RAS testing assessment in patients with metastatic colorectal cancer in 2014

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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.

Study objectives

Principal 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).

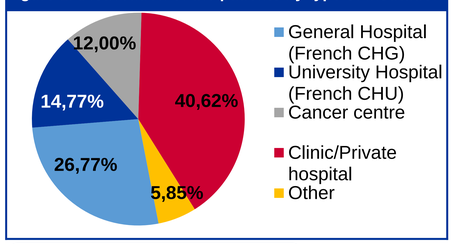
Secondary objectives:

- To describe the change in the rate of prescribing of KRAS gene mutation tests (exon 2) 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.

Patients and methodology

French national epidemiological, observational and retrospective study conducted between 15 June and 30 September 2014

Figure 1: Distribution of the patients by type of institution



A total of 104 institutions
➔406 patients included*
➔375 patients analysed.
*31 patients not analysed (7.6%) due to major deviation from the protocol.

Inclusion criteria: patients with mCRC diagnosed after 01 March 2014 and having started a 1st line treatment between 01 March 2014 and 30 June 2014.

Results: Patient characteristics

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%	- FOLFIRINOX: 6.4%
- Others: 1.3%	- No data: 0%
L1 associated with another target therapy (n, %)	198 (53.2%)

Results : Principal criterion

➔ 90.1% (CI [87.1%; 93.2%]) of patients (338 patients) benefited from genotyping of one or more biomarkers of the RAS gene while their first line therapy management was being decided.
➔ Rates are increasing compared with 2011 (p<0.001, using goodness of fit Chi2).

Fig. 2: Changes in rates of requests for genotyping of biomarkers between 2011 and 2014, according to standards at the time:

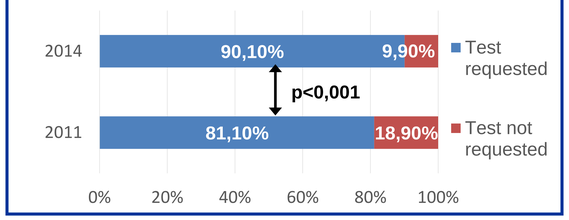
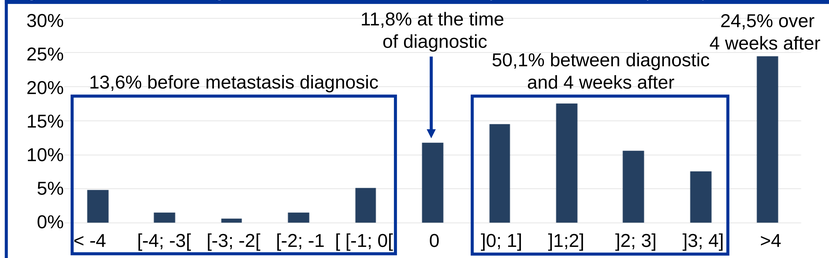


Fig. 3: Time between diagnosis of first metastases and request of RAS tests (weeks)



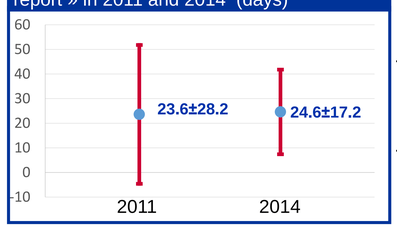
Note: 0 months = at the moment of metastasis (date of prescription = date of 1st metastases

➔ 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, more than one month after the diagnosis of the first metastases, does not seem to be compatible with a fully informed decision on 1st line treatment.

Results: Timing of RAS genotyping

Change in the Turn around time (time between test request and receipt of result) between 2011 (Flash-KRAS) and 2014 (Flash-RAS):

Fig. 4: Mean time «Prescription – Receipt of report » in 2011 and 2014 (days)



➔ Median and mean times to receipt 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 not analysable for 2, transmission problem for 3, missing data for 5).

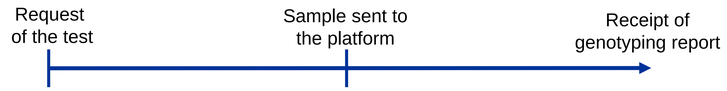
Table 2: Interval « Request - Receipt of report » in 2011 and in 2014

	Flash-KRAS (n= 362)	Flash-RAS (n=298*)
Year	2011	2014
Nb of exons tested	1	6
N	344	280
Mean ± SD (days)	23.6 ± 28.2	24.6 ± 17.2
Median (days)	19	20
Min ; Max (days)	0 ; 450	1; 118
Missing	18	18

*Requests for which there is a result for both KRAS and NRAS + request for RAS test for which there is at least one KRAS result

Results: Timing of RAS genotyping

Fig. 5: Turn around time (time between test request and receipt of result)



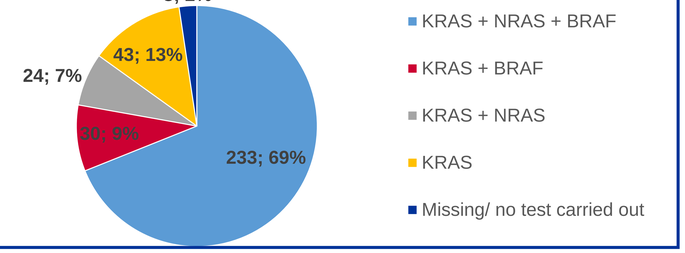
N / Missing	237 / 67	N / Missing	244 /54
Mean ±SD (days)	7.7 ±11.3	Mean ±SD (days)	19.5 ±15.8
Median (days)	4	Median (days)	15
Min ; max (days)	0 ; 65	Min ; max (days)	1 ; 112

N/ Missing	280 / 18
Mean ±SD (days)	24.6 ± 17.2
Median (days)	20
Min ; max (days)	1; 118

New techniques for analysis of RAS status currently being developed will probably lead to more rapid availability of genotyping test results.

Results: Genotyping pattern

Fig. 6: If genotyping requested (n=338), conduct of KRAS, NRAS, BRAF (association) tests



The BRAF mutation status was determined in 77,8% of patients.
The combination KRAS, NRAS, and BRAF was requested for most patients (69%, n=233).

Conclusion

- In 2014, RAS genotyping has become routine practice for the management of patients with a recent diagnosis of 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 turn around time was stable between 2011 (19 days) and 2014 (20 days), despite the increase in the number of mutation 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 very great reactivity of each stakeholder of mCRC patients management in the deployment of these new tests.
- New techniques for the assessment of RAS status currently being tested will probably improve and homogenize the turn around time to obtain RAS status.

Acknowledgment and Disclosures

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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)