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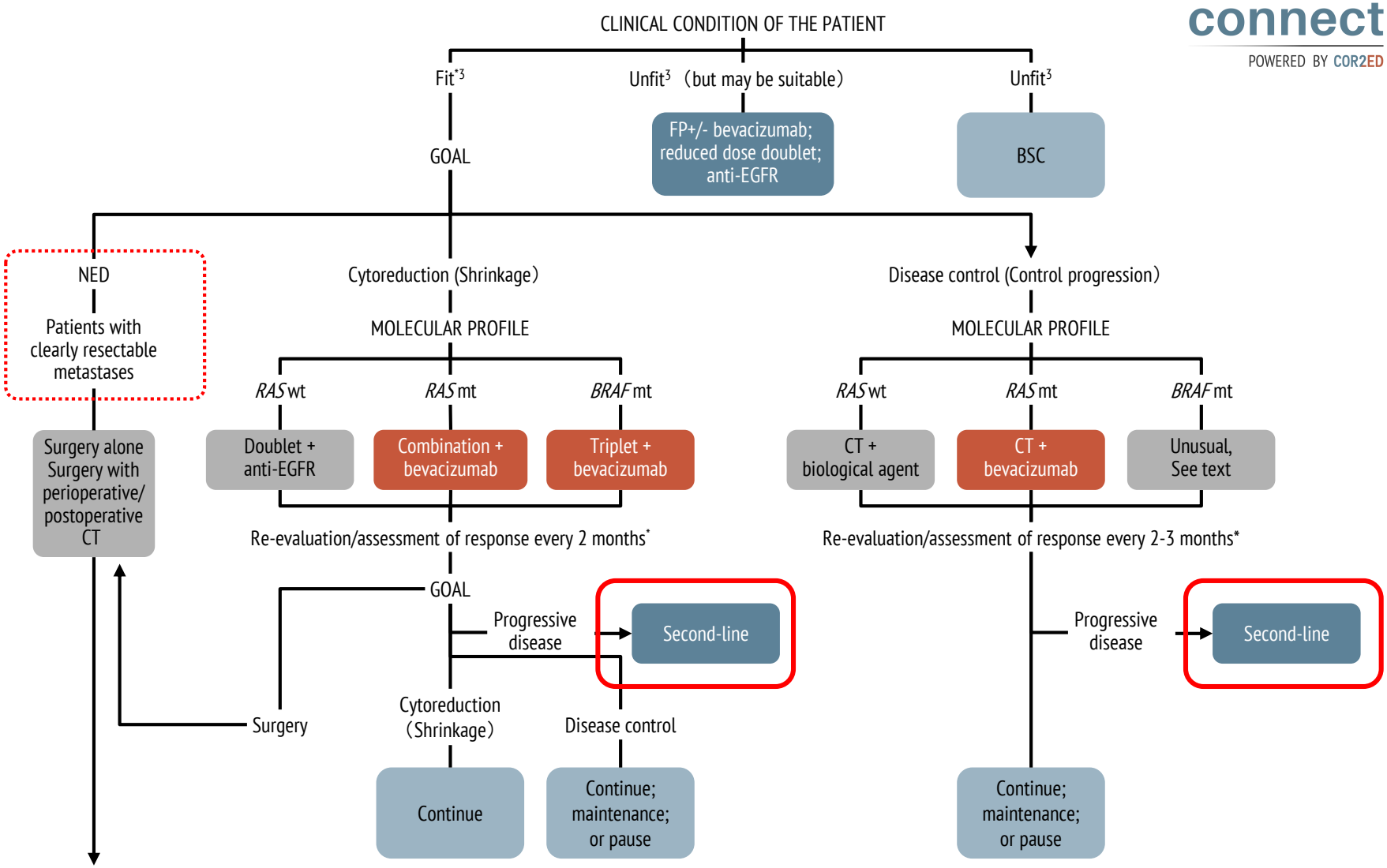
WHICH TARGETED DRUG (BEV, RAM, AFL, OR ANTI-EGFR?) IS BETTER FOR RAS-WT PATIENTS IN SECOND LINE TREATMENT AFTER BEV THERAPY?

Assoc. Prof. Yu Sunakawa, St. Marianna Univ, Japan
Ass. Prof. Joleen Hubbard, Mayo Clinic, USA

ESMO CONSENSUS GUIDELINES



Van Cutsem E et al. Ann Oncol, Aug 2016

SECOND-LINE COMBINATIONS WITH TARGETED AGENTS: ESMO

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- Patients who are bevacizumab naïve should be considered for treatment with an antiangiogenic (bevacizumab or aflibercept) second line
- Patients who received bevacizumab first line should be considered for treatment with:
  - Bevacizumab post-continuation strategy
  - Aflibercept or ramucirumab (in combination with FOLFIRI) when treated in first line with oxaliplatin
  - EGFR antibodies in combination with FOLFIRI/irinotecan for patients with RAS wild-type (*BRAF* wild-type) disease
- Relative benefit of EGFR antibodies is similar in later lines compared with second line

Van Cutsem E et al. Ann Oncol, Aug 2016

CLINICAL QUESTION:

WHICH ANTI-ANGIOGENIC COMPOUND SHOULD BE CONSIDERED FOR SECOND-LINE TREATMENT?

BEVACIZUMAB BEYOND PROGRESSION (BBP)

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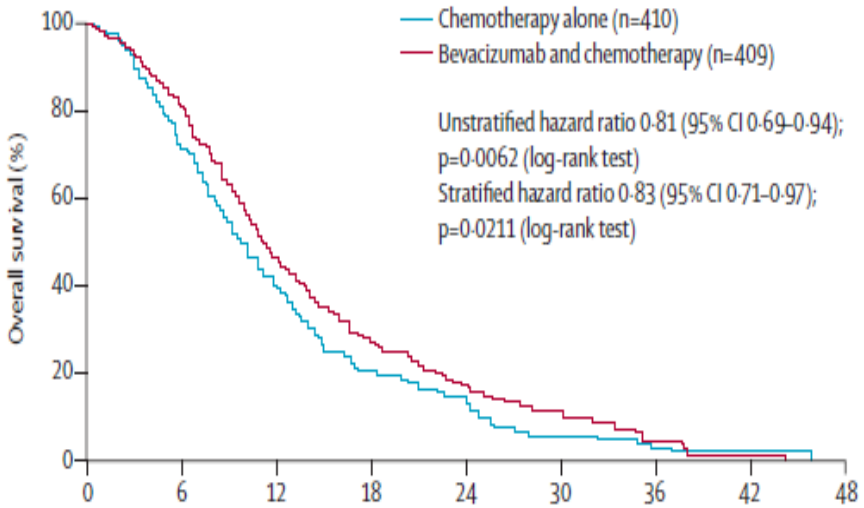
Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial

*Jaafar Bennouna, Javier Sastre, Dirk Arnold, Pia Österlund, Richard Greil, Eric Van Cutsem, Roger von Moos, Jose Maria Viéitez, Olivier Bouché, Christophe Borg, Claus-Christoph Steffens, Vicente Alonso-Orduña, Christoph Schlichting, Irmarie Reyes-Rivera, Belguendouz Bendahmane, Thierry André, Stefan Kubicka, on behalf of the ML18147 Study Investigators**



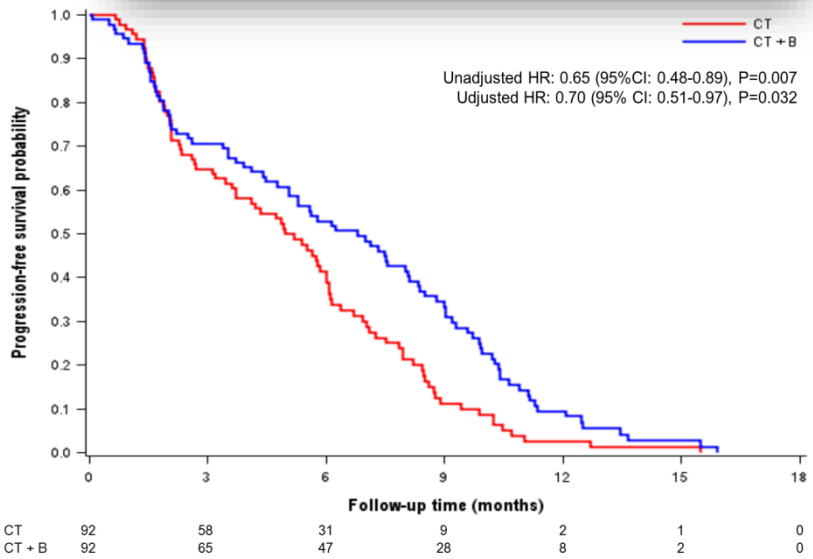
G.O.N.O
Gruppo Oncologico del Nord Ovest

A randomized study evaluating the continuation of bevacizumab beyond progression in metastatic colorectal cancer patients who received bevacizumab as part of first-line treatment: results of the BEBYP trial by the Gruppo Oncologico Nord Ovest (GONO).

G. Masi[1], F. Loupakis[1], L. Salvatore[2], L. Fornaro[1], C. Cremolini[1], M. Schirripa[1], E. Fea[2], C. Granetto[2], L. Antonuzzo[3], E. Giommoni[3], G. Allegrini[4], S. Cupini[5], C. Boni[6], M. Banzi[6], S. Chiara[7], C. Sonaglio[7], C. Valsuani[8], A. Bonetti[9], L. Boni[10], A. Falcone[2,11]

1) Pisa, Italy; 2) Cuneo, Italy; 3) Firenze, Italy; 4) Pontedera, Italy; 5) Livorno, Italy 6) Reggio Emilia, Italy; 7) Genova, Italy; 8) Lido di Camaiore, Italy; 9) Legnago, Italy; 10) Istituto Toscano Tumori, Firenze, Italy; 11) Università di Pisa, Italy.

VIENNA 2012 ESMO congress www.esmo2012.org



BBP IS NOT FOR "ALL" PATIENTS

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MAIN ELIGIBILITY CRITERIA

Inclusion

- Patients ⩾18 years with histologically confirmed diagnosis of mCRC
- Eastern Cooperative Oncology Group (ECOG) PS 0–2
- PD (⩾1 measurable lesion according to RECIST v1 assessed by investigator, documented by CT or MRI), ⩽4 weeks prior to start of study treatment
- Previously treated with BEV plus standard first-line CT, not candidates for primary metastasectomy

Exclusion

- Diagnosis of PD >3 months after last BEV administration
- First-line patients with PFS in first line of <3 months
- Patients receiving <3 consecutive months of BEV in first-line

ML18147 (Arnold D et al. ASCO 2012)

RAISE TRIAL (AFTER 1ST-LINE BEV)

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Patients with mCRC who progressed after 1L bevacizumab, oxaliplatin and fluoropyrimidine

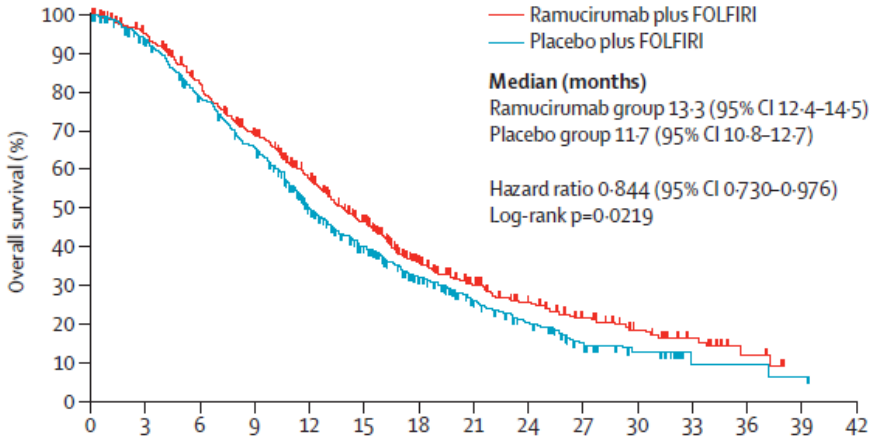
(n=1,072)

R

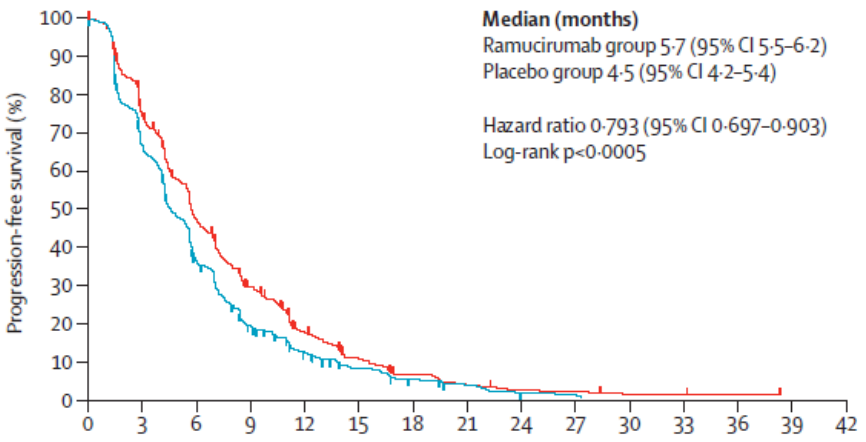
Ramucirumab + FOLFIRI (n=536) → **PD**

FOLFIRI (n=536) → **PD**

Primary endpoint: OS



Secondary endpoint: PFS



Tabernero et al. Lancet Oncol 2015

VELOUR TRIAL

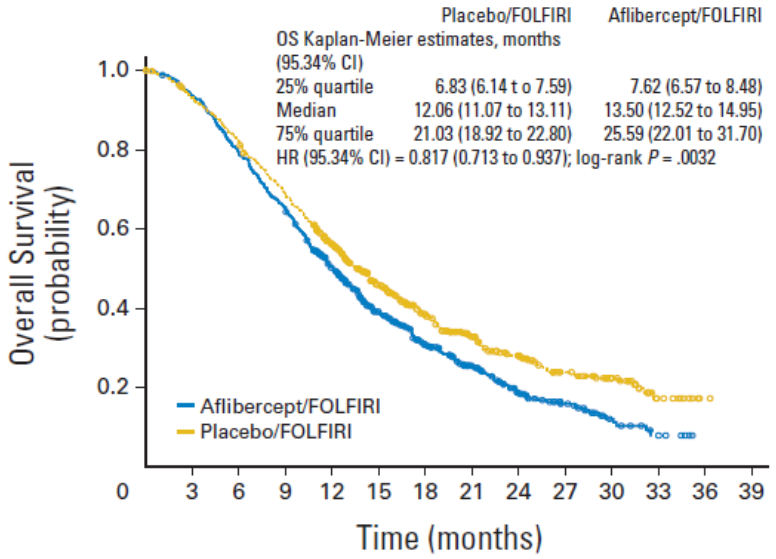
Patients with mCRC who progressed after 1L oxaliplatin and fluoropyrimidine ±bev

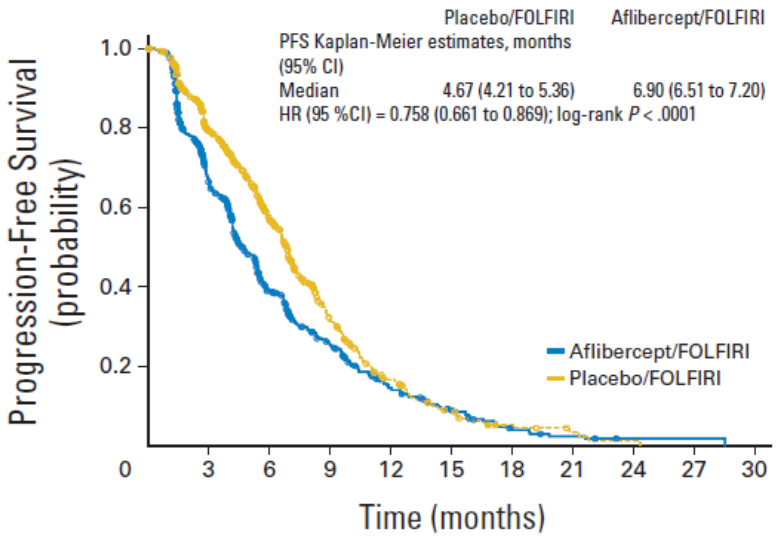
(n=1,226)

R

Aflibercept + FOLFIRI (n=612) → **PD**

Placebo + FOLFIRI (n=614) → **PD**





BEV VS. RAM VS. AFL IN SECOND LINE

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Trial	ECOG 3200 n=829 <bev-naïve>	TML18147 n=820 <bev-progressors>	TML18147-subanalysis-n=343 <Oxa-bev progressors>	RAISE n=1072 <Oxa-bev progressors>	VELOUR n=373 <Oxa-bev progressors>
Regimen	FOLFOX-bev vs. FOLFOX	CT-bev vs. CT	FOLFIRI-bev vs. FOLFIRI	FOLFIRI-ram vs. FOLFIRI	FOLFIRI-AFL vs. FOLFIRI
Response rate	22.7% vs. 8.6%	5% vs. 3%	5.5% vs. 2.9%	13.4% vs. 12.5%	11.7% vs. 8.4%
Progression-free survival	7.3m vs. 4.7m HR 0.61	5.7m vs. 4.1m HR 0.68 p<0.0001	6.2m vs. 4.2m	5.7m vs. 4.5m HR 0.79 p=0.0005	6.7m vs. 3.9m HR 0.66
Overall survival	12.9m vs. 10.8m HR 0.75	11.2m vs. 9.8m HR 0.81 p=0.0062	12m vs. 10m	13.3m vs. 11.7m HR 0.84 p=0.022	12.5m vs. 11.7m HR 0.86

bev, bevacizumab; CT, 5-FU+irinotecan/oxaliplatin; ram, ramucirumab; aflib, aflibercept

Bennouna et al. Lancet Oncol 2013;14:29–37; Kubicka et al. ASCO-GI 2014 #520
Tabernero et al. Lancet Oncol 2015;16:499–508; Tabernero et al. ESMO 2011

SAFETY SUMMARY, GRADE 3–4

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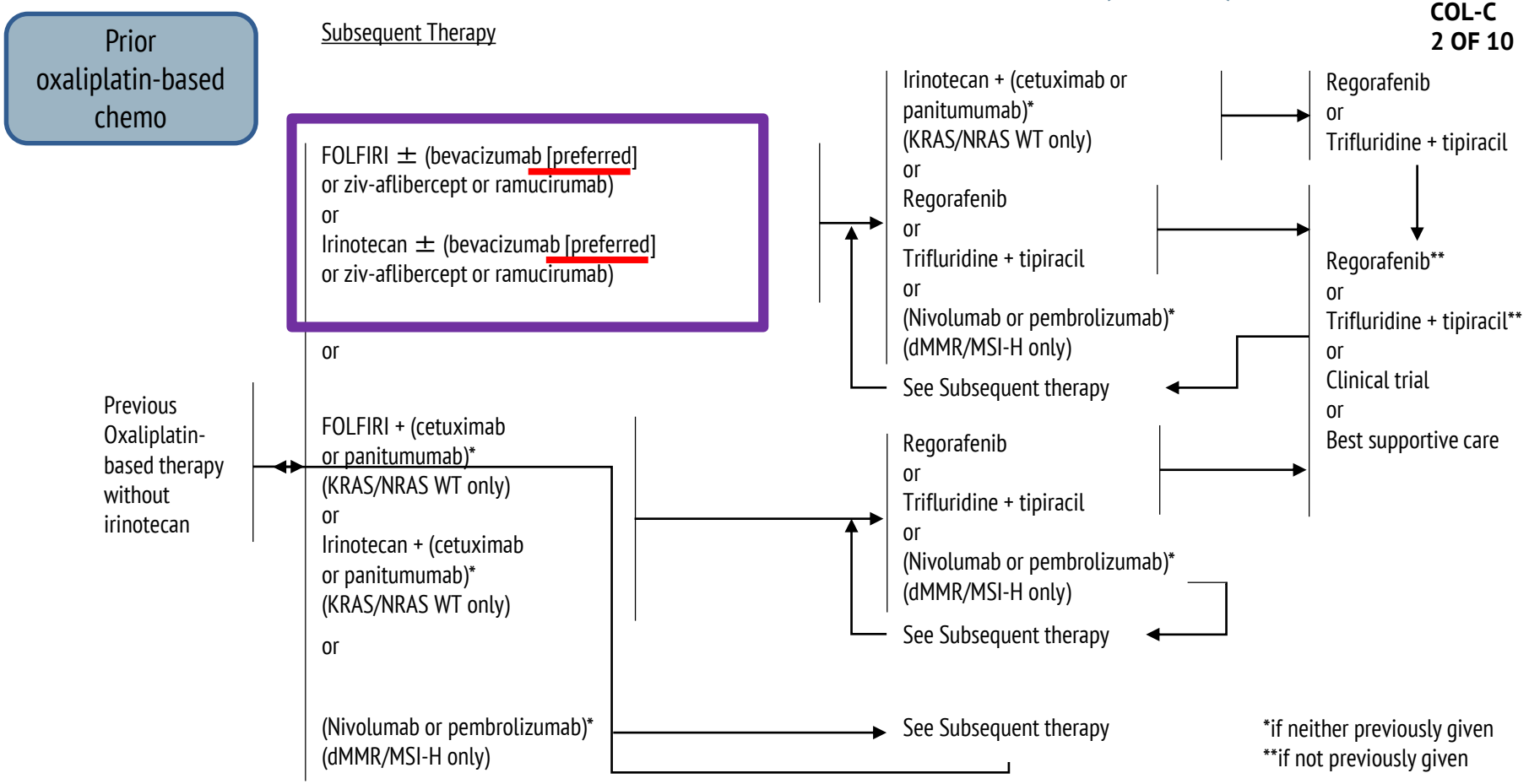
	ML18147		ML Sub-group		RAISE		VELOUR	
Grade >3 (%)	Chemo n=409	Chemo+Bev n=401	FOLFIRI n=174	FOLFIRI+Bev n=169	FOLFIRI+PL n=528	FOLFIRI+RAM n=529	FOLFIRI+PL n=605	FOLFIRI+AFL n=611
Neutropenia	13	16	NR	NR	23.3	38.4	29.5	36.7
Fatigue	2	3	NR	NR	7.8	11.5	NR	NR
Diarrhea	8	10	NR	NR	9.7	10.8	7.8	19.3
Mucositis	1	3	NR	NR	2.3	3.8	5.0	13.8
Abdominal pain	3	4	NR	NR	3.6	3.4	3.3	5.4
Thrombocytopenia	NR	NR	NR	NR	0.8	3.0	1.6	3.4
Vomiting	3	3	NR	NR	2.5	2.8	3.5	2.8
Nausea	3	3	NR	NR	2.7	2.5	3.0	1.8
Anorexia	2	1	NR	NR	1.9	2.5	1.9	3.4
Anemia	NR	NR	NR	NR	3.6	1.5	4.3	3.8
Constipation	NR	NR	NR	NR	1.5	0.9	1.0	0.8
Hypertension	1	2	0	1	2.8	10.8	1.5	19.3
Bleeding	<1	2	<1	3	1.7	2.5	1.7	3.0
Proteinuria	-*	<1*	0	<1	0.2	3.0	1.2	7.8
VTE	3	5	5	7	2.1	4.2	6.2	7.8
ATE	1	<1	0	<1	1.1	0.8	0.5	1.8
GI perforation	<1	2	<1	2	0.6	1.7	0.4	0.5

Bennouna J, et al. Lancet Oncol 2013;14:29–37; Kubicka S, et al. ASCO-GI 2014 #520;
Tabernero J, et al. Lancet Oncol 2015;16:499–508; *Arnold, et al. J Clin Oncol 30, 2012 (suppl; abstr CRA3503)

CONTINUUM OF CARE – CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE: (PAGE 2 of 10)



Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

See footnotes COL-C 6 of 10

NCCN GUIDELINES VERSION 1.2017
COLON CANCER

CONTINUUM OF CARE – CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE: (PAGE 2 of 10)

Prior oxaliplatin-based chemo

Subsequent Therapy

FOLFIRI ± (bevacizumab [preferred] or ziv-aflibercept or ramucirumab)
or
Irinotecan ± (bevacizumab [preferred] or ziv-aflibercept or ramucirumab)

or

Previous Oxaliplatin-based therapy without

FOLFIRI + (cetuximab or panitumumab)* (KRAS/NRAS WT only)

Irinotecan + (cetuximab or panitumumab)* (KRAS/NRAS WT only)
or
Regorafenib
or
Trifluridine + tipiracil
or
(Nivolumab or pembrolizumab)* (dMMR/MSI-H only)
See Subsequent therapy

Regorafenib
or
Trifluridine + tipiracil

Regorafenib
or
Trifluridine + tipiracil

Regorafenib**
or
Trifluridine + tipiracil**
or
Clinical trial
or
Best supportive care

COL-C 6 OF 9
"Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost."

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

See footnotes COL-C 6 of 10

SUB-ANALYSIS BY DURATION OF 1ST LINE: WHO ARE "FAST PROGRESSORS"?

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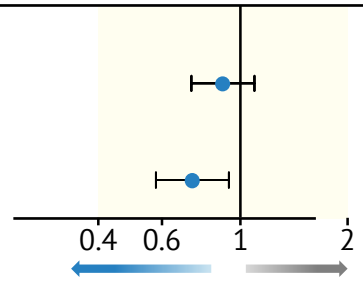
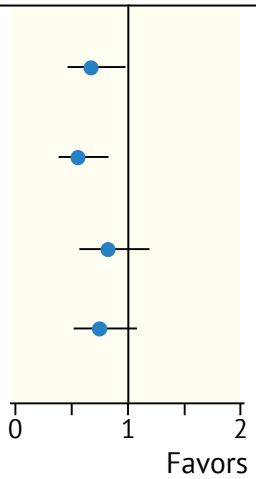
TML (BEV)

	1 st line PFS (m)	N	HR(95% CI)
OS	≤9	449	0.89(0.73-1.09)
	>9	369	0.73(0.58-0.92)



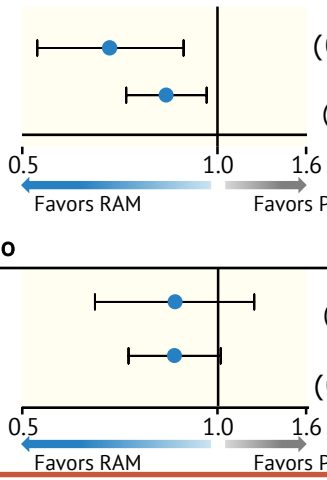
VELOUR (Afl)

	(m)	N	HR (95%CI) (prior BEV)
PFS	PFS-1st line PFS:<9	155	0.67 (0.46-0.97)
	PFS-1st line PFS:≥9	201	0.56 (0.39-0.82)
OS	OS-1st line PFS:<9	155	0.82 (0.58-1.18)
	OS-1st line PFS:≥9	201	0.75 (0.52-1.08)



RAISE (RAM)

	(m)	RAM	Placebo	HR (95% CI)
PFS	<6	125	129	0.681 (0.524-0.886)
	≥6	411	407	0.833 (0.721-0.962)
OS	<6	125	129	0.855 (0.644-1.134)
	≥6	411	407	0.855 (0.726-1.007)



Van Cutsem E et al, Target Oncol, 2016, epub, DOI 10.1007/s11523-015-0402-9.
Tabernero J et al, Lancet Oncol, 2015, 16:499-508
Giantonio BJ et al , JCO, 2007, 25:1539-1544. Bennouna J et al, Lancet Oncol 2013, 14: 29–37

POTENTIAL BIOMARKERS IDENTIFIED FROM THE VELOUR STUDY

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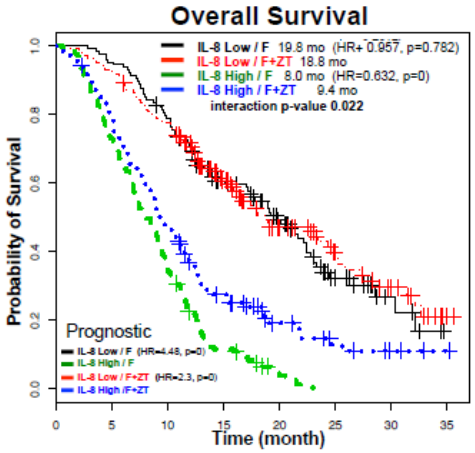
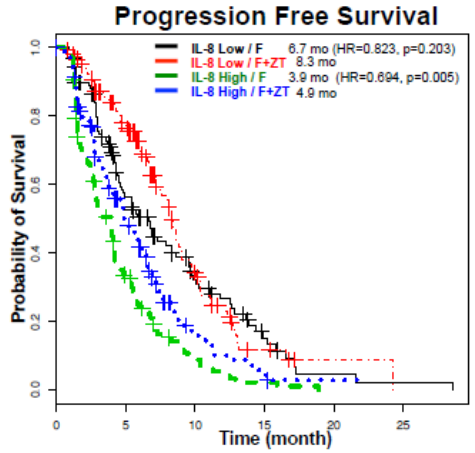
IL-8 may be a predictive & prognostic biomarker





Potentially Predictive Markers (HR <0.7, interaction p<0.01)

Biomarker	Median	High or Low biomarker group	Hazard Ratio (ZT vs control)	p-value*	Interaction p-value
IL-8	20 pg/ml	High	0.63	0.0004	0.022
MIF	0.3 ng/ml	High	0.67	0.003	0.087
VEGF	142 pg/ml	High	0.64	0.0013	0.056
VEGFR2	4.2 pg/ml	High	0.69	0.0082	0.157^
VEGFR3	35 ng/ml	High	0.69	0.0061	0.177^
SPD	7.7 ng/ml	Low	0.60	0.0003	0.003

Potentially Prognostic Markers (HR >1, p<0.01 on both control and ZT arms)

Biomarker	Median	Control treated		ZALTRAP treated	
		Hazard Ratio (High vs Low)	p-value	Hazard Ratio (High vs Low)	p-value
IL-8	20 pg/ml	4.481	<0.001	2.3189	<0.001
CRP	9.4 µg/ml	2.7732	<0.001	2.5535	<0.001
NRP1	160 ng/ml	2.0324	<0.001	2.104	<0.001
ANG2	3.9 ng/ml	1.5447	0.002	1.8293	<0.001

*Logrank p-values were adjusted for FDR; ^VEGF-R2 and VEGF-R3 fall below levels of significance for interaction

TUMOR GROWTH INHIBITION INDUCED BY AFLIBERCEPT OCCURRED MORE FREQUENTLY IN PDX MODELS COMPARED WITH BEVACIZUMAB

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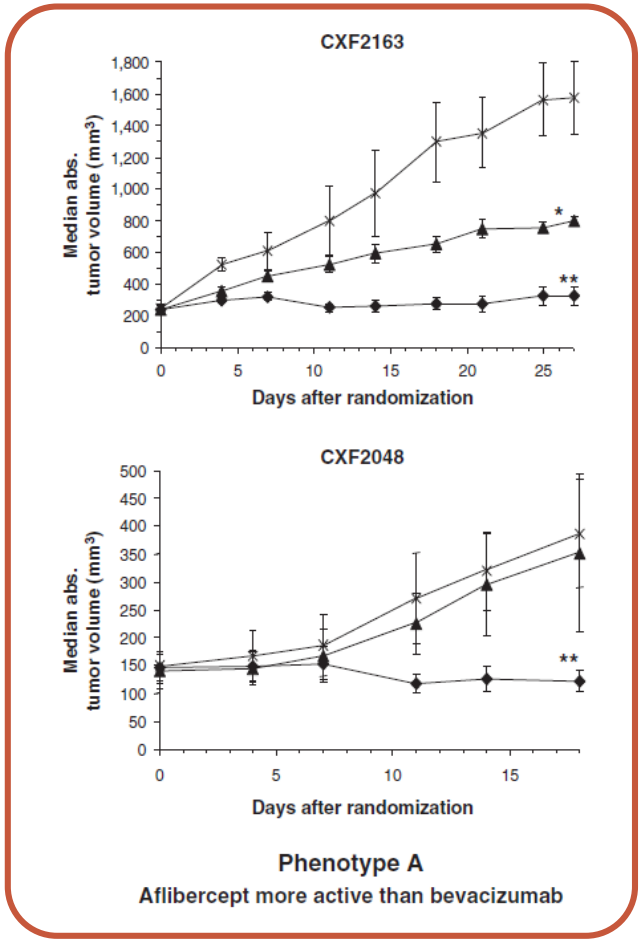

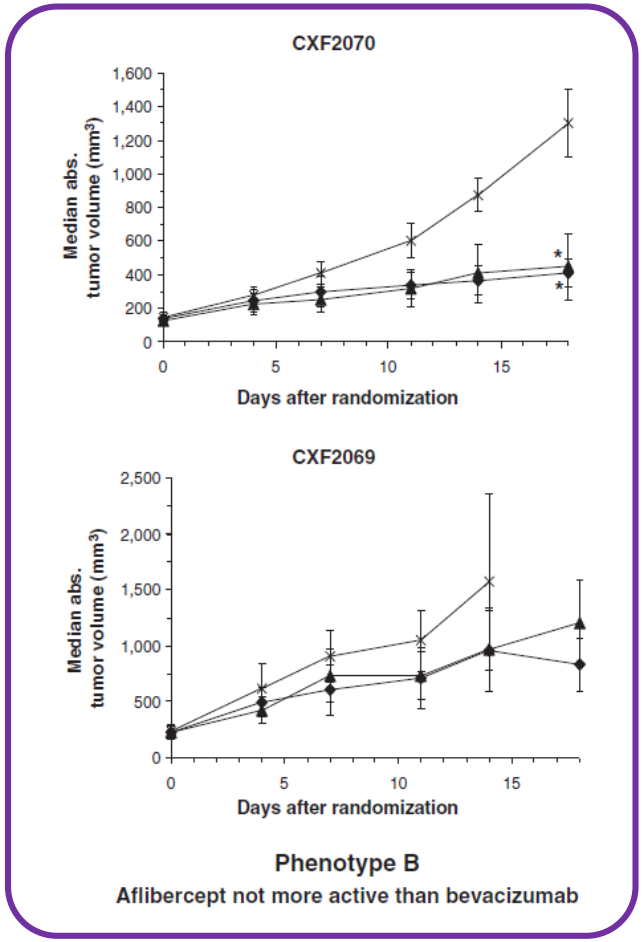

- Control; 10 mL/kg/day s.c.; days 0, 3, 7, 10, 14, 17, 26
- Aflibercept; 25 mg/kg/day s.c.; days 0, 3, 7, 10, 14, 17, 26
- Bevacizumab; 25 mg/kg/day i.v.; days 0, 3, 7, 10, 14, 17, 26

Chiron M, et al. Mol Cancer Ther 2014

WHICH ANTI-VEGF DRUG IS BETTER?

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- 4 trials have reported a gain in OS by the addition of an antiangiogenic compound, irrespective of the various first-line regimens
- Patients who are fast progressors on first-line bevacizumab containing regimens should be considered for treatment with aflibercept or ramucirumab

NEED CERTAIN BIOMARKERS TO USE MORE PROPER ANTI-VEGF DRUG FOR SECOND-LINE TREATMENT AFTER BEVACIZUMAB

ANALYSIS OF PLASMA VEGF-D EXPRESSION FOR RAMUCIRUMAB EFFICACY IN THE RAISE TRIAL

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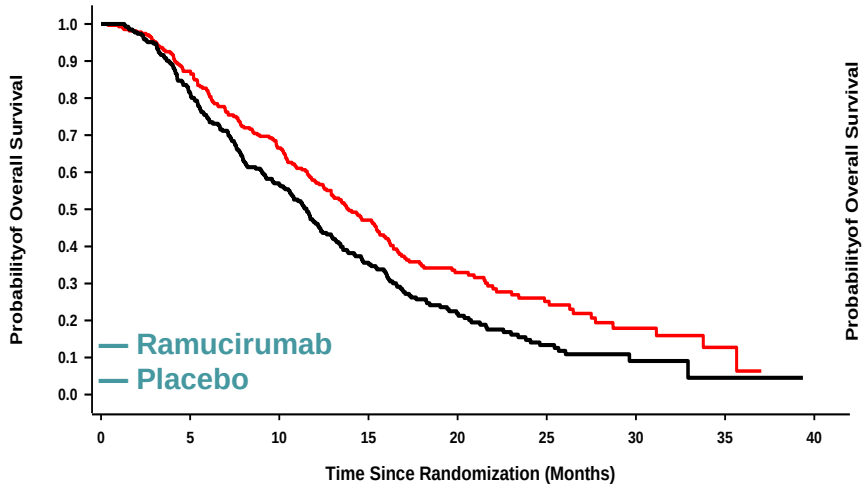
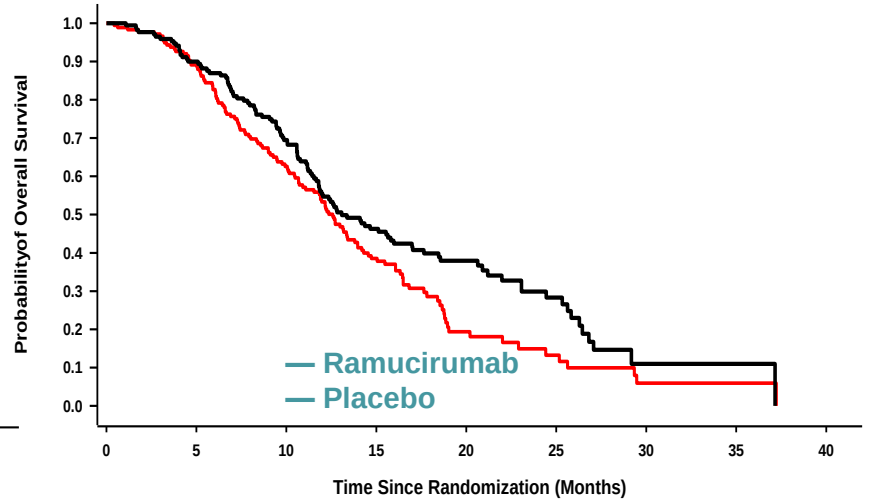
High VEGF-D (⩾115 pg/mL)

	Ramucirumab + FOLFIRI (n=270)	Placebo + FOLFIRI (n=266)
Median, months (95% CI)	13.9 (12.5-15.6)	11.5 (10.1-12.4)
Δ	2.4 month	
HR (95% CI)	0.73 (0.60-0.89)	
P-value (likelihood ratio)	0.0022	

Low VEGF-D (<115 pg/mL)

	Ramucirumab + FOLFIRI (n=176)	Placebo + FOLFIRI (n=172)
Median, months (95% CI)	12.6 (10.7-14.0)	13.1 (11.8-17.0)
Δ	-0.5 month	
HR (95% CI)	1.32 (1.02-1.70)	
P-value (likelihood ratio)	0.0344	





Tabernero J, et al: ESMO2017 abstract555

RANDOMIZED P-II TRIALS TO EVALUATE BEVACIZUMAB VS. ANTI-EGFR MAB

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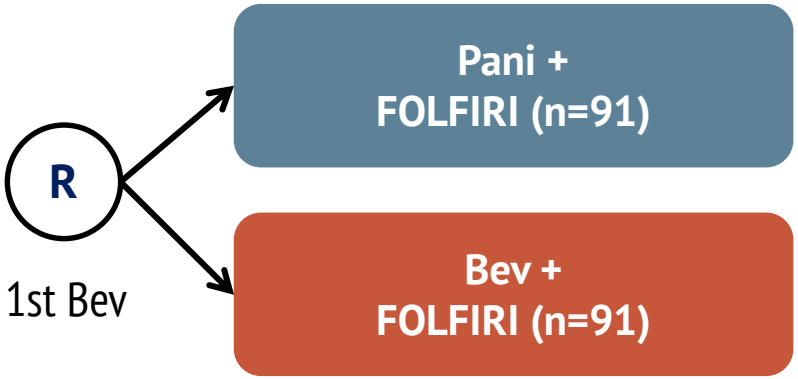
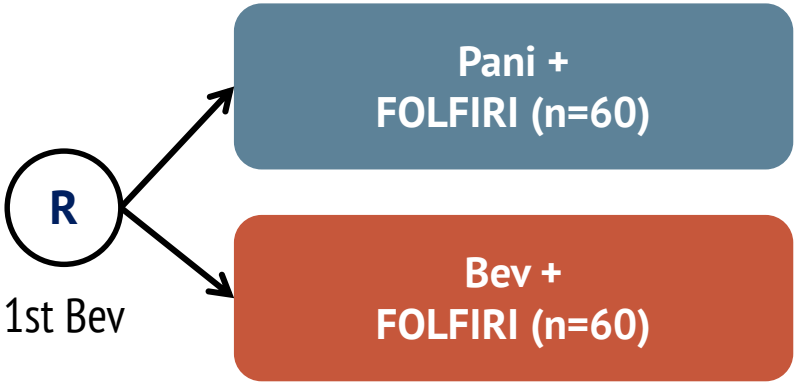
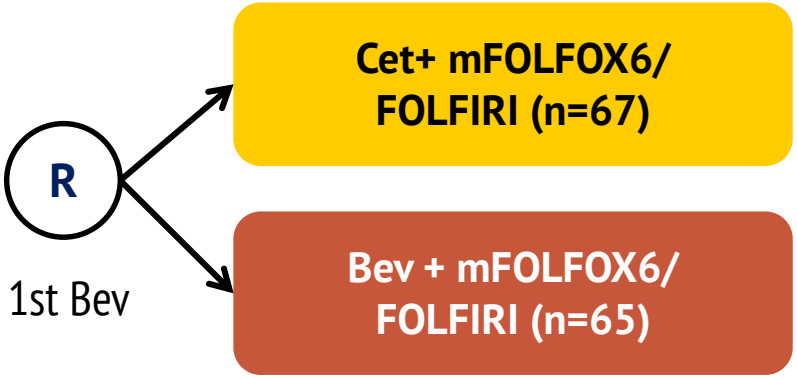
SPIRITT (n=182)



WJOG6210G (n=120)



PRODIGE18 (n=133)



Hecht JR, et al. Clin Colorectal Cancer. 2015; 14(2):72–80; Shitara K, et al. 2016 ASCO #3567; Bennouna J. et al. ESMO 2017 #4770

RANDOMIZED P-II TRIALS OF 2ND-LINE BEV VS. ANTI-EGFR MAB: PFS

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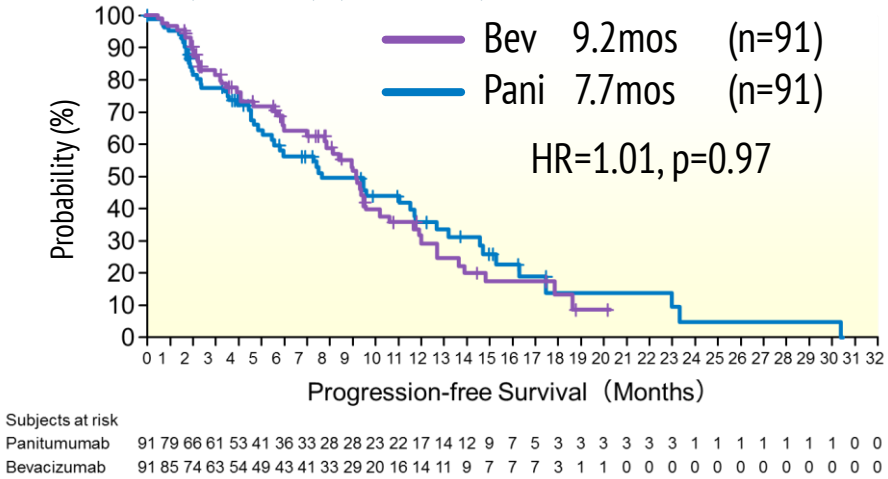
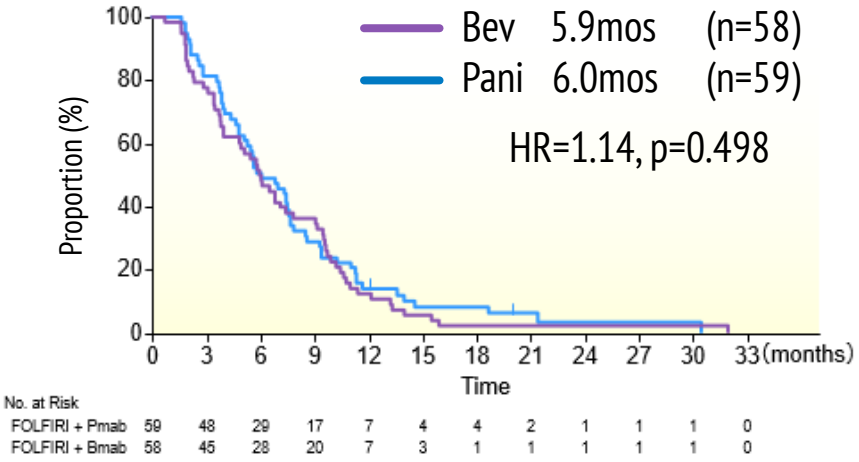
SPIRITT (n=182) (primary)



WJOG6210G (n=120) (secondary)

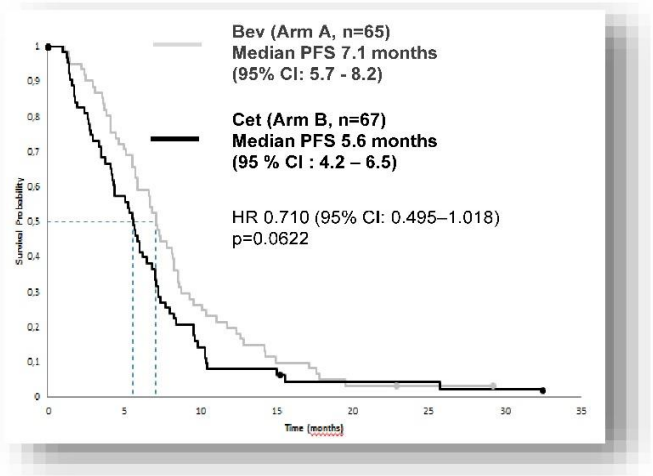


PRODIGE18 (n=132) (primary)

Progression free survival at 4 months

	Arm A (Bev) n=65	Arm B (Cet) n=67
PFS at 4 months 95% IC	80.3% (68.0%–88.3%)	66.6% (53.6%–76.8%)

Progression-Free Survival



RANDOMIZED P-II TRIALS OF 2ND-LINE BEV VS. ANTI-EGFR MAB: OS

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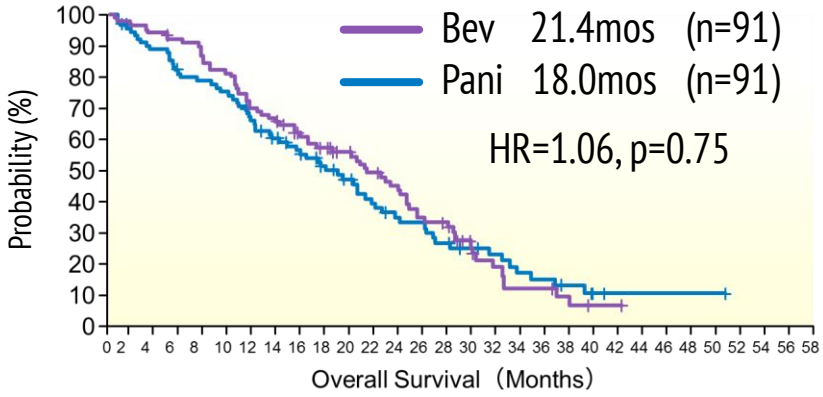
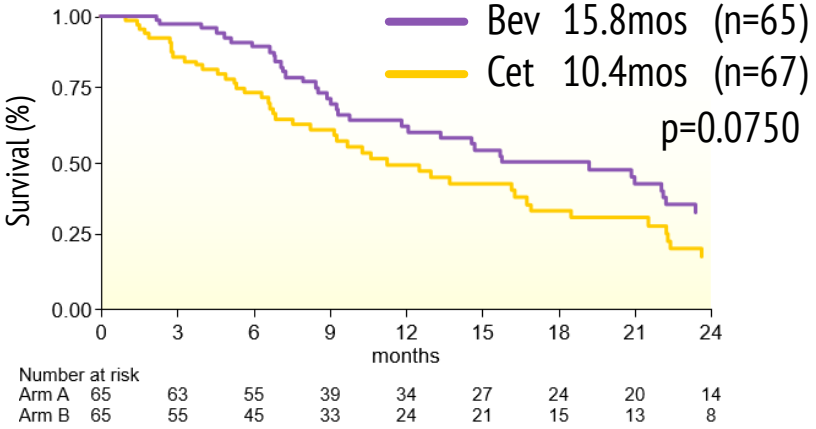
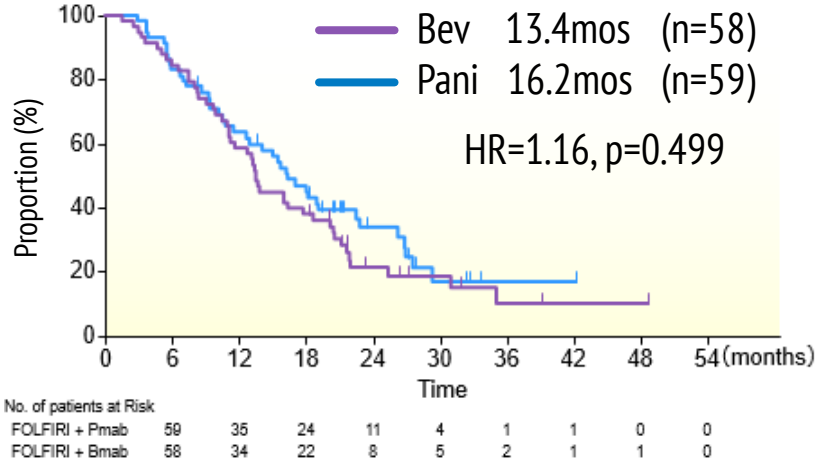
SPIRITT (n=182) (secondary)



PRODIGE18 (n=132) (secondary)



WJOG6210G (n=120) (primary)



Hecht JR, et al. Clin Colorectal Cancer. 2015; 14(2):72–80; Shitara K, et al. 2016 ASCO #3567; Bennouna J. et al. ESMO 2017 #4770

RANDOMIZED P-II TRIALS OF 2ND-LINE BEV VS. ANTI-EGFR MAB: SUMMARY

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Study	Treatment arm	PFS (m)		OS (m)		ORR (%)
SPIRITT	Pani+FOLFIRI	7.7	HR=1.01 p=0.97	18.0	HR=1.06 p=0.75	32
	Bev+FOLFIRI	9.2		21.4		19
WJOG6210G	Pani+FOLFIRI	6.0	HR=1.14 p=0.498	16.2	HR=1.16 p=0.499	46.2
	Bev+FOLFIRI	5.9		13.4		5.7
PRODIGE18-ACCORD22	Cet+Chemo	5.6	p=0.062	10.4	HR: N/A p=0.075	32.3
	Bev+Chemo	7.1		15.8		24.6

NO SURVIVAL BENEFIT IN ANTI-EGFR MAB COMPARED TO BEV, BUT BETTER RESPONSE RATE

Hecht JR, et al. Clin Colorectal Cancer. 2015; 14(2):72–80; Shitara K, et al. 2016 ASCO #3567; Bennouna J. et al. ESMO 2017 #4770

BEV FOLLOWED BY CET VS. CET FOLLOWED BY BEV

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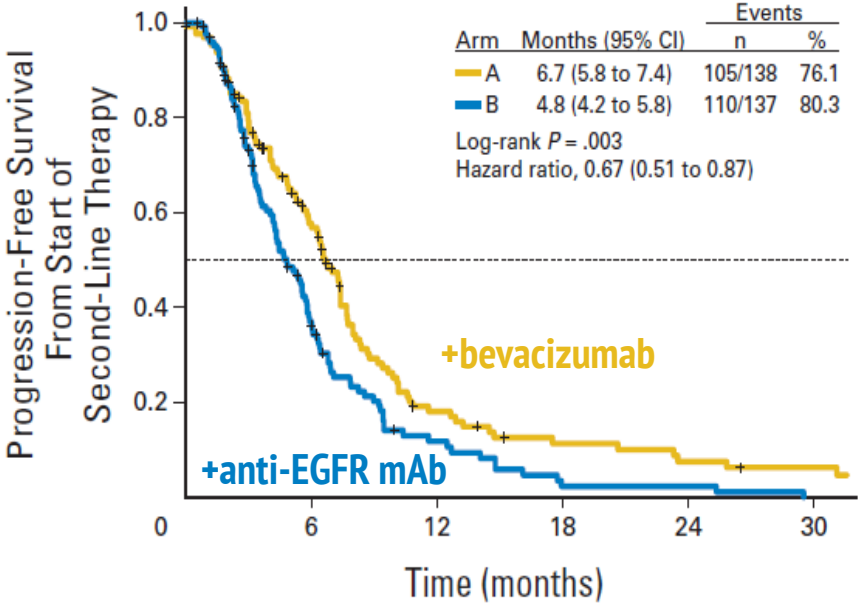
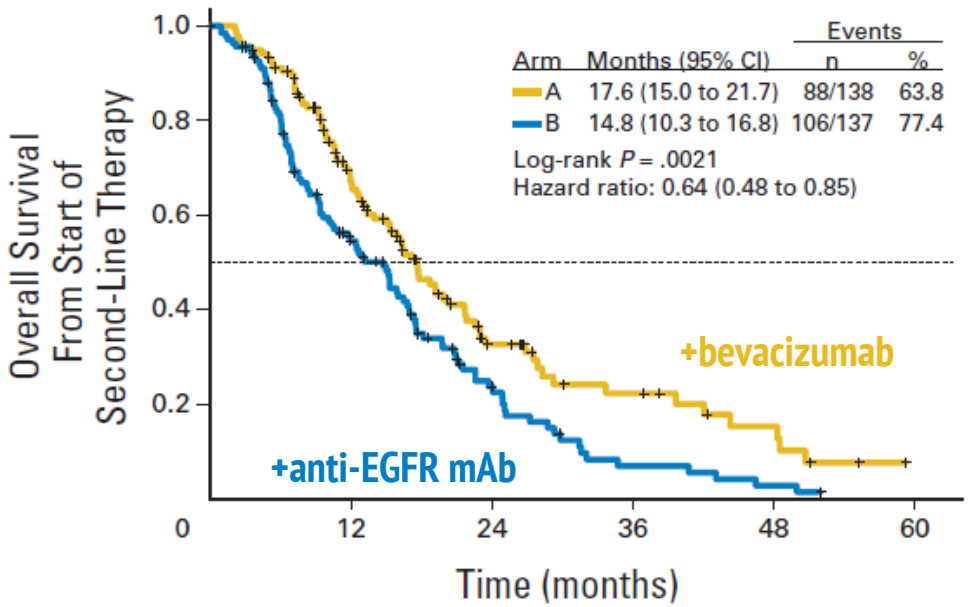
SUBSEQUENT THERAPY ANALYSIS OF THE FIRE-3

Second-line PFS



Second-line OS



IT SEEMS THAT THE SEQUENTIAL APPLICATION OF ANTI-EGFR AGENTS FOLLOWED BY SECOND-LINE ANTI-VEGF THERAPY ACHIEVES MORE FAVORABLE RESULTS THAN THE REVERSE SEQUENCE

Modest DP, et al. J Clin Oncol 2015

ANTI-VEGF VS. ANTI-EGFR FOR 2ND-LINE

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- There is a similar relative benefit when anti-EGFR mAb is used in later lines compared with 2nd-line, which was confirmed in a recent randomized trial
- EGFR inhibitors may be considered for patients with RAS wild-type disease, especially
  - when a higher response rate is desired
  - for patients who are fast progressors on first-line bevacizumab containing regimens

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GI CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Antoine Lacombe
Pharm D, MBA
Phone: +41 79 529 42 79
antoine.lacombe@cor2ed.com

Dr. Froukje Sosef
MD
Phone: +31 6 2324 3636
froukje.sosef@cor2ed.com