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IGF-1 Receptor Inhibitors in Clinical Trials—Early Lessons

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Abstract

The insulin-like growth factor pathway plays a major role in cancer cell proliferation, survival and resistance to anti-cancer therapies in many human malignancies, including breast cancer. As a key signaling component of IGF system, the IGF-1 receptor is the target of several investigational agents in clinical and pre-clinical development. This review will focus on the rationale for targeting the IGF-1 receptor and other components of the IGF-1 system. In addition, we will examine the role of IGF-1 signaling in resistance to clinically important breast cancer therapies, including cytotoxic chemotherapy, hormonal therapy and erbB targeted agents. We will also review the completed and ongoing clinical investigations with IGF-1 receptors inhibitors to date and the utility of these early data in designing future breast cancer studies with IGF-1 signaling inhibition strategies.

Keywords

Receptor; IGF Type I; IGF-1R inhibition; Monoclonal antibody; Tyrosine kinase inhibitors; Clinical trials-Phase I; Clinical trials-Phase II; Drug resistance; Receptor crosstalk

Therapeutic Potential of Targeting IGF Signaling

IGF system as a drug target

Targeting the IGF signaling pathway represents a promising strategy in the development of novel anti-cancer therapeutics. As a drug target, the IGF system has a number of key features that lends itself to being appealing. The expression of IGF-1R, the major signal transducing receptor of the pathway, appears to be necessary for malignant transformation in preclinical models [1]. Indeed, forced overexpression of IGF-1R increases the timing and frequency of tumor development in animal models [2,3]. Also, IGF-1 deficient mice have greatly reduced capacity to support tumor growth and metastasis [4].

An important feature of the IGF system is its near ubiquitous presence in most solid and hematologic malignancies, including expression of the IGF-1R [5]. In breast cancer in particular, the expression of IGF-1R may approach 90% [6,7]. Compared to HER2 + breast cancers, which represent 20–25% of all breast cancers, this represents a much broader potential group of patients that may be candidates for targeted therapy. In addition to IGF-1R, there are also several components of the system, including activating ligands IGF-1 and IGF-II, that may serve as ‘druggable’ targets, allowing various approaches to be evaluated for clinical activity. Whether or not, however, the IGF system, which is important for a number of normal physiologic processes, is dispensable in normal tissues to the extent that signaling can be attenuated to allow anti-tumor activity is less clear. In addition to the critical importance of IGF system signaling on growth and development, several key physiologic functions including

energy systems integration, glucose/insulin regulation, mammary development and lactation, bone health, neuronal maintenance [8,9]. While these processes are tightly regulated in normal tissues (described elsewhere in this issue), perturbed regulation of this system contributes to a growth and survival advantage of cancer cells. This review will focus on the translation of the importance of IGF system signaling in cancer to the clinical development of inhibitors and how early results from these studies may help design future investigations.

Proliferative signaling

The therapeutic potential of targeting the IGF signaling pathway is derived from the role it plays in the promotion of cell growth and inhibition of apoptosis. These oncogenic properties are mediated through the signal transduction crosstalk between two IGF-R-activated pathways: Ras/Raf/MEK/ERK/MAPK (Ras pathway) and PI3K/AKT (AKT pathway). The Ras and AKT pathways have been shown to upregulate key cell-cycle checkpoint proteins like cyclin D1 and CDK4, resulting in the phosphorylation of retinoblastoma protein, subsequent release of E2F transcription factor, and expression of downstream target genes like cyclin E [10–12]. In addition, IGF-1R inhibits the expression of a cell cycle suppressor gene p27^{kip1} [13] and thus, may promote cellular proliferation through more than one pathway. Through its antiproliferative activity, inhibitors of the IGF-1R system may provide a number of clinically important benefits. For instance, maintenance therapy, aimed at suppressing growth of residual, subclinical disease, could have a major impact if IGF system signaling is a critical factor, as suggested by prognostic data in patients with breast and ovarian cancer [14–17]. This strategy should also be more tolerable than typical cytotoxic regimens. Additionally, the antiproliferative effects could be useful in patients with metastatic disease, as an alternative to cytotoxic chemotherapy. Indeed, in the phase I dose escalation, single agent study of CP-751,871, the majority of solid tumor patients, all who progressed on cytotoxic chemotherapy, derived clinical benefit with relatively little adverse effects [18].

Pro-survival signaling

In addition to the mitogenic properties of IGF-1R signaling, activation of this system is a powerful pro-survival stimulus. Thus, dysregulation of the IGF system in tumor cells may be a key mechanism by which the balance of pro-survival and pro-apoptotic signaling shift in favor of survival. This pro-survival predisposition may also have a dramatic impact on the anti-tumor therapies that are used in clinical practice that rely on activating programmed cell death: cytotoxic chemotherapy, biological therapies, hormonal therapies and radiation therapy. From this perspective, blocking IGF system signaling has the potential for numerous clinically useful effects, including increasing the proportion, extent and duration of clinical responses from cytotoxic therapies when used in combination. For instance, in the neoadjuvant treatment of triple negative breast cancer, pathologic complete responses are an important prognostic marker for superior overall survival [19] and enhancement of the pathological complete response rate by combining chemotherapy with IGF-1R blockade could have a large impact on overall survival. Patients with tumors expressing IGF-1R are much less likely to obtain a clinical response to neoadjuvant therapy than non-expressors of IGF-1R [20]. Taken together, IGF-1R plays an important role in the promotion of cellular proliferation and survival, providing a growth advantage to IGF responsive cells.

The Role of IR in Targeting IGF-1R

Insulin receptor isoform A

Targeting the IGF-1R with a monoclonal antibody has been the most pursued method of blocking IGF system signaling employed in clinical investigations to date. This strategy is attractive, due to the fact that IGF-1R is the primary mitogenic receptor that is responsible for transducing IGF-I and/or IGF-II. However, the extent of mitogenic IGF signaling is not limited

to IGF-1R. Additional complexity related to targeting the IGF signaling pathway stems from the IR, the varying biological activity of its two isoforms, and their ability to form hybrid receptors with IGF-1R [21,22]. The classic form of the IR is IR isoform B (IR-B), which binds only insulin at physiologic concentrations leading to predominantly metabolic effects [23]. In contrast, as splice variant of IR is IR isoform A (IR-A), which can bind insulin and IGF-II at physiologic concentrations and has a predominantly proliferative effect [24].

IR-IGF-1R hybrids

Due to the high level of homology between IR and IGF-1R, heterodimers or so-called hybrid receptors (Hybrid-Rs) may also form [22]. Hybrid-Rs consist of one alpha/beta monomer of IR and one of IGF-1R. There are two types of Hybrid-Rs, Hybrid-RA and -RB, characterized by the heterodimerization of IGF-1R with either IR-A or -B, respectively. Although both hybrids are able to bind IGF-I and activate downstream targets to promote cellular proliferation, only Hybrid-RA is capable of binding IGF-II and insulin with any appreciable effect [22]. Proliferative signaling through IR-A or Hybrid-RA receptors may be important, particularly in tumors with a high IR-A to IGF-1R ratio [25]. Furthermore, hyper-insulinemic states may directly stimulate IR-A or Hybrid-RA and increase the bioavailability of IGF-1 [26–28].

Importance of hybrid receptors and IR-A

The precise role of Hybrid-Rs in the initiation and/or progression of human cancer is still unclear. An over-expression of Hybrid-Rs has been reported in thyroid, breast and colon cancer [21,29,30] and a likely mechanism by which it promotes cellular proliferation is mediated through the well-known mitogenic properties of IGF and IGF-1R. It is hypothesized that these Hybrid-Rs provide additional binding sites for the mitogenic stimulation of cells by IGF-I and -II. This may provide a growth advantage to a subset of cells overexpressing IR-A, IGF-1R, or both, and thus would have important implications in carcinogenesis.

Data from investigations in breast cancer tissues have found that IR expression is higher in breast tumors than normal breast tissue in as many as 80% [31]. Breast cancer patients that express high levels of IR have significantly worse disease free survival than patients that have even relatively moderate amounts of IR [32]. Additionally, many breast cancer tumors bind IGF-II with higher affinity than insulin, suggesting that IR-A is the predominant isoform activating cellular proliferation through Hybrid-RA [33].

Potential Targets for Inhibiting IGF Signaling

Receptor–ligand interaction

In evaluating the possible clinically feasible strategies to employ to block IGF system signaling as an anti-cancer therapeutic, there are three main strategies (Fig. 1): receptor blockade (A), kinase inhibition (B) and ligand sequestration (C). Receptor blockade with the use of monoclonal antibody therapies against the IGF-1R have been the most clinically investigated approach to date. In general, these therapies effectively block the binding of IGF-1 and IGF-II to the IGF-1R and down regulate the expression of IGF-1R and Hybrid-R. As Hybrid receptor heterotetramers are linked covalently through disulfide bonds, the IGF-1R/IR receptor pairs are downregulated as functional unit [25]. However, it should be noted that the effect of ability of the various IGF-1R monoclonal antibodies undergoing clinical development have not all demonstrated in a rigorous fashion the ability to block both IGF-1 and IGF-II binding and downregulate both IGF-1R homoreceptor pairs and hybrid receptor pairs. As the ratio of Hybrid:IGF-1R may be an important predictor of sensitivity to tumors to IGF system blockade, this may become a critical point [25]. As the epitope recognition for these IGF-1R monoclonal antibody antagonists are very specific, there is, in theory, no binding of the insulin receptor. This is important for concerns of insulin resistance and hyperglycemia incited by targeting the

IR-B receptor. However, monoclonal antibodies targeting the IGF-1R will not block activation of IR-A, which is a potential liability if indeed IR-A is an important mechanism of IGF signaling that can overcome IGF-1R blockade.

Receptor tyrosine kinase activity

Tyrosine kinase inhibition is another strategy being employed with several agents in clinical and preclinical development. In general, these therapies will indiscriminately inhibit the kinase domains of all IGF system receptors, as their primary sequences share 84% identity in the kinase domain with near absolute conservation in the ATP binding pocket [34]. The exception to this is the NVP-AEW541 and NVP-ADW742, which has 15–30 fold increased potency for IGF-1R kinase inhibition compared to IR kinase inhibition in cellular assays [35,36]. Additionally, the cyclolignan picropodophyllin (PPP) inhibits the IGF-1R tyrosine kinase but not IR [37]. Ironically, while the pharmaceutical industry has gone at great lengths to identify compounds that do not inhibit the IR tyrosine kinases, the potential benefit of tyrosine kinase inhibitors over antibody therapies targeting IGF-1R may be in their ability to block IR-A. Of course, this comes at the expense of blocking IR-B, which may represent a significant metabolic liability [38]. Though, it should be pointed out that hyperglycemia and evidence of insulin resistance, perhaps through a growth hormone-related mechanism, are observed clinically with the IGF-1R monoclonal antibody therapies [18].

Ligand bioavailability

Ligand sequestration through the use of monoclonal antibodies against ligand(s) or recombinant IGF-BPs is a third potential approach. Such therapies would have the potential benefits of the first two therapeutic categories: blockade of both IR-A, IGF-1R and Hybrid-R activation, without the metabolic liability of blocking IR-B. However, if insulin was able to stimulate mitogenic signaling in IR-A containing receptors, a potential mechanism for overcoming this therapy would also be plausible. This strategy has precedence clinically as evidenced by the FDA approval of the monoclonal antibody therapy, bevacizumab. Bevacizumab is an antibody antagonist of the VEGF ligand and is currently approved in the United States for use in colorectal, lung and breast cancers [39]. There are as yet no disclosed therapies in development that are currently employing this approach.

Resistance to Cancer Therapeutics

Cytotoxic chemotherapy

Perhaps the greatest impact IGF system signaling inhibition can make in the treatment of human cancers is the reversal or prevention of resistance to clinically useful anti-cancer therapies. Resistance to chemotherapy is a common occurrence among cancer patients. Malignant cells within a tumor mass are markedly heterogeneous in terms of genetic or chromosomal abnormalities. When tumors are exposed to cytotoxic chemotherapy, a broadly accepted theory is that susceptible cells die, while a subset of resistant cells persist and will continue to proliferate. Additionally, malignant cells may also acquire resistance after the initiation of treatment through the induction of other genes, which promote proliferation and inhibit apoptosis. The IGF system is an example and has been implicated in chemotherapy resistance. For instance, HBL100 human breast cancer cells become resistant to 5-fluorouracil, methotrexate, and camptothecin when treated with IGF-1 [40]. Similarly, IGF-1 administration rescues MCF-7 cells from doxorubicin and paclitaxel treatment [41]. In both studies, IGF provided a growth advantage by either promoting cell proliferation or inhibiting apoptosis. Alternatively, IGF may affect the response to chemotherapy by altering the efficacy of the drug. In hepatocellular carcinoma cells for example, IGF-1 upregulates the expression of glutathione transferase, thus quenching the redox-cycling potential of doxorubicin [42]. Ewing's sarcoma, through the t [11,22] translocation may take advantage autocrine and

paracrine production of IGF1 to activate IGF-1R to overcome chemotherapy sensitivity [43]. Indeed, Ewing's sarcoma tumor growth in vivo results in significant growth inhibition with vincristine and the IGF-1R inhibitor NVP-AEW541, compared to the single agents [44]. Modulation of IGF has also been shown to enhance the antitumor activity of doxorubicin [44–47], supporting the role for combination chemotherapy in the treatment of Ewing's sarcoma. Several Phase II studies (Table 1, bold) are being planned or are ongoing to test the hypothesis of whether IGF-1R inhibition will enhance the activity of cytotoxic chemotherapy in breast cancer. For instance, a randomized phase II study investigating docetaxel +/- the IGF-1R monoclonal antibody CP-751,871 will be testing this hypothesis in patients with metastatic breast cancer.

Hormonal therapy

Estrogen signaling is a major pathway by which breast cancers grow and survive, which has been taken advantage of clinically. An estimated 65–75% of breast cancers are ER positive [48]. Selective estrogen receptor modulators like tamoxifen, aromatase inhibitors like letrozole, anastrozole, and exemestane, and selective estrogen receptor down-regulators like fulvestrant have all been designed to inhibit the biological effects of ER signaling. Despite the discovery of targeted therapies for the treatment of breast cancer, drug resistance continues to be problematic [49,50] and may be partially explained by crosstalk between the ER and the IGF systems. Growth of HBL 100 cells is inhibited by tamoxifen but concomitant treatment with IGF-1 increases survival [40]. One mechanism by which IGF-1-treated breast cancer cells escape tamoxifen-induced apoptosis may be through the IGF-mediated activation of AKT and subsequent phosphorylation of ER at serine-167, which leads to the ligand-independent activation of ER [51]. Moreover, if the IGF system is inhibited by an anti-IGF-1R antibody, like alpha-IR-3 [52], or IGF-1R tyrosine kinase inhibitor, like AG1024 [53]. Growth of tamoxifen-resistant MCF-7 cells declines. Additionally, IGF-1R inhibition or knockdown significantly inhibits estrogen-stimulated breast cancer growth. Indeed, in estrogen receptor positive breast cancer xenografts, the IGF-1R monoclonal antibody, CP-751,871 enhances the anti-tumor activity of tamoxifen in vivo [54]. The mechanism by which IGF-1R promotes tamoxifen resistance may be through a direct interaction between IGF-1R and ER [55]. Further discussions about the importance of IGF and estrogen interdependence are described elsewhere in this issue. Whether IGF system inhibition can overcome or prevent resistance to IGF-1R inhibition is being tested in phase II clinical trials (Table 1, bold).

HER/erbB receptor therapy

Data has also accumulated to suggest that a bi-directional crosstalk pathways between the erbB family of receptors and IGF-1R exists and may be responsible to resistance to targeting these receptor pathways. In SKBR3, HER2 positive breast cancer cell line, sensitivity to trastuzumab can be overcome by expression of IGF-1R [56]. Similarly, SKBR3 breast cancer cells exhibited enhanced cytotoxic effects with trastuzumab when cultured in combination with an anti-IGF1 receptor antibody [57]. In addition, both activated EGFR and HER2 are sufficient for conferring resistance to the dual kinase IGF-1R/IR inhibitor, BMS-536924 [58]. These data suggest that resistance to both the IGF-1R and erbB receptor pathways may occur in a reciprocating fashion, suggesting simultaneous inhibition of HER receptors and IGF system receptors. This concept is being investigated in a phase II clinical trial in HER2 positive breast cancer patients comparing the efficacy of lapatinib and capecitabine +/- the IGF-1R monoclonal antibody IMC-A12 (Table 1). Further discussions regarding crosstalk between IGF and erbB signaling is discussed elsewhere in this issue.

Clinical Investigations Targeting IGF-1R

Monoclonal antibody therapies

To date, the vast majority of clinical trials have investigated new therapies that target the extracellular domains of the IGF-R. The agent most intensively studied and reported thus far has been CP-751,871. The first in human dose-escalation clinical trial enrolled 47 patients with multiple myeloma (Table 1) [59]. If suboptimal response was seen, patients were also given salvage dexamethasone or rapamycin at the discretion of the investigator. While no objective responses were seen with single agent CP-751,871, 28 patients had stable disease and nine had objective response with dexamethasone (six PR, three MR). Although there was no dose-limiting toxicity, adverse events included anemia and elevated AST among the most common. Nausea, diarrhea, and rash were less frequently reported. Interestingly, only one event of hyperglycemia occurred with CP-751,871 alone (grade 3) and two events in combination with dexamethasone. In the phase I single agent study of CP-751,871 in solid tumors, similar adverse events were observed with a few exceptions [18]. The most striking may be that hyperglycemia was the most frequent adverse event, though all but one event was grade 1. Other adverse events seen in this phase I, not seen in the first in human study was anorexia, fatigue and hyperuricemia. At the maximal feasible dose, ten of 15 patients experienced stability of their disease and three of these patients had long term (+10 months) stability. In a patient on study for 500+ days, incremental increases in insulin were observed, with only mild hyperglycemia until insulin increased to over 100 μ IU/ml).

A phase I/II clinical trial comparing carboplatin and paclitaxel with and without CP-751,871 in stage IIIB and IV NSCLCA has been reported and recently updated at the ASCO Annual Meeting 2008 [60]. The response rate in the study was 54% (52/97) with the combination of CP-751,871 and chemotherapy compared to 41% (22/53) for chemotherapy alone. Furthermore, subset analyses revealed that patients with squamous cell carcinoma histologies had a response rate of 78%. There was also additional evidence of single agent activity with CP-751,871 in patients with squamous cell histology. These findings were partially explained by the higher expression of IGF-1R in squamous-subtypes of NSCLCA compared to adenocarcinomas or NOS [61]. Three phase III study in NSCLA are now planned, including a randomized study of paclitaxel and carboplatin +/- CP-751,871 as front line therapy in non-adenocarcinomas, erlotinib + CP-751,871 in recurrent non-adenocarcinomas and a frontline study of gemcitabine and cisplatin +/- CP-751,871 in all non-NOS histologies.

Phase I studies of other monoclonal antibody therapies have also recently been reported. The results of a Phase I dose-escalation phase I study of IMC-A12 have revealed the adverse events included hyperglycemia, which was dose limiting. Additional adverse events were mild and included pruritis, rash and skins changes, stool changes, anemia and an infusion reaction. Of the 15 patients on study, one patient had a great than 25% reduction in PSA and four had stable disease (two greater than 9 months) [62]. The phase I results of AMG-479 were also recently reported. Unlike most of the other monoclonal antibodies described, the dose limiting toxicity for this agent was thrombocytopenia, suggesting the mechanism of action for this agent and MK0646, which also has thrombocytopenia as a grade 4 toxicity, may be unique. Additional adverse events included arthralgia, diarrhea, transaminitis, and hyperglycemia. Auto-antibody production and an infusion reaction were also observed with this therapy. Of the 33 patients enrolled on this study, three objective responses and five stable responses were observed. One of these objective responses included a dramatic complete response in a patient with Ewing's Sarcoma, supporting the pre-clinical data demonstrating the importance of IGF system in this tumor type [43]. Additional clinical investigations in sarcomas were recently reported, demonstrating a partial response and six stable responses in 22 patients receiving CP-751,871 [63]. The additional two responses seen in the phase I with AMG-479 were in neuroendocrine tumors, which have stimulated interest in further investigating this tumor type. The tolerability

of AMG-479 in combination with chemotherapy and biological therapy has also been reported [64]. The dose limiting toxicity of the combination of gemcitabine and AMG-479 is neutropenia, which was seen in half of the patients receiving treatment. The dose limiting toxicity of the combination of AMG-479 and panitumumab was hyperglycemia. Evidence of activity was suggested in these combinations with one partial response and five stable responses in the panitumumab arm (10 pts) and four patients with stable disease in the gemcitabine arm (8 pts).

The phase I study of two treatment schedules of MK-0646 have been reported [65,66]. The dose limiting toxicities for this agent are tumor pain and purpura, which were observed on the weekly schedule. Interestingly, hyperglycemia was only observed on the weekly schedule. Additional adverse events on the weekly schedule include chills, nausea, rash, asthenia and pyrexia. An infusion reaction was also observed on this schedule. On the every 2-week schedule the adverse events included thrombocytopenia, GI bleeding, pneumonitis, transaminitis, fatigue, vomiting, nausea, constipation, diarrhea, weight loss, abdominal pain. Stable disease was seen in patients on both single agent regimens, with two patients on the every 2-week schedule having stability of disease for over 1 year.

The single agent phase I study of R1507 reported similar adverse events to many of the other monoclonal antibody therapies, including fatigue, rash, fever, arthralgia, cough, diarrhea, and pain [67]. The lack of hyperglycemia is notable with this particular agent. Of the 26 patients treated on study, 11 had stable disease for greater than 15 weeks. The phase I studies of the humanized monoclonal antibody AVE-1642 in both solid tumors and multiple myeloma have been reported separately [68,69]. The most common adverse events observed are hyperglycemia, hypersensitivity reactions, asthenia, anemia, nail disorders, paresthesia, and pruritis. In the 14 solid patients treated, a reduction in the burden of metastatic nodules in a patient with breast cancer was observed. Additionally, four patients experience stability of their disease at four cycles of therapy. Of the 14 patients with refractory multiple myeloma treated, one patient experience benefit by decreased bone pain and improved proteinuria.

Small molecule inhibitors

To date, clinical data is available for only one non-monoclonal antibody therapy: INSM18 [70]. INSM18 is a small molecule inhibitor of the IGF-1R that also has activity against the HER2 receptor tyrosine kinase. The mechanism of action of this agent is unclear. This therapy appeared to be well tolerated among the 15 prostate cancer patients that received this treatment with transaminitis being the only reported adverse event. Evidence of activity was demonstrated with one patient that had a greater than 50% PSA decline. An additional patient had a reduction in PSA doubling time. We will anxiously await the results of additional small molecules including tyrosine kinase inhibitors and agents with novel mechanisms of actions (Table 2).

Effect on biomarkers

As many tumor types appear to rely of the IGF system for growth, proliferation and resistance to anti-tumor therapies, a major focus of clinical research in biomarker identification. The clinical trials to date have identified that IGF-1 and IGFBP3 serum levels increase in response to IGF-1R targeted therapy. In addition, IGF-1R expression in tumor tissue, circulating tumor cells and peripheral blood mononuclear cells have been described [65,66,71,72]. While these changes demonstrated a pharmacodynamic effect of the individual agents, it is unclear whether these changes will be helpful in predicting which patient are more or less likely to have tumors that dependent on IGF signaling. Several of these early clinical trial also conducted imaging studies to investigate the pharmacodynamic effects as measured by FDG-PET response. For example, in patients on the phase I study of AMG-479, the majority of the patients had

radiological responses by PET imaging [72]. Three metabolic responses following treatment with MK-0646 were also described [66]. At this early stage of development, there was no clear correlation of these radiological responses and ultimate clinical outcome. The utility of such imaging studies for obtaining clinical information beyond pharmacodynamic assessments is unclear.

Future of Investigations Targeting IGF-1R in Breast Cancer

Tolerability

The lessons learned to date with therapies targeting the IGF system may be of use as we continue to go forward conducting clinical investigations in breast cancer. As a whole, the novel therapies tested to date that target the IGF pathway have been very well tolerated, with most adverse events experienced mild and self-limiting. It should be noted however that there does appear to be small, but discernable differences between the IGF-1R targeted monoclonal antibodies. Thrombocytopenia—a dose limiting toxicity for AMG479 and observed with MK0646 and CP-751,871 (multiple myeloma patients only), had not been observed in the single agent phase I studies of the other therapies reported (Table 1). The mechanism of this toxicity is unclear and will need further evaluation if future studies, particularly in combination with cytotoxic chemotherapy. Another interesting adverse event that appears to differ among the agents in development is hyperglycemia. While this has not been described for R1507, hyperglycemia occurs in varying degrees with the other monoclonal antibodies reported. The mechanism of the hyperglycemic effects of IGF-1R targeted monoclonal antibodies is unclear, though it is not likely due to non-specific binding of the insulin receptor. A potential mechanism involves the neoglycogenic effects of human growth hormone, which appears to be upregulated in response to IGF-1R inhibition in some patients [72]. Additionally, hyperglycemia may result from inhibiting the hypoglycemic effects of IGF-1 through blockade of its receptor. The majority of hyperglycemic episodes have been mild and reversible. Anecdotes of oral hypoglycemics and insulin use have been presented, but data regarding the efficacy and necessity is lacking.

Maximizing the potential of IGF system blockade

Full dose chemotherapy, biological and hormonal therapy has been tolerated reasonably well in combination with full dose IGF-1R inhibitors. This point may be particularly important, as it appears, despite the anecdotal response with single agent therapy, combination therapies will likely be necessary to extract the full benefits of IGF system inhibition. Thus, in breast cancer, the greatest gains to be realized with therapy targeting the IGF system are combinations with hormonal, erbB-targeted agents and cytotoxic chemotherapy. At this time, little data is available about the clinical activity of TKI inhibitors of the IGF-1R +/- IR. The hope is that these agents will also be tolerated as well as the monoclonal antibody therapies, but this remains to be seen. Furthermore, it will be necessary to further define the role of the insulin receptor in breast cancer. As noted above, IR expression is very high in breast cancer samples that have been evaluated to date and the role of IR-A isoform in breast cancer could potentially be more important in the setting of hyperglycemia. Thus, through correlative studies, it will be important to investigate the role of IR-A isoforms in predicting sensitivity to IGF-1R targeting monoclonal antibodies and TKIs that target the IR have a therapeutic advantage that outweighs the metabolic liability.

Due to the complexity of the IGF system signaling pathway, a reasonable assumption would be that the relative expression of IGF-1R, outside of its absence, is not predictive of response to therapies targeting IGF-1R. Nonetheless, a compelling argument has been made by Gualberto et al. that relative expression, which is 'high' in squamous cell carcinomas of the lung, is potentially important and explains the high response rate of paclitaxel, carboplatin and

CP-751,871 is this sub-population [72]. While these findings must be validated, it will be important to gather this information in breast cancer patients treated with IGF-1R inhibitor therapies to be able to establish if this correlation also holds true as investigations combined with hormonal therapies, biological therapies and chemotherapy moves forward.

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Abbreviations

ACC	adrenocortical carcinoma
ALL	acute lymphocytic leukemia
AST	aspartate aminotransferase
ASCO	American Society of Clinical Oncology
CDK4	cyclin-dependent kinase 4
CML	chronic myelogenous leukemia
CR	complete response
CRC	colorectal cancer
DLT	dose limiting toxicity
ER	estrogen receptor
FDG-PET	14fluoro deoxyglucose-positron emission tomography
FIH	first in human
GGT	gamma-glutamyltransferase
HER2	human epidermal growth factors receptor 2
H&N	

	head and neck cancer
HRPC	hormone refractory prostate cancer
IGFBP	insulin-like growth factor binding protein
IGF-1R	insulin-like growth factor-1 receptor
IR	insulin receptor
mab	monoclonal antibody
MFD	maximal feasible dose
MFH	malignant fibrous histiocytoma
MR	minor response
NHL	non-Hodgkin's lymphoma
NOS	not otherwise specified
NSCLCA	non-small cell lung cancer
PI3K	phosphoinositidyl-3 kinase
PNET	peripheral neuroendocrine tumor
PPP	picropodophyllin
PR	partial response
PSA	prostate specific antigen
RR	response rate
SD	stable disease
TKI	tyrosine kinase inhibitor

VEGF

vascular endothelial growth factor

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Figure 1. Model of IGF system inhibition strategies. **a** Monoclonal antibody strategy; **b** tyrosine kinase inhibitor strategy; **c** ligand sequestration strategy.

Table 1
Clinical data for IGF system targeted therapy (breast cancer studies in bold).

Agent description, company				
Agent	Phase	Tumor Type	Adverse Events (gr3/4/# or %)	Response Ref.
CP-751,871	Fully human, monoclonal antibody (IgG2), Pfizer I/II	Multiple myeloma	Diarrhea, anemia (2.1%/-), thrombocytopenia, increase AST, hyperglycemia (2.1%/-), nausea, rash	47 patients were treated with single agent CP and 27 in combination with dexamethasone. 28 had SD with single agent. 9 of the 27 combo pts had a response [59,73]
	I	Solid tumors/ACC, sarcoma expansion cohorts	Hyperglycemia, anorexia, elevated GGT/AST (1/-), nausea, fatigue (1/-), arthralgia (1/-), hyperuricemia (-/1), DVT (1/-)	24 patients treated. Three long term SD (> 10 months). At MFD, 7 of 12 had SD. -In Sarcoma cohort 1/22 PR, 6/22 SD [18]
	I	Breast, neoadjuvant		Pending
	I/II	Sarcoma, Ewing's family		Pending
	II	CRC		Pending
Paclitaxel/carboplatin +/- CP (TC vs TCI)	Ib/II	NSCLCA	Hyperglycemia (15%/5%), fatigue (10%, -), neutropenia (18%, 12%), anorexia (7%/-), thrombocytopenia (6%/1%), neuropathy (5%/1%)	97 patients treated with TCI and 53 patients TC. Response rate: TCI-54%; TC-41%. Subset of squamous cell carcinoma on TCI-78% RR (18/23) [39]
+Sunitinib	I	Solid tumors		Pending
+Gemcitabine/cisplatin	I	NSCLCA—non-adeno		Pending
+PF-299804	I	Solid tumors/NSCLCA cohort		Pending
+Paclitaxel/carboplatin/erlotinib	I/II	Expansion cohort, NSCLCA		Pending
+Docetaxel	II	Breast		Pending
+Docetaxel/prednisone	II	Prostate		Pending
+Exemestane	II	Breast		Pending
Paclitaxel/carboplatin +/- CP	III	NSCLCA—non-adeno		Pending
Erlotinib +/- CP	III	NSCLCA—non-adeno		Pending
IMC-A12	Fully human, monoclonal antibody (IgG1), ImClone I	Solid Tumor	Hyperglycemia-DLT (#?/-), pruritis, rash, discolored feces, anemia, psoriasis, infusion reaction.	15 patients treated. 4/11 had SD. 2 had SD >9 months. 1 had >25% PSA reduction. [62]

Agent description, company				
Agent	Phase	Tumor Type	Adverse Events (gr3/4/# or %)	Response Ref.
	II	HRPC		Pending
	II	Sarcoma, Ewing's, PNET		Pending
	II	Hepatocellular		Pending
+Cetuximab	II	CRC, H&N		Pending
+Tensirolimus	II	Solid tumors, breast		Pending
+Adriamycin	II	Sarcoma, Soft tissue, MFH		Pending
+/- Antiestrogens	II	Breast		Pending
Lapatinib/capecitabine +/-A12	II	Breast		Pending
Gemcitabine/erlotinib +/- A12	II	Pancreatic		Pending
Mitoxantrone/prednisone/A12 or 1121B (VEGFR2 mab)	II	Prostate		Pending
AMG-479	Fully human, monoclonal antibody (IgG1), Amgen			
	I	Solid tumors, NHL	Thrombocytopenia-DLT (9%/ 3%), arthralgia (3%/-), diarrhea (3%/-), transaminitis (2%/-), hyperglycemia, autoantibody production, infusion reaction	33 patients treated. 1 CR (Ewing's sarcoma), 1 PR and 1 MR (both neuroendocrine), 5 SD. 1 mixed response (breast). 17/26 patients had evidence of decreased metabolic activity by PET [72]
	II	Sarcoma, Ewing's		Pending
	II	Ovarian, platinum sensitive		Pending
+Gemcitabine (G) or panitumumab (P)	Ib	Solid tumors	+ P: hyperglycemia-DLT (10%), rash (20%), hypomagnesemia (30%), anemia, nausea, vomiting, anorexia, fatigue, diarrhea, dizziness, thrombocytopenia. +G: neutropenia-DLT (50%), thrombocytopenia, fatigue, anemia, nausea, vomiting, anorexia, rash, hypomagnesemia	18 patients treated (10 with P); 1 PR in P arm (Colon). 9/18 SD (5 in P arm, 4 in G arm) [64]
+gemcitabine	I/II	Pancreatic		Pending
+exemestane or fulvestrant	II	Breast		Pending
paclitaxel/carboplatin +/- AMG	II	Ovarian		Pending
MK-0646	Humanized monoclonal antibody, Merck			

Agent description, company				
Agent	Phase	Tumor Type	Adverse Events (gr3/4/# or %)	Response Ref.
	I	Solid tumors, multiple myeloma, breast	Q2w schedule: Thrombocytopenia (−/1), GI bleeding (1/−), pneumonitis (1/−), transaminitis (1/−), fatigue, vomiting, nausea, constipation, diarrhea, weight loss, abdominal pain. QW schedule: Tumor pain-DLT (2%/−), purpura-DLT (2%/−), hyperglycemia (6%/−), chills (4%/−), nausea (2%/−), rash (2%/−), asthenia (2%/−), pyrexia (2%/−), infusion reaction	Q2w: 36 patients, 5 pts with SD>4 months, 2 greater than 1 year. [65,66] QW: 53 patients. Decrease IGF-1R expression and signaling (e.g. AKT) identified in paired biopsies, 3 PEI/metabolic responses. One mixed radiologic response (Ewing's sarcoma), 3 patients SD>3 months
+MK8669 (deforolimus) +erlotinib +Cetuximab/irinotecan R1507	II	Neuroendocrine		Pending
	I	Solid tumors		Pending
	I/II	NSCLCA		Pending
	II	CRC		Pending
	Fully human, monoclonal antibody (IgG1), Roche			
	I	Solid tumors—adult, children	Adults: Infection, fatigue, rash, fever, arthralgia, cough, diarrhea, abdominal and back pain	26 patients, 11 SD>15 weeks. [67]
	II	Sarcomas		Pending
	II	NSCLCA		Pending
+Erlotinib AVE-1642	Humanized monoclonal antibody, Sanofi-Aventis			
	I	Solid tumors (combined with docetaxel after cycle 1), multiple myeloma	Hyperglycemia, hypersensitivity reactions, asthenia, anemia, nail disorders, paresthesia, pruritis	14 patients (solid tumors), 1 reduction in skin nodules (breast), 4 SD confirmed at cycle 4 -14 patients (multiple myeloma). 1 decrease bone pain/proteinuria [68,69]
OSI-906 +/-Erlotinib SCH-717454	Tyrosine kinase inhibitor-reversible ATP competitive inhibitor, OSI			
	I	Solid tumors—continuous, intermittent dosing		Pending
	I	Solid tumors		Pending
Fully human, monoclonal antibody, Schering-Plough				

Agent	Agent description, company			
	Phase	Tumor Type	Adverse Events (gr3/4/# or %)	Response
Chemo +/- SCH XL-228	II	Sarcomas, Osteosarcoma, Ewing's		Pending
	II	Recurrent CRC		Pending
	Tyrosine kinase inhibitor of IGF-1R, abl and src, Exelixis			
INSM-18 (NDGA)	I	CML/ALL, Solid tumors, lymphoma, multiple myeloma		Pending
	Tyrosine kinase inhibitor of IGF-1R, HER2/neu, Insmed			
	I	Prostate cancer	Transaminitis	15 patients. 1 had >50% PSA decline. 1 had reduction in PSA doubling time. [70]
BIIB022	Fully human, monoclonal antibody (IgG4.P), Biogen Idec			
	I	Solid tumors		Pending
BMS-754807	Tyrosine kinase inhibitor-reversible ATP competitive inhibitor, Bristol-Myers Squibb			
	I/IIH	Solid tumors		Pending

Table 2

Anti-IGF receptor therapies in pre-clinical development.

Agent	Description	Company	Status/Notes	Ref
BVP.51004	Tyrosine kinase inhibitor, non-ATP competitive	Biovitrium	Cyclolignan PPP. Downregulated IGF-1R, without insulin receptor inhibition. Development status not disclosed.	[63]
rhIGFBP3	IGF binding protein	Insmed	Awaiting clinical investigations	
NVP-ADW742	Tyrosine kinase inhibitor, reversible ATP competitive	Novartis	No clinical investigations currently ongoing.	[36]
NVP-AEW541	Tyrosine kinase inhibitor, reversible ATP competitive	Novartis	No clinical investigations currently ongoing.	[35]
BMS-536924	Tyrosine kinase inhibitor, reversible ATP competitive	Bristol-Myers Squibb	IGF-1R inhibitor BMS-754807 currently undergoing phase I investigations	[2,74]
BMS-554417	Tyrosine kinase inhibitor, reversible ATP competitive	Bristol-Myers Squibb	IGF-1R inhibitor BMS-754807 currently undergoing phase I investigations	[38]
ANT-429	Pharmacophore	Antrya	Preclinical investigations	
ATL-1101	Antisense oligonucleotides	Asntisense Therapeutics	Beginning clinical investigations for dermatologic conditions and cancer.	
Tyrphostin AG1024	Tyrosine kinase inhibitor	—	Not in clinical development	[75]
α -IR3	Mouse monoclonal antibody	—	Not in clinical development	[76]