Combination mTOR and IGF-1R Inhibition: Phase I Trial of Everolimus and Figitumumab in Patients with Advanced Sarcomas and Other Solid Tumors

Richard Quek1, Qian Wang2, Jeffrey A. Morgan1, Geoffrey I. Shapiro3, James E. Butrynski1, Nikhil Ramaiya4, Tarsha Huftalen1, Nicole Jederlinic1, Judith Manola5, Andrew J. Wagner1, George D. Demetri6, and Suzanne George1

Abstract

Purpose: Preclinical models demonstrate synergistic antitumor activity with combination blockade of mTOR and IGF-1R signaling. We aimed to determine the safety, tolerability, and recommended phase II dose (RP2D) of the combination of figitumumab, a fully human IgG2 anti-insulin-like growth factor-1 receptor (IGF-1R) monoclonal antibody (Pfizer) and the mTOR inhibitor, everolimus (Novartis). Pharmacokinetics and preliminary antitumor effects of the combination were evaluated.

Experimental Design: Phase I trial in patients with advanced sarcomas and other solid tumors. Initial cohort combined full phase 2 dose figitumumab (20 mg/kg IV every 21 days) with full dose everolimus (10 mg orally once daily). Intercohort dose de-escalation was planned for unacceptable toxicities. Dose modifications were allowed beyond cycle 1.

Results: No DLTs were observed in the initial cohort during cycle one, therefore full dose figitumumab and everolimus was declared the RP2D. In total, 21 patients were enrolled on study. Most toxicities were grade 1 or 2, and were similar to reported toxicities of the single agents. Mucositis was the most frequently observed grade 3 toxicity. Median time on study was 104 days (range 17–300). Of 18 patients evaluable for response, best response was partial response in 1 patient with malignant solitary fibrous tumor and, stable disease in 15 patients. There were no apparent pharmacokinetic interactions between everolimus and figitumumab.

Conclusions: Combination figitumumab plus everolimus at full doses appears safe and well tolerated with no unexpected toxicities. Dose reductions in everolimus may be required after prolonged drug administration. This regimen exhibits interesting antitumor activity warranting further investigation.

Clin Cancer Res; 17(4); 871–9.

Introduction

Dysregulation of both insulin-like growth factor-1 receptor (IGF-1R) signaling and the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathways are biologically important in a variety of cancers, including many subtypes of sarcomas (1–3). IGF-1R, a trans-membrane tyrosine kinase, is widely expressed on normal human tissue and plays important role in growth, development, and angiogenesis. Preclinical studies have shown that fibroblasts lacking IGF-1R cannot be transformed by most oncogenes but this susceptibility is restored if IGF-1R expression is reinstituted (4, 5). Consequent to binding of IGF-1 or IGF-2 ligands, IGF-1R signaling activates the PI-3-kinase/AKT/mTOR as well as the Ras/Raf/MAPK signal transduction cascades. Interruption of these signals results in antiproliferative effects seen in both malignant cell cultures and tumor xenograft models (6, 7). Several inhibitory monoclonal antibodies targeting IGF-1R have demonstrated clinical benefit in certain sarcoma subsets, most notably Ewing sarcomas, and remain in active clinical development (8–10).

mTOR is a serine/theroine tyrosine kinase which functions as a key regulatory protein in normal cell growth, development, metabolism, as well as angiogenic pathways. It is downstream of PI3K–AKT signaling pathway and can be activated in response to mitogens, nutrients, and growth factor receptor signals, thereby playing crucial roles in the control of normal cellular growth and function as well as cancer cell proliferation and angiogenesis (11). Many mechanisms can result in constitutive activation of the PI3K–AKT–mTOR pathway, leading to cancer development (11), and it is reported that the mTOR pathway is aberrantly activated in a significant proportion of human cancers (12), making mTOR an attractive target for...
Translational Relevance

Inhibition of the IGF-1R and mTOR pathways are of significant interest in cancer therapeutics. IGF-1R and mTOR inhibitors have been studied through phases II and III trials as single agents. Preclinical data suggest combination therapy with mTOR and IGF-1R inhibition leads to enhanced antineoplastic efficacy against sarcomas and other solid tumors likely through IGF-1R inhibition of complex feedback loops activated by mTOR inhibition. This phase I trial of figitumumab and everolimus aimed to evaluate the toxicity profile of this combination, and to explore antitumor effects within a heterogeneous solid tumor patient population. Our results demonstrate this combination is feasible, and there is disease stability in the majority of patients as well as activity in patients with malignant solitary fibrous tumor, a disease which is likely driven by aberrant signaling through the IGF-1R pathway. These results justify further study of this novel blockade of two signaling pathways in sarcomas and other solid tumors.

Methods

Patients and study design

The study was a single center, investigator initiated, phase I, open label trial of daily oral everolimus in combination with figitumumab in patients with advanced sarcomas and other malignant solid tumors. This was conducted under an Investigator-held Investigational New Drug (IND) permit with the US FDA. Key eligibility criteria included: histologically proven advanced sarcoma or other malignant solid tumor without any curative therapy; at least 2 lines of established therapy, if such treatment exists or refusal of such treatment; age ≥18 years, Eastern Cooperative Oncology Group performance status of 0 or 1, adequate bone marrow, renal, and hepatic function (absolute neutrophil count ≥1,500/mm³ unsupported by growth factors, platelets ≥100,000/mm³, creatinine ≤1.5 times institutional upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, aspartate aminotransferase/alanine aminotransferase ≤2.5 times ULN, fasting serum cholesterol ≤7.75 mmol/L, and fasting triglycerides ≤2.5 times ULN); recovery from toxicities of prior anticancer therapy to grade 1 or less or returned to baseline; and use of adequate contraception in patients with reproductive potential. Key exclusion criteria included prior systemic anticancer therapy within 3 weeks of study drug administration, kinase inhibitors within 2 weeks for patients with gastrointestinal stromal tumor (GIST), prior radiotherapy or major surgery within 2 weeks concurrent use of any anticancer therapies; symptomatic or uncontrolled brain or central nervous system metastases; pregnant or nursing women; concomitant use of chronic high dose corticosteroids (>100 mg of prednisone or >40 mg dexamethasone per day) within 2 weeks of study entry or any inhibitors or inducers of CYP3A; uncontrolled diabetes mellitus as defined by fasting serum glucose >1.5 times ULN; significant active cardiac disease, serious active infection, other uncontrolled significant medical illness, psychiatric illness, or social situation that would preclude study participation. The study protocol was reviewed by the FDA and was approved by the institutional review board of Dana-Farber Cancer Institute. Written informed consent was obtained from all participants. This study is registered with ClinicalTrials.gov, number NCT00927966.

Procedures

This study employed a dose de-escalation design. Because no overlapping dose limiting toxicities were expected from prior studies of single-agent everolimus and figitumumab, the initial dose level combined the recommended full dose of figitumumab (20 mg/kg IV repeated every 21 days) with the standard approved dose of everolimus (10 mg orally once daily) (18–20). Study participants were enrolled in a standard 3+3 cohort design. Drug doses would be escalated in subsequent cohorts if DLT was observed in either ≥2 of the first 3 patients enrolled or ≥2 of the first 6 patients enrolled. Fifteen additional patients were to be enrolled at the recommended phase II dose (RP2D). This cohort size was selected to provide an estimation of toxicity rates with a 90% confidence interval no wider than ±23%. Study participants were allowed to continue combined study drug administration as long as there were no unacceptably severe adverse effects and there was no evidence of disease progression.
Dose modifications were allowed beyond cycle 1 for patients with stable disease or better response who developed a treatment related grade 3 toxicity or asymptomatic grade 2 toxicity. If dose modification was required, everolimus was reduced from 10 mg daily to 5 mg daily. If toxicity recurred, dose reduction of figitumumab from 20 to 10 mg/kg was planned.

Dose delays were required for grade 2 or higher toxicities until resolution of all toxicities to grade 1 or less. Safety and tolerability assessments, including clinical and laboratory evaluations, were performed during each drug administration cycle. All patients receiving at least 1 dose of either study drug were evaluable for toxicity. Treatment-related adverse events were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Dose-limiting toxicity was defined as any treatment-related adverse event that occurred in cycle 1, days 1 to 21, which resulted in one of the following: (a) Grade ≥ 2 noninfectious pneumonitis; (b) Grade 3 or higher nonhematological toxicities (excluding asymptomatic, uncomplicated hyperlipidemia, hyperglycemia, and/or nausea and vomiting manageable with drug therapy; (c) Grade 3 or 4 febrile neutropenia; (d) Grade 4 neutropenia or thrombocytopenia; or (e) study drug-related death. Tumor response was assessed at baseline and after every 2 cycles per Response Evaluation Criteria in Solid Tumours (RECIST; version 1.0).

Blood samples were also obtained for limited pharmacokinetic (PK) analysis. Predosing (trough) blood samples for everolimus plasma levels were collected in potassium-EDTA tubes during cycle 1 on days 1, 8, and 15 and cycle 2 day 1. Blood samples to assess circulating levels of figitumumab were collected in sodium heparin-containing tubes obtained before dosing and 1 hour after the end of infusion on cycle 1 day 1; additional samples to assess trough levels were drawn in cycle 1, days 8 and 15, and cycle 2, day 1, before figitumumab dosing.

Statistical analysis
Descriptive statistics were used to characterize patients at study entry. Ninety percent 2-sided exact binomial confidence intervals were computed for the partial response rate, stable disease rate, progressive disease rate, and severe toxicity rate. The area under the plasma concentration–time curve in cycle 1 (AUC0–22) was calculated for figitumumab using the trapezoidal method as implemented in SAS. The terminal disposition half-life was not estimated due to lack of data. All statistical analyses were done with SAS (version 9.2).

Role of funding source
This study was designed and written by the investigators with limited support from Novartis and Pfizer in providing study drugs, pharmacokinetic assessment, and nonstandard investigations as part of screening procedures. The investigators alone were responsible for data collection and analysis of the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Patients
Twenty-one patients were enrolled between August 2009 and February 2010. Patient demographics are summarized in Table 1. Median age was 56 years (range 25–77) with 12 of the 21 patients being males. Nineteen of 21 study participants (90%) had some form of sarcoma. Non-sarcoma patients included 1 patient with colon cancer and 1 patient with adrenal cortical carcinoma. Patients were heavily pretreated having received a median of 4 prior chemotherapy regimens (range 1–8). The most common sarcoma histologies enrolled were leiomyosarcoma (n = 4), malignant solitary fibrous tumor (n = 4), osteosarcoma (n = 3), and undifferentiated spindle cell sarcoma (n = 2).

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Number % or range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in years</td>
<td>56 25–77</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>9 43</td>
</tr>
<tr>
<td>Male</td>
<td>12 57</td>
</tr>
<tr>
<td>Prior chemo regimen</td>
<td>4 1–8</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>4 19</td>
</tr>
<tr>
<td>Solitary fibrous tumor</td>
<td>4 19</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>3 14</td>
</tr>
<tr>
<td>Spindle cell sarcoma</td>
<td>2 10</td>
</tr>
<tr>
<td>Ewing’s Sarcoma</td>
<td>1 5</td>
</tr>
<tr>
<td>GIST</td>
<td>1 5</td>
</tr>
<tr>
<td>Extraskeletal Myxoid</td>
<td>1 5</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>1 5</td>
</tr>
<tr>
<td>Chordoma</td>
<td>1 5</td>
</tr>
<tr>
<td>PEComa</td>
<td>1 5</td>
</tr>
<tr>
<td>Myxofibrosarcoma</td>
<td>1 5</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>1 5</td>
</tr>
<tr>
<td>Adrenal cortical carcinoma</td>
<td>1 5</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>19 90</td>
</tr>
<tr>
<td>Asian</td>
<td>1 5</td>
</tr>
<tr>
<td>Other</td>
<td>1 5</td>
</tr>
<tr>
<td>Baseline ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0 (Fully active)</td>
<td>10 48</td>
</tr>
<tr>
<td>1 (Restricted activity but ambulatory)</td>
<td>11 52</td>
</tr>
<tr>
<td>Total number of cycles completed</td>
<td>96</td>
</tr>
<tr>
<td>Median number of cycles completed for off-study patients (n = 18)</td>
<td>3.5 0–8</td>
</tr>
<tr>
<td>Median number of cycles completed for patients remaining on treatment (n = 3)</td>
<td>11 7–12</td>
</tr>
</tbody>
</table>
Safety and determination of RP2D

Of the first 6 patients enrolled in the initial dose cohort, no DLTs were observed, therefore the RP2D for this combination regimen was declared as figitumumab, 20 mg/kg IV every 21 days, with everolimus, 10 mg orally once daily. Per the protocol plans, an additional 15 patients were subsequently enrolled at this RP2D to gain additional safety and PK data. A total of 96 cycles of treatment have been administered as of August 1, 2010; the median number of cycles completed for all patients is 4 (range 0–12), and 3 patients continue to receive study drugs. Eighteen patients have been removed from study for the following reasons, progressive disease (n = 12), unacceptable toxicity (n = 3), clinical progression (n = 1), physician’s decision to remove patient from study (n = 1) and death due to disease (n = 1).

Twenty (21%) of the 96 cycles of study drug administered were delayed due to toxicity. The most common reason for dose delay was platelet count less than 100,000 on the planned d1, which occurred in 6 cycles (6%). Seven patients (33%) required everolimus dose modification per protocol (dose decreased from 10 to 5 mg daily) after a median of 4 cycles of study drug administration (range 2–11 cycles). No patient required dose reduction of figitumumab. Hematological toxicities were mild, all grades 1 to 2 in severity. All treatment related toxicities occurring in greater than 10% of patients, are listed in Table 2. Of note, grade 2 hyperglycemia was reported in 4 patients, with only 1 grade 3 event as the most severe examples of this potentially mechanism-based toxicity. Eleven patients [52%, 90% exact binomial CI

<table>
<thead>
<tr>
<th>Toxicity types</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Muco/stomatitis</td>
<td>11</td>
<td>52.4</td>
<td>7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>66.7</td>
<td>2</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>8</td>
<td>38.1</td>
<td>4</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>7</td>
<td>33.3</td>
<td>4</td>
</tr>
<tr>
<td>Platelets</td>
<td>6</td>
<td>28.6</td>
<td>5</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>8</td>
<td>38.1</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>33.3</td>
<td>1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>7</td>
<td>33.3</td>
<td>2</td>
</tr>
<tr>
<td>Rash: acne/acneiform</td>
<td>5</td>
<td>23.8</td>
<td>3</td>
</tr>
<tr>
<td>Taste disturbance</td>
<td>5</td>
<td>23.8</td>
<td>3</td>
</tr>
<tr>
<td>AST-SGOT</td>
<td>6</td>
<td>28.6</td>
<td>1</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>4</td>
<td>19.0</td>
<td>2</td>
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<tr>
<td>Neutrophils</td>
<td>4</td>
<td>19.0</td>
<td>2</td>
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<tr>
<td>Diarrhea w/o prior colostomy</td>
<td>4</td>
<td>19.0</td>
<td>1</td>
</tr>
<tr>
<td>Nose- hemorrhage</td>
<td>6</td>
<td>28.6</td>
<td>0</td>
</tr>
<tr>
<td>ALT- SGPT</td>
<td>5</td>
<td>23.8</td>
<td>1</td>
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<tr>
<td>Weight loss</td>
<td>5</td>
<td>23.8</td>
<td>0</td>
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<tr>
<td>Dry skin</td>
<td>5</td>
<td>23.8</td>
<td>0</td>
</tr>
<tr>
<td>GI-other</td>
<td>4</td>
<td>19.0</td>
<td>1</td>
</tr>
<tr>
<td>Ocular surface disease</td>
<td>5</td>
<td>23.8</td>
<td>0</td>
</tr>
<tr>
<td>Joint pain</td>
<td>5</td>
<td>23.8</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3</td>
<td>14.3</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>14.3</td>
<td>0</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>4</td>
<td>19.0</td>
<td>0</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>3</td>
<td>14.3</td>
<td>1</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>4</td>
<td>19.0</td>
<td>0</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>4</td>
<td>19.0</td>
<td>0</td>
</tr>
<tr>
<td>Head/headache</td>
<td>4</td>
<td>19.0</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>3</td>
<td>14.3</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus/itching</td>
<td>3</td>
<td>14.3</td>
<td>0</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>3</td>
<td>14.3</td>
<td>0</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>3</td>
<td>14.3</td>
<td>0</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>1</td>
<td>4.8</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal/soft tissue-other</td>
<td>3</td>
<td>14.3</td>
<td>0</td>
</tr>
<tr>
<td>Extremity limb pain</td>
<td>3</td>
<td>14.3</td>
<td>0</td>
</tr>
</tbody>
</table>
experienced 20 episodes (median 1; range 1–3) of grade 3 toxicities (Table 3). All episodes occurred outside of the DLT window. Grade 3 toxicities occurring more than once included mucositis/stomatitis, nausea, asymptomatic hypophosphatemia, and fatigue which resolved with appropriate medical therapy and/or temporary discontinuance and reduction of study drug dosing. Three patients came off study for unacceptable toxicities thought to be at least possibly related to study drugs; adverse events included grade 3 pneumonitis, grade 3 esophagitis/duodenal ulcer/enteritis, and grade 3 noninfectious wound complication in 1 patient each. The patient removed from study for grade 3 esophagitis/duodenal ulcer/enteritis was ultimately found to have a small bowel obstruction, unrelated to study drug. Once surgically repaired, all symptoms resolved. There were no grade 4 nonhematological toxicities reported. Of the 21 patients enrolled on study, 2 patients (9.5%), both in the expansion cohort, were removed from study due to toxicity during cycle 1.

**Preliminary evidence of antitumor activity**

Figure 1 summarizes the best response observed in the 18 of 21 patients (86%) evaluable for response. Three patients were not evaluable for response assessment due to removal

<table>
<thead>
<tr>
<th>Case</th>
<th>Disease type</th>
<th>Toxicity type</th>
<th>Cycle</th>
<th>Outcome of toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adrenal cortical carcinoma</td>
<td>Nausea</td>
<td>6</td>
<td>Continued without dose adjustment, antiemetics increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stomach-pain</td>
<td>7</td>
<td>Everolimus dose reduced, continued on study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Osteosarcoma</td>
<td>Muco/stomatitis</td>
<td>4</td>
<td>Everolimus dose reduced, continued on study</td>
</tr>
<tr>
<td>5</td>
<td>Ewing’s Sarcoma</td>
<td>Hypophosphatemia</td>
<td>2</td>
<td>Continued without dose adjustment</td>
</tr>
<tr>
<td>7</td>
<td>Leiomyosarcoma</td>
<td>Dehydration</td>
<td>3</td>
<td>Everolimus dose reduced at cycle 2, Removed from study during C3 for disease progression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diarrhea w/o prior colostomy</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypophosphatemia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muco/stomatitis</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Solitary fibrous tumor</td>
<td>Lymphopenia</td>
<td>10</td>
<td>Continued without dose adjustment</td>
</tr>
<tr>
<td>9</td>
<td>Solitary fibrous tumor</td>
<td>Pneumonitis/pulmonary infiltrates</td>
<td>1</td>
<td>Removed from study due to toxicity</td>
</tr>
<tr>
<td>12</td>
<td>Leiomyosarcoma</td>
<td>Fatigue</td>
<td>4</td>
<td>Removed from study due to clinical disease progression</td>
</tr>
<tr>
<td>13</td>
<td>Spindle cell sarcoma</td>
<td>Hyperglycemia</td>
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<td>Death due to disease</td>
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<tr>
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<td>Spindle cell sarcoma</td>
<td>Fatigue</td>
<td>3</td>
<td>Everolimus dose reduced, continued on study</td>
</tr>
<tr>
<td>16</td>
<td>Leiomyosarcoma</td>
<td>Enteritis</td>
<td>2</td>
<td>Removed from study due to toxicity*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Esophagitis</td>
<td>2</td>
<td></td>
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<tr>
<td></td>
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<td>Ulcer-duodenum</td>
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<td>20</td>
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<td>Removed from study due to toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wound–non-infectious</td>
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</tr>
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</table>

*Patient was ultimately found to have a chronic bowel obstruction, unrelated to study drug. When surgically repaired, all symptoms resolved.
from study before reimaging, all in the expansion cohort. One patient developed clinical disease progression during cycle 2, and 2 patients were removed for toxicity during cycle 1 (1 patient with grade 3 pneumonitis, and 1 patient with wound healing complications). Best response of partial response (PR) per RECIST version 1.0 was observed in 1 patient [5%, 90% CI (0–21%)], stable disease (SD) in 15 patients [71%, 90% CI (51–87%)], and progressive disease was noted in 2 patients [10%, 90% CI (2–27%)]. Of the 16 patients with either PR or SD 7 exhibited decrease in tumor size, ranging from 1% to 30% per RECIST 1.0, in a wide spectrum of sarcomas including solitary fibrous tumor (SFT), Ewing’s sarcoma, undifferentiated spindle cell sarcoma, leiomyosarcoma, and myxoid chondrosarcoma. One patient with bulky metastatic SFT demonstrated an impressive radiological response (Fig. 2) with significant reduction in tumor density and clinical improvement in tumor-related symptoms posttreatment. The patient has received 12 cycles of study drug and remains on study. Time on study for 3 patients with SFT range from 104 to 300 days; the 4th patient was withdrawn early from study because of grade 3 pneumonitis prior to 1st restaging scan. Eleven (52%) patients were on study drug for more than 100 days (Fig. 3).

Pharmacokinetic profiling of study drugs
Pharmacokinetic studies were performed at limited time points in this study. Blood samples of everolimus were available in all 21 patients on days 1 and 8 of cycle 1, with 3 missing on cycle 1 day 15 and cycle 2 day 1. Blood samples of figitumumab were available at 1 hour after the end of infusion on cycle 1 day 1 in 20 of the 21 patients, with 1, 2, and 2 missing on cycle 1 day 1, cycle 1 day 15, and cycle 2 day 1, respectively. There was no evident pharmacologic interaction between study drugs, and drug levels were comparable to levels expected based on single-agent trial reports. Everolimus steady-state plasma level (trough) at day 15 was 10.3 ± 6.5 ng/mL (n = 18). Figitumumab Cmax at 1 hour was 364 ± 78 mg/L (n = 20). Figitumumab mean AUC0–24 was 86,110 ± 16,811 mg hr/L for the population (n = 19). This is slightly lower than what has been reported previously, although the confidence intervals remain wide and overlapping (9, 21).

Discussion
Combined blockade of the mTOR and IGF-1R signaling pathways is an attractive and biologically rational approach to development of anticancer therapy for sarcomas and other solid tumors. Separately, both pathways appear to be relevant in multiple forms of cancer, and preclinical models suggest synergistic antitumor activity with combined inhibition of these pathways (14, 17).

Our study demonstrated that it is safe to combine figitumumab and everolimus at full doses recommended for each agent individually. Two other recently reported phase I studies evaluating combined mTOR and IGF-R inhibition using different combinations of agents have corroborated...
that this combination blockade is feasible in patients (22, 23). The toxicities encountered in the current combination phase I study were similar to those reported with each drug individually, and no new safety concerns were detected (9, 15, 18, 19, 24). Prolonged study drug administration was associated with need for dose modification in some patients. The toxicities observed were consistent with what is expected from prolonged administration of full dose everolimus and dose reduction of everolimus successfully managed these toxicities. Although concerns regarding cardiac toxicities have been raised with IGF-1R antibodies when combined with cytotoxic chemotherapy, we did not observe any treatment-related cardiac events. Because of the theoretically worse induction of hyperglycemia with these 2 agents, close monitoring of fasting blood glucose was performed. In a large phase III study, treatment-emergent hyperglycemia was reported in 50% of everolimus treated-patients, of which approximately a third of patients had grade 3 hyperglycemia (20). Similarly in single agent figitumumab dose escalation studies, hyperglycemia was a common adverse event (19). In this study we observed asymptomatic hyperglycemia in 13 patients (62%) but the majority were grade 1 in nature, with only 4 patients (19%) in whom grade 2 hyperglycemia occurred. One episode grade 3 hyperglycemia was observed in 1 patient. Mucositis was the predominant adverse event in our study; 33% and 14% experienced grades 2 and 3 mucositis respectively, and is consistent with the known side effects of mTOR inhibitors. We found this toxicity to be manageable with temporary dose interruptions, local therapy and, in some instances, dose reduction of everolimus. Although thrombocytopenia was the most commonly observed reason for treatment delay, likely related to both figitumumab and everolimus, thrombocytopenia observed was grade 1 or grade 2, did not require dose modification and typically was not a recurring toxicity for individual patients.

A number of patients on study experienced prolonged disease stability, including patients with metastatic solitary fibrous tumor, Ewing’s sarcoma, high-grade spindle cell sarcoma, osteosarcoma, adrenal cortical carcinoma, and leiomyosarcoma, suggesting that the combination may be impacting tumor proliferation despite the lack of tumor shrinkage sufficient to reach formal objective response.

Figure 2. Dramatic radiological response in a patient with solitary fibrous tumor. Computed tomography scans performed at (A) baseline and (B) after 8 cycles of study drugs showing dramatic tumor response with reduction in tumor density posttreatment.

Figure 3. Time on study among all patients. Median time on study is 104 days (range is 17–300 days). Asterisk (*) indicates patients who remain on study; double asterisks (**) indicates patients unevaluable for response.
Previous studies have implicated either the IGF-1R or PI3K–AKT–mTOR pathway as relevant to these histologies, suggesting that inhibition of these target pathways may lead to disease control (8–10, 25, 26–28). The most pronounced antitumor signal we observed in this heterogeneous population was in a patient with advanced bulky metastatic SFT who achieved a PR per RECIST criteria. Solitary fibrous tumor is an uncommon mesenchymal neoplasm. Although SFT may behave in a benign manner, approximately 20% of SFTs exhibit malignant behavior. There is no standard systemic therapy for this disease, although recent reports have suggested perhaps limited activity with tyrosine kinase inhibitors and anti-angiogenic regimens (29, 30). Malignant SFTs have been shown to secrete unprocessed insulin-like growth factor 2, which through activation of the insulin receptor may result in decreased hepatic gluconeogenesis, leading to the clinical hypoglycemia which has characterized this disease when metastatic as a paraneoplastic syndrome (31, 32). It has been suggested that this tumor-related activation of insulin receptor signaling may play an oncogenic role in SFTs, and that resection of metastases, if possible, may eliminate tumor-related hypoglycemia (33, 34). Importantly, IGF-2 is also capable of binding to and activating IGF-1 receptors, implying that the IGF-1 axis may also be a relevant target in this tumor type. Recently, Stacchiotti and colleagues reported high expression and phosphorylation of IGF-1R and activation of AKT in SFT, as well as a radiographic response to fititumumab alone in SFT, further supporting this hypothesis (30).

A limitation of this study is the lack of biomarkers to assess the status of the IGF-R, mTOR–PI3K–AKT pathway in the patient population studied. As the primary aim of this investigation was to assess the safety of this novel combination, these investigations were not included, however, further assessment of tumor efficacy and predictors of response should be included in future studies.

In conclusion, our results show that fititumumab and everolimus can be administered in combination at the full recommended doses for each individual agent. Toxicities observed are of similar character and severity as those reported for each single agent, and no drug–drug pharmacologic interactions were noted. Dose modification of everolimus may be required with continued dosing. Intriguing antitumor activity was seen in a patient with solitary fibrous tumor, as well as a reasonably high percentage of patients with stable disease. Further studies are justified to define efficacy in specific patient populations, as well as to further evaluate potential predictors of response to this novel blockade 2 separate but interacting signaling pathways.

Disclosure of Potential Conflicts of Interest

SG has received research funding from, and have served in a consultant or advisory role for Novartis and Pfizer. AJW has received research funding from Genentech, Prolepsyx, Arqule, and Exelixis, and have served in a consultant or advisory role for Genentech. GDD has received research funding from Novartis, Pfizer, and Ariad; served in a consultant or advisory role for Novartis, Pfizer, Ariad, Amgen, and Genentech; received honoraria from Novartis, Pfizer; and has provided expert testimony for Novartis, Pfizer, and Ariad. All other authors declared no conflicts of interest.

Author Contributions

R. Quek, Q. Wang, G.D. Demetri, and S. George were responsible for the conception and design of the study. J.A. Morgan, G.I. Shapiro, J.E. Butrynski, A.J. Wagner, G.D. Demetri, and S. George were responsible for the provision of study materials or patients. R. Quek, Q. Wang, J.A. Morgan, G.I. Shapiro, J.E. Butrynski, N. Ramaiya, T. Hufkelen, N. Jederlinic, A.J. Wagner, G.D. Demetri, and S. George were responsible for the collection and assembly of data. R. Quek, Q. Wang, J.A. Morgan, G.I. Shapiro, J.E. Butrynski, N. Ramaiya, A.J. Wagner, G.D. Demetri, and S. George were responsible for data analysis and interpretation. All authors contributed materially to drafts, revisions, and manuscript; all authors gave their final approval to the manuscript.

Grant Support

Research drugs and pharmacokinetic assay support were provided by Novartis and Pfizer.

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Received September 29, 2010; revised December 20, 2010; accepted December 20, 2010; published OnlineFirst December 22, 2010.

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Published OnlineFirst December 22, 2010; DOI: 10.1158/1078-0432.CCR-10-2621

Phase I Study of Everolimus and Figitumumab

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Richard Quek, Qian Wang, Jeffrey A. Morgan, et al.


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