Multicenter, Phase II Study of Axitinib, a Selective Second-Generation Inhibitor of Vascular Endothelial Growth Factor Receptors 1, 2, and 3, in Patients with Metastatic Melanoma

John Fruehauf1, Jose Lutzky2, David McDermott3, Charles K. Brown4, Jean-Baptiste Meric5, Brad Rosbrook6, David R. Shalinsky6, Katherine F. Liau6, Andreas G. Niethammer6, Sinil Kim6, and Olivier Rixe7

Abstract

Purpose: This multicenter, open-label, phase II study evaluated the safety and clinical activity of axitinib, a potent and selective second-generation inhibitor of vascular endothelial growth factor receptors (VEGFR)–1, 2, and 3, in patients with metastatic melanoma.

Experimental Design: Thirty-two patients with a maximum of one prior systemic therapy received axitinib at a starting dose of 5 mg twice daily. The primary endpoint was objective response rate.

Results: Objective response rate was 18.8% [95% confidence interval (CI), 7.2–36.4], comprising one complete and five partial responses with a median response duration of 5.9 months (95% CI, 5.0–17.0). Stable disease at 16 weeks was noted in six patients (18.8%), with an overall clinical benefit rate of 37.5%. Six-month progression-free survival rate was 33.9%, 1-year overall survival rate was 28.1%, and median overall survival was 6.6 months (95% CI, 5.2–9.0). The most frequently (>15%) reported nonhematologic, treatment-related adverse events were fatigue, hypertension, hoarseness, and diarrhea. Treatment-related fatal bowel perforation, a known class effect, occurred in one patient. Axitinib selectively decreased plasma concentrations of soluble VEGFR (sVEGFR)-2 and sVEGFR-3 compared with soluble stem cell factor receptor (sKIT). No significant association was noted between plasma levels of axitinib and response. However, post hoc analyses indicated potential relationships between efficacy endpoints and diastolic blood pressure of 90 mm Hg or higher as well as baseline serum lactate dehydrogenase levels.

Conclusions: Axitinib was well tolerated, showed a selective VEGFR-inhibitory profile, and showed single-agent activity in metastatic melanoma. Further evaluations of axitinib, alone and combined with chemotherapy, are ongoing. Clin Cancer Res; 17(23); 7462–9. ©2011 AACR.
Axitinib (AG-013736), a potent and selective second-generation inhibitor of vascular endothelial growth factor (VEGF) receptors (VEGFR)–1, 2, and 3. Preclinical studies strongly implicated the involvement of VEGF signaling pathway in melanoma progression, and elevated levels of VEGFR were found to be associated with poor outcome in patients with melanoma, providing the rationale for testing axitinib in the clinical setting. In this phase II clinical trial in patients with metastatic melanoma, single-agent axitinib showed antitumor activity comparable with that observed with current standard therapies. Axitinib was generally well tolerated; most adverse events were mild to moderate in severity and were manageable. In addition, the study showed preferential decreases in plasma levels of soluble VEGFR-2 and 3, indicating selective targeting of VEGF receptors. These results show the efficacy and safety of axitinib in the treatment of metastatic melanoma and support further evaluation of axitinib either alone or in combination with other agents.

Axitinib in Metastatic Melanoma

Translational Relevance

Axitinib has shown single-agent activity in several malignancies characterized by high levels of angiogenesis, including metastatic renal cell carcinoma and advanced thyroid cancer, with ORRs ranging from 30% to 44% (28, 29). Recently, a phase III study evaluating axitinib in comparison to sorafenib in patients with cytokine- or tyrosine kinase inhibitor–refractory renal cell carcinoma (NCT00678392; AXIS trial) showed an improvement in PFS for patients treated with axitinib (33). We investigated the tolerability and efficacy of axitinib in a multicenter, phase II, single-arm study in patients with metastatic melanoma.

Materials and Methods

Patients

Patients aged 18 years or older with histologically confirmed metastatic melanoma, who had received no more than one prior systemic therapy for metastatic disease, were eligible for enrollment. Other eligibility criteria included measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST), adequate major organ function, and no evidence of brain metastases, major surgical procedure or radiation therapy within 4 weeks of treatment.

Study design

This study was approved by the Institutional Review Board of each participating center and was carried out in accordance with the International Conference on Harmonization Good Clinical Practice guidelines protocol, as well as applicable local laws and regulatory requirements. Written informed consent was obtained prior to patients entering the study. The study is registered at ClinicalTrials.gov (NCT00094107).

Study treatment

Axitinib (5 mg) was self-administered orally twice a day with doses spaced approximately 12 hours apart in 4-week treatment cycles. Dose escalations of 20% were administered to patients who were not responding to therapy and if no grade ≥II adverse events (National Cancer Institute Common Terminology Criteria for Adverse Events, www.aacrjournals.org Clin Cancer Res; 17(23) December 1, 2011 7463

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version 3.0) were observed for 8 weeks. Treatment was interrupted in patients with adverse events grade ≥II that was not controlled by supportive medication and was resumed at the same dose after resolution to grade I or baseline levels. Treatment was resumed at a 20% lower dose after resolution to grade I or baseline levels for nonhematologic adverse events grade ≥II, grade IV hematologic adverse events, or recurrent subjectively intolerable toxicity. Dose interruptions also occurred because of uncontrolled elevated blood pressure, hemoptysis, or proteinuria. Treatment was continued until disease progression, significant toxicity, or withdrawal of consent. Patients deriving clinical benefit could continue to receive treatment after meeting criteria for study completion.

**Study assessments**

Blood pressure measurements were collected at each clinic visit. Blood pressure monitors were provided to all patients for daily blood pressure monitoring at home. Patients informed the treating physician for further clinical evaluation in the event of systolic blood pressure above 150 mm Hg or dBP above 90 mm Hg; however, only in-clinic blood pressure measurements were collected in the project database for data analyses. Tumors were measured using computed tomography or MRI at baseline and at least every 8 weeks. Blood samples were collected on day 1 (predose) and every 8 weeks thereafter for analysis of soluble proteins.

**Analysis of blood-based soluble proteins**

Proteins were analyzed with ELISA kits (R&D Systems) as previously reported (34). The VEGF-A ELISA assay measured the VEGF-A (165) and VEGF-A (121) isoforms. The extracellular domain of soluble VEGFR-2 (sVEGFR-2), sVEGFR-3, and soluble stem cell factor receptor (sKIT) were each measured via ELISA as well, after calibration against recombinant proteins consisting of the full-length extracellular domains of the respective receptors. Although, the structural details of sVEGFR-2 and sVEGFR-3 remain to be established, plasma-derived sVEGFR-2 has been reported to be heavily glycosylated and to have a molecular weight of approximately 90 kDa (35). All ELISA assays were run under Good Laboratory Practice conditions and performance specifications of each ELISA were validated as per established guidelines.

**Statistical methods**

The study was conducted using a 2-stage Simon Minimax design (36). Because of lower response rates to conventional chemotherapy for this indication, the p0 and p1 were set at 5% and 20%, respectively. The α and β error rates were set at 0.10 and 0.10, respectively. These criteria resulted in a sample size of 18 patients in stage I and additional 14 patients in stage II (based on Power Analysis and Sample Size 2002 software). At least one confirmed response (i.e., PR or CR) was needed in stage I to allow expansion of the trial to stage II.

Safety and efficacy analyses included all patients who received at least one dose of axitinib and had a baseline assessment of disease. Patients who died, progressed, or discontinued treatment before experiencing a CR or PR were classified as nonresponders. In an unplanned analysis of the subset of patients with or without dBP of 90 mm Hg or higher, survival–time comparisons were conducted using a Cox proportional hazards model, with onset of dBP of 90 mm Hg or higher as a time-dependent covariate. This methodology was used to adjust for covariates that change or vary with time during subject follow-up and controlled for the potential bias of patients who live longer or have greater drug exposure, as well as a greater opportunity to develop high blood pressure. An exploratory analysis of the relationship between outcomes and baseline serum lactate dehydrogenase (LDH) normalized to the median of each laboratory normal range was done using Spearman's correlation coefficient. An analysis for constructing the historical control OS distribution using prognostic variables (performance status, presence of visceral disease, brain metastases, and gender) was done based on an alternative calculation method described by Korn and colleagues (37).

**Results**

**Patient characteristics**

Thirty-two patients were enrolled in the study and received at least one dose of axitinib. Patient baseline characteristics are summarized in Table 1. All patients had stage IV disease from various types of melanoma including superficial spreading, nodular, lentigo maligna, and uveal melanoma (Table 1). Primary sites were cutaneous (n = 18), uveal (n = 3), mucosal (n = 1), and unknown (n = 10). Twenty-one patients (65.6%) had prior surgery; nearly two thirds of patients (n = 20; 62.5%) had received prior systemic treatment for any disease stage and 50% (n = 16) had prior systemic treatment for metastatic disease. Lung, lymph nodes, and liver were the most common metastatic disease sites. Seventeen patients (53.1%) had elevated baseline LDH levels and 25 patients (78.1%) were classified as M1C at baseline.

The median duration of treatment was 3.8 months (range, 0.4–33.8) with 19 patients (59.4%) receiving therapy for 3.7 months or longer. The median daily dose was 9.5 mg/d (range, 1.7–11.6), with one patient undergoing dose escalation to 14 mg/d. Treatment discontinuation occurred in all patients and was because of lack of efficacy (72.0%; including one patient who withdrew because of disease progression), death (15.6%), and nonfatal adverse events (9.4%) and one patient (3.1%) continued study therapy on a separate treatment-access protocol.

**Clinical activity**

The ORR was 18.8% [95% confidence interval (CI), 7.2–36.4], comprising one CR (3.1%) and 5 PRs (15.6%). The maximum percentage change in target lesion size is shown in Fig. 1. One patient with uveal melanoma experienced a PR. Responding tumor sites included lymph nodes (n = 4) and liver and lung (n = 1 each). Six patients (18.8%) had a best response of stable disease at least 16 weeks in duration,
yielding an overall clinical benefit rate (percentage of patients with a best response \( \geq \) stable disease) of 37.5%. An additional 14 patients (43.8%) had progressive disease, 3 patients (9.4%) had stable disease less than 16 weeks, and 3 patients (9.4%) had missing data. The median duration of response was 5.9 months (95% CI, 5.0–17.0; Fig. 2A). Median PFS was 3.9 months (95% CI, 2.3–6.7; Fig. 2B), and median OS was 6.6 months (95% CI, 5.2–9.0). OS ranged from 0.8 to 42.8 months. Six-month PFS rate was 33.9% and 1-year OS rate was 28.1%. One patient discontinued study after 16.2 months and continued therapy with axitinib on a separate treatment-access study for 1 year; however, additional data were not included in primary PFS or OS analysis.

On the basis of recent findings that VEGF plays a role in resting blood pressure and that blockade of VEGF-mediated upregulation of endothelial and neuronal nitric oxide

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics at baseline</th>
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<tr>
<td><strong>Axitinib (N = 32)</strong></td>
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<td>Median age, y</td>
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<td>Range</td>
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<td>Sex, n (%)</td>
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<td>ECOG performance status, n (%)</td>
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<td>Histology, n (%)</td>
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<td>Metastatic stage, n (%)</td>
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<td>Baseline serum LDH level, n (%)</td>
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<tr>
<td>Common ((\geq)20%) metastatic sites,(^b) n (%)</td>
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<td>Prior therapy,(^c) n (%)</td>
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Abbreviation: ECOG, Eastern Cooperative Oncology Group.
\(^b\)Includes dermoplastic melanoma, in situ, adenocarcinoma, liver metastasis, ocular (mixed type), epithelioid melanoma of the choroids, and choroidal melanoma (cell type unspecified).
\(^c\)Patients may be in more than one category.

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**Figure 1.** Maximum percentage change in target lesion size, based on RECIST (\(n = 27\)). Five patients without postbaseline scans were excluded.

**Figure 2.** Kaplan–Meier estimates of response duration (\(n = 6\); A), PFS in all patients (\(n = 32\); B), and OS in patients who had transient dBP measurements of 90 mm Hg or higher (\(n = 14\); C) compared with patients with dBP less than 90 mm Hg (\(n = 18\)).
synthase by axitinib may lead to hypertension (38), we considered dBP to be a potential pharmacodynamic marker of axitinib action in individual patients. In an unplanned subgroup analysis with a Cox model that used the onset of dBP of 90 mm Hg or higher as a time-dependent covariate, the relative risk of death was lower in patients with at least one dBP measurement of 90 mm Hg or higher than in patients with dBP less than 90 mm Hg (HR, 0.679; P = 0.387). Median OS in patients who experienced dBP of 90 mm Hg or higher during treatment was 10.7 months (95% CI, 5.9 to not estimable; n = 14) compared with 5.8 months in patients with a dBP less than 90 mm Hg (95% CI, 3.6–6.8; n = 18; Fig. 2C). Median PFS in patients who experienced dBP of 90 mm Hg or higher during treatment was 7.0 months (95% CI, 3.7–14.8) compared with 2.8 months in patients with a dBP less than 90 mm Hg (95% CI, 1.8–4.0). ORR for patients who had at least one dBP of 90 mm Hg or higher during treatment was 21.4% (95% CI, 4.7–50.8) compared with 11.1% (95% CI, 1.4–34.7).

In post hoc analyses, baseline serum LDH levels were also found to be significantly associated with efficacy endpoints. In patients with normal baseline LDH levels (n = 15), median OS was 18.6 months (95% CI, 6.5–not estimable) compared with 5.9 months (95% CI, 2.6–7.4) in patients with baseline LDH levels higher than the normal range (n = 17). Similarly, median PFS of 7.3 months (95% CI, 4.0–14.8) in patients with normal LDH levels was longer than 2.2 months (95% CI, 1.8–4.2) in those with elevated LDH levels. ORR was 26.7% for patients with normal LDH level compared with 11.8% for those with elevated LDH level [treatment difference = 14.9% (95% CI, −12.2% to 42.0%)]. Outcomes for patients with higher baseline LDH levels were worse than those for patients with baseline LDH levels within normal limits, which is consistent with other trials evaluating metastatic melanoma. OS based on prognostic variables of performance status, presence of visceral disease, brain metastases, and gender was similar to historical control for this population of 32 patients (data not shown).

### Safety

The most frequently (>15%) reported nonhematologic, treatment-related adverse events included fatigue, hypertension, hoarseness, and diarrhea (Table 2). The majority of these events were grade I/II. The most common grade ≥III adverse event was fatigue (n = 7; 21.9%). Hypertension was reported in 14 patients (43.8%), most of which was mild to moderate in severity (grade I/II). Grade III hypertension was reported in 3 patients (9.4%). There were no other grade III adverse events that were considered treatment related. Grade II treatment–related proteinuria was reported in 2 patients (6.3%), on the basis of laboratory data. Two patients (6.3%) experienced grade I/II hemoptysis, of which only one case was assessed as treatment related. No grade III/IV hematologic laboratory abnormalities were observed. Grade III clinical chemistry abnormalities were observed in 5 patients and no grade IV findings were reported.

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Number of Patients, N = 32, n (%)</th>
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<tbody>
<tr>
<td>Fatigueb</td>
<td>19 (59.4) 7 (21.9)</td>
</tr>
<tr>
<td>Hypertensionb</td>
<td>14 (43.8) 3 (9.4)</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>11 (34.4) 0</td>
</tr>
<tr>
<td>Diarrheab</td>
<td>10 (31.3) 0</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (25.0) 0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6 (18.8) 0</td>
</tr>
<tr>
<td>Appetite decreasedb</td>
<td>5 (15.6) 0</td>
</tr>
<tr>
<td>Mucosal inflammationb</td>
<td>5 (15.6) 0</td>
</tr>
<tr>
<td>Pain in limb</td>
<td>5 (15.6) 0</td>
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<tr>
<td>Stomatitis</td>
<td>5 (15.6) 0</td>
</tr>
<tr>
<td>Vomitingb</td>
<td>5 (15.6) 0</td>
</tr>
<tr>
<td>Weakness</td>
<td>5 (15.6) 0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>5 (15.6) 0</td>
</tr>
</tbody>
</table>

#### Table 2. Safety findings: treatment-related adverse events reported by at least 15% of patients

Seven patients (21.9%) had axitinib dose reductions because of adverse events and 22 patients (68.8%) had treatment interruptions because of adverse events, the most common of which were fatigue (n = 6), hypertension (n = 6), arthralgia (n = 3), and hand–foot syndrome (n = 3). Adverse events related to study treatment and resulting in discontinuation were grade IV fatigue, grade I hemoptysis, and grade V bowel perforation (n = 1 each).

Eight patients (25.0%) died because of an adverse event during the active treatment period or within 28 days of their last axitinib dose. Six of these patients (19%) died because of disease progression or disease-related symptoms that were unrelated to study treatment. One patient died because of cerebrovascular accident deemed unrelated to study treatment by the investigator. One death was assessed as treatment-related and occurred in a 56-year-old female who experienced a grade V bowel perforation, although tumor progression could not be excluded as a cause of death.

### Modulation of blood-based soluble proteins

Plasma concentrations of sVEGFR-2 and sVEGFR-3 were decreased to the greatest extent after 2 cycles of axitinib therapy (mean ratio to baseline ± SEM: sVEGFR-2 = 0.58 ± 0.03, P < 0.0001 and sVEGFR-3 = 0.61 ± 0.05, P < 0.0005).
and plateaued thereafter (Fig. 3; n = 15). In comparison, plasma concentrations of soluble stem cell factor receptor (sKIT; n = 7–25) were slightly decreased after 2 cycles of axitinib therapy (mean ratio to baseline ± SEM: sKIT = 0.82 ± 0.05; P < 0.002) and were not consistently decreased after cycle 3 day 1 (Fig. 3; n = 7–15). In contrast, plasma VEGF concentrations increased after 2 treatment cycles (mean ratio ± SEM to baseline: VEGF = 4.84 ± 1.03; P < 0.05). These results indicate that primary pharmacodynamic activity of axitinib is aimed at selectively inhibiting VEGFRs compared with KIT.

Exploratory pharmacodynamic analysis of changes in sVEGFR-2 and sVEGFR-3 did not show an association with clinical response (data not shown). Pharmacokinetic analysis of axitinib blood levels also failed to yield a significant relationship with response (data not shown).

Discussion

These results show that axitinib has single-agent activity in patients with stage IV melanoma of which 78% were classified as poor prognoses M1C and 53% had elevated baseline serum LDH levels. Antitumor activity was observed with an ORR of 18.8%, including one CR and 5 PRs, with responses persisting for a median duration of 5.9 months. An additional 6 patients (18.8%) experienced stable disease lasting at least 16 weeks. This response rate is comparable to the 8% to 13% ORR provided by standard single-agent dacarbazine or temozolomide, or combination therapy with carboplatin and paclitaxel for advanced disease and falls within the ORR range of 10% to 20% associated with IFN-α and IL-2 (3–5, 8). Although a 6-month PFS rate of 33.9% falls along the 95% CI boundary described by Korn and colleagues (37) in a meta-analysis of phase II melanoma trials, this study provides evidence that axitinib alone has clinical activity in advanced melanoma and a potential rationale for combining axitinib with other agents.

Although dose escalations were permitted on the basis of individual patient tolerability (no grade II adverse events for 8 weeks), few patients received a dose of more than 5 mg twice a day for the majority of the study. However, experience with axitinib in other studies indicates that, in many cases, dose escalations beyond 5 mg twice a day are feasible. Intrapatient dose escalation to elicit a surrogate marker of response, reach maximum tolerated dose for an individual patient, and potentially increase response rate is currently common practice with cetuximab in colon cancer, following the EVEREST dose-escalation study (39). A similar strategy may enhance the efficacy of axitinib.

Hypertension has emerged as a potential marker for axitinib activity (40). In the current study, patients who experienced dBP of 90 mm Hg or higher (grade I hypertension) during treatment had a longer survival time than those who did not (median OS, 10.7 vs. 5.8 months, respectively). Notably, although treatment-related hypertension as an adverse event was reported in 43.8% of patients, only 3 cases were grade III or higher, and none of these cases led to discontinuation. A retrospective analysis exploring the association between elevated dBP and increased OS across 5 additional phase II axitinib studies similarly showed an association between transient increases in dBP and increased survival in other cancer types including nonsmall cell lung cancer, metastatic renal cell carcinoma, and thyroid cancer (40). Hypertension has been reported with other angiogenesis inhibitors (41, 42) and is usually manageable with standard antihypertensive agents (43).

Axitinib was generally well tolerated, with most adverse events of mild to moderate severity (grades I/II). Overall, adverse events were consistent with those previously reported for axitinib therapy (28, 29). Most were manageable through treatment interruptions, dose reductions, and/or standard medical interventions. Hypertension was reported in nearly half of patients, but, as previously noted, was generally grade I/II and did not interfere with therapy. The incidence of grade II proteinuria was also low (n = 2). One fatal bowel perforation assessed as treatment related occurred in a patient with abdominal and pulmonary cavity metastases. The most likely cause of the bowel perforation was tumor necrosis of metastatic masses with transmural invasion of the hollow organ. Similar events have been described with other angiogenic agents (44).

Analysis of soluble plasma proteins showed that axitinib therapy preferentially decreased sVEGFR-2 and sVEGFR-3 levels and increased plasma concentrations of VEGF. The same pattern of modulation has been reported for other agents targeting VEGF and VEGFRs (45), but multitargeted inhibitors of class III/V kinase receptors, such as sunitinib, also inhibit sKIT concentrations, reflecting a broader profile of signaling inhibition (34). Preclinical studies have shown that these changes are dose dependent and can correlate with antitumor activity, although they may occur in both naive non–tumor-bearing and tumor-bearing mice (46). Changes that occur in naive mice invoke a mechanism(s) independent of preclinical tumors. In this clinical trial, the use of soluble proteins was to serve as pharmacodynamic markers. The findings reported here provide clinical pharmacodynamic evidence of the selectivity of axitinib for
VEGFRs relative to KIT at systemic exposures in patients with melanoma. In conclusion, axitinib has clinical activity as a single agent in metastatic melanoma and was generally well tolerated. Axitinib preferentially decreased sVEGFR-2 and sVEGFR-3 plasma concentrations compared with sKIT levels, showing its selective targeting of VEGFRs. Further evaluation in combination with other agents is warranted for this disease and additional exploration of the potential relationship between transient increases in dBP of 90 mm Hg or higher, serum LDH levels, and clinical activity of axitinib will also be of interest.

Disclosure of Potential Conflicts of Interest

J. Lutzky received a commercial research grant from Pfizer Inc. O. Rixe has honoraria from speakers' bureau of Pfizer Inc. D. McDermott is a consultant for Pfizer Inc. B. Rosbrook, A.G. Niederhammer, and S. Kim are employees of Pfizer Inc. and B. Rosbrook and S. Kim own Pfizer stock. D. R. Shalinsky was a Pfizer employee during the time of this study and owns Pfizer stock; she is currently a paid contractor to Pfizer Inc. as a clinical scientist. J. Fruehauf, C.K. Brown, and J.-B. Meric have no conflict of interests to disclose.

Acknowledgments

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