First-in-Human Study of CH5132799, an Oral Class I PI3K Inhibitor, Studying Toxicity, Pharmacokinetics, and Pharmacodynamics, in Patients with Metastatic Cancer

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Abstract

**Purpose:** This phase I dose-escalation study investigated the maximum-tolerated dose (MTD), dose-limiting toxicities (DLT), safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary clinical activity of CH5132799.

**Experimental Design:** Patients with metastatic solid tumors were eligible for the study. CH5132799 was administered orally once daily or twice daily in 28-day cycles.

**Results:** Thirty-eight patients with solid tumors received CH5132799 at 2 to 96 mg once daily or 48 to 72 mg twice daily. The MTD was 48 mg on the twice-daily schedule but was not reached on the once daily schedule. DLTs were grade 3 elevated liver function tests (LFT), grade 3 fatigue, grade 3 encephalopathy, grade 3 diarrhea, and grade 3 diarrhea with grade 3 stomatitis; all DLTs were reversible. Most drug-related adverse events were grade 1/2. Diarrhea (34%) and nausea (32%) were the most common events. Mean Cmax and AUC0-24 in steady state at MTD were 175 ng/mL and 1,550 ng h/mL, respectively, consistent with efficacious exposure based on preclinical modeling. Reduction in SUVmax with [18F] fluorodeoxyglucose positron emission tomography (FDG-PET) was observed in 5 of 7 patients at MTD. A patient with PI3KCA-mutated clear cell carcinoma of the ovary achieved a partial response by GCIG CA125 criteria and further, a heavily pretreated patient with triple-negative breast cancer had marked improvement in her cutaneous skin lesions lasting six cycles.

**Conclusion:** CH5132799 is well tolerated at the MTD dose of 48 mg twice daily. At this dose, the drug had a favorable PK and PD profile and preliminary evidence of clinical activity. *Clin Cancer Res;* 20(23); 5908–17. 
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Introduction

The intracellular phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway regulates cellular functions such as cell survival, proliferation, growth, apoptosis, protein synthesis, and glucose metabolism (1–6). Of the three classes of PI3K (I to III), class IA is implicated most in cancer (5). Class IA PI3K heterodimers comprise a p85-regulatory and a p110-catalytic subunit with several isoforms (5). Mutation or amplification of PI3K (p110α) promotes oncogenic activation of the PI3K pathway and occurs frequently in human cancers such as ovarian cancer and breast cancer (1, 6–12). Phosphatase and tensin homolog (PTEN), a key negative regulator of AKT, can be inactivated via mutations, downregulation, or loss of protein expression, and is associated with tumorigenesis in prostate, gastric, and other cancers (1, 13–19). Moreover, it is likely that PI3K pathway activation is associated with resistance to both chemotherapy (20–22) and...
Phase I Study of the Class I PI3K Inhibitor, CH5132799

**Translational Relevance**

CH5132799 is an oral pan-PI3 kinase inhibitor designed to target both alpha and beta isoforms of PI3K, which are frequently deregulated in cancer due to activating mutations in the oncogene PIK3CA or loss of function of the tumor-suppressor gene, PTEN. The dosing schedule was to be determined by toxicity, PK, and PD parameters and started with a once daily schedule followed if necessary by a twice-daily schedule. The trial started with CH5132799 administered orally once a day but a formal MTD was not reached at 96 mg; however, there were no significant increments in AUC above a dose of 56 mg once daily and p-AKT showed recovery at 24 hours. Therefore, the dosing schedule was modified to include twice a day dosing. A dose of 48 mg twice daily was declared the recommended phase II dose, at which dose a patient with PIK3CA-mutant clear cell ovarian cancer responded.

Targeted agents (23–26). Selective inhibition of the PI3K–AKT–mTOR pathway in cancer represents a promising therapeutic approach and has been the focus of significant research efforts, including the clinical development of novel agents targeting this pathway [1, 19, 27–37].

CH5132799 (Chugai Pharmaceutical Co Ltd.) is an oral PI3K inhibitor with specific and potent activity against class I PI3Ks, especially demonstrated in wild-type and mutant PI3Kα isoforms, and PI3Kγ, at nanomolar concentrations (38). CH5132799 has no inhibitory activity against class III PI3K, or mTOR (38). In vitro experiments demonstrated a strong antiproliferative effect of CH5132799 on human cancer cell lines with alterations in the PI3K pathway (38, 39). In vivo, CH5132799 demonstrated significant antitumor activity in human tumor xenograft models with PIK3CA mutations, with good correlation between CH5132799 exposure and inhibition of PI3K signaling (39).

The primary objective of this first-in-human, phase I, dose-escalation study was to determine the MTD of CH5132799 using a continuous oral schedule in patients with advanced solid tumors. Secondary objectives included the characterization of CH5132799 PK, and the PD profile of PI3K inhibition in tumor and in surrogate tissues such as peripheral blood samples, and by [18F] fluoro-deoxyglucose positron emission tomography (FDG-PET).

**Patients and Methods**

**Study population**

Patients had been diagnosed with advanced solid tumors that were not amenable or were refractory to standard therapy. Patients of ages ≥18 years with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and adequate bone marrow, renal, hepatic, and cardiac function (see Supplementary data for detailed inclusion and exclusion criteria) and a life expectancy of ≥12 weeks were enrolled.

This study was approved by an independent ethics committee (The Royal Marsden Research Ethics Committee, London, United Kingdom) and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP). Written informed consent was obtained from all patients before carrying out any study-related procedures.

**Study design and CH5132799 dose escalation**

This open-label dose-escalation study was conducted at four centers. Before the first treatment cycle, CH5132799 was administered as a single oral dose followed by a 5- to 7-day washout (run-in period). A classic "3+3" design was used for dose escalation with once daily to the early patient cohorts, and then twice daily to others, continuously in 4-week cycles. Dose escalation was determined by the nature and grade/severity of toxicities.

The primary objective was to determine the MTD of CH5132799 based on DLTs observed during the run-in period and first 4-week cycle. The MTD was defined as the highest dose level at which no more than 1 of 6 patients experienced a DLT. A starting dose of 2 mg was chosen on the basis of the highest nonsevere toxic dose in a nonrodent species and the severely toxic dose (10% lethal dose) in rat, which means 7.8-fold and 30-fold safety margins were applied to the two metabolically/kinetically relevant animal species, respectively.

**Assessments**

Medical history and demographic data were collected at baseline. Physical examination, monitoring of vital signs, and other safety assessments were performed throughout the study. All toxicities were documented using Common Terminology Criteria for Adverse Events (CTCAE) V4.03 (40). DLTs were defined as grade ≥3, nonhematologic toxicity despite adequate treatment; grade 4, neutropenia lasting ≥7 days; and febrile neutropenia, grade 4 thrombocytopenia lasting ≥7 days or requiring a platelet transfusion.

Tumor response was assessed according to Response Evaluation Criteria In Solid Tumors (RECIST; version 1.1) with imaging at baseline and every two cycles (41).

**PK and PD**

Plasma PK samples were collected on cycle 0, day 1, followed by cycle 1, days 1, 8, 15, and 22. Plasma concentrations of CH5132799 were measured by a validated LC-MS/MS assay method (Chugai Pharmaceutical Co. Ltd.; data on file) and PK parameters calculated by noncompartmental analysis with first-order oral absorption (WinNonlin Version 5.3 and Phoenix WinNonlin Version 6.1; Pharsight Corporation). The CH5132799-related inhibition of AKT phosphorylation (pAKT) was studied in platelet-rich plasma (PRP). Blood for PRP samples was collected at 0 (predose), 1, 2, 6, 24, 48, and 72 hours postdose on day 1 of the run-in period (cycle 0, day 1) and at 0 (predose) on cycle 1, day 15. Blood samples were
collected into BD Vacutainer sodium citrate coagulation
tubes and centrifuged at 200 × g at 4°C for 15 minutes. The
isolated PRP layer was incubated with PhosSTOP (Roche) to
stabilize the phosphorylation signals and then lysed using
the Cell Lysis Buffer (Cell Signaling Technology) containing
phenylmethane sulfonyl fluoride (Sigma-Aldrich) and then
snap-frozen on dry ice. PD analysis with PRP was performed
by The Institute of Cancer Research. All PRP samples were
analyzed for the levels of phosphorylated and total forms of
PD biomarker AKT by a Mesoscale Discovery electroche-
miluminescent (ECL) assay. The assay was modified into a
GCP-compliant quantitative assay for AKT by inclusion of a
standard curve of recombinant active AKT protein on every
plate. The quality, accuracy, and precision of the assays were
monitored using quality control (QC) samples created by
spiking three known quantities of recombinant AKT into
10% human plasma.

Biopsies were performed at screening and at cycle 1, day
15. Flash frozen tumor biopsies were homogenized using a
micro tissue grinder in the Cell Lysis Buffer (w/v) containing
PhosSTOP. The tumor lysates were centrifuged to remove
debris and the protein concentration measured using the
BCA assay (Pierce). Tumor biopsy samples were analyzed
for the levels of phosphorylated and total forms of PD
biomarker AKT by a quantitative ICR-modified GCP com-
pliant Mesoscale Discovery ECL assay. FDG-PET imaging
was performed within 28 days before the first dosing of
CH5132799, cycle 1, day 8, and cycle 3, day 1. Lesions with
the highest degree of FDG uptake were selected for quan-
titative analysis and a circular/spherical region of interest
drawn. A SUVmax was measured for each selected lesion and
the delta change in SUVmax was calculated. Tumor biopsies
were taken after FDG-PET scanning to avoid interference of
biopsy on FDG uptake.

Detection of mutations

PIK3CA/KRAS/BRAF mutations were studied with the
OncoCarta panel v1.0 and detected by mass ARRAY System.

Statistical analyses

Descriptive statistics were used for the analysis of PK, PD,
safety, and tumor response data.

Results

Thirty-eight patients received at least one dose of
CH5132799 (Table 1), of whom 23 received CH5132799
once daily (2–96 mg/day). The decision to dose twice daily
was made as there had been no DLTs and no significant
increase in drug concentrations at doses above 56 mg once
daily along with PD measures, i.e., recovery of p-AKT after
12 hours. Subsequently, 15 further patients then received
CH5132799 twice daily (96–144 mg/day). Overall, patients
received a median of 2 cycles (range, 0–6), with a median
duration of 52 days of treatment (range, 1–164 days).
Archival tumor samples were available in 30 patients.
PIK3CA mutations were found in 10% (3 of 30) of the
samples studied (Table 1).

DLTs

DLTs were observed in 5 of 38 evaluable patients who
received CH5132799 twice daily and completed the first
cycle (Table 2). Of 7 patients at 48 mg twice daily, 1

Table 1. Patient demographics and clinical
characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total patients (N = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (26%)</td>
</tr>
<tr>
<td>Female</td>
<td>28 (74%)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>58.5</td>
</tr>
<tr>
<td>Range</td>
<td>41–76</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>White</td>
<td>32 (84%)</td>
</tr>
<tr>
<td>Baseline ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>12 (32%)</td>
</tr>
<tr>
<td>1</td>
<td>25 (66%)</td>
</tr>
<tr>
<td>2</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Prior anticancer therapies, median (range)</td>
<td>3 (1–8)</td>
</tr>
<tr>
<td>Primary tumor site and mutational status</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>10 (26%)</td>
</tr>
<tr>
<td>No mutation</td>
<td>8</td>
</tr>
<tr>
<td>Unknown mutational status</td>
<td>2</td>
</tr>
<tr>
<td>Ovarian</td>
<td>6 (16%)</td>
</tr>
<tr>
<td>KRAS G12D</td>
<td>1</td>
</tr>
<tr>
<td>PIK3CA H1047R</td>
<td>1</td>
</tr>
<tr>
<td>No mutation</td>
<td>3</td>
</tr>
<tr>
<td>Unknown mutational status</td>
<td>1</td>
</tr>
<tr>
<td>Esophageal and esophageal-gastric adenocarcinoma</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>KRAS G12D</td>
<td>1</td>
</tr>
<tr>
<td>EGFR S768I</td>
<td>1</td>
</tr>
<tr>
<td>No mutation</td>
<td>3</td>
</tr>
<tr>
<td>Duodenal and large intestine</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>KRAS G12A</td>
<td>1</td>
</tr>
<tr>
<td>KRAS G12D and PIK3CA E545K</td>
<td>1</td>
</tr>
<tr>
<td>No mutation</td>
<td>2</td>
</tr>
<tr>
<td>Gastric*</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Lung*</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Endometriatia*</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Vagina*</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Myometrium*</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Vulva*</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Bladder*</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Pancreas*</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Prostate*</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Unknown primary origin</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>PIK3CA E545K</td>
<td>1</td>
</tr>
</tbody>
</table>

*No mutation or mutational status not known.
A patient with hepatocellular carcinoma experienced grade 3 elevated transaminases. Although the patient had liver metastases with elevated LFTs (grade 2) at baseline, a causal link to CH5132799 could not be excluded because clear evidence of disease progression in liver metastasis was not observed. At the next dose level, 2 of 3 patients receiving 72 mg twice daily had DLTs. One had grade 3 fatigue that was resolved following cessation of CH5132799 and she restarted CH5132799 with reduced dose when fatigue had been resolved and she did not experience the event later on, whereas the other developed grade 3 posterior reversible encephalopathy syndrome (PRES) that was presented with seizures. The diagnosis was made on characteristic MRI findings and the symptoms resolved on cessation of CH5132799 as well as instigation of supportive care without restarting CH5132799. Two of 5 patients receiving the intermediate dose of 56 mg twice daily had grade 3 diarrhea, the other grade 3 diarrhea with grade 3 stomatitis, which resolved following cessation of CH5132799 and instigation of supportive treatment; in both cases, study treatment was then restarted at a reduced dose without further DLTs. Therefore, the MTD and recommended phase II dose (RP2D) of CH5132799 administered orally was established at 48 mg twice daily.

**Safety**

The most common AEs were diarrhea, nausea, stomatitis, fatigue, and rash, which occurred in 34%, 32%, 29%, 29%, and 24% of patients, respectively (Table 3). Diarrhea was predominantly grade 1 or 2, with no grade 4 diarrhea reported. Four patients experienced grade 3 diarrhea (96 mg once daily, n = 2; 56 mg twice daily, n = 2). One patient experienced grade 3 nausea (96 mg once daily). No grade ≥3 gastrointestinal AEs occurred in the cohort who received CH5132799 at the RP2D (48 mg twice daily). Hyperglycemia was predicted because of the mechanism of action of CH5132799. Five patients experienced grade ≥3 hyperglycemia in the twice-daily dosing schedule, suggesting a dose-dependent effect (48 mg twice daily, n = 1; 56 mg twice daily, n = 2; 72 mg twice daily; n = 2 including one grade 4). No episodes of diabetic ketoacidosis occurred and hyperglycemia was controlled with oral metformin as required. No drug-related deaths were reported.

### Table 2. DLTs seen on the study

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose</th>
<th>N</th>
<th>DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>7b</td>
<td>48 mg BID</td>
<td>7</td>
<td>Grade 3 elevated LFT at cycle 1 day 8</td>
</tr>
<tr>
<td>8</td>
<td>72 mg BID</td>
<td>3</td>
<td>Grade 3 cerebral encephalopathy at cycle 1, day 14</td>
</tr>
<tr>
<td>9</td>
<td>56 mg BID</td>
<td>5</td>
<td>Grade 3 fatigue at cycle 1 day 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 3 diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 3 diarrhea and stomatitis (&lt;75% of the total scheduled dose)</td>
</tr>
</tbody>
</table>

Abbreviation: BID, twice daily.

### Table 3. Treatment-related toxicities occurring in ≥10% patients by CH5132799 dose level

<table>
<thead>
<tr>
<th>AE</th>
<th>QD (n = 3)</th>
<th>BID (n = 3)</th>
<th>Total (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 mg (n = 3)</td>
<td>4 mg (n = 3)</td>
<td>8 mg (n = 3)</td>
</tr>
<tr>
<td>Grade 1–2 3–4</td>
<td>1–2 3–4</td>
<td>1–2 3–4</td>
<td>1–2 3–4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Dry skin</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
PK
Following oral administration of a single dose of CH5132799, plasma concentrations peaked with a $T_{\text{max}}$ at 2.60 hours and $t_{1/2}$ of 10.2 hours at the MTD (Fig. 1A). Dose proportionality of AUC was shown in the dose range of 2 to 56 mg (Fig. 2B). Steady state was reached by cycle 1, day 8 at the latest with little subsequent accumulation; there was no further increase in AUC at higher doses. At the MTD of 48 mg twice daily, mean $C_{\text{max}}$ and $AUC_{\text{last}}$ were 172 ng/mL and 1,270 ng·h/mL after a single dose, respectively. Mean $C_{\text{max}}$ and $AUC_{0-24h}$ were 175 ng/mL and 1,550 ng·h/mL at steady state, respectively (Table 4).

PD
Significant inhibition of PI3K signaling was observed in PRP, with reduction of AKT phosphorylation at doses of 32 mg and above (Fig. 2A). The temporal relationship between reduction in phosphorylation of AKT and dosing administration with CH5132799 suggested target engagement for less than 24 hours (Fig. 2B). This observation contributed to the decision to increase dosing frequency to twice daily.

Pre- and posttreatment tumor biopsies were optional and the minimum number to be conducted during the study was not based on statistical assumptions. Tumor biopsy samples were collected before and after CH5132799 from 3 patients (one patient each on 56 mg once daily, 96 mg once daily, and 56 mg twice daily). There was a more than 50% reduction in normalized p-AKT levels in 2 of the 3 patients. A decrease in FDG avidity between baseline and cycle 1, day 8 was observed in 74% of patients (17 of 23) who underwent serial PET imaging (Fig. 2D). It was interesting that 5 of 7 patients at the RP2D who had pre- and postcycle 1, day 8 treatment PET scans showed a reduction in maximum standardized uptake value ($SU V_{\text{max}}$); 2 had a reduction in $SU V_{\text{max}}$ of 55% and 44%.
Phase I Study of the Class I PI3K Inhibitor, CH5132799

Figure 2. PD parameters of CH5132799. A, mean percentage change of phosphorylated AKT normalized to total AKT compared with pretreatment control values, 2 hours following a single dose of CH5132799. B, the temporal course of plasma concentration of CH5132799 and the percentage change of p-AKT normalized to total AKT compared with pretreatment control values following a single dose of the recommended phase II dose of CH5132799 (48 mg). C, percentage change of p-AKT normalized to total AKT in tumor biopsies when compared with pretreatment samples. D, SUVmax changes on FDG-PET scans in patients who had evaluable pre- and posttreatment FDG-PET scans.

Table 4. Summary of PK of CH5132799 in patients following oral administration

<table>
<thead>
<tr>
<th>Regimen</th>
<th>AUClasta (ng*h/mL)</th>
<th>Cmax (ng/mL)</th>
<th>t1/2 (h)</th>
<th>AUC0-24h b (ng*h/mL)</th>
<th>Cmax (ng/mL)</th>
<th>Accumulation ratio c</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg (QD)</td>
<td>53.0 (3)</td>
<td>10.0 (3)</td>
<td>7.52 (3)</td>
<td>48.8 (3)</td>
<td>9.92 (3)</td>
<td>0.912 (3)</td>
</tr>
<tr>
<td>4 mg (QD)</td>
<td>112 (3)</td>
<td>17.2 (3)</td>
<td>8.30 (3)</td>
<td>167 (3)</td>
<td>22.5 (3)</td>
<td>1.54 (3)</td>
</tr>
<tr>
<td>8 mg (QD)</td>
<td>133 (3)</td>
<td>41.1 (3)</td>
<td>23.7 (3)</td>
<td>159 (2)</td>
<td>46.3 (2)</td>
<td>1.22 (2)</td>
</tr>
<tr>
<td>16 mg (QD)</td>
<td>883 (1)</td>
<td>113 (1)</td>
<td>13.7 (1)</td>
<td>621 (2)</td>
<td>100 (3)</td>
<td>0.972 (1)</td>
</tr>
<tr>
<td>32 mg (QD)</td>
<td>859 (4)</td>
<td>165 (4)</td>
<td>12.2 (4)</td>
<td>1,740 (2)</td>
<td>345 (3)</td>
<td>1.57 (2)</td>
</tr>
<tr>
<td>56 mg (QD)</td>
<td>969 (3)</td>
<td>163 (3)</td>
<td>14.5 (3)</td>
<td>748 (3)</td>
<td>184 (3)</td>
<td>1.07 (3)</td>
</tr>
<tr>
<td>96 mg (QD)</td>
<td>1,650 (4)</td>
<td>206 (4)</td>
<td>23.2 (3)</td>
<td>691 (3)</td>
<td>103 (3)</td>
<td>0.640 (3)</td>
</tr>
<tr>
<td>48 mg (BID)</td>
<td>1,270 (4)</td>
<td>172 (5)</td>
<td>10.2 (4)</td>
<td>1,550 (5)b</td>
<td>175 (5)</td>
<td>1.10 (2)</td>
</tr>
<tr>
<td>56 mg (BID)</td>
<td>3,030 (5)</td>
<td>428 (5)</td>
<td>16.3 (5)</td>
<td>5,940 (2)b</td>
<td>331 (3)</td>
<td>1.72 (2)</td>
</tr>
<tr>
<td>72 mg (BID)</td>
<td>2,480 (3)</td>
<td>265 (3)</td>
<td>18.3 (3)</td>
<td>5,580 (1)b</td>
<td>631(1)</td>
<td>2.25 (1)</td>
</tr>
</tbody>
</table>

NOTE: Mean value and number (noted in parenthesis) are represented for each pharmacokinetic parameter.
Abbreviations: BID, twice daily; Cmax, maximum concentration measured; QD, once daily; t1/2: elimination half-life.
aAUClast in single dose represented AUC0-72h.
bAUC0-24h in BID regimen of repeat dose were calculated on the basis of the data from 0 to 12 hours (AUC0-12h).
cAccumulation ratio represents AUC0-24h/0-12h in repeat dose/AUC0-24h/0-12h in single dose.
There was no correlation between the PD changes in the limited number of biopsies, PET responses, or PRP inhibition.

**Efficacy**

There were no RECIST partial or complete responses, but 1 patient with *PIK3CA H1047R*-mutated clear cell ovarian cancer had a GCIG CA125 response having been treated at 48 mg twice daily and remained on study for 6 cycles (Fig. 3A). A second patient with heavily pretreated triple-negative breast cancer bearing no *PIK3CA* or *AKT* mutations who was treated at the 72 mg twice daily dose level had marked symptomatic and objective improvement in her cutaneous skin lesions and remained on treatment for 6 cycles (Fig. 3B). Disease stabilization was seen in 8 patients up to week 16 (approximately 4 cycles), including 2 patients with *PIK3CA* mutation.

**Discussion**

We report the first-in-human study of an oral PI3K class I inhibitor CH5132799. No DLTs occurred at the once daily schedule, but the twice-daily schedule was selected on the basis of the duration of target inhibition observed in platelet-rich plasma and the lack of dose-dependent incremental elevation in concentrations of drug above 56 mg once daily. The twice-daily schedule of CH5132799 was well tolerated and showed evidence of clinical and PD activity with a RP2D of 48 mg twice daily.

The most frequently observed toxicities were gastrointestinal, including diarrhea, nausea, and stomatitis. These have been described previously in studies of PI3K, AKT, and m-TOR inhibitors (28, 30–38). Reversible grade 3 LFT elevation was observed in 1 of 7 patients treated at the MTD of 48 mg twice daily. This patient with hepatocellular carcinoma had liver metastases and had previously undergone hepatic resection; therefore, the event was possibly caused by disease progression and/or overload of a liver with insufficient metabolic capability. No other cases of drug-related LFT abnormalities were noted, although they have been described in trials of other PI3K inhibitors (30–32, 34, 42). Of note, we observed one case of PRES at a dose above the MTD. This has not been reported previously in the trials of other drugs in this class; nevertheless, it raised the possibility that CH5132799 crosses the blood–brain barrier, which may be of future relevance in the treatment of patients with intracerebral malignancies. Mood alterations have been described as AEs in with other PI3 kinase inhibitors (30, 42), however, was not seen in this trial. Although skin-related toxicities have been frequently observed in the trials of other PI3K inhibitors (28–30, 32, 33, 35–37, 42–44), CH5132799 was associated with only
mild-to-moderate skin toxicities at a lower frequency. On-target toxicity such as hyperglycemia was observed with CH5132799, as with other PI3K, AKT, and m-TOR inhibitors (28–30, 35–37, 43, 44) and was not associated with ketoadiposis. The hyperglycemia was well controlled by metformin. The favorable toxicity profile of CH5132799 may make it suitable to combine with other targeted agents such as epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) or MAPK/ERK kinase (MEK) inhibitors.

The PK data show that it was possible to attain CH5132799 concentrations in patients that had been efficacious in xenograft models (39). The AUC increased proportionally with dose from 2 to 56 mg. The PD data indicated target modulation using phosphorylation of AKT at Sr473 as a proof-of-mechanism biomarker. Levels of p-AKT were reduced in PRP consistently at dose levels 8 to 96 mg. The maximal inhibition was approximately 50% compared with baseline and this was achieved at dose levels of 32 mg. p-AKT levels in PRP frequently recovered by 24 hours following the treatment. The duration of PD biomarker changes in normal tissue and the fact that there was no significant further reduction in p-AKT levels after the 32 mg cohort, along with the fact that the AUC of CH5132799 did not rise significantly above 56 mg, led us to explore a twice-weekly schedule, despite not reaching an conventional MTD at 96 mg on the once-daily dosing cohorts. At the recommended phase II dose of 48 mg twice daily, levels of p-AKT were reduced in PRP and in a limited number of posttreatment tumor biopsies. There was a reduction in levels of p-AKT (Ser473) in 2 of 3 post-treatment tumor biopsies at the higher dose levels, but there was considerable variation in reduction between patients (Fig. 2C). The degree of p-AKT reduction in the tumor from patients was less than what was seen in xenograft models (39), however, this could reflect different platforms to assess AKT phosphorylation and other factors such as intratumoral heterogeneity.

Further evidence of tumor target modulation was observed with FDG-PET scans with all patients at recommended dose. All 5 patients scanned at the RP2D had a reduction in $SUV_{\text{max}}$ and two of them achieved a PET response by PERCIST criteria (45). Although the number of patients is too small to draw definitive conclusions, these PD data are highly encouraging. There was no correlation between the PD changes in the limited number of biopsies and PET responses or PRP inhibition. The FDG PET was done pretreatment and on day 8 of treatment, whereas tumor biopsies were performed pretreatment and day 15 of treatment, while the detailed p-AKT studies in PRP were done on day 1 of treatment. The small number of biopsies and the disparities in the days when tests were conducted could have led to the lack of correlation between p-AKT levels in tumor, PRP, and changes in $SUV_{\text{max}}$ on PET.

The 8 study participants (21%) showing a best response of stable disease by RECIST included 2 participants who had clear clinical responses. In reports of other PI3K, AKT, and mTOR inhibitors as single agent in patients with solid tumors, disease stabilization was observed, but only a few cases of radiologic response have been reported (28–32, 34–36, 43). Therefore, there was clinical evidence as well as PD activity for CH5132799. These results indicated that CH5132799 was comparable with other PI3K, AKT, and m-TOR inhibitors in terms of single-agent activity.

Three patients were found to have PIK3CA mutations. Although there were no objective radiologic responses, it was interesting that 1 of these patients (with clear cell ovarian cancer) had a GCIG-defined partial response in her CA125 tumor marker. Another patient with triple-negative breast cancer had a visible response in cutaneous metastases. This patient with breast cancer did not have a PIK3CA mutation, although triple-negative breast cancer was known frequently to diseases associated with other perturbations in the PI3K pathway (46). Preclinical models suggest that PIK3CA mutations predict for sensitivity to PI3K inhibitors as either single agents (47, 48) or in combination (49). This was also seen with preclinical studies of CH5132799 (39). However, the clinical correlation between PIK3CA mutations and PI3K inhibitors to this has not been fully realized (50) in the clinic, and it is possible that other activating mutations (51) or intratumoral heterogeneity (52) may play a role.

We conclude that CH5132799 at RP2D of 48 mg twice daily is well tolerated and attains drug concentrations that show evidence of achieving target engagement in both normal tissues and tumor. CH5132799 has clinical, as well as PD activity, with evidence of proof of mechanism from a clinical response in 1 patient with PIK3CA-mutant ovarian cancer. The favorable toxicity profile and activity observed with single-agent CH5132799 suggests that it is suitable for combination with other targeted therapies and for exploration in subsets of patients with cancers harboring pre-defined mutations.

Disclosure of Potential Conflicts of Interest
U. Banerji reports receiving a commercial research grant from Chugai Pharma Europe Ltd. No potential conflicts of interest were disclosed by the other authors.

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References


Correction: First-in-Human Study of CH5132799, an Oral Class I PI3K Inhibitor, Studying Toxicity, Pharmacokinetics, and Pharmacodynamics, in Patients with Metastatic Cancer

In this article (Clin Cancer Res 2014;20:5908–17), which was published in the December 1, 2014, issue of Clinical Cancer Research (1), one of the authors' names was misprinted. The corrected name should read as follows: "Aurelius Omlin." The publisher regrets this error.

Reference

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