Panitumumab combined with irinotecan for patients with KRAS wild-type metastatic colorectal cancer refractory to standard chemotherapy: a GERCOR efficacy, tolerance, and translational molecular study

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Background: The purpose of this study was to evaluate the combination of panitumumab and irinotecan in patients with KRAS wild-type metastatic colorectal cancer refractory to standard chemotherapy (oxaliplatin, fluoropyrimidines–irinotecan and bevacizumab).

Patients and methods: KRAS status was first determined locally but subsequent validation of KRAS status and additional screenings (rare KRAS, NRAS, BRAF mutations and EGFR copy number) were centrally assessed. Patients received panitumumab (6 mg/kg) and irinotecan (180 mg/m²) every 2 weeks.

Results: Sixty-five eligible patients were analyzed. The objective response rate (ORR) was 29.2% [95% confidence interval (95% CI) 18.2–40.3]. Median progression-free and overall survivals were 5.5 and 9.7 months, respectively. Most frequent grade 3/4 toxic effects were skin 32.3%, diarrhea 15.4% and neutropenia 12.3%. Tissue samples were available for 60 patients. For the confirmed KRAS wild-type population codon 12 or 13 mutation (n = 54), ORR was 35.2% (95% CI 22.4–47.9). Thirteen patients had a NRAS, a BRAF or a rare KRAS mutation, and no tumor response was observed in this subgroup when compared with 46.3% (95% CI 31.1–61.6) ORR in the subgroup of 41 patients with no identified mutation.

Conclusion: Panitumumab and irinotecan is an active third-line regimen in a well-defined population based on biomarkers.

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Key words: irinotecan, kRAS NRAS BRAF mutations, metastatic colorectal cancer, panitumumab, translational research

introduction

Advances in the understanding of molecular mechanisms involved in carcinogenesis led to the development of targeted therapies in metastatic colorectal cancer (mCRC) treatment [1]. The epidermal growth factor receptor (EGFR) is a validated therapeutic target [2], and two monoclonal antibodies, cetuximab and panitumumab that target the EGFR have been approved in mCRC [3–5]. In the pivotal BOND-1 study, the combination of cetuximab and irinotecan in patients with refractory mCRC to prior irinotecan-containing regimens induced an objective response rate (ORR) in 22.9% of patients versus 10.8% with cetuximab alone, and the hazard ratio (HR) for progression-free survival (PFS) in favor of the combination-therapy group was 0.54 suggesting that cetuximab could restore irinotecan sensitivity [3]. Surprisingly, EGFR expression levels showed no correlation with response to anti-EGFR antibodies [3, 6] and the exploration of other predictors of response revealed the dramatic role of Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation status as a negative

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predictive biomarker [7]. Cetuximab [5] and panitumumab [4] have been tested as a single agent versus best supportive care (BSC) in patients with chemotherapy refractory mCRC. The retrospective analysis of these two large randomized studies confirmed that KRAS-mutated tumors did not benefit from anti-EGFR antibodies [8, 9]. In the cetuximab study, for patients with WT KRAS, the ORR was 12.8%, and PFS and overall survival (OS) were improved [9]. In the panitumumab study as third-line therapy for patients with WT KRAS, the ORR was 17% and PFS was improved compared with BSC, without improvement in OS [8]. However, still <20% of patients with KRAS codon 12 or 13 wild-type tumors will respond to cetuximab or panitumumab monotherapy suggesting that other genetic alterations may also have a predictive role [8, 9]. Among the other genetic alterations, downstream effectors of the EGFR pathway have been shown mutated in mCRC, and these alterations were associated with drug resistance [10]. Indeed, rare KRAS mutations (codon 59, 61, 117 and 146 principally), NRAS and BRAF alterations contribute to the activation of the EGFR pathways downstream of the receptor. This multicenter, phase II study evaluates the efficacy and safety of irinotecan–panitumumab combination in heavily pretreated patients with KRAS WT mCRC and is associated to a translational research to explore other potentially predictive genetic alterations.

patients and methods

This is a phase II, single-arm, multicenter study. The study protocol was approved by an independent ethics committee, and all patients provided written informed consent for participation, translational research before study and evaluation of tumor samples.

patients eligibility

Patients with pathologically confirmed mCRC, KRAS codon 12 and 13 WT, previously treated with irinotecan, oxaliplatin, fluoropyrimidines ± bevacizumab when noncontraindicated were eligible. All patients progressed on irinotecan-based chemotherapy (by investigator, no central review). Concerning oxaliplatin, some patients did not progress on oxaliplatin-based chemotherapy but progressed on fluoropyrimidines (Optimox strategy). Some patients could not receive reintroduction of fluoropyrimidines and oxaliplatin in relation to neurotoxicity or previous other toxicity related to oxaliplatin (allergy).

Eligibility was based on local assessment of KRAS status as for standard care purpose. Pretreatment paraffin-embedded tumor tissue or unstained tumor slides from the primary tumor or metastasis had to be available for molecular central review and translational research. Eligibility criteria also include age ≥18 ears, Eastern Cooperative Oncology Group performance status of zero to two; life expectancy ≥3 months; normal hematopoietic, hepatic (bilirubin ≤1.5 ULN) and renal functions, normal magnesium; measurable disease; no coexisting medical problem of sufficient severity to limit study compliance; no history of brain metastases; and no prior treatment with anti-EGFR antibodies.

doseage and administration

Panitumumab at a dose of 6 mg/kg on day 1 was administered as a 60-min intravenous infusion, just before the administration of irinotecan 180 mg/m² in 90 min on day 1 of each fortnightly cycle (cycles are every 14 days). Patients received this regimen until disease progression or unacceptable toxic effects. If irinotecan was discontinued, the administration of panitumumab alone was allowed.

efficacy and safety assessment

Tumor response was assessed by the investigator using the modified Response Evaluation Criteria in Solid Tumors (m-RECIST), every 8 weeks until disease progression or withdrawal from the trial [11]. Responses were confirmed no <28 days after the criteria for response were first met. Adverse events (AEs) were collected during the treatment period and safety follow-up phases and were graded using NCI–CTCAE v3.0. Follow-up was estimated using the reverse Kaplan–Meier method [12]. PFS and OS were analyzed based on the Kaplan–Meier method using all enrolled patients and the quartiles, and the event rates at various weeks are presented with 95% confidence intervals (CIs) for each end point.

translational researches

The study was designed to centrally genotype tumor samples to avoid discrepancies inherent in the use of different methods. Tumor specimens of all eligible patients were gathered for central laboratory assessment of KRAS and other molecular tests of other components of the EGFR pathway (rare KRAS codon 61, 117 and 146 mutations, BRAF p.V600E and NRAS codons 12, 13 and 61). Tissue blocks were cut for hematoylin–eosin–safran staining, quantification of tumor cells and DNA extraction was done using the QIAamp DNA Mini Kit (Qiagen, Courtaboeuf, France) following the manufacturer’s instruction. DNA were quantified by spectrophotometry (NanoDrop ND-100 instrument, Thermo Fisher Scientific, Waltham, MA) and normalized to 20 ng/μl. KRAS frequent mutations (p.G12A, p.G12V, p.G12C, p.G12D, p.G12S and p.G12R), and BRAF p.V600E were analyzed as previously described with TaqMan® probes [7, 13]. Briefly, reactions were done in 5-μl final volumes using TaqMan genotyping master mix, run on an ABI 3900 HD thermocycler and analyzed with SDS software (Applied Biosystems). KRAS codon 59, 61, 117 and NRAS mutations were screened using direct sequencing of short amplicons (bp <120) and analyzed using Sequencer software (Genes Codes Cooperation, Ann Arbor, MI). Primers and protocols are available on request [14]. Fluorescent in situ hybridization (FISH) were performed as previously described [14]. EGFR copy number was defined as described by Hirsch (tumors with four or more copies of the EGFR gene in ≥40% of the cells (high polysomy)) or tumors with EGFR gene amplification (gene-to-chromosome ratio ≥2 or presence of gene cluster or ≥10 gene copies in ≥10% of the cells) were considered to be FISH+, whereas all other tumors were considered to be FISH− [15]. Tumors with EGFR ≥20 gene copies in ≥10% of the cells were considered highly amplified.

study population

Data of all eligible patients (local assessment of KRAS status) are reported. According to the translational research, we defined a confirmed WT KRAS codons 12 and 13 population and an ‘all WT’ population: confirmed WT KRAS (codons 12 and 13, 61, 117 and 146), WT BRAF (codon V600E) and WT NRAS (codons 12, 13 and 61).

statistical analysis

The primary objective of this study was to evaluate the ORR of the combination in KRAS WT (local assessment) mCRC patients (codons 12 and 13). The ORR was estimated and a CI of 95% was calculated. An ORR of 30% was anticipated in the study. Given a sample size of 60 subjects, the expected CI for ORR would be no wider than 18.2–41.8% assuming an observed ORR of 30%. Secondary objectives were to assess safety and efficacy of the combination: PFS and OS in intention to treat (ITT), and to
determine ORR and survival in the different subgroup of patients defined by translational data.

results

From July 2008 to October 2010, 69 patients were enrolled in the study. Four patients were not eligible. Figure 1 represents the flow chart. Baseline demographics and disease characteristics of the 65 eligible patients are listed in Table 1.

molecular analysis

Tissue samples were available for 60 patients, four samples were not sent to central laboratory due to the paucity of tissue specimens available, and one sample had insufficient DNA quality, resulting in the exclusion of five patients from the translational subgroup analyses. KRAS mutation status and extend genotyping were centrally determined after local assessment at inclusion. Five samples out of the 60 had <20% tumor cells and were enriched by microdissection before extraction, others were extracted directly. De novo typing showed that six (10%) of 60 samples harbor a KRAS mutation at codon 12. Among those without KRAS codon 12 and 13 mutations, 13 tumors displayed additional alterations, 4 (6.6%) were rare KRAS mutations, 4 BRAF (6.6%) and 5 (8.3%) NRAS mutations. The description of patients harboring mutated tumors is given in Table 2. All mutations were exclusive. Overall, 29.2% of the patients selected in the study to receive anti-EGFR antibodies had at least one genetic alteration involving EGFR pathway genes. EGFR amplification status was determined in 50 of the 60 patients using the Hirsch score as cutoff. The dropout was due to an absence of available tumor tissue block for 10 patients. Nineteen samples were FISH+ among which 3 were KRAS, BRAF and NRAS mutated, 31 were FISH− among which 2 were KRAS, 2 NRAS and 3 BRAF mutated. Four of the 19 FISH+ patients were considered highly amplified; one was a BRAF-mutated tumor. Among the ‘all WT’ population (n = 41), Hirsh score was available for 37 patients (Figure 1) and 13 (32%) had EGFR amplification or polysomy (FISH+). Among the patients with KRAS, NRAS or BRAF mutation (n = 19), six (31.5%) had EGFR amplification or polysomy (FISH+).

efficacy

Efficacy parameters are reported for the whole eligible population and for the subgroups defined by tumor genotypes (Table 3).

At cut-off date (January 2012), median follow-up was 25.6 months (95% CI 20.0–29.9). For the 65 eligible patients, ORR was 29.2% (95% CI 18.2–40.3), median PFS 5.5 months (95% CI 3.7–7.6) and median OS 9.7 months (95% CI 6.6–15.8). ORR, PFS and OS for the 54 patients with confirmed WT KRAS codon 12 and 13 and for ‘all WT’ population are reported in Table 3 and Figure 2.

In patients with mutated tumors (n = 19), no response was observed, median PFS was 1.9 months and a median OS 4.6 months (Table 3). Individual data for these 19 patients are summarized in Table 2. Among the four patients with high EGFR amplification, there were two partial responses, one stabilization and one progression corresponding to the BRAF mutated/Hirsh+. Among the three patients who achieved complete response, none had an FISH+ tumor. Restricting our analysis to KRAS, BRAF and NRAS WT tumors (n = 41), we tested the association between EGFR amplification or high polysomy (FISH+) and PFS and OS (supplementary Figure S4, available at Annals of Oncology online). Curves did not show a benefit for FISH+ tumor.

safety

The incidence of AEs was 55.3% for worst grade 3/4 treatment-related (as assessed by the investigator), no serious AE nor toxic death was reported in the eligible population (n = 65). No grade 3/4 panitumumab-related infusion reactions occurred.

codon 12 and 13 and for ORR, PFS and OS for the 54 patients with confirmed WT KRAS codon 12 and 13 and for ‘all WT’ population are reported in Table 3 and Figure 2.

Table 1. Demographics and disease characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>n = 65</th>
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<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39 (60.0)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (40.0)</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Median</td>
<td>62</td>
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<tr>
<td>Min–max</td>
<td>(34–84)</td>
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<tr>
<td>WHO performance status, n (%)</td>
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<tr>
<td>0</td>
<td>25 (38.5)</td>
</tr>
<tr>
<td>1</td>
<td>33 (50.8)</td>
</tr>
<tr>
<td>2</td>
<td>7 (10.8)</td>
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<tr>
<td>Primary tumor type, n (%)</td>
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<tr>
<td>Colon</td>
<td>45 (69.2)</td>
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<tr>
<td>Rectum</td>
<td>17 (26.1)</td>
</tr>
<tr>
<td>Both</td>
<td>3 (4.6)</td>
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<tr>
<td>Number of metastatic sites, n (%)</td>
<td></td>
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<tr>
<td>1</td>
<td>37 (56.9)</td>
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<tr>
<td>&gt;1</td>
<td>28 (43.1)</td>
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<tr>
<td>Sites of metastatic disease, n (%)</td>
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<tr>
<td>Liver</td>
<td>46 (70.8)</td>
</tr>
<tr>
<td>Lung</td>
<td>25 (38.5)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>11 (16.9)</td>
</tr>
<tr>
<td>Others</td>
<td>21 (32.3)</td>
</tr>
<tr>
<td>Adjuvant chemotherapy, n (%)</td>
<td></td>
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<tr>
<td>Yes</td>
<td>17 (26.1)</td>
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<tr>
<td>Time between diagnosis of primary tumor and inclusion, n (%)</td>
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</tr>
<tr>
<td>&lt;12 months</td>
<td>13 (20)</td>
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<tr>
<td>12–24 months</td>
<td>21 (32.3)</td>
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<tr>
<td>&gt;24 months</td>
<td>31 (47.7)</td>
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<tr>
<td>First-line chemotherapy, n (%)</td>
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<tr>
<td>Oxaliplatin-based therapy</td>
<td>42 (64.7)</td>
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<tr>
<td>Irinotecan-based therapy</td>
<td>22 (33.8)</td>
</tr>
<tr>
<td>Oxaliplatin- and irinotecan-based therapy</td>
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</tr>
<tr>
<td>Second-line chemotherapy, n (%)</td>
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<tr>
<td>Oxaliplatin-based therapy</td>
<td>14 (21.5)</td>
</tr>
<tr>
<td>Irinotecan-based therapy</td>
<td>43 (66.2)</td>
</tr>
<tr>
<td>No second line*</td>
<td>8 (12.3)</td>
</tr>
<tr>
<td>Prior treatment with bevacizumab, n (%)</td>
<td></td>
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<tr>
<td>No (contraindication)</td>
<td>12 (18.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>53 (81.5)</td>
</tr>
</tbody>
</table>

*All of these patients received oxaliplatin and 5-FU/leucovorin as adjuvant therapy.
Grade 3/4 AEs of interest are skin toxicity: n = 20 (32.3%); neutropenia n = 8 (12.3%); diarrhea n = 10 (15.4%); mucositis n = 1 (1.5%).

discussion

This study prospectively analyzed the effect of panitumumab combined with irinotecan administered to previously heavily treated WT KRAS mCRC (codon 12 and 13). Sixty-five patients were eligible (ITT) with a 29.2% ORR with acceptable toxicity. Fifty-four patients had no mutation by central review of KRAS WT genotype (codons 12 and 13) with a 35.2% ORR. Our results are confirming the data of the randomized study comparing cetuximab alone to cetuximab and irinotecan in a pretreated non-KRAS WT-selected population [3]. More recently, Peeters et al. compared the combination of
panitumumab, irinotecan and 5-fluorouracil (5-FU)/leucovorin (FOLFIRI) to FOLFIRI alone as second-line treatment in mCRC patients [16]. In the subgroup of patients with WT KRAS, PFS was 5.9 months for panitumumab with FOLFIRI versus 3.9 months for FOLFIRI alone (HR = 0.73, \( P = .004 \)), and ORR was 35% versus 10% [16]. There is an unquestionable OS advantage for anti-EGFR monoclonal antibodies alone in third-line therapy in the WT-KRAS population [5, 9]. The randomized BOND study shows the superiority of the combination of irinotecan and cetuximab, compared with cetuximab alone, in patients with irinotecan-refractory tumors, further suggesting that cetuximab may circumvent irinotecan resistance. Our study, with the limitation of a single-arm phase II, seems to confirm this fact with panitumumab. Cells acquire irinotecan resistance by several mechanisms, like abrogating drug efflux, restoring apoptosis or impairing DNA-repair activity [17–19]. EGFR inhibition induced by anti-EGFR antibodies may overcome this resistance.

Since the identification of KRAS mutation as a biomarker of resistance to anti-EGFR antibodies, all patients with mCRC are now routinely profiled for KRAS common alterations [7, 20]. Therefore, this study was designed to include patients with KRAS WT tumor based on local molecular determination of the mutational status done in routine diagnosis. In order to further explore the selection of patient that will respond to anti-EGFR antibodies, other EGFR pathway alterations such as
BRAF mutation have been studied in retrospective studies [10, 14]. Therefore, in this prospective series of patients, tumors were analyzed for KRAS rare mutations, BRAF, NRAS and EGFR copy number was quantified (Hirsh score) to analyze whether tumor genotypes could still impact the response when panitumumab was administrated with irinotecan. Our first finding was the discovery by central validation of KRAS codon 12 mutations in six included patients (10% of the routinely defined KRAS WT tumor patients). It demonstrates inaccuracy of genotyping methods in analyzing KRAS status on paraffin-embedded specimens. Discrepancies between laboratories and technologies have already been reported [21]. External quality assessment for KRAS testing has been setup and should improve the quality of the KRAS genotyping [21]. In this study, central laboratory used an allelic discrimination strategy based on TaqMan mutation-specific probes for KRAS screening. This technology was shown to be robust on fixed samples and sensitive with a cutoff of mutation identification determined on serial dilution of cell line DNA found between 5 and 10% [7]. The French government through the National Cancer Institute (INCa) financed and licensed 28 public molecular genetic platforms, to handle theranostic tests. The number of KRAS test increased from 1100 in 2007 to 17,246 in 2009. Recent analyses showed that despite the absence of harmonization in KRAS mutation detection methods, interlaboratory Kappa values were >0.8 demonstrating a high agreement, i.e. a very good reproducibility and suggesting that incorrect KRAS screening were due to a lack of expertise of a subset of laboratories at the start of KRAS genotyping and can explain 10% incorrect KRAS mutation in this study.

Among the potential targets, patients with BRAF-mutated tumors clearly have a poorer prognosis and lower response rates to anti-EGFR antibodies when compared with other subgroups of patients [10, 22, 23]. Concerning rare KRAS, NRAS or PIK3CA mutations, evidence of a link with a low response to therapy is based on a small number of patients and retrospective studies [10]. Finally, EGFR amplification or high chromosome 7 polysomy was related to positive tumor response although EGFR expression has never been related to treatment efficacy [14, 24]. Concerning panitumumab, evidence for EGFR-related pharmacogenetic testing other than KRAS is still very limited. Recently, a large molecular study based on a phase III and an open-label extension study testing panitumumab as a single agent in third-line treatment revealed that other EGFR pathway-related genes could be of importance in strengthening patient’s selection. Indeed, none of the patients with KRAS (codon 12, 13), BRAF or NRAS mutations responded to treatment and only one-sixth of patients with
**KRAS** codon 61 alteration achieved partial response [25]. Moreover, their results did not support the role of PIK3CA mutation as a negative predictive biomarker of response, and for this reason, we did not evaluate PIK3CA mutational status in our study [25].

Frequencies of other pathway gene alterations are in accordance to previous findings although NRAS mutation frequency could be higher in our series [7, 25]. Mutated tumors did not respond to treatment and had a statistically lower PFS and OS as compared with nonmutated ones showing that, as seen previously for KRAS common alterations, other *EGFR* pathway gene mutations have a strong impact on treatment even though chemotherapy is added to anti-*EGFR* antibody. One patient with a NRAS p.G13C tumor mutation showed long OS. KRAS p.G13D mutation was recently related to better outcome in patients with colorectal cancer [25]; whether similar association exists for NRAS remains to be analyzed. Response to treatment was found highly dependent on tumor mutation status, indeed none of the mutated tumors showed an objective response. In our study, in all wild-type population, 17% of patients had progression at first evaluation compared with 73% for patients with any mutation (Table 3). Concerning the need of increasing screening to rare mutations, this report shows that in this population of CRC patients, there is no response in patients with KRAS, NRAS or BRAF mutations. De Roock et al. showed that there is an improvement in ORR prediction when multiple genes are tested for genetic alterations [26]. If validated in larger series of patients, the gain of information from enlarge screenings will have to be weighed against the cost and feasibility on FFPE samples. Technologies should be available in the near future.

Concerning *EGFR* quantification some studies suggested that increased *EGFR* copy number is uncommon in mCRC [27, 28] although the frequency of high copy number could increase in chemorefractory patients. High copy number was shown to be linked to response to treatment by anti-*EGFR* antibodies [14, 24]. In the ‘all WT’ sub group, among three patients with a high amplification of *EGFR*, two were considered as responders. Nevertheless, as already suggested [14], High amplification of *EGFR* does not seem to improve PFS or OS (supplementary Figure S4, available at Annals of Oncology online). The prognostic value of *EGFR* copy number is suggested in other malignancies (gliomas). In CRC, increased expression of *EGFR* at the invasive margins was recently shown to be linked with tumor progression [29].

The addition of cetuximab or panitumumab to chemotherapy as first-line therapy increases PFS between 0 and 1.6 months [30–32]. Cetuximab or panitumumab as third-line therapy versus BSC alone increases PFS between 1.2 and 2.8 months [8, 9]. In patients with mCRC refractory to chemotherapy, the activity of irinotecan and anti-*EGFR* antibodies suggested that previous chemotherapy regimens could render cell addicted to *EGFR* activation [3, 16]. Previous lines of chemotherapy could result in an increased dependence of cancer cells to *EGFR* pathways and, indirectly, renders cancer cells more sensitive to anti-*EGFR* therapy. In *in vitro* studies have reported that *EGFR* overexpression is frequently observed in chemoresistant cell lines of various tumor types in comparison with parental cell lines [33–35]. Interestingly, *EGFR* pathway upregulation was associated with an increased sensitivity to anti-*EGFR* therapy [34] with synergistic effect with irinotecan [35]. In colon cancer cells, the exposure to cytotoxic drugs, in particular 5-fluorouracil, leucovorin and irinotecan, was able to increase the cell surface expression of *EGFR*, resulting in an increased sensitivity of cancer cells to cetuximab [33]. Nevertheless, these results suggest that anti-*EGFR* antibodies approved for mCRC treatment could be more efficient when used in advanced treatment line than in first line. Future studies should investigate this point and could help to define the best place of anti-*EGFR* antibodies in the therapeutic strategy of mCRC.

In conclusion, panitumumab–irinotecan appeared to have acceptable safety profile with convenient administration and may represent a new treatment option in patients with WT KRAS mCRC resistant to standard chemotherapy. The high ORR, respectively, observed in the centrally controlled WT KRAS patients and in the all ‘WT’ subgroup of patients in our study underlined the importance of molecular biomarkers of response, with quality control for KRAS determination. Indeed, response was highly dependent on tumor mutation status. Extended genotyping, including KRAS rare mutants, BRAF and NRAS, could strengthen personalized medicine and avoid unnecessary treatment to patient with a nonresponse genotype (Figure 3).

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### disclosures

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references


