K-RAS EXON 2 MUTATIONS IN ADVANCED COLORECTAL CANCER: ARE THEY REALLY SO BAD PROGNOSTIC INDICATORS?

A mono-institutional retrospective study

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Abstract P-237

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> BACKGROUND

Prognostic role of K-RAS codon 12 and 13 mutations and their possible differential impact on survival are still discussed. Larger studies suggest a negative impact on cancer specific survival, although no data on metastatic population (mCRC) are available. This mono-institutional retrospective series investigates the real life impact of mCRC codon 12 and 13 mutations.

> METHODS

All mCRC patients treated between 2008 and 2014 carrying K-RAS exon 2 mutations were included in the study.
Primary endpoint was to determine difference in OS between codon 12 and 13 mutations. Secondary endpoints included PFS, OS according to treatment received, OS in liver-limited disease (LLD) according to codon mutation and surgery of metastases.

Baseline Characteristics	Codon 12 - (%)	Codon 13 - (%)
Total patients /562 tested	156 (27,7)	42 (7,4)
Primary Site		
Ascending colon	60 (38,5)	16 (39,0)
Descending colon / Sigmoid	59 (37,8)	13 (30,5)
Rectum	37 (23,7)	13 (30,5)
Metastatic Features		
Synchronous/Metachronous	108 /48	31/11
Liver-Limited Disease	50 (32,0)	15 (35,7)
M+ sites (diagnosis)		
1	77 (49,3)	24 (57,1)
2	57 (36,5)	11 (26,2)
≥3	22 (14,7)	7 (16,7)
Systemic treatments received		
1	57 (36,5)	11 (26,2)
2	45 (28,9)	17 (40,4)
≥3	52 (33,3)	14 (33,3)
- *Oxa + CPT11 received*	83 (53,2)	29 (69,0)
- *Bevacizumab treatment*	103 (66,0)	33 (78,5)
- *First Line Bevacizumab*	88 (56,4)	26 (61,9)

> RESULTS

> 198/562 mCRC patients analysed for K-RAS exon 2 carried a mutation (35,2%), n.156 at codon 12 (27,7%), n.42 at codon 13 (7,4%). Baseline characteristics and allocation of systemic treatments resulted similar in both groups.

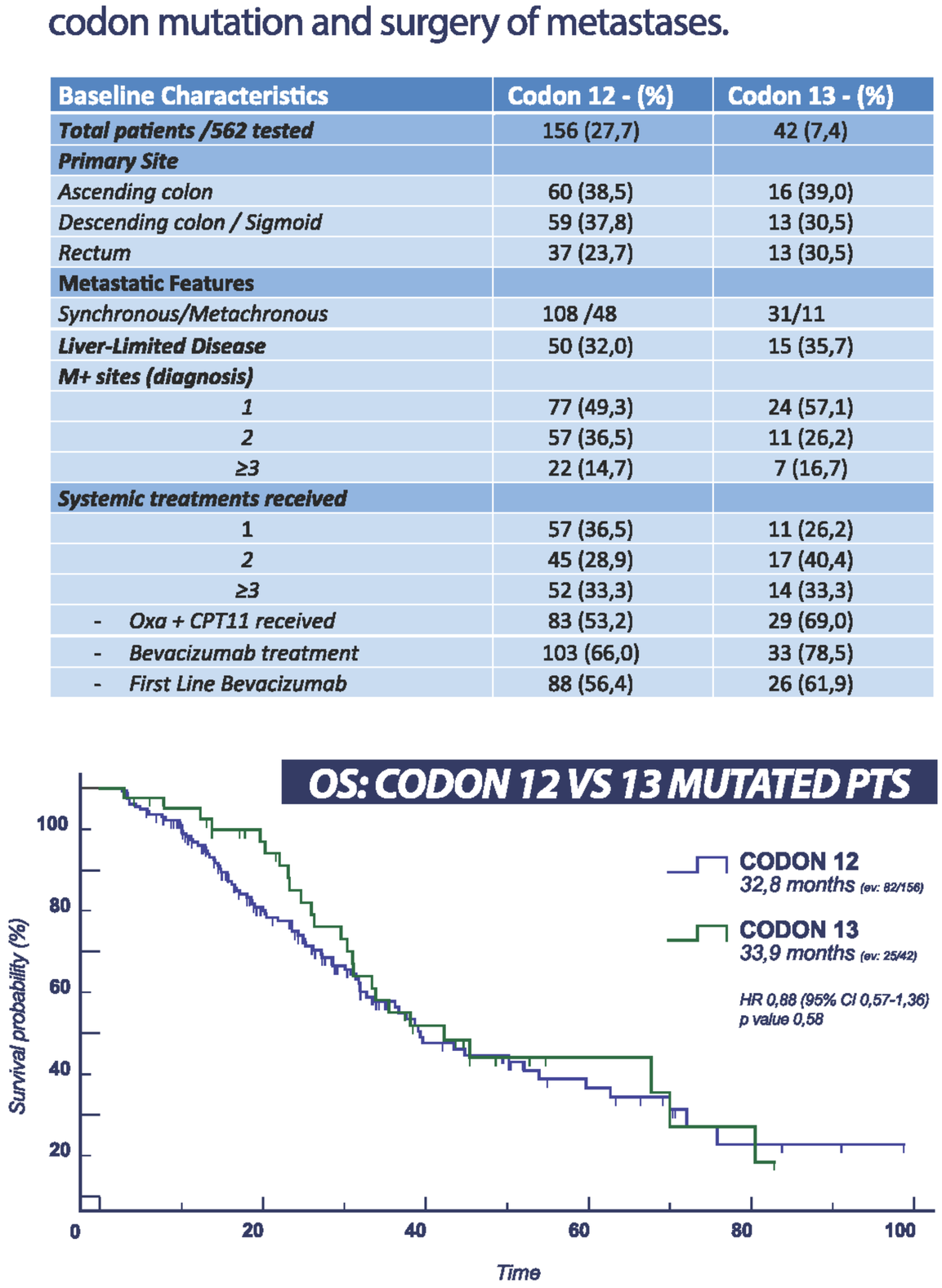
> OS reached no statistically significant difference: 32.8 months (codon 12) and 33.9 months (codon 13).

> PFS reached 10.8 months in both populations (no differences between first line Oxa vs Iri, with or without Bevacizumab).

> In LLD, hepatic surgery was attempted in 41/65 patients (63.1%): in these pts, median OS has not been reached after a median follow-up of 24.8 months (estimate 62.7 months after 25/66 events). OS in non-LLD patients was quite high too, reaching 31.0 months, with 28% of patients (37/132) undergone to surgery of metastases, mainly pulmonary (median OS 44.8 vs 24.3 months in resected vs unresected patients, p<0.001).

Endpoints Data	All pts	Codon 12	Codon 13
OS - months	**32,8** (107/198)	**32,8** (82/156)	**33,9** (25/42)
PFS - months	**10,8** (169/198)	**10,8** (132/156)	**10,8** (37/42)
Objective Response Rate - %	**50,5**	**50**	**52,4**
OS according to LLD - months			
LLD patients	**62,7** est. (25/66)	**53,9** est. (20/51)	**80,5** est. (5/15)
non-LLD patients	**31** (82/132)	**30,8** (62/105)	**31** (20/27)
Surgery of Metastases (%)	**78/198** (39,4)	**60/156** (38,5)	**18/42** (45,2)
Surgery in LLD patients (%)	**41/65** (63,1)	**31/50** (62,0)	**10/15** (66,7)
OS according to M+ surgery			
M+ resected	**62,7** est. (29/79)	**59,7** est. (22/60)	**67,7** est. (7/19)
M+ unresected	**23,6** (78/119)	**23,6** (60/96)	**26,3** (18/23)
OS according to Beva treatment			
Chemo Only	**33,4** (32/62)	**21,8** (28/53)	**ne** (4/9)
Chemo + Bevacizumab	**32,8** (75/136)	**33,6** (54/103)	**31,0** (21/33)
Chemo + Bevacizumab first line	**32,8** (63/114)	**32,8** (47/88)	**31,1** (16/26)

OS: CODON 12 VS 13 MUTATED PTS



> CONCLUSIONS

No OS difference between K-RAS codon 12/13 mutated pts was found. OS of our patients favourably compares with pan-RAS wild type patients of recent randomized studies, even when LLD patients are excluded. Considering the high proportion of patients in which surgery was attempted, we argue that therapeutic aggressiveness (both medical and surgical) could counterbalance the lack of therapeutic tools such as anti-EGFR

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