

REVIEW OF THE CURRENT STATUS OF RAS MUTATION TESTING IN PATIENTS WITH METASTATIC COLORECTAL CANCER (mCRC): FLASH-RAS STUDY

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Introduction

In 2008, it was shown that the presence of a somatic mutation in exon 2 of the gene KRAS was predictive of resistance to anti-EGFR antibodies.

The test for these mutations (KRAS test) thus became necessary before prescribing an anti-EGFR antibody and was incorporated into the Marketing Authorisation (MA) of EGFR inhibitors.

At the end of 2013, these MAs were updated: henceforth, mutation testing must also involve exons 3 and 4 of the KRAS gene and exons 2, 3 and 4 of the NRAS gene, these mutations also having been identified as predictive markers of resistance to anti-EGFR antibodies.

In order to assess the impact of this modification and the real-life conditions in which the tests are carried out, it was decided to set up a French epidemiological study called Flash-RAS. This study follows the Flash-KRAS study conducted in 2011 on KRAS exon 2 genotyping only.

Figure 1: Mechanism of action of EGFR inhibitors & RAS mutation

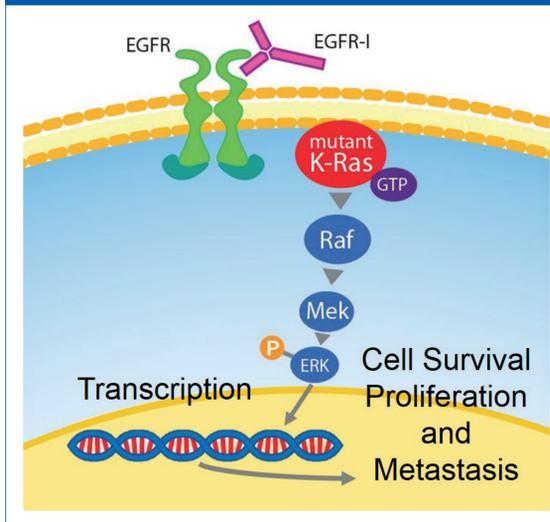
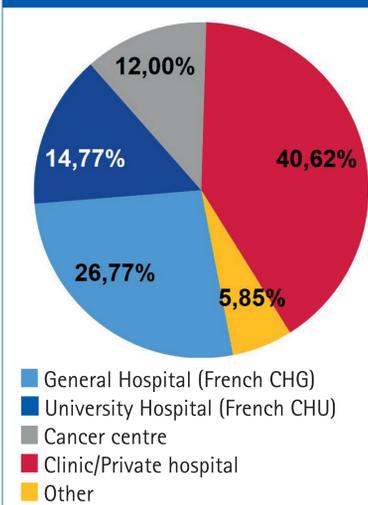
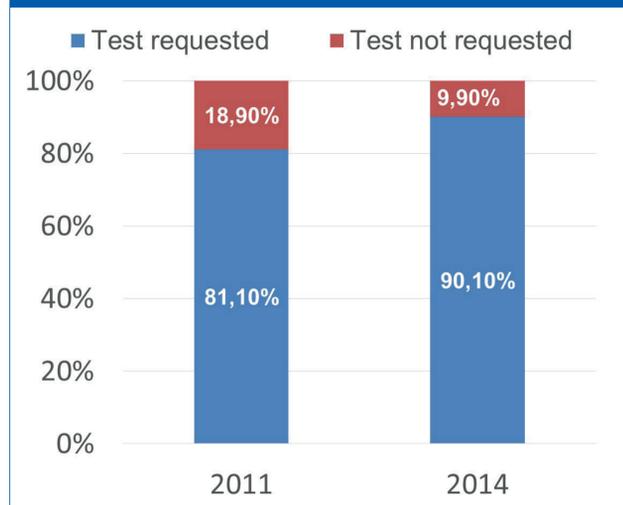


Figure 3: Distribution of patients by type of centers



The distribution by type of centers is representative of the French practice.

Figure 4: Prescription rate of RAS gene mutation between 2011 and 2014



91.1% (CI 95% = [87.1% ; 93.2%]) of patients benefited from genotyping of the RAS gene when their 1st line therapy management was being decided. Prescription rates are higher compared to 2011.

Study objectives

Primary objective:

To assess the rate of prescribing and conduct of RAS gene mutation tests (KRAS and NRAS exons 2, 3 and 4) in patients recently diagnosed with metastatic colorectal cancer (mCRC).

Secondary objectives:

- To describe the change in the rate of prescribing of KRAS gene mutation tests (exons 2, 3 and 4) between 2011 and 2014;
- To describe the reasons for prescribing and non-prescribing these tests depending on the characteristics of the doctors and the patients;
- To analyse the impact of the availability of the KRAS (exons 2, 3 and 4) and NRAS (exons 2, 3 and 4) tests in anatomical pathology laboratories, the impact of their results, the BRAF result, on the therapeutic choice of the doctor or its modification;
- To describe and analyse the clinical characteristics of the patients and the treatments scheduled and received as first line metastatic therapy;
- To describe the technique used for the analysis, the type of mutation sought (if available) and the method of reporting the result to the clinicians (analytical report);
- To describe and analyse the time taken to obtain the results of the KRAS and NRAS tests the circuit (who made the request and when) and the therapeutic approach adopted during this period.

Figure 5: Mean time "Prescription - Receipt of report" in 2011 and 2014 (days)



- Median and mean times to receive the genotyping report did not increase between 2011 and 2014, despite the increase in the number of exons tested (1 exon versus 6)
- The decrease in the standard deviation of the mean between 2011 and 2014 indicates a greater uniformity in the times required to receive a genotyping report.
- The report was available for 323 (96.4%) of the 338 genotyping requests (not received for 5 patients, sample could not be analyzed for 2, transmission problem for 3, missing data for 5).

Methods

National multicenter retrospective observational study

To prevent a selection bias, each participating physician had to screen all patients seen as part of a routine normal clinic visit, during the 'Enrolment Period' and who had to meet all the following inclusion criteria:

- Metastatic colorectal cancer histologically-confirmed after March 2014 (launch of NRAS tests in French centers)
- Seen by the physician between 15 June 2014 and 30 September 2014
- First-line therapy of metastatic disease initiated between 1 March 2014 and 30 June 2014

Exclusion criteria:

- <18 years
- Refused to participate
- Active participation in an interventional study.

Figure 2: flow chart of population



Figure 6: Time required between test request and receipt of result

	Request of the test	Sample sent to the platform	Receipt of genotyping report
N / Missing data	237 / 67		244 / 54
Mean ±SD (days)	7.7 ±11.3		19.5 ±15.8
Median (days)	4		15
Min ; max(days)	0 ; 65		1 ; 112
	N/ Missing		280 / 18
	Mean ±SD (days)		24.6 ± 17.2
	Median (days)		20
	Min ; max (days)		1 ; 118

Conclusion

In 2014, RAS genotyping has become routine practice for the management of patients recently diagnosed with mCRC. The percentage of requests for genotyping in 2014 (90.1%) has increased since 2011 (81.1%).

For a large majority of patients (75.5%), the request for genotyping is done before or not later than one month after the diagnosis of the first metastases. However, for 24.5% of patients, the date of the request for genotyping, more than one month after the diagnosis, does not seem to be compatible with a fully informed decision on 1st line treatment.

The median time to complete the tests was stable between 2011 (19 days) and 2014 (20 days), despite the increase in the number of mutations tested (1 exon versus 6). A narrower standard deviation of the mean confirms a trend for the times to become more uniform. This shows the great reactivity of each stakeholder involved in mCRC patient management in implementing these new tests.

New techniques for the assessment of RAS status currently being tested will probably reduce and homogenize the time required to obtain RAS status.

Disclosure/Acknowledgment

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Disclosures: M. Ducreux (Bayer, Amgen, Merck Serono, Sanofi, Roche, Novartis, Lilly, Pfizer); P. Artru (Roche, Merck Serono, Amgen, Sanofi); A. Lièvre (Merck Serono, Amgen, Roche, Sanofi); J.L. Merlin (Merck Serono, Amgen, Roche, Sanofi, Bayer); J.C. Sabourin (Merck Serono and Boehringer-Ingelheim, Roche, Amgen, AstraZeneca); P. Laurent-Puig (Amgen, Boehringer, Merck Serono, Integragen)

Results

Table 1: patients characteristics	N=375
Sex Male / Female	57.8 / 42.2
Median age (years)	67 (31 - 92)
Synchronous metastases	270 (73.6)
Primary tumour: colon / rectum / colorectal	76.2 / 23.2 / 0.5
Interval to diagnosis of the first metastases - L1 treatment (months)	Median: 1.0 (0.0; 3.6)
L1 chemotherapy:	
- FOLFOX / XELOX: 49.6	- FOLFIRI / XELIRI: 30.7
- 5 FU / Xeloda: 10.7	- Others: 1.3
- FOLFIRINOX: 6.4	- Missing data: 0
L1 associated with another target therapy (n, %)	198 (53.2)