INTEGRATING BIOMARKERS AND TARGETED THERAPY INTO COLORECTAL CANCER MANAGMENT

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MAYO CLINIC

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CONFLICTS OF INTEREST

RESEARCH FUNDING

Boston Biomedical
Mirna
Sunbiopharma
Senhwa
Medimmune
Bioline
Agios
Halozyme
Threshold
Celgene
Toray
Dicerna
Sillajen
Eisai
Taiho
Ionis
EMD Serono
Incyte
ARIAD
Imclone
Adaptimmune
Redhill Biopharma

CONSULTANT

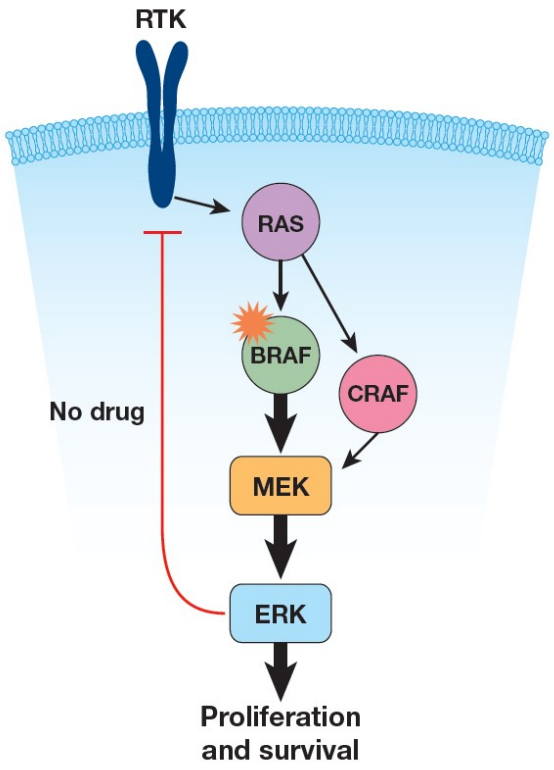
G1 Therapeutics
TD2
Fujifilm
Insys
Novartis
Arqule
Celgene
Inspyr
Halozyme
Exelixis

ADVANCES IN PRECISION MEDICINE

- *BRAF V600E*
- *HER2* (*ERBB2*) amplification
- *MSI-high*
- *KRAS G12C*
- *NTRK 1/2/3* and other rare fusions

BRAF V600E MUTATIONS

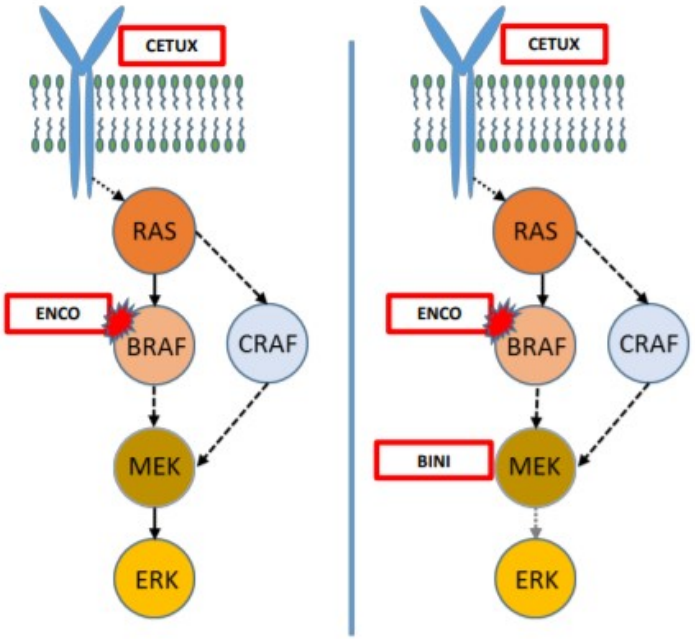
BRAF MUTATIONS IN METASTATIC CRC



- ~7% of CRC
- Right sided
- Poor prognosis (median OS ~ 12 months)
- Limited benefit from anti-EGFR therapy
- Limited response to single agent BRAF inhibition

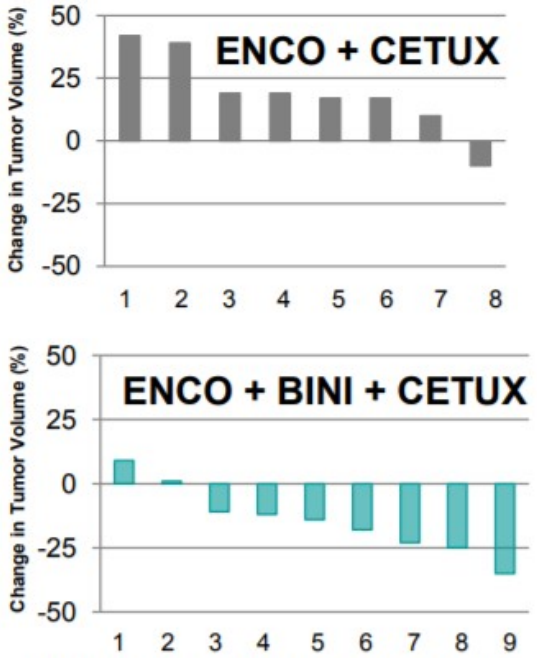
RATIONALE FOR TRIPLE MAPK PATHWAY INHIBITION

MAPK Signaling in Colorectal Cancer[1]



1.Adapted From: Strickler JH. *Cancer Treatment Reviews*. 2017; 60:109-119

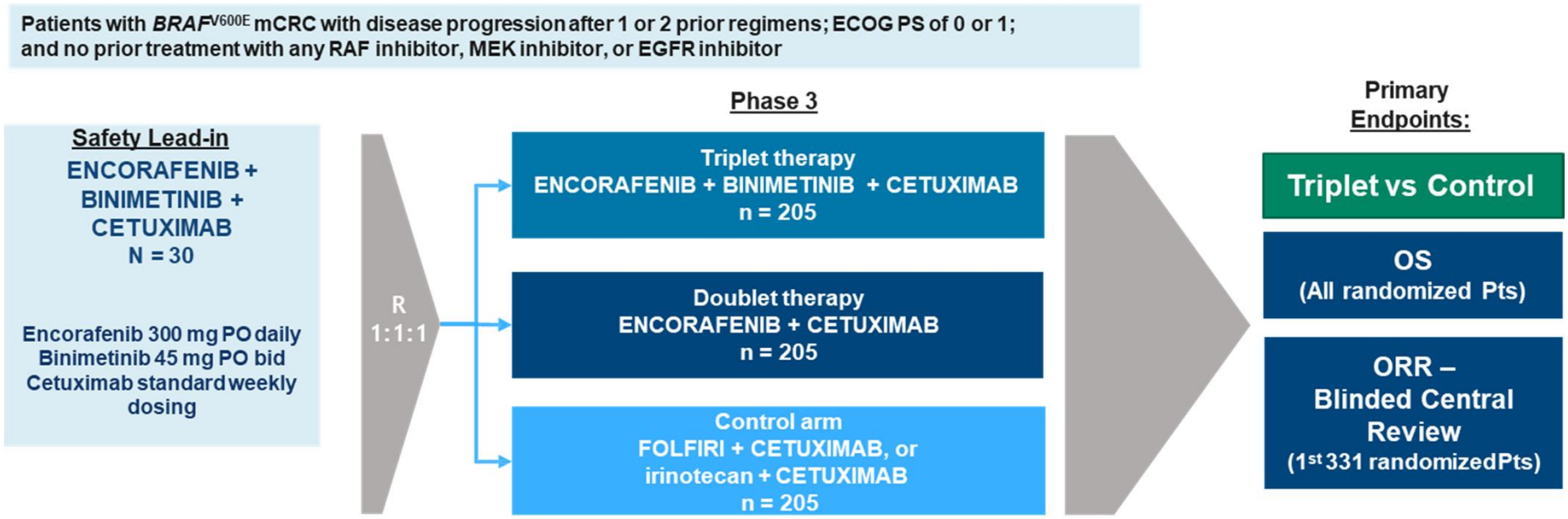
HT-29 *BRAF*^{V600E} colorectal xenografts[2]



Each bar represents change in tumor volume in one animal at day 21.
The control group showed increases in tumor size for all animals, with mean increase in tumor volume versus baseline of 285%.

2. Data on File. Array BioPharma Inc.

BEACON CRC PHASE 3 STUDY DESIGN

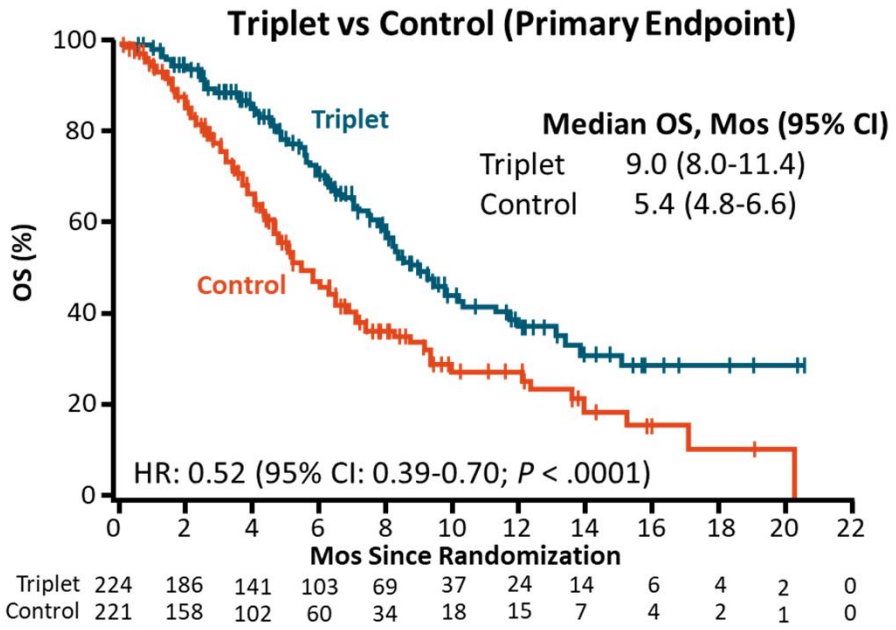


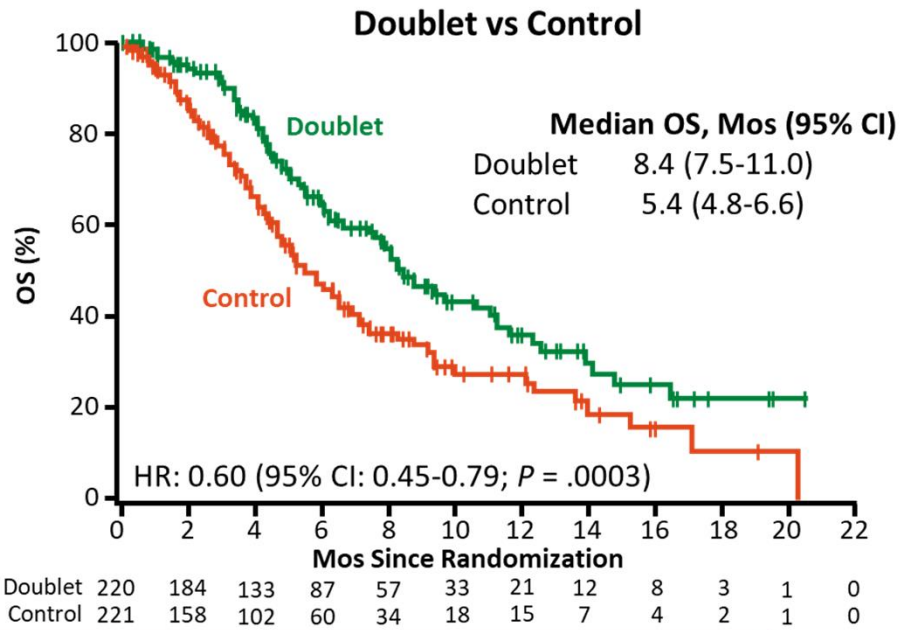
Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved)

Secondary Endpoints: Doublet vs Control and Triplet vs Doublet - OS & ORR, PFS, Safety

QOL Assessments: EORTC QOL Questionnaire (QLQ C30), Functional Assessment of Cancer Therapy Colon Cancer, EuroQol 5D5L, and Patient Global Impression of Change).

BEACON: OVERALL SURVIVAL AND RESPONSE RATE

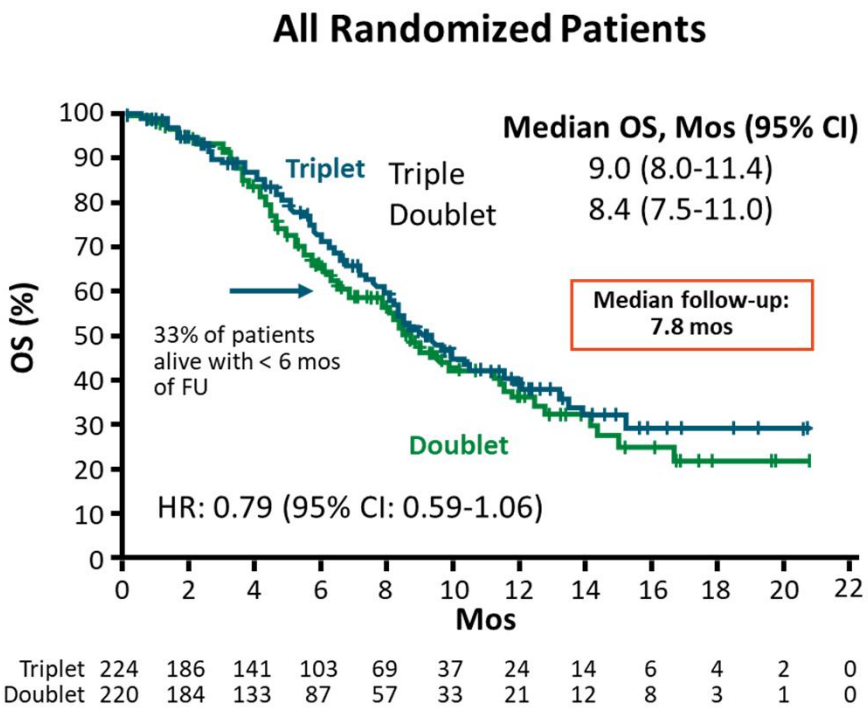


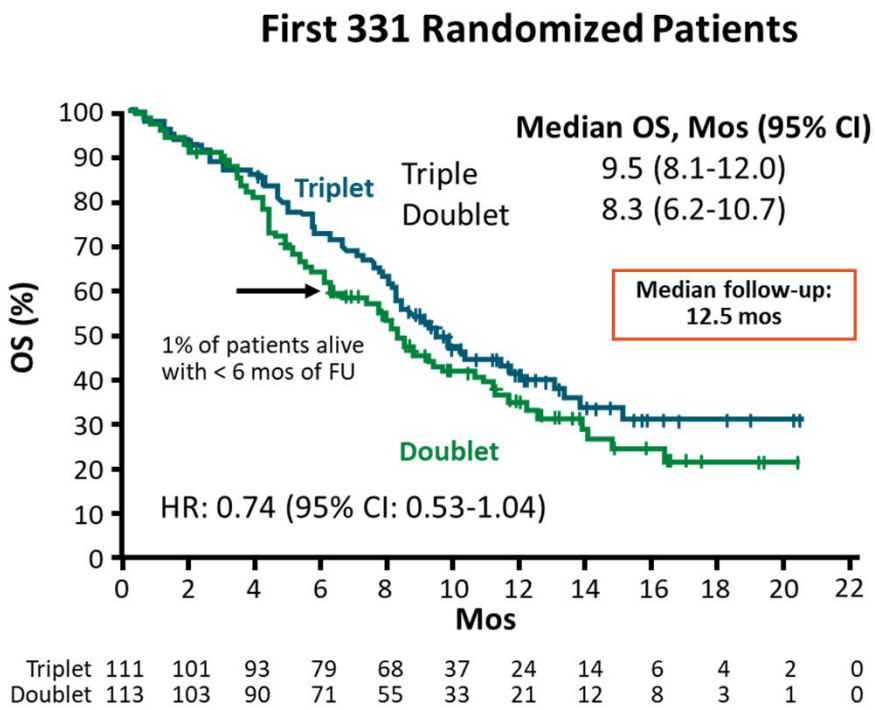


Confirmed Response by BICR	Triplet Regimen (n = 111)	Doublet Regimen (n = 113)	Control (n = 107)
ORR, % (95% CI)	26 (18-35)	20 (13-29)	2 (< 1-7)
P value (vs control)	< .0001	< .0001	

KOPETZ ET AL, NEJM 2019

OVERALL SURVIVAL: TRIPLET VS. DOUBLET

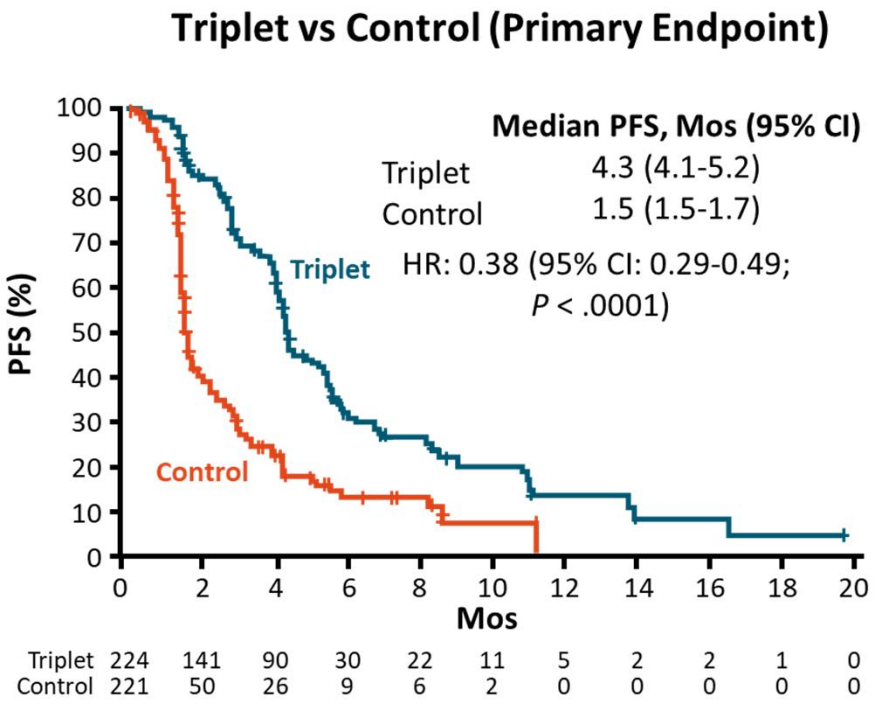


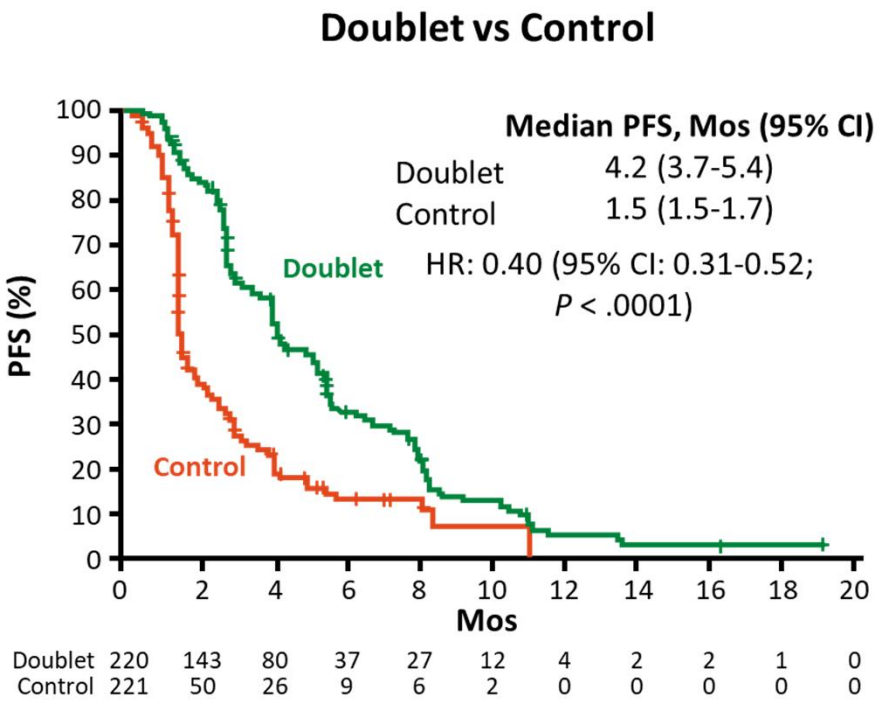


Study design not powered to formally compare OS in triplet vs doublet treatment arms

KOPETZ ET AL, NEJM 2019

BEACON: PROGRESSION FREE SURVIVAL





KOPETZ ET AL, NEJM 2019

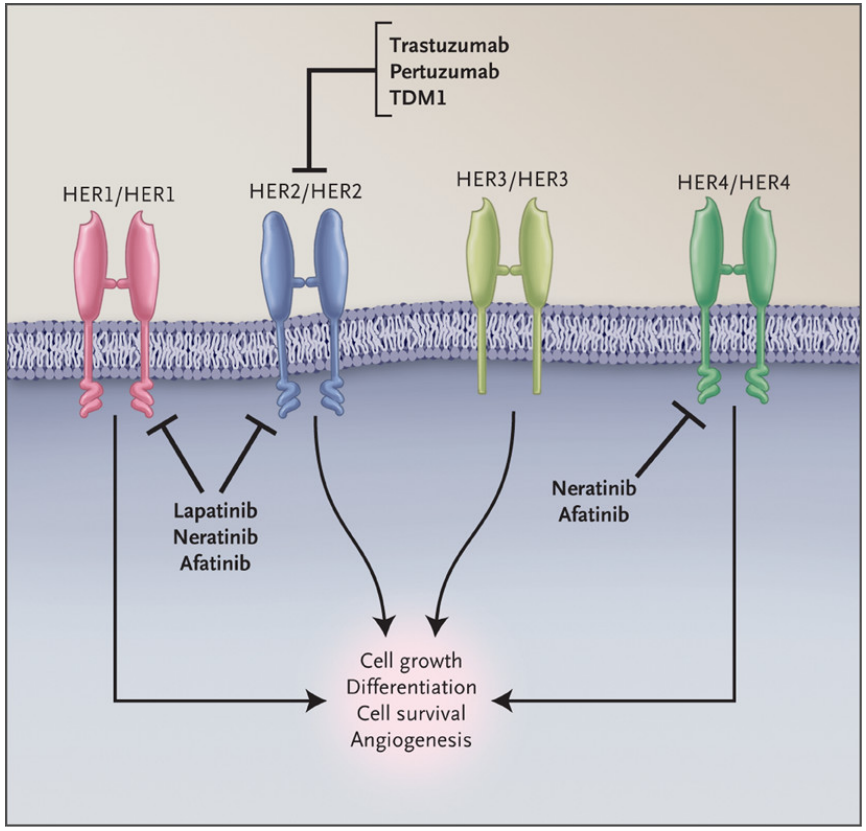
BEACON: CONCLUSIONS

- Encorafenib + binimetinib + cetuximab is superior to current SOC
- The triplet regimen was well-tolerated by most patients
- Triplet might be superior to doublet, but possible increase in toxicity
- BEACON results support a new approach to management of *BRAF V600E* mutated metastatic CRC

HER2 AMPLIFICATIONS

HER2 AS A TARGET

- HER2 is a RTK encoded by *ERBB2*
- HER2 receptor has no soluble ligand
- HER2 heterodimerizes with other ligand-bound HER family members
- HER2–HER3 heterodimer is a potent driver of PI3K signaling
- Multiple therapies target HER2 and/or HER2 heterodimers



PREVALENCE OF HER2 AMPLIFICATIONS IN COLORECTAL CANCER

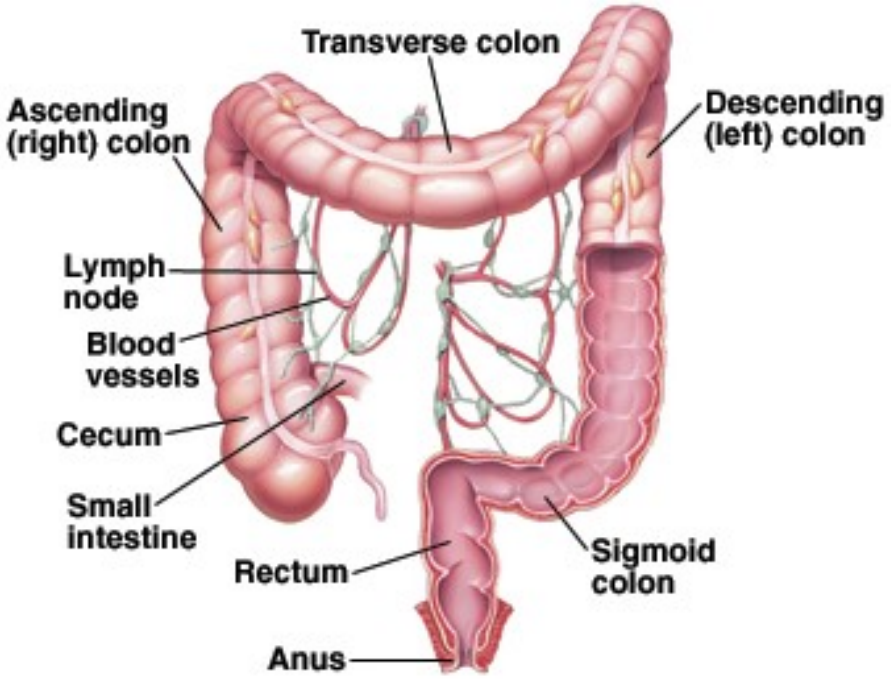
Dataset	Patient population (n)	*ERBB2* amplified
TCGA	615 unselected patients Source: online bioportal	3.1%
CARIS Life Sciences	1,226 unselected patients with metastatic disease Source: J Clin Oncol 32, 2014 (suppl; abstr e22200)	3.8%
Foundation Medicine	5,127 unselected patients with metastatic disease Source: J Clin Oncol 34, 2016 (suppl 4S; abstr 630)	3.0%

HER2 AMPLIFICATION IS MORE COMMON IN RAS/RAF WT COLORECTAL CANCER PATIENTS

Dataset	Patient population (n)	*ERBB2* amplified
HERACLES	914 KRAS exon 2 WT metastatic CRC patients Source: Sartore-Bianchi, Andrea et al., Lancet Oncol, 17(6) 738 - 746	5.3%
MDACC	114 NRAS/KRAS WT CRC patients 97 KRAS/NRAS/BRAF WT CRC patients Source: J Clin Oncol 34, 2016 (suppl; abstr 3517)	12.2% 14.4%
NCT02008383	76 RAS WT CRC patients (Guardant360) – Strickler et al series (unpublished)	11.8%

HER2 IN METASTATIC COLORECTAL CANCER

- Usually left sided
- Homogeneous HER2 expression
- Primary resistance to EGFR monoclonal antibodies (cetuximab, panitumumab)
- Not mutually exclusive with *RAS* or *BRAF* mutations
- Not associated with worse prognosis



RESULTS OF DUAL ANTI-HER2 CLINICAL TRIALS IN PATIENTS WITH REFRACTORY HER2^{AMP} METASTATIC COLORECTAL CANCER

Clinical trial	Therapies	Patients (N)	Response Rate	Time to Progression (median)
HERACLES	Lapatinib + Trastuzumab	27	30%	4.9 months
MyPathway	Pertuzumab + Trastuzumab	37	38%	4.6 months

Sartore-Bianchi et al., *Lancet Oncology* 2016 17, 738-746
Hurwitz et al., *J Clin Oncol* 35, 2017 (suppl 4S; abstract 676)
Hainsworth et al., *J Clin Oncol* 2018, 36, 536-542

MYPATHWAY: BIOMARKERS OF SENSITIVITY/RESISTANCE

	ORR n (%, 95% CI)	Median PFS Months (95% CI)	Median OS Months (95% CI)
All patients (n=57)	18 (32%, 20-45)	2.9 (1.4-5.3)	11.5 (7.7-NE)
KRAS status			
Wild-type (n=43)	17 (40%, 25-56)	5.3 (2.7-6.1)	14.0 (8.0-NE)
Mutated (n=13)	1 (8%, 0.2-36)	1.4 (1.2-2.8)	8.5 (3.9-NE)
PIK3CA status			
Wild-type (n=40)	17 (43%, 27-59)	5.3 (2.8-6.1)	14.0 (8.5-NE)
Mutated (n=8)	1 (13%, 0.3-53)	1.4 (1.1-5.7)	7.3 (1.2-12.6)
Previous anti-EGFR*			
Any (n=31)	11 (36%, 19-55)	4.1 (1.6-8.2)	11.5 (7.2-22.1)
None (n=12)	6 (50%, 21-79)	5.6 (1.3-14.7)	NE (3.2-NE)

Meric-Bernstam *et al*., Lancet Oncol Vol 20, Issue 4, April 2019, 518-530

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a]

[j] Larotrectinib or entrectinib are treatment options for patients with metastatic colorectal cancer that is *NTRK* gene fusion positive.
[n] If neither previously given
[o] If no previous treatment with a checkpoint inhibitor
[r] If no previous treatment with HER2 inhibitor.
[t] If not previously given

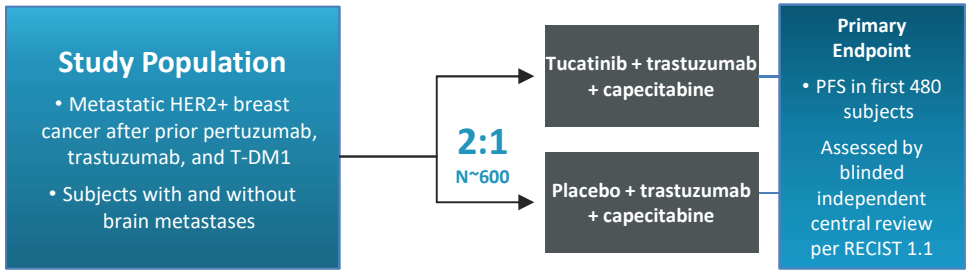
See footnotes on COL-D (7 of 13)

TUCATINIB : HIGHLY SELECTIVE HER2 TKI

- Oral, small molecule TKI that targets HER2 (Seattle Genetics, Inc.)
- Highly selective for the HER2 receptor
- Selectivity may improve tolerability (skin rash, diarrhea, etc.) compared to non-selective TKIs
- Potential for enhanced target inhibition, patient compliance, and opportunity for combinations with other drugs

TKI	Cellular Potency and Selectivity		
	pHER2 IC50 (nM): BT-474 cells	pEGFR IC50 (nM): A431 cells	Mechanism of Action
Tucatinib[1]	8	>4,000	Reversible
Neratinib[1]	7	8	Irreversible
Lapatinib[1]	49	31	Reversible
Poziotinib[2]	1	0.9	Irreversible
Tesavatinib[3]	552	1	Reversible

HER2CLIMB PIVOTAL TRIAL – TUCATINIB/TRASTUZUMAB BREAST CANCER



Tucatinib + trastuzumab + capecitabine

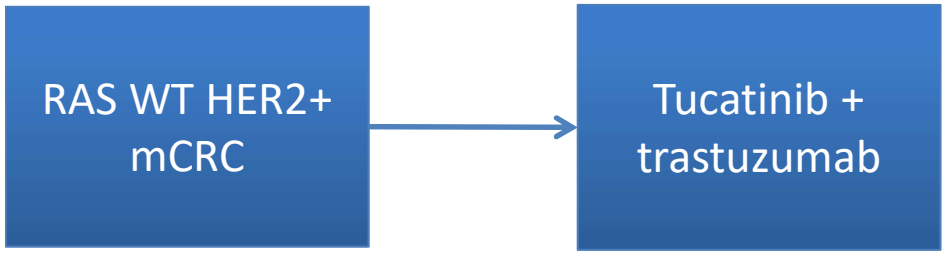
vs

Placebo + trastuzumab + capecitabine

- PFS: HR=0.54 (95% CI: 0.42-0.71); p<0.00001)
- Overall survival: HR=0.66 (95% CI: 0.50-0.88); p=0.0048)

Murthy et al., N Engl J Med 2019

MOUNTAINEER – TRASTUZUMAB/TUCATINIB IN HER2+ COLORECTAL CANCER

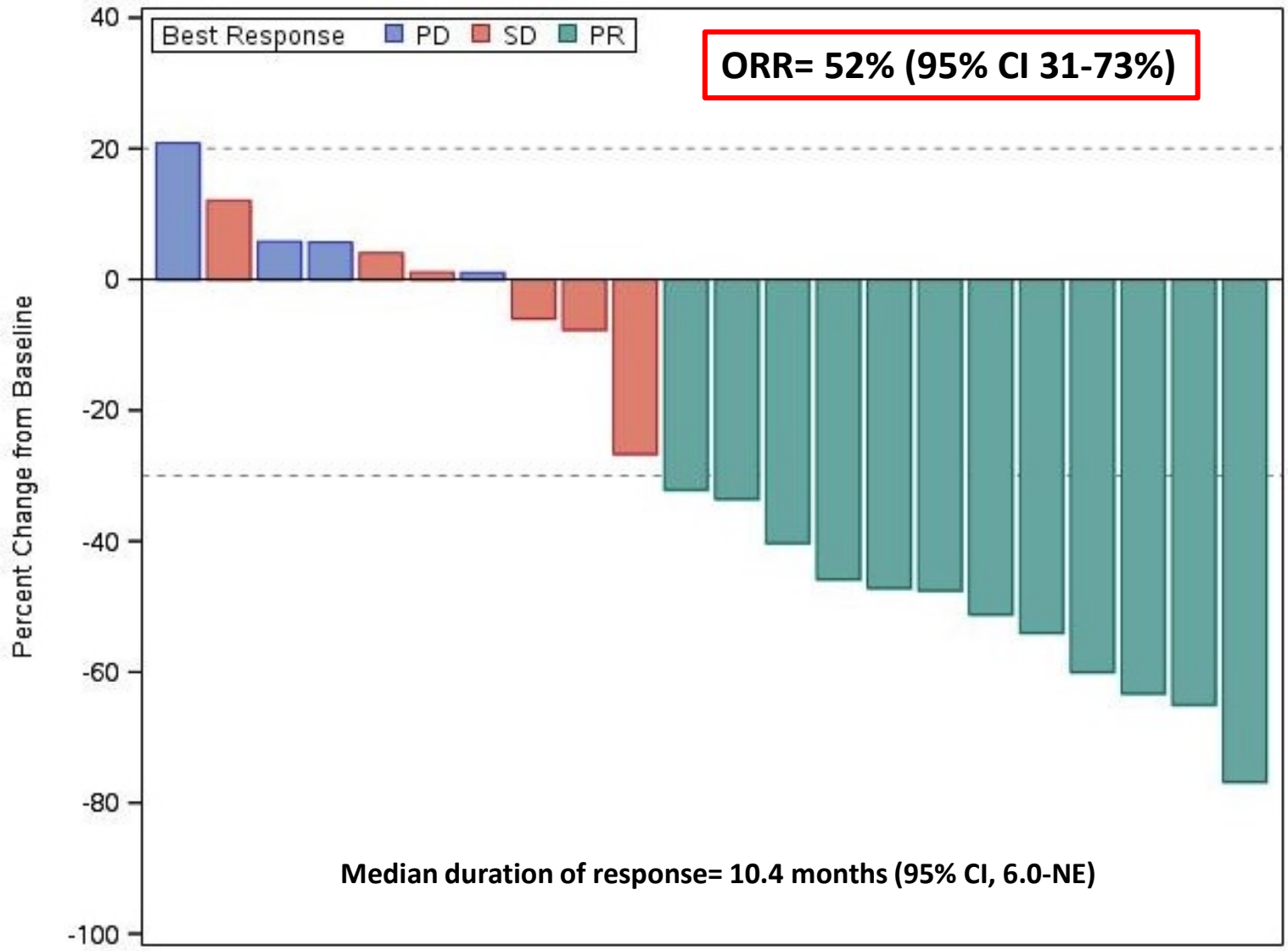


- Primary objective: ORR
- Secondary objectives: OS, PFS, duration of response, clinical benefit rate, safety, tolerability

Key eligibility

- Prior progression on 5FU, oxaliplatin, irinotecan, and an anti-VEGF monoclonal Ab
- Prior anti-EGFR NOT required
- Molecular testing confirming that tumor tissue has at least one of the following:
  - HER2 overexpression (IHC=3+ or IHC=2+ and amplified by FISH/CISH)
  - *ERBB2* amplification by *in situ* hybridization assay signal ratio > 2.0 or gene copy number > 6
  - *ERBB2* amplification by NGS sequencing assay
- Prior anti-HER2 therapy excluded

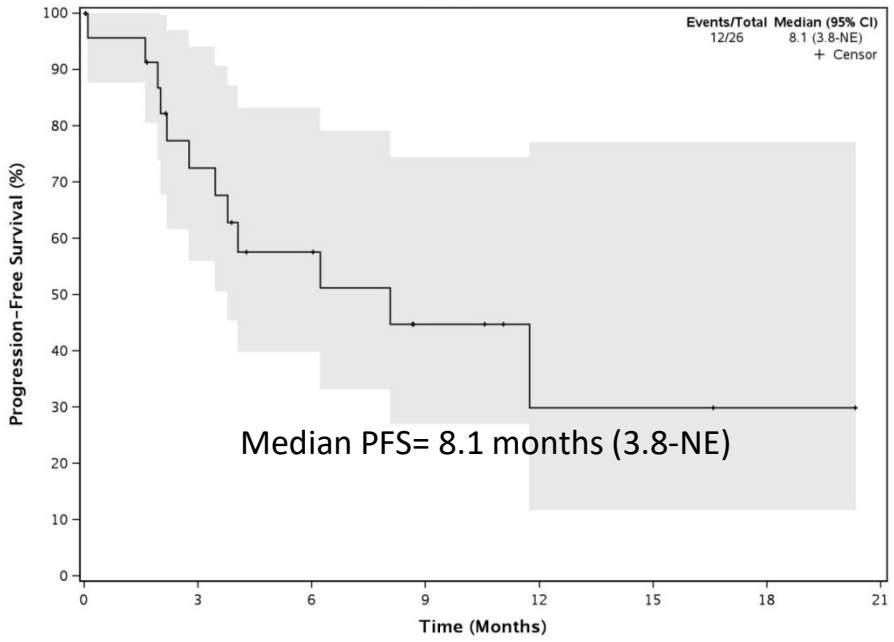
MOUNTAINEER – BEST PERCENT CHANGE FROM BASELINE



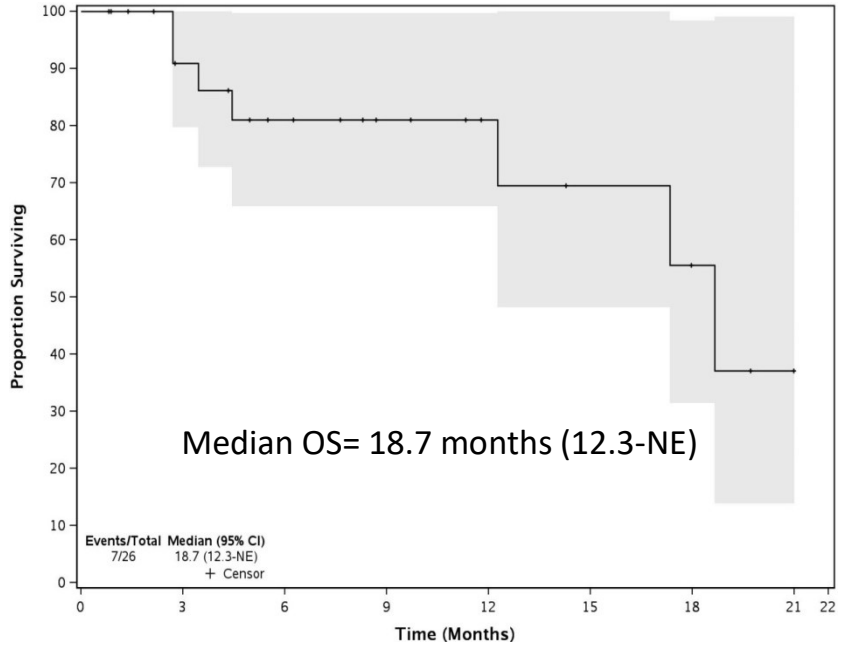
Strickler *et al*., Annals of Oncology 30, 2019 (suppl 5; abstr 527PD). ESMO, 2019

MOUNTAINEER – PFS AND OS

PFS



OS



Strickler *et al*., Annals of Oncology 30, 2019 (suppl 5; abstr 527PD). ESMO, 2019

MOUNTAINEER – RESULTS

	ORR n (%, 95% CI)	Median PFS Months (95% CI)	Median OS Months (95% CI)
Evaluable patients (n=23)	12 (52.2%, 30.6-73.2)	8.1 (3.8-NE)	18.7 (12.3-NE)
Treated patients* (n=26)	12 (46.2%, 26.6-66.6)	8.1 (3.8-NE)	18.7 (12.3-NE)
Primary Tumor Site			
Left/rectum (n=17)	11 (64.7%, 38.3-85.8)	11.7 (4.0-NE)	NE (18.7-NE)
Transverse (n=3)	1 (33.3%, 0.8-90.6)	2.0 (1.9-8.1)	17.3 (2.7-17.3)
Right (n=4)	0 (0%, 0-60.2)	NE (2.2-NE)	12.3 (NE-NE)
Overlapping (n=2)	0 (3.9%, 0-84.2)	2.8 (NE-NE)	3.5 (NE-NE)

Strickler *et al*., Annals of Oncology 30, 2019 (suppl 5; abstr 527PD). ESMO, 2019

MOUNTAINEER – TREATMENT RELATED TOXICITIES

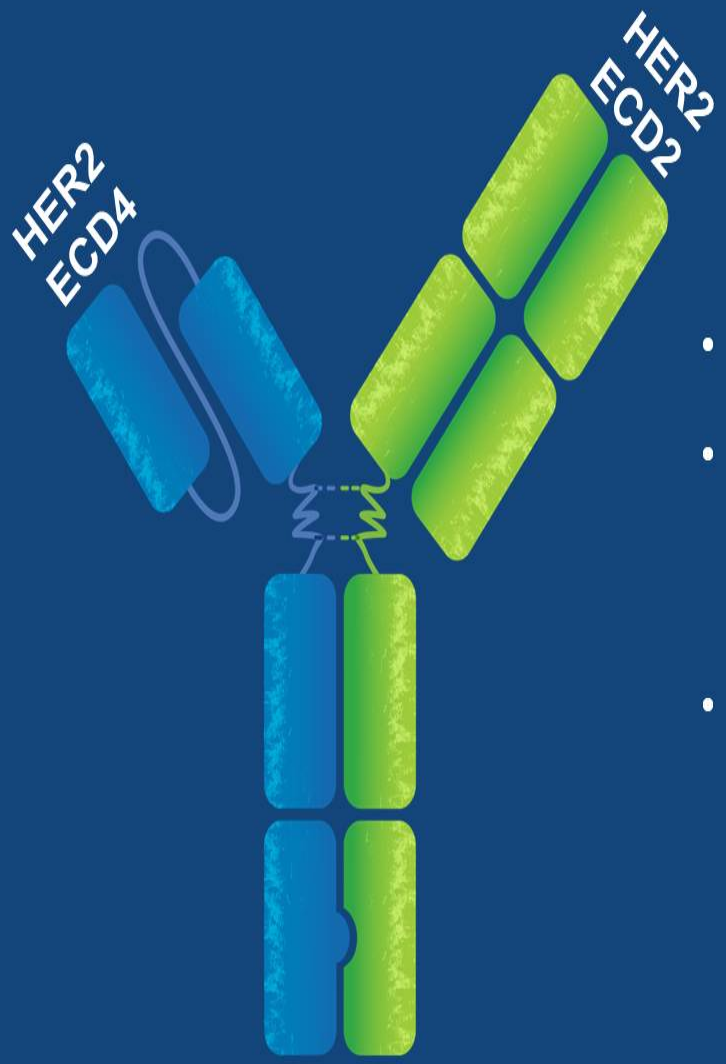
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Any Grade	
Toxicity	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Any AE	**6**	**23.1**	**10**	**38.5**	**2**	**7.7**	**-**	**-**	**-**	**-**	**18**	**69.2**
Aspartate aminotransferase increased	10	38.5									10	38.5
Alanine aminotransferase increased	6	23.1									6	23.1
Diarrhea	1	3.8	4	15.4	1	3.8					6	23.1
Fatigue	3	11.5	2	7.7							5	19.2
Infusion related reaction			3	11.5							3	11.5
Anemia	1	3.8	1	3.8							2	7.7
Blood bilirubin increased	2	7.7									2	7.7
Creatinine increased	2	7.7									2	7.7
Hypertension			1	3.8	1	3.8					2	7.7

Strickler *et al*., Annals of Oncology 30, 2019 (suppl 5; abstr 527PD). ESMO, 2019

MOUNTAINEER – CONCLUSIONS

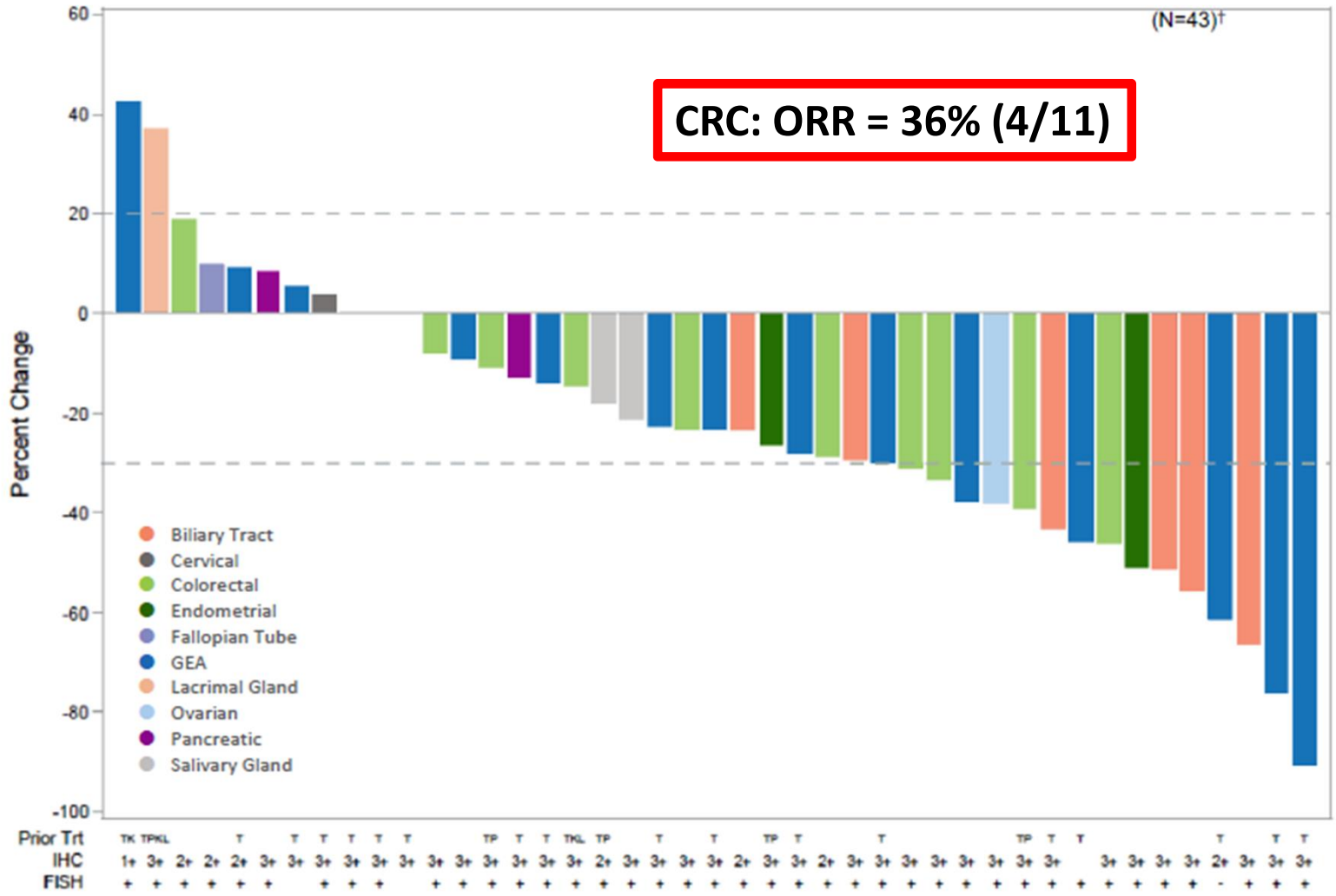
- The combination of tucatinib and trastuzumab is well tolerated and has met its primary efficacy endpoint
- Responses concentrated in patients with left-sided colon/rectal tumors
- Further expansion of the study in patients with *HER2* amplified *RAS* WT mCRC

ZW25: Azymetric™ Bispecific HER2-Targeted Antibody



- Designed using the Azymetric bispecific platform
- Biparatopic - simultaneously binds two HER2 epitopes
  - ECD4 (trastuzumab binding domain)
  - ECD2 (pertuzumab binding domain)
- Unique binding results in novel mechanisms of action

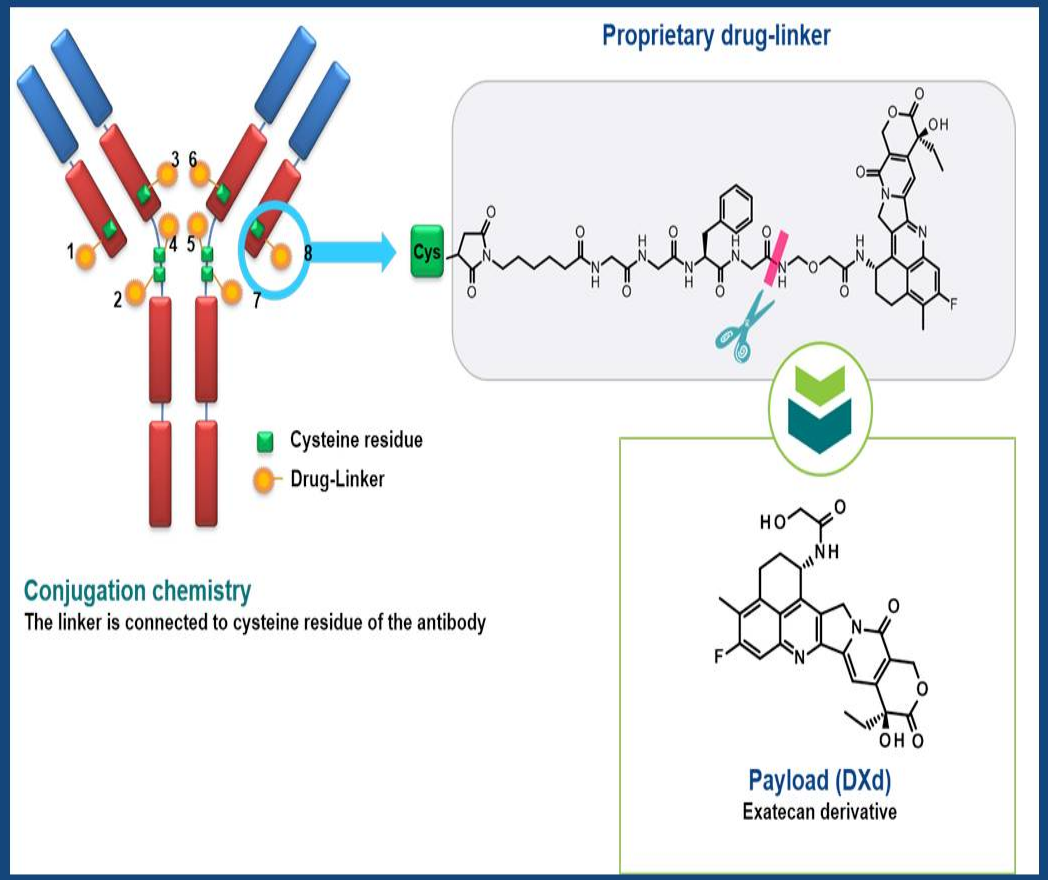
ZW25 IN ADVANCED SOLID TUMORS



† 3 of the 46 response-evaluable patients had no post-baseline disease assessment of their target lesions

Meric-Bernstam *et al.*, Annals of Oncology 30, 2019 (suppl 5; abstr 3575). ESMO 2019

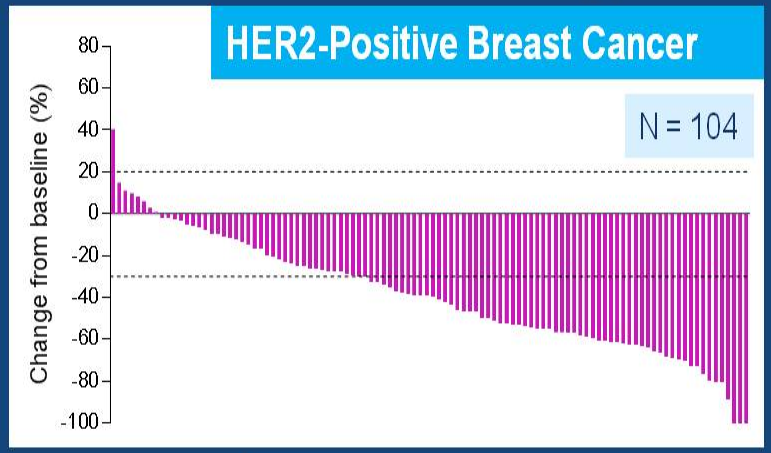
DS-8201a Structure and Mechanism of Action

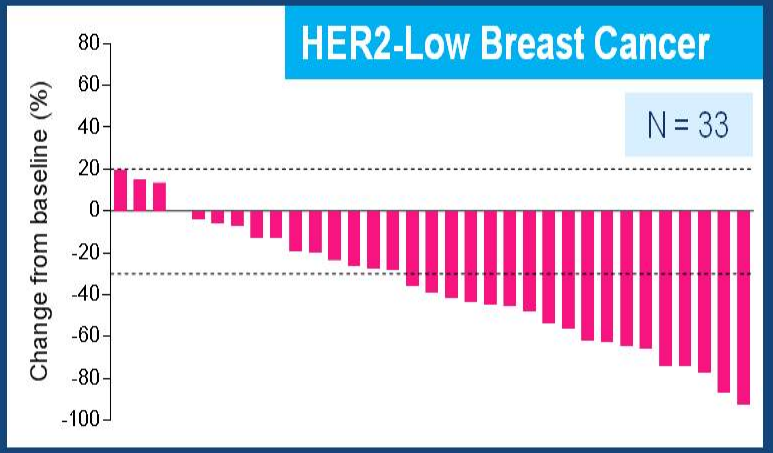


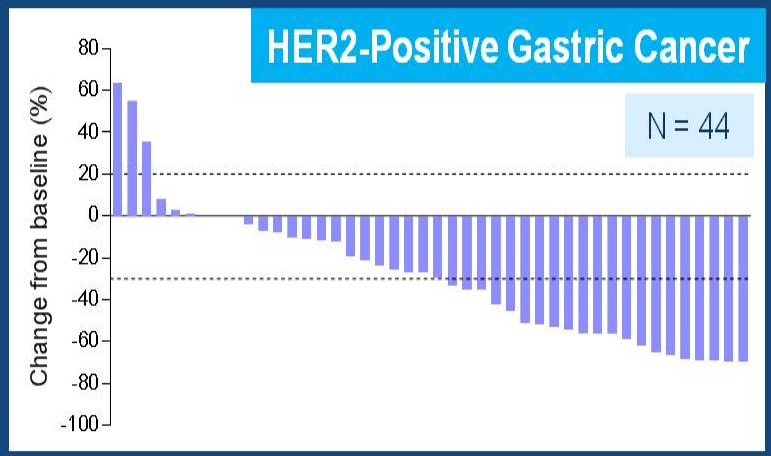
- *Payload with a different mechanism of action*
- *High potency of payload*
- *Payload with short systemic half-life*
- *Bystander effect*
- *Stable linker-payload*
- *Tumor-selective cleavable linker*
- *High drug-to-antibody ratio*

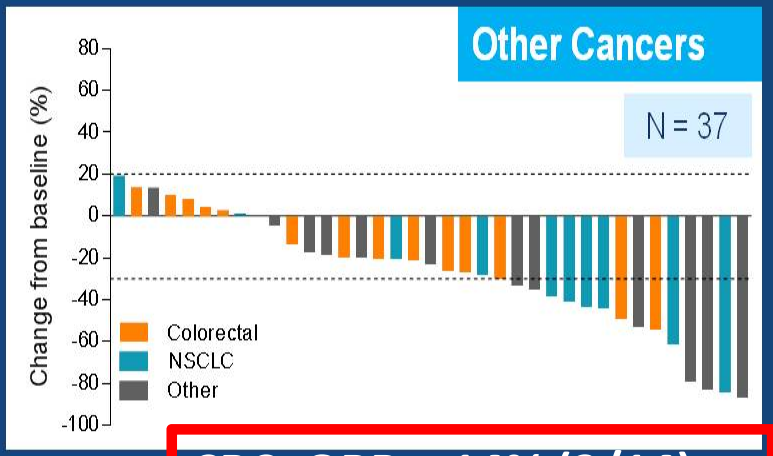
- DS-8201a was designed with the goal of improving critical attributes of an ADC

Consistent Tumor Shrinkage Across Tumor Types: (5.4 or 6.4 mg/kg)









- Overall, 86.3% of subjects experienced tumor shrinkage
- Confirmed ORR* in the overall population is 49.3%

CRC: ORR = 14% (2/14)
ESMO update 16% (3/19)

Includes subjects who had ≥1 postbaseline scan. Dotted lines denote 20% increase and 30% reduction in tumor size, respectively.
*Confirmed response includes subjects who had ≥2 postbaseline scans, progressive disease, or discontinued treatment for any reason prior to second postbaseline scan. Data cutoff is April 18, 2018.

MSI-HIGH

Pembrolizumab Versus Chemotherapy for Microsatellite Instability-High/Mismatch Repair Deficient Metastatic Colorectal Cancer: The Phase 3 KEYNOTE-177 Study

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] 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]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

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

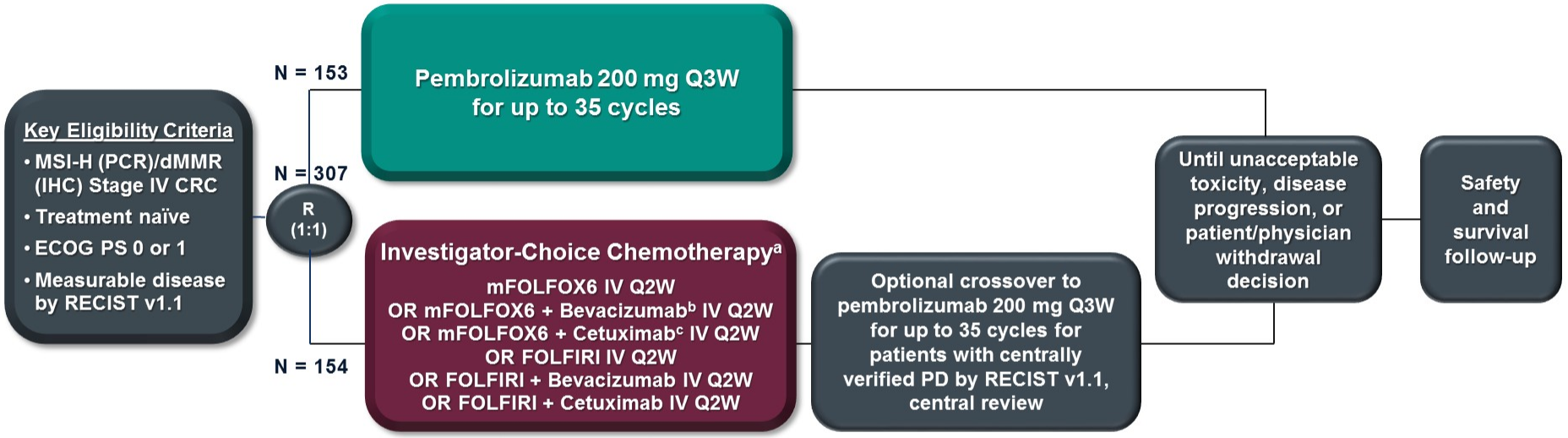
PRESENTED BY: Thierry Andre, MD

Colorectal Cancer: Two Different Diseases

CIN+ (85%) Chromosomal Instability	MSI-H (15%) Genetic (Microsatellite) Instability
Aneuploidy, loss of heterozygosity/loss of genetic material	Diploidy, no loss of heterozygosity
Proficient Mismatch Repair system Microsatellite stable (MSS)	Deficient Mismatch repair system Microsatellite instability (MSI)
Sporadic or Familial Adenomatous Polyposis (FAP)	Sporadic or Lynch syndrome
95% of metastatic colorectal cancer	5% of metastatic colorectal cancer Prognosis and chemosensitivity of MSI seems worse vs MSS[1-3]
More prevalent in distal location	More prevalent in proximal location
Frequent mutation of KRAS	Frequent mutation of $BRAF^{V600E}$
Tumor mutation burden low	Tumor mutation burden high Increased immune infiltration, higher tumour neo-antigens
No clear efficacy of immune check point inhibitor[4]	Efficacy of immune check point inhibitor in phase I and II[4-7]

1. Venderbosch S et al. *Clin Canc Res* 2014;20:5322-30; 2. Innocenti F et al. *J Clin Oncol* 2019;37:1217-1227; 3. Tougeron D et al., *Int J Cancer* 2020;Epub; 4. Le DT et al. *N Engl J Med.* 2015;372:2509-20; 5. Le D et al. *J Clin Oncol* 2020;38:11-19; 6. Overman M et al. *Lancet Oncol* 2017;18:1182-91; 7. Overman M et al. *J Clin Oncol* 2018;36:773-79.

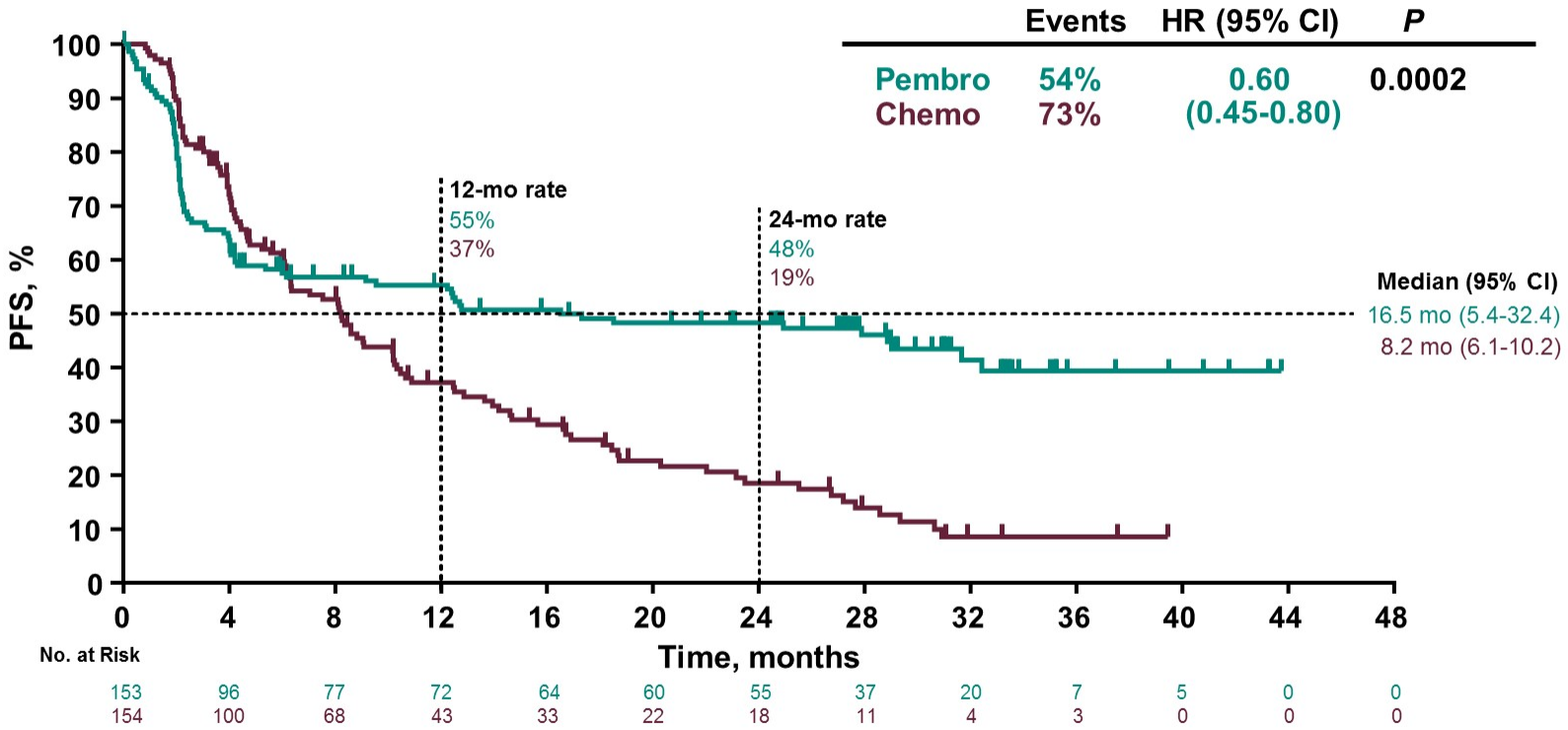
KEYNOTE-177 Study Design (NCT02563002)



- 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
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

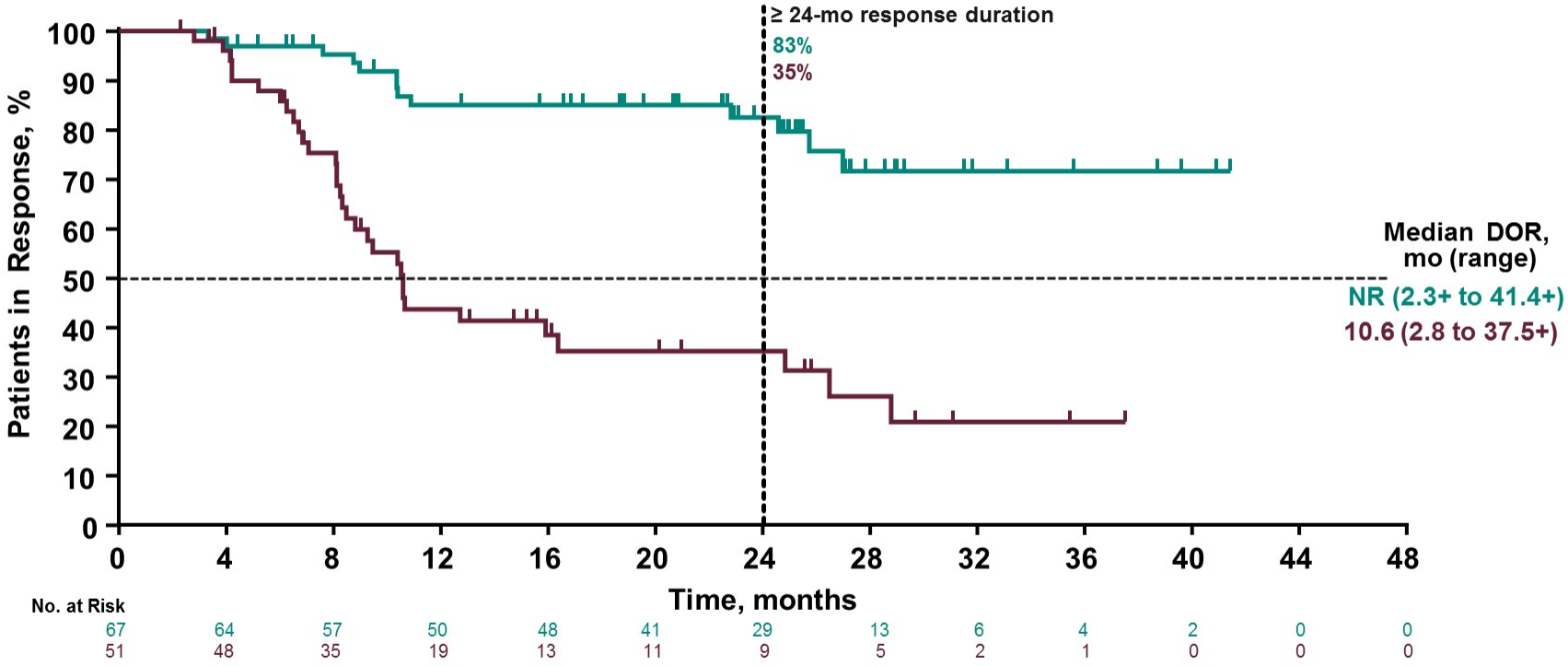
[a]Chosen before randomization; [b]Bevacizumab 5 mg/kg IV; [c]Cetuximab 400 mg/m2 over 2 hours then 250 mg/mg^2 IV over 1 hour weekly.
IHC: immunohistochemistry with hMLH1, hMSH2, hMSH6, PMS2; PCR: polymerase chain reaction; PFS, progression-free survival; OS: overall survival; ORR: overall response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

Progression-Free Survival



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.

Duration of Response



Duration of Response assessed per RECIST v1.1 by BICR; Data cut-off: 19Feb2020.

SUMMARY AND CONCLUSIONS

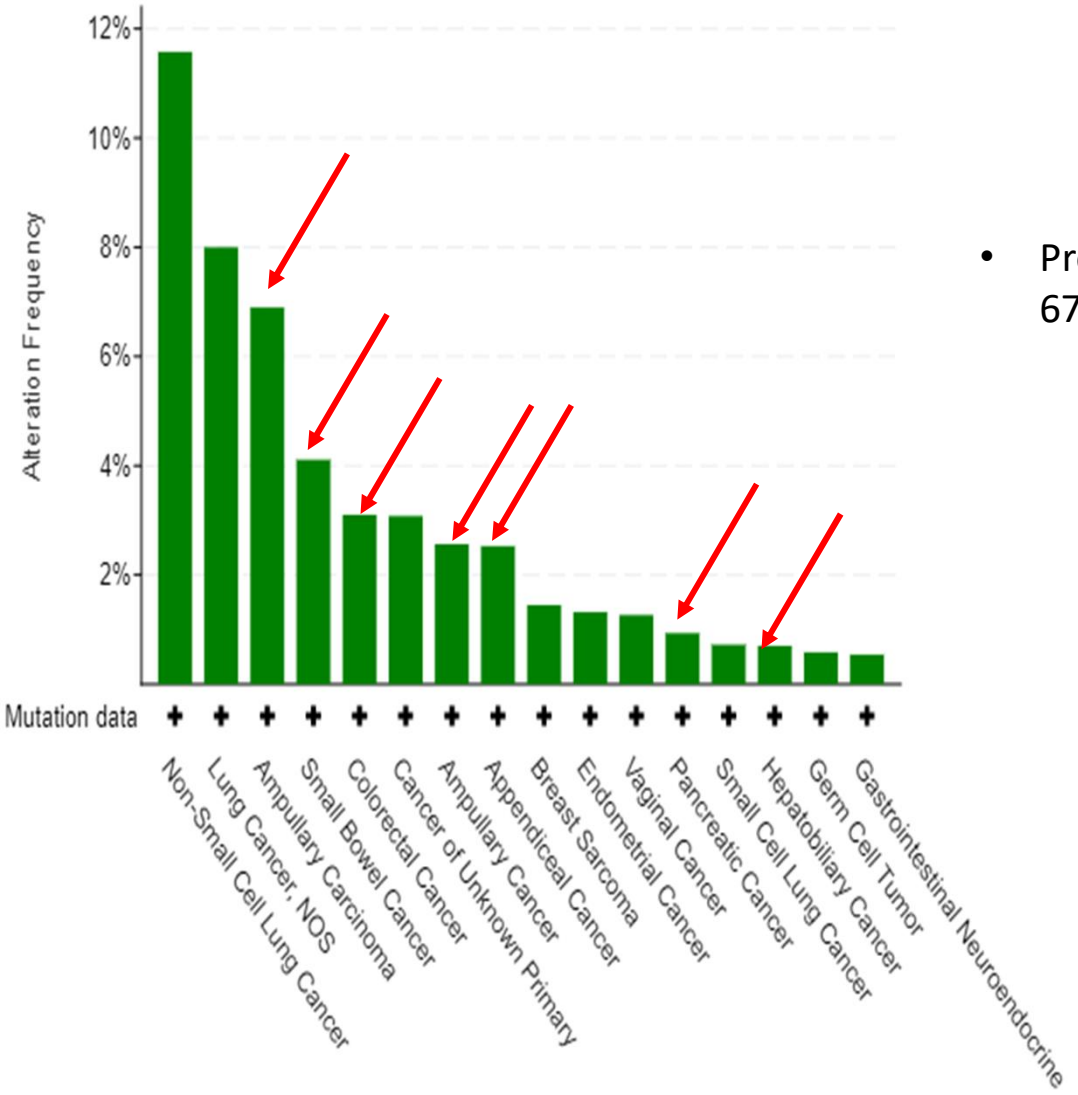
- Pembrolizumab provided a clinically meaningful and statistically significant improvement in PFS over chemotherapy in patients with MSI-H mCRC

- Responses were more durable with pembrolizumab

- ***Take-home:*** ***Pembrolizumab is the new standard-of-care as first-line therapy in patients with MSI-H mCRC***

KRAS G12C MUTATIONS

KRAS G12C: GI TUMORS WELL REPRESENTED

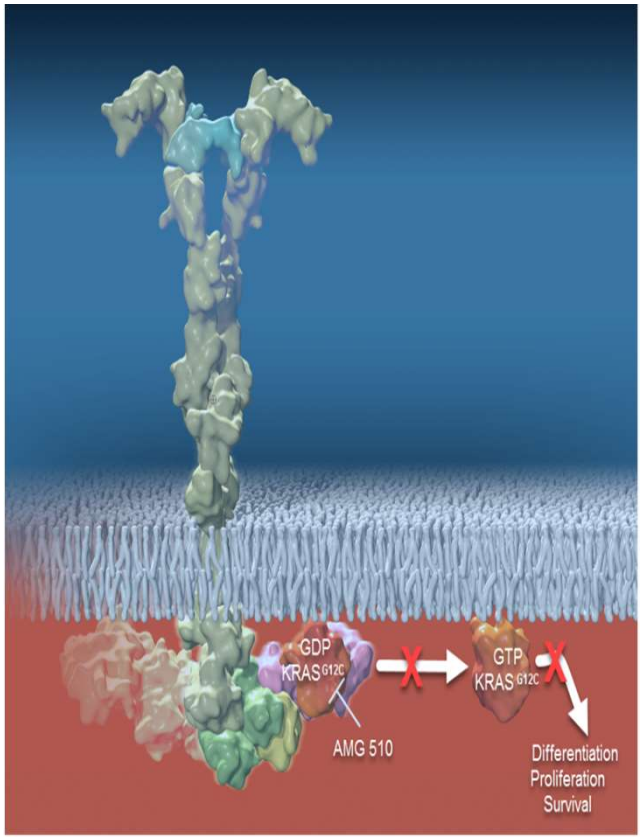


- Profiling results from 67,309 patients

https://genie.cbioportal.org/GENIE Cohort v6.1-public

AMG 510 is a First-in-Class KRAS^{G12C} Inhibitor

- KRAS is a GTP-binding protein that links receptor tyrosine kinase activation to intracellular signaling [1,2]
- Mutation of KRAS favors the GTP-bound active state, leading to constitutive activation of downstream signaling cascades that regulate differentiation, proliferation, and survival[3]
- *KRAS G12C* mutation has been identified as an oncogenic driver of tumorigenesis
- *KRAS G12C* mutation is found in approximately 13% of lung cancer[4], 3% of colorectal (CRC)[5] and appendix cancer, and 1-3% of other solid tumors[6]
- Currently, there is no approved therapy targeting this mutation
- AMG 510 is a novel, first in class, small molecule that specifically and irreversibly inhibits KRAS^{G12C} by permanently locking it in an inactive GDP-bound state



Govindan et al., *Annals of Oncology*, Volume 30, Issue Supplement_5, October 2019. ESMO 2019

Baseline Characteristics

Baseline Characteristics	N = 76
Median age (range) – years	59.0 (33.0–78.0)
Female – n (%)	40 (52.6)
Primary tumor type – n (%) NSCLC CRC SCLC Appendiceal cancer Endometrial cancer Small bowel cancer	 34 (44.7) 36 (47.4) 1 (1.3)[a] 3 (3.9) 1 (1.3) 1 (1.3)
ECOG performance at baseline – n (%) 0 1 2	 20 (26.3) 53 (69.7) 3 (3.9)
Prior lines of systemic anticancer therapy – n (%) 1 2 > 2	 5 (6.6) 9 (11.8) 62 (81.6)
Median No. of prior systemic anticancer therapy – n (range)	4.0 (1–10)

Govindan et al., *Annals of Oncology*, Volume 30, Issue Supplement_5, October 2019. ESMO 2019

Patient Incidence of Adverse Events (AEs): Summary

960mg oral daily dose was identified as the expansion dose and recommended phase 2 dose

	All AEs N = 76 n (%)	All treatment-related AEs N = 76 n (%)
Any grade Grade ≥ 2 Grade ≥ 3 Grade ≥ 4	57 (75.0) 44 (57.9) 24 (31.6) 8 (10.5)	**26 (34.2)** **14 (18.4)** **6 (7.9)** **0 (0.0)**
Dose limiting toxicity	0 (0)	**0 (0)**
Serious adverse events	17 (22.4)	**0 (0)**[c]
Fatal adverse events	7 (9.2)[a]	**0 (0)**
AEs leading to treatment discontinuation	2 (2.6)[b]	**0 (0)**

- No dose limiting toxicities were reported
- No treatment-related serious or fatal AEs were reported
- There were no treatment-related AEs leading to treatment discontinuation

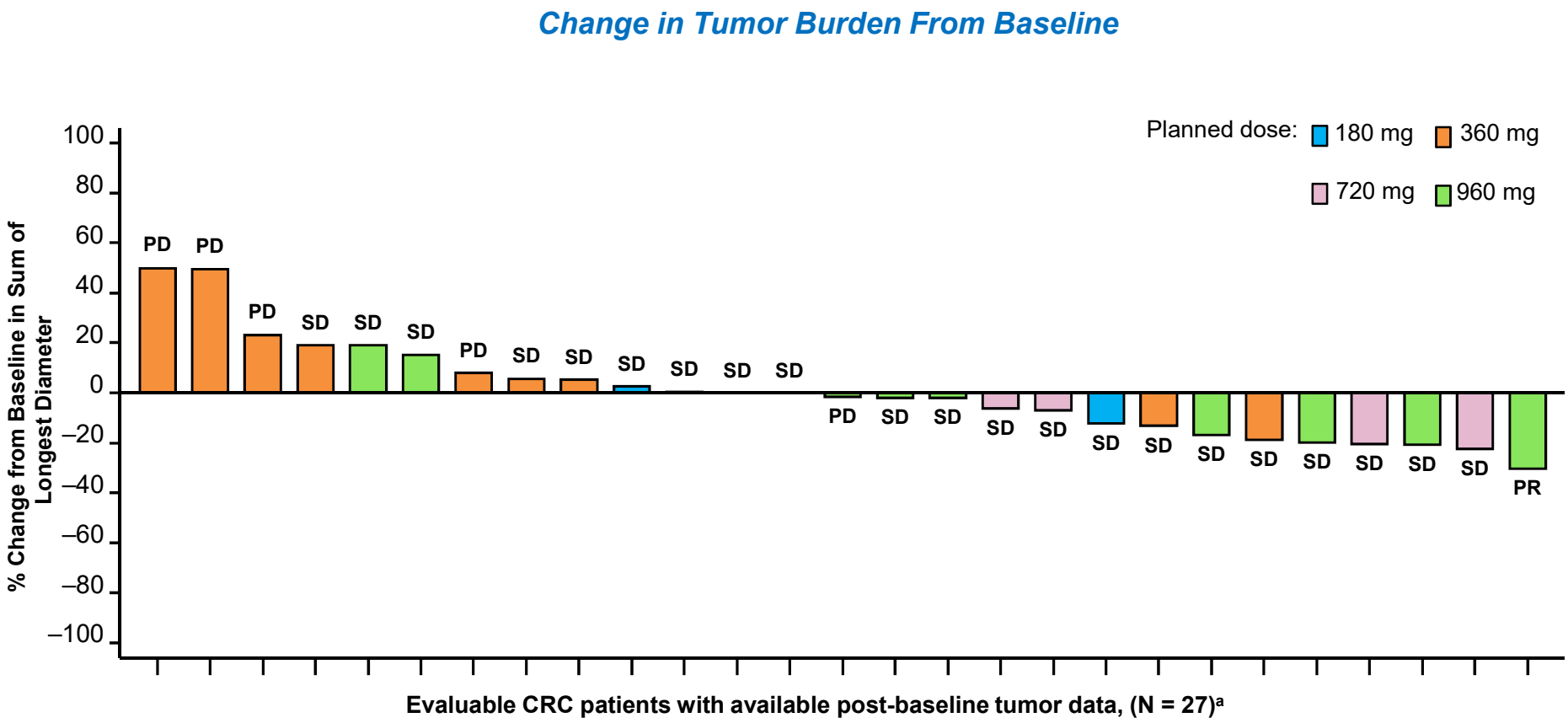
Govindan et al., *Annals of Oncology*, Volume 30, Issue Supplement_5, October 2019. ESMO 2019

Best Tumor Response With All Dose Levels, All Tumor Types

Efficacy outcomes	NSCLC, evaluable patients N = 23	CRC, evaluable patients N = 29	Other tumor types, evaluable patients N = 3
Best overall response			
Partial response – No. (%)	11 (48)	1 (3.4)	1 (33.3)[b]
Stable disease – No. (%)	11 (48)	22 (75.9)	1 (33.3)[c]
Progressive disease – No. (%)	1 (4)	6 (20.7)	1 (33.3)[d]
Objective response rate – %	**48%**	**3%**	**N/A**
Disease control rate[a] – %	**96%**	**79%**	**N/A**

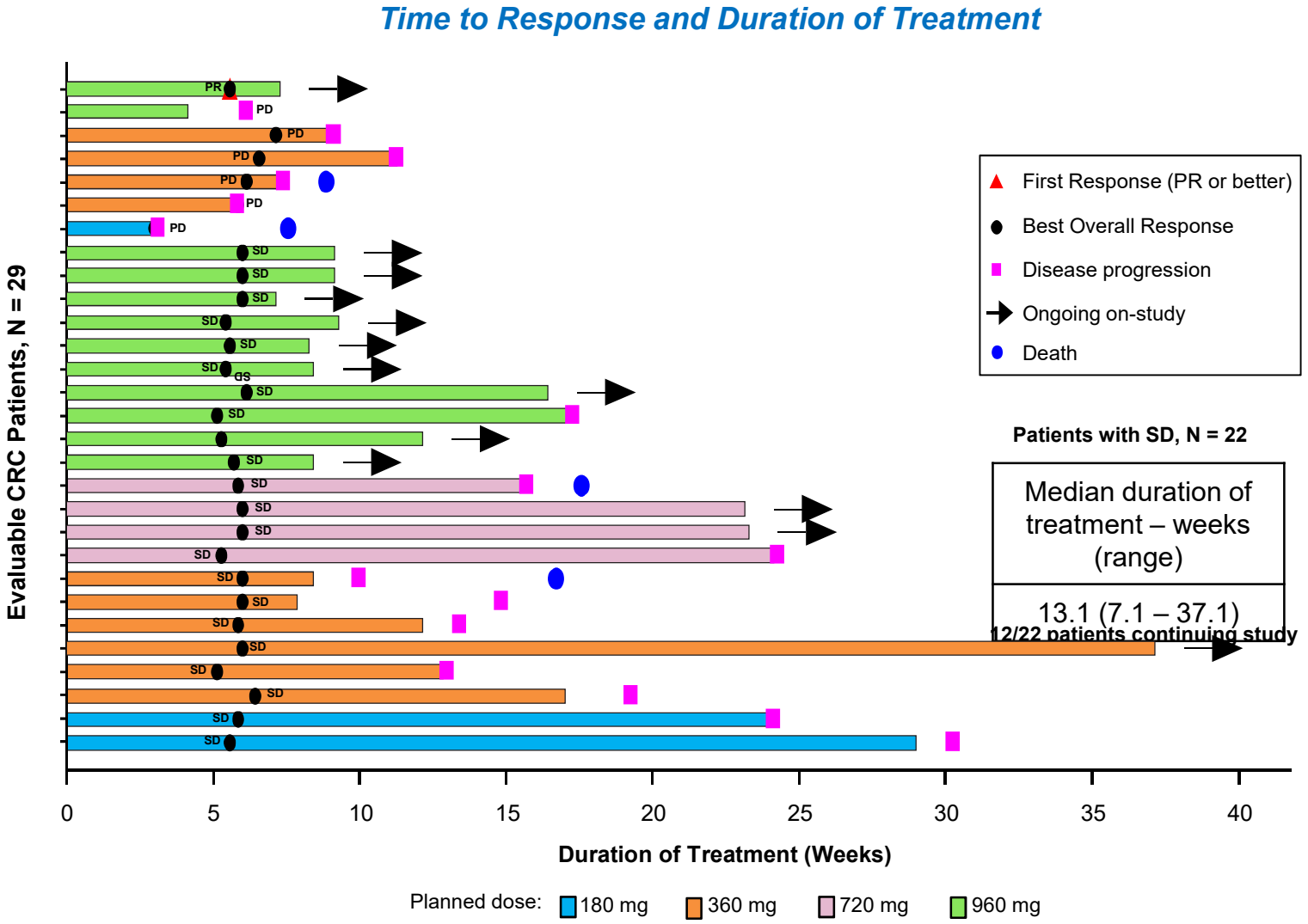
Govindan et al., *Annals of Oncology*, Volume 30, Issue Supplement_5, October 2019. ESMO 2019

Efficacy in CRC



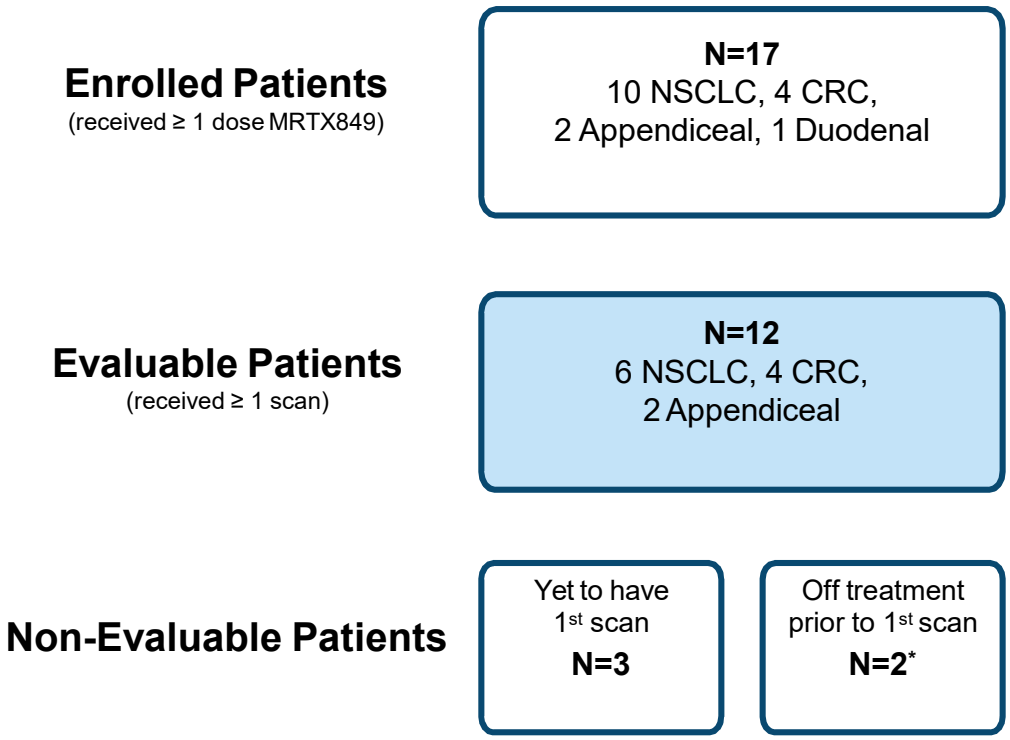
Govindan et al., *Annals of Oncology*, Volume 30, Issue Supplement_5, October 2019. ESMO 2019

Efficacy in CRC



Govindan et al., *Annals of Oncology*, Volume 30, Issue Supplement_5, October 2019. ESMO 2019

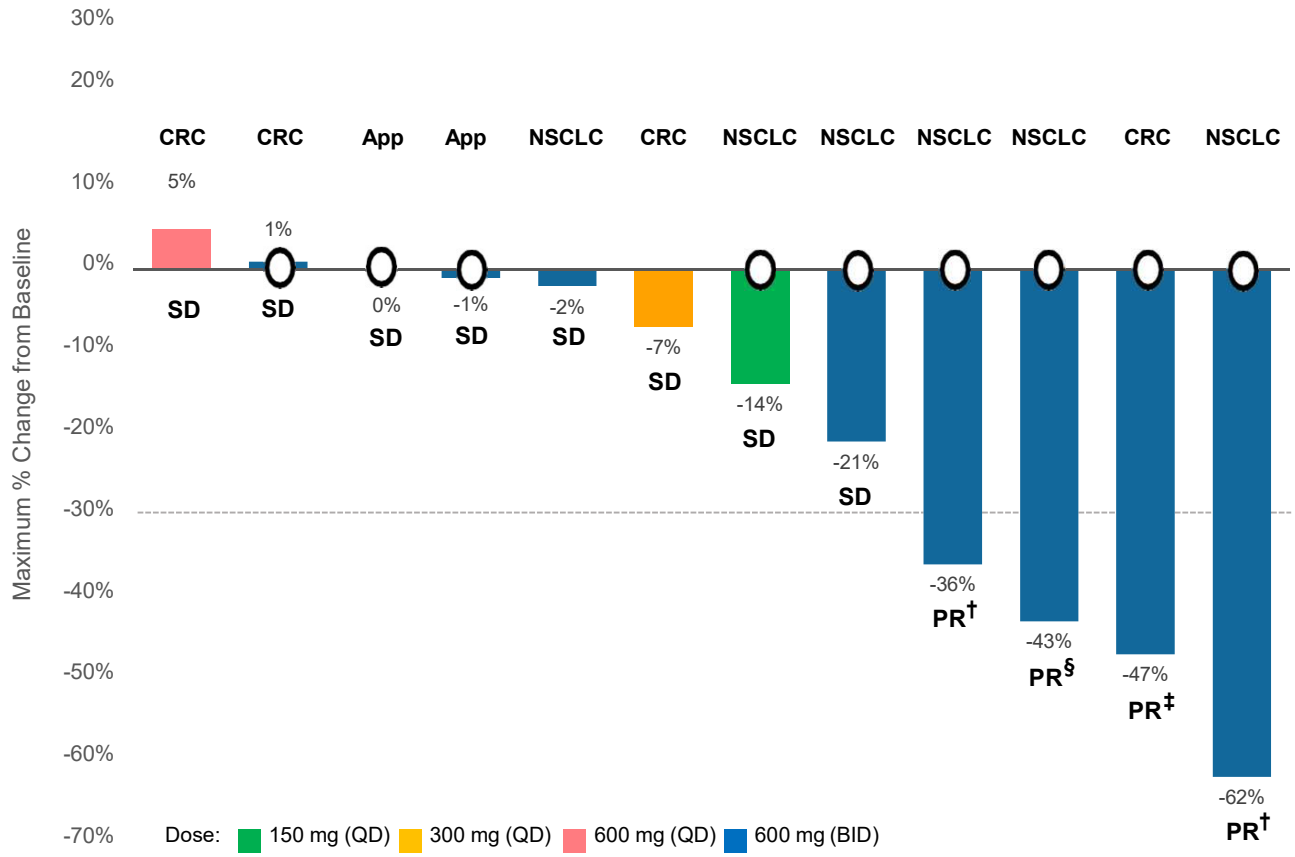
MRTX849 Patient Disposition



* 1 patient withdrew consent prior to 1st scan (1200 mg QD);
1 patient discontinued treatment due to an unrelated AE prior to 1st scan (600 mg QD)

Janne et al., Presented at AACR-NCI-EORTC International Conference on Molecular Targets, October 28,2019

All Evaluable Patients: Best Tumor Response* (N = 12)



Evaluable Patients at All Doses	
NSCLC	ORR: 3/6 DCR: 6/6
CRC	ORR: 1/4 DCR: 3/4
Append	ORR: 0/2 DCR: 2/2

DCR: Disease Control Rate (SD+PR at 6 weeks)

* Based on local radiographic scans every 6 weeks using RECIST 1.1 criteria

‡ Confirmed response (1st scan: -37%, 2nd scan: -47%); † Response yet to be confirmed (on study but only 1 scan)

§ Patient had confirmed PR post data cut-off (1st scan: -33%, 2nd scan:-43%)

o Patient on study (off study patients: 1 progressive disease, 1 global deterioration of health, 1 patient withdrawal of consent)

Data cut-off date: 11-Oct-2019

Janne et al., Presented at AACR-NCI-EORTC International Conference on Molecular Targets, October 28,2019

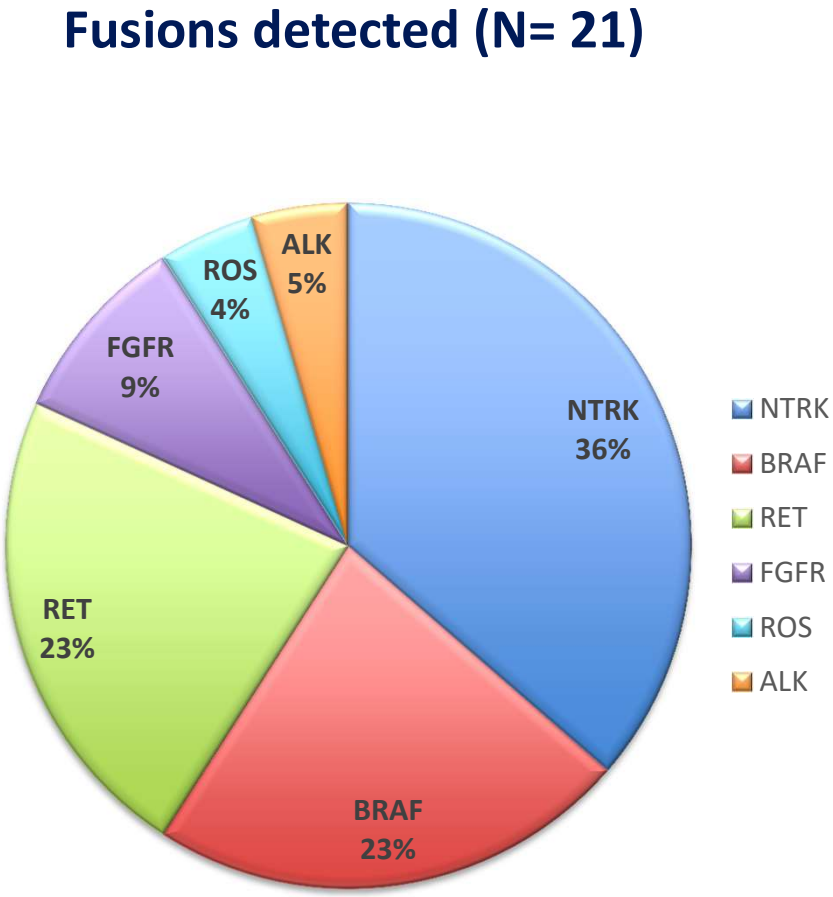
KRAS G12C: Actionable Target

- *KRAS G12C* inhibitors have entered the clinic
- Single-agent activity has been demonstrated
- Limited toxicity suggests potential for combination strategies to improve depth and duration of response
- More anti-KRAS strategies could be on the horizon (e.g. SHP2 inhibitors)

NTRK 1/2/3 AND OTHER FUSIONS

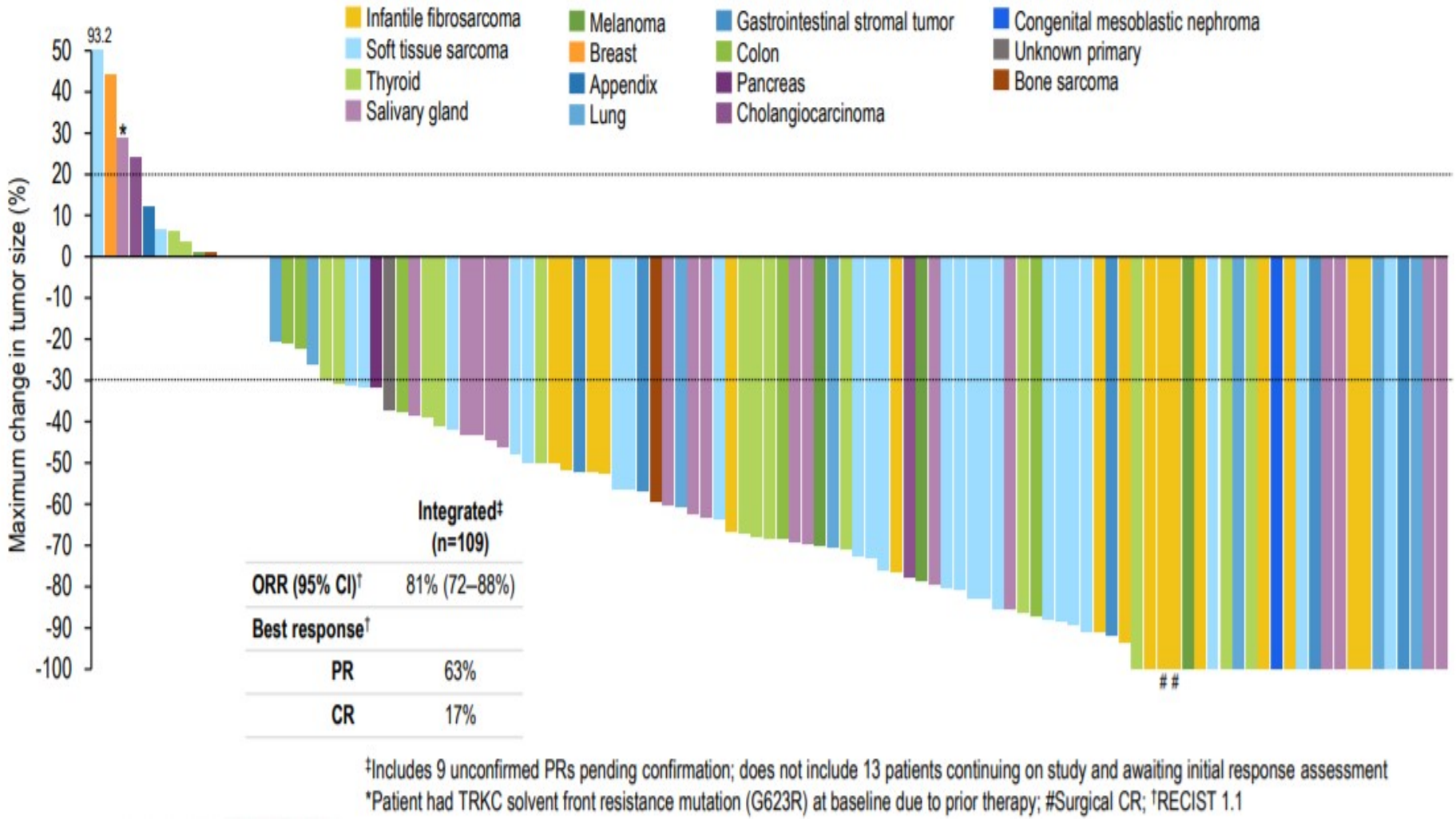
CRC Fusions: Actionable but rare

- In a series of 2,314 CRC cases profiled at MSKCC, 21 fusions detected (0.9%)
  - 8 NTRK 1/2/3 fusions
  - 5 BRAF fusions
  - 5 RET fusions
  - 2 FGFR fusions
  - 1 ROS fusion
  - 1 ALK fusion



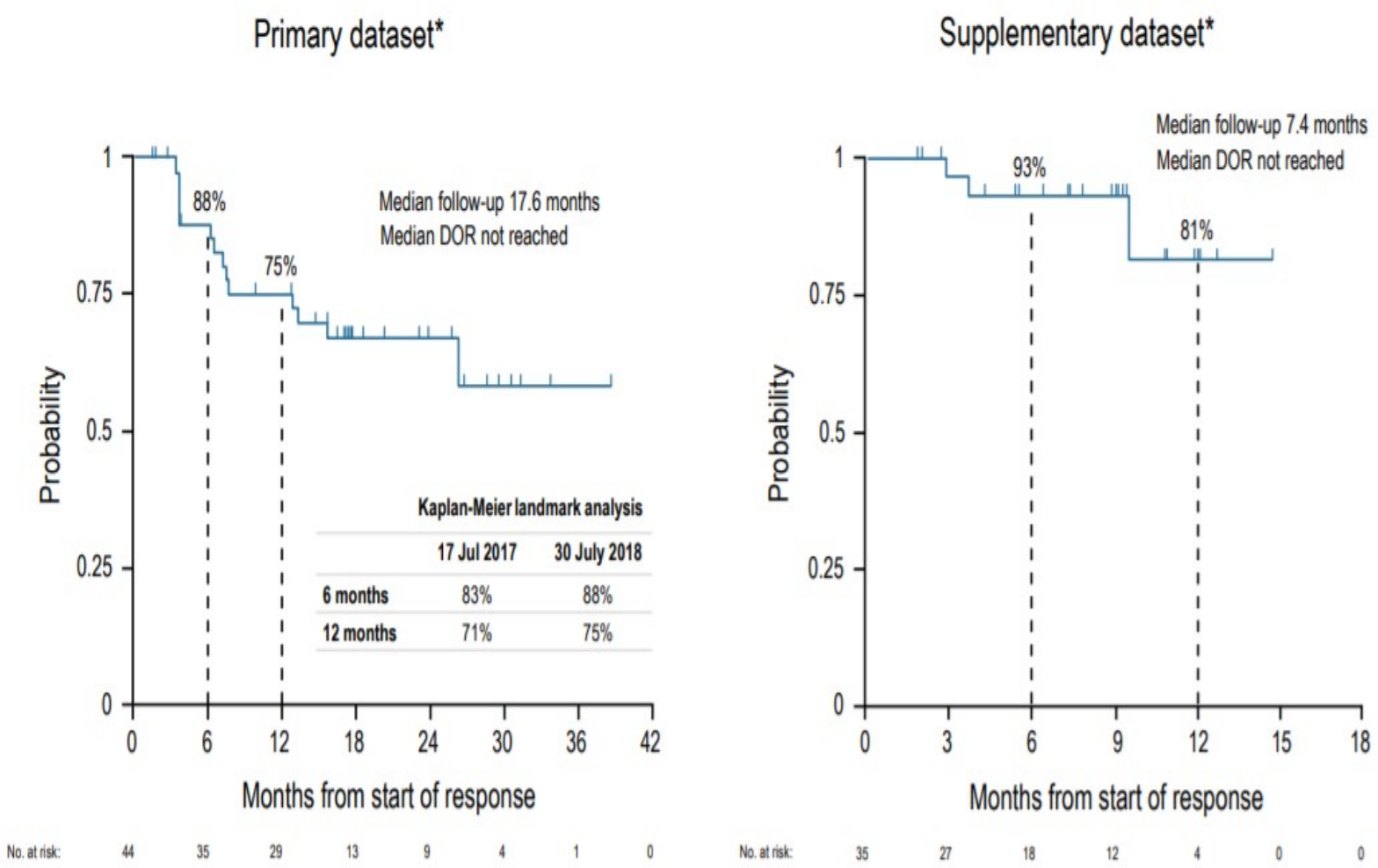
Cocco et al., Cancer Research 2019 Mar 15;79(6):1047-1053.

Larotrectinib: Best Response



Lassen et al, ESMO 2018

Larotrectinib: PFS and OS

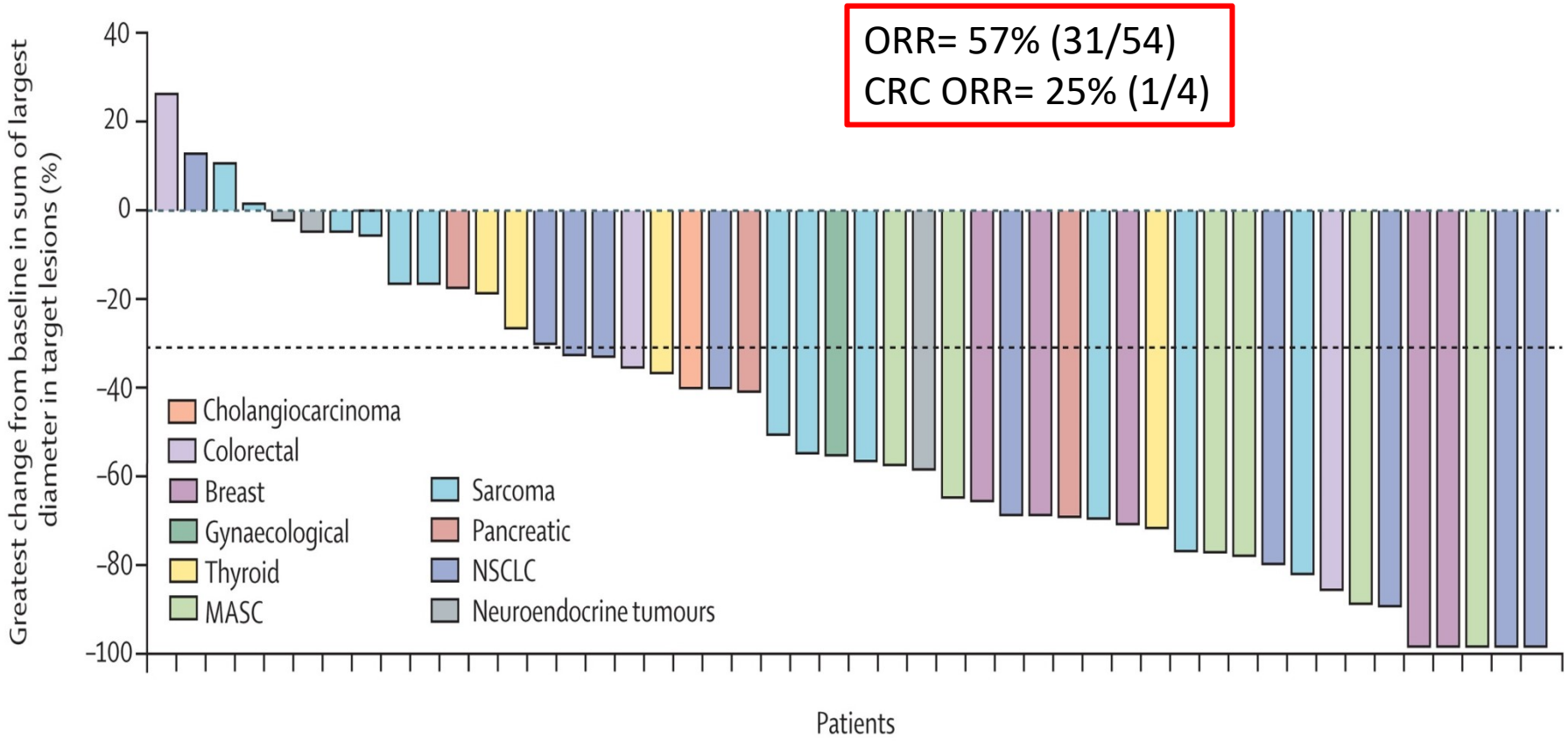


Lassen et al, ESMO 2018

Entrectinib: Overview

- Entrectinib exhibits potent anti-proliferative activity in all *NTRK* and *ROS1* fusion partners
- Tumor regressions demonstrated in multiple cell line and patient-derived xenograft *NTRK*- and *ROS1* tumour models
- Entrectinib achieves therapeutic levels in CNS with antitumor activity in multiple intracranial tumour models

Entrectinib: Best Response in Patients with *NTRK* fusion+ Advanced Solid Tumors by Tumor Type



Doebele et al., Lancet Oncology 2019

Fusions most likely to be found in MSI-H patients

Table 1. Spectrum and molecular characteristics of kinase fusions in colorectal carcinoma

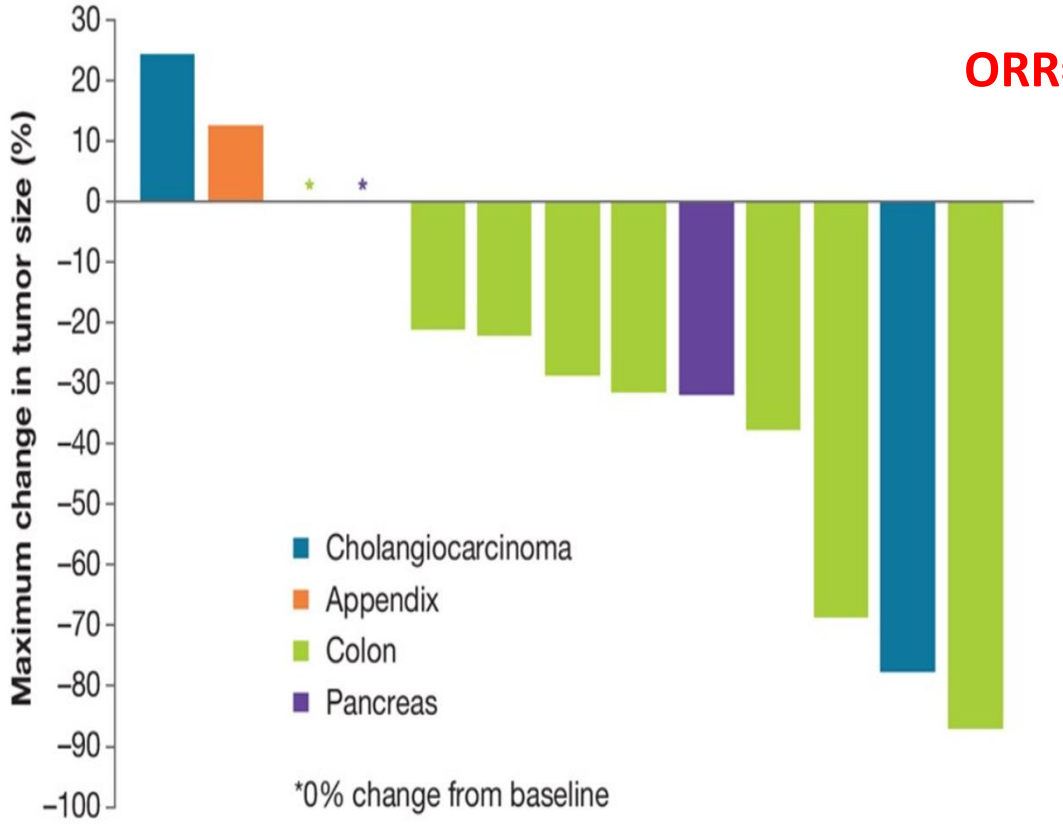
Case	Partner gene	Exon	Kinase gene	Exon	MMR IHC	MSI status	MLH1 promoter hypermethylation	Fusion detected by
1	*LMNA*	8	*NTRK1*	12	MMR-D (MLH1/PMS2)	MSI-H	Positive	IMPACT
2	*CCDC*	8	*RET*	12	MMR-D (MLH1/PMS2)	MSI-H	Positive	IMPACT + Archer
3	*TPM3*	10	*NTRK1*	9	MMR-D (MLH1/PMS2)	MSI-H	Positive	IMPACT
4	*LMNA*	2	*NTRK1*	11	MMR-D (MLH1/PMS2)	MSI-H	Positive	IMPACT
5	*ETV6*	6	*NTRK3*	15	MMR-D (MLH1/PMS2)	MSI-H	Positive	IMPACT
6	*SPTBN1*	7	*ALK*	20	MMR-D (MLH1/PMS2)	MSI-H	N/A	IMPACT
7	*GEMIN5*	24	*RET*	12	MMR-D (MLH1/PMS2)	MSI-H	Positive	IMPACT + Archer
8	*TPM3*	8	*NTRK1*	10	MMR-D (MLH1/PMS2)	N/A	Positive	IMPACT + Archer
9	*AGAP3*	10	*BRAF*	9	MMR-D (MLH1/PMS2)	MSI-H	Positive	IMPACT
10	*EML4*	2	*NTRK3*	14	MMR-D (MLH1/PMS2)	MSI-H	Positive	Archer (IMPACT Negative)
11	*TPM3*	8	*NTRK1*	10	MMR-D (MLH1/PMS2)	N/A	N/A	Archer (IMPACT Insufficient)
12	*TRIM24*	14	*BRAF*	9	MMR-D (MLH1/PMS2)	MSI-H	Positive	IMPACT + Archer
13	*NCOA4*	10	*RET*	12	MMR-P	MSS	Positive	IMPACT
14	*LMNA*	12	*NTRK1*	12	MMR-P	MSS	Negative	IMPACT + Archer
15	*GOPC*	4	*ROS1*	36	MMR-P	MSS	Negative	IMPACT + Archer
16	*NCOA4*	8	*RET*	12	MMR-P	MSS	Negative	IMPACT
17	*CUL1*	7	*BRAF*	9	MMR-P	MSS	N/A	IMPACT
18	*MKRN1*	3	*BRAF*	10	N/A	MSS	N/A	IMPACT + Archer
19	*AGAP3*	9	*BRAF*	9	MMR-P	MSS	N/A	IMPACT
20	*FGFR3*	17	*STAB1*	51	MMR-P	MSS	N/A	Archer (IMPACT Negative)
21	*FGFR2*	14	*MYH15*	31	MMR-P	MSS	N/A	Archer (IMPACT Negative)

Abbreviation: N/A, testing was not performed.

Cocco et al., Cancer Research 2019 Mar 15;79(6):1047-1053.

Larotrectinib in NTRK+ GI Cancers

Best change in tumor size, by tumor type



ORR= 43%

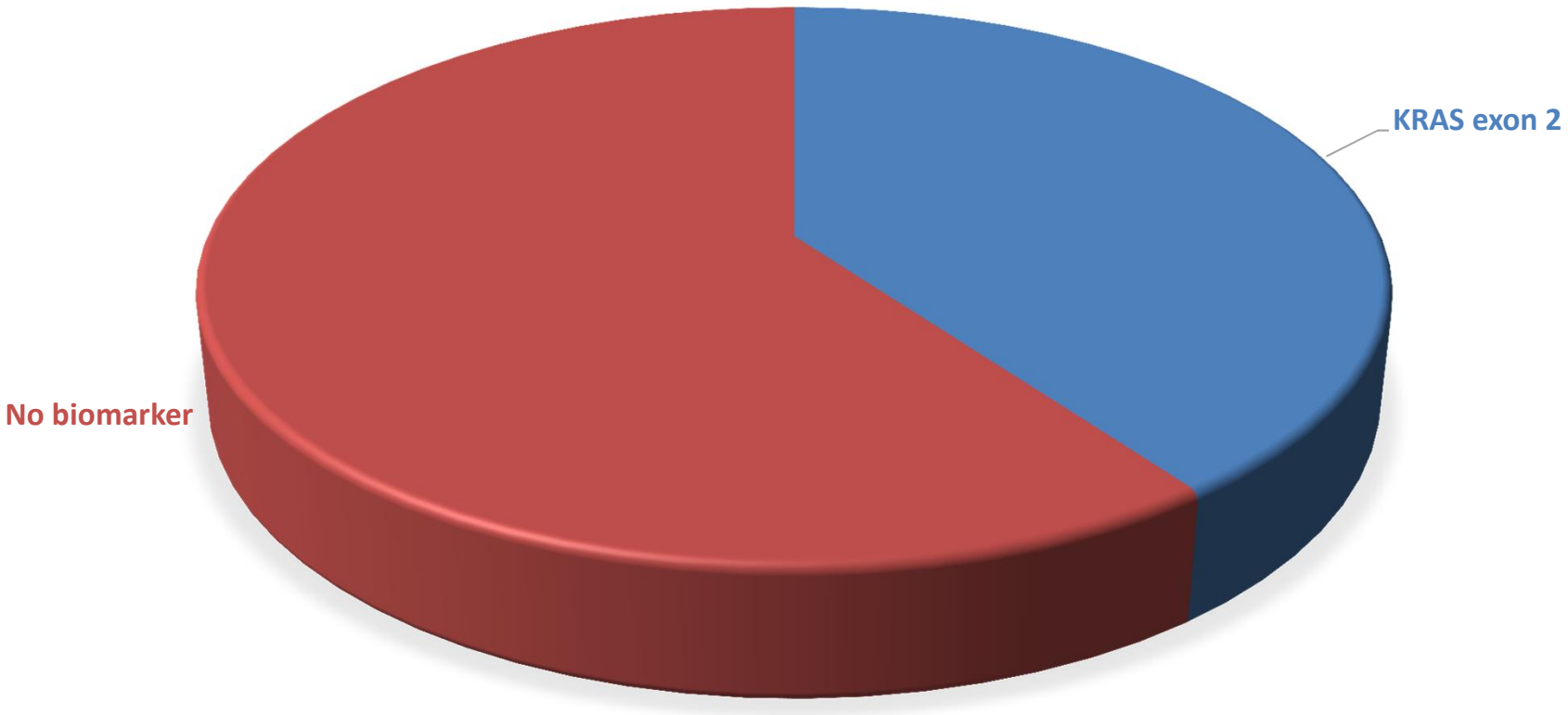
- 7/8 patients with NTRK+ CRC also had MSI-H tumors

Berlin et al., J Clin Oncol 38, 2020 (suppl 4; abstr 824).

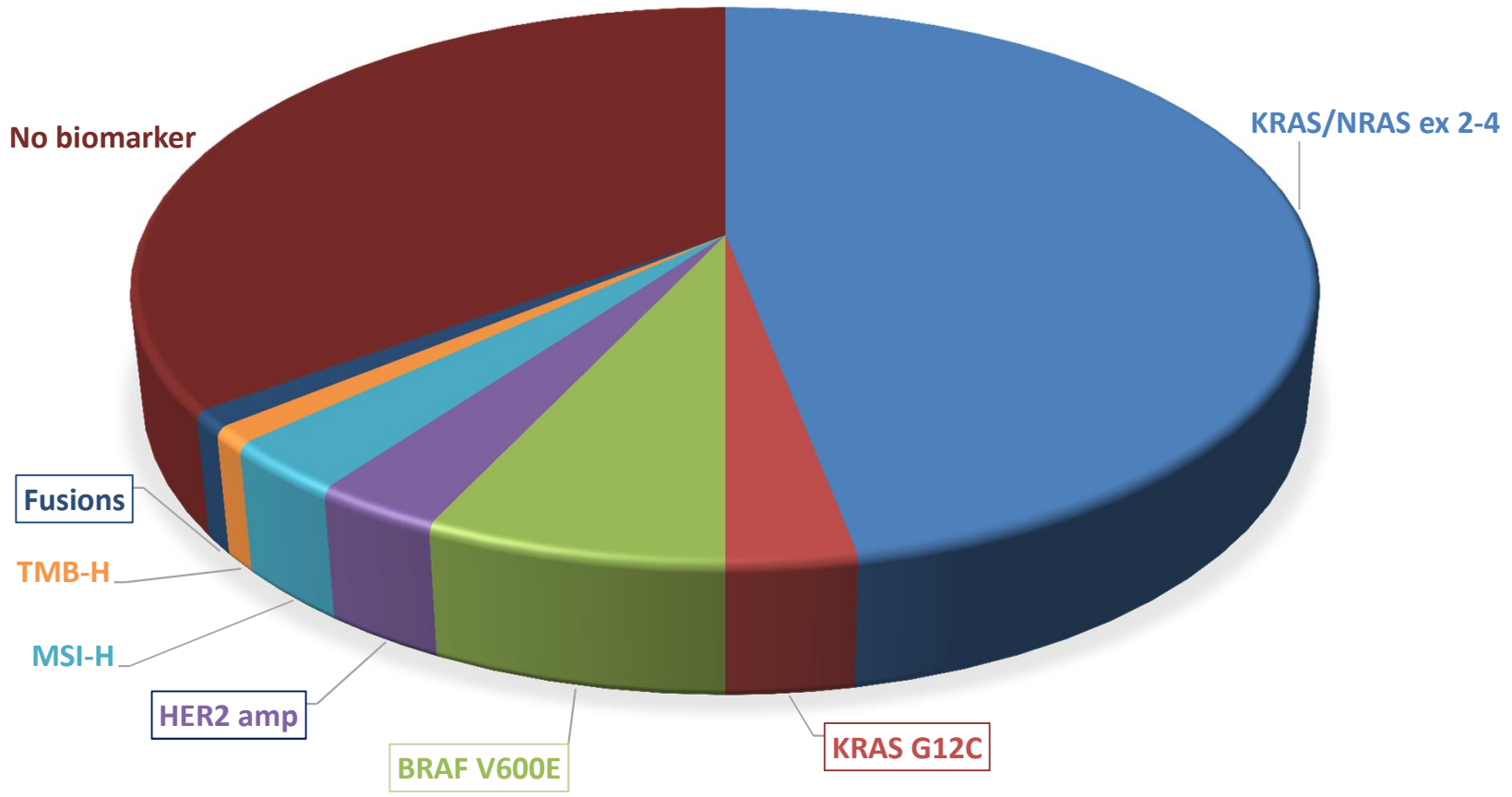
Conclusions

- Comprehensive molecular profiling is essential for all patients with metastatic CRC
- The number of “actionable” targets is growing – precision cancer medicine has finally arrived for metastatic CRC
- The key to finding a rare target is knowing who to test and how to test it
- The complexity of precision cancer medicine highlights the need for an active institutional molecular tumor board

ACTIONABLE COLORECTAL CANCER TARGETS IN 2010



ACTIONABLE COLORECTAL CANCER TARGETS IN 2020



THANK YOU !