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RESEARCH ARTICLE

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A phase II study of clinical activity of SCH 717454 (robatumumab) in patients with relapsed osteosarcoma and Ewing sarcoma

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Abstract

Background: Robatumumab (19D12; MK-7454 otherwise known as SCH717454) is a fully human antibody that binds to and inhibits insulin-like growth factor receptor-1 (IGF-1R). This multiinstitutional study (P04720) determined the safety and clinical efficacy of robatumumab in three separate patient groups with resectable osteosarcoma metastases (Group 1), unresectable osteosarcoma metastases (Group 2), and Ewing sarcoma metastases (Group 3).

Procedure: Robatumumab infusions were administered every 2 weeks and were well tolerated with minimal toxicity. Centrally reviewed response data were available for 144 patients.

Results: Low disease burden was important for osteosarcoma response: three of 31 patients had complete response or partial response (PR) by Response Evaluation Criteria in Solid Tumors (RECIST) in resectable patients (Group 1) versus zero of 29 in unresectable patients (Group 2); median overall survival was 20 months in Group 1 versus 8.2 months in Group 2. In centrally reviewed patients with Ewing sarcoma with PET-CT data (N = 84/115), there were six PR, 23 stable disease, and 55 progression of disease by RECIST at 2 months. Patients with Ewing sarcoma had a median overall survival of 6.9 months. However, responding patients with Ewing sarcoma were allowed to continue on treatment after study closure. A minority of patients with metastatic Ewing sarcoma showed clinical responses and have remained healthy after receiving 25–115 doses of robatumumab with remissions of >4 years duration (N = 6).

Conclusions: These findings show that although the IGF-1R remains an attractive treatment target, additional research is needed to identify responders and/or means to achieve durable remissions in order to successfully exploit IGF-1R signal blockade in Ewing sarcoma (clinicaltrials.gov: NCT00617890).

KEYWORDS

antibody therapy of cancer, bone sarcoma, Ewing sarcoma, osteosarcoma, resistance, tumor growth factor

1 | INTRODUCTION

Insulin-like growth factor receptor-1 (IGF-1R) is a rational target for Ewing sarcoma therapy because IGFR-1R is involved in growth regulation and cell signaling.[1–5] Indeed, cellular proliferation, metabolism, and resistance to apoptosis of a wide variety of cancers in addition to bone sarcomas involve IGF-1R signals.[6–11]

Wang et al. developed a fully human anti-IGFR-1 antibody (MK-7454 otherwise known as SCH717454; robatumumab) with very high affinity (3.8 pmol/l) for the receptor. This antibody also inhibits proliferation of a number of cell lines in soft agar as well as in vivo in the human ovarian tumor xenograft model.[12] These observations were extended to pediatric cancers including osteosarcoma and Ewing sarcoma in preclinical experiments.[3,4,13,14] About this time, it was shown that improved lymphocyte recovery following chemotherapy was associated with improved prognosis in patients with Ewing sarcoma[15,16]; similar observations also have been made for osteosarcoma patients.[17] Thus, better immune function may affect survival in both Ewing sarcoma and osteosarcoma.

Because of the dismal prognosis associated with metastases of osteosarcoma and Ewing sarcoma,[18–21] the current study was performed to examine the safety and efficacy of robatumumab in patients diagnosed with metastatic osteosarcoma with a low (i.e., resectable metastases) versus high disease burden (i.e., unresectable metastases) as well as metastatic Ewing sarcoma. This multinational clinical trial treated >200 patients with these rare bone sarcomas with robatumumab. The study was terminated early due to reprioritization of the sponsor's oncology product portfolio following the merger/acquisition of Schering Plough and Merck & Co., Inc. (Kenilworth, NJ). At that time, several other IGF-1R phase 2 studies were being conducted and have subsequently published their final results.[1–5] Nevertheless, at the time of termination, target enrollment in the robatumumab study was complete and patients who had not yet met protocol discontinuation criteria were allowed to continue receiving study therapy and be seen by the investigator according to usual standard of care, provided the investigator felt that such treatment was in the patient's best interest. This report describes the principal results of this large, phase 2A, multicenter study.

2 | METHODS

This was a multicenter study (Merck & Co., Inc., MK-7454/SCH717454, Protocol number P04720; clinicaltrials.gov: NCT00617890) involving 75 centers in the United States, Germany, Italy, Spain, Portugal, France, Netherlands, United Kingdom, Hungary, Canada, Sweden, Norway, Australia, New Zealand, Taiwan, South Korea, Turkey, Brazil, Guatemala, Argentina, Chile, Peru, Colombia, and Mexico. This study was conducted in conformance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. The primary study period began January 2007 and ended October 2011, with the last subject treated in July 2013. Robatumumab was supplied by Schering-Plough (now Merck & Co., Inc.) and was infused intravenously over 60 min every 14 ± 3 days. Following the Schering-Plough and Merck & Co., Inc. merger, this study was terminated early due to duplication of anti-IGFR-1 efforts and reprioritization of the oncology portfolio. However, patients already enrolled and responding to treatment were allowed to continue on therapy at the discretion of the study investigator. The data set was considered complete in April 2013. Drug supply for responding patients was exhausted in July 2013.

2.1 | Study design

Group 1 osteosarcoma patients were 11 years of age or older and had relapsed, resectable recurrences within 6 months of prior definitive treatment after an initial regimen containing a platinum agent and doxorubicin. Group 1 patients were stratified based on number of relapses (1–2 and >2) and randomly assigned in a 1:1 ratio to double-blind treatment with either a very low dose of robatumumab (0.3 mg/kg) or a standard dose (10 mg/kg) prior to resection after the first dose and PET-CT. This cohort then received subsequent dosing IV over 1 hr every 2 weeks, had tumor resected after second dose of antibody, then continued every 2 week antibody infusions until documented disease progression. If progression occurred in patients randomized to the low dose arm, subsequent treatment with the standard dose was allowed. Subjects were required to have a tumor sample obtained within 8 months of study entry to assess historical tumor proliferation rate. The prior surgical specimen was chosen because of not only challenges of getting lung biopsies, but also potential delay in therapy posed by a biopsy requirement in this group of resectable patients would be not allowed for ethical reasons.

Group 2 osteosarcoma patients were 11 years of age or older and had relapsed metastases that were clinically unresectable (e.g., bone, hilar, or too many metastases to justify resection) after an initial regimen containing a platinum agent and doxorubicin. These patients received nonrandomized, open-label robatumumab 10 mg/kg IV over 1 hr every 2 weeks until progression. Imaging of measurable lesions was done every 8 weeks.

Group 3 patients were 11 years of age or older and had Ewing sarcoma that had recurred or was refractory after treatment with at least three standard agents (e.g., ifosfamide + etoposide alternating with vincristine + cyclophosphamide + doxorubicin; vincristine, doxorubicin, and ifosfamide). Most had also received a second- or third-line treatment regimen (e.g., temozolomide + irinotecan; topotecan + cyclophosphamide). This chemotherapy resistant/refractory Ewing sarcoma cohort was treated with nonrandomized, open-label robatumumab 10 mg/kg IV over 1 hr every 2 weeks. Imaging of measurable disease with computer tomography or magnetic resonance imaging was done every 8 weeks until progression using Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

For all groups, subjects between 4 and 10 years of age were considered for enrollment on a site-by-site basis following approval of Protocol Amendment #3 (April 17, 2009). All patients were required to have measurable disease at study entry and to have Eastern Cooperative Oncology Group scores of ≤2 for patients >16 years of age or

Karnofsky performance status/Lansky play performance status of between 50% and 100% for patients ≤16 years of age. All patients had adequate organ function prior to study entry as defined by Hb ≥ 8 g/dl, ANC ≥ 1,500/mm^3, platelets ≥ 50,000/mm^3, creatinine < 1.5 upper limit of normal (ULN), total bilirubin < 1.5 × ULN, AST and ALT < 3 × ULN.

The treatment for Group 1 continued until disease progression or until a year of dosing at the same dose level (including two dose reductions allowed during the study) for patients who underwent surgery. If no relapse was noted after 1 year of treatment, follow-up continued in order to better define the relapse-free interval. Patients in Groups 2 and 3 who did not undergo surgery continued until documented disease progression.

2.2 | Statistical considerations

Primary endpoints were Ki-67 tumor cell proliferation compared to prior historical sample in Group 1 patients. Ki-67 proliferation marker reduction is exploratory; a cut point of 25% was chosen because of preclinical data showing correlation of growth inhibition of 40% and 53% in xenografts experiencing high growth inhibition compared to no significant change in ki-67 in three xenograft models exhibiting low or no growth inhibition after SCH717454 treatment. The proportions of patients whose tumor cell proliferation was reduced by ≥25% from baseline following exposure to robatumumab 0.3 mg/kg and 10 mg/kg were to be compared using a chi-square test. For Groups 2 and 3, the primary endpoint was tumor response as determined by RECIST and World Health Organization criteria. Response rate for Group 2 was defined as the proportion of patients who achieved complete response (CR), partial response (PR), or stable disease (SD) for ≥6 months. Response rate for Group 3 was defined as the proportion of patients who achieved SD for ≥6 months, or a CR or PR. Secondary objectives in all groups included overall survival, as well the assessment of safety and tolerability of the investigational agent.

For Group 1, the study had planned approximately 80% power to detect a true difference of approximately 25% (30% vs. 5%) in response rate for tumor proliferation (measured by Ki67) between the robatumumab doses with enrollment of 64 evaluable subjects (i.e., 32 per dose group). For Groups 2 and 3, a total of 25 evaluable subjects were required to be enrolled at the first stage to detect a radiologic tumor response using a Simon two-stage design. If no response was observed after the first 25 patients, accrual was stopped. If at least one response was observed, 29 additional evaluable patients were enrolled. If ≥5 responses were observed among all 54 patients, the null hypothesis (i.e., radiological response rate of ≤5%) was rejected. For Group 3 only, after enrollment of 54 subjects, if ≥5 responses was observed, up to 50 additional evaluable patients were to be enrolled to obtain a more precise estimate of the response rate. A follow-up period of up to 6 months would be required to obtain sufficient efficacy and safety data. During this period, enrollment was to continue.

With respect to secondary endpoints, the Kaplan–Meier method was used to estimate distributions of time to relapse for both doses of robatumumab (Group 1), duration of response (Groups 2 and 3), time to progression (Groups 2 and 3), and overall survival (all groups).

Safety and tolerability were assessed through physical examinations, vital signs, recording of adverse events (AEs) and routine hematology, chemistry, and urinalysis surveillance. AEs were tabulated by treatment using descriptive statistics.

Due to the early termination of the study, predefined efficacy endpoints could not be evaluated. The response rate, the proportion of subjects who achieved CR, PR, or SD, was summarized using descriptive statistics. CR and PR were determined by two observations not less than 4 weeks apart. Kaplan–Meier plot of overall survival was produced for all three groups. For the Ki-67 analysis, it was centrally reviewed and data analyzed the percent positive nuclei change from baseline was calculated for each subject.

2.3 | Follow-up and lesion measurement

Centrally reviewed radiology data were available in 144 subjects. Survival data were available until April 2012 in all patients and until December 2013 in patients with prolonged responses. Of six responding patients with Ewing sarcoma, two had infusions for 1 year (USA) and four had infusions stopped in July 2013 after >100 infusions per patient when drug supply was exhausted (non-USA) and their oncologists were contacted for additional details of these remarkable cases.

2.4 | Cluster analysis of genes associated with response

Gene expression patterns in responders with Ewing sarcoma (CR + PR; N = 8) and nonresponders (N = 26) were compared to normal controls (normal samples on Affymetrix Genome-Wide Human SNP 6.0 arrays that passed quality control thresholds) across 1,450 gene signatures. RNA extraction was performed using Ambion Recover ALL kits (Life Technologies, Carlsbad, CA) for use on formalin-fixed paraffin embedded (FFPE) tumor tissue material. The isolated RNA was then reversed transcribed by using the Nugen Technologies, Inc. (San Carlos, CA) WT-Ovation^{TM} FFPE system, and gene expression profiling data were generated using a Merck custom Affymetrix GeneChip.

The samples of patients with Ewing sarcoma profiled were classified as responder or nonresponders based on RECIST criteria. The area under the curve and overall patient survival were compared for both responders/nonresponders. A *t*-test was performed on the individual genes and for a set of pathway gene signatures collected from a Merck & Co., Inc. proprietary database. Ranking by lowest *P*-values identified top genes and pathways most associated with response or nonresponse to the IGFR inhibitor.

3 | RESULTS

3.1 | Demographics

The median age of the overall population was 20 years (range 9–79 years). Males accounted for 63% (N = 138) and females 37% (N = 81) of the enrolled population. The majority of patients enrolled in this study were Caucasian (N = 175; 80%). The median body weight was 64 kg.

TABLE 1 Overall patient disposition summarized by group

	Group 1		Group 2	Group 3	
	0.3 mg/kg	10 mg/kg	10 mg/kg	10 mg/kg	Total
Enrolled	35 (100)	33 (100)	35 (100)	116 (100)	219 (100)
Discontinued treatment[1]	31 (89)	28 (85)	35 (100)	110 (95)	204 (93)
Administrative reasons	0	0	1 (3)	0	1 (<1)
Adverse event	1 (3)	0	3 (9)	8 (7)	12 (5)
Did not meet protocol eligibility	3 (9)	1 (3)	0	1 (1)	5 (2)
Lost to follow-up	0	0	1 (3)	2 (2)	3 (1)
Progression of disease	23 (66)	26 (79)	30 (86)	97 (84)	176 (80)
Subject did not wish to continue	4 (11)	1 (3)	0	2 (2)	7 (3)
Completed treatment as per primary therapy period[2]	4 (11)	5 (15)	0	1 (1)	10 (5)
Completed treatment as per July 2013[3]	–	–	–	6 (5)	–

[1]This category includes three subjects who were enrolled but never treated (i.e., two patients in protocol ineligibility and one patient in administrative).
[2]Between 2007 and 2013.
[3]Clinical supplies were exhausted in 2013.
Values are n (%). Group 1, osteosarcoma with disease resected by day 14 of study; Group 2, unresectable osteosarcoma; Group 3, Ewing sarcoma; –, not applicable.

TABLE 2 Overall incidences of adverse events summarized by group

	Group 1		Group 2	Group 3	
	0.3 mg/kg (n = 34)	10 mg/kg (n = 33)	10 mg/kg (n = 34)	10 mg/kg (n = 115)	Total (n = 216)
Patients with any treatment-emergent AE	30 (88)	30 (91)	31 (91)	112 (97)	203 (94)
Patients with any ≥Grade 3 treatment-emergent AE	16 (47)	10 (30)	14 (41)	67 (58)	107 (50)
Patients with any SAE	14 (40)	8 (24)	12 (34)	57 (49)	91 (42)
Patients with any drug-related treatment-emergent AE	16 (47)	16 (48)	16 (47)	58 (50)	106 (49)
Patients with any ≥Grade 3 drug-related treatment-emergent AE[1]	1 (3)	1 (3)	3 (9)	16 (14)	21 (10)
Patients with any drug-related SAE	1 (3)[2]	0	2 (6)[3]	8 (7)[4]	11 (5)
Patients with any AE leading to death	4 (12)	1 (3)	1 (3)	14 (12)	20 (9)

[1]AE = adverse event; SAE = serious adverse event (may or may not be treatment related).
[2]Including 1 haemorrhagic shock in 1 patient.
[3]Including two thrombocytopenia in one patient, one hyperglycaemia in one patient.
[4]Including one anemia in one patient, one arthralgia in one patient, one unilateral blindness in one patient, one anorexia in one patient, one pneumothorax in one patient, one respiratory distress in one patient, one tachycardia in one patient, and three thrombocytopenia in one patient.
Values are n (%). Group 1, osteosarcoma with disease resected by day 14 of study; Group 2, unresectable osteosarcoma; Group 3, Ewing sarcoma; AE, adverse event; SAE, serious adverse event (may or may not be treatment related).

3.2 | Patient disposition

Table 1 provides the overall disposition of patients in each of the patient groups. Discontinuation due to an AE while on study medication was a rare occurrence (N = 12; 5% across all the groups and <10% within each group). The majority of patients who discontinued treatment did so due to disease progression (80% across all the groups and >65% within each group). Overall the discontinuations and reasons for discontinuation appeared similar across the different patient groups as well as across robatumumab doses within Group 1.

3.3 | Toxicity and tolerance of antibody infusions

Overall 94% of patients experienced one or more AE during this study (Table 2). The incidences of Grade 3 or greater AEs were generally similar across the different patient groups (47% and 30% for 0.3 and 10 mg/kg doses, respectively, within Group 1; 41% for Group 2; and 58% for Group 3); however, Group 1 patients with resectable osteosarcoma receiving 10 mg/kg experienced slightly fewer of these AEs compared with those receiving robatumumab 0.3 mg/kg and the other patient groups. Nearly half of all patients in each of the groups had AEs that were deemed to be related to treatment by the study

TABLE 3 Central review of RECIST/WHO best response to robatumumab (N = 144)

	Group 1		Group 2	Group 3
	0.3 mg/kg (n = 19)	10 mg/kg (n = 12)	10 mg/kg (n = 29)	10 mg/kg (n = 84)
CR + PR	1 (5)	2 (17)	0 (0)	6 (7)
Stable disease	10 (52)	7 (58)	6 (21)	23 (27)
Progression	8 (42)	3 (25)	23 (79)	55 (66)

Values are n (%) unless otherwise noted. Group 1, osteosarcoma with disease resected by day 14 of study; Group 2, unresectable osteosarcoma; Group 3, Ewing sarcoma; CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization.

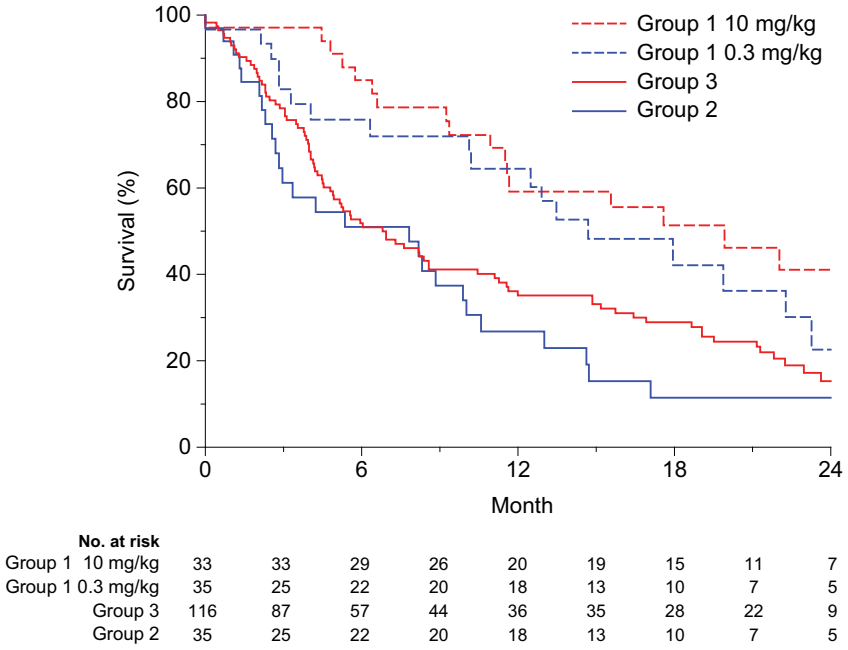

FIGURE 1 Kaplan–Meier curve of overall survival for osteosarcoma patients with low disease burden (resectable metastases, Group 1 [10 mg/kg and 0.3 mg/kg infusions]) and unresectable osteosarcoma metastases (Group 2, 10 mg/kg infusions). At 18 months, about 50% Group 1 were still alive versus 10% Group 2. Although patients with Ewing sarcoma (Group 3, 10 mg/kg infusions) had a higher disease burden (unresectable) and relatively poor short-term survival, about 30% were still alive 1.5 years into the study and a minority (N = 6, see Table 4) seem to have achieved long-term survival

investigators. Treatment-related AEs of Grade 3 or greater had a generally low incidence rate in this study across the patient groups (<15% for all groups). Of the bone sarcoma patients with measurable disease, 42% of them had reportable SAEs the majority of which were disease related and not related to study drug (e.g., abnormal lab tests, pain, fever, unexpected hospitalization). The incidences of drug-related SAEs were low and similar across the groups (3% and 0% for 0.3 and 10 mg/kg doses within Group 1, 6% for Group 2, and 8% for Group 3).

A total of 151 patients died during the study (35 in Group 1 [18 and 17 in the 0.3 and 10 mg/kg groups, respectively], 28 in Group 2 and 88 in Group 3); the primary reason of death was disease progression (121/125; 97%). The incidences of AEs leading to death were low and similar across the groups (12% and 3% for 0.3 and 10 mg/kg doses, respectively, within Group 1; 3% for Group 2; and 12% for Group 3). These AEs leading to death were disease related and not drug related.

3.4 | Ki67 proliferation data

Only a small subset of patients (11/68 [16%]) in Group 1 had Ki67 data both at baseline and endpoint. Most patients in both dose levels showed either no change or a decrease from baseline in Ki67 staining of tumor samples. Nevertheless, the sample size was not adequate to make definitive conclusions about the effect of robatumumab 0.3 mg/kg and 10 mg/kg on tumor proliferation.

3.5 | Centrally reviewed tumor response data

Centrally reviewed tumor response data were available in 144 of 219 patients. In Group 1, there were three patients with PRs (one in the 0.3 mg/kg and two in the 10 mg/kg cohort), 17 patients had SD (10 in 0.3 mg/kg and seven in 10 mg/kg), and 11 patients showed documented disease progression (eight in 0.3 mg/kg and three in 10 mg/kg). Although no objective tumor responses were seen in the unresectable osteosarcoma cohort (Group 2), six patients had SD per RECIST criteria. Twenty-three patients had documented disease progression. Of the patients with Ewing sarcoma (Group 3), six had PR, 23 SD, and 55 disease progression. The tumor response findings are summarized in Table 3.

TABLE 4 Patients with Ewing sarcoma who experienced prolonged responses after robatumumab

Site	Number of doses	Duration of response	Current status and comments
Minnesota	25	>4	CR, NED; no apparent late effects
Texas	25	>5	CR, NED s/p resection of one additional lung nodule 2013; new (resectable) 1 cm nodule 2015 with stable disease on pazopanib 2016; no apparent late effects
Brazil	>100	>4	CR, NED; no apparent late effects
Hungary	>100	>4	CR, NED; no apparent late effects
Norway	>100	>4	CR, NED; no apparent late effects
Spain	115	>4	CR, NED; no apparent late effects

CR, complete response; NED, no evidence of disease.

3.6 | Patient survival

Overall survival is summarized by patient group in Supplementary Table S1 and Fig. 1. Since Group 1 had low burden of disease after surgical intervention, superior survival was seen in this group (0.3 mg/kg: median overall survival 18 months [95% CI: 13–30]; 10 mg/kg: median overall survival 22 months [95% CI: 12, could not be estimated] versus the unresectable osteosarcoma cohort: median overall survival 8 months [95% CI: 3–11]). Patients with Ewing sarcoma who relapsed tended to do so in a manner that resulted in relatively short survival time (7 months). Figure 1 shows patterns of overall survival in the 3 patient cohorts. A total of six patients with Ewing sarcoma demonstrated prolonged and/or durable disease control (>4 years). Information on these patients is presented in Table 4.

3.7 | Genes associated with response and survival to IGF-1R

Gene signatures associated with better overall survival in responders after robatumumab included those related to direct mTOR downregulation, T cells, apoptosis, and downregulation of AKT and NK cells (Table 5). Notably, IGF-1, IGF1-R expression, indirect mTOR inhibition/suppression genes, pERK, and TH1 cytokines were not different in responders surviving longer (Table 5).

4 | DISCUSSION

IGF-1R is an important pathway for growth of Ewing sarcoma and other cancers.[2–5,22–28] Furthermore, Pediatric Preclinical Testing Program showed osteosarcoma cell lines with high IGF-1R had CR in *in vivo* models; thus a trial such as this one in advanced osteosarcoma and also resectable osteosarcoma to see if anti-IGF-1R therapy was effective was warranted.[3] A variety of clinical trials with anti-IGF-1R antibodies have been tested with low response rates as demonstrated by RECIST including R1507 and cixutumumab (IMCA-12) with a 10–11% in Ewing sarcoma, figitumumab, and ganitumab.[29–34] AE profiles have been favorable and were reviewed by Ma et al.[35]

IGF-1R signal inhibition was not sufficient to induce durable remissions in most bone sarcoma patients in our study and other single agent studies.[27,36,37] In osteosarcoma patients with resectable disease (Group 1), no dose response was detected for Ki-67 proliferation index or number of patients remaining alive after tumor resection. This group had best overall survival (18 months). In the unresectable osteosarcoma (Group 2) cohort, all of these patients had progression of disease by RECIST; no durable remissions were seen. Nevertheless, overall survival was similar for the unresectable osteosarcoma cohort (Group 2) if not slightly longer than the Ewing sarcoma cohort (8 months vs. 7 months). It would seem that in osteosarcoma metastases, a population of cancer stem cells may escape inhibition of IGF-1R relatively rapidly thereby necessitating other means (e.g., surgery) for achieving durable remissions.[38]

The unique long-term follow up that took place in this study permitted us to demonstrate durable remissions (>4 years) in a minority of unresectable patients with Ewing sarcoma. Further, we were able to show that long-term anti-IGF-1R administration (>4 years) was associated with few, if any, long-term side effects resulting from chronic anti-IGF-1R inhibition. In this group of patients, five of six remaining patients had continuous relapse-free remission. One has had surgery for isolated lung metastases once and is currently responding to 1 year of pazopanib for a >1 cm indicator lesion and two smaller indeterminate lesions (Table 5).

The combination of anti-IGF-1R antibodies and mTOR inhibition has demonstrated some success in Ewing sarcoma,[39,40] but mucositis is a problem.[41,42] Morphoproteomic profiling of two patients relapsing after anti-IGF1-R therapy, then following combined anti-IGF-1R + mTOR inhibition, showed two potential patterns of escape through AKT and ERK pathways. One patient showed both pAKT and mTOR and the other mTOR activation, which may explain the emergence of resistance after initial anti-IGF-1R therapy. After combined anti-IGF-1R + mTOR inhibition with temsirolimus, a metastasis showed activation of the ERK pathway when resistance emerged. Biomarkers including IGF-2 and IGFBP-2 seem predictive for effects from ganitumab.[11] Indeed, IGF-2 can reverse potent inhibition of angiogenesis by robamutumab, the antibody used in our study.[43] Of the six patients in this study who experienced long-term durable responses, the cluster analysis showed that immune response genes often were differentially expressed in responders versus nonresponders. This is consistent with results previously reported for trastuzumab and suggests that changes in the expression of immune genes may predict response to robatumumab.[44]

Synergy of ganitumab and cisplatin against ovarian cancer xenografts was recently shown.[45] Combinations of anti-IGF-1R

TABLE 5 Gene expression comparisons* of Ewing sarcoma responders and nonresponders (N = 26) versus normal expression and relationship to overall survival after robatumumab treatment

Column/Signature #	Name of gene(s) analyzed	AUC response[1]/NR2	Overall survival[2] *P* value
Genes associated with better overall survival			
4/1,326	Thymic ($CD4^+$, $CD8^+$, $CD3^-$) up	0.26	0.00005
7/427	TRIB1 mTORi PD down	0.32	0.00006
10/546	MKI67 sign up	0.30	0.0001
19/1,342	T-helper	0.28	0.0002
23/429	mTOR down	0.37	0.0003
30/143	p53	0.30	0.0004
39/564	Apoptosis	0.23	0.0007
41/269	AKTi MK-6673 postdose down	0.34	0.0008
47/1,320	Th2, up	0.37	0.001
62/435	OD24hr MEKi down	0.26	0.002
68/138	PARP enhancers (18 probes)	0.33	0.004
69/213	PARP enhancers that cluster	0.33	0.004
70/560	Apoptosis:gset06 Staurosporine	0.32	0.004
73/277	AKTi resistance down	0.21	0.004
74/436	MEKPD up	0.62	0.005
80/483	RAS pathway down	0.60	0.006
88/1,143	PIKi sensitivity down	0.29	0.007
95/1,381	IGF1PD sig up	0.32	0.009
136/299	Pro-apoptosis set 1	0.44	0.02
147/557	Apoptosis gset03 CASP8PD up	0.34	0.02
151/555	Apoptosis gset01 CASP3PD up	0.30	0.02
Genes with no apparent difference in overall survival			
688/1,403	IGF-1 sig up	0.30	0.3
722/1,382	IGF-1 PD sign down	0.61	0.4
892/819	IGF-1R protein correlation down	0.53	0.5
933/486	pERK up	0.39	0.6
1,034/487	pERK down	0.47	0.6
1,206/1,416	Th1 cytokines and related genes	0.66	0.9
1,302/816	MK-0646 lung cell line sensitivity	0.66	0.9
1,385/286	mTORi up	0.43	0.9
1,402/273	mTORi supressors	0.37	0.9
1,423/1,880	AKT up	0.60	1.0

*Selected genes from analysis of 1,450 gene signatures.
[1]Area under curve (AUC) (total expression compared to normal) of responders (N = 8)/nonresponders (N = 28).
[2]Overall survival after start of robatumumab treatment (Cox).

antibody dalotuzimub and ridaforlimus was very promising in a phase I trial including 10 of 23 patients with breast cancer[46]; dose-limiting toxicities were stomatitis and asthenia. Compared to the gemcitabine control arm (50% 6-month survival), the addition of ganitumab improved survival in pancreas cancer.[47] Although the best combinations remain to be determined, pairing known effective agents against Ewing sarcoma with an IGF-1R antibody would seem to be a very attractive strategy. However, IGF-1R inhibition seems to have no effect on chemotherapy resistance *in vitro*.[48] Short-term IGF-1R incubation was shown to increase survival kinase AKT and x-linked inhibitor of apoptosis (XIAP), which is associated with Apo2L/TNF-related apoptosis-inducing ligand (TRAIL) resistance. However, long-term IGF-1R inhibition resulted in XIAP repression and eventual Apo2L/TRAIL sensitization.[48] Patience with long-term anti-IGF-1R inhibition could be a virtue in therapy of Ewing sarcoma; it is possible that eventual Apo2L/TRAIL sensitization may be important for durable responses in a subset of patients. Thus, not only mTOR inhibition but also a novel agent that can inhibit both the AKT and ERK pathways to result in TRAIL induction may become another means to more effectively inhibit escape without toxicity to normal cells in which TRAIL is not expressed.[49] Indeed, one such agent, Onc201, has recently completed phase I clinical trials as a single agent.[50]

The results of our study are subject to the limitation of early study closure before all study data were collected according to the predefined study protocol. Although patients were allowed to continue study treatment at the discretion of the investigator, all study assessments were not completed per protocol hence limiting the ability to make definitive conclusions about the efficacy and safety/tolerability profile of robatumumab in these various osteosarcoma and Ewing sarcoma cohorts. Nevertheless, the study was fully enrolled at the time a decision was made to terminate this study, thus enabling the assessment of the primary efficacy endpoints in two of three patient groups. The efficacy bar was not met in the group of patients with unresectable osteosarcoma refractory to standard therapy (Group 2), since there were no responses among the first 25 evaluable patients. In contrast, there were at least five responses among the initial 54 evaluable subjects in Group 3, according to the Simon two-stage design, thereby meeting the efficacy threshold in patients with Ewing sarcoma. For Group 1, the limited availability of Ki67 in patients makes it difficult to draw any conclusions regarding differences in the efficacy of robatumumab 0.3 mg/kg versus 10 mg/kg on the response rate for tumor proliferation.

In summary, this study conducted in a large (>200 patients) multinational trial of robatumumab in bone sarcomas did not show significant benefit when administered as a single agent in patients with metastatic osteosarcoma. However, follow-up of responding patients with Ewing sarcoma treated with robatumumab showed encouraging long-term clinical benefit with no apparent deleterious safety/toxicity effects in a small subset of patients with Ewing sarcoma receiving treatment for >4 years. This finding warrants further study to explore the potential benefits of combination therapy with anti-IGF-1R antibody treatment. Currently, these findings are being evaluated in pediatric patients as part of a clinical study being conducted by Children's Oncology Group in which the anti-IGF-1R antibody, ganitumab, is being tested in combination with standard chemotherapy consisting of vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide (COG EWS1221; clinicaltrials.gov: NCT02306161). Results of this trial will attempt to discern long-term clinical benefit of IGF-1R inhibition in newly diagnosed patients with metastatic Ewing sarcoma.

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AUTHORS' CONTRIBUTIONS

All authors are responsible for the work described in this paper; involved in at least one of the following: conception, design, acquisition, analysis, statistical analysis, and interpretation of data, and drafting the manuscript and/or revising/reviewing the manuscript for important intellectual content; and provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

A. Lassaletta reports consulting honoraria for Takeda and clinical trial payments from Merck & Co., Inc. S. S. Bielack reports payment to his institution from Schering Plough Corp. for the conduct of the study and personal fees from Celgene, Chugai, Bayer, Clinigen, and Lilly. N. C. Daw reports funding from Schering Plough Corp. for the conduct of the study. K. Skubitz reports grants from Merck and Co., Inc. and Schering Plough Corp. for the conduct of the study, as well as consulting fees for Amgen, Ariad/Merck, Novartis, Johnson & Johnson, Pfizer/Schering-Plough, Systems Medicine, and Seattle Genetics; stock ownership in Johnson & Johnson; research funding received from Amgen, Novartis, GSK, Ariad/Merck, Celgene, Cell Therapeutics, Systems Medicine, Infinity, Schering-Plough Corp., Bayer, Pfizer, and Daiichi; and provided expert testimony on the role of bisphosphonates in osteonecrosis of the jaw. R. G. Gorlick reports stock options with Oncolytics, Inc. and meeting travel support from Bayer Inc. J. Rubino, K. Pathiraja, D. A. Hille, M. Ayers, S.-L. Yao, M. Nebozhyn, B. Lu, and D. Mauro are former or current employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., and may own stock or stock options in the company. B. Lu reports current employment at Celgene. P. M. Anderson, C. Herzog, E. Boldrini, O. R. Monge, and Z. Papai have nothing to disclose.

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ABBREVIATIONS

AE	Adverse event
CR	complete response
FFPE	formalin-fixed paraffin embedded
IGF-1R	insulin-like growth factor receptor-1
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SD	stable disease
TRAIL	TNF-related apoptosis-inducing ligand
ULN	upper limit of normal
XIAP	x-linked inhibitor of apoptosis

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