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A phase I study of selumetinib (AZD6244/ARRY-142866), a MEK1/2 inhibitor, in combination with cetuximab in refractory solid tumors and *KRAS* mutant colorectal cancer

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Abstract

Background—*KRAS* mutations are clinically important predictors of resistance to EGFR-directed therapies in colorectal cancer (CRC). Oncogenic activation of the RAS/RAF/MEK/ERK signaling cascade mediates proliferation independent of growth factor signaling. We hypothesized that targeting MEK with selumetinib could overcome resistance to cetuximab in *KRAS* mutant CRC.

Methods—A phase I study (NCT01287130) was undertaken to determine the tolerability, and pharmacokinetic profiles of the combination of selumetinib and cetuximab, with an expanded cohort in *KRAS*-mutant CRC.

Results—15 patients were treated in the dose escalation cohort and 18 patients were treated in the expansion cohort. Two dose-limiting toxicities were observed. One grade 3 acneiform rash and one grade 4 hypomagnesemia occurred. The most common grade 1 and 2 adverse events included rash, nausea/vomiting, diarrhea, and fatigue. The maximum tolerated dose was established at selumetinib 75 mg PO BID and cetuximab 250 mg/m^2 weekly following a 400 mg/m^2 load. Best clinical response in the dose escalation group included 1 unconfirmed partial response in a patient with CRC and stable disease (SD) in 5 patients (1 squamous cell carcinoma of the tonsil, 1 non-small cell lung cancer, and 3 CRC), and in the *KRAS*-mutant CRC dose expansion cohort, of the 14 patients who were evaluable for response, 5 patients had SD and 9 patients had progressive disease.

Conclusions—The combination of selumetinib and cetuximab is safe and well tolerated. Minimal anti-tumor activity was observed in *KRAS*-mutant refractory metastatic CRC. Further investigations might be warranted in other cancer subtypes.

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Conflict of interest

The authors declare that they have no conflict of interest.

Keywords

selumetinib; AZD6244; cetuximab; phase I; KRAS; colon cancer

INTRODUCTION

The clinical significance of certain mutations for the treatment of metastatic colorectal cancer (CRC) is being better understood. Most notably, patients whose tumors express mutant *KRAS* are largely unresponsive to epidermal growth factor receptor (EGFR) directed therapies [1, 2]. Unfortunately there are currently limited therapeutic options once these cancers have progressed after oxaliplatin and irinotecan-based regimens.

KRAS mutations occur in approximately 40% of patients with mCRC and most commonly occur in codons 12, 13, and 61 [3-5]. These alterations lock the protein in the guanosine triphosphate (GTP) bound conformation and decrease the response to guanosine triphosphatase-activating proteins (GAPs) maintaining RAS in the constitutively active form. This leads to resistance to EGFR-directed therapies secondary to the oncogenic activation of cellular signaling cascades independent of EGFR, including the RAF/MEK/ERK pathway, among others [3, 6]. Thus, targeting the RAF/MEK/ERK pathway downstream of activating *KRAS* mutations could result in inhibition of this signaling cascade and suppression of cellular proliferation.

Cancer cells with activating mutations of the RAF/MEK/ERK signaling cascade have been shown to be dependent on these mutations to maintain their malignant phenotype [3]. Selumetinib (AZD6244/ARRY-142866, AstraZeneca), an oral highly selective and potent uncompetitive inhibitor of mitogen-activated protein kinase 1/2 (MEK1/2) was able to prevent ERK1/2 mediated growth factor-independent survival [7]. In other preclinical studies, selumetinib has shown activity against melanoma, non-small cell lung cancer, pancreatic cancer, hepatocellular carcinoma, and colorectal cancer [8]. Two single agent phase I studies of selumetinib have been completed in patients with advanced cancers [9, 10]. Inhibition of ERK phosphorylation was observed in peripheral blood mononuclear cells and in tumor biopsies following selumetinib treatment. The most common toxicities with selumetinib treatment included rash, diarrhea, edema, fatigue, and mild to moderate reversible hepatic transaminase elevation. The maximum tolerated dose (MTD) of selumetinib in the solid formulation was determined to be 75 mg orally twice daily [10].

Colorectal cancer cells which are known to possess *KRAS* mutations were found to have minimal response to cetuximab (Erbitux, Bristol-Myers Squibb) *in vitro*, however a significant decrease in growth was noted with the combination of cetuximab and a MEK1/2 inhibitor, PD98059 [3]. In this clinical study, we will examine the toxicities and efficacy of selumetinib in combination with cetuximab in patients with treatment-refractory solid tumors and more specifically, in third line or greater treatment of *KRAS*-mutated colorectal cancer.

PATIENTS AND METHODS

Patient selection

The protocol was approved by the Health Sciences Institutional Review Board at the University of Wisconsin-Madison. Informed consent was obtained from each patient before participating in the study. In the dose escalation cohort patients were considered eligible if they had histologically confirmed metastatic or unresectable malignancy refractory to standard therapies or with no other existing curative or palliative measures. Histology was based on either the primary tumor or metastases. In the MTD expansion cohort patients were required to have *KRAS* mutant metastatic colorectal cancer that had progressed on at least 2 prior standard therapies. *KRAS* (exon 2) mutation status was verified by a CLIA-certified laboratory.

Other key eligibility criteria included: ≥ 18 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, adequate hematologic, hepatic and renal functions (WBC ≥ 3,000/μl, absolute neutrophil count ≥ 1,500/μl, platelets ≥ 100,000/μl, total bilirubin within institutional normal limit, AST/ALT ≤ 2.5 x the institutional upper limit of normal, creatinine ≤ 1.5 mg/dl or measured creatinine clearance ≥ 60 ml/min/1.73m^2 for patients with creatinine levels about institutional normal), and life expectancy greater than 12 weeks.

Patients were excluded if they were unable to swallow and retain selumetinib capsules, had untreated brain metastasis, were treated within 4 weeks with chemotherapy or radiation therapy, had a history of uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, prior cardiomyopathy, LVEF <50%, unstable angina pectoris, cardiac arrhythmia (i.e. atrial fibrillation), or psychiatric illness/social situations that would limit compliance with study requirements. All patients were required to practice effective birth control. Patients taking high doses (more than recommended daily dose) of vitamin E were excluded. Patients serologically positive for HIV or viral hepatitis were also excluded.

Study design and patient treatment

This open-label, dose escalation phase 1 trial was designed to determine the safety and tolerability of selumetinib in combination with cetuximab. Patients were enrolled at the University of Wisconsin–Carbone Cancer Center and the Medical Branch of the National Cancer Institute. Treatment was administered on an outpatient basis. Treatment started at dose level 1 and dose escalation proceeded according to the traditional 3+3 design. Once the recommended phase 2 dose/MTD was identified, an additional 12 patients with *KRAS*-mutant metastatic colorectal cancer were enrolled at that dose level, in an effort to more fully characterize pharmacokinetic characteristics of this combination.

Selumetinib in the oral capsule formulation was administered orally twice daily (BID) according to the dose escalation scheme (Table 2) on an empty stomach, at least 1 hour before or 2 hours after meals. The morning dose was given at least 1 hour before cetuximab. Premedication with diphenhydramine 50 mg intravenously (IV) and acetaminophen 650 mg orally were administered 30-60 minutes prior to cetuximab. Cetuximab was administered at standard doses of 400 mg/m^2 IV loading dose over 120 minutes on cycle 1 day 1 followed

by 250 mg/m^2 over 60 minutes IV weekly. Cycles were repeated every 28 days. The MTD was defined as the dose level in which one or fewer of six patients developed a dose limiting toxicity (DLT) within the first cycle.

Since rash is noted with both selumetinib and cetuximab as single agents, treatment guidelines for the treatment of rash were included. For grade 1 rash no specific treatment, topical hydrocortisone 1% or 2.5 % cream twice daily to affected areas, or clindamycin 1% gel topically twice daily to affected areas could be prescribed. For grade 2 rash, topical hydrocortisone 1% or 2.5 % cream twice daily to affected areas or clindamycin 1% gel topically twice daily to affected areas in addition to doxycycline 100mg orally BID or minocycline 100mg orally BID were recommended. For grade ≥3 or intolerable grade 2, topical hydrocortisone 1% or 2.5 % cream twice daily to affected areas or clindamycin 1% gel topically BID to affected areas plus doxycycline 100mg orally BID or minocycline 100mg orally BID plus methylprednisolone (Medrol) dose pack orally were recommended.

Dose modification

Dose modifications were considered for toxicities that were at least possibly attributable to selumetinib or cetuximab. If the toxicity was at least possibly related to both selumetinib and cetuximab, then both drugs required modification. On the day of treatment, the absolute neutrophil count was required to be ≥ 1000, and platelets ≥ 75,000. All previous drug-related toxicities needed to be resolved to grade 1 or baseline. If treatment was delayed for greater than 28 days for any reason, the patient was required to have a repeat staging CT or MRI scan. If the patient's disease did not meet criteria for progression, treatment could continue. If a patient was off treatment for any reason for more than 42 days, they would subsequently be removed from the study protocol.

Patient evaluations and follow-up

History, physical examination, weight, evaluation of ECOG performance status, and routine laboratory studies were obtained from all patients at baseline and at the beginning of subsequent cycles. Tumor assessment was obtained at baseline and every cycle if measured by physical examination, or every other cycle if measured by radiographic imaging. Other pre-registration studies included measurement of height, serum pregnancy testing for women of childbearing age and an EKG. In addition, a CBC with differential was obtained on days 8 and 15 of each cycle.

All toxicity grades were according to NCI Common Terminology Criteria for Adverse Events Version 4.0. A DLT was defined as a toxicity that was considered probably or definitely related to selumetinib in combination with cetuximab, and met the following criteria: ≥ grade 3 non-hematologic toxicity (excluding nausea, vomiting, or diarrhea); ≥ grade 3 nausea; vomiting, or diarrhea uncontrolled by maximal anti-emetic/anti-diarrheal therapy; inability to deliver more than 75% of the protocol-specified cycle 1 treatment due to a toxicity considered at least possibly related to study treatment; dose delay of > 14 days on day 1 of cycle 2 due to a toxicity considered at least possibly related to study treatment, grade 4 neutropenia lasting > 7 days; grade 4 neutropenia and fever of > 38.5°; ≥ grade 3

neutropenia with ≥ grade 3 infection; thrombocytopenia of any grade associated with a clinically significant or life-threatening bleed; grade 4 thrombocytopenia.

For MTD determination, only toxicities occurring during the first cycle (treatment days 1 through 28) were utilized, including residual treatment toxicities at cycle 2, day 1. Any patient who did not complete the first scheduled cycle of therapy due to toxicity, but did not meet criteria for a DLT, would be considered unevaluable and be replaced.

All patients who completed at least one treatment cycle followed by 2 weeks of observation were considered evaluable. The determination of antitumor efficacy was based on objective tumor assessments made according to the Response and Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1) [11]. Baseline imaging-based tumor assessments were performed within 28 days prior to the start of treatment, and all tumor assessments were re-evaluated every 8 weeks thereafter. All patients with responding tumors (complete response (CR) and partial response (PR)) were required to have response confirmed 4 weeks after the first documented response.

Duration of study treatment

In the absence of treatment delays due to adverse events, treatment could continue until one of the following criteria applied: disease progression; intercurrent illness preventing further administration of treatment; unacceptable adverse event(s); patient decision to withdraw from the study; general or specific changes in the patient's condition rendering the patient unacceptable for further treatment in the judgment of the investigator; delayed recovery from toxicity preventing re-treatment in ≤ 42 days of scheduled therapy; or patient requiring more than two dose reductions of selumetinib and cetuximab.

Pharmacokinetic analysis

Selumetinib—EDTA plasma samples for the analysis of selumetinib were collected at baseline, 0.5, 1, 1.5, 2, 3, 4, 8 and 12 hours after selumetinib administration on cycle 1 day 1. Trough levels were obtained at C1D8, 15, 22 and on D1 of ensuing cycles. An LC-MS/MS assay for the analysis of selumetinib was developed and validated based on a previously published method [9]. Following acetonitrile extraction, samples were analyzed with an Agilent 1200 HPLC coupled to a model API4000 triple quadrupole mass spectrometer equipped with a Turbo V™ atmospheric pressure ionization source. MS/MS data were obtained in positive ion mode with m/z 459→m/z 301. The standard curve was linear from 15.62 to 4000 ng/ml, r2 =0.998 with an intraday variability of 9.62% for high standard (2000 ng/ml), n=3 and 5.61% for low standard (250 ng/ml), n = 3. Inter-day variability was 10.7% for low standard (250 ng/ml), n=5 and 9.04% for high standard (2000 ng/ml), n = 5 over 30 days. The LOD was 3.91 ng/ml and the LLOQ was 15.62 μg/ml. Recovery from plasma as compared to water was 66.3% for the low standard (250 ng/ml) and 117% for the high standard (2000 ng/ml).

Cetuximab—EDTA plasma samples for the analysis of cetuximab were collected at baseline on day 1 and trough levels were obtained at C1D8, 15, 22 and on D1 of ensuing cycles. Cetuximab was evaluated by a validated ELISA assay as previously described [12].

Briefly, the cetuximab standard curve was linear from 0.16-2.50 ng/mL. The intra-day and inter-day coefficients of variation (CV) were <11.7% and <15.1%, respectively. Correlation coefficient (R2) values for the linear range of the dilution curves were 0.99 for day 0, 0.98 for day 7, and 0.97 for day 14.

Statistical methods

Demographic information and clinical outcomes were analyzed descriptively and summarized in terms of frequencies and percentages for categorical variables or medians and ranges for continuous variables. Pharmacokinetic analysis for selumetinib was performed by noncompartmental methods using the WinNonlin, Version 6.3, Phoenix 64 (Pharsight, Cary, NC), and data are summarized using geometric means and coefficient of variations (CV) for Cmax and AUC. Tmax, T1/2 Cl/F, V/F and log-transformed AUC and Cmax values were summarized in terms of means ± standard. Comparisons of PK parameters between dose levels were conducted using a log-normal model (Cmax and AUC) and ttwo-sample t-test (dose normalized AUC and Cmax). All P-values are two-sided and $p < 0.05$ is used to define statistical significance.

RESULTS

Patient characteristics

Thirty-three patients, 24 male and 9 female, with a median age of 57 years (range 37-89) were enrolled and received a total of 62 courses of therapy (median of 2 cycles; ranging from 1 to 6 cycles). The majority of patients were heavily pretreated, having received a mean of 3.4 prior chemotherapy regimens. Baseline characteristics are outlined in Table 1.

Dose escalation and MTD

Three dose levels of selumetinib (50 mg daily, 50 mg BID and 75 mg BID) with cetuximab 250 mg/m^2 IV weekly following a 400 mg/m^2 load were assessed (Table 2). Treatment was started with dose level 1 at 50 mg daily of selumetinib. There was one reported DLT of hypomagnesemia at dose level 1 during cycle 1, and an additional three patients were enrolled at this dose level for a total of 6 evaluable patients, without additional dose-limiting toxicities. There was one unevaluable patient at dose level 1 due to not completing the first cycle, per patient preference. Dose level 2 enrolled a total of 4 patients at 50 mg BID of selumetinib with 250 mg/m^2 IV weekly following a 400 mg/m^2 load. No DLTs were reported at this level. One patient was unevaluable at this dose level for not receiving at least 75% of the planned selumetinib. Dose level 3 examined 75mg BID of selumetinib with standard dosing of cetuximab. The dose of selumetinib examined at this dose level is the single agent MTD. A total of 4 patients were enrolled at this dose level and no DLTs were reported at this level. One patient was unevaluable at this dose level due to removal from the study at the discretion of the treating physician prior to completing cycle 1. The MTD for the combination was established at selumetinib 75 mg PO BID and cetuximab 250 mg/m^2 weekly following a 400 mg/m^2 load, which is the single agent MTD for both drugs individually.

Safety and Tolerability

In general this regimen was very well tolerated. The most common adverse events reported as at least possibly attributed to selumetinib or cetuximab per patient during cycle 1 are listed in Table 3. One DLT of grade 4 hypomagnesemia occurred in the dose escalation group during the first cycle, and no other grade 4 toxicities were seen. Hypomagnesemia was attributed to cetuximab, as this is a well-known adverse reaction of the drug, seen in up to 55% of patients on it; and although selumetinib cannot be ruled out as a possible cause, this would be less likely.

Grade 3 toxicities were observed in 30% of patients and included acneiform rash, diarrhea, nausea, fatigue, hyponatremia, headache and transaminitis. The most common grade 1 and 2 adverse events during cycle 1 included acneiform rash (97%), nausea/vomiting, (76%), diarrhea (58%), fatigue (55%), dry skin (21%), fever (15%), and hypomagnesemia (12%). Most patients (60%) required no dose modifications during cycle 1. At dose level 3 and in the expansion cohort, 4/22 (18%) of patients received 4 or more cycles of therapy. Reported grade 2 and 3 adverse events in this subgroup of patients receiving 4 or more cycles included: one patient with grade 2 vomiting, one patient with grade 3 anemia and another patient with grade 3 INR elevation, representing late adverse events of this combination of drugs. A second DLT for grade 3 acneiform rash was observed in the expansion cohort

Efficacy

Out of 33 patients enrolled in the study, 26 were evaluable for assessment of tumor response. Patients underwent disease assessment within 28 days prior to the start of treatment, and all were re-evaluated at 8 week intervals thereafter. Best clinical responses are listed in Table 4 by dose level. In the dose escalation phase, an unconfirmed partial response was seen in a patient with metastatic CRC. This patient had previously had cetuximab-sensitive disease then underwent hepatectomy and was enrolled in this study after being diagnosed with disease recurrence. In addition, stable disease was seen in 5 patients in the dose escalation phase (1 SCC of the tonsil, 1 NSCLC, and 3 CRC). In the treatment-refractory advance *KRAS*-mutant CRC dose expansion cohort 14 patients were evaluable for response. No complete or partial responses were observed. Stable disease was identified in 36% (5/14) and progressive disease in 74% (9/14). Patients in the expanded cohort received a median of 2 cycles of therapy (range 1-6).

Selumetinib and cetuximab pharmacokinetics

Selumetinib pharmacokinetic parameters by dose level are found in Table 5. Geometric mean Cmax ranged from 1324 (dose level 2)) to 1504 ng/mL (dose level 3), while the geometric mean AUC ranged 3213 to 5200 ng/mL × hr. The coefficient of variations for Cmax ranged from 0.13 to 0.40 and from 0.12 to 0.58 for AUC. Since subjects in dose level 1 and 2 received the same dose, these levels were combined and compared to dose level 3. Cmax and AUC were higher in subjects receiving the 75mg dose when compared to the 50mg dose. Geometric mean Cmax was 1212 ng/mL in patients receiving a 50mg dose compared to 1504 ng/mL in those receiving the 75 mg dose(p=0.08), while the geometric mean AUC was 3448 ng/mL × hr in those receiving the 50mg dose compared to 5200 ng/mL × hr in those receiving the 75 mg dose (p=0.01). As expected, dose-normalized

Cmax and AUC did not vary. See Table 6. Cetuximab steady state concentrations of approximately 18-20 μg/mL were achieved by day 8 after the loading dose and can be found in Table 7.

DISCUSSION

RAS mutated tumors are resistant to anti-EGFR therapies, likely through the activation of growth factor signaling pathways independent of EGFR signaling [1, 2]. The RAF/MEK/ERK signaling cascade is a major effector of RAS signaling. Pre-clinical studies with CRC cell lines and human tumor mouse xenograft models treated with selumetinib alone or in combination with cytotoxic agents showed both anti-proliferative and pro-apoptotic effects [7, 8]. *In vitro* studies with CRC cell lines possessing *KRAS* mutations demonstrated a significant treatment response with the combination of cetuximab and a MEK1/2 inhibitor [3]. Target inhibition was observed in phase I clinical trials of selumetinib at the doses achieved in this study [9, 10]. The rationale for this study was based on the premise that inhibition downstream of RAS at MEK1/2 would overcome mutant *KRAS*-induced resistance to cetuximab therapy.

This phase I study examined the combination of selumetinib and cetuximab in patients with advanced and treatment refractory solid tumors. This combination was well-tolerated. Common toxicities included acneiform rash, diarrhea, fatigue, and nausea. The MTD was determined to be 75 mg BID of selumetinib in combination with cetuximab 400 mg/m^2 IV load followed by 250 mg/m^2 IV weekly. These doses are the single agent MTDs for both drugs. In the dose escalation phase a PR was noted in one patient who had recurrent cetuximab sensitive CRC. In addition, some patients developed stable disease. Unfortunately, the dose expansion cohort did not show a meaningful anti-tumoral response in patients with *KRAS*-mutant CRC.

Even though the RAF/MEK/ERK pathway is important for RAS signaling and likely plays an important role for KRAS-mediated resistance to anti-EGFR therapies, this study proves that inhibition of MEK alone is not sufficient to overcome mutant *KRAS*-mediated resistance to cetuximab. Other signaling pathways are also implicated in the neoplastic effects of RAS signaling and likely contributed to the lack of benefit seen with the combination of selumetinib and cetuximab. These alternate signaling pathways include the phosphatidylinositol 3-kinase (PI3K)/AKT, Ral-GEF and JAK/STAT pathways [13]. Inhibitors of these pathways are in development and additional combination strategies could be entertained for this treatment-refractory population. In addition to compensatory activation of alternate signaling pathways, concomitant mutations in these pathways might have been present activating these pathways in parallel to RAS signaling. Activating mutations of the *PIK3CA* gene and loss of PTEN commonly occur concurrently with *KRAS* mutations and could also lead to resistance to MEK inhibition. Comprehensive mutation profiling is needed for future studies investigating therapies targeting this patient population.

Though blockade of EGFR and MEK is not beneficial for *KRAS*-mutant CRC, it may have potential for other CRC subtypes. *BRAF* mutations occur in 10% of CRC and are mutually exclusive of *KRAS* mutations. These mutations have also been shown to lead to resistance to

anti-EGFR therapies [3, 6]. MEK1/2 is the only recognized substrate for BRAF and *BRAF* mutant cell lines have been shown to be sensitive to MEK inhibition [7, 8]. Similar regimens are currently being investigated in phase I/II studies in *BRAF*-mutant CRC. These studies are evaluating different combinations of BRAF inhibitors given with EGFR inhibitors (either cetuximab or panitumumab), in association with or without MEK inhibitors, PI3K inhibitors and cytotoxic chemotherapy, as a continued attempt to overcome tumor activation of alternate escape pathways [14-17]. These studies show encouraging preliminary data with partial responses ranging from 12 to 80% of patients, including some complete responses, thought the sample sizes are still small and further research is ongoing in this area.

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References

1. Ciardiello F, Tortora G. EGFR antagonists in cancer treatment. N Engl J Med. 2008; 358:1160–74. [PubMed: 18337605]
2. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med. 2008; 359:1757–65. [PubMed: 18946061]
3. Benvenuti S, Sartore-Bianchi A, Di Nicolantonio F, et al. Oncogenic activation of the RAS/RAF signaling pathway impairs the response of metastatic colorectal cancers to anti-epidermal growth factor receptor antibody therapies. Cancer Res. 2007; 67:2643–8. [PubMed: 17363584]
4. Souglakos J, Philips J, Wang R, et al. Prognostic and predictive value of common mutations for treatment response and survival in patients with metastatic colorectal cancer. Br J Cancer. 2009; 101:465–72. [PubMed: 19603024]
5. Yokota T, Ura T, Shibata N, et al. BRAF mutation is a powerful prognostic factor in advanced and recurrent colorectal cancer. Br J Cancer. 2011; 104:856–62. [PubMed: 21285991]
6. Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol. 2008; 26:5705–12. [PubMed: 19001320]
7. Yeh TC, Marsh V, Bernat BA, et al. Biological characterization of ARRY-142886 (AZD6244), a potent, highly selective mitogen-activated protein kinase kinase 1/2 inhibitor. Clin Cancer Res. 2007; 13:1576–83. [PubMed: 17332304]
8. Davies BR, Logie A, McKay JS, et al. AZD6244 (ARRY-142886), a potent inhibitor of mitogen-activated protein kinase/extracellular signal-regulated kinase kinase 1/2 kinases: mechanism of action in vivo, pharmacokinetic/pharmacodynamic relationship, and potential for combination in preclinical models. Mol Cancer Ther. 2007; 6:2209–19. [PubMed: 17699718]
9. Adjei AA, Cohen RB, Franklin W, et al. Phase I pharmacokinetic and pharmacodynamic study of the oral, small-molecule mitogen-activated protein kinase kinase 1/2 inhibitor AZD6244 (ARRY-142886) in patients with advanced cancers. J Clin Oncol. 2008; 26:2139–46. [PubMed: 18390968]
10. Banerji U, Camidge DR, Verheul HM, et al. The first-in-human study of the hydrogen sulfate (Hyd-sulfate) capsule of the MEK1/2 inhibitor AZD6244 (ARRY-142886): a phase I open-label multicenter trial in patients with advanced cancer. Clin Cancer Res. 2010; 16:1613–23. [PubMed: 20179232]
11. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45:228–47. [PubMed: 19097774]

12. Ikesue H, Vermeulen LC, Hoke R, et al. Stability of cetuximab and panitumumab in glass vials and polyvinyl chloride bags. Am J Health Syst Pharm. 2010; 67:223–6. [PubMed: 20101065]
13. Ballif BA, Blenis J. Molecular mechanisms mediating mammalian mitogen-activated protein kinase (MAPK) kinase (MEK)-MAPK cell survival signals. Cell Growth Differ. 2001; 12:397–408. [PubMed: 11504705]
14. Corcoran RB, Atreya CE, Falchook GS, et al. Phase 1-2 trial of the BRAF inhibitor dabrafenib (D) plus MEK inhibitor trametinib (T) in BRAF V600 mutant colorectal cancer (CRC): Updated efficacy and biomarker analysis. J Clin Oncol. 2014; 32(5s) suppl; abstr 3517.
15. Bendell JC, Atreya CE, Theirry A, et al. Efficacy and tolerability in an open-label phase I/II study of MEK inhibitor trametinib (T), BRAF inhibitor dabrafenib (D), and anti-EGFR antibody panitumumab (P) in combination in patients (pts) with BRAF V600E mutated colorectal cancer (CRC). J Clin Oncol. 32(5s) suppl; abstr 3515.
16. Van Geel R, Elez E, Bendell JC, et al. Phase I study of the selective BRAFV600 inhibitor encorafenib (LGX818) combined with cetuximab and with or without the α-specific PI3K inhibitor BYL719 in patients with advanced BRAF-mutant colorectal cancer. J Clin Oncol. 2014; 32(5s) suppl; abstr 3514.
17. Hong DS, Van Karlyle M, Fu S, et al. Phase 1B study of vemurafenib in combination with irinotecan and cetuximab in patients with BRAF-mutated advanced cancers and metastatic colorectal cancer. J Clin Oncol. 2014; 32(5s) suppl; abstr 3516.

Table 1

Baseline patient characteristics

	Dose escalation	Dose expansion
Number of patients	15	18
Median Age, years (range)	60 (41-73)	55 (27-89)
Gender, n (%)		
Male	9 (60)	15 (83)
Female	6 (40)	3 (17)
Race, n (%)		
Caucasian	15 (100)	16 (89)
African-American	0	2 (11)
ECOG PS, n (%)		
0	7 (47)	3 (17)
1	8(53)	15 (83)
Primary Tumor Type, n (%)		
Colorectal Cancer	11 (73)	18 (100)
Non Small Cell Lung Cancer	2 (13)	0 (0)
Head and Neck Cancer	2 (13)	0 (0)
Prior Systemic Therapy		
Mean number of regimens (range)	4.7 (1-8)	2.8 (2-4)
KRAS Mutation Status, n (%)		
Mutant	8 (53)	18 (100)
Wild-type	2 (13)	0 (0)
Unknown	5 (34)	0 (0)
Prior EGFR-directed Therapy, n (%)	5 (33)	2 (11)

Table 2

Dose escalation schema and frequency of dose limiting toxicities

Dose level	Total n of patients	Selumetinib, oral dose	Cetuximab, IV load/week	N of courses	N of unevaluable patients[a]	N of patients with DLTs	DLT description
1	7	50mg Daily	400mg/250mg	16	1	1	Hypomagnesemia
2	4	50mg BID	400mg/250mg	12	1	0	
3[b]	22	75mg BID	400mg/250mg	34	7	1[c]	Acneiform rash

[a] Patients were unevaluable due to not receiving at least 75% scheduled of selumetinib and cetuximab during cycle 1.

[b] Includes patients at dose level 3 and the dose expansion cohort

[c] This DLT was observed in the *KRAS* mutant CRC dose expansion cohort.

Table 3

Drug-related adverse events, worst grade per patient per cycle 1.

	Dose level 1 (n = 7)			Dose level 2 (n = 4)			Dose level 3[a] (n = 22)			Total (n = 33), %
Selected Toxicities	**G1**	**G2**	**G3/4**	**G1**	**G2**	**G3/4**	**G1**	**G2**	**G3/4**	
Hematologic										
Neutropenia								1		3
Anemia								3		9
Thrombocytopenia							1			3
Non-Hematologic										
Nausea		2					10	1	1	42
Vomiting	1			1			5	5		36
Diarrhea	3			3			7	5	1	58
Acneiform Rash	5	2		1	3		12	8	1*	97
Dry Skin	2	1		1			2	1		21
Headache			1	1			2			12
Fever	3						1	1		15
Fatigue	1	1		2			9	4	1	55
Mucositis		1					2			9
Blurry Vision				1			3			12
Hypokalemia							2			6
Hypophosphatemia								1		3
Hyponatremia								1	2	9
Hypomagnesemia			1*				4			15
Transaminitis				2			3		3	24

AEs at least possibly related to drug were included.

[a] Includes patients at dose level 3 and the dose expansion cohort

* DLT

Table 4

Best response per dose level

Dose level	Total n of patients	Selumetinib, oral dose	Cetuximab, IV Load/Week	Best response, n		
				PR	SD	PD
1	5	50mg Daily	400mg/250mg	0	2	3
2	4	50mg BID	400mg/250mg	1	1	2
3	3	75mg BID	400mg/250mg	0	2	1
Expansion cohort	14	75mg BID	400mg/250mg	0	5	9

Table 5

Summary pharmacokinetic parameters of selumetinib on day1 of cycle 1

Dose level	N	Cmax (ng/mL)	Tmax (hr)	AUC 0-∞ (ng/mL × hr)	T ½ (hr)	Cl/F (L/hr)	V/F (L)
1	6*	1324 (CV 0.13)	1.13 ± 0.25	3213 (CV 0.23)	2.28 ± 0.55	23.9 ± 5.48	76.9 ± 18.1
2	4	1143 (CV 0.28)	1.92 ± 1.28	3614 (CV 0.12)	2.31 ± 0.55	21.0 ± 2.53	70.4 ± 19.7
3[a]	22	1504 (CV 0.40)	1.64 ± 0.73	5200 (CV 0.58)	2.97 ± 0.89	16.4 ± 7.08	65.2 ± 24.3

Data are shown as geometric mean and coefficient of variation (CV) for Cmax and AUC, and as mean ± standard deviation for Tmax T 1/2 , Cl/F and V/F.

[a] Includes patients at dose level 3 and the dose expansion cohort

* Pks were unevaluable in one patient due to hemolyzed samples

Table 6

Summary pharmacokinetics parameters of selumetinib on day 1 of cycle 1

	Dose level 1 and 2 combined (N=10)	Dose level 3 (N=22[a])	p-value
Cmax (ng/mL)	1212 (CV 0.24)	1504 (CV 0.40)	0.08
AUC 0-∞ (ng/mL × hr)	3448 (CV 0.17)	5200 (CV 0.58)	0.01
Log (Cmax (ng/mL) – dose normalized	3.19 ± 0.23	3.00 ± 0.43	0.20
Log(AUC 0-∞ (ng/mL × hr) – dose normalized	4.23 ± 0.17	4.24 ± 0.54	0.97

Data are shown as geometric mean and coefficient of variation (CV) for Cmax and AUC, and as mean ± standard deviation for log-transformed, dose normalized Cmax and AUC.

[a]Includes patients at dose level 3 and the dose expansion cohort

Table 7

Cetuximab Plasma Concentrations

Cycle	Day	N	Mean	SD
1	1	32	0	0
1	8	31	18.36	17.43
1	15	28	20.68	17.21
1	22	26	18.66	20.85
2	1	32	21.31	19.80
3	1	18	16.99	33.70
4	1	7	7.73	3.25
5	1	5	7.28	4.21
6	1	1	9.16	NA
7	1	1	8.18	NA

NA, not applicable.