Phase I Dose-escalation Study of the Safety, Pharmacokinetics and Pharmacodynamics of the MEK Inhibitor RO4987655 (CH4987655) in Patients with Advanced Solid Tumours

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Translational relevance

The phase I and pharmacological study has shown preliminary proof of principle that tumours with selected mutations are sensitive to MEK inhibition. PET scan analysis and ERK phosphorylation measurement supported concentration-dependent target engagement. In addition, prolonged patient benefit could be demonstrated in these patients. This may guide future development of the MEK inhibitor RO4987655. Evidence of pharmacological activity, as demonstrated by invasive and non-invasive biomarkers, combined with documented anti-tumour activity in this phase I study are an excellent basis for targeted development in phase II and III studies. Furthermore, despite the reported toxicities, continuous treatment at adequate levels of drug exposure was feasible in the great majority of patients.
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Abstract

Purpose: This Phase I study of the MEK inhibitor RO4987655 (CH4987655) assessed its maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), safety, pharmacokinetics (PK)/pharmacodynamics (PD) profile and anti-tumour activity in patients with advanced solid tumours.

Patients and Methods: An initial dose-escalation was performed using a once-daily (QD) dosing schedule, with oral RO4987655 administered at doses of 1.0–2.5 mg QD over 28 consecutive days in 4-week cycles. Doses were then escalated to 3.0–21.0 mg (total daily dose [TDD]) using a twice-daily (BID) dosing schedule.

Results: Forty-nine patients were enrolled. DLTs were blurred vision (n=1) and elevated creatine phosphokinase (n=3). The MTD was 8.5 mg BID (TDD, 17.0 mg). Rash-related toxicity (91.8%) and gastrointestinal disorders (69.4%) were the most frequent adverse events. The pharmacokinetic profile of RO4987655 demonstrated dose-linearity and a half-life of ~4 hours. At the MTD, target inhibition, assessed by suppression of ERK phosphorylation in peripheral blood mononuclear cells, was high (mean 75%) and sustained (90% of time >IC50). Of the patients evaluable for response, clinical benefit was seen in 21.1%, including two partial responses (one confirmed and one unconfirmed). 79.4% of patients demonstrated a reduction in fluorodeoxyglucose uptake by positron emission tomography between baseline and Day 15.

Conclusion: In this population of heavily pre-treated patients, oral RO4987655 demonstrated manageable toxicity, a favourable PK/PD profile and promising preliminary anti-tumour activity, which has been further investigated in specific population of patients with RAS and/or RAF mutation driven tumours.
Introduction

Constitutive activation of the Ras-regulated mitogen-activated protein kinase (MAPK) signalling cascade has been identified in various human cancers. The MAPK cascade comprises three enzymes (RAF/MEK/ERK) involved in regulation of cell proliferation, differentiation, survival and migration (1;2). Mutations of the Ras proto-oncogenes (KRAS, HRAS and NRAS) have been found in ~30% of cancers (3), while BRAF gene mutations have been identified in up to 66% of malignant melanomas (4).

MAP kinase kinase (MEK) is the only known kinase capable of phosphorylating ERK; therefore, inhibition of MEK can potentially block the activation of multiple downstream pathways. Several small-molecule inhibitors of MEK are currently being investigated (5-14). RO4987655 is a highly selective adenosine triphosphate non-competitive oral MEK inhibitor that has shown promising anti-tumour activity in a series of human cancer xenograft models (non-small cell lung cancer [NSCLC], pancreatic cancer and hepatocellular carcinoma) (15). RO4987655 has a unique ring structure with a high metabolic stability and slow dissociation from MEK which may confer better clinical efficacy compared with other MEK inhibitors (15). In a study of healthy volunteers, once-only single doses of oral RO4987655 (0.5–4 mg) were found to be safe and well tolerated (16). Toxicity was typically mild/moderate, the most common adverse events (AEs) being skin-related or gastrointestinal (16). Target effect was assessed by measuring the level of phosphorylated ERK (pERK) in peripheral blood mononuclear cells (PBMCs), which demonstrated pERK inhibition of >80% at higher RO4987655 doses (16).

The objectives of this study were to determine the maximum tolerated dose (MTD), dose limiting toxicities (DLTs), the pharmacokinetics (PK)/pharmacodynamic (PD) profile, safety and tolerability, and preliminary anti-tumour activity of RO4987655 in a population of patients with advanced cancers (17).
Methods

Patient selection

Patients were aged ≥18 years with advanced or metastatic solid tumours for which no standard therapy was available. All patients had an Eastern Cooperative Oncology Group performance status (ECOG-PS) of ≤1, evaluable and/or measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST, v1.0) (18), a life expectancy of ≥12 weeks, and adequate organ functions (see Supplementary Information for full inclusion/exclusion criteria). Patients with a history of ocular disorders or other known risk factors were excluded, as were patients who had received recent corticosteroids or hormone therapy (within 2 weeks of first planned RO4987655 dose) or recent major surgery, chemotherapy, radiotherapy, immunotherapy or investigational agent (within 4 weeks). Unlimited prior systemic therapy for metastatic disease was permitted.

Study design and dose escalation

This Phase I, open-label, dose-escalation study (NCT00817518) was conducted at four European centres, was approved by an Independent Ethics Committee and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all patients prior to performing any study-related procedure. RO4987655 was administered as oral capsules at least two hours after a light meal, followed by at least one hour before the next meal.

Initial escalation was performed using a once-daily (QD) dosing schedule with oral RO4987655 administered over 28 consecutive days in 4-week cycles. Based on data from a toxicity study in cynomolgus monkeys (15) and clinical data from healthy volunteers (16), a starting dose of 1.0 mg/day was chosen. A regimen of twice-daily (BID) dosing was also investigated, with starting dose based on interim PK data from the QD regimen. A classical 3+3 dose-escalation design was used, with the dose escalated according to the
grade/severity of toxicity during Cycle 1. Dose escalation was performed in 100% increments (according to nearest capsule strength) until the occurrence of Grade 2 toxicity, after which subsequent escalation took place in increments of 50%. Following the occurrence of a Grade 3 toxicity that was not a DLT, dose-escalation was performed in increments of 33% until the first DLT was observed. This cohort was expanded to six patients and if further DLTs were not observed in these six patients, dose escalation continued by 25% increments. Escalation was stopped if two or more patients in a given cohort developed a DLT and the preceding dose level expanded to six patients to confirm the MTD (defined as the dose level below the lowest dose at which ≥2 DLTs were seen).

No dose reductions were permitted during the first 28 days of the study (DLT evaluation period). For any given patient, a maximum of one dose reduction or interruption was allowed after Day 28 of Cycle 1. Re-escalation was permitted for Grade ≥3 skin toxicity which improved to Grade ≤2 and for diarrhoea or any other toxicity which improved to Grade ≤1 within 14 days. Patients were treated at their assigned dose until disease progression, unacceptable toxicity or patient withdrawal, whichever occurred first.

Assessments

Demographics and medical history were collected during screening. Physical examination, vital signs and safety assessments (ECOG-PS, 12-lead electrocardiogram [ECG], haematology/biochemistry, echocardiography/multigated acquisition [MUGA] scan and ophthalmological examination [fundoscopy]) were performed at baseline/screening and throughout treatment: ECG on Day 8 of Cycle 1 (pre-dose and 2 and 4 hours after drug administration); echocardiography/MUGA on Day 1 of Cycle 3; and all other assessments were done pre-dose on Days 1, 8, 15 and 22 of Cycle 1, Days 1 and 15 of Cycles 2 and 3, and thereafter on Day 1 of each cycle and at final visit. Following observation of creatine phosphokinase (CPK) elevation in one patient (17.0 mg, total daily dose), CPK was
measured in all subsequent patients and retrospectively in blood collected from patients receiving lower doses.

**Safety**

AEs were graded according to the National Cancer Institute Common Toxicity Criteria (v3.0) (19). DLTs were defined as: Grade ≥3 non-haematological toxicity; Grade ≥3 nausea/vomiting, skin rash and/or diarrhoea (despite adequate supportive care); Grade ≥3 skin toxicity that does not revert to Grade ≤2 within 14 days of the scheduled start date; febrile neutropenia (absolute neutrophil count [ANC] <1.0 x 10^9/L and fever ≥38.5°C), and/or documented infection (ANC <1.0 x 10^9/L); Grade 4 thrombocytopenia or bleeding requiring a platelet transfusion.

**Pharmacokinetics/pharmacodynamics**

Blood samples (4 mL in potassium EDTA vacutainers) were collected prior to dosing on Days 1 and 15 of Cycle 1 for PK analysis and at 1, 3, 7 and 12 hours following drug administration. Trough PK sampling was performed pre-dose on Days 8 and 22 of Cycle 1. The plasma concentration of RO4987655 was determined by a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method (16). PK parameters were calculated via standard non-compartmental methods using WinNonlin V6.1 (Pharsight Corporation, Mountain View, CA) and PK measurements were fitted to a PK/PD model of pERK inhibition in PBMCs using NONMEM vVI (ICON, Maryland, US).

**pERK inhibition**

Target inhibition of 4 beta-phorbol 12-myristate 13-acetate (PMA)-induced pERK was measured in PBMCs (collected Days 1 and 15, Cycle 1 from all patients) using flow cytometry as described previously (16). NONMEM was used to fit PK/PD data to a model of serum and effect compartment RO4987655 concentration versus pERK inhibition in PBMCs (Supplementary Information). pERK inhibition was calculated as the percentage decrease in mean fluorescent intensity between pre- and post-dose samples, with adjustment for non-

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PMA stimulated pre-dose values. The antibody phospho-p44/42 MAPK (ERK1/2; Thr202/Tyr204; clone D13.14.4E, Cell Signaling Technology, Beverly, MA) was used to detect endogenous levels of p44 and p42 MAPK (ERK1 and ERK2) when phosphorylated either individually or dually at Thr202 and Tyr204 of ERK1 (Thr185 and Tyr187 of ERK2).

The effect of RO4987655 on cellular proliferation (Ki67 labelling) and target inhibition (pERK expression) was investigated by immunohistochemistry (IHC) in optional skin and tumour biopsies (collected at baseline/screening and on Day 15 of Cycle 1). Apoptosis was analysed in tumour biopsies by terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL) assay. A ≥20% change in PD biomarkers between baseline and Day 15 was considered significant. Mutational analyses for KRAS, NRAS, BRAF (V600), HRAS, PI3KCA and PTEN loss were performed if archival tumour samples were available.

Immunohistochemistry

Skin and tumour biopsies were formalin-fixed and paraffin-embedded according to standard procedures. Immunohistochemistry for Ki67 was performed using the ultraView detection kit (Ventana Medical Systems Inc, Tuscon, AZ) on a Ventana Benchmark XT platform according to the manufacturer's instructions. Slides were dewaxed, pretreated with mild Cell Conditioning 1 buffer (CC1, Ventana) and incubated for 12 minutes with a primary antibody against Ki67 (clone 30.9, Ventana). Slides were then counterstained with haematoxylin and bluing reagent, dehydrated and mounted. For pERK immunohistochemistry, the iView detection kit (Ventana) was used on a Ventana Benchmark XT platform. Slides were dewaxed and pretreated as before, and incubated for 1 hour with a phospho-p44/42 MAPK primary antibody (ERK1/2; Thr202/Tyr204; clone D13.14.4E, Cell Signaling Technology). To reduce non-specific staining by endogenous biotin present in cells and tissues, the Endogenous Biotin Blocking Kit (Ventana) was also used. Slides were counterstained and mounted as before.
Terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL) assay
Formalin-fixed tissue sections were dewaxed and washed in phosphate buffered saline. Sections were incubated in 3% citric acid for 1 hour to decalcify the tissue and, after three washes with water, epitope retrieval was performed using proteinase K (Roche). Slides were again washed in water, and incubated with 100 µl of TUNEL reaction mixture (containing FITC-dUTP) at 37°C for 1 hour. Following another wash, slides were treated with 3% hydrogen peroxide for 15 minutes to block endogenous peroxidase activity before incubating with a secondary antibody (anti-FITC-HRP, Roche) for 45 minutes. Finally, slides were washed and 3-Amino-9-Ethylcarbazole substrate was added for 10 minutes. Counterstaining was performed using haematoxylin for 30 seconds and slides were mounted using a gelatin-glycerin mounting medium.

Mutation analysis
Mutational analysis was performed centrally using formalin-fixed tissue. Biopsies were first assessed to ensure at least 50% tumour cell content and manually microdissected if required. Real-time polymerase chain reaction with fluorescently-labelled, sequence-specific probes was used to distinguish the wild-type \textit{BRAF} (V600) sequence (GTG) from the mutant sequence (GAG). \textit{KRAS} mutations were identified using an investigational assay based upon PCR and melting temperature analysis, with fluorescently-labelled, sequence specific probes designed to distinguish the wild-type sequence from mutation bearing sequences in exon 2 (specifically at codons 12 and 13) and in exon 3 (specifically at codon 61). All assays were performed on the cobas 4800 system (Roche Molecular Systems, Inc.) according to manufacturer's instructions. \textit{NRAS} (in melanoma), \textit{HRAS}, and \textit{PI3K} mutations were screened for by standard sequencing methods and \textit{PTEN} loss was determined by IHC (antibody clone 138G6, Cell Signaling Technology).

FDG-PET
Metabolic activity of tumours was investigated by fluorodeoxyglucose positron emission tomography (FDG-PET; at baseline; Day 15, Cycle 1; Day 1, Cycle 3). Baseline and follow-
up PET scans were performed using a single scanner and under the same conditions (administered $^{18}$F-FDG activity for all scans was maintained within 10% of the calculated activity administered at baseline and the same acquisition time per bed position was used for all scans for each individual patient). Low-dose CT scans were performed for all PET scans for attenuation correction. Independent analysis of PET images was performed centrally based on European Organisation for Research and Treatment of Cancer guidelines (20). Lesions with the highest degree of FDG uptake were selected for quantitative analysis (up to five) and a 10 mm circular/spherical region of interest drawn. A standardised uptake value (SUV) was measured for each selected lesion and the delta change in SUV between baseline and Day 15 of Cycle 1 was calculated for each patient. FDG-PET scanning took place before tumour biopsies to avoid interference on FDG uptake. Patients with a recent history of diabetes were excluded from FDG-PET analysis.

**Tumour response**

Tumour assessments according to RECIST criteria (version 1) were performed at screening, every 2 cycles and on suspicion of disease progression.

**Statistical analyses**

PK/PD, safety, and tumour response data were analysed by descriptive statistics. Correlations between specific AEs and anti-tumour activity or PK were assessed by logistic regression and Analysis of Variance (ANOVA).
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Results

Forty-nine patients were enrolled between January 2009 and June 2010 (Table 1), all received at least one dose of RO4987655. The most common tumour types were melanoma (n=27, 55.1%; including choroidal melanoma, n=9) and colorectal cancer (CRC, n=11, 22.4%). None of the patients had previously received treatment with a MEK inhibitor.

Thirteen patients received RO4987655 QD (1.0–2.5 mg) and 36 received RO4987655 BID (3.0–21.0 mg total daily dose [TDD]; Supplementary Figure 1). Patients received a median of two treatment cycles (range 0–12; 93.8% of patients completed at least one cycle), with a median duration of treatment of 57 days (range 2–337).

Four DLTs were observed during the first 28 days of treatment, all with BID dosing (Table 2). At 8.5 mg BID (TDD, 17 mg) one patient experienced Grade 3 elevated CPK. No further DLTs were observed when this cohort was expanded to nine patients in total. After escalation to 10.5 mg BID (TDD, 21 mg), three patients experienced DLTs (Grade 3 blurred vision, Grade 3 elevated CPK and Grade 4 elevated CPK). Accordingly, 8.5 mg BID (TDD 17.0 mg) was defined as the MTD. All DLTs were reversible.

Safety

Patients experienced 189 treatment-related AEs, including 20 Grade 3 AEs (in 17 patients) and two Grade 4 AEs (in two patients). The most common AEs (≥10% of patients, Table 2) were skin toxicity (rash-related, n=45 [92% of patients]; dry skin, n=7 [14%]; skin fissures, n=6 [12%]) and gastrointestinal (diarrhoea, n=16 [33%]; nausea, n=7 [14%]; vomiting, n=6 [12%]; stomatitis, n=5 [10%]). Grade 3/4 AEs were primarily limited to BID dosing of ≥5.0 mg. Among the rare (<10% patients) Grade ≥3 toxicities, isolated and reversible Grade 3 neutropenia occurred in two patients in the 1.5 mg and 10 mg dose cohorts and one case of reversible Grade 3 anaemia occurred in the 13 mg dose cohort treated by transfusion on Day 63. One patient was reported with a Grade 3 left ventricle ejection fraction decrease in the 13 mg dose cohort which occurred on Day 56 when drug was stopped due to
progression of the disease. The other Grade 3 toxicities included general disorders (asthenia, depression, decreased appetite) and skin disorders (Table 2). Most rash-related toxicities were Grade 1/2, with six patients experiencing Grade 3 events and no Grade 4 events reported. Median time to development of Grade 3 rash was 49.5 days (range 9–146). Skin toxicity developed primarily in the face, upper trunk and back; comprising red papulopustules and crusts, occasionally accompanied by swelling (mainly the nose). Severe psychological impacts were reported in patients experiencing substantial alterations in appearance.

Sixteen eye-related AEs occurred in 13 [27%] patients (including blurred vision, photopsia, corneal erosion, dry eyes, periorbital oedema, chorioretinopathy, punctate keratitis and retinal vein occlusion [RVO]). Blurred vision was associated with fluid accumulation in the sub-retinal space, identified by optical coherence tomography (OCT), resulting in serous retinal detachment (SRD) in one patient. Two patients experienced Grade 3 ocular toxicity (RVO [8.5 mg BID] and blurred vision [10.5 mg BID]). Median time-to-onset of ocular toxicity was 12 days (range 1–175 days), and median duration of toxicity was 14 days (range 2–104 days). Ocular toxicity resolved either spontaneously or with drug interruption (two Grade 2 and two Grade 3) except for one patient with Grade 3 visual disturbances associated with RVO who improved to Grade 1 at study completion, and one with Grade 1 blurred vision whose condition remained unresolved at study completion.

Nine [18%] patients experienced elevated CPK including four Grade 3 (one at 2.0 mg BID, two at 8.5 mg BID and one at 10.5 mg BID) and two Grade 4 events (at 8.5 mg BID and 10.5 mg BID). CPK elevation was reversible with drug interruption and was asymptomatic in most patients and not associated with either clear rhabdomyolysis symptoms or cardiac dysfunction. Three cases of Grade 1 myalgia (in three patients), one Grade 1 joint swelling, one Grade 2 joint stiffness, one Grade 2 neck pain, one Grade 1 pain in extremity, and one Grade 2 muscular weakness were reported in association with CPK elevation.
Eight patients experienced dose reductions due to treatment-related AEs (one patient at 1.5 mg QD and 4.0/3.5 mg BID, and three patients at 8.5 mg BID and 10.5 mg BID), including five patients who experienced more than one AE-related dose interruption (one patient at 1.5 mg QD and two patients each at 8.5 mg BID and 10.5 mg BID). Of the nine patients receiving RO4987655 at the RP2D (8.5 mg BID), the median duration of dosing was 87.5 days (range 50–194) in the six patients who did not undergo dose modification. Median time to dose modification in the remaining three patients was 37 days (range 14–51).

Eleven patients experienced temporary drug interruptions due to AEs (one each at 1.5 mg QD, 2.0 mg QD, 4.0/3.5 BID and 5.0 mg BID; two at 6.5 mg BID and 10.5 mg BID and three patients at 8.5 mg BID). The median duration of interruption was 7 days; range 1–21; Supplementary Table 1).

Seven patients experienced eight treatment-related serious AEs (SAEs; all Grade 2/3; Table 2). Five of the SAEs were resolved, two with dose modifications, two without dose modifications and one with treatment discontinuation. The remaining three SAEs were unresolved. Two deaths following disease progression were not considered to be treatment-related.

**Anti-tumour activity**

Clinical benefit (defined as partial response [PR] or stable disease [SD] lasting ≥16 weeks) was seen in eight of the 38 evaluable patients (21.1%; Figure 1), including one confirmed and one unconfirmed PR in patients with skin melanomas (mutational status unknown). These patients received treatment with RO4987655 for 113 and 224 days (mean 168.5 days) and responses lasted for 48 and 168 days (mean 108 days). Six other patients achieved SD lasting >16 weeks: three patients with melanoma, two patients with choroidal melanoma, and one patient with a rectal adenocarcinoma. The median percentage change in tumour size at maximum reduction from baseline in evaluable patients was 9.8% (range –66.9% to 101.4%).
**Pharmacokinetics**

Pharmacokinetics were assessed in 43 patients (87.8%). Plasma concentrations of RO4987655 increased rapidly following oral administration. For the majority of patients, $C_{\text{max}}$ was reached $\sim30–60$ minutes after dosing (Figure 2A, Table 3). Mean terminal half-life was $\sim4$ hours. Plasma exposure increased approximately dose-proportionally on Day 1 (Figure 2B) and increased linearly with dose at steady state (Figure 2C). Intra-patient variability in plasma exposure was limited (Table 3). At the MTD, $C_{\text{max}}$ and $AUC_{0–12\text{hr}}$ were 425 ng/mL and 1660 ng·hr/mL, respectively, at Day 1 and 530 ng/mL and 2577 ng·hr/mL, respectively, at steady state. The mean accumulation index ($AUC_{\text{Day 15}}/AUC_{\text{Day 1}}$) was 1.53 (range 1.15–1.96). Increased steady-state plasma exposure was significantly associated with occurrence of Grade 2/3 rash (logistic regression, $p=0.01$) and showed a trend towards association with CPK elevation (ANOVA; $p=0.07$).

**Pharmacodynamics**

**pERK inhibition in peripheral blood lymphocytes**

Assessment of target suppression was evaluated by measuring the extent of pERK inhibition in a surrogate tissue, PBMC. The relationship between exposure (RO4987655 plasma concentration) and PD effect (pERK inhibition in PBMCs) was characterised by a direct link PK/PD (effect compartment) model which revealed 70–80% pERK inhibition at plasma concentrations of $>200$ ng/mL (Figure 3A).

**Tumour/skin biopsies**

Between baseline and Day 15, pERK expression in tumour biopsies decreased by $\geq20\%$ in six of seven evaluable patients and increased by $\geq20\%$ in the other (Figure 3B, Supplementary Table 2). One tumour demonstrated $>90\%$ reduction in pERK expression. Paired pre- and post-treatment normal skin biopsies were available from 20 patients; five showed a decrease in pERK expression of $\geq20\%$ by Day 15, 14 showed no change, and IHC failed in one patient (Figure 3B, Supplementary Table 2). One skin biopsy demonstrated
>90% pERK reduction. Most tumour and skin biopsies showed no change in cell proliferation (Ki67 labelling) between baseline and Day 15 (Supplementary Table 2). Three of five paired tumour biopsies demonstrated no change in apoptotic signal between baseline and Day 15 (TUNEL assay; Supplementary Table 2). No correlations were observed between changes in biomarker levels and tumour response, mutational status, or exposure.

**Mutational analysis**

Mutational analyses were performed for tumour samples from a total of 30 patients; 22 samples were suitable for assessment of *BRAF V600* and *KRAS* mutations, 21 were suitable for *NRAS*, 18 for *HRAS* and *PI3K*, and 10 samples were suitable for assessment of *PTEN* loss. Of the 30 tumour samples assessed, eight revealed mutations (Table 1) including two melanomas with *BRAF* (V600) mutation, five CRC with *KRAS* mutation and one CRC with both *KRAS* and *PI3K* mutations. Figure 1 shows the mutational status of tumours that were evaluable for tumour response.

**FDG-PET**

FDG-PET was performed in 34 patients. Between baseline and Day 15, 27 patients (79.4%, QD, n=1; BID, n=26) demonstrated a reduction in FDG uptake (Figure 3C). In most cases, reductions in FDG uptake were maintained until at least Week 8 in patients not progressing between assessments. Excluding one outlier, there was a positive relationship between dose/exposure and change in FDG uptake between baseline and Day 15 in the overall population. This relationship was more pronounced in melanoma patients, where larger changes in FDG uptake were observed as dose increased. Change in FDG-PET uptake was weakly correlated with tumour response (RECIST). All patients achieving a PR or SD (>16 weeks) demonstrated a reduction in FDG uptake by Day 15 (see Supplementary Figure 2). Larger reductions in FDG uptake between baseline and Day 15 were observed with increased pERK inhibition in PBMCs.
Discussion

In patients with advanced solid tumours, oral RO4987655 was moderately tolerated with manageable toxicity and demonstrated a favourable PK/PD profile and encouraging anti-tumour activity. The safety profile of RO4987655 in this study was consistent with data from healthy volunteers with no new safety signals being identified. The management and treatment of safety events was facilitated by the short half-life of RO4987655. The MTD of RO4987655 was 8.5 mg BID (17.0 mg TDD). DLTs were Grade 3 blurred vision (n=1) and Grade 3/4 elevated CPK (n=3); all of which were reversible without treatment.

The most frequent RO4987655-related AEs were skin toxicity and gastrointestinal disorders. MEK inhibitor class effects included rash (91.8%) and eye-related toxicity (26.5%). Previous studies with MEK inhibitors have reported rash, diarrhoea, nausea, fatigue and visual disturbances as the most common treatment-related AEs (5;8;13;21;22). An indirect comparison between RO4987655 and the Phase I published data from other MEK inhibitors suggests that RO4987655 has a comparable safety profile with a higher frequency of rash-related toxicity (92% vs. 38–79%), but a generally lower incidence of diarrhoea (32% vs. 32–55%), nausea (14% vs. 29–54%) and eye-related toxicity (27% vs. 33–50%) (5;8;13;21;22), while CPK elevation which was observed regularly in this study, has so far not been observed with other MEK inhibitors (5;13;21;23).

Ocular toxicity is a known class effect of MEK inhibitors and was also observed in this study. Two episodes of blurred vision even occurred very early in treatment, after one or two days of dosing. The majority of visual symptoms reported in this study were due to SRD, but OCT was not systematically performed, preventing accurate evaluation of the incidence of associated SRD. Although ocular toxicities can be alarming for both patients and physicians, all cases of SRD reported in this study were reversible without any specific treatment and without long-term damage. This is in line with blurred vision reported in other studies (5;8;13). Other class-related ocular complications in this study occurred less frequently than
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SRD and include ocular hypertension, which can be detected by regular measure of intraocular pressure, and RVO, that can be detected early by regular fundus photographs. Since the pathogenesis of MEK-related eye disorders remains unknown and experience with chronic administration of MEK inhibitors is limited, careful monitoring of ocular disorders should be implemented in further clinical trials with MEK inhibitors to ensure adequate management of patients.

CPK elevation was reported in this study and considered related to RO4987655. Systematic measurement of CPK in this study may have generated a higher incidence of reports. Most elevated CPK episodes were asymptomatic and no RO4987655-related cardiovascular disorders or rhabdomyolysis were observed. The mechanism behind the observed CPK elevation remains unknown at present. A direct role of MEK inhibition cannot be excluded as the MAPK pathway plays a key role in regulation of muscle cell signalling (24-27).

RO4987655 monotherapy demonstrated encouraging anti-tumour activity as measured by RECIST. Like other MEK inhibitors, RO4987655 showed clinical activity against melanoma (13;21-23). Seven of the eight patients who achieved clinical benefit with RO4987655 had melanoma tumours, including two PRs (one confirmed, one unconfirmed; both at 8.5 mg BID). No clear correlation existed between response and mutational status; however, the number of patients with mutation data was limited. Based on the safety and PK/PD profile data presented here, a dose-regimen of 8.5 mg BID (17.0 mg TDD) RO4987655 is recommended for Phase II studies.

Pharmacokinetic analyses showed that RO4987655 was absorbed rapidly, reaching $C_{\text{max}}$ 0.5–1 hour after dosing, and that plasma concentration and exposure increased approximately dose-proportionally. The PK of RO4987655 were linear, time-independent, and consistent with an earlier study in healthy volunteers, with the exception of terminal half-life, which was much shorter than previously reported (~4 hours vs. 25 hours, respectively) (16). While the reason for this remains unclear, it may indicate that the longer sampling period employed previously allowed for a more accurate assessment of the terminal phase.
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half-life: RO4987655 was monitored for 72 hours post-dosing in healthy volunteers but only 12 hours in this study due to the inclusion of BID dosing. The influence of food on the absorption of RO4987655 remains to be determined. Data from recent studies with other MEK inhibitors are conflicting; while administration with a high-fat meal was shown to increase exposure to the oral inhibitor CI-1040, exposure to selumetinib was reduced when administered with food (28;29). Patients in this study were lightly fasted prior to dosing with RO4987655; the effect of food on the exposure to RO4987655 will be investigated during further development of this compound.

Although higher plasma concentrations of RO4987655 were associated with greater pERK inhibition in PBMCs and almost all tumour samples demonstrated a significant decrease in pERK expression by Day 15(Cycle 1), target suppression in skin biopsies was observed in only a quarter of cases. Overall, skin and tumour biopsies showed no change in either tumour cell proliferation or apoptosis between baseline and Day 15, possibly reflecting the RO4987655’s cytostatic nature. Data on inhibition of tumour cell proliferation and induction of apoptosis in response to MEK inhibition are limited; decreased tumour Ki67 has been demonstrated in response to treatment with AZD6244 and PD-0325901 (5;13). The exact mechanism by which apoptosis is induced by MEK inhibition has not been identified and better understanding will be important in the development of strategies to overcome treatment resistance (30;31).

Evidence of biological activity was demonstrated by FDG-PET, particularly in melanoma where decrease in FDG uptake appeared to be associated with dose and drug exposure. In addition, a weak relationship was observed between change in FDG uptake (between baseline and Day 15) and RECIST tumour assessment. All patients achieving a PR or SD lasting >16 weeks demonstrated a reduction in FDG uptake by Day 15, suggesting that an FDG decrease was necessary, but not sufficient, for later tumour response. Furthermore, FDG-PET data correlated with PBMC pERK inhibition; larger changes from baseline were associated with increased inhibition of pERK. Clinical studies investigating other signal
transduction inhibitors like imatinib (in gastrointestinal stromal tumours and soft-tissue sarcomas) (32;33) and erlotinib (in NSCLC) (34;35) and the chemotherapy agent irinotecan (in CRC) (36), have supported the role of FDG-PET as a predictive marker of clinical activity, although this needs large-study confirmation.

There is currently an unmet need for effective treatment of patients with tumours containing KRAS mutations and patients with wild-type BRAF melanoma (37-41). While the mutational analysis in this study was limited, MEK inhibition may offer a therapeutic option independent of KRAS and BRAF mutation state, most likely in combination with chemotherapy and/or another targeted agent. Recent preclinical data demonstrate that combined RAF/MEK inhibitors can block ERK activation in resistant cells and may delay emergence of resistance (42;43). Studies with other MEK inhibitors are investigating combinations with AKT inhibitors, PI3K inhibitors, and chemotherapy agents such as paclitaxel and docetaxel (44-48). The optimum partners for RO4987655 remain to be determined; however, in vitro and in vivo data demonstrate that combination with PI3-kinase pathway inhibitors (mTOR, PI3K inhibitors) (15), other targeted agents, or chemotherapy agents (cisplatin, paclitaxel and gemcitabine) may potentiate RO4987655’s anti-tumour activity.

Single-agent RO4987655 is currently under investigation in an expansion of this study in four parallel patient cohorts including patients with: (1) melanoma tumours carrying the BRAF (V600) mutation, (2) melanoma tumours not carrying the BRAF (V600) mutation, (3) NSCLC carrying KRAS mutations, and (4) CRC carrying KRAS and/or BRAF (V600) mutations. The primary endpoint of this expansion cohort study will be to investigate the efficacy of single-agent RO4987655 in these specific tumour genotypes, using approximately 20 patients per cohort. Further development of RO4987655 will involve combination with chemotherapy or other signal transduction inhibitors.

In summary, oral RO4987655 was reasonably well tolerated in patients with advanced or metastatic solid tumours, but often resulted in skin toxicity (91.8%; primarily facial, and with psychosocial impact reported). RO4987655 revealed a safety profile comparable with other
MEK inhibitors. The main DLTs were reversible blurred vision and elevated CPK. At the RP2D, high (~70%) and sustained (>IC\textsubscript{50} for >90% of time) pERK inhibition was observed in PBMCs, and plasma drug concentrations were in the range predicted to be efficacious in preclinical models. Metabolic and anatomic responses were observed in all tumour types, but particularly in patients with melanoma tumours.

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Reference List


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# TABLES

## Table 1: Patient demographics and clinical characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Total patients n=49</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30 (61%)</td>
</tr>
<tr>
<td>Female</td>
<td>19 (39%)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>53</td>
</tr>
<tr>
<td>Range</td>
<td>22–79</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>48 (98%)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Baseline ECOG performance status</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>23 (47%)</td>
</tr>
<tr>
<td>1</td>
<td>25 (51%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Prior anti-cancer therapies, median (range)</strong></td>
<td>3 (1–9)</td>
</tr>
<tr>
<td><strong>Primary cancer site and mutational status</strong></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>27</td>
</tr>
<tr>
<td><em>BRAF</em> (V600)</td>
<td>2</td>
</tr>
<tr>
<td>No mutation</td>
<td>7</td>
</tr>
<tr>
<td>Unknown</td>
<td>18</td>
</tr>
<tr>
<td>Colon/large intestine and rectum</td>
<td>11</td>
</tr>
<tr>
<td><em>KRAS</em></td>
<td>6(^a)</td>
</tr>
<tr>
<td><em>PI3KCA</em></td>
<td>1(^a)</td>
</tr>
<tr>
<td>No mutation</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
</tr>
<tr>
<td>Lung</td>
<td>3(^b)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>2(^b)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1(^b)</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>1(^b)</td>
</tr>
<tr>
<td>Thymoma</td>
<td>1(^b)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1(^b)</td>
</tr>
<tr>
<td>Cervix</td>
<td>1(^b)</td>
</tr>
<tr>
<td>Clear-cell sarcoma</td>
<td>1(^b)</td>
</tr>
</tbody>
</table>

**FOOTNOTE:** \(^a\)One tumour contained both a *KRAS* and *PI3KCA* mutation; \(^b\)Mutational status unknown. ECOG, Eastern Cooperative Oncology Group.
Table 2: Treatment-related toxicity

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Total daily dose (mg)</th>
<th>QD dosing*</th>
<th>BID dosing*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>1.5 (n=4)</td>
<td>3 (n=3)</td>
<td>4 (n=3)</td>
</tr>
<tr>
<td></td>
<td>5.5 (n=4)</td>
<td>7.5 (n=4)</td>
<td>10 (n=4)</td>
</tr>
<tr>
<td></td>
<td>13 (n=4)</td>
<td>17 (n=9)</td>
<td>21 (n=4)</td>
</tr>
</tbody>
</table>

**DLTs**
- Grade 3 blurred vision (n=1)
- Grade 3 elevated CPK (n=2)
- Grade 4 elevated CPK (n=1)

**Treatment-related AEs**

<table>
<thead>
<tr>
<th>AEs (all grades)</th>
<th>n</th>
<th>%</th>
<th>AEs (Grade 3–4 only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash-related†</td>
<td>45</td>
<td>91.8</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>16</td>
<td>32.7</td>
<td>1</td>
</tr>
<tr>
<td>Eye-related*</td>
<td>13</td>
<td>26.5</td>
<td>1</td>
</tr>
<tr>
<td>Elevated CPK</td>
<td>9</td>
<td>18.4</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8</td>
<td>16.3</td>
<td>1</td>
</tr>
<tr>
<td>Dry skin</td>
<td>7</td>
<td>14.3</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>14.3</td>
<td>1</td>
</tr>
<tr>
<td>Skin fissures</td>
<td>6</td>
<td>12.2</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>12.2</td>
<td>2</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>5</td>
<td>10.2</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>3</td>
<td>6.1</td>
<td>1</td>
</tr>
<tr>
<td>Asthenia</td>
<td>3</td>
<td>6.1</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
<td>6.1</td>
<td>1</td>
</tr>
<tr>
<td>Anaemia</td>
<td>2</td>
<td>4.1</td>
<td>1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2</td>
<td>4.1</td>
<td>1</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
<td>2.0</td>
<td>1</td>
</tr>
<tr>
<td>Decreased Ejection Fraction</td>
<td>1</td>
<td>2.0</td>
<td>1</td>
</tr>
</tbody>
</table>

**Treatment-related SAEs (all grades)**

<table>
<thead>
<tr>
<th>SAEs (all grades)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Retinal vein occlusion</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Chorioretinopathy</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Elevated CPK</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>1</td>
<td>2.0</td>
</tr>
</tbody>
</table>

1
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FOOTNOTE: Data cut-off: January 28th 2011. Only the most severe intensity was counted for multiple occurrences of the same AE in one individual. Adverse events occurring in >10% of patients are shown above the dotted line. AEs, adverse events; BID, twice daily; CPK, creatine phosphokinase; DLT, dose-limiting-toxicity; QD, once daily; SAEs, serious adverse events.

*aOnly one Grade 3 toxicity (neutropenia) was reported in only one dosing-cohort in the QD regimen (1.5 mg QD);

*bThe most common AEs were reported at Grade 3 or 4 severity in the BID dosing cohorts. Two Grade 4 AEs occurred, both elevated CPK (8.5 mg and 10.5 mg, BID). No Grade 5 AEs occurred. Nausea/vomiting, skin rash and/or diarrhoea were only considered a DLT if they reached Grade ≥3 severity despite adequate supportive care measures. SAEs were defined as any AE which was fatal; life-threatening; required in-patient hospitalization or prolongation of existing hospitalisation; resulted in persistent or significant disability/incapacity; was a congenital anomaly/birth defect; was medically significant or required intervention to prevent one or other of the outcomes listed above. No SAEs occurred in once-daily dosing cohorts;

*cNo further DLTs were observed when the 17.0 mg (BID) cohort was expanded to nine patients;

dIncludes dermatitis aciform, rash, dermatitis, papular rash, folliculitis, and genital rash;

*eIncludes blurred vision, photopsia, corneal erosion, dry eyes, periorbital oedema, chorioretinopathy, punctate keratitis and retinal vein occlusion;

*fNo signs of chronic or acute gastrointestinal bleeding were observed and no haemoglobinuria was recorded.
## Table 3: Summary of pharmacokinetics of RO4987655 in patients following oral administration

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Day 1</th>
<th>Day 15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>AUC&lt;sub&gt;0-12h&lt;/sub&gt; ng•hr/mL (% CV)</td>
</tr>
<tr>
<td>1.5 mg (BID)</td>
<td>4</td>
<td>278 (27%)</td>
</tr>
<tr>
<td>2.0 mg (BID)</td>
<td>3</td>
<td>321 (7%)</td>
</tr>
<tr>
<td>3.0 mg (BID)</td>
<td>4</td>
<td>596 (44%)</td>
</tr>
<tr>
<td>4.0 mg (BID)</td>
<td>4</td>
<td>608 (38%)</td>
</tr>
<tr>
<td>5.0 mg (BID)</td>
<td>4</td>
<td>797 (64%)</td>
</tr>
<tr>
<td>6.5 mg (BID)</td>
<td>3</td>
<td>1005 (35%)</td>
</tr>
<tr>
<td>8.5 mg (BID)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9</td>
<td>1660 (39%)</td>
</tr>
<tr>
<td>10.5 mg (BID)</td>
<td>4</td>
<td>2282 (43%)</td>
</tr>
</tbody>
</table>

**FOOTNOTE:** <sup>a</sup>Accumulation index represents AUC<sub>Day 15</sub>/AUC<sub>Day 1</sub>; <sup>b</sup>Maximum tolerated dose. AUC, area under the plasma concentration time curve; BID, twice daily; C<sub>max</sub>, maximum plasma drug concentration; CV, coefficient of variation; t<sub>1/2</sub>, plasma half-life.
TABLE AND FIGURE LEGENDS

Table 1. Patient demographics and clinical characteristics

Table 2. Treatment-related toxicity

Table 3. Summary of pharmacokinetics of RO4987655 in patients following oral administration

Figure 1. Relative change (%) in sum of lesion size from baseline at best overall response.

FOOTNOTE: Thirty-eight patients were evaluable for tumour response. Target lesions were not measured in seven patients, three patients were not evaluable at Day 1 of Cycle 3 and tumour assessment was not completed for one patient. By the end of the study, 44 patients had progressed. All patients were eventually withdrawn from treatment: 43 due to disease progression, five due to AEs and one due to refusal of treatment. Tumour response assessments were performed according to RECIST criteria (version 1). Dotted line indicates the RECIST cut-off for partial response (~30%). The figure also depicts mutation status for patients with response data: BRAF (*), KRAS (▲); wild type (○), PI3K (■); one melanoma patient with BRAF mutation and two CRC patients with KRAS mutation were not evaluable for response and are not shown. BID, twice daily; CRC, colorectal cancer; QD, once daily; RECIST, Response Evaluation Criteria In Solid Tumours

Figure 2. Mean plasma concentration (A) and plasma exposure (B) on Day 1 and plasma exposure on Day 15 (C) of RO4987655 following oral administration.

FOOTNOTE: Blood was collected for PK assessment from 43 patients on Day 1: pre-dose (0 hours) and 1, 3, 7 and 12 hours post-dose. For patients on BID dosing cohorts, PK parameters were measured after the first daily dose. Figure 2A (mean plasma concentration): Data points represent the mean plasma concentrations on Day 1. Cmax was reached approximately 0.5–1 hour after dosing. Mean terminal half-life was ~4 hours. The figure legend shows administered dose, rather than total daily dose. Figures 2B (plasma exposure on Day 1) and 2C (plasma exposure on Day 15): Steady-state conditions were reached by Day 15 and drug accumulations were assessed by the plasma...
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exposure (AUC$_{0-12h}$). Data points represent mean plasma exposure and error bars represent standard deviation.

Figure 3A. (A) RO4987655 plasma and effect concentrations versus PBMC pERK inhibition (all doses); (B) Case study: pERK expression in paired tumour (i and ii) and normal skin (iii and iv) biopsies obtained prior to treatment with RO4987655 (baseline) and on Day 15 of Cycle 1; (C) Relative change (%) in FDG-PET from baseline to Day 15 of Cycle 1.

FOOTNOTE: Figure 3A: Measurements were fitted to an effect compartment PK/PD model of pERK inhibition in PBMCs (Supplementary material). 70–80% inhibition of pERK was observed at RO45987655 plasma concentrations of >200 ng/mL. Half maximal inhibitory concentration (IC$_{50}$), 53 ng/mL; 90% inhibitory concentration (IC$_{90}$), 480 ng/mL. Average regression is represented by the blue line, and 90% confidence intervals of the mean regression are shown as purple lines. A time delay of ~3 hours was observed between C$_{max}$ and the maximum effect generated by the PK/PD model.

FOOTNOTE: Figure 3B: Representative images depicting immunohistochemistry for pERK in paired tumour biopsies taken from a patient with melanoma. This patient received RO4987655 at a dose of 8.5 mg BID (17.0 mg TDD) and the patient achieved stable disease lasting for 28 weeks. In this case study, reductions in nuclear pERK expression of 65% and 97% were observed in the tumour and skin biopsies, respectively, between baseline and Day 15.

FOOTNOTE: Figure 3C: * +320% change from baseline (PET % change) was trimmed at +125% for aesthetic purposes); **, patients who achieved partial responses (the patient initially treated at 10.5 mg BID underwent a dose reduction to 8.5 mg BID due to a DLT [CPK elevation]). FDG-PET was performed at baseline and on Day 15 of Cycle 1 in 34 patients (69.4%; three patients received RO4987655 QD and 31 received RO4987655 BID). BID, twice daily; CRC, colorectal cancer.
Percentage change from baseline (sum of the longest diameter)

- **BRAF V600**
- **KRAS**
- **Melanoma**
- **CRC**
- **Other**
- **PI3K**

(RECIST cutoff for PR, 30%)
**A**

Plasma concentration of RO4987655 (ng/mL) vs Time (hr)

Dose (mg): 10.5 mg, 8.5 mg, 6.5 mg, 5 mg, 4 mg, 3 mg, 2 mg, 1.5 mg

**B**

AUC$_{0-12	ext{hr}}$ (ng•hr/mL) vs Dose (mg)

**C**

AUC$_{0-12	ext{hr}}$ (ng•hr/mL) vs Dose (mg)
Clinical Cancer Research

Phase I Dose-escalation Study of the Safety, Pharmacokinetics and Pharmacodynamics of the MEK Inhibitor RO4987655 (CH4987655) in Patients with Advanced Solid Tumours

Suzanne Leijen, Mark R. Middleton, Patricia Tresca, et al.

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