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.

**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.

**Results**

<table>
<thead>
<tr>
<th>Table 1: patients characteristics</th>
<th>N=375</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex Male / Female</td>
<td>57.8 / 42.2</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>67 (31 – 92)</td>
</tr>
<tr>
<td>Synchronous metastases</td>
<td>270 (73.6)</td>
</tr>
<tr>
<td>Primary tumour: colon / rectum / colorectal</td>
<td>762 / 232 / 0.5</td>
</tr>
<tr>
<td>Interval to diagnosis of the first metastases – L1 treatment (months)</td>
<td>Median: 1.0 (0.0; 3.6)</td>
</tr>
<tr>
<td>L1 chemotherapy</td>
<td>- FOLFIRINOX + XELOX: 49.6</td>
</tr>
<tr>
<td></td>
<td>- FOLFOX + XELOX: 30.7</td>
</tr>
<tr>
<td></td>
<td>- 5 FU + Xeloda: 10.7</td>
</tr>
<tr>
<td></td>
<td>- Others: 1.3</td>
</tr>
<tr>
<td></td>
<td>- FOLFOXIRINOX: 6.4</td>
</tr>
<tr>
<td>L1 associated with another targeted therapy (n, %)</td>
<td>198 (52.2)</td>
</tr>
</tbody>
</table>

**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 (80.1%) 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, AstraZeneca) ; P. Laurent-Puig (Amgen, Boehringer, Merck Serono, Interstagen)