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DOES LOCATION MATTER IN COLORECTAL CANCER: LEFT VS RIGHT?

By:
Dr. Dominik Modest, Medical Department III, Hospital of the University of Munich, Germany

Dr. Andrea Sartore-Bianchi, Niguarda Cancer Center, Milano, Italy

Dr. Sebastian Stintzing Medical Department III, Hospital of the University of Munich, Germany

RIGHT AND LEFT COLON: ANATOMY

The **large intestine** can be divided into **right** and **left sides**. Although the anatomical limits are not standardised in the literature, **the right colon comprises the caecum, ascending colon and transverse colon up to the splenic flexure**; the **left colorectum comprises the splenic flexure, descending colon, sigmoid colon and rectum** (the rectum is sometimes included as left colorectum and sometimes considered a separate entity).

Right (proximal) colon	Left (distal) colorectum
Transverse colon	Splenic flexure
Hepatic flexure	Descending colon
Ascending colon	Sigmoid colon
Caecum	Rectum

Lee GH, et al. Eur J Surg Oncol 2015; Li F, Lai M. J Zhejiang Univ Sci B 2009; Iacopetta B. Int J Cancer 2002

RIGHT AND LEFT COLON: ANATOMY AND GENETIC FEATURES

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- The right colon and left colorectum have **different embryonic origins and vascular supplies**:
  - the **right** colon originates from the midgut and blood is supplied by branches of the superior mesenteric artery and the capillary network is multi-layered; innervation derives from the vagus nerve
  - the **left** colorectum originate from the hindgut and blood is supplied by tributaries from the inferior mesenteric artery and innervation is from fibres of S2–S4
- Genetic profiling of normal right and left colon mucosa has confirmed major differences between colorectal sites; 351 genes have been identified as differentially expressed between the right and left colon: 157 overexpressed in the right colon and 194 in the left colon

Li F, J Zhejiang Univ Sci B 2009; Missiaglia E, et al. Ann Oncol 2014

RIGHT AND LEFT COLORECTAL CANCER

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- The site distribution of colorectal tumours is 28% (range 19–38%) for the right colon and 72% (range 63–81%) for the left colorectum
  - In Western countries, there is evidence that the incidence of right-sided tumours has increased while that of left-sided tumours has decreased over time
- Symptoms associated with tumours in the right colon are often subtle, whereas those associated with tumours in the left colorectum may be more pronounced, such as rectal bleeding or changes in bowel habit
- Patients with right-sided tumours typically present with more advanced tumour stage than those with left-sided disease
- More common features of right-sided tumours compared with left include high TNM stage, large tumour size, vascular invasion, mucinous type, high grade and invasive tumour border
- Right-sided colon tumours appear to be more common in women than in men

Lee GH, et al. Eur J Surg Oncol 2015; Riihimäki M, et al. Sci Rep 2016; Benedix F, et al. Dis Colon Rectum 2010; Brenner H, et al. Int J Cancer 2012; Li F, Lai M. J Zhejiang Univ Sci B 2009; Icopetta B. Int J Cancer 2002

RIGHT AND LEFT COLORECTAL CANCERS: DIFFERENCES IN MOLECULAR BIOMARKERS

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- There are associations between tumour location and the frequency of gene mutations or expression levels of proteins involved in CRC signalling pathways
- In a retrospective analysis of data from a US cohort of mCRC patients whose tumours underwent molecular testing between 2007 and 2010 (n=431)
  - BRAF mutations were significantly more common in the right colon (14%) than either the left colon (5%) or rectum (2%) ($P < 0.001$)
  - KRAS mutations were observed at similar frequencies across the colon and rectum ($P = 0.51$)
  - VEGFR2 expression levels were significantly higher in rectal tumours (1.77; range, 0.23–13.00) than left-sided colon (1.24; range, 0.18–7.66) or right-sided colon (1.10; range, 0.24–6.10) tumours ($P < 0.001$ for both comparisons)
- In another study, important signalling pathways including MAPK and ErbB were more frequently mutated in tumours from the right colon compared with the left. Analysis of genes differentially expressed between right-sided and left-sided colon tumours revealed EREG (EGF ligand) to be among the most over-expressed genes in distal carcinomas

Maus MKH, et al. Pharmacogenomics J 2015;15:354–62; Missiaglia E, et al. Ann Oncol 2014;25:1995–2001

SIDENESS AND RESPONSE TO TARGETED THERAPY

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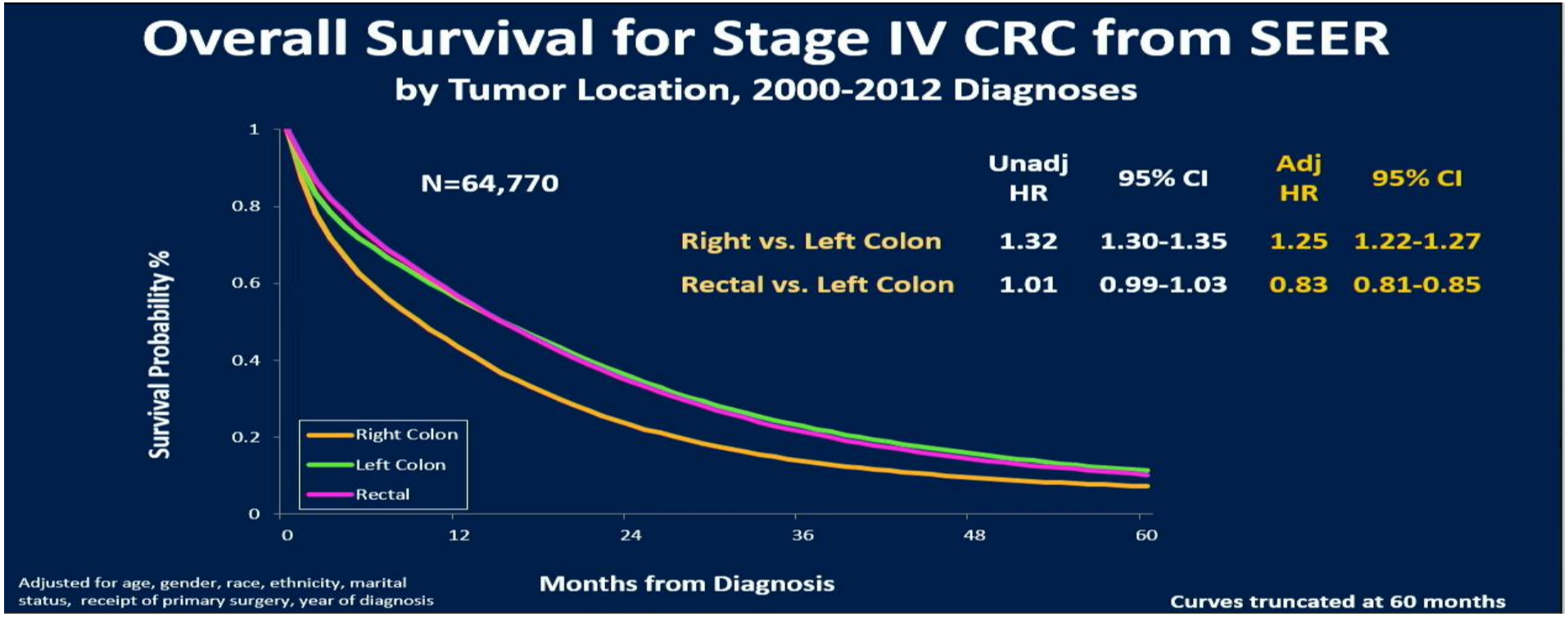
- Given the different genetic make-up of colon arising in the left versus right side, differential outcomes have been reported with the use of EGFR- or VEGF-targeted treatments according to sideness
- Here we will present these data and their impact on results from phase III trials in mCRC

PROGNOSTIC IMPACT OF SIDENESS IN CRC-SEERS DATA



Presented by D Schrag at ASCO 2016

FIRE-3: RIGHT-SIDED TUMOURS AND EFFICACY OF MABS

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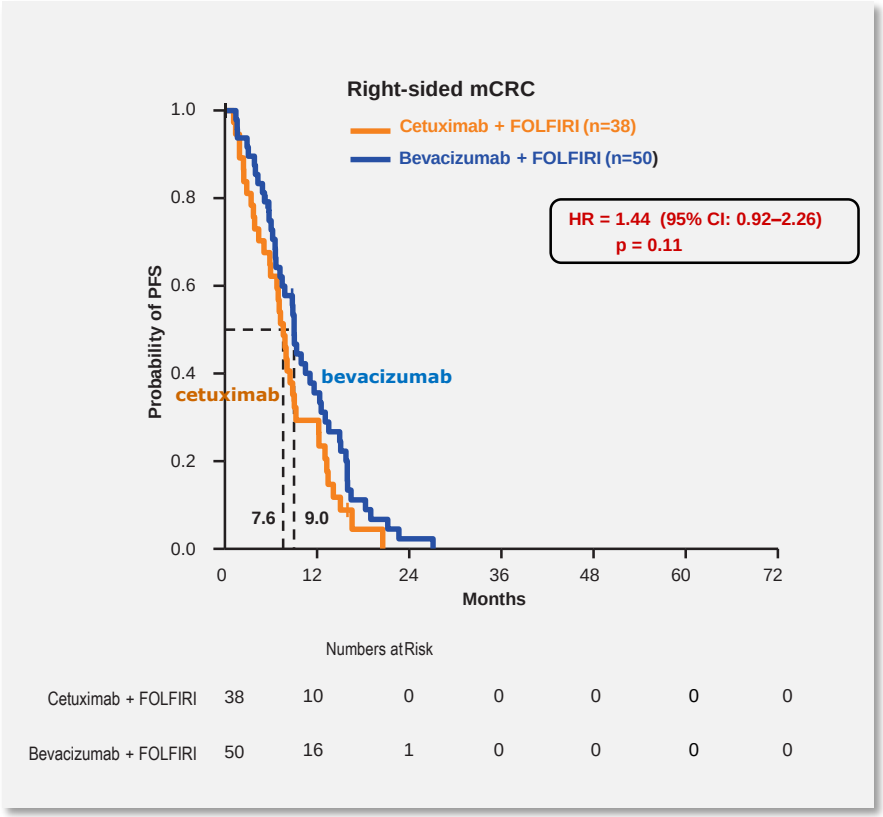
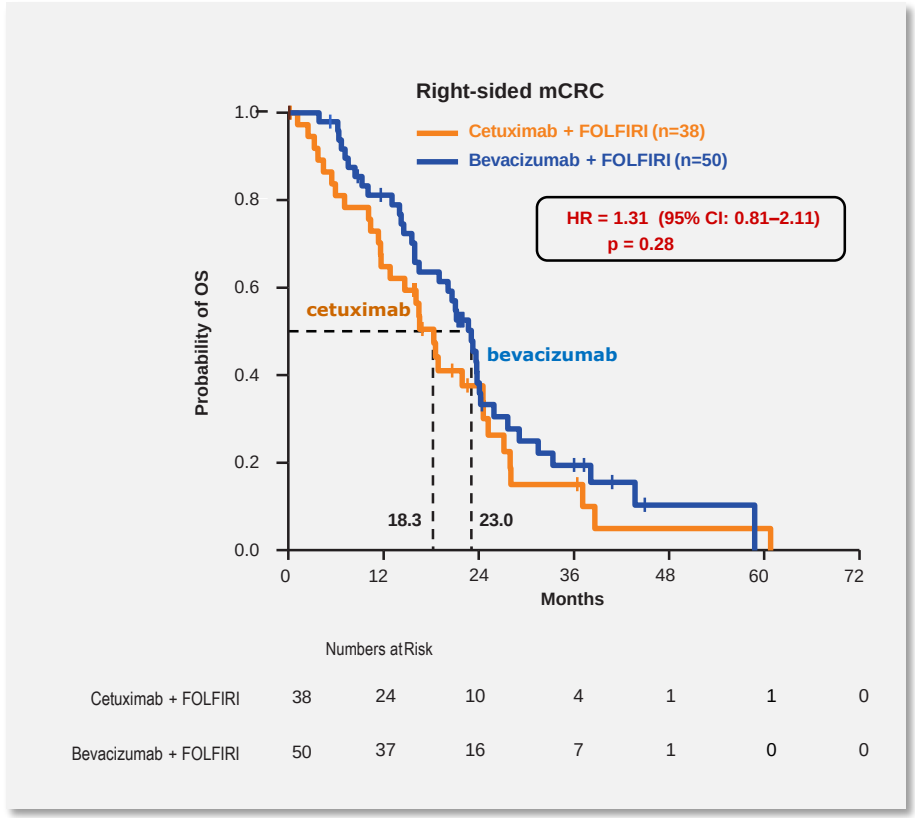
Progression-free survival



Overall survival



Tejpar et al, JAMA Oncol 2017

FIRE-3: LEFT-SIDED TUMOURS AND EFFICACY OF MABS

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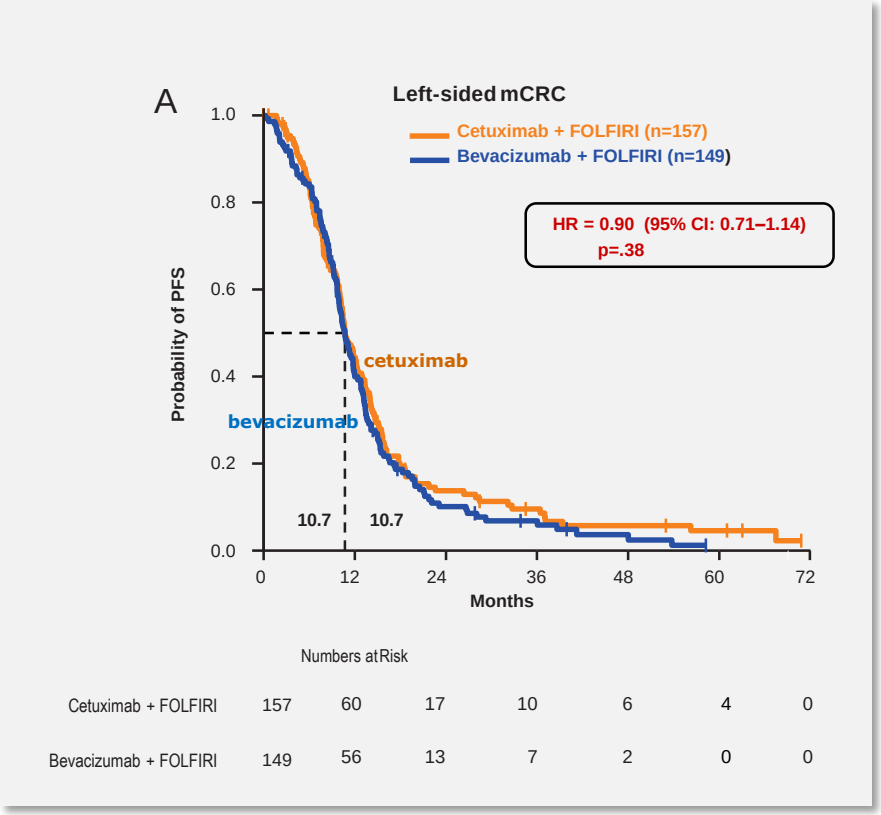
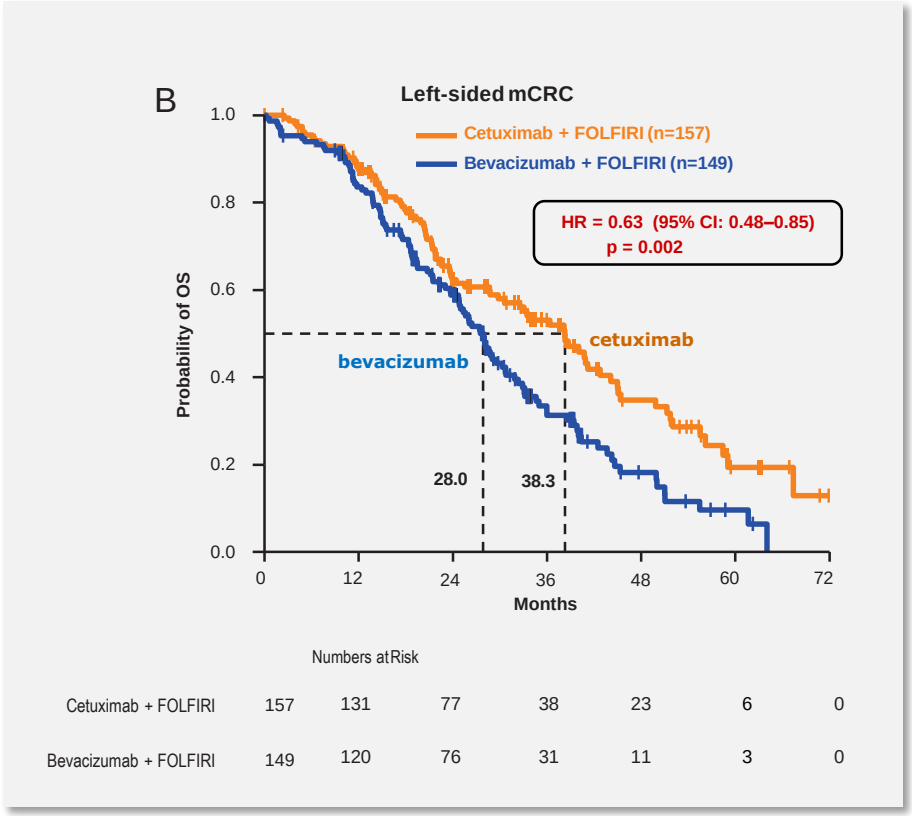
Progression-free survival

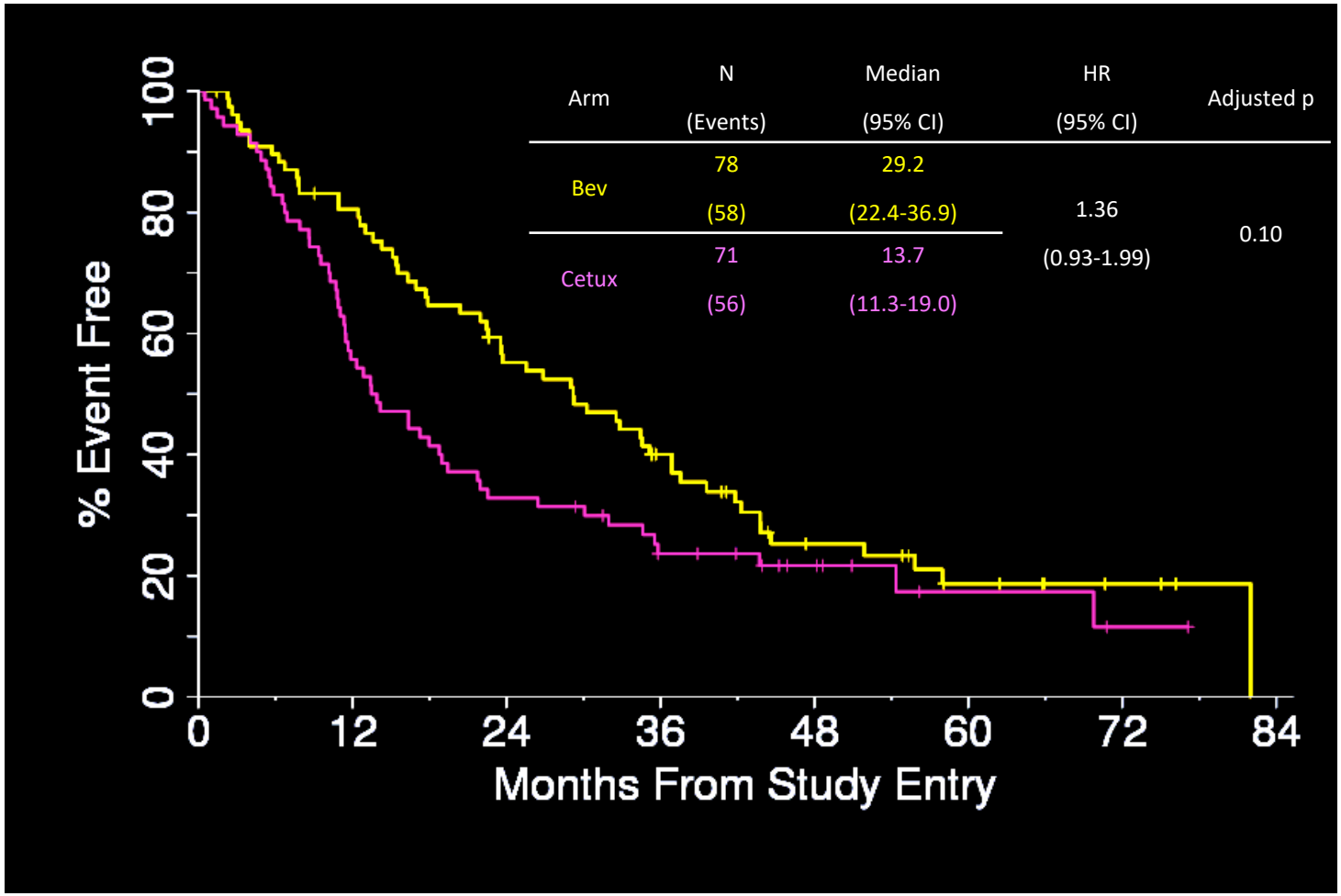


Overall survival



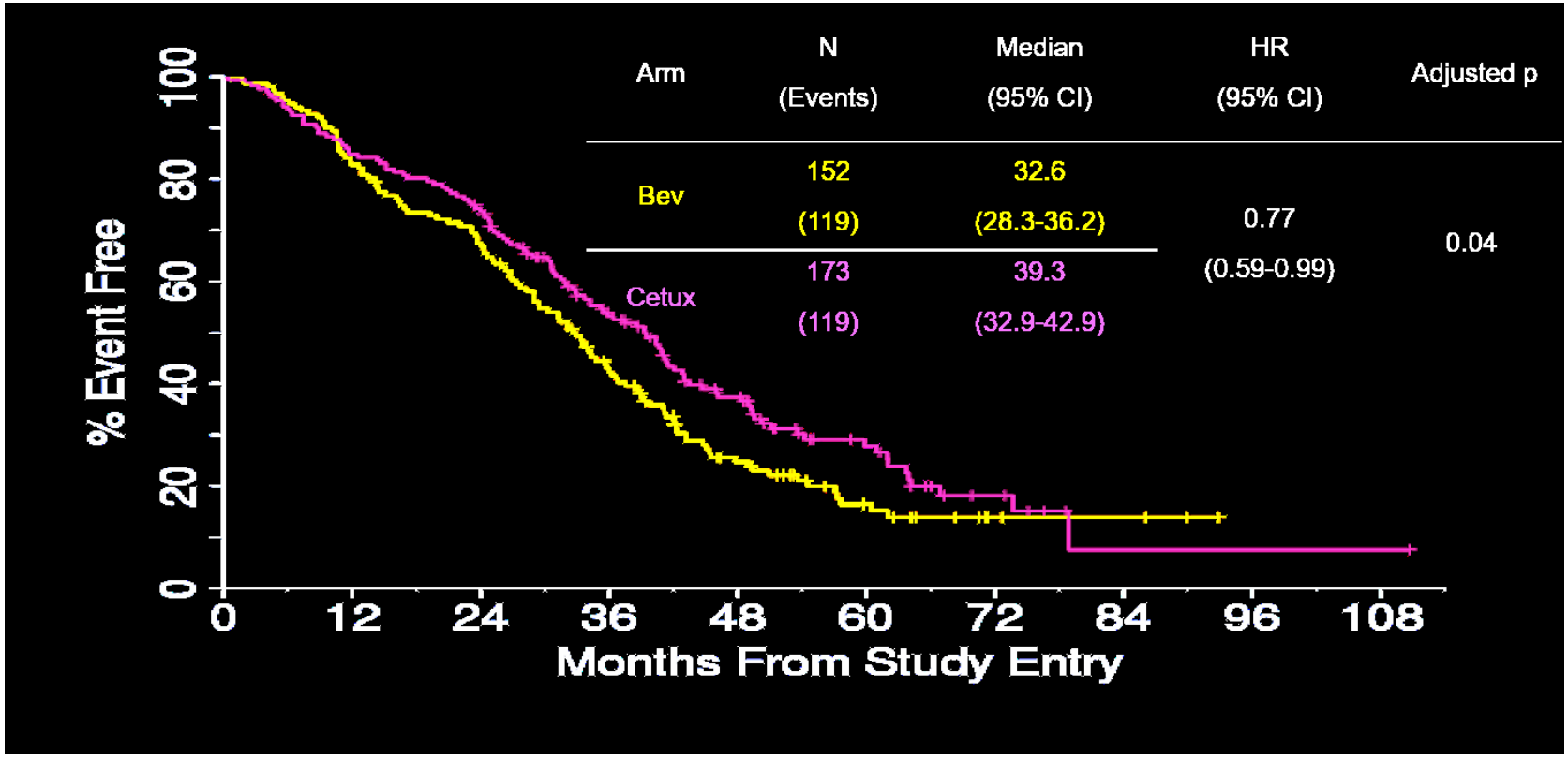
Tejpar et al, JAMA Oncol 2017

CALGB/SWOG 80405 [FOLFOX OR FOLFIRI +MAB]: OVERALL SURVIVAL BY BIOLOGIC (RIGHT SIDED PRIMARY)



Presented by Lenz et al, ESMO 2016

CALGB/SWOG 80405 [FOLFOX OR FOLFIRI +MAB]: OVERALL SURVIVAL BY BIOLOGIC (LEFT SIDED PRIMARY)



Presented by Lenz et al, ESMO 2016

PRIME – OS – FIRST LINE

EFFICACY OF PANITUMUMAB BY SIDEDNESS

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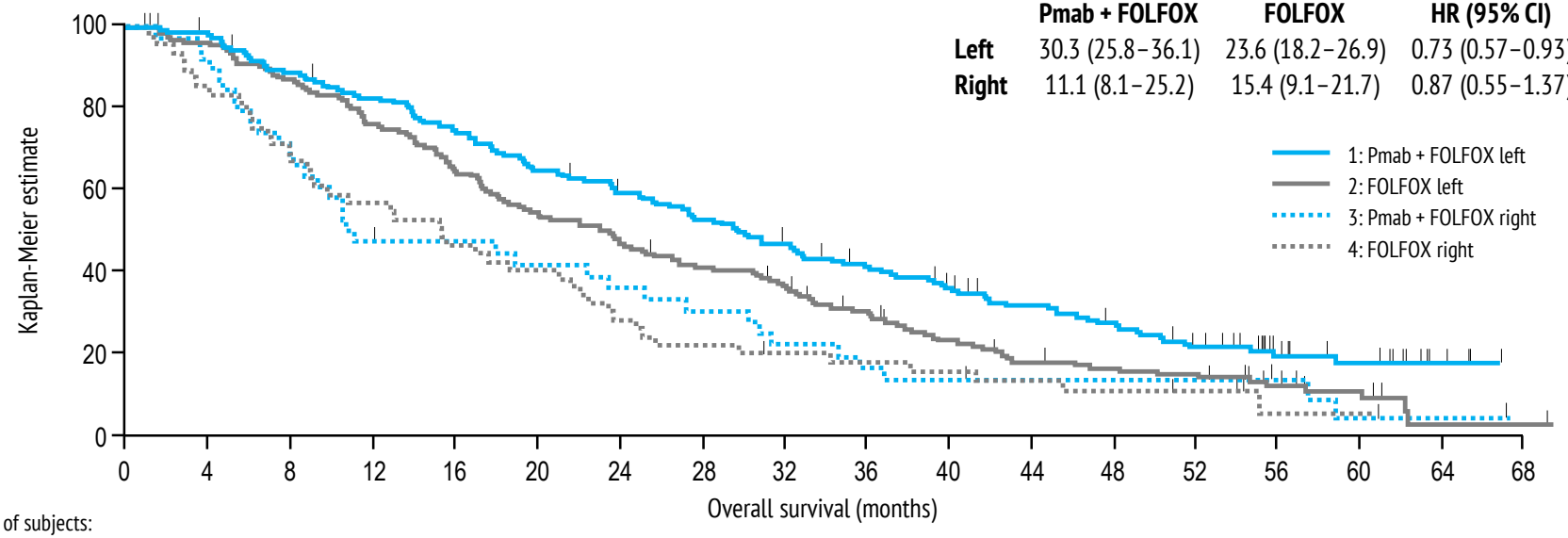
	Median OS (95% CI), months		
	Pmab + FOLFOX	FOLFOX	HR (95% CI)
Left	30.3 (25.8–36.1)	23.6 (18.2–26.9)	0.73 (0.57–0.93)
Right	11.1 (8.1–25.2)	15.4 (9.1–21.7)	0.87 (0.55–1.37)



No. of subjects:

1:	169	164	147	136	124	107	97	86	77	66	56	46	39	30	16	11	3	0
2:	159	151	137	120	103	86	76	64	56	44	32	24	21	19	11	6	1	1
3:	39	36	26	18	17	15	13	11	8	6	5	4	4	4	3	1	1	0
4:	49	42	34	28	23	20	14	11	9	8	7	6	5	4	1	1	0	

Censor indicated by vertical bar

HR, hazard ratio; OS, overall survival; Pmab, panitumumab

Presented by Peeters et al, ESMO 2016

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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