

PARTIAL ACCESS ORIGINAL REPORTS January 21, 2009



# Impact of FcγRIIa-FcγRIIIa Polymorphisms and KRAS Mutations on the Clinical Outcome of Patients With Metastatic Colorectal Cancer Treated With Cetuximab Plus Irinotecan

Authors: [Frédéric Bibeau](#) , [Evelyne Lopez-Crapez](#), [Frédéric Di Fiore](#), [Simon Thezenas](#), [Marc Ychou](#), [France Blanchard](#), [Aude Lamy](#), [Frédérique Penault-Llorca](#), [Thierry Frébourg](#), [Pierre Michel](#), [Jean-Christophe Sabourin](#), and [Florence Boissière-Michot](#) | [AUTHORS INFO & AFFILIATIONS](#)

*J Clin Oncol* 27, 1122-1129(2009) [Volume 27, Number 7](#)  
DOI: 10.1200/JCO.2008.18.0463

**3,289 / 439** **10** PDF

## Abstract

### Purpose

The antiepidermal growth factor receptor antibody cetuximab shows activity in irinotecan-refractory metastatic colorectal cancer (mCRC), mainly in wild-type KRAS tumors. Cetuximab may also exert antitumor effects through antibody-dependent cell-mediated cytotoxicity (ADCC) in which antibody Fc portion interacts with Fc

receptors (FcγRs) expressed by immune cells. ADCC is influenced by FcγRIIa-H131R and FcγRIIIa-V158F polymorphisms that are clinically relevant in follicular lymphoma and metastatic breast cancer treated with rituximab and trastuzumab, respectively. We investigated the association of FcγR polymorphisms and KRAS mutation with the outcome of irinotecan-refractory mCRC patients treated with cetuximab plus irinotecan.

### Patients and Methods

## ASCO® Career Center

ASCO Career Center

Employed Hem Onc | UNC Community Hospital | Regional Cancer Center | NC

North Carolina | Competitive Salary and Benefits Package

Highlights: - Established team of physicians and APPs. 4-day work week, minimal after-hours phone call only. - Accredited Comprehensive Cancer Cent...

Employer: Jackson Physician Search [Apply for this job](#)

Hematology/Oncology near Fort Collins, CO | 4 Day Week | 30k Annually for Loans

Wyoming | Competitive Salary and Benefits Package

A thriving 200-bed regional medical center just 40 minutes from Fort Collins, CO is seeking a BE/BC Hematology/Oncology physician to join their

## Recommended Articles

GASTROINTESTINAL CANCER | SEPTEMBER 2016

**[FCGR2A and FCGR3A Polymorphisms Associated With Clinical Outcome of Epidermal Growth Factor Receptor-Expressing Metastatic Colorectal Cancer Patients Treated With Single-Agent Cetuximab](#)**

TUMOR BIOLOGY AND HUMAN GENETICS | MAY 2008

**[Association of FcγRIIa and FcγRIIIa polymorphisms with clinical outcome in metastatic colorectal cancer patients \(mCRC\) treated with cetuximab and irinotecan](#)**

CANCERS OF THE COLON AND RECTUM | FEBRUARY 2011

**[Distributions of FcγRIIa-131 and FcγRIIIa-158 polymorphisms and clinical response to cetuximab in Japanese patients with metastatic colorectal cancer \(mCRC\)](#)**

Tumor and normal tissues from 69 patients were screened for *KRAS* mutations using a sensitive multiplex assay and

### Impact of FcγRIIa-FcγRIIIa Polymorphisms and *KRAS* Mutations on

polymerase chain reaction, respectively. The results were correlated with response and progression-free survival (PFS).

### Results

*KRAS* mutations were associated with lower response rate (4% v 27% in nonmutated patients;  $P = .021$ ) and shorter PFS (3.0 v 5.3 months;  $P = .021$ ). Patients with FcγRIIa-131H/H and/or FcγRIIIa-158V/V genotypes had longer PFS than 131R and 158F carriers (5.5 v 3.0 months;  $P = .005$ ). The difference remained significant for mutated-*KRAS* patients. By multivariate analysis, *KRAS* mutation and FcγR combined status were independent risk factors for PFS.

### Conclusion

Combined FcγRIIa/FcγRIIIa polymorphisms are prognostic factors for disease progression in mCRC patients treated with cetuximab plus irinotecan. As these polymorphisms are also clinically relevant in mutated-*KRAS* mCRC, an important role of ADCC in cetuximab efficacy is presumed.

### Introduction

Cetuximab (Erbix; ImClone Systems Inc, Branchburg, NJ), a chimeric immunoglobulin 1 (IgG1) monoclonal antibody (mAb), targeted against the extracellular domain of the epidermal growth factor receptor (EGFR) has shown efficacy in patients with metastatic colorectal cancer (mCRC) in several phase II trials, leading to US Food and Drug Administration approval in 2004 for the treatment of irinotecan-refractory mCRC.<sup>1,2</sup> Recent randomized phase III clinical trials showed that cetuximab has significant clinical activity when given in

Colorectal Cancer (more)

CORRESPONDENCE | SEPTEMBER 2016



### Patients, and for an FcγRIIIa-Restricted Influence on the Response to Therapeutic Antibodies

HEMATOLOGIC MALIGNANCIES | SEPTEMBER 2016

### Polymorphisms in FcγRIIIA (CD16) Receptor Expression Are Associated With Clinical Response to Rituximab in Waldenström's Macroglobulinemia



combination with irinotecan as first- or second-line agent.<sup>3,4</sup> Moreover, cetuximab significantly extended median survival as third-line monotherapy for refractory mCRC compared to best supportive care alone.<sup>5</sup>

The molecular mechanisms underlying the clinical response or resistance to cetuximab remain the subject of intense ongoing basic and clinical investigations. It becomes necessary, for ethical and economical reasons, to better define the subpopulation of patients who truly benefit from cetuximab. Unlike the predictive value of HER2 overexpression for trastuzumab therapy in breast cancer, the efficacy of cetuximab in mCRC does not appear to be linked to the tumor expression of the target itself (as assessed by immunohistochemistry) and response can be obtained in tumors that do not express EGFR.<sup>6,7</sup> Currently, some biologic markers involved in the EGFR intracellular signaling pathways have been investigated as potential predictors of response to cetuximab.<sup>8</sup> To date, *KRAS* status is the most relevant molecular marker of cetuximab sensitivity. Several retrospective clinical studies have clearly demonstrated that a *KRAS* mutation confers resistance to mCRC patients.<sup>9-13</sup> Other factors such as activated EGFR,<sup>14</sup> EGFR amplification,<sup>13,15,16</sup> phosphatase protein homolog to tensin (PTEN) expression,<sup>13</sup> low vascular endothelial growth factor receptor (VEGFR) expression,<sup>17</sup> nuclear factor- $\kappa$ B tumor expression,<sup>18</sup> or epiregulin and amphiregulin expression<sup>12</sup> were also found to predict response to cetuximab, but results need to be confirmed in larger series of mCRC patients.

Modulation of the immune response could be another important mechanism of cetuximab sensitivity. The immunological mechanism antibody-dependent cellular cytotoxicity (ADCC) mediated through Fc receptors (Fc $\gamma$ R) carried by immune cells such as macrophages and natural killer (NK) cells plays an important role in the antitumor effect of IgG1 antibody.<sup>19</sup> Constitutional polymorphisms have been demonstrated on genes encoding for the activating receptors Fc $\gamma$ RIIIa (CD 32, mainly expressed on macrophages) and

FcγRIIIa (CD16, expressed on NK cells and macrophages), affecting their affinity to human IgG: a histidine (H)/arginine (R) polymorphism at position 131 for FcγRIIa and a valine (V)/phenylalanine (F) polymorphism at position 158 for FcγRIIIa.<sup>20</sup> On the basis of the different binding affinities, patients harboring FcγRIIa-131H/H and FcγRIIIa-158V/V genotypes would be expected to mediate a more potent ADCC antitumor response after mAb treatment.<sup>21-23</sup> Clinical studies have shown that FcγRIIa-131H/H<sup>24,25</sup> and FcγRIIIa-158V/V genotypes<sup>24-26</sup> were associated with better clinical outcome to rituximab as first-line treatment of follicular lymphoma and to trastuzumab-based therapy in metastatic breast cancer. In vitro studies have shown that cetuximab was able to induce ADCC.<sup>27-29</sup> Recently, in a series of 39 EGFR-expressing mCRC patients treated with single-agent cetuximab, Zhang et al<sup>30</sup> found that FcγRIIa-H131R and FcγRIIIa-V158F polymorphisms were independently associated with PFS. However, opposed to results with rituximab, FcγRIIIa-158V/V genotype was associated with unfavorable clinical outcome.

This study was designed to evaluate the influence of FcγRIIa and FcγRIIIa polymorphisms and *KRAS* mutations on the outcome of 69 patients with irinotecan-resistant mCRC treated with cetuximab plus irinotecan.

## Patients and Methods

### Eligible Patients

Sixty-nine patients (46 males; 23 females; median age, 60 years) with histologically proven colorectal adenocarcinoma, who had been treated with cetuximab for mCRC in two French centers (Val d'Aurelle Institute, Montpellier and University Hospital, Rouen) from 2002 to 2007, were included in this study ([Table 1](#)). All patients but one were white. They all failed one irinotecan-based chemotherapy regimen and the majority of patients (78%) received at least two previous lines for metastatic disease. Among these patients, 55 had received oxaliplatin and seven had received bevacizumab therapy previously to cetuximab. All patients were treated with

cetuximab at standard dosage combined with irinotecan, except one patient who also received fluorouracil/folinic acid. All patients received glucocorticoids as premedication. Tumor response was evaluated every 2 to 3 months by computerized tomodensitometry according to the Response Evaluation Criteria in Solid Tumors<sup>31</sup> and classified as complete (CR), partial response (PR), stable disease (SD), or progressive disease (PD). For the statistical analysis, the best tumor response was selected. The median follow-up time was 19.3 months (95% CI, 0.3 to 34.4 months). This retrospective analysis was approved by our local research boards and all data were anonymized.

**Table 1.** Characteristics of mCRC Patients Treated With Cetuximab Plus Irinotecan (N = 69)

Characteristic	No.	%
Age, years		
Median	60	
–		

Abbreviations: mCRC, metastatic colorectal cancer; FcγR, fragment cy receptor; H, histidine allele; R, arginine allele; V, valine allele; F, phenylalanine allele.

## DNA Extraction

Two appropriate paraffin-embedded samples were selected for each patient. The first one contained exclusively normal tissue whereas the other was either primary (n = 53), metastatic (n = 15) or local recurrence (n = 1) tumor tissue. DNA was extracted according to manufacturer's recommendations from 10-µm thin sections by using the QIAamp DNA Mini Kit (Qiagen, Courtaboeuf, France).

## KRAS Mutation Analysis

Polymerase chain reaction (PCR)–amplified *KRAS* exon 2 was analyzed twice for the presence of *KRAS* mutations at nucleotides c.34, c.35, c.37, and c.38, using the ABI PRISM SNaPshot Multiplex kit (Applied Biosystems, Foster City, CA) and four primers including at their 5' end, an additional tail allowing their simultaneous detection according to Di Fiore et al.<sup>11</sup>

### **FcγRIIIa-H131R Genotyping**

A specific 360-basepair fragment was PCR amplified then cycle sequenced. Oligonucleotides for PCR amplification were chosen to amplify the *FcγRIIIa* gene and not the highly homologous *FcγRIIIb* and *FcγRIIIc* genes (sequences available on request).

PCR reactions were carried out by using 1.5 mmol/L MgCl<sub>2</sub>, 200 μmol/L of each dNTP (GE Healthcare, Orsay, France), 0.4 μmol/L of each primer, 1 U of Taq Platinum DNA polymerase (Invitrogen, Illkirch, France), and 50 ng genomic DNA. After an initial denaturation step, samples were submitted to 35 PCR cycles (15 seconds at 95°C, 30 seconds at 55°C, and 40 seconds at 72°C). Purified PCR products were then sequenced by using the Big Dye terminators version 1.1 cycle sequencing kit (Applied Biosystems, Courtaboeuf, France) and the 3130 Genetic Analyzer (Applied Biosystems). All sequencing reactions were performed twice by using two independent PCRs.

### **FcγRIIIa-158 V/F Genotyping**

Extracted DNA was analyzed after amplification by a multiplex allele-specific PCR as previously described,<sup>32</sup> but with some modifications. A FcγRIIIa-specific common forward primer was used in combination with a short FcγRIIIa-V specific reverse and a long FcγRIIIa-F specific reverse primer (sequences available on request). The PCR reaction was performed in a final volume of 25 μL containing 2 mmol/L MgCl<sub>2</sub>, 200 μmol/L of each dNTP, 0.4 μmol/L of each primer, 1 U of Taq Platinum DNA polymerase and 50 ng genomic DNA. After an initial

DNA polymerase and 50 ng genomic DNA. After an initial denaturation step, samples were submitted to 35 PCR cycles (40 seconds at 95°C, 20 seconds at 56°C, and 30 seconds at 72°C). The amplification products, which are 70 and 117 basepairs long for the homozygous FcγRIIIa-158V and the homozygous FcγRIIIa-158F samples respectively, were electrophoresed in 8% polyacrylamide gels and visualized after SYBR Gold (Invitrogen, Illkirch, France). Multiplex allele specific PCR was carried out in duplicate for each patient and previously characterized cell lines with homozygous or heterozygous genotype were run in parallel. A negative control performed without DNA was used to discriminate primer dimers from the smallest PCR product.

## Statistical Analysis

Categorical variables were reported by means of contingency tables. Furthermore, for continuous variables, the means, the median, and range were computed. To investigate the association between biologic and clinical features (*KRAS* mutation, FcγRIIIa and FcγRIIIa polymorphisms and response to cetuximab), univariate statistical analyses were performed using Pearson's  $\chi^2$  test or Fisher's exact test if applicable. PFS was measured as time from the first day of cetuximab infusion until the first observation of tumor progression or death from any cause. Survival rates were estimated according to the Kaplan-Meier method. Survival curves were drawn, and the log-rank test was performed to assess differences between groups.

Cox's proportional hazards regressions using a stepwise selection procedure were applied to investigate known prognostics factors. Hazard ratios (HR) with 95% CI are presented to display reductions of risk. All *P* values reported are two sided. For all statistical tests, differences were considered as significant at the 5% level. Statistical analysis was performed using the STATA 9.0 software (Stata Corporation, College Station, TX).

## Results

Under cetuximab plus irinotecan–based chemotherapy, 11 patients had PR (16%), 29 had SD (42%), and 29 progressed (42%), whereas no patient showed CR (Table 1). The median PFS was 4.0 months (95% CI, 3.0 to 5.3 months).

**KRAS Mutations**

A KRAS mutation was detected in the tumor of 27 patients (39%) and five patients (7%) were not assessable (Table 1). One of the 27 patients with a KRAS mutation had a response to cetuximab, whereas 10 of the 37 nonmutated patients were responders (4% v 27%; P = .021; Table 2). Patients without KRAS mutation had significantly longer median PFS compared to mutated patients (ie, 5.3 months [95% CI, 4.0 to 8.4 months] v 3.0 months [95% CI, 2.2 to 3.2 months]; P = .021; Fig 1A) and showed a trend to longer overall survival (OS;

Appendix Table A1, online only).

**Table 2.** KRAS Mutations and Outcome of mCRC Patients Treated With Cetuximab Plus Irinotecan

KRAS	Total	Response		
		PR	SD	PD

EXPAND TABLE

Abbreviations: mCRC, metastatic colorectal cancer; PR, partial response; SD, stable disease; PD, progressive disease; CI, confidence interval; HR, hazard ratio.

\* Fisher's exact test.

† Log rank test.

‡ Cox's proportional hazards regression.



**Fig 1.** Progression-free survival for patients with metastatic colorectal cancer (mCRC) according to the presence or absence of (A) *KRAS* mutation and to the (B) FcγR polymorphisms combination.

### FcγR Polymorphisms

The influence of FcγRIIa-H131R polymorphism, FcγRIIIa-V158F polymorphism, and both combined, on the tumor response and PFS after cetuximab therapy is reported in [Table 3](#). OS

data are reported online only in Appendix Table A2. Because the presence of a tumor *KRAS* mutation was significantly associated with resistance to cetuximab and a lower PFS, we analyzed the relationship between FcγR polymorphisms and

PFS in stratified wild-type (wt) and mutated *KRAS* tumor subtypes.

**Table 3.** Outcome of Patients Treated With Cetuximab According to FcγR Polymorphisms and *KRAS* Mutations

Polymorphism	Total No. of Patients	Resp			
		PR		SD	
		No.	%	No.	%
<div style="border: 1px solid black; border-radius: 15px; padding: 5px; display: inline-block;">           ▼ EXPAND TABLE         </div>					

NOTE. — indicates +infinity.

Abbreviations: FcγR, fragment cy receptor; PR, partial response; SD, stable disease; PD, progressive disease; HR, hazard ratio; H, histidine allele; R, arginine allele; F, phenylalanine allele; V, valine allele; wt, wild-type; mut, mutated.

### FcγRIIa-H131R Polymorphism

Overall, 17 patients (28%) were homozygous for FcγRIIa-131H allele, 27 patients (44%) were heterozygous (131H/R), and 17 patients (28%) were homozygous for 131R allele ([Table 1](#)). No statistically significant difference in response to cetuximab or PFS based on the FcγRIIa-H131R polymorphism was observed, whatever the *KRAS* status ([Table 3](#)).

### FcγRIIIa-V158F Polymorphism

Overall, 10 patients (15%) were homozygous for FcγRIIIa-158V allele, 43 patients (63%) were heterozygous (158V/F), and 15 patients (22%) were homozygous for 158F allele ([Table 1](#)). No statistically significant difference in response to cetuximab based on the FcγRIIIa-V158F polymorphism was observed ([Table 3](#)). A statistically significant difference was observed for PFS for 158V/V patients compared to F carriers (6.9 v 3.2

months;  $P = .047$ ). The difference remained significant for patients with mutated *KRAS* (5.5 months for 158V/V patients v 2.8 months for F carriers;  $P = .039$ ). For this subpopulation of patients, response rate tended to be higher for 158V/V patients compared to F carriers (20% of responders v 0%;  $P = .052$ ).

## **Combination of FcγRIIa and FcγRIIIa Polymorphisms**

Overall, 22 patients (32%) were homozygous for 131H and/or 158V allele, 39 patients (56%) carried both F and R alleles and eight patients (12%) were not assessable. No significant difference was observed for tumor response between 131H and/or 158V homozygous patients and other patients whatever

the *KRAS* status ([Table 3](#)). Patients with 131H/H and/or 158V/V genotypes had a significantly longer median PFS than the other patients for the whole population (5.5 v 3.0 months;  $P = .005$ ; [Fig 1B](#)) as well as for the subpopulation of patients with wt-*KRAS* (9.6 v 4.6 months;  $P = .015$ ) and with mutated *KRAS* (3.2 v 2.8 months;  $P = .015$ ). 131 H/H and/or 158V/V polymorphisms also demonstrated significant association with OS for whole group ( $P = .032$ ) and wt-*KRAS* patients ( $P = .027$ ; Table A2).

## **Prognostic Factors for PFS**

A multivariate Cox regression model, adjusted for baseline characteristics showed that only FcγR combined polymorphisms and *KRAS* mutation status were independent risk factors for disease progression ([Table 4](#)). Patients with a *KRAS* mutation ( $P = .001$ ) and patients with FcγRIIa-131R and FcγRIIIa-158F polymorphisms ( $P = .001$ ) showed a higher risk of disease progression. This allowed for the constitution of three groups of patients according to a prognostic index (PI): PI = 0, patients with two favorable prognostic factors (wt-*KRAS* and 131H/H and/or 158V/V polymorphisms; median PFS: 9.6 months; 95% CI, 3.0 to 12.7 months;  $n = 14$ ); PI = 1, patients with only one favorable prognostic factor (wt-*KRAS* and 131R and 158F polymorphisms; mutated *KRAS* and 131H/H

and/or 158V/V polymorphisms; median PFS: 4.6 months; 95% CI, 3.0 to 5.6 months; n = 27), and PI = 2, patients with no favorable prognostic factor (mutated *KRAS* and 131R and 158F polymorphisms; median PFS: 2.8 months; 95% CI, 1.9 to 3.0 months; n = 17; [Fig 2](#)).

**Table 4.** Prognostic Factors for Progression-Free Survival

Parameter	Progression-Free Survival		
	Hazard Ratio	95% CI	P
<i>KRAS</i> status			.001

▼ EXPAND TABLE

NOTE. Variables used in the multivariate model were sex (H v F), age (< 60 v 60+), FcγR combined (F&R v VV/HH), FcγRIIIa polymorphisms (VV v VF/FF), FcγRIIa polymorphisms (HH v HR/RR), anatomic site (colon v rectum) and *KRAS* mutation (wild-type v mutated).

Abbreviations: FcγR, fragment cy receptor; H, histidine allele; V, valine allele; F, phenylalanine allele; R, arginine allele.

**Fig 2.** Progression-free survival curves were plotted according to a prognostic index (PI). PI = 0: patients with two favorable prognostic factors (ie, wild-type [wt]-*KRAS* and FcγRIIa-131H/H and/or FcγRIIIa-158V/V genotypes, n = 14). PI = 1: patients with one favorable prognostic factor (ie, wt-*KRAS* and FcγRIIa-131R and FcγRIIIa-158F genotypes; mutated *KRAS* and FcγRIIa-131H/H and/or FcγRIIIa-158V/V genotypes, n = 27). PI = 2: patients with no favorable prognostic factors (ie, mutated *KRAS* and FcγRIIa-131R and FcγRIIIa-158F genotypes, n = 17).

## Discussion

Since 2004, the marked variability of response to cetuximab has clearly shown the need for translational approach to identify relevant predictive molecular markers. Although *KRAS* mutation has been unambiguously identified as a marker of resistance by several studies,<sup>9-13</sup> the complete mechanism of cetuximab sensitivity remains partially understood. *KRAS* is a G protein that plays a key role in the Ras/mitogen-activated protein kinase (MAPK) signaling pathway, downstream of EGFR and many other growth factor receptors, and is involved in cell proliferation and colorectal carcinogenesis. Numerous studies showed, in mCRC patients treated with cetuximab-based therapy, that *KRAS* mutations were linked to an absence of response and to poor prognosis.<sup>9,10-13,33,34</sup> Our data confirm that the presence of *KRAS* mutation in tumors is highly predictive of a nonresponse to a cetuximab-based therapy. In our series of 69 mCRC patients, *KRAS* mutation was significantly associated with lower response rate and shorter PFS. In addition, 32% of progressive patients displayed a wt-*KRAS* status and one patient with *KRAS* mutation experienced a PR. Such observations have also been reported by others<sup>13,15,16,35</sup> suggesting that *KRAS* mutation is not the only genetic alteration conferring resistance to cetuximab. Somatic

alterations hitting other downstream effectors of the EGFR transduction cascade may have a similar effect.<sup>8</sup>

The strongest evidence supporting ADCC as a clinically meaningful mechanism of certain therapeutic mAb is based on studies evaluating the impact of different allelic variations of FcγRs on clinical response. FcγRIIIa-158V/V, alone or in combination with FcγRIIa-131H/H genotype, was significantly associated with better response rate and PFS in follicular lymphoma and metastatic breast cancer patients treated by rituximab or trastuzumab-based therapy, respectively.<sup>24-26</sup> These results were in part similar in the Zhang et al study carried out on 39 mCRC patients, who failed previous irinotecan- and oxaliplatin-based therapy, treated with single-agent cetuximab. As observed for rituximab and trastuzumab, patients with FcγRIIa-131H genotype had a longer PFS compared to those with homozygous 131R genotype.<sup>30</sup> However, the FcγRIIIa-158V homozygous genotype was surprisingly associated to a shorter PFS compared to FcγRIIIa-158F carriers. It should be noticed that the FcγRIIIa-158V/V genotype was also associated with a lower response rate to rituximab and alemtuzumab in two small series of chronic lymphocytic leukemia, with nevertheless no significant difference between the different genotypes.<sup>36,37</sup>

In our series, FcγRIIa-131H and FcγRIIIa-158V were favorable alleles, as observed in the studies with rituximab and trastuzumab. Our results are in favor of a more effective ADCC antitumor response on cetuximab treatment as it has been clearly demonstrated that human IgG1 binds more strongly to homozygous FcγRIIIa-158V NK cells than to homozygous FcγRIIIa-158F or heterozygous NK cells.<sup>20,22</sup> Explanation of the discrepancy in FcγRIIIa polymorphism observed between Zhang's study and ours remains unclear. The main differences between the two studies involved cetuximab treatment (single-agent in Zhang's study v combination with irinotecan in ours) and a smaller series in Zhang's study with only two responders to cetuximab. The type and level of pretreatment of patients could also be involved since cytotoxic drugs were

known to delete NK cell function to a varying degree.<sup>38</sup> Thus, cetuximab was given as third-line monotherapy in the Zhang study contrarily to our series where 22% of the patients received cetuximab combined to irinotecan as second-line agent. Further in vitro and in vivo studies are necessary to elucidate the exact relationship between FcγRIIIa-V158F polymorphism and cetuximab efficacy. On that point, the role of inhibitory receptor FcγRIIb and the ratio of FcγRIIIa to FcγRIIb as potent regulators of ADCC and predictors of IgG1 in vivo activity should be further investigated.<sup>39,40</sup>

In our study, FcγR polymorphisms did not show a significant association with response to cetuximab but response rate tended to be better for FcγRIIIa-131H/H and FcγRIIIa-158V/V genotypes. The significant effect on PFS was noted for patients with FcγRIIIA-158V/V genotype compared to F carriers and for patients with FcγR-131H/H and/or 158V/V favorable alleles whatever the *KRAS* status. The limitation of our study is the absence of control arm that does not allow to definitely conclude that FcγR polymorphisms are linked to cetuximab efficacy. However, in vitro and in vivo data did not evidence any clinical impact of these polymorphisms in patients who did not receive IgG1 therapy, strongly suggesting their predictive value.<sup>25,41-42</sup> The relevance of FcγR polymorphisms after IgG2 antibody treatment, such as panitumumab, would also been interesting to assess, since IgG2 is assumed to trigger less effective in vitro ADCC than IgG1.<sup>43</sup>

The combined analysis of *KRAS* mutation status and FcγR polymorphisms showed that median PFS increased with the number of favorable prognostic factors (ie, wt-*KRAS* and FcγRIIIa-131H/H and/or FcγRIIIa-158V/V genotypes): patients with two favorable prognostic factors had a longer PFS than patients with only one (intermediate PFS) or no favorable factor (shortest PFS).

The role of ADCC in metastatic cancer patients who mostly have suppressed immune function remains a debated question.<sup>23</sup> Early-stage CRC patients treated with cetuximab in an adjuvant setting may be more suitable study candidates.

Two studies support the in vivo role for immune responses in the mechanism of action of trastuzumab in breast cancer or rituximab in follicular lymphoma at an early stage of the disease.<sup>42,44</sup> These studies evidenced the immune cells recruitment within tumors after antibody-based therapy. Thus, in situ analysis of immune cell response in the neoadjuvant setting could help to demonstrate the role of ADCC in cetuximab efficacy.

In conclusion, our study confirms that *KRAS* mutation in tumors is highly predictive of nonresponse to a cetuximab-based therapy. Combined FcγRIIa and FcγRIIIa polymorphisms (131H/H and/or 158V/V genotypes) are prognostic factors for PFS in mCRC patients treated with cetuximab plus irinotecan. As these polymorphisms are also clinically relevant in mutated *KRAS* mCRC in which EGFR pathway is constitutively activated, an important role of ADCC in cetuximab efficacy can be presumed. Given the retrospective design of this study, ancillary studies to larger prospective clinical trials are needed to assess the impact of FcγR polymorphisms on cetuximab efficiency.

---

## **Authors' Disclosures of Potential Conflicts of Interest**

*Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*

**Employment or Leadership Position:** None **Consultant or Advisory Role:** Marc Ychou, Merck Lipha Santé (C) **Stock Ownership:** None **Honoraria:** Frédéric Bibeau, Merck Lipha Santé, Amgen Inc; Frédéric Di Fiore, Merck Lipha Santé, Amgen Inc; Marc Ychou, Merck Lipha Santé, Pfizer Inc, Amgen Inc; Frédérique Penault-Llorca, Merck Lipha Santé; Jean-Christophe Sabourin, Merck Lipha Santé **Research Funding:**

Christophe Sabbatini, Merck Lipha Santé Research Funding.  
Frédérique Penault-Llorca, Merck Lipha Santé **Expert**  
**Testimony:** None **Other Remuneration:** Frédérique Penault-Llorca, Merck Lipha Santé

## References

1. D Cunningham, Y Humblet, S Siena, etal: Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 351: 337–345,2004

[← Go to Citation](#) | [View](#) | [PubMed](#) | [Google Scholar](#)

2. L Saltz, NJ Meropol, PJ Loehrer, etal: Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. *J Clin Oncol* 22: 1201–1208,2004

[← Go to Citation](#) | [View](#) | [PubMed](#) | [Google Scholar](#)

3. E Van Cutsem, M Nowacki, I Lang, etal: Randomized phase III study of irinotecan and 5-FU/FA with or without cetuximab in the first line treatment of patients with metastatic colorectal cancer: The CRYSTAL trial. *J Clin Oncol* 25: 164s,2007 suppl abstr 4000

[← Go to Citation](#) | [View](#) | [Google Scholar](#)

[SHOW ALL REFERENCES](#)

## Appendix

The Appendix is included in the full-text version of this article, available online at [www.jco.org](http://www.jco.org). It is not included in the PDF version (via Adobe® Reader®).

Table A1. KRAS Mutations and Overall Survival of mCRC Patients

**Table A1. KRAS Mutations and Overall Survival of mCRC Patients**

Treated With Cetuximab Plus Irinotecan

KRAS Status	No.	Overall Survival			
		Median		Cox Regression	
		Months	95% CI	HR	95% CI
Wild type	37	10.8	7.5 to —	1	Reference
Mutated	27	8.7	4.9 to 15.9	1.6	0.8 to 2.9
<i>P</i>		.147*		.151†	

NOTE. — indicates +infinity.

Abbreviations: mCRC, metastatic colorectal cancer; No., total number of patients; HR, hazard ratio.

\* Log-rank test.

† Cox's proportional hazards regression.

**Table A2. Overall Survival of Patients Treated With Cetuximab According to FcγR Polymorphisms and KRAS Mutations**

Polymorphism	No.	Overall Survival		
		Median		Log-Rank Test <i>P</i>
		Duration (months)	95% CI	

EXPAND TABLE

NOTE. — indicates +infinity.

Abbreviations: FcγR, fragment cy receptor; No., total number of patients; PR, partial response; SD, stable disease; PD, progressive disease; HR, hazard ratio; H, histidine allele; R, arginine allele; F, phenylalanine allele; V, valine allele; wt, wild-type; mut, mutated; NR; median not reached.

[View full text](#) | [Download PDF](#)

**JOURNALS**

Journal of Clinical  
Oncology  
JCO Oncology Practice  
JCO Global Oncology  
JCO Clinical Cancer  
Informatics  
JCO Precision  
Oncology  
JCO Oncology  
Advances

**ASCO**

About ASCO  
Press Center  
Meetings & Education  
Contact Us

**PUBLICATIONS**

ASCO Educational Book  
ASCO Daily News  
ASCO Connection  
The ASCO Post  
ASCO Podcasts

**ASCO WEBSITES**

asco.org  
ASCO Career Center  
Conquer Cancer

**CONTENT**

Journal Podcasts  
Topics  
Meeting Abstracts  
ASCO Guidelines

**INFORMATION**

Author Center  
Subscriber Center  
Permissions  
Reprints  
Advertise  
E-Alerts  
View My Profile  
About ASCO Journals

**FOLLOW US**

JCO\_ASCO  
JCOOP\_ASCO  
JCOGO\_ASCO  
JCOPO\_ASCO  
JCOCC\_ASCO  
JCOOA\_ASCO