Phase I, First-in-Human, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Vorolanib in Patients with Advanced Solid Tumors

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TRIAL INFORMATION

• ClinicalTrials.gov Identifier: NCT01296581
• Sponsor(s): Sarah Cannon Development Innovations
• Principal Investigator: Johanna C. Bendell
• IRB Approved: Yes

LESSONS LEARNED

• Pharmacokinetic results underscore that the vorolanib (X-82) study design was successful without the need for further dose escalation beyond 400 mg once daily (q.d.).
• Therefore, the recommended dose of X-82 as a single agent in patients with advanced cancer is 400 mg q.d.

ABSTRACT

Background. Vorolanib (X-82) is a novel, oral, multikinase vascular endothelial growth factor (VEGF) receptor/platelet-derived growth factor (PDGF) receptor inhibitor that was developed on the same chemical scaffold as sunitinib, but designed to improve upon the safety profile while maintaining the efficacy of sunitinib. By targeting the VEGF and PDGF receptors, X-82 was expected to disrupt tumor angiogenesis and be active in a broad spectrum of solid tumors. Therefore, we determined the maximum tolerated dose (MTD) and characterized the preliminary pharmacokinetics and clinical tumor response of X-82 as a single agent in patients with advanced solid tumors.

Methods. Adult patients with advanced solid tumors received X-82 as tablets or capsules (once daily [q.d.] or b.i.d.) every 4 weeks. Patients were evaluated for response every 8 weeks, and continued treatment until disease progression or intolerable toxicity.

Results. Fifty-two patients received study treatment in 17 cohorts. X-82 capsule dosing was as follows: cohorts 1–6 (20–400 mg q.d.) and cohorts 7–8 (140–200 mg b.i.d.). Patients in cohorts 9–17 received 50–800 mg q.d. tablet dosing. The median time on treatment was 58 days. X-82 blood pharmacokinetics appeared dose-independent with a $t_{1/2}$ of 5.13 hours and 6.48 hours for capsule and tablet formulations, respectively. No apparent accumulation was observed after 21 days of daily dosing.

Conclusion. X-82 had a safety profile consistent with its mechanism of action. It has a short half-life and was well tolerated by most patients. Study enrollment ended prior to the determination of the MTD because of the apparent saturation of absorption at 400–800 mg. The recommended dose of X-82 as a single agent in patients with advanced cancer is 400 mg q.d. The Oncologist 2018;23:1–9

DISCUSSION

The study planned to determine the MTD and preliminary pharmacokinetic (PK) characteristics of X-82, administered as a single agent in a continuous daily dosing schedule, in patients with advanced solid tumors. The study began with a capsule formulation of X-82. To improve the absorption
and exposure of X-82, a tablet formulation was available with protocol Amendment 3, and patients receiving capsules had the option to switch to the tablet formulation based on availability.

Patients on cohorts 1–6 received 20–400 mg once-daily capsule dosing and patients on cohorts 7 and 8 received 140–200 mg twice-daily capsule dosing. Patients on cohorts 9–17 received 50–800 mg once-daily tablet dosing. Patients were enrolled sequentially into these cohorts. No dose-limiting toxicities were observed in the dose levels explored. However, enrollment was stopped prior to determination of the MTD because of the apparent saturation of absorption at 400–800 mg. The recommended dose of X-82 monotherapy in patients with advanced cancer is 400 mg once daily.

To achieve the PK/pharmacodynamic (PD) model reported by Mendel et al., X-82 was designed to have a short $t_{1/2}$ and no accumulation in humans. The results underscore that our X-82 study design was successful without the need for further dose escalation beyond 400 mg once daily. In summary, X-82 was well tolerated by most patients, with the most common treatment-related grade 3 adverse event (AE) being proteinuria (4%). There were no grade $\geq 4$ AEs or deaths thought to be related to X-82. This safety profile is consistent with the mechanism of action. Further improvements in the treatment of advanced cancers with X-82 will likely await identification of and successful combination with other agents.

### Table 1. Treatment-related adverse events (incidence $\geq$5%; $n = 52$)

| Adverse event               | Grade 1/2 | Grade 3 | Total |
|-----------------------------|-----------|---------|-------|
| Dysphagia                   | 3 (6)     | —       | 3 (6) |
| Decreased appetite          | 3 (6)     | —       | 3 (6) |
| Dehydration                 | 3 (6)     | —       | 3 (6) |
| Myalgia                     | 3 (6)     | —       | 3 (6) |
| Dysgeusia                   | 3 (6)     | —       | 3 (6) |
| Headache                    | 3 (6)     | —       | 3 (6) |
| Mucosal inflammation        | 3 (6)     | —       | 3 (6) |
| Neuropathy peripheral       | 3 (6)     | —       | 3 (6) |
| Proteinuria                 | 1 (2)     | 2 (4)   | 3 (6) |
| Epistaxis                   | 3 (6)     | —       | 3 (6) |
| Hypertension                | 3 (6)     | —       | 3 (6) |
| Asthenia                    | 6 (12)    | —       | 6 (12) |
| Edema peripheral            | 6 (12)    | —       | 6 (12) |
| Rash                        | 6 (12)    | —       | 6 (12) |
| Vomiting                    | 7 (14)    | —       | 7 (14) |
| Hair color changes          | 8 (15)    | —       | 8 (15) |
| Diarrhea                    | 11 (21)   | 1 (2)   | 12 (23) |
| Nausea                      | 12 (23)   | 1 (2)   | 13 (25) |
| Fatigue                     | 15 (29)   | 1 (2)   | 16 (31) |
| Treatment-related deaths    | 0         |         |       |

Data are presented as $n$ (%). Abbreviation: —, no occurrence.

Figure 1. Best response as change from baseline for the sum of target lesions ($n = 49$). Two patients stopped study treatment during Cycle 1 because of clinical progression and were not reassessed for response. †Hurthle cell carcinoma. ††Pancreatic cancer.
### TRIAL INFORMATION

| Disease                  | Advanced cancer/solid tumor only |
|--------------------------|----------------------------------|
| Stage of Disease/Treatment | Metastatic/advanced              |
| Prior Therapy            | More than two prior regimens     |
| Type of Study – 1        | Phase 1                          |
| Type of Study – 2        | 3 + 3                            |
| Primary Endpoint         | Maximum tolerated dose           |
| Secondary Endpoint       | Pharmacokinetics                 |
| Secondary Endpoint       | Safety                           |
| Secondary Endpoint       | Efficacy                         |
| Secondary Endpoint       | Proportion of patients with an overall tumor response (complete response + partial response) |
| Secondary Endpoint       | Duration of response             |
| Secondary Endpoint       | Proportion of patients with stable disease |

Additional Details of Endpoints or Study Design

Additional Notes on Prior Therapy: Dose escalation phase: There was no limit on the amount of prior chemotherapy; dose expansion phase: ≤3 prior cytotoxic treatment regimens, and at least 1 regimen must have included a platinum-containing agent.

Dose Escalation Schema: Once-daily dosing regimen used an accelerated titration scheme that evaluated at least one patient per 28-day cycle before escalation to the next dose level. This accelerated titration scheme was to be followed by a 3 + 3 dose escalation (see Protocol Amendment 2). However, based on preliminary PK data from patients in this study, an apparent saturation in absorption of the drug capsule was observed, with a plateau in drug exposure at q.d. doses ≥160 mg. As a result, b.i.d. dosing was employed to further increase exposure and evaluate toxicity (Protocol Amendment 2). A new X-82 tablet formulation was introduced at a starting dose of 50 mg once or twice daily depending on data evaluation from the prior cohort using a 3 + 3 design.

Investigator’s Analysis

Active and should be pursued further

### DRUG INFORMATION

**Drug 1**

| Generic/Working Name | X-82 |
|----------------------|------|
| Trade Name           | Vorolanib |
| Company Name         | Equinox Sciences, LLC |
| Drug Type            | Small molecule |
| Drug Class           | Angiogenesis - antivascular |
| Dose                 | X-82 Capsule formulation: 20 mg and 100 mg (for patients enrolled prior to amendment 3); Tablet formulation: 50 mg and 100 mg (for patients enrolled after amendment 3) |
| Route                | p.o. |

### DOSE ESCALATION TABLE

| Dose level | Dose of drug: X-82 | Number enrolled | Number evaluable for toxicity |
|------------|--------------------|-----------------|-------------------------------|
| Capsule    |                    |                 |                               |
|            | 20 mg q.d.         | 1               | 1                             |
|            | 40 mg q.d.         | 1               | 1                             |
|            | 80 mg q.d.         | 1               | 1                             |
|            | 160 mg q.d.        | 1               | 1                             |
|            | 300 mg q.d.        | 2               | 2                             |
|            | 400 mg q.d.        | 3               | 3                             |
|            | 140 mg b.i.d.      | 3               | 3                             |
|            | 200 mg b.i.d.      | 4               | 4                             |
| Tablets   |                    |                 |                               |
|            | 50 mg q.d.         | 3               | 3                             |
|            | 100 mg q.d.        | 3               | 3                             |
Each X-82 dose was a cohort. For the 150 mg q.d., there were two cohorts: Cohort 11, 150 mg q.d., five patients; and Cohort 12, 150 mg q.d., three patients.

### PATIENT CHARACTERISTICS

|                  |          |
|------------------|----------|
| Number of Patients, Male | 38 (73%) |
| Number of Patients, Female | 14 (27%) |
| Stage            | Advanced |
| Age              | Median (range): 64 (40–80) |
| Number of Prior Systemic Therapies | Median (range): not collected |
| Performance Status: ECOG | 0 — 34 (65%)
  1 — 18 (35%)
  2 — 0
  3 — 0
  Unknown — 0 |
| Other            | Race: white, 49 (94%); black, 1 (2%); American Indian/Alaskan Native, 2 (4%) |
| Cancer Types or Histologic Subtypes | Breast, 1 (2%)
  Lung, non-small cell, 1 (2%)
  Lung, small cell, 2 (4%)
  Ovarian - platinum sensitive, 3 (6%)
  Ovarian - primary platinum resistant, 2 (4%)
  Ovarian - secondary platinum resistant, 2 (4%)
  Ovarian - platinum refractory, 3 (6%)
  Pancreatic, 1 (2%)
  Endometrial, 6 (12%)
  Colorectal, 8 (15%)
  Sarcoma, 2 (4%)
  Renal, 3 (6%)
  Gastrointestinal stroma, 1 (2%)
  Other*, 17 (33%)

*Carcinoid (3, 6%); cervical (2, 4%); clear cell ovary; gastric, Hurthle cell carcinoma of right thyroid; liver; melanoma; neuroendocrine carcinoid tumor; parotid gland; squamous cell carcinoma of the vulva; thyroid; unknown primary; uterine; and vagina (1 patient each, 2%).

### PRIMARY ASSESSMENT METHOD

|                  |          |
|------------------|----------|
| Title            | Assessment |
| Number of Patients Enrolled | 52 |
| Number of Patients Evaluable for Toxicity | 52 |
| Number of Patients Evaluated for Efficacy | 49 |
| Evaluation Method | RECIST 1.1 |
| Response Assessment CR | $n = 1$ (2%) |
| Response Assessment PR | $n = 1$ (2%) |
| Response Assessment SD | $n = 25$ (51%) |
| Response Assessment PD | $n = 20$ (41%) |
| Response Assessment OTHER | $n = 2$ (4%) |
**Median Duration Assessments PFS**
2 months, CI: 95%

**Median Duration Assessments TTP**
2 months, CI: 95%

**Median Duration Assessments Response Duration**
5 months

**Median Duration Assessments Duration of Treatment**
58 days

**Outcome Notes**
Other = missing, 2 (4%). Note that 11 patients (22%) had stable disease and were on study for at least six cycles.

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### Adverse Events

| Name                                           | All Cycles | NC/NA | 1   | 2   | 3   | 4   | 5   | All grades |
|------------------------------------------------|------------|-------|-----|-----|-----|-----|-----|------------|
| Dehydration                                    |            | 94%   | 2%  | 4%  | 0%  | 0%  | 0%  | 6%         |
| Dysphagia                                      |            | 94%   | 6%  | 0%  | 0%  | 0%  | 0%  | 6%         |
| Myalgia                                        |            | 94%   | 6%  | 0%  | 0%  | 0%  | 0%  | 6%         |
| Dysgeusia                                      |            | 94%   | 6%  | 0%  | 0%  | 0%  | 0%  | 6%         |
| Headache                                       |            | 94%   | 6%  | 0%  | 0%  | 0%  | 0%  | 6%         |
| Peripheral sensory neuropathy                  |            | 94%   | 4%  | 2%  | 0%  | 0%  | 0%  | 6%         |
| Proteinuria                                    |            | 94%   | 0%  | 2%  | 4%  | 0%  | 0%  | 6%         |
| Epistaxis                                      |            | 94%   | 6%  | 0%  | 0%  | 0%  | 0%  | 6%         |
| Hypertension                                   |            | 94%   | 2%  | 4%  | 0%  | 0%  | 0%  | 6%         |
| Fatigue                                        |            | 58%   | 27% | 13% | 2%  | 0%  | 0%  | 42%        |
| Edema limbs                                    |            | 88%   | 12% | 0%  | 0%  | 0%  | 0%  | 12%        |
| Vomiting                                       |            | 86%   | 8%  | 6%  | 0%  | 0%  | 0%  | 14%        |
| Diarrhea                                       |            | 76%   | 10% | 12% | 2%  | 0%  | 0%  | 24%        |
| Nausea                                         |            | 75%   | 17% | 6%  | 2%  | 0%  | 0%  | 25%        |
| Gastrointestinal disorders - Decreased appetite|            | 94%   | 4%  | 2%  | 0%  | 0%  | 0%  | 6%         |
| Gastrointestinal disorders - Mucosal inflammation|      | 94%   | 6%  | 0%  | 0%  | 0%  | 0%  | 6%         |
| Skin and subcutaneous tissue disorders - Rash  |            | 88%   | 12% | 0%  | 0%  | 0%  | 0%  | 12%        |
| General disorders and administration site conditions - Hair color changes | | 85% | 15% | 0%  | 0%  | 0%  | 0%  | 15% |

Abbreviation: NC/NA, no change from baseline/no adverse event.

### Serious Adverse Events

| Serious adverse event              | Grade | Attribution |
|------------------------------------|-------|-------------|
| Pancreatitis acute                 | 3     | Definite    |
| Deep vein thrombosis               | 2     | Definite    |
| Death                              | 5     | Unrelated   |
| Anemia                             | 3     | Unrelated   |
| Left hip fracture                  | 3     | Unrelated   |
| Pancreatic abscess                 | 3     | Unrelated   |
| Pleural effusion                   | 3     | Unrelated   |
| Drug reaction to denosumab (Xgeva) | 3     | Unrelated   |
| Abdominal pain                     | 3     | Unrelated   |
| Spinal fracture                    | 3     | Unrelated   |
| Hyperbilirubinemia                 | 4     | Unrelated   |
| Atrial fibrillation                | 3     | Unrelated   |
| Sciatic pain                       | 2     | Unrelated   |
| Right humeral fracture             | 3     | Unrelated   |
| Weakness                           | 3     | Unrelated   |
| Dyspnea                            | 3     | Unrelated   |
Vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) are cell surface tyrosine kinase receptors that represent targets for anticancer therapy in solid tumors. The combined effect on VEGFR and PDGFR with similar potency is thought to contribute to the increased efficacy of sunitinib (SU11248) over other tyrosine kinase inhibitors (TKIs) such as sorafenib, in patients with renal cell carcinoma, that primarily target VEGFR [1]. Vorolanib (X-82) was developed on the same chemical scaffold as sunitinib, targets all isoforms of VEGFR and PDGFR, and was designed to improve the safety profile while maintaining the efficacy of sunitinib.

Clinical studies showed that sunitinib has a long $t_{1/2}$ (>40 hours) as well as large distribution and accumulation in various tissues [2]. This observation required sunitinib dosing holidays as reflected in the U.S. Food and Drug Administration-approved dose of 50 mg once daily with 4 weeks on and 2 weeks off (4/2) treatment in metastatic renal cell carcinoma [3]. However, murine pharmacokinetic (PK)/pharmacodynamic (PD) studies of sunitinib suggested that constant inhibition of VEGFR2 and PDGFRβ phosphorylation was not required for efficacy; at highly efficacious doses, inhibition was sustained for 12 hours of a 24-hour dosing interval [4]. With a $t_{1/2}$ of about 2 hours in mice, sunitinib displayed intermittent inhibition with daily dosing; however, as the $t_{1/2}$ in humans is much longer, daily dosing results in constant inhibition. X-82 was designed to have a short $t_{1/2}$ in humans to meet the PK/PD requirement of intermittent inhibition with daily dosing. X-82 was also designed to have a smaller volume of distribution in tissues because its therapeutic targets, VEGFR and PDGFR, are in blood vessels. It was hypothesized that if X-82 had a short $t_{1/2}$ and did not accumulate in tissues, it would meet the requirement of intermittent inhibition and minimize the potential for toxicity, while maintaining antitumor activity similar to sunitinib.

The objective of this study was to determine the maximum tolerated dose (MTD) and preliminary PK of single-agent X-82 in patients with advanced solid tumors. The expectation was that an improved safety profile would allow daily dosing of X-82 and permit combination modalities currently precluded by safety concerns with sunitinib. Enrollment was stopped prior to determination of the MTD because of the apparent saturation of absorption at 400–800 mg. We believe that X-82 proved to be less toxic, as proteinuria (two patients, 4%) was the most common treatment-related adverse event reported. Additionally, we considered the intermittent suppression to be clinically effective. In a small phase I/II trial in patients with renal cell carcinoma (about half TKI naïve, half received prior TKI), its efficacy was comparable to other TKIs, but much better tolerated, consistent with the PK/PD model. Finally, the drug sponsor, Xcovery, LLC, has three clinical trials ongoing to investigate the X-82 combination with anti-programmed cell death protein 1 therapies (NCT03511222, NCT03583086, NCT03602547).

**Not** Note that two patients experienced a serious adverse event of grade 3 anemia that was unrelated to X-82. In addition, two patients experienced a serious adverse event of grade 3 dyspnea that was unrelated to X-82.

**Assessment, Analysis, and Discussion**

| Completion | Terminated Reason | Investigator’s Assessment |
|------------|-------------------|--------------------------|
| Study terminated before completion | Did not fully accrue | Active and should be pursued further |

**Fever**

| Small bowel (jejunal) obstruction | 3 | Unrelated |
| Esophageal ulcer | 3 | Unrelated |
| Esophagitis | 3 | Unrelated |
| Pneumothorax | 3 | Unrelated |
| Anemia | 2 | Unrelated |
| Fistula | 3 | Unrelated |
| Hyponatremia | 3 | Unrelated |
| Hematuria | 3 | Unrelated |
| Back pain | 3 | Unrelated |
| Constipation | 3 | Unrelated |
| Colon perforation | 4 | Unrelated |
| Fever | 4 | Unrelated |

Note that two patients experienced a serious adverse event of grade 3 anemia that was unrelated to X-82. In addition, two patients experienced a serious adverse event of grade 3 dyspnea that was unrelated to X-82.

**Acknowledgments**

Medical writing assistance was provided by Candice A. Shaifer, Ph.D., from Sarah Cannon; however, the authors retained editorial control of the manuscript.

**Disclaimers**

**Johanna C. Bendell:** Tyrogenix (RF); **Manish R. Patel:** Pfizer, Exelixis, Celgene, Bayer, Janssen (H); **Kathleen N. Moore:** AstraZeneca, Genentech/Roche, Immunogen, Tesaro, Clovis, OncoMed, Janssen, Merck, Aravive (C/A), PTC Therapeutics, Lilly (RF); **Hendrik-Tobias Arkenau:** Sarah Cannon/HCA (E), Guardant, Roche, Servier (C/A, H); **Gary Dukart:** Xcovery Holdings, Inc. (C/A, OI); **Kim Harrow:** Xcovery Holdings, Inc. (E, OI [company owns stock in Equinox Sciences, LLC]); **Chris Liang:** Xcovery Holdings, Inc. (E). The other author indicated no financial relationships. (C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patient holder; (SAB) Scientific advisory board

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FIGURES AND TABLES

Figure 2. Cycle 1 Day 22 arithmetic mean plasma concentration time curves with tablet formulation of X-82.
Table 2. Cycle 1 Day 22 mean PK parameters in patients administered X-82 tablets

| PK parameter | Cohort (X-82 dose/fasting or fed state) |
|--------------|----------------------------------------|
|              | 50 mg/fast | 100 mg/fast | 150 mg/fast | 150 mg/fed | 200 mg/fed | 300 mg/fed | 400 mg/fed | 600 mg/fed | 800 mg/fed |
| AUC(0–24), ng × hour/mL | 1,300 | 2,940 | 3,360 | 6,410 | 4,360 | 5,870 | 10,200 | 8,270 | 5,950 |
| t_{1/2}, hours | 8.4 | 7.3 | 8.5 | 5.0 | 5.8 | 7.8 | 6.0 | 5.6 | 4.2 |
| C_{max}, ng/mL | 118 | 315 | 346 | 560 | 446 | 646 | 804 | 936 | 727 |
| T_{max}, hours | 2.1 | 4.0 | 2.5 | 6.0 | 4.0 | 1.0 | 4.0 | 3.0 | 3.0 |

Abbreviations: AUC, area under the plasma-concentration time curve from time zero to 22 days; C_{max}, peak drug concentration; fast, fasting; fed, with meal; PK, pharmacokinetic; T_{max}, time to maximum observed concentration; t_{1/2}, terminal half-life.

Table 3. Cancer antigen 125 response (n = 14)

| Best overall response | n (%) |
|-----------------------|-------|
| Complete response     | 0     |
| Partial response      | 0     |
| Stable disease\(^a\)  | 7 (50) |
| Progressive disease   | 2 (14) |
| Unknown               | 0     |
| Missing               | 5 (36) |

Overall response rate (complete response + partial response) 0

\(^a\)One patient achieved stable disease and remained on treatment for at least six cycles.

Figure 3. Time to progression (TTP). Sample size, 49 patients; median progression-free survival (95% confidence interval [CI]): 2.00 (1.8–3.7); median TTP (95% CI): 2.00 (1.8–3.7).
Figure 4. Progression-free survival. Sample size, 49 patients; median progression-free survival (95% confidence interval): 2.00 (1.8–3.7).