Safety and efficacy of the addition of simvastatin to panitumumab in previously treated *KRAS* mutant metastatic colorectal cancer patients

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Panitumumab has proven efficacy in patients with metastatic or locally advanced colorectal cancer patients, provided that they have no activating *KRAS* mutation in their tumour. Simvastatin blocks the mevalonate pathway and thereby interferes with the post-translational modification of KRAS. We hypothesize that the activity of the RAS-induced pathway in patients with a *KRAS* mutation might be inhibited by simvastatin. This would theoretically result in increased sensitivity to panitumumab, potentially comparable with tumours with wild-type *KRAS*. A Simon two-stage design single-arm, phase II study was designed to test the safety and efficacy of the addition of simvastatin to panitumumab in colorectal cancer patients with a *KRAS* mutation after failing fluoropyrimidine-based, oxaliplatin-based and irinotecan-based therapy. The primary endpoint of this study was the proportion of patients alive and free from progression 11 weeks after the first administration of panitumumab, aiming for at least 40%, which is comparable with, although slightly lower than, that in KRAS wild-type patients in this setting. If this 40% was reached, then the study would continue into the second step up to 46 patients. Explorative correlative analysis for mutations in the KRAS and related pathways was carried out. One of 14 patients was free from progression at the primary endpoint time. The median progression-free survival was 8.4 weeks and the median overall survival status was 19.6 weeks. We conclude that the concept of mutant *KRAS* phenotype expression modulation with simvastatin was not applicable in the clinic. *Anti-Cancer Drugs* 26:872–877

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Introduction

The epidermal growth factor receptor (EGFR) inhibitors panitumumab and cetuximab have proven efficacy in the third-line treatment of colorectal cancer (CRC) patients failing 5-FU-based, oxaliplatin-based and irinotecan-based regimens [1,2], but only in patients with tumours not harbouring an activating *KRAS* mutation in codon 12, 13 or 61 [3–5] or, more recently published, several other *RAS* mutations [6]. At the time of design of this study, the available literature showed that *KRAS* mutations are found in tumour tissue of 40% of CRC patients, at least 90% located on codon 12 or 13 of the *KRAS* gene [4]. Patients harbouring these mutations in their tumour were left with little therapeutic options after failing standard therapy. This raised the question of whether *KRAS* mutations can be modulated, thereby making *KRAS* mutated tumours sensitive to EGFR inhibitor therapy. The possible target for the simvastatin modulation is the mevalonate pathway, as we have discussed previously [7].

Statins (HMG-CoA-reductase inhibitors) inhibit cholesterol synthesis by inhibiting the mevalonate pathway, a metabolic cascade also responsible for syntheses of farnesylated and geranylgeranylated proteins (C15 and C17), both essential for post-translation activation of the KRAS protein [8]. As statins also inhibit the synthesis of C15 and C17, they may inhibit post-translational activation of RAS proteins. Therefore, statins may inhibit the expression of the mutant *KRAS* phenotype and normalize the phenotype into *KRAS* wild-type, rendering sensitivity to panitumumab.

This single-arm, multicentre phase II study was designed to test the safety and efficacy of the addition of simvastatin to panitumumab in previously treated CRC patients with a *KRAS* mutation in their tumour.

Methods

Patients

Eligible patients had advanced or metastatic CRC with a mutation in codon 12, 13 or 61 of the *KRAS* gene (either on tissue of the primary tumour or of a metastasis), after failure of fluoropyrimidine-based, oxaliplatin-based and irinotecan-based regimens, or after failure of oxaliplatin

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therapy and unable to tolerate irinotecan. In patients with progressive disease within 6 months after the start of adjuvant therapy, these therapies were considered to be treatment for metastatic disease.

Other eligibility criteria included the following: age 18 years or older, WHO performance score of 0–2 and progression of disease in the 3 months before inclusion. Exclusion criteria were symptomatic brain metastases, previous treatment with EGFR inhibitors, history of toxicity during statin use or another malignancy during the past 4 years (with the exception of nonmelanoma skin cancer and adequately treated preinvasive carcinoma of the cervix).

The study protocol was approved by the ethics committees of all participating hospitals and all study procedures were in accordance with the 1964 Helsinki declaration and its later amendments. Written informed consent from the patient was obtained before any study-related interventions.

Treatment schedule

Panitumumab 6 mg/kg was administered intravenously once every 2 weeks. The first administration was scheduled at least 1 week after starting simvastatin. Simvastatin 80 mg once daily was started at baseline and continued throughout the entire study, although dose reductions or temporary interruptions were allowed in case of toxicity. This starting dose of simvastatin was chosen for the following reasons: inhibitory effect on the mevalonate pathway (and not high-dose antitumour effect by itself), tolerability and the need for continuous administration of the statin during the entire study. Statins in cancer therapy have been studied in clinical trials in solid [9–19] and haematologic [20–22] malignancies, both as monotherapy as well as additional to standard therapy. Statin doses from 20 up to 35 mg/kg-/day were used in various intermittent schedules. In continuous dosing schedules, simvastatin was used at a maximum of 80 mg/day. The aim of this study was to modulate KRAS during the entire treatment with panitumumab; therefore, a continuous exposure to simvastatin was needed and a dose of 80 mg/day was selected to achieve the maximum effect while minimizing the risk of toxicity. Patients who were already using statins before inclusion had to switch to simvastatin. Treatment was continued until progression of disease according to Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1, clinical signs of progression according to the investigators' assessment, unacceptable toxicity, signs of rhabdomyolysis or panitumumab toxicity requiring interruption of treatment.

Tumour response was measured 7 weeks after baseline and every two cycles thereafter using computed tomography scans and according to RECIST, version 1.1. These intervals were based on historical data on progression-free survival (PFS) of *KRAS* wild-type CRC patients treated with panitumumab [3]. Scans of patients free from progression at the time of the primary endpoint were centrally reviewed. All patients were followed for survival once every 3 months after termination of study participation. Adverse events were monitored on an ongoing basis per cycle and toxic effects were categorized using the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

Endpoints

The primary endpoint was the proportion of patients alive and free from progression at 11 weeks after the first administration of panitumumab in combination with simvastatin. Our hypothesis was that at least 40% of patients would be free from progression at 11 weeks, comparable with although slightly lower than the proportion of *KRAS* wild-type patients who remains free from progression at 11 weeks when treated with panitumumab [3].

The secondary endpoints were overall survival, objective response rate, PFS and safety of simvastatin combined with panitumumab in this population and to evaluate the correlation between skin toxicity and response to treatment. Exploratory endpoints were to investigate the role of cholesterol as a possible biomarker during this treatment and whether *PIK3CA* status correlates with response to panitumumab in this population.

Mutational analysis

KRAS mutational status was reconfirmed centrally, testing for the seven most frequent mutations in codon 12 and 13 as described in detail elsewhere [23]. In addition, we tested for the three most common mutation in the *PIK3CA* gene: in exon 9 [c.1624G > A (p.E542K) and c.1633G > A (pE545K)] and exon 20 [c.3140A > G (p.H1047R)]. Although *KRAS* and *BRAF* mutations are known to be mutually exclusive [24], all tissue was tested for the activating hotspot mutation p.V600E.

Design and statistics

This phase II, single-arm, multicentre study was carried out using a Simon two-stage design [25]. In the first stage, 15 patients were included, after which an interim analysis was carried out. Results of this analysis would determine whether the combination of simvastatin and panitumumab may have clinical benefit in this group of CRC patients, thus justifying the second stage up to 46 patients in total.

The sample size was chosen on the basis of previously published data of CRC patients with *KRAS* wild-type tumours treated with panitumumab [3], aiming for at least six out of 15 patients free from progression at 11 weeks after the start of combination panitumumab and simvastatin treatment in patients with *KRAS* mutant-type tumours. Combined with an α of 0.05 and a power of

0.80, an interim size of 15 and a total sample size of 46 patients were required. An interim analysis was to be carried out after the inclusion of 15 evaluable patients. Only when at least 40% (i.e. six patients) were free from progression at the 11 weeks, another 31 patients would be enrolled during the second stage of the study.

Results

Patients

From April 2010 to May 2012, 17 patients were included. Notably, 17 instead of 15 patients were included because two patients were considered to be unevaluable (both showed clinical signs of progression before the first infusion of panitumumab). However, after review, three instead of two patients were unevaluable (Fig. 1). The third unevaluable patient had a second malignancy that was first discovered at the baseline computed tomography scan. As none of the three unevaluable patients received panitumumab, all three were excluded in the efficacy and safety analysis. Baseline characteristics of the remaining 14 patients are listed in Table 1. One patient only received oxaliplatin/5-FU-based chemotherapy before study participation. None were receiving any kind of statin before study participation. Table 2 shows the type of *KRAS* mutation per patient, along with *PIK3CA* mutational status. Tumour tissue was available in all except one patient. Two patients had a *PIK3CA* mutation on tumour tissue, one located in exon 20 and one in exon 9. Eleven patients had a *KRAS* codon 12 mutant tumour and two patients had a *KRAS* codon 13 mutant tumour.

Table 1 Baseline characteristics

Age (years)	
Mean	59
Range	33–77
Sex [*n* (%)]	
Male	5 (36)
Female	9 (64)
WHO performance score [*n* (%)]	
0	7 (50)
I	5 (36)
II	2 (14)
Site of primary tumour [*n* (%)]	
Colon	8 (57)
Rectum	6 (43)
Prior lines of chemotherapy [*n* (%)]	
1	1 (7)
2	8 (57)
3	2 (14)
Not reported	3 (22)
Prior surgery [*n* (%)]	9 (64)
Prior radiotherapy [*n* (%)]	5 (36)

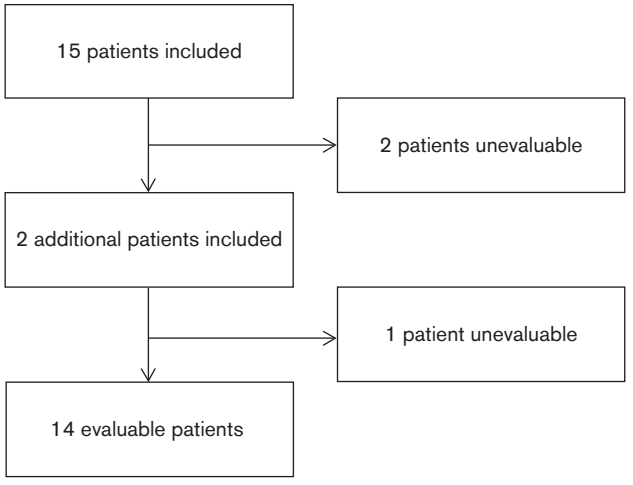
Table 2 Mutational status per patient

Study number	KRAS	PIK3CA
1	G12V	Wild-type
2	G12D	Wild-type
3	G12C	Wild-type
4	G12V	Wild-type
5	G12D	Wild-type
7	G12V	Wild-type
8	G12A	Wild-type
9	G12A	Wild-type
10	G12V	Mutation in exon 20
11	G12D	Wild-type
13	G13D	Mutation in exon 9
14	G13D	Wild-type
15	G12V	Wild-type
17	Missing	Missing

Efficacy

One study participant was free from progression at the primary endpoint. The percentage of patients alive and free from progression 11 weeks after the first administration of panitumumab is therefore 7%. The predefined criteria to proceed to the second stage of the study were not fulfilled; therefore, no further patients were included. Time to progression in this particular patient was 17 weeks; the median time to progression was 8.4 weeks (mean 8.7, range 5–17, Fig. 2a). The median overall survival was 19.6 weeks (mean 24.2, range 8.3–71.1, Fig. 2b). The objective response rate was 0% as none of the patients had a (partial) remission. Analysis of a correlation between skin toxicity and efficacy was not feasible because of the absence of responders.

Fig. 1



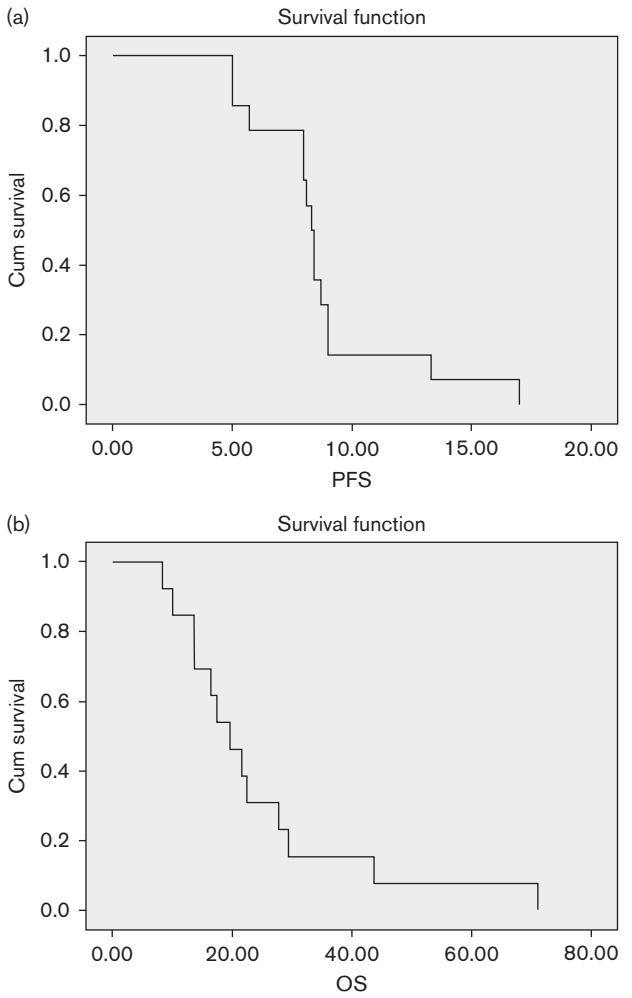
Flow chart of the inclusion of patients.

Exposure to panitumumab was equal in all patients; none required dose reductions or delays. Two patients needed a 50% dose reduction of simvastatin, both after the second infusion of panitumumab. The reason for dose reduction was an increase in liver enzymes in one patient. In the other patient, the reason for dose reduction was not specified, although liver enzymes were stable in this specific patient and myalgia was not reported.

Toxicity

The most frequently reported adverse events on study were fatigue ($n=10$), anaemia ($n=9$) and hypomagnesaemia ($n=9$). The incidence of severe adverse events is shown in

Fig. 2



(a) Kaplan–Meier plot for progression-free survival in weeks of CRC patient treated with 80 mg of simvastatin in combination with panitumumab. (b) Kaplan–Meier plot for overall survival in weeks of CRC patients treated with 80 mg of simvastatin in combination with panitumumab. CRC, colorectal cancer; OS, overall survival; PFS, progression-free survival.

Table 3. Skin toxicity occurred in 10 patients. Acneiform rash was reported in seven patients and none had grade 3 acneiform rash, although one case of grade 3 folliculitis was reported. Myopathy occurred in three patients. Grade 3 myopathy was reported in one patient and the patient terminated study participation for this reason. Increase in CK was reported in all three patients with myopathy (up to 3917 U/l in one patient) and in two additional patients.

Table 3 Severe (grade 3) adverse events

Event	Number (%)
Fatigue	3 (21)
Nausea	2 (14)
Pruritis	1 (7)
Vomitus	1 (7)
Myalgia	1 (7)
Folliculitis	1 (7)
Paronychia	1 (7)

Discussion

To the best of our knowledge, this is the first clinical trial of combined treatment with simvastatin and panitumumab in CRC patients with a *KRAS* mutation in tumour tissue, testing the theoretical concept of *KRAS* modulation by statins. As only one out of 14 patients was alive and free from progression at the time of the primary endpoint, study enrolment was terminated after the first stage of the study and it was concluded that simvastatin does not render sensitivity to panitumumab in this specific population.

The current study is not the first to hypothesize on statins and their inhibitory effect on the activity of RAS and its downstream pathway. However, all except one previous report are on preclinical research. Lovastatin was shown to inhibit RAS activation in *KRAS* transformed thyroid cells through inhibition of its farnesylation, thereby inhibiting activity of the downstream pathway [26]. Furthermore, it was shown that lovastatin and simvastatin inhibited downstream activity in breast cells with mutated *HRAS*, known to induce an invasive phenotype, possibly by inhibiting membrane localization of HRAS. The effect was reversed by farnesyl pyrophosphate, indicating that the effect was related to prenylation of RAS [27]. More recently, simvastatin was shown to restore cetuximab resistance *in vitro* and *in vivo* [28]. On the basis of these results, it may be questioned whether a higher dose of simvastatin would have been necessary to overrule *KRAS* mutation and render sensitivity to EGFR inhibitor therapy. As mentioned above, statin doses up to 35 mg/kg/day have been prescribed in clinical trials, although higher doses were not used continuously as was essential in the current design. Preclinical data research showed a significant reduction in cell growth of *KRAS* mutant CRC cell lines using 0.2 μmol/l simvastatin, the equivalent of 2 mg/kg/day in humans [28]. Moreover, in cardiovascular disease, the registered dose of 80 mg of simvastatin significantly reduced cholesterol serum levels. It is reasonable to assume that this dose will also affect the formation of the C15 and C17 groups and subsequently the prenylation of the KRAS protein. Furthermore, we question whether higher doses will be feasible in terms of safety.

The lack of effect in the current study is in striking contrast with the original reported data by Lee *et al.* [29], testing the addition of simvastatin 40 mg once daily to third-line therapy with cetuximab plus irinotecan in CRC patients harbouring a *KRAS* mutation. Their original report showed indeed a low response rate (one out of 52 patients achieved a partial remission); however, PFS was 7.6 months, which is even higher than the historical results of third-line cetuximab plus irinotecan in *KRAS*

wild-type CRC patients [30,31]. However, in a recent erratum, Lee *et al.* [29] reported corrected measurements of PFS in their population. The corrected mean PFS was 3.7 months (range 2.1–5.3), significantly lower than the previous reports of cetuximab plus irinotecan as third-line therapy in *KRAS* wild type [30,31]. In summary, both our study as well as the study by Lee and colleagues show that simvastatin does not render sensitivity to EGFR inhibitor therapy.

Mutational status of *PIK3CA* is also related to response to EGFR inhibitor-based therapy. The majority of *PIK3CA* mutations are located in exon 9 and exon 20, and those mutations may occur in patients with or without *KRAS* mutation in tumour tissue. Only *PIK3CA* mutations in codon 20 are associated with lower objective response rate and PFS [4]. If statins can induce a *KRAS* wild-type phenotype in our population, a high incidence of *PIK3CA* mutations might still lead to low PFS. However, as only two patients harboured a *PIK3CA* mutation (one in exon 9 and one in exon 20), this is not likely to (partly) explain the results of the current study.

Toxicity of this dose of simvastatin in CRC patients failing standard chemotherapy was relatively mild, with only two patients requiring dose reduction and only one patient experiencing severe myopathy. Panitumumab was also well tolerated, in line with previous data of panitumumab as third-line therapy [2].

Conclusion

The present study showed that simvastatin 80 once daily does not render sensitivity to panitumumab in CRC patients with a *KRAS* mutation failing oxaliplatin-based, 5-FU-based and irinotecan-based therapy. The theoretical concept of *KRAS* modulation using statins does not seem to be feasible in the clinic. Recently, regorafenib was registered for these patients (and for *KRAS* wild-type patients after failing third-line therapy with an EGFR inhibitor); however, PFS gain is limited [32]. New therapeutic strategies for these patients are needed.

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Conflicts of interest

There are no conflicts of interest.

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