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Cetuximab in treatment of metastatic colorectal cancer: final survival analyses and extended *RAS* data from the NORDIC-VII study

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Background: The NORDIC-VII study is a randomised phase III trial of cetuximab plus continuous or intermittent fluorouracil, folinic acid, and oxaliplatin (Nordic FLOX) *vs* FLOX alone in first-line treatment of metastatic colorectal cancer. The present report presents an updated and final survival analysis with *BRAF* and extended *RAS* mutational status, 5 years after the primary analysis.

Methods: A total of 566 patients were included in the intention-to-treat (ITT) population of the NORDIC-VII study. Updated survival status was obtained from 176 patients who were alive in the primary survival analyses. Samples from 223 tumours previously found to be *KRAS* (exon 2) and *BRAF* (V600E) wild-type, were re-analysed for *KRAS* (exons 3 and 4) and *NRAS* (exons 2–4) mutations.

Results: Including the extended *RAS* analyses, *RAS* and *BRAF* mutational status was available from 457 patients (81% of the ITT population). *RAS* was mutated in 46% and *BRAF* in 12% of the tumours. *RAS* and *BRAF*, if mutated, were negative prognostic factors. The updated analyses confirmed the finding of the primary report that cetuximab did not provide any additional benefit when added to FLOX in patients with *RAS/BRAF* wild-type tumours, neither on progression-free nor overall survival. However, the outcomes in a subset of patients, which, after the first eight treatment cycles, received cetuximab alone, suggested a beneficial effect of cetuximab monotherapy.

Conclusions: Adding cetuximab to Nordic FLOX did not provide any clinical benefit, but the data suggested an effect of cetuximab monotherapy in patients with *RAS/BRAF* wild-type tumours in the NORDIC-VII cohort. The data were compatible with a negative interaction between cetuximab and the Nordic FLOX chemotherapy backbone.

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Several studies have shown that adding EGFR antibodies to chemotherapy in first-line treatment of metastatic colorectal cancer (mCRC) improves outcome (Bokemeyer *et al*, 2009; Van Cutsem *et al*, 2009; Douillard *et al*, 2010). Initially, the effect was reported to be restricted to patients with *KRAS* (exon 2) wild-type tumours. Extended *RAS* analyses have demonstrated lack of response to EGFR antibodies also in patients with tumours harbouring other *KRAS* (exons 3 and 4) or *NRAS* mutations (Douillard *et al*, 2013; Bokemeyer *et al*, 2015; Van Cutsem *et al*, 2015).

The NORDIC-VII study (Tveit *et al*, 2012), randomised phase III trial, investigated the effect of adding cetuximab to a regimen of bolus 5-fluorouracil (5-FU)/folinic acid (FA) and oxaliplatin (Nordic FLOX) in first-line therapy of mCRC (Sorbye *et al*, 2004). In the intention-to-treat (ITT) population of 566 patients there was no statistically significant difference in overall response rate (ORR), progression-free survival (PFS), or overall survival (OS) between the treatment arms, and no effect of adding cetuximab to Nordic FLOX was demonstrated in patients with *KRAS* (exon 2) wild-type tumours (Tveit *et al*, 2012). These results were unexpected, however, the COIN trial also showed lack of effect when adding cetuximab to an oxaliplatin–capecitabine regimen in *KRAS* wild-type cases, while combination of cetuximab with the commonly used FOLFOX regimen gave a minor benefit (Maughan *et al*, 2011). Theoretically, the lack of effect of cetuximab in NORDIC-VII might have at least two explanations, a negative influence of the companion chemotherapy regimen used or a patient population in this study that was non-responsive to anti-EGFR antibodies. On the basis of the results of a bolus 5-FU/FA regimen in the NORDIC-VII study, and the majority of patients in the COIN trial who received capecitabine, it has been suggested that when an EGFR antibody is added to fluoropyrimidine–oxaliplatin chemotherapy, the type of fluoropyrimidine regimen may influence treatment outcome (Grothey and Lenz, 2012; Mahipal and Grothey, 2016).

An updated OS analysis of NORDIC-VII is reported here, 5 years after the primary survival analysis. The impact of *RAS* (*KRAS* exons, 2, 3, and 4, and *NRAS* exons 2, 3, and 4) and *BRAF* (V600E) mutation status on prognosis and treatment outcome was investigated. Moreover, to investigate whether cetuximab might have an effect when given alone also in this patient population, we have examined the outcome in patients who received cetuximab in the absence of FLOX as maintenance therapy after eight cycles of treatment.

MATERIALS AND METHODS

Study design, treatments, and data collection. The NORDIC-VII study is a randomised phase III trial investigating the effect of adding cetuximab to the Nordic FLOX regimen of bolus 5-FU/FA and oxaliplatin in previously untreated patients with mCRC. Patients were randomly assigned to receive FLOX (arm A), cetuximab plus FLOX (arm B), or continuous cetuximab combined with intermittent FLOX (arm C). In arms A and B, treatment was continued until progressive disease (PD) or unacceptable toxicity. In arm C, FLOX was usually stopped after eight courses (16 weeks of treatment), and in cases of objective response or stable disease, cetuximab was continued as maintenance therapy. After recording PD in arm C, FLOX was reintroduced and continued together with cetuximab until PD or unacceptable toxicity (Tveit *et al*, 2012). Between May 2005 and October 2007, 571 patients from 32 centres were enrolled in the study and 566 were evaluable in the ITT population. In the primary report, patients were followed for PFS and OS analyses up to 12 and 18 months, respectively, after inclusion of the last patient (Tveit *et al*, 2012).

Updated OS data were obtained from 176 out of 182 patients reported alive in the primary analysis. The updated OS analysis had censoring date 30 April 2014. Four patients (three in arm A and one in arm C) were lost to follow-up and two had withdrawn their consent before the primary analysis, and for these the

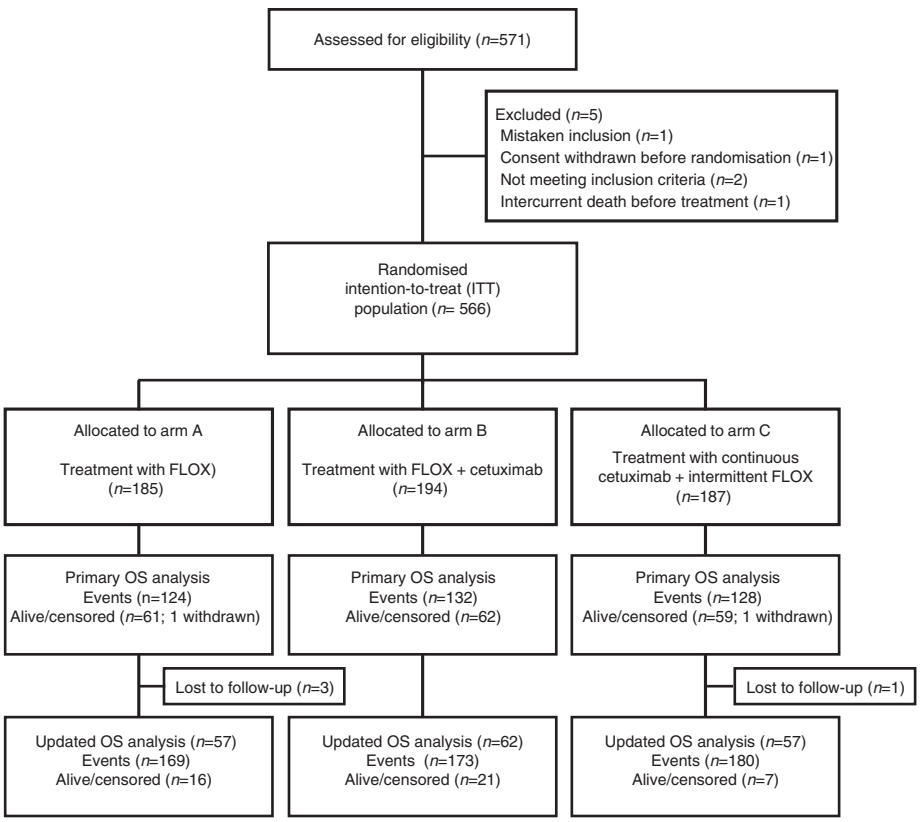

Figure 1. CONSORT diagram of the study design.

censoring date was the last date they were known to be alive and not withdrawn (Figure 1).

Mutation analysis of *KRAS*, *NRAS*, and *BRAF*. In the primary analysis, *KRAS* (exon 2) mutation status was available for 498 patients. From this cohort with known *KRAS* (exon 2, codons G12D, G12A, G12V, G12S, G12C, G12R, and codon G13D) and *BRAF* (exon 15, V600E) mutation status, tumour DNA of 457 patients (81% of the ITT population) was available for extended *RAS* mutation testing. In all, 179 patients (39%) had tumours with known *KRAS* (exon 2) mutations, and 55 (12%) had tumours with *BRAF* mutation. As *KRAS* and *BRAF* mutations were considered to be mutually exclusive (Rajagopalan *et al*, 2002), tumour DNA from the remaining 223 *KRAS* (exon 2)/*BRAF* wild-type patients was analysed for the other *KRAS* mutations (in exons 3 and 4) and *NRAS* mutations (in exons 2, 3, and 4).

Tumour DNA extraction from formalin-fixed, paraffin-embedded (FFPE) tumour tissue and analyses of mutations in *KRAS* (exon 2) and *BRAF* have been previously reported (Tveit *et al*, 2012). DNA was screened for the presence of the *KRAS* mutations Q61H, Q61L, and Q61R in exon 3, and K117X (K117N 351A>C, K117N 351A>T, and K117R, K117E) and A146X (A146T, A146P, and A146V) in exon 4, using the *KRAS* Mutation Analysis Kit for Real-Time PCR (exons 2, 3, and 4) by EntroGen (Woodland Hills, CA, USA). The *NRAS* mutations G12C, G12D, G12S, G13V, G13R, Q61K, Q61R, Q61L, Q61H, and A146T in exons 2, 3, and 4 were analysed using the *NRAS* Mutation Analysis Kit (EntroGen). The mutation detection assays and the analysis of the results were done in accordance with the manufacturer's instructions. Input in the *KRAS* (exons 3 and 4) and *NRAS* assays were 10 and 20 ng of whole-genome DNA from FFPE material, respectively.

Ethics. The NORDIC-VII study (http://clinicaltrials.gov/show/NCT00145314) was approved by the national ethics committees and governmental authorities in each country and conducted in accordance with the Declaration of Helsinki. All patients had provided written informed consent.

Statistical analysis. The statistical analyses, using IBM SPSS (version 23, IBM Corp., Armonk, NY, USA), were performed in the ITT population and in subsets of patients based on *RAS* and *BRAF* mutation status. Demographic data were described with median and range (continuous variables) and proportions and

Table 1. Baseline patient demographics and clinical characteristics

	Study population									
	ITT	*RAS*/*BRAF* status unknown	Tested for *RAS* and *BRAF* mutations				*RAS*/*BRAF* wild-type			
	Total (*n* = 566)	Total (*n* = 109)	Total (*n* = 457)	Arm A (*n* = 146)	Arm B (*n* = 158)	Arm C (*n* = 153)	Total (*n* = 192)	Arm A (*n* = 64)	Arm B (*n* = 66)	Arm C (*n* = 62)
Age (years)										
Median (range)	62 (24–75)	62 (30–75)	62 (24–75)	60 (35–75)	61 (24–74)	64 (33–75)	62 (24–75)	60 (40–75)	60 (24–74)	65 (36–75)
Gender, *n* (%)										
Male	334 (59)	61 (56)	273 (60)	80 (55)	98 (62)	95 (62)	126 (66)	30 (47)	51 (77)	45 (73)
Female	232 (41)	48 (44)	184 (40)	66 (45)	60 (38)	58 (38)	66 (34)	34 (53)	15 (23)	17 (27)
WHO PS, *n* (%)										
0	380 (67)	73 (67)	307 (67)	102 (70)	108 (68)	97 (63)	129 (67)	48 (75)	44 (67)	37 (60)
1	162 (29)	32 (29)	130 (28)	38 (26)	44 (28)	48 (31)	54 (28)	11 (17)	19 (29)	24 (39)
2	24 (4)	4 (4)	20 (4)	6 (4)	6 (4)	8 (5)	9 (5)	5 (8)	3 (5)	1 (2)
Site of primary tumour, *n* (%)										
Colon	333 (59)	58 (53)	275 (60)	83 (57)	91 (58)	101 (66)	111 (58)	36 (56)	33 (50)	42 (68)
Rectum	233 (41)	51 (47)	182 (40)	63 (43)	67 (42)	52 (34)	81 (42)	28 (44)	33 (50)	20 (32)
Previous treatment, *n* (%)										
Primary tumour resected	382 (68)	35 (32)	347 (76)	114 (78)	118 (75)	115 (75)	146 (76)	51 (80)	49 (74)	46 (74)
Adjuvant chemotherapy	51 (9)	5 (5)	46 (10)	14 (10)	16 (10)	16 (11)	21 (11)	6 (9)	9 (14)	6 (10)
Preoperative radiotherapy	80 (14)	10 (9)	70 (15)	18 (12)	29 (18)	23 (15)	29 (15)	6 (9)	17 (26)	6 (10)
Timing of metastases, *n* (%)										
Synchronous	402 (71)	94 (86)	308 (67)	97 (66)	106 (67)	105 (69)	129 (67)	43 (67)	45 (68)	41 (66)
Metachronous	164 (29)	15 (14)	149 (33)	49 (34)	52 (33)	48 (31)	63 (33)	21 (33)	21 (32)	21 (34)
Number of metastatic sites, *n* (%)										
1 site	162 (29)	26 (24)	136 (30)	44 (30)	53 (34)	39 (26)	67 (35)	24 (38)	23 (35)	20 (32)
>1 sites	404 (71)	83 (76)	321 (70)	102 (70)	105 (67)	114 (75)	125 (65)	40 (63)	43 (65)	42 (68)
Type of metastases, *n* (%)										
Liver only	107 (19)	17 (16)	90 (20)	31 (21)	34 (22)	25 (16)	53 (28)	19 (29)	17 (26)	17 (27)
Liver plus other	312 (55)	69 (63)	243 (53)	69 (47)	76 (48)	98 (64)	92 (48)	25 (39)	31 (47)	36 (58)
Non-liver	147 (26)	23 (21)	124 (27)	46 (32)	48 (30)	30 (20)	47 (25)	20 (31)	18 (27)	9 (15)
Investigations, *n* (%)										
Normal alkaline phosphatase level	298 (53)	48 (44)	250 (55)	86 (59)	82 (52)	82 (54)	100 (52)	38 (59)	34 (52)	28 (45)
Platelet count $<400\,nl^{-1}$	398 (70)	70 (64)	328 (72)	100 (69)	115 (73)	113 (74)	142 (74)	45 (70)	51 (77)	46 (74)
White blood cell count $<10\,nl^{-1}$	428 (76)	69 (63)	359 (79)	118 (81)	123 (78)	118 (77)	152 (79)	51 (80)	53 (80)	48 (77)

Abbreviations: ITT = intention to treat; PS = performance status; WHO = World Health Organisation.

percentages (categorical variables). The PFS and OS were compared between treatment groups using the log-rank test, and treatment effects were estimated using Kaplan–Meier plots and Cox proportional hazards model. Separate univariable analyses of the effect of the WHO performance status, alkaline phosphatase (ALP), and *RAS* and *BRAF* mutation status were performed. Only variables statistically significant in univariable analyses were included in the multivariable analyses, and models were thereafter restricted to include statistically significant variables only.

RESULTS

Patients. In all, 566 patients were evaluable and included in the ITT population in the primary analysis of the NORDIC-VII study. Baseline characteristics were well balanced between the three treatment arms (Tveit *et al*, 2012). In the present study of 457 patients with available results for *RAS* and *BRAF* mutation status, the patient groups were well balanced and representative for the ITT population (Table 1 and Supplementary Table S1).

Updated OS. The median OS for the overall ITT population ($n = 566$) was 20.1 months, and there was no statistically significant difference between the treatment arms (Figure 2A). In all, 38 out of 44 censored patients were registered alive in the updated analysis, 12 (7%), 21 (11%), and 5 (3%) in arm A, B, and C, respectively. Of the 38 patients reported alive, 18 (47%) had stopped study treatment due to secondary complete surgical resection of metastases, 5 of 12 in arm A, 11 of 21 in arm B, and 2 of 5 in arm C.

Extended *RAS* and *BRAF* mutations. The mutation analyses are reported in Table 2. In the cohort of 457 patients, 210 (46%) had tumours with (any) *RAS* mutations, 55 (12%) had *BRAF* mutation, and 192 (42%) were *RAS/BRAF* wild-type. The frequency and distribution of *RAS* and *BRAF* mutations were similar in the three treatment arms A, B, and C, with any *RAS* mutations in 63 (43%), 72 (46%), and 75 (49%), respectively, and *BRAF* mutations in 19 (13%), 20 (13%), and 16 (10%), respectively.

Survival related to *RAS* and *BRAF* mutation status. The patient population with known *RAS* and *BRAF* mutation status had almost identical OS compared to the ITT population (Figure 2B), and, as shown in Figure 2C, there was no statistically significant difference between the treatment arms in patients with *RAS/BRAF* wild-type tumours (27.3, 23.5, and 23.7 months, respectively). These data are

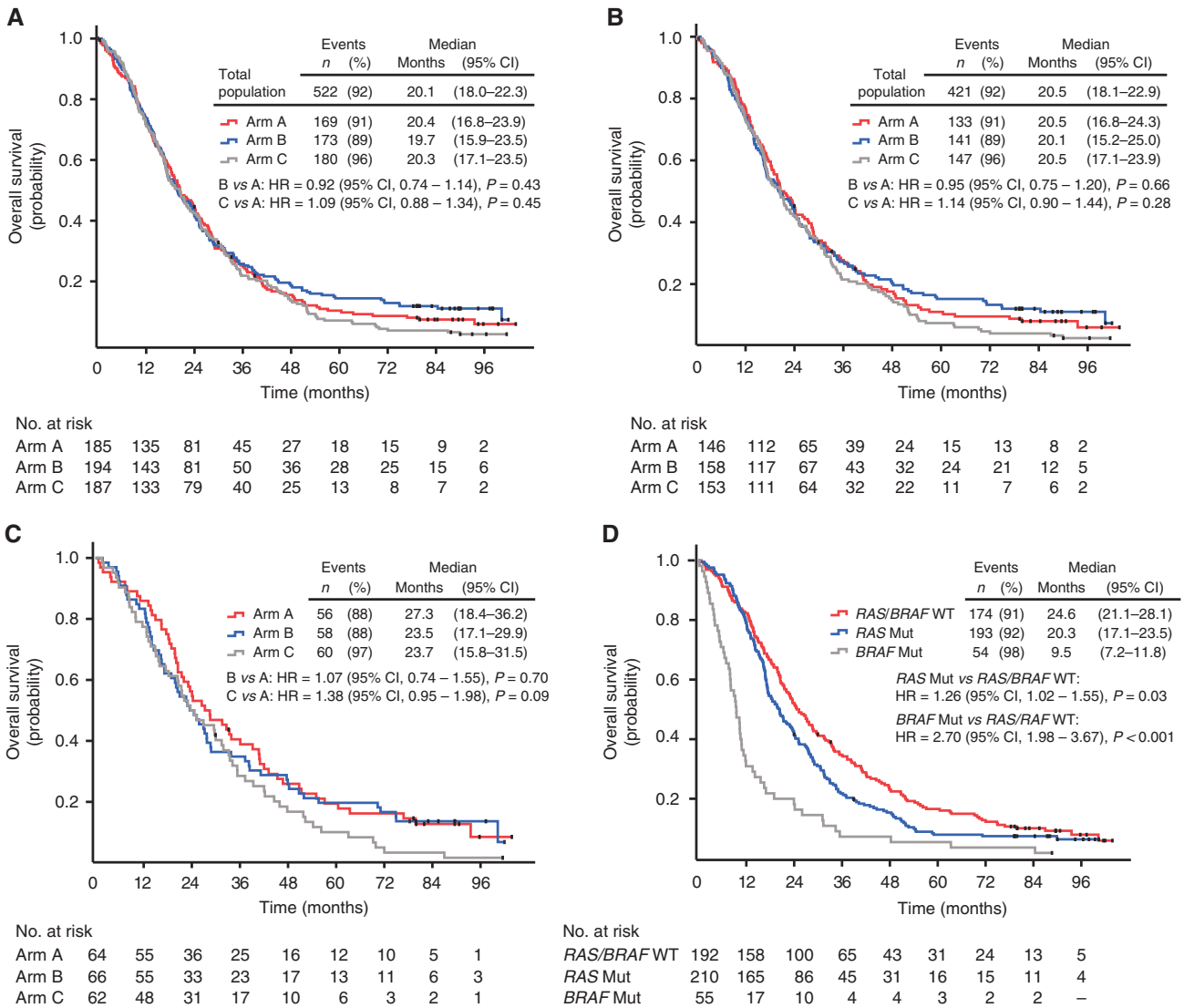

Figure 2. Survival curves. Overall survival in the three different treatment arms: (**A**) intention-to-treat population; (**B**) *RAS*- and *BRAF*-tested population; and (**C**) *RAS* and *BRAF* wild-type population. (**D**) Overall survival in patients with *RAS* and *BRAF* wild-type, *RAS* mutant, and *BRAF*-mutated tumours. CI = confidence interval; HR = hazard ratio; Mut = mutation; WT = wild-type.

in agreement with the previously published findings (Tveit *et al*, 2012).

Prognostic value of *RAS* and *BRAF* mutations. The outcome in the patients, depending on the mutational status of their tumours, is shown in Figure 2D. The median OS for those with *RAS/BRAF* wild-type tumours was 24.6 months, while it was shorter for those with tumours harbouring mutations in *RAS* (20.3 months) and, particularly, in patients with *BRAF*-mutated tumours (9.5 months). The prognostic value of *RAS* or *BRAF* mutation was further demonstrated in a Cox regression model for OS, which included the WHO performance status and ALP level registered before start of treatment as explanatory variables. Similar results were obtained when OS was censored at start of treatment with EGFR antibodies as second- or third-line therapy (Supplementary Table S2).

Response rates and PFS related to *RAS* and *BRAF* mutation status. Confirmed ORR values in the ITT population, the *RAS*- and *BRAF*-tested population, and subgroups by mutation status are listed in Supplementary Table S3. Numerically, ORR was highest in patients with *RAS/BRAF* wild-type tumours, and in this cohort ORR was somewhat higher (not statistically significant) for patients in arm B (61%) or arm C (60%), compared to those in arm A (50%).

The median PFS was 8.3, 8.2, and 7.4 months for arms A, B, and C, respectively, in the population with known *RAS* and *BRAF* mutation status (Figure 3A). In patients with *RAS/BRAF* wild-type tumours, the curves for arms A, B, and C were similar, with median PFS of 9.3, 9.5, and 9.2 months, respectively (Figure 3B). In patients with *RAS* mutant tumours, there was no statistically significant difference between the median PFS of 8.3 months in arm B compared to 7.9 months in arm A (HR, 0.84 (0.59–1.19); $P = 0.32$).

Progression-free survival in patients treated with cetuximab in the absence of FLOX. From the start of treatment, patients in arm A were randomised to receive FLOX, while those in both arms B and C received cetuximab plus FLOX. After eight cycles of chemotherapy (~16 weeks of treatment), the patients in arm C were treated with cetuximab only, while those in arm A continued the therapy with FLOX. This fact allowed a comparison of the outcome of cetuximab monotherapy with FLOX treatment from cycle 9 of 159 patients with known *RAS* and *BRAF* mutation status. Progression-free survival was calculated from the start of cycle 9 to event (progression or death) or censoring. Figure 3C shows that for patients with *RAS/BRAF* wild-type tumours the outcome in arm A and C was closely similar, 5.8 *vs* 6.3 months. In contrast, for patients with *RAS*-mutated tumours, PFS was markedly shorter in those receiving cetuximab monotherapy (arm C) compared to patients treated with FLOX (arm A), 2.3 *vs* 4.4 months ($P = 0.003$, Figure 3D). There was a positive interaction between treatment arms, A and C, and *RAS/BRAF* mutation status ($P = 0.046$)

Third-line treatment with EGFR antibodies. Figure 4 shows the treatment outcome of 82 patients with known *RAS* and *BRAF* mutation status who received therapy with EGFR antibodies (cetuximab or panitumumab) as second- or third-line therapy after end of treatment in NORDIC-VII. The patients with *RAS/BRAF* wild-type tumours had a median survival of 10.1 months from start of later-line treatment with EGFR antibodies, while the median survival of patients with *RAS* or *BRAF* mutant tumours was 6.6 months.

Colon *vs* rectum. Outcome stratified on the origin of primary tumour was examined (Supplementary Table S4). In the ITT population, patients with colon cancer had shorter median OS compared to those with their primary tumour in rectum, 18.6 *vs* 22.3 months (HR, 0.83 (0.70–0.99); $P = 0.04$). A similar trend was observed in subpopulations based on *RAS/BRAF* mutation status. There was no statistically significant difference in PFS or OS between the treatment arms neither in colon nor in rectal cancer. Location of primary tumour within colon was not registered in this study.

Table 2. *RAS* and *BRAF* mutation status

	Study population			
Genotype	Total ($n = 457$) *n* (%)	Arm A ($n = 146$) *n* (%)	Arm B ($n = 158$) *n* (%)	Arm C ($n = 153$) *n* (%)
Wild-type (*RAS* and *BRAF*)	192 (42.0)	64 (43.8)	66 (41.8)	62 (40.5)
RAS mutant	210 (46.0)	63 (43.2)	72 (45.6)	75 (49.0)
KRAS exon 2 mutant	179 (39.2)	55 (37.7)	67 (42.4)	57 (37.3)
KRAS G12A	16 (3.5)	5 (3.4)	5 (3.2)	6 (3.9)
KRAS G12R	3 (0.7)	1 (0.7)	1 (0.6)	1 (0.7)
KRAS G12D	62 (13.6)	14 (9.6)	27 (17.1)	21 (13.7)
KRAS G12C	16 (3.5)	4 (2.7)	7 (4.4)	5 (3.3)
KRAS G12S	11 (2.4)	5 (3.4)	4 (2.5)	2 (1.3)
KRAS G12V	30 (6.6)	11 (7.5)	11(7.0)	8 (5.2)
KRAS G13D	41 (9.0)	15 (10.3)	12 (7.6)	14 (9.2)
KRAS exon 3 mutant	9 (2.0)	2 (1.4)	2 (1.3)	5 (3.3)
KRAS Q61H	3 (0.7)	0	1 (0.6)	2 (1.3)
KRAS Q61L	5 (1.1)	2 (1.4)	1 (0.6)	2 (1.3)
KRAS Q61R	1 (0.2)	0	0	1 (0.7)
KRAS exon 4 mutant	7 (1.5)	2 (1.4)	1 (0.6)	4 (2.6)
KRAS K117X	1 (0.2)	0	0	1 (0.7)
KRAS A146X	6 (1.3)	2 (1.4)	1 (0.6)	3 (2.0)
NRAS exon 2 mutant	8 (1.8)	2 (1.4)	1 (0.6)	5 (3.3)
NRAS G12S	1 (0.2)	1 (0.7)	0	0
NRAS G12C	6 (1.3)	0	1 (0.6)	5 (3.3)
NRAS G13V	1 (0.2)	1 (0.7)	0	0
NRAS exon 3 mutant	7 (1.5)	2 (1.4)	1 (0.6)	4 (2.6)
NRAS Q61L	2 (0.4)	0	0	2 (1.3)
NRAS Q61K	3 (0.7)	1 (0.7)	1 (0.6)	1 (0.7)
NRAS Q61R	2 (0.4)	1 (0.7)	0	1 (0.7)
BRAF mutant (V600E)	55 (12.0)	19 (13.0)	20 (12.7)	16 (10.5)

DISCUSSION

The updated survival analysis showed no statistically significant difference between OS for the three treatment arms, in the ITT, *RAS/BRAF* tested, or *RAS/BRAF* double wild-type populations. Similarly, in the population of patients with known *RAS* and *BRAF* mutation status and in patients with *RAS/BRAF* double wild-type tumours, there was no statistically significant difference in PFS between the treatment arms. However, in arm B there was a numerically higher number of long-term survivors and a higher number of patients with complete surgical resection of metastases. In the primary analysis of NORDIC-VII an unexpected trend towards increased PFS was found in patients with tumours harbouring *KRAS* (exon 2) mutations who received FLOX plus cetuximab, as compared to FLOX alone (arm B *vs* arm A). This difference in PFS was less pronounced in analyses based on the extended *RAS* mutation status, further suggesting that the previously reported result was an incidental finding. Taken together, the analyses based on *RAS* status and updated survival data did not change the conclusion from the primary report that cetuximab did not add any significant benefit to the Nordic FLOX regimen in first-line treatment of mCRC (Tveit *et al*, 2012).

Patients with colon cancer had shorter median OS compared to those with rectal cancer, in line with other trials (Tejpar *et al*, 2017). Recently, pooled data from two randomised phase III trials have emphasised that clinical benefit of cetuximab treatment is significantly higher in patients with left-sided colon and rectum tumours compared to right-sided (Tejpar *et al*, 2017). Precise location of the primary tumour within colon was not registered in this study, and as no effect of adding cetuximab to FLOX was observed in the population of colon or rectal cancer patients in NORDIC-VII, a possible difference in outcome between right and left colon cancer was not further examined.

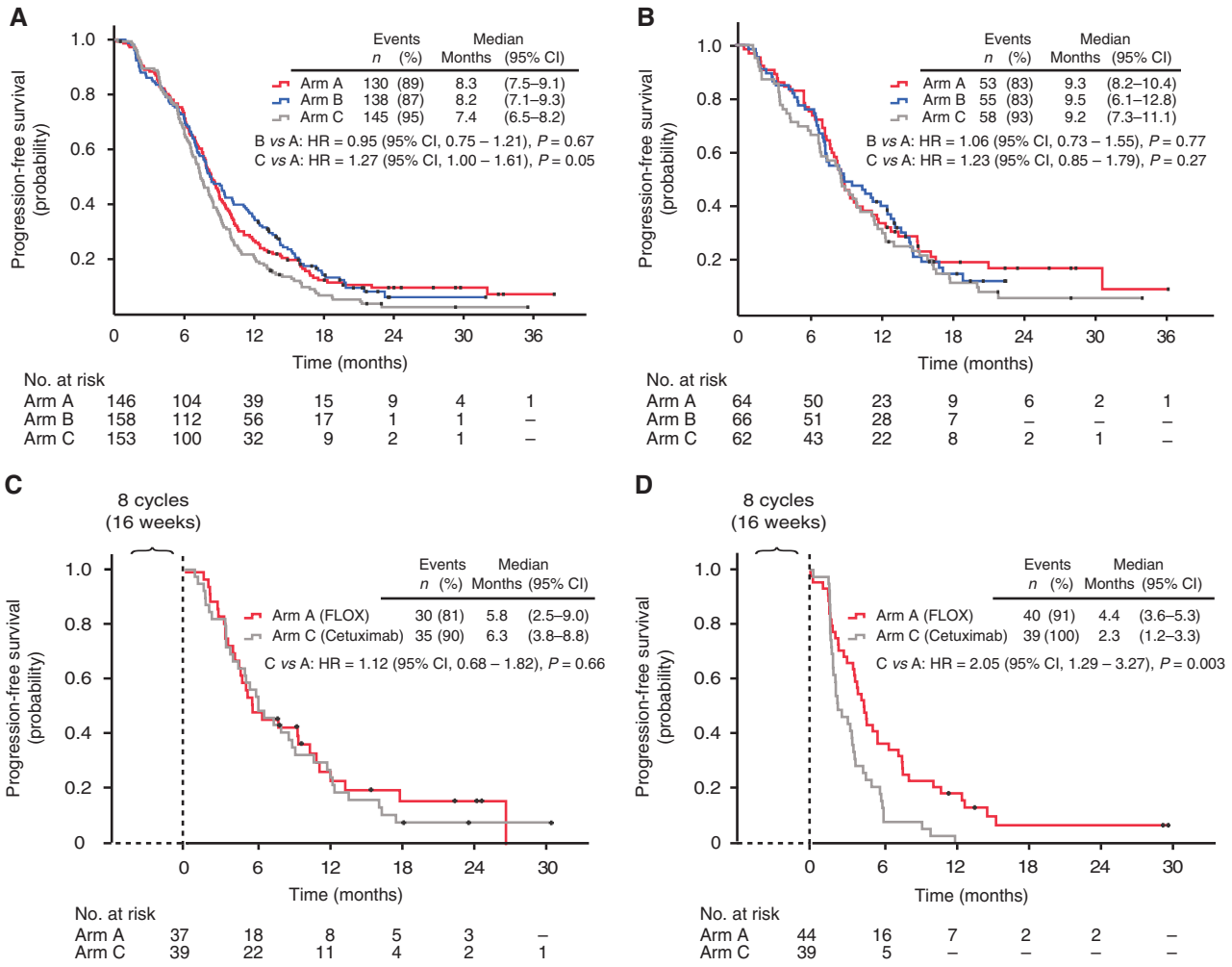

Figure 3. Survival curves. Progression-free survival in the three different treatment arms: (**A**) *RAS*- and *BRAF*-tested population; (**B**) *RAS* and *BRAF* wild-type population. Progression-free survival from start of treatment cycle 9 in arms A (FLOX) and C (maintenance treatment with cetuximab) in patients with (**C**) *RAS/BRAF* wild-type tumours and (**D**) *RAS*-mutated tumours. CI = confidence interval; HR = hazard ratio.

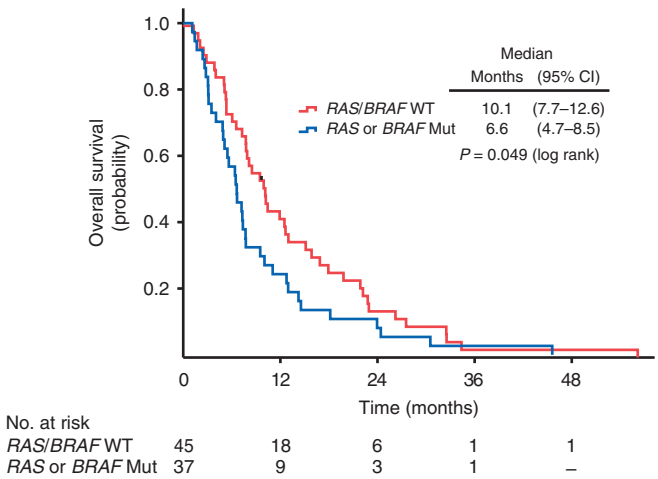

Figure 4. Kaplan–Meier estimate of overall survival from start of second- or third-line treatment with EGFR antibodies, cetuximab (*n* = 75), or panitumumab (*n* = 7), in 82 patients with known *RAS/BRAF* status. Mut = mutation; WT = wild-type.

The frequency of the *RAS* mutations was in agreement with those reported in other trials (Douillard *et al*, 2013; Bokemeyer *et al*, 2015; Van Cutsem *et al*, 2015), and patients with tumours harbouring *RAS* or *BRAF* mutations showed impaired outcomes compared to those with *RAS/BRAF* wild-type tumours, also in line with results reported from recent first-line chemotherapy trials in mCRC (Maughan *et al*, 2011; Cremolini *et al*, 2015). Thus, it is unlikely that the reason for lack of effect of cetuximab in this trial was that the NORDIC-VII cohort differed fundamentally from other patient populations studied.

After eight cycles of chemotherapy, the patients in arm C were treated with cetuximab only, while those in arm A continued the therapy with FLOX. This study design allowed a comparison of cetuximab monotherapy with FLOX treatment from cycle 9. In patients with double wild-type tumours the PFS from cycle 9 was quite similar for the patients receiving FLOX (arm A) and those treated with cetuximab only (arm C). In contrast, in patients with *RAS*-mutated tumours, the PFS was significantly reduced in those who received cetuximab monotherapy compared with FLOX. On the basis of the assumption that chemotherapy (FLOX) received from cycle 9 improved the outcome in patients with *RAS/BRAF* wild-type as well as in *RAS*-mutated tumours, these results strongly suggest that also for the NORDIC-VII cohort, in patients with *RAS/BRAF* wild-type tumours, unlike *RAS*-mutated, cetuximab may exert an effect as single agent. These results also suggest that maintenance cetuximab therapy, as given in arm C, provides an alternative approach to ongoing chemotherapy in the relevant biomarker-selected group, in line with the results of the COIN-B trial (Wasan *et al*, 2014).

To further elucidate the effects of anti-EGFR therapy in this patient population, survival of patients who received such therapy as part of second- or third-line treatment was analysed. This treatment was mainly offered before the demonstration that effect of EGFR antibodies was restricted to KRAS wild-type tumours (Amado *et al*, 2008; Karapetis *et al*, 2008). Patients with *RAS*/*BRAF* wild-type tumours, previously treated in NORDIC-VII, had significantly longer median OS from start of this treatment compared to those with *RAS* or *BRAF* mutations, consistent with outcome reported by others (Amado *et al*, 2008; Karapetis *et al*, 2008). These results are based on observational data and should be interpreted with caution as *RAS* and *BRAF* mutations affect prognosis and comparison with no EGFR antibody therapy was not possible. However, it may be hypothesised that a 3.5 month difference in median OS from start of second- or third-line EGFR antibody therapy reflects some effect of this treatment in the wild-type patients. The prognosis reflected by the *RAS*/*BRAF* mutation status was sustained in a Cox regression model where OS was censored at start of second- or third-line treatment with EGFR antibodies if the patients had received such treatment.

In view of the results of NORDIC-VII, together with the data from COIN and the New EPOC trials (Maughan *et al*, 2011; Primrose *et al*, 2014), as compared to trials where cetuximab was combined with irinotecan-based regimens (Van Cutsem *et al*, 2009), it may be discussed whether cetuximab and oxaliplatin are good partners. We have no clinical data to answer this question directly. However, preclinical studies have mechanistically demonstrated an antagonistic modulation of cetuximab on the effect of oxaliplatin (Dahan *et al*, 2009; Santoro *et al*, 2015). It should, however, be noted that in the TAILOR trial a significant benefit in terms of ORR, PFS, and OS was reported with the addition of cetuximab to FOLFOX (Qin *et al*, 2016). It has been suggested that the type of fluoropyrimidine regimen has influence on treatment outcome when an EGFR antibody is added to fluoropyrimidine–oxaliplatin chemotherapy (Grothey and Lenz, 2012), and so far, a benefit has only been demonstrated with the FOLFOX regimen (Bokemeyer *et al*, 2009; Douillard *et al*, 2010; Qin *et al*, 2016). In the NORDIC-VII study, a bolus 5-FU/FA regimen was used, and in the COIN trial, the majority of patients received capecitabine. Thus, there might be a positive pharmacodynamic synergism between the anti-EGFR antibodies and 5-FU administered via the FOLFOX regimens (Harstrick *et al*, 1998; Skvortsov *et al*, 2008; Kim *et al*, 2009 Bijnsdorp *et al*, 2010), which was not achieved when the Nordic FLOX bolus regimen was used as the chemotherapy backbone.

In conclusion, the patient population of NORDIC-VII seems to be comparable with other cohorts of mCRC patients who start first-line therapy. The lack of effect of cetuximab when added to the Nordic FLOX regimen strengthens the notion that this combination is not favourable and strongly suggests a negative interaction between the FLOX regimen and cetuximab.

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CONFLICT OF INTEREST

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