A First-in-Human Phase I Study of OPB-111077, a Small-Molecule STAT3 and Oxidative Phosphorylation Inhibitor, in Patients with Advanced Cancers

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TRIAL INFORMATION

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LESSONS LEARNED

• OPB-111077 is a novel inhibitor of STAT3 and mitochondrial oxidative phosphorylation that exhibited promising anticancer activity in preclinical models.
• In this first-in-human phase I study of OPB-111077 in unselected advanced cancers, treatment-emergent adverse events, most frequently nausea, fatigue, and vomiting, were generally mild to moderate in intensity and could be medically managed.
• Overall, only modest clinical activity was observed after OPB-111077 given as monotherapy. Notable antitumor activity was seen in a subject with diffuse large B-cell lymphoma.

ABSTRACT

Background. OPB-111077 is a novel inhibitor of STAT3 and mitochondrial oxidative phosphorylation with promising anticancer activity in preclinical models.

Methods. Open-label, phase I trial of OPB-111077 in advanced cancers with no available therapy of documented benefit. Initial dose escalation in unselected subjects was followed by dose expansion. Patients received oral OPB-111077 daily in 28-day cycles until loss of clinical benefit.

Results. Eighteen subjects enrolled in dose escalation, and 127 in dose expansion. Dose-limiting toxicities were observed at 300 mg and 400 mg QD; maximum tolerated dose was defined as 250 mg QD. Frequently reported treatment-emergent adverse events (TEAEs) included nausea, fatigue, and vomiting. TEAEs were generally mild to moderate and could be medically managed. OPB-111077 reached micromolar drug concentrations, had an elimination half-life of approximately 1 day, and reached steady-state by day 8. A durable partial response was observed in one subject with diffuse large B-cell lymphoma. Seven subjects with diverse tumor types had stable disease or minor responses for at least eight treatment cycles (224 days).

Conclusion. OPB-111077 is generally well tolerated, and its pharmacokinetic profile is sufficient for further clinical development. Notable clinical activity was observed in a subject with diffuse large B-cell lymphoma. Overall, modest efficacy was observed against unselected tumors. The Oncologist 2018;23:658–e72

DISCUSSION

Previous studies showed that STAT3 can promote tumorigenesis by at least two mechanisms: first, by acting as a nuclear transcription factor that alters expression of pro-tumorigenic gene-regulatory networks [1–8]; and second, by acting as a regulator of oxidative phosphorylation (OXPHOS) via interaction with complexes I and II of the mitochondrial electron transport chain [9–13]. OPB-111077 is an oral, small-molecule, new chemical agent that has been shown to be a potent, high-specificity inhibitor of STAT3 in preclinical models (Otsuka Pharmaceuticals, Inc., 9704 Medical Center Drive, Rockville, Maryland, USA. Telephone: 609-356-9459; e-mail: rocke@macrogenics.com)
The current study assessed the safety, pharmacokinetics, and preliminary antitumor activity of OPB-111077 in patients with unselected advanced cancers that, based on prior genetic and molecular studies, were thought to have potential for a therapeutic response to an anti-STAT3 agent. Results demonstrated that OPB-111077 was generally well tolerated in human subjects with advanced cancers. During dose escalation, none of 10 subjects receiving OPB-111077 at or below the 250-mg maximum tolerated dose developed a dose-limiting toxicity or other serious TEAE. Most reported TEAEs were reversible and could be medically managed. Common TEAEs included nausea, vomiting, and fatigue. Following single- and multiple-dose daily oral OPB-111077 in the range of 100–400 mg, OPB-111077 reached micromolar levels, which was in the range that correlated with antitumor activity in preclinical models.

In the study’s efficacy evaluations, one ongoing subject with diffuse large B-cell lymphoma achieved a partial response per RECIST, Version 1.1. Seven subjects maintained stable disease for at least eight treatment cycles (gastric cancer, cholangiocarcinoma, prostate cancer, renal cell carcinoma, KRAS-mutant colon cancer, esthesioneuroblastoma, and B-cell lymphoma; Fig. 1). Nine (60%) and thirty (32.3%) subjects had best overall responses of stable disease during the dose escalation and expansion stages, respectively.

Anticancer activity of OPB-111077 was therefore, in general, modest in this study, and further development of the drug will require identification of specific sensitive cancer subtypes. Given that OPB-111077 blocks OXPHOS, it seems feasible, for instance, that cancer cells sensitive to metabolic inhibition might be sensitive to OPB-111077 therapy. Notably, chemotherapy-resistant and cancer stem cells have been reported to be dependent on OXPHOS [14, 15], and drug combinations with OPB-111077 can be envisioned to exploit this observation [16, 17]. It is important to note, however, that it remains unclear whether effects other than those on OXPHOS were required for the observed anticancer effect of OPB-111077 in the current study population of advanced cancer patients.

In conclusion, OPB-111077 can be administered safely. Its pharmacokinetic profile is acceptable for further clinical development. Although notable clinical activity was observed in a subject with diffuse large B-cell lymphoma, monotherapy demonstrated minimal clinical activity against unselected tumors overall. Research continues to identify drivers of OPB-111077 clinical activity and synergistic combinations.

Figure 1. Maximum change in measured tumor size versus duration of OPB-111077 therapy per patient. (A): Maximum percent change in tumor size in 101 subjects who completed postbaseline tumor measurements in stage 2. (B): Days of OPB-1110777 treatment in the same patients. Note that the bars in the top graph and the bars in the bottom graph represent the subjects in the same order. Abbreviation: NSCLC, non-small cell lung cancer.
### Trial Information

| Category                              | Details                                      |
|---------------------------------------|----------------------------------------------|
| Disease                               | Advanced cancer                              |
| Stage of Disease/Treatment            | Metastatic/advanced                          |
| Prior Therapy                         | No designated number of regimens             |
| Stage 1                               | Phase I - Dose escalation                    |
| Stage 2                               | Phase I - Dose expansion                     |
| Primary Endpoint                      | Safety                                       |
| Primary Endpoint                      | Tolerability                                 |
| Secondary Endpoint                    | Pharmacokinetics                             |
| Secondary Endpoint                    | Pharmacodynamic                              |
| Secondary Endpoint                    | Efficacy                                     |
| Secondary Endpoint                    | Maximum tolerated dose                       |
| Secondary Endpoint                    | Recommended phase II dose                    |
| Secondary Endpoint                    | Food-effect substudy                         |
| Investigator's Analysis               | Drug tolerable, hints of efficacy            |

### Drug Information for Phase I Dose Escalation (Stage 1)

| Category                              | Details                                      |
|---------------------------------------|----------------------------------------------|
| Generic/Working Name                  | OPB-111077                                   |
| Trade Name                            | NA                                           |
| Company Name                          | Otsuka Pharmaceutical                         |
| Drug Type                             | Small molecule                               |
| Drug Class                            | STAT3 and OXPHOS inhibitor                   |
| Dose                                  | 100–400 mg per flat dose                     |
| Route                                 | p.o.                                         |
| Schedule of Administration            | Every morning under fasting conditions in 28-day cycles. |

### Drug Information for Phase I Expansion (Stage 2)

| Category                              | Details                                      |
|---------------------------------------|----------------------------------------------|
| Generic/Working Name                  | OPB-111077                                   |
| Trade Name                            | NA                                           |
| Company Name                          | Otsuka Pharmaceuticals                        |
| Drug Type                             | Small molecule                               |
| Drug Class                            | STAT3 and OXPHOS inhibitor                   |
| Dose                                  | 250 mg per flat dose                         |
| Route                                 | p.o.                                         |

### Patient Characteristics for Phase I Dose Escalation (Stage 1)

| Category                              | Details                                      |
|---------------------------------------|----------------------------------------------|
| Number of Patients, Male              | 12                                           |
| Number of Patients, Female            | 6                                            |
| Stage                                 | All advanced                                 |
| Age                                   | Mean years (standard deviation [SD]) = 64.4 (11.4) |
| Performance Status: ECOG              | 0 — 7                                        |
|                                       | 1 — 11                                       |
|                                       | 2 — 0                                        |
|                                       | 3 — 0                                        |
|                                       | Unknown — 0                                  |

### Other

| Category                              | Details                                      |
|---------------------------------------|----------------------------------------------|
| Prior surgery, n (%)                  | 15 (83.3)                                    |
| Prior radiotherapy, n (%)             | 9 (50.0)                                     |
| Prior chemotherapy/hormone, n (%)     | 16 (88.9)                                    |
### Patient Characteristics for Phase I Expansion (Stage 2)

| Characteristic                              | Value     |
|---------------------------------------------|-----------|
| Number of Patients, Male                    | 59        |
| Number of Patients, Female                  | 68        |
| Age                                         | Mean age (SD) = 60.9 (11.6) |
| Performance Status: ECOG                    |           |
| 0 — 3                                       | 5         |
| 1 — 6                                       | 6         |
| 2 — 6                                       |           |
| 3 — 0                                       |           |
| Unknown                                     | 0         |
| Other                                       |           |
| Prior surgery, n (%)                        | 107 (84.3)|
| Prior radiotherapy, n (%)                   | 69 (54.3)|
| Prior chemotherapy/hormone, n (%)           | 127 (100)|

### Primary Assessment Method for Phase I Dose Escalation (Stage 1)

| Title                                      | Value     |
|--------------------------------------------|-----------|
| Number of Patients Screened                | 19        |
| Number of Patients Enrolled                | 18        |
| Number of Patients Evaluable for Toxicity  | 18        |
| Number of Patients Evaluated for Efficacy  | 15        |
| Evaluation Method                          | RECIST 1.1|
| Response Assessment CR                     | n = 0 (0%)|
| Response Assessment PR                     | n = 0 (0%)|
| Response Assessment SD                     | n = 10 (67%)|
| Response Assessment PD                     | n = 5 (33%)|
| Response Assessment OTHER                  | n = 0 (0%)|

### Primary Assessment Method for Phase I Expansion (Stage 2)

| Title                                      | Value     |
|--------------------------------------------|-----------|
| Number of Patients Screened                | 145       |
| Number of Patients Enrolled                | 127       |
| Number of Patients Evaluable for Toxicity  | 127       |
| Number of Patients Evaluated for Efficacy  | 93        |
| Evaluation Method                          | RECIST 1.1|
| Response Assessment CR                     | n = 0 (0%)|
| Response Assessment PR                     | n = 0 (0%)|
| Response Assessment SD                     | n = 30 (32%)|
| Response Assessment PD                     | n = 54 (58%)|
| Response Assessment OTHER                  | n = 9 (10%)|
### Adverse Events

| Name               | NC/NA | 1    | 2    | 3    | 4    | 5    | All Grades | n  |
|--------------------|-------|------|------|------|------|------|------------|----|
| Nausea             | 40    | 50   | 32   | 5    | 0    | 0    | 0          | 87 | 127 |
| Fatigue            | 51    | 30   | 42   | 4    | 0    | 0    | 0          | 76 | 127 |
| Vomiting           | 66    | 44   | 13   | 4    | 0    | 0    | 0          | 61 | 127 |
| Constipation       | 80    | 27   | 17   | 3    | 0    | 0    | 0          | 47 | 127 |
| Dizziness          | 87    | 31   | 8    | 1    | 0    | 0    | 0          | 40 | 127 |
| Anorexia           | 97    | 16   | 14   | 0    | 0    | 0    | 0          | 30 | 127 |
| Diarrhea           | 102   | 17   | 7    | 1    | 0    | 0    | 0          | 25 | 127 |
| Hypothyroidism     | 103   | 11   | 13   | 0    | 0    | 0    | 0          | 24 | 127 |
| Dehydration        | 104   | 4    | 19   | 0    | 0    | 0    | 0          | 23 | 127 |
| Aspartate aminotransferase increased | 109 | 8 | 2 | 8 | 0 | 0 | 0 | 18 | 127 |
| Anemia             | 111   | 2    | 8    | 6    | 0    | 0    | 0          | 16 | 127 |
| GGT increased      | 111   | 2    | 7    | 6    | 1    | 0    | 0          | 16 | 127 |
| Dyspnea            | 112   | 8    | 5    | 2    | 0    | 0    | 0          | 15 | 127 |
| Hyponatremia       | 113   | 5    | 0    | 8    | 1    | 0    | 0          | 14 | 127 |
| Cough              | 113   | 9    | 5    | 0    | 0    | 0    | 0          | 14 | 127 |
| Abdominal pain     | 114   | 5    | 7    | 1    | 0    | 0    | 0          | 13 | 127 |

Treatment-emergent adverse events reported in ≥10% of subjects in stage 2 (expansion); n = 127.

Abbreviations: GGT, gamma-glutamyltransferase; NC/NA, no change from baseline/no adverse event.

### Serious Adverse Events

| Event                      | Number of subjects (%) | Number of events reported |
|----------------------------|------------------------|---------------------------|
| Cardiac disordera          | 8 (6)                  | 8                         |
| Gastrointestinal           | 12 (8)                 | 19                        |
| Nausea                     | 3 (2)                  | 4                         |
| Infections and infestations | 6 (4)                 | 7                         |
| Respiratory                | 12 (8)                 | 16                        |
| Pulmonary embolism         | 3 (2)                  | 3                         |

aOne cardiac event (grade 3 right ventricular dysfunction) was judged possibly related. The rest were unrelated to study medication.

### Pharmacokinetics/Pharmacodynamics

| Dose level | Dose of drug: OPB-111077 | Number enrolled | C\text{max} (µg/L) mean ± SD | T\text{max} (h) (min–max) | AUC\text{∞} (hr·µg/mL) mean ± SD | T\text{1/2} (h) mean ± SD |
|------------|---------------------------|-----------------|-----------------------------|--------------------------|----------------------------------|--------------------------|
| Cycle 1, day 1 | 100 mg                  | 1               | 1.10 (0.427)                | 0.50 (4.08–4.08)         | 26.6 (8.13)                      | 22.2 (5.7)               |
| 2          | 200 mg                  | 3               | 1.90 (0.20)                | 4.08 (1.25–8.07)         | 58.4 (26.9)                      | 25.0 (8.0)               |
| 3          | 250 mg                  | 6               | 3.17 (2.02)                | 4.08 (2.08–4.18)         | 112 (30.9)                       | 32.8 (16.8)              |
| 4          | 300 mg                  | 6               | 3.48 (1.09)                | 4.08 (1.08–10.05)        | 63.2 (NA)                        | 24.7 (NA)                |
| 5          | 400 mg                  | 2               | 2.67 (NA)                 | 5.57 (0.50–2.00)         | 223 (112)                        | 28.7 (10.3)              |

Cycle 2, day 1

| Dose level | Dose of drug: OPB-111077 | Number enrolled | C\text{max} (µg/L) mean ± SD | T\text{max} (h) (min–max) | AUC\text{∞} (hr·µg/mL) mean ± SD | T\text{1/2} (h) mean ± SD |
|------------|---------------------------|-----------------|-----------------------------|--------------------------|----------------------------------|--------------------------|
| 1          | 100 mg                  | 1               | 2.33 (0.804)                | 10.00 (1.00–8.10)        | 157 (70.5)                       | 23.0 (8.7)               |
| 2          | 200 mg                  | 3               | 4.85 (0.846)                | 5.02 (0.50–2.00)         | 223 (112)                        | 28.7 (10.3)              |
| 3          | 250 mg                  | 5               | 6.36 (NA)                 | 0.53 (0.50–2.00)         | 226 (NA)                         | 24.3 (NA)                |

Abbreviations: AUC\text{∞}, area under the concentration-time curve from time 0 to infinity; C\text{max}, peak (maximal) concentration of drug in plasma; hr, hours; NA, nonapplicable; SD, standard deviation; T\text{max}, time to maximum (peak) plasma concentration; T\text{1/2}, terminal phase elimination half-life.
Previous studies have shown that STAT3 promotes tumorigenesis by at least two mechanisms: first, by acting as a nuclear transcription factor that alters expression of pro-tumorigenic gene-regulatory networks [1–8]; and second, by acting as a regulator of oxidative phosphorylation (OXPHOS) via interaction with complexes I and II of the mitochondrial electron transport chain [9–13]. Given this broad involvement in tumorigenesis, significant effort has been devoted to the discovery of small-molecule STAT3 inhibitors [18–20]. One agent that showed early promise was OPB-31121, which binds with high affinity to STAT3 (Kd = 10 nM), blocks STAT3 activity without upstream kinase inhibition, and inhibits growth of diverse malignant cells at nanomolar concentrations in various preclinical models [21, 22]. A phase 1 study, however, found that the bioavailability of OPB-31121 was low, and further development of the agent was discontinued [23].

The same phase 1 study found that the primary metabolite of OPB-31121, designated OPB-111077, accumulated at higher tissue levels [23]. Subsequent in vitro studies found that OPB-111077 had significant growth inhibitory effect in a variety of cancer models (Otsuka Pharmaceuticals, unpublished). Following up on these observations, the current study was designed to assess safety, pharmacokinetics, and preliminary antitumor activity of OPB-111077 in patients with advanced cancers that, based on prior genetic and molecular studies, were thought to have potential for a therapeutic response to an anti-STAT3 agent. The study consisted of a dose escalation phase (n = 18), followed by a dose expansion phase at the maximum tolerated dose (MTD; n = 127; Tables 1–3). All patients received oral OPB-111077 once daily until loss of clinical benefit.

During dose escalation, no dose-limiting toxicities (DLTs) were observed in the 100-mg, 200-mg, and 250-mg dose cohorts (Table 4). Two DLTs were observed in the 300-mg dose cohort (grade 3 dizziness and grade 3 nausea/vomiting) and in the 400-mg dose cohort (two cases of grade 3 vomiting). The MTD and recommended phase II dose were thus determined to be 250 mg QD. All 18 subjects reported at least one treatment-emergent adverse event (TEAE) during dose escalation, and 125 of 127 subjects (98.4%) reported at least one such event during dose expansion. Frequently reported TEAEs included nausea, vomiting, and fatigue (Table 5). At doses ≥300 mg, vomiting was dose limiting despite optimal antiemetic therapy, whereas nausea and vomiting at the MTD could be controlled by antiemetics. Grade 1 or 2 hypothyroidism was reported in 20% of study participants, nearly all of which (27 of 29 [93.1%] cases) were thought to be drug-related. Four subjects (22%) in dose escalation and 45 (35.4%) in dose expansion had serious TEAEs. Frequently reported serious adverse events (SAEs) were cardiac, gastrointestinal, and respiratory disorders (Table 6). With the exception of a grade 3 cardiac event, none of these SAEs were considered related to study medication.

OPB-111077 exposure increased linearly after single and multiple ascending daily doses (Table 7). Tmax, at the MTD was about 4 hours. Steady-state concentrations were observed by day 8, consistent with the observed elimination half-life of about 1 day. AUC0–24h and Cmax accumulation ratios were about 2–3.

Among 15 subjects in dose escalation evaluated for best overall response, 9 (60%) had stable disease, and 5 (33.3%) had progressive disease (at least eight cycles on study therapy) [24]. An additional subject continued treatment in the dose escalation stage as of the database cutoff date (May 27, 2015) and had stable disease on initiating his 26th cycle at 300 mg. In dose expansion, 93 subjects were assessed for efficacy and 89 were evaluated for best overall response. In best overall response analysis, 30 subjects (32.3%) had stable disease, 54 (58.1%) had progressive disease, 3 (3.2%) were not evaluable, and 2 (2.2%) were missing an assessment.

Maximum change in tumor size versus duration of OPB-111077 therapy is shown in Figure 1. Eight subjects met protocol-defined antitumor activity thresholds. These responses included an individual with diffuse large B-cell lymphoma (with BCL2 amplification only on fluorescence in situ hybridization studies and no amplification of BCL6 or MYC) on OPB-111077 for 17 months who achieved a partial response (Fig. 2). In addition, a renal cell carcinoma patient had 35% shrinkage in lung metastases but progressed with brain metastasis. Another seven subjects met stable disease criteria for at least eight treatment cycles. Tumor types and stable disease durations were as follows: gastric cancer (two subjects for 8 months), cholangiocarcinoma (8 months), prostate cancer (10 months), renal cell carcinoma (10 months; subject had 35% shrinkage of lung metastasis, but developed brain metastases), KRAS-mutant colon cancer (14 months), and esthesioneuroblastoma (48 months).

Given its modest efficacy in this trial, further development of OPB-111077 will require identification of specific cancer subtypes sensitive to STAT3 inhibition. Because OPB-111077 blocks OXPHOS, it seems feasible that cancer cells sensitive to metabolic inhibition might be particularly sensitive to the drug. Chemotherapy-resistant and cancer stem cells have both been reported to be dependent on OXPHOS [14, 15], and drug combinations with OPB-111077 might build on this observation [16, 17]. Conversely, it remains unconfirmed what effects led to the observed anticancer effect of OPB-111077 in the current trial.

This study was limited by the absence of pharmacodynamic confirmation of OPB-111077 effect. An assay to assess inhibition of IL6-stimulated Y705 phosphorylation of STAT3 in peripheral blood mononuclear cells has been developed using a phospho-specific monoclonal antibody, but it was not used here due to the difficulty of maintaining analytic validity when the IL6-stimulation protocol was deployed at trial sites. Bearing in mind this caveat, this first in-human study of OPB-111077 has shown that this new anti-STAT3 agent can be administered safely and its pharmacokinetic profile is acceptable for further clinical development. Notable clinical activity was observed in a subject with diffuse large B-cell lymphoma, although monotherapy had minimal clinical activity against unselected tumors.
overall. Research continues to identify drivers of OPB-111077 clinical activity and synergistic combinations.

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FIGURES AND TABLES

Figure 2. Partial response in diffuse large B-cell lymphoma. A 78-year-old man with diffuse large B-cell lymphoma diagnosed 3 years and six chemotherapy regimens before study entry. (A): Baseline computed tomography (CT) scan showing red arrow pointing to bulky left axillary mass. (B): End of cycle 2 positron emission tomography (PET) scan showing persistent left axillary glucose uptake in areas of lymphoma. (C): End of cycle 4 PET scan showing complete metabolic response. (D, E): End of cycle 14 PET and CT scans with red arrows pointing to ongoing complete metabolic response and nonpathologic residual nodes, respectively. After a gradual 90% decline in measured disease, at month 17 the subject’s disease progressed distantly in the thigh, and study therapy was stopped.

Table 1. Patient demographics and baseline characteristics

| Characteristics          | Dose escalation (stage 1), (n = 18) | Expansion (stage 2), (n = 127) |
|--------------------------|------------------------------------|--------------------------------|
| Age, years, mean (SD)    | 64.4 (11.4)                        | 60.9 (11.6)                     |
| Male, n (%)              | 12 (66.7)                          | 59 (46.5)                       |
| Diagnosis, n (%)         |                                    |                                |
| Rare cancers             | 8 (44.4)                           | 42 (33.1)                       |
| NSCLC                    | 1 (5.6)                            | 13 (10.2)                       |
| Breast                   | 0 (0.0)                            | 13 (10.2)                       |
| Kidney                   | 2 (11.1)                           | 11 (8.7)                        |
| Ovarian                  | 0 (0.0)                            | 11 (8.7)                        |
| Colorectal               | 2 (11.1)                           | 10 (7.9)                        |
| Prostate                 | 3 (16.7)                           | 8 (6.3)                         |
| Gastric                  | 0 (0.0)                            | 7 (5.5)                         |
| Lymphoma                 | 1 (5.6)                            | 8 (6.3)                         |
| Cervical                 | 1 (5.6)                            | 3 (2.4)                         |
| Myeloma                  | 0 (0.0)                            | 1 (0.8)                         |
| ECOG performance status, n (%) |                                  |                                |
| 0                        | 7 (38.9)                           | 35 (27.6)                       |
| 1                        | 11 (61.1)                          | 86 (67.7)                       |
| 2                        | 0 (0.0)                            | 6 (4.7)                         |
| Prior surgery, n (%)     | 15 (83.3)                          | 107 (84.3)                      |
| Prior radiotherapy, n (%)| 9 (50.0)                           | 69 (54.3)                       |
| Prior chemotherapy/hormone, n (%) | 16 (88.9)                       | 127 (100)                       |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; SD, standard deviation.
Table 2. Subject disposition during dose escalation (stage 1)

| Subjects                        | OPB-11107 Dose cohort | 100 mg, n (%) | 200 mg, n (%) | 250 mg, n (%) | 300 mg, n (%) | Totala, n (%) |
|--------------------------------|-----------------------|---------------|---------------|---------------|---------------|---------------|
| Screened                       |                       |               |               |               |               | 19            |
| Enrolled                       |                       | 1 (100.0)     | 3 (100.0)     | 2 (100.0)     | 6 (100.0)     | 18 (100.0)    |
| Treated                        |                       | 1 (100.0)     | 3 (100.0)     | 2 (100.0)     | 6 (100.0)     | 18 (100.0)    |
| Completed per protocolb        |                       | 1 (100.0)     | 3 (100.0)     | 1 (50.0)      | 5 (83.3)      | 15 (83.3)     |
| Discontinued prior to C2 D1    |                       | 0 (0.0)       | 0 (0.0)       | 1 (50.0)      | 1 (16.7)      | 3 (16.7)      |
| Discontinued after C2 D1       |                       | 1 (100.0)     | 3 (100.0)     | 1 (50.0)      | 5 (83.3)      | 14 (77.8)     |
| Analyzed for safetyc           |                       | 1 (100.0)     | 3 (100.0)     | 2 (100.0)     | 6 (100.0)     | 18 (100.0)    |
| Analyzed for efficacyd         |                       | 1 (100.0)     | 3 (100.0)     | 1 (50.0)      | 5 (83.3)      | 15 (83.3)     |

*As of the report cutoff date (May 27, 2015), one subject (subject 0010110) in the 300-mg group was ongoing on treatment in the dose escalation stage.

Subjects who completed cycle 2 day 1 assessments were defined as completers.

Subjects who received any OPB-111077 were included in safety analysis.

Subjects who received at least one cycle of OPB-111077 were analyzed for efficacy.

Abbreviation: C2 D1, cycle 2 day 1.

Table 3. Subject disposition during dose expansion (stage 2)

| Subjects                        | NSCLC, n (%) | Kidney, n (%) | Rare cancers, n (%) | Gastric, n (%) | Prostate, n (%) | Colorectal, n (%) | Lymphoma, n (%) | Breast, n (%) | Cervical, n (%) | Ovarian, n (%) | Myeloma, n (%) | Total, n (%) |
|--------------------------------|--------------|---------------|---------------------|---------------|----------------|-------------------|---------------|--------------|----------------|----------------|----------------|---------------|
| Screened                       |              |               |                     |               |                |                   |               |              |                |                |                | 145           |
| Enrolled                       | 13 (100.0)   | 11 (100.0)    | 42 (100.0)          | 7 (100.0)     | 8 (100.0)      | 10 (100.0)        | 8 (100.0)     | 13 (100.0)   | 3 (100.0)      | 11 (100.0)     | 1 (100.0)      | 127 (100.0)   |
| Food-effect substudy          | 0 (0.0)      | 0 (0.0)       | 3 (7.1)             | 1 (14.3)      | 0 (0.0)        | 1 (10.0)          | 0 (0.0)       | 1 (7.7)      | 0 (0.0)        | 1 (9.1)        | 0 (0.0)        | 7 (5.5)       |
| Treated                       | 13 (100.0)   | 11 (100.0)    | 42 (100.0)          | 7 (100.0)     | 8 (100.0)      | 10 (100.0)        | 8 (100.0)     | 13 (100.0)   | 3 (100.0)      | 11 (100.0)     | 1 (100.0)      | 127 (100.0)   |
| Food-effect substudy          | 0 (0.0)      | 0 (0.0)       | 3 (7.1)             | 1 (14.3)      | 0 (0.0)        | 1 (10.0)          | 0 (0.0)       | 1 (7.7)      | 0 (0.0)        | 1 (9.1)        | 0 (0.0)        | 7 (5.5)       |
| Completed per protocola       | 8 (61.5)     | 10 (90.9)     | 32 (76.2)           | 6 (85.7)      | 7 (87.5)       | 8 (80.0)          | 5 (62.5)      | 7 (53.8)     | 2 (66.7)       | 7 (63.6)       | 1 (100.0)      | 93 (73.2)     |
| Discontinued prior to C2 D1   | 5 (38.5)     | 1 (9.1)       | 10 (23.8)           | 1 (14.3)      | 1 (12.5)       | 2 (20.0)          | 3 (37.5)      | 6 (46.2)     | 1 (33.3)       | 4 (36.4)       | 0 (0.0)        | 34 (26.8)     |
| Discontinued after C2 D1      | 8 (61.5)     | 10 (90.9)     | 31 (73.8)           | 6 (85.7)      | 7 (87.5)       | 8 (80.0)          | 4 (50.0)      | 7 (53.8)     | 2 (66.7)       | 7 (63.6)       | 1 (100.0)      | 91 (71.7)     |
| Analyzed for safetyb          | 13 (100.0)   | 11 (100.0)    | 42 (100.0)          | 7 (100.0)     | 8 (100.0)      | 10 (100.0)        | 8 (100.0)     | 13 (100.0)   | 3 (100.0)      | 11 (100.0)     | 1 (100.0)      | 127 (100.0)   |
| Analyzed for efficacyb        | 8 (61.5)     | 10 (90.9)     | 32 (76.2)           | 6 (85.7)      | 7 (87.5)       | 8 (80.0)          | 5 (62.5)      | 7 (53.8)     | 2 (66.7)       | 7 (63.6)       | 1 (100.0)      | 93 (73.2)     |

*Subjects who completed cycle 2 day 1 assessments were defined as completers.

Subjects who received any IMP were included in safety analysis.

Subjects who received at least one cycle of IMP were analyzed for efficacy.

Abbreviations: C2 D1, cycle 2 day 1; IMP, investigational medicinal product; NSCLC, non-small cell lung cancer.

Table 4. Dose-limiting toxicities as a function of OPB-111077 dose

| OPB-111077 dose cohort | 100 mg | 200 mg | 250 mg | 300 mg | 400 mg |
|------------------------|--------|--------|--------|--------|--------|
| n                      | 1      | 3      | 6      | 6      | 2      |
| DLTs                   | —      | —      | —      | Dizziness (grade 3) | Nausea/vomiting (grade 3) | Vomiting (grade 3) (two cases) |

Abbreviations: —, no data; DLT, dose-limiting toxicity.
Table 5. Treatment-emergent adverse events reported in ≥10% of subjects in stage 2 (expansion)

| Adverse event                      | Number of subjects (%) |
|------------------------------------|------------------------|
| Nausea                             | 87 (68.5)              |
| Fatigue                            | 76 (59.8)              |
| Vomiting                           | 61 (48.0)              |
| Constipation                       | 47 (37.0)              |
| Dizziness                          | 40 (31.5)              |
| Decreased appetite                 | 29 (22.8)              |
| Diarrhea                           | 25 (19.7)              |
| Hypothyroidism                     | 24 (18.9)              |
| Dehydration                        | 23 (18.1)              |
| Aspartate aminotransferase increased | 18 (14.2)           |
| Anemia                             | 16 (12.6)              |
| Gamma glutamyl-transferase increased | 15 (11.8)            |
| Dyspnea                            | 15 (11.8)              |
| Hyponatremia                       | 14 (11.0)              |
| Abdominal pain                     | 13 (10.2)              |
| Cough                              | 13 (10.2)              |

Total number of subjects = 127.

Table 6. Most frequently reported serious adverse events

| Event                               | Number of subjects (%) | Number of events reported |
|-------------------------------------|------------------------|---------------------------|
| Cardiac disorder<sup>a</sup>        | 8 (6)                  | 8                         |
| Gastrointestinal                    | 12 (8)                 | 19                        |
| Nausea                              | 3 (2)                  | 4                         |
| Infections and infestations         | 6 (4)                  | 7                         |
| Respiratory                         | 12 (8)                 | 16                        |
| Pulmonary embolism                  | 3 (2)                  | 3                         |

<sup>a</sup>One cardiac event (grade 3 right ventricular dysfunction) was judged possibly related. The rest were unrelated to study medication.

Table 7. OPB-111077 pharmacokinetics

| Parameter                  | 100 mg | 200 mg | 250 mg | 300 mg | 400 mg |
|----------------------------|--------|--------|--------|--------|--------|
| Cycle 1 day 1              |        |        |        |        |        |
| n                          | 1      | 3      | 6      | 6      | 2      |
| C<sub>max</sub> (µg/mL)    | 1.10   | 1.90 (0.427) | 3.17 (2.02) | 3.48 (1.09) | 2.67 (NA) |
| t<sub>max</sub> (hr)<sup>a</sup> | 0.50   | 4.08 (4.08) | 4.08 (1.25–8.07) | 4.08 (2.08–4.18) | 5.57 (1.08–10.05) |
| t<sub>1/2,z</sub> (hr)     | 32.3   | 22.2 (5.7) | 25.0 (8.0) | 32.8 (16.8) | 24.7 (NA) |
| AUC<sub>∞</sub> (hr·µg/mL) | 26.6   | 58.4 (8.13) | 81.2 (26.9) | 112 (30.9) | 63.2 (NA) |
| Cycle 2 day 1              |        |        |        |        |        |
| N                          | 1      | 3      | 5      | 2      | —      |
| C<sub>max</sub> (µg/mL)    | 2.33   | 4.85 (0.804) | 6.36 (0.846) | 7.24 (NA) | —      |
| t<sub>max</sub> (hr)<sup>a</sup> | 10.00  | 5.02 (1.00–8.10) | 0.53 (0.50–2.00) | 2.26 (0.50–4.02) | —      |
| t<sub>1/2,z</sub> (hr)     | 25.8   | 23.0 (8.7) | 28.7 (10.3) | 24.3 (NA) | —      |
| AUC<sub>∞</sub> (hr·µg/mL) | 102    | 157 (70.5) | 223 (112) | 226 (NA) | —      |

Shown are mean (SD) values, unless otherwise designated. Subjects received single doses of OPB-111077 on cycle 1 day 1 and cycle 2 day 1; blood samples were collected over subsequent treatment-free intervals until day 4 in each cycle.

<sup>a</sup>Values are median (minimum–maximum).

Abbreviations: —, no data; AUC<sub>∞</sub>, area under the concentration-time curve from time 0 to infinity; C<sub>max</sub>, peak (maximal) concentration of drug in plasma; hr, hours; NA, nonapplicable; SD, standard deviation; t<sub>max</sub>, time to maximum (peak) plasma concentration; t<sub>1/2,z</sub>, terminal phase elimination half-life.

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