Radiological tumor size decrease at week 6 is a potent predictor of outcome in chemorefractory metastatic colorectal cancer treated with cetuximab (BOND trial)

H. Piessevaux1, M. Buyse2, W. De Roock3, H. Prenen3, M. Schlichting4, E. Van Cutsem3 & S. Tejpar3*

1Service de Gastro-entérologie, Cliniques universitaires Saint-Luc, Université catholique de Louvain, Brussels; 2International Drug Development Institute, Louvain-la-Neuve, Belgium and Center for Statistics, Universiteit Hasselt, Diepenbeek; 3Digestive Oncology Unit, University Hospital Gasthuisberg, Leuven, Belgium and 4Merck KGaA, Darmstadt, Germany

Received 20 October 2008; revised 25 December 2008; accepted 8 January 2009

Background: Early radiological tumor shrinkage may be associated with better long-term outcome in chemorefractory metastatic colorectal cancer (cmCRC) treated with cetuximab. We aimed at validating this in a large and independent series.

Patients and methods: Of the 329 patients, 289 had a measurement both at baseline and week 6. Tumor shrinkage was expressed as a relative decrease compared with baseline and categorized according to a previously reported cut-off value (10%) or used as a continuous variable.

Results: Median time to progression (TTP) was 6.1 [95% confidence interval (CI) 5.1–7.2] versus 1.5 months (95% CI 1.4–1.7) in patients with [99 patients (34.3%)] or without [190 patients (65.7%)] tumor shrinkage, respectively, at week 6 [hazard ratio (HR) 0.23 (95% CI 0.17–0.32)]. The median overall survival (OS) was 13.7 (CI NA) versus 6.9 months (95% CI 6.1–7.7) [HR 0.21 (95% CI 0.14–0.32)], respectively. In a multivariate model, early tumor decrease outperformed skin toxicity as a predictor of long-term outcome.

Conclusions: Tumor shrinkage at 6 weeks is a strong predictor of TTP and OS in cmCRC patients treated with cetuximab with or without irinotecan. This suggests early tumor shrinkage is the hallmark of efficacy of cetuximab and reliably identifies the subpopulation that is sensitive to the drug. Early tumor shrinkage can be used as a marker of efficacy in clinical practice, as such or in combination.

Key words: cetuximab, metastatic colorectal cancer, tumor measurements

introduction

Some novel targeted cancer therapies are particularly effective in a subpopulation of patients. Clinicians are therefore in need of predictors of therapeutic benefit at the patient level. It is now clearly established that patients having a KRAS mutant colorectal tumor will not respond or have long-term benefit when treated with anti-epidermal growth factor receptor (EGFR) mAbs such as cetuximab [1–4] and panitumumab [5]. Importantly, while ~60% of the tumors are KRAS wild type (WT), only ~4% of chemorefractory KRAS WT patients will respond to an anti-EGFR antibody. Some additional molecular predictors of response within the KRAS WT group, such as the expression of the EGFR ligands, epiregulin and amphiregulin, are under assessment [6].

In the absence of pretreatment predictors of response, early on-treatment changes may help identify those patients in whom continuation of therapy is worthwhile. Cetuximab-related skin toxicity is an example of such a parameter. Patients developing skin toxicity are more likely to benefit from the treatment [7]. Unfortunately, the time of appearance of the skin manifestations is too variable to be used for early therapy discontinuation and there is a lack of uniform grading. Recent correlations between biomarkers and radiological data have shown that KRAS WT tumors clearly differ from KRAS mutant in terms of tumor size changes [1, 5]. Specifically, we showed that a decrease in tumor size of ~10% at 6 weeks was associated with clinical benefit in chemorefractory metastatic colorectal cancer (cmCRC), was associated with the KRAS WT status and could differentiate patients with favorable outcome within the KRAS WT group [1].

From these data, we hypothesize that tumor decrease at week 6 is a marker of sensitivity to cetuximab and could be used to predict long-term benefit of this drug.

The aim of this study was to (i) validate the value of early tumor shrinkage in predicting time to progression (TTP) and overall survival (OS) in a large and independent series and (ii)
patients and methods

BOND trial

The patients’ characteristics, treatment regimens and results of the BOND trial have been reported previously [8]. In this open-label, randomized trial, 329 patients with metastatic colorectal cancer, whose disease had progressed during or within 3 months after treatment with an irinotecan-based regimen, were randomized to receive either cetuximab and irinotecan (218 patients) or cetuximab monotherapy (111 patients). Tumor response was evaluated every 6 weeks for the first 24 weeks and thereafter every 3 months with the use of computed tomography (CT) or magnetic resonance imaging. Tumor response assessment was carried out by the investigators (INV) who used the unidimensional RECIST and by an independent review committee (IRC) who used the bidimensional modified World Health Organization (WHO) criteria. As reported in the original paper, the objective response (OR) and TTP were calculated from the IRC data [8].

statistical analysis

Data were extracted from the anonymized BOND trial database (Merck, Darmstadt, Germany). Both the successive measurements of the target lesions by the INV and the IRC were available to us. Changes in tumor size were expressed as a relative change of the sum of the longest diameter of the target lesions. Using a cut-off point of 10% decrease at week 6, the patients were dichotomized for the presence or absence of early tumor shrinkage. The correlation between early tumor shrinkage and OR [complete remission (CR) or partial remission (PR)] or disease stabilization [CR or PR and stable disease (SD)] (as evaluated by the IRC, following the WHO criteria, or the INV using the RECIST criteria) was assessed using a χ² test. In objective responders, the time to achieve response was calculated. The best radiological tumor response was calculated as the relative change at the nadir size over the whole trial duration. The bivariate correlation between early and best tumor shrinkage was evaluated using Spearman’s correlation. Wasserfall plots were constructed for tumor size change at week 6 and for best tumor change. Kaplan–Meier plots were constructed for TTP and OS according to the early tumor shrinkage. The correlation between early tumor shrinkage and OR was assessed by intraclass correlation coefficient (ICC). The agreement between continuous measurements was assessed by intraclass correlation coefficient (ICC). The agreement between early tumor shrinkage status, as evaluated by the IRC or the INV, was measured using a k statistic. The k statistic was also used to quantify the level of agreement of the early tumor shrinkage status determined with a maximum of 10 target lesions to the status determined with a lower number of target lesions. The results presented hereafter pertain to the measurements carried out on a maximum of 10 target lesions, unless indicated otherwise.

results

Of the 329 intent-to-treat patients, 289 had a measurement made by the INV both at baseline and at week 6 (192 cetuximab + irinotecan and 97 cetuximab) and 284 had both measurements from the IRC available (188 cetuximab + irinotecan and 96 cetuximab). Of the 45 patients without both measurements available for IRC, one had progressive disease (PD) early on, 17 died before week 6 and 33 were protocol violators.

relationship between tumor shrinkage at week 6 and outcome

univariate analysis. Early tumor shrinkage and OR correlated very well (χ²: P < 0.005). Whereas early radiological tumor shrinkage is assessed at 6 weeks, 34 of 62 (55%) patients who achieved an OR did so after 6 weeks (range 1.0–5.5 months). Additional tumor shrinkage beyond week 6 was present in 109 (37.7%; INV) and 107 (37.7%; IRC) patients. Correlation of early tumor shrinkage with disease control (OR and SD) was also excellent (χ²: P < 0.005). There was an excellent correlation between early and best tumor size decrease obtained on therapy [Spearman’s ρ 0.96 (INV) and 0.93 (IRC); both P < 0.005]. The magnitude of tumor size changes at week 6 and at the time of best response for each individual is depicted in waterfall plots (Figure 1).

According to Kaplan–Meier analysis, there was a significantly longer TTP in patients with early tumor shrinkage [INV measures: HR 0.23 [95% confidence interval (CI) 0.17–0.32], log-rank test P < 0.001; IRC measures: HR 0.28 (95% CI 0.21–0.39), log-rank test P < 0.001] (Figure 2). Similarly, the OS was significantly longer in patients with early tumor shrinkage [INV measures: HR 0.21 (95% CI 0.14–0.32), log-rank test P < 0.001; IRC measures: HR 0.30 (95% CI 0.20–0.43), log-rank test P < 0.001] (Figure 2). These differences in OS and TTP were equally present in patients treated with cetuximab + irinotecan or with cetuximab alone (Table 1).

twivariate analysis. A Cox regression model, including the following additional prognostic variables: age, sex, Karnofsky performance status, treatment arm, maximum grade of skin toxicity and number of prior treatment regimens, revealed early tumor shrinkage to be the main predictor of TTP and OS (Table 2). Additional significant variables retained in the model were number of prior treatment regimens, grade of skin toxicity and treatment arm. We found no interaction between any of these predictor variables. Interestingly, our findings show that the well-known predictor skin toxicity and early tumor shrinkage provide additional and independent information.

performance parameters in clinical practice

predictive accuracy. To evaluate the predictive value of early tumor size measurement on relevant outcomes in current clinical practice, we studied only patients treated in the combination arm (cetuximab + irinotecan) and used only the original investigator’s radiological assessments. TTP but not OS was used because of numerous censored OS data in the database.

The predictive performances [positive and negative predictive values (PPV and NPV)] of dichotomized early tumor shrinkage for different outcomes are presented in Table 3. As shown, very good predictive parameters were obtained.
strength of the relationship between tumor decrease at week 6 and outcome. To use the full informative value of early tumor shrinkage, in the following sections we have expressed tumor shrinkage at week 6 as a continuous (nondichotomized) variable.

To evaluate the discriminatory power of early tumor decrease to predict outcome, we constructed a ROC curve with TTP >4 months (median TTP in cetuximab + irinotecan) as the dependent variable. We found an area under the ROC curve of 0.87, suggesting strong discriminatory power of this variable (Figure 3). The ROC analysis also allows the choice of different cut-off values such as an optimized NPV usually preferred in clinical practice.

Figure 1. (A) Magnitude of the changes in tumor size at week 6 as assessed by the INV. This waterfall plot represents the ranked changes in tumor size at first radiological evaluation (range −93 to +193%). It indicates that tumor shrinkage may be a very early event. (B) Waterfall plot representing the ranked best tumor shrinkage with color coding according to presence/absence of tumor shrinkage at week 6 (cut-off 10%) [as assessed by the investigator (INV)].
A predictive model based on the tumor size change at week 6 as a continuous variable and other predictive factors. A Cox regression model was built including measurement of early tumor shrinkage as a continuous variable and other potential predictor variables identified in the BOND trial (age, sex, performance status, number of prior chemotherapy regimens).

Figure 2. Kaplan–Meier plot representing the proportion of patients free of progression (panel A) or surviving (panel B) over time according to the presence or absence of early tumor shrinkage, as measured by the investigator. Number of subjects at risk:

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early tumor shrinkage time to progression</td>
<td>99</td>
<td>87</td>
<td>74</td>
<td>26</td>
<td>17</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>No early tumor shrinkage time to progression</td>
<td>190</td>
<td>64</td>
<td>38</td>
<td>8</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early tumor shrinkage overall survival</td>
<td>99</td>
<td>99</td>
<td>94</td>
<td>85</td>
<td>82</td>
<td>50</td>
<td>26</td>
</tr>
<tr>
<td>No early tumor shrinkage overall survival</td>
<td>190</td>
<td>181</td>
<td>138</td>
<td>112</td>
<td>78</td>
<td>26</td>
<td>10</td>
</tr>
</tbody>
</table>
and skin toxicity (up to week 6). This model identified three significant covariates: number of prior regimens, grade of skin toxicity at or before week 6 and early tumor decrease, all of which are measurable at 6 weeks. To evaluate the combined impact of these covariates for a given patient, we defined a predictive index (PI) based on the Cox regression coefficients:

\[ PI = 0.33 \text{[number of prior regimens]} - 0.20 \text{[grade of skin toxicity at week 6]} + 0.017 \text{[relative change in the sum of the longest diameters (\%)]}. \]

With this PI calculated for a patient, the clinician can estimate the probability to remain free of progression at different time points, using the normogram provided in Figure 4. The calculated PI is reported on the x-axis. The y-value at the cut point with the plotline of the time point of interest will reveal the probability of remaining free of progression at that time point. This method easily allows representation of the impact of the three parameters that are available at 6 weeks on the probability of remaining free of progression at determined time points.

**discussion**

The search for markers predicting efficacy in mCRC treated with cetuximab is still ongoing. Tumoral KRAS mutant status was shown to be a strong negative predictor of response to anti-EGFR antibodies [2]. Therefore, it has rapidly become standard of care to reserve these treatments for KRAS WT patients. Unfortunately, in the KRAS WT subpopulation, there still is only a 40% chance of responding, indicating that the KRAS WT status alone is a necessary but not a sufficient condition for response.

As an alternative to pretreatment predictive markers determined on the primary tumor, characteristics of the metastatic lesions during therapy can be used as predictors of outcome. With antiangiogenic drugs, for example, it has been suggested that changes in blood flow on treatment may be predictive of outcome [9, 10]. If changes on therapy are linked to the mode of action of the drug, theoretically they may be used to identify drug responders.

**Table 1.** Median TTP and OS estimates according to the Kaplan–Meier method in patients presenting without or with early tumor shrinkage

<table>
<thead>
<tr>
<th></th>
<th>Radiological decrease at week 6 (INV)</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10%</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>Cetuximab + irinotecan</td>
<td>TTP (months) median (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.6 (1.3–1.9)</td>
<td>7.0 (5.1–8.9)</td>
</tr>
<tr>
<td></td>
<td>OS (months) median (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.3 (5.5–8.1)</td>
<td>13.4 (11.7–15.1)</td>
</tr>
<tr>
<td>Cetuximab alone</td>
<td>TTP (months) median (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.5 (1.4–1.6)</td>
<td>4.1 (2.3–6.0)</td>
</tr>
</tbody>
</table>

**Table 2.** Result of a Cox regression model on TTP and OS in 289 patients with 217 (TTP) and 182 (OS) events

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Significance</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of prior regimens</td>
<td>0.007</td>
<td>0.74</td>
<td>0.59–0.92</td>
</tr>
<tr>
<td>Early tumor shrinkage</td>
<td>&lt;0.001</td>
<td>0.22</td>
<td>0.16–0.31</td>
</tr>
<tr>
<td>Worst grade of skin toxicity</td>
<td>&lt;0.001</td>
<td>0.66</td>
<td>0.55–0.79</td>
</tr>
<tr>
<td>Treatment arm</td>
<td>&lt;0.001</td>
<td>0.50</td>
<td>0.36–0.68</td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance status</td>
<td>&lt;0.001</td>
<td>0.42</td>
<td>0.27–0.67</td>
</tr>
<tr>
<td>Early tumor shrinkage</td>
<td>&lt;0.001</td>
<td>0.21</td>
<td>0.14–0.32</td>
</tr>
<tr>
<td>Worst grade of skin toxicity</td>
<td>&lt;0.001</td>
<td>0.66</td>
<td>0.54–0.79</td>
</tr>
</tbody>
</table>

Covariates were presence of early tumor shrinkage, age, sex, performance status, treatment arm, maximum grade of skin toxicity and number of prior treatment regimens. The hazard ratios must be interpreted per change in unit of the covariate, i.e. for number of prior treatment regimens: per increase in one regimen; for early tumor shrinkage: absence versus presence; for maximum grade of skin toxicity: per increase in one grade of toxicity; for treatment arm: cetuximab + irinotecan arm versus cetuximab alone arm. TTP, time to progression; OS, overall survival.
In a previous study, we identified a cut-off value of decrease in tumor size of \( \geq 10\% \) at 6 weeks to optimally predict prolonged survival [1]. The present study was undertaken to validate the predictive power of early tumor shrinkage in an independent, large and well-documented cohort. First, we confirmed that early tumor shrinkage is a strong predictor of outcome in cmCRC treated with cetuximab with adjusted HRs of 0.23 for TTP and 0.21 for OS. Secondly, we show that this relationship is also strongly present when early changes of tumor size are expressed as a continuous variable, thereby alleviating the constraints of a predetermined cut-off point to predict outcome. Thirdly, we found that the tumor measurements were reliable and accurate. The agreement between the INV and IRC shrinkage measurements was excellent (\( \kappa = 0.67 \)). Discordances occurred in either direction, suggesting there was no systematic bias in the INV measurements. All HRs for long-term outcome, build on INV or IRC measurements, were of the same magnitude. We found that the use of five lesions, instead of all 10 measured by the IRC, was sufficient to accurately classify the patient. These findings are consistent with the idea that central review is unnecessary and that the number of lesions to be measured can be substantially decreased from the current 10 (RECIST) [11].

We have confronted our parameter with other known on-treatment and baseline predictive markers available in the BOND study. Occurrence of skin toxicity on therapy is a known strong outcome predictor [1, 3, 12]. We constructed a predictive model combining a baseline and on-treatment markers (number of previous lines of chemotherapy, early skin toxicity and early tumor shrinkage). Our findings not only show that early tumor shrinkage is relatively more powerful in predicting outcome than skin toxicity but also show that these markers provide independent predictive information with regard to long-term outcome. The combined model now explains a large proportion of the variability of cetuximab efficacy seen in daily clinical practice.

Grothey et al. [13] have recently shown that tumor response was not predictive of OS benefits for the frequently used fluoropyrimidine/oxaliplatin and bevacuzimab-containing regimens. On the other hand, Karrison et al. [14] initiated the concept that small changes early on therapy with novel biologicals (Raf inhibitor sorafenib and EGFR inhibitor erlotinib) may be used as outcome variable. However, to be valid as a predictor, an early tumor size change that is not in itself of benefit to the patient has to be conclusively shown to be linked to a long-term outcome. Our work confirms that this is indeed the case for cetuximab. This suggests that rapid and important decrease in tumor load is a hallmark of activity of cetuximab and this may be in sharp contrast to other agents.

We show that tumor shrinkage at week 6 is a very potent independent predictor of both TTP and OS in cmCRC treated with cetuximab. To validate early tumor shrinkage as a surrogate for OS, several conditions need to be met [15]: (i) the candidate surrogate end point needs to predict the ultimate outcome (OS). In our study, this is the case. (ii) There needs to be a correlation between the potential surrogate and OS. Unfortunately, the BOND trial was underpowered to demonstrate an OS benefit. Moreover, interpretation would be hazardous because of the crossover design after failure of cetuximab monotherapy. For all these reasons, while being an excellent candidate, early tumor shrinkage will need prospective randomized trials to be validated as a surrogate end point.

In our previous study in cmCRC treated with cetuximab in clinical trials, we combined the KRAS status and radiological data [1]. We found tumor shrinkage of \( \geq 10\% \) at 6 weeks to...
optimally predict prolonged survival, even in KRAS WT patients. This is not entirely unexpected as tumor dynamics are strongly linked to the molecular state of the tumor. In our previous study, 5 of 39 of the KRAS mutants had a decrease more than $\sim$10% at week 6 but only two of these had a progression-free survival >12 weeks [1]. In the KRAS WT group, however, 35 of 62 had a decrease more than $\sim$10% and had long-term benefit (HR: 0.23 for OS). Similarly, in the panitumumab trial, only 1 of 62 KRAS mutant patients had a decrease of tumor size $>10\%$ [5]. In the current BOND dataset, no tumor material was collected for KRAS genotyping; however, our previous findings may apply here as they were obtained from patients treated in an identical setting.

We believe our findings have several implications. If small and early tumor size changes are to be used as predictors of long-term outcome, their predictive power needs to be demonstrated conclusively for every drug in every clinical situation [16]. Our data clearly establish the relationship between early tumor shrinkage and outcome for cetuximab-treated cmCRC. As suggested by Karrison et al. [14], these findings can facilitate trial designs as end points measured as early as at 6 weeks can be used to assess efficacy and adapt further treatments accordingly. New combinations of cetuximab with inhibitors of ERK or drugs enhancing the efficacy in KRAS WT patients need to be explored. Our findings provide the tools for adaptive trial designs, where patients could be started on cetuximab and depending on their tumor shrinkage at week 6 be continued on cetuximab or randomized to novel combinations. To be able to predict outcome earlier than 6 weeks we believe, morphological evaluations only will not be sensitive enough and will need to be combined with metabolic information such as available in positron emission tomography–CT or with tumor markers.

In the cmCRC setting, treating according to KRAS status will soon be mandatory for all EGFR inhibitors. In the meantime or if KRAS genotyping is not accessible, early tumor shrinkage can already be used as a reliable tool to predict outcome. Based on our previous work, we propose that early tumor shrinkage may provide additional information within the KRAS WT group; however, this needs to be validated in the recent trials where KRAS status is available. Future studies will also need to assess the impact of early tumor shrinkage on outcome when chemotherapy is added to the regimen in a chemonaive setting.

In conclusion, tumor shrinkage at week 6 is a novel, reliable and easily accessible tool to predict efficacy of cetuximab for cmCRC. The prognostic impact of early tumor shrinkage is probably far more important than with treatment regimens without cetuximab. We believe this finding will be applicable to other clinical settings and may help identify the distinct subgroup of tumors responding to cetuximab.

**funding**

WDR is supported by the institute for the Promotion of Innovation by Science and Technology in Flanders (IWT).

**acknowledgements**

ST and EVC are senior clinical investigators of the Fund for Scientific Research, Flanders (Belgium)(FWO). This study was presented in part at the 2008 American Society of Clinical Oncology annual meeting.

**references**


[Figure 4. Estimated probability of remaining free of progression at 2, 4, 6, 8 and 10 months, as a function of the predictive index in patients treated with cetuximab + irinotecan. The predictive index (PI) of an individual patient is calculated as follows: $\text{PI} = -0.33 \times \text{number of prior regimens} - 0.20 \times \text{maximum grade of skin toxicity at or before week 6} + 0.017 \times \text{relative change in the sum of the longest diameters (\%)}.\]