

13° CONGRESSO NAZIONALE AIOM GIOVANI  
**2019 NEWS IN ONCOLOGY**



**HOT TOPIC IN TEMA DI NEOPLASIE DEL COLON**

*Scelta del trattamento  
di prima linea  
nel tumore del colon metastatico*

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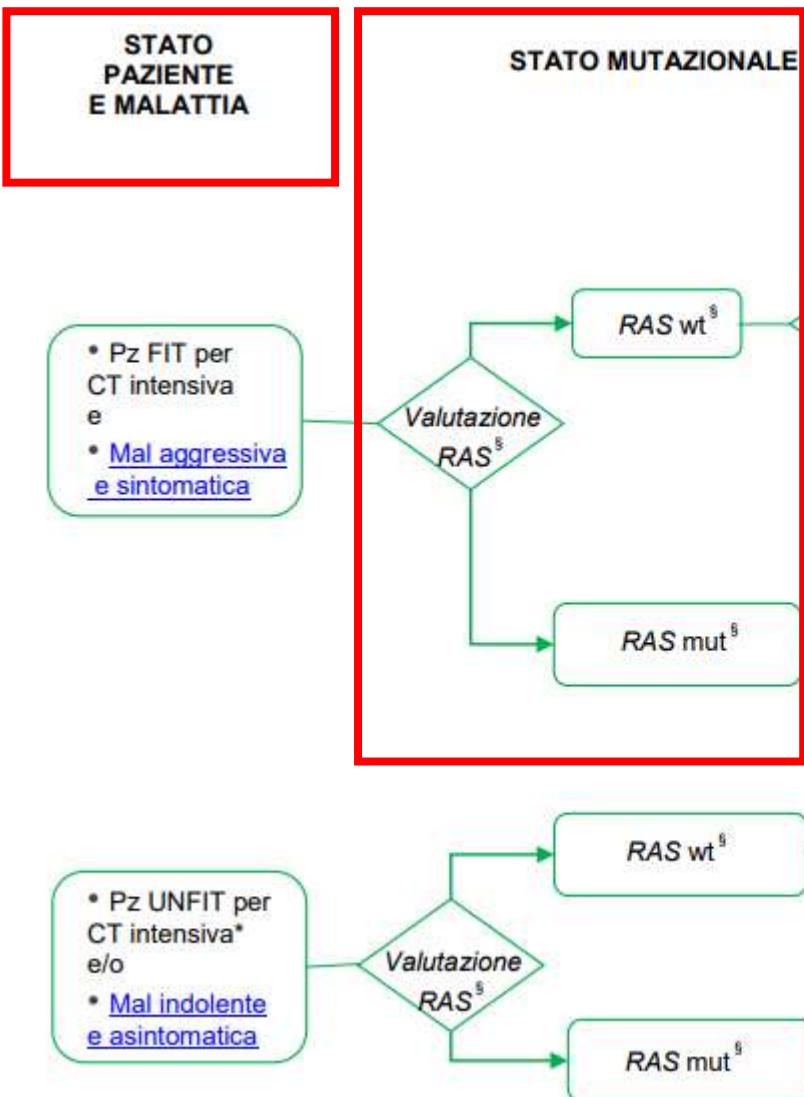


## Disclosures

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- ✓ Roche, AMGEN, Merck, Servier, Bayer, Lilly

# LINEE GUIDA AIOM 2018



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## STATO PAZIENTE E MALATTIA

- Pz FIT per CT intensiva e
- Mal aggressiva e sintomatica

- Pz UNFIT per CT intensiva\* e/o
- Mal indolente e asintomatica

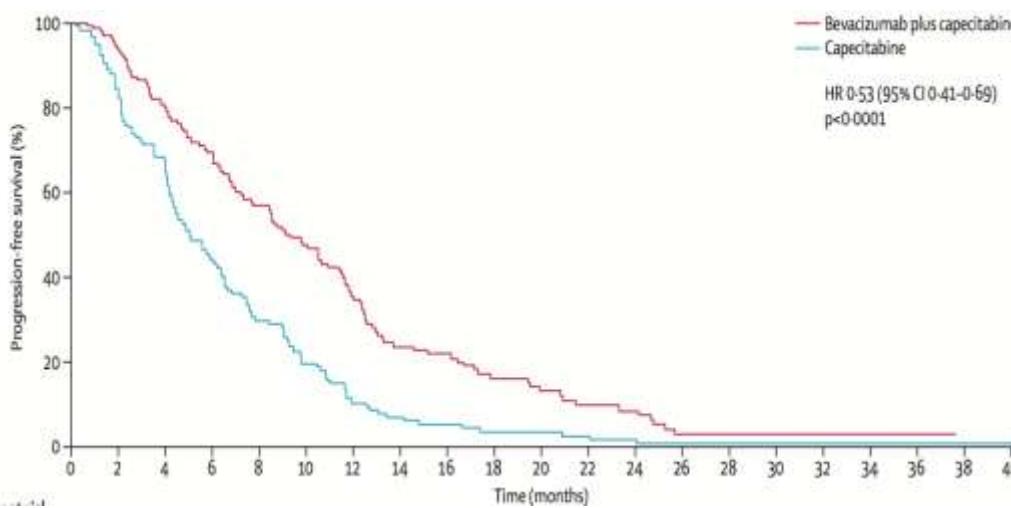
- Tailored CT + Bev\*\* o
- Tailored CT + anti-EGFR\*\*

- Tailored CT + Bev\*\*

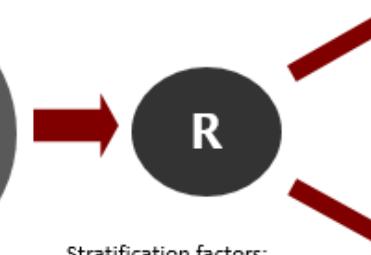


# If you need to go for the monotherapy

AVEX

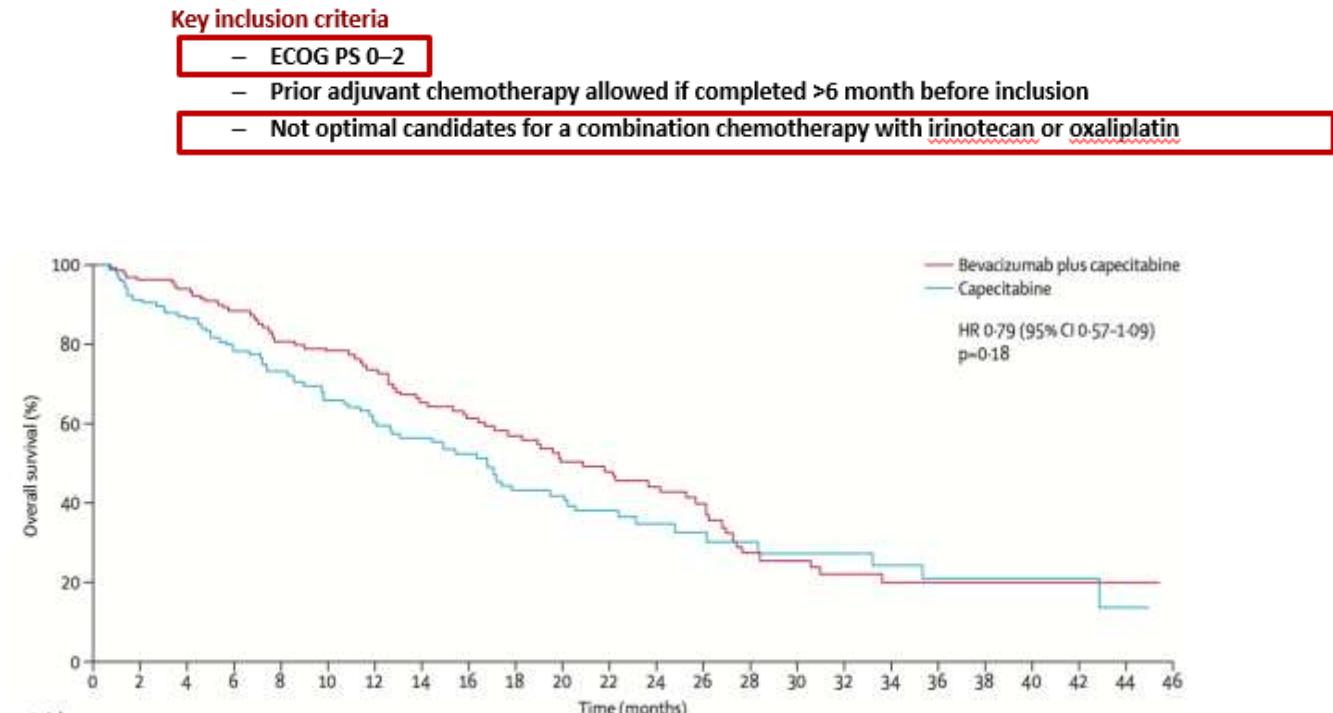


280 mCRC pts  
1st line mCRC  
AGE □ 70 years

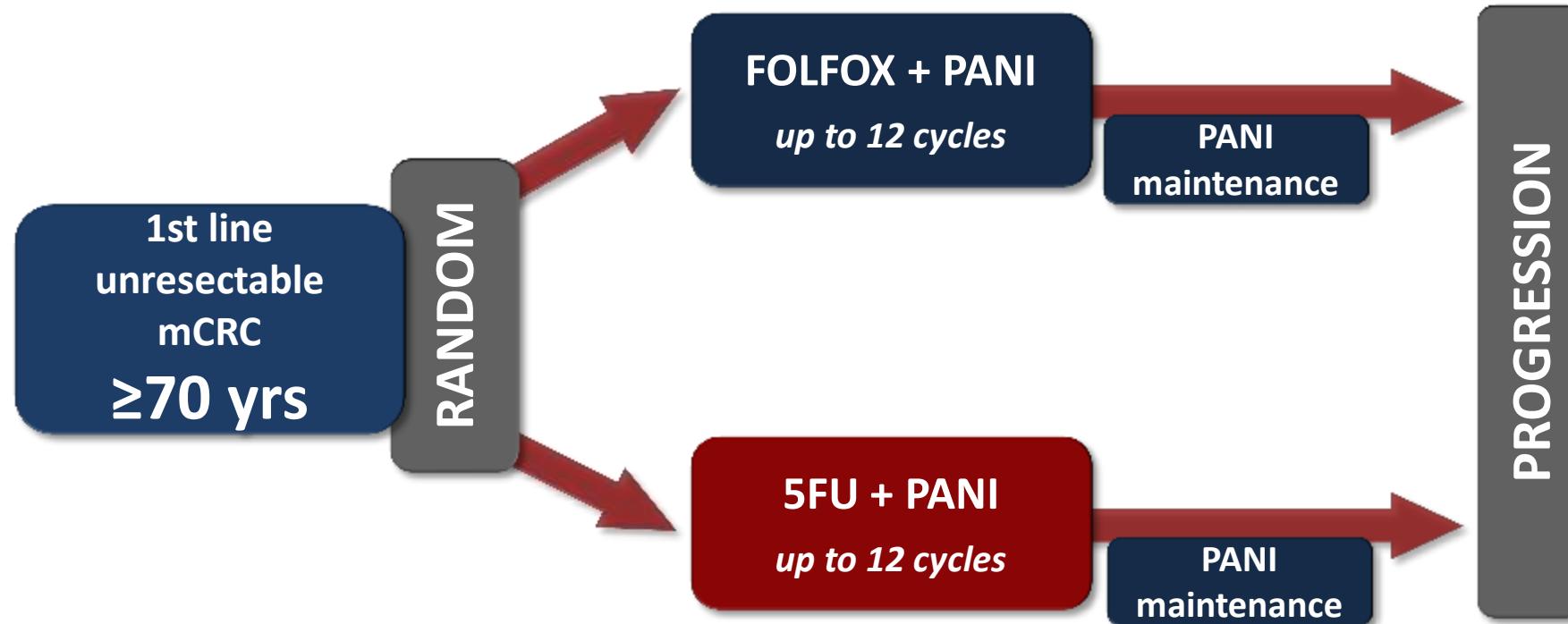


Capecitabine + bev

Capecitabine



# Waiting for PANDA



**Primary endpoint:** median PFS

p0: mPFS  $\leq$  6.0 months (literature-based), mPFS  $\geq$  9.5 months  
Design: Fleming single-stage  
Alpha error: 0.05, Beta error: 0.10



# LINEE GUIDA AIOM 2018



## STATO PAZIENTE E MALATTIA

- Pz FIT per CT intensiva e
- Mal aggressiva e sintomatica



## STRATEGIA TERAPEUTICA

- Tripletta + Bev o
- Doppietta + Bev o
- Doppietta + anti-EGFR o  
Quesito 13, Quesito 11, Quesito 10a
- Studi clinici

- Doppietta + anti-EGFR o  
Quesito 13, Quesito 11, Quesito 10a
- Tripletta + Bev o
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- Doppietta + Bev o
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- Pz UNFIT per CT intensiva\* e/o
- Mal indolente e asintomatica

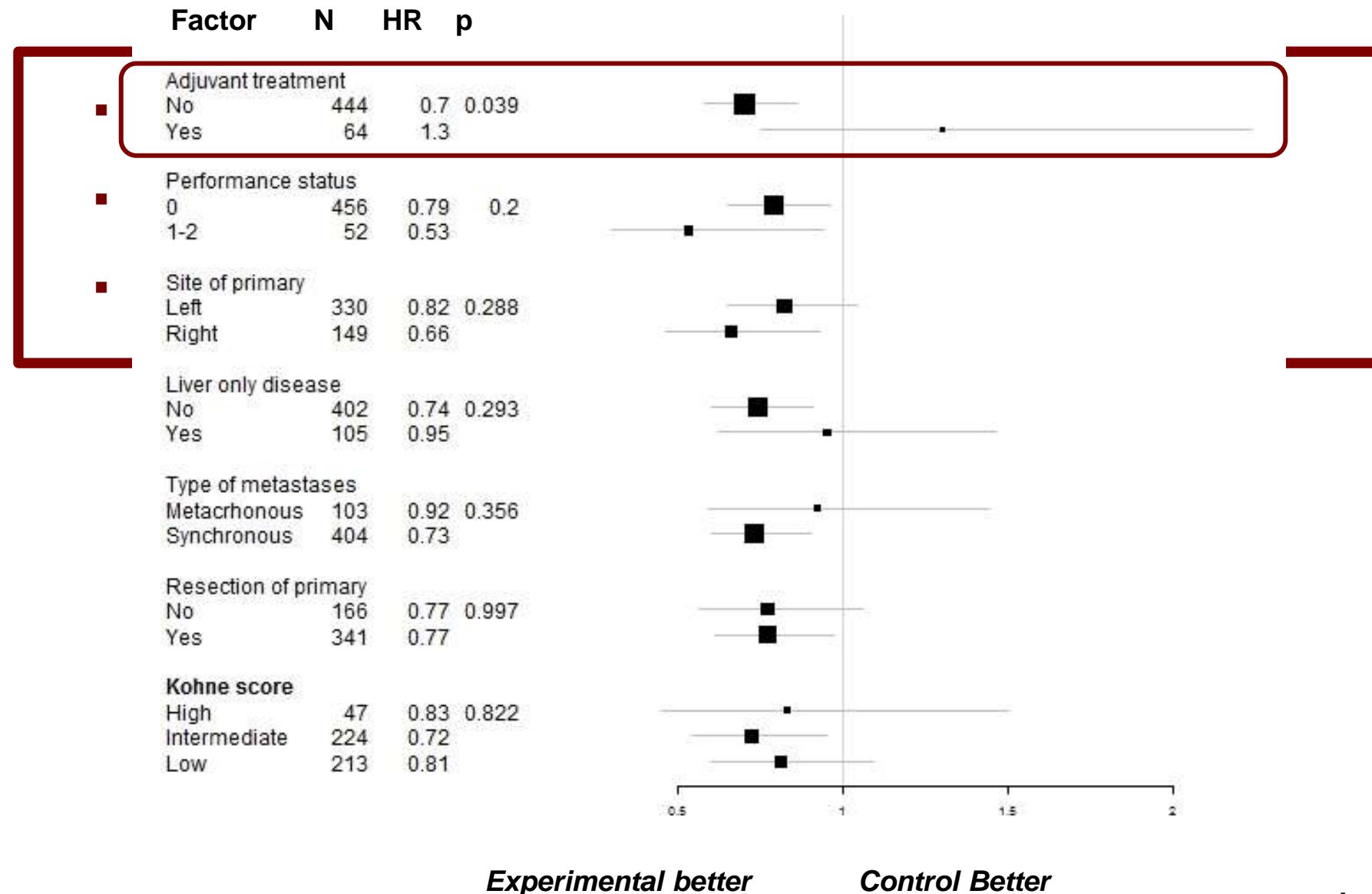
# Consistent and confirmatory results with FOLFOXIRI plus bev

...in previously untreated, unresectable mCRC



	FOIB N = 57	TRIBE N=252	OPAL N=97	STEAM N=93
<b>Response Rate</b>	77%	65%	64%	60%
<b>Disease Control Rate</b>	100%	90%	87%	91%
<b>Median PFS, mos</b>	13.1	12.3	11.1	11.7
<b>Median OS, mos</b>	30.9	29.8	32.2	Too early

# FOLFOXIRI+bev: Is it for everyone?

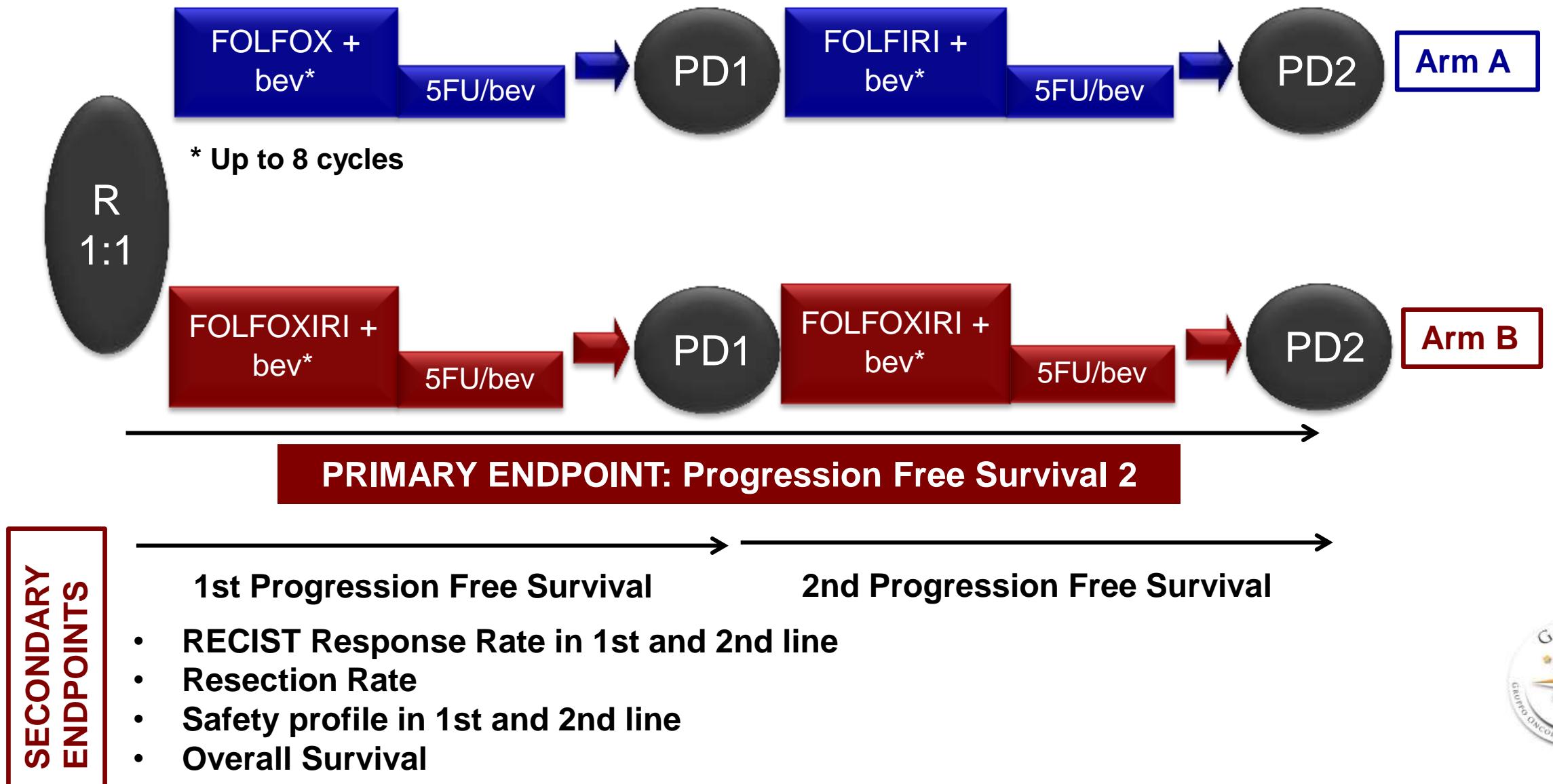




**TRIBE 2**

**Anti EGFRs + Triplet**

# TRIBE2: Study design

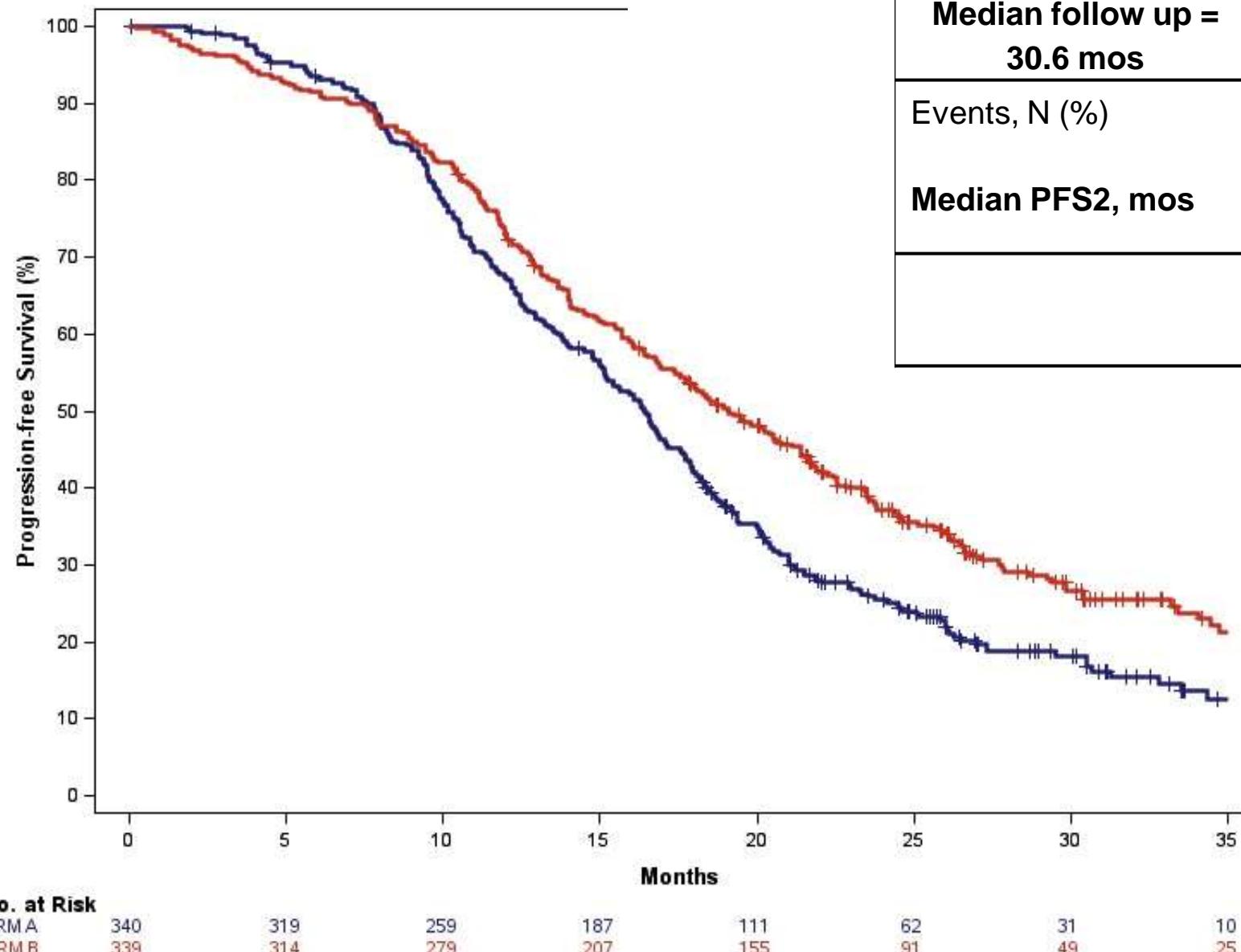


# Patients' characteristics – ITT population

N=679

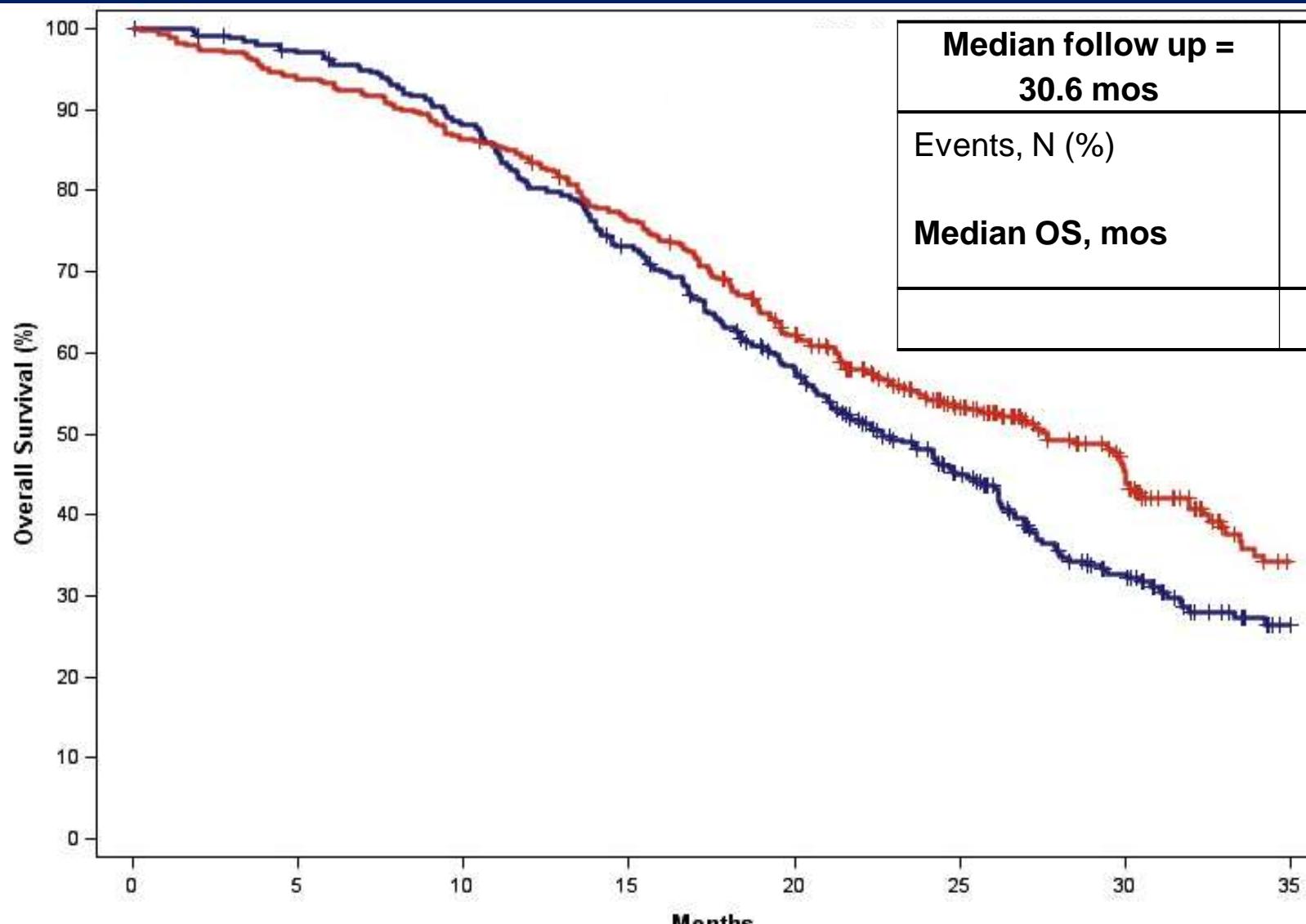
<b>Characteristic, % patients</b>	<b>Arm A N = 340</b>	<b>Arm B N = 339</b>
<b>Sex (M / F)</b>	61 / 39	54 / 46
<b>Median Age (range)</b>	61 (30 – 75)	60 (33 – 75)
<b>ECOG PS (0 / 1-2)</b>	85 / 15	86 / 14
<b>Synchronous Metastases (Y / N)</b>	89 / 11	89 / 11
<b>Prior Adjuvant CT (Y / N)</b>	2 / 98	2 / 98
<b>Number Metastatic Sites (1 / &gt;1)</b>	38 / 62	45 / 55
<b>Liver Only Disease (Y / N)</b>	29 / 71	32 / 68
<b>Primary Tumor Side (right / left)</b>	38 / 62	38 / 62
<b>RAS/BRAF (RAS mut / BRAF mut / wt / NE)</b>	65 / 10 / 20 / 5	63 / 10 / 22 / 5
<b>Right AND/OR RAS/BRAF mut / Left AND RAS/BRAF wt / NA</b>	<b>79 / 16 / 5</b>	<b>78 / 17 / 5</b>

# Primary endpoint: Progression Free Survival 2



Median follow up = 30.6 mos	Arm A N = 340	Arm B N = 339
Events, N (%)	272 (80%)	242 (71%)
Median PFS2, mos	<b>17.5</b>	<b>19.1</b>
HR = 0.74 [95% CI: 0.62-0.88] p<0.001		

# Overall Survival – preliminary results



Median follow up = 30.6 mos	Arm A N = 340	Arm B N = 339
Events, N (%)	217 (64%)	191 (56%)
Median OS, mos	22.6	27.6
HR = 0.81 [95%CI: 0.67-0.98] p=0.033		

## No. at Risk

ARM A	340	325	294	242	184	117	64	29
ARM B	339	318	293	256	201	137	83	37

## Conclusions

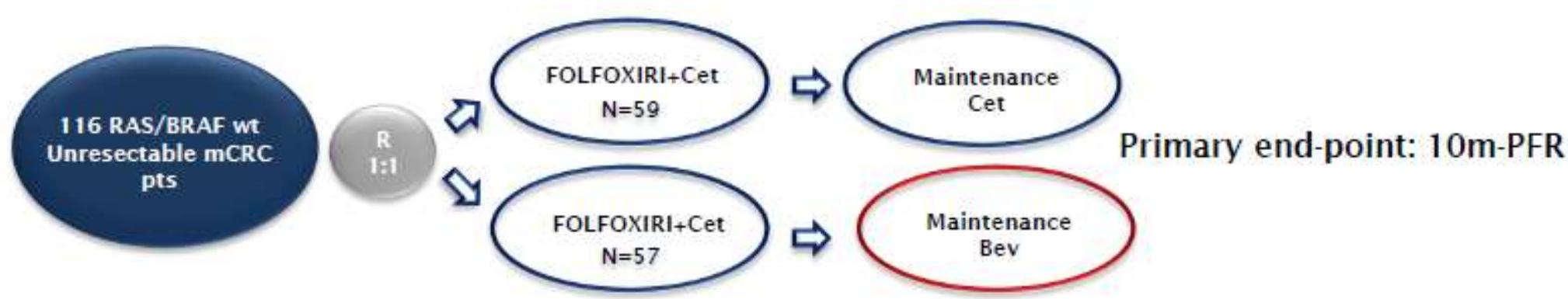
- ✓ First-line treatment with FOLFOXIRI/bev does not impair the feasibility and the efficacy of therapies after progression and may positively affect patients' long-term outcome
- ✓ Safety, activity and efficacy results reported with FOLFOXIRI/bev (4 months, followed by 5FU/LV maintenance) are highly consistent with those from the previous phase III TRIBE study (6 months, followed by 5FU/LV maintenance)
- ✓ When feasible, the reintroduction of FOLFOXIRI/bev after PD may provide a further benefit with modest additional toxicities
- ✓ These data support the use of FOLFOXIRI/bev as the best first-line option for most fit patients with right-sided and/or *RAS/BRAF* mutated mCRC



**TRIBE 2**

**Anti EGFRs + Triplet**

# FOLFOXIRI+Cet: MACBETH trial



Activity	Arm A N = 59	Arm B N = 57	All N = 116
RECIST Response Rate	68%	75%	<b>72%</b>
Disease Control Rate	92%	89%	<b>91%</b>
<i>Early tumor shrinkage (ETS)</i>	Arm A N = 54	Arm B N = 53	All N = 107
ETS ≥ 20%	74%	77%	<b>76%</b>

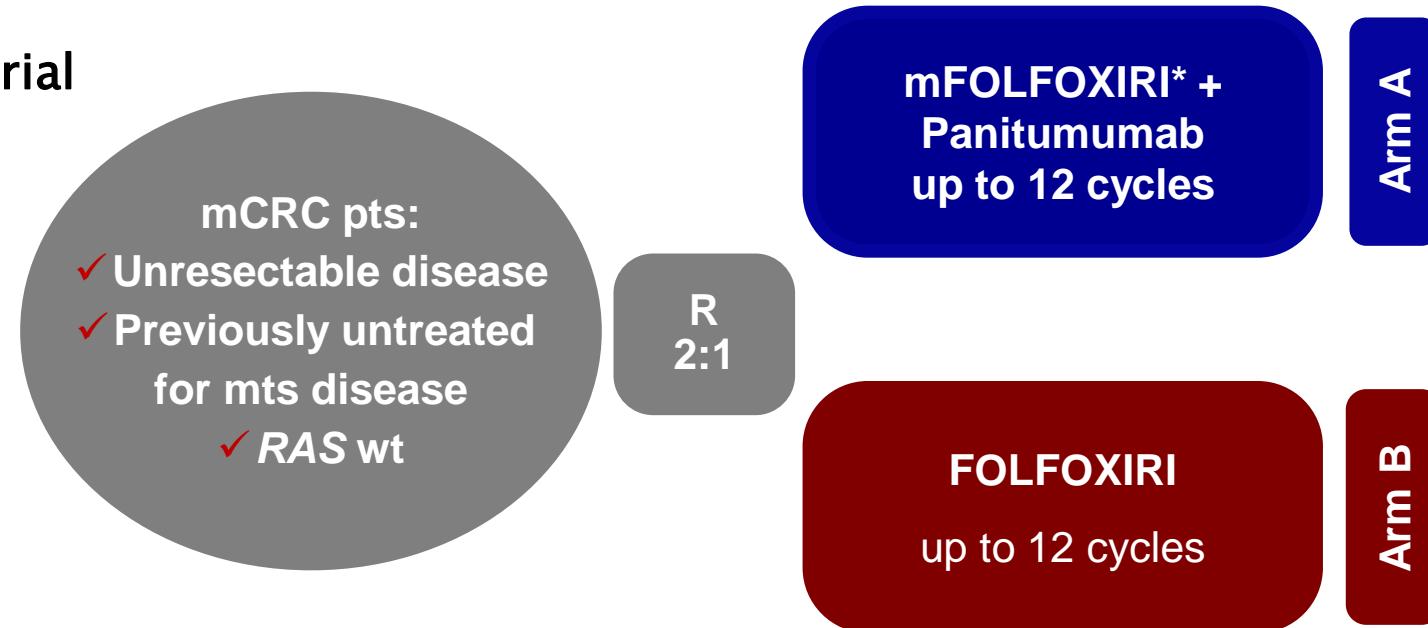
Resection Rate	Arm A N = 59	Arm B N = 57	All N = 117
R0/R1/R2 surgery	45.8%	29.8%	<b>37.9%</b>
R0 secondary surgery	32.2%	22.8%	<b>27.6%</b>
<i>Liver-only subgroup</i>	N = 28	N = 24	
R0/R1/R2 surgery	71.4%	58.3%	<b>65.4%</b>
R0 secondary surgery	53.6%	45.8%	<b>50.0%</b>

# MACBETH: Safety

<b>G3/4 adverse events, % patients</b>	<b>Arm A N = 59</b>	<b>Arm B N = 57</b>	<b>Overall N = 116</b>
Nausea	1.7%	0%	<b>0.9%</b>
Vomiting	3.4%	1.0%	<b>2.6%</b>
Diarrhea	20.3%	15.8%	<b>18.1%</b>
Stomatitis	6.8%	5.3%	<b>6.0%</b>
Neutropenia	28.8%	33.3%	<b>31.0%</b>
Febrile neutropenia	3.4%	1.8%	<b>2.6%</b>
Skin rash	18.6%	12.3%	<b>15.5%</b>

# FOLFOXIRI+Pani: VOLFI trial

Phase II randomized trial



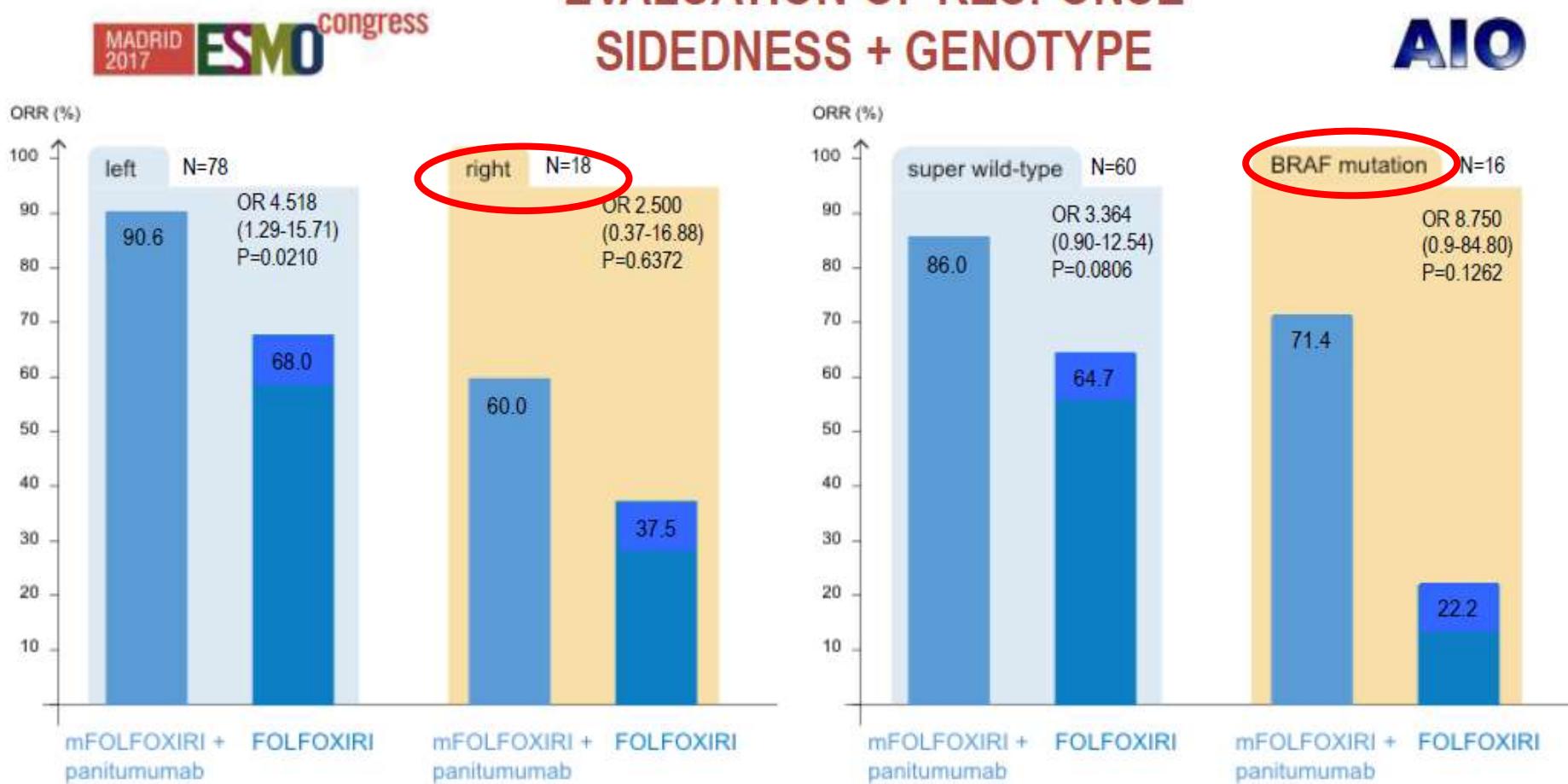
\*irinotecan 150mg/sqm;  
oxaliplatin 85 mg/sqm;  
LV 200 mg/sqm;  
5-FU: 3000 mg/sqm

**Primary endpoint: Objective Response Rate**

# FOLFOXIRI+Pani: activity in VOLFI

	mFOLFOXIRI+ pan N=63	FOLFOXIRI N=33	OR	p
<b>Response Rate</b>	87.3%	60.6%	4.47	0.004
<b>Resection Rate</b>	33.3%	12.1%	3.63	0.02
<b>Definitive non-resectable</b>	<b>N=43</b> 14.0%	<b>N=22</b> 0%	7.80	0.08
<b>Potentially resectable</b>	<b>N=20</b> 75.0%	<b>N=11</b> 36.4%	5.25	0.05

# VOLFI: Results



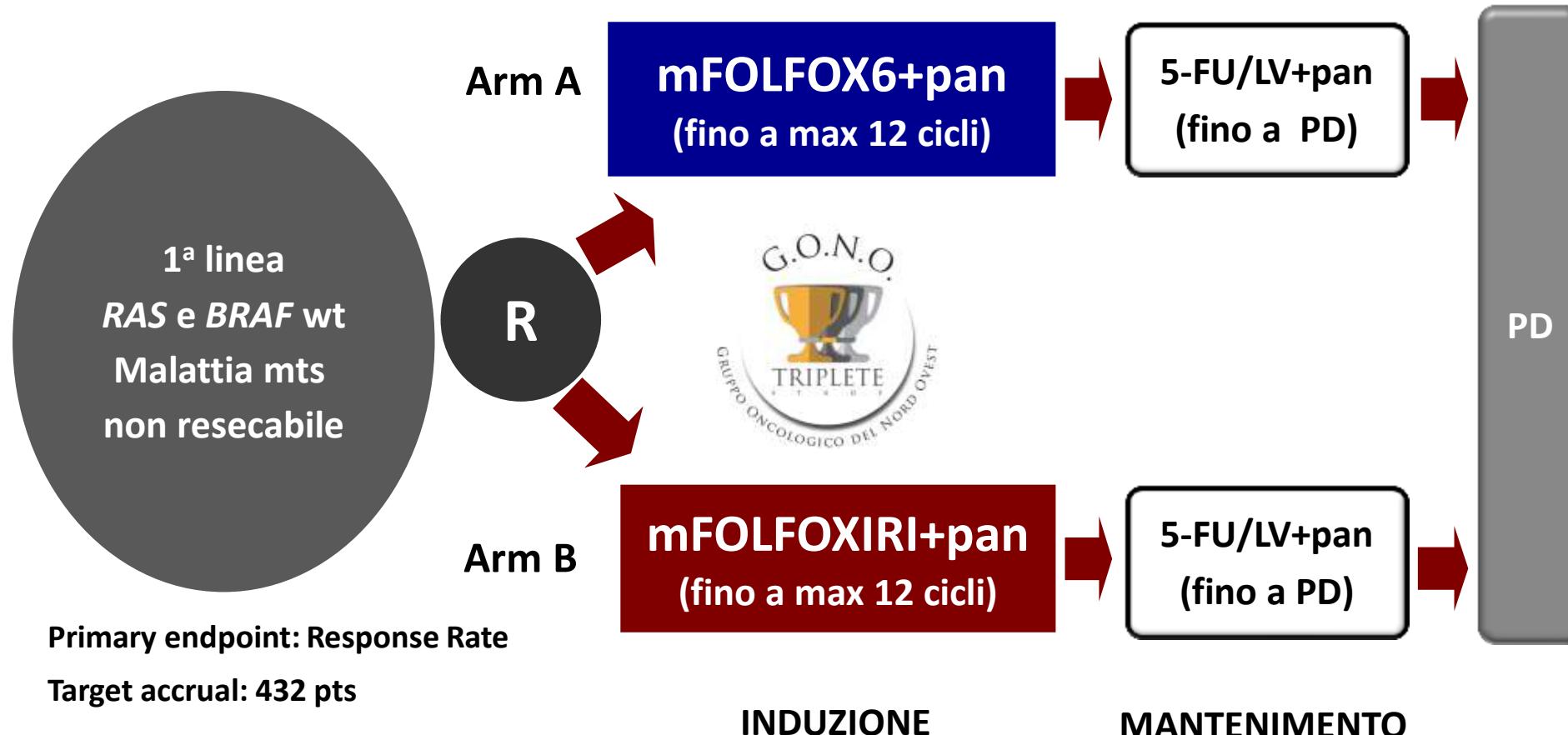
## First-line triplet plus anti-EGFR

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- ✓ A modified schedule of FOLFOXIRI plus anti-EGFR is confirmed to be safe and feasible
- ✓ Remarkable activity results translate into high secondary resection rate
- ✓ The intensification of the chemotherapy backbone plus anti-EGFR emerges as an appealing treatment, especially when a rapid and deep tumor shrinkage is required
- ✓ Volfi trial met its primary endpoint, but failed its secondary endpoints of PFS and OS
- ✓ BRAF mutated?

# TRIPLETE: Study Design

## Fase III randomizzato



### Fattori di stratificazione:

- ECOG PS: 0 vs 1-2
- →Sede del T primitivo: colon dx (dal ceco al trasverso) vs colon sx (dalla flessura sx al retto)
- Metastasi limitate al fegato: si vs no

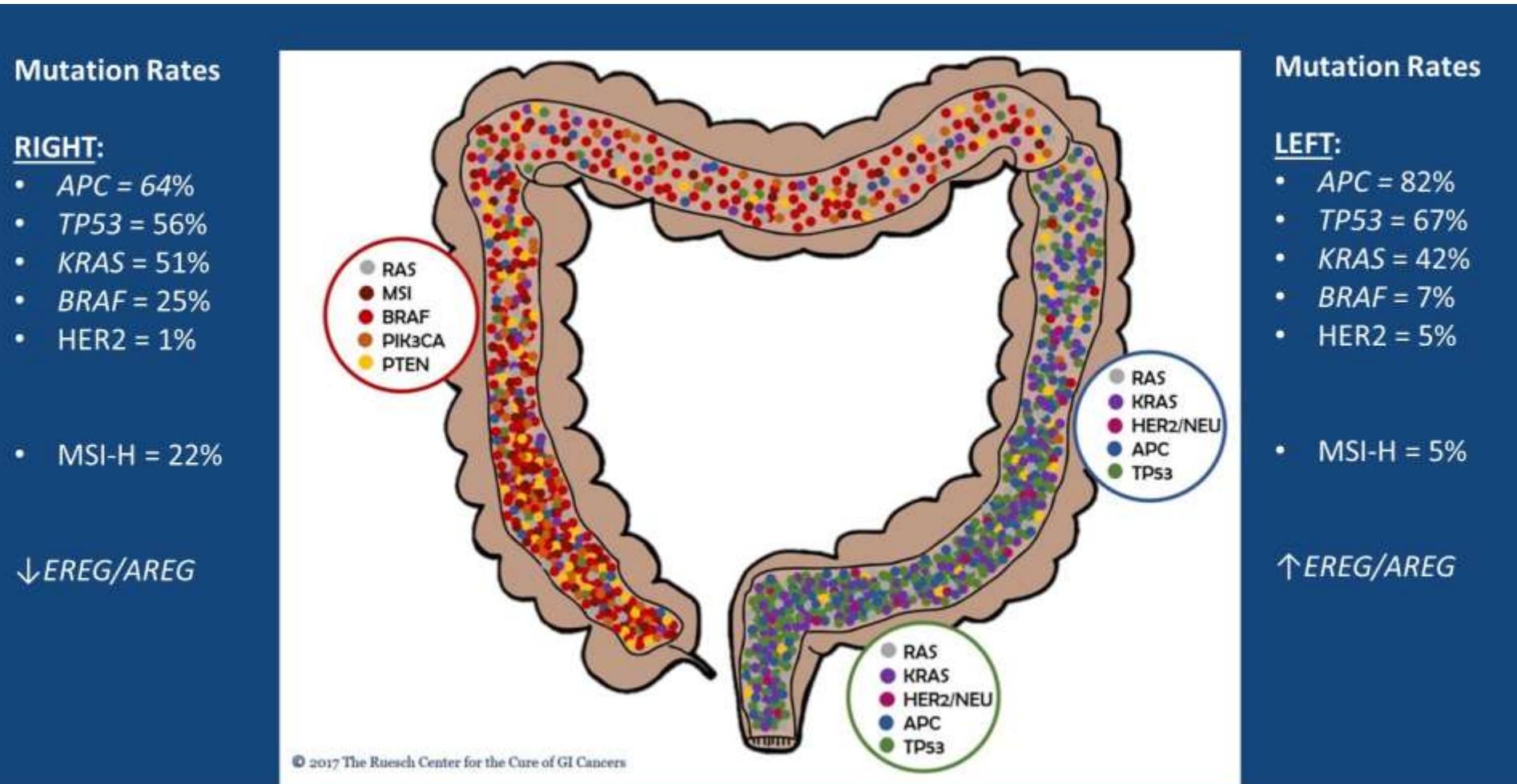


# **How to optimize the first-line therapy in wt mCRC pts?**

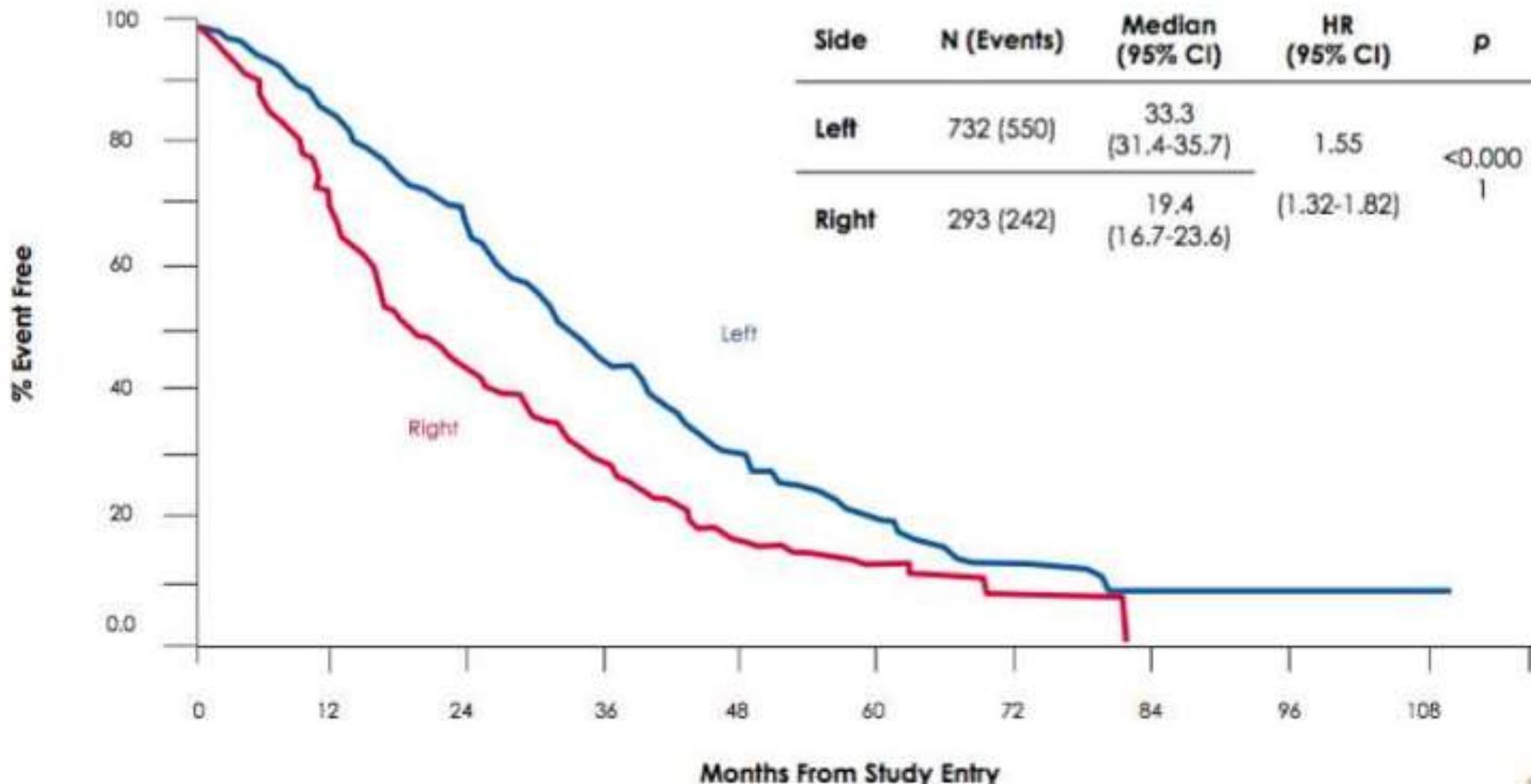
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- 1) Tumor Sideness?**
- 2) Molecular selection for anti-EGFRs**

# Right versus Left: molecular make-up



# Right versus left: prognostic!

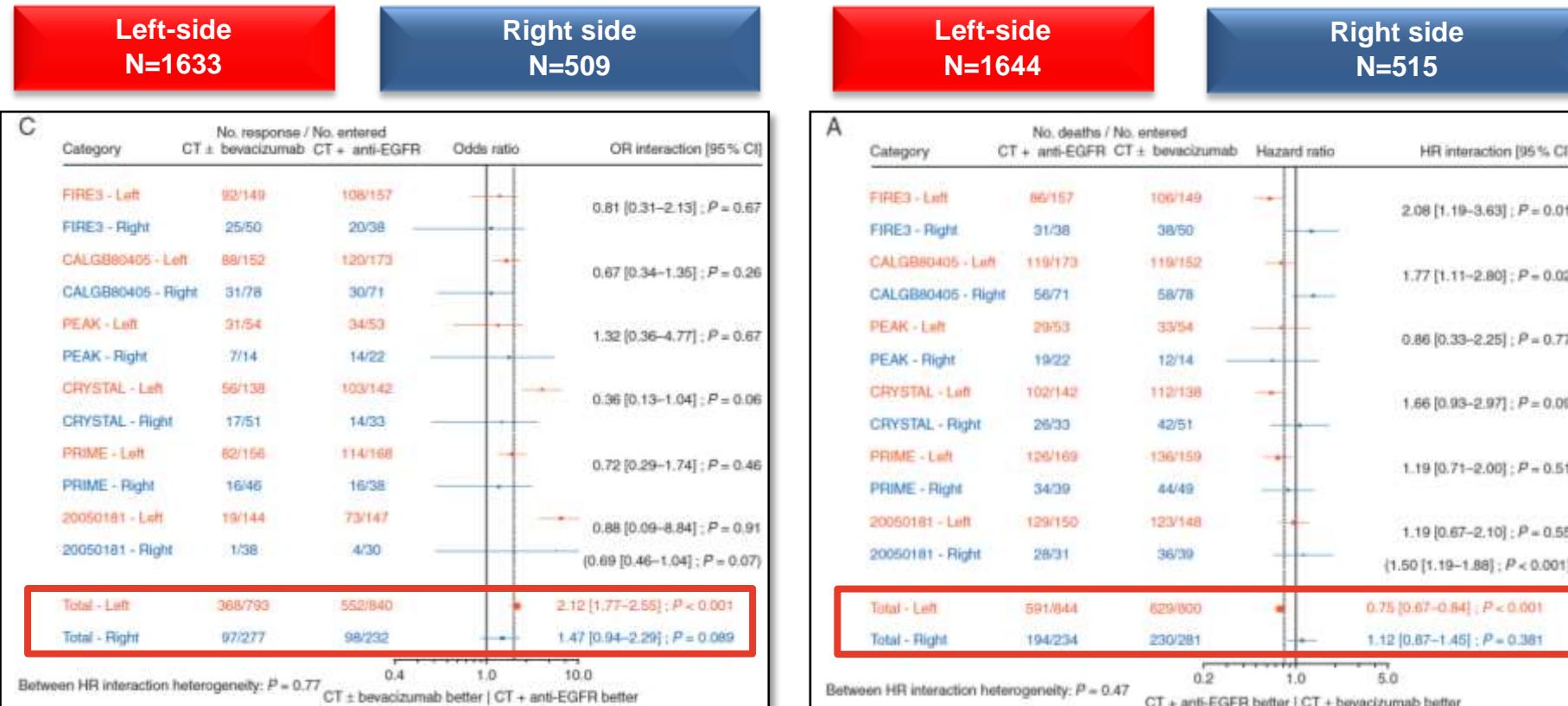


**... Is Primary Tumor Location Predictive for bev or anti-EGFRs?**

# Primary tumor location as a surrogate marker

*A retrospective analysis of 6 randomized trials:  
CRYSTAL, FIRE-3, CALGB 80405, PRIME, PEAK and 20050181*

**2159 patients with All RAS wt mCRC treated with anti-EGFR**



**Objective Response Rate**

**Overall Survival**

## CRC sidedness ...

- ✓ Right-sided tumors have worse prognosis
  - ✓ No different benefit from BEV for right versus left
  - ✓ Great benefit from anti-EGFRs in left-sided tumors
  - ✓ Primary tumor location should be considered among other drivers for the choice of the first-line
- ***Location is clearly a surrogate of several molecular markers ...  
KNOWLEDGE OF TUMOR BIOLOGY SHOULD BE STRONGLY  
IMPROVED!!!***

# **How to optimize the first-line therapy in wt mCRC pts?**

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- 1) Tumor Sideness?**
- 2) Molecular selection for anti-EGFRs**

# BRAF mutated tumors

**RAS wt**



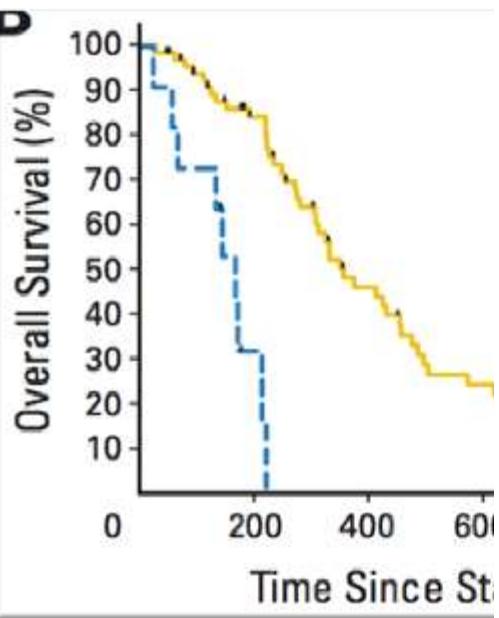
**BRAF mut**  
**10-15%**

- ✓ Poor prognosis
- ✓ More frequent in women and in right colon tumors
- ✓ Often poor performance
- ✓ Often mucinous hystotype and microsatellite instability (MSI)
- ✓ Peritoneal and nodes metastases more frequent
- ✓ Characteristic gene signature

# Benefit from anti-EGFRs: still a debated issue

\* $P < .05$  ( $P = .029$ )

	Mutant <i>BRAF</i> 11/79 (14%)	Wild-Type <i>BRAF</i> 68/79 (86%)
Responders	0/11 (0%)*	22/68 (32%)*
Nonresponders	11/11 (100%)*	46/68 (68%)*



Di Nicolantonio et al, J Clin Oncol '08

Pietrantonio et al, Eur J Cancer '15

# TRIBE: OS outcome according to molecular subgroups

FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study

Chiara Cremolini\*, Fotios Loupolis\*, Carlotta Antoniotti, Cristian Lupi, Elisa Sensi, Sara Lainardi, Silvia Mezi, Gianluca Tornaxelli, Monica Ronzoni, Alberto Zaniboni, Giuseppe Tonini, Chiara Carliomagno, Giacomo Allegri, Silvana Olara, Mauro D'Amico, Cristina Grisotto, Marina Cozzaniga, Luca Boni, Gabriella Fontanini, Alfredo Falcone

	N	FOLFIRI + bev Median OS	FOLFOXIRI + bev Median OS	HR [95% CI]	p
RAS and BRAF wt	93	33.5	41.7	0.77 [0.46-1.27]	
RAS mutated	236	23.9	27.3	0.88 [0.65-1.18]	0.522*
BRAF mutated	28	10.7	19.0	0.54 [0.24-1.20]	

\* p for interaction

# Molecular selection for anti-EGFRs



Annals of Oncology 0: 1–6, 2017  
doi:10.1093/annonc/mdx546  
Published online 25 September 2017

ORIGINAL ARTICLE

Negative hyper-selection of metastatic colorectal cancer patients for anti-EGFR monoclonal antibodies: the PRESSING case-control study

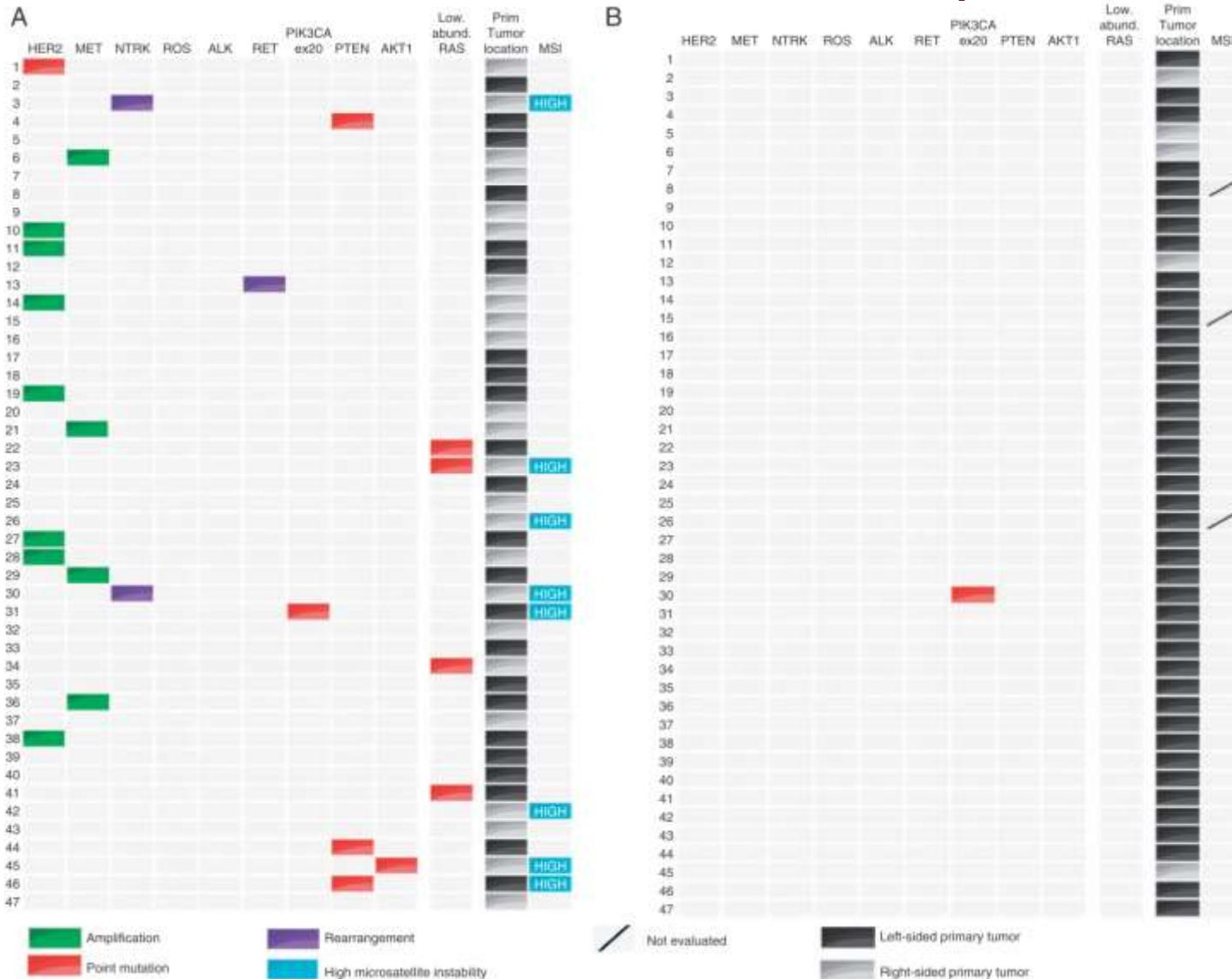
To demonstrate the negative predictive impact of a panel of genomic alterations in *RAS* and *BRAF* wild-type mCRC

## PRESSING Panel

- *HER2* amplification or mutations
- *MET* amplification
- *ALK/ROS1/NTRKs* and *RET* fusions
- *PI3K/PTEN/Akt* and *MAPKs* pathways' activating mutations

# PRESSING panel: results

## Primary resistant pts



**PRESSING panel alterations are more frequent:**  
**Resistant vs sensitive pts,  $p<0.001$**   
**Right-sided vs left-sided tumors,  $p=0.030$**

## First Line Options : “Cytoreduction Intent”

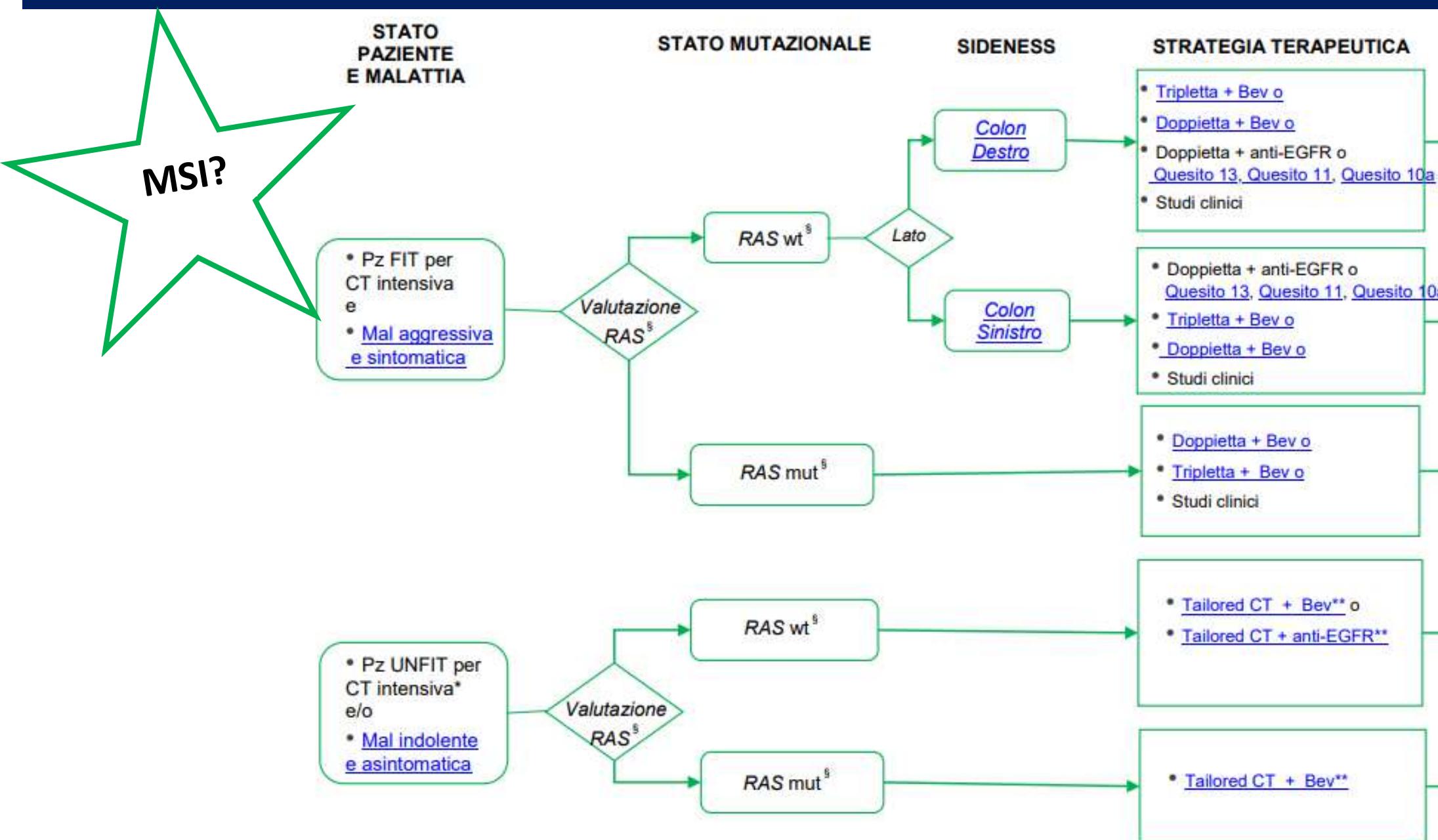
Goal / condition	Molecular	Preferred 1st line regimen
<b>Cytoreduction</b>	<b>all WT</b>	<b>Left:</b> Doublet/anti-EGFR <b>Right:</b> FOLFOXIRI/beva (Doublet/anti-EGFR)
	<b>RAS mut</b>	FOLFOXIRI (Doublets)/beva
	<b>BRAF mut</b>	FOLFOXIRI/beva

Waiting for more robust data with triplet plus anti-EGFR

## First Line Options : “Disease Stabilization Intent”

Goal / condition	Molecular	Preferred 1st line regimen
Disease stabilization	all WT	Left: Doublet/anti-EGFR Right: Doublet/bev (FOLFOXIRI/bev)
	RAS mut	Doublet/bev
	BRAF mut	FOLFOXIRI/bev

# LINEE GUIDA AIOM 2018



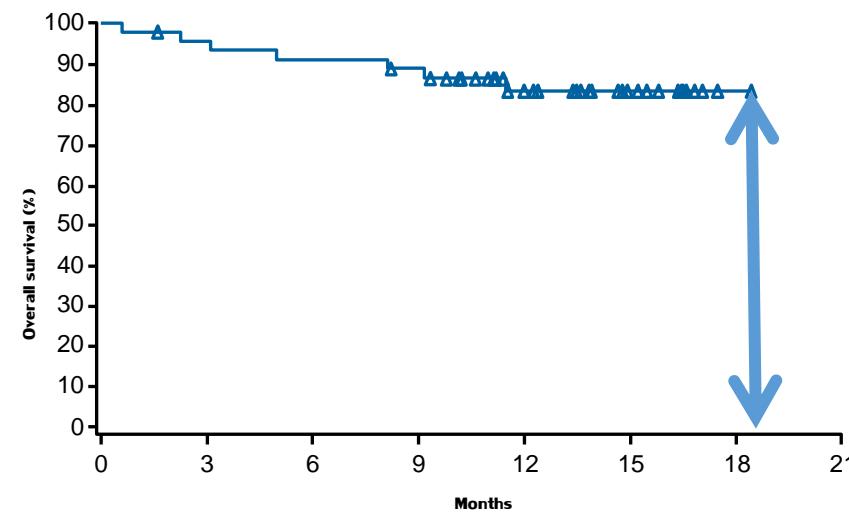
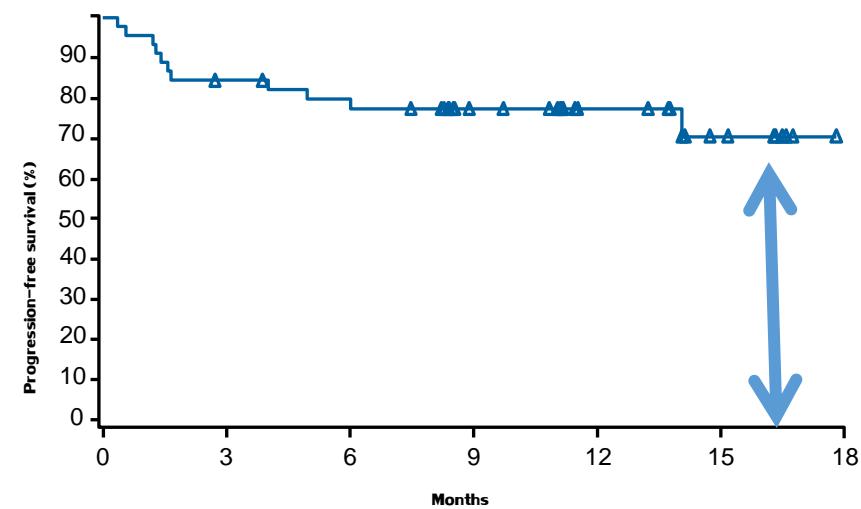
# CheckMate 142: first-line Ipi+Nivo



Objective Response Rate: 60%

PFS	NIVO3 (Q2W) + IPI1 (Q6W) N = 45
Median PFS, months (95% CI)	NR (14.1–NE)
9-mo rate (95% CI), %	77 (62.0–87.2)
12-mo rate (95% CI), %	77 (62.0–87.2)

OS	NIVO3 (Q2W) + IPI1 (Q6W) N = 45
Median OS, months (95% CI)	NR (NE)
9-mo rate (95% CI), %	89 (74.9–95.1)
12-mo rate (95% CI), %	83 (67.6–91.7)



No. at risk

45

37

34

24

15

7

7

45

42

40

38

24

13

1

0

## Conclusions

- ✓ The choice of the first-line treatment has a crucial mission in mCRC: to achieve disease control, in order to allow further interventions (systemic treatments and locoregional tools)
- ✓ Though recognizing the importance of exposing mCRC patients to all available treatment options across different lines of treatment (sequencing, continuum of care...), the impact of the first-line treatment on the disease history is the most relevant
- ✓ Today a mix of clinical and molecular factors contribute to the therapeutic decision-making process...the contribution of molecular markers will probably increase in the next future

