Clinical Development of Inhibitors of the Insulin-like Growth Factor Receptor in Oncology

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Abstract: The insulin-like growth factor I receptor (IGF-IR) pathway plays a major role in cancer growth, tumor cell survival and resistance to therapy. Ancillary evidence that targeting the IGF-IR may be useful in the treatment of cancer has been accumulating for almost two decades. Today, more than two dozen compounds have been developed and clinical trials are underway for at least 12 of those. The ability to pharmacologically control the IGF-IR pathway holds not only promising therapeutic implications but also the possibility to gather a better understanding of the role of the IGF axis in tumor initiation and progression. This review focuses on the preclinical rationale for targeting the IGF-IR and other components of the IGF-I system, early clinical results observed to date, biomarker approaches employed and the lessons from these early results for future study design. Early clinical trials reveal an acceptable safety profile together with pharmacodynamic evidence of receptor targeting. Instances of single-agent activity during phase I evaluations have been well documented and a recently reported randomized phase II study indicates that co-administration of an anti-IGF-IR antibody with chemotherapy improves objective response rate and progression-free survival in non-small cell lung cancer patients. These early results support ongoing research across a broad range of cancer indications.

Keywords: A12, cixutumumab, AMG-479, AVE1642, AXL1717, BIIB022, BMS-754807, CP-751,871, figitumumab, MK0646, OSI-906, R1507, robatumumab, Sch717454, XL228.

INTRODUCTION

Numerous model systems have provided evidence for important roles in neoplasia of insulin-like growth factors (IGFs) and their receptors [1-4]. Key examples include genetic ligand [5-15] and receptor knock-down methods [16]. One important theme that emerged from this work was the notion that multiple oncogenes require the presence of the IGF I receptor (IGF-IR) to achieve cellular transformation [17, 18]. Another was that IGF-I signaling confers resistance to many therapies that currently constitute the standard of care in oncology [19, 20].

Interest in IGF-IR targeting increased with evidence linking IGF-I signaling with the onset of neoplasia. Such evidence include associations between circulating IGF-I and cancer risk [21], between IGF-I and mammographic breast density [22], between growth rate in adolescence (which is IGF-I mediated) and cancer risk [23], and the observation that IGF-II overexpression was among the most common molecular derangements in colorectal cancer [24]. More than two dozen drug candidates targeting the IGF-IR have been investigated pre-clinically [7-13, 15, 25-29]. Here, we summarize the available clinical data from twelve of these therapeutics that are currently in clinical trial development; other recent reviews [4, 7-15] have focused on pathophysiology.

To the best of our knowledge, 12 IGF-IR inhibitors are currently in clinical development. These include the anti-IGF-IR antibodies A12, AMG-479, AVE1642, BIIB022, CP-751,871, MK0646, OSI-906, R1507, and Sch717454 (Table 1A), and the small-molecule inhibitors BMS-754807, Axl1717, OSI-906 and XL228 (Table 1B).

MONOCLONAL ANTIBODIES AGAINST THE IGF-IR

The anti-IGF-IR monoclonal antibodies are further in development than small molecule inhibitors.

PHASE I AND PHASE II CLINICAL DRUG DEVELOPMENT

A12

A12 (cixutumumab) is fully human IgG1 anti-IGF-IR antibody in development by ImClone Systems. Phase I trials evaluating the safety and maximum tolerated dose of A12 given weekly or every 2 weeks (q2weeks) at doses of 3-27 mg/kg are being conducted in patients with refractory solid tumors (NCT00785538, NCT00785941) [30, 31]. Toxicity reported included grade 3 hyperglycemia and grade 2 anemia, psoriasis, hyperglycemia, and infusion-related reaction.

Mean half-lives of 205 hours for 10 mg/kg on weekly dosing and 211 hours at 15 mg/kg on q2weeks dosing were reported. Consistent elevations of IGF-I and IGF binding protein (IGFBP) 3 post-A12 dosing were observed. No objective responses have been yet reported but 2 disease stabilizations >9 months (1 male breast cancer, 1 hepatocellular cancer) were observed on weekly dosing (Table 1A).

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Table 2 summarizes the ongoing clinical plan for A12 and other IGF-IR inhibitors. Eighteen additional clinical trials of A12 are listed in ClinicalTrials.gov. Single-agent studies include those evaluating the activity of A12 in Ewing’s and other sarcomas (NCT00668148), advanced liver cancer (NCT00639509), and metastatic prostate cancer prior to chemotherapy (NCT00520481). A trial for children with relapsed or refractory solid malignancies has commenced enrollment (NCT00609141). Combination trials include those of A12 given with cetuximab in patients with metastatic colorectal cancer who have failed prior anti-epidermal growth factor receptor (EGFR) therapy (NCT00503685) or in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (NCT00617734). A12 is also being tested with the mammalian target of rapamycin (mTOR) inhibitor temsirolimus (CCI-779) in patients with advanced breast cancer (NCT00699491) and other solid tumors (NCT00678223); with erlotinib in advanced non-small cell lung cancer (NSCLC; NCT00778167); with gemcitabine and erlotinib in patients with metastatic pancreatic cancer (NCT00617708); with antiestrogens in metastatic breast cancer patients who have progressed on antiestrogen therapy (NCT00728949); with mitoxantrone and prednisone in docetaxel-refractory hormone-independent prostate cancer (NCT00683475); with androgen deprivation therapy in pre-surgical prostate cancer (NCT00769795); with mitotane in adrenocortical carcinoma (ACC; NCT00778817); with octreotide in patients with carcinoid or islet cell cancer (NCT00781911); and with doxorubicin in soft tissue sarcoma (NCT00720174).

AMG-479

AMG-479 is a fully human anti-IGF-IR IgG1 monoclonal antibody in development for oncologic indications by
<table>
<thead>
<tr>
<th>Indication</th>
<th>Agent/Combination</th>
<th>Clinicaltrials.gov identifier</th>
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<tbody>
<tr>
<td>ACC</td>
<td>+mitotane (A12)</td>
<td>NCT00778817</td>
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<tr>
<td>ALL</td>
<td>XL228</td>
<td>NCT00464113</td>
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<tr>
<td>BC</td>
<td>+antiestrogens (A12)</td>
<td>NCT00728949</td>
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<td>+ exemestane (CP-751, 871)</td>
<td>NCT00372996</td>
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<td>+ exemestane or fulvestrant (AMG-479)</td>
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<td>NCT00683475</td>
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<td>+ doxorubicin (A12)</td>
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ACC, adrenocortical carcinoma; ALL, acute lymphocytic leukemia; BC, breast cancer; CML, chronic myeloid leukemia; CRC, colorectal carcinoma; HCC, hepatocellular carcinoma; H&N, head and neck; IGF-IR, insulin-like growth factor type I receptor; NSCLC, non-small cell lung cancer.
Amgen (and Takeda within Japan). The safety of single-agent AMG-479 was studied in a phase I dose-escalation trial of AMG-479 given intravenously (IV) at doses of 1-20 mg/kg q2weeks [32]. Sixteen patients with advanced malignancies were treated for a median number of 3 cycles (range, 1 to 16). Grade 3 thrombocytopenia was considered dose limiting at 20 mg/kg. Other grade 3/4 non-hematologic toxicities were observed in 2 patients; however, hyperglycemia greater than grade 2 was not observed. Anti-AMG-479 antibodies were detected in 1 patient. One additional patient had an infusion reaction (grade 2).

AMG-479 exhibited dose-linear pharmacokinetics in the 1-20 mg/kg dose range, reaching steady state at cycle 3 with a mean terminal half-life of 7-11 days. Pharmacodynamic studies showed a trend to dose-proportional occupancy of IGF-IR in neutrophils and to increased levels of serum IGF-I and IGFBP-3. By Response Evaluation Criteria in Solid Tumors (RECIST), 1 patient with Ewing’s sarcoma had a complete response, 1 patient with a neuroendocrine tumor had a partial response, and 5 patients had stable disease [32].

Early results from a phase Ib combination study of AMG-479 with either panitumumab or gemcitabine have been also reported (NCT00788957, NCT00630552) [33]. Patients with advanced solid tumors and no prior gemcitabine (in the gemcitabine arm only), received panitumumab (6 mg/kg) q2weeks or gemcitabine (1000 mg/m²) on days 1, 8, and 15 q4weeks in combination with AMG-479 at 6 or 12 mg/kg q2weeks. Grade 3/4 toxicities observed included AST/ALT elevations and neutropenia in 4 of 8 patients dosed with AMG-479 and gemcitabine, and one case of grade 3 hyperglycemia, and stomatitis and hypomagnesemia in 2 and 3 of 10 patients, respectively, dosed with AMG-479 and panitumumab. A partial response by World Health Organization (WHO) criteria was observed when AMG-479 12 mg/kg was combined with panitumumab in a patient with KRAS wild-type colon cancer who had previously progressed on cetuximab. Stable disease as best response (WHO) was noted in 9 of 11 evaluable patients. Another partial response was also WHO) was seen in a patient with hormone-resistant prostate cancer (HRPC) treated with AMG-479 and gemcitabine. Panitumumab or gemcitabine did not appear to affect the pharmacokinetics of AMG-479 (12 mg/kg).

An ongoing study is investigating the activity of AMG-479 as a single agent in refractory Ewing’s sarcoma in patients 16 years of age or older (NCT00563680). Single-agent AMG-479 is also being evaluated in recurrent platinum-sensitive ovarian cancer (NCT00719212). The activity of AMG-479 in combinations is being investigated in multiple trials: in combination with exemestane or fulvestrant as first- or second-line treatment of postmenopausal women with estrogen receptor-positive metastatic breast cancer (NCT-00626106); in combination with platinum-based chemotherapy in extensive disease small cell lung cancer (NCT-00791154); in combination with panitumumab in metastatic colorectal cancer (NCT00788957); in combination with gemcitabine as first-line therapy for metastatic pancreatic cancer (NCT00630552); in combination with carboplatin and paclitaxel for the first-line treatment of patients with optimally debulked epithelial ovarian cancer (NCT00-718523).

AVE1642

AVE1642 is a humanized anti-IGF-IR IgG1 monoclonal antibody licensed from ImmunoGen Corp in development by Sanofi-Aventis. Two phase I studies with this product, one in multiple myeloma and another in solid tumors, have been reported so far. An open-label, dose-escalation phase I study of AVE1642 given q3weeks was conducted in patients with refractory multiple myeloma [34]. Fourteen patients were dosed 3-12 mg/kg of AVE1642 for a median of 3 cycles (range, 1 to 8). AVE1642 was well tolerated. Two grade 3 hyperglycemias were observed in diabetic patients. No hypersensitivity during infusion was reported. No anti-drug antibodies were detected. One patient with Bence-Jones protein-positive myeloma experienced a decrease in proteinuria and relief of bone pain.

In the second study, AVE1642 (3-12 mg/kg) was administered q3weeks as single agent at cycle 1 and then combined with docetaxel (75 mg/m²) at cycle 2 and beyond in patients with advanced solid tumors [35]. No dose-limiting toxicity (DLT) was reported in the initial 14 patients enrolled. Grade 1/2 toxicity included hyperglycemia (1 case) and hypersensitivity reactions (2 cases). No anti-drug antibodies were detected. Four patients had stable disease but no objective responses were reported. AVE1642 concentrations increased dose-proportionally in the dose-range study and its half-life was estimated to be approximately 9 days.

A combination of AVE1642, 12 mg/kg q3weeks with bortezomib in patients with advanced multiple myeloma has been proposed [34]. Additional studies include combinations with fulvestrant in postmenopausal patients with hormone-dependent advanced breast cancer (NCT00774878), and with sorafenib and erlotinib in patients with locally advanced or metastatic liver carcinoma (NCT00791544).

BIIB022

BIIB022 (Biogen) is a human anti-IGF-IR non-glycosylated IgG4 antibody. A phase I dose-escalation study of BIIB022 given q3weeks to patients with relapsed or refractory solid tumors is currently underway (NCT00555724).

CP-751,871

CP-751,871 (figitumumab), a fully human IgG2 developed by Pfizer, was the first IGF-IR-targeting agent to be evaluated in clinical trials, and over one thousand patients have participated in trials of this antibody. Several studies have provided data on the safety and tolerability of CP-751,871 alone or in combination with chemotherapy. The first-in-human study of CP-751,871 was a phase I dose escalation (0.025-20 mg/kg) of this product given q4weeks to patients with refractory multiple myeloma [36]. Forty-seven patients were enrolled. No DLT was observed. Grade 3 events attributed to CP-751,871 included hyperglycemia and anemia (1 case each). The effective half-life of CP-751,871 at the 20 mg/kg dose was estimated to approach that of an endogenous IgG2, approximately 20 days. Several pharmacodynamic endpoints were investigated. The IGF-IR level on granulocytes was observed to decrease in a dose-dependent manner, with sustained down-regulation at doses ≥0.8 mg/kg. In addition, there was a substantial dose-dependent
increase in circulating IGF-I and IGFBP-3 levels, with >10-fold elevations to approximately 3-fold, 5-fold, and >10-fold from baseline levels at doses of 6, 10, and 20 mg/kg, respectively. No objective responses were seen, but 6 patients exhibited disease stabilization ≥6 months, despite progressive disease at study entry. Patients with a suboptimal response to CP-751,871 were eligible to receive CP-751,871 in combination with dexamethasone (3 x 40 mg q4weeks) or dexamethasone plus rapamycin (2 mg/day daily) while continuing to receive the antibody. Nine responses by European Group for Blood and Marrow Transplant criteria were noted in 27 patients receiving the CP-751,871/dexamethasone combination, including 2 patients refractory to dexamethasone regimens at study entry.

Further phase I single-agent experience with this agent has been reported (NCT00474760) [37]. This trial involved a dose escalation of CP-751,871 (3-20 mg/kg) given q3weeks in patients with refractory solid tumors and included assessment of pharmacokinetic endpoints and endocrine effects. In addition, two extension cohorts at the 20 mg/kg dose, one in ACC patients (N = 21) and one in patients with sarcoma (N = 26), were conducted [38-40]. In the phase I dose-escalation portion of the study, 110 cycles were administered to 24 patients. Again, no DLTs were observed. Grade 3 events included elevated gamma-glutamyltransferase (GGT), fatigue, and arthralgia. Greater than doubling of baseline growth hormone levels was observed, indicating systemic inhibition of the IGF-IR with blockade and loss of regulatory feedback of IGF-I through IGF-IR at the pituitary (discussed below). Treatment-associated elevations in growth hormone and insulin levels were greater in magnitude than elevations of fasting glucose levels which were modestly (<120% of pretreatment values) increased in most subjects [41]. Pharmacokinetic analysis revealed a dose-dependent increase in CP-751,871 levels with an approximately 2-fold accumulation on repeated dosing (21-day cycles), further supporting an estimated half-life of 20 days. No objective responses were observed in the dose escalation, but at the 20 mg/kg dose, 10 of 15 patients had a best response of stable disease with 2 of them experiencing long-term (>1 year) stability. Adverse events in the sarcoma cohort included one grade 4 uric acid elevation and one grade 3 bilateral deep-vein thrombosis. In ACC patients, one grade 4 GGT elevation and several grade 3 elevations of liver function tests were observed. In patients evaluable for response (RECIST), one complete response was observed in a patient with Ewing’s sarcoma. Stable disease (≥8 weeks) was seen in 12 of 20 evaluable (RECIST) patients with sarcoma, and in 9 of 13 evaluable patients with ACC.

An additional phase Ib study investigated the safety of CP-751,871 (0.1-20 mg/kg) in combination with docetaxel (75 mg/m²) in 27 patients with advanced malignancies [42]. Grade 3/4 toxicities reported were attributed to docetaxel and included neutropenia (n = 18) and diarrhea (n = 3). Of 20 HRPC patients treated, 8 had confirmed prostate-specific antigen (PSA) responses. This study also included the assessment of the number of circulating tumor cells expressing the IGF-IR (IGF-IR CTCs) [43]. IGF-IR CTCs were detectable in 50% of HRPC patients and their decline post-treatment appeared to be associated with PSA response.

Additional phase I studies currently investigate the safety of CP-751,871 in combination with sunitinib (NCT0072-9833); with paclitaxel and carboplatin in Asian patients with advanced NSCLC (NCT00603538); with gemcitabine/cisplatin or pemetrexed/cisplatin also in advanced NSCLC (NCT00560573); and with the EGFR inhibitor PF-299804 (NCT00728390). A phase I biomarker study involving tissue and magnetic resonance imaging biomarker endpoints is also underway in the setting of neoadjuvant breast cancer treatment (NCT00635245).

The safety and efficacy of CP-751,871 in combination with paclitaxel and carboplatin was investigated in a phase Ib/II study (NCT00147537) [44, 45]. The range of CP-751,871 doses evaluated in the phase Ib portion of the study was 0.8-20 mg/kg given q3weeks. Eight cohorts with a total of 42 patients, including 36 NSCLC patients, were enrolled. No DLTs were identified. Grade 3 events possibly related to CP-751,871 treatment were: GGT elevation, diarrhea, asthenia, and hyperglycemia (1 case each). CP-751,871 exposure parameters increased with dose and pharmacokinetic characteristics were consistent with target mediated disposition. Blood and tissue markers of the IGF-IR pathway were investigated. IGF-IR CTCs were cleared from blood upon treatment and reappeared in some patients upon disease progression. Sustained decreases in circulating cleaved soluble IGF-IR (sIGF-IR) as well as (free) IGF-I and IGFBP-3 accumulation were observed at CP-751,871 doses ≥ 6 mg/kg. Fifteen objective responses were observed, 10 of them in 24 (42%) advanced NSCLC patients dosed 6-20 mg/kg CP-751,871. An additional phase Ib extension cohort currently investigates the safety and tolerability of the combination of erlotinib (150 mg daily) with CP-751,871 (20 mg/kg) and standard doses of paclitaxel and carboplatin.

The phase II portion of the study was a 2:1 randomization of treatment-naïve NSCLC patients to paclitaxel, carboplatin, and CP-751,871 or to paclitaxel/carboplatin alone. Two doses of CP-751,871 were investigated in the experimental arm: 10 and 20 mg/kg in two sequential cohorts. Both treatment regimens were given q3weeks for up to 6 cycles. Patients receiving chemotherapy and CP-751,871 could continue CP-751,871 treatment upon chemotherapy discontinuation. Patients that progressed on paclitaxel/carboplatin treatment were eligible to receive CP-751,871 alone or in combination with chemotherapy at the investigator’s discretion. Safety and efficacy information has been reported for 151 of the phase II patients [45]. Forty-eight patients received chemotherapy and CP-751,871 at 10 mg/kg and 50 at 20 mg/kg. Twenty of a total 53 paclitaxel/carboplatin patients received CP-751,871 upon progression on chemotherapy. The combination regimen was well tolerated. Forty-two and 54% of patients receiving respectively chemotherapy and chemotherapy with CP-751,871 had objective responses. Exploratory analyses of response by dose and histology revealed an apparent dose-response relationship for patients with squamous cell and adenocarcinoma histologies. Response rates of the combined squamous cell and adenocarcinoma population for chemotherapy alone and with CP-751,871 at 10 and 20 mg/kg were respectively 33, 43, and 62% (n = 98, P = 0.0478 for chemotherapy and 20 mg/kg of CP-751,871 versus chemotherapy alone). Of note, 14 of 18 squamous patients responded to combination therapy, including 9 ob-
jective responses in bulky disease. Responses were also observed in 2 squamous patients receiving CP-751,871 upon chemotherapy discontinuation. In contrast, no incremental benefit by the addition of CP-751,871 to chemotherapy was seen in patients with large cell or unspecified histology. Upon completion of the randomized portion of the study, an additional non-randomized, single-arm extension cohort has enrolled 56 patients, including 47 with squamous cell carcinoma tumor histology in order further to verify the activity of CP-751,871 (20 mg/kg) and chemotherapy in NSCLC. The efficacy endpoint of this extension cohort is currently under evaluation. The combination regimen was well tolerated with a low incidence of treatment-related grade 3/4 toxicities. Grade 3/4 hyperglycemia was seen in 15% of patients receiving paclitaxel/carboplatin and CP-751,871 and 8% of patients receiving paclitaxel/carboplatin alone. Hyperglycemia resulted in study discontinuation in 3 patients receiving CP-751,871 treatment but it was manageable with insulin, metformin, or other oral anti-diabetic agents in the rest. Insulin was used in 23 patients, including 4 paclitaxel/carboplatin patients. Of note, 11 patients reported a history of diabetes at enrollment and 5 of these developed grade 3/4 hyperglycemia on study, including 1 patient in the reference arm. No hypersensitivity reactions to CP-751,871 were reported.

Additional phase II studies of this agent are ongoing. Two phase II protocols test the activity of CP-751,871 as single agent; one in refractory metastatic colorectal cancer (NCT00560560) and another in refractory Ewing’s sarcoma (NCT00560235). Combination phase II studies include those testing CP-751,871 as first treatment for hormone-refractory metastatic prostate cancer in combination with docetaxel and prednisone (NCT00313781), and a combination with exemestane in advanced oestrogen receptor-positive breast cancer (NCT00372996). Both trials are not yet mature but initial data indicate that the combinations are well tolerated [46, 47].

**MK0646**

MK0646 is a humanized IgG1 monoclonal anti-IGF-IR antibody in development by Merck. The safety and tolerability of MK0646 as a single agent was investigated in two phase I studies (NCT00282737, NCT00701103). In the first study, 48 patients with chemotherapy-refractory IGF-IR-expressing tumors were given MK0646 weekly at doses of 1.25-20 mg/kg [48]. Sequential (baseline and day 14) skin and tumor biopsies were collected and fluorodeoxyglucose positron emission tomography (FDG-PET) performed prior to and on treatment. One DLT of grade 3 thrombocytopenia was noted at 5.0 mg/kg. Grade 1/2 hyperglycemia responding to metformin occurred in 10% of patients. Pharmacokinetic data supported dose proportionality with a mean terminal half-life of approximately 4 days. For patients with evaluable paired tumor biopsies (n = 13), decreases in IGF-IR protein level, and downstream signaling were clearly documented at doses >5 mg/kg. FDG-PET metabolic responses occurred in 3 patients but no objective responses were observed. Three patients had stable disease for >3 months.

In the second phase I study, 29 patients were enrolled in 3 stages (NCT00635778) [49]. In stages 1 and 2, patients were treated with loading doses of MK0646 from 2.5 to 20.0 mg/kg IV followed by maintenance doses from 2.5 to 15.0 mg/kg q2weeks. In stage 3 (not completed at the time of the report), patients will be treated at a 15 mg/kg loading dose and 10 mg/kg maintenance dose. One DLT of grade 4 thrombocytopenia was observed at the 15 mg/kg loading dose, 5.0 mg/kg maintenance cohort. Grade 3 toxicity included thrombocytopenia, gastrointestinal bleeding, pneumonitis, and increase in liver function tests. Pharmacokinetic analyses suggested a terminal half-life of approximately 100 hours (range, 54 to 296). Although no objective responses to single-agent treatment were observed, 2 patients have had prolonged stabilization and have remained on study for longer than 1 year.

A pharmacodynamic study in breast cancer patients (NCT00759785) and a phase II in patients with neuroendocrine tumors (NCT00610129) further study the effects of MK0646 as a single agent. Combination studies include a phase I with the mTOR inhibitor deforolimus (MK88699) in patients with advanced solid tumors and phase IIIs with gemcitabine and erlotinib in advanced pancreatic cancer (NCT00769483), with pemetrexed and cisplatin in advanced NSCLC (NCT00799240), and with erlotinib, also in NSCLC (NCT00654420). This latter study is complemented by a phase I PET imaging study to characterize the erlotinib/MK0646 response (NCT00729742).

**R1507**

The safety and pharmacokinetics of weekly and q3weeks administrations of the human anti-IGF-IR IgG1 antibody R1507 (robotumumab, Roche) were explored in a phase I study in patients with advanced solid tumors or lymphomas (NCT00400361) [50]. Twenty-one patients were enrolled in 4 dose-escalation cohorts (1-16 mg/kg) of weekly R1507. One grade 3 hyperglycemia and one grade 3 CD4-positive lymphopenia were reported. Other adverse events included infection (n = 6) and fatigue (n = 4). Pharmacokinetic analysis estimated a half-life of approximately 8 days at the 16 mg/kg dose. At 1 mg/kg an average 80% reduction (range, 13 to 34%) in IGF-IR expression on peripheral blood mononuclear cells (PBMC) was seen on day 8 (n = 7). The q3weeks dose escalation has been also reported [51]. Thirty-four patients were enrolled at 3 dose levels (1-9 mg/kg). Two adverse events, a cerebrovascular accident and hyperbilirubinemia, classified as possibly related to study drug were reported at the 9 mg/kg dose. No hyperglycemia was reported; however, new glucose tolerance test abnormalities were observed in 2 of 17 patients at week 7. Half-life estimates increased from 3.4 to 6.2 days at the highest dose. Two objective responses were reported in 2 patients with Ewing’s sarcoma in the 9 mg/kg cohort. Stable disease was reported in another 2 of 8 evaluable Ewing’s sarcoma patients. Overall, 10 patients showed stable disease of median duration 18 weeks (range, 12 to 48).

Additional single-agent studies include a dose-finding trial in pediatric patients with advanced solid tumors (NCT00560144), and a single-arm phase II study of R1507 9 mg/kg weekly in patients with recurrent or refractory sarcoma (NCT00642941). R1507 combination studies include phase IIIs with erlotinib in advanced NSCLC who failed at
least one standard chemotherapy regimen (NCT00760929) and in those who failed prior erlotinib (NCT00773383), and a combination with letrozole in postmenopausal women with advanced breast cancer (NCT00796107).

Sch717454

Sch717454 (19D12) is a fully human anti-IGF-IR IgG1 monoclonal antibody in development by Schering-Plough. A phase I, single-dose study of Sch717454 0.3-20 mg/kg was conducted in 32 healthy volunteers with no adverse events reported up to 8 weeks post-dosing [52]. Two phase II clinical trials are currently ongoing to test the efficacy of Sch717454 q2weeks. In the first of these trials, patients ≥11 years old with relapsed osteosarcoma that can be treated with surgery, will be randomized to Sch717454 administered at one of two dose levels. Patients will receive Sch717454, have surgery performed, and continue to receive treatment with Sch717454. A second cohort of patients with unresectable osteosarcoma or Ewing’s sarcoma will receive Sch717454 until disease progression (NCT00617890). An additional trial investigates the activity of Sch717454 in patients with advanced colorectal cancer (NCT00551213).

PHASE III CLINICAL DRUG DEVELOPMENT

CP-751,871

Two phase III studies are being conducted to compare the activity of combination therapies that include CP-751,871 to currently approved treatments for advanced NSCLC. Study 1018 (NCT00673049) is a randomized, open-label, phase III trial of erlotinib alone or in combination with CP-751,871 in patients with recurrent or refractory NSCLC. Study 1016 (NCT00596830) is a randomized, open-label, phase III trial of paclitaxel and carboplatin alone or in combination with CP-751,871 in chemotherapy-naïve advanced NSCLC patients. Both studies employ a CP-751,871 dose regimen of 20 mg/kg q3weeks and target patients with histology other than adenocarcinoma. Additional studies targeting the NSCLC adenocarcinoma population are currently in the planning stages. (reviewed in [53]).

MK0646

This agent is being evaluated in a randomized, double-blind, placebo-controlled phase II/III protocol investigating the activity of MK0646 in combination with cetuximab and irinotecan in metastatic colorectal cancer that progressed on prior irinotecan and oxaliplatin therapy (NCT00614939). Two MK0646 regimens are being investigated in the phase II portion of the study: 10 mg/kg weekly, and 7.5 mg/kg q2weeks with a loading dose of 15 mg/kg in cycle 1, with one of these two regimens to be investigated in the phase III portion of the study [54].

SMALL MOLECULAR WEIGHT IGF-IR INHIBITORS

AXL1717

AXL1717 (Axelar) is a small molecule IGF-IR inhibitor investigated in phase I trials. Structurally, AXL1717 is based on a cyclopignan derivative, picropodophyllin, that appears to have some selectivity for the IGF-IR versus other tyrosine kinases, including the IR [55]. No clinical information was yet released.

BMS-754807

BMS-754807 (Bristol-Myers) is a small molecule antagonist of the IGF-IR administered orally. A multiple-dose study of the safety of BMS-754807 in patients with advanced solid tumors (NCT00569036) has been initiated with a starting dose of 4 mg/day.

OSI-906

OSI-906 (OSI Pharmaceuticals) is an oral small molecular weight tyrosine kinase inhibitor of the IGF-IR. Two phase I trials are underway investigating continuous (NCT00514007) and intermittent (1 to 3, 5, 7 days or 2 weeks) dosing (NCT00514306). Thirty patients received OSI-906 at 10-150 mg qd with 1 grade 3 hyperglycemia and 1 grade 3 lipase elevation reported. Twenty five patients were dosed at 10-450 mg, days 1-3/q2weeks without severe toxicity. Disease stabilization >6 months was observed in 1 thymic carcinoma, 1 ACC and 2 colorectal patients receiving OSI-906 in continuous dosing, and 1 myxoid chondrosarcoma, 1 ACC and 1 refractory NSCLC patients receiving OSI-906 40 mg days 1-3 q2weeks. Trends for increases in insulin levels with increasing OSI-906 plasma concentrations were observed [56].

XL228

XL228 (Exelixis) is a small-molecule tyrosine kinase inhibitor of IGF-IR, Src, fibroblast growth factor receptor, and BCR-Abl. A phase I dose-escalation of XL228 administered intravenously once or twice weekly was conducted in patients with advanced malignancies (NCT00526838) [57]. Data have been reported for 4 study cohorts (13 patients) receiving XL228 weekly at 0.45-3.6 mg/kg. There were no DLTs reported. Pharmacokinetic analysis of the first 3 cohorts has demonstrated a slightly greater than dose-proportional increase in exposure, with the mean terminal half-life of the first three cohorts ranging from 47 to 55 hours, and marked tissue distribution. There were substantial changes in phosphorylation of Src kinase substrates in PBMC after XL228 infusion; decreases of up to 20-70% were measured in Pyk2 Y402, Src Y416, and p56Dok2 Y351 phospho-epitopes. Rapid and transient increases in plasma glucose and insulin levels after infusion suggested inhibition of IGF-IR/insulin receptor. Twelve evaluable patients remained on study at the time of the report and continued to receive XL228 weekly; the longest time on study was experienced by a patient with small cell lung cancer (7+ cycles) and perirectal leiomyosarcoma (4+ cycles).

An additional study is investigating the safety of similar dose schedules in patients with chronic myeloid leukemia (CML) or Philadelphia-chromosome-positive (Ph+) acute lymphocytic leukemia (ALL; NCT00464113). XL228 is administered as a 1-hour IV infusion once or twice weekly in patients with Ph+ leukemias who harbor the T315I mutation or who are resistant to or intolerant of at least two prior BCR-ABL-inhibitor therapies. Dose levels to be tested are
0.45-10.8 mg/kg once weekly and 3.6 mg/kg twice weekly. Thirty-five patients have received one or more doses of XL228 and 7 patients have shown signs of clinical activity: 2 patients with chronic-phase CML patients demonstrated a complete cytogenetic response, including 1 patient with a T315I mutation, 2 patients experienced a major cytogenetic response, including a patient with Ph+ ALL harboring the T315I mutation, and 3 patients with accelerated-phase CML have experienced a return to chronic-phase CML. Adverse events have generally been of grade 1 or 2 severity and manageable. Serious adverse events reported included tumor lysis syndrome, syncope, neutropenia, thrombocytopenia, anemia, fever, and infections. DLTs of syncope and hyperglycemia were observed in the 10.8 mg/kg weekly cohort. Evidence of inhibition of BCR-ABL (including T315I), IGF-IR, and Src kinase pathways was demonstrated by the assessment of phosphoprotein markers in circulating leukocytes [58].

CHARACTERISTICS, DIFFERENTIATION, AND KNOWLEDGE GAPS WITHIN THE IGF-IR CLASS

Differences Between Antibodies and Small Molecule Inhibitors

Experience gained from clinical trials targeting the EGFR shows that it can be difficult to predict differences in efficacy between anti-receptor antibodies and small-molecule receptor tyrosine kinase inhibitors against the same target [59]. Most tyrosine kinase inhibitors directed against IGF-IRs have a broader activity than anti-IGF-IR antibodies (which were designed to spare the insulin receptor). They have inhibitory activity against the insulin receptor, the IGF-I receptor, and hybrid receptors, and therefore might be expected to be more effective antineoplastic agents than the anti-IGF-IR antibodies, particularly if insulin directly influences neoplastic behaviour (discussed below).

However, drug candidates that target the insulin receptor may have more serious metabolic toxicity than those that spare it. Monoclonals that are able to target hybrid receptors, such as Sch717454 or CP-751,871, may be able to block insulin signaling in cancer cells that is mediated by hybrid receptors [10, 60, 61].

Of note, tyrosine kinase inhibitors may allow the investigation of drug sequencing and intermittent dosing more conveniently than antibodies, but this is an area of investigation that has not been addressed in detail for insulin/IGF-IR targeting. The question of tissue distribution of small-molecule IGF-I/insulin receptor kinase inhibitors and their metabolites is important with respect to both potential toxicity (particularly central nervous system) and efficacy. While considerable information is already available regarding safety of anti IGF-IR antibodies, results of ongoing phase I studies of tyrosine kinase inhibitors are eagerly awaited.

SAFETY

Experience to date with several anti-IGF-IR antibodies administered alone or in combination with other agents for periods of up to or even exceeding a year has not revealed a degree of toxicity that would discourage further clinical trials. In fact, early trial results have revealed a rather favourable toxicity profile relative to other antineoplastic agents. Most reported adverse effects are mild and manageable.

Endocrine changes induced by anti-IGF-IR treatment appear to be characteristic of the class and include significant elevations in levels of circulating IGF-I, growth hormone, insulin, and glucose. From a safety viewpoint it is noteworthy that the metabolic consequences of IGF-IR inhibition have been reported only rarely to be associated with DLT, although in some patients co-administration of insulin or oral anti-diabetic agents has been necessary to control blood glucose levels. Mild elevations in blood glucose are seen in about 25% of patients treated with anti-IGF-IR antibodies. There is no evidence to support the simplistic notion that the hyperglycemia is attributable to cross reactivity of the antibodies with the insulin receptor. These agents were all designed to spare the insulin receptor, and there is convincing evidence that this has been achieved. Importantly, while several antibodies do target “half receptors” (comprising a “half receptor” composed of insulin receptor-alpha and -beta chains, complexed with a “half receptor” composed of IGF-IR-alpha and -beta chains), these receptors are more responsive to IGFs than to insulin, and do not play a central role in the regulation of glycemia [62, 63].

Available data are consistent with the more complex mechanism to account for the hyperglycemia outlined in Fig. 1. Anti-IGF-IR antibodies are not specific for receptors present on neoplastic cells; they act on normal tissues as well. In particular, IGF-IRs in the hypothalamic-pituitary axis that are involved in homeostatic feedback control are also targeted. This results in a loss of feedback inhibition of growth hormone secretion, which in turn leads to elevations in growth hormone. The elevated growth hormone levels stimulate increased IGF-I production by the liver, accounting for the observed elevations in IGF-I in the circulation. Furthermore, the elevations in growth hormone likely lead to growth hormone-induced liver gluconeogenesis as well as insulin resistance in muscle, liver, and adipose tissue [64]. This could result in hyperglycemia, similar to the growth hormone-dependent hyperglycemia seen in acromegalic patients. However, in most patients treated with IGF-IR inhibitors, hyperglycemia appears to be limited by increased pancreatic secretion of insulin (accounting for the observed elevation in insulin levels), which compensates to some extent for the insulin resistance and increased hepatic glucose production. Consequently, severe hyperglycemia is a rare event in studies in which IGF-IR antibodies are given as single agent [36, 37]. In contrast, up to 20% of severe hyperglycemia is seen in studies in which anti-IGF-IR antibodies are given with agents that require pre-medication with steroids that are themselves strong hyperglycemic agents [45]. Particular caution should therefore be taken with these combinations, but with physician awareness of the issues, these combinations can be safely administered. Of note, a combination of CP-751,871 with high-dose steroids in patients with multiple myeloma did not report high frequency or severity of hyperglycemia [36]. This may be due to the fact that when given at high doses in myeloma treatment, as distinct from antiemetic doses, steroids significantly interfere with the growth hormone-IGF-I axis at the hypothalamic, pituitary, and target organ levels [65], further indicating the complexities of the control systems involved.
The hormonal consequences of IGF-IR inhibition can in a sense be regarded as pharmacodynamic evidence of effective receptor targeting. This is conceptually analogous to the raised estrogen levels seen in premenopausal patients treated with tamoxifen. Caution is required in the interpretation of the magnitude of secondary hormonal changes as a function of dose of IGF-IR targeting agent. This is because the changes in growth hormone and IGF-I levels are likely dependent on a number of variables in addition to drug dose or degree of downregulation of IGF-IR signalling. For example, the degree to which growth hormone levels rise for a fixed degree of IGF-IR inhibition would be expected to vary with the pituitary reserve capacity of the patient. An elderly patient might have a less robust compensatory increase in growth hormone secretion than an adolescent. Similarly, there is likely person-to-person variability in the degree of insulin response to growth hormone-induced insulin resistance, leading to variability in treatment-induced hyperglycemia that is not directly attributable to drug exposure. This is important as there may be a natural temptation to try to establish relationships between hyperglycemia and efficacy.

The medical consequences of high growth hormone and IGF-I levels, hyperinsulinemia, and occasionally hyperglycemia require careful consideration. These changes are not desirable, but it appears that they are all tolerable, at least for treatment durations of ~1 year, beyond which there is little experience. Hyperglycemia appears usually to be easily controllable with metformin and other anti-diabetic agents [45, 48]. Metformin likely acts primarily to lower hepatic gluconeogenesis, which reduces circulating glucose, and results in secondary decline in insulin without effecting the elevated growth hormone or IGF-I levels [66]. An alternative approach might be the use of the growth hormone antagonist pegvisomant or agents that may decrease total or free IGF-I levels [67-70].

Importantly, there is no evidence that the significant elevation of IGF-I levels that occurs with IGF-IR targeting agents is sufficient to overcome the desired IGF-IR inhibition of IGF-IR signaling [36]. This may be due in part to the fact that parallel elevations of IGF binding proteins (which can reduce IGF bioactivity) have been observed [31, 32, 36], although one early report showed that the free IGF-I fraction increased in response to anti-IGF-IR treatment [71]. Poten-

**Fig. (1).** Legend. IGF-I production by the liver is stimulated by GH, and IGF-I negatively regulates GH secretion by the pituitary. In the setting of IGF-IR blockade, this feedback inhibition is lifted, and GH and consequently IGF-I levels rise. Elevation in GH can lead to insulin resistance in classic insulin target organs, and increased gluconeogenesis, leading to elevations in glucose. This in turn results in increased insulin secretion, which may vary from patient to patient, and which commonly corrects hyperglycemia. (See text for details). GH, growth hormone; IGFBP, insulin-like growth factor binding protein; IGF-IR, insulin-like growth factor type I receptor; IR, insulin receptor.
tial effects of high IGF-I levels on the insulin receptor in this setting are not well understood. In addition, despite reports of growth hormone receptor expression by human cancers [72], there is not yet clear evidence that growth hormone has an important direct action on neoplastic cells, so the elevations in growth hormone are unlikely to attenuate the anti-neoplastic activity of IGF-IR-targeting drugs.

On the other hand, elevations of insulin level associated with IGF-IR targeting deserve attention. There is clear evidence for insulin receptor expression by human cancers [73, 74] and experimental evidence for insulin acting through its own receptor to attenuate the effects of IGF-IR targeting [73, 75]. There is also evidence that high insulin secretion is associated with adverse prognosis of common cancers [10, 76-78]. However, preliminary reports indicate that patients with high insulin levels post anti-IGF-IR treatment fare in general as well as or better than other patients [79]. Likewise, better outcomes are not seen in patients who develop hyperglycemia [45]. Nevertheless, it will be of interest to examine the possibility that the benefits of IGF-IR targeting are attenuated by high insulin levels. Should hyperinsulinemia or IGF-I elevations be found to be associated with reduced clinical benefit from IGF-IR targeting, there would be clear justification for examining combinations of the IGF-IR antibodies with metformin or pegvisomant, as well as exploring in more detail the tyrosine kinase inhibitors that target both insulin and IGF-I signalling.

Early data raise the possibility that there could be differences in hematologic toxicity between the anti-IGF-IR antibodies, but the number of events described was overall low and comparative data are not yet available [38, 39]. Fully human IgG2 and IgG4 antibodies such as CP-751,871 and BIIB022 are poor activators of antibody mediated cytotoxicity and complement fixation [60]. If future applications involve combinations of IGF-IR targeting agents with aggressive chemotherapy, additive or synergistic complement-mediated hematologic toxicity may become an important issue. Of course, it is plausible that antibody-mediated cytotoxicity may contribute to anti-tumor activity in certain contexts and therefore represent an advantage, but there is also no definitive clinical data yet reported to support this possibility.

Pediatric trials were initiated with 5 of the anti-IGF-IR monoclonals (Table 2). Prolonged therapy could result in growth delay, but this would be of little clinical significance if the treatment was effective for life-threatening cancers, particularly as it is possible that growth recovery would occur following treatment discontinuation. Of note, no growth effects have yet been described in adolescents and young adults treated with anti-IGF-IR antibodies [38, 39].

Hypersensitivity reactions have been rare for anti-IGF-IR antibodies as a class. Experience with long-term (>1 year) treatment duration is limited, but might be expected to associate with changes in body composition reminiscent of the syndrome of growth hormone deficiency, including increased adiposity and decreased muscle mass. An additional particular concern would be adverse central nervous system effects associated with those drug candidates that accumulate in the brain, as IGF-I signaling has neuroprotective effects [80].

PHARMACOKINETICS

In keeping with current practice for other receptor-targeting agents in clinical use, clinical development of IGF-IR-targeting agents to date has been in the context of continuous exposure, with a goal of long-term continuous reduction in signaling. Target-mediated disposition has been demonstrated for some of the antibodies.[36, 37, 81] Of note, population pharmacokinetics conducted with CP-751,871 identified body weight as a significant covariate for plasma clearance whereas age, sex, and albumin or bilirubin concentrations showed no apparent effects [81]. These data validated the appropriateness of body weight-based dosing for at least this monoclonal antibody. As expected, chemotherapy agents do not appear to affect the pharmacokinetic properties of anti-IGF-IR monoclonals [33, 42, 45]. It is also noteworthy that the effective half-lives and dosage intervals of the anti-IGF-IR antibodies differ from each other. The half-life of CP-751,871 of approximately 20 days is longer than other monoclonal antibodies in clinical trials [7, 82]. A mean terminal half-life estimates of approximately 4 days has been reported for MK0646 [48]. Half-life estimates of 6 days [51], 7 to 11 days [32], and 9 days [30] have been reported respectively for R1507, AMG-479, and A12 (Table 1A). Differences in half-life could be explained in part by the antibody backbone, but also by selection for optimal pharmacological properties during preclinical lead product development [83].

PHARMACODYNAMICS

Downregulation of IGF-IR levels detected on circulating leukocytes by IGF-IR-targeting agents, as demonstrated for several of the antibodies (Table 1A), demonstrates that the target is influenced by the drug, at least in a surrogate tissue. Early results with CTCs suggest that CP-751,871 has similar effects on neoplastic cells [43]. More detailed pharmacodynamic endpoints on tumor biopsy specimens obtained pre and post-therapy were generated as part of a phase I study of MK0646 [48]. At weekly doses >5 mg/kg, decreased levels of IGF-IR, pAKT, pMAPK, and pS6 were observed. This result is in keeping with data from preclinical models where similar observations were made. Furthermore, this observation provides key evidence that despite the fact that many tumors have several receptor kinases upstream of pAKT and pMAPK, targeting the IGF-IR is sufficient to perturb downstream signaling.

The availability of biomarkers that may identify a subset of tumors of a defined histology likely to respond to a targeted therapy can be of key importance, as efficacy for the subset may be greatly superior to that of unselected patients, and lead to approval for an indication defined by the biomarker. In the case of CP-751,871, improvement in response rate to chemotherapy alone by adding the antibody in unselected patients is comparable to the improvement observed for addition of trastuzumab to chemotherapy (from 32 to 50%) in the subset of patients defined by HER2/neu overexpression. If future research were to show that survival endpoints are consistent with the response rate endpoint, then defining a molecular predictor of response would not be critical. Nevertheless, there is interest in defining subpopulations most likely to benefit from IGF-IR-targeting agents and early data raise the possibility that receptor and ligand levels...
may be independent predictors for response to anti-IGF-IR therapy. Receptor amplification was detected in some tumors [84–86], but does not appear to be a common event [87]. Sensitivity to targeting could correlate with receptor activation, but methods of measurement are not yet perfected. In NSCLC, differential IGF-IR expression was seen across histologies, with higher IGF-IR expressed in differentiated tumors, particularly squamous cell carcinoma [79, 88]. In colorectal cancer and other tumors, the role of KRAS and EGFR status and its relationship to the activity of IGF-IR inhibitors should be object of investigation. Similarly, more research is required to understand the potential effects of p53 and PTEN inactivation on anti-IGF-IR therapy [10, 27].

**Efficacy Testing**

Encouraging phase II results have been observed with the anti-IGF-IR antibody CP-751,871 in NSCLC as summarized above [45]. Phase I responses have been reported in Ewing’s sarcoma and other tumors (Table 1A) with the anti-IGF-IR monoclonals when given as single agents. However, it is premature to reach formal conclusions on efficacy at this time. The biological rationale for IGF-IR-targeting agents suggests the possibility of indication in a wide range of cancers with several different combination therapies for each of these indications. While this broad relevance increases enthusiasm for the target, it also presents challenges in planning and prioritization of trials. Sixteen tumor types and almost 30 combinations are listed in (Table 2). Certain indications are the subject of competing clinical trials by several drug candidates, but other hypotheses involving specific disease settings or drug combinations are being addressed at least initially in a non-overlapping fashion. Some potential indications for which pre-clinical rationale is available (including mesothelioma or renal cancer, for example) are not yet the subject of phase II clinical trials.

Most targeted agents in oncology are used in combinations, and many of these combinations were developed empirically. Instances of impressive single-agent activity by anti-IGF-I antibodies were seen in early studies. Although rare, these are important observations as they provide clear evidence of the relevance of the target and the efficacy of the targeting approaches. However, in common with many other novel targeting agents in oncology, most of the ongoing interest is not related to single-agent activity, but rather to clinical trials evaluating combinations with chemotherapy and/or other targeted agents.

A reality in the field is that there are multiple plausible hypotheses, often with interesting but non-definitive preclinical support, for a number of combinations for each of many disease sites. This represents a considerable challenge, as it would be impractical to evaluate all of these simultaneously in clinical trials. Preclinical work does suggest that combinations with cytotoxic agents, EGFR family inhibitors, hormonal steroids, mTOR inhibitors and radiation may translate to supra-additive effects and therefore deserve prioritization [10, 20, 60, 89–98].

There are important gaps in knowledge concerning the optimum way to combine cytotoxics with receptor kinase-targeting drugs in general, including those that target the IGF-IR. Questions concerning the pros and cons of co-administering as compared to sequencing receptor targeting agents with cytotoxics are difficult to address experimentally, and the optimum combination regimens have not been rigorously established even for approved agents. Possibilities that intermittent, pulsed, or sequenced regimens of receptor targeting in combination with cytotoxic agents may or may not have advantages over continuous exposure, are being explored.

**Conclusions**

IGF-IR-targeting agents are a fast emerging class of compound currently in development in Oncology. Based on the biology of this target and the encouraging results observed to date, extended clinical programs are ongoing for multiple drug candidates. Safety profiles have been favorable. Hyperglycemia appears to be common in this class of compounds, but it is usually manageable. Other adverse events require further characterization and may constitute a key differentiation factors. Pharmacokinetic properties vary extensively among the compounds in the class. Longer half-lives are, as expected, characteristic of the monoclonal antibodies. Both, safety and pharmacokinetics, may be key factors in the ability of these drug candidates to combine with standard of care regimens. Use of pharmacodynamic biomarkers has complemented well clinical development and there is compelling evidence, at least for some of the anti-IGF-IR antibodies, that receptor inhibition and ligand accumulation is achieved in the clinic. Further work is needed in this area in order to define appropriate predictive markers. Importantly, it is likely that IGF-IR activation may occur by different mechanisms at different tumors. It is clearly too early to reach firm conclusions regarding efficacy. However, impressive instances of major responses to single-agent anti-IGF-IR therapies in heavily pre-treated patients in phase I studies have been observed, particularly in patients with Ewing’s sarcoma. Current phase II evidence that co-administration of one of the anti-IGF-IR antibody enhances response rate to chemotherapy for lung cancer, have raised the interest level and have led to further clinical development. Challenges at this stage include the large number of potential indications, careful study design (optimum dose, regimen, schedules, and endpoint) and execution, and the need simultaneously to evaluate candidate biomarkers for resistance and sensitivity.

Two decades ago, there was speculation that it might be possible to design IGF-IR-targeting agents, and that they might have utility in cancer treatment. Recent efforts have shown that such drugs can indeed be synthesized, and the intense clinical trial and translational research activity presently underway will soon provide data concerning their efficacy in cancer treatment.

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**Conflict of Interest**

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