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Anthony J. Olszanski, Fox Chase Canc Ctr
David C. Smith, University of Michigan
Luis H. Camacho, Ctr Oncol & Blood Disorders
John Thompson, Seattle Cancer Care Alliance
Suresh S Ramalingam, Emory University
R Donald Harvey, Emory University
Luis Campos, Oncol Consultants
David Ferry, Eli Lilly & Co
Shande Tang, Eli Lilly & Co
Ling Gao, Eli Lilly & Co

Only first 10 authors above; see publication for full author list.

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Electrocardiographic Characterization of Ramucirumab on the Corrected QT Interval in a Phase II Study of Patients With Advanced Solid Tumors

ANTHONY J. OLSZANSKI,a DAVID C. SMITH,b LUIS H. CAMACHO,c JOHN THOMPSON,d SURESH S. RAMALINGAM,e R. DONALD HARVEY,e LUIS CAMPOS,f DAVID FERRY,g SHANDE TANG,g LING GAO,g HOWARD SAFRANh

aFox Chase Cancer Center, Philadelphia, Pennsylvania, USA; bUniversity of Michigan, Ann Arbor, Michigan, USA; cCenter for Oncology and Blood Disorders, Houston, Texas, USA; dSeattle Cancer Care Alliance, Seattle, Washington, USA; eWinship Cancer Institute of Emory University, Atlanta, Georgia, USA; fOncology Consultants, Houston, Texas, USA; gEli Lilly and Company, Bridgewater, New Jersey, USA; hRhode Island Hospital, Providence, Rhode Island, USA

TRIAL INFORMATION

- ClinicalTrials.gov Identifier: NCT01017731
- Sponsor: Eli Lilly and Company
- Principal Investigator: Anthony J. Olszanski
- IRB Approved: Yes

LESSONS LEARNED

- Cardiotoxicity can be a serious complication of anticancer therapies. To enable earlier identification of drug-related cardiac effects, the International Conference on Harmonization (ICH) adopted the ICH E14 Guidelines for evaluating the potential for QT/corrected QT (QTc) interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs.
- The results of the evaluation of ramucirumab on the QT/QTc interval show a lack of effect on QTc prolongation in patients with advanced cancer.

ABSTRACT

Background. Ramucirumab is a human immunoglobulin G1 monoclonal antibody that specifically blocks vascular endothelial growth factor receptor-2 and is approved for the treatment of advanced gastric, non-small cell lung, and colorectal cancers. This phase II study was conducted to determine if treatment with ramucirumab causes prolongation of the corrected QT interval using Fridericia’s formula (QTcF) in patients with advanced cancer.

Methods. Patients received intravenous ramucirumab (10 mg/kg) every 21 days for 3 cycles. The first 16 patients received moxifloxacin (400 mg orally), an antibiotic associated with mild QT prolongation as a positive control. Determination of QTcF prolongation was made with triplicate electrocardiograms at multiple time points to compare with baseline.

Results. Sixty-six patients received therapy; 51 patients completed 9 or more weeks of therapy for the complete QTcF evaluation period. The upper limit of the 90% two-sided confidence intervals for the least square means of change from baseline for QTcF values was less than 10 milliseconds at all study time points in cycle 3 (Fig. 1). Concentration-QTcF analysis showed a visible, but not significant, negative association between ramucirumab concentration and QTcF change from baseline.

Conclusion. Ramucirumab at a dose of 10 mg/kg administered every 21 days for 3 cycles did not produce a statistically or clinically significant prolongation of QTcF. The Oncologist 2016;21:402–403f

DISCUSSION

QTcF correction change from baseline was the primary endpoint for this study. Fifty-one patients received at least 9 weeks of ramucirumab (10 mg/kg) plus diphenhydramine treatment (the complete corrected QT [QTc] evaluation period). Using the time-matched QTcF values from day −1 as the baseline, repeated-measures analysis of covariance showed that the upper limit of the two-sided 90% confidence intervals of the least square means of change from baseline for QTcF values was less than 10 milliseconds at all time study points in cycle 3 (Fig. 1). Concentration-QTcF analysis showed a visible, but not significant, negative association between ramucirumab concentration and QTcF change from baseline.

Correspondence: Anthony J. Olszanski, M.D., Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, Pennsylvania 19111, USA. Telephone: 215-214-1676; E-Mail: anthony.olszanski@fccc.edu. Received November 13, 2015; accepted for publication February 17, 2016; published Online First on March 16, 2016. ©AlphaMed Press; the data published online to support this summary is the property of the authors. http://dx.doi.org/10.1634/theoncologist.2015-0467

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The relationship between ramucirumab concentrations and change in QTcF was assessed using data from time points at which both the electrocardiogram data and the concentration data were available; the time-matched mean change from baseline QTcF was analyzed for correlation with the serum concentration of ramucirumab, using linear mixed models (Fig. 2). The slope of the model in this analysis was not statistically significantly different from zero. The estimated value of the slope was $-0.00207$, showing a small negative association between concentration of ramucirumab and the change from baseline in QTcF.

Mean ramucirumab concentration-time profiles at cycles 1 and 3 were very similar, with slightly higher mean concentrations for cycle 3, reflecting a small amount of accumulation following 3 doses of ramucirumab.

Safety analyses included all treated patients ($n = 66$). Most treatment-emergent adverse events (TEAEs) in patients receiving ramucirumab were consistent with the known adverse event (AE) profile. Sixty-five patients experienced at least one TEAE, regardless of causality. Forty-two patients (63.6%) experienced at least one TEAE considered related to ramucirumab; the most common were headache (16.7%; 1.5% grade 3), nausea (15.2%), hypertension (10.6%; 4.5% grade 3), and vomiting (10.6%).

This phase II study demonstrated that ramucirumab did not produce a prolongation of QTcF. The 90% two-sided (95% one-sided) upper confidence limit did not exceed 10 milliseconds. This conclusion is also supported by concentration-QTcF modeling, which showed a visible but not significant negative association between concentration of ramucirumab and change from baseline in QTcF.
### Drug Information

| Generic/Working name | Ramucirumab |
|----------------------|-------------|
| Trade name           | Cyramza     |
| Company name         | Eli Lilly and Company |
| Drug type            | Antibody    |
| Drug class           | Angiogenesis - VEGF |
| Dose                 | 10 mg/kg    |
| Route                | IV          |
| Schedule of Administration | Every 21 days |

### Patient Characteristics

| Number of patients, male | 37 |
| Number of patients, female | 31 |
| Age | Median (range): 63.5 years (19–86 years) |
| Performance Status: ECOG | 0 — 17 |
| | 1 — 46 |
| | 2 — 3 |
| | Unknown — 2 |

### Primary Assessment Method

| Control Arm: Total Patient Population |
|--------------------------------------|
| Number of patients screened | 76 |
| Number of patients enrolled | 68 |
| Number of patients evaluable for toxicity | 66 |
| Number of patients evaluated for efficacy | 0 |

### Adverse Events

| Name                  | *NC/NA | 1   | 2   | 3   | 4   | 5   | All Grades |
|-----------------------|--------|-----|-----|-----|-----|-----|------------|
| Fatigue               | 68%    | 15% | 14% | 3%  | 0%  | 0%  | 32%        |
| Nausea                | 67%    | 17% | 14% | 2%  | 0%  | 0%  | 33%        |
| Dyspnea               | 69%    | 12% | 14% | 5%  | 0%  | 0%  | 31%        |
| Abdominal pain        | 72%    | 9%  | 11% | 8%  | 0%  | 0%  | 28%        |
| Headache              | 72%    | 18% | 5%  | 5%  | 0%  | 0%  | 28%        |
| Diarrhea              | 76%    | 21% | 3%  | 0%  | 0%  | 0%  | 24%        |
| Vomiting              | 77%    | 9%  | 11% | 3%  | 0%  | 0%  | 23%        |
| Dehydration           | 81%    | 2%  | 11% | 6%  | 0%  | 0%  | 19%        |
| Constipation          | 84%    | 8%  | 6%  | 2%  | 0%  | 0%  | 16%        |
| Dizziness             | 84%    | 14% | 2%  | 0%  | 0%  | 0%  | 16%        |
| Hypertension          | 85%    | 0%  | 9%  | 6%  | 0%  | 0%  | 15%        |
| Fever                 | 85%    | 12% | 3%  | 0%  | 0%  | 0%  | 15%        |
| Anorexia              | 67%    | 17% | 14% | 2%  | 0%  | 0%  | 33%        |
| Edema limbs           | 81%    | 12% | 5%  | 2%  | 0%  | 0%  | 19%        |
| Cough                 | 79%    | 18% | 3%  | 0%  | 0%  | 0%  | 21%        |

**Adverse Events Legend**
- Treatment-emergent adverse events reported for ≥10 patients regardless of causality (safety population, n = 66)
- *No Change from Baseline/No Adverse Event
**SERIOUS ADVERSE EVENTS**

| Name                              | Grade | Attribution |
|-----------------------------------|-------|-------------|
| Gastrointestinal hemorrhage       | 2     | Possible    |
| Infusion-related reaction         | 2     | Probable    |
| Hepatic failure                   | 4     | Possible    |
| Dehydration                       | 3     | Unrelated   |
| Pulmonary embolism                | 3     | Unrelated   |
| Deep vein thrombosis              | 3     | Possible    |
| Hypertension                      | 2     | Definite    |

**Serious Adverse Events Legend**  
Serious adverse events considered related to study drug (safety population, \( n = 66 \))

**PHARMACOKINETICS/PHARMACODYNAMICS, CYCLE 1**

| \( n \) | 61 |
|---------|----|
| \( C_{\text{max}} \) | 485 \( \mu \)g/mL |
| \( \text{AUC} \) | 67,400 \( \mu \)g \( \times \) h/mL |
| Half-life | 148 hours |
| Volume of distribution | 2,290 mL |
| Clearance | 11.6 mL/h |

**PHARMACOKINETICS/PHARMACODYNAMICS, CYCLE 3**

| \( n \) | 47 |
|---------|----|
| \( C_{\text{max}} \) | 571 \( \mu \)g/mL |
| \( \text{AUC} \) | 69,900 \( \mu \)g \( \times \) h/mL |
| Half-life | 189 hours |
| Volume of distribution | 2,560 mL |
| Clearance | 10.7 mL/h |

Note: Please refer to Table 2 for summary of major pharmacokinetic parameters.

**ASSESSMENT, ANALYSIS, AND DISCUSSION**

Completion: Study completed  
Pharmacokinetics / Pharmacodynamics: Correlative Endpoints Met  
Investigator’s Assessment: Active and should be pursued further

Vascular endothelial growth factor (VEGF) and VEGF receptor-2 (VEGFR-2) contribute to angiogenesis, which plays a role in tumor growth and metastasis. Ramucirumab is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody that specifically binds to VEGFR-2, inhibiting VEGF-mediated signaling [1]. The International Conference on Harmonization E14 guidance specifies that all drugs should undergo a formal clinical evaluation early in clinical development to assess the potential for QT/QTc prolongation [2]. The exact timing of QT/QTc prolongation following ramucirumab administration, if existent, was not known before initiating this study. This study was a multicenter, open-label, single active-arm, phase II study to determine if treatment with ramucirumab (10 mg/kg) caused prolongation of the QT/QTc interval in patients with advanced cancer.

A total of 68 patients (37 men and 31 women) between the ages of 19 and 86 years with advanced cancer of solid-tumor origin enrolled in this study (Table 1). Patients with an implantable pacemaker or automatic implantable cardioverter defibrillator were not eligible for this study. Patients with a congenital long QT syndrome; a prolonged QTc interval on pretreatment electrocardiogram (ECG) of longer than 450 milliseconds, using both Bazett’s (QTcB) and Fridericia’s (QTcF) QT correction; a clinically relevant abnormality on the ECG that prevented an accurate measurement of the QT interval; or using a medication that was known to prolong the ECG QT interval were excluded. Patients with a history of risk factors for ventricular tachycardia or torsades de pointes, fainting, unexplained loss of consciousness, or convulsions were also excluded from participation. Patients received 10 mg/kg of ramucirumab every 21 days. Sixty-six patients received at least one dose of study drug and comprised the safety population. Fifty-one patients received at least 9 weeks of therapy (the complete QTc evaluation period). Patients who experienced ongoing clinical benefit may have continued to receive study therapy until there was documented progression of disease, intolerable toxicity, or withdrawal of consent. A follow-up evaluation was conducted, including adverse event assessment. Routine monitoring, including radiographic evaluation of disease, was continued as necessary to confirm patient eligibility to continue in the trial.

Serial blood samples were taken from patients following the initial infusion (cycle 1) and the third infusion (cycle 3).
Ramucirumab serum concentrations were measured by a bridging enzyme-linked immunosorbent assay, as previously described [3]. Profiles were very similar, with slightly higher mean concentrations for cycle 3, reflecting the small amount of accumulation following 3 doses of ramucirumab (Fig. 3). Major pharmacokinetic parameters following intravenous infusion of 10 mg/kg ramucirumab in cycles 1 and 3 are summarized in Table 2.

The QTcF change from baseline was the primary endpoint for this study. QT/QTc prolongation was determined with triplicate ECGs at multiple time points after the initial dose, and at steady state at a therapeutic dose level. The first 16 patients enrolled in the study received 1 dose of moxifloxacin (400 mg orally), an antibiotic associated with mild QTc prolongation, 1 week before receiving ramucirumab treatment, to demonstrate assay sensitivity. The mean moxifloxacin-induced QTcF prolongation exceeded 10 milliseconds and the lower 95% confidence intervals (CIs) exceeded 5 milliseconds at 8 postdose time points (Fig. 4).

Pretreatment with diphenhydramine (25–50 mg) was required before the administration of ramucirumab for cycles 1–4. The 90% CI of change from time-matched baseline (day −1) for QTcF at cycle 3 is shown in Figure 1. The diphenhydramine infusion occurred between 00:00 and 00:15, and the ramucirumab infusion occurred between 00:15 and 1:15. Using the time-matched QTcF values from day −1 as the baseline, repeated-measures analysis of covariance showed that the upper limit of the two-sided 90% CI of the least square means of change from baseline for QTcF values was less than 10 milliseconds at all study time points in cycle 3. Categorical outlier analysis for cycle 3 showed 2 patients (3 time points) with a QTcF value of longer than 450 milliseconds and no longer than 480 milliseconds. No patient had a QTcF value of longer than 480 milliseconds or QT, QTcB, or QTcF values of 500 milliseconds or longer in this population.

Time-matched concentration change from baseline in QTcF analysis demonstrated the slope of the model in this analysis was not statistically significantly different from zero. The estimated value of the slope was −0.00207, showing a small negative association between ramucirumab concentration and the change from baseline in QTcF (Fig. 2). The estimated value of mean change in QTcF was 2.8 milliseconds (90% CI: −3.8 to 9.5) at a geometric mean maximum serum concentration (Cmax) of 571 µg/mL (range: 272–1820 µg/mL) during cycle 3.

Sixty-five patients experienced at least one treatment-emergent adverse event (TEAE), regardless of causality. The TEAEs, regardless of causality, reported for at least 10% of patients are presented in Table 3. Forty-two patients (63.6%) had at least 1 TEAE that was considered related to ramucirumab. The most common grade 3 TEAE considered related to ramucirumab was hypertension (n = 3; 4.5%). Eleven patients (16.7%) experienced at least 1 serious adverse event (SAE) considered related to ramucirumab; 8 (12.1%) were grade ≥3 (Table 4). Thirty-two patients (48.5%) experienced at least 1 SAE regardless of causality. Sixteen patients died during the study. Eleven patients died within 30 days of the last dose of ramucirumab; 5 patients died more than 30 days after the last dose of ramucirumab. Disease progression was indicated as the primary cause of all of these deaths.

Ramucirumab is approved by the U.S. Food and Drug Administration for metastatic gastric cancer ( REGARD and RAINBOW trials), non-small cell lung cancer (REVEL trial), and metastatic colorectal cancer (RAISE trial) [4–7]. Some VEGF inhibitors can prolong the QTc interval. Vandetanib, which inhibits VEGFR and epidermal growth factor receptor signaling, significantly prolonged QTc interval [8]. An evaluation of sunitinib, a multitargeted tyrosine kinase inhibitor, demonstrated a dose-dependent effect on QT interval [9]. Based on the overall assessment, this study demonstrated that ramucirumab at a dose of 10 mg/kg administered every 21 days for 3 cycles did not produce a prolongation of QTcF. This was also supported by time-matched concentration change from baseline in QTcF analysis, which showed a visible but not significant negative association between ramucirumab concentration and change from baseline in QTcF.

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**Figures and Tables**

**Figure 3.** Mean ramucirumab concentration-time profiles following the first (cycle 1) or third (cycle 3) dose of 10 mg/kg ramucirumab.

**Figure 4.** Graph showing 90% confidence interval of change from baseline for QTcF after moxifloxacin treatment. Red dotted line and blue dotted line indicate 10- and 5-millisecond time points, respectively. The scale of the x-axis (time) is non-uniform following the 4-hour measurement.

Abbreviation: QTcF, QT corrected by Fridericia’s formula.
Table 1. Baseline patient characteristics (enrolled population, \( n = 68 \))

| Characteristic | \( n \) (%) |
|----------------|------------|
| **Sex**        |            |
| Male           | 37 (54.4)  |
| Female         | 31 (45.6)  |
| **Age, years** |            |
| Median (range) | 63.5 (19–86) |
| 18 to <65      | 41 (60.3)  |
| ≥65            | 27 (39.7)  |
| **Race**       |            |
| White          | 62 (91.2)  |
| Black          | 5 (7.4)    |
| Asian          | 1 (1.5)    |
| **Ethnicity**  |            |
| Hispanic or Latino | 4 (5.9) |
| Non-Hispanic or Latino | 64 (94.1) |
| **ECOG PS**    |            |
| 0              | 17 (25.0)  |
| 1              | 46 (67.6)  |
| ≥2             | 3 (4.4)    |
| Missing        | 2 (2.9)    |

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Table 2. Summary of ramucirumab pharmacokinetic parameters following administration of 10 mg/kg ramucirumab

| PK parameter                  | Cycle 1: first dose (\( N_{PK} = 61 \))^a | Cycle 3: third dose (\( N_{PK} = 47 \))^b |
|-------------------------------|------------------------------------------|------------------------------------------|
| \( C_{\text{max}} \) or \( C_{\text{max,ss}} \) (\( \mu g/mL \)) | 485 (43)                                  | 571^b (41)                               |
| \( t_{1/2} \) (hours)         | 148^a (36)                                | 189^b (33)                               |
| \( \text{AUC}_{\text{i} = 0} \) or \( \text{AUC}_{t,\text{ss}} \) (\( \mu g \times h/mL \)) | 67,400^a (38)                            | 69,900^b (41)                            |
| \( \text{CL} \) or \( \text{CL}_{\text{ss}} \) (mL/h) | 11.6^a (35)                               | 10.7^b (41)                              |
| \( V_{ss} \) (mL)            | 2,290^a (36)                              | 2,560^b (46)                             |
| \( R_{A,\text{Cmax}} \)      | 1.12^b (57)                               |                                          |
| \( R_{A,AUC} \)              | 1.11^b (38)                               |                                          |

^a\( n_{PK} = 59 \) for \( t_{1/2} \); \( n_{PK} = 58 \) for \( \text{AUC}_{\text{i} = 0} \); \( \text{CL} \), and \( V_{ss} \).

^b\( n_{PK} = 45 \) for \( \text{C}_{\text{max,ss}} \); \( n_{PK} = 43 \) for \( \text{AUC}_{\text{t,ss}} \); \( n_{PK} = 37 \) for \( t_{1/2} \); \( n_{PK} = 34 \) for \( V_{ss} \).

Abbreviations: AUC, area under the concentration-time curve; \( \text{AUC}_{\text{i} = 0} \); AUC from time 0 extrapolated to infinity; \( \text{AUC}_{t,\text{ss}} \); AUC over the dosing interval at steady state; \( \text{CL} \), total body clearance of drug calculated after intravenous administration; \( \text{CL}_{\text{ss}} \), clearance at steady state; \( \text{C}_{\text{max}} \), maximum observed serum concentration; CV%, percent coefficient of variation; \( N_{PK} \), number of subjects used in pharmacokinetic analysis; \( n_{PK} \), number of pharmacokinetic observations; PK, pharmacokinetic; \( R_{A,\text{Cmax}} \); accumulation ratio based on \( \text{C}_{\text{max}} \); \( R_{A,AUC} \), accumulation ratio based on \( \text{AUC} \); \( t_{1/2} \), apparent terminal elimination half-life; \( V_{ss} \), volume of distribution at steady state.
Table 3. Treatment-emergent adverse events reported for at least 10% of patients regardless of causality (safety population, \( n = 66 \))

| Preferred term       | Any grade,\( ^* n \) (%) | Grade \( \geq 3, ^* n \) (%) |
|----------------------|----------------------------|-------------------------------|
| Decreased appetite   | 21 (31.8)                  | 1 (1.5)                       |
| Fatigue              | 21 (31.8)                  | 2 (3.0)                       |
| Nausea               | 21 (31.8)                  | 1 (1.5)                       |
| Dyspnea              | 20 (30.3)                  | 3 (4.5)                       |
| Abdominal pain       | 18 (27.3)                  | 5 (7.6)                       |
| Headache             | 18 (27.3)                  | 3 (4.5)                       |
| Diarrhea             | 16 (24.2)                  | 0 (0.0)                       |
| Vomiting             | 15 (22.7)                  | 2 (3.0)                       |
| Cough                | 14 (21.2)                  | 0 (0.0)                       |
| Dehydration          | 12 (18.2)                  | 4 (6.1)                       |
| Edema peripheral     | 12 (18.2)                  | 1 (1.5)                       |
| Constipation         | 10 (15.2)                  | 1 (1.5)                       |
| Dizziness            | 10 (15.2)                  | 0 (0.0)                       |
| Hypertension         | 10 (15.2)                  | 4 (6.1)                       |
| Pyrexia              | 10 (15.2)                  | 0 (0.0)                       |
| Chills               | 9 (13.6)                   | 0 (0.0)                       |
| Abnormal weight loss | 8 (12.1)                   | 1 (1.5)                       |
| Arthralgia           | 7 (10.6)                   | 0 (0.0)                       |
| Asthenia             | 7 (10.6)                   | 0 (0.0)                       |
| Depression           | 7 (10.6)                   | 0 (0.0)                       |

\(^*\)National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 was used for adverse event grading [10].

Table 4. Serious adverse events considered related to study drug (safety population, \( n = 66 \))

| Serious adverse event          | Any grade, \( n \) (%) | Grade \( \geq 3, \ n \) (%) |
|--------------------------------|-------------------------|-----------------------------|
| Patients with any adverse event| 11 (16.7)               | 8 (12.1)                    |
| Gastrointestinal hemorrhage    | 1 (1.5)                 | 0 (0.0)                     |
| Infusion-related reaction      | 1 (1.5)                 | 0 (0.0)                     |
| Hepatic failure                | 1 (1.5)                 | 1 (1.5)                     |
| Dehydration                    | 1 (1.5)                 | 1 (1.5)                     |
| Pulmonary embolism             | 1 (1.5)                 | 1 (1.5)                     |
| Deep vein thrombosis           | 2 (3.0)                 | 2 (3.0)                     |
| Hypertension                   | 1 (1.5)                 | 0 (0.0)                     |