POST ESMO from Barcelona to Real World

Roma, 2 Dicembre 2019

Nuove Prospettive

COLON - RETTO

Daniele Rossini

Department of Translational Research and New Technologies in Medicine and Surgery

Unit of Medical Oncology 2

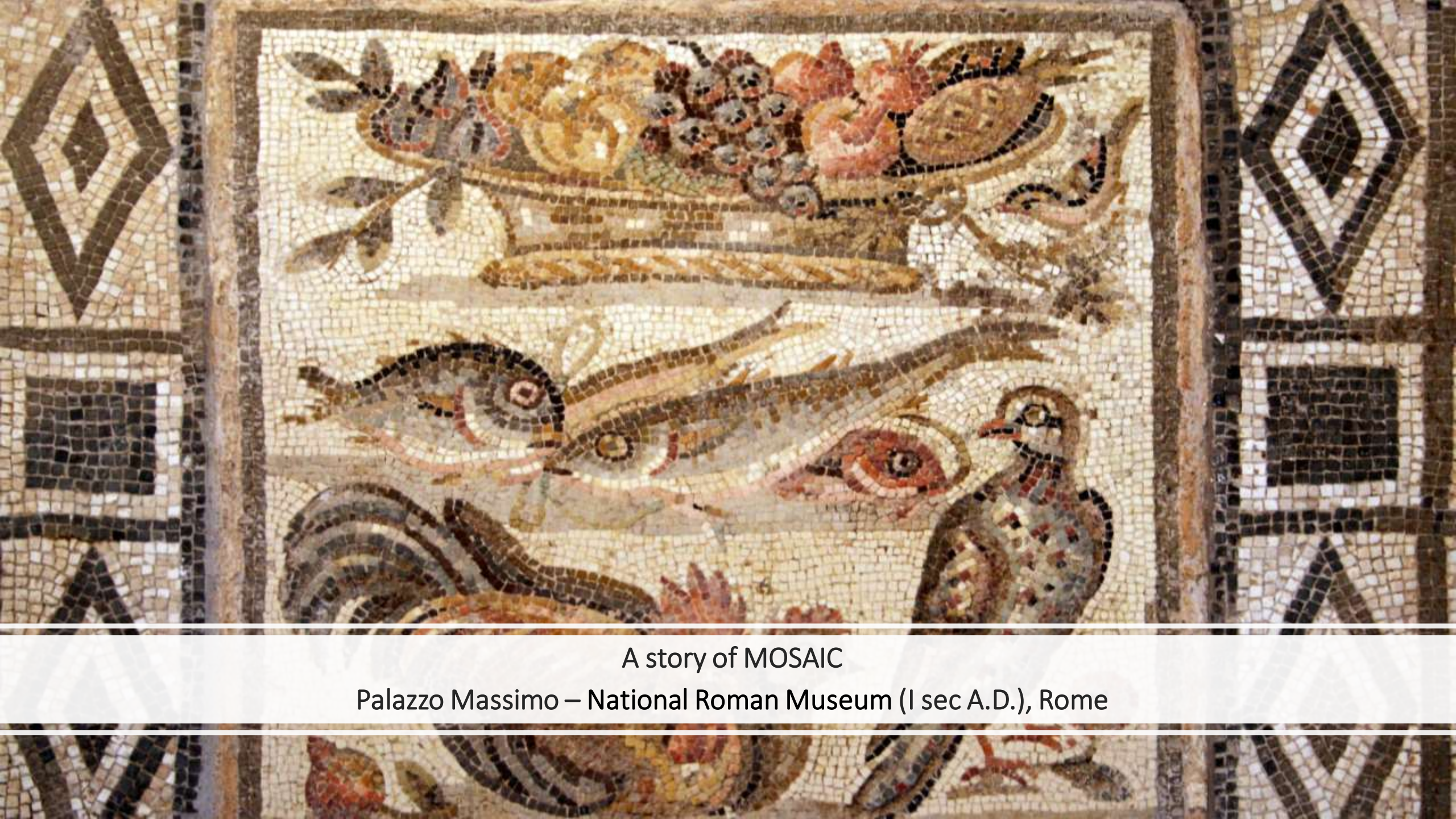
Azienda Ospedaliera Universitaria Pisana

Pisa (Italy)

Conflict of Interest

Honoraria: Takeda Pharmaceutical Co.

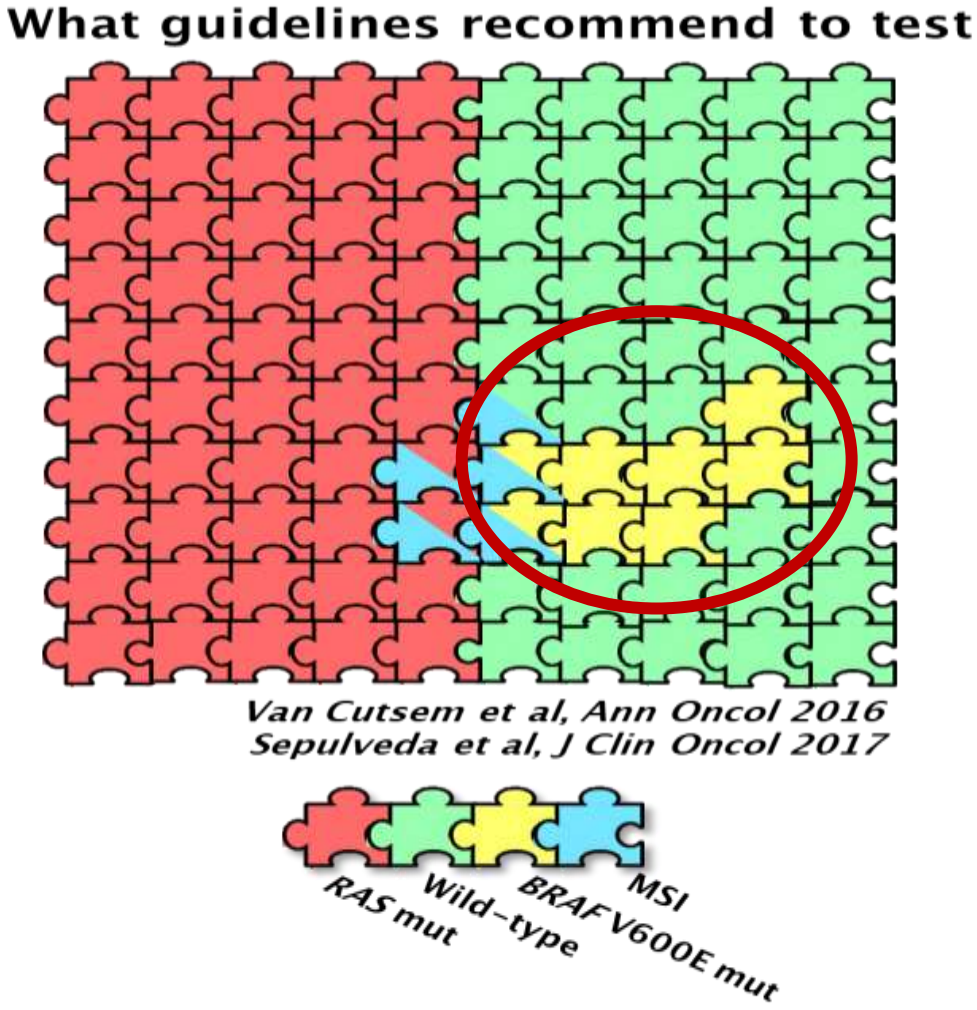
Travel, Accommodations, Expenses: Takeda Pharmaceutical Co.



A story of MOSAIC

Palazzo Massimo – National Roman Museum (I sec A.D.), Rome

Genomic markers in mCRC



- **BRAF V600E occurs in 8-12% of patients with a mCRC**
- **BRAF V600E are associated with resistance to anti-EGFRs**
- **BRAF mutations were observed in 34.6% of patients with MSI tumours, whereas among BRAF-mt tumours 21.2% showed MSI**
- **Patients that are right-sided primary, female and mucinous had an 81% chance to bear a *BRAF V600E*-mutant tumour**

Taieb et al, BJC 2019
Seymur et al, Lancet Oncol 2013
Pietrantonio et al, Eur J Cancer 2015
Venderbosch et al, Clin Cancer Res 2014
Loupakis et al, Bjc 2016

How to target *BRAF?*

BEACON: Study Design

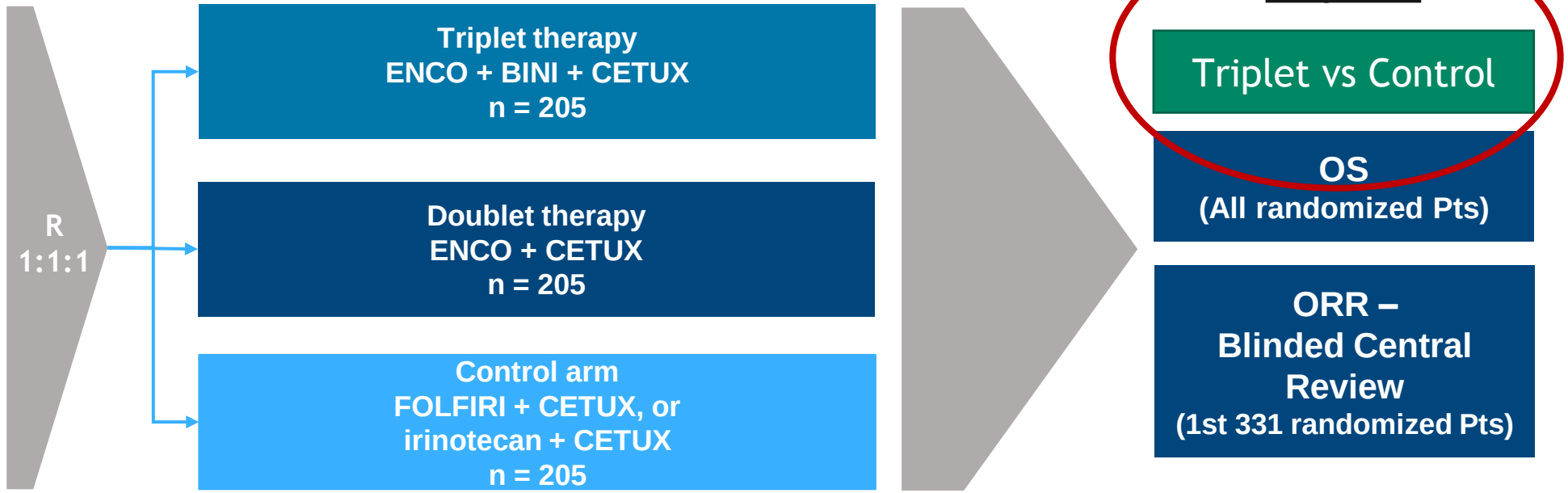
Patients with *BRAF*^{V600E} mCRC with disease progression after 1 or 2 prior regimens; ECOG PS of 0 or 1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor

Safety Lead-in

ENCO + BINI + CETUX
N = 30

Encorafenib 300 mg PO daily
Binimetinib 45 mg PO bid
Cetuximab standard weekly dosing

A separate Safety Lead-in cohort of n=7 in Japan was enrolled subsequently. Results will be reported at a later time.



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

Van Cutsem et al, J Clin Oncol 2019

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

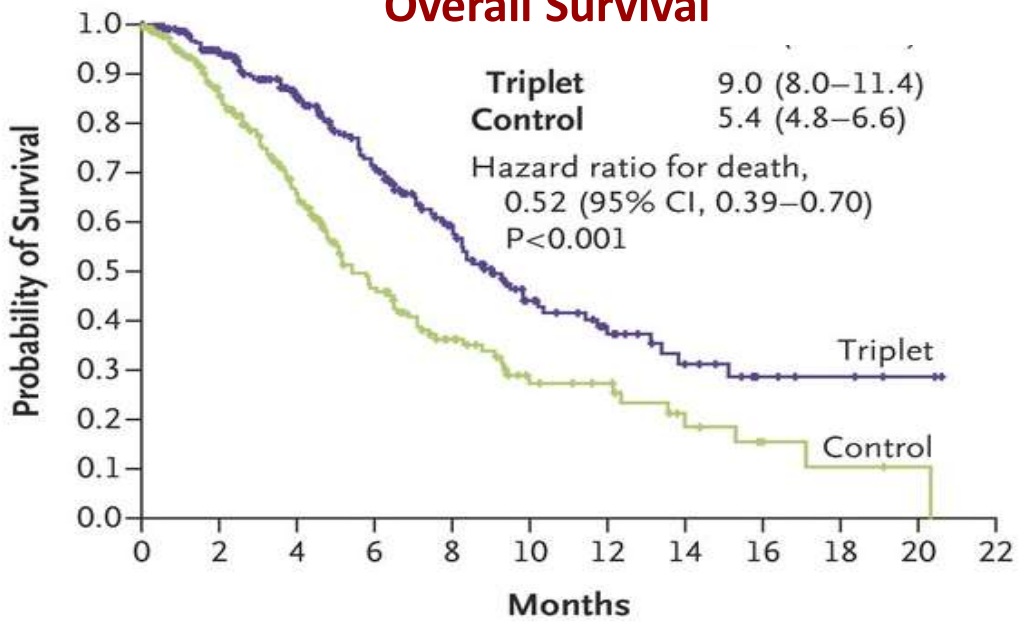
QOL Assessments: EORTC QOL Questionnaire (QLQ C30), Functional Assessment of Cancer Therapy Colon Cancer, EuroQol 5D5L, and Patient Global Impression of Change).

OS analysis conducted in all patients; ORR analysis conducted in the first 331 randomized patients.

BARCELONA 2019 ESMO congress

Results
Triplet vs Control

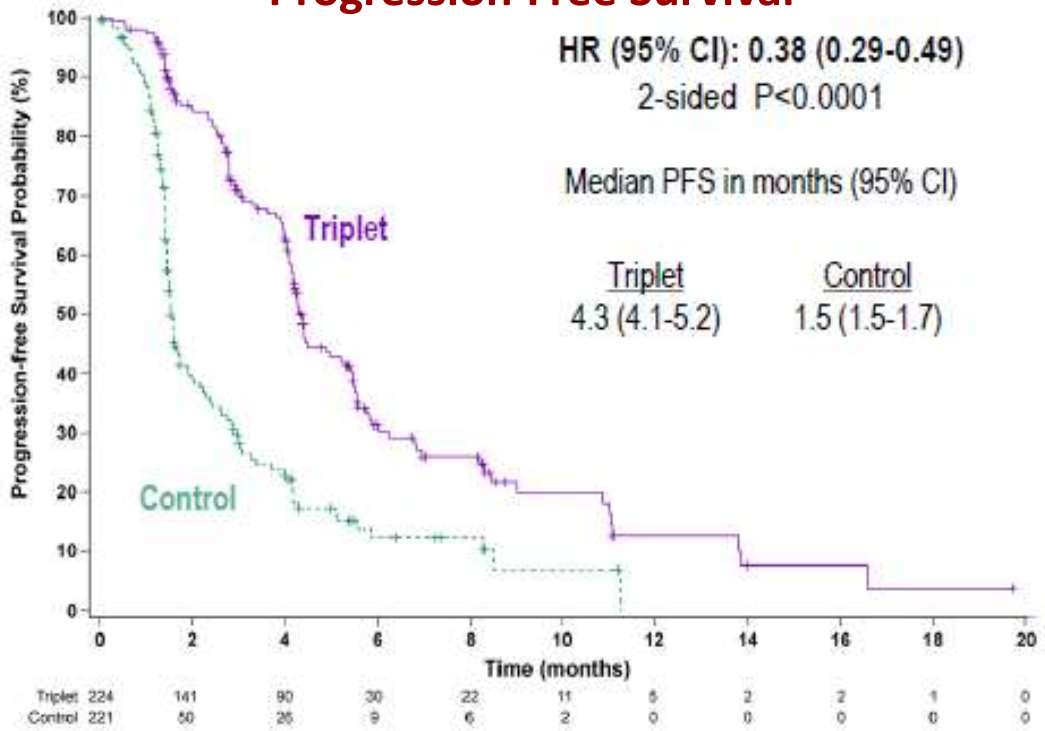
Overall Survival

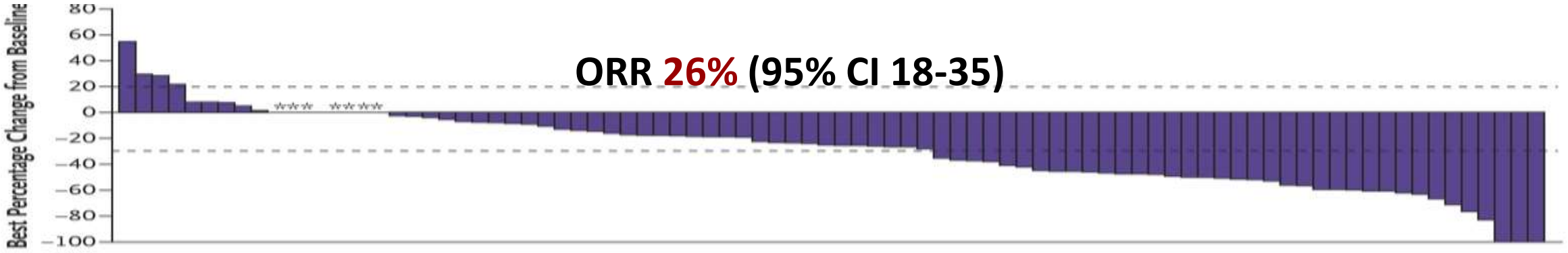


No. at Risk

Triplet	224	186	141	103	69	37	24	14	6	4	2	0
Control	221	158	102	60	34	18	15	7	4	2	1	0

Progression Free Survival



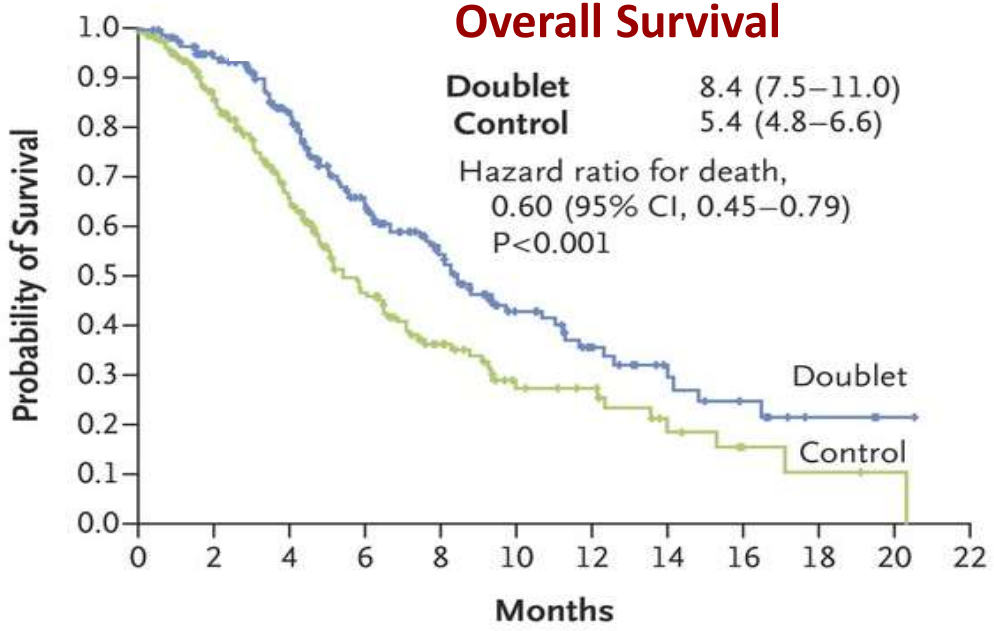


ORR 26% (95% CI 18-35)

Kopetz S. et al, NEJM 2019

Results
Doublet vs Control

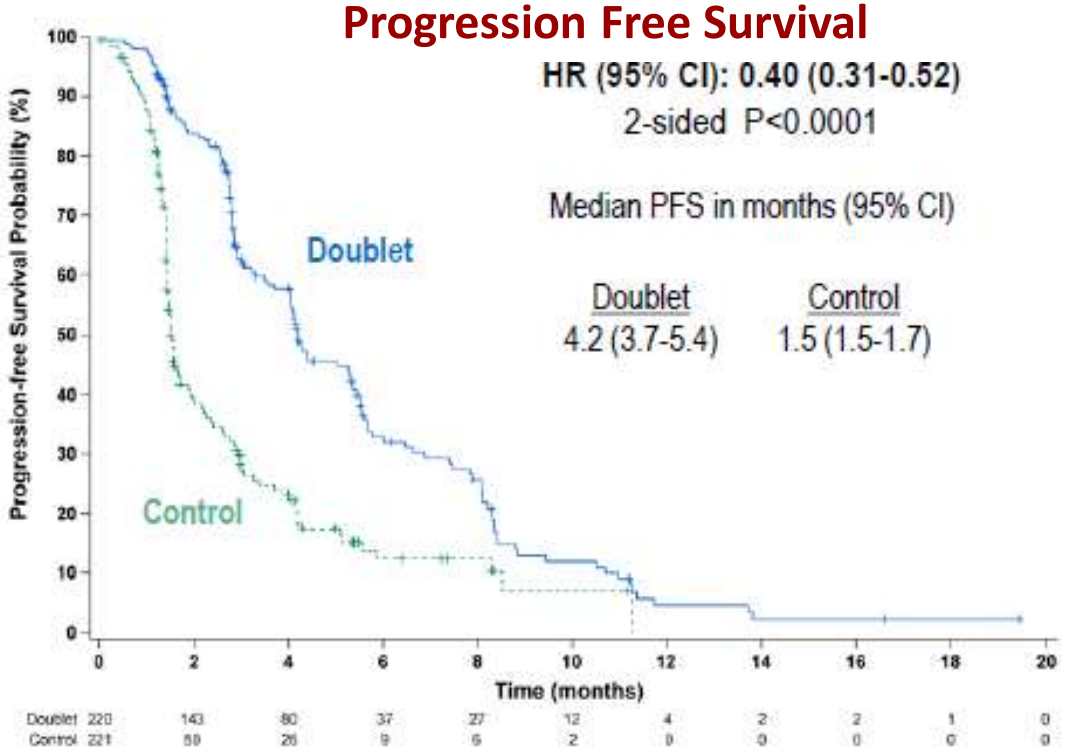
Overall Survival

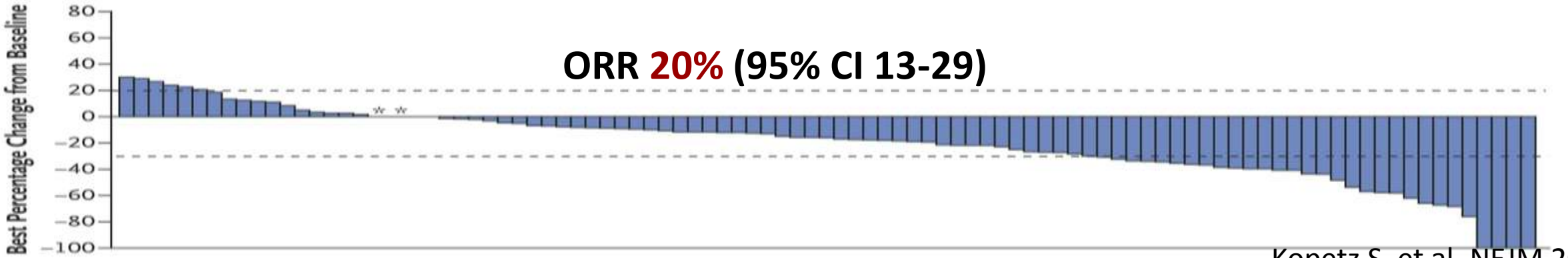


No. at Risk

Doublet	220	184	133	87	57	33	21	12	8	3	1	0
Control	221	158	102	60	34	18	15	7	4	2	1	0

Progression Free Survival





ORR 20% (95% CI 13-29)

Kopetz S. et al, NEJM 2019

Results: ORR
Doublet vs Control

Confirmed Response by BICR	Triplet N=111	Doublet N=113	Control N=107
Objective Response Rate	**26%**	**20%**	**2%**
95% (CI)	(18, 35)	(13, 29)	(<1, 7)
p-value vs. Control	<0.0001	<0.0001	
Objective Response Rate			
1 prior line of therapy	**34%**	**22%**	**2%**
>1 prior line of therapy	14%	16%	2%
Best Overall Response			
Complete Response	4%	5%	0
Partial Response	23%	15%	2%
Stable Disease	42%	54%	29%
Progressive Disease	10%	7%	34%
Non Evaluable by RECIST	22%	19%	36%
Clinical progression or adverse event[a]	14%	17%	16%
Insufficient information to assess response[b]	8%	2%	20%

Tabernero J. et al, ESMO 2019

What's New?

BARCELONA 2019 ESMO congress

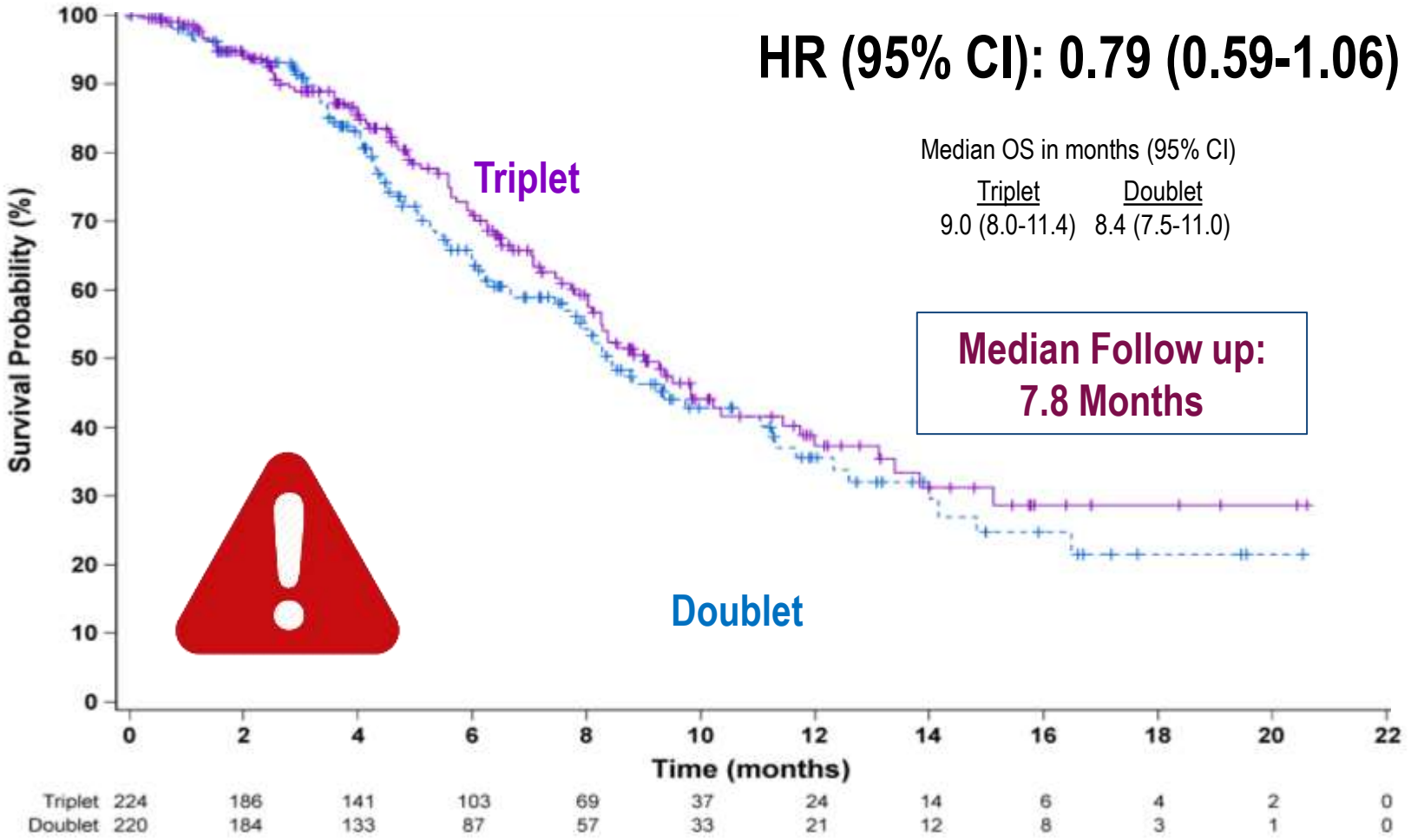
TRIPLET vs DOUBLET

ENCORAFENIB
BINIMETINIB
CETUXIMAB

VS

ENCORAFENIB
CETUXIMAB

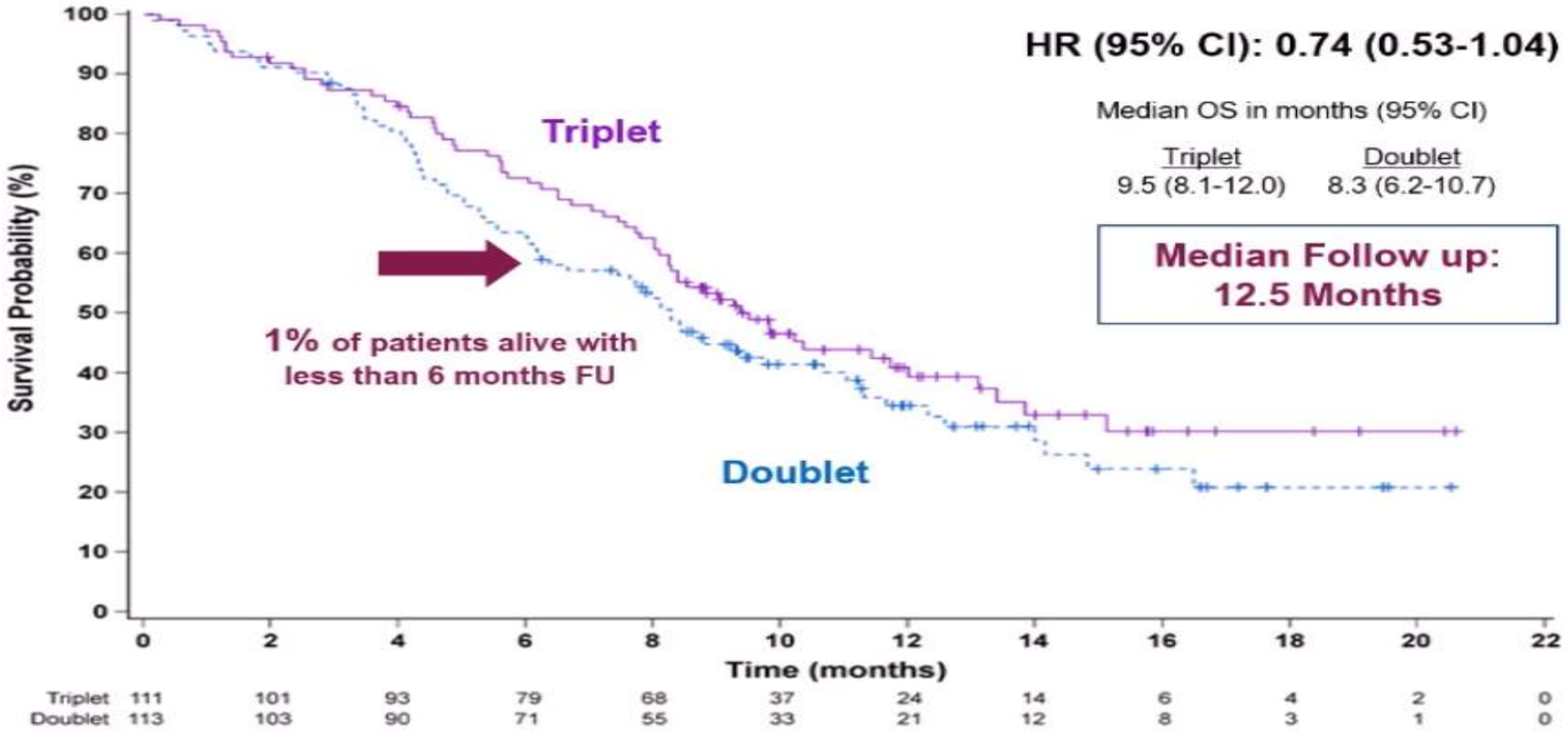
Overall Survival: Triplet vs Doublet (All Randomized Patients)



BARCELONA 2019 ESMO congress

Tabernero J. et al, ESMO 2019

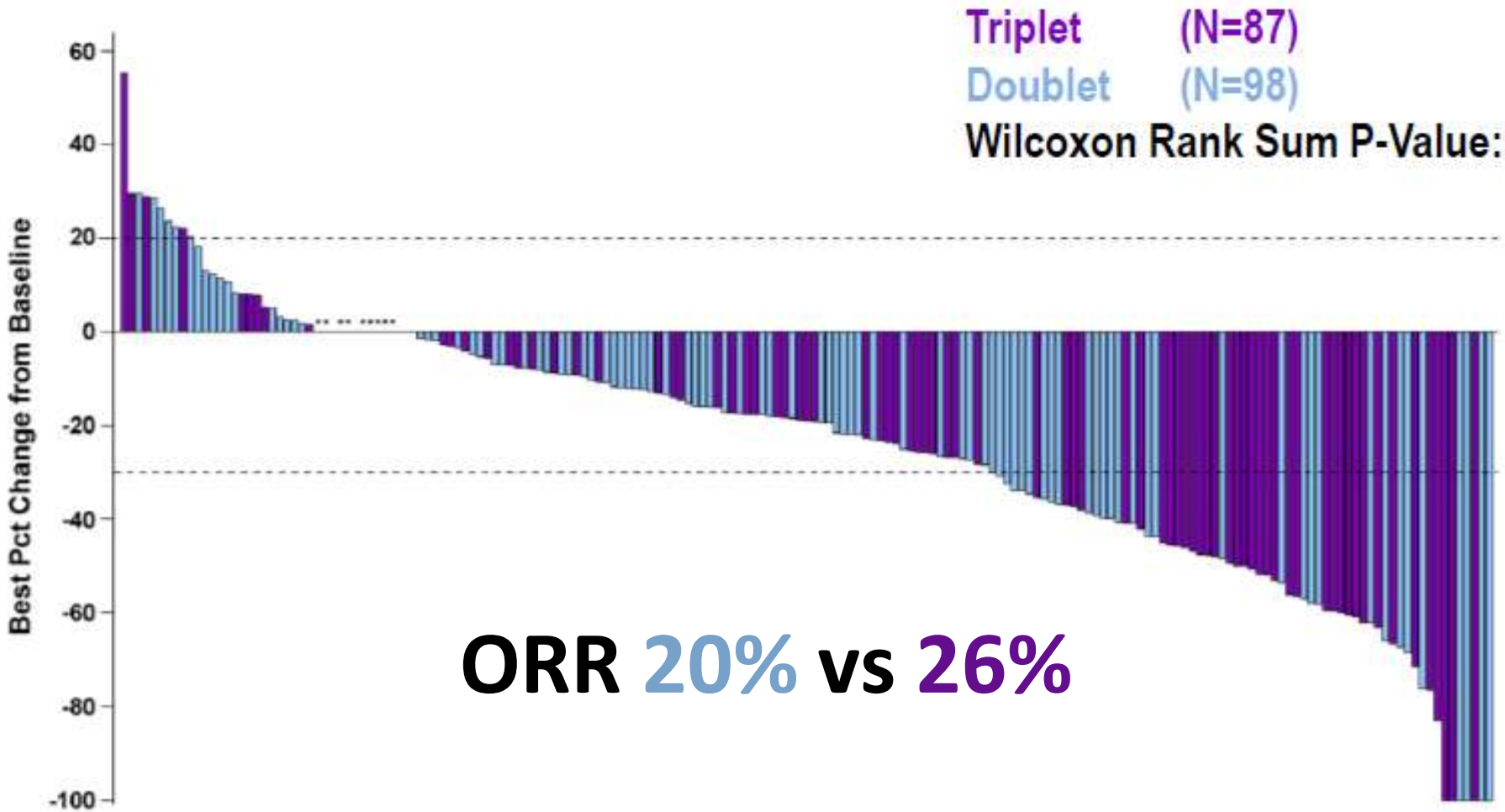
Overall Survival: Triplet vs Doublet



BARCELONA 2019 ESMO congress

Tabernero J. et al, ESMO 2019

Results: RR
Doublet vs Control



ORR 20% vs 26%

Kopetz S. et al, NEJM 2019

Safety Results
Doublet vs Control

Adverse events of grade 3 or higher were observed in 58% of patients in the triplet-therapy group, in 50% in the doublet-therapy group, and in 61% in the control group.

Preferred Term	ENCO + BINI + CETUX N = 222		ENCO + CETUX N = 216		Difference in Percent Incidence (All Grades) (%)
	All Grades n (%)	Grade 3+ n (%)	All Grades n (%)	Grade 3+ n (%)	
Diarrhea	137 (62)	22 (10)	72 (33)	4 (2)	28
Anemia	80 (36)	37 (17)	35 (16)	10 (5)	20
Dermatitis acneiform	108 (49)	5 (2)	63 (29)	1 (<1)	19
Vomiting	85 (38)	9 (4)	46 (21)	3 (1)	17
Nausea	100 (45)	10 (4)	74 (34)	1 (<1)	11
Dry skin	46 (21)	2 (1)	24 (11)	0	10
Constipation	55 (25)	0	33 (15)	0	9
Blood CK increased	20 (9)	8 (4)	1 (<1)	0	8
Stomatitis	31 (14)	1 (<1)	12 (6)	0	8
PPE syndrome	28 (13)	0	9 (4)	1 (<1)	8
Vision blurred	25 (11)	0	8 (4)	0	8
Rash	42 (19)	1 (<1)	25 (12)	0	7
Abdominal pain	65 (29)	13 (6)	49 (23)	5 (2)	7
Muscle spasms	17 (8)	1 (<1)	3 (2)	0	6
Blood creatinine increased	18 (8)	5 (2)	4 (2)	1 (<1)	6

Abbreviations: BINI = binimetinib; CETUX = cetuximab; CK = creatine phosphokinase; ENCO = encorafenib; PPE = palmar-plantar erythrodysesthesia;
Preferred terms are presented by descending order of difference in percent incidence between the Randomized Phase 3 ENCO+BINI+CETUX and the ENCO+CETUX all-grades column.

Tabernero J. et al, ESMO 2019

Safety Results
Doublet vs Control

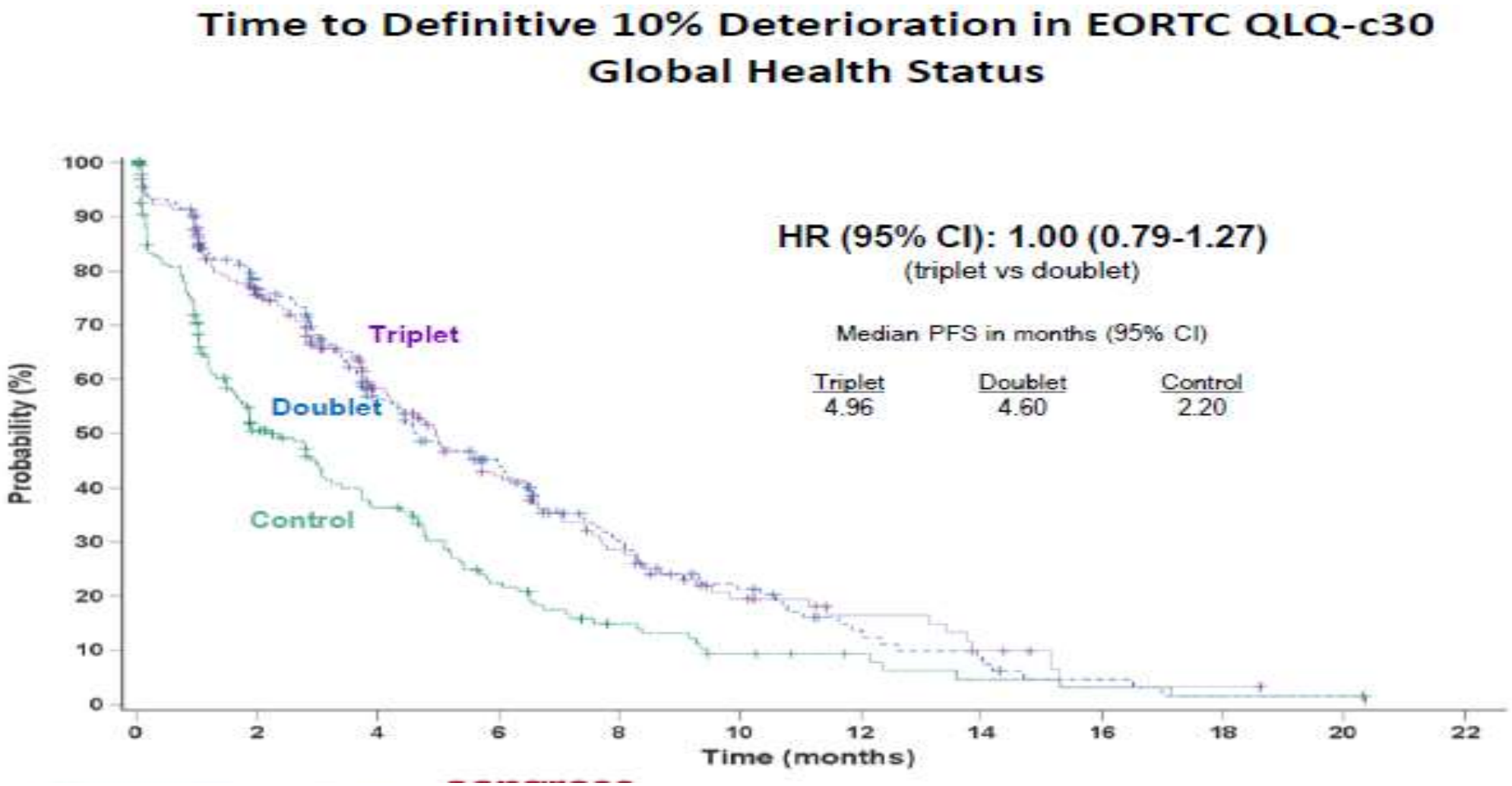
Preferred Term	ENCO + BINI + CETUX N = 222		ENCO + CETUX N = 216		Difference in Percent Incidence (All Grades) (%)
	All Grades n (%)	Grade 3+ n (%)	All Grades n (%)	Grade 3+ n (%)	
Skin papilloma	0	0	11 (5)	0	-5
Myalgia	18 (8)	0	29 (13)	1 (<1)	-5
Insomnia	11 (5)	0	24 (11)	0	-6
Skin hyperpigmentation	1 (<1)	0	16 (7)	0	-7
Infusion related reaction	5 (2)	1 (<1)	20 (9)	2 (1)	-7
Skin lesion	1 (<1)	0	17 (8)	0	-7
Arthralgia	23 (10)	0	41 (19)	2 (1)	-9
Musculoskeletal pain	6 (3)	0	27 (12)	0	-10
Headache	16 (7)	0	42 (19)	0	-12
Melanocytic naevus	1 (0)	0	31 (14)	0	-14

Abbreviations: BINI = binimetinib; CETUX = cetuximab; CK = creatine phosphokinase; ENCO = encorafenib; PPE = palmar-plantar erythrodysesthesia;

Preferred terms are presented by descending order of difference in percent incidence between the Randomized Phase 3 ENCO+BINI+CETUX and the ENCO+ CETUX all-grades column.

Tabernero J. et al, ESMO 2019

Safety Results
Doublet vs Control



Recapping & Consideration

- Data suggest that the Triplet (Encorafenib+Binimetinib+Cetuximab) vs the Doublet (Encorafenib+Cetuximab) has some improved efficacy with a modest increase in toxicity and no detrimental effect in QoL
- The Triplet will become the new standard in previously treated mCRC $BRAF^{V600E}$ mut pts
- Probably we need a deeper insight on:
  - MSI-H Pts
  - BM1 and BM2

ANYWAY

The «story» of BEACON represents a good example of

«bench to bedside»

BRAF inhibition in first-line or with immunotherapy

Study	Phase	N pts	Line of therapy	Microsatellite status	Drugs	Primary endpoint	Country
NCT03693170 Anchor-CRC	II	90	previously untreated	unselected	**Encorafenib Binimetinib Cetuximab**	ORR	
NCT03668431	II	25	previously untreated and treated	unselected	**Dabrafenib Trametinib Spartalizumab***	ORR and safety	
NCT04017650	I/II	38	previously treated (at least one therapy before)	MSS/pMMR	**Encorafenib Cetuximab Nivolumab**	ORR and safety	
NCT04044430	I/II	38	previously treated (at least one therapy before)	MSS/pMMR	**Encorafenib Binimetinib Nivolumab**	ORR and safety	

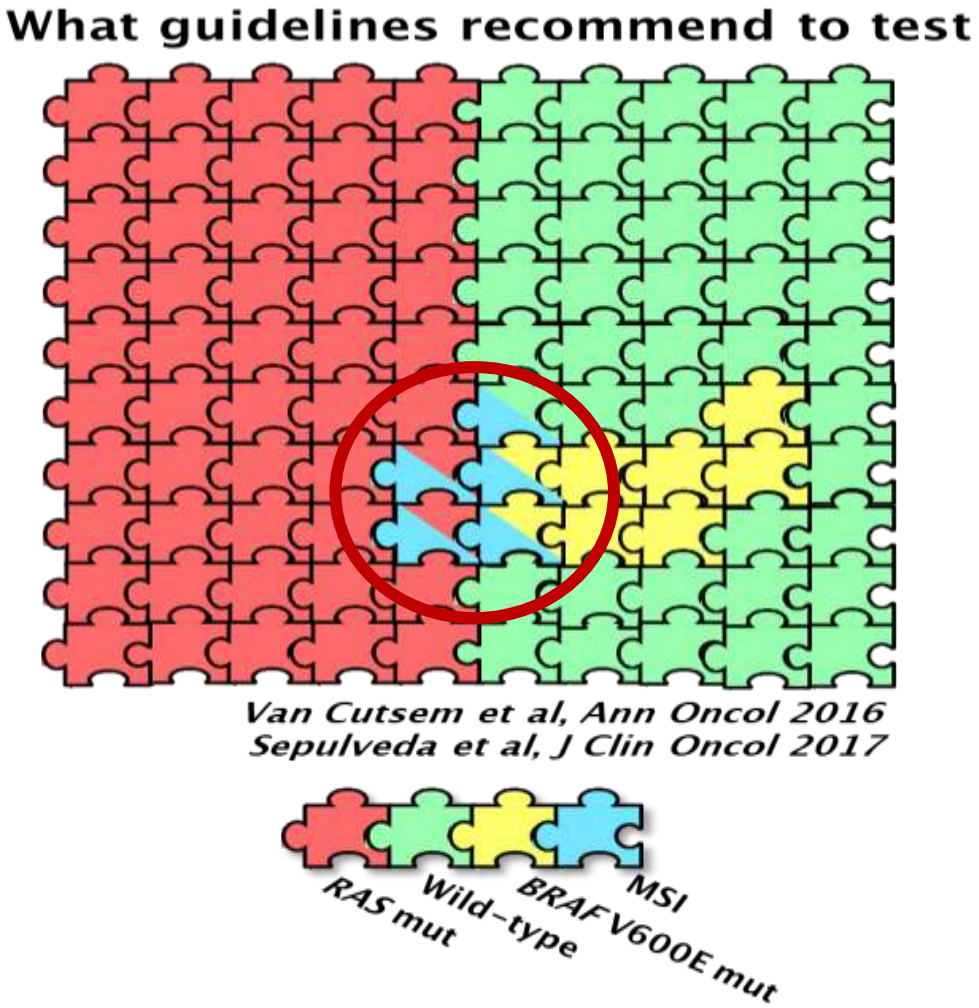
BARCELONA 2019 ESMO congress

* anti-PD-1 monoclonal antibody [PDR-001]

Courtesy of Prof. A. Falcone

http://clinicaltrials.gov

Genomic markers in mCRC

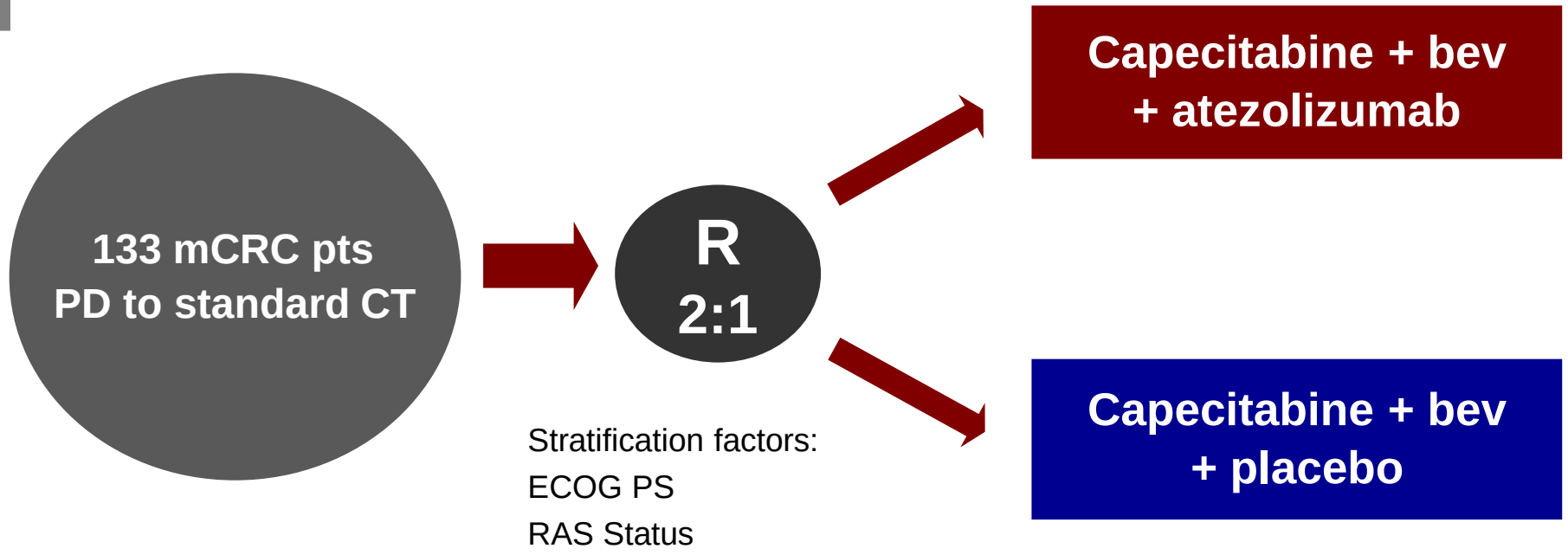


BARCELONA 2019 ESMO congress

Modify from C. Antoniotti

Immunotherapy: BACCI Trial

Phase II



Dosage:

- Capecitabine 850 or 1000 mg/m² d1-14
- Bevacizumab 7.5 mg/kg d1
- Atezolizumab 1200 mg d1

Cycle Length: d1 in 21 day cycles.

Primary End-Point:

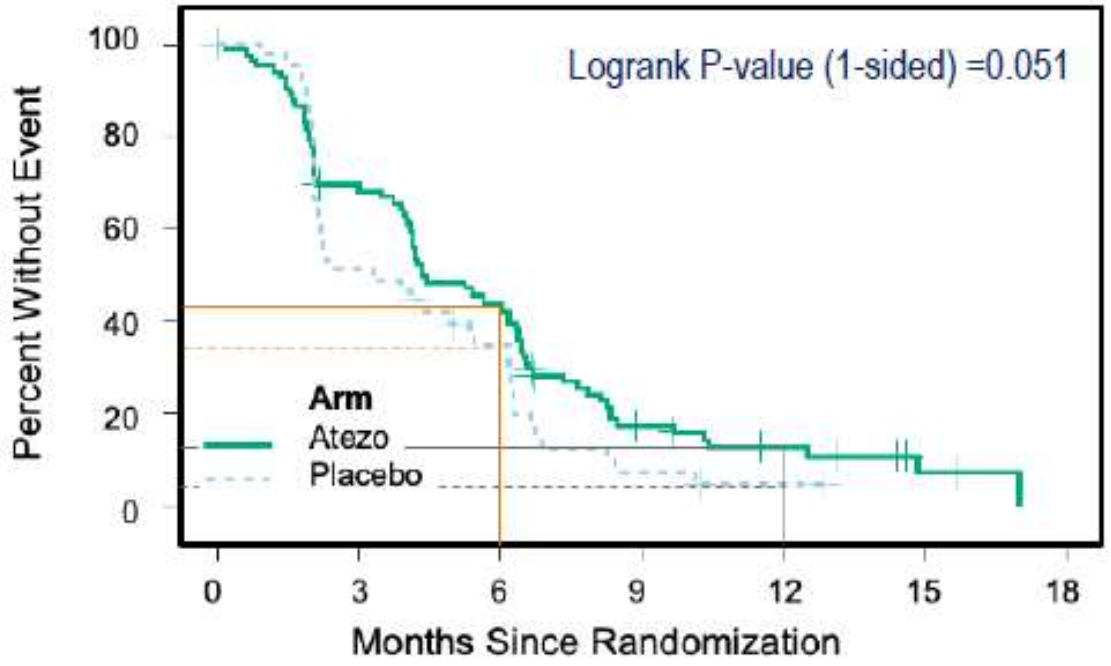
- Progression free survival (PFS)

Secondary End-Point:

- Overall survival (OS)
- Safety/tolerability.

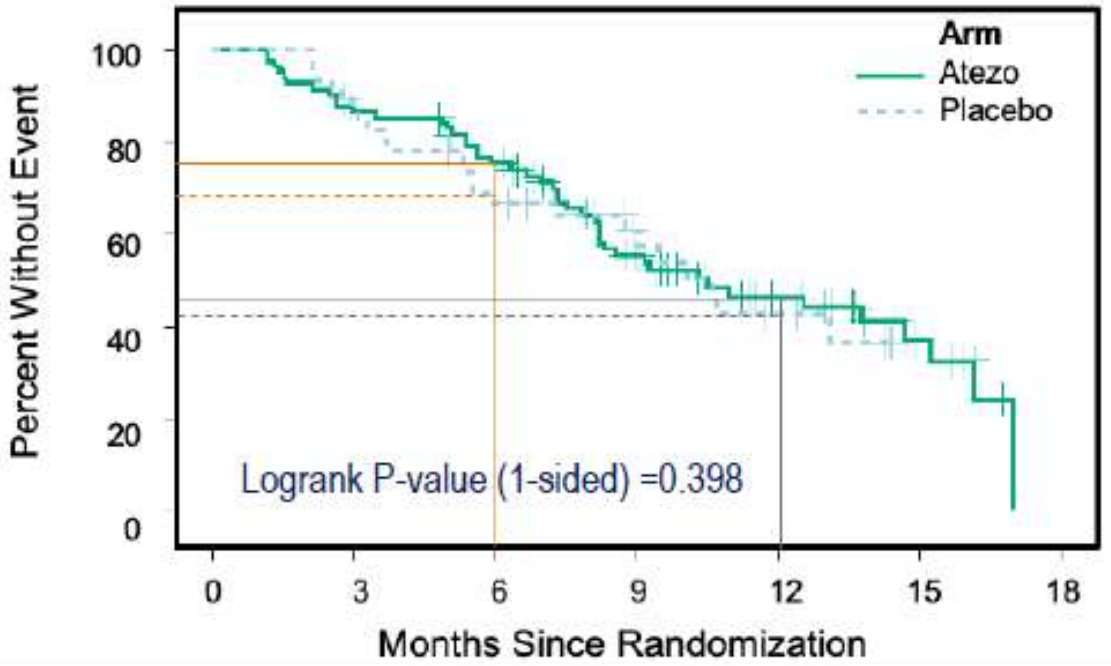
BACCI TRIAL: PFS & OS

PROGRESSION FREE SURVIVAL



Arm	Event / Total	Median (95% CI)	Survival Estimates (95% CI)	HR (95% CI)
Atezo	72/82	4.4 (4.1-6.4)	6 mo: 43.4 (33.9-55.7%) 12 mo: 12.9 (7.1-23.5%)	0.73 (0.49-1.07)
Placebo	41/46	3.3 (2.1-6.2)	6 mo: 34.8 (23.2-52.2%) 12 mo: 5.0 (1.3-19.1%)	

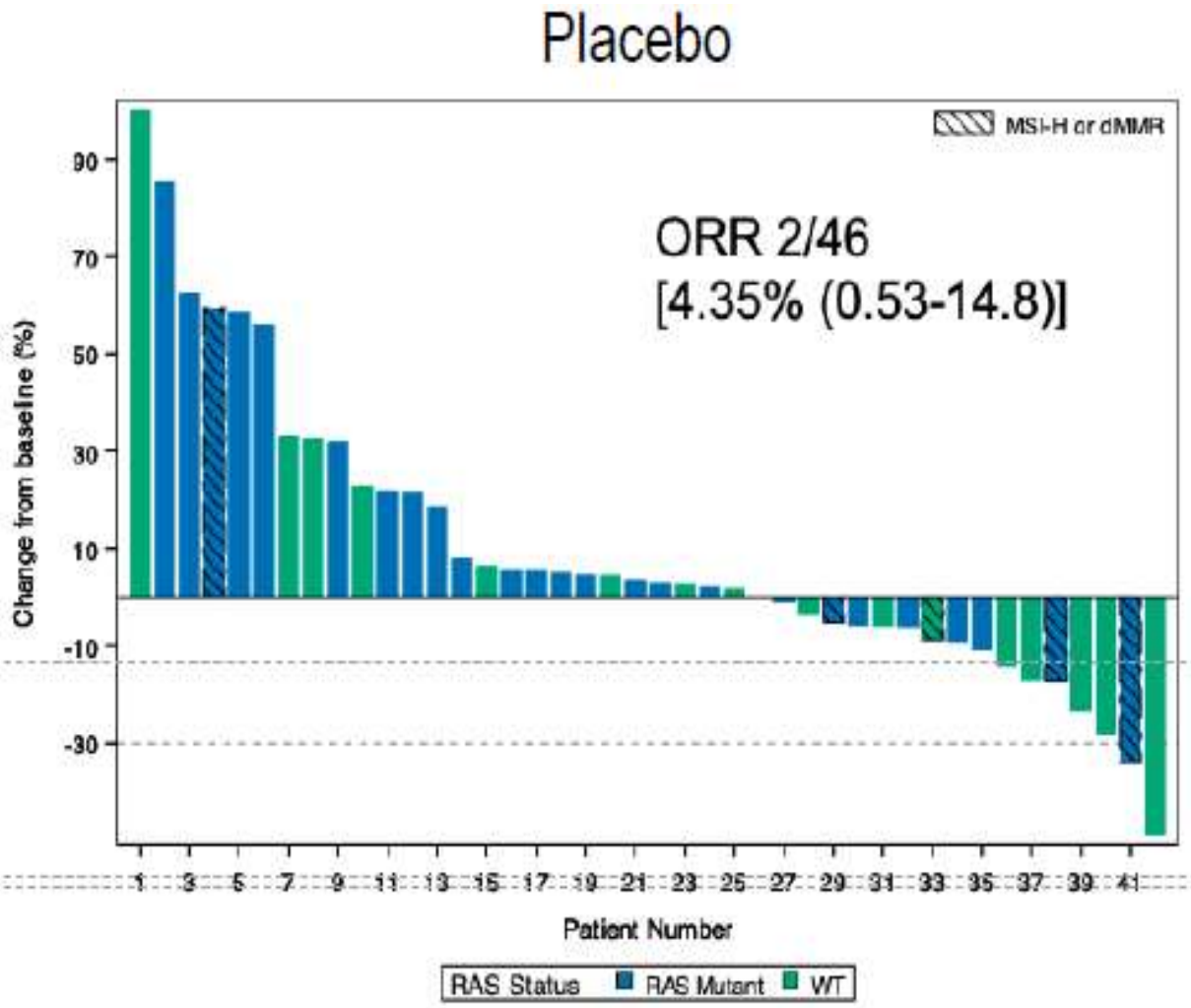
OVERALL SURVIVAL

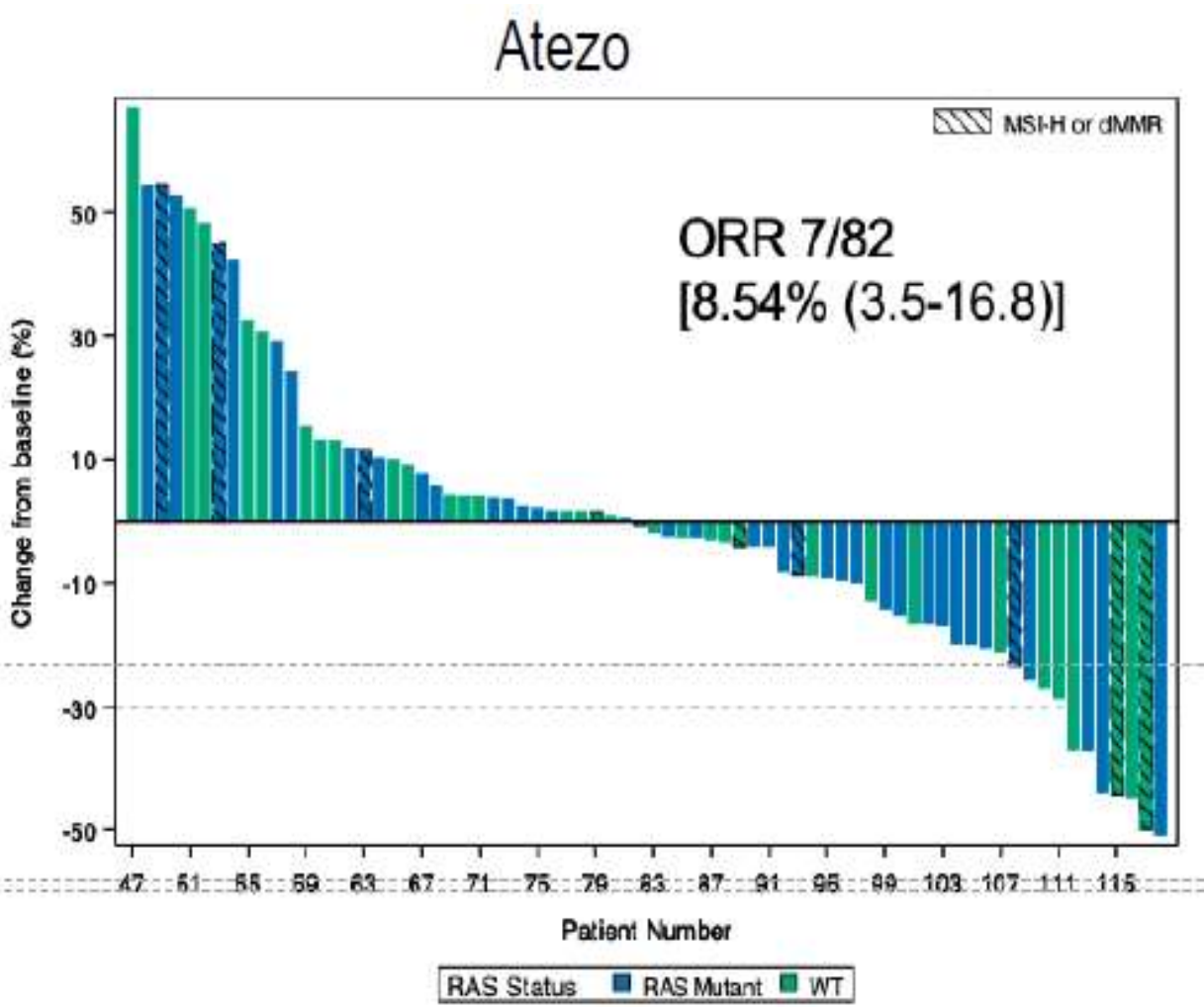


Arm	Event / Total	Median (95% CI)	Survival Estimates (95% CI)	HR (95% CI)
Atezo	45/82	10.5 (8.2-17.0)	6 mo: 75.2 (66.3-85.3%) 12 mo: 46.4 (35.9-60.0%)	0.94 (0.56-1.56)
Placebo	23/46	10.6 (8.8-NE)	6 mo: 68.8 (56.5-83.8%) 12 mo: 42.7 (28.7-63.5%)	

Mettu B et al, ESMO 2019

BACCI TRIAL: Overall Response Rate



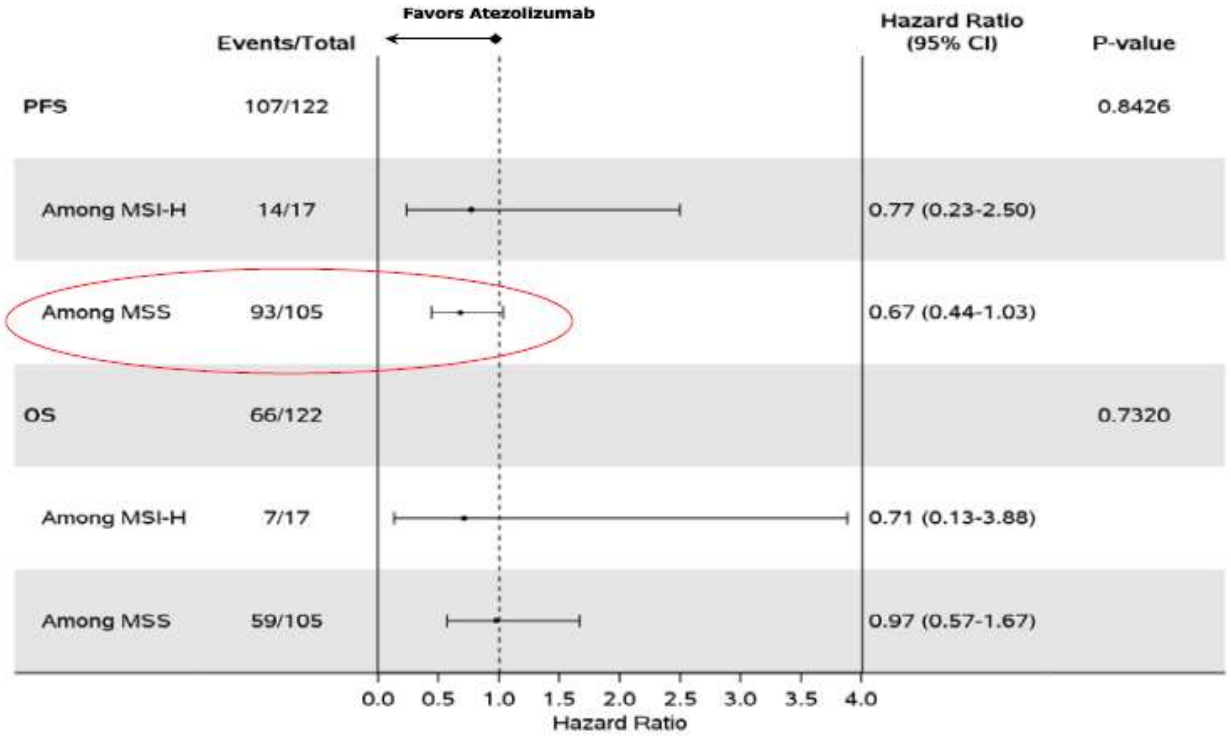


P=.05

Mettu B et al, ESMO 2019

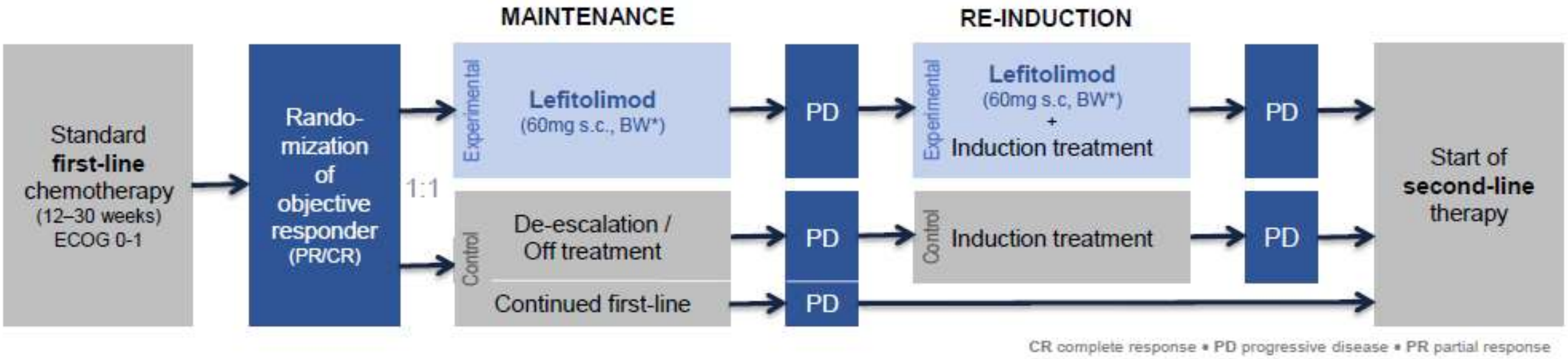
BACCI Trial: The Role of Microsatellite

Characteristic	Cape/Bev + Placebo (n=46)	Cape/Bev + Atezo (n=82)	Total (n=128)
Mean Age (yrs)	56.5	59.6	58.5
Male Gender	30 (65.2%)	47 (57.3%)	77 (60.2%)
White Race	36 (78.3%)	66 (80.5%)	102 (79.7%)
ECOG 0	21 (45.7%)	39 (47.6%)	60 (46.9%)
Colon Rectum	27 (58.7%) 19 (41.3%)	57 (69.5%) 25 (30.5%)	84 (65.6%) 44 (34.4%)
RAS mutant RAS wildtype	25 (54.3%) 21 (45.7%)	49 (59.8%) 33 (40.2%)	74 (57.8%) 54 (42.2%)
MSI Missing MSS/pMMR MSI-H/dMMR	1 39 (86.7%) 6 (13.3%)	5 66 (85.7%) 11 (14.3%)	6 105 (86.1%) 17 (13.9%)



Mettu B et al, ESMO 2019

IMMUNOTHERAPY: Lefitolimod



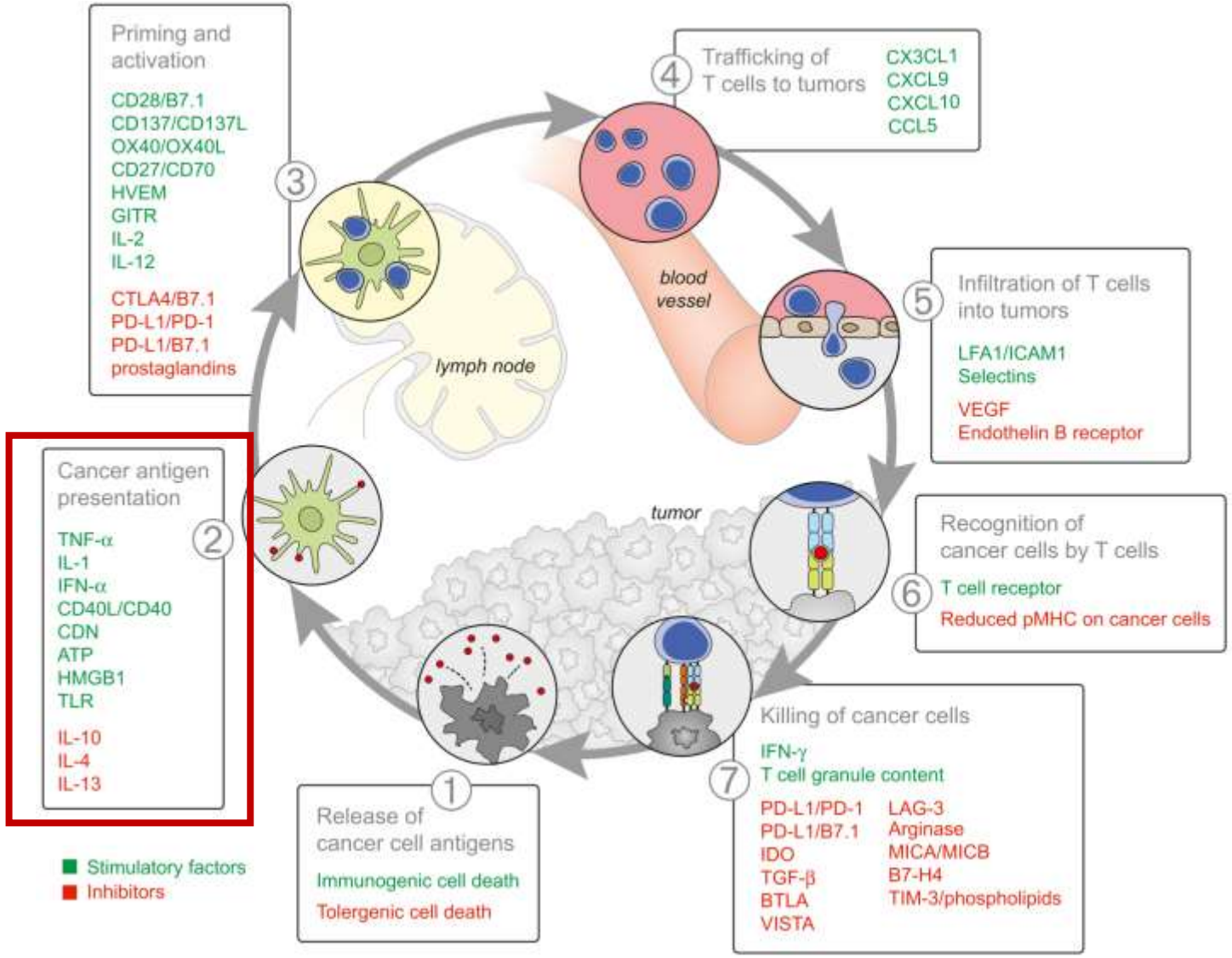
- Open-label, randomized, controlled, two-arm, multinational phase III trial
- 549 patients randomized in 121 sites in 8 European countries
- Supported by AIO, TTD and GERCOR

→ Phase III trial evaluating maintenance therapy with lefitolimod for prolongation of overall survival (OS)

Mettu N. et al, ESMO 2019

Lefitolimod: attractive new mechanism of action

DNA-based TLR9 agonist
<u>Positive</u> regulator of innate and adaptive immune response

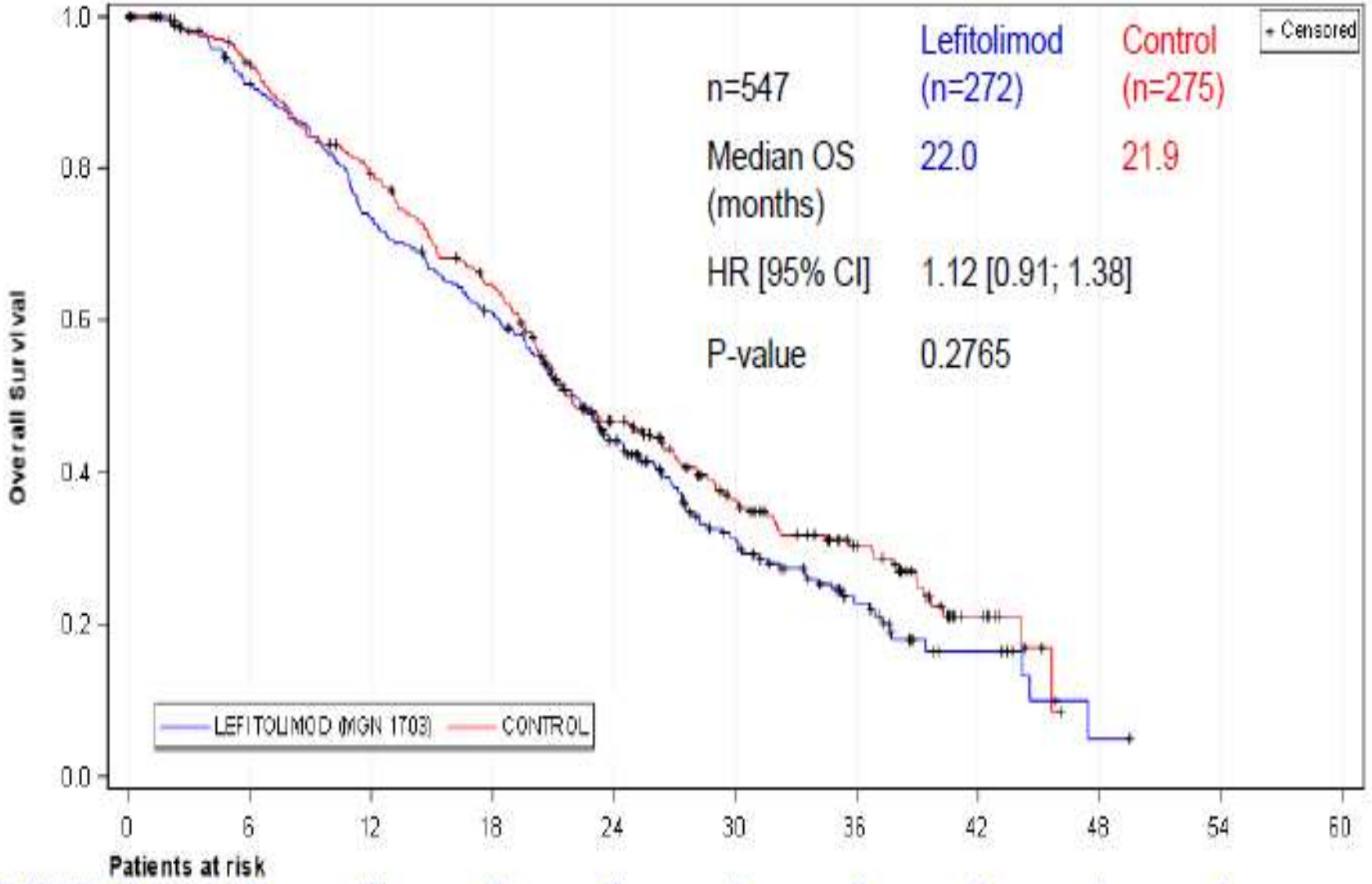


Chen et al, Immunity 2013
Wittig et al, Crit Rev Hemat and Oncol 2015

IMPALA Trial: Overall Survival Results

OS from randomization (ITT study population)

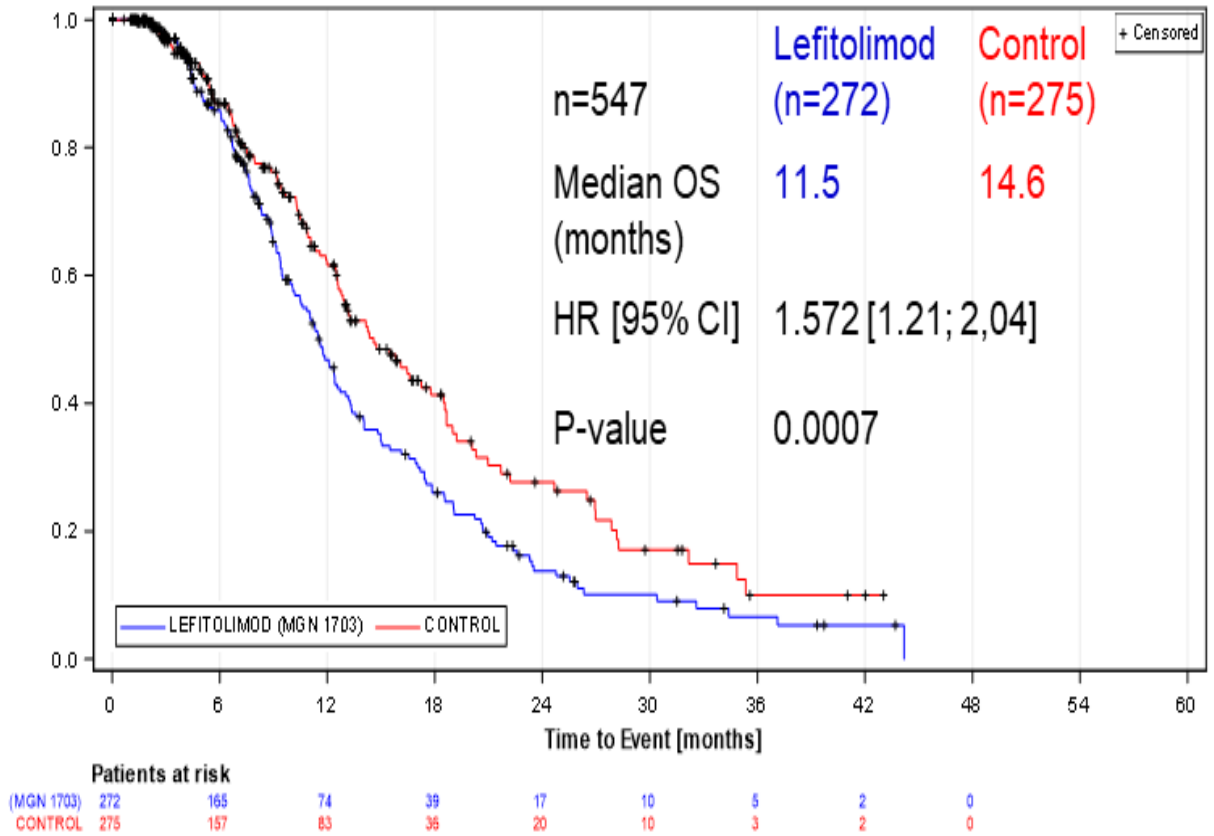
- Data mature
  - 547 Patients recruited
  - 365 events (median follow-up 35 mo)



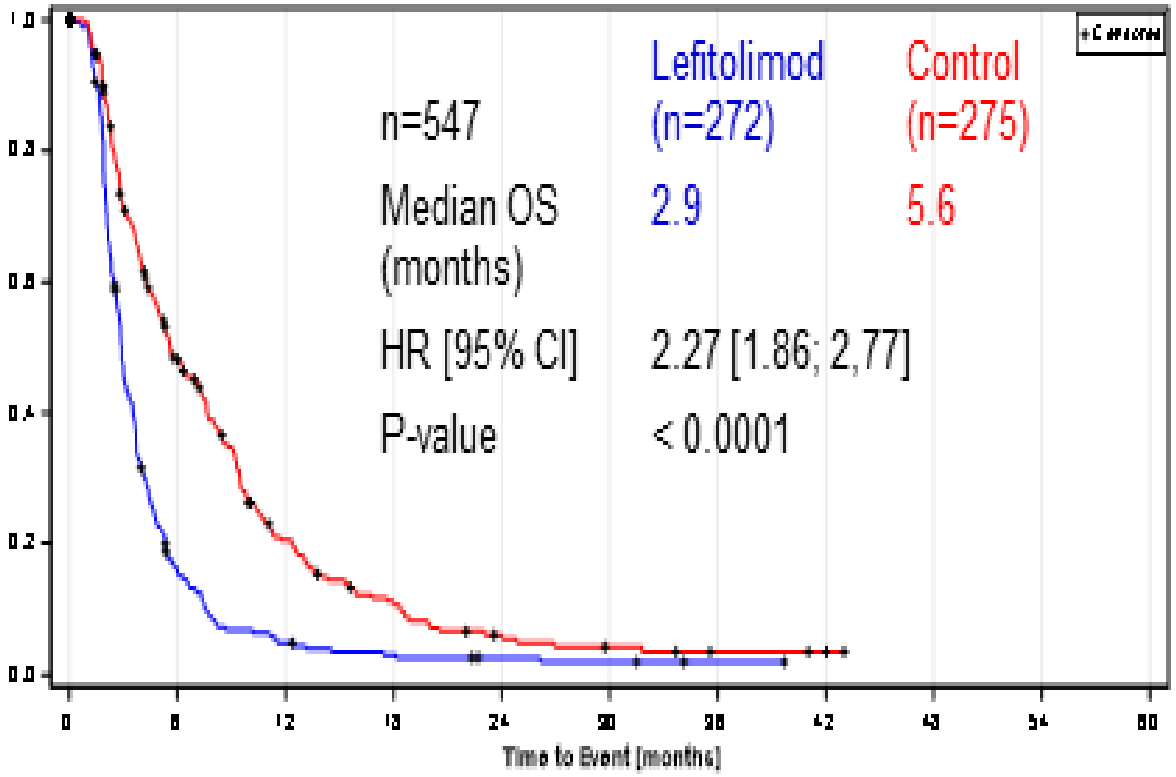
Mettu N. et al, ESMO 2019

IMPALA study: PFS– secondary endpoint

PFS on study (Time to second progression)



PFS in maintenance (Time to first progression)

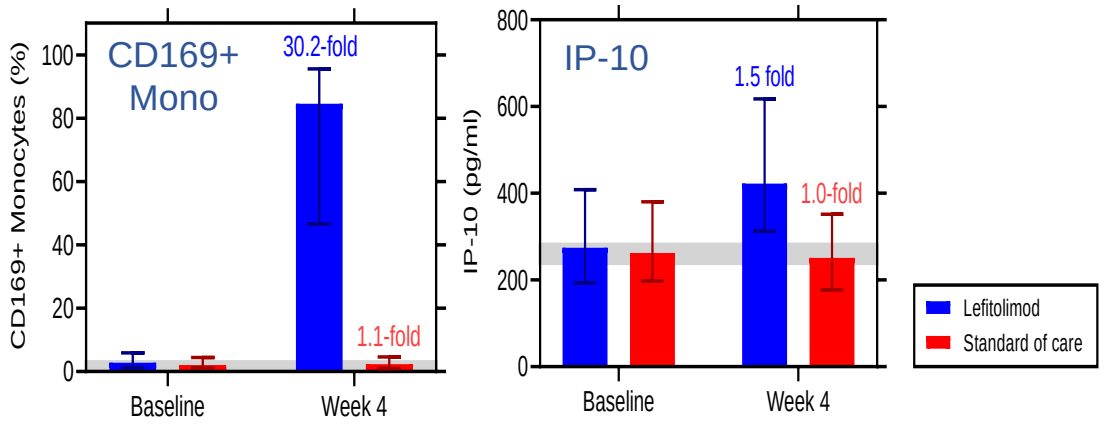


Mettu N. et al, ESMO 2019

… however immunological effects are observed

Assessment of pharmacodynamic parameters:

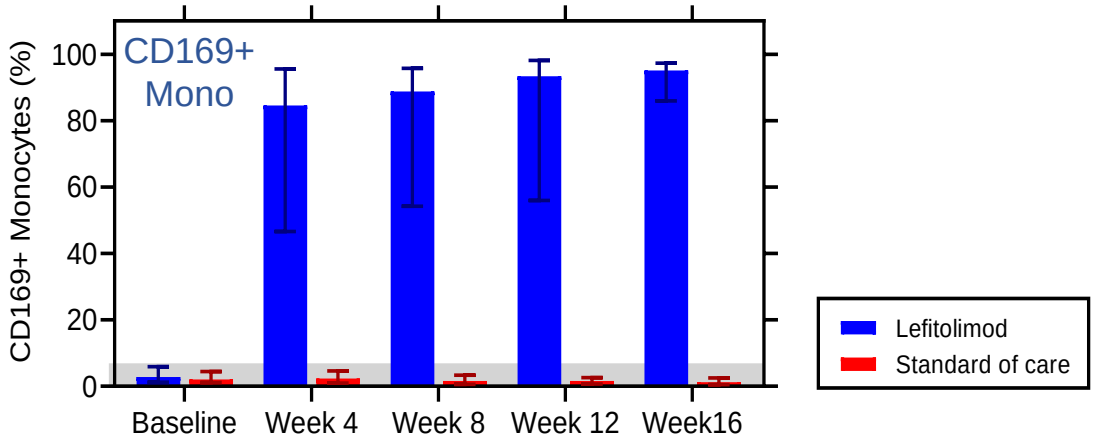
- Activation of CD169+ monocytes and IP-10 chemokine in patients treated with lefitolimod
- Analysis of peripheral blood samples



→ Pharmacodynamic data confirm the immunological mode-of-action of lefitolimod

Assessment of continuous immune activation:

- Activation of CD169+ monocytes
- Analysis of peripheral blood samples
- Samples taken over course of study



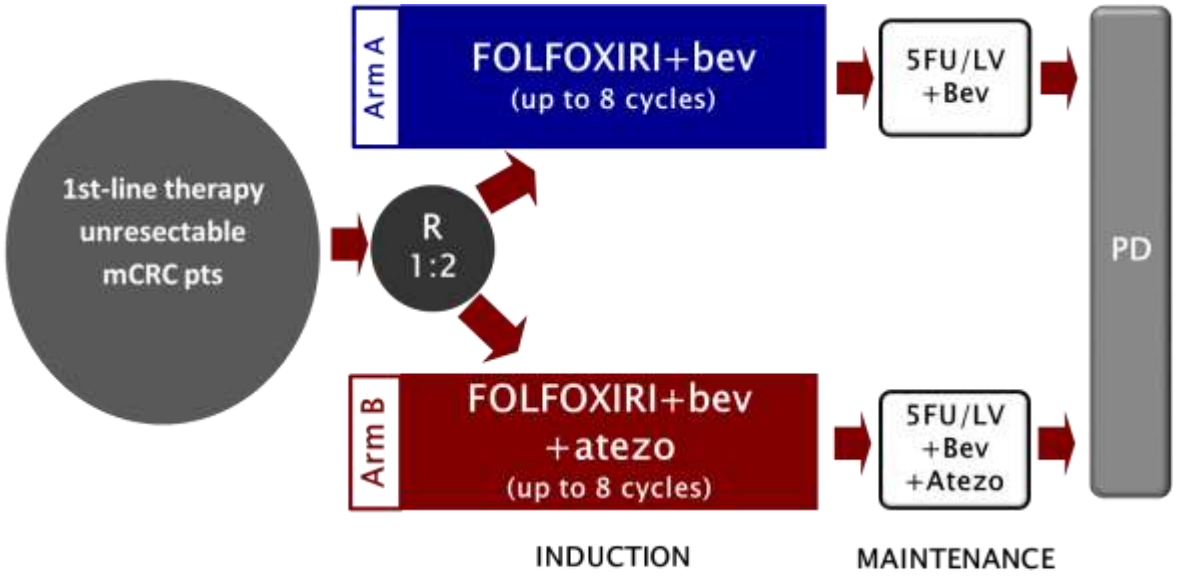
→ No decrease of immune activation during the study

BARCELONA 2019 ESMO congress

Courtesy of Prof. A. Falcone

We do not have to give-up to study immunotherapy in MCRC: some ongoing studies

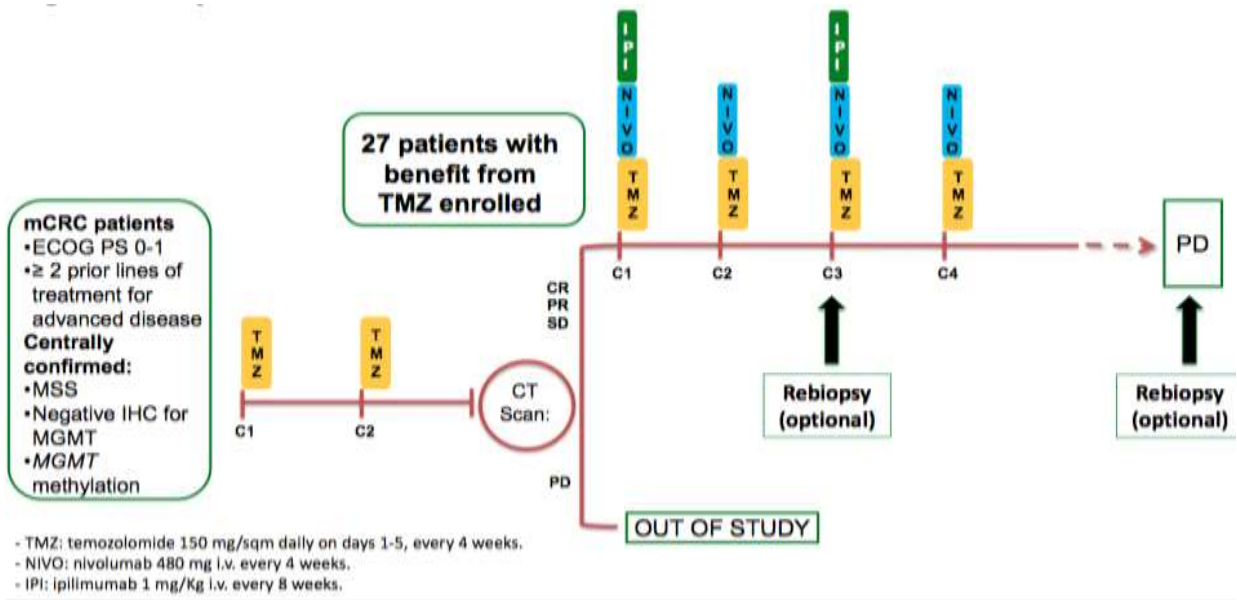
Phase II AtezoTRIBE study (GONO group PI: Cremolini)



Stratification factors:
- Site
- ECOG PS 0 *versus* 1–2;
- Primary tumour location (right colon *versus* left colon/rectum);
- Previous adjuvant therapy (yes *versus* no)

Primary endpoint: PFS
Target accrual: 201 patients

Phase II MAYA study (INT Milan PI: Pietrantonio)

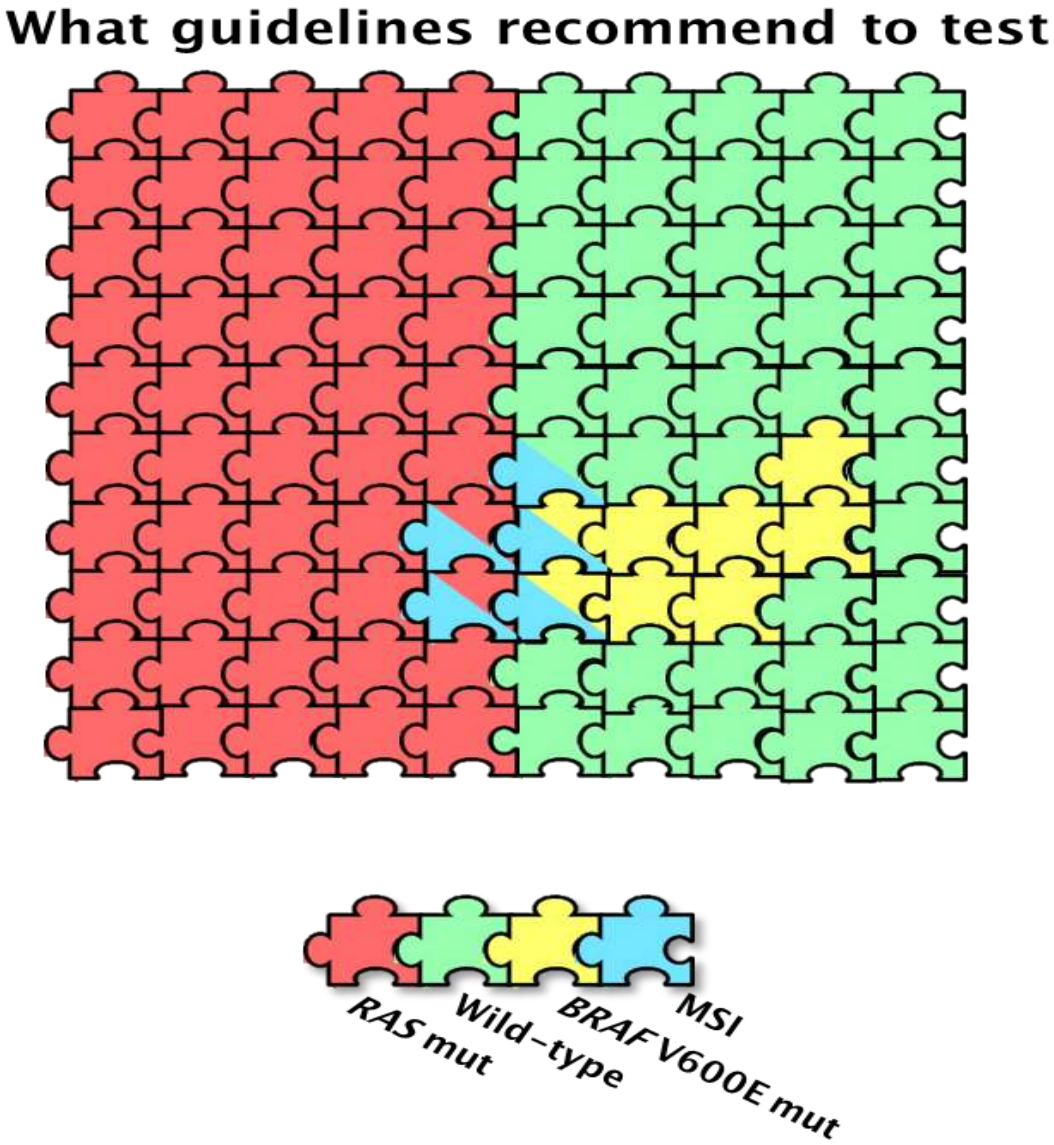


- TMZ: temozolomide 150 mg/sqm daily on days 1-5, every 4 weeks.
- NIVO: nivolumab 480 mg i.v. every 4 weeks.
- IPI: ipilimumab 1 mg/Kg i.v. every 8 weeks.

BARCELONA 2019 ESMO congress

http://clinicaltrials.gov

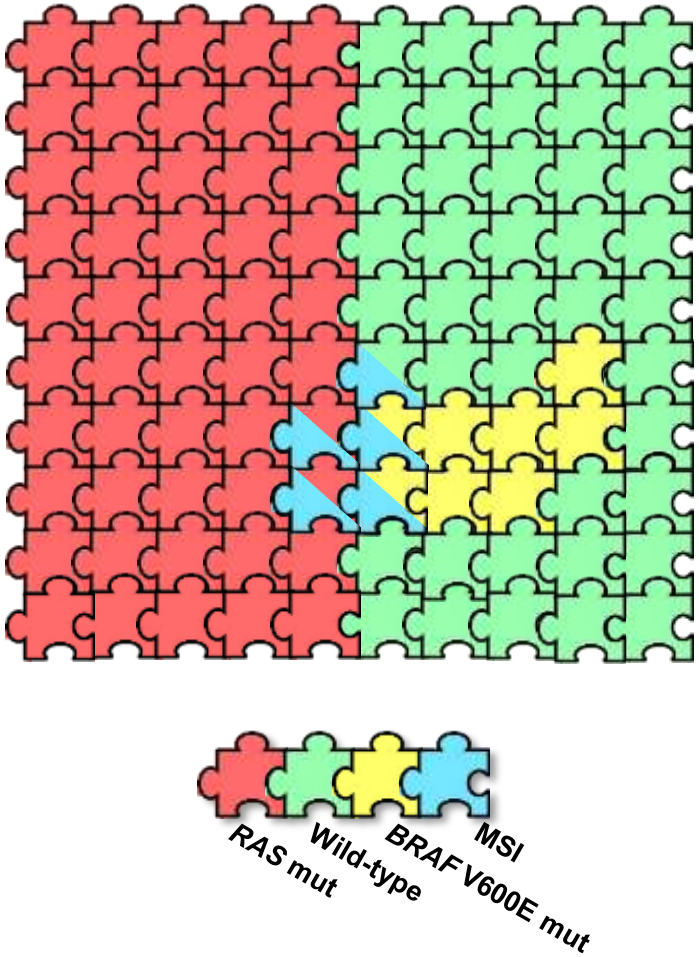
Genomic markers in mCRC



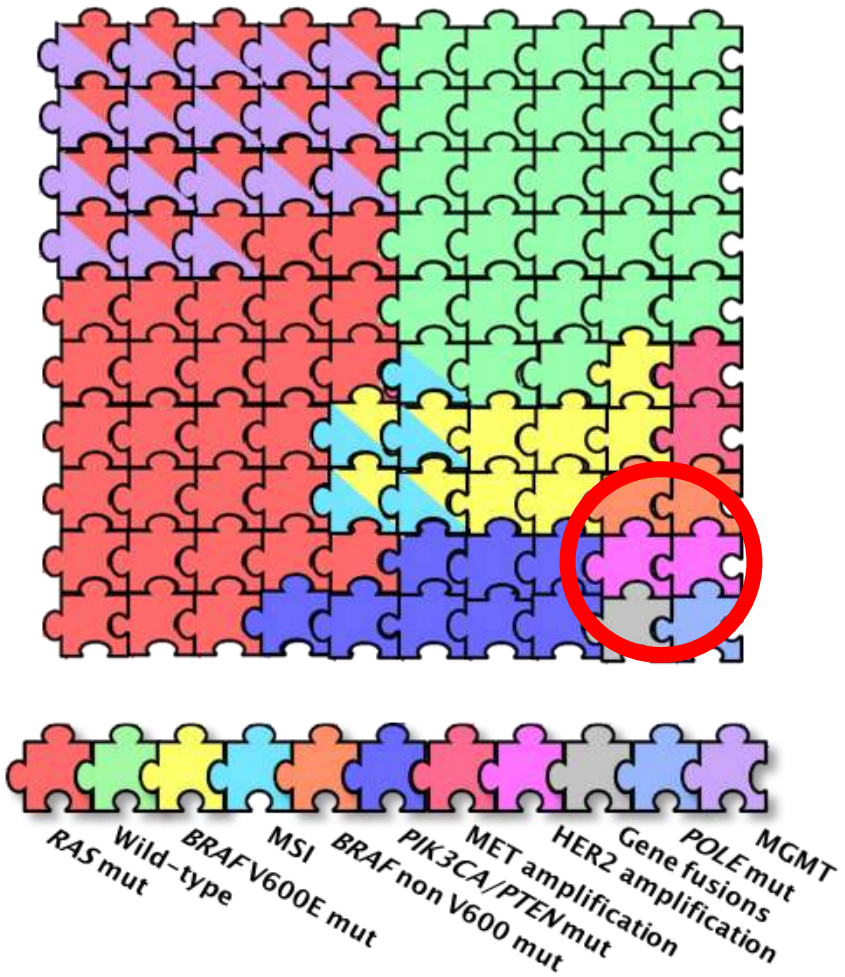
Courtesy of C. Antoniotti

Genomic markers in mCRC

What guidelines recommend to test



The most updated molecular puzzle



Modify from C. Antoniotti

HER2: a successful story

Prevalence: ≈2-5%

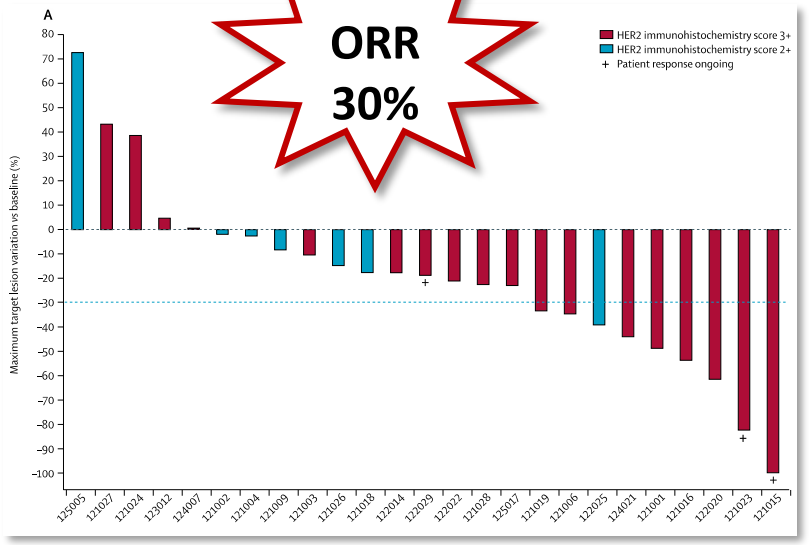
HER-2+ mCRC pts

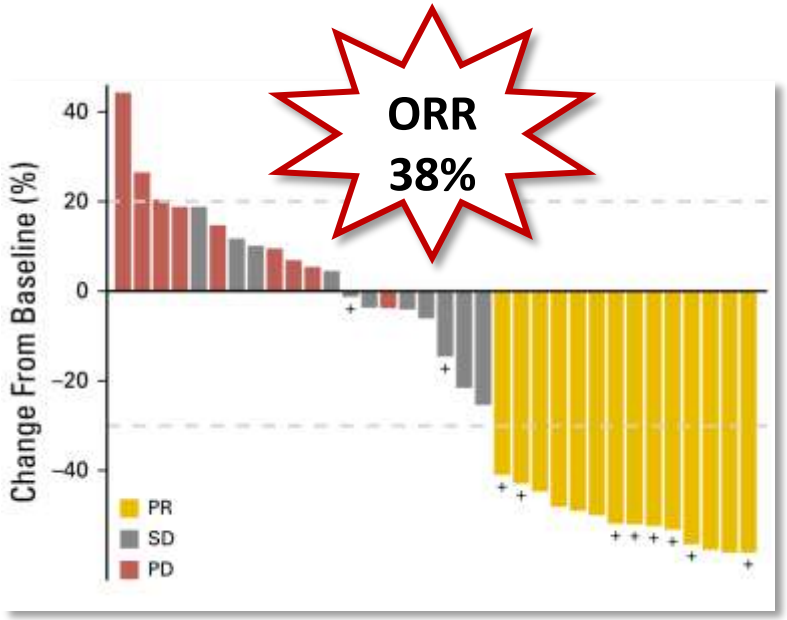
HERACLES TRIAL

Trastuzumab + Lapatinib

MyPATHWAY TRIAL

Trastuzumab + Pertuzumab





Sartore Bianchi et al, Lancet Oncology 2016

Hainsworth et al, J Clin Oncol 2018

HER-2: ESMO 2019

LBA35

Phase II Study of Pertuzumab and Trastuzumab-emtansine (T-DM1) in Patients with HER2-positive Metastatic Colorectal Cancer: the HERACLES-B (HER2 Amplification for Colo-rectaL cancer Enhanced Stratification - cohort B) Trial

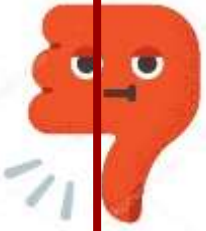
#526PD

TRIUMPH: Primary Efficacy of a Phase II Trial of Trastuzumab (T) and Pertuzumab (P) in Patients (pts) with Metastatic Colorectal Cancer (mCRC) with HER2 (*ERBB2*) Amplification (amp) in Tumor Tissue or Circulating Tumor DNA (ctDNA): A GOZILA Sub-study (EPOC1602)

#527PD - Trastuzumab and tucatinib for the treatment of HER2 amplified metastatic colorectal cancer (mCRC): Initial results from the MOUNTAINEER trial

Sartore-Bianchi A. et al. ESMO 2019
Nakamura Y. et al, ESMO 2019
Strickler J.H. et al., ESMO 2019

ESMO 2019: HER-2



	HERACLES n=30	TRIUMPH n=19	ONTANIEER n=26
Study Type	Phase II	Phase II	Phase II
Regimen	Pertuzumab 420 mg+ TDM-1 3.6 mg/kg 1q21	Pertuzumab 420 mg+ Trastuzumab 6 mg/kg 1q21	Tucatinib 300 mg+ Trastuzumab 6 mg/kg 1q21
Selection	IHC=3+ IHC=2+ and FISH/SISH Ampl RAS/RAF Wild-Type	IHC=3+ IHC=2+ and FISH/SISH Ampl RAS/RAF Wild-Type	IHC=3+ IHC=2+ and FISH/SISH Ampl HER2 ampl by NGS RAS Wild-Type
Methods	TISSUE	TISSUE Liquid Biopsy	TISSUE
ORR	10 % (0-28)	35% (14 – 62)	52% (31 – 73)
DCR	80% (50-85)	65% (38 -86)	64 %
Secondary endpoint	PFS 4.9 mos (1.2-12.0)	PFS 4.0 mos (1.4 – 5.6)	PFS 8.1 mos (3.8-NE) OS 18.7 mos (12.3-NE)

Umbrella & Basket Clinical Trials (IIT Only to be listed) based on NGS-Based Liquid Screening

GOZILA Project

Guardant Originates in Zipangu Liquid biopsy Arrival

Nationwide Genome Screening Project

SCRUM-Japan GI-SCREEN

26 sites

CRC Only

CRC cohort, N = 1,500
- Before anti-EGFR, N = 500
- Refractory to anti-EGFR, N = 500

Non-CRC cohort, N = 1,500
- Gastric cancer, N = 300
- Esophageal cancer, N = 150
- Hepatocellular carcinoma, N = 100
- Biliary tract cancer, N = 150
- Pancreatic cancer, N = 100
- Neuroendocrine tumor/carcinoma, N = 50
- GIST, N = 100
- Others, N = 50

Non-GI Cancer cohort, N = 1,000

Organ-Specific approach

ctDNA analysis (Guardant360)

- HER2 Positive → Trastuzumab + Pertuzumab (TRIUMPH)
- *BRAF* V600E MT → Eribulin (BRAVERY)
- *BRAF* Non-V600E MT → Binimetinib+ Encorafenib + Cetuximab (BIG BANG)
- *MET* Amplification → Cabozantinib ± Panitumumab (METBEIGE)
- *RAS* WT → Re-challenge with anti-EGFR mAb (PURSUIT)

- *HER2* amplification → DS-8201a (HERB)

Tumor-agnostic approach

Pan cancer

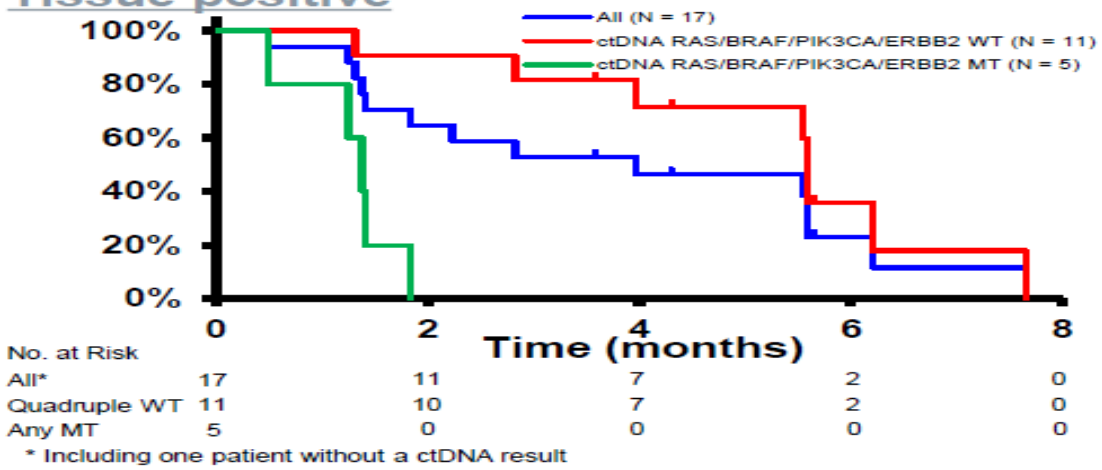
ctDNA analysis (Guardant360)

- bTMB-High Cancer → Nivolumab (TMB-H basket)
- Any *FGFR* alteration → TAS-120 (TiFFANY)
- *HER2* amplification → DS-8201a (HERALD)
- *ROS1* fusion → Brigatinib (Barossa)

Nakamura Y, Yoshino T. Oncologist. 2018, Revised

ESMO 2019: TRIUMPH Trial Results

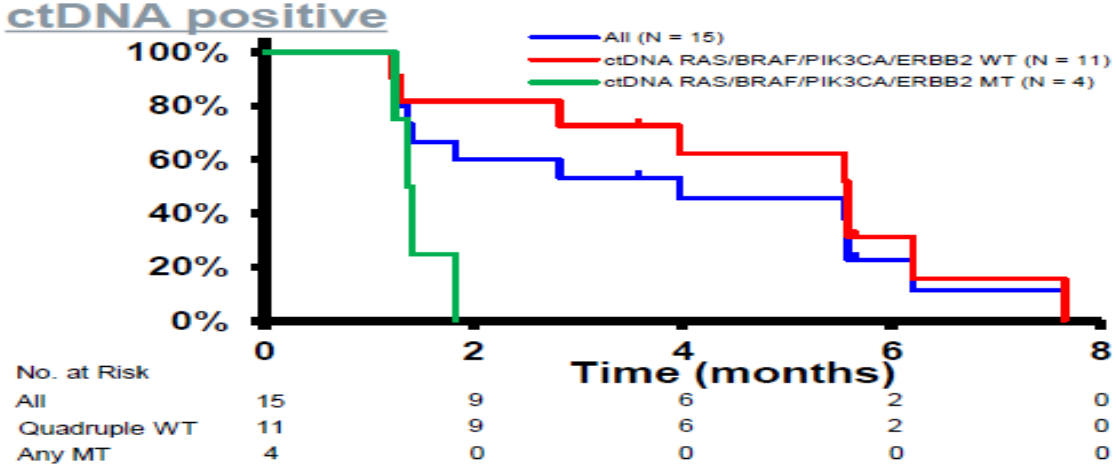
Tissue positive



* Including one patient without a ctDNA result

	Median PFS, months (95% CI)
All	4.0 (1.4-5.6)
ctDNA *RAS/BRAF/PIK3CA/BRAF* WT	5.6 (2.8-7.7)
ctDNA *RAS/BRAF/PIK3CA/BRAF* MT	1.4 (0.5-1.8)

ctDNA positive



	Median PFS, months (95% CI)
All	4.0 (1.3-5.6)
ctDNA *RAS/BRAF/PIK3CA/BRAF* WT	5.6 (1.3-6.2)
ctDNA *RAS/BRAF/PIK3CA/BRAF* MT	1.4 (1.2-1.8)

	ORR N (% [95% CI])	DCR N (% [95% CI])
Tissue positive group (N = 17)		
All	6 (**35.3** [14.2-61.7])	11 (**64.7** [38.3-85.8])
ctDNA *RAS/BRAF/PIK3CA/ERBB2**		
WT (N = 11)	6 (**54.5** [23.4-83.3])	10 (**90.9** [58.7-99.8])
MT (N = 5)	0 (**0.0** [0.0-52.2])	0 (**0.0** [0-52.2])
ctDNA positive group, N = 15		
ctDNA *RAS/BRAF/PIK3CA/ERBB2*		
WT (N = 11)	5 (**45.5** [16.7-76.6])	9 (**81.8** [48.2-97.7])
MT (N = 4)	0 (**0.0** [0.0-60.2])	0 (**0.0** [0.0-60.2])

Nakamura Y. et al, ESMO 2019

anti-HER2 strategies in HER2+ mCRC: ongoing trials

Study	Phase	N pts	Drugs	Primary endpoint	Country
HERACLES RESCUE	II	13	**T-DM1**	ORR	Italy
MODUL - maintenance	II	-	**Trastuzumab + Pertuzumab + Capecitabine**	PFS	worldwide
NSABP FC-11	II	35	**Neratinib + Trastuzumab vs Neratinib + Cetuximab**	ORR	USA
NCT03384940	II	90	**Trastuzumab deruxtecan (DS-8201a)**	ORR	worldwide
NCT03843749	Interve ntional	30	**Pyrotinib + Trastuzumab**	ORR	China
NCT03185988	II	100	**Trastuzumab + CT (CPT-11 +/- Cape)**	ORR	China
NCT03821233	I	69	**ZW49**	DLTs AE	USA

http://clinicaltrials.gov

Conclusions

- The "bench to bedside" studies are now reality and are increasing in number (MGMT, ALK / ROS, PolE, KRAS, MSI)
- We are progressively adding tesserae to a complex mosaic
  - Trials on HER-2 confirmed the possibility of a new strategies
  - The triplet will become the new standard in previously treated mCRC $BRAF^{V600E}$ mut pts
- We need further study to understand the correct use of these treatments

Thank you!

danielerossini87@gmail.com