
GI
connect®
POWERED BY COR2ED

GI CONNECT EXPERTS KNOWLEDGE SHARE: HOW DO WE IDENTIFY AND TREAT PATIENTS WITH *BRAF*-MUTATED mCRC TODAY AND TOMORROW?

Dr. Scott Kopetz (USA), Dr. Armin Gerger (Austria) and Dr. Joleen Hubbard (USA)

Monday October 19th and Thursday October 22nd 2020

Supported by an Independent Educational Grant from Bayer

EXPERTS KNOWLEDGE SHARE

GI connect® POWERED BY COR2ED

OBJECTIVE: Discuss how we identify and treat patients with *BRAF*-mutated mCRC

- Your opportunity to discuss and share learnings on challenging questions within the area of GI oncology
- A chance to hear the experts provide their perspectives and interpretation
- A forum for you to ask the experts and allow them to answer the questions that are important to you
- Review and discuss your own patient scenarios along with any questions

BRAF, B-Raf proto-oncogene; GI, gastrointestinal; mCRC, metastatic colorectal cancer

INTRODUCTION TO MAPK SIGNALLING PATHWAY AND THE ROLE OF *BRAF*

Dr. Scott Kopetz

MD Anderson Cancer Center, Houston, TX, USA

BRAF, B-Raf proto-oncogene; MAPK, mitogen-activated protein kinase

DISCLAIMER AND DISCLOSURES

Please note: The views expressed within this presentation are the personal opinions of the expert. They do not necessarily represent the views of the author's academic institution or the rest of the GI CONNECT group.

Disclosures: Dr. Scott Kopetz has the following information to disclose:

Advisory Boards

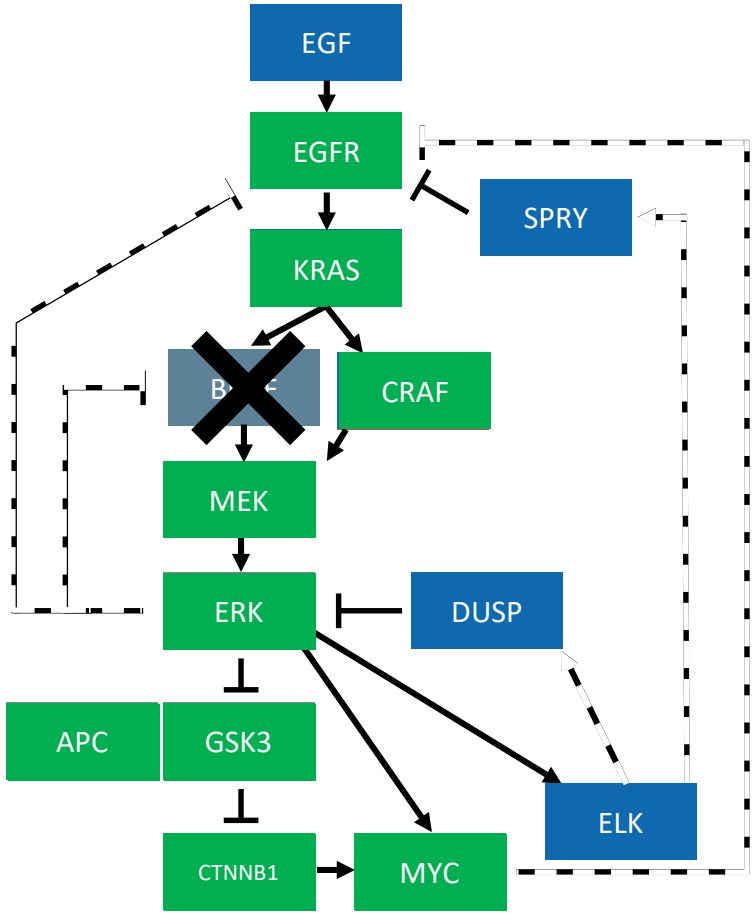
- Amal Therapeutics, Amgen, AstraZeneca/Medimmune, Bayer Health, Biocartis, Boehringer Ingelheim, Boston Biomedical, EMD Serono/Merck KGA, Holy Stone, Karyopharm Therapeutics, Lilly, Merck, Navire Pharma, Novartis, Pfizer, Pierre Fabre, Roche/Genentech, Symphogen

Research funding

- Amgen, Biocartis, Boehringer Ingelheim, EMD Serono, Genentech/Roche, Guardant Health, MedImmune, Novartis, Sanofi

TARGETING MAPK: ADAPTIVE RESISTANCE

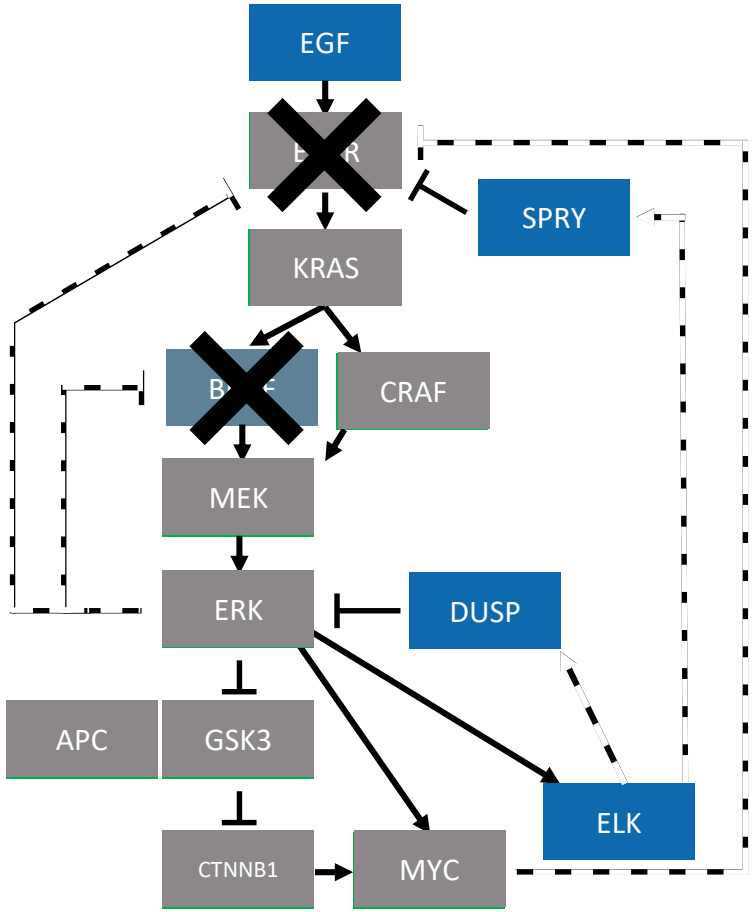
RAF kinase family = key components of the RAS–RAF–MEK–ERK signalling cascade
Like RAS, the serine/threonine-protein kinase *BRAF* is a downstream signalling protein in the epidermal growth factor receptor (EGFR)-mediated pathway



BRAF, B-Raf proto-oncogene; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase

TARGETING MAPK: ADAPTIVE RESISTANCE

RAF kinase family = key components of the RAS–RAF–MEK–ERK signalling cascade
Like RAS, the serine/threonine-protein kinase *BRAF* is a downstream signalling protein in the epidermal growth factor receptor (EGFR)-mediated pathway



BRAF, B-Raf proto-oncogene; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase

SEQUENCING TREATMENT APPROACH IN PATIENTS WITH *BRAF*-MUTATED mCRC: EU PERSPECTIVE

Dr. Armin Gerger
Medical University Graz, Austria

BRAF, B-Raf proto-oncogene; EU, European Union; mCRC, metastatic colorectal cancer

DISCLAIMER AND DISCLOSURES

Please note: The views expressed within this presentation are the personal opinions of the expert. They do not necessarily represent the views of the author's academic institution or the rest of the GI CONNECT group.

Disclosures: Dr. Armin Gerger has the following information to disclose:

Advisory Boards

- Advisory Board: Roche, Merck, Amgen, Servier, Bayer, Pierre Fabre, AsrtraZeneca, Boehringer Ingelheim, Eli Lilly, Sanofi

Research funding

- Research Funding: Roche, Merck, Amgen, Pierre Fabre, Servier, Sanofi

AGENDA

- *RAS* and *BRAF* biomarkers testing in EU
- FOFOXIRI + bev defined SoC in first-line treatment for *BRAF*-mutant mCRC
- Key clinical results in second-line treatment for *BRAF*-mutant mCRC
- Immunotherapy clinical data for MSI-H *BRAF*-mutant mCRC
- Key clinical results in third-line treatment for *BRAF*-mutant mCRC
- Next key clinical development programs
- ESMO guidelines and recommendations

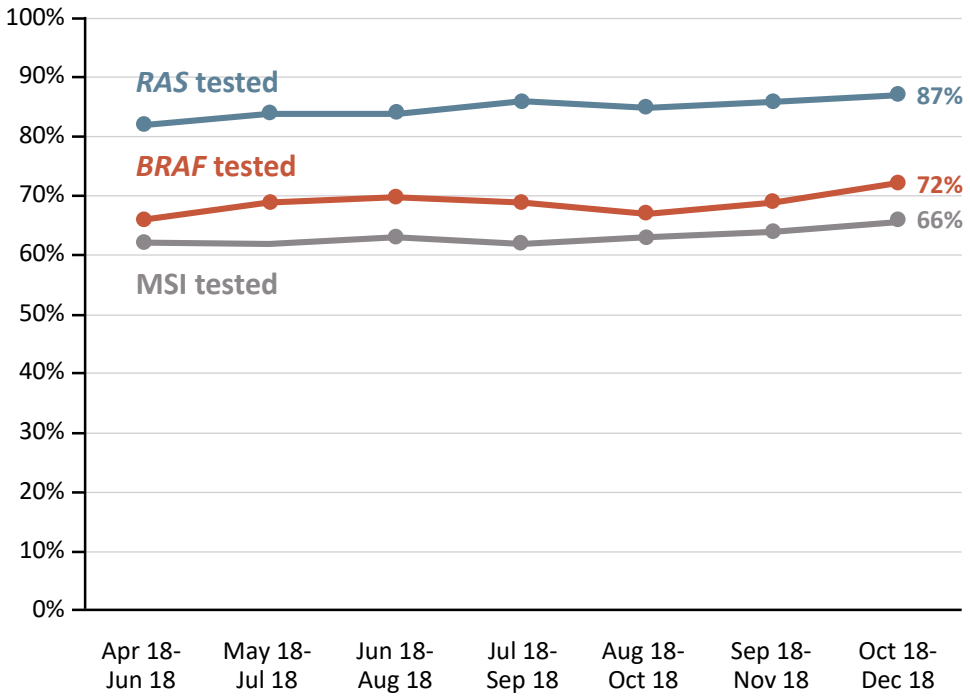
bev, bevacizumab; BRAF, B-Raf proto-oncogene; ESMO, European Society for Medical Oncology; EU, European Union; FOLFOXIRI, folinic acid + fluorouracil + oxaliplatin + irinotecan; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; SoC, standard of care

RAS AND *BRAF* TESTING IN EU

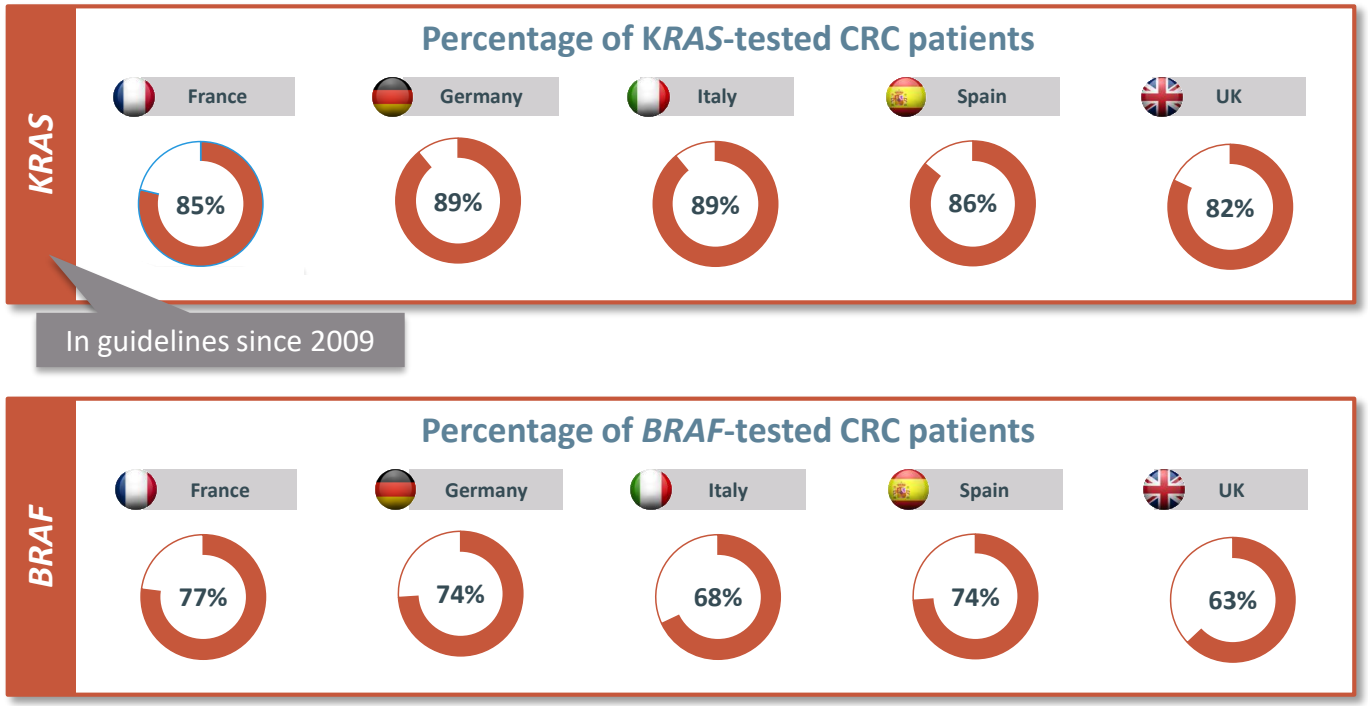
BRAF, B-Raf proto-oncogene; EU, European Union

RAS- AND *BRAF*-TESTING IN CLINICAL ROUTINE SETTING IN THE FIVE EU COUNTRIES*

1



2



→ *KRAS* and *BRAF* testing is low

* Germany, France, Italy, Spain and UK

BRAF, B-Raf proto-oncogene; CRC, colorectal cancer, EU, European Union; MSI microsatellite instability

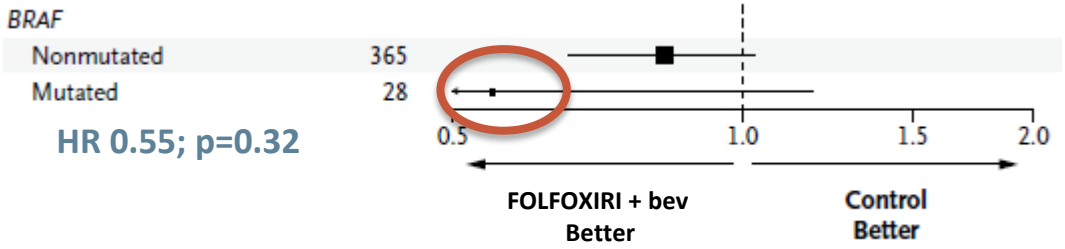
1. IPSOS. Pierre Fabre commissioned quantitative market research Q4 2018. Shared with the permission of Pierre Fabre
2. IPSOS. Pierre Fabre commissioned quantitative market research in June 2019. Shared with the permission of Pierre Fabre

FOLFOXIRI + BEV DEFINED 1ST LINE STANDARD OF CARE FOR *BRAF*-MUTANT mCRC

bev, bevacizumab; BRAF, B-Raf proto-oncogene; FOLFOXIRI, folinic acid + fluorouracil + oxaliplatin + irinotecan; mCRC, metastatic colorectal cancer

SUBGROUP ANALYSIS OF TRIBE STUDY SHOWED EFFICACY IN *BRAF*-MUTANT mCRC

Baseline characteristics of the patients in the ITT population		
Characteristic	**FOLFIRI + bev (N=256)**	**FOLFOXIRI + bev (N=252)**
***BRAF* status, n (%)**		
Non mutated	183 (71.5)	182 (72.2)
Mutated	**12 (4.7)**	**16 (6.3)**
No definable	6 (2.3)	7 (2.8)
Missing data	55 (21.5)	47 (18.7)



Efficacy results in *BRAF*-mutation positive subgroup		
	FOLFIRI + bev (N=12)	**FOLFOXIRI + bev (N=16)**
Median OS		
Months (95% CI)	10.7 (3.1–24.8)	19.0 (8.2–28.6)
HR (95% CI)	0.54 (0.24–1.20)	
Median PFS		
Months (95% CI)	5.5 (1.6–11.2)	7.5 (5.1–15.0)
HR (95% CI)	0.57 (0.27–1.23)	
ORR		
n (%)	5 (42%)	9 (56%)
Odds ratio (95% CI)	1.82 (0.38–8.78)	

In *BRAF*-mutant mCRC patients, the role of FOLFOXIRI + bevacizumab looked promising but was not confirmed in further clinical investigations

bev, bevacizumab; BRAF, B-Raf proto-oncogene; CI, confidence interval; FOLFIRI, folinic acid + fluorouracil + irinotecan; FOLFOXIRI, folinic acid + fluorouracil + oxaliplatin + irinotecan; HR, hazard ratio; ITT, intention to treat; mCRC, metastatic colorectal cancer; ORR, overall response rate; OS, overall survival, PFS, progression-free survival
Loupakis F, et al. N Engl J Med 2014;371(17):1609-18, Cremolini C, et al. Lancet Oncol 2015;16(13):1306-15

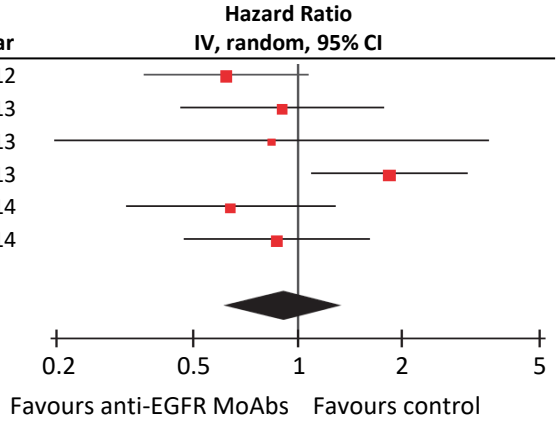
ROLE OF *BRAF* MUTATIONS IN THE ACTIVITIES OF *EGFR* INHIBITORS IN mCRC PATIENTS IN 1L AND 2L SETTINGS

OS for anti-EGFR treatment in *BRAF*-mutant mCRC patients

Study or Subgroup	Log (Hazard Ratio)	SE	Weight	Hazard Ratio IV, random, 95% CI	Year
Bokemeyer 2012	-0.478	0.275	20.7%	0.62 (0.36-1.06)	2012
Douillard 2013	-0.105	0.342	17.0%	0.90 (0.46-1.76)	2013
Karapetis 2013	-0.174	0.736	6.0%	0.84 (0.20-3.56)	2013
Seymour 2013	0.61	0.263	21.5%	1.84 (1.10-3.08)	2013
Peeters 2014	-0.446	0.354	16.4%	0.64 (0.32-1.28)	2014
Stintzing 2014	-0.139	0.314	18.5%	0.87 (0.47-1.61)	2014
Total (95% CI)			**100.0%**	**0.91 (0.62-1.34)**	

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 10.09$, df = 5 (p=0.07); $I^2 = 50\%$

Test for overall effect: Z = 0.48 (p=0.63)



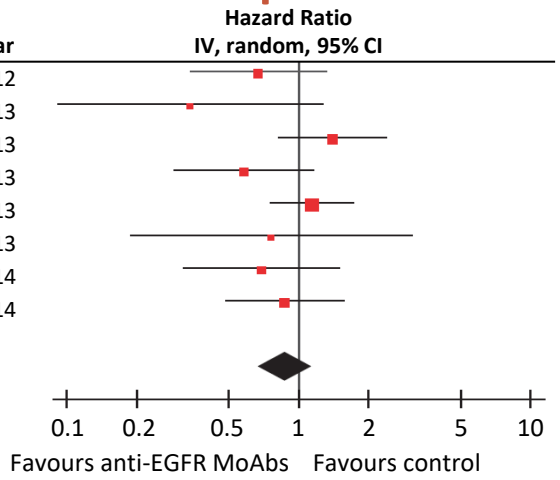
HR: 0.91

PFS for anti-EGFR treatment in *BRAF*-mutant mCRC patients

Study or Subgroup	Log (Hazard Ratio)	SE	Weight	Hazard Ratio IV, random, 95% CI	Year
Bokemeyer 2012	-0.4	0.34	12.6%	0.67 (0.34-1.31)	2012
Peeters 2013	-1.079	0.669	3.8%	0.34 (0.09-1.26)	2013
Seymour 2013	0.336	0.273	17.5%	1.40 (0.82-2.39)	2013
Douillard 2013	-0.545	0.351	12.0%	0.58 (0.29-1.15)	2013
Smith 2013	-0.131	0.207	25.1%	1.14 (0.76-1.71)	2013
Karapetis 2013	-0.274	0.711	3.4%	0.76 (0.19-3.06)	2013
Peeters 2014	-0.371	0.392	10.0%	0.69 (0.32-1.49)	2014
Stintzing 2014	-0.139	0.297	15.5%	0.87 (0.49-1.56)	2014
Total (95% CI)			**100.0%**	**0.88 (0.67-1.14)**	

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 8.88$, df = 7 (p=0.26); $I^2 = 21\%$

Test for overall effect: Z = 0.98 (p=0.33)



HR: 0.88

Meta-analysis of 10 trials including 463 *BRAF*-mutant CRC patients

The addition of cetuximab and panitumumab **in *BRAF*-mutant CRC patients**:

- **did not increase OS** compared with chemotherapy or BSC (HR, 0.91; 95% CI, 0.62–1.34; p=0.63)
- **did not increase PFS** compared with chemotherapy or BSC (HR, 0.88; 95% CI, 0.67–1.14; p=0.33)
- **did not favour anti-EGFR agents in front-line setting**

BRAF, B-Raf proto-oncogene; BSC; best supportive care; CI, confidence interval; CRC, colorectal cancer; df, degrees of freedom; EGFR, epidermal growth factor receptor; HR, hazard ratio; IV, inverse variance; mCRC, metastatic CRC; MoAbs, monoclonal antibodies; OS, overall survival; PFS, progression-free survival; SE, standard error

Pietrantonio F, et al. Eur J Cancer 2015;51(5):587-94

KEY CLINICAL RESULTS IN 2ND LINE THERAPY FOR *BRAF*-MUTANT mCRC

BRAF, B-Raf proto-oncogene; mCRC, metastatic colorectal cancer

CHEMOTHERAPY BASED APPROACHES FOR *BRAF*-MUTANT mCRC IN ≥2ND LINE

Ref. or study name (identification number)	Therapy	*BRAF*-mutant (n)	ORR (%)	PFS (months)	OS (months)
PICCOLO[1] (ISRCTN93248876)	irinotecan +panitumumab /irinotecan	37/31	11/6	NR/NR	NR/NR
Loupakis F. et al. 2009[2]	irinotecan + cetuximab	13	0	2.6	4.1
Mitani S. et al. 2019[3]	CTX	51	7	2.5	6.5
Peeters M. et al. 2014[4]	FOLFIRI +panitumumab /FOLFIRI	22/23	NR/NR	2.5/1.8	4.7/5.7
Saridaki Z. et al. 2013[5]	CTX + Anti-EGFR	42	NR	2.2	4.3
Ulivi P. et al. 2012[6]	CTX + cetuximab	12	8.3	2.8	5.8
De Roock W. et al. 2010[7]	CTX + cetuximab	36	8.3	1.8	6

Clinical benefit of chemotherapy-based approaches is low

1. Seymour MT. et al, Lancet Oncol 2013;14(8):749-59. 2. Loupakis F. et al, Br J Cancer 2009;101(4):715-21. 3. Mitani S. et al, Ther Adv Med Oncol 2019;11:1758835918820298. 4. Peeters M. et al, J Clin Oncol 2014;32(15_suppl): Abstract #3568. 5. Saridaki Z. et al, PLoS One 2013;8(12):e84604. 6. Ulivi P. et al, J Transl Med 2012;10:87. 7. De Roock W. et al, Lancet Oncol 2010;11(8):753-62

BRAF, B-Raf proto-oncogene; CTX, chemotherapy; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

THE PHASE 3 BEACON COLORECTAL CANCER STUDY DESIGN

Role of binimetinib, encorafenib, and cetuximab triplet therapy for patients With *BRAF*^{V600E}-mutant mCRC in 2L or 3L settings

NCT02928224

Data cut-off date: August 15, 2019

Eligibility criteria

- mCRC
- BRAF V600E mutation
- Progression after 1 or 2 regimens
- ECOG PS 0-1
- No prior treatment with any RAF/MEK or EGFR inhibitor

R 1:1:1

Triplet Arm
encorafenib + binimetinib + cetuximab
N=224

Doublet Arm
encorafenib + cetuximab
N=220

Control Arm
irinotecan + cetuximab
OR FOLFIRI + cetuximab
N=221

Primary endpoints:

- Triplet arm vs control arm
  - OS (all randomised patients)
  - ORR BICR (1st 331 randomised patients)

Secondary endpoints:

- Doublet arm vs control arm and triplet arm vs doublet arm:
  - OS and ORR
  - PFS
  - Safety
  - QoL

2L, second-line, 3L, third-line; BICR, blinded independent central review; BRAF, B-Raf proto-oncogene; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FOLFIRI, folinic acid + fluorouracil + irinotecan; mCRC, metastatic colorectal cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; R, randomisation

Kopetz S, et al. N Engl J Med 2019;381(17):1632-43, Kopetz S, et al. J Clin Oncol 2020;38(4_suppl):8-8

THE PHASE 3 BEACON COLORECTAL CANCER STUDY: INITIAL ORR AND UPDATED ORR RESULTS

GI connect® POWERED BY COR2ED

Data cut-off date: February 11, 2019[1]

Confirmed response by BICR	Triplet arm (N=111)	Doublet arm (N=113)	Control arm (N=107)
ORR* (95% CI)	26% (18-35)	20% (13-29)	2% (<1-7)
p value vs control	<0.001	<0.001	

Data cut-off date: August 15, 2019[2]

Confirmed response by BICR	Triplet arm (N=224)	Doublet arm (N=220)	Control arm (N=221)
ORR (95% CI)	27% (21-33)	20% (15-25)	2% (<1-5)
Best overall response			
Complete response	4%	3%	0%
Partial response	23%	16%	2%
Stable disease	48%	56%	29%
Progressive disease	11%	10%	34%
No evaluable by RECIST	14%	15%	32%

Triplet combination demonstrated improved outcome compared to historical data with higher response rate in *BRAF*-mutant mCRC patients in 2L and 3L settings

* ORR with the first 331 randomised patients

BICR, blinded independent central review; BRAF, B-Raf proto-oncogene; CI, confidence interval; ORR, objective response rate; RECIST, response evaluation criteria in solid tumours

1. Kopetz S, et al. N Engl J Med 2019;381(17):1632-43, 2. Kopetz S, et al. J Clin Oncol 2020;38(4_suppl):8-8

IMMUNOTHERAPY CLINICAL DATA IN MSI-H AND *BRAF*-MUTANT mCRC

BRAF, B-Raf proto-oncogene; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high

IMMUNOTHERAPY IN MSI-H *BRAF*-MUTANT mCRC

CheckMate 142[1]

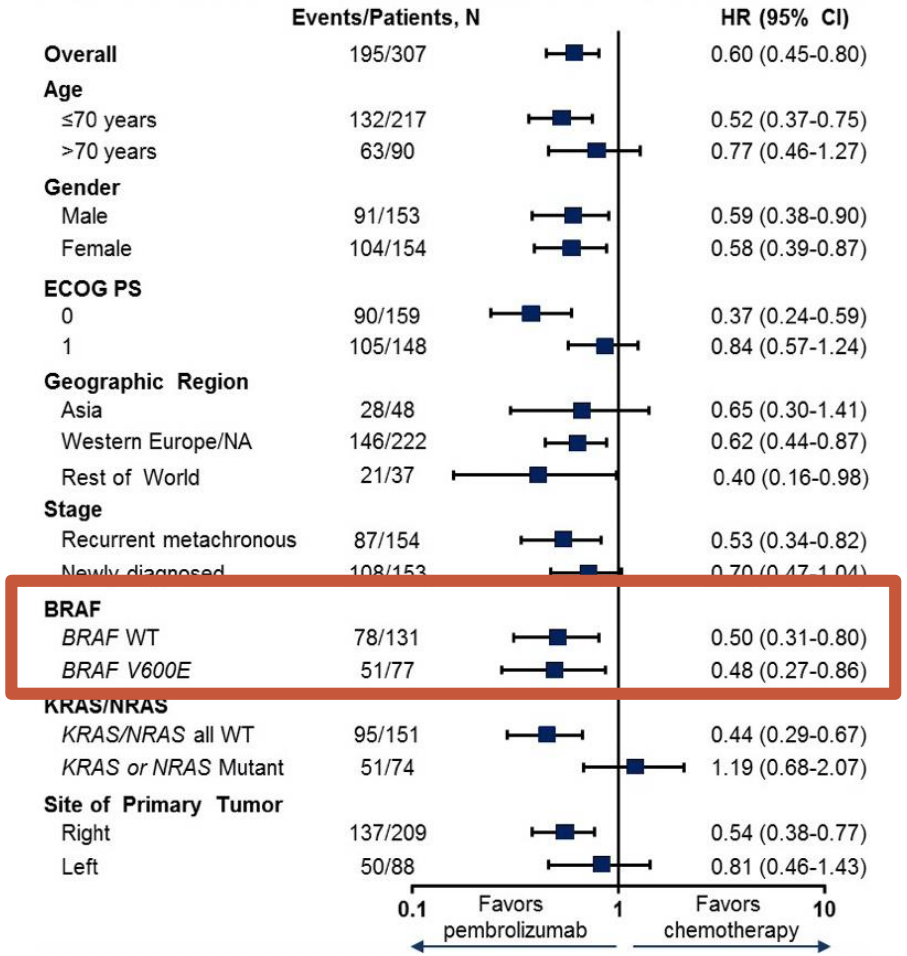
ORR AND DCR IN BIOMARKER-DEFINED PATIENT POPULATIONS PER INVESTIGATOR ASSESSMENT (N=119)

Biomarker	No. (%)	
	ORR	Disease control for ≥12 Weeks
Tumor PD-L1 expression		
≥1% (n=26)	14 (54)	20 (77)
<1% (n=65)	34 (52)	51 (78)
Unknown (n=28)	17 (61)	24 (86)
Mutation status		
BRAF/KRAS wild type (n=31)	17 (55)	24 (77)
BRAF-mutant (n=29)	16 (55)	23 (79)
KRAS mutant (n=44)	25 (57)	37 (84)
Unknown (n=15)	7 (47)	11 (73)
Clinical history of Lynch syndrome*		
Yes (n=35)	25 (71)	30 (86)
No (n=31)	15 (48)	25 (81)
Unknown (n=53)	25 (47)	40 (75)

* Lynch syndrome designation was based on the clinical records of the patients at sites in countries where this reporting was permitted (excluded Italy)

KEYNOTE-177[2]

PROGRESSION-FREE SURVIVAL IN KEY SUBGROUPS



Immunotherapy activity in patients with MSI-H/dMMR mCRC patients is independent of *BRAF* mutation status

BRAF, B-Raf proto-oncogene; DCR, disease control rate; dMMR, mismatch repair deficiency; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; NA, North America; ORR, objective response rate; PD-L1, programmed death-ligand 1; WT, wild type

1. Overman MJ, et al. J Clin Oncol 2018;36(8):773-9, 2. Andre T, et al. J Clin Oncol 2020;38(18_suppl):LBA4

KEY CLINICAL RESULTS IN 3RD LINE THERAPY FOR *BRAF*-MUTANT mCRC

BRAF, B-Raf proto-oncogene; mCRC, metastatic colorectal cancer

NEARLY NO EFFICACY DATA IN 3RD LINE TREATMENT OPTIONS IN *BRAF*-MUTANT mCRC

GI connect® POWERED BY COR2ED

TAS102:

PRECONNECT study (**NCT03306394**)[1]

In the open-label, multicentre, single arm, phase 3b study, in pre-treated mCRC 793 patients were treated with TAS102 and among the 227 RAS WT patients 4% (9) had *BRAF* mutations

Regorafenib:

CORRELATE study (**NCT02042144**)[2]

In the real-world observational study, in pretreated mCRC 1037 patients were treated with regorafenib with 4% having *BRAF* mutations

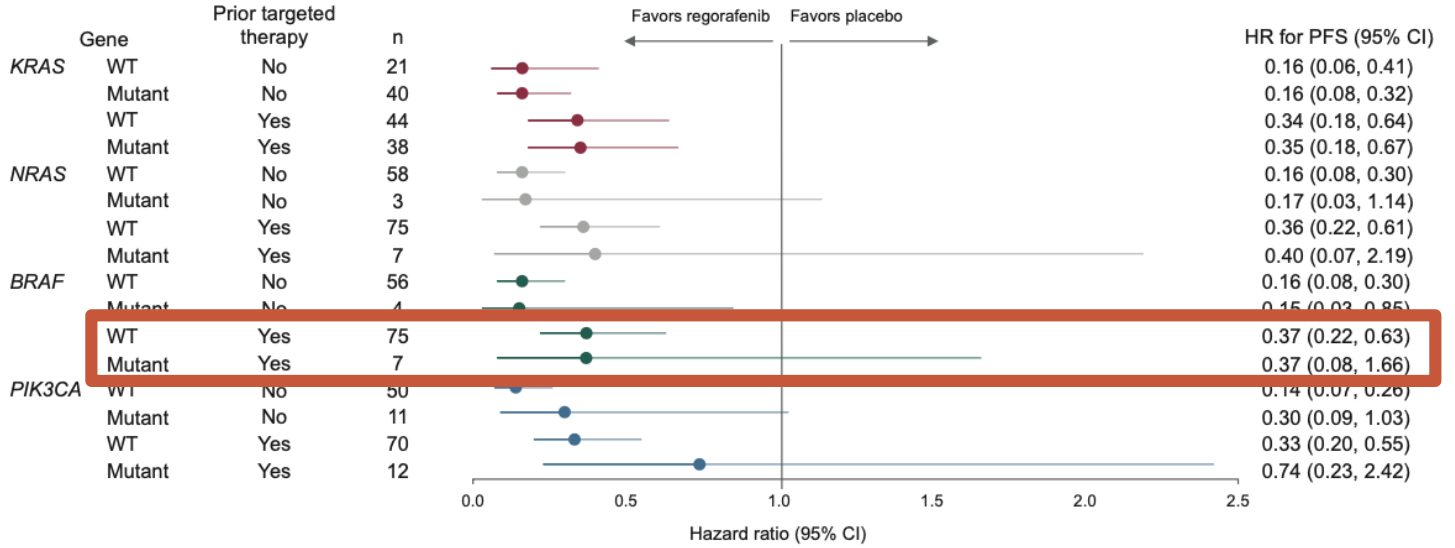
Regorafenib:

CONCUR study (**NCT01584830**)[3]

In the randomised double-blind placebo controlled phase 3 trial, 204 pretreated mCRC Asian patients
were randomly assigned to receive regorafenib (136) or placebo (68)

CONCUR in Asian patients[4]

SUBGROUPS ANALYSIS OF PFS BY MUTATION STATUS (CTDNA) AND PRIOR TARGETED THERAPY



BRAF, B-Raf proto-oncogene; CI, confidence interval; ctDNA, circulating tumour DNA; HR, hazard ratio; mCRC, metastatic colorectal cancer; PFS; progression-free survival; TAS102: trifluridine/tipiracil, WT, wild type

1. Bachet JB, et al. ESMO Open 2020;5(3):e000698, 2. Ducreux M, et al. Eur J Cancer 2019;123:146-54, 3. Li J, et al. Lancet Oncol 2015;16:619-29. 4. Teufel M. et al, Eur Cancer Congress 2015, Abstract#P003

NEXT KEY CLINICAL DEVELOPMENT PROGRAM

ANCHOR CRC – PHASE 2 STUDY IN 1L *BRAF*^{V600E} mCRC DESIGN & RESULTS FOR STAGE 1

Eligibility criteria

- mCRC with BRAF^{V600E} mutation
- Untreated in metastatic setting
- No prior treatment with any RAF/MEK/anti-EGFR inhibitors
- ECOG PS 0-1

STAGE 1 (N=40)
encorafenib + binimetinib + cetuximab

STAGE 2 (N=50)
Encorafenib + binimetinib + cetuximab

Treatment until
- **Disease progression**
- **Unacceptable toxicity**
- **Consent withdrawal**

Continued follow up for survival every 3 months

Primary objective and endpoint: confirmed ORR (investigator assessed)
Secondary endpoints: PFS, OS, safety, QoL, PK

Cut off date: 6 February 2020. n=41; 9 ongoing (22%), 32 discontinued (78%) due to progressive disease (54%)/ AEs (10%)/physician decision (7%)/death (5%)/protocol deviation (2%)

Primary endpoint	Patients (N=40), n (%) [95% CI]
Confirmed ORR	20 (50%) [34–66]
Best overall confirmed response	
Complete response	0
Partial response	20 (50%)
Stable disease	14 (35%)
Progressive disease	4 (10%)
Not evaluable	2 (5%)

Median time on treatment: 4.9 months

Secondary endpoint	Patients (N=40)
Median PFS (95% CI), months	4.9 (4.4–8.1)

DCR= 85%

Data are promising in the assessment of the triplet combination in the 1L setting

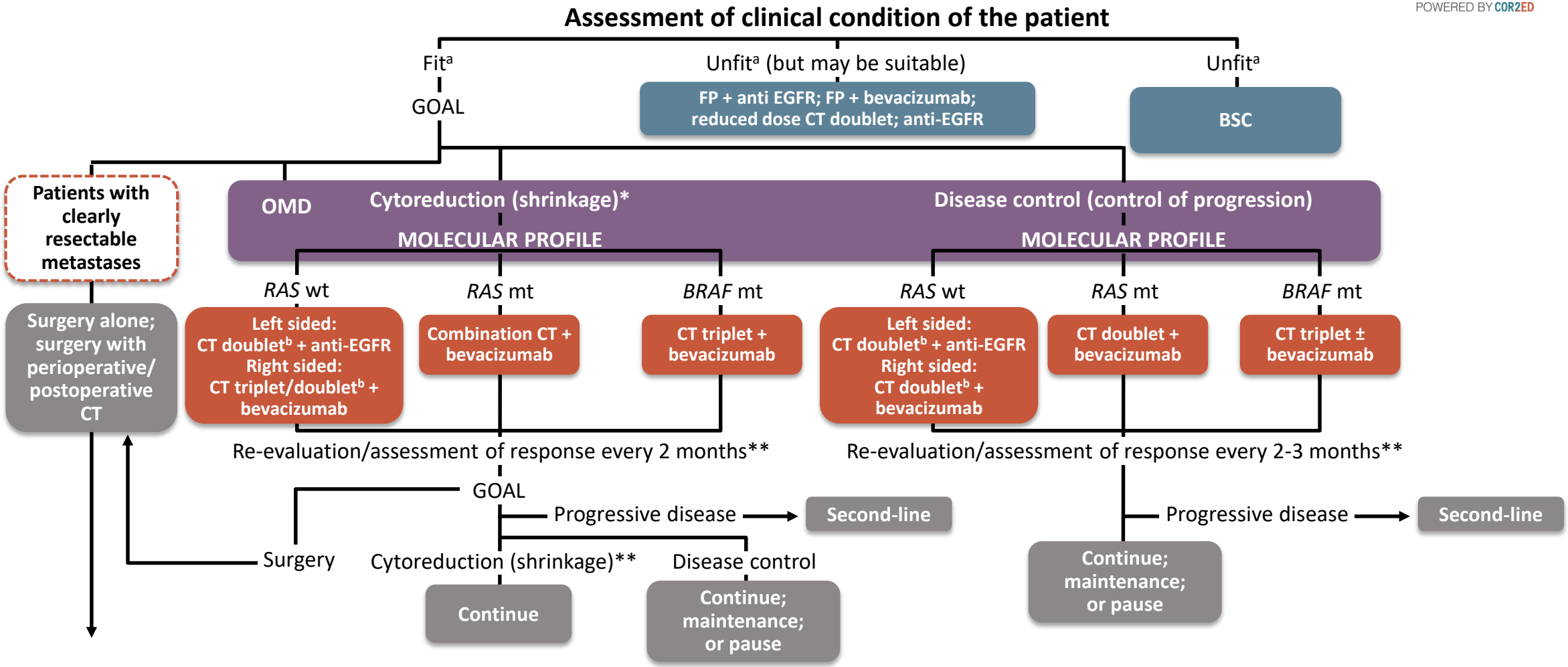
1L, first-line; AEs, adverse events; BRAF, B-Raf proto-oncogene; CI, confidence interval; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; QoL, quality of life

Grothey A, et al. Ann Oncol 2020;31(S3):S242-S243

EU GUIDELINES RECOMMENDATIONS FOR *BRAF*-MUTANT mCRC PATIENTS TREATMENT

BRAF, B-Raf proto-oncogene; EU, European Union; mCRC, metastatic colorectal cancer

JSMO/ESMO CONSENSUS GUIDELINES



BSC, best supportive care; BRAF, B-Raf proto-oncogene; CT, chemotherapy; EGFR, epidermal growth factor receptor; ESMO, European Society of Medical Oncology; FP, fluoropyrimidine; JSMO, Japanese Society of Medical Oncology; LAT, local ablative treatment; mt, mutant; OMD, oligometastatic disease; wt, wild-type.

[a] Patients assessed as fit or unfit according to medical condition not due to malignant disease; [b] CT doublet, SOX (S-1 plus oxaliplatin) is an alternative to FOLFOX (infusional 5-fluorouracil, leucovorin and oxaliplatin) or, CAPOX (capecitabine plus oxaliplatin), and S-1 plus irinotecan is an alternative to FOLFIRI (infusional 5-fluorouracil, leucovorin and irinotecan). * Includes two sub- groups: (1) those for whom intensive treatment is appropriate with the goal of cytoreduction (tumour shrinkage) and conversion to resectable disease; (2) those who need an intensive treatment, although they will never make it to resection or LAT, since they need a rapid reduction of tumour burden because of impending clinical threat, impending organ dysfunction, severe symptoms. ** After two re-evaluations, consider maintenance
.Yoshino T, et al. Ann Oncol 2018;29: 44–70

SEQUENCING TREATMENT APPROACH IN PATIENTS WITH *BRAF*-MUTATED mCRC: US PERSPECTIVE

Dr. Joleen Hubbard

Mayo Clinic, Rochester, MN, USA

BRAF, B-Raf proto-oncogene; mCRC, metastatic colorectal cancer; US, United States

DISCLAIMER AND DISCLOSURES

Please note: The views expressed within this presentation are the personal opinions of the expert. They do not necessarily represent the views of the author's academic institution or the rest of the GI CONNECT group.

Disclosures: Dr. Joleen Hubbard has the following information to disclose:

- Advisory Board (honorarium to institution):
  - Bayer
- Research funding (to Mayo) from:
  - Merck, Boston Biomedical, Treos Bio, Taiho, Senhwa Pharmaceuticals, Bayer, Incyte, TriOncology, Seattle Genetics, Hutchison MediPharma

AGENDA

- **Biomarkers testing in the US**
- **Key clinical study results for:**
  - First-line treatment for *BRAF*-mutant mCRC
  - Second-line treatment for *BRAF*-mutant mCRC
- **Immunotherapy approach for:**
  - MSI-H *BRAF*-mutant mCRC
- **US-based guidelines and recommendations**

ASCO, American Society of Clinical Oncology; BRAF, B-Raf proto-oncogene; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; NCCN, National Comprehensive Cancer Network; US, United States

BIOMARKERS TESTING IN THE US

BIOMARKERS TESTING IN THE UNITED STATES

- Very limited published data
- Available evidence suggests that many patients with mCRC are not receiving the recommended biomarker testing
- Data from 1497 pts with mCRC from 23 practices across the US (community and academic centers) from 2013 – 2017

Jan 2009 NCCN
- Limited *KRAS* (codons 12 and 13) testing recommended for all pts with mCRC

March 2010 NCCN
- *BRAF* testing can be considered for *KRAS* wt mCRC

Aug 2014 NCCN
- All pts with mCRC should be tested for *RAS* (*KRAS* and *NRAS*) mutations
- Insufficient data to recommend *BRAF* testing
- MSI or IHC should be considered for all pts with CRC ≤ 70 years or those meeting Bethesda guidelines

Nov 2015 NCCN
- All pts with mCRC should be tested for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations
- MSI testing is recommended for all pts with mCRC

Jan 2018 NCCN
- MSI testing may be done as part of a validated NGS panel
- Anti-EGFR + BRAF inhibitor combination therapy option added for *BRAF* V600E + mCRC

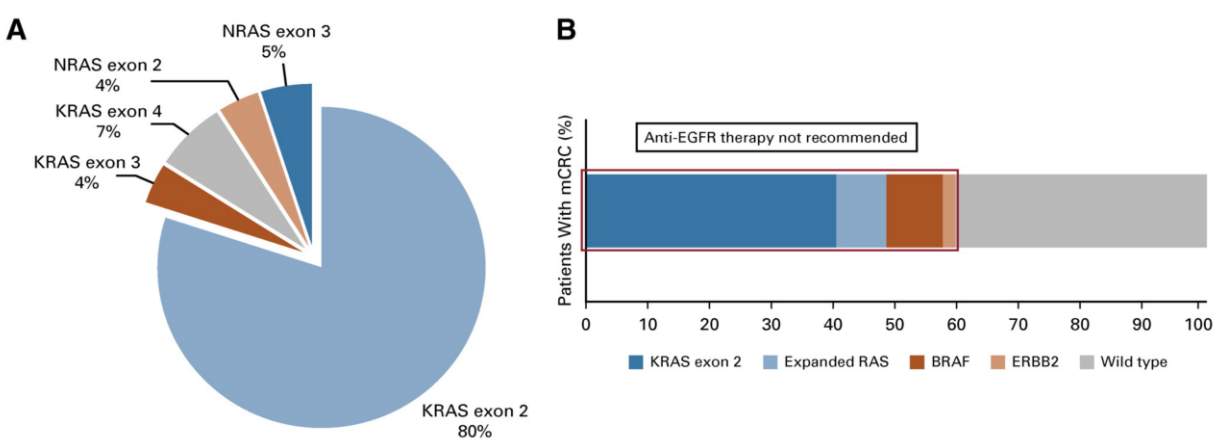
Feb 2009 ASCO
- All patients with mCRC who are candidates for anti-EGFR antibody therapy should have *KRAS* testing

Nov 2011 NCCN
- Testing for MMR proteins should be considered for all pts < 50 years and stage II considering FU
- Stage II MSI-H CRC may not benefit from FU

Oct 2015 ASCO
- Anti-EGFR should only be considered in *RAS* wt pts after extended *RAS* testing *KRAS* and *NRAS* exons 2 (codons 12 and 13), 3 (codons 59 and 61), and 4 (codons 117 and 146)

Nov 2016 NCCN
- MMR or MSI testing recommended for all patients with colon or rectal cancer

May 2019 NCCN
- Trastuzumab and pertuzumab therapy option added for *ERBB2* (HER2) amplified and *RAS* wt colon cancer
- *NTRK* gene fusion testing is recommended



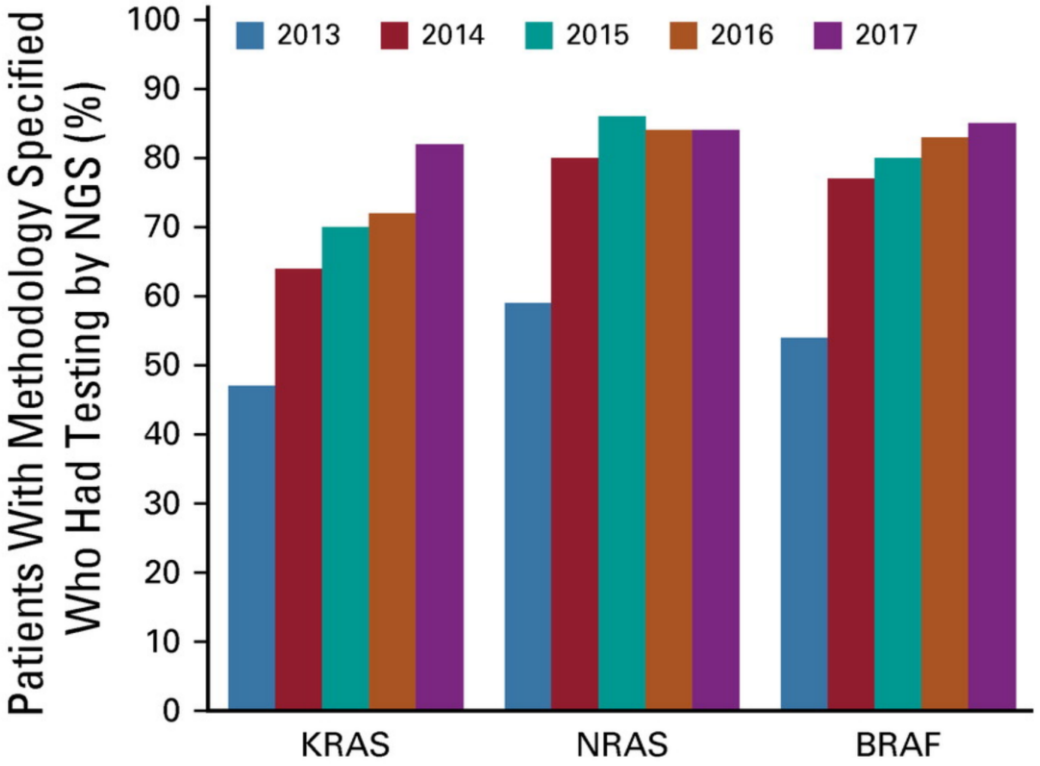
Prevalence of negative predictors to anti-EGFR therapy

EGFR, epidermal growth factor receptor; FU, fluorouracil; IHC, immunohistochemistry; mCRC, metastatic colorectal cancer; MMR, impaired DNA mismatch repair; MSI, microsatellite instability; NGS, next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase; wt, wild-type

Gutierrez ME. et al, JCO Precision Oncology 2019

BIOMARKERS TESTING IN THE UNITED STATES

- *Testing rates:*
  - *RAS 41%*
  - *BRAF 43%*
    - 2016-2017 after *BRAF* testing recommended
  - MSI/MMR 51%
- Biomarker testing more likely
  - Academic center
  - Newly diagnosed metastatic disease
  - Female
  - Age < 65
- Among the 177 patients (12%) who received EGFR inhibitors
  - 50 (28%) had biomarker testing



EGFR, epidermal growth factor receptor; MMR, impaired DNA mismatch repair; MSI, microsatellite instability

Gutierrez ME. et al, JCO Precision Oncology 2019

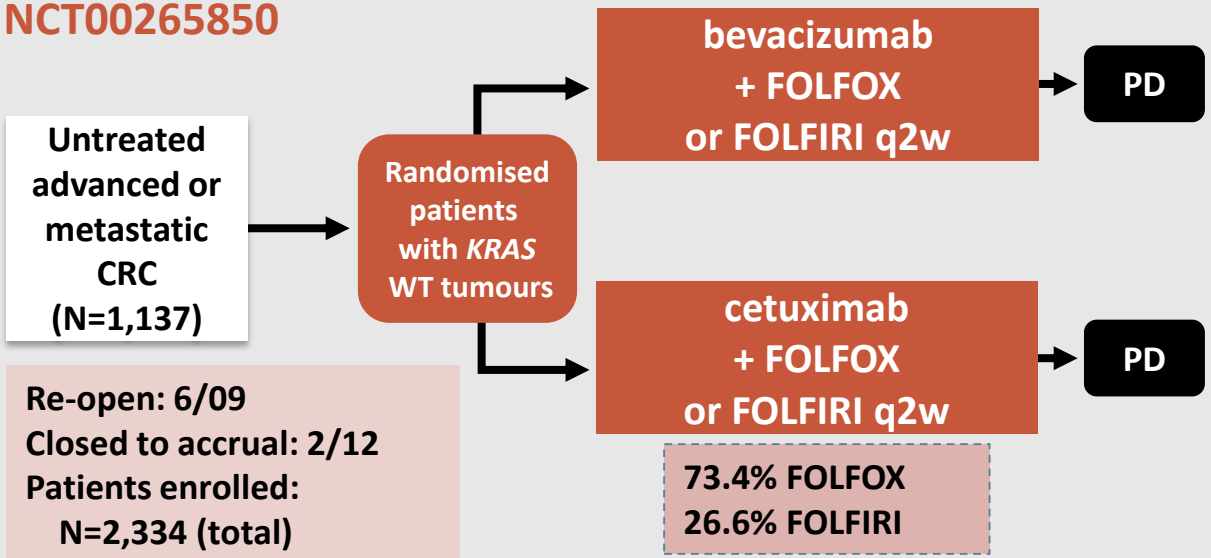
KEY CLINICAL RESULTS IN 1ST LINE THERAPY FOR *BRAF*-MUTANT mCRC

BRAF, B-Raf proto-oncogene; mCRC, metastatic colorectal cancer

CALGB/SWOG 80405: BEVACIZUMAB VS CETUXIMAB IN 1L *KRAS* WT mCRC

GI connect® POWERED BY COR2ED

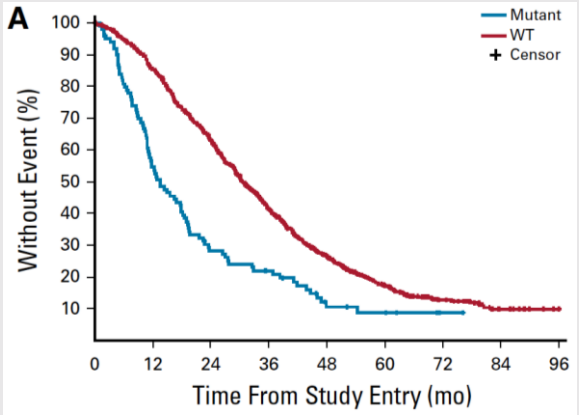
NCT00265850



Re-open: 6/09
Closed to accrual: 2/12
Patients enrolled:
N=2,334 (total)
N=1,177 (final endpoint)

- **Primary endpoint:**
  - OS: superiority trial with 90% power to detect an OS HR of 1.25 (2-sided α=0.05)
- **Secondary endpoints:**
  - ORR, PFS, TTF, DOR, and safety

Effect of *BRAF* mutation on OS



	BRAF analysis population (N=843)	
	BRAF-mutant (N=100)	*BRAF* WT (N=743)
Median OS, months	13.5	30.6
HR (95% CI)	2.01 (1.49 to 2.71)	
p value	<0.001	
Median PFS, months	7.6	11.4
HR (95% CI)	1.72 (1.30 to 2.29)	
p value	<0.001	

Demonstrated the negative prognostic effect of *BRAF*^{V600E} mutation in a clinical trial in the 1L setting of mCRC

1L, first-line; BRAF, B-Raf proto-oncogene; CI, confidence interval; CRC, colorectal cancer; DOR, duration of response; FOLFIRI, folinic acid + fluorouracil + irinotecan; FOLFOX, folinic acid + fluorouracil + oxaliplatin; HR, hazard ratio; mCRC, metastatic CRC; mo, months; ORR, objective response rate; OS, overall survival; PD; progression disease; PFS, progression-free survival; q2w, every 2 weeks; TTF, time to treatment failure; WT, wild type

Venook AP, et al. J Clin Oncol 2014;32(15_suppl):LBA3, Innocenti F, et al. J Clin Oncol 2019;37(14):1217-27

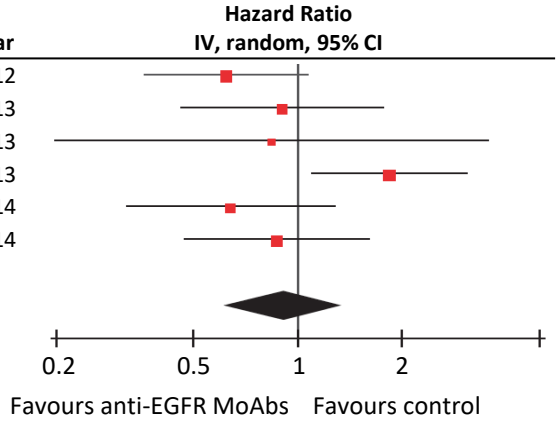
ROLE OF *BRAF* MUTATIONS IN THE ACTIVITIES OF *EGFR* INHIBITORS IN mCRC PATIENTS IN 1L AND 2L SETTINGS

OS for anti-EGFR treatment in *BRAF*-mutant mCRC patients

Study or Subgroup	Log (Hazard Ratio)	SE	Weight	Hazard Ratio IV, random, 95% CI	Year
Bokemeyer 2012	-0.478	0.275	20.7%	0.62 (0.36-1.06)	2012
Douillard 2013	-0.105	0.342	17.0%	0.90 (0.46-1.76)	2013
Karapetis 2013	-0.174	0.736	6.0%	0.84 (0.20-3.56)	2013
Seymour 2013	0.61	0.263	21.5%	1.84 (1.10-3.08)	2013
Peeters 2014	-0.446	0.354	16.4%	0.64 (0.32-1.28)	2014
Stintzing 2014	-0.139	0.314	18.5%	0.87 (0.47-1.61)	2014
Total (95% CI)			**100.0%**	**0.91 (0.62-1.34)**	

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 10.09$, df = 5 (p=0.07); $I^2 = 50\%$

Test for overall effect: Z = 0.48 (p=0.63)



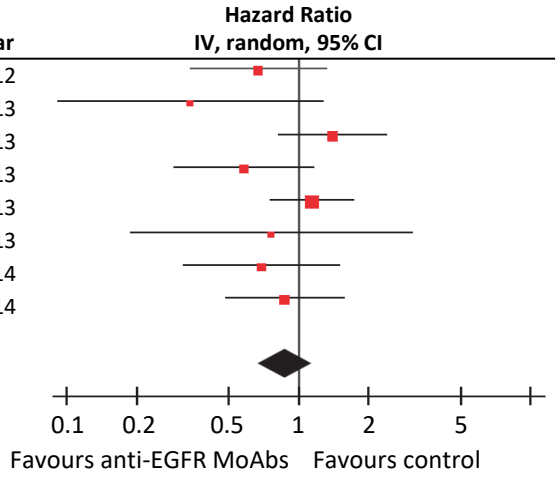
HR: 0.91

PFS for anti-EGFR treatment in *BRAF*-mutant mCRC patients

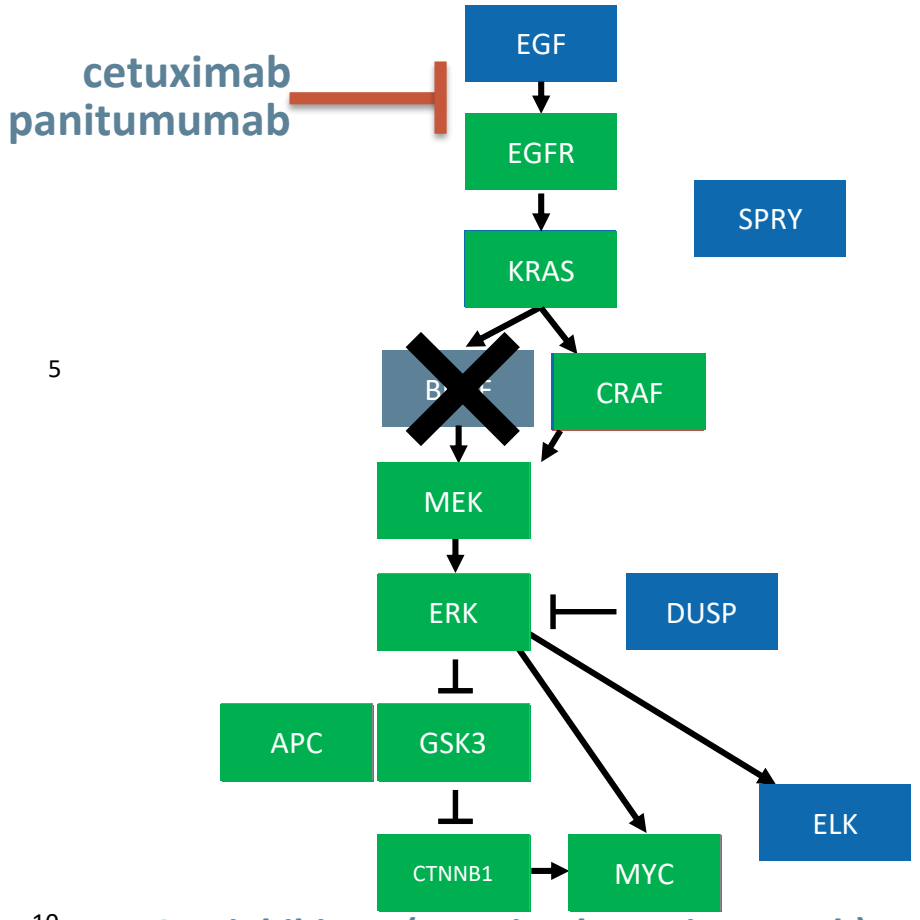
Study or Subgroup	Log (Hazard Ratio)	SE	Weight	Hazard Ratio IV, random, 95% CI	Year
Bokemeyer 2012	-0.4	0.34	12.6%	0.67 (0.34-1.31)	2012
Peeters 2013	-1.079	0.669	3.8%	0.34 (0.09-1.26)	2013
Seymour 2013	0.336	0.273	17.5%	1.40 (0.82-2.39)	2013
Douillard 2013	-0.545	0.351	12.0%	0.58 (0.29-1.15)	2013
Smith 2013	-0.131	0.207	25.1%	1.14 (0.76-1.71)	2013
Karapetis 2013	-0.274	0.711	3.4%	0.76 (0.19-3.06)	2013
Peeters 2014	-0.371	0.392	10.0%	0.69 (0.32-1.49)	2014
Stintzing 2014	-0.139	0.297	15.5%	0.87 (0.49-1.56)	2014
Total (95% CI)			**100.0%**	**0.88 (0.67-1.14)**	

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 8.88$, df = 7 (p=0.26); $I^2 = 21\%$

Test for overall effect: Z = 0.98 (p=0.33)



HR: 0.88



EGFR inhibitors (cetuximab, panitunumab) are not efficient in the treatment of *BRAF*-mutant mCRC patients

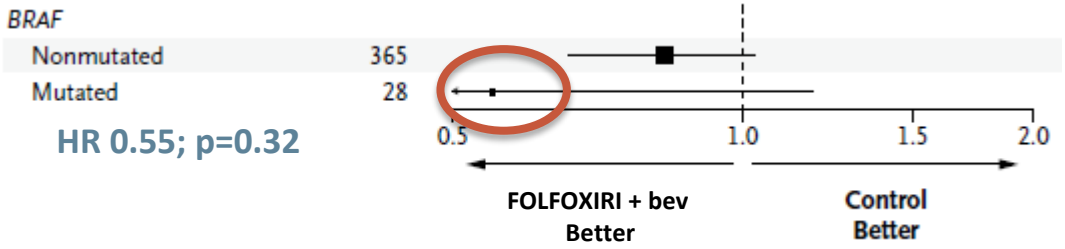
BRAF, B-Raf proto-oncogene; BSC; best supportive care; CI, confidence interval; CRC, colorectal cancer; df, degrees of freedom; EGFR, epidermal growth factor receptor; HR, hazard ratio; IV, inverse variance; mCRC, metastatic CRC; MoAbs, monoclonal antibodies; OS, overall survival; PFS, progression-free survival; SE, standard error

Pietrantonio F, et al. Eur J Cancer 2015;51(5):587-94

SUBGROUP ANALYSIS OF TRIBE STUDY

Could FOLFOXIRI + bevacizumab be the optimal choice for 1L therapy for *BRAF*-mutant mCRC?

Baseline characteristics of the patients in the ITT population		
Characteristic	**FOLFIRI + bev (N=256)**	**FOLFOXIRI + bev (N=252)**
***BRAF* status, n (%)**		
Non mutated	183 (71.5)	182 (72.2)
Mutated	**12 (4.7)**	**16 (6.3)**
No definable	6 (2.3)	7 (2.8)
Missing data	55 (21.5)	47 (18.7)



Efficacy results in *BRAF*-mutation positive subgroup		
	FOLFIRI + bev (N=12)	**FOLFOXIRI + bev (N=16)**
Median OS		
Months (95% CI)	10.7 (3.1–24.8)	19.0 (8.2–28.6)
HR (95% CI)	0.54 (0.24–1.20)	
Median PFS		
Months (95% CI)	5.5 (1.6–11.2)	7.5 (5.1–15.0)
HR (95% CI)	0.57 (0.27–1.23)	
ORR		
n (%)	5 (42%)	9 (56%)
Odds ratio (95% CI)	1.82 (0.38–8.78)	

In *BRAF*-mutant mCRC patients, the role of FOLFOXIRI + bevacizumab deserves further investigations

1L, first-line; bev, bevacizumab; BRAF, B-Raf proto-oncogene; CI, confidence interval; FOLFIRI, folinic acid + fluorouracil + irinotecan; FOLFOXIRI, folinic acid + fluorouracil + oxaliplatin + irinotecan; HR, hazard ratio; ITT, intention to treat; mCRC, metastatic colorectal cancer; OS, overall survival, ORR, overall response rate; PFS, progression-free survival

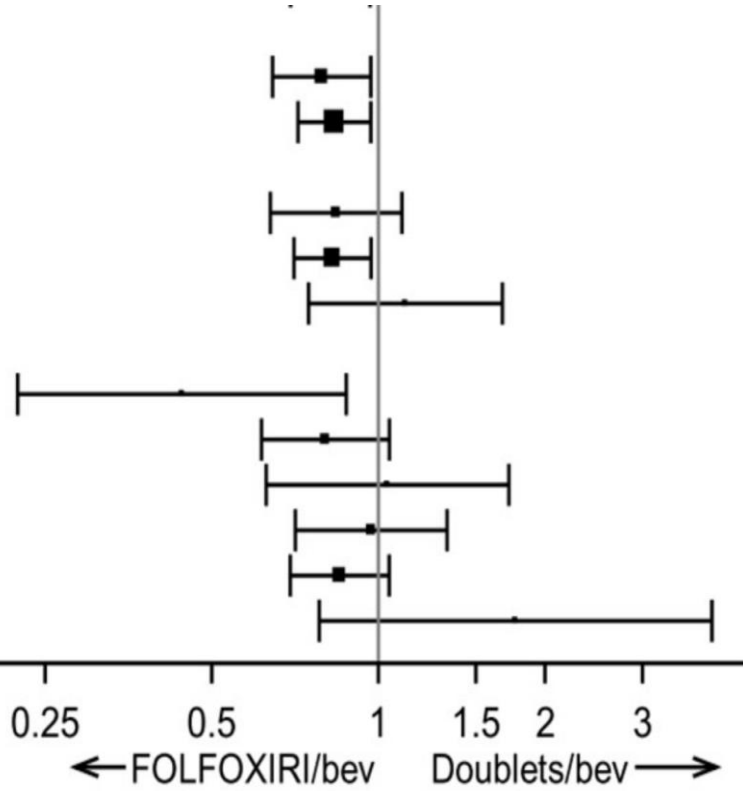
Loupakis F, et al. N Engl J Med 2014;371(17):1609-18, Cremolini C, et al. Lancet Oncol 2015;16(13):1306-15

ROLE OF FOLFOXIRI + BEVACIZUMAB INVESTIGATIONS

- No increased benefit in TRIBE2 study
- Meta-analysis of five trials evaluating OS with FOLFOXIRI + bev vs doublet + bev (CHARTA, OLIVIA, STEAM, TRIBE, TRIBE2)

Subgroup	Doublets + bev Events/N (%)	FOLFOXIRI + bev Events/N (%)	HR (95% CI)
Tumour site			
Right	185/255 (72.5)	193/295 (65.4)	0.79 (0.64-0.97)
Left/rectum	367/535 (68.6)	317/496 (63.9)	0.83 (0.72-0.97)
RAS			
RAS-BRAF wt	107/172 (62.2)	99/177 (55.9)	0.84 (0.64-1.10)
RAS mut	316/430 (73.5)	289/422 (68.5)	0.83 (0.70-0.97)
BRAF mut	43/54 (79.6)	53/61 (86.9)	1.12 (0.75-1.68)
Site–RAS/BRAF			
Right-*RAS/BRAF* wt	21/31 (67.7)	21/44 (47.7)	0.44 (0.22-0.88)
Right-*RAS* mut	110/149 (73.8)	113/168 (67.3)	0.80 (0.62-1.05)
Right-*BRAF* mut	33/40 (82.5)	34/39 (87.2)	1.04 (0.63-1.72)
Left-*RAS/BRAF* wt	79/134 (59.0)	78/132 (59.1)	0.97 (0.71-1.33)
Left-*RAS* mut	199/273 (72.9)	173/250 (69.2)	0.85 (0.69-1.05)
Left-*BRAF* mut	9/13 (69.2)	19/22 (86.4)	1.77 (0.78-4.01)

OS



The role of FOLFOXIRI + bevacizumab was not confirmed

bev, bevacizumab; BRAF, B-Raf proto-oncogene; CI, confidence interval; FOLFOXIRI, folinic acid + fluorouracil + oxaliplatin + irinotecan; HR, hazard ratio; mut, mutation; OS, overall survival; WT, wild type

Cremolini C, et al. Lancet Oncol 2020;21(4):497-507, Cremolini C, et al. J Clin Oncol 2020;38(15_suppl):4015-4015

KEY CLINICAL RESULTS IN 2ND LINE THERAPY FOR *BRAF*-MUTANT mCRC

BRAF, B-Raf proto-oncogene; mCRC, metastatic colorectal cancer

THE PHASE 3 BEACON COLORECTAL CANCER STUDY DESIGN

Role of binimetinib, encorafenib, and cetuximab triplet therapy for patients With *BRAF*^{V600E}-mutant mCRC in 2L or 3L settings

NCT02928224

Data cut-off date: August 15, 2019

Eligibility criteria

- mCRC
- BRAF V600E mutation
- Progression after 1 or 2 regimens
- ECOG PS 0-1
- No prior treatment with any RAF/MEK or EGFR inhibitor

R 1:1:1

Triplet Arm
encorafenib + binimetinib + cetuximab
N=224

Doublet Arm
encorafenib + cetuximab
N=2220

Control Arm
irinotecan + cetuximab
OR FOLFIRI + cetuximab
N=221

Primary endpoints:

- Triplet arm vs control arm
  - OS (all randomised patients)
  - ORR BCR (1st 331 randomised patients)

Secondary endpoints:

- Doublet arm vs control arm and triplet arm vs doublet arm:
  - OS and ORR
  - PFS
  - Safety
  - QoL

BICR, blinded independent central review; BRAF, B-Raf proto-oncogene; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FOLFIRI, folinic acid + fluorouracil + irinotecan; mCRC, metastatic colorectal cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; R, randomisation

Kopetz S. et al, N Engl J Med 2019;381(17):1632-1643, Kopetz S, et al. J Clin Oncol 2020;38(4_suppl):8-8

THE PHASE 3 BEACON COLORECTAL CANCER STUDY: INITIAL OS & UPDATED OS RESULTS

At the initial data cut-off date: February 11, 2019[1]

Median OS follow up = 7.8 months

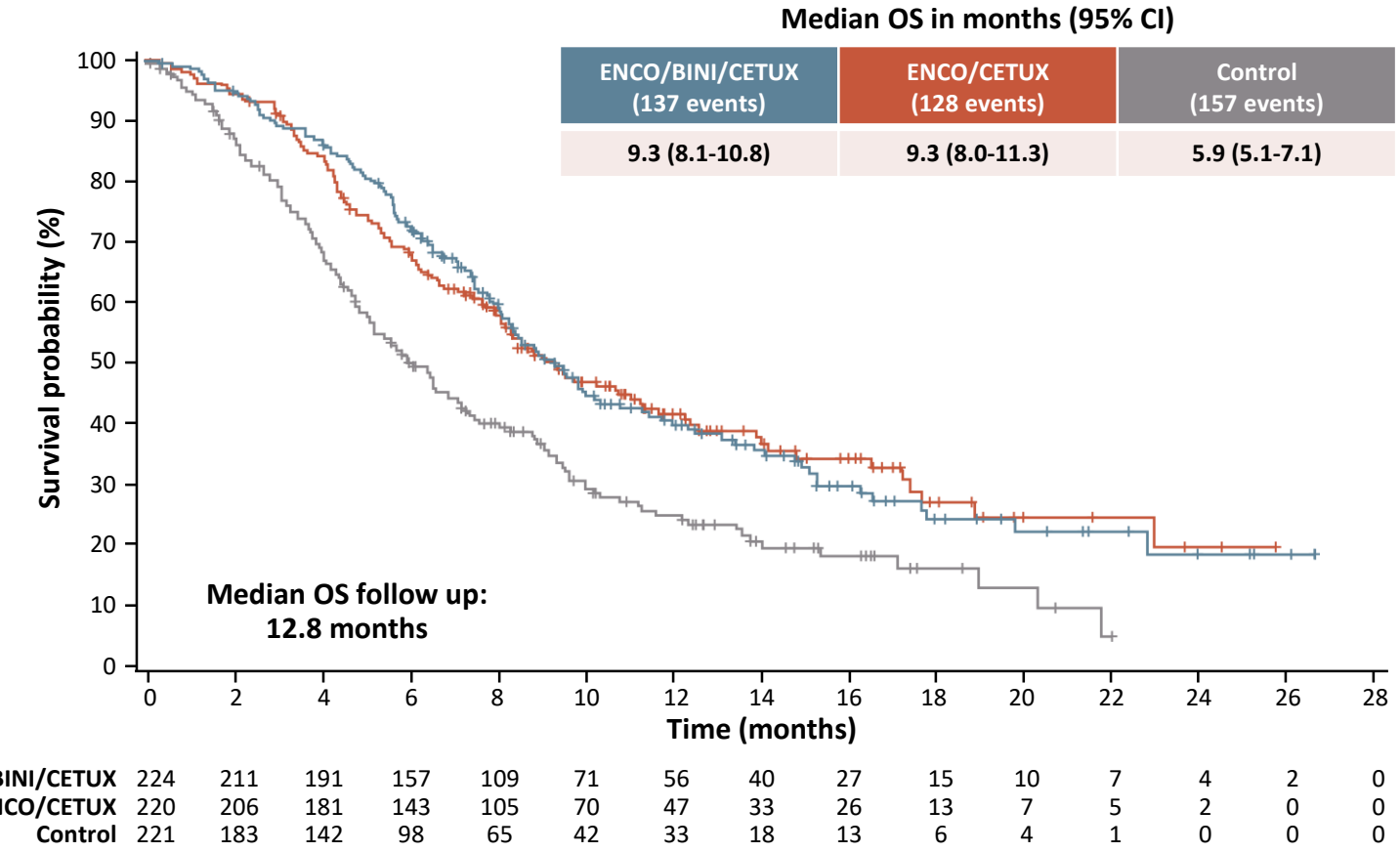
Median OS:

Triplet arm: 9.0 months (95% CI: 8.0-11.4)

Doublet arm: 8.4 months (95% CI: 7.5-11.0)

Control arm: 5.4 months (96% CI: 4.8-6.6)

At the update data cut-off date: August 15, 2019[2]



Bini, binimetinib; CI, confidence interval; CETUX, cetuximab; ENCO, encorafenib; OS, overall survival

1. Kopetz S, et al. N Engl J Med 2019;381(17):1632-43, 2. Kopetz S, et al. J of Clin Oncol 2020;38(4_suppl):8-8

IMMUNOTHERAPY APPROACH FOR MSI-H *BRAF*-MUTANT mCRC

BRAF, B-Raf proto-oncogene; mCRC, metastatic colorectal; MSI-H microsatellite instability high

KEYNOTE-177 – TO EVALUATE THE EFFICACY AND SAFETY OF PEMBROLIZUMAB VS SOC IN 1L THERAPY FOR DMMR OR MSI-H mCRC

KEYNOTE-177 (NCT02563002)

Some eligibility criteria
- Treatment naive mCRC
- dMMR or MSI-H
- ECOG PS 0-1
- No active brain metastases

307 patients

Randomisation 1:1

Pembrolizumab
200 mg IV Q3W
N=153

Investigator's choice*
mFOLFOX6 +/- bev or cetuximab
FOLFIRI +/- bev or cetuximab
N=154

Treatment Duration: until PD, unacceptable toxicity, patient/ investigator decision to withdraw, or completion of 35 cycles (pembrolizumab only)

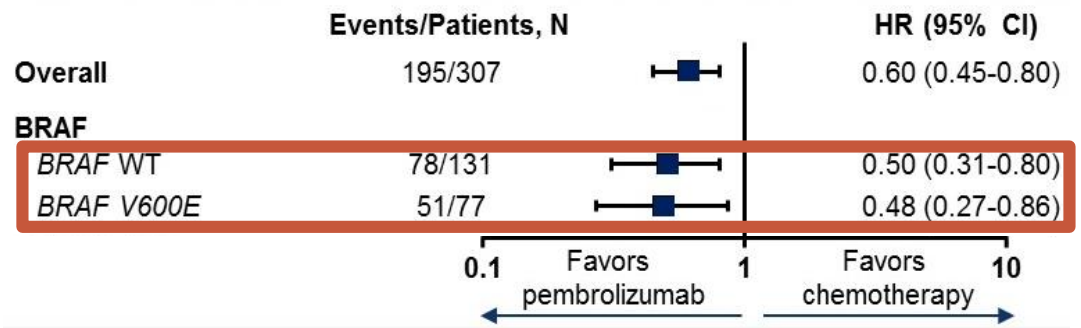
Primary endpoints: **PFS** (RECIST v1.1, central review) and **OS**
Secondary endpoints: **ORR** (RECIST v1.1, central review) and **safety**

* Patients with progressive disease have the option of receiving pembrolizumab 200 mg IV q3wk

Data cut-off date: Feb 19, 2020

Primary endpoint	Pembro	Chemo
Median PFS (months)	**16.5**	**8.2**
HR (95% CI)	**0.60 (0.45-0.80)**	
P-value	**0.0002**	
12-months PFS rates	55.3%	37.3%
24-months PFS rates	48.3%	18.6%

PFS results in *BRAF* status subgroups



1L, first-line; bev, bevacizumab; BRAF, B-Raf proto-oncogene; chemo, chemotherapy; CI, confidence interval; dMMR, mismatch repair deficiency; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ration; FOLFIRI, leucovorin + irinotecan + 5- fluorouracil; IV, intravenously; mFOLFOX6, modified oxaliplatin + leucovorin + 5-fluorouracil; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; ORR, overall response rate; OS, overall survival; PD, disease progression; pembro, pembrolizumab; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, response evaluation criteria in solid tumours; SOC, standard of care; WT, wild type

Andre T, et al. J Clin Oncol 2020;38(18_suppl):LBA4

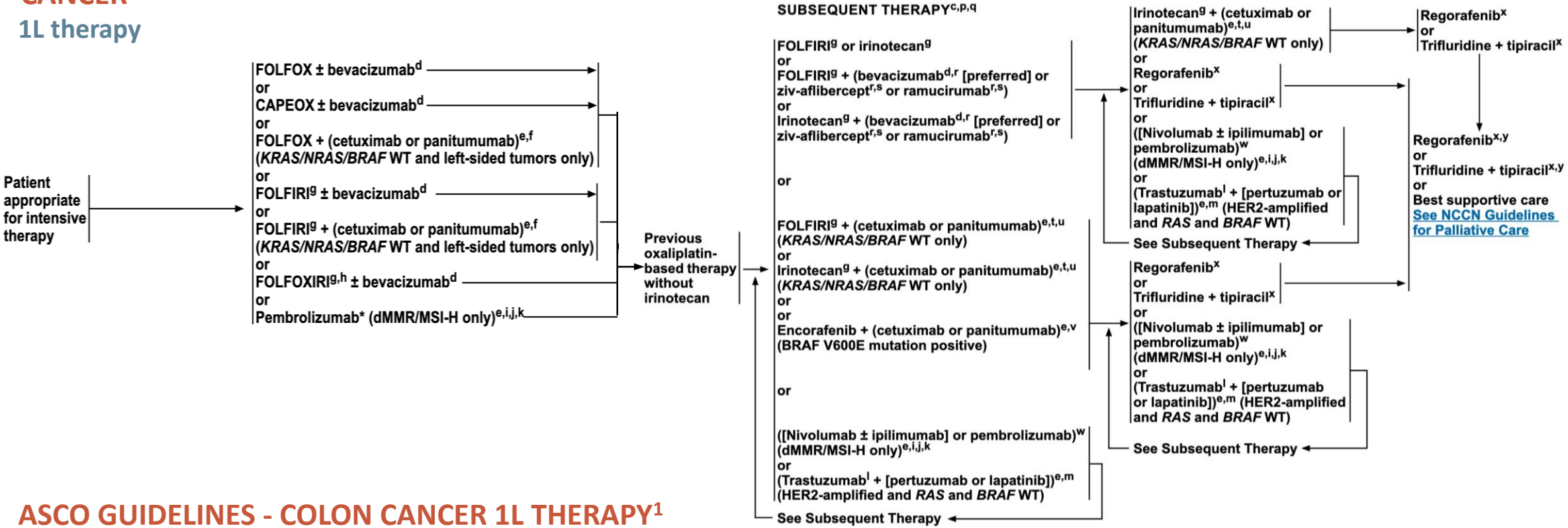
US-BASED GUIDELINES & RECOMMENDATIONS

US, United States

NCCN AND ASCO GUIDELINES

NCCN GUIDELINES VERSION 4.2020 – COLON CANCER

1L therapy



ASCO GUIDELINES - COLON CANCER 1L THERAPY[1]

TREATMENT OF PATIENTS WITH LATE-STAGE COLORECTAL CANCER: ASCO RESOURCE-STRATIFIED GUIDELINE					
Population	**Basic**	**Limited**	**Enhanced**	**Maximal**	**Strength of Recommendations**
RAS WT ± BRAF MUT, patients with good PS and without major comorbidities, and/or when tumour shrinkage is the goal	N/A	N/A	Triplet chemotherapy	Triplet chemotherapy ± anti-VEGF (bevacizumab)	Strong (chemotherapy) Moderate (chemotherapy + anti-VEGF)

1L, first-line; ASCO, American Society of Clinical Oncology; BRAF, B-Raf proto-oncogene; CAPEOX, oxaliplatin + capecitabine; dMMR, mismatch repair deficiency; FOLFIRI, folinic acid + fluorouracil + irinotecan; FOLFOX, infusional 5-fluorouracil, leucovorin and oxaliplatin; FOLFOXIRI, folinic acid + fluorouracil + oxaliplatin + irinotecan; MUT, mutant; N/A, not applicable; NCCN, National Comprehensive Cancer Network; MSI-H, microsatellite instability-high; PS, performance status; VEGF, vascular endothelial growth factor; WT, wild type

1. Summary of Recommendations www.asco.org/resource-stratified-guidelines©American Society of Clinical Oncology 2020

MY PROPOSED RECOMMENDATIONS IN THE SEQUENCING STRATEGY FOR PATIENTS WITH *BRAF*-MUTANT mCRC IN THE US:

GI connect® POWERED BY COR2ED

MSS, *BRAF*-mutant

Very fit[1] (low risk for toxicity from cancer treatment)

- 1st line FOLFOXIRI + bev
- 2nd line BRAF inhibitor + EGFR inhibitor
- 3rd/4th line Rego/TAS102

Fit[1] (medium risk for toxicity from cancer treatment)

- 1st line FOLFOX + bev
- 2nd line BRAF inhibitor + EGFR inhibitor
- 3rd line FOLFIRI + bev
- 4th/5th line Rego/TAS102

Less Fit[1] (high risk for toxicity from cancer treatment)

- 1st line fluoropyrimidine + bev
- 2nd line BRAF inhibitor + EGFR inhibitor

MSI-H, *BRAF*-mutant

- 1st line pembrolizumab
- 2nd line FOLFOX + bev
- 3rd line *BRAF* inhibitor + EGFR inhibitor
- 4th line FOLFIRI + bev
- 5th/6th line Rego/TAS102

April 8, 2020, the FDA approved encorafenib in combination with cetuximab for the treatment of adult patients with mCRC with a BRAF V600E mutation, detected by an FDA-approved test, "after prior therapy."[2]

- **What are the unmet medical need for patients with *BRAF*-mutated mCRC?**

bev, bevacizumab; BRAF, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; FOLFIRI, folinic acid + fluorouracil + irinotecan; FOLFOX, infusional 5-fluorouracil, leucovorin and oxaliplatin; FOLFOXIRI, folinic acid + fluorouracil + oxaliplatin + irinotecan; mCRC, metastatic colorectal cancer; rego, regorafenib; TAS102, trifluridine/tipiracil; US, United States; USPI, US Product Information

1. NCCN guidelines Version 1.2020 Older Adult Oncology MS-41220. 2. USPI for encorafenib dated April 2020

REACH GI CONNECT VIA TWITTER, LINKEDIN, VIMEO & EMAIL OR VISIT THE GROUP'S WEBSITE

http://www.giconnect.info

Follow us on Twitter
@giconnectinfo

Follow the
GI CONNECT
group on LinkedIn

Watch us on the
Vimeo Channel
GI CONNECT

Email
antoine.lacombe@cor2ed.com

GI connect®
POWERED BY COR2ED

GI CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Froukje Sosef MD

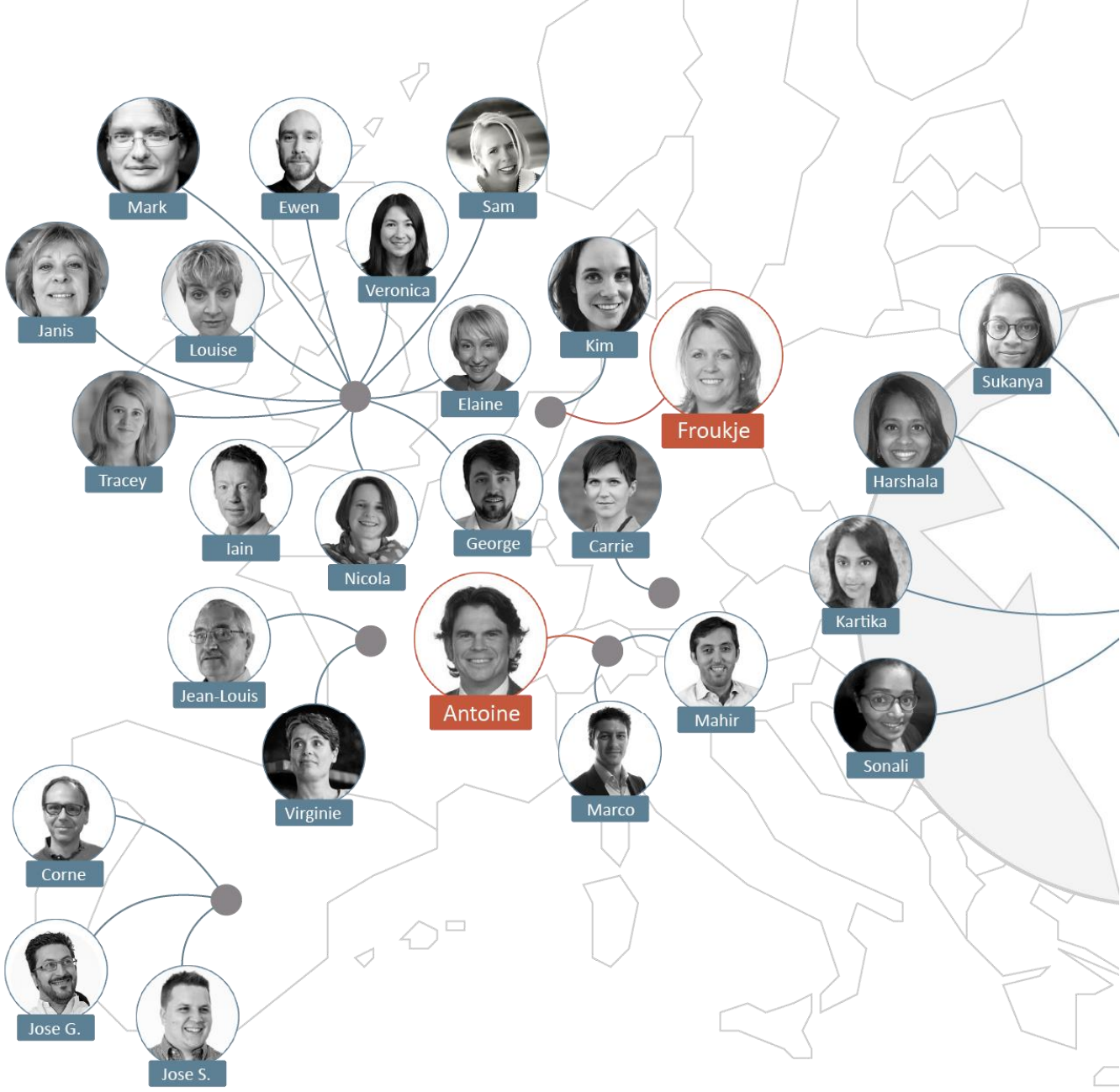
+31 6 2324 3636

froukje.sosef@cor2ed.com

Dr. Antoine Lacombe Pharm D, MBA

+41 79 529 42 79

antoine.lacombe@cor2ed.com



Heading to the heart of Independent Medical Education Since 2012