Metastatic CRC

BIOLOGICAL AGENT

New emerging field

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APPROVED IN EUROPE DRUGS FOR mCCR FROM 1957 UNTIL NOW

YEAR	DRUG	NAME
1957	**thymidilate synthetase inhibitor**	5-FLUOROURACIL
1997	**TOPOISOMERASE 1 INHIBITOR**	IRINOTECAN
1997	SPECIFIC TS INHIBITOR	TOMUDEX
1999		
2001		E
2004		
2005		B
2007		B
2013		B
2016 (FDA 20[illegible])		T RAMUCIRUMAB (*)
2017	**Trifluridine and Tipiracil**	TAS-102
(FDA 2017)	**Anti PD-1**	PEMBROLIZUMAB (*)

SINCE 5 YEARS WITH DEBATE ON ANTI-EGFR OR ANTI-VEGFR IN FIRST LINE
NO REAL NEWS FOR TREATMENT WITH BIOLOGICAL AGENT

NOW BIOMARKER DIRECTED TRIAL WITH OLD AND NEW BIOLOGICAL AGENT

BIOMARKERS testing for mCRC in 2020 (SOC)

aberration	%	Therapeutic option
KRAS/BRAF/NRAF WT	40	Cetuximab panitumumab
BRAF V600E mut	8	Encorafenib+cetuximab Encorafenib+panitumumab
HER2 positive **IHC 3+/2+ with +ISH or NGS**	3(all) 5-10 (RAS WT)	If KRAS-NRAS WT Trastuzumab + pertuzumab Trastuzumab+lapatinib (Trastuzumab+tucatinib)(Abst)
MSI-high (PCR or NGS panel)/Deficient Mismatch Repair	8	Pembrolizumab Nivolumab Nivo+Ipi
NTRK gene fusion	< 0,5	Larotrectinib/Entrectinib
KRAS G12 C mutation	3	
BRAF non V600E mut	4	
Pole mutation	<1	
Others rare like FGFR fusion,RET fusion,ALK fusion	<1	

ABSTRACT 4002:PANDA trial in elderly

ABSTRACT 4001:BEACON update
Bitherapy confirmed (FDA/EMA)

ABSTRACT 4000:Destinity CRC01
New drug: trastuzumab deruxtecan

PLENIERE:Keynote 177
1st line chemo vs Pembro

ABSTRACT 4018: CodeBreak 100
New Drug:AMG 510
NEJM SEP 2020

ESMO Colloquium:RET inhibition
PRALSETINIB/SELPERCATINIB

ASCO 2020:ABSTRACT 4002 PANDA TRIAL

Biomarker directed trial in elderly patient

First-line FOLFOX plus Panitumumab versus 5FU plus Panitumumab in RAS-BRAF wild-type metastatic colorectal cancer elderly patients: the PANDA study. Phase II non comparative randomised design.

1st line
Unresectable mCRC
RAS BRAF wt
≥ 70 Y
N=185

R

OXALI 85 mg/msq
5FU 2400/msq/48H ci
PANI 6 mg/KG q2weeks (up to 12 cycles)

PANI maintenance until PD

5FU 2400/msq/48H ci
PANI 6 mg/KG q2weeks(up to 12 cycles)

PANI maintenance until PD

STRATIFICATION FACTORS:
Age: ≤ 75 vs >75 years
Ps 0-1 vs 2
G8 ≤ 14 vs > 14

Primary endpoint:PFS of each arm compared to a literature based historic control of ≥ 6 mo (null hypothesis in each arm median PFS ≤ 6 month;alternative hypothesis PFS ≥ 9,5 months ,**no formal comparison between the 2 arms was planned**
Secondary endpoints:ORR,safety,OS,association between G8 score and clinical outcome, association between G8 score and severe toxicity (grade ¾),association between CRASH score risk categories and severe toxicity (grade ¾), translational analyses.

S Ionardi,GONO TRIAL

ASCO 2020:ABSTRACT 4002 PANDA TRIAL

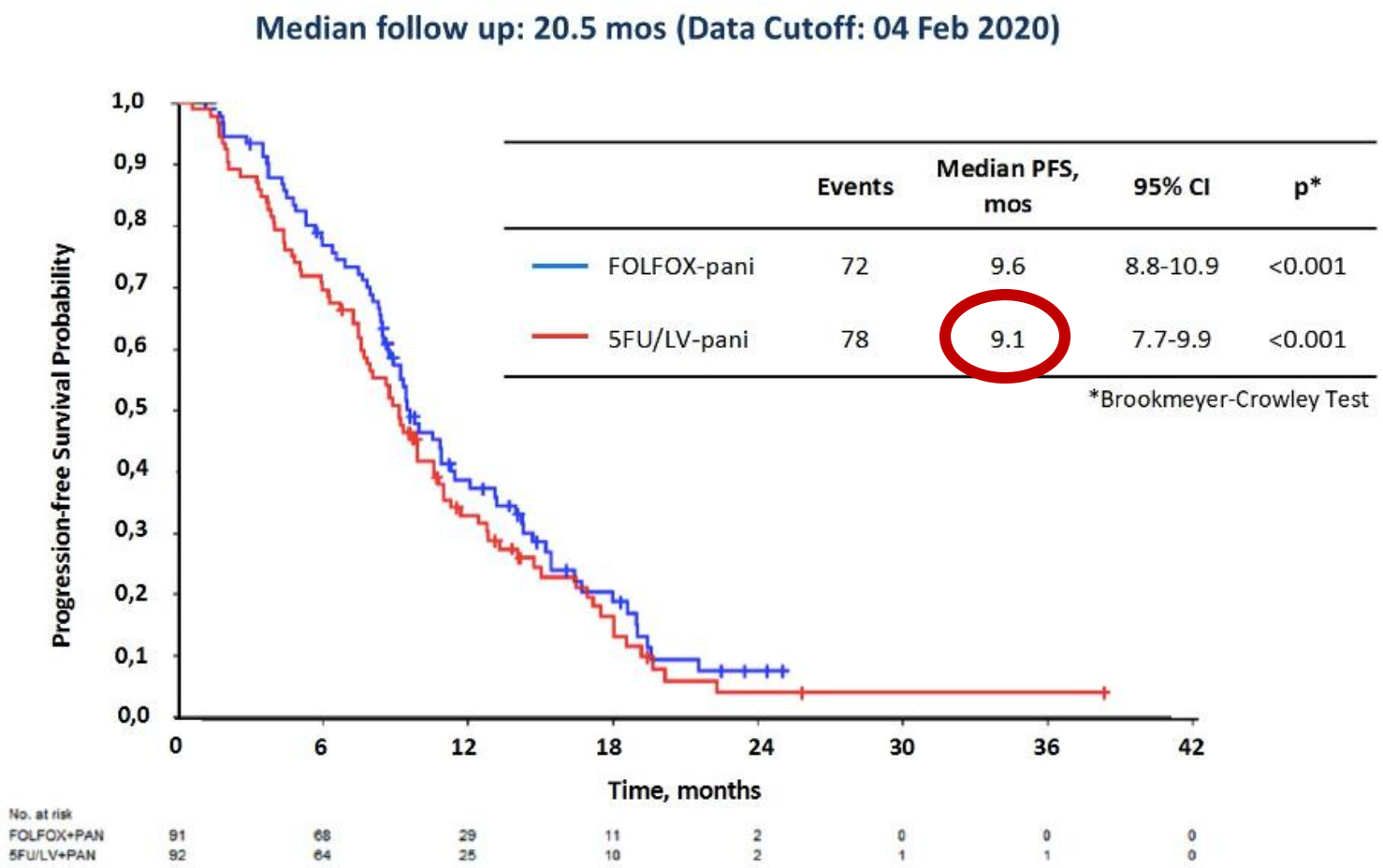
Main baseline characteristics/treatment administration/toxicity

	FOLFOX + PANI N=91 %	5FU/LV + PANI N=92 %
Median age	77 Y	77 Y
Male/Female	66/34	61/39
ECOG PS 0:1-2	51/49	45/55
G8 score ≤ 14 / > 14/ NA	68/31/1	70/30/0
Synchronous met Y/N	74/26	71/29
Prior adjuvant CT Y/N	16/84	14/86
Primary tumor side,right,left,rectum	23/46/31	21/44/35
Number of met sites 1,>1	43/57	41/59
Patient with treatment delay Patient with dose reduction	80,4 75	70,3 45,1
AE grade ¾ Leukopenia/Diarrhea/stomatitis,neurotoxicity Fatigue/skin rash/hypomagnesemia	 9,6 /16,3 /9,8 /3,3 6,5/25/3,3	 1,1/1,1/4,4/- 4,4/24,2/7,7

S Ionardi,GONO TRIAL

ASCO 2020:ABSTRACT 4002 PANDA TRIAL

Primary endpoint median PFS



Secondary endpoint ORR

	FOLFOX PANI N=91	5FU/LD PANI N=92
Overall response rate (CR+PR)	65 %	57 %
Disease control rate (CR+PR+SD)	88 %	86 %

PANDA trial met its primary endpoint both in combination and monotherapy arm
Safety profile is in favor of monotherapy arm

S Ionardi,GONO TRIAL

OTHER DATA IN FIRST LINE ELDERLY PATIENT ?

Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial

- **Untreated metastatic CRC aged ≥ 70 years not suitable for combination chemo**
- **Excluded if comorbidities (clinically significant CV disease,remote history of thromboembolic disease,proteinuria or recent anticoagulation;**

Cunningham Lancet Onco 2013

Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial

- **Untreated mCRC not candidate for standard full dose combination chemotherapy**
- **No upper or lower age limit (22 % less than 70 Y)**
- **4 arms (5F/LV vs FOLFOX,cape vs CAPOX) at reduced doses**

Seymour,Lancet Onco 2011

OTHER DATA IN FIRST LINE ELDERLY PATIENT ?

Data with anti EGFR in first line are scarce.

FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial

- **Subgroup analysis presented at ASCO 2019**
- **Age > 70 years and right or left side**
- **Fit patient**

Heinnemann, ASCO 2019, ABST 3541

OTHER DATA IN FIRST LINE ELDERLY PATIENT ?

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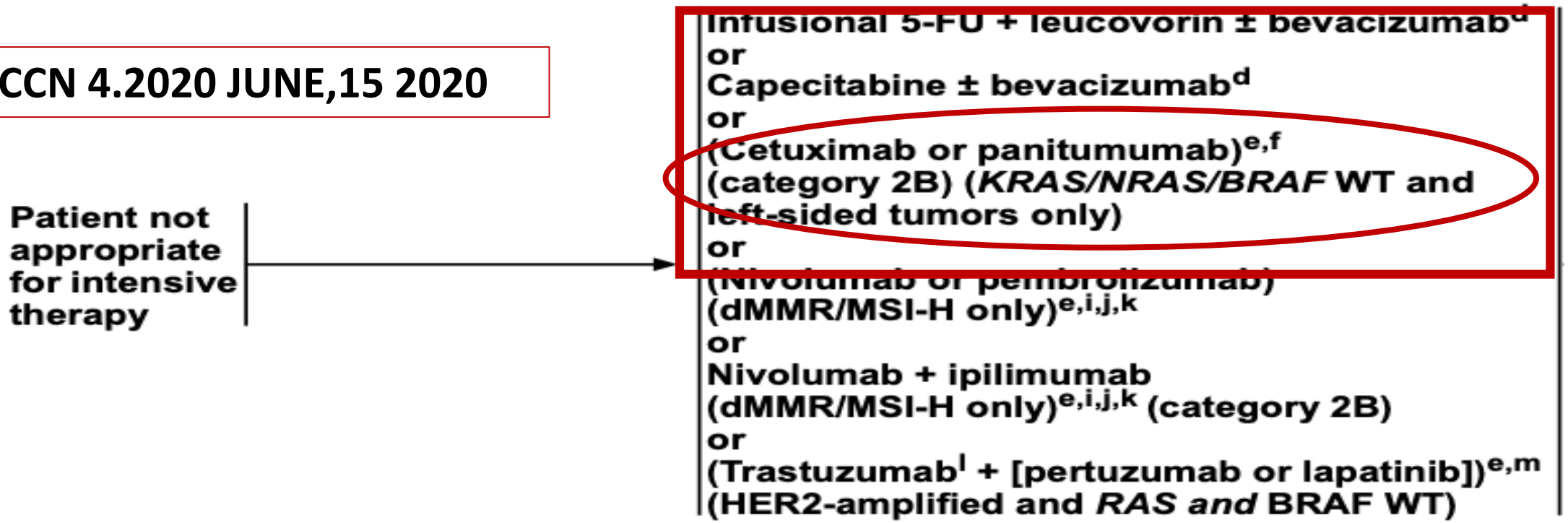
trials	PANDA FOLFOX+ PANI N=91	PANDA 5FU/LV+PANI N=92	FOCUS 2 5FU/LV N=115	FOCUS 2 5FU/OXALI N=115	AVEX CAPE+BEV N+140	AVEX CAPE N+140	FIRE 3 RAS WT > 70 Right-side N=31 FOLFIRI BEV N=16 FOFIRI CET N=15	FIRE 3 RAS WT > 70 Left-Side N=80 FOLFIRI BEV N=34 FOFIRI CET N=46
mPFS	9,6 mo	9,1 mo	3,5 mo	5,8 mo	9,1 mo	5,1 mo	8,6 mo 7,1 mo	10,7 10,2
mOS	Immature	immature	10,1	10,7	20,7	16,8	23,7 14,7	26,1 30,6
ORR	65 %	57 %	11 %	38 %	19 %	10 %	46,2 % 66,7 %	67,9 % 73,8 %

PANDA trial:practice changing ??

NCCN 4.2020 JUNE,15 2020



PANDA trial

Not comparative trial but showed increased toxicity with oxaliplatine with minimal difference in outcome ..

OS and geritric assessment is waiting

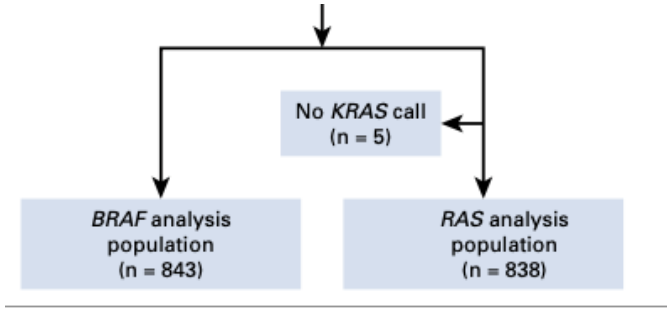
5FU/anti EGFR to be considered in less fit elderly patient and left sided tumor ?

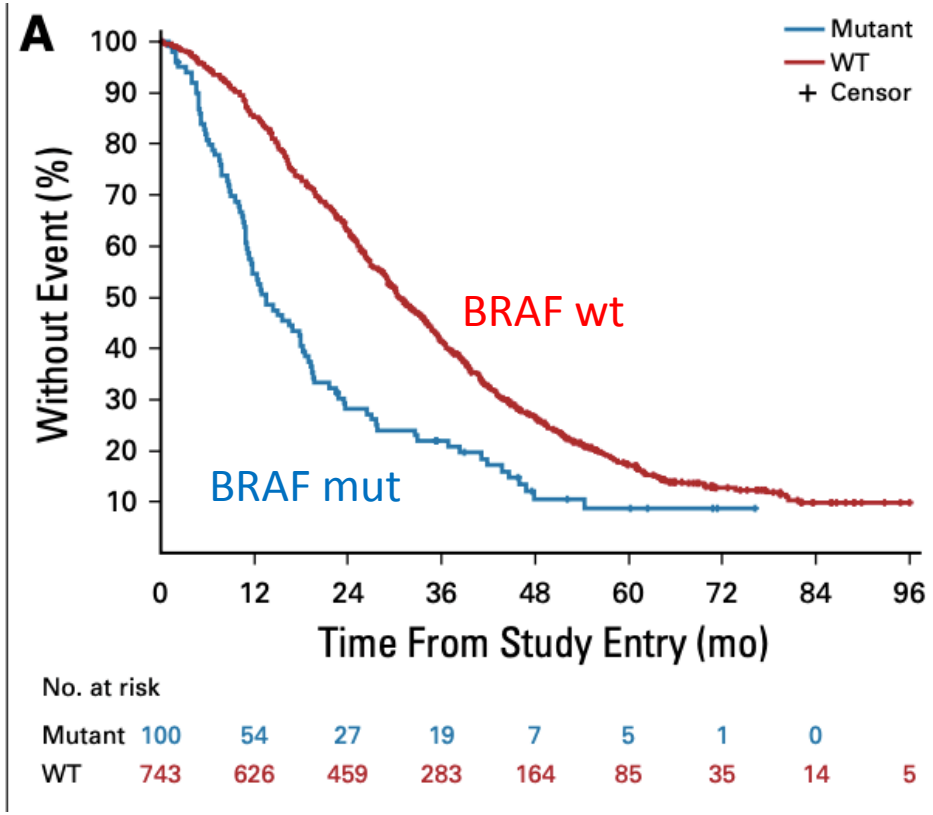
BRAF and CRC

Innocenti,JCO,2019

Trial CALGB/SWOG 80405 (mCRC in first line Chemo+ beva vs chemo +cetuximab): biomarkers study

BRAF population N=843





TRIAL 80405 BRAF analysis N=843	Median OS
BRAF mut N=100 (12 %) 98 % BRAF V600E	13,5 mo
BRAF WT N= 743	30,6 mo

BRAf mut CRC has poor prognosis

BEACON STUDY PHASE 3

ESMO 2019 Median FU for all patients 7,8 months
ASCO 2020 Median FU for all patients 12,5 months

N=615

B-RAF V600E mCRC after 1 or 2 prior regimen,
ECOG ps 0-1
No prior treatment with RAF/MEK or EGFR inhibitor

R1:1:1

Triplet therapy
Encorafenib+binimetinib + cetuximab
N=205

Doublet therapy
Encorafenib + cetuximab
N=205

Control arm
FOLFIRI+ cetuximab or irinitecan + cetuximab
N=205

PRIMARY ENDPOINTS:
- **TRIPLET VS CONTROL**
- **OS (ALL PATIENTS)**
- **ORR BLINDED CENTRAL REVIEW (FIRST 331 PTS)**

SECONDARY ENDPOINTS:
- **DOUBLET VS CONTROL**
- **TRIPLET VS DOUBLET**
- **OS,ORR,PFS,SAFETY**

Stratification:
ECOG PS 0 vs 1
Prior use of irinotecan yes vs no
Cetuximab source:US-licenced vs EU approved

Median follow-up time for OS for all patients was 7.8 months
Median follow-up time for OS for the 1st 331 randomized patients was 12.5 months

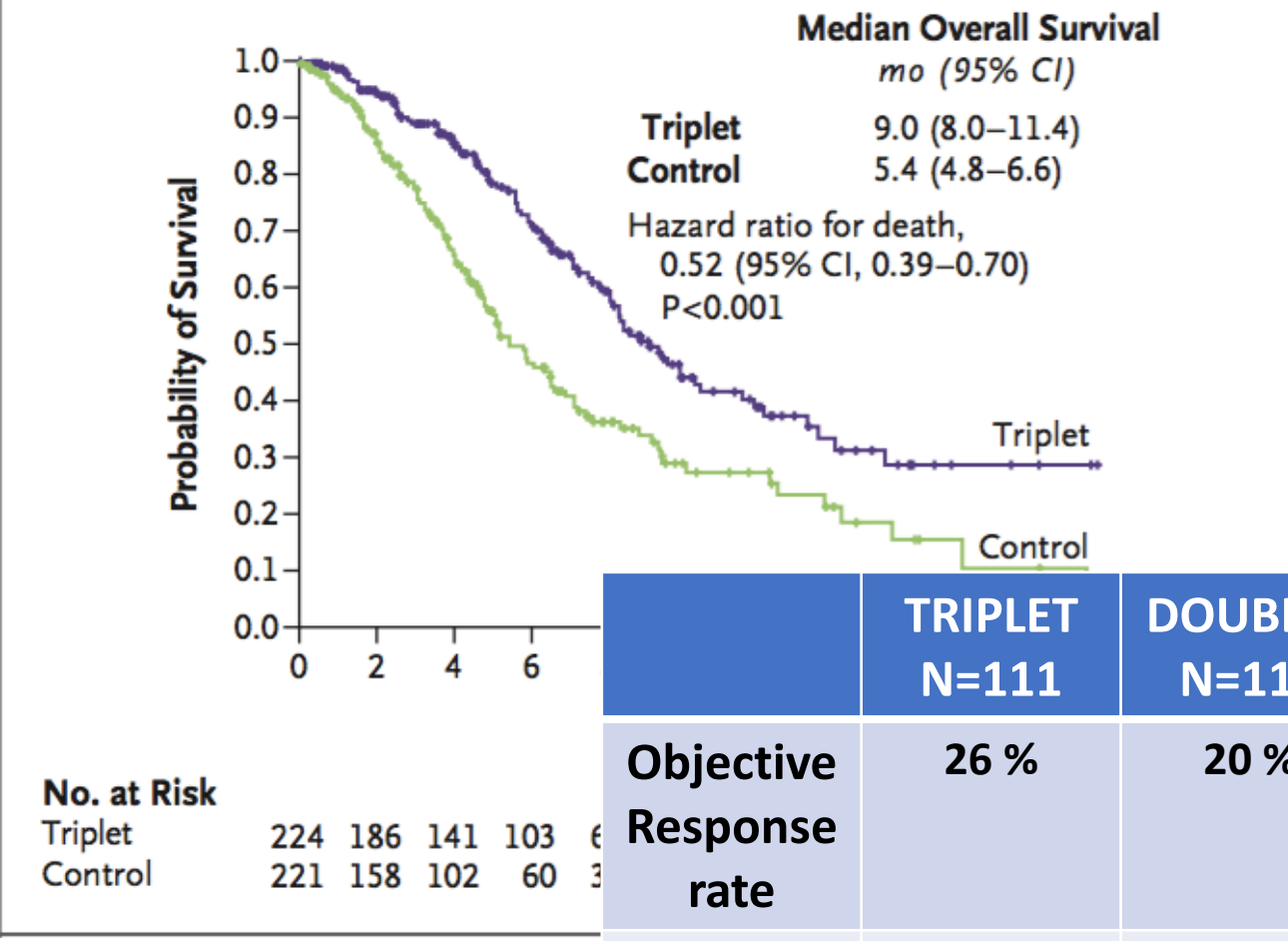
TABERNO,ESMO 2019,LBA32

BEACON STUDY

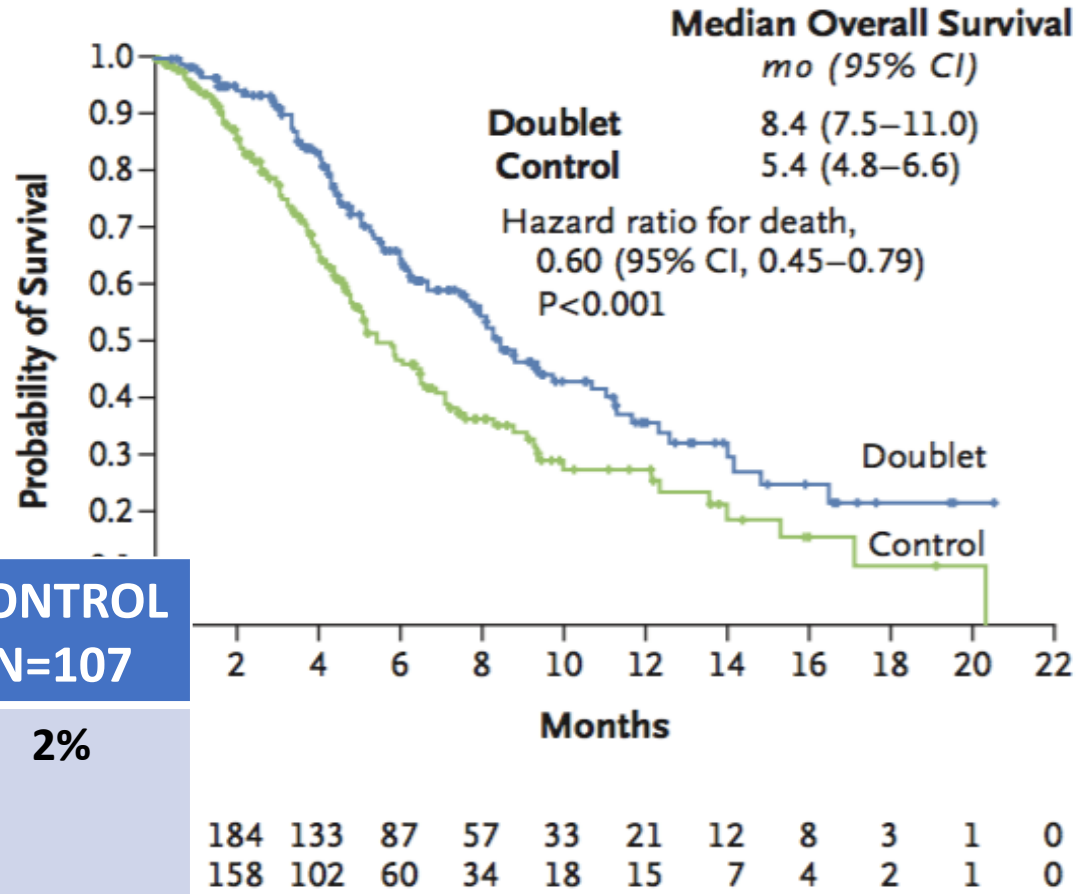
PRIMARY ENDPOINT (A) WAS MET;ALSO SECONDARY (B,ORR)

ESMO GI 2019
NEJM SEP 2019

A Overall Survival, Triplet Regimen vs. Control



B Overall Survival, Doublet Regimen vs. Control



	TRIPLET N=111	DOUBLET N=113	CONTROL N=107
Objective Response rate	26 %	20 %	2%
P-value vs control	<0,0001	<0,0001	<1,7

TABERNO,ESMO 2019,LBA32

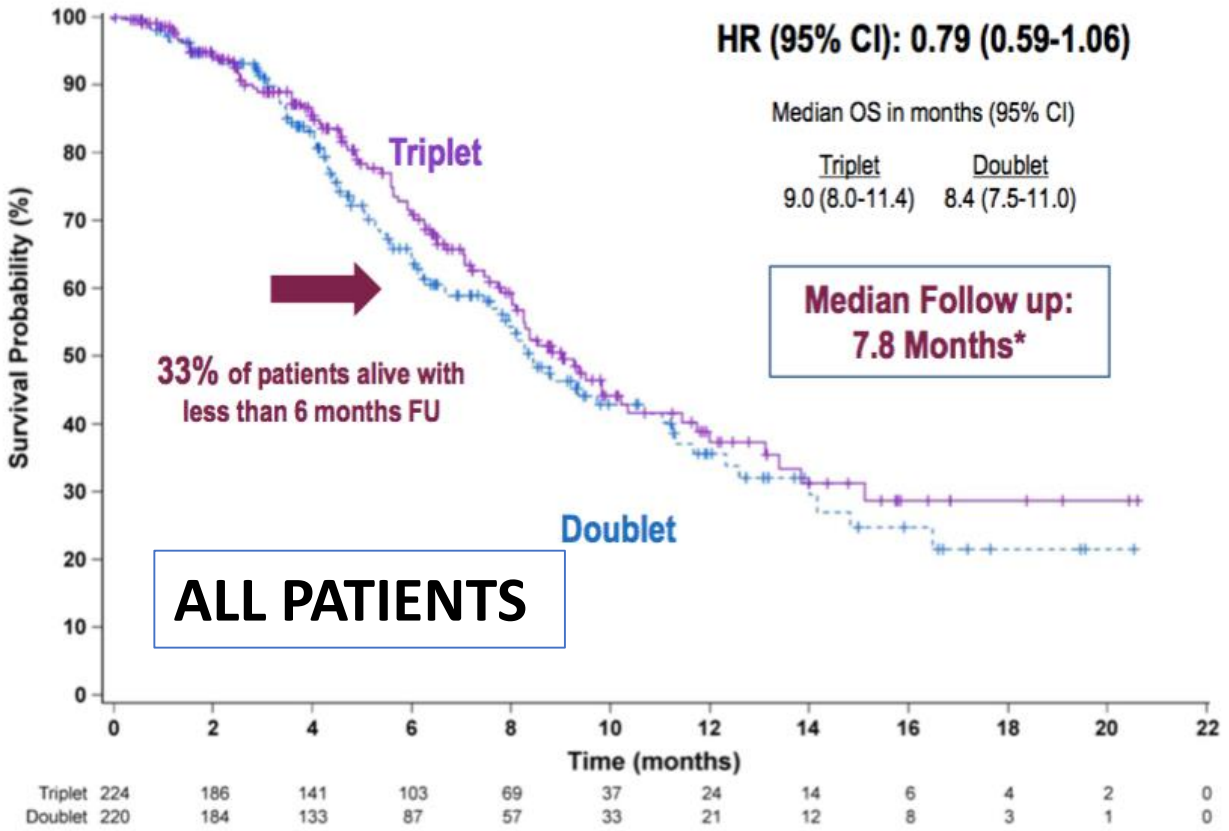
BEACON STUDY

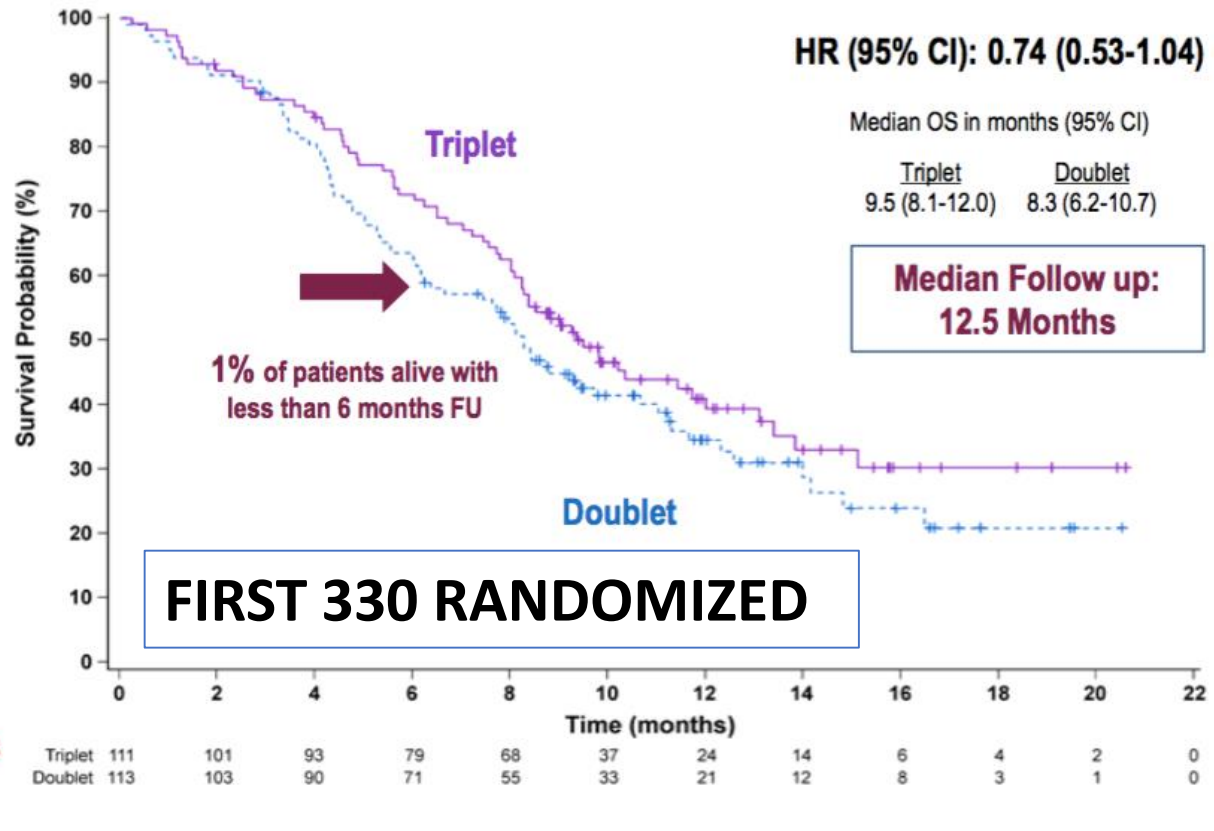
ESMO GI 2019
NEJM SEP 2019

OS: TRIPLET VS DOUBLET

Triplet vs Doublet efficacy analysis was prospectively defined (not formally powered)

TABERNO,ESMO 2019,LBA32



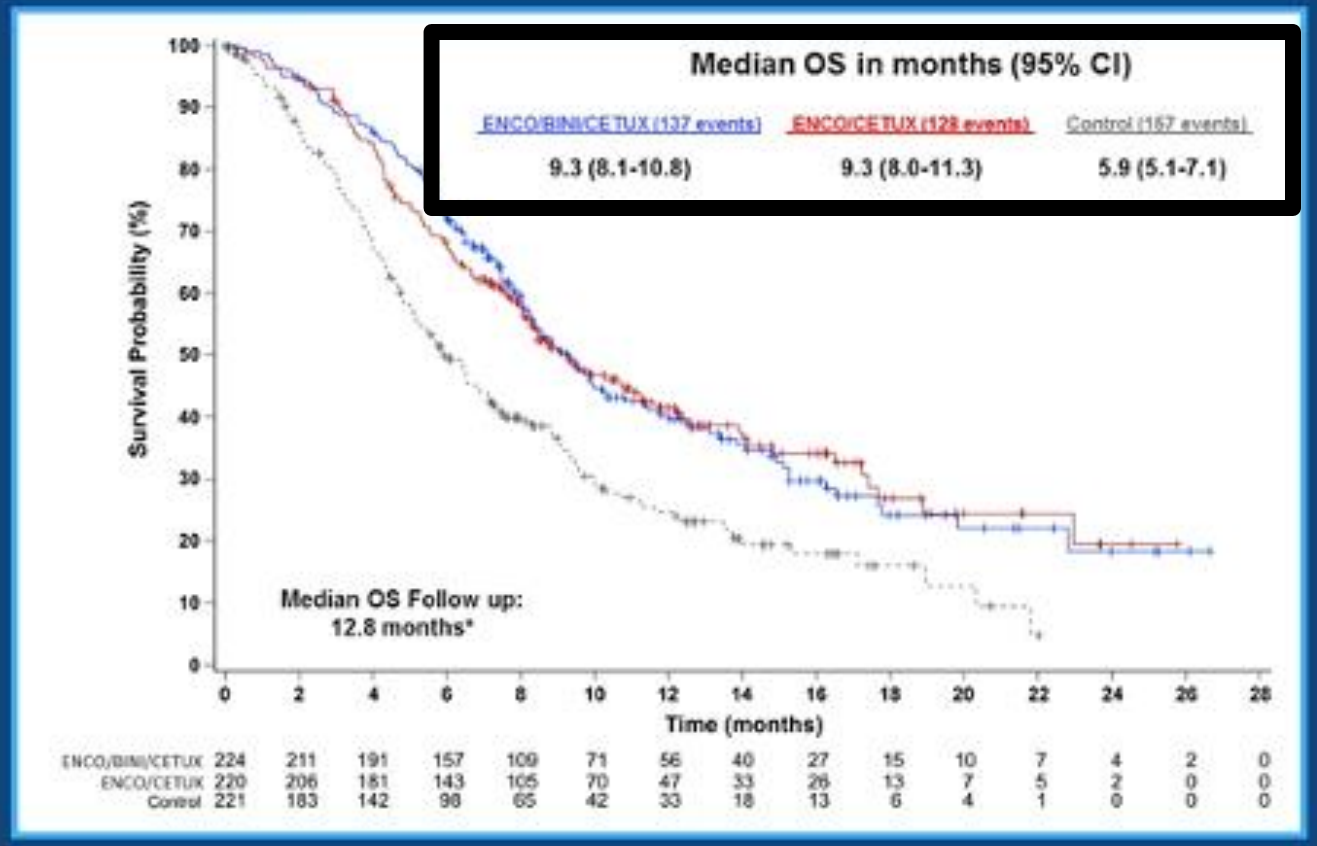


BEACON STUDY

KOPETZ,ASCO 2020 ORAL SESSION

MEDIAN FU TIME FOR OS FOR ALL PATIENTS=12,8 MONTHS

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



BEACON STUDY

KOPETZ,ASCO 2020 ORAL SESSION

Updated Grade ≥3 Adverse Events and Laboratory Abnormalities*

Consistent with previously r[illegible] 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%

Doublet therapy was well tolerated and allow maintenance of high dose intensity

*Occurring in at least 2% of patients in either ENCO/BINI/CETUX or ENCO/CETUX arms

†Kopetz et al. N Engl J M[illegible] 2019; 381:1632-1643

**Selected laboratory abnormalities associated with adverse events

PRACTICE CHANGING

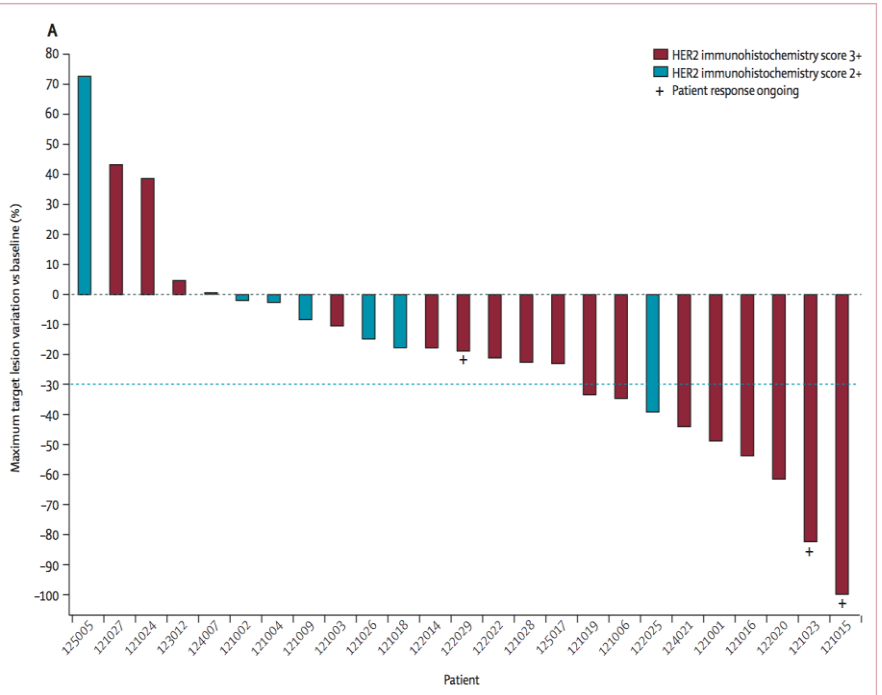
In 2+ lines BRAF V600E mutated mCRC,new standard= doublet therapy with cetuximab and encorafenib
Trials in progress in first line (ANCHOR-CRC)

FDA 8/4/2020
EMEA 3/6/2020

Background: HER2 POSITIVE CHEMOREFRACTORY CRC

3 % ALL CRC
5-10 % RAS WT CRC

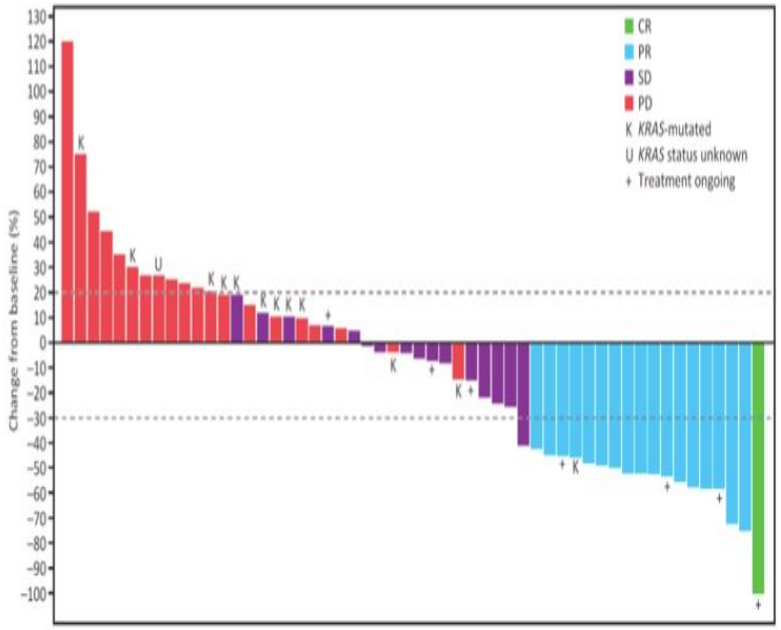
HERACLES TRIAL

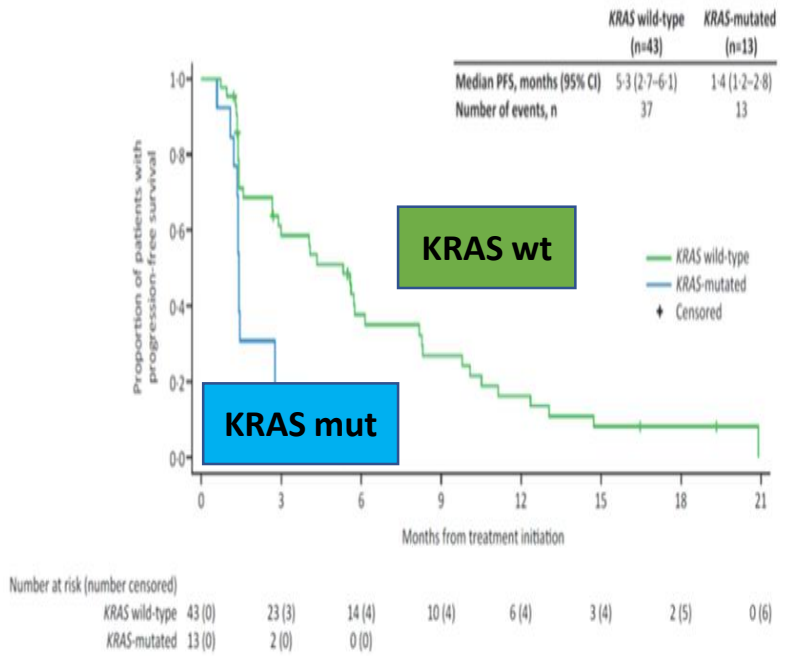


mCRC > 3 LINES
Trastuzumab+lapatinib
Sreened 914 pts KRAS exon 2 WT 5 %
HER2+ (IMMUNO and FISH)
N=48
ORR 30 %
Median duration of response:8,7 mo

SARTORE-BIANCHI,LANCET ONCO,2016

MYPATHWAY





Median of 4 prior lines
Trastuzumab+Pertuzumab
N=57
ORR 40 % in KRAS wt (8 % in KRAS mut)
Median duration of response: 6,1 mo
Median PFS 5,3 (1,4 in KRAS mut

MERIC-BERNSTAM,LANCET ONCO,2019

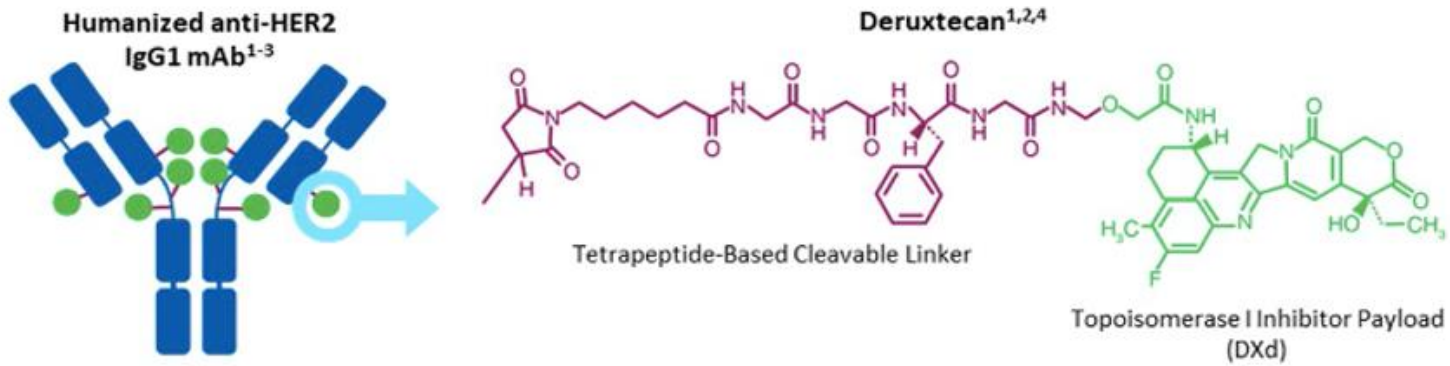
ASCO 2020:ABSTRACT 4000: DESTINY-CRC01

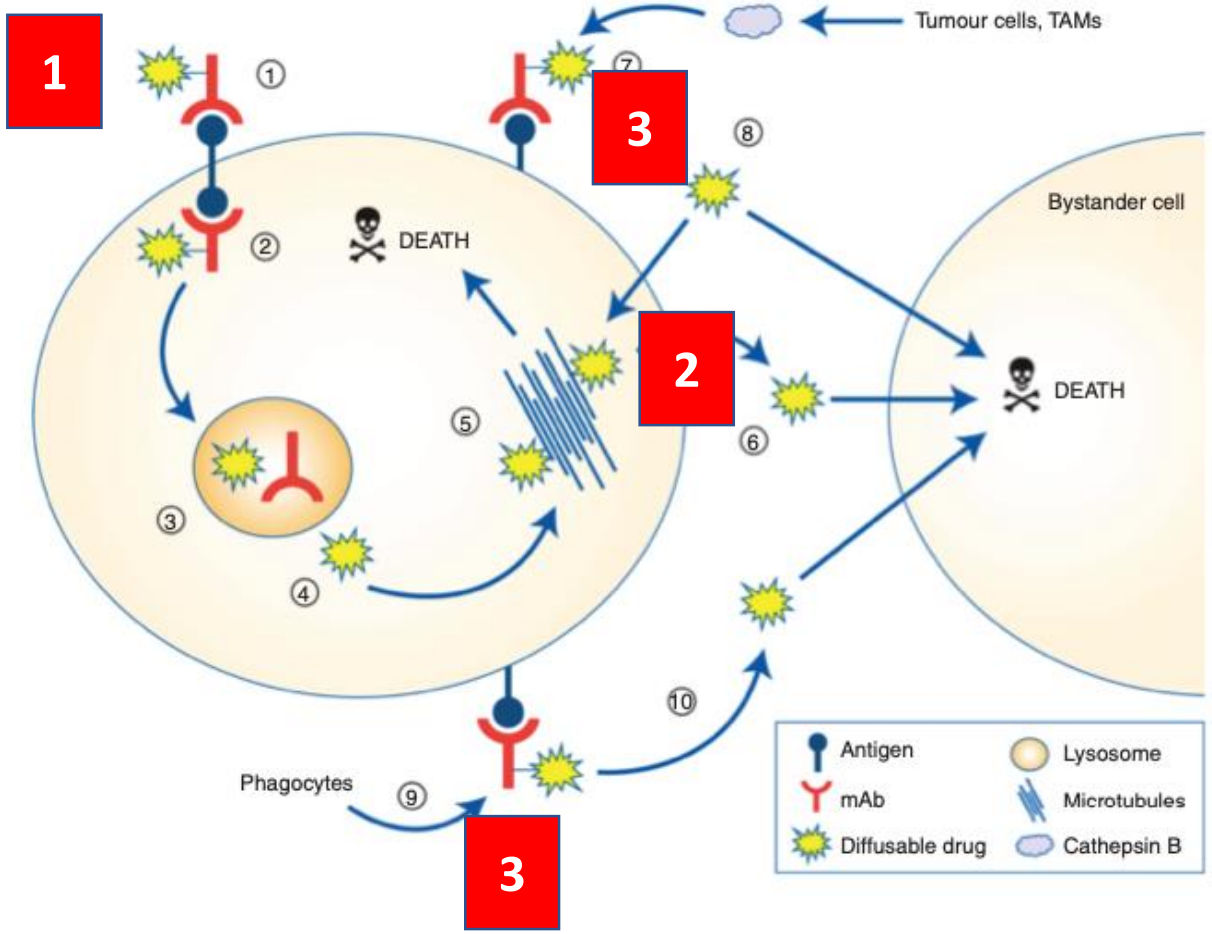
A Phase 2, Multicenter, Open-Label Study of Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients With HER2-Expressing Metastatic Colorectal Cancer: DESTINY-CRC01

Salvatore Siena, Maria Di Bartolomeo, Kanwal Raghav, Toshiki Masuishi, Fotios Loupakis, Hisato Kawakami, Kensei Yamaguchi, Tomohiro Nishina, Marwan Fakih, Elena Elez, Javier Rodriguez, Fortunato Ciardiello, Kapil Saxena, Eriko Yamamoto, Emarjola Bako, Yasuyuki Okuda, Javad Shahidi, Axel Grothey, Takayuki Yoshino

S Sienna,ASCO 2020,,Abst 4000

Antibody drug conjugate (ADC)





- Topoisomerase inhibitor active after internalisation (1)
- High drug to antibody ratio:8
- Tumor selective Cleavable linkers
- Membrane-permeable payload (2) allows for bystander effect
  - → Drug may kill AG positive target cell but also surrounding Ag negative cells
  - → Internalisation not necessary
  - → Alternative route:cleavage by extracellular enzyme (3°

Staudacher,BJC,2017

ASCO 2020:ABSTRACT 4000: DESTINY-CRC01

Keys eligibility criteria

- Unresectable and/or mCRC
- HER2 expressing
- RAS/BRAF WT
- ≥2 prior regimens
- Prior anti HER2 treatment allowed
- Excluded patients with a history of/or current/suspected interstitial lung disease

T-DX 6,4 mg/Kg / 3 W (approved in Breast at 5,4 mg/Kg)

Cohort A (N= 53) HER2 positive (IHC3+ or IHC 2+/ISH +)

A futility monitoring was done after ≥ 20 patients in cohort A had 12 weeks FU to open 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 in cohort A

Data cutoff : 9 augustus 2019

- 38,5 %remained on treatment
- 61,5 % discontinued for profressive disease and clinical progression

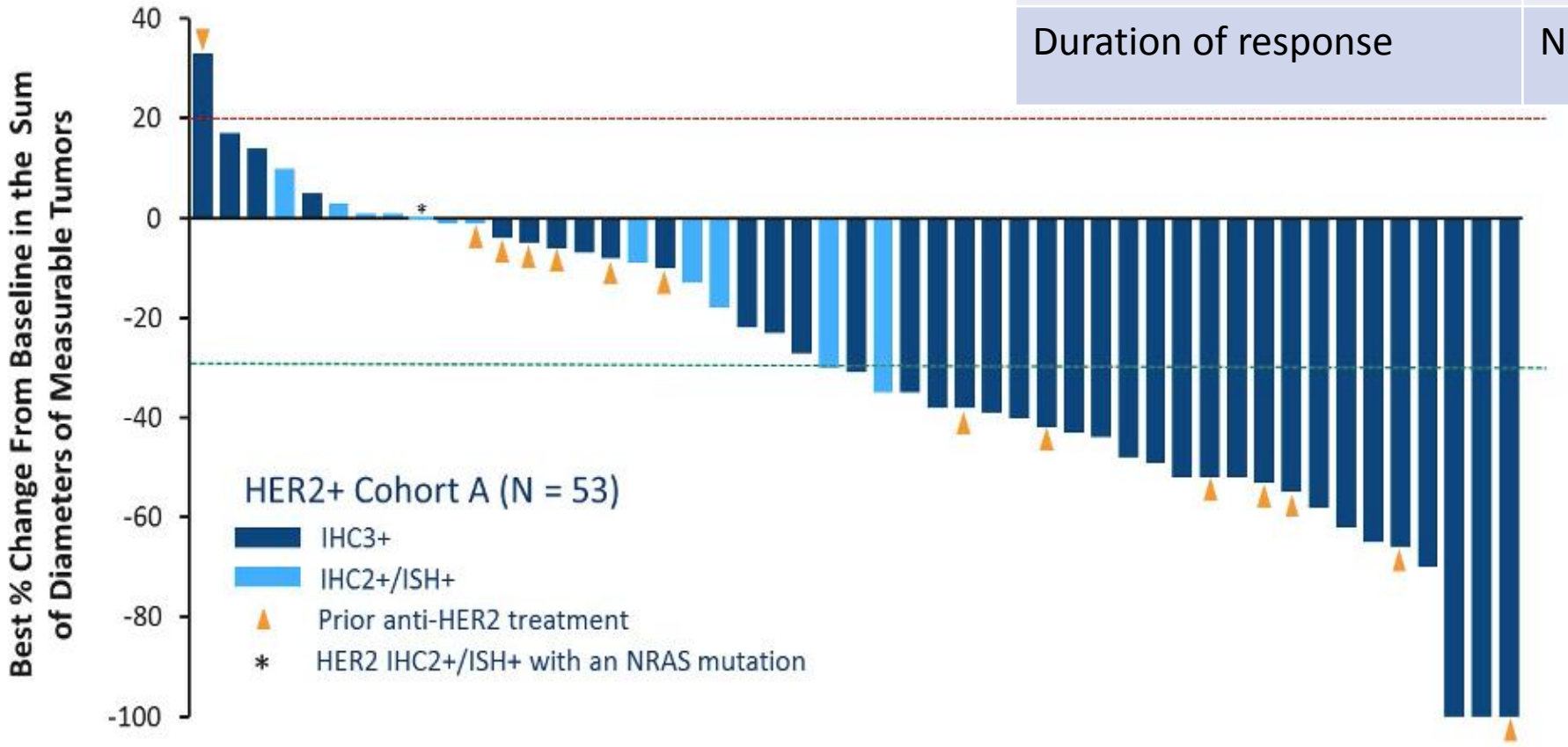
S Sienna,ASCO 2020,,Abst 4000C

ASCO 2020:ABSTRACT 4000: DESTINY-CRC01

cohorts	HER2 cohort A N=53	All patients N=78
Median age,years	57 (27-79)	58,5 (27-79)
Female ,%	52,8	47,4
Europe/Asia/North Amrica %	52,8/28,3/18,9	52,6/32,1/15,4
ECOG PS 0/1/2 %	69,8/30,2/0	62,8/35,9/1,3
Primary tumor site left/right %	88,7/11,3 %	89,7/10?3
Microsatellite stable/unknown %	81,1/18,9	79,5/20,5
RAS WT %	98,1	98,7
BRAF wt %	100	98,7
HER2 IHC 3+/IHC 2+;ISH+ HER2 IHC 2+/IHC 1+	75,5/24 5 0/0	51,3/16,7 25,6/23,1
Prior treatment % Irinotecan/oxaliplatin FU/Capecitabine Cetuximab or panitumumab Bevacizumab Prior anti HER2 agents(Pertu:24,5 %;Trastu:22,6 %;T-DMI:5,7 %;Lapatinib:5,7 %;Tucatinib:1,9 %)	 100/100 100/54,7 100 75,5 30,2	 100/100 98,7/53,8 98,7 79,5 20,5

ASCO 2020:ABSTRACT 4000: DESTINY-CRC01

	HER2+ Cohort A (N=51)
Confirmed ORR by ICR %	45,3 %
Disease control rate	83,0 %
Duration of response	Not reached at 4,2 mo



SAME RESPONSE IF PRIOR HER2 THERAPY
MEDIAN OS NOT REACHED

S Sienna,ASCO 2020,,Abst 4000

DESTINY CRC 01 trial: practice changing ??

Impressive results in heavy pretreated population and seems superior to SOC in such refractory population (all these drugs are expansive in the same range)

	PFS mo	OS mo	ORR %
regorafenib	1,9	6,4	1
TAS-102	2	7,1	1,6
T-DXD	6,9	NR	45,3 %

Toxicity is in line of previous studies in Breast and gastric cancer

Low grade GI and hematologic AE were common

At dosage of 6,4 , Interstitial lung disease: 6,4 % with 2,6 % grade 5

Maybe practice changing…but we need more data
Clinical trial with different dosage

CONCLUSIONS

IN 2020,we need a full testing of biomarkers in mCRC and access to clinical trial .

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New Drug:AMG 510
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ESMO Colloquium:RET inhibition
PRALSETINIB/SELPERCATINIB

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