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A randomized study of KRAS-guided maintenance therapy with bevacizumab, erlotinib or metronomic capecitabine after first-line induction treatment of metastatic colorectal cancer: the Nordic ACT2 trial

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Background: Maintenance treatment (mt) with bevacizumab (bev) ± erlotinib (erlo) has modest effect after induction chemotherapy in metastatic colorectal cancer (mCRC). We hypothesized the efficacy of erlo to be dependent on KRAS mutational status and investigated this by exploring mt strategies with bev ± erlo and low-dose capecitabine (cap).

Patients and methods: Included patients had mCRC scheduled for first-line therapy, Eastern Cooperative Oncology Group (ECOG) 0–1 and no major comorbidities. Treatment with XELOX/FOLFOX or XELIRI/FOLFIRI + bev was given for 18 weeks. After induction, patients without progression were eligible for randomization to mt; KRAS wild-type (wt) patients were randomized to bev ± erlo (arms wt-BE, $N = 36$ versus wt-B, $N = 35$), KRAS mutated (mut) patients were randomized to bev or metronomic cap (arms mut-B, $N = 34$ versus mut-C, $N = 33$). Primary end point was progression-free survival (PFS) rate (PFSr) at 3 months after start of mt. A pooled analysis of KRAS wt patients from the previous ACT study was performed.

Results: We included 233 patients. Median age was 64 years, 62% male, 68% ECOG 0, 52% with primary tumor *in situ*. A total of 138 patients started mt after randomization. PFSr was 64.7% versus 63.6% in wt-B versus wt-BE, $P = 1.000$; and 75% versus 66.7% in mut-B versus mut-C, $P = 0.579$, with no significant difference in median PFS and overall survival (OS). In the pooled cohort, median PFS was 3.7 months in wt-B ($N = 64$) and 5.7 months in wt-BE ($N = 62$) (hazard ratios 1.03, 95% confidence interval 0.70–1.50, $P = 0.867$). The frequency of any grade 3/4 toxicities during mt was: 28%/58%/18%/15% (wt-B/wt-BE/mut-B/mut-C).

Conclusions: Addition of erlo to bev as mt in KRAS wt mCRC did not significantly improve PFS or OS, but it did increase toxicity. KRAS status does not seem to influence the outcome of treatment with erlotinib. Metronomic cap warrants further investigation in mt strategies, given our explorative results.

ClinicalTrials.gov: NCT01229813.

Key words: metastatic colorectal cancer, maintenance treatment, bevacizumab, erlotinib, capecitabine, metronomic chemotherapy

introduction

The therapeutic mainstay in the management of incurable metastatic colorectal cancer (mCRC) is combination chemotherapy, with or without targeted agents [1].

In recent years, efforts have been put into establishing more tolerable maintenance strategies to be initiated before the dose-limiting toxicity of combination chemotherapy occurs. The aim is to prolong survival with sustained quality of life. Low-dose continuous capecitabine, i.e. metronomic chemotherapy, has only been described in retrospective, nonrandomized studies in this setting, e.g. by Sun et al. [2], whereas targeted therapies have been investigated in several randomized mCRC maintenance trials [3–6]. A combination of the antiangiogenic antibody

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bevacizumab and erlotinib, a tyrosine-kinase inhibitor (TKI) of the epithelial growth factor receptor (EGFR), has shown synergistic effects in preclinical tests and promising results in clinical trials on nonsmall-cell lung cancer (NSCLC) and in mCRC [7–9].

However, not all patients benefit from this treatment and predictive markers are needed. At the time of initiation of the present study, mutation in KRAS exon 2 had been identified as a negative predictive factor for the efficacy of EGFR-inhibiting antibodies in mCRC [10], but also for the efficacy of EGFR TKIs (gefitinib and erlotinib) in NSCLC [11]. This study was designed to investigate whether addition of erlotinib to bevacizumab leads to improved outcome compared with bevacizumab alone as maintenance treatment in mCRC patients with KRAS wild-type (wt) tumors. In patients with KRAS mutated (mut) tumors, metronomic capecitabine was explored as maintenance in comparison with bevacizumab.

patients and methods

patient population

Eligible patients were ≥18 years of age, Eastern Cooperative Oncology Group (ECOG) 0–1, with histologically confirmed untreated mCRC and paraffin-embedded tumor tissue available for KRAS mutation analysis. Other inclusion and exclusion criteria were equally consistent with the preceding Nordic ACT trial and included standard criteria for first-line mCRC trials involving bevacizumab as study treatment [3]. Prior adjuvant chemotherapy for CRC was allowed if ended at least 6 months before inclusion.

study design

The ACT2 study was an open-label, phase III, randomized clinical trial recruiting patients at 11 sites in Sweden and one in Denmark between October 2010 and May 2012. The study was approved by ethics committees and medical products agencies in both countries and was conducted in accordance with the International Conference of Harmonization guideline for Good Clinical Practice and with the Declaration of Helsinki. All patients signed written informed consent. The trial was investigator sponsored with financial support from Roche. A representative from Roche took part in designing the study protocol but Roche had no role in validation or analysis of the data.

induction treatment

First-line induction treatment was given with XELOX/XELIRI or FOLFOX/FOLFIRI (investigator's choice) plus bevacizumab (for treatment schedules, see supplementary Material S1, available at *Annals of Oncology* online). After 18 weeks of induction treatment, patients without progressive disease (PD) were eligible for randomization to maintenance treatment. Patients were divided by KRAS mutational status and in the randomization process stratified by best response in induction, i.e. partial response (PR) versus stable disease (SD), and to whether or not oxaliplatin had been used in induction. Mutational analyses were carried out with validated standard assays at each study site. Tumors were classified as KRAS mut if any mutation was identified in codons 12 or 13 of exon 2.

maintenance treatment

Patients with KRAS wt tumors were randomized (1:1) between bevacizumab 7.5 mg/kg i.v. once every 3 weeks alone (arm wt-B) or in combination with oral erlotinib 150 mg once daily (arm wt-BE). Patients with KRAS mut tumors were randomized (1:1) to bevacizumab alone (arm mut-B), or oral capecitabine 500 mg twice daily continuously (arm mut-C). Maintenance therapy was given until PD, intolerable toxicity, planned surgery, noncompliance, serious protocol deviation, consent withdrawn or lost to follow-up.

dose modification of study drugs

Dose modifications of bevacizumab and erlotinib during maintenance phase were allowed as previously described in the Nordic ACT trial [3]. In case of capecitabine-related toxicity grade ≥2, maintenance treatment was interrupted until toxicity resolved to grade ≤1, other dose adjustments were not allowed. If interruption of dosing was required by more than 3 weeks for treatment with any study drug, the patient was withdrawn from the study.

evaluation of response and safety

Tumor response was evaluated according to RECIST 1.0 with a computed tomography scan of the thorax and abdomen within 28 days before enrollment, after 8–12 weeks of induction treatment, before randomization and every 9 weeks during the maintenance phase. Toxic effects were recorded according to National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0. Follow-up was documented every third month until death or study data cutoff (14 November 2014).

statistical methods

The aim of the study was to evaluate whether maintenance treatment with erlotinib plus bevacizumab (wt-BE) increases the progression-free survival (PFS) compared with bevacizumab alone (wt-B) in a mCRC KRAS wt population. The study was designed to detect a difference in 3-month PFS rate (PFSr) from 50% in arm wt-B to 80% in arm wt-BE at a two-sided significance level of 5% and a power of 80%, requiring 40 patients in each arm. It was estimated that 60% were KRAS wt and that 70% would be randomized. Accordingly, inclusion of 181 patients was planned. During the course of the study, an unexpectedly high attrition rate was observed, why the study population was increased to 233 patients by a protocol amendment in January 2012. The primary end point (PFSr) was analyzed within the KRASwt and the KRASmut populations, respectively, by a two-sided Fisher's exact test. Subjects censored before 3 months were excluded from the primary end point analysis.

Secondary end points included PFS, defined as time from start of maintenance treatment until first occurrence of PD or death from any cause, overall survival (OS) from study inclusion and safety. PFS and OS were calculated in the full analysis set (FAS), defined as all randomized patients that started treatment in maintenance phase, and in the per-protocol (PP) population, including all FAS patients compliant with the protocol. Median OS was also analyzed in the intention-to-treat (ITT) population defined as all included patients who started treatment in induction phase with the intention to be evaluated for maintenance treatment if eligible for randomization. Pooled analyses of PFS and OS were carried out according to protocol including arms wt-B and wt-BE from the current study and data from KRAS evaluable wt patients from our first Nordic ACT trial [3]. This was justified by the identical eligibility criteria and treatment design.

For the survival analyses, the Kaplan–Meier method was used and hazard ratios (HRs) were calculated by the Cox regression model. A two-sided log-rank test was used for comparison between study arms. The median follow-up-time was calculated as Kaplan–Meier estimate of potential follow-up. Toxicity in the induction phase was listed for the safety analysis population (SAP), defined as patients who had received at least one dose of induction treatment, and in the maintenance phase for the FAS population. Analyses were done with SAS (version 9.2).

results

patient characteristics

The study enrolled 233 patients. Two patients were withdrawn from the study before any data were recorded and were excluded from the ITT population (Figure. 1A). The baseline characteristics were similar between treatment arms, but some differences were noted (Table 1). In the wt-BE arm, a smaller proportion of patients (19%) had rectum as primary cancer location compared with 54% in the wt-B arm and fewer patients had received previous adjuvant treatment in wt-BE (6% versus 21%).

efficacy and safety

induction treatment. In the ITT population ($N = 231$), the frequencies of each induction chemotherapy backbone used were XELOX (36%), FOLFIRI (33%), FOLFOX (21%) and XELIRI (10%). Response rates in induction phase among assessable patients were PR (43%), SD (51%) and PD (6%). Best response on induction for FAS populations is presented in Table 1, with no statistical differences between the study arms (χ^2 test). In the safety population, 104 patients (45.5%) presented with at least one grade 3/4 adverse event (AE) during induction therapy. There were four cases of gastrointestinal perforation reported in induction phase; three were grade 3 and one was fatal.

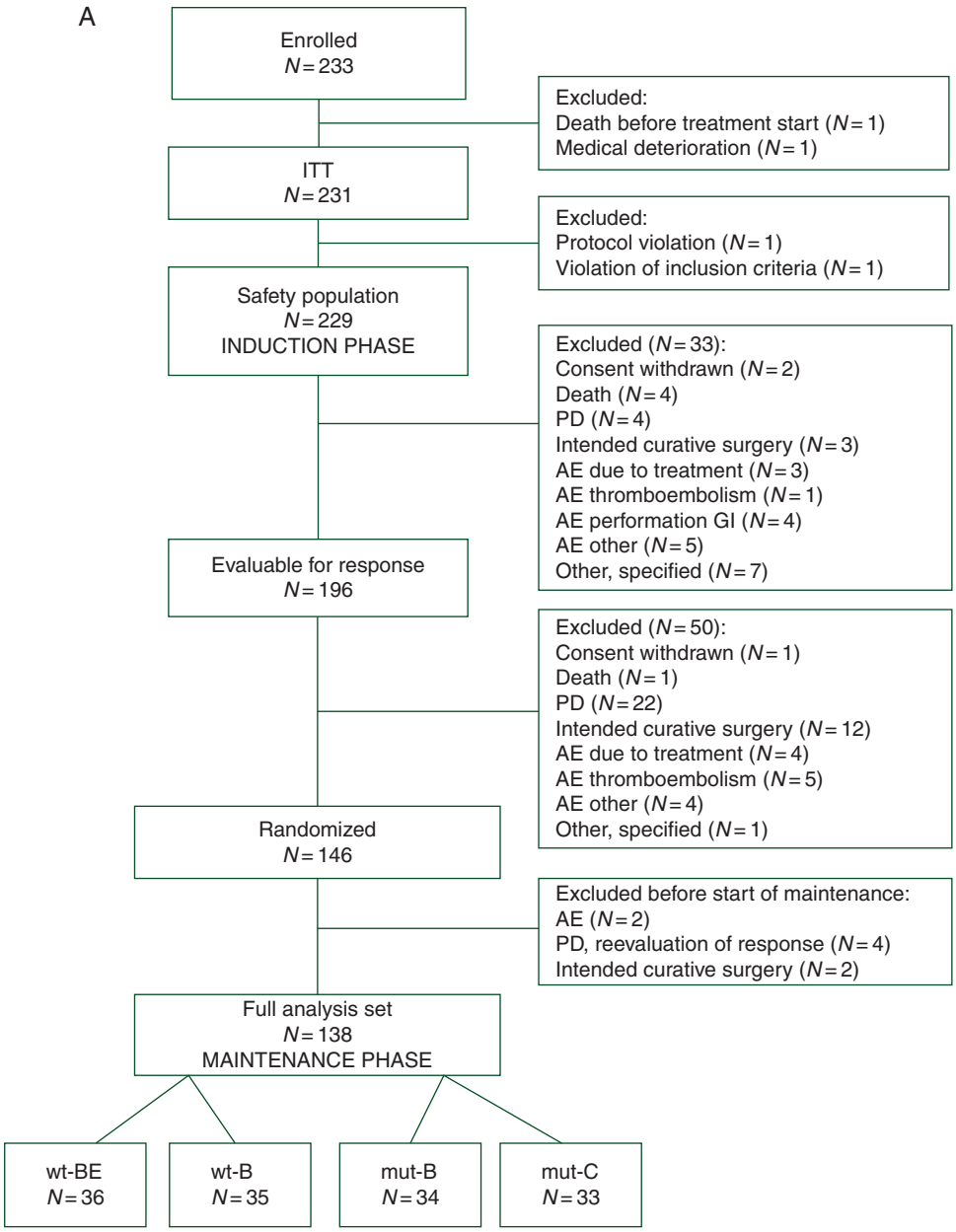

Figure 1. CONSORT diagrams of (A) the present ACT2 trial and (B) the pooled population KRAS wild-type (wt) patients from the Nordic ACT and ACT2 trials. ITT, intent-to-treat population; PD, progressive disease; AE, adverse event. Definition of arms: B, bevacizumab; BE, bevacizumab+erlotinib; C, metronomic capecitabin.

maintenance treatment. Of the 146 randomized patients, 138 started treatment in maintenance phase (FAS) (Figure. 1A). Owing to failure of performing obligatory laboratory tests at inclusion, 11 patients were excluded from the PP population.

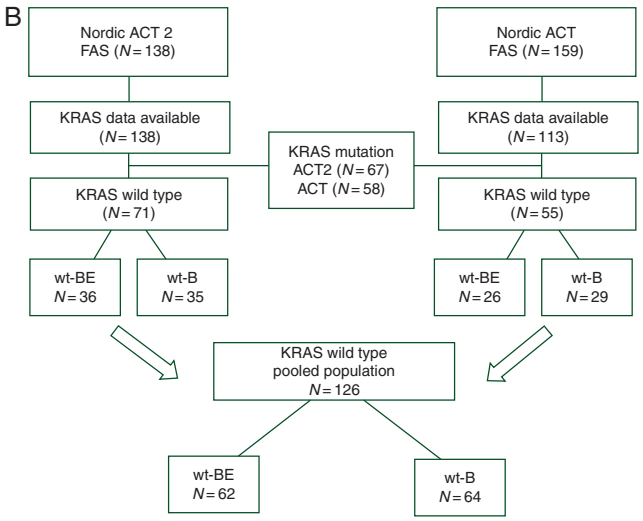

Fig. 1 *Continued*

Since the outcome in the PP population did not differ significantly from that in FAS, only results from the FAS population will be presented.

The PFSr at 3 months was 63.6% in the wt-BE arm ($N = 33$) compared with 64.7% in the wt-B arm ($N = 34$), with no statistically significant difference ($P = 1.000$). The median PFS was 5.7 months in wt-BE and 3.6 months in wt-B [HR 0.93, 95% confidence interval (CI) 0.56–1.56, $P = 0.787$] (Figure. 2A). The 3-month PFSr was 75% in mut-B ($N = 32$) and 66.7% in mut-C ($N = 30$) ($P = 0.579$). The median PFS was 3.9 months in mut-B and 3.7 months in mut-C (HR 1.19, 95% CI 0.72–1.97, $P = 0.501$) (Figure. 2B).

The median duration of maintenance treatment was 4.7 months (wt-BE), 4.1 months (wt-B and mut-B) and 3.9 months (mut-C). 94.4% of the patients in wt-BE had at least one AE of any grade during maintenance treatment, compared with 88.6% in wt-B, 82.4% in mut-B and 66.7% in mut-C, respectively. AEs grade 3/4 in the maintenance phase are presented in Table 2. Three patients had intestinal perforations during maintenance phase; one grade 4 included in Table 2 and two additional patients had fatal perforations (grade 5), one in mut-B and one in mut-C. One patient in arm wt-B died of cerebral infarction, considered unlikely related to study drug.

Maintenance treatment was discontinued due to toxicity in a total of five patients (4%) in FAS, three of them were in wt-BE.

Table 1. Patient characteristics at baseline

	ITT	Full analysis set			
	Total	KRAS wild type		KRAS mutated	
		wt-B	wt-BE	mut-B	mut-C
	$N = 231$	$N = 35$	$N = 36$	$N = 34$	$N = 33$
Age, years					
Median (range)	64 (32–83)	61 (32–76)	65 (38–74)	65 (44–75)	63 (45–79)
Gender					
M/F	62/38%	66/34%	64/36%	53/47%	70/30%
ECOG					
0/1	68/32%	77/23%	67/33%	82/18%	61/39%
Primary tumor site					
Colon	56%	46%	75%	50%	50%
Rectum	41%	54%	19%	44%	47%
Both	3%	0%	6%	6%	3%
Primary tumor *in situ*	52%	43%	58%	56%	49%
Metastatic sites					
1	39%	34%	50%	35%	33%
>1	61%	66%	50%	65%	67%
Liver metastases					
Total	75%	81%	83%	62%	76%
Liver mets. only	23%	20%	39%	12%	15%
Previous adjuvant treatment					
Total	15%	21%	6%	24%	15%
Oxaliplatin	10%	17%	6%	15%	12%
Best response induction					
PR	n.a.	46%	61%	41%	55%
SD	n.a.	54%	39%	59%	45%

ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat population; PD, progressive disease; SD, stable disease; n.a., not applicable (not all patients of the ITT population were evaluable for response); definition of arms: B, bevacizumab; BE, bevacizumab+erlotinib; C, metronomic capecitabine; wt, KRAS wild type; mut, KRAS mutated.

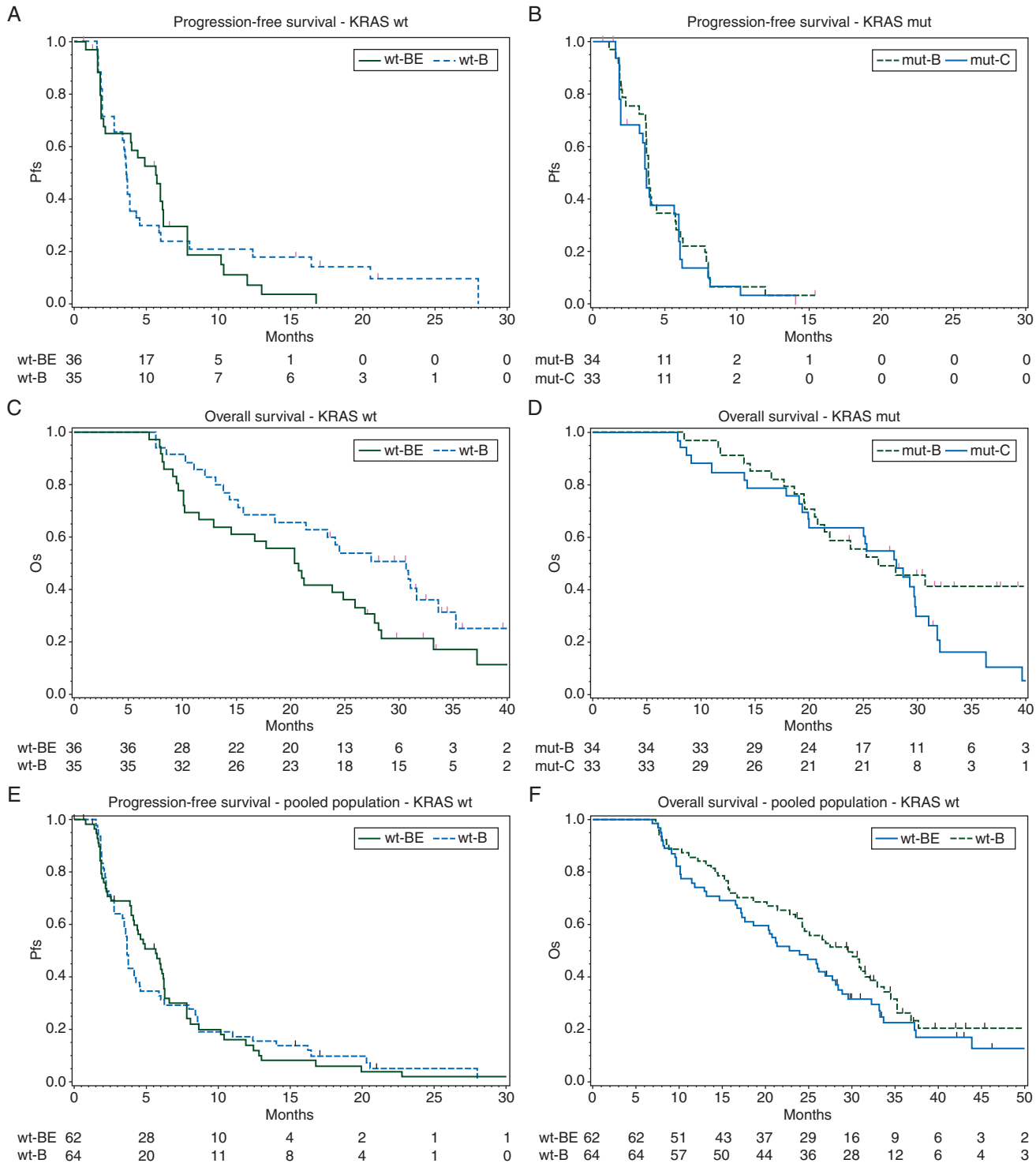

Figure 2. Progression-free survival (PFS) of (A) the KRAS wild-type (wt) population and (B) the KRAS mutated (mut) population from start of maintenance treatment in the ACT2 full analysis set (FAS) population. Overall survival (OS) of the KRAS wt (C) and the KRAS mut (D) patients from start of induction treatment. Corresponding PFS (E) and OS (F) in the pooled KRAS wild-type FAS population of the ACT and ACT2 trials. Definition of arms: wt, KRAS wild type; mut, KRAS mutated; B, bevacizumab; BE, bevacizumab+erlotinib; C, metronomic capecitabin.

Other reasons of end of treatment in FAS were PD (86%), death (2%), intended curative surgery (2%) and withdrawn consent (1%).

overall survival. With a median follow-up time of 34.5 months (95% CI 32.3–37.7), 184 patients in the ITT population and 101 in the FAS population had died. Median OS from date of informed consent was 19.5 months in the ITT population and 25.3 months in the FAS. Within the FAS randomized populations, median OS from date of informed consent was 20.6 months in wt-BE and 30.7 months in wt-B (HR 0.58, 95% CI

Table 2. Adverse events grade 3/4 in the maintenance phase

	wt-BE		wt-B		mut-B		mut-C	
	N = 36		*N* = 35		*N* = 34		*N* = 33	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
	n	*n*	*n*	*n*	*n*	*n*	*n*	*n*
Appetite disorders	1		1					
Asthenic conditions/fatigue	2		2					
Disturbances in consciousness	1						1	
Hypertension	1		1		3			
Thrombosis and pulmonary embolism					1	1		
Gastrointestinal ulcers and perforation								1[a]
GI stenosis and obstruction	1	2					1	2[a]
Diarrhea	3						2	
Nausea and vomiting			1					
Gastrointestinal disorders other	3		3					
Infections	3				1			1[a]
Skin and subcutaneous tissue disorders	5							
Peripheral neuropathies			1		1			
Hepatic and hepatobiliary disorders	2							
Hypokalemia	1							
Renal and urinary disorders (ureteric obstruction)	1						1	
Musculoskeletal and connective tissue disorders	1		1		2			
Any AE grade 3/4	21 (58.3%)		9 (25.7%)		7 (20.6%)		5 (15.2%)	

Adverse events grade 3 or 4 according to NCI-CTCAE version 3.0 [adverse events were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes and preferred terms].

[a]Three of the grade 4 toxicities were related to the same medical event in one patient.

AE, adverse events; definition of arms: wt, KRAS wild type; mut, KRAS mutated; B, bevacizumab; BE, bevacizumab+erlotinib; C, metronomic capecitabin.

0.34–1.01, $P = 0.0510$) (Figure. 2C). In mut-B, the median OS was 26.4 months and in mut-C 28.0 months (HR 1.57, 95% CI 0.87–2.84, $P = 0.128$) (Figure. 2D).

pooled analyses. Data from the KRAS wt FAS population of the present trial and our first Nordic ACT trial [3] were evaluated in a combined analysis (Figure. 1B). Median PFS from start of maintenance treatment was 3.7 months in the pooled wt-B group compared with 5.7 months in the pooled wt-BE group (HR 1.03, 95% CI 0.70–1.50, $P = 0.867$) (Figure. 2E). The median OS from informed consent was 29.4 months in the pooled wt-B group and 23.3 months in the pooled wt-BE group, with no statistically significant difference (HR 0.76, 95% CI 0.51–1.14, $P = 0.197$) (Figure. 2F).

post-study treatment. Most patients (89%) in the FAS population received further anticancer drugs after termination of the maintenance treatment (supplementary Material S2, available at *Annals of Oncology* online). In the KRAS wt cohort, the use of an EGFR-inhibitor in subsequent treatment lines was similar, 37% and 31% in wt-B and wt-BE, respectively.

discussion

According to our results, maintenance treatment with bevacizumab plus erlotinib does not improve PFS significantly compared with bevacizumab alone in mCRC KRAS wt patients.

A potential criticism of this trial could be its limited size. If erlotinib is to gain wide acceptance as a maintenance treatment, then the efficacy has to be substantial. We decided that a rather large increase in 3-month PFS from 50% to 80% in the KRASwt cohort would be clinically meaningful to detect. Consequently, the sample size could be limited. The final shortage of assessable patients (71 versus estimated 80) is explained by a higher than expected attrition rate before randomization (40% versus predicted 30%) and more (49%) KRAS mut tumors than the expected 40%. Despite an increase of the study population, the high dropout rate was unfortunately not fully compensated for. To increase the power, we carried out a preplanned pooled analysis with data from KRAS wt patients in the preceding Nordic ACT trial. No significant difference between the pooled population arms was found, but there was a numerical increase in median PFS from 3.7 to 5.7 months favoring the addition of erlotinib (Figure. 2E). This is in the same order of magnitude as seen in non-KRAS selected patients both in Nordic ACT [3] (HR 0.79, $P = 0.19$) and in the similar GERCOR DREAM study (HR 0.77, 95% CI 0.62–0.94; $P = 0.012$) [9]. These findings, supported by previous preliminary results from the GERCOR group [12], indicate that KRAS exon 2 mutation is not a good predictor for the efficacy of erlotinib in this setting, as opposed to NSCLC in which KRAS wt patients in the ATLAS trial were more likely to benefit from the addition of erlotinib to bevacizumab, at least in terms of PFS [13].

If a maintenance treatment is to gain wide acceptance, it should preferably also affect OS. Preliminary results from the DREAM trial showed a statistically significant OS gain of 3 months with the addition of erlotinib to bevacizumab whereas,

in our first Nordic ACT study, no significant difference in OS was seen. In the present study, there is a somewhat surprising tendency for worse OS in the combination arm compared with the bevacizumab single arm (Figure 2C and F). The reason for this is unclear. Subsequent anticancer treatments were well balanced between the arms (supplementary Material S2, available at *Annals of Oncology* online). Differences in baseline features, such as age, ECOG status, primary tumor location and history of adjuvant treatment, may have influenced the OS (Table 1).

The design of the study may be criticized due to lack of comparison with a 'standard maintenance' or observation arm. The ACT2 trial was launched as an extension of and in direct succession to the first Nordic ACT trial, which justifies analyses of a pooled dataset. Recent studies have shown that maintenance treatment with bevacizumab alone in mCRC is of limited value, whereas capecitabine + bevacizumab has shown to be an active maintenance strategy [4–6]. Whether metronomic capecitabine has a future role in this setting and what doses should be used is unclear.

In the current study, capecitabine was administered at a dose of 500 mg twice daily, i.e. much lower than the conventional dose, based on a retrospective study exploring fixed low doses of capecitabine to facilitate maintenance treatment and limit toxicity [2]. In an early randomized phase II trial, a continuous capecitabine dose of 625 mg/m^2 twice daily was found almost as effective and less toxic compared with the intermittent schedule with 1250 mg/m^2 twice daily for 2 weeks of 3, that later became the preferred standard [14]. The capecitabine dose of 625 mg/m^2 twice daily was later used as maintenance in the CAIRO3 trial, in combination with bevacizumab [5], but to our knowledge we are first to present a randomized comparison between bevacizumab and single metronomic capecitabine.

The results on metronomic capecitabine in our trial must be interpreted with caution due to the exploratory nature and small sample size, but PFS and OS were not clearly inferior to bevacizumab, and given the limited toxicity, simple administration and low cost, metronomic capecitabine could be of interest to explore in future maintenance trials, including identification of optimal doses. In summary, this study shows that KRAS status does not seem to have an important role in the selection of mCRC patients for treatment with erlotinib. In light of our negative results, including increased toxicity, the combination of erlotinib and bevacizumab is not yet to be broadly implemented as maintenance treatment in mCRC. However, subsequent research should focus on exploring other possible biomarkers to identify subgroups that may benefit from the addition of erlotinib in this setting.

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disclosure

The authors have declared no conflicts of interest.

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