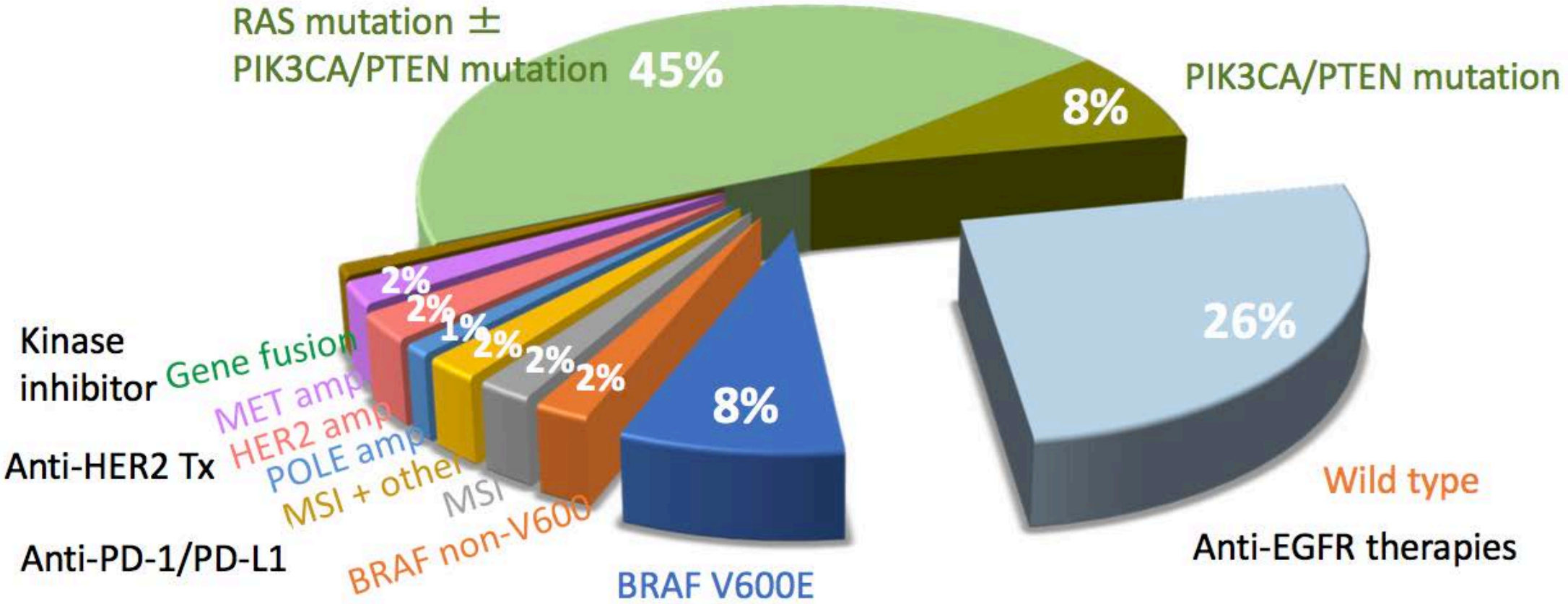
New Developments in the Use of Biomarker-Based Treatment for Metastatic Colorectal Cancer (mCRC)

Kristen K. Ciombor, MD, MSCI
Assistant Professor of Medicine
Vanderbilt-Ingram Cancer Center

VANDERBILT UNIVERSITY
MEDICAL CENTER

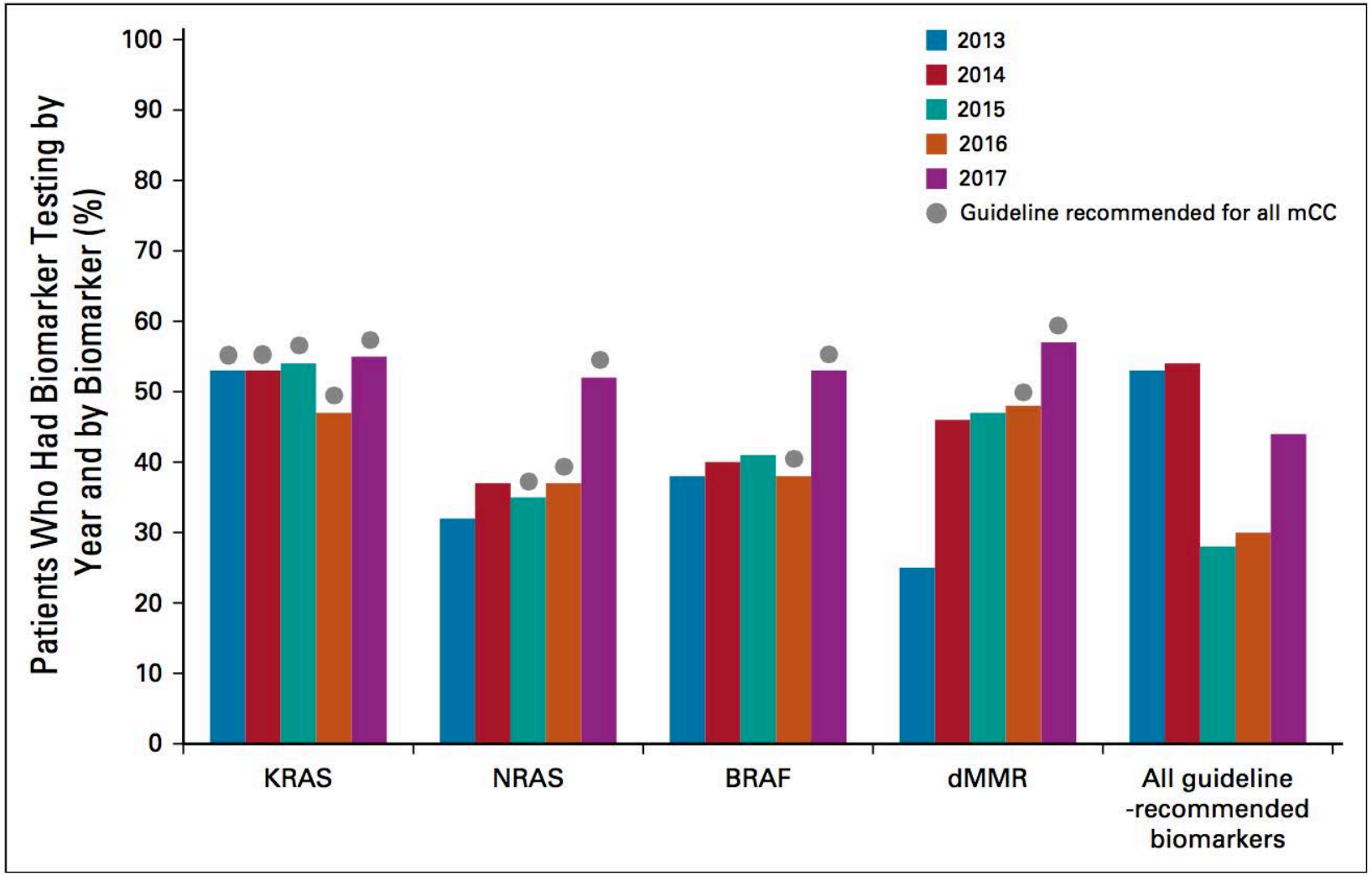
Genomic Markers in CRC



Dienstmann. ASCO Ed Book. 2018.

Courtesy of Kristen K Ciombor, MD, MSCI

Molecular Profiling in Metastatic Colon Cancer



VANDERBILT UNIVERSITY MEDICAL CENTER

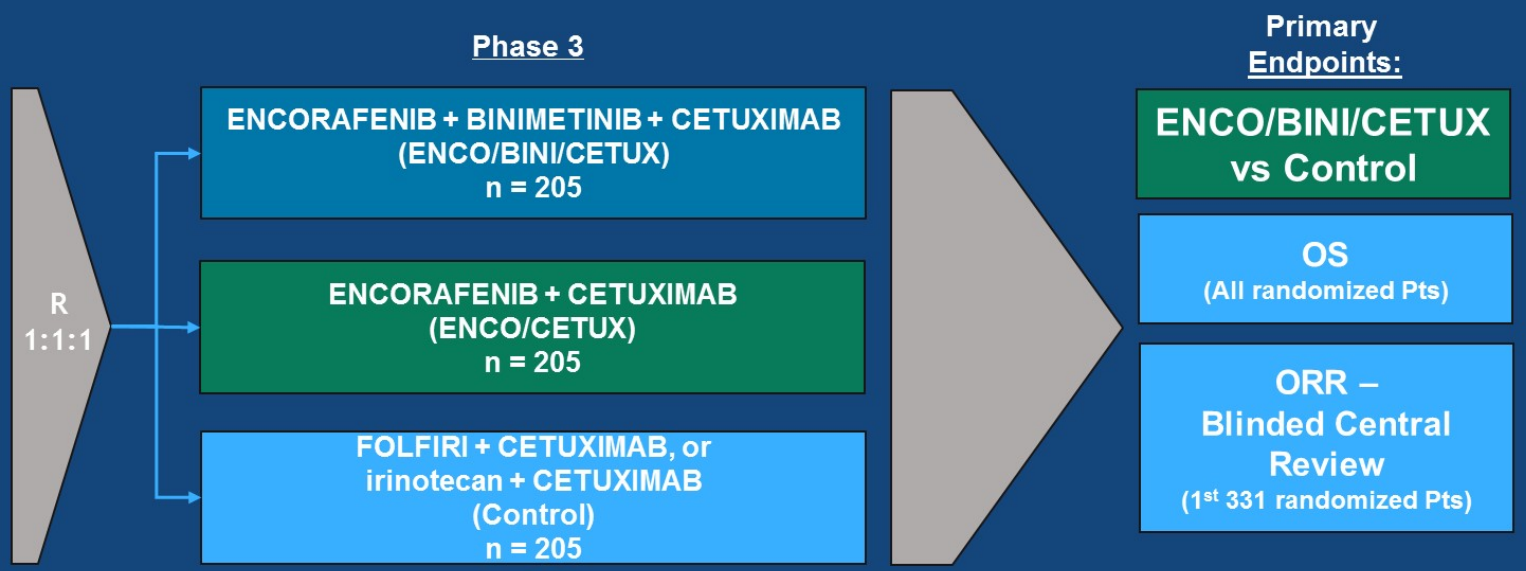
Gutierrez ME, et al. *JCO Precision Oncology.* 2019. doi:10.1200/PO.19.00274.

Courtesy of Kristen K Ciombor, MD, MSCI

Phase III BEACON CRC Trial

Study Design

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



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

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

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

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Scott Kopetz, MD, PhD

VANDERBILT UNIVERSITY MEDICAL CENTER

Presented By Scott Kopetz at ASCO 2020

Courtesy of Kristen K Ciombor, MD, MSCI

BEACON CRC

Updated Objective Response Rates

Confirmed Response by BICR	ENCO/BINI/CETUX N=224	ENCO/CETUX N=220	Control N=221
Objective Response Rate[a]	**27%**	**20%**	**2%**
95% (CI)	(21, 33)	(15, 25)	(<1, 5)
Best Overall Response[b]			
Complete Response (CR)	4%	3%	0%
Partial Response (PR)	23%	16%	2%
Stable Disease[c]	48%	56%	29%
Progressive Disease	11%	10%	34%
Non Evaluable by RECIST[d]	14%	15%	32%

BICR=blinded independent central review.

a. Confirmed responses per RECIST 1.1; Objective Response Rate equals the percentage of patients with a complete response or a partial response.

b. Best overall response percentage may not add up to 100% due to rounding.

c. Stable disease includes measurable disease patients who were either stable disease or non-measurable disease patients who were non-complete response/non-progressive disease per RECIST 1. Patients with only non-measurable disease, whose best non-target lesion response was Non-CR/non-PD and did not have any new lesions.

d. This category refers to patients who discontinued the trial regimen because of adverse events or whose disease could not be assessed centrally but who had clinical or radiologic disease progression according to local assessment.

Presented By Scott Kopetz at ASCO 2020

Courtesy of Kristen K Ciombor, MD, MSCI

BEACON CRC

Updated Grade ≥3 Adverse Events and Laboratory Abnormalities*

Consistent with previously reported safety profile†

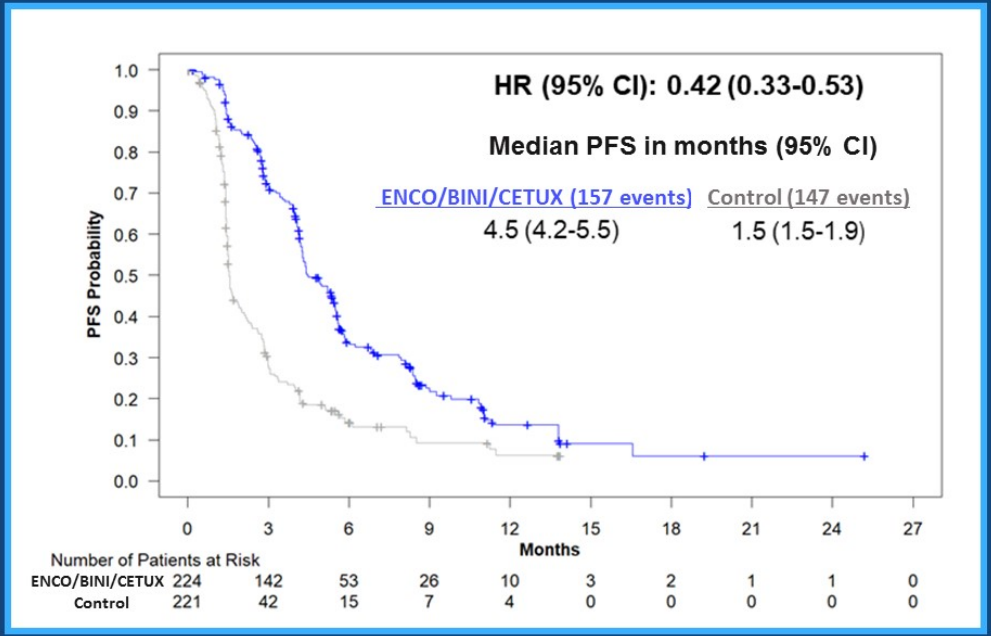
Adverse Event (Preferred term)	ENCO/BINI/CETUX N=222 Grade ≥3	ENCO/CETUX N=216 Grade ≥3	Control N=193 Grade ≥3
Diarrhea	11%	3%	10%
Abdominal pain	6%	3%	5%
Nausea	5%	<1%	2%
Vomiting	5%	1%	3%
Intestinal obstruction	5%	5%	3%
Pulmonary embolism	4%	1%	5%
Asthenia	4%	4%	5%
Acute kidney injury	3%	2%	<1%
Dermatitis acneiform	3%	<1%	3%
Fatigue	2%	4%	5%
Ileus	2%	2%	2%
Urinary tract infection	1%	2%	1%
Cancer pain	<1%	2%	<1%
Laboratory Abnormality**			
Hemoglobin (g/L), hypo	23%	6%	5%
Creatinine (μmol/L), hyper	5%	3%	1%
Creatine Kinase (IU/L), hyper	4%	0%	<1%
Bilirubin (μmol/L), hyper	3%	3%	3%

*Occurring in at least 2% of patients in either ENCO/BINI/CETUX or ENCO/CETUX arms. † Kopetz et al. N Engl J Med 2019; 381:1632-1643 **Selected laboratory abnormalities associated with adverse events.

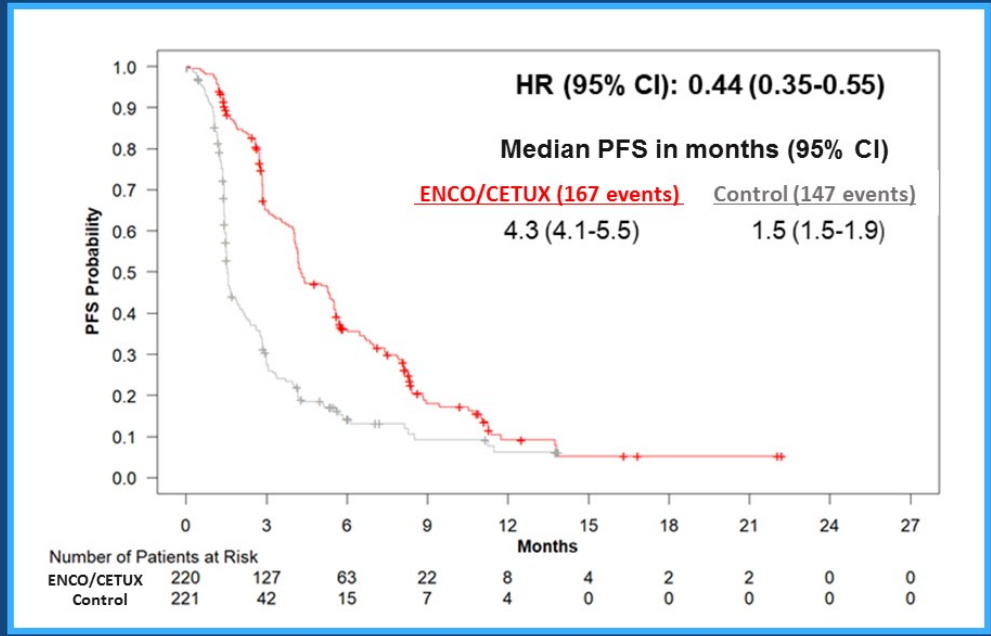
BEACON CRC

Updated Progression Free Survival*

ENCO/BINI/CETUX vs Control



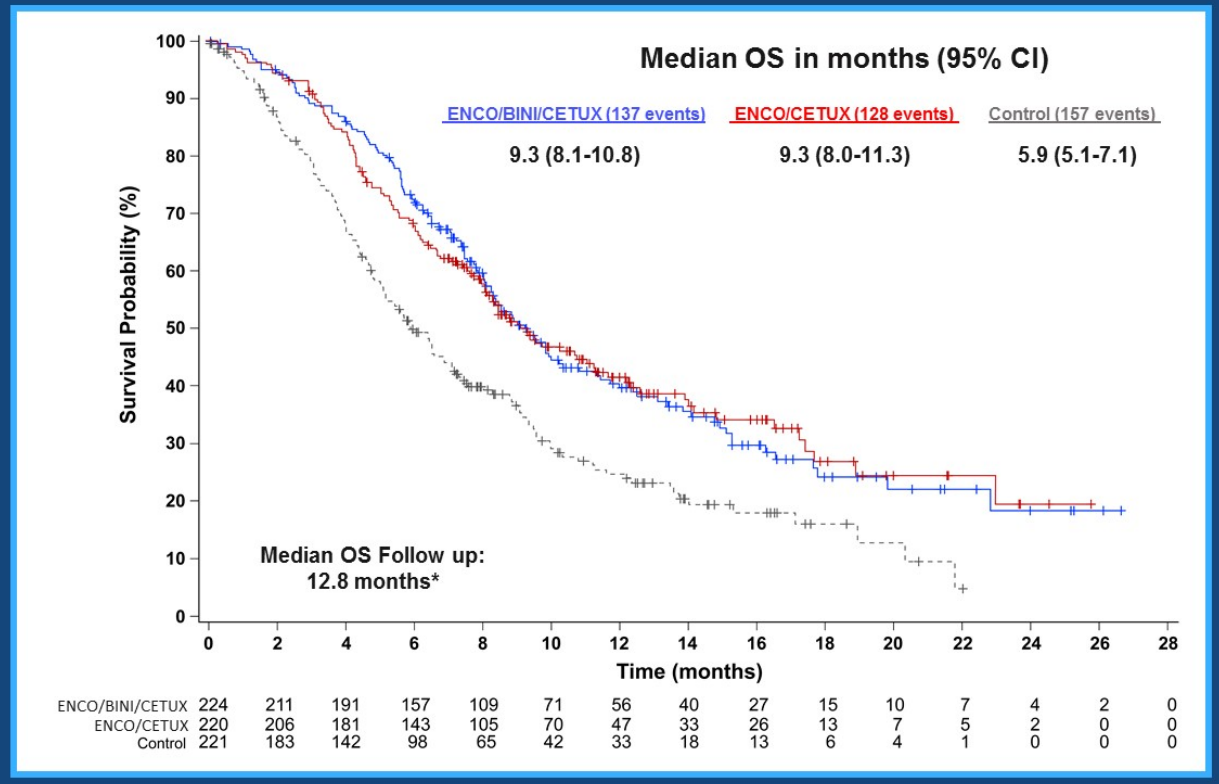
ENCO/CETUX vs Control



*PFS by BICR (blinded independent central review).

BEACON CRC

Updated Overall Survival: ENCO/BINI/CETUX vs ENCO/CETUX vs Control



PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Scott Kopetz, MD, PhD

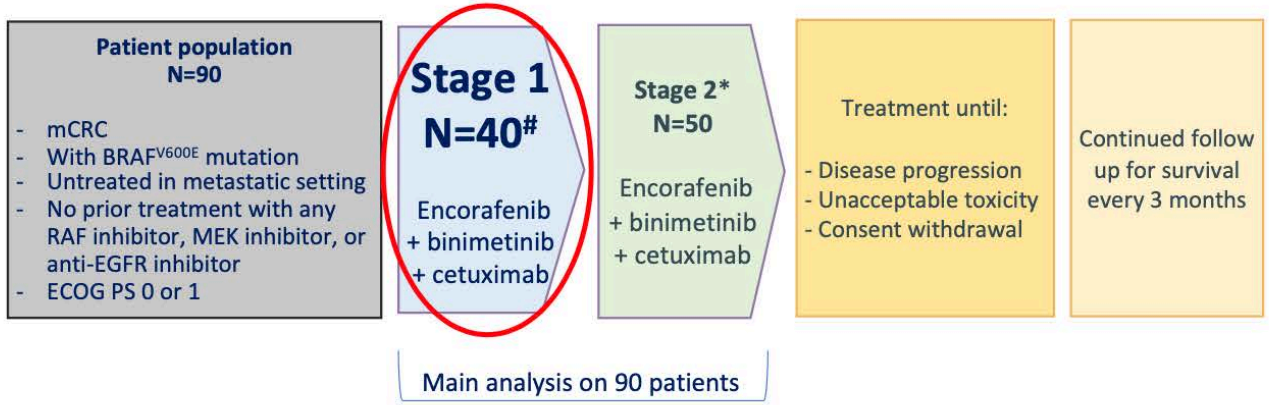
VANDERBILT UNIVERSITY MEDICAL CENTER

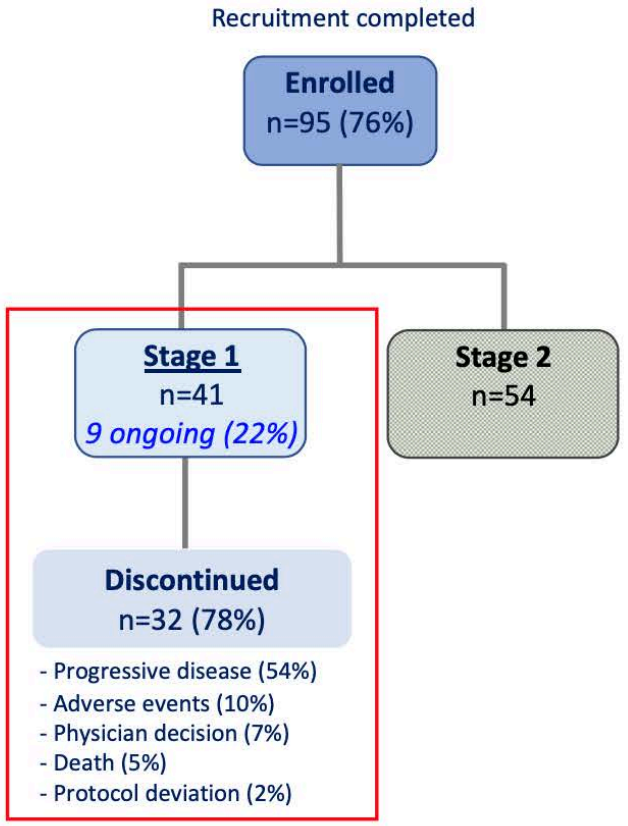
Presented By Scott Kopetz at ASCO 2020

Courtesy of Kristen K Ciombor, MD, MSCI

ANCHOR CRC, Phase 2 study in FIRST LINE BRAF^{V600E} mCRC

2-STAGE DESIGN[1]





Primary objective & endpoint: confirmed ORR (investigator assessed)

Secondary endpoints: PFS, OS, Safety, QoL, PK

1. Grothey A, et al. *Annals Oncol*. 2019;30(suppl 4):P-400
#Futility analysis
*Stage 2 enrolment only after ≥ 12 responses observed in stage 1
cORR=confirmed objective response rate, OS=overall survival, PK=pharmacokinetics, PFS=progression free survival, QoL=quality of life

Cut-off date: 06-Feb-2020

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

ESMO WORLD CONGRESS ON Gastrointestinal Cancer 2020 VIRTUAL

VANDERBILT UNIVERSITY MEDICAL CENTER

Courtesy of Kristen K Ciombor, MD, MSCI

Confirmed Objective Response Rate (primary endpoint) for Stage 1

Investigator's assessment, median time on treatment: 4.9 months

	Patients (N=40[#]), n (%)	
Confirmed Objective Response Rate	**20 (50%)**	
95% CI	[34 ; 66]	
Best Overall Confirmed Response		
Complete response	0	
Partial response	20 (50%)	**DCR = 85%**
Stable disease	14 (35%)	
Progressive disease	4 (10%)	
Not evaluable*	2 (5%)	

# 1 patient has been excluded from the efficacy analysis as the BRAF mutation was not confirmed by central lab
DCR=Disease Control Rate
* 1 patient with no adequate post-baseline assessment
1 patient with 1st CT-scan performed < 6 weeks (32 days after study drug start, stable disease) and discontinued due to AE (myocardial infarction)

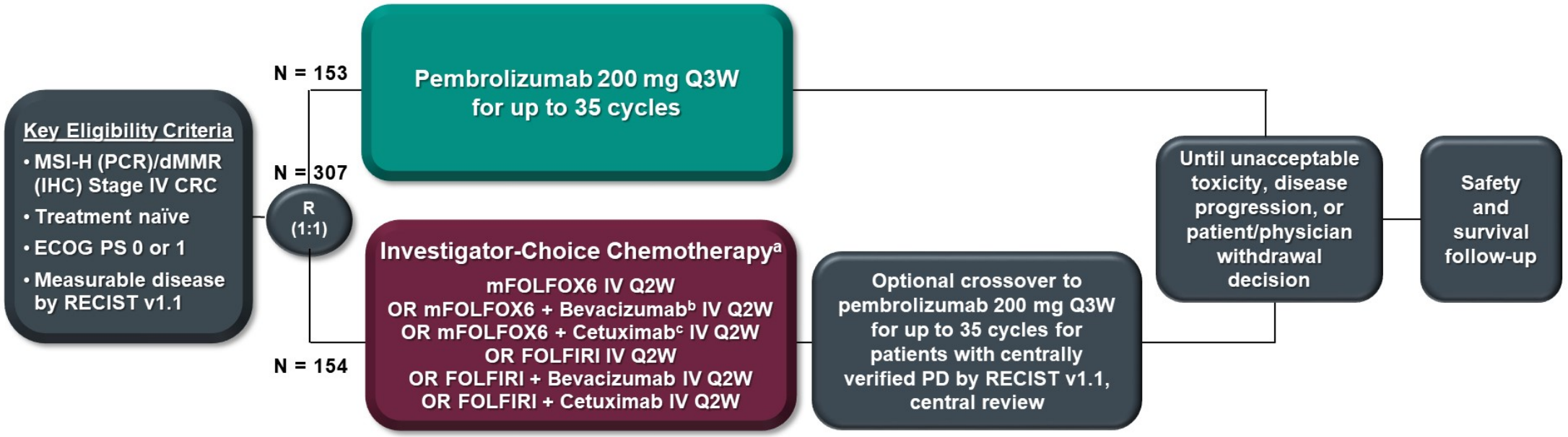
ESMO WORLD CONGRESS ON Gastrointestinal Cancer | 2020 VIRTUAL

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

VANDERBILT UNIVERSITY MEDICAL CENTER

Courtesy of Kristen K Ciombor, MD, MSCI

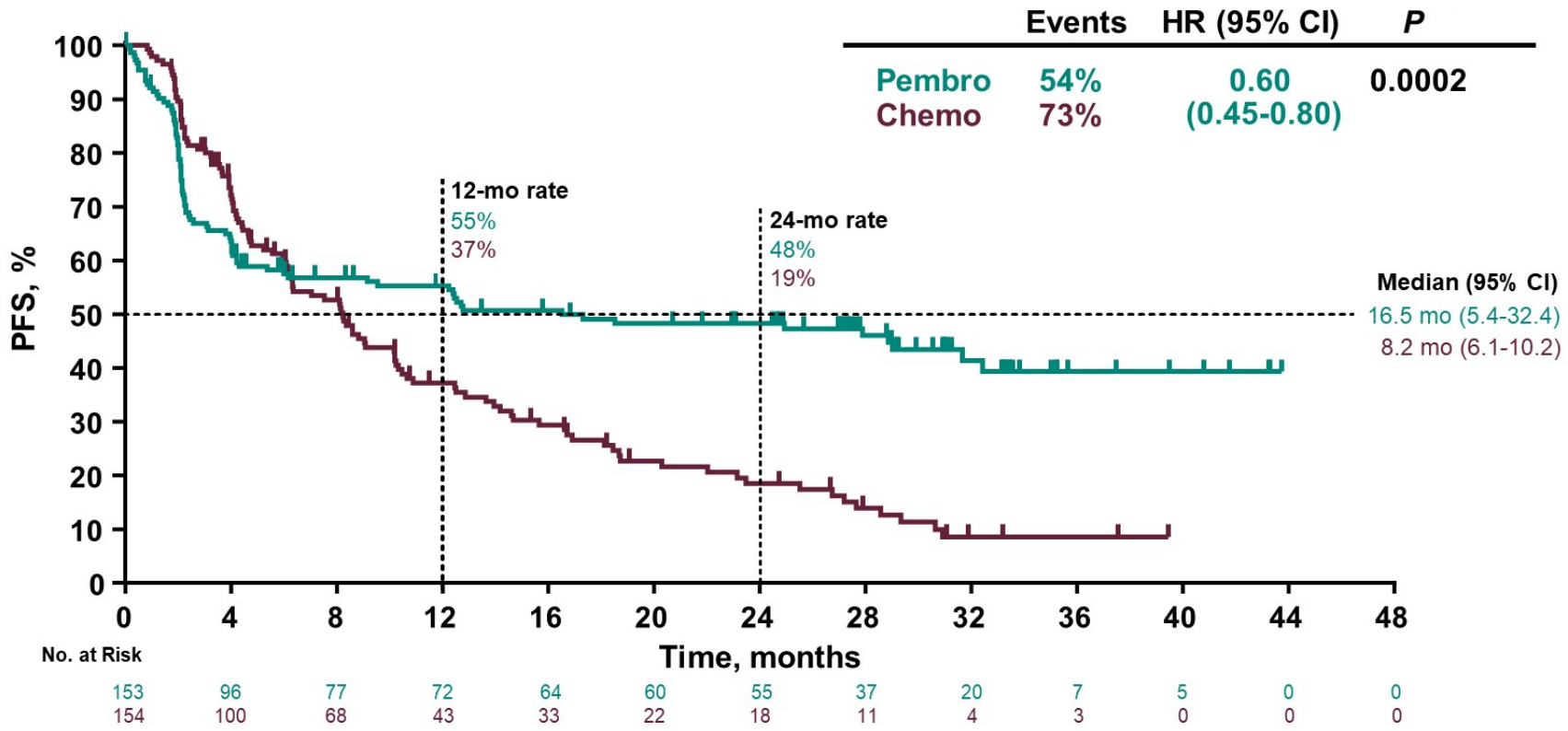
KEYNOTE-177 Study Design (NCT02563002)



- 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
- 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

KEYNOTE-177

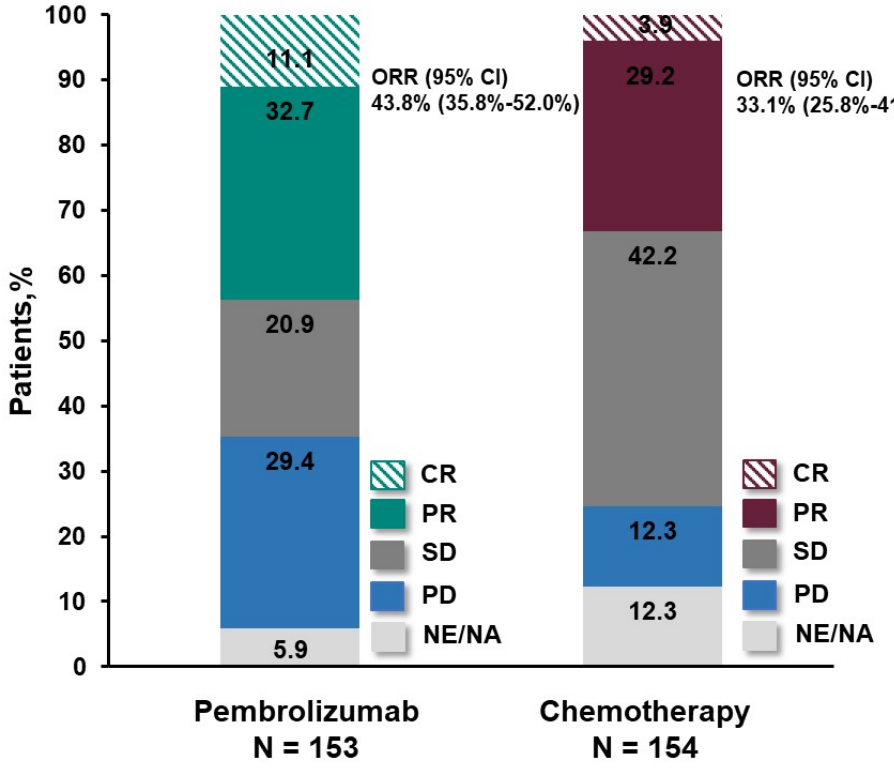
Progression-Free Survival

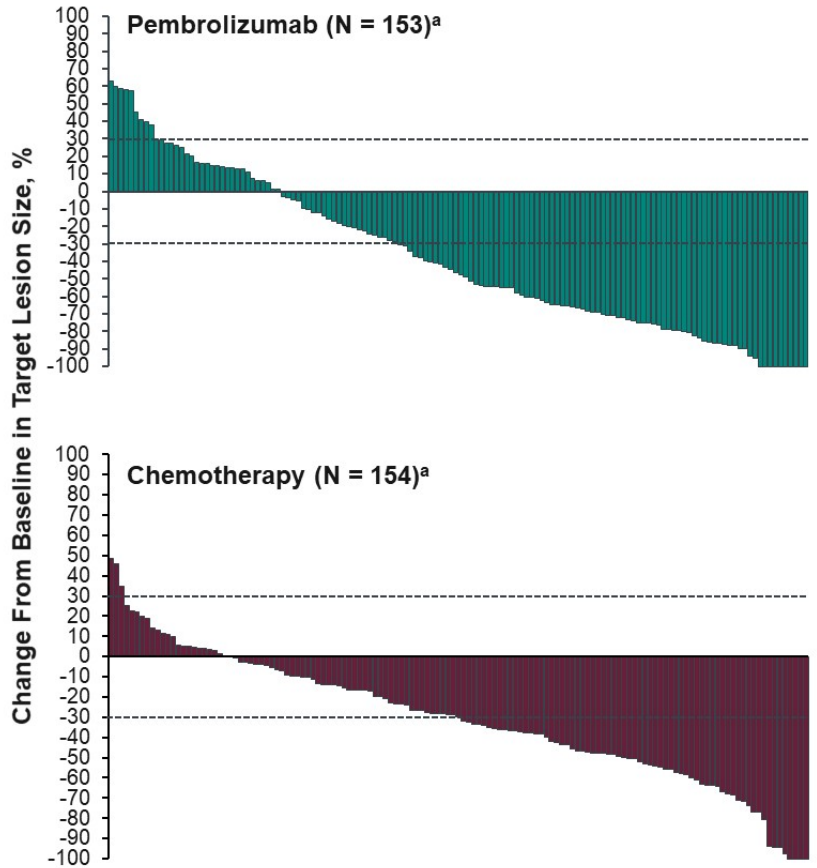


Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR. Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

KEYNOTE-177

Summary of Best Anti-Tumor Response



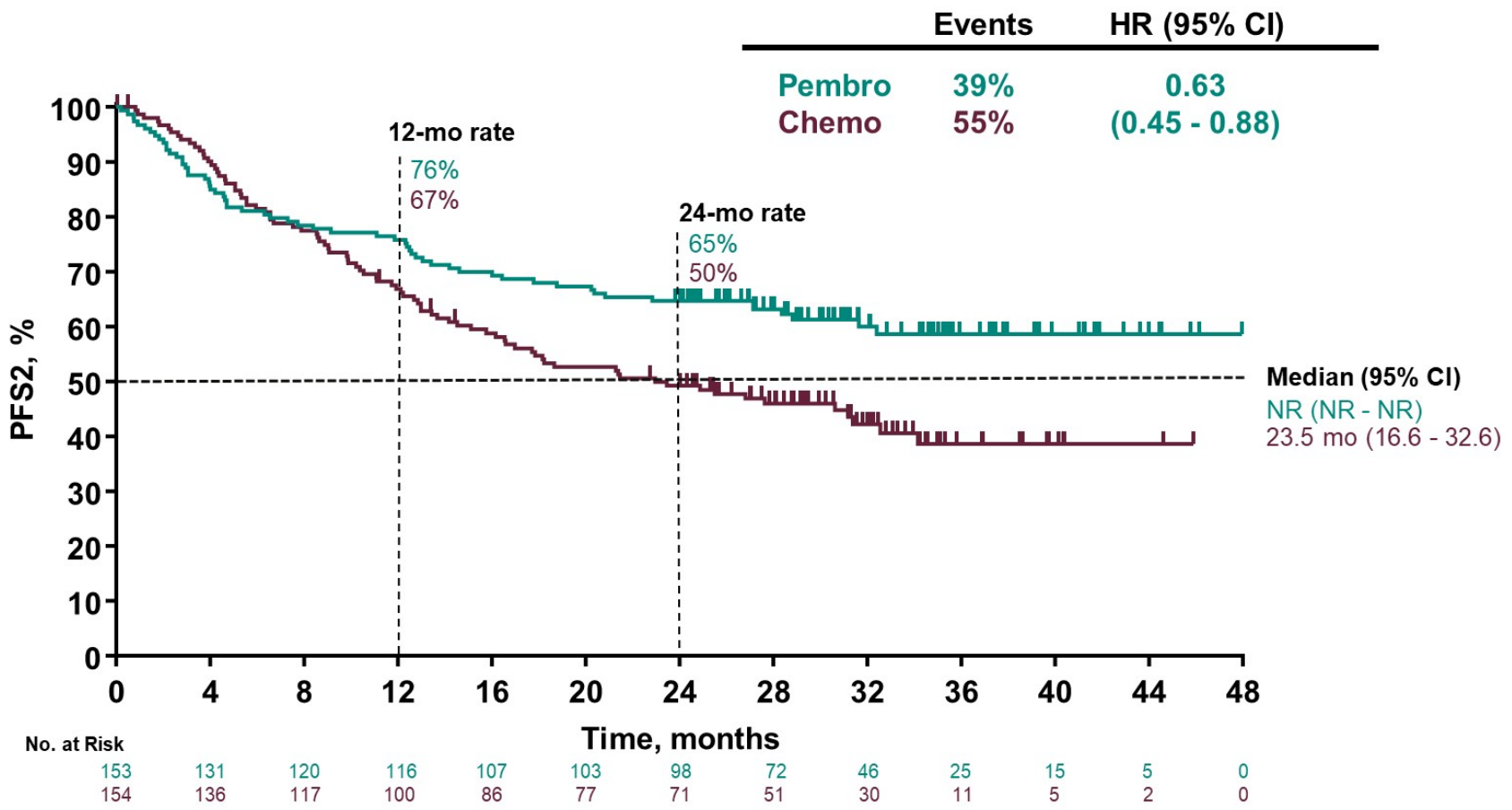


9 (6%) patients in the pembrolizumab arm and 19 (12%) in the chemotherapy arm were not evaluable (NE) or had no assessment (NA); [a]104 of 138 (75%) evaluable patients in the pembrolizumab arm and 111 of 135 (82%) evaluable patients in the chemotherapy arm had a reduction from baseline in target lesion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

KEYNOTE-177

Progression-Free Survival 2

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

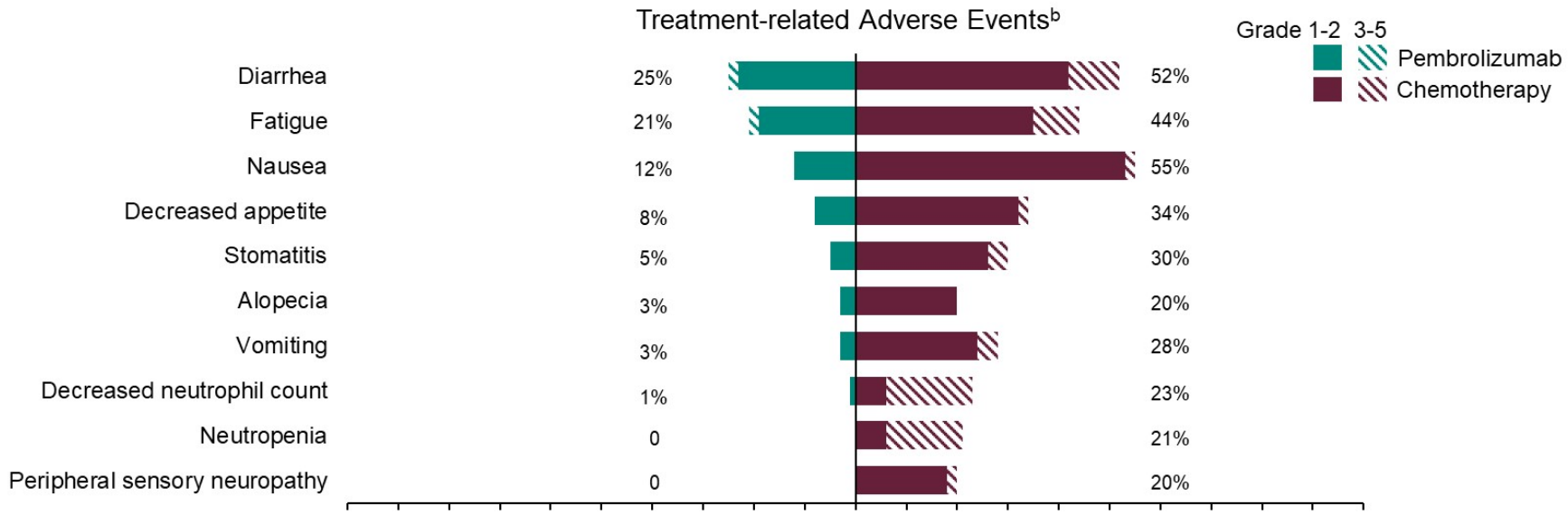


Data cut-off: 19Feb2020; PFS2 assessed per RECIST v1.1 by investigator.

KEYNOTE-177

Adverse Events (AEs) in All Treated Patients

Events	Pembrolizumab N = 153	Chemotherapy N = 143
All AEs	97%	99%
Treatment-related	80%	99%
Grade ≥3	22%	66%
Death	0	1%[a]
Discontinued	10%	6%



[a]One grade 5 event of intestinal perforation; [b]Incidence ≥20% in any group; Data cut-off: 19Feb2020.

VANDERBILT UNIVERSITY MEDICAL CENTER

Presented By Kai-Keen Shiu at 2021 Gastrointestinal Cancers Symposium

Courtesy of Kristen K Ciombor, MD, MSCI

KEYNOTE-177

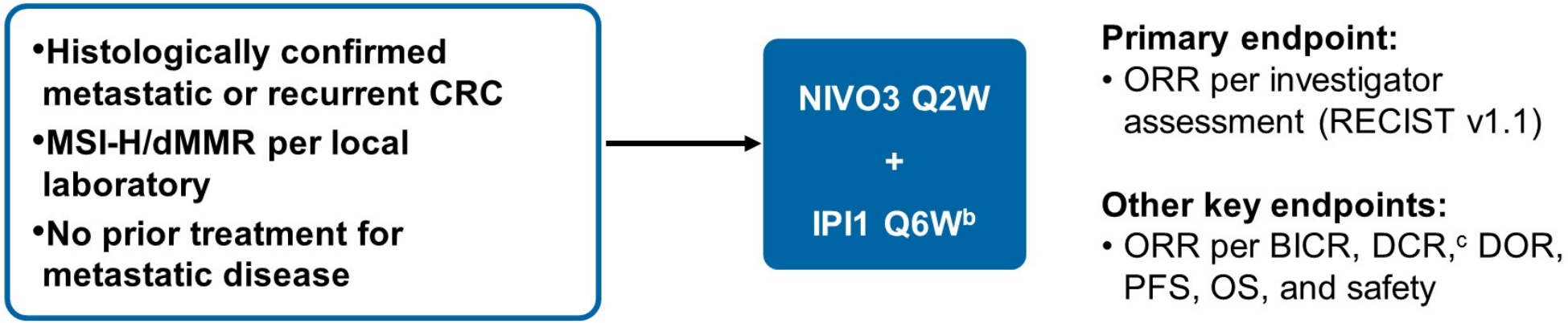
Immune-Mediated AEs and Infusion Reactions

	Pembrolizumab N = 153		Chemotherapy N = 143	
All	31%		13%	
Grade ≥3	9%		2%	
Discontinued	7%		0	
Died	0		0	
Incidence >0%	**All**	**Grade ≥3**	**All**	**Grade ≥3**
Hypothyroidism	12%	0	2%	0
Colitis	7%	3%	0	0
Hyperthyroidism	4%	0	0	0
Pneumonitis	4%	0	1%	0
Adrenal insufficiency	3%	1%	0	0
Hepatitis	3%	3%	0	0
Infusion reactions	2%	0	8%	1%
Hypophysitis	1%	0	0	0
Myositis	1%	0	0	0
Nephritis	1%	0	0	0
Pancreatitis	1%	1%	0	0
Severe skin reactions	1%	1%	1%	1%
Thyroiditis	1%	0	0	0
Type 1 Diabetes Mellitus	1%	1%	0	0
Myocarditis	0	0	1%	0

Based on a list of terms specified by the sponsor and included by the investigator regardless of attribution to study treatment or immune relatedness; Data cutoff: 19Feb2020.

CheckMate 142 NIVO3 + IPI1 1L Cohort Study Design

- CheckMate 142 is an ongoing, multi-cohort, nonrandomized phase 2 study evaluating the efficacy and safety of nivolumab-based therapies in patients with mCRC[a]



- Median duration of follow-up (defined as time from first dose to data cutoff) was 19.9 months (range, 15.1–24.6)

[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 a CR, PR, or SD for ≥ 12 weeks divided by the number of treated patients.
BICR, blinded independent central review; CRC, colorectal cancer; DCR, disease control rate; IPI1, ipilimumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

CheckMate 142

Response, Disease Control, and Durability

	NIVO3 (Q2W) + IPI1 (Q6W) N = 45[a]	
	BICR-assessed	Investigator-assessed
ORR,[b] n (%) [95% CI]	26 (58) [42–72]	29 (64) [49–78]
Best overall response, n (%)		
CR	8 (18)	4[c] (9)
PR	18 (40)	25 (56)
SD	10 (22)	9 (20)
PD	7 (16)	6 (13)
Not determined	2 (4)	1 (2)
DCR,[d] n (%) [95% CI]	35 (78) [63–89]	38 (84) [71–94]
Median TTR (range), months	1.6 (1.2–16.3)	2.6 (1.2–13.8)
Median DOR (range), months	NR (3.3+ to 20.8+)	NR (1.4+ to 20.8+)

[a]Median follow-up of 19.9 months; [b]Patients with CR or PR divided by the number of treated patients; [c]One patient was incorrectly reported as CR instead of PR. CR was based on surgical pathology and not RECIST v1.1; [d]Patients with a CR, PR, or SD for ≥ 12 weeks divided by the number of treated patients.
CI, confidence interval; NR, not reached; PD, progressive disease; TTR, time to response.

DESTINY-CRC01 Study Design

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

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+

Primary endpoint

- Confirmed ORR by independent central review (ICR) in Cohort A

Data cutoff: August 9, 2019

- 38.5% (30/78) remained on treatment
- 61.5% discontinued, primarily for progressive disease (41.0%) and clinical progression (9.0%)

PRESENTED BY: Prof Salvatore Siena; Università degli Studi di Milano, Milan, Italy; salvatore.siena@unimi.it

DESTINY-CRC01 Cohort A

Efficacy

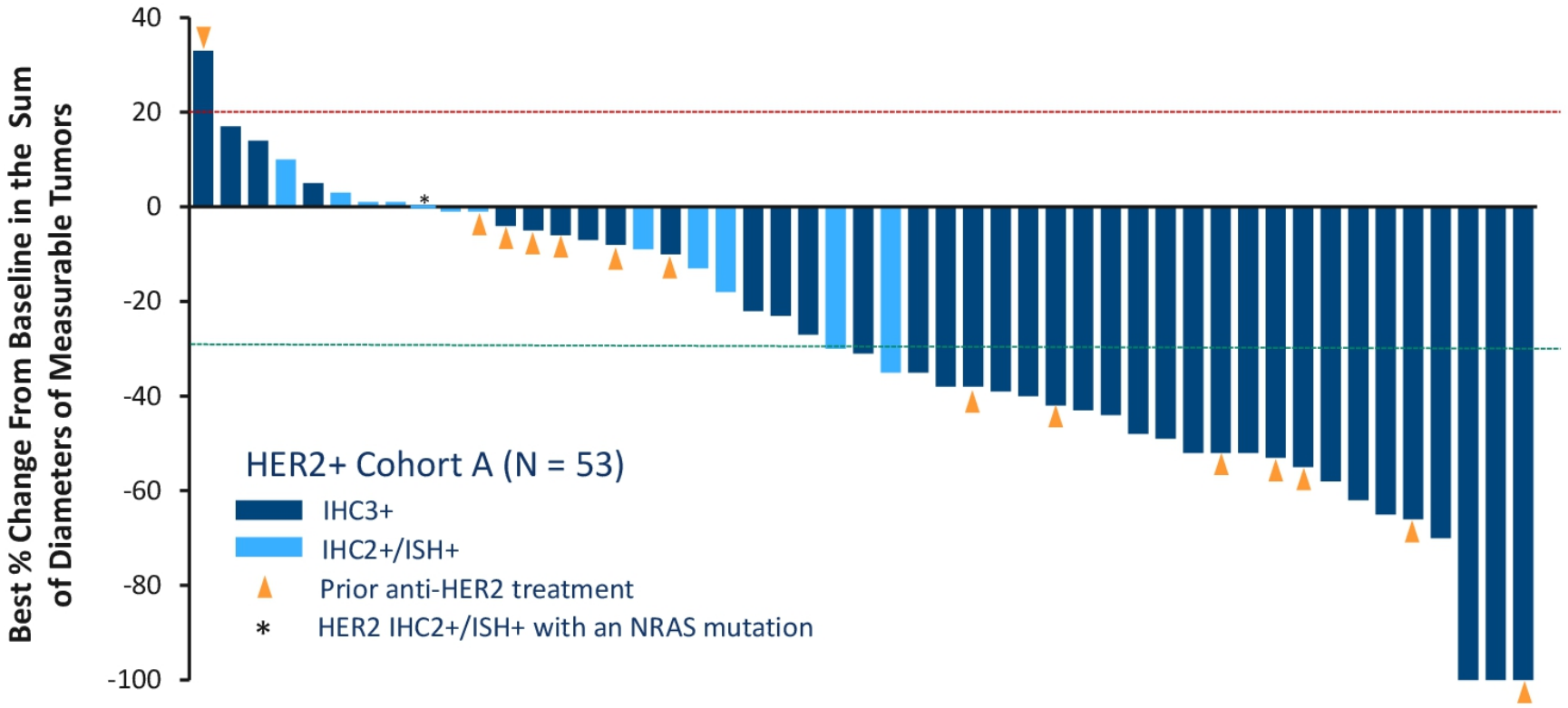
	HER2+ Cohort A (N = 53)
Confirmed ORR by ICR	**45.3% (n = 24)** (95% CI, 31.6%-59.6%)
CR	1.9% (n = 1)
PR	43.4% (n = 23)
SD	37.7% (n = 20)
PD	9.4% (n = 5)
Not evaluable	7.5% (n = 4)[a]
Disease control rate	83.0% (95% CI, 70.2%-91.9%)
Duration of response, median	Not reached (95% CI, 4.2 months-NE)

[a] Patients were missing postbaseline scans.
Median study duration, 5.0 months (range, 0.6-10.5 months). There were no confirmed responses by ICR in Cohort B or C.

PRESENTED BY: Prof Salvatore Siena; Università degli Studi di Milano, Milan, Italy; salvatore.siena@unimi.it

DESTINY-CRC01 Cohort A

Best Change in Tumor Size



PRESENTED BY: Prof Salvatore Siena; Università degli Studi di Milano, Milan, Italy; salvatore.siena@unimi.it

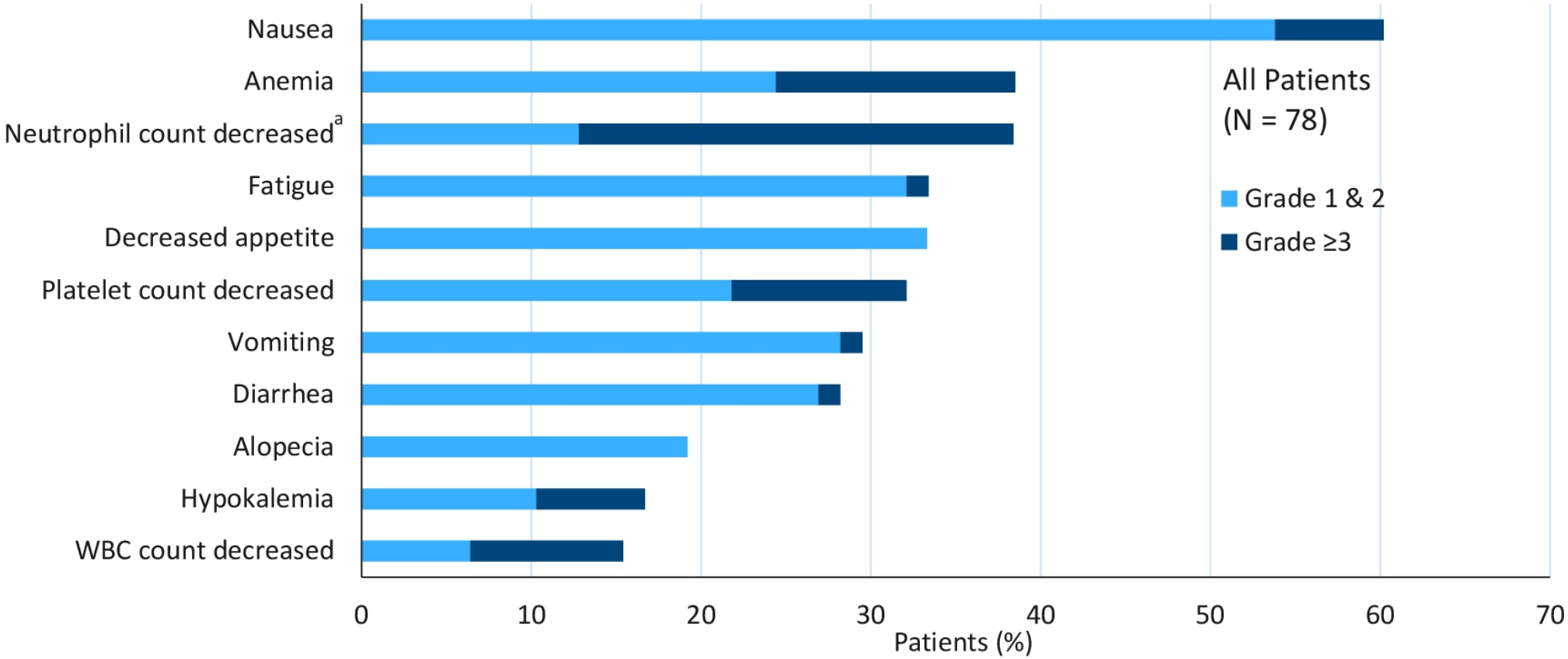
VANDERBILT UNIVERSITY MEDICAL CENTER

Presented By Salvatore Siena at TBD

Courtesy of Kristen K Ciombor, MD, MSCI

DESTINY-CRC01

Treatment-Emergent Adverse Events in >15% of Patients



[a] Grade ≥3 neutrophil count decreased, 25.6%; no patients had febrile neutropenia.

PRESENTED BY: Prof Salvatore Siena; Università degli Studi di Milano, Milan, Italy; salvatore.siena@unimi.it

VANDERBILT UNIVERSITY MEDICAL CENTER

Presented By Salvatore Siena at TBD

Courtesy of Kristen K Ciombor, MD, MSCI

DESTINY-CRC01

AEs of Special Interest: Interstitial Lung Disease

	All Patients (N = 78)					
Preferred Term, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/ Total
Interstitial Lung Disease	0	2 (2.6)	1 (1.3)	0	2 (2.6)	5 (6.4)

Among the 5 total events:

- Median time to investigator-reported onset was 80 days (range, 22-132)
- 5 of 5 patients with grade ≥ 2 ILD received corticosteroids
- 2 patients recovered, 1 did not recover (later died due to disease progression), and 2 died
- In the 2 fatal cases, onset was from 40-126 days, both received steroids as part of treatment, and death occurred 6-18 days after diagnosis

Protocol recommendations: Monitor for symptoms. Hold T-DXd and start steroids as soon as ILD is suspected

Drug related; ILD was determined by an Independent ILD Adjudication Committee based on 44 preferred terms.
One additional grade 5 ILD case in Cohort B was reported after the data cutoff. This case was adjudicated after data cutoff as drug-related ILD.

PRESENTED BY: Prof Salvatore Siena; Università degli Studi di Milano, Milan, Italy; salvatore.siena@unimi.it

Anti-HER2 Tx in mCRC

		N	ORR	Median PFS	Median OS
HERACLES-A	Trastuzumab + Lapatinib ^	27	30% (14-50)	4.8 mo (3.7-7.4)	10.6 mo (7.6-15.6)
MyPathway (*KRAS* WT subgroup)	Trastuzumab + Pertuzumab ^	43	40% (25-56)	5.3 mo (2.7-6.1)	14.0 mo (8.0-NE)
TRIUMPH	Trastuzumab + Pertuzumab ^	17 (Tissue)	35% (14-62)	4.0 mo (1.4-5.6)	
TAPUR (no RAS data)	Trastuzumab + Pertuzumab ^	28	25% (11-45)	4.0 mo (2.6-6.3)	25.0 mo (6.0-NE)
MOUNTAINEER	Trastuzumab + Tucatinib	23	52% (31-73)	8.1 mo (3.8-NE)	18.7 mo (12.3-NE)
DESTINY-CRC01 *	**T-DXd**	**54**	**45% (32-60)**	**6.9 mo (4.1-NE)**	**NE (0.74-NE)**
HERACLES-B #	T-DM1 + Pertuzumab	30	10% (0-28)	4.8 mo (3.6-5.8)	

* ORR in subgroup **with prior HER2 rx 43.8% (19.8-70.1)**; without prior HER2 rx 45.9% (29.5-63.1)
# Did not meet primary endpoint. T-DM1 had 0% response rate in MATCH Arm Q and MSKCC basket trial
^ In NCCN guidelines

Sartore-Bianchi A, Lancet Oncol 2016; Meric-Bernstam F, Lancet Oncol 2019; Nakamura Y, ESMO 2019; Gupta R, GI ASCO 2020; Strickler J, ESMO 2019; Sartore-Bianchi A, ESMO 2019; Siena S, ASCO 2020; Jhaveri KL, Ann Oncol 2019; Li BT, ASCO 2018

Case 1

- 53 year old woman with abdominal pain
- CT A/P in ER showed multiple liver lesions, portal LAD
- Cscope: distal ascending colon mass; MD adenocarcinoma, pMMR; liver biopsy c/w mCRC
- CEA 52.7
- NGS: MSS, KRAS/NRAS wt, BRAF V600E mut, FGFR1 amp
- FOLFOX/bev with great response x 10 cycles; dropped oxali for PN and eventually bev for mucosal bleeding
- At PD: encorafenib/panitumumab x 8 months
- FOLFIRI → FOLFOXIRI → Y90

Courtesy of Kristen K Ciombor, MD, MSCI

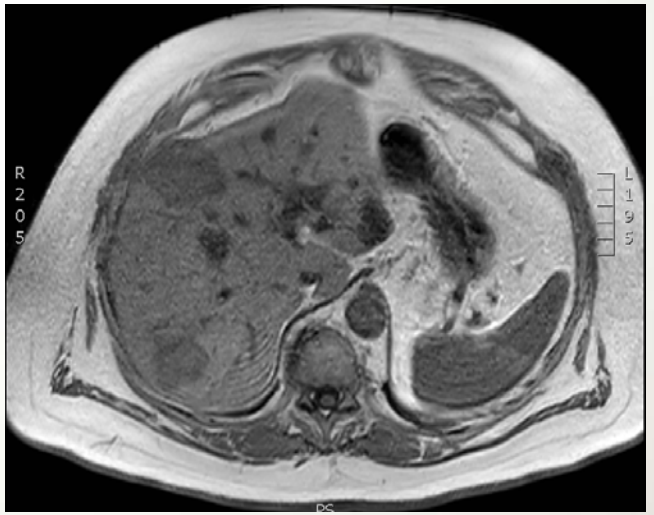
Case 2

- 51 year old woman with HTN, DM; rectal bleeding
- Colonoscopy: rectal tumor at 5 cm from anal verge; dMMR (loss of MLH1, PMS2)
- MRI pelvis: T3bN1; MRI liver: multiple liver lesions, R>L, L lesion on L hepatic vein (unresectable)
- Nivo 3 mg/kg q2 weeks, ipi 1 mg/kg q6 weeks (2 cycles)
- Genetic testing: VUS in MLH1, TSC1
- CEA 44.5→43.4→27.9→7.8→3.1→2.1
- Developed appendicitis – diagnosed with adrenal insufficiency, thyroiditis
- Imaging: marked improvement; liver mets resectable

Courtesy of Kristen K Ciombor, MD, MSCI

Case 3

- 34 year old man with rectal bleeding, weight loss
- Colonoscopy: nearly obstructing tumor 15 cm from anal verge; path: adenocarcinoma, pMMR
- CT C/A/P: multiple liver lesions, unresectable
- NGS: MSS, KRAS/NRAS/BRAF wt, HER2+
- FOLFOX/bev x 6 months → partial response
- Dropped oxali for PN
- FOLFIRI/bev upon PD → 8 mos
- Initial PR, then mixed response
- Tucatinib/trastuzumab – SD at 6 wks
- PD at 10 wks



Courtesy of Kristen K Ciombor, MD, MSCI