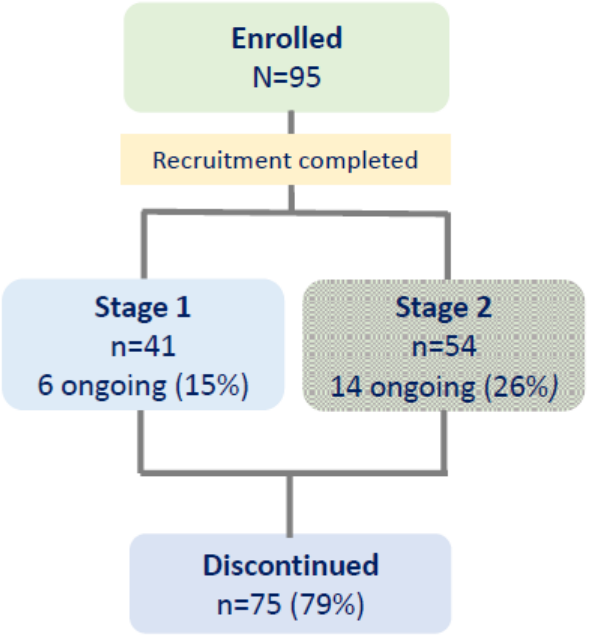
AEs in ≥25% of Patients in Experimental Arm, %	Triplet Regimen (n = 222)		Doublet Regimen (n = 216)		Control (n = 193)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE	99.1	65.8	98.1	57.4	98.4	64.2
Diarrhea	66.2	10.8	38.4	2.8	48.7	10.4
Acneiform dermatitis	50	2.7	30.1	0.5	39.9	2.6
Nausea	48.2	4.5	38.0	0.5	43.5	1.6
Vomiting	44.1	5.4	27.3	1.4	31.6	3.1
Abdominal pain	34.2	6.3	27.8	3.2	28.0	5.2
Fatigue	33.3	2.3	33.3	4.2	28.0	4.7
Decreased appetite	29.7	1.8	31.0	1.4	29.0	3.1
Constipation	28.4	0.5	18.1	0	20.2	1.0
Asthenia	27.9	3.6	24.1	3.7	27.5	5.2

Taberno. ESMO 2019. LBA32. Kopetz. NEJM. 2019;381:1632.

ANCHOR CRC: First-line Encorafenib + Binimetinib + Cetuximab in BRAF V600E mutant mCRC

Two-stage study design[1]





- PD, n=48 (64%)
- Adverse events, n=16 (21%)
- Physician decision, n=6 (8%)
- Other, n=5 (7%)

Primary objective and endpoint: cORR (investigator-assessed)
H0 rejection if lower limit of the 95% CI for cORR ≥30% (≥37 confirmed responses in 90 patients)
Secondary endpoints: PFS, OS, safety, QoL, PK

#Futility analysis; *Stage 2 enrolment only after ≥12 responses observed in Stage 1. cORR, confirmed objective response rate; ECOG PS, Eastern Cooperative Oncology Group performance status; mCRC, metastatic colorectal cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; QoL, quality of life.

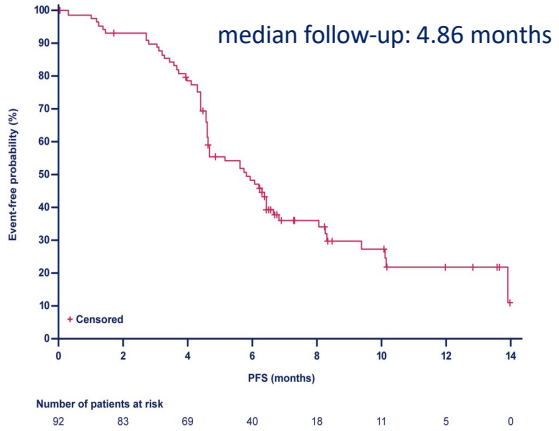
1. Grothey A, et al. *Annals Oncol*. 2019;30(suppl 4):P-400.

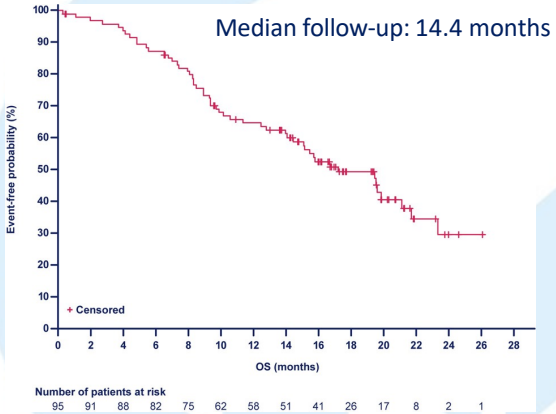
ClinicalTrials.gov Identifier: NCT03693170

Cut-off date: 29 June 2020

The ANCHOR-CRC Study

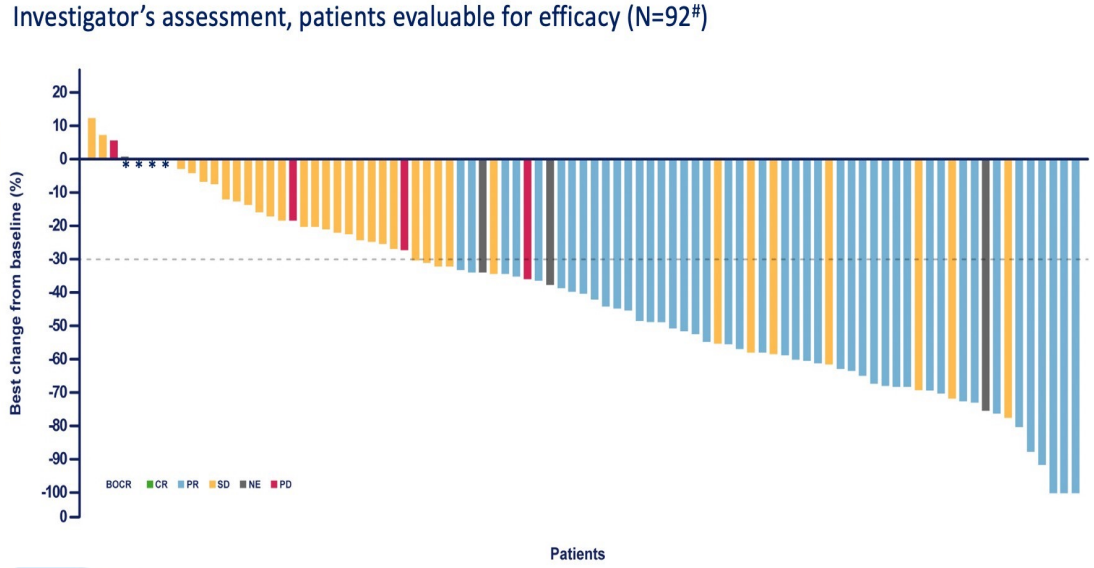
Secondary Endpoints: PFS / OS





E/C/B	N	Number of events	Median (months - 95% CI)
OS	N=95	52 (54'7%)	17'2 (14'1-21'1)
PFS	N=92	61 (66'3%)	5'8 (4'6-6'4)

Primary Endpoint: cORR (investigator assessed)



The study met its primary endpoint, as the observed cORR was 47.8% with a lower limit of the 95% CI of 37.3%, exceeding the pre- specified rate of at least 30% required to reject the null hypothesis

Overall, the results reported are similar to that observed with recommended chemotherapy-based regimens in 1st line BRAF-mutant mCRC"

Frontline BRAF V600E Phase III RCT

BREAKWATER Study Schema

Safety Lead-in

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

Encorafenib + Cetuximab + mFOLFOX6
N=30
Encorafenib + Cetuximab + FOLFIRI
N=30

Doses:
Encorafenib- 300 mg PO QD
Cetuximab- 500 mg/m^2 IV Q2W
FOLFOX- full doses IV Q2W
FOLFIRI- full doses IV Q2W

ENDPOINTS

- Incidence of DLTs, Adverse events, dose modifications/discontinuations due to AEs
- PK including drug-drug interactions

Phase 3

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

Randomize 1:1:1*

Arm A**
Encorafenib + Cetuximab
N=290

Arm B**
Encorafenib + Cetuximab + FOLFOX or FOLFIRI$^{\beta}$
N=290

Control Arm§ Physicians Choice: FOLFOX, FOLFIRI, FOLFOXIRI, CAPOX, all +/- anti-VEGF antibody
N=290

1° ENDPOINTS

- PFS (BICR) Arm A v. Control
  AND
- PFS (BICR) Arm B v. Control

(BICR-blinded independent central review)

KEY 2° ENDPOINTS

- OS Arm A v. Control AND
- OS Arm B v. Control

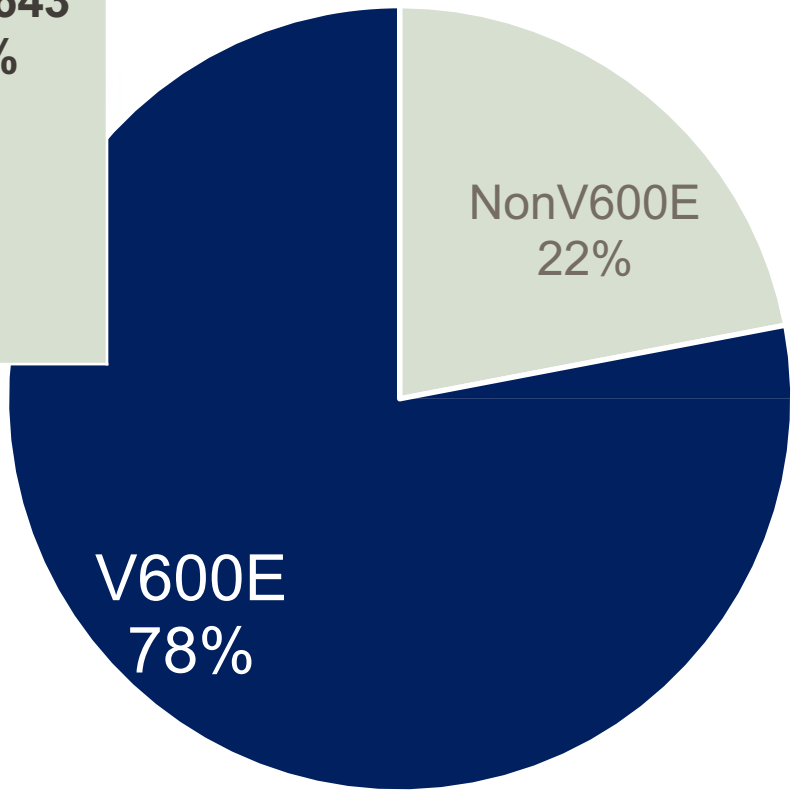
*Stratified by: ECOG PS 0 v. 1, Region US/Canada v. Europe v. ROW

**Same dosing as SLI; $^{\beta}$FOLFOX or FOLFIRI based on SLI results; § No crossover

FOLFOX: Folinic acid (leucovorin), Fluorouracil (5-FU)- infusional, Oxaliplatin (Eloxatin) FOLFIRI: Folinic acid (leucovorin), Fluorouracil (5-FU)- infusional, Irinotecan (Camptosar), CAPOX: Capecitabine (Xeloda), Oxaliplatin (Eloxatin) FOLFOXIRI: Folinic acid (leucovorin), Fluorouracil (5-FU), Oxaliplatin (Eloxatin), Irinotecan (Camptosar)

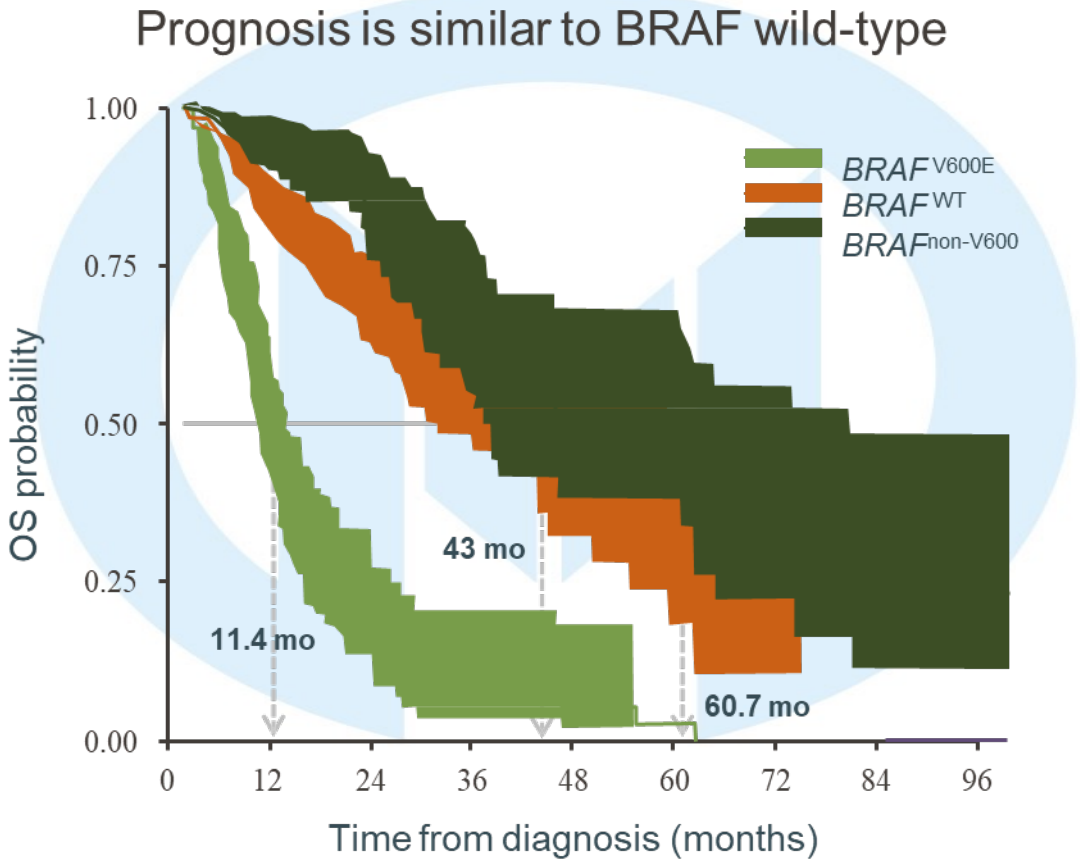
Prevalence of Non-V600E BRAF mutations in CRC

	MC	MDA	FM	Totals	All BRAF mut %	% of all BRAF mut which are non-V600	% of total CRC which are non-V600
Total CRC Cases	1014	2276	6353	9643	**1147/9643 11.9%**	**207/940 22%**	**207/9643 2.1%**
Total BRAF Mutations	137	334	469	940			
Non-V600 BRAF	27	54	126	207			



Jones et al., JCO '16

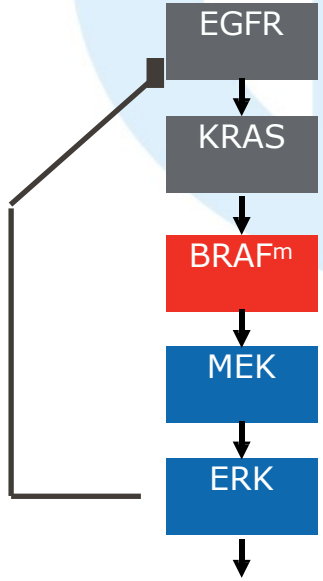
Atypical (Non-V600E) BRAF mutations

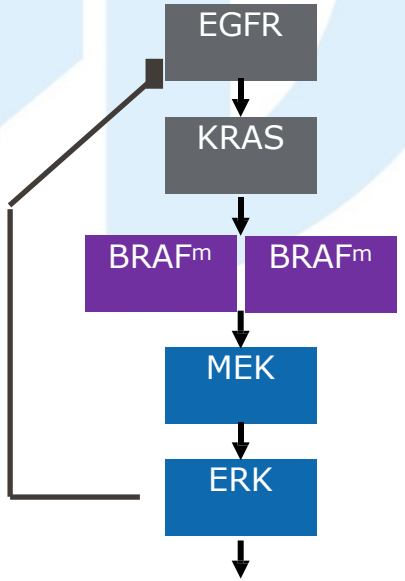


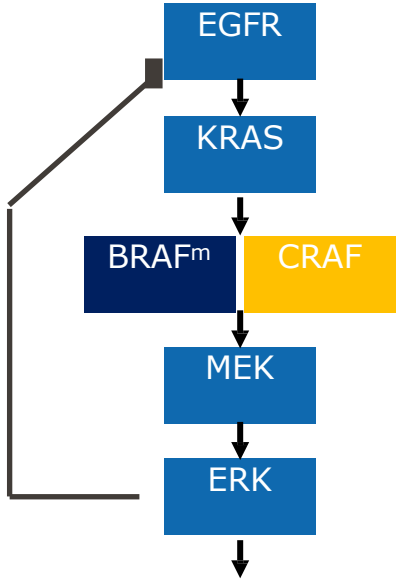
Jones JC, et al. J Clin Oncol 2017;35:2624–30.

Understanding Class II and Class III Non-V600E *BRAF*^{mut}

	BRAF V600E Class I	Class II BRAF	Class III BRAF
Structure	BRAF monomer	BRAF dimers	BRAF/CRAF dimers
RTK (EGFR) Dependency	No	No	Yes
Kinase activity	High	High/Intermediate	Low
EGFRi sensitivity	No	Unlikely	Likely
Potential Strategy	BRAF, MEK, EGFR	RAF dimer inhibitors	RTK, MAPK combinations





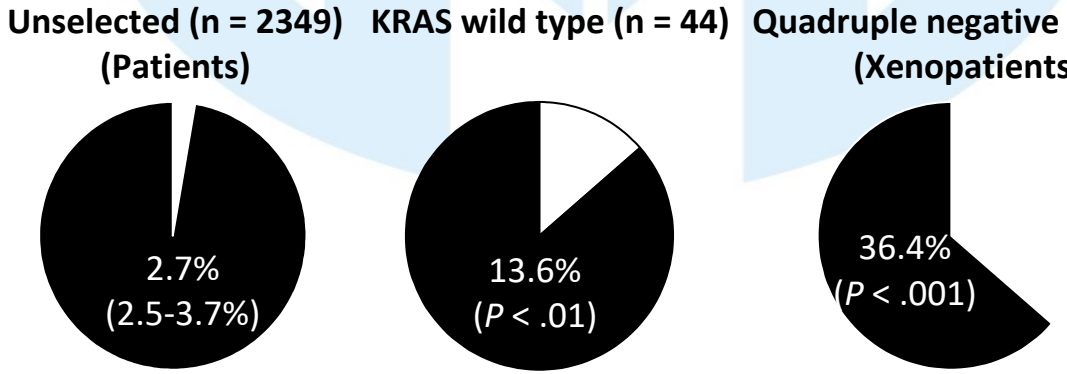


Yao et al Nature '17

HER2 Amplification in CRC

- Resistance marker for EGFR antibodies
- Defines patients who are candidates for HER2-targeted therapy

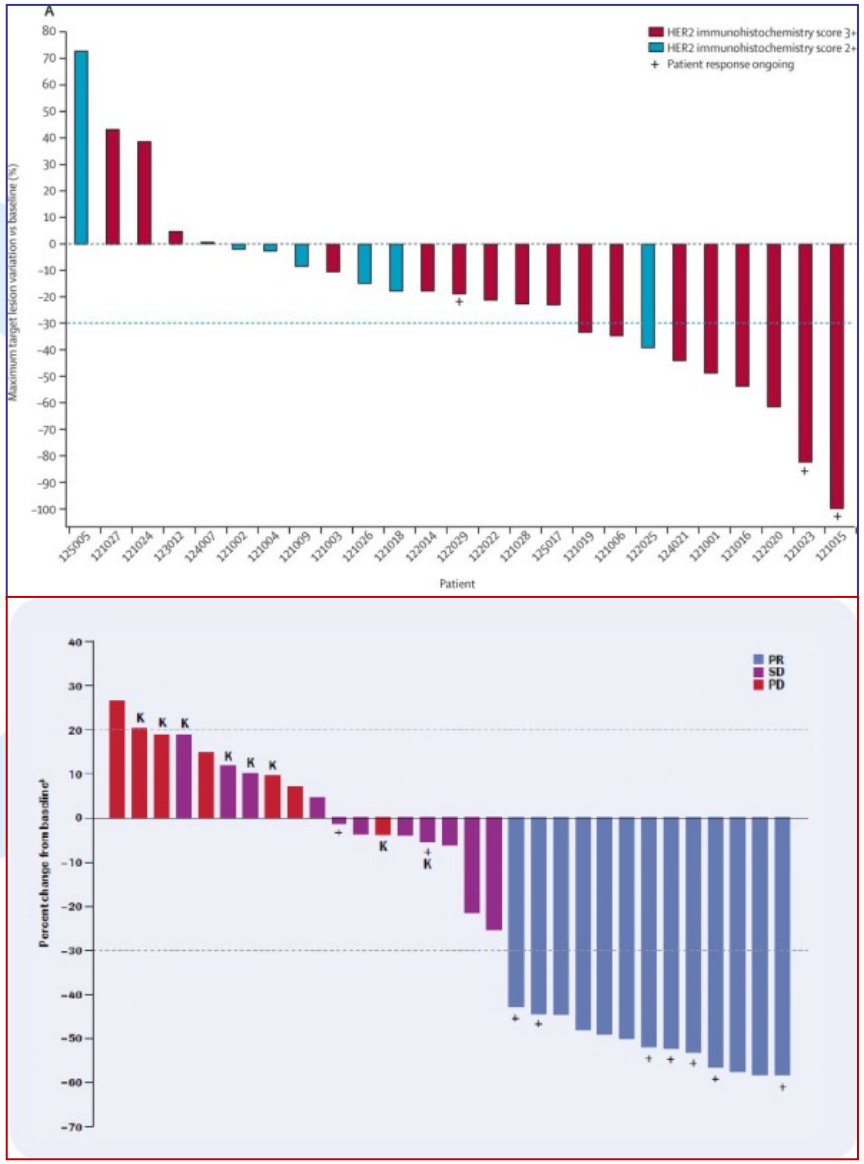
- 5.3% *HER2* amplification in HERACLES study (screened = 1299)[1]
- *HER2* amplification enriched in KRAS, NRAS, BRAF, and PIK3CA WT tumors[2,3]



1. Siena. AACR 2017. Abstr CT005. 2. Bertotti. Cancer Discovery. 2011;1:508. 3. Kuwada. Int J Cancer. 2004;109:291.

HER2 Amplification and mCRC

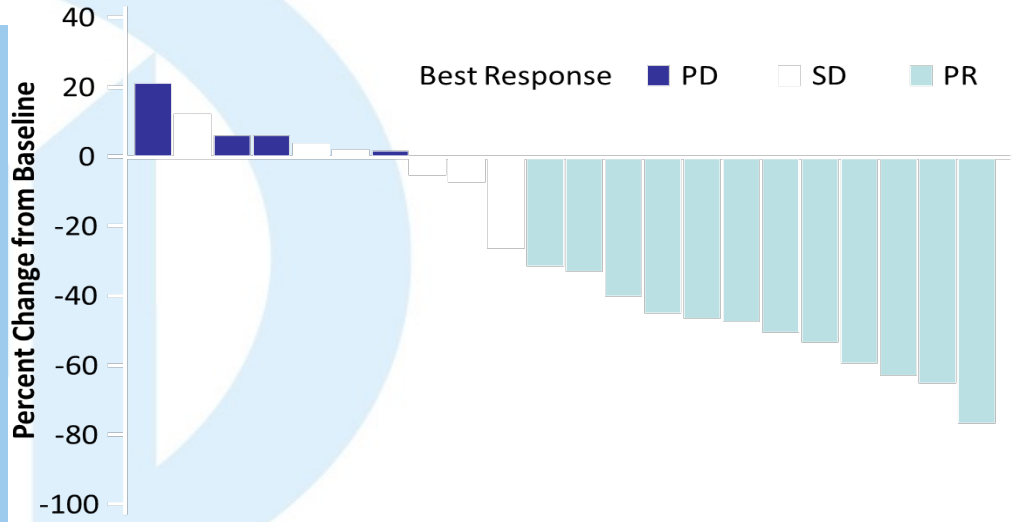
- Dual anti-HER2 Inhibition: Early single-arm phase II studies in refractory HER2 amplified mCRC:
  - HERACLES Study (Siena et. al. 2016):
    - Trastuzumab + Lapatinib
    - ORR: 30% (8/27) (95% CI: 14%–50%)
    - Median PFS: 21 weeks (95% CI: 16-32 weeks)
- My Pathway Study (Hurwitz et. al. 2016):
  - *Trastuzumab + Pertuzumab*
  - *ORR: 38% (13/34) (95% CI: 24%–55%)*
  - *Median TTP: 4.6 months*



MOUNTAINEER: Trastuzumab With Tucatinib for *HER2*-Amplified mCRC

- Single-arm phase II for patients with *RAS* wt, *HER2*-amplified mCRC (n = 26)
  - Primary tumor site of origin: right colon (n = 4), left colon/rectum (n = 17), transverse colon (n = 3), and overlapping (n = 2)

	Evaluable Patients (n = 22)
Overall response rate	55%
Clinical benefit rate	64%
Median PFS	6.2 months
Median OS	17.3 months
Median DOR	Not reached

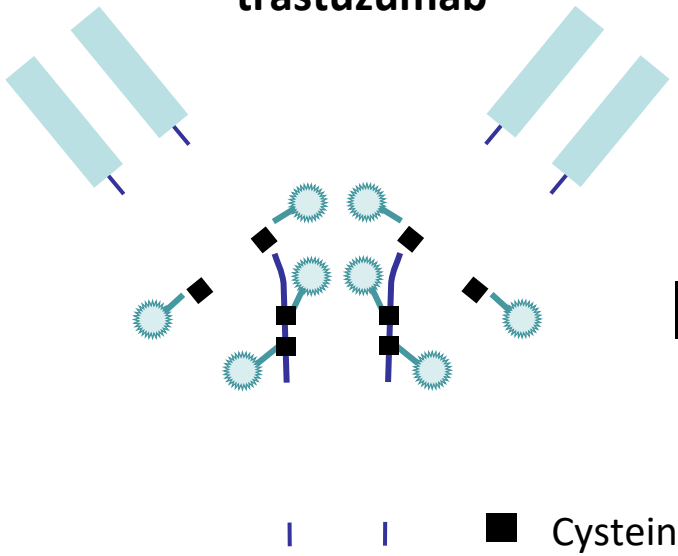


- Median follow-up = 10.6 months
- Grade 3 treatment-related AEs (TRAEs) = 9% (no grade 4/5 TRAEs)
- Most common TRAEs: AST elevation (48%; all G1), ALT elevation (30%; all G1), and diarrhea (26%)

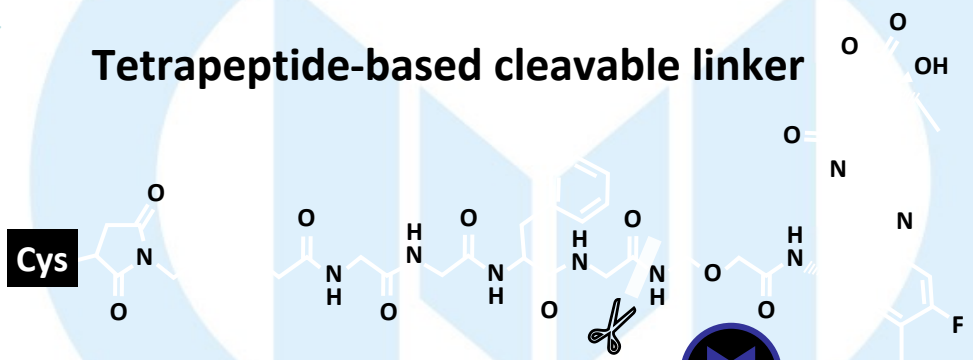
Strickler JH, et al. ESMO 2019. Abstract 527PD.

HER2-Targeted ADC: Trastuzumab Deruxtecan (DS-8201)

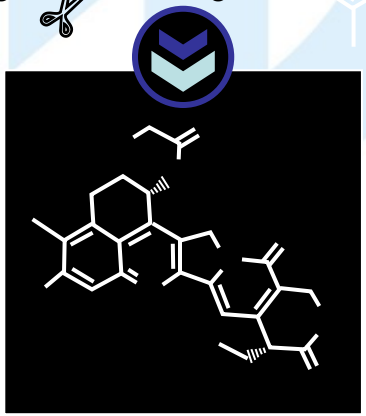
Humanized HER2 IgG1 mAb with same AA sequence as trastuzumab



Tetrapeptide-based cleavable linker



Topoisomerase I inhibitor (DXd) payload
(exatecan derivative)



- High drug:antibody ratio: ~ 8
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect

Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Trail. Pharmacol Ther. 2018;181:126. Ogitani. Cancer Sci. 2016;107:1039.

DESTINY-CRC01

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

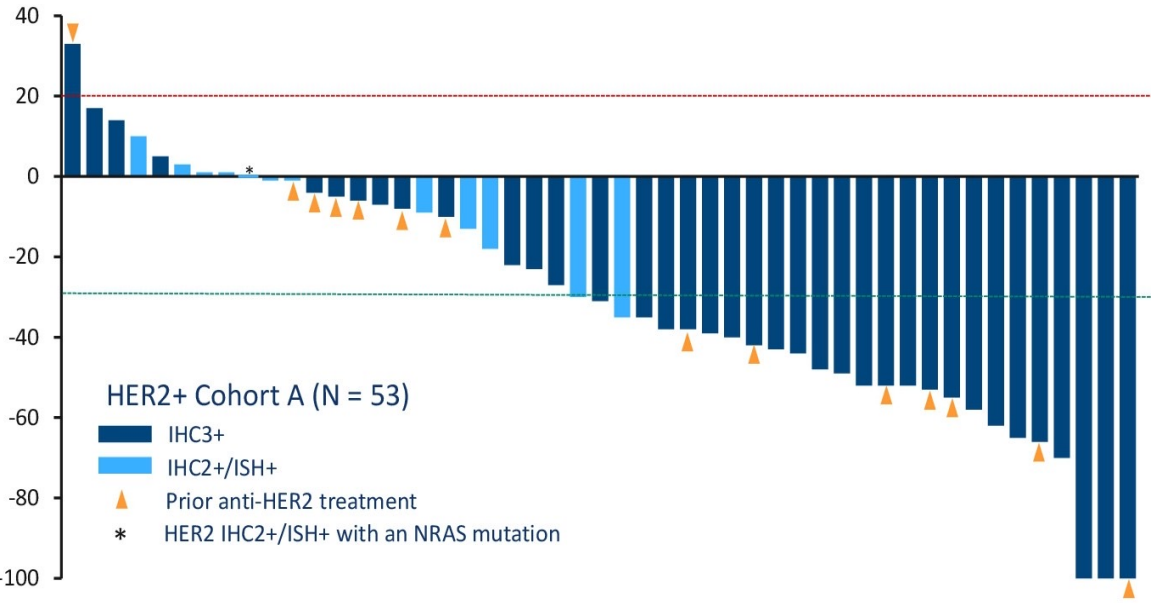
T-DXd 6.4 mg/kg q3w

Cohort A (n = 53)
HER2 Positive (IHC 3+ or IHC 2+/ISH+)

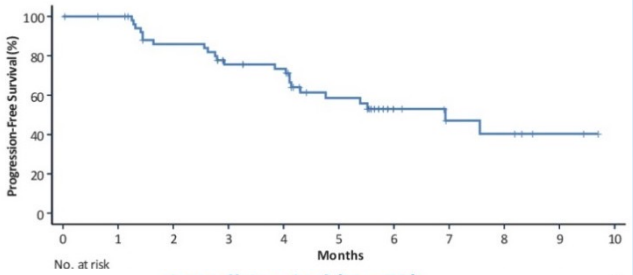
A futility monitoring was done after ≥20 patients in Cohort A had 12 weeks of follow-up to inform opening of Cohorts B and C

Cohort B (n = 7)
HER2 IHC 2+/ISH−

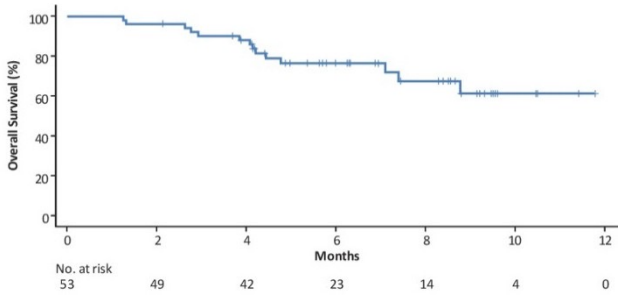
Cohort C (n = 18)
HER2 IHC 1+



Progression-Free Survival (N = 53)
Median: 6.9 months
(95% CI, 4.1-NE)



Overall Survival (N = 53)
Median: Not reached
(overall 95% CI, 0.74-NE)



Overall Safety Summary

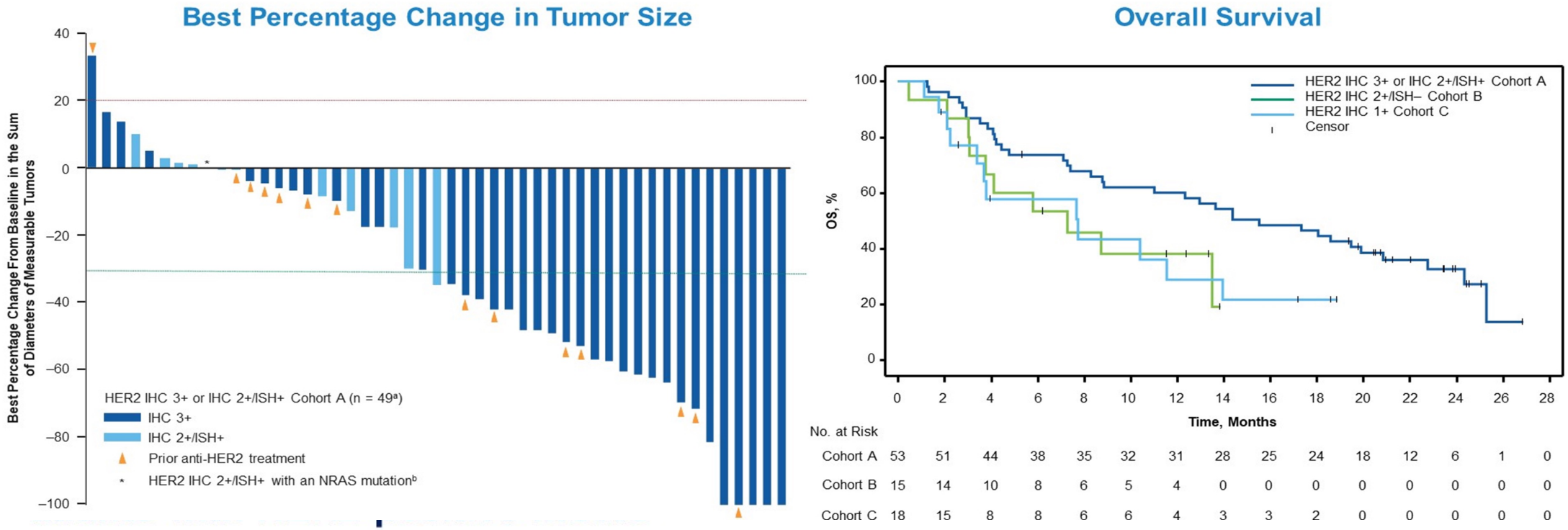
Type of Adverse Event, n (%)[a]	HER2+ Cohort A (n = 53)	All Patients (N = 78)
Any TEAE	53 (100)	78 (100)
Drug-related	51 (96.2)	73 (93.6)
TEAE grade ≥3	32 (60.4)	48 (61.5)
Drug-related	27 (50.9)	38 (48.7)
Serious TEAE	18 (34.0)	26 (33.3)
Drug-related	12 (22.6)	14 (17.9)
Dose adjustments		
TEAE associated with discontinuation	5 (9.4)	7 (9.0)
Drug-related	2 (3.8)	2 (2.6)
TEAE associated with dose reduction	11 (20.8)	15 (19.2)
Drug-related	10 (18.9)	14 (17.9)
TEAE associated with dose interruption	20 (37.7)	27 (34.6)
Drug-related	15 (28.3)	19 (24.4)
Death		
TEAE associated with death[b]	5 (9.4)	7 (9.0)
Drug-related	2 (3.8)	2 (2.6)

Siena et al, ASCO 2020

Updated results from GI ASCO 2022

DESTINY-CRC01

Best Percentage Change in Tumor Size in Cohort A and OS in All Cohorts



- For cohort A, confirmed ORR was 45.3% (95% CI, 31.6-59.6), median DOR was 7.0 months (95% CI, 5.8-9.5), median PFS was 6.9 months (95% CI, 4.1-8.7), and median OS was 15.5 months (95% CI, 8.8-20.8)

Yoshino et al, GI ASCO 2022

Synopsis of HER2-targeted trials in mCRC

Trial	n	Molecular selection	Her2-directed regimen	ORR	PFS (months)
HERACLES-A	27	*KRAS* WT	Trastuzumab + lapatinib	30%	4.9
MyPathway	57	none	Trastuzumab + pertuzumab	32%*	2.9**
HERACLES-B§	30	*RAS/BRAF* WT	Pertuzumab + T-DM1	10%	4.8
MOUNTAINEER§	23	*RAS* WT	Trastuzumab + tucatinib	52.2%	8.1
TRIUMPH§	17	*RAS* WT	Trastuzumab + pertuzumab	35.3%	4.0
DESTINY-CRC01§	53	*RAS* WT¥	T-DXd	45.3%	6.9

§ Abstract only
*40% in *KRAS* WT; **5.1 in *KRAS* WT; ¥1 patient had an *NRAS* mutation

Sartore-Bianchi et al, *Lancet Oncol* 2016
Meric-Bernstam F et al, *Lancet Oncol* 2019
Sartore-Bianchi et al, ESMO 2019 LBA
Strickler et al, ESMO 2019 LBA
Nakamura et al, ESMO 2019
Siena et al, ASCO 2020

Take Home Points

- NGS testing is essential to optimize clinical outcomes for patients with cancer. ALL pts should be tested.
- MSI-H mCRC - Pembrolizumab should be the standard of care treatment choice if possible in first line
- Encorafenib in combination with cetuximab is now FDA approved for use in patients with previously treated BRAF 600E mutant mCRC and is considered SOC.
- Treatment for KRAS G12C mutated mCRC is evolving, and initial data are promising
- Exciting data with trastuzumab combinations (lapatinib, pertuzumab, tucatinib) as well as trastuzumab deruxtecan
- Think about rare fusions (NTRK) !!

Thank you !

GI oncology questions

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