

Review

IGF-1R as an anti-cancer target—trials and tribulations

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Abstract

Type I insulin-like growth factor receptor (IGF-1R) has long been recognized for its role in tumorigenesis and growth, but only recently have the tools for targeting the IGF pathway become available. More than 10 IGF/IGF-1R inhibitors have entered clinical trials, and these belong to three main classes: (1) monoclonal antibodies against IGF-1R, (2) monoclonal antibodies against IGF-1R ligands (IGF-1 and IGF-2), and (3) IGF-1R tyrosine kinase inhibitors. These IGF-1R-targeting agents share common effects on IGF-1R signaling but differ in mechanisms of action, spectrum of target inhibition, and pharmacological features. Clinical activity of IGF-1R inhibitors has been demonstrated with sustained responses in a small number of patients with select tumor types, such as Ewing sarcoma and thymoma. However, many large clinical trials involving patients with adult tumors, including non-small cell lung cancer, breast cancer, and pancreatic cancer, failed to show clinical benefit in the overall patient population. Possible reasons for failure include the complexity of the IGF-1R/insulin receptor system and parallel growth and survival pathways, as well as a lack of patient selection markers. While IGF-1R remains a valid target for selected tumor types, identification of predictive markers and rational combinations will be critical to success in future development.

Key words IGF-1R, insulin receptor

Type I insulin-like growth factor receptor (IGF-1R) has been recognized for decades for its role in tumorigenesis and growth^[1]. Not until recently had advances in medicinal chemistry and biotechnology provided the tools for targeting the insulin-like growth factor (IGF) pathway in patients. To date, more than 10 IGF/IGF-1R inhibitors have entered clinical trials. Clinical validation of this target has been demonstrated in select tumor types. However, several large clinical trials failed to show clinical benefit in the overall patient population. In this review we focus on the two main classes of IGF-1R inhibitors in clinical development—monoclonal antibodies (mAbs) and small molecule tyrosine kinase inhibitors (TKIs)—and discuss the background, clinical experience, and lessons learned.

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IGF-1R

IGF-1R belongs to the insulin receptor (IR) family that includes the IR (a homodimer), IGF-1R (a homodimer), IGF-1R/IR (hybrid, heterodimeric receptors), and the mannose 6-phosphate receptor (also known as IGF-2R)^[1] (Figure 1). IGF-1R can be activated by the ligands insulin-like growth factor-1 (IGF-1) or insulin-like growth factor-2 (IGF-2). IGF-1R/IR hybrids preferentially signal with the IGF ligands. IR exists in two isoforms: IR-B, traditional insulin receptors, and IR-A, a fetal form that is re-expressed in selected tumors and preferentially binds IGF-2^[2]. IGF-2R is a non-signaling receptor that acts as a “sink” for IGF-2^[3]. These receptors may coexist in a given cell, with relative abundance and activation status varying by cell type, tissue type, and physiologic or pathologic conditions.

The ligands of IGF-1R, IGF-1 and IGF-2 are abundant in the serum of adults^[4] and have complex interactions with IGF-1R/IR receptors. IGF-1 is secreted primarily by the liver upon stimulation by human growth hormone (HGH), whereas IGF-2 is non-HGH dependent and is expressed in a variety of tissues. There are at

least 6 well-characterized IGF-binding proteins (IGFBP-1 through -6) that bind IGFs and prevent their action on the receptors. In serum, only approximately 2% of IGF ligands exist in the unbound form. At the tissue level, bioavailability of IGF-1 and IGF-2 is modulated by IGFBP protease and the presence of the non-signaling, IGF-2-binding IGF-2R. Intracellular signaling of IGF-1R is mediated through IR substrates (IRS-1 through -4) and Src-homology collagen protein (Shc)^[6], which in turn leads to activation of the mitogen-activated protein kinase (MAPK) pathway and the PI3K-AKT pathway (Figure 1B)^[3]. PI3K-AKT is considered the predominant downstream signaling pathway for the IR family.

IGF-1R is ubiquitously expressed in normal tissues and plays an important role in growth and various physiological functions, including those involving the

cardiac and neurological systems, as well as glucose homeostasis. The impact on glucose probably occurs through feedback down-regulation of GHG by circulating IGF-1 and the local effect of IGF-1 on IGF-1R in the muscles or kidneys to promote glucose uptake^[6,7].

Extensive *in vitro* and *in vivo* studies have implicated IGF-1R, IGF-1, and IGF-2 signaling in cancer development, maintenance, and progression. IGF-1R expression is critical for anchorage-independent growth, a well recognized property of malignant cells. IGF-1 and IGF-2 are strong mitogens in a wide variety of cancer cell lines, including prostate cancer^[8], breast cancer^[9-12], colon cancer^[13,14], and myeloma^[15]. High circulating levels of IGF-1 have been associated with increased risk of breast, prostate, and colon cancers^[1]. The IGF/IGF-1R pathway has also been shown to have extensive

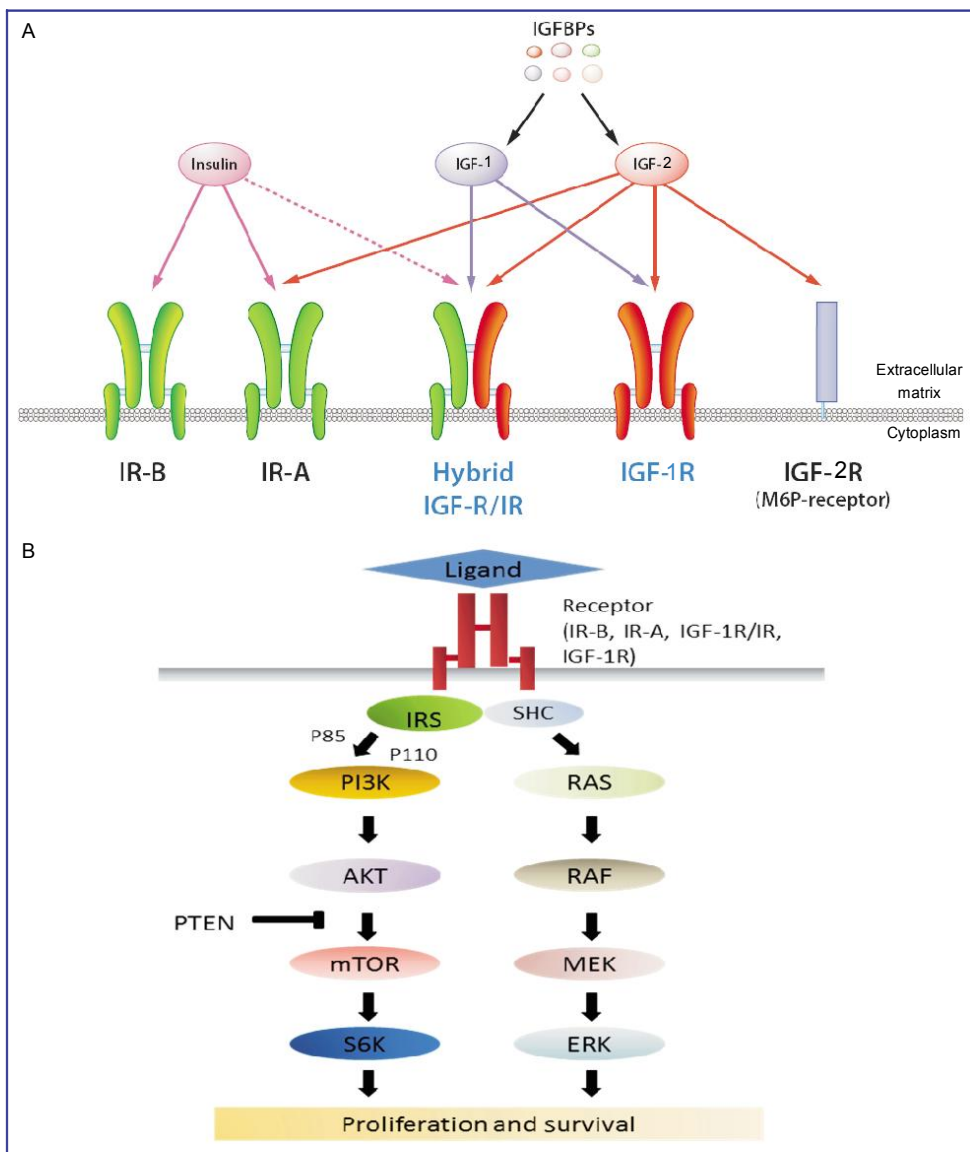


Figure 1 Insulin and insulin-like growth factor (IGF) receptors and downstream signaling. A, the insulin receptor family includes the insulin receptor (IR) in two isoforms (IR-A and IR-B), the type 1 insulin-like growth factor receptor (IGF-1R), and the mannose 6-phosphate (M6P) receptor (IGF-2R). IR and IGF-1R are expressed as preformed dimers, either homodimers or heterodimers. IGF-2R is a non-signaling receptor that acts as a “sink” for IGF-2. Insulin binds primarily to IR-A or IR-B, but also has weak affinity for IGF-1R. IGF-1 and IGF-2 are ligands for the IGF-1R and IGF-1R/IR hybrid receptor along with IR-A. Insulin-like growth factor binding proteins (IGFBPs) bind to and prevent IGF-1 and IGF-2 from activating receptor signaling cascades. B, signaling of the IGF-1R/IR system is mediated by the insulin receptor substrate (IRS) and Shc. PI3K-AKT activation is the predominant downstream event of IGF-1R/IR, but the MAPK pathway can also be activated.

cross-talk with the estrogen receptor (ER), epidermal growth factor receptor (EGFR), and human epidermal growth factor receptor 2 (HER-2) signaling pathways and to play an important role in the resistance mechanisms of cytotoxic drugs and EGFR/HER-2-targeted agents^[16]. More recent work also suggests a potential role for IGF-1R in the resistance to mTOR inhibitors^[17] and RAF-MEK inhibitors^[18].

IGF-1R can be detected in most solid tumors and hematological malignancies examined to date, and IGF-2 overexpression, IGF1R modulations, and IGF-2R down-regulation have also been seen in cancer cells^[5,19,20]. However, unlike other growth factor receptors such as EGFR and HER-2, activating mutations of the *IGF1R* gene have not been reported, and gene amplification is extremely rare in the tumors that have been tested^[21]. On the other hand, several genetic abnormalities can lead indirectly to IGF/IGF-1R overexpression and signaling. For example, in Ewing sarcoma (EWS), the EWS/friend leukemia integration-1 (FLI-1) translocation product can interact with the *IGFBP3* promoter and repress its expression, and IGF-1R is required for transformation by the fusion protein. Some tumor types, including hepatocellular carcinoma and breast cancer, have been associated with loss of heterozygosity of the *IGF2R* gene^[22]. Loss of imprinting of IGF-2 (loss of methylation resulting in biallelic expression), first described in Wilms tumor, has since been identified in adult tumors and is associated with an increased risk of colon cancer^[23,24]. These genetic changes may increase IGF-2 production or its bioavailability for IGF-1R signaling.

IGF-1R Inhibitors in Clinical Development

Several approaches to inhibit IGF-1R signaling have been investigated. Agents in current clinical develop-

ment belong to three main classes (Tables 1 and 2): monoclonal antibodies (mAbs) against IGF-1R, mAbs against IGF-1R ligand (IGF-1 and IGF-2), and IGF-1R tyrosine kinase inhibitors (TKIs). At least eight human or humanized anti-IGF-1R mAbs entered clinical trials (Table 1), though several clinical development programs have since been discontinued. These antibodies are highly specific to IGF-1R and do not bind IR. Common mechanisms of action include blockade of the receptor from ligand binding and internalization/degradation of IGF-1R^[25]. In addition, anti-IGF-1R mAbs also down-regulate the IGF-1R/IR hybrid receptor^[26].

Currently, MEDI-573 is the only monoclonal antibody in clinical development that targets the ligands IGF-1 and IGF-2^[27]. MEDI-573 inhibits IGF-induced IGF-1R and IR-A activation, but does not affect insulin signaling. Several small molecule TKIs against IGF-1R are under clinical investigation. Among them, OSI-906 and BMS-754807 are the most specific, whereas others also inhibit receptor tyrosine kinases beyond the IGF-1R and IR family (Table 2). Because of the high degree of homology between IGF-1R and IR, even the most specific IGF-1R TKIs have some degree of inhibitory effect on the IR. For example, OSI-906 has a half maximal inhibitory concentration (IC_{50}) of 0.018 $\mu\text{mol/L}$ against IGF-1R and 0.054 $\mu\text{mol/L}$ against IR^[28,29]. At clinically relevant doses, this agent is expected to inhibit IGF-1R and IR simultaneously. Co-inhibition of IR and IGF-1R may confer a better anti-tumor effect because IR signaling induced by insulin or IGF-2 has been implicated in a number of preclinical tumor models^[30], including breast cancer^[31]. Furthermore, when IGF-1R signaling is disrupted, cells may respond with an increase in IR activity^[32]. However, IR inhibition is expected to impact insulin signaling and may increase the risk of toxicities, particularly hyperglycemia.

In summary, the three classes of IGF-1R-targeting agents share common effects on IGF-1R signaling, but differ in mechanisms of action, spectrum of target

Table 1. Monoclonal antibodies that target the type I insulin-like growth factor receptor (IGF-1R) pathway

Target	Agent name	Sponsor	Status	Class	Phase 2 dose
IGF-1R	Cixutumumab (IMC-A12) ^[49,84]	ImClone	Phase 2	IgG1	6 mg/kg qw, 10 mg/kg q2w
IGF-1R	Figitutumumab (CP-751,871) ^[35,36,59]	Pfizer	Discontinued after Phase 3	IgG2	20 mg/kg q3w
IGF-1R	Dalotuzumab (MK-0646; h7C10) ^[85,86]	Pierre Fabre and Merck	Phase 3	IgG1	10 mg/kg q2w
IGF-1R	Ganitumab (AMG 479) ^[33]	Amgen	Phase 3	IgG1	18 mg/kg q3w
IGF-1R	R1507 ^[41]	Roche	Phase 2	IgG1	9 mg/kg qw
IGF-1R	SCH 717454 (19D12) ^[37]	Schering Plough	Discontinued after Phase 1	IgG1	NA
IGF-1R	AVE1642 (EM164) ^[38]	ImmunoGen/Sanofi	Discontinued	IgG1	8 mg/kg q4w, 12 mg/kg q3w
IGF-1R	BIIB022 ^[37,88]	Biogen-IDEC	Discontinued after Phase 1	IgG4	NA
IGF-1 and IGF-2	MEDI-573 ^[27,89]	MedImmune	Phase 1	IgG2	NA

qw, every week; q2w, every 2 weeks; q3w, every 3 weeks; q4w, every 4 weeks; NA, not available.

Table 2. Small molecule tyrosine kinase inhibitors (TKI) against IGF-1R

Agent	Sponsor	Class (route)	IC ₅₀ (μmol/L) against			Sponsor
			IGF-1R	IR	Others ^a	
Linsitinib (OSI-906) ^[28,29]	OSI	TKI (oral) ATP-competitive	0.018	0.054	None	Phase 3
BMS-754807 ^[90]	BMS	TKI (oral) ATP-competitive	<2 nmol/L	<2 nmol/L	11 other kinases <100 nmol/L	Phase 2
BVP 51004 ^[91]	Biovitrum	Small molecule (oral) Not ATP-competitive	0.038 μmol/L	No effect	None	Phase 1
XL228 ^[92]	Exelixis	TKI (IV) ATP-competitive	1.6 nmol/L (cellular)	NA	<ul style="list-style-type: none"> • Bcr-Abl: 5 nmol/L • Bcr-Abl T315I: 1.4 nmol/L • Src: 6.1 nmol/L • Aurora A: 3.1 nmol/L • LYN: 2 nmol/L (all cellular) 	Phase 1
INSM-18 (NDGA) ^[93,94]	Insmed	Phenolic compound isolated from creosote bush <i>Larrea divaricata</i>	31 μmol/L (cellular)	NA	HER-2: 15 μmol/L (cellular)	Phase 1

^a Targets for which IC₅₀ is <50 fold of the IC₅₀ for IGF-1R. IGF-1R, type I insulin-like growth factor receptor; IR, insulin receptor; TKI, tyrosine kinase inhibitor; IC₅₀, half maximal inhibitory concentration; IV, intravenous; NDGA, nordihydroguaiaretic acid; OSI, OSI Pharmaceutical; BMS, Bristol-Meyers Scribb; HER-2, human epidermal growth factor receptor 2.

inhibition, and pharmacological features (Table 3). For example, anti-IGF-1R mAbs only block signaling through IGF-1R and IGF-1R/IR hybrids, whereas IGF-1/2-neutralizing mAb prevents IGF signaling through both homodimers and heterodimers of IGF-1R and IR-A, but spares insulin signaling. IGF-1R TKIs can potentially block all receptors responsible for IGF/insulin signaling. The differing spectrum of target blockade may potentially translate into different toxicity and/or activity profiles.

Clinical Experience with IGF-1R Inhibitors

IGF-1R-targeting mAbs

The maximum tolerated dose for monotherapy was not reached at the conclusion of the phase 1 trials for any of the anti-IGF-1R mAbs. Selection of the phase 2 doses was largely based on feasibility and the target steady-state drug levels extrapolated from preclinical *in vivo* tumor models. Table 1 lists the recommended phase 2 doses for monotherapy with different IGF-1R mAbs. Anti-IGF-1R mAbs are generally well tolerated as monotherapy. Common treatment-emergent adverse events include hyperglycemia, the classic side effect of all anti-IGF-1R mAbs. Hyperglycemia, which occurs in about 20% patients, is mostly grades 1–2 and can be controlled with oral diabetic medications with continued mAb treatment.

Pharmacodynamic changes tested in early clinical trials with anti-IGF-1R mAbs have shown evidence of target modulation, including down-regulation of IGF-1R in granulocytes and circulating tumor cells^[33,34], a significant

increase in HGH and IGF-1, and a variable increase in the insulin level^[33,35-38]. Decrease in the standardized uptake values of (18)F-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) has also been observed in anecdotal cases^[33].

The most notable activity of anti-IGF-1R mAbs was demonstrated in EWS, with reports of complete responses (CRs) or partial responses (PRs) and prolonged stable disease (SD) in phase 1 trials^[33,39-41]. These promising results led to a series of phase 2 evaluations in the indication (Table 4). The largest EWS-specific phase 2 trial used R1507^[42]. In this trial, 115 patients with recurrent or refractory EWS older than 2 years of age were treated at either 9 mg/kg once a week ($n = 109$) or 27 mg/kg every 3 weeks ($n = 6$). The overall CR/PR rate was 10% (1 CR, 10 PRs), with a median response duration of 29 weeks (range, 12 to 94 weeks) and a median overall survival of 7.6 months (95% confidence interval, 6 to 9.7 months). Ganitumab (AMG 479) was also tested in patients with refractory EWS ($n = 19$) or desmoplastic round cell tumors ($n = 16$)^[43], and the results were reported together. PR was noted in one patient with EWS (censored at 47 weeks) and one patient with desmoplastic round cell tumor. Overall, five additional patients had SD for more than 24 weeks. Recently, Malempati *et al.*^[44] reported the results of a Children's Oncology Group (COG) trial involving 47 pediatric patients treated with cixutumumab (IMC-A12) at 6 mg/kg or 9 mg/kg weekly on 28 day cycles. Of the 35 patients in the EWS expansion cohorts with heavily pretreated disease, 3 patients had confirmed PRs. As with other mAbs, the median progression-free survival (PFS) in the overall patient population was short (44 days in 9 mg/kg dose cohort)^[44]. The overall experience

Table 3. Main features of monoclonal antibodies and small molecule tyrosine kinase inhibitors against the IGF/IGF-1R pathway

Features of interest	mAb against IGF-1R	mAb against IGF-1 and -2	Small molecule TKI
Mechanism of action	<ul style="list-style-type: none"> Block IGF-1R from ligand binding Receptor degradation of IGF-1R homodimer and IGF-1R/IR hybrids Possible ADCC (if IgG1) 	<ul style="list-style-type: none"> Neutralizing ligand from binding to IGF-1R and IR-A 	<ul style="list-style-type: none"> Kinase inhibition intracellular ▲(also inhibit ligand-independent activation, if relevant)
Signaling affected	<ul style="list-style-type: none"> Specific Inhibit signaling of: <ul style="list-style-type: none"> ▲IGF-1R ▲IGF-1R/IR-A hybrid No effect on IR-A or IR-B 	<ul style="list-style-type: none"> Specific Inhibit IGF-1 or IGF-2 signaling through: <ul style="list-style-type: none"> ▲IGF-1R ▲IGF-1R/IR-A ▲IR-A No effect on insulin signaling 	<ul style="list-style-type: none"> Less specific Inhibit signaling of RTKs (by any ligand): <ul style="list-style-type: none"> ▲IGF-1R ▲IGF-1R/IR ▲IR (to a lesser degree than for IGF-1R) May inhibit targets beyond IGF-1R and IR (XL228; INSM-18)
Pharmacokinetics	<ul style="list-style-type: none"> Long $t_{1/2}$ (days to weeks) PK interaction less likely in combination regimens Poor CNS uptake 	<ul style="list-style-type: none"> Long $t_{1/2}$ (days to weeks) PK interaction less likely in combination regimens Poor CNS uptake 	<ul style="list-style-type: none"> Short $t_{1/2}$ (hours)

IGF-1R, type I insulin-like growth factor receptor; IR, insulin receptor; mAbs, monoclonal antibodies; TKIs, tyrosine kinase inhibitors; ADCC, antibody-dependent cell-mediated cytotoxicity; RTKs, receptor tyrosine kinases; PK, pharmacokinetics; $t_{1/2}$, half life; CNS, central nervous system.

in EWS suggests that IGF-1R inhibition with mAb has major activity in this indication, but the benefit was restricted to a small subset of patients. Further studies are warranted to explore markers predictive of response, mechanisms of resistance, and combination strategies.

Phase 1 trials of IGF-1R-targeting mAbs have also shown objective responses in patients with neuroendocrine tumors^[45] and prolonged SD in patients with hepatocellular carcinoma, thymoma, and prostate cancer. A phase 2 trial of cixutumumab was initiated in patients with thymoma and thymic carcinoma^[46]. For the 30 evaluable patients with thymoma, 4 patients had PRs, 23 had SDs, and only 3 had progressive disease. No response was observed in the thymic carcinoma cohort. Of note, 8 of 33 patients with thymoma developed autoimmune symptoms, 4 of which were new onset, while on study, including immune thrombocytopenic purpura, myositis, myocarditis, colitis, pure red cell aplasia, and a food allergy. The underlying mechanism of the autoimmune phenomena is unclear.

IGF-1R-targeting mAbs have shown less single agent activity in other tumors. Abou-Alfa *et al.*^[47] reported the results of a phase 2 trial of cixutumumab in hepatocellular carcinoma. In that trial with 22 evaluable patients, no objective responses were observed; 7 (29%) had SD for at least four months. The median overall survival (OS) was 8 months. Similarly, 14 patients with adrenal cortical cancer were treated with figitumumab in

a phase 2 trial, in which eight patients had stable disease, but none had objective responses^[48]. A phase 2 trial of cixutumumab in 31 patients with metastatic castration-resistant prostate cancer showed no objective responses, although the result was considered promising as some patients achieved stabilization of their initially progressing tumors^[49,50]. The median time to progression was 3.8 months, with 9 patients showing SD for more than 6 months. Combination regimens in castration-sensitive prostate cancer are currently being explored.

IGF-1R TKIs

Phase 1 trials of the IGF-1R TKI OSI-906 explored two main schedules: continuous oral dosing (once or twice daily without interruption) and intermittent oral dosing (days 1–3 every 14 days)^[51–53]. DLTs included: grade 3 hyperglycemia, grade 3 QT prolongation, and grade 4 ALT/AST elevation. Daily dosing up to 300 mg indicated a linear PK, with median terminal $t_{1/2}$ of 2–4 h. The recommended phase 2 doses were determined to be 150 mg, twice per day, 500 mg daily, or 600 mg daily on Day 1 to Day 3 in 14-day cycles. The plasma concentrations in the phase 1 trials exceeded the “efficacious” concentration (IC_{50}) in the *in vitro* models (1 μ mol/L).

Table 4. Activity of IGF-1R monoclonal antibodies

Tumor type	Agent	Trial and regimen	Phase of trial	Activity	Reference
EWS	Figitumumab	Monotherapy	Phase 1 (<i>n</i> =14)	1 CR, 1 PR, 8 SD	[95]
EWS	Cixutumumab (IMC-A12)	Monotherapy	Phase 1/2 (<i>n</i> =35 on EWS expansion)	3 PRs	[44]
EWS	R1507	Monotherapy	Phase 2 (<i>n</i> =115)	1 CR, 10 PR	[42]
EWS and DRCT	Ganitumab (AMG 479)	Monotherapy	Phase 2 (<i>n</i> =16)	1 PR in EWS, 1 PR in DRCT, 5 SD	[43]
HCC	Cixutumumab	Monotherapy	Phase 2 (<i>n</i> =24)	No PR/CR, 7 SD for > 4 months	[47]
ACC	Figitumumab	Monotherapy	Phase 2 (<i>n</i> =14)	No PR, 8 SD	[48]
Metastatic castration-resistant prostate cancer	Cixutumumab	Monotherapy	Phase 2 (<i>n</i> =31 in q2w dose cohort and <i>n</i> =10 in q3w dose cohort)	9 patients had SD > 6 months in q2w cohort; 3 patients had SD	[50]
Thymoma	Cixutumumab	Monotherapy	Phase 2 (<i>n</i> =30)	4 patients had PRs, 23 had SD	[46]
NSCLC (squamous cell)	Figitumumab	Chemotherapy ± figitumumab	Phase 3	Experimental vs. control; OS: 8.5 vs. 10.3 months	[60]
NSCLC		Erlotinib ± figitumumab	Phase 3	Early termination for futility	[71]
		Erlotinib ± R1507	Phase 2	No difference in 12-week PFS	[70]
Pancreatic cancer	Ganitumab	Gemcitabine ± ganitumab	Phase 2	Increase in PFS and OS	[55]
	Cixutumumab	Gemcitabine + erlotinib ± cixutumumab	Phase 2	No difference in PFS and OS	[56]
Colorectal cancer	Dalotuzumab	Irinotecan-cetuximab ± dalotuzumab	Phase 2/3	No difference in PFS	[72]
Breast cancer	Ganitumab	Exemustane or fulvestrant ± ganitumab	Phase 2	No difference in ORR or PFS	[65]

IGF-1R, type I insulin-like growth factor receptor; EWS, Ewing sarcoma; DRCT, desmoplastic round cell tumor; HCC, hepatocellular carcinoma; ACC, adrenocortical carcinoma; NSCLC, non-small cell lung cancer; CR, complete response; PR, partial response; SD, stable disease; PFS, progression-free survival; OS, overall survival; ORR, overall response rate.

OSI-906's target effect was reflected by a dose-dependent increase in the insulin levels. SD more than 12 weeks in duration was seen in patients with thymic, adrenocortical, and colorectal cancer. Interestingly, in the phase 1 trial for the intermittent schedule^[51], 1 of the 3 patients with adrenocortical carcinoma had a confirmed PR in the primary tumor and multiple lung metastases, whereas another patient had prolonged SD of 32 weeks.

Currently, OSI-906 is being tested in combination with erlotinib in patients with NSCLC with EGFR activating mutation, in pancreatic cancer for combination with standard of care, and in head and neck cancer for combination with cetuximab. A phase 3 study comparing OSI-906 versus placebo in patients with advanced adrenocortical cancer is ongoing.

IGF-Neutralizing mAb

The only IGF-1-neutralizing mAb in clinical trials, MEDI-573, is still in the early stage of development. In a phase 1 trial of MEDI-573, the drug was well tolerated in

the 25 patients treated, and the maximum tolerated dose was not reached. Hyperglycemia occurred in 2 patients^[54]. No objective responses were seen in the phase 1 trial. Phase 2 trials are ongoing in breast cancer for combination with endocrine therapy.

Combination of IGF-1R Inhibitors and Chemotherapy or Targeted Agents

Combination with chemotherapy

A number of clinical trials have been initiated involving the combination of anti-IGF-1R mAbs and standard chemotherapies in multiple tumor types. In pancreatic cancer, the randomized phase 2 trial for gemcitabine with or without ganitumab revealed a statistically significant improvement in the combination arm in PFS [median of 5.1 months vs. 2.1 months, hazard ratio (HR) = 0.6, *P* = 0.07] and OS (median of 8.7 vs. 5.9 months, HR = 0.67, *P* = 0.12)^[56]. On the other hand, no difference in PFS was observed when

cixutumumab was added to gemcitabine and erlotinib as the backbone regimen in pancreatic cancer^[56]. The reason for the differing outcomes of the two trials is unclear. Interestingly, a population pharmacokinetics (PK) analysis in the ganitumab trial in pancreatic cancer showed a positive association between OS and PFS with higher exposure of ganitumab^[57]. Unfortunately, a definitive phase 3 trial in advanced pancreatic cancer for gemcitabine with or without ganitumab was recently halted because the independent data monitoring committee concluded that the addition of ganitumab is unlikely to result in a statistically significant improvement in the primary endpoint of OS. More data from that trial will be forthcoming in the final analysis^[58].

Data from a randomized phase 2 trial for figitumumab in combination with carboplatin and paclitaxel in advanced, treatment-naïve non-small cell lung cancer (NSCLC) showed promising results with higher overall response rates and PFS, particularly in patients with squamous cell carcinoma^[59], but this result was not confirmed in a large, international phase 3 trial. The trial was terminated early after interim analysis indicated an increase in early deaths as well as futility of the experimental arm^[60]. Biomarker exploration indicated an association between IGF-1 with toxicity and efficacy. Patients with low baseline free IGF-1 had worse survival with the addition of figitumumab (HR = 1.6, $P = 0.006$), whereas patients with high free IGF-1 had better outcomes with figitumumab and chemotherapy compared to chemotherapy alone (HR = 0.62, $P = 0.13$). Confirmation for this marker is limited at this time.

Combination with anti-estrogen therapy

A key growth and survival mechanism of estrogen-dependent tumors is the functional cross-talk and co-dependence between IGF/IGF-1R and ER^[16,61,62]. Anti-IGF-1R agents are highly active in estrogen-dependent, tamoxifen-responsive cell lines but generally ineffective in tamoxifen-resistant cells^[63]. Furthermore, addition of anti-IGF-1R antibodies to tamoxifen enhanced the anti-tumor activity in T61 and MCF-7 tamoxifen-sensitive breast cancer models^[26,63,64].

These results support the clinical evaluation of addition of IGF-1R inhibitors to anti-estrogen therapies. However, results from clinical trials combining IGF-1R mAbs and antiestrogen agents have been disappointing. The combination of ganitumab and fulvestrant or exemestane did not delay or reverse resistance to hormonal therapy^[65]. Reasons for the failure of this trial are unclear but could be related to intrinsic or induced activation of IR and/or lack of patient selection. Given the important role of IR in breast cancer, evaluation of receptor-targeting antibodies with IGF-1R TKIs or IGF-1- and IGF-2-neutralizing mAbs would be interesting.

Combination with EGFR or HER-2 inhibitors

IGF-1R signaling has been causally linked to *de novo* or acquired resistance to trastuzumab (Herceptin®) and EGFR-targeting agents in numerous models^[16]. *In vitro* and *in vivo* tumor models have also demonstrated direct interactions between IGF-1R, EGFR/HER-2^[16,62,66-68], and, in some studies, co-localization of IGF-1R and HER-2^[68,69]. Treatment of resistant cells with IGF-1R inhibitors was shown to inhibit transactivation of HER-2 and restore sensitivity to trastuzumab^[16,68,69]. Similarly, addition of anti-IGF-1R agents to EGFR TKIs or anti-EGFR mAbs has been shown to prevent, delay, or reverse resistance to EGFR inhibitors^[66,67]. The preclinical rationale supported clinical evaluations for the combination of IGF-1R and EGFR inhibitors in NSCLC, colorectal cancer, and head and neck cancers, as well as the combination of anti-IGF-1R mAb with lapatinib in HER2-positive breast cancer.

Clinical results from the combination of IGF-1R and EGFR inhibitors have been disappointing. A randomized phase 2 trial of erlotinib with or without the anti-IGF-1R mAb R1507 failed to show difference in the primary endpoint of 12-week PFS. Intriguingly, in 36 patients with *KRAS* mutation (27% of the patients who were evaluable for mutation status), the 12-week PFS appeared better in the R1507 group as compared with the erlotinib-alone arm (36% vs. 0%), although this result was based on retrospective analysis on a fraction of the patients^[70]. A phase 3 trial of figitumumab and erlotinib versus erlotinib alone in unselected NSCLC, not including adenocarcinoma patients, was closed early after an interim analysis suggesting futility and toxicity concerns^[71].

A randomized phase 2 trial in colorectal cancer with dalotuzumab (MK-0646) in combination with cetuximab and irinotecan also had a negative outcome^[72]. A subsequent analysis of biomarkers suggested that patients with high tumor expression of IGF-1R may derive benefit from the addition of dalotuzumab, whereas those with IGF-2R overexpression were likely to be resistant to anti-IGF-1R mAb^[73]. These intriguing results remain to be confirmed and warrant further studies.

Combination with mTOR inhibitors

Recent studies in preclinical models and tumor biopsies from patients demonstrate that treatment with mTOR inhibitors leads to up-regulation of AKT phosphorylation^[74,75]. They further suggest that the IGF/IGF-1R pathway mediated feedback activation of AKT and that combining rapamycin and IGF-1R inhibitors enhanced antitumor effects^[74,75]. The most significant synergism was observed in pediatric tumor models such as those for EWS and osteosarcoma,

where the combination of an anti-IGF-1R mAb and rapamycin led to complete tumor regression, whereas single agents only induced modest growth delay^[76].

This combination strategy has been pursued with several IGF-1R antibody agents^[77-81] and TKIs^[82]. A phase 1 trial with cixutumumab and temsirolimus (CCI-779, Torisel®) has shown that the combination is feasible at the full doses of both agents^[80]. Mucositis was the most common toxicity. In a preliminary study of efficacy in the expansion for 20 patients with heavily pretreated EWS, 35% patients achieved either CR/PR or SD for five months. Interestingly, 1 patient who had progressed on a previous anti-IGF-1R mAb achieved a CR that lasted for more than 20 months^[77]. In another phase 1 trial for the same strategy, with ganitumab and everolimus, CR was observed in 2 patients with refractory NSCLC^[78]. Efficacy data were also promising for patients with ER-positive breast cancer in a phase 1 trial for dalotuzumab and ridaforolimus, warranting further studies for the combination in the indication^[79]. A phase 2 evaluation of the combination is ongoing in pediatric malignancies, neuroendocrine tumors, and breast cancer.

Combination with MEK inhibitor

Preclinical work suggested activation of IGF-1R as a potential mechanism of escape from treatment with MAPK inhibitors^[18]. Also, MEK and IGF-1R inhibitors had additive effects in preclinical models with *RAF* or *RAS* mutations^[18]. Ahmed *et al.*^[83] recently reported the first clinical experience with combined IGF-1R and MEK inhibition in a National Cancer Institute (NCI)-sponsored trial of cixutumumab and selumetinib (AZD6244). Dose-limiting toxicities included visual changes, requiring dose reduction of selumetinib to 50 mg twice daily in combination with full dose cixutumumab (20 mg/kg every 3 weeks) at maximum tolerated dose. Pharmacodynamic endpoints and preliminary efficacy evaluations are ongoing in the expansion cohort.

Considerations in Predictive Markers and Resistance Mechanisms

Experience with IGF-1R inhibitors indicates that the pathway is a valid target in human cancers, but the clinical benefit seems to be restricted to a small subset of patients. Identifying patient selection markers is a critical step for success in IGF-1R inhibitor development. Several factors may also confer *de novo* or acquired resistance, including absence or biological irrelevance of the intended target, IGF-1R; escape mechanisms within or outside the IGF-1R/IR system; or constitutively activate downstream effector molecules.

At the current time, no predictive markers for IGF-1R inhibitors are available. In view of the complexity of the IGF-1R and IR family, as well as their extensive interaction with several other signal transduction pathways, it may be difficult to identify a uniform set of predictive markers for all tumor types and molecular contexts, and for all classes of IGF/IGF-1R inhibitors. Ongoing studies focus on the following areas:

- Genomic alterations within the IGF-1R axis in tumors;
- Genetic alterations outside the IGF-1R axis that may affect the IGF-1R signaling (e.g., chromosomal translocations resulting in transcriptional modulations of ligands or receptors);
- Absolute and relative levels as well as phosphorylation status of IGF-1R and IR; conformations of the receptors (homodimers or heterodimers)
- Bioavailability of ligands (including IGF-1, IGF-2, IGFBP3, and decoy receptor IGF-2R);
- Activating mutations of downstream molecules such as *AKT*, *PI3K*, *RAS*, and *RAF*;
- Markers related to parallel pathways such as EGFR and vascular endothelial growth factor (VEGF); and
- Markers related to epithelial-mesenchymal transition.

Preliminary data based on a limited number of patients suggested a few markers—free IGF-1 in the circulation and tumor expression of IGF-1, IGF-1R, and IR—warrant research and confirmation in prospective randomized trials is required. Additional studies on tumor biology and the molecular consequences of IGF-1R blockade are needed to provide guidance for patient selection and combination strategies.

Summary

The three classes of IGF/IGF-1R inhibitors—anti-IGF-1R mAbs, IGF-1- and IGF-2-neutralizing mAbs, and IGF-1R TKIs—have distinct mechanisms of actions and potentially different resistance/escape mechanisms. Given the complexity of the IGF-1R/IR family and the dynamic predominance of specific receptors and ligands in individual tumors, each class of anti-IGF/IGF-1R agents may have unique advantages in selected tumor settings and different toxicity profiles.

Currently available clinical data with anti-IGF-1R mAbs and TKIs have demonstrated that these targeting approaches are feasible and can induce strong anti-tumor activities in several tumor types, including rare tumors refractory to standard therapies. However, the efficacy is likely to be limited to a small patient subset.

A variety of mechanisms may confer intrinsic or acquired resistance, highlighting the need for rational combination strategies. Preliminary data support further studies for the combination of IGF-1R-specific inhibitors

with insulin/IR-targeting agents, mTOR inhibitors, and MEK inhibitors. Critical tasks for future research include deeper and broader understanding of the biology of IGF-1R, exploration of predictive markers, and most importantly, integration of biomarker studies in all clinical

investigations of these agents and combination regimens.

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