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Research Letter to Editor

The effect of *BRAF*^{V600E} mutation on survival and treatment efficacy in vulnerable older patients with metastatic colorectal cancer – A post-hoc exploratory analysis of the randomized NORDIC9-study

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1. Introduction

Colorectal cancer is common, with the highest incidence and mortality rate observed in adults ≥70 years [1]. Through the past decades, survival has substantially improved in young and fit patients with metastatic colorectal cancer (mCRC) eligible for intensive treatment including chemotherapy combinations (doublet/triplet) and monoclonal antibodies, e.g., vascular endothelial growth factor receptor inhibitors (VEGFi), and epidermal growth factor receptor-1 inhibitors (EGFRi). While all patients are considered candidates for the VEGFi bevacizumab (bev) during the continuum of care, only subgroups according to *RAS* and *BRAF* mutation status are suitable for treatment with EGFRi [2]. *RAS/BRAF* wild type (*RAS/BRAF*wt) tumors have a better prognosis in general and gain benefit of EGFRi [2,3], whereas, *RAS* or *BRAF*^{V600E} mutations (*RAS*mt, *BRAF*mt) are associated with shorter survival and resistance to EGFRi [2,4,5].

The survival benefit of intensive chemotherapy with or without targeted agents is less clear in older patients, especially in those considered vulnerable or frail [6]. Thus, therapeutic recommendations based on randomized controlled trials (RCTs) cannot be directly

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extrapolated to these patients. Moreover, the tumor biology may be more indolent in older adults allowing a less intensive or sequential treatment approach manifesting in a reduced-dose combination or single agent first-line chemotherapy with or without bev [7]. The investigator-initiated NORDIC9-study randomized vulnerable older patients with mCRC to receive either reduced-dose combination chemotherapy ± bev or full-dose monotherapy ± bev irrespective of the *RAS/BRAF* mutation status.

We have already published the study protocol, survival outcomes, quality of life, functional status, and the biomarker analyses of the NORDIC9-study [8–11]. Here, we present post-hoc exploratory analyses on the effect of *RAS/BRAF* mutation status on survival and treatment efficacy.

2. Patients and Methods

2.1. Study Design, Participants, and Interventions

The NORDIC9-study, a randomized phase 2 study, was conducted in four Nordic countries and included patients ≥70 years with mCRC not eligible for full-dose combination chemotherapy. Patients were randomized (1:1) to reduced-dose SOx (S1 (Teysuno), 20 mg/m^2 orally twice daily and oxaliplatin 100 mg/m^2 intravenously on day 1, q3w) or full-dose S1 monotherapy (30 mg/m^2 orally twice-daily on days 1–14, q3w). The addition of bev (7.5 mg/kg intravenously, q3w) was optional. Patients were treated until unacceptable toxicity or progression.

2.2. Statistics

We applied descriptive statistics for baseline demographic and clinical characteristics; data were presented as median (interquartile range [IQR]) or n (%). We used the Wilcoxon Mann-Whitney test analyzing continuous numerical variables; for categorical variables, χ^2-test, or Fischer's exact test was applied.

2.3. Survival Analyses

Outcomes were defined as overall survival (OS) and progression-free survival (PFS); survival curves were estimated by the Kaplan-Meier method. The subgroups according to *RAS/BRAF* status were compared by log-rank test. Hazard ratios (HR) and corresponding 95% confidence intervals (95%CI) were estimated by Cox proportional hazard regression. We evaluated the prognostic value of *RAS/BRAF* status applying C-statistics and calculated Harrell's C with 95%CIs. We considered two-sided *p*-values ≤0.05 statistically significant.

2.4. Sample Size

Formal sample size calculation for this particular analysis was not performed; all patients with known *RAS/BRAF* status ($n = 116$) were included from the intention-to-treat (ITT) population consisting of all randomized patients.

3. Results

Between March 2015 and October 2017, 160 patients were enrolled with a median age of 78 years (IQR: 75–81) [9]. The median follow-up was 23.8 months (IQR: 18.8–30.9). *RAS* and *BRAF* status were established with the following distribution: *RAS/BRAF*wt was registered in 36 (31%), *RAS*mt in 59 (51%), and *BRAF*mt in 21 patients (18%). Baseline clinical and demographic characteristics were balanced between the treatment arms; however, we found significant differences regarding weight-loss and plasma C-reactive protein (CRP) (Supplementary Table 1). The patient flow is presented by a CONSORT diagram (Supplementary Fig. 1).

3.1. Prognostic Value of RAS/BRAF Mutation Status

Although formally not statistically significantly different in the univariate analyses, patients with *BRAF*mt had statistically significantly shorter OS and PFS in the multivariable analysis (OS: HR = 2.78 (95%CI: 1.37–5.64), $p = 0.005$; PFS: HR = 1.93 (95%CI: 1.04–3.56), $p = 0.037$) (Table 1). Estimating C-statistics, the model indicated good prognostic value for OS (Harrell's C: 0.73 (95%CI: 0.69–0.78).

3.2. The Predictive Role of RAS/BRAF Mutation Status Regarding Treatment Arms and Regimens

Univariate efficacy analyses comparing reduced-dose SOx with or without bev vs full-dose S1 ± bev showed significant OS benefit in patients with *BRAF*mt tumors in favor of the SOx arm: 21.4 vs 5.7 months (95%CI: [4.2-not estimable (NE)] vs [3.3–10.6], HR = 0.13 [95%CI: 0.04–0.49], $p = 0.003$) (Fig. 1, Supplementary Table 2). The difference remained statistically significant when adjusting for weight-loss and CRP; HR = 0.20 (95%CI: 0.05–0.84), $p = 0.028$).

4. Discussion

Our post-hoc exploratory analysis demonstrated a clear OS benefit for patients with *BRAF*mt tumors receiving reduced dose combination chemotherapy with or without bev compared to those who received full-dose monotherapy with or without bev. To the best of our knowledge, of the very few RCTs investigating the efficacy of different chemotherapy approaches in vulnerable older adults with mCRC, none has reported specific outcomes in the *BRAF*mt population.

While *BRAFmt* is a well-established prognostic marker for short survival and a predictive factor for no/less benefit of EGFRi in younger patients with mCRC [2,4,5], its significance in older adults, especially in vulnerable ones, is less clear. It might be explained by an over-representation of *BRAF*mt and mismatch repair deficient/microsatellite instable (dMMR/MSI) tumors in older adults [7].

Among the strengths of our analyses is the prospective randomized setting including vulnerable older patients reflecting most patients treated in the "real-world" setting. Furthermore, the distribution of molecular subtypes including the relative high proportion of *BRAF* mutation (18%) is representative for the Nordic population [12].

We acknowledge that our analyses have limitations. In 44 patients, the mutational status was not established (chiefly because the amount of tumor material was too small) limiting our sample size and possibly affecting the statistical analysis. Furthermore, we found imbalance between the treatment arms regarding weight-loss and CRP. We consider that occurring rather by chance than posing a selection bias, in particular, considering that this imbalance was not present in the ITT population. Reflecting on the emerging role of the mismatch repair (MMR) status in the current state-of-the-art mCRC; having information about MMR status, especially in patients with *BRAF*mt, might have improved our understanding and the applicability of our data. However, when the NORDIC9-tudy was planned in 2013, MMR status was not part of the routine diagnostic work-up. Despite us making significant efforts, we could not establish the MMR status. We consider our results as rather hypothesis generating than practice changing and they should, thus, be interpreted carefully. Further validation of our findings is required on larger cohorts. Despite the limitations, we consider our findings clinically relevant owing that the largest and steeply expanding group of adults with cancer comprising patients ≥70 years [13], and *BRAF*mt mCRC is more frequent than seen in clinical trials or at referral hospitals [12]. Moreover, our findings emphasize the importance of molecular testing. At the time of diagnosis, testing older adults for molecular alterations such as *RAS* and *BRAF* mutations and MMR genes is paramount; it might significantly affect their treatment and outcomes. About 30% of the tumors harboring *BRAF*^{V600E} are dMMR/MSI where the effect of fluoropyrimidine monotherapy is uncertain. These patients rather

Table 1
The prognostic value of RAS/BRAF mutational status on overall survival and progression-free survival in the NORDIC9-study. The multivariable model was adjusted for age, sex, treatment allocation, bevacizumab, the Eastern Cooperative Oncology Group performance status (ECOG PS), number of metastatic sites, primary tumor in situ, weight loss, and serum C-reactive protein.

Multivariable analysis adjusted for age, sex, treatment allocation, bevacizumab, ECOG PS, number of metastatic sites, primary tumor in situ, weight-loss, and plasma C-reactive protein							
RAS/BRAF status	n	Progression-free survival			Overall survival		
		Hazard ratio (95%CI)	p-value	Harrell's C (95%CI)	Hazard ratio (95%CI)	p-value	Harrell's C (95%CI)
RAS and *BRAF* wild type	36	1.00	NA		1.00	NA	
RAS mutated	59	1.19 (0.75–1.88)	0.463	**0.69 (0.66–0.73)**	1.13 (0.65–1.95)	0.675	**0.73 (0.69–0.78)**
BRAF mutated	21	**1.93 (1.04–3.56)**	**0.037**		**2.78 (1.37–5.64)**	**0.005**	

NA: non-applicable; CI: confidence interval.

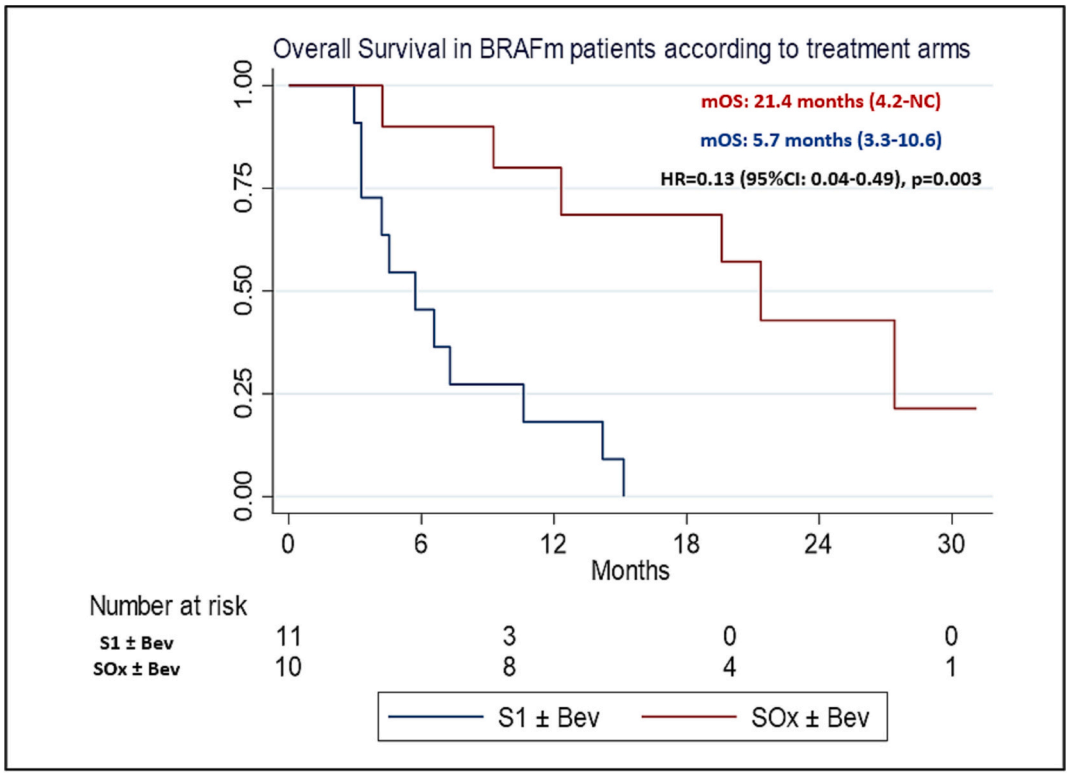

Fig. 1. Kaplan-Meier curve demonstrating overall survival in patients harboring *BRAF*^{V600E}mutation comparing reduced-dose SOx ± bevacizumab (bev) vs full-dose S1 ± bev in the NORDIC9-study.

should receive first-line ICI; if ICI is not available, doublet chemotherapy is the treatment of choice. Thus, chemotherapy is still considered an important and widely available option for patients with *BRAF*mt despite the significant therapeutic advances achieved in the recent years [2,14,15]. The availability of the new treatment options remains limited worldwide due to their high cost affecting survival, especially in low- and middle-income countries emphasizing the importance of an effective first-line chemotherapy option.

5. Conclusion

Reduced-dose combination chemotherapy might be a promising first-line treatment option for vulnerable older patients with mCRC harboring *BRAF*^{V600E} mutation. Molecular testing for RAS, BRAF, and MMR genes may significantly affect first-line treatment and outcomes also in this population. Further prospective studies are needed to confirm our findings.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Regional Scientific Ethical Committee (project ID: S-20140020, date of approval: 08.05.2014), the Danish Health and Medicines Authority (journal nr.: 2014023387), and the Danish Data Protection Agency (number of approval: 2008-58-0035). EudraCT-number: 2014–000394-39. Finland: Operatiivinen eettinen toimikunta at Helsinki University Hospital (357/13/03/02/14, the date of approval: 21.10.2015). Norway: Regional Committee for

Medical and Health Research Ethics, REC West, Norway (2014/598, the date of approval: 22.05.2014). Sweden: Regionala Etikprovningsnämnden, Uppsala (2014/288, the date of approval: 19.11.2014).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Author Contributions

Gabor Liposits: Conceptualization, Methodology, Software, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition. **Stine B. Winther:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Jesper Ryg:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Funding acquisition. **Halla Skuladottir:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision. **Sören Möller:** Conceptualization, Methodology, Software, Writing – original draft, Writing – review & editing. **Eva Hofsli:** Writing – review & editing. **Carl-Henrik Shah:** Writing – review & editing. **Laurids Østergaard Poulsen:** Writing – review & editing. **Åke Berglund:** Writing – review & editing. **Camilla Qvortrup:** Writing – review & editing. **Pia Osterlund:** Writing – review & editing. **Bengt Glimelius:** Writing – review & editing, Supervision. **Halfdan Sorbye:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision. **Per Pfeiffer:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors have no competing interest to declare. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results. CHS is employed by Roche AB.

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Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2023.101632.

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