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Publication date:
2023

Document version:
Final published version

Document license:
Unspecified

Citation for pulished version (APA):
Liposits, G. (2023). *The effect of RAS/BRAF mutation status on survival and treatment efficacy in vulnerable older patients with metastatic colorectal cancer a post-hoc exploratory analysis of the randomized NORDIC9-study*. Poster session presented at Wold Congress on Gastrointestinal Cancer 2023, Barcelona.

The effect of *RAS/BRAF* mutation status on survival and treatment efficacy in vulnerable older patients with metastatic colorectal cancer

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WORLD CONGRESS ON Gastrointestinal Cancer

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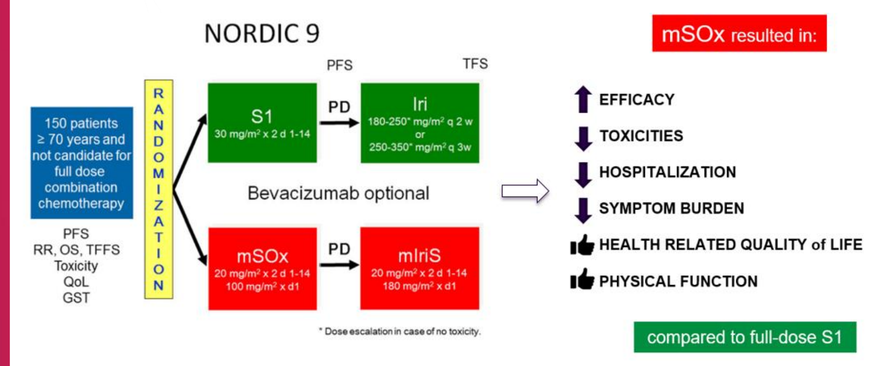
BACKGROUND



AIM

Here, we present the post-hoc exploratory analysis of the *RAS/BRAF* mutation status on survival and treatment efficacy in a cohort comprising vulnerable older patients with mCRC.

Of the very few randomized trials investigating the efficacy of chemotherapy in older adults with mCRC, none has reported specific outcomes in a *BRAF*^{V600E} mutated population.

METHOD

Overall survival (OS) and progression-free survival (PFS) for subgroups based on *RAS/BRAF* status were compared by log-rank test. Hazard ratios (HR) and 95% confidence intervals (95%CI) were estimated by Cox regression.

The prognostic value of *RAS/BRAF* status was evaluated by C-statistics.

For multivariate analyses, Cox proportional hazards regression models were applied.

CONCLUSIONS

We demonstrated a substantial difference in OS favoring patients with *BRAF*^{V600E} mutated tumors receiving reduced-dose combination chemotherapy (± bev) compared to those treated with full-dose monotherapy (± bev). The relatively high proportion of patients with *BRAF* mutation is representative for the Nordic population.

IMPORTANCE

- The largest group of adults with cancer is ≥70 years.
- *BRAF*^{V600E} mCRC is more frequent than seen in clinical trials
- Availability of BEACON doublet and ICIs remains limited in low- and middle-income countries
- Emphasizing the need for effective chemotherapy option for *BRAF*^{V600E} mutated patients

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RESULTS

Between 2015 and 2017, 160 patients were enrolled; the median age was 78 years (IQR): 75-81). *RAS* and *BRAF* status were established in 116 patients with the following distribution: *RAS/BRAF* wild type 31%, *RAS* mutation 51%, and *BRAF*^{V600E} mutation in 18% of the patients.

The prognostic value of *RAS/BRAF* mutation status

mOS for *RAS/BRAF*wt, *RAS*mut, and *BRAF*mut subgroups were 16.0, 14.5, and 10.8 months. In multivariable analysis, *BRAF*mut patients had higher risk for shorter survival.

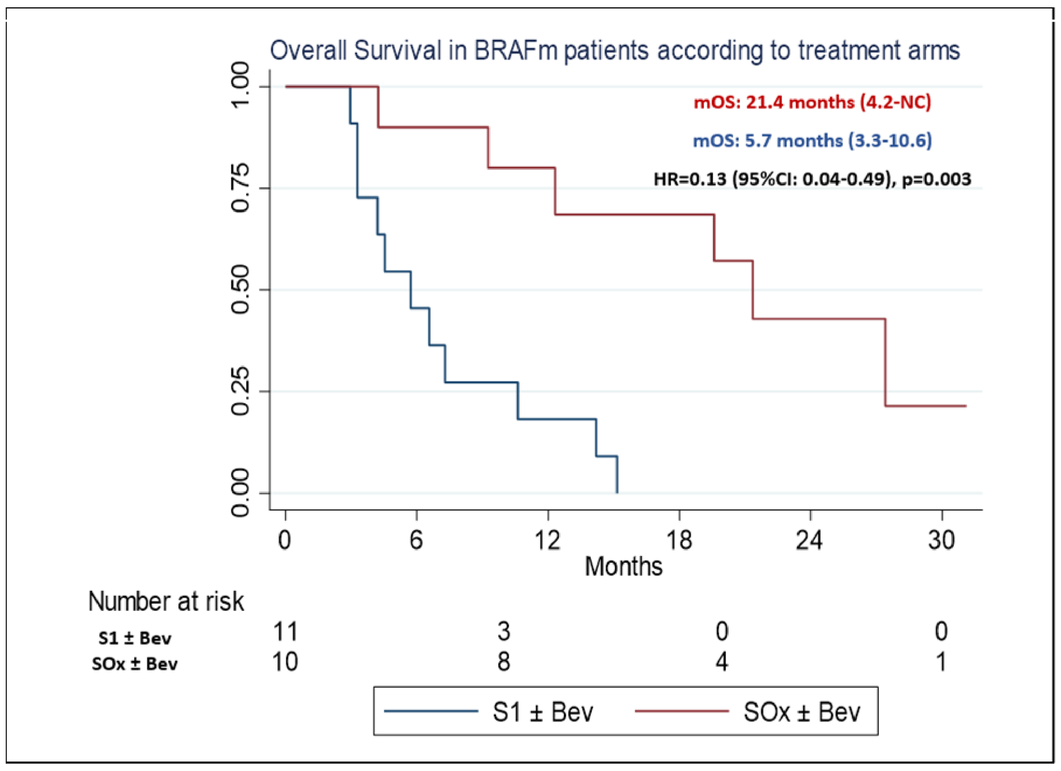
Multivariable analysis adjusted for age, sex, treatment allocation, bevacizumab, ECOG PS, number of metastatic sites, primary tumor in situ, weight-loss, and plasma C-reactive protein

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	**0.69 (0.66-0.73)**	1.00	NA	**0.73 (0.69-0.78)**
RAS mutated	59	1.19 (0.75-1.88)	0.463		1.13 (0.65-1.95)	0.675	
BRAF mutated	21	**1.93 (1.04-3.56)**	**0.037**		**2.78 (1.37-5.64)**	**0.005**	

The predictive value of treatment approach on survival according to the *RAS/BRAF* status

In the BRAF^{V600E} subgroup, patients receiving SOx±Bev had a significant longer OS compared to those treated with S1±Bev.

The difference remained statistically significant using multivariate analysis: HR=0.20 (95%CI: 0.05-0.84), p=0.028).



Univariate analysis of OS and PFS according to treatment regimens and *RAS/BRAF* status
(Abbreviations: bev: bevacizumab, 95%CI: 95% confidence interval, NA: non-applicable, NE: not estimable)

Progression-free and Overall Survival according to *RAS/BRAF* status and treatment regimens
Univariate analyses

Treatment arms	n	Progression-free Survival			Overall Survival		
		Months (95%CI)	Hazard ratio (95%CI)	p-value	Months (95% I)	Hazard ratio (95%CI)	p-value
***RAS/BRAF* wild type**	36						
S1 ± bev	21	6.8 (4.8-9.0)	1.00	0.48	19.5 (10.4-27.3)	1.00	0.602
SOx ± bev	15	6.7 (4.2-10.2)	0.77 (0.38-1.58)		15.4 (8.8-NE)	1.24 (0.55-2.78)	
***RAS* mutated**	59						
S1 ± bev	30	5.4 (3.1-8.0)	1.00	0.238	10.2 (5.9-20.5)	1.00	0.256
SOx ± bev	29	8.2 (5.3-9.8)	0.73 (0.43-1.24)		15.5 (12.9-NE)	0.69 (0.36-1.31)	
***BRAF* mutated**	21						
S1 ± bev	11	3.1 (2.0-4.7)	1.00	0.052	5.7 (3.3-10.6)	1.00	**0.003**
SOx ± bev	10	6.2 (2.0-11.5)	0.36 (0.13-1.00)		**21.4 (4.2-NE)**	**0.13 (0.04-0.49)**	