Targeting insulin and insulin-like growth factor signalling in oncology

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The family of insulin/insulin-like growth factor (IGF) receptors regulates many crucial aspects of cellular and whole-organism physiology. Evidence that targeting these receptors may be useful in cancer treatment was first recognized more than 20 years ago. Drug development began relatively recently, justified both by laboratory studies and by circumstantial clinical evidence that this receptor family is involved in the molecular pathophysiology of neoplasia. Pharmacologic targeting strategies include both small molecule receptor tyrosine kinase inhibitors and anti-receptor antibodies. More than a dozen drug candidates have been studied preclinically, and several are now being evaluated in clinical trials. These trials have provided evidence suggesting safety of the anti-IGF-I receptor antibodies, a few anecdotes of impressive single-agent activity, and early evidence for a significant improvement in response rate to chemotherapy for lung cancer with co-administration of an anti-IGF-I receptor antibody. This experience has justified expanded clinical trials programs to evaluate several of the IGF-I receptor targeting agents in many different areas of clinical need. Most of these trials will involve assessing activity of rational combinations of IGF-I receptor targeting agents with currently approved drugs.

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Recognition of the target: history

The fact that insulin is mitogenic for neoplastic cells in culture was known before the development of the paradigm that targeting peptide growth factor receptors represents a useful strategy for cancer drug development. A representative study, one from the laboratory of Marc Lippman published in 1976 [1] showed clear evidence of increasing thymidine uptake by breast cancer cells exposed to increasing concentrations of insulin. Even earlier *in vivo* work (for example [2]), although crude by current standards, suggested that tumor growth is impaired in insulin deficient as compared with intact hosts. These provocative results, however, were not pursued with regards to their potential clinical relevance. To understand why, it is necessary to recognize that the general notion of targeting peptide growth factor receptors was not developed at the time. Even if it had existed as a theoretical concept, there were no practical pharmacological strategies available, as there were no examples of drugs that inhibited receptor tyrosine kinase activity, and the use of anti-receptor antibodies as drugs had not been demonstrated.

Insulin-like growth factors (IGFs) and their receptors were well characterized in the 1980s, and the first report of the presence of IGF-I receptors on primary human neoplastic tissue was published in 1987 [3•]. This fact, together with tissue culture data showing that IGF-I stimulated proliferation of cultured neoplastic cells (for example [4]), led us to speculate that the paradigm of therapeutic exploitation of hormonal dependence of neoplasia may be extended from gonadal steroids to peptide growth factors [3•].

Only one year later, Arteaga *et al.* demonstrated inhibition of *in vivo* growth of breast cancer xenografts by an anti-IGF-IR antibody [5••]. Although impressive, this result was not generally regarded as a clue for drug development, as the concept of targeting peptide receptors was still in its infancy. Around this time, important progress was being made in characterizing the roles of the epidermal growth factor receptor family in neoplasia, and this line of research eventually led to the development of trastuzumab, an anti-HER2/neu antibody [6]. This not only represented a major therapeutic advance, but also provided a precedent that legitimized the concept that in general, receptor tyrosine kinases deserved attention in the search for new therapeutic approaches in oncology.

Even at this point, neither the insulin receptor nor the IGF-I receptor were prioritized as molecular targets. However, by the late 1990s, general interest in these receptors in the context of neoplasia increased because of epidemiologic evidence for a relationship between circulating levels of IGF-I and cancer risk (for example [7•]), and also because of increasing laboratory evidence (for example [8–10], reviewed in [11,12]) for a role for IGF-I receptors in neoplastic growth. In addition, attention was given to the considerable amount of circumstantial evidence linking insulin and IGF physiology to neoplasia. Examples included positive relationships between circulating levels

of c-peptide (an insulin surrogate) and prostate cancer mortality [13], between circulating IGF-I levels and mammographic breast density (a strong breast cancer risk factor) [14], between diet-induced hyperinsulinemia and *in vivo* tumor growth [15], and between rate of acceleration of growth in adolescence (thought to be IGF-I-mediated) and cancer risk [16]. This finally led to drug development programs, and then to many reports of preclinical antineoplastic activity of drug candidates (reviewed below).

In recent months, early data from phase II clinical trials of some of these agents have been reported (for example [17,18,19••]). Results have been encouraging enough to justify greatly expanded clinical trial programs, including large phase III studies.

Background biology concerning the target

General background information regarding insulin receptor and insulin-like growth I receptor structure and signalling have been the subject of many reviews (for example [20,21]), and these topics will not be further addressed here in detail. However, a few specific points deserve mention.

Evolutionary aspects

Insulin is conventionally described in medical text books as a hormone that plays key roles in the regulation of carbohydrate metabolism, while the insulin-like growth factors are described as important regulators of pre and post natal growth. In fact, an insulin-like signal transduction system is present in simple organisms such as *C. elegans*, where it regulates fundamental cellular processes such as longevity and energy metabolism [22]. The emergence of distinct insulin and IGF-I receptors and the use of these signalling systems to regulate blood glucose concentration is a relatively recent evolutionary development.

The signalling pathways downstream of the insulin and IGF-I receptors are similar. Different cell types may express the insulin receptor and the IGF-I receptor at different levels, resulting predominantly in sensitivity to IGFs on the one hand or to insulin on the other. For example, hepatocytes express more insulin receptors than IGF-I receptors, and this is consistent with the fact that hepatocyte glycogen metabolism is more responsive to insulin than to IGFs. On the contrary, chondrocytes in epiphyseal growth plates express more IGF-I receptors than insulin receptors, and are more responsive to IGFs than to insulin. All this is physiologically appropriate, because in higher organisms there is a need to regulate long-term growth and development independently of regulation of short-term energy metabolism according to variations in energy intake.

Complexity of the receptor family

Insulin and IGF-I receptors share similar tetrameric structures [20]. Each is composed of two 'half receptors'. A 'half insulin receptor' is composed of a predominately extracellular alpha chain and a beta chain, which comprises the intracellular tyrosine kinase domain. Both chains are derived by proteolytic processing of the product of the insulin receptor gene. Similarly, a 'half IGF-I receptor' is composed of alpha and beta chains derived from the protein product of the IGF-I receptor gene. At the cell surface, there is evidence for the presence of not only insulin receptors composed of two 'half insulin receptors' and IGF-I receptors composed of two 'half IGF-I receptors', but also for the presence of hybrid receptors composed of a 'half insulin receptor' and a 'half IGF-I receptor'. A further level of complexity relates to the presence of two insulin receptor isoforms, IR-A and IR-B, which differ by a 12 amino acid sequence in the c-terminal region of the alpha chain [23,24•]. This leads to six possible receptor species, excluding the so-called IGF-II receptor that does not transduce a signal, but rather acts as a tumor suppressor gene by sequestering IGF-II ligand away from the IGF-I receptor [25]. Description of details of the relative affinity of each these receptors for ligands is an ongoing research topic, but several generalities are clear. IGF-I and IGF-II are ligands for the IGF-I receptor as well as hybrid receptors, but have relatively low affinity for the insulin receptor [26]. Insulin binds to the insulin receptor but at physiological concentrations has low affinity for IGF-I or hybrid receptors. There is recent evidence that the A isoform of the insulin receptor can bind IGF-II [24•].

In terms of therapeutic targeting, inhibitory activity of antibodies and tyrosine kinase inhibitors for each member of the receptor family remains incompletely described. Most antibodies were designed to spare the insulin receptor and have achieved this goal. Many of these antibodies target both IGF-I receptors and hybrid receptors (for example [27]). While some kinase inhibitors were originally designed to spare the insulin receptors and achieved some degree of differential inhibition *in vitro*, it is possible that they inhibit all receptor family members to some extent *in vivo*, but detailed dose–response data of *in vivo* inhibitory activity for the various receptor types in a series of normal and neoplastic tissues has not yet been published.

Physiology and pathophysiology

Organism level

Regulation of carbohydrate metabolism requires activation of insulin receptors of the 'classic' insulin target tissues, namely liver, muscle, and fat by circulating insulin secreted by pancreatic beta cells. Insulin deficiency leads to type I diabetes, which can lead to fatal hyperglycemia if not treated. Type II diabetes is complex and often involves chronic excess caloric intake, obesity, insulin resistance in classic insulin responsive tissues, and hyperinsulinemia as well as hyperglycemia.

Most circulating IGF-I and IGF-II is produced by the liver, where production is subject to a number of regulatory influences including (particularly for IGF-I) stimulation by growth hormone level and inhibition by malnutrition. While insulin expression is largely restricted to pancreatic beta cells, IGF-I and IGF-II are expressed in an autocrine or paracrine manner in many target tissues. Thus insulin is a classic 'endocrine' hormone, while IGF-I and IGF-II have characteristics of both hormones and tissue growth factors.

Importantly in the context of the development of inhibitors, IGF-I receptors are present in the hypothalamic–pituitary axis, and pituitary growth hormone secretion is subject to feedback inhibition by circulating IGF-I. IGF-I excess, usually attributable to excess growth hormone secretion by pituitary tumors, leads to acromegaly. Growth hormone deficiency or rarer molecular pathology involving growth hormone or IGF-I insensitivity lead to syndromes that involve growth retardation [28].

Cellular and molecular levels

It is clear that most cancers express IGF-I receptors, but there is little evidence for major molecular pathology in signal transduction. In contrast to HER2-NEU, where it is common for the gene to be amplified, the receptor to be greatly overexpressed, and activation to be ligand-independent, amplification or mutation of the IGF-I receptor is rare, receptor expression levels are relatively close to normal, and receptor activation remains ligand dependent. This has implications for targeted therapies: in common with certain established targets (such as VEGF) but in contrast to others (such as HER2/NEU), one would predict that much administered anti-IGF-IR may bind specifically to its intended molecular target, but in non-neoplastic tissues.

On the contrary, there is evidence that autocrine and/or paracrine expression of ligands, particularly IGF-II, is deranged in malignancy [29]. IGF-II is an imprinted gene, and loss of imprinting is one of several mechanisms that lead to IGF-II overexpression. *IGF-II* is the single most overexpressed gene in colorectal cancer relative to normal colorectal mucosa [30•], strongly implying that high levels of IGF-II in the tumor microenvironment confer a selective advantage.

A complex family of IGF binding proteins modulate IGF ligand bioavailability [31,32]. There is considerable evidence that the action of a variety of growth inhibitors or tumor suppressor genes (including, for example p53 [33], TGFbeta [34], retinoids [34], antiestrogens [35], and vitamin D [36] involve increased IGF binding protein expression, with decreased ligand bioavailability and decreased receptor activation. However, the expression of certain IGF binding proteins, notably IGFBP-2, is increased with loss of function of PTEN, and the details of molecular pathophysiology in this area represent an active research topic [37].

A key finding initially reported by Baserga and co-workers [38••] and extended by many others (for example [39]) is that many important oncogenes require intact IGF-I signalling in order to transform cells. This suggests the possibility that the neoplastic phenotype of cancers that involve a variety of different molecular pathologies may share a degree of dependence on IGF-I receptor function. The basis for this finding may relate to the strong survival signal associated with IGF-IR activation, which would be expected to increase the probability that oncogene activation will result in transformation rather than cell death due to oncogene stress.

Targeting strategies

Targeting strategies include on the one hand reduction of ligand levels or bioactivity, and on the other inhibition of receptor function using anti-receptor antibodies or small molecule tyrosine kinase inhibitors.

First generation anti-ligand approaches included approaches such as the use of somatostatin analogs to reduce circulating IGF-I levels, and were unsuccessful. One of the largest trials of this approach [40] fortunately included a translational science component that showed that the desired suppression of ligand levels was not achieved, so the negative results represent a failure of a particular strategy, rather than evidence that the target is unimportant. Other approaches, such as anti-ligand antibodies [41], show interesting preclinical activity.

Many tyrosine kinase inhibitors of varying specificity that are designed to inhibit the IGF-I receptor have been designed and evaluated preclinically [42–45]. Data from phase I studies are eagerly anticipated. Relative to the trials of anti-receptor antibodies, tyrosine kinase inhibitors may not only have certain additional risks, but also may have certain advantages, as discussed below.

Many anti-receptor antibodies have been studied preclinically, and several are being evaluated in clinical trials. To date, the largest clinical experience has been with the Pfizer antibody CP 751 871 [17,18,19••,46•,47–49]. In general, the toxicity has been acceptable, and early clinical results have not only revealed activity in terms of pharmacodynamic endpoints, but also have suggested that there is significant improvement in response rates to chemotherapy for non-small cell lung cancer when the antibody was co-administered. The most recent available update showed the largest improvement was in squamous cancers (response rate to chemotherapy alone, 41%; with antibody 72%), which were noted to have higher expression of the IGF-I receptor than other histological types. Ongoing research will reveal if this early result is

confirmed in phase III studies, and if it is associated with an effect on survival endpoints.

Additional anti-IGF-IR antibodies have been developed. Those in trials for which early clinical data have been reported include AMG479 (Amgen) [50,51], AVE1642 (Sanofi-Aventis) [52,53], A12 (Imclone) [54–56], MK0646 (Merck) [57,58•], and R1507 (Roche) [59].

There are common observations across early clinical trials of anti-IGF-I receptor antibodies. These include generally favorable toxicity profile without dose limiting toxicity, and disease stabilizations or responses in a minority of patients participating in phase I single agent trials. Several agents have been noted to achieve clinically impressive objective responses in metastatic chemotherapy-refractory Ewing's sarcoma, although some patients with this disease have not responded. AMG479 has been shown to be well tolerated in combination with panitumumab or gemcitabine, and a combination study of AVE1642 with bortezomib in multiple myeloma is planned. Early evaluation of MK0646 included pharmacodynamic studies on neoplastic tissue, which revealed reduction of phospho-AKT, phospho-S6, both of which are downstream of the receptor, as well as downregulation of receptor levels and reduction in proliferation as estimated by KI67 staining.

Gaps in knowledge

As is frequently the case in oncology drug development, targeting the IGF-I receptor is being studied in the absence of a complete description of the relevant pathophysiology. The following are examples of areas of active research that may impact drug development.

What is the role of the insulin receptor?

While activation of the insulin receptor on classic insulin sensitive tissues such as muscle, liver, and fat stimulates glucose uptake and energy storage by processes such as glycogen synthesis, the physiologic consequences of insulin receptor activation on normal or transformed epithelial cells are less clear. Glucose uptake may also increase, but the predominant consequences may involve increased proliferation and inhibition of apoptosis.

While several reports (for example [60•]) describe IGF-I receptor expression by neoplastic tissue, there is a surprising paucity of data concerning the expression of the insulin receptor by primary human cancers. Nevertheless, a survey of public gene expression databases suggests that this receptor is expressed by most if not all cancers at levels comparable to those seen in classic insulin sensitive tissues. Few immunohistochemical studies have been reported [61], and these are consistent with the gene expression data. However, neither the gene expression data nor immunohistochemical staining with conventional anti-insulin receptor antibodies can reliably distinguish between hybrid receptors and insulin receptors. A further gap in knowledge concerns the relative expression of the two insulin receptor isoforms by malignant cells.

The partitioning of insulin 'half receptors' between 'pure' insulin receptors and hybrid receptors depends largely on the relative expression of the genes encoding the IGF-I receptor and the insulin receptor. If gene expression, mRNA translation, and post translation processing result in an equal number of insulin 'half receptors' and IGF-I 'half receptors' being delivered to the cell surface, then one would anticipate that 50% of the receptors would be hybrid, and 25% would be classic insulin receptors and 25% would be classic IGF-I receptors; imbalance in the production rates of the of 'half receptors' would influence these ratios. This topic was until recently a relatively obscure one, but has become important as many anti-IGF-I receptor antibody drug candidates have been designed to have activity against IGF-I receptors and hybrid receptors, but not insulin receptors, in order to avoid the anticipated metabolic toxicity of blockade of insulin receptors. Therefore, there is increasing interest in the role of the insulin receptors on cancer cells. On the one hand, preclinical and early clinical evidence suggests that antineoplastic activity is present even with therapeutic approaches that spare the insulin receptor; on the other, a model of insulin-receptor-mediated resistance to IGF-I receptor targeting has been described [62••].

Positron emission tomographic (PET) scanning using labelled glucose analogs is based on the high level of glucose uptake by malignant cells. In many non-transformed tissues, glucose uptake is insulin dependent, and this raises the possibility that in malignancy, insulin-stimulated glucose uptake is widespread and denotes an important role for insulin signalling within malignant cell. However, this line of reasoning may be simplistic: while some glucose uptake by cancer cells may indeed be insulin-stimulated, in other cases there is evidence that it is constitutive and insulin-independent.

What are the key toxicity issues?

Experience to date with several anti-IGF-I receptor antibodies used as single agents or in combinations with cytotoxics has not revealed clinically important toxicity, at least over periods of administration of several months. Endocrine changes induced by treatment include significant elevations in levels of circulating growth hormone and IGF-I, which result as a consequence of the compensatory homeostatic response to blockade of receptors in the hypothalamic–pituitary axis. There is no evidence that the elevation of IGF-I is sufficient to overcome the desired inhibitory effect on signalling. However, the elevation in growth hormone levels may result in insulin resistance in classic insulin-sensitive organs (as is seen clinically in acromegaly), with resulting hyperglycemia and secondary hyperinsulinemia. Hyperglycemia arising

from this mechanism is a common side effect of treatment, but rarely is severe enough to require cessation of treatment, and often responds to metformin therapy. In theory, more severe hyperglycemia and metabolic consequences may be associated with administration of tyrosine kinase inhibitors that directly inhibit the insulin receptor *in vivo*. Whether this theoretical possibility will be observed clinically will be revealed by ongoing phase I studies.

In pediatric settings, long-term therapy would be predicted to result in growth retardation, but this would be of limited clinical significance if the treatment were effective for life-threatening cancers, particularly as it is possible that 'catch up' growth would occur following completion of treatment.

Experience with long-term (>1 year) treatment duration is limited, but this might be associated with changes reminiscent of the syndrome of growth hormone deficiency. An additional particular concern would be adverse CNS effects associated with those drug candidates that accumulate in the brain, as IGF-I signalling may have key neuroprotective effects [63].

Other observed adverse effects including leukopoenia, lassitude, and anorexia are generally modest and not dose limiting.

Will there be clinically important differences between the drugs being developed?

Experience with targeting the EGF receptor shows that it can be difficult to predict differences in efficacy between different drug candidates that share a receptor target. At this time, there are insufficient data to allow comparison between IGF-I receptor targeting agents, but there are some grounds for speculation.

Tyrosine kinase inhibitors that are active against all members of the insulin receptor/insulin-like growth factor receptor family might be expected to be more effective than the anti-IGF-I receptor antibodies, particularly if it is confirmed, as implied by some studies, that insulin directly influences neoplastic behavior. On the contrary, drug candidates that target the insulin receptor may have more serious metabolic toxicity than those that spare it; while considerable information is already available regarding safety of anti-IGF-I receptor antibodies, results of ongoing phase I studies of tyrosine kinase inhibitors are eagerly awaited.

The different anti-IGF-I receptor antibodies are expected to have profiles more similar to each other than to the kinase inhibitors. While there may be differences in pharmacokinetics, recognized epitopes, and antibody subclass, at this point of time (without direct comparisons available) no major differences in efficacy have been noted.

What resistance mechanisms are anticipated and can reliable predictors of sensitivity be developed?

The target receptors are so commonly expressed in cancers that it is unlikely that their presence can be used to define a subgroup sensitive to targeting. It is too early to be certain if a quantitative measurement of receptor expression level will be of predictive value with regards to responsivity, but since the levels of receptor expression vary within a range that is much smaller than that of the HER2/neu receptor, it is unlikely that an all-or-none cutoff will be found. It is plausible that sensitivity to targeting may correlate with levels of receptor activation, but the methods involved in these measurements in primary human tissue are not perfected.

Efforts to identify predictors of response are being embedded in ongoing clinical trials. Some approaches involve undirected surveys of gene expression variation in relation to response, while others are hypothesis driven. An example of the latter is the notion that intra-tumoral overexpression of IGF-II may indicate the presence of an autocrine loop, which implies 'addiction' to receptor activation and a higher probability of response to a therapeutic strategy that is able to block the involved receptor [21]. Notwithstanding efforts to develop novel molecular markers of sensitivity, early phase II results evaluating the Pfizer anti-IGF-IR antibody CP 751 871 in lung cancer have yielded early data, suggesting response rate may vary by simple histopathologic criteria, with higher activity seen in squamous cancers than other lung cancer histologies [19••].

More research is required to clarify the role of molecular pathology downstream of the IGF-I receptor in resistance to therapies. It is plausible, for example, that PTEN loss of function may result in constitutive downstream pathway activation, rendering receptor targeting futile. In this case, PTEN loss of function would be a resistance marker. However, there is some evidence that PTEN loss of function results in hypersensitivity to upstream stimulation rather than to constitutive pathway activation, and that it is not necessarily associated with resistance to treatment [64].

How should optimum dose and schedule be determined?

For the anti-IGF-I receptor antibodies, choosing the highest tolerated dose in phase I for efficacy studies is not an effective strategy because the drugs are well enough tolerated that one could escalate to impractical dose ranges. Choosing a dose for efficacy studies is therefore not a trivial issue. One approach is to aim for a serum concentration in humans that was observed to be associated with activity in animal models. Another is to rely on pharmacodynamic endpoints, including for example, degree of elevation of growth hormone secretion or IGF-I level, degree of receptor down regulation in

leukocytes [46•] or degree of pathway inhibition in neoplastic tissue. However, none of these methods can be regarded as definitive. In the case of the Pfizer antibody CP 751 871, phase II experience with a response rate endpoint raises the probability that 20 mg/kg dosing is more active than 10 mg/kg [19••]. For the kinase inhibitors, it is possible that dose-limiting toxicity will indeed be demonstrated in phase I, and this information will guide dose in efficacy studies.

For both classes of agent, scheduling also is a complex area. It is conceivable that continuous antibody treatment is not equivalent to pre-chemotherapy or post-chemotherapy pulses. It is unclear at this time if IGF-I receptor targeting will find an application in long-term therapy analogous to steroid hormone targeting agents used in breast or prostate cancer, or will typically be given over a period limited to several months in conjunction with chemotherapy.

What combinations deserve study?

Although there have been multiple anecdotes of single-agent activity of anti-IGF-I receptor antibodies in Ewing's sarcoma, it is commonly assumed on the basis of the experience with other receptor kinase inhibitors that combination therapies will be important. This view is based on evidence that IGF-I receptor activation tends to reduce responsiveness to many antineoplastic therapies. A few represent obvious priorities. Early experience suggests that combining cytotoxics with IGF-I receptor blockade may be useful [19••]. There is evidence that insulin receptors and/or IGF-I receptors can play a role in conferring resistance to rapamycin and other rapalogs [65,66••]; therefore there is interest in combining these with IGF-I receptor-targeting agents. Similarly, there is considerable evidence that IGF-I receptor-mediated signalling confers resistance to therapies that target EGF receptor family members (for example [67••,68••]), so simultaneous inhibition of these receptor families is of interest. Combined inhibition of steroid signal transduction and IGF-I receptor is also proposed for breast and prostate cancer on the basis of preclinical models. The combination of a growth hormone receptor antagonist [69] with an anti-IGF-I receptor antibody would be of interest as this may reduce the growth hormone induced insulin resistance, hyperglycemia, and hyperinsulinemia associated with IGF-I receptor targeting, as described above, thereby improving tolerability and/or efficacy. Finally, there is also evidence that IGF-I receptor signaling is facilitated by heat shock protein 90 [70] which provides a rationale for investigation of combinations of HSP90 inhibitors with IGF-IR targeting agents.

Conclusion

In retrospect, clues that the insulin receptor/IGF-I receptor family represents an interesting molecular target for cancer treatment have been available for at least 20 years. However, only recently has the role of this receptor family in neoplasia moved from a topic of strictly academic interest to one that has led to drug development by the pharmaceutical industry. These efforts have successfully yielded dozens of drug candidates. Not only have preclinical evaluations of several of these been impressive enough to justify clinical trials, but early results from initial clinical studies have provided data that in turn have justified the launch of expanded clinical trial programs.

Thus, efforts to exploit this molecular target have not so far failed at the steps that commonly provide a reason to cancel the vast majority of drug development programs. There is increasing excitement in the field [71], leading to an increasing amount of clinical trial activity and increasing resources being devoted to address the important remaining gaps in knowledge. In stark contrast to earlier examples of development of targeted agents such as trastuzumab, where the targeting hypothesis was initially evaluated using one agent, the IGF-I receptor target is now being simultaneously addressed by more than a dozen competing drug development programs, and clinical trials of many compounds are in progress. The most successful clinical trial designs will not only test hypotheses regarding antineoplastic activity, but also provide information related to mechanisms of sensitivity or resistance.

Anecdotal evidence of major responses of chemotherapy-refractory metastatic Ewing's sarcoma to several different anti-IGF-I receptor antibodies (used as single agents) has raised hope that there may be a class of neoplasms for which IGF-IR targeting will provide major clinical benefit. Initial reports of significant improvement response rates to chemotherapy in lung cancer by co-administration of an anti-IGF-IR antibody has led to interest in the possibility that further research may show improvements in survival endpoints for common cancers as a result of adding an anti-IGF-IR agent to current therapies. Nevertheless, despite the increasing pace of research, several more years will be required to determine if this line of investigation will or will not in the end yield new agents approved for cancer treatment. At this stage, potential applications involve many organ sites and many drug combinations. This implies the possibility of many indications, but makes the process of prioritizing clinical trials challenging.

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