Evaluating intermittent schedules of the oral RAF-MEK inhibitor CH5126766 in patients with *RAS/RAF*-mutated solid tumours and multiple myeloma: a single-centre, phase 1 trial.

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Abstract

Background

CH5126766 (VS-6766, RO5126766), a novel MEK/pan-RAF inhibitor, has antitumor activity across various solid tumours but initial development was limited by toxicity. We aimed to investigated the safety and toxicity profile of intermittent schedules of CH5126766 and its antitumour activity in patients with solid tumours and multiple myeloma (MM) harbouring RAS-RAF-MEK pathway mutations.

Methods

In this open-label, dose-escalation and basket expansion, phase 1 study conducted at a UK centre, we recruited patients (aged ≥ 18 years) with World Health Organisation performance status of 0 or 1, who had solid tumours or MM refractory to conventional therapy or for whom no conventional therapy existed. Eligible patients for the basket expansion had tumours harbouring RAS-RAF-MEK pathway mutations. During dose-escalation, we evaluated three intermittent oral schedules (28-day cycles) in patients with solid tumours: i) 4·0 mg thrice-weekly (TIW, Mon/Wed/Fri); ii) 4·0 mg twice-weekly (BIW, Mon/Thu or Tue/Fri); iii) toxicity-guided treatment interruption schedule where treatment at the recommended phase 2 dose (RP2D) was de-escalated to 3 weeks on, 1 week off if patients experienced pre-specified toxicities. In the expansion, we evaluated antitumour activity at the RP2D in biomarker-selected baskets: non-small cell lung cancer (NSCLC), gynaecological malignancies (GM), colorectal cancers (CRC), melanoma, and MM. The primary endpoints were RP2D at which no more than one out of six patients experienced a treatment-related dose-limiting toxicity (DLT), and safety and toxicity profile for each schedule. The key secondary endpoint was response rate in the expansion phase. All analyses were per protocol. This trial is registered with ClinicalTrials.gov, NCT02407509. The study was subsequently amended to combine CH5126766 with everolimus; recruitment to this arm ongoing.

Findings

Between June 5, 2013 to January 10, 2019, 58 eligible patients were enrolled (29 dose-escalation; 29 dose-expansion). Median follow-up at the time of data cut-off was 2·3 months (Interquartile range: 1·6-3·5 months). DLTs, including grade 3 bilateral retinal pigment epithelial detachment occurred at 4·0 mg TIW, grade 3 rash (in two patients) and grade 3 creatinine phosphokinase (CPK) elevation occurred at 3·2 mg TIW; 4·0 mg BIW was established as the RP2D. Out of the 57 safety-evaluable patients, the most common treatment-related adverse events (TRAEs) (in ≥30% of population) were rash (50, 87·7%), CPK elevation (42, 73·7%), visual disturbance (25, 43·9%), diarrhoea (23, 40·4%), fatigue (21, 36·8%), and peripheral oedema (18, 31·6%). The most common grade 3-4 TRAEs (in ≥5% of patients) were rash (11, 19·3%), CPK elevation (6, 10·5%), hypoalbuminemia (6, 10·5%), and fatigue (4, 7·0%). Five (8·8%) patients experienced treatment-related serious adverse events. There was no treatment-related death. Seven (26·9%) of 26 response-evaluable patients in the basket expansion achieved objective responses, with response rates in patients with NSCLC, GM, CRC, melanoma, and MM being 3/10 (30·0%), 3/5 (60·0%), 0/4 (0·0%), 0/1 (0·0%), and 1/6 (16·7%), respectively. All patients with *KRAS*-mutant solid tumours had non-G12C mutations.

Interpretation

To our knowledge, this is the first study to show that highly intermittent schedules of a RAF-MEK inhibitor has antitumour activity across various cancers with RAF-RAS-MEK pathway mutations and is tolerable. CH5126766 monotherapy and in combinations warrant further evaluation.

Funding

Chugai Pharmaceutical

Research in Context

Evidence before the study

We searched PubMed using the terms “clinical trial” AND “adult” AND “neoplasm” AND (“RAF” OR “MEK” OR “RAS” OR “ERK” OR “BRAF” OR “NRAS” OR “KRAS” OR “HRAS” OR “MAPK” OR “MAP kinase”) NOT “review” with no time restriction for reports published in English. CH5126766 is the only known dual RAF and MEK inhibitor. We previously showed that CH5126766 had promising antitumour activity in solid tumours but development was limited by toxicity. Our search yielded clinical studies of direct inhibitors of MEK, RAF, and ERK, as well as inhibitors of farnesyltransferase across various cancers. KRAS (G12C) inhibitors have recently shown antitumour activity in non-small-cell lung cancers harbouring this mutation and represent the first breakthrough in direct RAS targeting. Our search also yielded studies of combinations of MEK or RAF inhibitors with other targeted therapies or chemotherapy. BRAF inhibitor or the combination of BRAF and MEK inhibitors are licensed for use in $BRAF^{V600}$-mutant melanoma and the triplet combination of BRAF, MEK and EGFR inhibitors is provisionally approved for the treatment of $BRAF^{V600E}$ colorectal cancer.

Added value of this study

To our knowledge, this is the first study to show proof-of-concept single agent activity of a RAF-MEK inhibitor, administered as an intermittent twice-weekly schedule, across a wide range of RAS/RAF-driven cancers including multiple myeloma.

Implications of all the available evidence

This expands the possibility of the use of RAF-MEK inhibitor monotherapy and in rational combination with targeted therapies in RAS-RAF-MEK pathway mutation-driven cancers.

Introduction

The mitogen-activated protein kinase (MAPK) pathway is the most commonly mutated oncogenic pathway in human malignancies, implicated in over a third of solid tumours and around half of multiple myeloma (MM) [1,2]. Aberrant signalling through the MAPK pathway drives tumour cell proliferation, differentiation, survival, and migration [1].

KRAS driver mutations have been considered a difficult target to drug[3]. Inhibition of downstream signalling such as through MEK or farnesyltransferase have shown limited success[4,5]. AMG510 is the first agent to directly target KRAS(G12C) and has demonstrated antitumour activity in *KRAS*^{G12C} non-small cell lung cancer (NSCLC)[6]. Among the *RAF*-mutant malignancies, combined BRAF and MEK inhibition has improved overall survival in patients with *BRAF*^{V600}-mutant melanoma [7]. Triplet BRAF, MEK and EGFR inhibition has also been shown to improve overall survival in *BRAF*^{V600E} colorectal cancer (CRC)[8]. Overall, there remains an unmet need to develop targeted therapies which have efficacy beyond selective inhibition of BRAF(V600) or KRAS(G12C) as this unserved population of cancers constitute the majority of malignancies harbouring RAS-RAF-MEK pathway mutations.

CH5126766/VS-6766, previously named RO5126766, is a first-in-class MEK inhibitor with concomitant functional RAF inhibitory activity[9]. Henceforth in this manuscript, the agent will be referred to as CH5126766. CH5126766 allosterically inhibits MEK and prevents its phosphorylation by RAF through the formation of a stable RAF-MEK complex, thereby also prevents MEK from activating downstream ERK [9]. A first-in-human (FIH) study of CH5126766 recommended a phase 2 dose of 2·7 mg taken for four continuous days every week. Although three patients with melanoma achieved objective responses, common toxicities such as rash (all grades: 94%), raised creatinine phosphokinase (CPK) (all grades: 56%) and diarrhoea (all grades: 52%) led to difficulty developing this drug further [10].

Side effects of tyrosine kinase inhibitors (TKIs) have been mitigated by intermittent dosing schedules and toxicity-guided treatment interruptions, or drug holidays, without diminishing antitumour activity

[11,12]. In keeping with the long half-life of CH5126766 of approximately 55 hours, pharmacokinetic simulation of CH5126766 administered twice-weekly (BIW, Mon/Thu or Tue/Fri) or thrice-weekly (TIW, Mon/Wed/Fri) showed highly intermittent schedules could provide clinically relevant drug exposure (Appendix p 3)[10].

We hypothesised that twice or thrice-weekly schedules would allow adequate drug exposure with improved toxicity profiles to facilitate the exploration of antitumour activity in biomarker-selected cohorts. To our knowledge, this is the first study to evaluate the clinical activity of a dual RAF-MEK inhibitor using a highly intermittent schedules in patients with solid tumours or MM bearing RAS-RAF-MEK pathway mutations.

Methods

Study Design and Participants

This was an open-label, dose-escalation and dose-expansion, phase 1 study of CH5126766 conducted at The Royal Marsden NHS Foundation Trust, United Kingdom. Patients eligible for the dose-escalation cohort had histologically or cytologically confirmed advanced or metastatic solid tumours. In the expansion cohorts, eligible patients had advanced or metastatic solid tumours or MM harbouring RAS-RAF-MEK pathway mutations. The MM cohort (10 patients) was added following a protocol amendment on February 18, 2016. All eligible patients were aged ≥18 years; had cancers that were refractory to conventional treatment or for which no conventional therapy existed; had World Health Organisation performance status of 0 or 1; life-expectancy of ≥12 weeks; had adequate bone marrow, liver, renal, and coagulation function. Solid tumours had to be measurable according to Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST v1·1).

Patients were excluded if they had systemic therapy or non-palliative radiotherapy within 28 days or hormone therapy within 14 days of starting the trial treatment, except if hormone therapy was indicated for prostate cancer; malabsorptive or bowel disorder; ocular disorder; known infection with HIV, hepatitis B or hepatitis C, or a significant intercurrent illness. The exclusion criteria was

amended on November 22, 2013 to allow the entry of patients with grade 1 toxicities related to prior treatment, a history of gallbladder disorders, and on December 4, 2016 to allow the entry of patients on CYP3A4 inducers. See Study Protocol for the complete eligibility criteria (appendix p 7).

Regulatory approvals were obtained before trial activation from the Medicines and Healthcare products Regulatory Agency and the local institutional Research Ethics Committee. The study was run in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all participants. A Safety Review Committee evaluated the safety and tolerability of each schedule at regular intervals and after recruitment of six patients to a schedule. All protocol amendments were approved by the sponsor and Research Ethics Committee.

Procedures

During dose-escalation, patients received CH5126766 4·0 mg BIW (Mon/Thu or Tue/Fri) or TIW (Mon/Wed/Fri) orally over 28-day cycles. A minimum of six patients per dose schedule were required to evaluate toxicity over a 28-day dose-limiting toxicity (DLT) evaluation period. The dose escalation phase was rule based with an initial three patients enrolled per dose level and further three patients recruited following review by the Safety Review Committee (SRC). The dose at which no more than one of six patients experienced a DLT was defined as the recommended phase 2 dose (RP2D). The study was amended on November 22, 2013 so that if the 4·0 mg TIW schedule was intolerable, a single dose reduction to 3·2 mg TIW could be implemented with six additional patients. A dose level lower than 4·0 mg was not planned in the BIW schedule. If the reduced 3.2 mg TIW and the 4·0 mg BIW schedule were both tolerated, the RP2D would be selected based on pharmacokinetic and pharmacodynamic data; if the 3.2 mg TIW schedule was intolerable, and the 4·0 mg BIW schedule was tolerated, the 4·0 mg BIW schedule would be the RP2D. Upon defining the RP2D, a toxicity-guided treatment interruption arm was instituted where upon the occurrence of grade 2 or higher diarrhoea, rash, or CPK elevation, treatment was de-intensified to three weeks on, one week off. This toxicity-guided treatment interruption arm was added following a protocol amendment on August 9, 2017, and intended to explore a regimen which could be used to treat heavily comorbid

patients or in combination regimens. The SRC evaluated the safety and tolerability of each schedule and determined the optimum schedule for the expansion study. The study was subsequently amended on July 9, 2018 to combine CH5126766 with everolimus; recruitment to this arm is ongoing.

During expansion, patients with solid tumours were treated at the RP2D. Patients with MM were treated three weeks on, one week off, and were allowed to continue on dexamethasone (up to 20 mg per week) at physician's discretion (Figure 1).

In both cohorts, treatment was continued until disease progression, intolerance, or withdrawal of consent. Patients could also be removed from the trial for serious protocol violation, clinical reasons as per the investigator, or if the trial was terminated.

Adverse events (AEs) were monitored continuously and graded using the National Cancer Institute Common Terminology Criteria, version 4·0 (CTCAE v4·0) until 28-days after the discontinuation of study treatment or, in the event of a persistent drug-related AE, until its resolution. Investigators used their own judgment to determine whether or not an adverse event was related to the study drug.

DLTs were defined as per protocol (appendix p 7). Notably, grade 3 or higher skin toxicity recurring after dose reduction or failing to improve to grade 2 or less within two weeks of optimal treatment was considered a DLT.

Solid tumour responses were evaluated by investigators using computer tomography or magnetic resonance imaging (MRI) at baseline, eight-weekly for the first six months, and could occur less frequently thereafter, until disease progression, death, or patient withdrawal. For MM patients, paraprotein levels, bone marrow aspirate and trephine (BMAT), and whole-body diffusion-weighted MRI (DW-MRI) were performed at baseline and, where indicated, at the time of disease progression. During treatment, paraprotein levels were repeated every cycle. DW-MRI and BMAT were repeated every three cycles.

Blood samples for pharmacokinetics analyses were collected from all patients enrolled to the dose-escalation cohorts and from selected patients (first eight) in the basket expansion. Optional paired fresh tumour samples were collected at baseline, then one to four hours post-dosing on cycle 1 day

15 from patients in the expansion cohorts. Prespecified immunohistochemical evaluation for phosphorylated MEK (pMEK), phosphorylated ERK (pERK), and Ki67 were graded using the histo-score (H-score)[13]. DNA was extracted for targeted next generation sequencing for RAS-RAF-MEK pathway mutations.

Serial blood samples for cell-free DNA (cfDNA) collected as part of a parallel, non-interventional, tumour molecular characterisation study were analysed post-hoc for long-term responders (> 6 months).

Outcomes

The primary endpoint was to establish a RP2D at which no more than one out of six patients experience a TRAEs and to determine the safety and toxicity profile of each schedule. Secondary endpoints were: response rate (partial or complete) in patients with solid tumours or MM with RAS-RAF-MEK pathway mutations, as determined by the RECIST v1·1 for patients with solid tumours and the International Myeloma Working Group (IMWG) Uniform Response Criteria for patients with MM[14,15] and pharmacokinetic parameters (maximum concentration [C_{max}], area under the curve, and half-life). Pharmacodynamic changes in tumour biopsies were a tertiary endpoint.

Statistical Analysis

Patients who received at least one dose of CH5126766 were evaluable for the primary endpoints. Safety variables were summarised by descriptive statistics. Patients who received at least two cycles of the trial medication and have undergone baseline disease assessment were evaluable for response. For the activity analysis, investigator-assessed objective response was determined with the corresponding two-sided 95% CIs (calculated via the exact binomial method). All endpoints were evaluated by per protocol analysis. As antitumour activity was a secondary endpoint, no formal power calculations were done for the expansion phase; the sample size (20 patients with solid tumours, 10 with MM) was chosen as feasible within timelines and sufficient for descriptive exploratory analysis. Changes in levels of tumour cfDNA and cfDNA mutant allele frequency amongst long-term responders were analysed post-hoc. We used STATA (version 15) for all statistical analyses.

This trial is registered on ClinicalTrials.gov, number NCT02407509.

Role of the funding source

The study was funded by Chugai Pharmaceutical Co., Ltd., Japan, and was an academic study jointly sponsored by The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust. The funder had no role in the study design or data collection. The funder was involved in the analysis and interpretation of the pharmacokinetics data and reviewed and commented on the manuscript. All authors had full access to all study data and the corresponding author had final responsibility for the decision to submit this publication.

Results

Between June 5, 2013 to January 10, 2019, 58 patients, including 51 patients with solid tumours and seven patients with MM, were enrolled at a single centre in the United Kingdom. The data cut-off for this report was April 15, 2019. Patient characteristics are summarised in Table 1.

Twenty-nine patients were enrolled in the dose-escalation study: seven patients were recruited to the CH5126766 4·0 mg TIW cohort, seven patients to the 3·2 mg TIW cohort, and eight patients to the 4·0 mg BIW cohort. More than six patients were enrolled per cohort as some patients progressed prior to completing 28 days of therapy. Seven patients were enrolled to the 4·0 mg BIW toxicity-guided treatment interruption schedule although one patient with NSCLC did not receive study drug so was excluded from analyses. Twenty-nine patients were enrolled in the basket expansion study: 22 patients with solid tumours and seven patients with MM harbouring *RAS* or *RAF* mutation received CH5126766 4·0 mg BIW (Figure 1). For the primary analysis, the median follow-up at data cut-off was 2·3 months (interquartile range: 1·6-3·5 months).

In the dose-escalation phase, four DLTs occurred in three (10·7%) of 28 patients. One patient experienced transient grade 3 bilateral RPED with associated grade 3 blurred vision hours after receiving one dose of CH5126766 (4·0 mg TIW). Blurred vision resolved after 24 hours of treatment

interruption and did not recur with re-treatment at 2·4 mg TIW. Return of visual acuity to baseline, and the resolution of retinal changes were confirmed before treatment re-initiation.

At 3·2 mg TIW, two patients experienced DLTs. One patient developed grade 3 rash by the third week of treatment despite having commenced topical hydrocortisone and clindamycin, and oral doxycycline (100 mg BD) for a grade 2 rash one week after starting treatment. The patient developed concurrent grade 3 CPK elevation (DLT) and the study drug was withheld. When the rash improved to grade 2 and CPK elevation to grade 1 after two weeks off treatment, the study drug was recommenced at a reduced dose (2·4 mg TIW), whilst the same management for rash continued. Recurrence of grade 3 rash and grade 2 CPK elevation after two weeks of treatment prompted another treatment interruption. After two weeks, rash improved to grade 1 and the treatment was recommenced at 3·2 mg BIW; treatment was permanently discontinued when grade 3 rash recurred after two weeks.

The second patient developed grade 3 rash which persisted for more than 14 days despite the use of topical hydrocortisone and clindamycin, and oral doxycycline (100 mg BD) when a grade 2 rash developed after one week of treatment. Treatment was permanently discontinued when the rash worsened to grade 3; rash improved to grade 2 after a 15-day treatment interruption. All DLTs were reversed by appropriate treatment, dose reduction and/or interruption. No DLT was observed at 4·0 mg BIW establishing it as the RP2D.

Among the 57 patients evaluable for safety, the most common TRAEs (in ≥ 30% of patients) were skin toxicity (50, 87·7%), CPK elevation (42, 73.7%), visual disturbance (25, 43·9%), diarrhoea (23, 40·4%), fatigue (21, 36·8%) and peripheral oedema (18, 31·6%). The most common grade 3-4 TRAEs (in ≥ 5% of patients) were rash (11, 19·3%), CPK elevation (6, 10·5%), hypoalbuminemia (6, 10·5%), and fatigue (4, 7·0%). Five (8·8%) of 57 patients had a treatment-related serious adverse event which were RPED (1, 1·8%), CPK elevation (2, 3·5%), rash (1, 1·8%), and bronchial infection (1, 1·8%). Twenty-two (38·6%) of 57 patients required one or more dose reductions for TRAEs. Four were part of the toxicity-guided dose-interruption cohort. Three (5·3%) patients discontinued

treatment due to toxicity; one patient discontinued treatment for grade 3 rash and CPK elevation and two discontinued treatment for grade 3 rash. There were eight deaths on trial due to disease progression; there was no treatment-related death (Table 2).

All cases of rash were reversible with appropriate management (i.e., topical steroids, topical clindamycin lotion and, in some cases, oral doxycycline). Eight (14·0%) of 57 patients required dose-reduction and/or treatment interruption. Median time to onset of rash was 11 days (range: 1-84 days). Thirty-five (61·4%) of 57 patients experienced treatment-related ocular AEs, which included blurred vision or change in colour vision (28 [49·1%] of 57 patients; grade ≥ 3: 1 [1·8%]), serous retinal pigment epithelial detachment (RPED) (17 [29·8%] of 57 patients; grade ≥ 3: 1 [1·8%]), retinal/subretinal oedema (4 [7·0%] of 57 patients, all grade 1-2), and blepharitis (5 [8·8%] of 57 patients, all grade 1-2). Serous RPED and/or retinal/subretinal oedema were detected by fundoscopy and OCT. All cases of RPED were self-limiting except for one patient who required dose-interruption followed by reduction.

CPK elevation was not associated with any clinical symptom or renal complication, and resolved either spontaneously, with treatment interruption and/or dose-reduction. Hypoalbuminemia resolved spontaneously or with treatment interruption. Median time to onset was 14 days (range: 1-42 days) for CPK elevation and 15 days (range: 7-49 days) for hypoalbuminemia. Median time to onset for diarrhoea was five days (range: 1-34 days); one patient required a dose reduction whilst other cases resolved spontaneously or with supportive measures. Three patients with grade 3 fatigue required dose interruptions. There was no significant difference in the overall rate of toxicity between patients treated at the RP2D and in the toxicity-guided treatment interruption arm.

In the part 1 dose-escalation, 24 (85·7%) of 28 patients who received the study drug were evaluable for response. One patient with metastatic apocrine cancer of the scalp with an $HRAS^{G12R}$ mutation (in the toxicity-guided treatment interruption cohort) had a partial response lasting 66 weeks at the time of data cut-off and remains on treatment (Appendix p 4)[16].

In the biomarker-selected basket expansion, 26 (89·7%) of 29 patients with solid tumours and MM harbouring different *RAS* or *RAF* mutations were evaluable for response. There was no patient with a solid tumour harbouring a $KRAS^{G12C}$ mutation, a subset of tumours that may respond to KRAS G12C inhibitors[17]. Overall, seven (26·9%) of 26 patients achieved an objective response (95% confidence interval [CI]: 11·6-47·8). Six (30·0%) of 20 patient with solid tumours (95% CI: 11·9-54·3) achieved an objective response (Figures 2, 3, Appendix p 4). Three (30·0%) of 10 patients in the NSCLC cohort had objective responses which all lasted over six months (Figure 3). Of note, the *KRAS* mutations in patients who responded in the NSCLC cohort were $KRAS^{G12V}$ (n=2) and $KRAS^{G12R}$ (n=1). Non-responders had NSCLC harbouring $KRAS^{G12D}$ (n=3), $KRAS^{G12V}$ (n=3), and $KRAS^{A146V}$ (n=1) mutations.

Responders in the GM cohort were all platinum resistant and had $KRAS^{G12D}$ low-grade serous ovarian cancer (LGSOC), $BRAF^{V600E}$ LGSOC, and $KRAS^{G12V}$ endometrial adenocarcinoma. The two non-responders in the GM cohort had $KRAS^{G12D}$ clear cell ovarian carcinoma and $KRAS^{G12V}$ uterine sarcoma. Both patients with LGSOC previously had durable responses to, then progressed on MEK inhibitors. No responses were seen in patients with CRC or melanoma. In all six responders with solid tumours, tumour shrinkage was observed at the time of the first restaging scan after two cycles of treatment, with partial responses confirmed after two to four cycles. Five of the six responses lasted more than six months.

Among the seven patients with *RAS-RAF*-mutant MM, six were response-evaluable; one was not evaluable due to early disease progression. One (16·7%) of six patients (95% CI: 0·4-64·1) achieved partial response with a progression-free survival of 30 weeks (Figures 2, 3). A second patient, who received five lines of prior therapy, remains on treatment after 72 weeks of disease stability. Patients with MM were heavily pre-treated, with two having had autologous stem cell transplants (Appendix p 2). Two non-responders continued on dexamethasone (one at 10 mg once weekly, one at 20 mg once weekly) during trial treatment.

Following oral administration of a single dose of CH5126766, plasma concentration increased rapidly with C_{max} being reached 1-2 hours after dosing. The mean terminal half-life was approximately 55 hours. Consistent with simulated plasma CH5126766 concentration at 4·0 mg BIW and 4·0 mg TIW, exposure was comparable across all three schedules evaluated in the dose-escalation study (Table 3; Appendix p 3).

We obtained matched, baseline and post-treatment biopsies from three patients (*NRAS*^{Q61R} melanoma, *RAS/RAF* wild-type high-grade serous ovarian cancer, and *NRAS*^{Q61R} CRC). Reduction in pMEK and pERK expression occurred in all three patients post treatment suggesting attenuation of RAF and MEK activity (Appendix p 5). There was no significant change in Ki67 expression (data not shown). No tumour shrinkage was observed in patients who underwent fresh tumour biopsies. Post-hoc analyses of serial cfDNA was performed on blood samples collected from the five patients with responses lasting greater than six months (Appendix p 6)

The study was not powered to compare antitumour activity between tumours and between different mutations. *KRAS*^{G12V} (n=9), *KRAS*^{G12D} (n=5), and *BRAF*^{V600E} (n=4) were the most common tumour mutations in the basket expansion. Objective responses occurred in six (31·6%) of 19 of patients with *KRAS*-mutant solid tumours (including MM). Notably, four (44·4%) of nine patients with *KRAS*^{G12V} malignancies, one (20·0%) of five patients with *KRAS*^{G12D} malignancies, and one (25·0%) of four patients with *BRAF*^{V600E} malignancies had objective responses.

Discussion

To our knowledge, this is the first clinical trial to demonstrate antitumour activity with a dual RAF/MEK inhibitor in biomarker-selected patients with solid tumours or MM harbouring RAS-RAF-MEK pathway mutations. Importantly, we describe a novel intermittent schedule that was devised based on the long half-life of CH5126766 and the need to establish better tolerability.

CH5126766 at the RP2D of 4·0 mg BIW was well-tolerated as per clinicians' assessment. Whilst the current study population is not directly comparable to that enrolled in the FIH study of CH5126766,

which used more frequent dosing, it is worth noting that the rate of grade 3 or higher toxicity was 44·0% among patients who received CH5126766 at 4·0 mg BIW compared with 63% patients in the FIH study[10]. The median age of the FIH study were lower, patients had better performance status, and fewer lines of prior therapy[10]. Expectedly, the toxicity profile is consistent with the FIH study. Visual disturbances due to serous RPED and retinal/subretinal oedema are consistent with reported class effects of MEK inhibitors[18,19]. Whilst there was no long-term clinical impact in the six patients who received more than six months of treatment and experienced ocular AEs, longer follow-up in larger cohorts is required.

Pharmacokinetics of the drug are in line with those previously reported[10]. In the three patients who underwent paired tumour biopsies, demonstration of pMEK and pERK downregulation was consistent with the mechanism of action of CH5126766, however, pharmacodynamics analyses in the current study are limited by the small number of patients who underwent tumor biopsies and the limited analyses performed. Given the drug's long half-life, there is likely partial target inhibition including on non-dosing days despite the intermittent schedules. However, intermittent reductions in exposure in the context of differential dependence of healthy versus tumour tissue on RAF-RAS-MEK pathway signalling may be sufficient to improve the therapeutic index. Further, off-target effects cannot be excluded although previous testing of CH5126766 on a panel of 256 kinases showed inhibition of CRAF and BRAF. Since the initial panel did not contain MEK1 and MEK2, separate analysis showed CH5126766 inhibited both MEK1 and MEK2[9]. These preclinical studies and absence of bone marrow toxicity and neurotoxicity associated with DNA/tubulin binding agents, suggest that the clinical activity of CH5126766 is unlikely to be driven predominantly by off-target effects. Detailed pharmacodynamics studies in PBMCs, skin and tumours were conducted in the FIH study[10].

We observed encouraging responses across different cancers, including NSCLC, LGSOC, endometrial adenocarcinoma, apocrine adenocarcinoma, and MM patients. These tumours harboured a range of *RAS* and *RAF* mutations including *KRAS*^{G12D}, *KRAS*^{G12V}, *KRAS*^{G12R}, *BRAF*^{V600E}, and

HRAS^{G12R}. For decades, KRAS has been considered extremely challenging to drug[3] and there remains no effective targeted therapy against the majority of *RAS*-mutant cancers. Approaches targeting prenylation of RAS by farnesyltransferases have been ineffective[5]. Inhibition of multiple nodes on the MAPK pathway have been shown to be efficacious in preclinical models, although cancer cells also develop resistance through dynamic pathway reprogramming and alternative signalling pathways[20,21]. There have been various attempts to combine MEK inhibitors with inhibitors of other oncogenic pathways, such as PI3K/AKT/mTOR signalling in the setting of *KRAS* mutations, but these have largely not been taken forward due to toxicity and/or lack of antitumour activity [22,23]. Recent reports of impressive antitumour activity with a KRAS(G12C) inhibitor in *KRAS*^{G12C} NSCLC has led to renewed fervour in KRAS-targeted therapies [6]. Whilst G12C mutations are present in approximately 13% of lung adenocarcinoma, they comprise a small proportion of CRC (~3%) and pancreatic adenocarcinoma (~2%), whereas other *KRAS* mutations are common[24,25]. Therefore, the antitumour activity of CH5126766 in non-*G12C* mutant tumours addresses an important area of unmet need.

In the heavily pre-treated MM cohort, we observed durable partial response in one patient and durable disease stabilisation in another. Both patients had *KRAS*-mutant MM. *KRAS*, *NRAS*, and *BRAF* mutations are detectable in approximately half of MM (although it is unclear what proportion lead to pathway activation), occur more frequently in relapsed/refractory MM, and is therefore a relevant therapeutic target in these diseases[2,26]. To our knowledge, our study represents the first prospective study to evaluate combined RAF and MEK inhibition in patients with *RAS*/*RAF*-mutant MM, and corroborates evidence from retrospective case reports and series which have shown responses to trametinib and vemurafenib (including intermittent dosing in one case) in patients with *RAS*/*RAF*-mutant MM [27-29].

Overall, the efforts of bringing together tolerability, pharmacokinetics, pharmacodynamics, and predictive biomarkers of response in this study are in alignment with the Pharmacologic Audit Trail that helps to optimise dose scheduling and precision oncology approaches in early phase clinical

trials[30]. However, there are a number of limitations to the study. First, whilst the RP2D was deemed tolerable based on clinicians' assessment with several patients remaining on study for more than six months, patient-reported outcomes and quality-of-life instruments are needed in future studies to evaluate the clinical impact of chronic low-grade toxicities. Second, given the various histologies and tumour mutations included, larger samples are required to evaluate antitumour activity in specific tumour types and mutations of interest. Finally, further pharmacodynamics studies in larger cohorts with and without RAS-RAF-MEK pathway mutations, evaluating on-target and potential off-target effects would shed light on the effects of highly intermittent dosing and whether certain tumour histologies or RAS-RAF-MEK pathway mutations that lead to pathway activation confer sensitivity to CH5126766. Since *RAS/RAF* mutations do not necessarily translate into downstream pathway activation[26], future biomarker development will likely need to incorporate orthogonal measures accounting for tumour type, mutation, clonality, expression of downstream effectors, and the activation of alternative signalling pathways.

MEK inhibitor combinations are currently licensed for the treatment of $BRAF^{V600}$-mutant melanoma and $BRAF^{V600E}$ CRC[7,8]. These agents are administered in continuous dosing schedules; however, few have shown single agent activity in intermittent schedules[7,8,31]. Intermittently dosed CH5126766 has now shown early proof-of-concept responses in a various *RAS/RAF*-mutant tumours. The intermittent dosing schedule explored in this study will allow testing of CH5126766 both as a single agent in *RAS/RAF*-mutant cancers such as *KRAS*-mutant NSCLC (NCT03681483) or in combination with small molecules such as the FAK inhibitor defactinib (NCT03875820) or the mTOR inhibitor everolimus (NCT02407509) in *KRAS*-mutant solid tumours.

Contributors

CG and UB performed the literature searches.

MP, AJT, EH, JSdB, and UB designed the study.

CG, MC-P, DR, MdM, SJH, IMC, PS, WX, MS, AC, NT, MK, and UB collected the data.

CG, JK, MP, AJT, LF, EH, YI, KN, JSL, AM, JSdB, and UB performed the data analysis.

CG, MC-P, DR, MdM, SJH, IMC, PS, WX, MS, AC, JK, MP, AJT, SC, RR, LF, EH, YI, KN, NT, BB, MK, JSL, AM, JSdB, and UB interpreted the data.

CG, JK, MP, AJT, SC, RR, LF, EH, KN, NT, JSL, and UB contributed to the figures.

MP, AJT, LF, EH, BB, JSL, AM, JSdB, and UB were involved in the supervision of the study.

All authors contributed to manuscript writing, approved the final version, and are accountable for all aspects of the work. All authors provided final approval to publish the manuscript.

Declaration of interests

IMC reports personal fees from Speaker fees: BMS, outside the submitted work. WX reports grants and personal fees from Merck Serono, speaker fees from MSD, conference travel support from AstraZeneca, outside the submitted work. EH reports grants from Chugai Pharmaceuticals, during the conduct of the study; grants from Merck Sharp & Dohm, grants and non-financial support from AstraZeneca, grants from Janssen-Cilag, grants and non-financial support from Bayer, grants from Aventis Pharma Limited (Sanofi), grants from Accuray, Inc., grants from Varian, grants from Roche Products, Ltd., outside the submitted work. YI reports employment with Chugai Pharmaceutical Co., Ltd., Japan, during the conduct of the study. KN reports employment with Chugai Pharmaceutical Co., Ltd., Japan, during the conduct of the study. MK reports grants and personal fees from Celgene and BMS, personal fees from Amgen, grants and personal fees from Janssen, personal fees from Takeda, personal fees from AbbVie, personal fees from GSK, personal fees from Karyopharm, outside the submitted work. JSL reports grants and non-financial support from Roche-Genentech, grants, personal fees and non-financial support from Basilea, grants from Genmab, outside the submitted work. AM reports personal fees from Merck, personal fees from Novartis Pharmaceuticals, personal fees from Faron Pharmaceuticals, personal fees from Bayer Pharmaceuticals, personal fees from Janssen Pharmaceuticals, personal fees from Imugene Pharmaceuticals, personal fees from LOXO Pharmaceuticals, outside the submitted work. JSdB reports personal fees and non-financial

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Data sharing

Qualified researchers can request access to the study documents that support the methods and findings in this report. Proposals should be directed to the corresponding author in the first instance.

The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust will share patient-level and study-level data after de-identification with qualified non-commercial, scientific, and medical researchers on the researcher's request. Requests for data sharing can be made to UB, including a detailed proposal for data meta-analysis, and must be approved by The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust. The Institute of Cancer Research will

endeavour to gain agreement with Chugai Pharmaceutical Co., Ltd., who currently has ownership of CH5126766 and funded this study before data is shared in response to approved research requests.

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Legends to figures

Figure 1. Consort diagram

BIW = twice per week. TIW = three times per week. RP2D = recommended phase 2 dose. CPK = creatinine phosphokinase

[a] Two patients were not evaluable for response.

[b] One patient was not evaluable for response.

[c] One patient did not receive the study drug and was not evaluable for safety or response.

[d] Toxicity-guided dose interruption arm where treatment was de-intensified to three weeks on, one week off upon the occurrence of grade 2 or higher diarrhoea, rash, or CPK elevation.

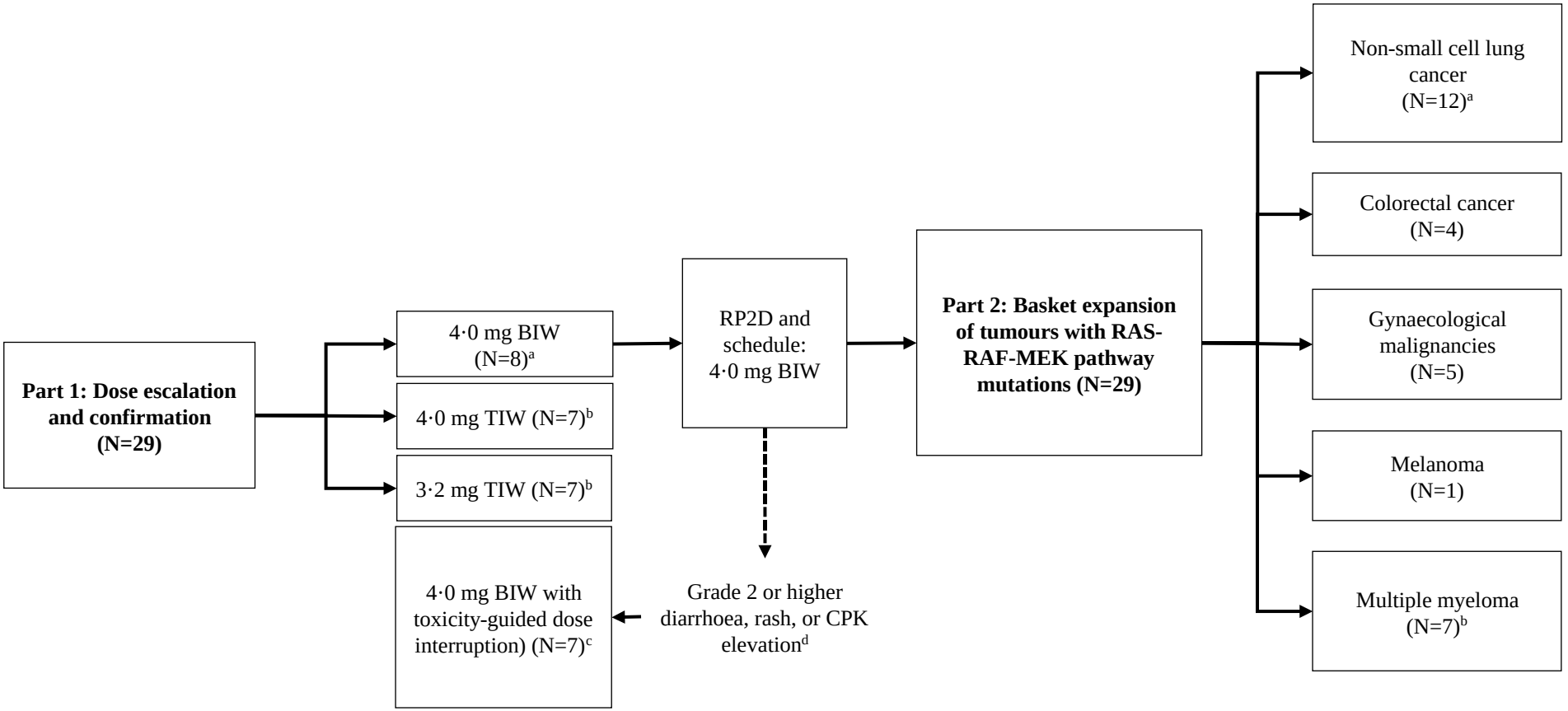
Figure 2. Changes in tumour size by cancer type

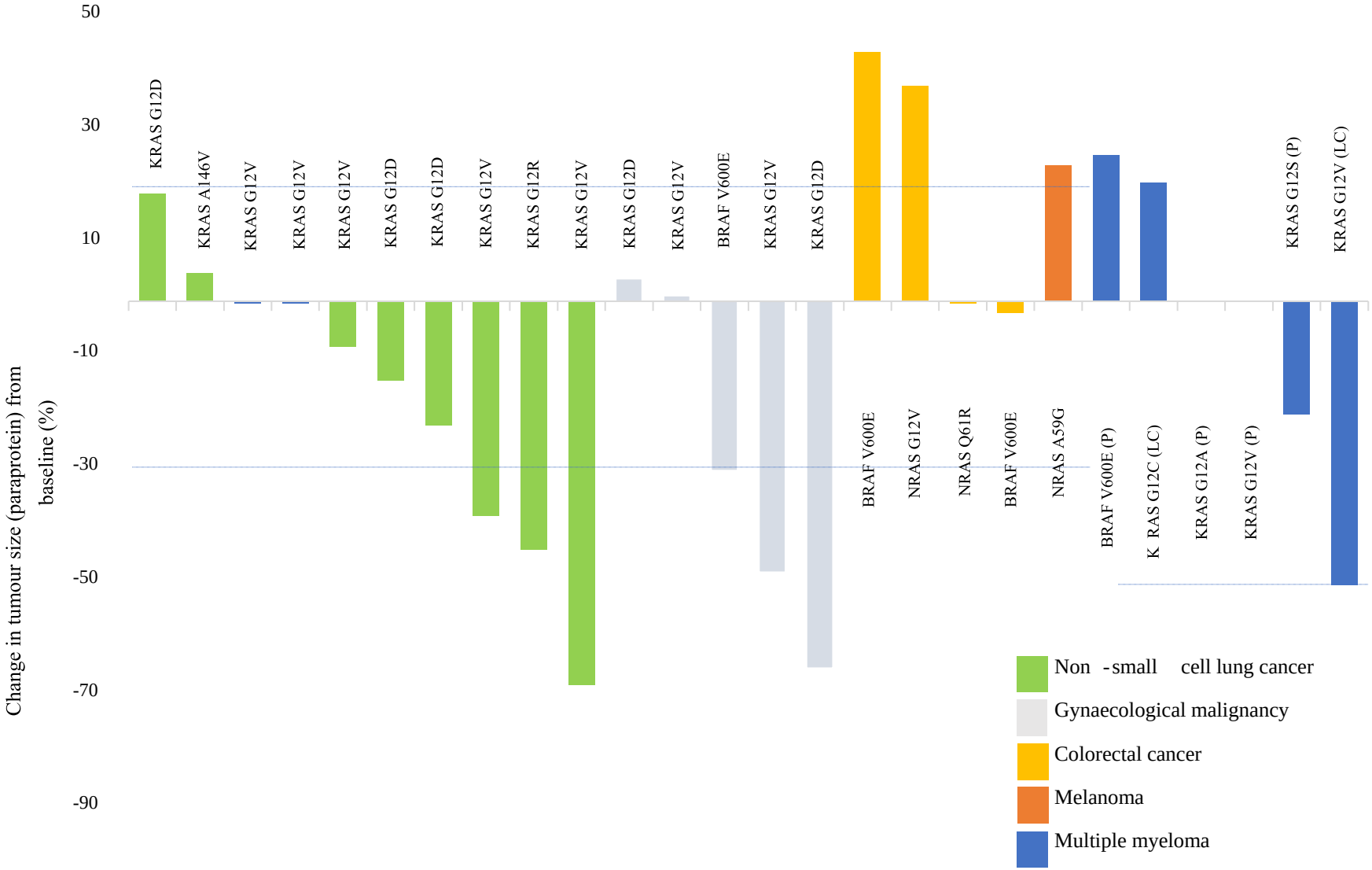
Individual patient data for best objective response according to RECIST v1·1 for the 20 evaluable patients with solid tumours and according to IMWG response criteria for the six evaluable patients with MM. Ten patients had non-small cell lung cancer (NSCLC) (green), five had gynaecological malignancies (grey), four had colorectal cancer (yellow) and one had melanoma (orange). Four patients with MM had detectable paraprotein (P) at baseline and two patients only had lambda light chains (LC) at baseline (blue). Three patients with NSCLC (two with $KRAS^{G12V}$ and one with $KRAS^{G12R}$), three patients with gynaecological malignancies (one with $KRAS^{G12D}$ and one with $BRAF^{V600E}$ low-grade serous ovarian cancer; one with $KRAS^{G12V}$ endometrial adenocarcinoma), and one patient with $KRAS^{G12V}$ MM (blue) had partial responses. Dashed lines represent the thresholds for partial response (≥ 30% decrease in target lesion diameter from baseline) for solid tumours; progressive disease (≥ 20% increase in target lesion diameter from baseline) for solid tumours; partial response (≥ 50% decrease in paraprotein from baseline) for MM. Tumour mutations are annotated.

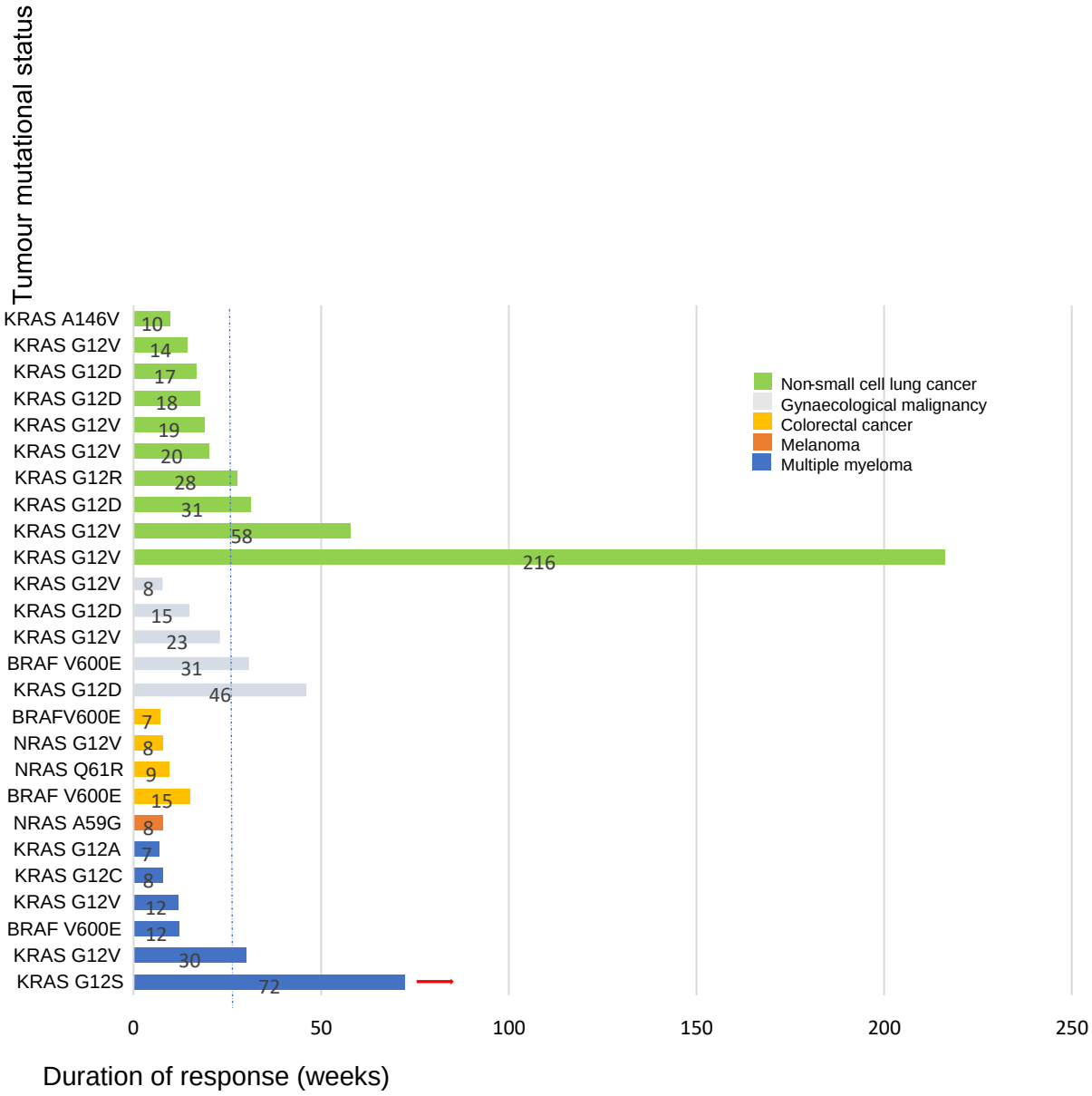
Figure 3. Duration of response

Duration of treatment measured from time of the first dose of treatment to the end of trial visit for all 26 response-evaluable patients with solid tumours or multiple myeloma harbouring RAS-RAF-MEK pathway mutations. Ten patients had non-small cell lung cancer (NSCLC) (green), five had

gynaecological malignancies (grey), four had colorectal cancer (yellow), one had melanoma (orange) and six patients had multiple myeloma (blue). Red arrow denotes ongoing response. All other patients have ceased trial treatment. Dashed line denotes six months from the time of the first dose of treatment.


Part 1: Dose escalation and confirmation (N=29)
4·0 mg BIW (N=8)a
4·0 mg TIW (N=7)b
3·2 mg TIW (N=7)b
4·0 mg BIW with toxicity-guided dose interruption) (N=7)c
Grade 2 or higher diarrhoea, rash, or CPK elevationd
RP2D and schedule: 4·0 mg BIW
Part 2: Basket expansion of tumours with RAS-RAF-MEK pathway mutations (N=29)
Non-small cell lung cancer (N=12)a
Colorectal cancer (N=4)
Gynaecological malignancies (N=5)
Melanoma (N=1)
Multiple myeloma (N=7)b


50
30
10
-10
-30
-50
-70
-90
Change in tumour size (paraprotein) from baseline (%)
KRAS G12D
KRAS A146V
KRAS G12V
KRAS G12V
KRAS G12V
KRAS G12D
KRAS G12D
KRAS G12V
KRAS G12R
KRAS G12V
KRAS G12D
KRAS G12V
BRAF V600E
KRAS G12V
KRAS G12D
BRAF V600E
NRAS G12V
NRAS Q61R
BRAF V600E
NRAS A59G
BRAF V600E (P)
K RAS G12C (LC)
KRAS G12A (P)
KRAS G12V (P)
KRAS G12S (P)
KRAS G12V (LC)
Non -small cell lung cancer
Gynaecological malignancy
Colorectal cancer
Melanoma
Multiple myeloma


Tumour mutational status
KRAS A146V
KRAS G12V
KRAS G12D
KRAS G12D
KRAS G12V
KRAS G12V
KRAS G12R
KRAS G12D
KRAS G12V
KRAS G12V
KRAS G12V
KRAS G12D
KRAS G12V
BRAF V600E
KRAS G12D
BRAFV600E
NRAS G12V
NRAS Q61R
BRAF V600E
NRAS A59G
KRAS G12A
KRAS G12C
KRAS G12V
BRAF V600E
KRAS G12V
KRAS G12S
10
14
17
18
19
20
28
31
58
216
8
15
23
31
46
7
8
9
15
8
7
8
12
12
30
72
Non-small cell lung cancer
Gynaecological malignancy
Colorectal cancer
Melanoma
Multiple myeloma
0
50
100
150
200
250
Duration of response (weeks)

~~Supplementary Table S1~~Table 1: Patient demographic and baseline characteristics, by cohort.

	Dose escalation (part 1)				Basket expansion (Part 2)		Total population
Schedule	**4·0 mg BIW (N=8)**	**4·0 mg TIW (N=7)**	**3·2 mg TIW (N=7)**	**Toxicity-guided treatment interruption (N=7)**	**Solid tumour 4·0 mg BIW (N=22)**	**Multiple myeloma 4·0 mg BIW 3 weeks on/1 week off (N=7)**	**(N=58)**
Sex							
Male	4	4	6	1	9	5	29
Female	4	3	1	6	13	2	29
Age median (range)	64 (39-74)	55 (42-74)	59 (46-80)	57 (43-64)	62 (39-80)	71 (53-81)	62 (39-80)
Prior lines of systemic therapy median (range)	3 (2-8)	3 (1-4)	3 (2-5)	5 (3-8)	3 (1-7)	6 (4-9)	3 (1-0)
ECOG PS							
0	3	2	3	0	3	0	11
1	5	5	4	7	19	7	47
Tumour type							
Non-small cell lung cancer	0	1	1	4	12	0	18
Gynaecological malignancy	1	2	0	0	5	0	8
Colorectal cancer	3	3	3	0	4	0	13
Ampullary adenocarcinoma	1	0	0	0	0	0	1
Pancreatic adenocarcinoma	0	0	1	0	0	0	1
Appendiceal carcinoma	0	1	0	0	0	0	1
Melanoma	2	0	2	1	1	0	6
Prostate adenocarcinoma	0	0	0	1	0	0	1
Mesothelioma	1	0	0	0	0	0	1
Apocrine adenocarcinoma	0	0	0	1	0	0	1
Multiple myeloma	0	0	0	0	0	7	7
Mutational status							
KRAS	3	4	3	4	16	6	36
NRAS	0	0	1	1	3	0	5
HRAS	0	0	0	1	0	0	1
BRAF	2	0	0	1	3	1	7
PIK3CA	0	1	0	0	0	0	1

* Not all patients in the part 1 dose escalation underwent assessment for RAS/RAF mutations

Table 21: Treatment-related adverse events

Adverse event, n (%)	Grade 1-2	Grade 3	Grade 4
Rash	39 (68%)	11 (19%)	0 (%)
CPK elevation	36 (63%)	5 (9%)	1 (2%)
Visual disturbance	24 (42%)	1 (2%)	0 (0%)
Diarrhoea	22 (39%)	1 (2%)	0 (0%)
Fatigue	17 (30%)	4 (7%)	0 (0%)
Peripheral Oedema	18 (32%)	0 (%)	0 (0%)
Retinal detachment	16 (28%)	1 (2%)	0 (0%)
Mucositis	16 (28%)	1 (2%)	0 (0%)
Dry skin	14 (25%)	0 (%)	0 (0%)
Hypoalbuminemia	5 (9%)	6 (11%)	0 (0%)
Nausea	11 (19%)	0 (%)	0 (0%)
Skin fissure	11 (19%)	0 (%)	0 (0%)
Pain	7 (12%)	0 (%)	0 (0%)
Paronychia	7 (12%)	0 (%)	0 (0%)
Facial oedema	6 (11%)	0 (%)	0 (0%)
Pruritis	6 (11%)	0 (%)	0 (0%)
Dehydration	6 (11%)	0 (%)	0 (0%)
Abdominal discomfort	6 (11%)	0 (%)	0 (0%)
Anaemia	2 (4%)	2 (4%)	0 (0%)
Bronchial infection	0 (%)	1 (2%)	0 (0%)
Hypokalaemia	0 (%)	1 (2%)	0 (0%)
Hypoxia	0 (%)	1 (2%)	0 (0%)

Treatment-related adverse events occurring in ≥10% of patients and all grade ≥3 treatment-related adverse events are shown. Common Terminology Criteria for Adverse Events (version 4·0) are used. There was no treatment-related death. CPK = creatine phosphokinase.

Table 3: Pharmacokinetics

Pharmacokinetic parameters (mean ± standard deviation)				
Cycle 1 day 1				
		AUC_{last}	**C_{max}**	**$t_{1/2}$**
	Number of patients	(ng·h/mL)	(ng/mL)	(h)
3·2 mg, TIW (Dose-escalation)	7	5·670±2·270	209±120	52·9±15·0
4·0 mg, TIW (Dose-escalation)	7	7·140±2·880	278±174	44·4±12·9
4·0 mg, BIW (Dose-escalation)	8	6·110±1·650	247±90·4	40·5±17·1
4·0 mg, BIW (Dose-expansion)	8	6·250±2·120	284±67·4	48·3±24·0
Cycle 1 day 15				
		AUC_{last}	**C_{max}**	**$t_{1/2}$**
	Number of patients	(ng·h/mL)	(ng/mL)	(h)
3·2 mg, TIW (Dose-escalation)	4	10·300±1·910	315±94·2	67·6±17·1
4·0 mg, TIW (Dose-escalation)	5	11·600±4·160	389±169	50·4±23·8
4·0 mg, BIW (Dose-escalation)	7	8·170±3·020	267±119	45·3±12·7
4·0 mg, BIW (Dose-expansion)	7	8·240±2·820	328±84·2	56·3±21·0

BIW = twice per week. TIW = three times per week. RP2D = recommended phase 2 dose. AUC_{last} = area under the plasma concentration-time curve from time zero to the last measurable concentration. C_{max} = maximum concentration. $t_{1/2}$ = half-life.