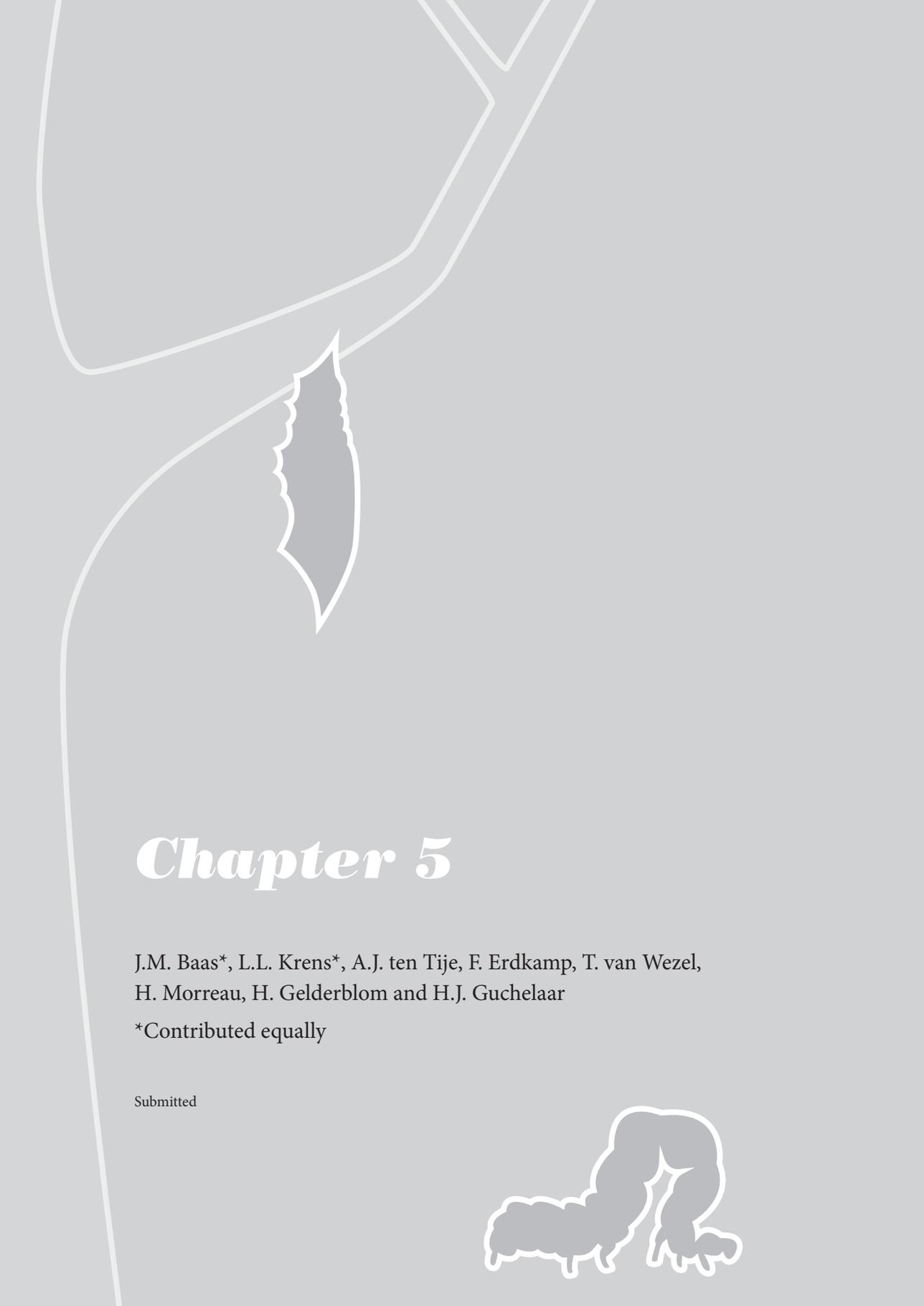Cover Page

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Author: Krens, Lisanne
Title: Refining EGFR-monoclonal antibody treatment in colorectal cancer
Issue Date: 2015-07-02

Chapter 5

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

Abstract

Introduction

Cetuximab is registered for use in CRC patient with **RAS** wild type tumours only. Simvastatin blocks the mevalonate pathway and thereby interferes with the post-translational modification (prenylation) of KRAS. We hypothesize that the activitated KRAS pathway in *KRAS* mutant tumors can be inhibited by simvastatin rendering these tumors sensitive to the EGFR inhibitor cetuximab.

Methods

A Simon two-stage, single-arm, phase II study was performed to test the efficacy and safety of the addition of simvastatin to cetuximab in patients with a *KRAS* mutation in their tumour who were previously treated with fluoropyrimidine, oxaliplatin and irinotecan based regimens. The primary endpoint of this study was to test the percentage of patients alive and free from progression 12.5 weeks after the first administration of cetuximab. Our hypothesis was that at least 40% was free from progression, comparable to, though slightly lower than in **KRAS** wild type patients.

Results

Four of 18 included patients (22.2%) were free from progression at the primary endpoint time. The time to progression in these 4 patients ranged from 20.3 to 47 weeks.

Conclusion

Based on the current study we conclude that the theoretical concept of KRAS modulation with simvastatin was not applicable in the clinic, as we were not able to restore sensitivity to cetuximab in patients harbouring a *KRAS* mutation.

Introduction

Colorectal cancer (CRC) is a major healthcare issue. Each year over 940.000 patients are diagnosed with CRC world-wide and over 500.000 people die of this disease[1]. In patients with advanced or metastatic colorectal treatment with monoclonal antibodies directed against the epidermal growth factor receptor (EGFR), cetuximab and panitumumab are proven to be active after failing fluoropyrimidine, oxaliplatin and irinotecan based regimens, though only in patients with tumours without a mutation in the *KRAS*[2;3] or more recently *RAS* gene[4]. At time of design of this study, patients with a *KRAS* mutation in their tumour were left with no therapeutic options after failing conventional therapy. This led to the question whether increased activation of KRAS signaling by KRAS mutations can be modulated, thereby making KRAS mutated tumours sensitive to EGFR inhibitor therapy. One possible target for modulation is the mevalonate pathway, as we have previously discussed[5].

The mevalonate pathway is a metabolic cascade with various end-products including cholesterol. Other end-products are farnesylated and geranylgeranylated proteins (C15 and C17), both essential for posttranslational prenylation of the RAS protein and its association with the cytoplasmic membrane, and thereby activation of the RAS protein (Figure 1). By using HMG-CoA reductase inhibitors not only the synthesis of cholesterol is inhibited, but also the formation of C15 and C17, thereby inhibiting posttranslational modification of RAS[5;6]. By blocking the mevalonate pathway in CRC patients with *KRAS* mutated tumours, the activated KRAS pathway might be inhibited. This would theoretically lead to increased sensitivity to cetuximab, potentially comparable to tumours with wild type *KRAS*.
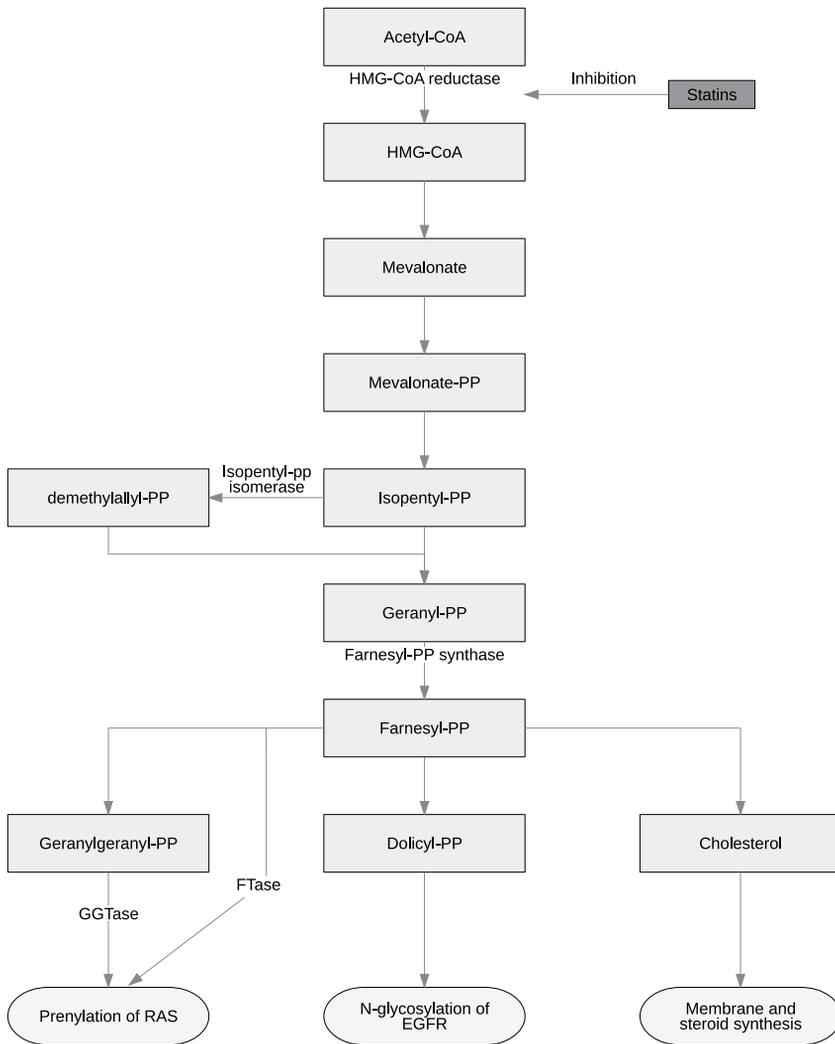
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Figure 1: Mevalonate pathway

This single-arm, phase II study was designed to test the safety and efficacy of the addition of simvastatin to cetuximab in patients with a *KRAS* mutation in their tumour who were previously treated with fluoropyrimidine, oxaliplatin and irinotecan based regimens.

Methods

Patients

Eligible patients had advanced or metastatic colorectal cancer 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 failing fluoropyrimidine, oxaliplatin and irinotecan based regimens, or after failure of oxaliplatin based therapy in patients who cannot be treated with irinotecan. In case of progressive disease within 6 months after start of adjuvant fluoropyrimidine, oxaliplatin, and irinotecan containing regimens the adjuvant therapy was considered to be treatment for metastatic disease.

Other eligibility criteria included age 18 years or older, World Health Organisation (WHO) performance score of 0 to 2 and progression of disease in the past three months prior to inclusion. Exclusion criteria included symptomatic brain metastases, previous treatment with EGFR inhibitors, history of toxicity during statin use and another malignancy during the past four years (with the exception of non-melanoma skin cancer and adequately treated pre-invasive carcinoma of the cervix).

The study protocol was approved by the Ethics Committees of all participating hospitals. Written informed consent was obtained prior to any study-related interventions.

Study design

This phase II, single-arm, multi-center study was performed using a Simon two-stage design[7]. In the first stage, 15 patients were included, followed by an interim analysis. Results of this analysis would determine whether the combination of simvastatin and cetuximab may have clinical benefit in this group of CRC patients, thus justifying the second stage and including up to 41 patients. If the first stage would suggest that this combination does not indicate clinical benefit, no additional patients would be exposed to this combination.

Treatment schedule

Cetuximab was first administered at least one week after start of simvastatin therapy. The initial cetuximab dose was 400 mg/m² (over 120 minutes) with subsequent weekly infusions of 250 mg/m² (over 60 minutes). Pretreatment with an antihistamine and a corticosteroid was mandatory before the first infusion of cetuximab and recommended for all subsequent infusions.

Simvastatin 80 mg orally once daily was started at start of study participation and continued throughout the entire study. This dose was chosen taken into consideration the need for continuous administration of the statin during the entire study, inhibitory effect on the mevalonate pathway and tolerability. Statins in cancer therapy have been studied in clinical trials in solid[8-18] and haematologic [19-21] malignancies, both as monotherapy as well as additional to chemotherapy. Statin doses from 20 mg/day up to 35 mg/kg/day were used, with only continuous use of statins when dosed at a maximum of 80 mg/day. Since the aim of this study is to modulate KRAS during the entire treatment with cetuximab and therefore a continuous exposure to simvastatin is needed, a dose of 80 mg/day was selected in order to obtain maximum effect while minimizing the risk of toxicity. Patients who were already using statins prior to inclusion had to switch to simvastatin in the above mentioned dose.

Treatment was continued until progression of disease, clinical signs of progression according to the investigators assessment, unacceptable toxicity or cetuximab toxicity requiring withholding of more than two subsequent infusions.

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Tumour response was every six weeks using CT-scans and according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. Scans of patients free from progression at time of primary endpoint were centrally reviewed. All patients were followed for survival once every 3 months after termination of study participation. All patients were assessed for toxicity prior to every administration of cetuximab.

Endpoints

Primary objective was to test the percentage of patients with *KRAS* mutant advanced or metastatic colorectal cancer alive and free from progression and alive at 12.5 weeks after the first administration of cetuximab in combination with simvastatin. Our hypothesis was that at least 40% of patients was free from progression, comparable to though slightly lower than in *KRAS* wild type patients[2].

Secondary objectives were to investigate overall survival (OS), objective response rate (ORR), progression free survival (PFS), and safety of simvastatin combined with cetuximab 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 correlate with response to cetuximab 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[22]. 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). Though *KRAS* and *BRAF* mutations are known to be mutually exclusive[23], we did test for the activating hotspot mutation p.V600E.

Statistics

Sample size was chosen based on previous published data of CRC patients with *KRAS* wild type tumours treated with cetuximab[2], aiming for a at least six out of 15 patients free from progression at 12.5 weeks after start of cetuximab treatment in patients with *KRAS* mutant type tumours (i.e., slightly lower than the effect in *KRAS* wild type patients). Combined with an alpha 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 performed after the inclusion of 15 evaluable patients. Only when at least 40% (i.e. 6 patients) were free from progression at the 12.5 weeks, another 31 patients would be enrolled during the second stage of the study.

Results

Patients

During the first stage of the study 18 instead of 15 patients were enrolled to account for patients that were thought to unevaluable for the primary endpoint. Baseline characteristics are listed in Table 1. Fifteen patients had previously been receiving two lines of chemotherapy, two patients were only treated with oxaliplatin/5FU based therapy prior to inclusion and 1 patient had received

three lines of chemotherapy (oxaliplatin and irinotecan based therapy and regorafenib during participation in a different trial). None of the patients were using statins prior to inclusion.

Table 2 shows type of *KRAS* mutation per patient, along with *PIK3CA* mutational status.

Table 1: Baseline characteristics

Age – years	
Mean	62
Range	52 – 75
Gender – n (%)	
Male	13 (72)
Female	5 (18)
WHO performance score – n (%)	
0	13 (72)
I	5 (18)
Site of primary tumour – n (%)	
Colon	12 (67)
Rectum	6 (33)
Prior lines of chemotherapy – n (%)	
1	2
2	15
3	1
Prior surgery – n (%)	13 (72)
Prior radiotherapy – n (%)	4 (22)

Table 2: *KRAS* and *PIK3CA* mutational status per patient

Study number	*KRAS* mutation	*PIK3CA* mutational status
1	G12D	Wild type
2	G12V	Wild type
3	G12V	Wild type
4	G12C	Wild type
5	G12V	Wild type
6	G12S	Wild type
7	*missing*	*Missing*
8	G12V	Wild type
9	G13D	Wild type
10	G13D	Wild type
11	G12D	Wild type
12	G12D	Wild type
13	*missing*	*Missing*
14	G12V	Wild type
15	G12A	Wild type
16	G12A	Wild type
17	G13D	Mutation in exon 9
18	G12D	Mutation in exon 9

Efficacy

Four of 18 patients were free from progression at the primary endpoint time, therefore the percentage of patients alive and free from progression 12.5 weeks after the first administration of cetuximab was 22%. The time to progression in these four patients ranged from 20.3 to 47 weeks. Drug exposure to simvastatin and cetuximab was equal for all patients since none of the patients required dose reductions while on study.
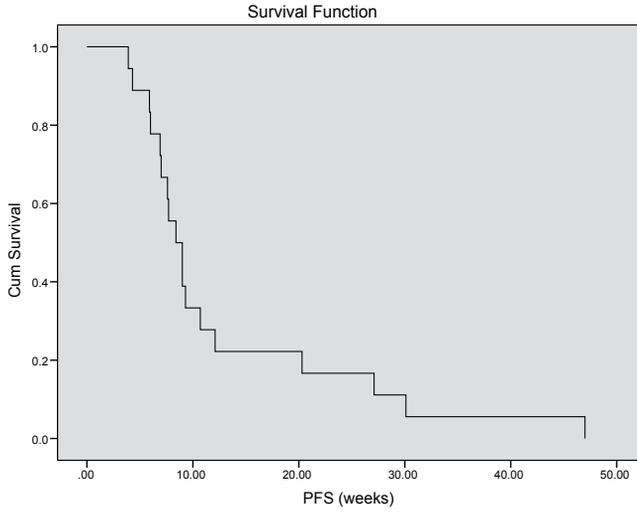

Figure 2a: Progression free survival in weeks for the addition of simvastatin to cetuximab in CRC patients failing standard therapy
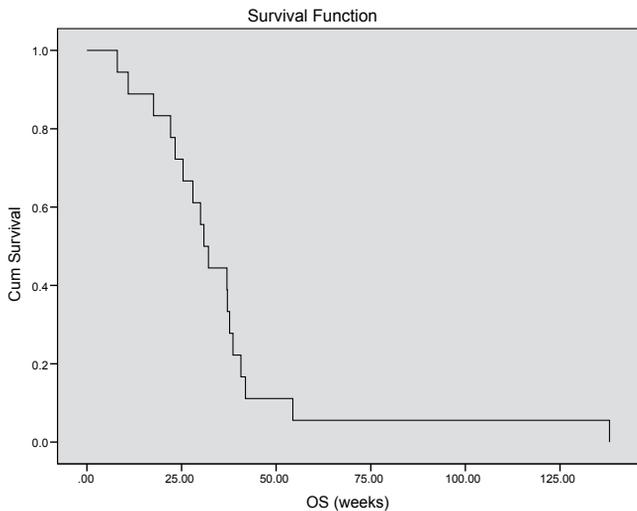

Figure 2b: Overall survival in weeks for the addition of simvastatin to cetuximab in CRC patients failing standard therapy

Figure 2 shows progression free (panel A) and overall survival (panel B). Median progression free survival was nine weeks (mean 12.9 weeks, range 3.9 - 47 weeks). Median overall survival was 31.5 weeks (mean 36.3, range 8-138.1). Objective response rate was 6% (partial remission in one patient). A true relation between skin toxicity and efficacy of treatment was not observed in this study though this may (partly) be due to the low number of patients and due to the improved knowledge of the efficacy of pre-emptive skin toxicity management.

Safety

Main symptoms and adverse events reported on study reported were fatigue (n=11), acne (n=10) and rash (n=6). Myopathy was not reported. Three patients had elevation of creatine kinase (CK) levels on study (grade 4 in one patient). Table 3 shows the most frequent reported adverse events. Skin toxicity occurred in 10 patients; the worst grade of acneiform rash was grade 3 in one patient, grade 2 in four patients and grade 1 in the remaining five patients. One patient experienced a severe (i.e. grade 3) allergic reaction during the first infusion of cetuximab. This was the only grade 3 infusion reaction reported during the entire study, and this patient did not experience any further reactions while on study. Hypomagnesaemia was reported in four patients, no cases of hypocalcaemia were reported.

Table 3: Adverse events occurring in > 10%

Event	Any grade	Grade 3-4
Fatigue	11 (61%)	1 (6%)
Acneiform rash	10 (56%)	1 (6%)
Anemia	9 (50%)	-
Rash (not acneiform)	6 (33%)	1 (6%)
Tumour-related pain	6 (33%)	1 (6%)
Pruritis	5 (28%)	-
Nausea	5 (28%)	-
Dyspnea	4 (22%)	-
Hypomagnesaemia	4 (22%)	-
Creatine kinase elevation	3 (17%)	1 (6%)
Constipation	3 (17%)	-
Fever	2 (11%)	-
Infusion related reaction	2 (11%)	1 (6%)
Thrombocytopenia	2 (11%)	-
Weight loss	2 (11%)	-
Thrombosis	2 (11%)	1 (6%)

One of the serious adverse events did precede the death of a participant. Upon the scheduled laboratory examination severe elevation of liver enzymes were observed soon after start of study medication. Rhabdomyolysis due to simvastatin was considered, (though on study CK levels were below 3.000 U/l) and so was progression of liver metastases with impaired liver function. Study medication was interrupted immediately, however the patient's situation did not improve and it was decided to terminate study participation permanently. Specific SNPs associated with increased risk of statin-induced myopathy (i.e. SLCO1B1 variants[24]) were considered though none were identified in this patient. The patient deceased few weeks later. Post-mortem examination did not occur.

Exploratory endpoints

Serum cholesterol was measured in all patients at baseline and in 15 patients on study. All showed cholesterol reduction, ranging from a maximum reduction of 0.8% to 64.4%. Cholesterol reduction on study did not differ between patients free from progression at time of primary endpoint compared to those who were not (mean reduction 37.1% versus 30.5%, p-value = 0.55). The percentage of cholesterol reduction did not correlate with progression free survival.

Tumour tissue of 15 patients was available for central review. Table 3 shows mutational status of KRAS and PIK3CA per patient. Thirteen patients had a mutation in codon 12 (most often G12D and G12V) and three in codon 13. A mutation in the *PIK3CA* gene was detected in 2 patients (both exon 9). Of the four patients responding to treatment, 3 had a *KRAS* mutation in codon 12 and one had a *PIK3CA* mutation. As expected in patients with a *KRAS* mutation in their tumour, all patients were *BRAF* wild type.

Discussion

To our knowledge, this is the first clinical trial testing the addition of simvastatin to cetuximab monotherapy in CRC patients harbouring a KRAS mutation in tumour tissue as an attempt to restore cetuximab sensitivity. While it was remarkable to notice a durable progression free survival in four patients, the interim analysis showed that the predefined criteria to proceed to the second stage of this study were not reached. Therefore, the current study suggests that high dose simvastatin does not render cetuximab sensitivity in *KRAS* mutant CRC.

Statines are one of several potential agents to modulate *KRAS* signaling, as we have previously reviewed[5]. 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 but one previous reports include only preclinical data. Lovastatin showed to inhibit RAS activation in KRAS transformed thyroid cells through inhibition of its farnesylation, and thereby inhibiting activity of the downstream pathway[25]. Furthermore, lovastatin and simvastatin inhibit 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 when adding farnesyl pyrophosphate, indicating the effect was related to prenylation of *RAS*[26]. More recently, simvastatin was shown to restore cetuximab resistance *in vitro* and *in vivo*[27]. Based on these results, one might wonder whether the negative outcome of the current study would have been different if using higher doses of simvastatin. As mentioned above, statin doses up to 35 mg/kg/day have been prescribed in clinical trials, though higher doses were not used continuously as was essential in the current design. Preclinical data showed a significant reduction in cell growth of *KRAS* mutant CRC cell lines using 0.2 µM simvastatin, the equivalent of 2mg/kg/day in humans[27]. Moreover, in cardiovascular disease the registered dose of 80 mg of simvastatin is significantly lowers cholesterol serum levels. It is reasonable 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.

A recent study of Lee et al tested the efficacy of the addition of the same dose of simvastatin (i.e. 80mg once daily) to cetuximab and irinotecan in *KRAS* mutant CRC patients failing prior oxaliplatin, fluoropyrimidine and irinotecan based therapy[28]. The initially reported PFS and OS (median 7.6 months and 12.8 months respectively) were considerably higher than historical results in chemotherapy refractory CRC patients with *KRAS* mutated tumours[29]

and chemotherapy refractory CRC patients in general[30-32]. Moreover, these results were in contrast with our findings and the authors concluded that simvastatin may overcome cetuximab resistance in patients with *KRAS* mutant tumours. However, a recent erratum published by this group showed that initial survival data were incorrect[33]. The corrected PFS and OS are in line with our results, providing no evidence for a modulating effect of simvastatin on the *KRAS* mutant phenotype.

The majority of patients had a *KRAS* mutation in codon 12 and only 3 in codon 13. It has been reported that tumours harbouring a G13D mutation in the *KRAS* gene might be sensitive to EGFR-inhibitors[34]. Moreover, none of our patients had a *PIK3CA* mutation in exon 20. Mutations in exon 20 of the PIK3CA gene might also be more likely to be sensitive to EGFR-inhibitors, contrary to mutations in exon 9[35]. However, while the number of patients in our study is low, of the four patients who were free from progression at time of the primary endpoint only one patients had a G13D mutation in the *KRAS* gene and none had a *PIK3CA* mutation in exon 20.

While one patient developed impaired liver function, it remains unclear whether this was related to simvastatin. Nonetheless, CK levels were clearly increased in this particular patient. However, none of the other patients reported statin related adverse events (e.g. myopathy) and CK levels were only mildly elevated in two patients. There was no need for dose reduction. Overall, simvastatin 80 mg once daily was considered well tolerated in the current population.

Conclusion

Based on the current study we conclude that the concept of KRAS modulation with simvastatin was not applicable in the clinic. Other strategies are needed for CRC patients with tumours harbouring a *KRAS* mutation who failed standard therapy. Recently regorafenib was registered for CRC patients failing standard therapy (including EGFR inhibitors if wild type *KRAS*), but the gain in survival is limited to 6 weeks[30]. Better treatment strategies are needed for this patient population.

Compliance with ethical standards

Conflict of interest
Jara M, Baas: none; Lisanne L. Krens: none; A.J. ten Tije: none; F. Erdkamp: none; Tom van Wezel: none; Hans Morreau: none; Henk-Jan Guchelaar: research funding by Amgen Inc and Merck BV; Hans Gelderblom: research funding by Amgen Inc en Merck BV.

Informed consent
The informed consent form was signed by the patient (and physician) prior to inclusion and according to the ICH guidelines on Good Clinical Practice.

Funding
This was an Investigator Initiated Study, made possible by a research grant offered by Merck Serono.

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References

1 Denters MJ, Deutekom M, Fockens P, Bossuyt PM, Dekker E. (2009) Implementation of population screening for colorectal cancer by repeated fecal occult blood test in the Netherlands. BMC Gastroenterol 9: 28.

2 Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, et al. (2008) KRAS mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 359: 1757-1765.

3 Amado RG, Wolf M, Peeters M, Van CE, Siena S, et al. (2008) Wild type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 26: 1626-1634.

4 Sorich MJ, Wiese MD, Rowland A, Kichenadasse G, McKinnon RA, et al. (2014) Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials. Ann Oncol .

5 Krens LL, Baas JM, Gelderblom H, Guchelaar HJ. (2010) Therapeutic modulation of KRAS signaling in colorectal cancer. Drug Discov Today 15: 502-516.

6 Swanson KM, Hohl RJ. (2006) Anti-cancer therapy: targeting the mevalonate pathway. Curr Cancer Drug Targets 6: 15-37.

7 Simon R. (1989) Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10: 1-10.

8 Hong JY, Nam EM, Lee J, Park JO, Lee SC, et al. (2014) Randomized double-blinded, placebo-controlled phase II trial of simvastatin and gemcitabine in advanced pancreatic cancer patients. Cancer Chemother Pharmacol 73: 125-130.

9 Manoukian GE, Tannir NM, Jonasch E, Qiao W, Haygood TM, et al. (2011) Pilot trial of bone-targeted therapy combining zoledronate with fluvastatin or atorvastatin for patients with metastatic renal cell carcinoma. Clin Genitourin Cancer 9: 81-88.

10 Han JY, Lim KY, Yu SY, Yun T, Kim HT, et al. (2011) A phase 2 study of irinotecan, cisplatin, and simvastatin for untreated extensive-disease small cell lung cancer. Cancer 117: 2178-2185.

11 Han JY, Lee SH, Yoo NJ, Hyung LS, Moon YJ, et al. (2011) A randomized phase II study of gefitinib plus simvastatin versus gefitinib alone in previously treated patients with advanced non-small cell lung cancer. Clin Cancer Res 17: 1553-1560.

12 Konings IR, van der Gaast A, van der Wijk LJ, de Jongh FE, Eskens FA, et al. (2010) The addition of pravastatin to chemotherapy in advanced gastric carcinoma: a randomised phase II trial. Eur J Cancer 46: 3200-3204.

13 Lee J, Jung KH, Park YS, Ahn JB, Shin SJ, et al. (2009) Simvastatin plus irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) as first-line chemotherapy in metastatic colorectal patients: a multicenter phase II study. Cancer Chemother Pharmacol 64: 657-663.

14 Graf H, Jungst C, Straub G, Dogan S, Hoffmann RT, et al. (2008) Chemoembolization combined with pravastatin improves survival in patients with hepatocellular carcinoma. Digestion 78: 34-38.

15 Knox JJ, Siu LL, Chen E, Dimitroulakos J, Kamel-Reid S, et al. (2005) A Phase I trial of prolonged administration of lovastatin in patients with recurrent or metastatic squamous cell carcinoma of the head and neck or of the cervix. Eur J Cancer 41: 523-530.

16 Lersch C, Schmelz R, Erdmann J, Hollweck R, Schulte-Frohlinde E, et al. (2004) Treatment of HCC with pravastatin, octreotide, or gemcitabine--a critical evaluation. Hepatogastroenterology 51: 1099-1103.

17 Kim WS, Kim MM, Choi HJ, Yoon SS, Lee MH, et al. (2001) Phase II study of high-dose lovastatin in patients with advanced gastric adenocarcinoma. Invest New Drugs 19: 81-83.

18 Kawata S, Yamasaki E, Nagase T, Inui Y, Ito N, et al. (2001) Effect of pravastatin on survival in patients with advanced hepatocellular carcinoma. A randomized controlled trial. Br J Cancer 84: 886-891.

19 Ahmed TA, Hayslip J, Leggas M. (2013)

Pharmacokinetics of high-dose simvastatin in refractory and relapsed chronic lymphocytic leukemia patients. Cancer Chemother Pharmacol 72: 1369-1374.

20 Hus M, Grzasko N, Szostek M, Pluta A, Helbig G, et al. (2011) Thalidomide, dexamethasone and lovastatin with autologous stem cell transplantation as a salvage immunomodulatory therapy in patients with relapsed and refractory multiple myeloma. Ann Hematol 90: 1161-1166.

21 van der Spek E, Bloem AC, Sinnige HA, Lokhorst HM. (2007) High dose simvastatin does not reverse resistance to vincristine, adriamycin, and dexamethasone (VAD) in myeloma. Haematologica 92: e130-e131.

22 van Eijk R., Licht J, Schrumpf M et al. (2011) Rapid KRAS, EGFR, BRAF and PIK3CA mutation analysis of fine needle aspirates from non-small-cell lung cancer using allele-specific qPCR. PLoS.One.; 6: e17791.

23 Tol J, Nagtegaal ID, Punt CJ. (2009)BRAF mutation in metastatic colorectal cancer. N.Engl.J.Med.; 361: 98-9.

24 Link E, Parish S, Armitage J, Bowman L, Heath S, et al. (2008) SLCO1B1 variants and statin-induced myopathy--a genomewide study. N Engl J Med 359: 789-799.

25 Laezza C, Fiorentino L, Pisanti S, Gazzerro P, Caraglia M, et al. (2008) Lovastatin induces apoptosis of KRAS-transformed thyroid cells via inhibition of ras farnesylation and by modulating redox state. J Mol Med (Berl) 86: 1341-1351.

26 Kang S, Kim ES, Moon A. (2009) Simvastatin and lovastatin inhibit breast cell invasion induced by H-Ras. Oncol Rep 21: 1317-1322.

27 Lee J, Lee I, Han B, Park JO, Jang J, et al. (2011) Effect of simvastatin on cetuximab resistance in human colorectal cancer with KRAS mutations. J Natl Cancer Inst 103: 674-688.

28 Lee J, Hong YS, Hong JY, Han SW, Kim TW, et al. (2014) Effect of simvastatin plus cetuximab/irinotecan for KRAS mutant colorectal cancer and predictive value of the RAS signature for treatment response to cetuximab. Invest New

Drugs 32: 535-541.

29 De Roock RW, Claes B, Bernasconi D, De SJ, Biesmans B, et al. (2010) Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. Lancet Oncol 11: 753-762.

30 Grothey A, Van CE, Sobrero A, Siena S, Falcone A, et al. (2013) Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 381: 303-312.

31 Jonker DJ, O'Callaghan CJ, Karapetis CS, Zalcberg JR, Tu D, et al. (2007) Cetuximab for the treatment of colorectal cancer. N Engl J Med 357: 2040-2048.

32 Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, et al. (2007) Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 25: 1658-1664.

33 Lee J, Hong YS, Hong JY, Han SW, Kim TW, et al. (2014) Erratum to: Effect of simvastatin plus cetuximab/irinotecan for KRAS mutant colorectal cancer and predictive value of the RAS signature for treatment response to cetuximab. Invest New Drugs .

34 Tejpar S, Celik I, Schlichting M, Sartorius U, Bokemeyer C, Van CE. (20120 Association of KRAS G13D tumor mutations with outcome in patients with metastatic colorectal cancer treated with first-line chemotherapy with or without cetuximab. J.Clin.Oncol.; 30: 3570-7.

35 Karapetis CS, Jonker D, Daneshmand M et al. (2014) PIK3CA, BRAF, and PTEN status and benefit from cetuximab in the treatment of advanced colorectal cancer--results from NCIC CTG/AGITG CO.17. Clin.Cancer Res.; 20: 744-53.

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