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Outcomes according to tumor *RAS* and *BRAF* mutation status in patients treated with cetuximab in 1st-line treatment of unresectable metastatic colorectal cancer (mCRC): updated results from EREBUS cohort

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Background

Cetuximab had initially demonstrated improved survival outcomes in metastatic colorectal cancer (mCRC) with *KRAS* exon 2 wild-type (wt) and more recently no benefit in mCRC with *KRAS* (exon 3 and 4) or *NRAS* (exon 2, 3 and 4) mutation. *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**

- Estimate the 2-years 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

➢ **Ancillary study: analysis according to *RAS* and *BRAF* tumor mutation status**

- Describe patient 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), response and surgical resection of metastases rates according to tumor mutation status

Methods

➢ **Study design**

- Observational cohort study, conducted in 65 French hospital centres

➢ **Recruitment process, inclusion criteria and follow-up**

- Identification of patients initiating cetuximab in 2009–2010 through hospital pharmacy registries
- Inclusion of KRASwt patients with unresectable mCRC, initiating cetuximab as 1st-line therapy
- Follow-up of 24 months from initiation date of cetuximab for PFS evaluation criterion, and 36 months for OS evaluation criterion

➢ **Additional data for ancillary study**

- Vital status at 5 years with participation of physicians in 50 centres
- Additional *RAS* (exons 2,3,4 *KRAS* and *NRAS*) and *BRAF* mutation testing and provided by 35 hospital molecular genetics platforms

Declaration of Interests

This study was supported by an unconditional grant from MERCK SERONO 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 to determine *RAS* tumor mutation status for 312 patients (80.2%), and *RAS/BRAF* tumor mutation status for 310 patients (79.7%).

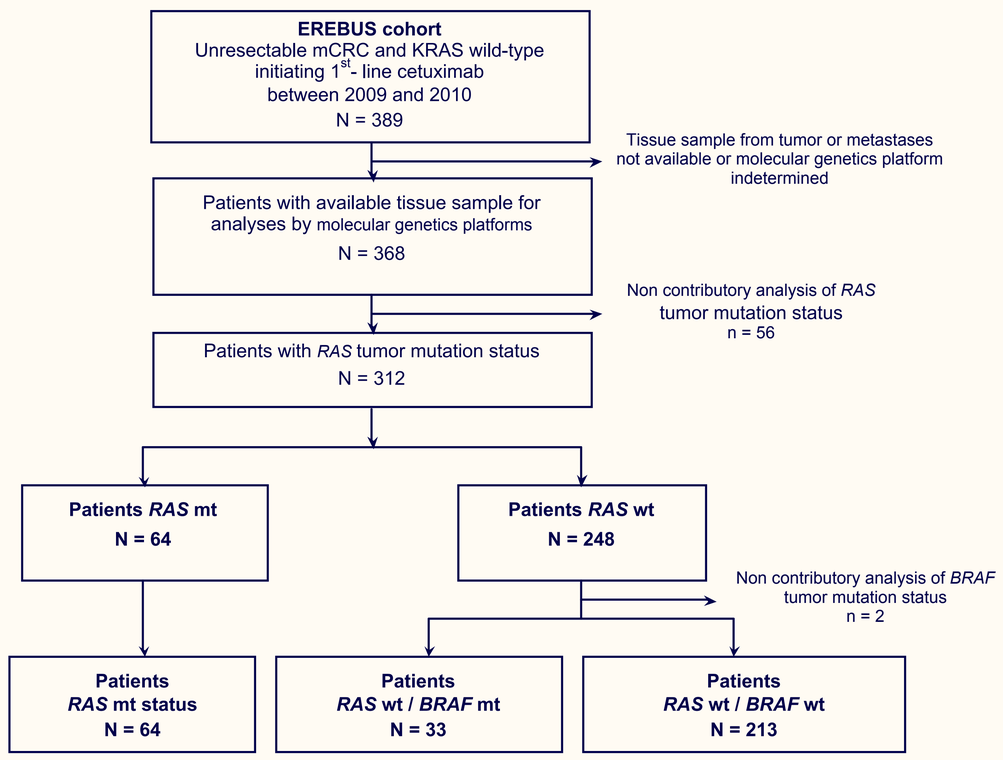

Figure 1 : Identification and selection of study populations

➢ **Baseline characteristics of study populations**

Baseline characteristics of patients are described according to *RAS* and *BRAF* tumor mutation status in Table 1.

Table 1. Baseline characteristics of patients

	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 concomitant chemotherapy use, months	4.9	3.4	6.3
[p25% – p75%]	[2.3 – 9.0]	[1.4 – 6.4]	[3.4 – 11.0]

➢ **Response to treatment and metastases resection rates**

Objective response to treatment and metastases resection rates are described in Table 2.

Table 2. Objective response to treatment and metastases resection rate according to tumor mutation status

	RAS mt n = 64	*RAS* wt / *BRAF* mt n = 33	*RAS* wt / *BRAF* wt n = 213
Objective response to treatment before surgery (partial + complete response), n (%)	26 (40.6)	10 (30.3)	131 (62.4)
[CI 95%]	[28.5 ; 53.6]	[15.6 ; 48.7]	[55.9 ; 68.9]
Metastases resection (whatever surgery result: CR RFq[2], R0, R1 or R2), n (%)	12 (18.8)	2 (6.1)	75 (35.2)
[CI 95%]	[10.1 ; 30.5][1]	[0.7 ; 20.2][1]	[28.8 ; 41.6]
Complete response rate after surgery (R0, R1 or CR RFq[2]), n (%)	8 (12.5)	2 (6.1)	47 (22.1)
[CI 95%]	[5.6 ; 23.2]	[0.7 ; 20.2]	[16.5 ; 27.6]

[1] CI 95% Clopper-Pearson [2] Complete response after radiofrequency ablation

➢ **Survival Outcomes**

PFS was evaluated at 2 years of follow-up and OS at 5 years of follow-up in study populations (PFS: table 3, and figure 2 ; OS: table 3, and figure 3), and in operated patients with mCRC *RAS* mt and *RAS* wt / *BRAF* wt (PFS: table 4, and figure 4 ; OS: table 4, and figure 5).

✓ *Study populations:*

Table 3. Survival outcomes of patients treated by cetuximab according to RAS and BRAF tumor mutation status

	RAS mt n = 64	*RAS* wt / *BRAF* mt n = 33	*RAS* wt / *BRAF* wt n = 213
2-yr PFS probability, % [CI 95%]	8.9 [3.5 ; 17.6]	3.3 [0.3 ; 14.5]	12.9 [8.8 ; 17.8]
Median PFS, months [CI 95%]	8.0 [5.9 ; 9.3]	6.0 [2.3 ; 7.2]	10.4 [9.5 ; 11.0]
5-yr OS probability, % [CI 95%]	11.9 [5.2 ; 21.6]	0.0 [. ; .]	27.1 [21.1 ; 33.5]
Median OS, months [CI 95%]	18.4 [10.9 ; 23.3]	9.7 [6.9 ; 16.6]	29.3 [26.3 ; 36.1]

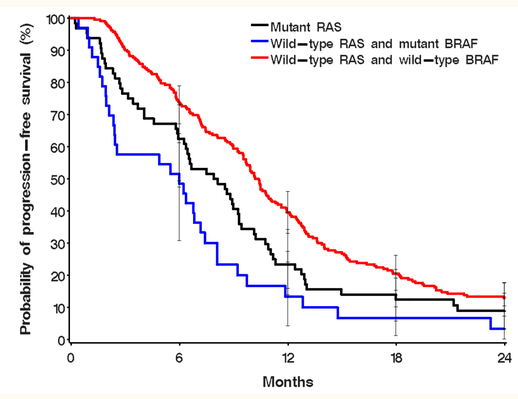

Figure 2. PFS according to RAS and BRAF tumor mutation status (Kaplan-Meier method)

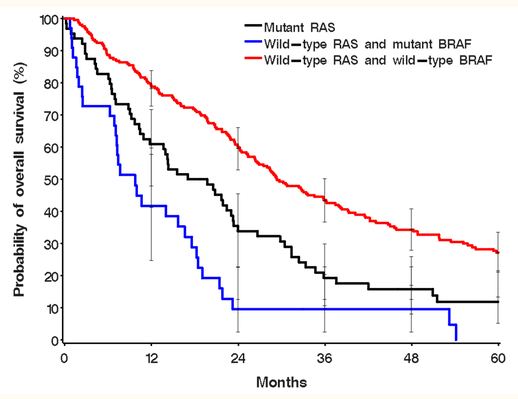

Figure 3. OS according to RAS and BRAF tumor mutation status (Kaplan-Meier method)

✓ *Operated patients:*

Table 4. Survival outcomes of operated patients and mCRC RAS mt and RAS wt / BRAF wt treated by cetuximab

	RAS mt n = 64	*RAS* wt / *BRAF* wt n = 213
2-yr PFS probability, % [CI 95%]	16.7 [2.7 ; 41.3]	23.2 [14.4 ; 33.3]
Median PFS, months [CI 95%]	11.0 [8.1; 21.2]	13.6 [11.6 ;15.3]
5-yr OS probability, % [CI 95%]	41.7 [15.3 ; 66.5]	50.5 [38.5; 61.4]
Median OS, months [CI 95%]	38.9 [20.5; 57.3]	*Not reached*

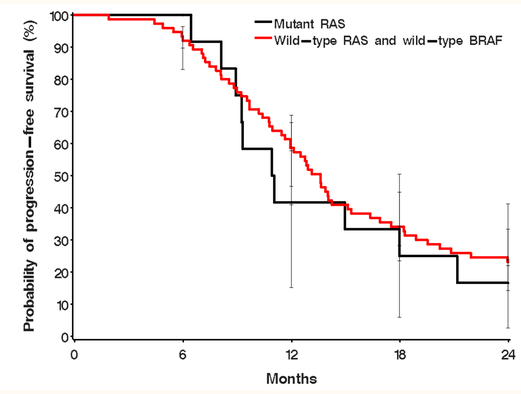

Figure 4. PFS in operated patients with mCRC RAS mt status and RAS wt / BRAF wt status (Kaplan-Meier method)

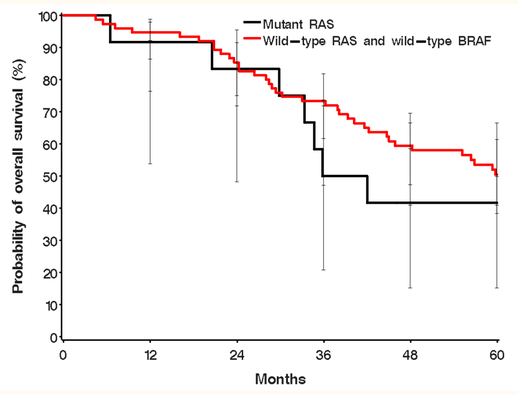

Figure 5. OS in operated patients with mCRC RAS mt status and RAS wt / BRAF wt status (Kaplan-Meier method)

Conclusion

In line with RCTs findings, these results support in real-life practice, the difference of benefit associated to tumoral *KRAS*, *NRAS,* and *BRAF* mutations in patients with unresectable mCRC treated with cetuximab as 1st- line treatment.