Outcomes of cetuximab in first-line therapy for metastatic colorectal cancer according to tumor RAS-BRAF mutation status from an update of EREBUS cohort

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Abstract

Background: Poor efficacy has been recently reported for patients with *RAS/BRAF* mutation (mt) treated with cetuximab. There are few data about cetuximab benefit in real-life according to tumor *RAS/BRAF* mt status.

Objectives: To evaluate objective response rate (ORR), metastases resection rate, progression-free survival (PFS) and overall survival (OS) according to tumor mt status: *RAS*mt (whatever *BRAF*mt status), *RAS*wt/*BRAF*mt and *RAS*wt/*BRAF*wt (i.e. 2xWT).

Methods: EREBUS is a multicenter (n=65) cohort study of *KRAS* wild-type (wt) unresectable metastatic colorectal cancer (mCRC) patients initiating cetuximab as 1st-line treatment from 2009 to 2010, followed for 2 years (up to 5 years for vital status). Kaplan-Meier method was used to describe 2-year PFS and 5-year OS. The association between the tumor mt status and the 1-year progression or the 3-year death was evaluated using multivariate Cox analyses adjusted on prognostic factors.

Results: 389 patients were included; tumor mt status was known for 310 (80%): 64 *RAS*mt (21%), 33 *RAS*wt/*BRAF*mt (11%) and 213 2xWT (69%). Respective baseline characteristics were: median age 65 years, 64 years and 63 years, male gender 63%, 64% and 69%, ECOG-PS 0-1 75%, 76% and 79%, liver only metastases 39%, 33% and 40%. ORR was 40.6% 95%CI [28.5-53.6] in *RAS*mt patients, 30.3% [15.6-48.7] in *RAS*wt/*BRAF*mt patients and 62.4% [55.8-69.0] in 2xWT patients. Metastases resection was performed in 12 *RAS*mt patients (18.8% [10.1-30.5]; 8 radical resections R0/R1/radiofrequency), 2 *RAS*wt/*BRAF*mt patients (6.1% [0.7-20.2]; 2 radical resections), and 75 2xWT patients (35.2% [28.8-41.6]; 47 radical resections). Median PFS (months) was 8.0 [5.9-9.3] in *RAS*mt patients, 6.0 [2.3-7.2] in *RAS*wt/*BRAF*mt patients, and 10.4 [9.5-11.0] in 2xWT patients. Median OS (months) was 18.4 [10.9-23.3] in *RAS*mt patients, 9.7 [6.9-16.6] in *RAS*wt/*BRAF*mt patients and 29.3 [26.3-36.1] in 2xWT patients. In adjusted multivariate analyses, progression (HR=2.69 [1.78-4.07]) and death (HR=3.13 [2.04-4.79]) were more likely for *RAS*wt/*BRAF*mt patients vs. 2xWT patients. In reference to 2xWT patients, HR for progression was 1.41 [0.98-2.04] (p=0.0618) for *RAS*mt/*BRAF*wt patients and HR for death 1.63 [1.13-2.35].

Conclusions: EREBUS confirms in real-life the difference in clinical outcomes with tumoral *RAS/BRAF* mutation in unresectable mCRC treated with 1st-line cetuximab, showing the greatest effectiveness in 2xWT patients.

Background

Cetuximab had initially demonstrated improved survival outcomes in metastatic colorectal cancer (mCRC) with *KRAS* exon 2 wild-type (wt). More recently, no benefit in mCRC with *KRAS* (exon 3 and 4) or *NRAS* (exon 2, 3 and 4) mutation was observed. *BRAF* mutation would also be an indicator of mCRC poor prognosis. Few data are available concerning cetuximab benefit in real-life practice according to tumor *RAS* and *BRAF* mutation status.

Objectives

EREBUS study

- Estimate the 2-year metastases resection rate in patients initiating cetuximab as 1st-line treatment of initially unresectable mCRC.
- Describe cetuximab use, safety, and effectiveness in real-life practice.

Secondary analysis according to *RAS* and *BRAF* tumor mutation status

- Describe patients characteristics according to tumor mutation status: mutant *RAS* (*RAS* mt), wild-type *RAS* and mutant *BRAF* (*RAS* wt / *BRAF* mt), and double wild-type (*RAS* wt / *BRAF* wt).
- Estimate progression-free survival (PFS), overall survival (OS), tumor response and metastases resection rates according to tumor mutation status.
- Identify factors associated to PFS and OS.

Methods

Study design

- Observational cohort study conducted in 65 French hospital centers.

Recruitment process, inclusion criteria and follow-up

- Identification of patients initiating cetuximab in 2009 and 2010 through hospital nominative dispensations.
- Inclusion of *KRAS*wt patients with unresectable mCRC, initiating cetuximab as 1st-line therapy.
- 2-year follow-up from initiation date of cetuximab (5-year for OS).

Additional data for secondary analysis

- Additional *RAS* (exons 2,3,4 *KRAS* and *NRAS*) and *BRAF* mutation status provided by 35 hospital molecular genetics platforms.

Statistical analysis

- Kaplan-Meier method was used to describe PFS and OS.
- The risks of progression and death were evaluated by multivariate analyses adjusted on prognostic factors at 1-year and 3-year follow-up. The tested variables at baseline were: RAS and BRAF tumor mutation, ECOG score, metastatic sites, initial resectability criteria of metastases, administration schedule of cetuximab. The time-dependent variables were: surgery of primary tumor, surgery of metastases, 2nd line treatment.

Conflict of interest statement

The EREBUS study was carried out by the Bordeaux PharmacoEpi platform and supervised by a Scientific Committee. This project was funded by an unconditional financial support from Merck Santé S.A.S., an affiliate of Merck KGaA, Darmstadt, Germany.

Results

➢ Study population

Among the 389 included patients, tissue sample from tumor or metastases was available for 312 patients (80.2%), and *RAS/BRAF* tumor mutation status for 310 patients (79.7%).

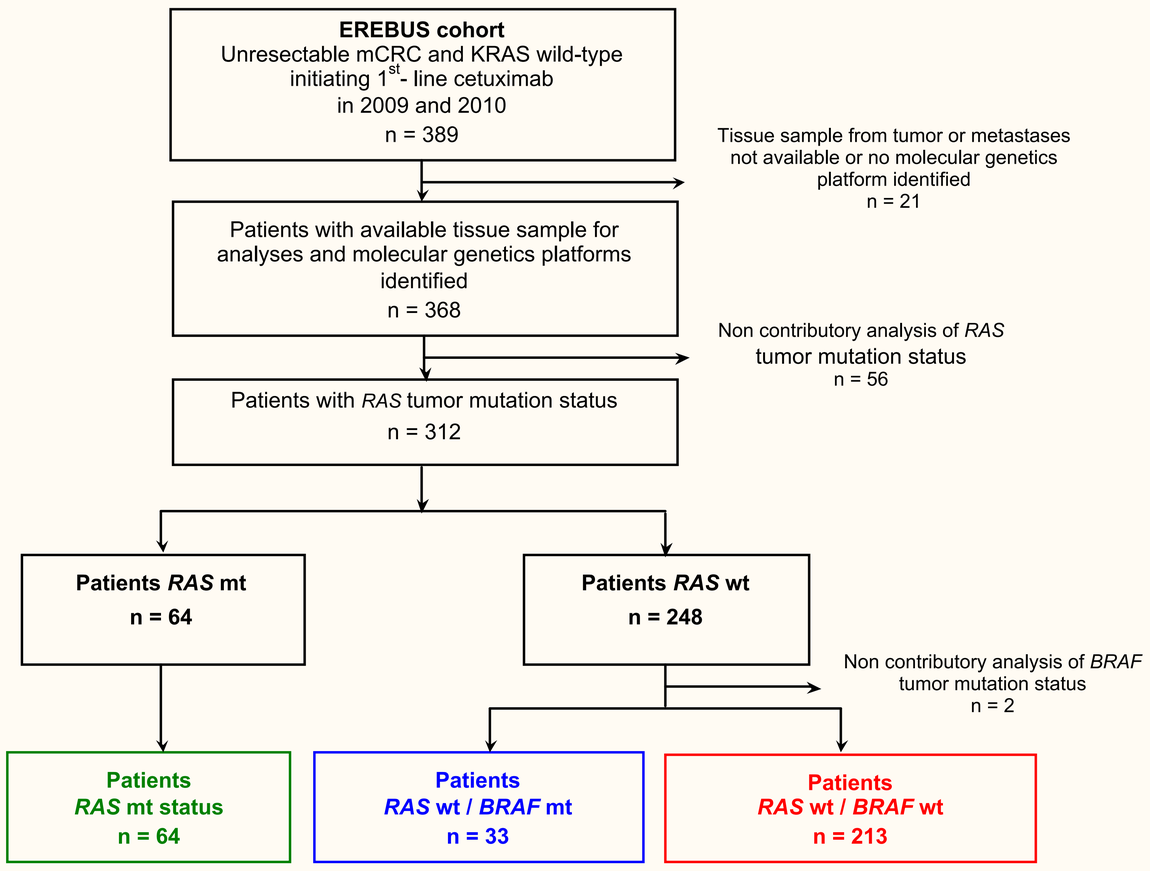

Figure 1. Identification and selection of study groups

➢ Baseline characteristics of study groups

Table 1. Baseline characteristics of patients according to RAS/BRAF tumor mutation status

	RAS mt n = 64	*RAS* wt / *BRAF* mt n = 33	*RAS* wt / *BRAF* wt n = 213
Median age at inclusion, years	64.5	64	63
[min – max]	[38 – 87]	[42 – 88]	[27 – 85]
Male, n (%)	40 (62.5)	21 (63.6)	147 (69.0)
Colon primary tumor, n (%)	44 (68.8)	25 (75.8)	163 (76.5)
ECOG = 0-1 Performance Status, n (%)	48 (75.0)	25 (75.8)	168 (78.9)
Exclusive liver metastases, n (%)	25 (39.1)	11 (33.3)	85 (39.9)
Median duration of cetuximab use, months	4.6	1.7	5.3
[p25% – p75%]	[1.8 – 7.6]	[0.8 – 6.0]	[2.5 – 9.7]
Median duration of chemotherapy use, months	4.9	3.4	6.3
[p25% – p75%]	[2.3 – 9.0]	[1.4 – 6.4]	[3.4 – 11.0]

➢ Tumor response and metastases resection rates

Table 2. Tumor response and metastases resection rates according to RAS/BRAF tumor mutation status

	RAS mt n = 64	*RAS* wt / *BRAF* mt n = 33	*RAS* wt / *BRAF* wt n = 213
Partial and complete tumor response before surgery, n (%)	26 (40.6)	10 (30.3)	131 (62.4)
[95% CI]	[28.5 ; 53.6]	[15.6 ; 48.7]	[55.9 ; 68.9]
Metastases resection[1], n (%)	12 (18.8)	2 (6.1)	75 (35.2)
[95% CI]	[10.1 ; 30.5][1]	[0.7 ; 20.2][1]	[28.8 ; 41.6]
Complete response rate after surgery[2], n (%)	8 (12.5)	2 (6.1)	47 (22.1)
[95% CI][3]	[5.6 ; 23.2]	[0.7 ; 20.2]	[16.5 ; 27.6]

[1] whatever surgery result: Complete response after radiofrequency ablation, R0, R1 or R2
[2] Complete response after radiofrequency ablation, R0 or R1
[3] CI 95% Clopper-Pearson

➢ Survival outcomes and multivariate analyses adjusted on prognostic factors

- Progression Free Survival (PFS)

Table 3. PFS of patients treated by cetuximab according to RAS/BRAF tumor mutation status

	RAS mt n = 64	*RAS* wt / *BRAF* mt n = 33	*RAS* wt / *BRAF* wt n = 213
2-year PFS probability, % [95% CI]	8.9 [3.5 ; 17.6]	3.3 [0.3 ; 14.5]	12.9 [8.8 ; 17.8]
Median PFS, months [95% CI]	8.0 [5.9 ; 9.3]	6.0 [2.3 ; 7.2]	10.4 [9.5 ; 11.0]

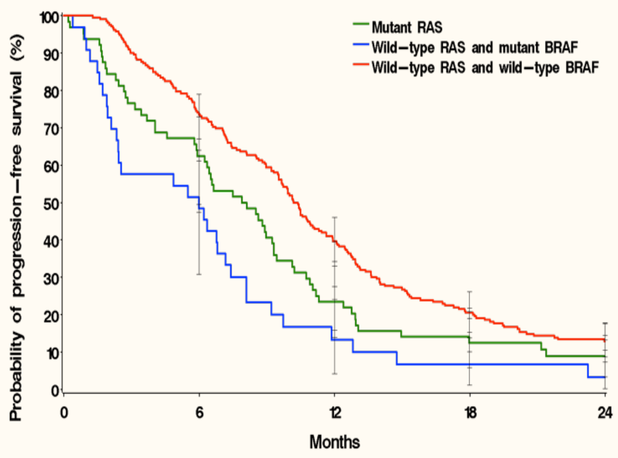

Figure 2. PFS at 2-year follow-up according to RAS and BRAF tumor mutation status (Kaplan-Meier method)

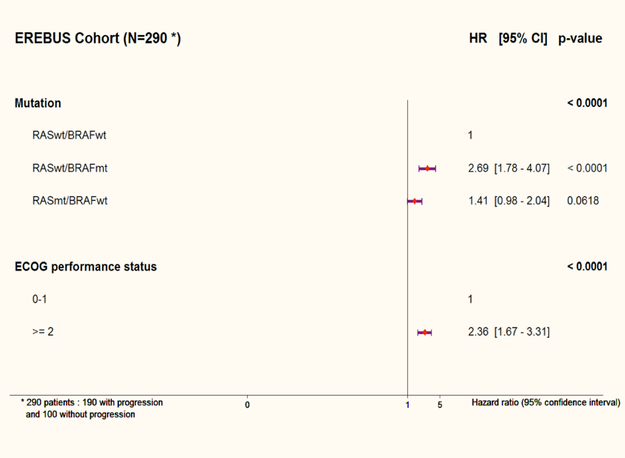

Figure 3. Factors associated with risk of progression at 1-year follow-up after the 1-st line treatment initiation (Multivariate Cox model)

- Overall Survival (OS)

Table 4. OS of patients treated by cetuximab according to RAS/BRAF tumor mutation status

	RAS mt n = 64	*RAS* wt / *BRAF* mt n = 33	*RAS* wt / *BRAF* wt n = 213
5-year OS probability, % [95% CI]	11.9 [5.2 ; 21.6]	0.0	27.1 [21.1 ; 33.5]
Median OS, months [95% CI]	18.4 [10.9 ; 23.3]	9.7 [6.9 ; 16.6]	29.3 [26.3 ; 36.1]

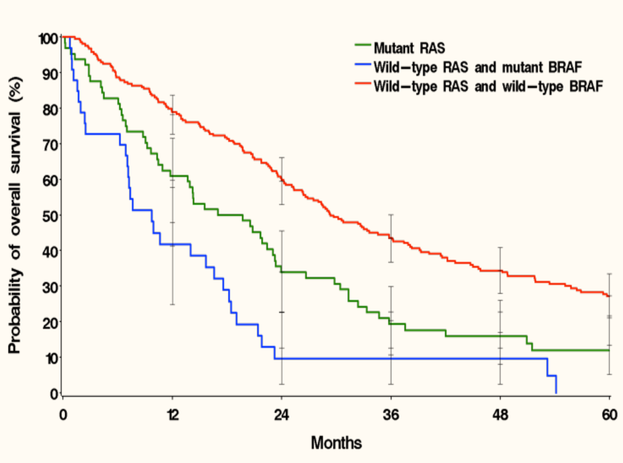

Figure 4. OS at 5-year follow-up according to RAS and BRAF tumor mutation status (Kaplan-Meier method)

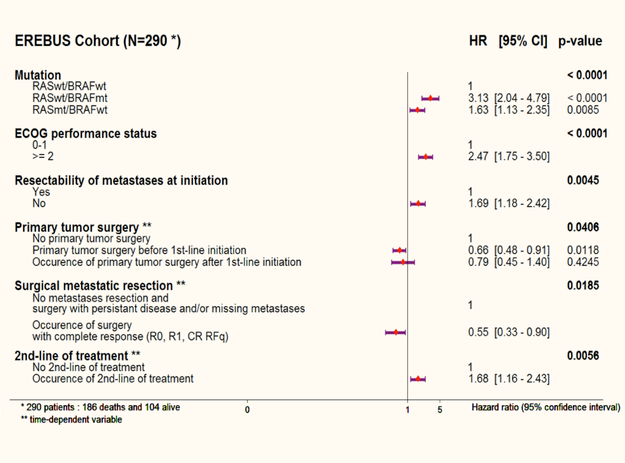

Figure 5. Factors associated with risk of death at 3-year follow-up after the 1-st line treatment initiation (Multivariate Cox model)

Conclusion

EREBUS confirms in real-life the difference in clinical outcomes with tumoral *RAS/BRAF* mutation in unresectable mCRC treated with 1st-line cetuximab, showing the greatest effectiveness in double wild-type (*RASwt / BRAFwt*) patients.

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